PROTOCOL A5481019

A PHASE 1 OPEN-LABEL PHARMACOKINETICS STUDY OF PALBOCICLIB, A CYCLIN-DEPENDENT KINASE 4 AND 6 (CDK4/6) INHIBITOR, IN POSTMENOPAUSAL CHINESE WOMEN WITH ER (+), HER2 (-) ADVANCED BREAST CANCER

STATISTICAL ANALYSIS PLAN (SAP)

Version: 2.0

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Date: 16 May 2016

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APPENDICES

1. AMENDMENTS FROM PREVIOUS VERSION(S)

This is the Version 2.0 (Amendment 1) of the Statistical Analysis Plan (SAP).

The following changes have been made to the previous Version 1.0.

- Updated the plan according to the protocol amendment 2 including the schedule of activites in Appendix 1.
- Removed the description of pharmacogenomic endpoints and analyses.
- Added the description of interim summary in Section 3.
- Added the categorical summary of vital signs as defined in Section 8.2.2.2.4.
- Revised the definition of actual dose intensity and intended dose intensity from dose per week to dose per day and clarified the calculation of relative dose intensity in Appendix 5.2.
- Added the definition of the programmatic data cut-off algorithm for interim reports in Appendix 6.

2. INTRODUCTION

Note: in this document any text taken directly from the protocol is ***italicised***. Any deviations from this analysis plan will be documented in the clinical study report.

This Phase 1 China-only PK study (A5481019) is intended to support the CFDA regulatory filing requirement of palbociclib, and is designed to evaluate the PK profile and safety of palbociclib as combination therapy with letrozole in Chinese patients with ER(+), HER2(-) ABC. In addition, efficacy will be evaluated as one of the secondary objectives.

2.1. Study Design

This is a single-country, non-randomized, open-label, single-arm, multicenter Phase 1 clinical trial which will evaluate PK, safety and efficacy of palbociclib in combination with letrozole in postmenopausal Chinese women with ER(+)/HER2 (-) ABC.

A minimum of approximately 25 patients will be enrolled to the study and patients may be replaced if there are less than 12 patients completing the single-dose and multiple-dose PK sample collections without dosing interruption or dose modification.

Single-dose PK (Lead-in phase, total 5 days) will be conducted prior to multiple-dose PK (Cycle 1). On Day 1 of the single-dose PK part (Lead-in phase), patients will receive a single oral dose of palbociclib 125 mg and letrozole 2.5 mg. From Day 2 to Day 5, patients will receive letrozole 2.5 mg alone once daily as a background therapy. From Cycle 1 Day 1 (C1D1), patients will receive palbociclib 125 mg once daily orally for 3 weeks followed by 1 week off treatment and letrozole 2.5 mg once daily orally continuously. Patients will remain on study treatment with combination treatment of palbociclib and letrozole until disease progression, unacceptable toxicity, withdrawal of

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

Patients will be screened within 28 days of the first dose of study medication. Patients will be admitted to the clinical research unit (CRU) at least 12 hours prior to Day 1 dosing in Lead-in phase and remain in the CRU until at least 72 hours post-dose on Day 4 in Lead-in phase for PK samplings before discharge (the duration of confinement is subject to change given the availability of CRU). Patients will return to the CRU as outpatient visits on Day 5 (Lead-in phase) for morning PK sample collection at 96 hours post-dose and on C1D1 for predose morning PK sample collection (120 hours post single dose). During Cycle 1, patients will visit the CRU for hematology evaluation on Day 14 and trough PK sample collection (predose) on Day 19. Patients will return to the CRU on C1D20 for trough PK sample collection (predose) and remain in the CRU until C1D24 for PK sample collection before discharge (the duration of confinement is subject to change given the availability of CRU). Patients will visit the CRU on Days 25, 26 of Cycle 1and C2D1 for morning trough PK sample collection (predose).

Blood samples for determination of palbociclib concentrations will be collected at 2, 4, 6, 8, 10, 24, 48, 72, 96, and 120 hours after single-dose palbociclib administration for single-dose PK in Lead-in phase and after palbociclib dose on C1D21 for multiple-dose PK. Trough blood samples (predose) for both palbociclib and letrozole will be collected on Days 19-21 of Cycle 1. An additional trough blood sample (predose) for letrozole will be collected on C2D1.

Disease assessments will be performed every 12 weeks (± 7 days) from C1D1. Patients with bone lesions identified at baseline will also have repeat bone scans performed every 24 weeks (± 7 days) from C1D1. Each assessment will be performed as scheduled according to the calendar regardless of any dosing delay to prevent the introduction of bias into the assessment of efficacy. Failure to perform any of the required disease assessments will result in the inability to determine disease status for that time point. Tumor assessments will be performed until radiographically and/or clinically (ie, for photographed or palpable lesions) documented disease progression as per RECIST v.1.1, study treatment discontinuation (for patients continuing treatment beyond RECIST-defined disease progression), initiation of new anticancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first. A series of incomplete disease assessments will result in censoring of PFS back to the time of the last full assessment that did not show disease progression.

The study also includes translational components aimed at characterizing alterations in proteins relevant to the cell cycle, drug targets, and patient response over time. Longitudinal monitoring of palbociclib pharmacodynamic marker modulation, such as

phosphorylated retinoblastoma protein (pRb) and Ki67 expression using skin biopsies and thymidine kinase (TK) activity using serum samples will allow characterizing the relationship among PK, biomarker, and patient clinical response. The duration and magnitude of cell cycle inhibition after palbociclib treatment may also be obtained. This biomarker analysis will be critical for better understanding of the mechanism of action of palbociclib in breast cancer patients, and may also potentially identify patients with better response to palbociclib treatment.

See for details of schedule of activities.

2.2. Study Objectives

Primary Objective

- *To determine single-dose and multiple-dose PK profiles of Palbociclib in combination with letrozole in Chinese patients with ER(+)/HER2(-) advanced breast cancer who have not received any prior systemic anti-cancer therapy for their advanced disease.*

Secondary Objectives

- *To evaluate safety of palbociclib in combination with letrozole in this patient population.*
- *To evaluate efficacy of palbociclib in combination with letrozole in this patient population.*
- *To evaluate trough plasma concentration of letrozole after multiple dosing.*
- *To evaluate biomarker changes post palbociclib treatment and their correlation with drug exposure and efficacy endpoints if data permit.*

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

Interim summary reports will be generated during the study for fulfillment of the regulatory submission requirement. See Appendix 3 for the programmatic data cut-off algorithm for interim summaries. Interim summaries will include the summary of subject information, PK data, and safety results, and may include the summary of efficacy results or biomarker data if deemed necessary.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

Not applicable.

4.2. Statistical Decision Rules

Not applicable.

5. ANALYSIS SETS

5.1. Full Analysis Set

The Full Analysis Set (FAS) is defined as all subjects enrolled.

5.2. 'Per Protocol' Analysis Set

The efficacy analysis set is defined as all enrolled patients who start the treatment of Cycle 1. This analysis set will be used for efficacy analysis. Sensitivity analyses may be conducted on patients in the efficacy analysis set without major protocol deviations for efficacy evaluation or other subsets of the efficacy analysis set (eg, with measurable disease at baseline) for certain efficacy endpoints if deemed necessary.

5.3. Safety Analysis Set

The safety analysis set is defined as all enrolled patients that receive at least one dose of study medication. This analysis set will be used for safety analysis.

5.4. Other Analysis Sets

5.4.1. PK Concentration Analysis Set

The PK concentration analysis population is defined as all patients enrolled and treated who have at least 1 PK concentration in single dose and/or multiple dose PK part.

5.4.2. PK Parameter Analysis Set

The PK parameter analysis population is defined as all patients enrolled and treated who have at least 1 of the PK parameters of primary interest in single dose and/or multiple-dose PK part.

5.4.3. PK Evaluable Analysis Set

The PK evaluable analysis set is defined as all patients in the PK parameter analysis set who complete both the single dose PK and multiple dose PK parts without major protocol deviations for PK evaluation.

5.4.4. Biomarker Analysis Set

A subset of enrolled and treated patients who have both pre-dose value and at least one post-dose value for at least one biomarker.

5.4.5. Ocular Analysis Set

A subset of enrolled and treated patients who have both baseline and at least one post-dose value for at least one ocular assessment. 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 as they do not undergo these ophthalmic procedures.

5.5. Treatment Misallocations

Not applicable.

