Protocol A5481037

A 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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1. AMENDMENTS FROM PREVIOUS VERSION(S)

The SAP is being amended to reflect the changes in Protocol Amendments 1 (April 13, 2015), 2 (August 14, 2015), 3 (May 31, 2016). Following changes were made in this amendment:

- Per the request from the Regulatory Agency in India, the primary objective of the study has been revised to include safety.
- Removed country limitation to make the study open to other countries.
- The number of patients to be enrolled in the study has been increased to approximately 300 patients.
- Removed Schedule of Activity from Appendices since it is in study protocol and could be amended over time.
- Other editorial modification of the analysis plan.

2. INTRODUCTION

This document describes the planned statistical analyses for Protocol A5481037 (dated September 24, 2014), Protocol Amendment 1 (April 13, 2015), Protocol Amendment 2 (August 14, 2015), and Protocol Amendment 3 (May 31, 2016). This analysis plan is meant to supplement the study protocol. Any deviations from this analysis plan will be described in the Clinical Study Report.

Oral palbociclib is a novel, first-in-class highly selective reversible inhibitor of cyclin dependent kinases (CDK) 4 and 6 that is being studied for use in the treatment of cancer. The compound inhibits cell proliferation by preventing progression of the cell cycle from G1 into the S phase.

Both pre-clinical and clinical study results indicate that the combination of palbociclib with letrozole demonstrated antitumor activity among patients with ER(+), HER2(-) advanced breast cancer. Additionally, the combination appears to have a manageable side effect profile.

The purpose of this study is to collect safety data while providing access to palbociclib before it becomes commercially available to post-menopausal patients with hormone receptor-positive [HR(+)], HER2-negative [HER2(-)] ABC who are deemed appropriate for letrozole therapy.

2.1. Study Design

This is an open-label, single arm, multi-center clinical trial. Patients will be enrolled and will continue to receive treatment with the combination therapy until disease progression,

symptomatic deterioration, unacceptable toxicity, death, withdrawal of consent, or at the time of commercial availability of palbociclib.

Upon marketing approval of palbociclib by the local health authorities in the participating countries, patients enrolled in Study A5481037 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 study-related assessments as outlined in the Schedule of Activities table. 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 last dose of study treatment will be recorded.

Tumor response will be assessed by investigator as per local practice. The overall tumor assessment will be collected on CRF. The date of tumor progression will be recorded. No statistical tests will be performed.

Patients enrolled in Australia will be subjected to additional assessments (Australian Sub-study). Patient reported health utility and general health status will be assessed in each patient using the EuroQol Group's EQ-5D Self-Report Questionnaire (EQ-5D). The questionnaire will be administered to each patient before starting the study treatment (baseline), at every clinical visit during study treatment and at the end of treatment.

2.2. Study Objectives

Primary Objective:

- To collect safety data while providing access to palbociclib to post-menopausal patients with hormone receptor-positive [HR(+)], HER2-negative [HER2(-)] ABC who are deemed appropriate for letrozole therapy.

Secondary Objectives:

- To gain additional anti-tumor activity data of the combination therapy of palbociclib with letrozole in postmenopausal HR(+)/HER2(-) population.
- To gain additional Patient Reported health utility and general health status (Australian patients only).

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

The study is designed as an open-label study to collect additional safety data while providing access to palbociclib to post-menopausal patients with hormone receptor-positive [HR(+)], HER2-negative [HER2(-)] ABC who are deemed appropriate for letrozole therapy. No

interim analyses are planned. 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

The purpose of this study is to collect safety data while providing access to palbociclib to post-menopausal patients with hormone receptor-positive [HR(+)], HER2-negative [HER2(-)] ABC who are deemed appropriate for letrozole therapy before it becomes commercially available to patients. There is no statistical hypothesis test for the study.

4.2. Sample Size Determination and Statistical Decision Rules

Due to the nature of the study, no sample size determination is made by statistical procedure and there are no statistical decision rules.

Approximately 300 patients will be enrolled in this study. Patients will continue to receive treatment with palbociclib and letrozole until disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurs first. Patients who permanently discontinue palbociclib for any reason will be off study.

Upon marketing approval of palbociclib by the local health authorities in the participating countries, patients enrolled in Study A5481037 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. When patients exit the study, all study related 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. The PRO-evaluable population will be defined as patients from the as-treated (AT) population who completed the EQ-5D at baseline and at least 1 visit post baseline. The PRO-evaluable population will be the primary population for analysis of change from baseline scores.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoints

Because of the nature of the study, no inferential analyses are planned, and no hypotheses are to be tested. However, some exploratory analyses may be conducted if data are available. Specifically, analyses on objective response (OR, assessed by investigator), and duration of clinical benefit may be conducted if appropriate.

Tumor assessments are to be performed at Screening and as per local practice and the

patient's clinical status thereafter. No uniformed assessment schedule is planned for patients across the sites. Tumor assessments will be evaluated as per local guidelines by investigators and their assessments will be collected in the CRF.

The OR rate will be provided along with the corresponding exact 95% 2-sided confidence interval using standard methods based on the binomial distribution.

Duration of Clinical Benefit: For patients who are taking palbociclib combination treatment in the study, 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.

6.2. Safety Data

Overall safety profile as characterized by type, frequency, severity of adverse events as graded by NCI Common Toxicity Criteria for Adverse Events version 4.03 (NCI CTCAE v.4.03), timing and relationship to treatment on each arm, and laboratory abnormalities observed.

Adverse events (AEs), hematology, blood chemistry will be assessed as described in the Schedule of Activities of the protocol.

