Protocol A5481053

STUDY OF PALBOCICLIB IN COMBINATION WITH LETROZOLE AS TREATMENT OF POSTMENOPAUSAL WOMEN WITH HORMONE RECEPTOR-POSITIVE, HER2-NEGATIVE ADVANCED BREAST CANCER FOR WHOM LETROZOLE THERAPY IS DEEMED APPROPRIATE

Statistical Analysis Plan (SAP)

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[redacted]

TABLE OF CONTENTS

1. AMENDMENTS FROM PREVIOUS VERSION(S)

Not Applicable

2. INTRODUCTION

This document describes the planned statistical analyses for Protocol A5481053 dated July 23, 2015. This analysis plan is meant to supplement the study protocol. Any deviations from this analysis plan will be described in the Clinical Study Report.

Palbociclib is being developed for the treatment of hormone receptor-positive (HR-positive), HER2-negative (human epidermal growth factor receptor 2 negative) breast cancer (BC).

The purpose of this study is to provide access to palbociclib in Mexico and in selected Latin American countries before it becomes commercially available to patients with HR-positive/HER2-negative ABC who are appropriate candidates for letrozole therapy.

2.1. Study Design

A5481053 is a multicenter, single-arm, open-label clinical study which will be conducted in Mexico and in selected Latin American countries.

Approximately 130 patients will be enrolled. This total number of patients will allow for enrollment of an adequate number of patients from each participating country. Patients will continue to receive treatment with palbociclib until disease progression, symptomatic deterioration, unacceptable toxicity, death, withdrawal of consent, or time of commercial availability of palbociclib, whichever occurs first.

Upon marketing approval of palbociclib by the local health authorities in the participating countries, patients enrolled in Study A5481053 will end participation in this study and be moved to commercially available palbociclib (if considered to be appropriate by the investigator), as soon as feasible.

Patients will receive palbociclib orally once a day at 125 mg/day for 21 days followed by 7 days off treatment for each 28-day cycle, in combination with letrozole 2.5 mg orally once a day continuously.

Patients will undergo AE monitoring as per local practice and per protocol. All grade, all causality AEs and all serious adverse events (SAEs) will be recorded on the CRF. All deaths occurring up to 28 days after palbociclib is discontinued will be recorded.

Hematology laboratory data will be recorded every 2 weeks for the first 2 cycles of therapy, then monthly at the start of each cycle thereafter. In the case of Grade ≥3 neutropenia, consider repeating complete blood count monitoring 1 week later in accordance with best

local practice and report on the CRF in order to document the level of neutropenia and the time to recovery of neutrophils to ≥1000 cells/mm^3. Re-treatment criteria are based on time to recovery of neutrophil count. For patients who develop Grade 3 or 4 neutropenia, refer to the dose modifications. The clinical actions taken as a result of Grade ≥3 neutropenia, including the use of granulocyte colony stimulating factor (G-CSF), if any, should be recorded.

Tumor response will be assessed as per local practice and only investigator tumor assessments will be collected. The date of tumor progression will be recorded. No statistical tests will be performed.

The end of the trial is defined by the time of regulatory approval and commercial availability of palbociclib for the treatment of advanced breast cancer. At that time, patients enrolled in the study will be moved to commercial supply. A separate patient assistance program is designed to cover all patients (ie, "no patient left behind"). There will be some time lag between approval and commercial availability of palbociclib; therefore, there will be a 4 month or more transition period after approval to allow patients to access locally available commercial drug.

2.2. Study Objectives

Primary Objective:

- To provide access to palbociclib in Mexico and in selected Latin American countries to postmenopausal patients with hormone receptor-positive (HR-positive), HER2-negative ABC who are deemed appropriate for letrozole therapy.

Secondary Objectives:

- To gain additional safety data of the combination of palbociclib with letrozole in the postmenopausal HR-positive/HER2-negative population.
- To gain additional antitumor activity data of the combination of palbociclib with letrozole in postmenopausal HR-positive/HER2-negative population.

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

This is an open-label study. No interim analysis is planned for this study. However, summaries of accumulating safety and efficacy data from the study may be presented at academic meetings during the course of the study, as appropriate. The final analyses will be performed at the time of study completion as determined by the Sponsor.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

Because of the nature of the study, no inferential analyses are planned, and no hypotheses will be tested.

4.2. Sample Size Determination and Statistical Decision Rules

Due to the nature of this study, the number of patients to be enrolled is not determined for the hypothesis testing. Based on the prevalence of the disease and eligible study population over the timelines of this study, it is estimated that the study will enroll 130 patients.