5.6. Protocol Deviations

Subjects who experience events that may affect their PK profile (eg, lack of compliance with dosing, issues with PK sample collections and/or sample handling procedures) may be excluded from the PK analysis. At the discretion of the pharmacokineticist, a concentration value may also be excluded if the deviation in sampling time is of sufficient concern or if the concentration is anomalous for any other reason.

A full list of protocol deviations for the study report will be compiled prior to database closer. Any significant deviation from the protocol will be reviewed prior to database closer and a decision will be taken regarding evaluation for each analysis population. A summary of important protocol deviations will be provided.

6. ENDPOINTS AND COVARIATES

6.1. PK Endpoints

PK endpoints are the primary endpoints.

Blood samples for PK analysis of palbociclib and letrozole will be collected according to the Schedule of Activities given in Appendix 1.

The following single dose PK parameters will be calculated for palbociclib from the plasma concentration-time data using standard noncompartmental methods:

Table 1 Noncompartmental PK Parameters Following Single Dose of Palbociclib

PK Parameter	Analysis Scale	Palbociclib
AUC_{10}	ln	D
AUC_{24} (=$AUC_{sd,\tau}$)	ln	D
AUC_{last}	ln	D
AUC_{inf}	ln	D
C_{max}	ln	D
T_{max}	R	D
CL/F	ln	D
$t_{1/2}$	R	D
MRT	R	D
Vz/F	ln	D
K_{el}	R	D

Key:D=displayed with descriptive statistics; ln=natural-log transformed; R=raw (untransformed).

The following multiple dose PK parameters at steady-state will be calculated for palbociclib from the plasma concentration-time data using standard non-compartmental methods:

Table 2 Noncompartmental PK Parameters Following Multiple Dose of Palbociclib

PK Parameter	Analysis Scale	Palbociclib
$AUC_{ss,\tau}$	ln	D
$C_{ss,max}$	ln	D
$C_{ss,min}$	ln	D
$C_{ss,av}$	ln	D
$T_{ss,max}$	R	D
CL/F	ln	D
Vz/F	ln	D
$t_{1/2}$	R	D
PTF (DF)	ln	D
R_{ac}	ln	D
R_{ss}	ln	D

Key:D=displayed with descriptive statistics; ln=natural-log transformed; R=raw (untransformed).

In addition, trough plasma concentration of palbociclib on Days 19-21 of Cycle 1 or a later cycle and trough plasma concentration of letrozole on Days 19-21 of Cycle 1 or a later cycle and Day 1 of Cycle 2 or a later cycle are also parameters of interest.

6.2. Efficacy Endpoints

Baseline tumor assessments are those collected within 28 days of enrollment (unless otherwise specified in the protocol).

Progression-free survival (PFS)

Progression-free survival is the time from C1D1 to date of first documentation of disease progression or death due to any cause, whichever occurs first. Documentation of progression must be by objective disease assessment as defined by the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1; Appendix 3).

If tumor progression data includes more than 1 date, the first date will be used. PFS (in months) will be calculated as (first event date – date of C1D1 +1)/30.4.

Censoring:

Patients last known to be 1) alive and 2) progression-free, are censored at the date of the last objective disease assessment that verified lack of disease progression (see Appendix 4 for determining the date in details). In addition,

- Patients with inadequate baseline disease assessment are censored at the date of C1D1.
- Patients with no on-study disease assessments are censored at the date of C1D1 unless death occurred within acceptable interval (in which case the death is an event).

- If a new anti-cancer treatment is started prior to progression and death, then censorship is at the date of the last objective disease assessment that verified lack of disease progression prior to the new treatment.

- If patients are removed from the study (withdrew the consent, lost to follow up, etc.) prior to progression and death, then censorship is at the date of the last objective disease assessment that verified lack of disease progression.

- Patients with documentation of progression or death after an unacceptably long interval (>2 consecutive assessments) since the last tumor assessment will be censored at the time of last objective assessment documenting no progression.

Objective Response (OR)

Objective response is defined as a complete response (CR) or partial response (PR) according to the RECIST version 1.1 recorded from C1D1 until disease progression or death due to any cause.

The OR rate (ORR) will be estimated by dividing the number of patients with objective response (CR or PR) by the number of patients in the efficacy analysis set.

Designation of best response of stable disease (SD) requires the criteria to be met at least 12 weeks after C1D1. Patients who do not have on-study radiographic tumor reevaluation, 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.

Tumor response will be determined from tumor assessment data (where data meet the criteria for CR or PR as described in Appendix 3).

Disease Control (DC)

Disease control (DC) is defined as complete response (CR), partial response (PR), or stable disease (SD) ≥24 weeks according to RECIST version 1.1 recorded in the time period between C1D1 and disease progression or death due to any cause.

The DC rate (DCR) will be estimated by dividing the number of patients with CR, PR, or SD ≥24 weeks by the number of patients in the efficacy analysis set.

Designation of best response of SD ≥24 weeks requires the criteria to be met at least 24 weeks after C1D1. Patients who do not have on-study radiographic tumor re-evaluation, who receive anti-tumor treatment other than the study medication prior to reaching a CR or PR, a best response of SD ≥24 weeks, or who die, progress, or drop out for any reason prior to achieving reaching a CR or PR and a best response of SD ≥24 weeks will be counted as non-responders in the assessment of DCR.

Tumor response will be determined from tumor assessment data (where data meet the criteria for CR or PR and best response of SD as described in Appendix 3).

Duration of Response (DR)

For patients with an objective response (CR or PR), duration of response (DR) is the time from first documentation of CR or PR to date of first documentation of objective progression or death.

If tumor progression data include more than 1 date, the first date will be used. DR (months) will be calculated as [the date response ended (ie, date of PD or death) – first CR or PR date + 1)]/30.4. DR will only be calculated for the subgroup of patients with an objective tumor response.

Censoring:

Patients last known to be 1) alive and 2) progression-free, are censored at the date of the last objective disease assessment that verified lack of disease progression. In addition,

- If a new anti-cancer treatment is started prior to progression and death, then censorship is at the date of the last objective disease assessment that verified lack of disease progression prior to the new treatment.
- If patients are removed from the study (withdrew the consent, lost to follow up, etc.) prior to progression and death, then censorship is at the date of the last objective disease assessment that verified lack of disease progression.
- Patients with documentation of progression or death after an unacceptably long interval (>2 consecutive assessments) since the last tumor assessment will be censored at the time of last objective assessment documenting no progression.

1-year PFS Probability

1-year PFS probability is defined as the probability of progression-free survival at 1 year after C1D1 based on the Kaplan-Meier estimate.

6.3. Safety Endpoints

6.3.1. Adverse Events

Adverse Events (AEs) will be graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Treatment-Emergent Adverse Events

An adverse event is considered treatment emergent if:

- The event occurs for the first time after the start of study treatment and within 28 days after final dose of study treatment and is not seen prior to the start of treatment or

- The event occurs prior to the start of treatment but increases in NCI CTCAE v4.0 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.

Treatment Related Adverse Events

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.

6.3.2. Laboratory Data

The laboratory results will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and summarized using the worst severity grade observed for each patient. For parameters for which an NCI CTCAE v.4.0 scale does not exist, results will be categorized as normal, abnormal or not done.

Baseline evaluations for laboratory data are those collected

- Within 28 days prior to the first day of study drug (prior to the first dose) and;

- Closest to but prior to dosing on the first day of study treatment, if there is more than one baseline evaluation.

6.3.3. Electrocardiogram (ECG)

ECG measurements will include PR interval, QT interval, RR interval, and QRS complex. ECGs obtained during the study will be evaluated for safety. The average of the triplicate ECG measurements will be used for the statistical analysis and all data presentations.

QT intervals will be corrected for heart rate (QTc) using standard correction factors (ie, Bazett's and Fridericia's).

Baseline evaluations for ECG data are those collected

- Within 28 days prior to the first day of study drug (prior to the first dose) and;

- Closest to but prior to dosing on the first day of study treatment, if there is more than one baseline evaluation.

6.3.4. Ocular Safety Assessment

Ocular assessments include visual acuity, intraocular pressure measurements, slit-lamp biomicroscopy, funduscopy, and lens grading.

6.3.5. Other Safety Assessments

Other safety assessments include physical examination, vital signs, and Eastern Cooperative Oncology Group (ECOG) performance status.

6.4. Other Endpoints

6.4.1. Biomarker Endpoints

Skin biopsy tissues and blood samples will be collected for biomarker assessments of palbociclib at pre-dose and at multiple post-dose time points during the single and multiple dose PK parts as specified in the protocol.

