I3Y-MC-JPCB Statistical Analysis Plan

Effects of Multiple Doses of Abemaciclib on the Pharmacokinetics of Cytochrome P450 (CYP) 1A2, CYP2C9, CYP2D6, and CYP3A Substrates (Caffeine, Warfarin, Dextromethorphan, and Midazolam) in Cancer Patients

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STATISTICAL ANALYSIS PLAN

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1. TABLE OF CONTENTS

2. ABBREVIATIONS

Abbreviations pertain to the Statistical Analysis Plan (SAP) only (not the tables, figures and listings [TFLs]).

AE	Adverse event
AUC	Area under the concentration versus time curve
AUC(0-t_{last})	Area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
AUC(0-∞)	Area under the concentration versus time curve from zero to infinity
%AUC(t_{last}-∞)	Percentage of AUC(0-∞) extrapolated
AUC_{INR}	Area under the INR curve
C_{max}	Maximum observed drug concentration
CI	Confidence interval
CL\F	Apparent total body clearance of drug calculated after extravascular administration
CRF	Case Report Form
CSR	Clinical Study Report
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
EC	Early Clinical
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
e.g.	For example (Latin: *exempli gratia*)
ICH	International Conference on Harmonisation
INR	International normalized ratio
INR_{max}	Maximum observed INR response
KIM-1	Kidney injury molecule-1
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NGAL	Neutrophil gelatinase-associated lipocalin

PD	Pharmacodynamic
PK	Pharmacokinetic
PRO	Patient reported outcomes
Q12H	Every 12 hours
SAP	Statistical Analysis Plan
SD	Standard deviation
SE	Safety extension
TFLs	Tables, Figures, and Listings
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
t_{max}	Time of maximum observed drug concentration
$V_{ss}\backslash F$	Apparent volume of distribution at steady state after extravascular administration
$V_z\backslash F$	Apparent volume of distribution during the terminal phase after extravascular administration
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 06 October 2015) and Protocol Amendment (a) (final version dated 21 December 2015).

This SAP describes the planned analysis of the safety, tolerability and pharmacokinetic (PK) and pharmacodynamic (PD) data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical, PD and PK analyses of data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement between Eli Lilly and Company and Covance Early Clinical (EC) Biometrics. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. This SAP must be signed off prior to first subject administration for this study. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon between Eli Lilly and Company and Covance EC Biometrics and identified in the CSR. Any minor deviations from the TFLs may not be documented in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials[1] and the ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports[2].

4. STUDY OBJECTIVES

4.1 Primary objective

The primary objective of this study is to assess the effect of abemaciclib on the PK of caffeine (CYP1A2 substrate), warfarin (CYP2C9 substrate), dextromethorphan (CYP2D6 substrate), and midazolam (CYP3A substrate) in cancer patients after multiple oral doses of abemaciclib.

4.2 Secondary objectives

The secondary objectives of this study are:

- to characterize the tolerability of coadministration of abemaciclib with caffeine, warfarin, dextromethorphan, and midazolam following multiple doses of abemaciclib in cancer patients.
- to assess the effect of abemaciclib on blood pressure and pulse rate following multiple doses of abemaciclib in cancer patients.

4.3 Exploratory objectives

The exploratory objectives of this study are:

- to determine the effect of abemaciclib on the PD of a single dose of warfarin as measured by international normalized ratio (INR).
- to assess the effect of abemaciclib on markers of renal function, including creatinine, cystatin-C, kidney injury molecule-1 (KIM-1), and neutrophil gelatinase-associated lipocalin (NGAL).
- to characterize bowel habits via a patient diary and a stool assessment tool (Bristol Stool Chart).
- to characterize diarrhea experienced via patient reported outcome data based on selected individual items from existing patient reported outcomes (PRO) scales (FACIT-D) as well as custom-generated PRO items.