When patients are moved to commercial supply of palbociclib, their participation in the study and clinical study data collection will be discontinued.

5. ANALYSIS SETS

The as-treated (AT) population or safety analysis set will include all patients who receive at least 1 dose of palbociclib treatment. The AT population will be the primary population for evaluating treatment administration/compliance and safety.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoints

Tumor assessments are to be performed at Screening and as per local clinical practice and the patient's clinical status thereafter. No uniformed assessment schedule is planned for tumor assessments across the sites. Tumor assessments will be evaluated as per local guidelines by investigators and the tumor responses which are based on their tumor assessments will be collected in the Investigator Overall Tumor assessment (IOTA) eCRF.

6.1.1. Objective Response (OR)

Objective response is defined as the overall complete response (CR) or partial response (PR). Objective Response Rate (ORR) is defined as the proportion of patients with CR or PR relative to all AT population. Patients who do not have on-study tumor re-evaluation, who receive anti-tumor treatment other than the study medication prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of ORR.

6.1.2. Duration of Clinical Benefit

Duration of clinical benefit is defined as the length of time patients remain on palbociclib treatment from the first day of treatment until the last day of treatment in this study. Duration of clinical benefit = (palbociclib last dose date – palbociclib 1st dose date +1)/7.02

6.2. Other Endpoints

6.2.1. Patient Disposition

The number of patients treated with palbociclib and/or letrozole, treated with palbociclib, treated with letrozole, and the number of patients who withdrew from the study, as well as their reasons for discontinuation, will be summarized in data table format.

6.2.2. Baseline Characteristics

Demographic characteristics such as age, race, prior medication, and physical examination results will be tabulated.

6.2.3. Treatment Administration and Compliance

Study drug administration will be described in terms of:

- Total and median number of weeks administered
- Reasons for dose interruptions

6.3. Safety Data

Adverse events (AEs), hematology, blood chemistry will be assessed as described in the Schedule of Activities of the protocol. The records will be excluded from the analysis if AE onset date and laboratory data collecting date fall 28 days after the final dose of treatment or at/after a new non-study treatment's starting date (whichever comes first). AE/SAE observed beyond 28 days and recorded in the database per Sponsor's agreement will be included and marked in the AE/SAE listings.

Adverse events will be classified using the MedDRA classification system. The severity of the toxicities will be graded according to the NCI CTCAE version 4.03. The hematologic and chemistry laboratory results will be graded according to the NCI CTCAE v.4.03 severity grade. For parameters for which an NCI CTCAE v.4.03 scale does not exist, the categories of values below, within, and above the normal range for the local lab will be used.

6.3.1. Treatment Emergent Adverse Event

An adverse event is considered treatment emergent if:

- The event occurs for the first time after the start of study treatment and before 28 days after final dose of study treatment and was not seen prior to the start of treatment, or
- The event was seen prior to the start of treatment but increased in NCI CTCAE toxicity grade during study treatment.
- Disease progression is not considered a treatment emergent adverse event unless the patient dies of disease prior to 28 days after discontinuation of treatment.

6.3.2. Treatment Related Adverse Event

Adverse events defined as treatment emergent adverse events with causality having 'YES/UNKNOWN related to study treatment' as judged by the investigator are defined as treatment related adverse events.

6.3.3. Laboratory Safety Assessments

Laboratory assessment will be assigned to cycle and week in the cycle based on the collection date of the sample relative to the study drug administration start date of each cycle.

Baseline evaluations for laboratory are those collected

- Within 28-30 days prior to or on first day of study drug and
- If there is more than one baseline evaluation, closest to but any time prior to the 1st dosing on the first day of study treatment.

Laboratory abnormalities

- For parameters which have an NCI CTCAE v.4.03 scale: CTC grade is graded according to the NCI CTCAE v.4.03 severity grade
- For parameters which do not have an NCI CTCAE v.4.03 scale: the categories of values below, within, and above the normal range for the local lab will be used

6.3.4. ANC

- Nadir ANC values during post-baseline
- Time-to-lowest ANC count during post-baseline
- Time-to-1st ANC count < 1000 cells/mm^3
- Time-to-recovery of ANC to ≥1000 cells/mm^3

6.3.5. ECOG

All ECOG values

6.3.6. Electrocardiogram (ECG)

All ECG tests

6.3.7. Death

- Death from any cause while on treatment and within 28 days of palbociclib discontinuation
- All reported deaths from any cause at any day (for death listing only)

6.4. Covariates and Stratification Factors

Not Applicable

7. HANDLING OF MISSING VALUES

7.1. Missing Dates

In compliance with Pfizer standards, if the day of the month is missing for any date used in a calculation, the 1st of the month will be used to replace the missing date. If the month is missing for any date used in a calculation, January will be used to replace the missing month. For any imputed post-baseline date, if the calculation results in a negative duration, then the date resulting in 1 day duration will be used (e.g., date of onset cannot be prior to day one date).