Retrospective testing of formalin fixed paraffin embedded (FFPE) tissue samples for phosphorylated retinoblastoma protein (pRb) and Ki67 expression will be performed in a central laboratory designated by the sponsor. Results from this assay will be used for exploratory analyses between PK and pharmacodynamics markers.

Retrospective testing of serum samples for thymidine kinase (TK) activity will be performed in a central laboratory designated by the sponsor. Results from this assay will be used for exploratory analyses between PK and pharmacodynamics markers.

6.5. Covariates

None.

7. HANDLING OF MISSING VALUES

7.1. Missing Dates

In compliance with Pfizer Data Standard, 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 (eg, 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.

7.2. Missing Tumor Assessments

If baseline tumor assessment is inadequate the patient cannot be assessed for response.

Inadequate baseline assessment may include

- Not all required baseline assessments are done ;
- Assessments are done outside the required window ;
- Measurements are not provided for one or more target lesions ;
- One or more lesions designated as target are not measurable.

If measurements for one or more target lesions are missing for an evaluation and disease does not qualify as progression (or symptomatic deterioration if applicable), the objective status for that evaluation is Indeterminate.

If non-target disease is not assessed, then a patient who qualifies for an objective status of CR based on target disease will be classified as PR. Otherwise, missing non-target disease assessments do not necessarily affect response determination. Such cases will be reviewed carefully.

If a lesion measurement is missing because it is documented as too small to measure, the value 5 mm will be assigned and objective status is calculated accordingly.

In the assessment of OR, patients who do not have on study radiographic tumor re-evaluations will be counted as non-responders.

7.3. Missing Data in PFS Derivation

PFS cannot be assessed in patients with inadequate baseline tumor assessment. PFS cannot be assessed in patients who have no on-study assessments unless death occurs within acceptable gap.

If a substantial number of patients have questionable failure or censorship dates for either PFS definition (such as progression or death not documented until after multiple missing assessments), scenarios such as best case (failure at time of documentation) and worst case (progression at earliest possible planned assessment date) will be investigated.

For PFS analysis, no values will be imputed for missing data. For time to event endpoints, non-event observations will be censored as defined in Section 6.2.

7.4. Missing QTc Data

For QTc analysis, no values will be imputed for missing data except for averaging of triplicate measurements. If one or two of the triplicate measurements for an ECG parameter are missed, the average of the remaining two measurements or the single measurement can be used in the analyses. If the triplicate is not good because of an artifact, then the triplicate repeated within about ± 15 minutes can be used at that nominal time.

7.5. Missing PK Data

Specifications on how missing values for PK analysis will be handled are given in Section 8.2.1.1 and 8.2.1.2 below.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

8.1.1. Analyses for Binary Endpoints

The percentage of response and the exact 95% confidence interval (CI) calculated using Clopper-Pearson method will be provided for binary efficacy endpoints.

8.1.2. Analyses for Continuous Endpoints

Descriptive statistics, including the mean, standard deviation, median, minimum, and maximum values, will be provided for continuous endpoints.

8.1.3. Analyses for Categorical Endpoints

The number and percentage of patients in each category will be provided for categorical variables.

8.1.4. Analyses for Time-to-event Data

Time-to-event endpoints will be summarized using the Kaplan-Meier method and displayed graphically. Median event time and the 2-sided 95% confidence interval (CI) for the median calculated using Brookmeyer and Crowley method will be provided.

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

8.1.5. Analyses for PK Endpoints

Descriptive statistics will be provided for PK endpoints.

8.1.6. Analyses for Ocular Assessment Data

Descriptive statistics will be provided for ocular assessment data as appropriate.

8.1.6.1. Visual Acuity and Refraction

Snellen visual acuity charts are commonly used for safety evaluations. In the most familiar acuity test, a Snellen chart is placed at a standard distance, twenty feet in countries where that is the customary unit of measure. This line, designated 20/20, is the smallest line that a person with normal acuity can read at a distance of twenty feet. Three lines above, the letters have twice the dimensions of those on the 20/20 line. The chart is at a distance of twenty feet, but a person with normal acuity could be expected to read these letters at a distance of forty feet. This line is designated by the ratio 20/40. If this is the smallest line a person can read, the person's acuity is "20/40," meaning, in a very rough kind of way, that this person needs to approach to a distance of twenty feet to read letters that a person with normal acuity could read at forty feet.

In countries using the metric system, the standard chart distance is six meters, normal acuity is designated 6/6, and other acuities are expressed as ratios with a numerator of 6.

Besides Snellen fraction (such as 20/20, 20/40), visual acuity can also be specified with several other scales, for example the decimal visual acuity and the logarithm of the minimal angle of resolution (LogMar). Decimal visual acuity is obtained by dividing the numerator of the Snellen fraction by the denominator. The logarithm of the reciprocal of this decimal visual acuity approximates the logarithm of the minimal angle of resolution. The table below displays equivalent visual acuity measurements.

CCI

[redacted]

CCI

[redacted]

In summary tables, proportion of subjects with visual acuity of improvement, no change, decrease by 1 line, 2 line and >2 lines will be displayed. If different visual acuity scales are used by different investigators, all visual acuity scores will be converted to LogMAR scale according the table above before data summarization. The change of 0.1 in LogMAR is equivalent to 1 line change Snellen chart.

$$\text{LogMAR} = -\log_{10}(\text{Decimal Fraction})$$

In the event of a decrease in visual acuity of 3 lines or more from baseline, refraction will be rechecked at all subsequent study visits. A change in refraction power (spherical or cylindrical) of +/– 1.25 diopters compared with the baseline examination will be reported in data listing.

8.1.6.2. Intraocular Pressure Measurement

Intraocular pressure (IOP) will be measured using a calibrated Goldmann applanation tonometer or a non-contact method (puff) with the Tonopen, Schiotz or Rebound tonometer. IOP data may be pooled together for analysis. 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.

8.1.6.3. Slit-lamp Biomicroscopy, Funduscopy (Ophthalmoscopy), and Lens Grading

Slit-lamp biomicroscopy results will be graded according to Intraocular Inflammation Grading Scale for Biomicroscopy criteria.

CCI

[redacted]

CCI

[redacted]

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

For lens grading, the Wisconsin AREDS 2008 Clinical Lens Opacity Grading Procedure will be used.[2]

8.2. Statistical Analyses

8.2.1. Primary Analyses

PK endpoints are the primary endpoints.

8.2.1.1. Concentrations below the Limit of Quantification

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. In listings, BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.

8.2.1.2. Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of the median values at each time point, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND (ie, not done) or NS (ie, no sample);
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

8.2.1.3. Pharmacokinetic Parameters

Summary of Pharmacokinetic parameters will be for PK parameter analysis set and PK evaluable analysis set. Actual PK sampling times will be used in the derivation of PK parameters.

The following PK parameters following single dose administration of palbociclib for lead-in phase will be listed and summarized descriptively.

Table 3 PK Parameters Following Single Dose Administration of Palbociclib to be Summarized Descriptively

PK Parameter	Summary Statistics
AUC_{10}, AUC_{24} (=$AUC_{sd,\tau}$), AUC_{last}, AUC_{inf}, C_{max}, CL/F, Vz/F	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%
T_{max}	N, median, minimum, maximum
$t_{1/2}$, MRT, K_{el}	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

The following PK parameters following multiple dose administration of palbociclib will be listed and summarized descriptively.

Table 4 PK Parameters Following Multiple Dose Administration of Palbociclib to be Summarized Descriptively

PK Parameter	Summary Statistics
$AUC_{ss,\tau}$, $C_{ss,max}$, $C_{ss,min}$, $C_{ss,av}$, CL/F, Vz/F, PTF (DF), R_{ac}, R_{ss}	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%
$T_{ss,max}$	N, median, minimum, maximum
$t_{1/2}$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

8.2.1.4. PK Concentrations

To assess the single dose and multiple dose PK profiles of palbociclib, PK concentrations will be listed, summarized and plotted for subjects in the PK concentration analysis set, where missing and BLQ values will be handled as detailed in Section 8.2.1.1 and Section 8.2.1.2 above.

Presentations for palbociclib will include:

- A listing of all concentrations sorted by subject ID, cycle, study day, and nominal time postdose for single dose and multiple dose PK, respectively. The listing of concentrations will include the actual times. Deviations from the nominal time will be given in a separate listing.
- A summary of concentrations by nominal postdose time points for single dose and multiple dose PK, respectively, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.
- Median concentrations time plots (on both linear and semi-log scales) against nominal time postdose (based on the summary of concentrations by time postdose) for single dose and multiple dose PK, respectively.