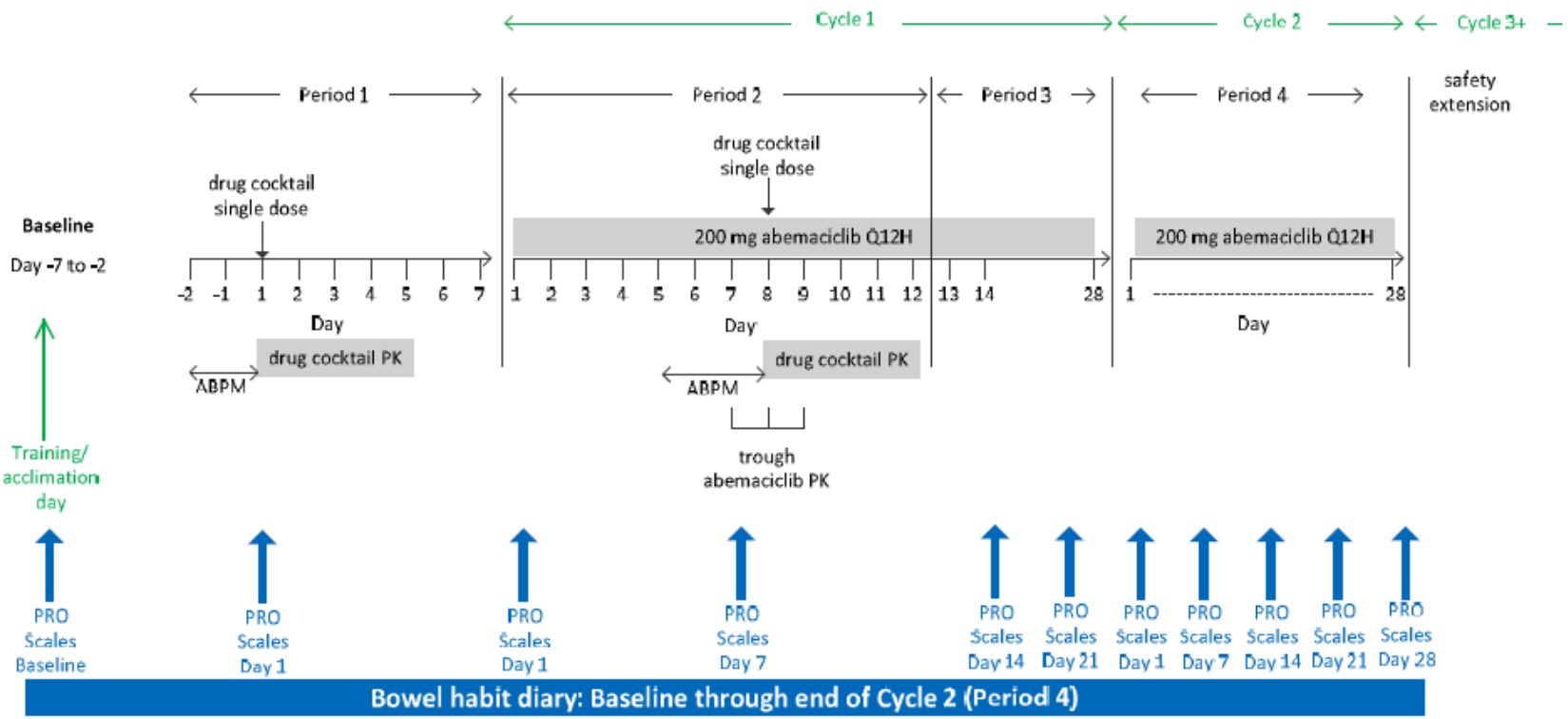
5. STUDY DESIGN

This will be an open-label, 4-period, fixed-sequence study, followed by a safety extension phase, in patients with advanced and/or metastatic cancer.

The drug cocktail of 100 mg caffeine, 10 mg warfarin, 30 mg dextromethorphan, and 0.2 mg midazolam will be administered orally as a single dose on 2 occasions: Day 1 in Period 1, and in combination with abemaciclib on Day 8 of Period 2, after 7 days of 200 mg abemaciclib every 12 hours (Q12H) dosing. After completing Period 2, patients will continue to receive abemaciclib at a dose of 200 mg Q12H (or a modified dose) through the end of Periods 3 and 4, in 28-day cycles, and then may continue in a safety extension phase until discontinuation criteria are met. Patients who do not complete dosing and PK sampling through Period 2 may be replaced.

Patients will be provided with a diary from the baseline visit through the end of Cycle 2 to record the time and date of abemaciclib administration, any constipation or anti-diarrhea medications taken, and bowel habits and any changes.

The study design is illustrated in Figure JPCB.6.1.