Missing dates for adverse events will be imputed based on the similar principle.

- For the start date, if the day of the month is missing, the 1st day of the month will be used to replace the missing date. If both day and month are missing, January 1 of the non-missing year will be used to replace the missing date. If the first dose date is later than this imputed date, then impute the start date again to the first dose date.
- For the stop date, if the day of the month is missing, the last day of the month will be used to replace the missing date. If both day and month are missing, December 31 of the non-missing year will be used to replace the missing date.

If the start date is missing for an AE, then AE is considered to be treatment emergent unless the non-missing month and year indicate the AE onset prior to the treatment start date.

7.2. Other Missing Data

Other missing non-date data will not be imputed or carried forward.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

For the continuous variable, descriptive statistics (n, mean, standard deviation, median, minimum, and maximum values) will be summarized.

For the categorical variables, the total patients count, number and percentage of patients in each category will be provided.

Time-to-event endpoints will be summarized using the Kaplan-Meier method and displayed graphically when appropriate. Median event times and 2-sided 95% confidence interval (log-log transformation function is used (Kalbfleisch and Prentice 1980[1])) for each median will be provided.

Individual patient data will be presented in data listings.

8.2. Statistical Analyses

8.2.1. Primary Efficacy Analysis

No formal efficacy analysis will be conducted.

- If applicable, ORR with will be summarized (N, n, %) in AT population along with the corresponding 2-sided 95% exact (Clopper-Pearson[2]) confidence intervals which are based on the binomial distribution.

- If applicable, descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) for the duration of clinical benefit (in weeks) will be provided.

8.2.2. Standard Analyses

Descriptive statistics will be used to summarize study conduct and patient disposition, baseline characteristics, and treatment administration/compliance.

- **Study Conduct and Patient Disposition** - the number and percentage of patients enrolled, accrual by study center, treated (treated-palbociclib or letrozole, treated-palbociclib, and treated-letrozole), assessed for AEs, laboratory data, etc. The number and percentage of patients: 1) discontinued from the study and the reason for the discontinuation, 2) discontinued from treatment-palbociclib and reasons for the discontinuation, 3) discontinued from treatment- letrozole and reasons for the discontinuation. Listing on patients along with the reason for their premature discontinuation from the study will be provided.

- **Baseline Characteristics** - patient characteristics such as patient age, height, weight, race, ethnicity, ECOG performance status, primary diagnosis, prior therapy (radiotherapy, surgery, systemic therapy), prior medication, medical history, and signs and symptoms at study entry (if applicable) will be summarized in frequency tables, and descriptive statistics will be provided for quantitative variables.

- **Treatment Administration and Compliance**
  Study drug administration will be described in terms of the total number of cycles administered, the median (range) of cycles administered, relative dose, relative dose intensity, dose modifications, dose interruptions, and reasons for dose interruptions.

- **Concomitant medications and Non-drug treatments**
  Concomitant drug and non-drug treatments will be listed. Granulocyte Colony Stimulating Factor (G-CSF) treatment for neutropenia will be summarized.

8.2.3. Safety Analyses

Listings of AE, SAE, death, lab data, ECOG, and physical examinations (if available in database) will be provided according to reporting standard.

8.2.3.1. Adverse Events

All patients treated with at least one dose of study treatment (i.e. palbociclib / letrozole) will be included in all the safety analyses.

Adverse events will be classified using the medical dictionary for regulatory activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE v.4.03 whenever possible (http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

Adverse events will be summarized 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 v.4.03 grade during the study.

Adverse events leading to death or discontinuation of study, events classified as NCI CTCAE v.4.03 Grade 3 or higher, trial drug related events, and serious adverse events will be considered with special attention.