- Mean concentrations time plots (on both linear and semi-log scales) against nominal time postdose (based on the summary of concentrations by time postdose) for single dose PK and multiple dose PK, respectively..
- Overlay individual concentration time plots on both linear and semi-log scales against actual time postdose (there will be separate spaghetti plots per scale) for single dose PK and multiple dose PK, respectively.
- Individual concentration time plots by patient on both linear and semi-log scales against actual time postdose (there will be separate plots for each patient per scale) for single dose PK and multiple dose PK, respectively.
- Individual and descriptive summary of palbociclib trough concentrations versus study day will also be plotted.

Presentations for letrozole will include:

- A listing of all concentrations sorted by subject ID, cycle, study day, and nominal PK sampling time. The listing of concentrations will include the actual times. Deviations from the nominal time will be given in a separate listing.
- A summary of concentrations by cycle, study day, and nominal PK sampling time, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.
- Individual and descriptive summary of letrozole trough concentrations versus study day will also be plotted.

  For summary statistics and median plots by sampling time, the nominal PK sampling time will be used. For individual subject plots by time, the actual PK sampling time will be used, while the predose time will be set to zero.

8.2.2. Secondary Analyses

8.2.2.1. Efficacy Analyses

All the efficacy analyses dependent on disease assessments will be based on investigator assessment of disease response and progression. All the efficacy analyses will be conducted using the efficacy analysis set. Sensitivity analyses may be conducted on patients in the efficacy analysis set without major protocol deviations or other subsets of the efficacy analysis set (eg, with measurable disease at baseline) for certain endpoints if deemed necessary.

Progression-Free Survival (PFS)

PFS will be summarized in the efficacy analysis set using the Kaplan-Meier method and displayed graphically. Median event time and the 2-sided 95% CI for the median calculated using Brookmeyer and Crowley method will be provided.

Objective Response (OR)

The number of patients achieving OR (CR or PR) will be summarized. The OR rate (ORR) will be estimated by dividing the number of patients with OR by the number of patients in the efficacy analysis set. An exact 2-sided 95% CI calculated using Clopper-Pearson method will be provided for ORR.

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

Disease Control (DC)

The number of patients achieving DC (CR, PR, or SD ≥24 weeks) will be summarized. The DC rate (DCR) will be estimated by dividing the number of patients with DC by the number of patients in the efficacy analysis set. An exact 2-sided 95% CI calculated using Clopper-Pearson method will be provided for DCR.

Duration of Response (DR)

DR will only be calculated for the subgroup of patients with an objective response. DR will be summarized in the efficacy analysis set using the Kaplan-Meier method and displayed graphically. Median event time and the 2-sided 95% CI for the median calculated using Brookmeyer and Crowley method will be provided.

1-year PFS Probability

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

8.2.2.2. Safety Analyses

The safety data will be summarized and listed according to Pfizer reporting standard. The safety analyses will be conduct on the safety analysis set.

8.2.2.2.1. Analysis of Adverse Events

Adverse Events (AEs) will be graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The focus of AE summaries will be on treatment-emergent adverse events, as defined in Section 6.3.1.

The number and percentage of patients who experience any AE, serious AE (SAE), treatment-related AE, and treatment-related SAE will be summarized according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle (Cycle 1 and Cycles > 1). Adverse events leading to death or discontinuation of study treatment, events classified as CTCAE version 4.0 Grade 3 or higher, study drug related events, and serious adverse events will be considered with special attention.

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

- Discontinuations due to adverse events including causality: all cause, treatment related, including relationship to specific study treatment of letrozole and palbociclib.
- Temporary discontinuations or dose reductions due to adverse events including causality and relationship to specific study treatment of letrozole and 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.4.0 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.

8.2.2.2.2. Analysis of Laboratory Tests

The number and percentage of patients who experience laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory assay based on the NCI CTCAE v4.0 severity grade. The analyses will summarize laboratory tests both on the entire study period and by cycle (Cycle 1 and Cycles > 1). For parameters for which an NCI CTCAE v.4.0 scale does not exist, results will be categorized as normal, abnormal or not done.

8.2.2.2.3. Analysis of Electrocardiogram Measurements

All ECGs obtained during the study will be evaluated for safety. The average of the triplicate ECG measurements will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates.

If any of the three individual ECG tracings has a QTc interval >500 msec, but the mean of the triplicates is not >500 msec, the data from the subject's individual tracing will be

described in a safety section of the study report in order to place the >500 msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 msec.

QT intervals will be corrected for heart rate (QTc) using standard correction factors (ie, Bazett's and Fridericia's). Data will be summarized and listed for QT, HR, RR, PR, QRS and QTc. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute QTc value and changes from baseline in QTc after treatment by day and time point. For each patient, the maximum change from baseline will be calculated as well as the maximum post-baseline value across time points. Categorical analysis of the QTc, PR, and QRS data will be conducted and summarized as follows:

- QT/QTc outlier values will be summarized and tabulated by the following CTCAE grade v.4.0.

Grade	1	2	3	4	5
Prolonged QTc interval	QTc 450 – 480 msec	QTc 481 – 500 msec	QTc ≥501 msec on at least two separate ECGs	QTc ≥501 or >60 msec change from baseline and Torsade de pointes or polymorphic Ventricular tachycardia or signs/symptoms of serious arrhythmia	Death

- The change from baseline will summarized by shift tables of maximum on-study CTC grades versus baseline grades.

- Individual QT and QTc values ≥ 501 msec from each ECG within a triplicate will be flagged in data listings.

- The number of and percentage patients with maximum post-dose QTcF/QTcB (<450, 450-480, 481-500, and ≥501 ms), including all scheduled and unscheduled ECG's.

- The number and percentage of patients with maximum increase from baseline in QTcF/QTcB (<30, 30- 59, and ≥60 ms), including all scheduled and unscheduled ECG's.

- PR changes from baseline ≥ 50% if absolute baseline value is < 200 ms, and ≥25% if absolute baseline value is > 200 ms.

- QRS changes from baseline ≥ 50% if absolute baseline value is < 100 ms, and ≥25% if absolute baseline value is > 100 ms.

8.2.2.2.4. Analysis of Vital Signs

Categorical summary of vitals signs will be provided.

- The number and percentage of patients with on study absolute value for systolic BP of >150mmHG or diastolic BP of >100 mmHg
- The number and percentage of patients with on study absolute value for systolic BP of >200 mmHg or diastolic BP of >110 mmHg
- The number and percentage of patients with systolic BP increases of ≥20, ≥40, and ≥60 mmHg from baseline and diastolic BP increases of ≥10, ≥20, and ≥30 mmHg from baseline
- The number and percentage of patients with pulse rate of <50 and >120 BPM

8.2.2.2.5. Other Safety Data

Other safety data including vital signs and physical examinations will be summarized and/or listed according to Pfizer reporting standard.

8.2.3. Standard Analyses

Descriptive statistics will be used to summarize study conduct and patient disposition, demographic and baseline characteristics, treatment administration/compliance, medical history, and prior and concomitant medications and non-drug treatments.

8.2.3.1. Treatment Administration and Compliance

- Extent of Treatment

  The extent of treatment (starting from C1D1) will be summarized as follows:

  - The number and % of patients on treatment and off for each reason
  - The number and percent of patients beginning 1, 2, 3, 4, 5+ cycles
  - The number of cycles started (median, minimum, maximum) will be reported.
  - Duration of treatment (weeks)
  - Cumulative dose and relative dose intensity (see Appendix 5 for details) (overall and by cycle)

- Treatment Delays and Dose Modifications

Dose reductions are not allowed for letrozole. Treatment delays and dose modifications of study treatments will be summarized as follows including number and percent (see Appendix 5 for details):

- The number of patients with at least one palbociclib dose reduction and the number of patients with at least one palbociclib or letrozole dose omission at any time during drug administration will be reported.
- The number of patients with at least one palbociclib dose reduction due to an adverse event will be reported.
- The number of patients with at least one palbociclib dose delay (ie, start of following cycle is delayed) and percentage due to each reason for the delay will be reported

8.2.4. Ocular Assessment Data Analyses

Ocular assessment will be conducted on ocular analysis set.

Snellen visual acuity data will be analyzed by using LogMAR value, reporting the maximum changes from baseline of LogMAR.

Any IOP increase of greater than 10 mmHg above baseline or any IOP that increases above 25 mm Hg will be reported in data listing.

Any new finding or deterioration from baseline findings in slit-lamp biomicroscopy, lens grading, and funduscopy will be reported in data listing.