Abbreviations: ABPM = ambulatory blood pressure monitoring; PK = pharmacokinetics; PRO = patient reported outcomes; Q12H = every 12 hours.
ABPM will be performed at following times: 12-hour acclimation period between Days -7 to -2 in Period 1, 24-hour period between Day -2 and dosing on Day 1 in Period 1, and 24-hour period between Days 5 to 8 in Period 2.

Figure JPCB.6.1. Study Design

6. TREATMENTS

The following is a list of the study treatment abbreviations that will be used in the safety TFLs.

Study Treatment Name	Abbreviation	Treatment order in TFLs
100 mg caffeine + 10 mg warfarin + 30 mg dextromethorphan + 0.2 mg midazolam	Drug cocktail (Period 1)	1
200 mg Abemaciclib Q12H	200 mg Abemaciclib (Period 2)	2
200 mg Abemaciclib Q12H + 100 mg caffeine + 10 mg warfarin + 30 mg dextromethorphan + 0.2 mg midazolam	200 mg Abemaciclib + Drug cocktail (Period 2)	3
XX mg Abemaciclib Q12H (200 mg or a modified dose)	XX mg Abemaciclib (Periods 3 and 4)	4
XX mg Abemaciclib Q12H (200 mg or a modified dose)	XX mg Abemaciclib (SE)	5

Drug cocktail = 100 mg caffeine + 10 mg warfarin + 30 mg dextromethorphan + 0.2 mg midazolam.
SE = Safety extension.

The following is a list of the study treatment abbreviations that will be used in the PK TFLs.

Study Treatment Name	Abbreviation	Treatment order in TFLs
100 mg caffeine + 10 mg warfarin + 30 mg dextromethorphan + 0.2 mg midazolam	Drug cocktail (Period 1)	1
200 mg Abemaciclib Q12H	200 mg Abemaciclib (Period 2)	2
200 mg Abemaciclib Q12H + 100 mg caffeine	200 mg Abemaciclib + 100 mg caffeine (Period 2)	3
200 mg Abemaciclib Q12H + 10 mg warfarin	200 mg Abemaciclib + 10 mg warfarin (Period 2)	4
200 mg Abemaciclib Q12H + 30 mg dextromethorphan	200 mg Abemaciclib + 30 mg dextromethorphan (Period 2)	5
200 mg Abemaciclib Q12H + 0.2 mg midazolam	200 mg Abemaciclib + 0.2 mg midazolam (Period 2)	6

7. SAMPLE SIZE JUSTIFICATION

Up to 48 patients may be enrolled in order that 22 patients complete Periods 1 and 2.

Caffeine

For caffeine area under the concentration time curve (AUC), the intra-subject variability (coefficient of variation [CV]) was estimated to be 21.0% (Blanchard & Sawers 1983); 22 patients will provide a precision of 0.13 on the log scale with 90% power.

Warfarin

For warfarin AUC, the intra-subject variability (coefficient of variation) was estimated to be 7% (Steinijans et al. 1995); 22 patients will provide a precision of 0.04, with 9 0% power, which corresponds to 4.4% on the log scale. For warfarin C_{max}, the intra-subject variability was estimated to be 8% (Steinijans et al. 1995); 22 patients will provide a precision of 5.0% on the log scale with 90% power.

Dextromethorphan

For dextromethorphan AUC, the intra-subject variability (coefficient of variation) was estimated to be 33.7% (derived from a previous study); 22 patients will provide a precision of 0.20, with 90% power, which corresponds to 22.4% on the log scale. For dextromethorphan C_{max}, the intra-subject variability was estimated to be 32.1% (derived from a previous study); 22 patients will provide a precision of 21.3% on the log scale with 90% power.

Midazolam

For midazolam AUC, the intra-subject variability (coefficient of variation) was estimated to be 16.1% (derived from a previous study); 22 patients will provide a precision of 0.10, with 90% power, which corresponds to 10.4% on the log scale. For midazolam C_{max}, the intra-subject variability was estimated to be 26.4% (derived from a previous study); 22 patients will provide a precision of 17.3% on the log scale with 90% power.