The following summaries of treatment emergent adverse events will also be provided:

- Discontinuations Due to Adverse Events including causality: all cause, treatment related, including relationship to specific study treatment of letrozole and /or palbociclib.
- Temporary Discontinuations or Dose Reductions Due to Adverse Events including causality and relationship to specific study treatment of letrozole, and /or palbociclib.
- Treatment-Emergent Adverse Events (All Causality, and Treatment Related) including the number of patients evaluable for adverse events, total number of adverse events (counting each unique preferred term across all patients), number of patients with serious adverse events, number of patients with Grades 3 and 4 adverse events, number of patients with Grade 5 adverse events, and number with dose reductions or temporary discontinuations due to adverse events
- Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term and Maximum NCI CTCAE v.4.03 Grade (All Causality, and Treatment related)
- Treatment-Emergent Adverse Events by MedDRA Preferred Term sorted by Descending Order of AE Frequency (All Causality, and Treatment related)
- Treatment-Emergent Adverse Events by Preferred Term – Grade 3/4/5 events with number of patients experienced Grade 3-5 AEs and total number of Grade 3-5 AEs, sorted by Descending Order of AE Frequency (All Causality, and Treatment Related)

A summary of Serious Adverse Events and listing of deaths reported as serious adverse events will be provided.

8.2.3.2. ECG

Only patient listing will be provided. Each patient's individual ECG tests with mean of 3 repeated ECG values of each test will be listed.

8.2.3.3. Death

All reported deaths are included. Total numbers of patients and percentage on cause of death and source of death will be summarized. Listing of all deaths will be provided.

8.2.3.4. Laboratory abnormalities

Laboratory data will be reported in data listing.

The hematologic and metabolic laboratory results will be summarized in descriptive statistics on change from baseline and % change from baseline by cycle and by week in each cycle.

The shift table from each patient's baseline to her worst grade during post-baseline for each hematologic and metabolic laboratory parameter will be provided, respectively.

Descriptive statistics on nadir ANC values during post-baseline and time-to-lowest ANC count during post-baseline in the AT population will be provided. Survival analyses using Kaplan-Meier method on time-to-1st ANC count < 1000 cells/mm^3 (i.e. 1st Grade ≥3 neutropenia) and time-to-recovery of ANC to ≥1000 cells/mm^3 will be provided. The median event time and 2-sided 95% confidence interval for the median will be included, if applicable. Time-to-recovery of ANC to ≥1000 cells/mm^3 is defined as the length of time (in week) from 1st ANC < 1000 cells/mm^3 to 1st recovery of ANC to ≥1000 cells/mm^3 in sub-AT population who ever have ANC < 1000 cells/mm^3 during the post-baseline.

8.2.3.5. ECOG **performance status**

ECOG performance status shift table from each patient's screening value to her end of study value will be provided. A listing of all ECOG data will be provided.

9. REFERENCES

1. J.D. Kalbfleisch and R.L. Prentice The statistical analysis of failure time data. John Wiley & Sons, Inc., New York, 1980
2. Collett, D. (1991), Modelling Binary Data, London: Chapman & Hall

10. APPENDICES

10.1. Schedule of Activities

Visit Identifier	Screening[a]	Treatment: One cycle = 28 days[b]		End of Treatment[d]	End of Study[d]
		Cycles 1 and 2	Cycles ≥3		

Study day **Time window**	**Within 28-30 days prior to randomization unless specified otherwise**	**Day 1**[c] **±2 days**	**Day 14** **±2 days**	**Day 1** **±2 days**		
Procedures at Screening						
Informed consent[e]	X					
Eligibility criteria evaluation[f]	X					
Registration[g]	X					
Medical/Oncological history[h]	X					
Procedures at Screening and on study						
Physical examination[i]	X	Per routine clinical practice				
ECOG performance status[j]	X	Per routine clinical practice			X	
12-Lead ECG[k]	X	As clinically indicated				
Treatments						
Palbociclib (PD-0332991[l])		Orally once daily from Day 1 to Day 21 of each cycle (Schedule 3/1)				
Letrozole[m]		Orally once daily (Schedule: continuous dosing)				
Clinical Assessments						
Tumor assessment (CT or MRI scans) [n]	X	Per routine clinical practice				
Adverse events[o]	X	X				X
Hematology (platelet count, ANC, WBC count, hemoglobin) [p]	X	X	X	X	X	
HbA1c[q]	X	Every 3 months			X	
Blood chemistry[r]	X	Per routine clinical practice				

Abbreviations: ECOG=Eastern Cooperative Oncology Group; ECG=electrocardiogram; CT=CAT scan; MRI=magnetic resonance imaging; ANC=absolute neutrophil count; WBC=white blood cell; HbA1c=Glycated hemoglobin.