8.2.5. Biomarkers Analyses

The biomarker analyses will be conducted on biomarker analysis set.

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

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

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

8.2.6. Pharmacokinetic and Pharmacodynamic Analyses

Individual palbociclib concentrations might be used to conduct a population PK analysis based on prior model practice. The relationship between PK and potential covariates on Chinese patients may be evaluated. All patients treated with palbociclib and for whom palbociclib plasma concentration data (from at least 1 visit) are available will be included in the analysis.

In addition, the relationship between palbociclib exposure, biomarker expression and efficacy/safety endpoints will be explored, as necessary, based on emerging biomarker, efficacy and safety data. The results of these modeling analyses may be reported separately from the clinical study report.

8.2.7. Summary of Efficacy Analyses

Endpoint	Analysis Set	Statistical Method	Missing Data
PFS	Efficacy analysis set	K-M method (median and 95% CI)	See details in Section 6.2 and Section 7.
ORR	Efficacy analysis set	Exact CI based on Clopper-Pearson method (95% CIs)	See details in Section 6.2 and Section 7.
DCR	Efficacy analysis set	Exact CI based on Clopper-Pearson method (95% CIs)	See details in Section 6.2 and Section 7.
DR	Efficacy analysis set; Patients with a CR or PR	K-M method (median and 95% CI)	See details in Section 6.2 and Section 7.
1-year PFS probability	Efficacy analysis set	K-M method (95% CI)	See details in Section 6.2 and Section 7.

Abbreviations:
CR: complete response; PR: partial response; DCR: disease control rate; DR: duration of response; ORR: objective response rate; PFS: progression-free survival.

9. REFERENCES

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

2. 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.

10. APPENDICES

Appendix 1. Schedule of Activities

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

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

Table 5. Schedule of Activities

Protocol Activity	Screening (≤ 28 days prior to study entry)		Single- Dose PK (Lead-in phase, Days 1-5)	Multiple Dose PK (Cycle 1)			Cycles ≥2			End of Treatment /Withdrawal (EOT) [a]	Follow-up
Study Day		Day -1 [a] From Day -4 to Day -1	Days 1~5 From Day -3 to Day 1	Day 1	Day 14	Day 21	Day 1 (±2d, only for cycle >2)	Day 14 (±2d)	Day 21 (±2d)	±7	
Baseline Documentation											
Informed Consent	X										
Medical/Oncology History	X	X									
Baseline Signs/Symptoms [b]	X	X									
Vital Signs and Physical Examination [c]	X	X		X						X	
ECOG Performance Status	X			X			X			X	
Laboratory Tests											
Hematology [d]	X	X	See Table 2 for detailed time points				X		X (only for Cycle 2)	X	
Blood Chemistry [d]	X	X		X	X		X	X (only for Cycle 2)		X	
HgbA1c [d]		X	Cycle 4 Day 1 and every 3 months thereafter							X	

Protocol Activity	Screening (≤ 28 days prior to study entry)		Single- Dose PK (Lead-in phase, Days 1-5)	Multiple Dose PK (Cycle 1)			Cycles ≥2			End of Treatment /Withdrawal (EOT) [z]	Follow-up
Study Day		**Day -1** [a] From Day -4 to Day -1	**Days 1~5** From Day -3 to Day 1	**Day 1**	**Day 14**	**Day 21**	**Day 1** (±2d, only for cycle >2)	**Day 14** (±2d)	**Day 21** (±2d)	±7	
Fasting Glucose and Fasting Insulin [d]		X				X	X (only for Cycle 2)			X	
Fasting Lipid Panel [d]		X								X	
Urinalysis [e]	X	X								X	
Coagulation [f]	X	X								X	
HbsAg, anti- HCV [g]	X										
HIV test [h]	X										
ECG (in triplicate) [i]	X	X		X	X		X	X (only for Cycle 2)		X	
Ocular Assessment [j]	X						See footnote for details			X	
Study Treatment											
Letrozole			Once daily continuously (from Lead-in phase Day 1)								
Palbociclib [k]			X (Only Day 1)	Once daily on Day 1 to Day 21 of each cycle followed by 7 days off							
Disease Assessments [l,z]											
CT/MRI Scans of Chest, Abdomen, Pelvis, any clinically indicated sites of disease, and of bone lesions; Clinical evaluation of superficial disease	X						Performed every 12 weeks (± 7 days) from C1D1			X	
Radionuclide Bone Scan, Whole Body	X						Performed every 24 weeks (± 7 days) from C1D1			X	
Other Clinical Assessments											
Drug Compliance [m]				X			X				
Adverse Event Reporting [n]	X	X	Assessed throughout the study							X	X

Protocol Activity	Screening (≤ 28 days prior to study entry)		Single- Dose PK (Lead-in phase, Days 1-5)	Multiple Dose PK (Cycle 1)			Cycles ≥2			End of Treatment /Withdrawal (EOT) [s]	Follow-up
Study Day		Day -1 [a] From Day -4 to Day -1	Days 1~5 From Day -3 to Day 1	Day 1	Day 14	Day 21	Day 1 (±2d, only for cycle >2)	Day 14 (±2d)	Day 21 (±2d)	±7	
Concomitant Medications/Treatments [o]	X	X	Assessed throughout the study							X	X
Pharmacokinetic Blood Sampling			See Table 6 for detailed time points								
Skin Biopsy [p]		X	See Table 6 for detailed time points								
Randomization [p]		X									
Thymidine Kinase Blood Test [q]		X	See Table 6 for detailed time points								

a. **Day -1:** Patients will be admitted to the Clinical Research Unit (CRU) on Day -1 and will be required to stay in the unit until at least 72 hours (on Day 4) following single dose of palbociclib based on the availability of CRU. In the case that screening and Day -1 occur on the same day, procedures scheduled on Day -1 do not need to be repeated.

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

c. **Vital Signs and Physical Examination:** A full physical examination including an examination of all major body systems, height (at screening only), weight, blood pressure and pulse rate, which may be performed by a physician, registered nurse or other qualified health care provider, will be required at screening, Day -1, Day 1 of Cycles 1 and 2 as well as the end of treatment (EOT). Physical examinations will not be required on Day -1 if an acceptable screening examination is performed within 7 days prior to Day -1. Symptom-directed physical examinations, blood pressure and pulse rate will be performed at subsequent visits.

d. **Hematology, and Blood Chemistry Panel:** Hematology includes hemoglobin (Hb), WBC, absolute neutrophils, platelet count and the assessments will be conducted regardless of food intake. Blood chemistry includes AST/ALT, alkaline phosphatase, sodium, potassium, magnesium, total calcium, total bilirubin, BUN (or urea), serum creatinine, albumin, hemoglobin A1c (HgbA1c), fasting glucose, fasting insulin, and fasting lipid panel. HgbA1c assessments will be conducted regardless of food intake; fasting glucose, fasting insulin and fasting lipid panel will be assessed following an overnight fast (at least 10 hours) ; samples for other blood chemistry tests should be collected following at least a 4-hour fast. Therefore, if all of these assessments are conducted together, they should be done before food intake. The hematology and blood chemistry assessment schedules should be referred to in Table 1 and Table 2. Additional hematology/chemistry panels may be performed as clinically indicated. HgbA1c, fasting lipid panel, fasting glucose and fasting insulin will be shipped to a central laborary designated by the Sponsor for analysis.