ABPM

Using an intra-subject standard error of 9.48 mmHg in systolic blood pressure from Study JPBA, a sample size of 22 completed patients will provide more than 90% coverage probability that the half-width of the 90% confidence interval (CI) for the difference in means will be approximately 6 mmHg. The intra-subject standard error of diastolic blood pressure was estimated to be 6.78 mmHg and will provide more than 90% coverage probability that the half-width of the 90% CI is in difference of means to be 4.3 mmHg.

8. DEFINITION OF ANALYSIS POPULATIONS

The “Safety” population will consist of all subjects who received at least one dose of study drug, and have at least one postdose safety assessment.

The "Pharmacokinetic" population will consist of all subjects who received at least one dose of study drug and have evaluable PK data. Subjects may be excluded from the PK summary statistics and statistical analysis if a subject has an adverse event (AE) of vomiting that occurs at or before 2 times median time to maximum concentration (t_{max}).

The "Pharmacodynamic" population will consist of all subjects who received at least one dose of study drug and have evaluable PD data. Subjects may be excluded from the PD summary statistics and statistical analysis if a subject has an AE of vomiting that occurs at or before 2 times median t_{max}.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when subjects are assigned to analysis populations.

9. STATISTICAL METHODOLOGY

9.1 General

Data listings will be provided for all data that is databased. Summary statistics and statistical analysis will only be presented for data where detailed in this SAP. For continuous data, summary statistics will include the arithmetic mean, arithmetic SD, median, min, max and N; for log-normal data (e.g. the PK parameters: AUCs and C_{max}) the geometric mean and geometric CV% will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all subjects up to the point of withdrawal, with any subjects excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for subjects included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Mean change from baseline is the mean of all individual subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The individual subject's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

Data analysis will be performed using SAS® Version 9.3 or greater.

9.2 Patient Characteristics

Subject disposition will be listed. The demographic variables age, sex, race, ethnicity, screening height and weight, and screening body mass index will be summarized and listed. All other demographic data will be listed only.

Baseline disease characteristics will be summarized and listed. Furthermore, prior disease-related therapies will be listed.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

The PK parameter estimates will be determined using non-compartmental procedures in validated software program (Phoenix WinNonlin Version 6.2.1 or later).

Plasma concentrations of caffeine, S-warfarin, dextromethorphan and midazolam will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC(0-t_{last})	ng•h/mL	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
AUC(0-∞)	ng•h/mL	area under the concentration versus time curve from zero to infinity
%AUC(t_{last}-∞)	%	percentage of AUC(0-∞) extrapolated
C_{max}	ng•h/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
$t_{1/2}$	h	half-life associated with the terminal rate constant (λz) in non-compartmental analysis
CL/F	L/h	Apparent total body clearance of drug calculated after extravascular administration
V_Z/F	L	Apparent volume of distribution during the terminal phase after extravascular administration
V_{SS}/F	L	Apparent volume of distribution at steady state after extravascular administration

Trough plasma concentrations of abemaciclib will be listed and summarised.

An alternative AUC measure, such as AUC to a common time point, may be calculated if AUC(0-∞) cannot be reliably calculated.

Additional PK parameters may be calculated, as appropriate. The software and version used for the final analyses will be specified in the CSR. Any exceptions or special handling of data will be clearly documented within the final study report.

Formatting of tables, figures and abbreviations will follow the Eli Lilly Global PK/PD/TS Tool: NON-COMPARTMENTAL PHARMACOKINETIC STYLE GUIDE. The version of the tool effective at the time of PK analysis will be followed.

General PK Parameter Rules

- Actual sampling times will be used in the final analyses of individual PK parameters, except for non-bolus predose sampling times which will be set to zero.

- The C_{max} and t_{max} will be reported from observed values. If C_{max} occurs at more than one time point, t_{max} will be assigned to the first occurrence of C_{max}.

- The AUC parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max} and then the logarithmic trapezoidal method will be used after t_{max}. The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}. Any AUC(0-∞) values where the percentage of the total area extrapolated is more than 20% will be flagged. Any AUC(0-∞) value excluded from summary statistics will be noted in the footnote of the summary table.

- Half-life ($t_{½}$) will be calculated, when appropriate, based on the apparent terminal log-linear portion of the concentration-time curve. The start of the terminal elimination phase for each subject will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in plasma concentrations. Half-life will only be calculated when a reliable estimate for this parameter can be obtained comprising of at least 3 data points. If $t_{½}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{½}$ value excluded from summary statistics will be documented in the footnote of the summary table.