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 frequency of patients with values below, within, and above the normal range for the local lab may be summarized.

Patients who start treatment are assessed for toxicities up to 28 days after the final dose of treatment. Toxicities observed up to 28 days after the last dose of treatment will be included in safety summaries.

6.2.1. 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.

6.2.2. Treatment Related Adverse Event

Adverse events defined as treatment emergent adverse events with cause possibly, probably or definitely related to treatment as judged by the investigator are defined as treatment related adverse events. Events that are continuation of baseline abnormalities are not considered treatment related unless there is an increase in grade, or if there is an increase following a decrease, and the increase is judged by the investigator to be caused by the treatment.

6.2.3. Laboratory Safety Assessments

Laboratory assessment will be assigned to cycles based on the collection date of the sample relative to the start dates of cycles from the study drug administration.

Baseline evaluations for laboratory are those collected

- Within 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.

6.2.4. Electrocardiogram (ECG)

Three consecutive 12-lead ECGs will be performed approximately 2 minutes apart at Screening. ECG could 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. ECGs performed during treatment will need to be available from the patient's medical record upon request by the Sponsor. In the case an ECG abnormality meets the definition of AE, it is captured on an AE CRF page.

6.3. Other Endpoints

6.3.1 Patient Reported Outcomes Endpoints

The patient reported outcomes endpoints will include health utility and general health status measured using the EQ-5D questionnaire .

The EQ-5D questionnaire consists of the EQ-5D descriptive system and a visual analogue scale (the EQ VAS). The EQ-5D descriptive system measures a patient's health state on 5 dimensions which include: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The respondent's self-rated health is assessed on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state) by the EQ-VAS.

6.4. Covariates and Stratification Factors

N/A

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 unless the calculation results in a negative time duration (e.g., date of onset cannot be prior to day one date). In this case, the date resulting in 1 day duration will be used. If the day of the month and the month is missing for any date used in a calculation, January 1 will be used to replace the missing 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, the AE is considered to be treatment emergent unless the collection date is prior to the treatment start date.

For the EQ-5D, in cases where two answers are given to one item, the item will be considered missing. For the EQ-5D, questions not answered will be considered missing items and will not be utilized.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

Descriptive statistics for continuous variables will include the mean, standard deviation, median, minimum, and maximum values.

For categorical variables, summary measures will include the number and percentage of patients in each category.

Missing data will not be imputed or carried forward. 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. Summary of OR, assessed by investigator, and duration of clinical benefit may be performed if appropriate.

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** - an accounting of the study patients will be tabulated including number of patients enrolled, treated, accrual by study center, assessed for AEs, laboratory data, etc. Patients not meeting the eligibility criteria will be identified. Patients not completing the study will be listed along with the reason for their premature discontinuation. Reasons for premature discontinuation will be summarized.

- **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 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, dose intensity, dose modifications, dose interruptions, and reasons for dose interruptions.

- **Concomitant medications and Non-drug treatments**

  Concomitant and non-drug treatments are not collected on the CRFs but will be available in patients' medical record files, except for Granulocyte Colony Stimulating Factor (G-CSF) treatment for neutropenia. G-CSF use will be documented in CRF and summarized in study report.

8.2.3. Safety Analyses

Listings of AE, SAE, death, lab data, 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 trial treatment, 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. Laboratory abnormalities

The hematologic laboratory results will be graded according to the NCI CTCAE v.4.03 severity grade. For parameters for which an NCI CTCAE v.4.0 scale does not exist, the frequency of patients with values below, within, and above the normal range for the local lab

may be summarized. Each patient will be summarized by the worst severity grade observed for a particular laboratory parameter.

Hematologic laboratory data will be summarized by maximum change from baseline. Chemistry data will be reported in data listing.

Patient Reported Outcomes Analyses

The PRO-Evaluable population will be the primary population for the analysis change from baseline. Visit windows will be applied for the analysis of the PRO endpoints.

The EQ-5D will be scored according to its scoring manual[1]. Each dimension of the health state profiles (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) will include the proportion of patients reporting "no health problems," "moderate health problems" and "extreme health problems". A health utility index score will be calculated using the standard algorithm for Australia provided in the manual.

Instrument Compliance Rates

At each time point, the number and percentage of patients who complete the EQ-5D will be summarized in a table, as will the reasons for non-completion. The questionnaire is considered complete if at least one item was answered by the patient.

Descriptive statistics by treatment arm will be reported for the actual score and change from baseline for health utility index and EQ-5D VAS scores. It will include the mean (and 95% CI), median (and range), and number of patients completing the scale for each arm at each time assessment after baseline A chart depicting the mean of actual score sand change from baseline scores along with the SE error bars at each time assessment will be provided.
To calculate overall actual scores and change from baseline scores repeated measures mixed-effects modelling will be carried for the EQ-5D health utility index and the general health status scores. Repeated measures over time will be accounted by unstructured covariance structure (using the REPEATED statement in PROC MIXED).

9. REFERENCES

1. The EuroQol Group. EQ-5D: A measure of health-related quality of life developed by the EuroQol Group: User Guide. V 5.0., Oct 2013.
2. Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Medical Care 2005; 43:203-220

10. APPENDICES

Euro Qol-5D (EQ-5D) (for Australian patients only)

[redacted]

Health Questionnaire

English version for the UK
(validated for Ireland)

[redacted]

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

Mobility

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

Self-Care

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

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

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

Pain/Discomfort

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

Anxiety/Depression

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

[redacted]

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

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

Your own health state today