e. **Urinalysis:** Urine protein and blood. Dipstick is acceptable. If positive, microscopic analysis will be performed and 24-hr urine samples will be collected (only for protein excretion). This assessment will not be required on Day -1 if an acceptable screening assessment is performed within 7 days prior to Day -1.
f. **Coagulation:** PT or INR, PTT or aPTT. Additional coagulation studies may be performed as clinically indicated. The assessment will not be required on Day -1 if an acceptable screening assessment is performed within 7 days prior to Day -1.
g. **HbsAg, anti-HCV:** Hepatitis B surface antigen (Hbs Ag) and antibody against hepatitis C virus (anti-HCV) tests.
h. **HIV test:** Human Immunodeficiency Virus test.
i. **ECG:** At each scheduled ECG evaluation, 3 consecutive 12-lead pre-dose ECGs will be performed approximately 2 minutes apart to determine the mean QTc interval. All the assessments will be made after at least a 10-minute rest in a supine position. If ECG and PK collections are scheduled on the same day (Cycle 2 Day 1), pre-dose ECG assessments should occur before PK collections. All ECG evaluations should be conducted before food intake.
j. **Ocular Assessment**: Ocular assessments should be conducted at screening and on study treatment after 3 months (Cycle 4 Day 1), 6 months (Cycle 7 Day 1), 12 months (Cycle 13 Day 1), every 12 months (Day 1 of Cycles 25, 37 etc.) thereafter, as well as at the EOT. Additional ocular assessments may be performed during the study as clinically indicated. The ocular assessments will include: best corrected distant visual acuity, refractive error associated with best corrected distant visual acuity, intraocular pressure (IOP – one reading), slit-lamp biomicroscopy of the anterior segment including cell count and flare grading, crystalline lens grading using the Wisconsin Age-Related Eye Disease Study (AREDS), 2008 Clinical Lens Opacity Grading procedure, and fundoscopy. All ocular assessments will be performed by ophthalmologists.
k. **Study Treatment Administration:** Palbociclib and letrozole should be administered together with food. On Day 1 in Lead-in phase and Day 21 in Cycle 1(intensive PK sampling days), similar breakfast will be provided to patients approximately 30 minutes prior to the administration of palbociclib (breakfast started at approximately 0930 AM). Breakfast will be consumed within a 20-minute period with study drugs administered approximately 10 minutes after completion of the meal. At least 80% of the provided breakfast should be consumed prior to palbociclib administration. The provided breakfast should be moderate-fat standard-calorie meal (approximately 15% protein, 50% carbohydrate, 35% fat diet for a total of 500-700 calories).
l. **Disease Assessments:** Refer to the tumor assessment requirement flowchart (Table 7) for details and timing of procedures.
m. **Drug Compliance:** Patients will be required to return the completed patient dosing diary and all bottles of palbociclib and letrozole including any unused capsules/tablets to the clinic for drug accountability at the beginning of each cycle. Drug accountability will be performed on Day 1 of every cycle prior to dispensing drug supply for the next cycle.
n. **Adverse Events:** For SAEs, the active reporting period begins from the time that the patient provides informed consent through and including 28 calendar days after the last administration of the investigational product. 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 CRF from the time the patient has taken at least one dose of study treatment through last patient visit.
o. **Concomitant Medications/Treatments:** Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 28 days after the last dose of study treatment. No Chinese or other herbal medicines will be allowed during PK portion. No Chinese anti-cancer herbal medicines will be allowed after the PK portion (Cycle 1). The use of herbal medicines is not recommended from Cycle 2. Any usage of Chinese or other herbal medicine should be recorded.
p. **Skin Biopsy:** Skin tissue samples are required to be collected from enrolled patients at pre-dose on Day -1. On Day -1, patients will be randomized into 2 groups for different collection schedules in Lead-in phase and Cycle 1. Refer to Table 2 for timing details of post-dose procedures.
q. **Thymidine Kinase Blood Test:** Blood samples will be collected for analysis of thymidine kinase (TK) activity at pre-dose on Day -1. Refer to Table 2 for timing details of post-dose procedures.

r. **End of Treatment/Withdrawal**: Obtain these assessments if not completed during the previous 4 weeks (or within the previous 8 weeks for disease assessments).

Table 6. Blood Sampling Time Points for PK, Hematology and Biomarker Evaluations During Single-Dose and Multiple-Dose PK Portion

Single- or Multiple-Dose PK[a]	Single-Dose PK (Lead-in phase)										C1[i]	Multiple-Dose PK in Cycle 1[f]														Cycle 2
Study Day	1						2	3	4	5	1	14	19	20	21						22	23	24	25	26	1
Hour post dose	0[b]	2	4	6	8	10	24	48	72	96	120[b,c]	0	0[b]	0[b]	0[b]	2	4	6	8	10	24	48	72	96	120	0[b]
PK blood collection for pabociclib[d]	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
PK blood collection for letrozole[d]													X	X	X											X
Hematology[e]									X		X	X			X								X			X
Skin Biopsy[g]						X	X													X	X	X	X	X	X	
Blood Samples for TK test[h]			X		X	X	X		X		X						X		X	X	X	X	X	X	X	X
Confinement	→	→	→	→	→	→	→	→	X					X	→	→	→	→	→	→	→	→	X			
Discharge from CRU									X														X			
Outpatient Visit										X	X	X	X											X	X	X

a. For both single-dose and multiple-dose PK collections, patients will be required to stay in the CRU for at least 72 hours following palbociclib dosing based on the availability of CRU, and come back for outpatient visits to provide PK samples as scheduled. For PK collections scheduled before 24 hours post-dose in CRU, deviation of required collection time within 10% of the nominal time (eg, within 6 minutes of a 60-minute sample) from dosing will not be captured as a protocol deviation, as long as the actual collection time is recorded. For samples scheduled after 24 hours post-dose, collections obtained within 10% of the sampling interval (ie, 24 hours in this study) will not be captured as a protocol deviation as long as the actual collection time is recorded. For the PK samples collected during outpatient visits, deviation of required collection time larger than 10% of sampling interval (ie, 24 hours in this study) may be acceptable as long as the actual collection time is recorded.
b. Pre-dose PK samples should be taken immediately prior to any palbociclib and letrozole morning dosing on that day (within approximately 15 minutes prior to the dosing). On these days, administration of palbociclib and letrozole should occur in the CRU to ensure the pre-dose PK samples can be collected; on Days 1, 19 and 20 in Cycle 1 and Day 1 in Cycle 2, patients should be instructed to bring the drug supply and administer the drugs in the CRU after completion of PK collection on that day.
c. On Cycle 1 Day 1, the post single dose PK sample at 120 hrs will be taken prior to dosing.
d. 2 mL of whole blood will be drawn into a tube containing K_2EDTA for each time point.
e. Hematology assessments will be evaluated at screening and/or Day -1, on Day 4 before discharge in Lead-in phase, on Cycle 1 Day 1 before dosing of palbociclib, on Cycle 1 Day 14, 21, 24 in Cycle 1, on Cycle 2 Day 1 and 21 as well as Day 1 in Cycles ≥3. On Day 1 of each cycle (at least for 4 subsequent cycles after the first 2 cycles), the assessments should be conducted before dosing to ensure the tolerability of patients. Actual time of assessments must be documented. Once complete blood count has stabilized, further monitoring should be conducted as clinically indicated.
f. PK sample collections scheduled after multiple dosing of palbociclib should be conducted given that there is no dosing interruption for at least 8 days prior to sample collection. If the sample collection is missed for any reason, or if the PK data collected are deemed not evaluable by the Sponsor, then the PK sample collection may be repeated during a later cycle.
g. Skin biopsy for biomarker assessments will be conducted. Samples will be collected from all enrolled patients at pre-dose on Day -1. In Lead-in phase and Cycle 1, patients will be randomized into 2 groups for different collection schedules: patients from Group 1 will be required to provide samples on Day 2 (24 hours post dose) in Lead-in phase, Days 22, 24 and 26 in Cycle 1; patients from Group 2 will be required to provide samples on Day 1 (10 hours post dose) in Lead-in phase, Days 21 (10 hours post-dose), 23 and 25 in Cycle 1. The biomarker sample collection should be conducted together with PK collection, and the actual collection time must be documented.
h. 3 mL of whole blood will be drawn into a tube at each scheduled time point right after collection of PK samples (no need to perform venipuncture again at the same time point). Actual collection time should be recorded.
i. C1 represent Cycle 1.

NOTE:

During the periods of intensive PK blood draws, an indwelling catheter is allowed if there is a need.