- A uniform weighting scheme will be used in the regression analysis of the terminal log-linear portion of the concentration-time curve.

- The parameters based on predicted C_{last} will be reported.

Individual PK Parameter Rules

- Only quantifiable concentrations will be used to calculate PK Parameters with the exception of special handling of certain concentrations reported below the lower limit of quantitation (BQL). Plasma concentrations reported as BQL will be set to a value of zero when all of the following conditions are met:

    - The compound is non-endogenous.

    - The samples are from the initial dose period for a subject or from a subsequent dose period following a suitable wash-out period.

    - The time points occur before the first quantifiable concentration.

- All other BQL concentrations that do not meet the above criteria will be set to missing.

- Also, where two or more consecutive concentrations are BQL towards the end of a profile, the profile will be deemed to have terminated and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

Individual Concentration vs. Time Profiles

- Individual concentrations will be plotted utilizing actual sampling times.

- The terminal point selections will be indicated on a semi-logarithmic plot.

Average Concentration vs. Time Profiles

- The average concentration profiles will be graphed using scheduled (nominal) sampling times.

- The average concentration profiles will be graphed using arithmetic average concentrations.

- The predose average concentration for single-dose data from non-endogenous compounds will be set to zero. Otherwise, only quantifiable concentrations will be used to calculate average concentrations.

- Concentrations at a sampling time exceeding the sampling time window specified in the protocol, or ± 10%, will be excluded from the average concentration profiles.

- Concentrations excluded from the mean calculation will be documented in the final study report.

- A concentration average will be plotted for a given sampling time only if 2/3 of the individual data at the time point have quantifiable measurements that are within the sampling time window specified in the protocol or ± 10%. An average concentration estimated with less than 2/3 but more than 3 data points may be displayed on the mean concentration plot if determined to be appropriate and will be documented within the final study report.

Treatment of Outliers during Pharmacokinetic Analysis

Application of this procedure to all PK analyses is not a requirement. Rather, this procedure provides justification for exclusion of data when scientifically appropriate. This procedure describes the methodology for identifying an individual value as an outlier for potential exclusion, but does not require that the value be excluded from analysis. The following methodology will not be used to exclude complete profiles from analysis.

Data within an Individual Profile

A value within an individual profile may be excluded from analysis if any of the following criteria are met:

- For PK profiles during multiple dosing, the concentration of the predose sample exceeds all measured concentrations for that individual in the subsequent post-dose samples.
- For PK profiles during single dosing of non-endogenous compounds, the concentration in a predose sample is quantifiable.
- For any questionable datum that does not satisfy the above criteria, the profile will be evaluated and results reported with and without the suspected datum.

Data between Individual Profiles

1. If $n<6$, then the dataset is too small to conduct a reliable range test. Data will be analyzed with and without the atypical value, and both sets of results will be reported.
2. If $n\geq6$, then an objective outlier test will be used to compare the atypical value to other values included in that calculation:
    a. Transform all values in the calculation to the logarithmic domain.
    b. Find the most extreme value from the arithmetic mean of the log transformed values and exclude that value from the dataset.
    c. Calculate the lower and upper bounds of the range defined by the arithmetic mean ±3*SD of the remaining log-transformed values.
    d. If the extreme value is within the range of arithmetic mean ±3*SD, then it is not an outlier and will be retained in the dataset.
    e. If the extreme value is outside the range of arithmetic mean ±3*SD, then it is an outlier and will be excluded from analysis.

If the remaining dataset contains another atypical datum suspected to be an outlier and $n \geq 6$ following the exclusion, then repeat step 2 above. This evaluation may be repeated as many times as necessary, excluding only one suspected outlier in each iteration, until all data remaining in the dataset fall within the range of arithmetic mean ±3*SD of the log-transformed values.

Reporting of Excluded Values

Individual values excluded as outliers will be documented in the final report. Approval of the final report will connote approval of the exclusion.

9.3.2 Pharmacokinetic Statistical Methodology

PK parameter estimates will be evaluated to delineate effects of drug interaction. Caffeine, warfarin, dextromethorphan, and midazolam administered in the absence of abemaciclib will represent the reference treatments and be analyzed separately. Each drug administered with abemaciclib will represent the test treatments. Log-transformed C_{max} and AUC(0-∞) estimates will be evaluated in a linear mixed-effects analysis of variance model with a fixed effect for treatment and a random effect for subject. The treatment differences will be back-transformed to present the ratios of geometric least squares (LS) means and the corresponding 90% CIs.