a. **Screening:** All assessments should be performed within 28-30 days prior to study randomization.
b. **Active Treatment Phase:** All assessments should be performed prior to dosing with study medications on the visit day unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headers. Clinical visits will be conducted as per local practice and as clinically indicated. Each subsequent cycle will begin 7 days after the last dose of study drug in the prior cycle to allow patients a 7-day washout period for each cycle.
c. **Cycle 1/Day 1:** Blood chemistry and hematology not required if acceptable screening assessment is performed within 7 days prior to randomization.
d. **End of Treatment/End of Study:** The End of Treatment (EOT) visit will be conducted when palbociclib is permanently discontinued for any reason. The indicated assessments are to be obtained if not completed in the last week of therapy. Patients who permanently discontinue palbociclib for any reason will also complete an End of Study (EOS) visit that will occur 28 days after last dose of palbociclib. An EOS visit will be completed if a patient will continue on commercial palbociclib. Adverse events should be followed up until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable".
e. **Informed Consent**: Must be obtained prior to undergoing any study specific procedures
f. **Eligibility Criteria Evaluation:** Patients must meet all of the eligibility criteria in the protocol.

g. **Registration:** Patient identification number will be attributed to each patient. Patients will be assigned a single subject identification number (SSID) which will be obtained at the time of screening using the automated registration system and retained throughout the study. A separate randomization number will be assigned by the automated registration system at Cycle 1 Day 1 and will be recorded on the CRF.

h. **Medical/Oncologic History:** Medical history includes history of disease process other than oncology (active or resolved). Oncological history includes date of primary diagnosis, information on prior antitumor treatments and radiotherapy, and oncologic surgeries.

i. **Physical Examination:** General clinical examination of major body systems. To be performed at Screening, and as per routine clinical practice during the treatment.

j. **ECOG Performance Status**: To be performed at Screening, as per routine clinical practice during the treatment, and at EOT. ECOG performance status scale is available in Appendix 1 of the Protocol.

k. **12-Lead ECG**: Three consecutive 12-lead ECGs will be performed approximately 2 minutes apart at Screening to verify eligibility. ECG to be repeated during the treatment, as clinically indicated. If the mean QTc is prolonged (value of >500 msec), then the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Only ECG at Screening will be recorded on the CRF (Case Report Form).

l. **Palbociclib Administration:** PD-0332991 will be administered orally once daily at the starting dose of 125 mg on Day 1 to Day 21, followed by 7 days off treatment (Schedule 3/1). The patient will receive drug supply at the clinical site that will be sufficient to last until their next cycle visit.

m. **Letrozole Administration:** Letrozole will be administered orally once daily at the dose of 2.5 mg (continuous daily dosing schedule). Locally obtained commercial supplies of letrozole will be used

n. **Tumor Assessments:** Tumor assessments are to be performed at Screening as per local practice and according to the patient's clinical status thereafter. Tumor assessment evaluation will be conducted as per local guidelines. Only investigator's assessments will be recorded on the CRF.

o. **Adverse Events**: Patients must be followed for adverse events (AEs) from the time they signed the informed consent until 28 days after the last treatment administration or until all palbociclib-related toxicities have resolved, whichever is later. AEs (serious and nonserious) should be recorded on the CRF from the time the patient has taken at least 1 dose of investigational product through the patient's last visit. AEs should be documented and recorded at each clinical visit using NCI CTC-AE version 4.03. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent through and including 28 calendar days after the last administration of the investigational product. SAEs experienced by 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 SAEs that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.

p. **Hematology:** To include platelet count, absolute neutrophil count (ANC), white blood cell (WBC) count, and hemoglobin. To be performed to check patient's eligibility at Screening, every 2 weeks (Days 1 and 14) of the first 2 cycles, then monthly on Day 1 of each subsequent cycle of treatment with palbociclib and at EOT. In the case of Grade ≥3 neutropenia consider repeating complete blood count monitoring 1 week later in accordance with best local practice and report on the CRF in order to document the ANC value at the time of severe neutropenia as well as the time to recovery of neutrophils to ≥1000 cells/mm3. Re-treatment criteria are based on time to recovery of neutrophil count. For patients who develop Grade 3 or 4 neutropenia, refer to the dose modifications described in Table 6 of Protocol. If granulocyte-colony stimulating factors (G-CSF) and/or antibiotics are administered, their use will be documented on the CRF.

q. **Glycated Hemoglobin (HbA1c):** To be assessed at Screening, every 3 months, and EOT, and will be documented on the CRF.

r. Blood Chemistry: To be performed to check patient's eligibility at Screening and as per routine clinical practice thereafter. Only laboratory data at Screening will be recorded on the CRF.