Table 7. Tumor Assessment Requirements Flow Chart

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

a. Screening scans must occur within 4 weeks (ie, 28 days) prior to study entry unless otherwise specified.
b. Tumor assessment must be done during the treatment period, every 12 weeks (± 7 days) from C1D1, bone scans (as applicable) every 24 weeks (±7 days) from C1D1 until radiographically and/or clinically (ie,for photographed or palpable lesions) documented PD as per RECIST v.1.1, study treatment discontinuation (for patients continuing treatment beyond RECIST-defined disease progression), initiation of new anticancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow up), whichever occurs first. The schedule of assessments should be fixed according to the calendar, regardless of treatment delays/interruptions. Imaging assessments are to be scheduled using the C1D1 date as the reference date for all time-points and are NOT to be scheduled based on the date of the previous imaging time-point. Imaging assessment delay to conform to treatment delay is not permitted. The same tumor assessment technique MUST be used throughout the study for a given lesion/patient.
c. Patients who have already demonstrated objective disease progression as per RECIST v.1.1 do not need to have scans repeated at the end of treatment visit.
d. The CT scans, including brain CT scan if applicable, should be performed with contrast agents unless contraindicated for medical reasons. If IV contrast is medically contraindicated, the imaging modality to be used to follow the disease (either CT without contrast or MRI) should be the modality which best evaluates the disease, and the choice should be determined by the investigator in conjunction with the local radiologist. MRI of the abdomen and pelvis can be substituted for CT if MRI adequately depicts the disease. However, MRI of the chest should not be substituted for CT of chest even if IV contrast is contraindicated. In such case CT will be performed without contrast. If MRI is used to follow-up bone lesion(s) it must be performed a few days before any treatment that may affect bone-marrow cellularity (eg, G-CSF).
e. Radiographic assessments obtained per the patient's standard of care prior to study entry do not need to be repeated and are acceptable to use as baseline evaluations, if (1) obtained within 28 days before study entry, (2) they were performed using the method requirements outlined in RECIST v.1.1 (3) the same technique/modality should be used to follow identified lesions throughout the trial for a given patient, and (4) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes.
f. Baseline brain scans are only required if signs and symptoms suggest presence of metastatic brain disease. Brain scans performed before the signing of

informed consent as routine procedures (but within 6 weeks before study entry) 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 should be used to follow identified lesions throughout the trial for a given patient (3) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes. Post-baseline repeat brain scans will only be required only if metastases are suspected.

g. Bone scans will be carried out at baseline for all patients within 12 weeks prior to study entry in order to detect bony sites of disease. Bone scans performed before the signing of informed consent as routine procedures (but within 12 weeks before study entry) 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 should be used to follow identified lesions throughout the trial for a given patient (3) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes.

h. Any suspicious abnormalities (ie, hotspots) identified on the bone scans at baseline and on subsequent bone scans MUST be confirmed by X-ray, CT scan with bone windows or MRI. The same modality must be used throughout the trial for confirmation for a given lesion/patient. Bone lesions identified at baseline will be followed up according to the same assessment schedule (ie, every 12 weeks ±7 days from C1D1) as for all other lesions. Areas that have received palliative radiotherapy cannot be used to assess response to study treatment.

i. If bone lesions were identified at baseline, then bone scans will be repeated during the active treatment phase every 24 week (±7 days) from the date of C1D1 and at the time of confirmation of CR. If no bone lesions were identified at baseline, then bone scans will only be repeated during the active treatment phase when clinically indicated (ie, patient describes new or worsening bone pain, or has increasing alkaline phosphatase level, or other signs and symptoms of new/progressing bone metastases) but are required at the time of confirmation of CR. New Abnormalities found on subsequent bone scans must also be confirmed by X-ray, CT scan with bone windows or MRI.

j. Clinical assessment of superficial disease must be carried out on the same date as the imaging studies and will include photographs of all superficial metastatic lesions. All lesion measurements must be recorded in the case report form (CRF).

Notes:

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

Appendix 2. Data Derivation Details

Study Day 1	Day 1 of the single-dose PK part (Lead-in phase), ie, the first day of dosing
Day 1 (cycle start date)	Day 1 of a cycle is every 28 days unless there is a dosing delay. Cycle 1 Day 1 is the start date of dosing recorded on CRF for Cycle 1, and also the start date to derive PFS.
Cycle length (all but final cycle)	Cycle length is 28 days (previous cycle length may exceed planned length if there is a delay in study treatment administration).
Final cycle	For patients off treatment, from Day 1 of final cycle to 28 days after final dose or until start of new anticancer treatment (whichever comes first). For patients on treatment, from Day 1 of the most recent cycle start to protocol specified cycle length.
Follow-up period for AEs	From 28 days after final dose until start of new anticancer treatment (whichever comes first).
Baseline laboratory test, ECG, and vital signs, ocular assessments, biomarker assessments	Baseline evaluations are those collected • Within 28 days prior to or on the first day of study drug (prior to the first dose) 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.
Tumor assessment baseline values	From date closest but prior to the first dose.
Measurable disease	Defined by RECIST
Adequate baseline tumor assessment	Within 35 (28 + 7) days prior to the first dose. Maximum diameter reported for each target lesion listed. Each target lesion is measurable, unless bone only disease. All required pre-treatment scans done.
Cycle k treatment delayed.	If study treatment administration is delayed for cycle k, then cycle k-1 is extended.

Appendix 3. RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1 Guidelines

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

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

Lesions that can be accurately measured in at least one dimension.

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

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

Non-measurable disease

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

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

Normal sites

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

RECORDING TUMOR ASSESSMENTS

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

Target lesions

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

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded..

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

Non-target disease

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

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION.

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

Target disease

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

Non-target disease

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

New Lesions

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

Supplemental Investigations

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

- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective progression

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

Table 1. Objective Response Status at each Evaluation

Target Lesions	Non-target Disease	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate, or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate, or Missing	No	Stable
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

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

Appendix 4. Rules for Determining PFS Status and Date

Situation	Date of Progression/Censoring[1]	Outcome
Inadequate baseline assessment	C1D1	Censored
No on-study assessments	C1D1	Censored
Alive and no Progression	Date of last objective tumor assessment documenting no progression	Censored
Progression Documented on or between scheduled tumor assessments	Date of first objective tumor assessment documenting objective progression	Progressed (Event)
Patients are removed from the study (withdrew the consent, lost to follow up, etc.) prior to progression or death	Date of last objective tumor assessment documenting no progression	Censored
New anticancer treatment prior to progression or death	Date of last objective tumor assessment documenting no progression prior to new anticancer treatment	Censored
Death prior to first planned tumor assessment	Date of death	Death (Event)
Death without objective progression prior to treatment discontinuation[2]	Date of death	Death (Event)
Death or progression after 2 or more missed tumor assessments	Date of last objective tumor assessment documenting no progression prior to the event	Censored

[1] For date of censorship, if a tumor assessment takes place over a number of days (eg, superficial lesions one day, scans another), the last date is used as the assessment date.

Appendix 5. Study Treatment Modification and Compliance

Appendix 5.1. Dose Modification

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

In the event of significant treatment-related toxicity, palbociclib/placebo dosing may be interrupted or delayed and/or reduced as described below.

- A **treatment delay** is defined as any delay of the cycle start date, based on the previous cycle's start date. Since letrozole is administered daily continuously, a treatment delay is not applied to letrozole.

A **dose reduction** is defined as a day when the actual dose taken is less than the initial prescribed dose for any reason with the exception that a day with total dose administered of 0mg is not considered a dose reduction.

A **dose interruptions/missed dose** is defined as a planned dosing day with 0 mg administered.

Appendix 5.2. Summarizing Relative Dose (RD) and Relative Dose Intensity (RDI)

The following types of summaries are proposed for administration of palbociclib and letrozole.

When palbociclib is administered in combination with letrozole (orally once daily continuously), on an orally once a day for 21 days of every 28-day cycle followed by 7 days off treatment (cyclical dosing), the following summaries can be presented:

- RDI for palbociclib: by Cycle and Overall
- RDI for letrozole: by Cycle and Overall

Note: the denominator for tables summarizing "letrozole" will be all patients who took at least a dose of letrozole and for tables summarizing "palbociclib" will be all patients who took at least a dose of palbociclib

Examples for the summaries described in above are included in the tables below.

Conventions:

- Regular Cycle or Complete Cycle: There is another cycle after the current one.
- Last Cycle: The treatment is permanently discontinued after the current cycle.

- Intended Total Dose Per Cycle is the same (2.5mg [once daily continuous] x 28 days for letrozole and 125mg [once a day for 21 days followed by 7 days break in a 28 days treatment cycle] x 21 days for palbociclib) for all regular cycles. The daily dose is fixed at the start of treatment rather than start of a cycle.
- Intended Dosed Days Per Cycle for palbociclib
  - 21 days for a regular cycle, or
  - Minimum of (21 days, actual treatment duration) for the last cycle
- Intended Treatment Duration is the same for the entire dosing period, except for the last cycle which is the actual duration of treatment up to 4 weeks. (eg, for a 3/1 dosing schedule, all cycles have an intended duration of 4 weeks)
  - 28 days for a regular cycle, or
  - Minimum of (28 days, actual treatment duration) for the last cycle.
- Actual Total Dose Per Cycle is the total dose a patient actually took in a cycle.
- Actual Treatment Duration is the treatment duration for a cycle.
  - Start date of next cycle – Start date of current cycle for a regular cycle
  - Last dose date – Start date of the cycle+1 for the last cycle