Example SAS code 1:

```
proc mixed data=pk;
    by parameter;
    class subject treatment;
    model log_pk = treatment / alpha=0.1 cl residual ddfm=kr;
    random subject;
    lsmeans treatment / alpha=0.1 cl pdiff;
    ods output lsmeans=lsmeans;
    ods output diffs=diffs;
run;
```

The t_{max} will be analyzed using a Wilcoxon signed rank test. Estimates of the median difference based on the observed medians, 90% CIs, and p-values from the Wilcoxon test will be calculated.

The inter- and intra-subject variability will be reported for each probe drug.

9.4 Pharmacodynamic Assessment

9.4.1 Pharmacodynamic Analysis

Area under the INR curve (AUC_{INR}) and maximum observed INR response (INR_{max}) will be calculated to quantify the action of warfarin.

9.4.2 Pharmacodynamic Statistical Methodology

The PD parameters AUC_{INR} and INR_{max} will be evaluated statistically to delineate the effect of INR response to warfarin dose. A linear mixed-effects model with log-transformed PD parameter as a response variable, predose INR as a covariate, treatment as a fixed effect, and subject as a random effect. For each of these PD parameters, the statistical inference will be made using the test treatment of warfarin + abemaciclib and the reference treatment of warfarin in the absence of abemaciclib. The geometric LS means for the treatments and the ratios of geometric LS means for AUC_{INR} and INR_{max}, between the test (Abemaciclib) and reference (Drug cocktail) treatments with 90% CIs will be established.

Example SAS code 2:

```
proc mixed data=pd;
    by parameter;
    class subject treatment;
    model log_pd = treatment pre_INR / alpha=0.1 cl residual ddfm=kr;
    random subject;
    lsmeans treatment / alpha=0.1 cl pdiff;
    ods output lsmeans=lsmeans;
    ods output diffs=diffs;
run;
```

Descriptive statistics will be presented for PD parameters by treatment.

9.5 Safety and Tolerability Assessments

9.5.1 Adverse events

All AEs will be coded by the Medical Dictionary for Regulatory Activities (MedDRA) version 18 and graded according to the National Cancer Institute (NCI) Comm on Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

Where changes in CTCAE grade are recorded in the Case Report Form (CRF), each separate grade of the AE will be reported in the listings, only the highest grade will be used in the summary tables. A pre-existing condition is defined as an AE that starts before the subject has provided written informed consent and is ongoing at consent. A non-treatment emergent AE is defined as an AE which starts after informed consent but prior to dosing. A treatment-emergent AE is defined as an AE which occurs postdose or which is present prior to dosing and its grade increases postdose.

All AEs will be listed. Treatment-emergent AEs will be summarized by treatment, grading and relationship to the study drug. The frequency (the number of AEs, the number of subjects experiencing an AE and the percentage of subjects experiencing an AE) of treatment-emergent AEs will be summarized by treatment, CTCAE v 4.0 grade and code, and MedDRA system organ class and preferred term. The summary and frequency AE tables will be presented for all causalities and those considered related to the study drug. Any serious AEs will be tabulated and any deaths will be listed.

9.5.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version WhoDrug September 2015). Concomitant medication will be listed and ongoing concomitant medications will be summarized.

9.5.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be listed and summarized by parameter and treatment together with changes from baseline, where basline is defined as Period 1 Day 7. Urinalysis data will be listed. Additionally clinical chemistry, hematology and urinalysis data outside the reference ranges will be listed.

Furthermore, shift tables for clinical chemistry, hematology and urinalysis data will be presented to show the changes in CTCAE grade by parameter.

Values for any clinical chemistry, hematology and urinalysis values outside the reference ranges will be flagged on the individual subject data listings.

Figures of absolute mean, mean changes from baseline, and mean percent changes from baseline will be presented for creatinine by treatment. Furthermore, individual profiles of absolute values, change from baseline, and percent change from baseline will be presented for all renal biomarkers by parameter.