Table 1

Treatment / Summary Type	Calculation of RD/RDI	Example
Cyclical palbociclib / Overall	$RD = \frac{Actual\ Total\ Dose}{Intended\ Total\ Dose} * 100\ \%$ *Actual Total Dose* = Sum over all cycles of the Actual Total Dose *Intended Total Dose* = Sum over all cycles of the Intended Total Dose† Note: Calculation of RD is optional † = Calculated based on prescribed dose at the beginning of the study	• Palbociclib is to be dosed at 125 mg QD on a 3/1 Schedule (21 days in a cycle of 28 days) • Actual palbociclib dosing: 21 days (3/1) in Cycle 1, 21 days out of 35 days (3/2) in Cycle 2 and 13 days (Day 1- Day 13) in Cycle 3 (the last cycle) Actual Total Dose = (125*21)*2 + (125*13) (same dosing in the first 2 cycles) = 2,625*2+1,625 = 6,875mg Intended Total Dose= (125*21)*2 + (125*13) = 6,875mg RD = (6,875 / 6,875) * 100% = 100%
	$RDI = \frac{Actual\ Overall\ Dose\ Intensity}{Intended\ Overall\ Dose\ Intensity} * 100\ \%$ *Actual Overall Dose Intensity* = (Sum over all cycles of the Actual Total Dose) / (Sum of overall Actual Treatment Duration) *Intended Overall Dose Intensity* = (Sum over all cycles of the Intended Total Dose) /(Sum of overall Intended Treatment Duration)	• Palbociclib is to be dosed at 125 mg QD on a 3/1 Schedule (21 days in a cycle of 28 days) • Actual palbociclib dosing: 21 days (3/1) in Cycle 1, 21 days out of 35 days (3/2) in Cycle 2 and 13 days (Day 1- Day 13) in Cycle 3 (the last cycle) Actual Overall Dose Intensity = (2,625 + 2,625 + 1,625) / (28 + 35 + 13) = 90.46 mg/day Intended Overall Dose Intensity = (2,625 + 2,625 + 1,625) / (28 + 28 + 13) = 99.64 mg/day RDI = (90.46 /99.64) *100% = 90.79%

Table 2

Treatment / Summary Type	Calculation of RD/RDI	Example
Cyclical palbociclib / By Cycle	$RDI = \frac{Actual\ Dose\ Intensity}{Intended\ Dose\ Intensity} * 100\%$ *Actual Dose Intensity (per day)* = (Actual Total Dose per cycle) / (Actual Treatment Duration for the cycle) For a regular cycle *Actual Treatment Duration for the Cycle* = Start date of next cycle – Start date of current cycle. For the last cycle *Actual Treatment Duration for the Cycle* = Last dose date – Start date of the cycle+1. *Intended Dose Intensity (per day)* = (Intended Total Dose per cycle) / (Intended Treatment Duration in cycle) For a regular cycle Intended Total Dose per cycle is always 125 * 21 = 2625 mg; Intended Treatment Duration is always 28 days For the last cycle Intended Total Dose in last cycle = 125 * [Min(21, actual treatment duration)] Intended Treatment Duration in last cycle = Min[(28, actual treatment duration)]	• Palbociclib is to be dosed at 125 mg QD on a 3/1 Schedule (21 days in a cycle of 28 days) • Actual palbociclib dosing: 21 days (3/1) in Cycle 1, 21 days out of 35 days (3/2) in Cycle 2 and 13 days (Day 1- Day 13) in Cycle 3 (the last cycle) Intended Dose Intensity in cycle 1, 2 = (125*21) / 28 = 93.75 mg/day Intended Dose Intensity in cycle 3 (last cycle)= (125*13) / 13 = 125 mg/day <u>Cycle 1:</u> Actual Dose Intensity = (125*21) / 28 = 93.75 mg/day RDI = (93.75/93.75)*100% = 100% <u>Cycle 2:</u> Actual Dose Intensity = (125*21) / 35 = 75 mg/day RDI = (75/93.75) * 100% = 80% <u>Cycle 3 (Last cycle):</u> Actual Dose Intensity = (125*13) / 13= 125 mg/wk RDI = (125/125) * 100% = 100%

Table 3

Treatment / Summary Type	Calculation of RD/RDI	Example
letrozole By Cycle & Overall	$RDI = \frac{Actual\ Dose\ Intensity}{Intended\ Dose\ Intensity} * 100\%$ *Actual Dose Intensity (per day)* = (Actual Total Dose per cycle) / (Actual Treatment Duration for the cycle) *Intended Dose Intensity (per day)* = (Intended Total Dose per cycle) / (Intended Treatment Duration for the cycle) $RDI = \frac{Actual\ Overall\ Dose\ Intensity}{Intended\ Overall\ Dose\ Intensity} * 100\%$ *Actual Overall Dose Intensity* = (Sum over all cycles of the Actual Total Dose) / (Sum of overall Actual Treatment Duration) *Intended Overall Dose Intensity = Intended Dose Intensity (per day)*	• letrozole is to be dosed at 2.5 mg daily continuously • Actual letrozole dosing: D1 to D28 on Cycle 1; D1 to D14 and D22 to D28 in Cycle 2 (ie, 7 days interruption) • Actual Dose is 2.5*28 = 70mg in Cycle 1 • Actual Dose is 2.5* 21 = 52.5mg in Cycle 2 • Actual Total Dose level is 70mg in Cycle 1 and 52.5mg in Cycle 2 <u>Cycle 1:</u> Actual Dose Intensity=70/28=2.5 mg/day Intended Dose Intensity = 70/28 = 2.5 mg/day RDI= (2.5 /2.5) * 100% =100% <u>Cycle 2:</u> Actual Dose Intensity = 52.5/28 = 1.875 mg/day Intended Dose Intensity = 70/28 = 2.5 mg/day RDI= (1.875 /2.5) * 100% =75% <u>Overall:</u> Actual Overall Dose Intensity = (70 + 52.5) / (28 + 28) = 2.1875 mg/day Intended Overall Dose Intensity = (70 + 70) / (28 + 28) = 2.5 mg/day RDI= (2.1875 / 2.5) *100%=87.5%

Appendix 6. Definition of the Programmatic Data Cut-Off Algorithm for Interim Reports

For any formal or regulatory reporting of this study when ongoing, a cut-off date will be set programmatically for reporting purposes. Data entered as of the agreed upon data snap-shot date for that deliverable will be extracted from the database. This data will then be subset programmatically using a data cut-off date. In general, data with an assessment date on or prior to the specific cut-off date defined for that deliverable will be included in the datasets used for reporting. Data with an assessment date after the cut-off date will be removed from the datasets for the specific reporting event and will be reported in the next update. Since the database is not locked for interim reporting, the data reported in interim reports may be updated in the database after interim reporting but prior to database lock.

In particular, the following steps will be taken to derive and report CRF data that might be potentially affected by the data cut-off date.

- For any CRF pages with an actual assessment or sample collection date collected (Pharmacokinetic data, Vital signs, ECGs, Laboratory data, Ocular safety assessments, Tumor assessments, IOTA, Biomarker assessments, etc…), only those assessments that were made or samples that were collected on or before the cut-off will be included in the datasets used to generate the TFLs.

- For the following CRFs, if a treatment starts on or before the data cut-off date and ends after the data cut-off date, the stop date will be set to missing and the status of "ongoing" will be programmatically reported in all relevant derived data sets and TFLs, including:

    1. Prior and Concomitant Drug Treatment
    2. Previous and Current Non-Drug Treatement/Procedure
    3. Prior Cancer Related Radiotherapy
    4. Concomitant Radiation Therapy
    5. Prior Cancer Related Surgey
    6. Concomitant Cancer Related Surgey
    7. Prior Systemic Therapy For Primary Diagnosis
    8. Prior Cancer Related Systemic Therapy

- For the Adverse Event (AE) and Medication Error (ME) CRF pages, if an AE starts on or before the data cut-off date and is resolved after the data cut-off date, the resolution date will be programmatically removed and the outcome of the AE will be set to "Still Present" at the data cut-off date in all relevant derived data sets and TFLs.

The same algorithm applies to the adverse event data extracted from ARGUS safety database.

- For the Dosing CRF pages, if a subject is still receiving the study medication as of the data cut-off date (with a stop date that is after the cut-off date), the dosing stop date will be programmatically set to the cut-off date in the raw and derived data sets for calculating dosing-related summary results (eg, treatment duration and dose intensity). If the stop date is missing, it will be imputed with the start date or the latest dosing date if available (whichever occurs later) from that record.

- For all other pages with no specific date associated with the field, the visit date in the CRF header is used in the algorithm for data cut-off.

Additional details around the specific variables used to apply the cut-off to each specific dataset will be detailed in the programming plan.