9.5.4 Vital signs

Vital signs data will be summarized by treatment together with changes from baseline, where baseline is defined as Period 1 Day 1 predose. Figures of mean vital signs and mean changes from baseline profiles will be presented by treatment. Furthermore, values for individual subjects will be listed.

9.5.5 Renal markers

Renal marker data will be listed and summarized by parameter and treatment together with changes from baseline, where baseline is defined as Period 1 Day 1 predose. Data outside the reference ranges will be listed and values outside the reference ranges will be flagged on the individual subject data listings.

Figures of mean renal biomarkers, mean changes from baseline, and mean percent changes from baseline will be presented by parameter and treatment. Furthermore, individual profiles of absolute values, change from baseline, and percent change from baseline will be presented for all renal biomarkers by parameter.

9.5.6 Ambulatory blood pressure monitoring (ABPM)

The mean ABPM data over 24 hours will be used for the secondary objective to assess the effect of abemaciclib on blood pressure and pulse rate. The mean 6 hour and 24 hour data will be summarized by treatment together with changes from baseline, where baseline is defined as Period 1 Day - 1. Figures of mean ABPM data and mean changes from baseline will be presented by treatment. Individual scatter plots over time will also be presented. Furthermore, a time-matched APBM measurement versus concentration plot will be presented.

Mean values over 24 hours for individual subjects will be listed.

9.5.7 Bowel habit data

The bowel habit data will include patient diaries and patient reported outcomes. The data will summarized and listed. Additional analyses may be performed if required.

9.5.8 Eastern Cooperative Oncology Group (ECOG) Questionnaire

The ECOG status data will be listed.

9.5.9 Tumor assessment

The tumour assessment data will be listed.

9.5.10 Genotyping sample

The genotyping sample data will be listed. Patients with uncommon metabolic status such as CYP2C9 poor metabolizers will be excluded from the warfarin analysis. CYP2D6 poor metabolizers will be excluded from dextromethorphan analysis.

9.5.11 Other assessments

All other safety assessments not detailed in this section will be listed but not sum marized or statistically analyzed.

9.5.12 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

An interim analysis, which will serve as the final analysis for the primary objective, is planned for this study. This interim analysis will be completed after the last patient has completed Period 2.

Patients will be allowed to continue receiving abemaciclib during Period 3, 4, and the safety extension phase until discontinuation criteria are met (such as progressive disease or unacceptable toxicity). A final analysis and final study report will be completed after t he last patient visit has occurred for this extension phase.

Two additional interim analyses may be conducted: one analysis will be conducted after approximately half of the patients have completed Periods 1 and 2, as a preliminary assessment of the magnitude of any observed effect on blood pressure. No changes to the study design are planned. Another analysis will be conducted after the last patient has completed Period 4 and a preliminary study report will be written.

Unplanned interims may be conducted if deemed necessary by Lilly study team.

This is an open-label study. Data may be analyzed while the trial is ongoing. An Assessment Committee will not be formed.

11. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

12. REFERENCES

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

3. Blanchard J, Sawers SJ. The absolute bioavailability of caffeine in man. *Eur J Clin Pharmacol.* 1983;24(1):93-8.

4. Steinijans VW, Sauter R, Hauschke D, Diletti E, Schall R, Luus HG, Elze M, Blume H, Hoffman C, Franke G et al. Reference tables for the intrasubject c oefficient of variation in bioequivalence studies. *Int J Clin Pharmacol Ther*. 1995;33(8):427-430.

13. DATA PRESENTATION

13.1 Derived Parameters

Individual derived parameters (e.g. PK parameters) and appropriate summary statistics will be reported to three significant figures. Observed concentration data, e.g. C_{max}, should be reported as received. Observed time data, e.g. t_{max}, should be reported as received. N and percentage values should be reported as whole numbers. Median values should be treated as an observed parameter and reported to the same number of decimal places as minimum and maximum values.

13.2 Missing Data

Missing data will not be displayed in listings.

13.3 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the centre of the table, such as, “No serious adverse events occurred for this study.”

Leo Document ID = 74c330f8-d8d6-479a-9147-a7a7c40f6998

Approver: PPD
Approval Date & Time: 03-Feb-2016 17:15:47 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 03-Feb-2016 17:16:55 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 03-Feb-2016 17:36:07 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 04-Feb-2016 15:46:05 GMT
Signature meaning: Approved