Statistical Analysis Plan Version 3 I3Y-MC-JPBA

Phase 1 Study of a CDK4/6 Dual Inhibitor in Patients with Advanced Cancer

NCT01394016

Approval Date: 22-Oct-2013

1. Statistical Analysis Plan: Phase 1 Study of a Dual CDK4/6 Inhibitor in Patients with Advanced Cancer

CDK4/6 Inhibitor (LY2835219)

This Phase 1 study is a single arm dose-escalation study of a dual CDK4/6 inhibitor in patients with advanced cancer.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol I3Y-MC-JPBA
Phase 1

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly: 17 FEB 2010
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly: 11 Jan 2011
Statistical Analysis Plan Version 3 electronically signed and approved by Lilly on date provided below.

Approval Date: 22-Oct-2013 GMT

2. Table of Contents

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved on February 17, 2010 prior to unblinding.

Statistical Analysis Plan Version 2 was created based on Protocol I3Y-MC-JPBA (JPBA) Amendment (c). Protocol JPBA Amendment (c) added a new dosing schedule, receiving study drug every 12 hours for Days 1 through 28 of a 28-day cycle to the study. It also added Melanoma patients in the tumor-specific expansion phases.

Statistical Analysis Plan Version 3 was created based on Protocol JPBA Amendments (f) and (g). This SAP includes the definitions of the analysis populations, the pharmacokinetics (PK), the pharmacodynamic (PD), efficacy and safety endpoints, the tables, listings and graphs for the analysis. It is based on Protocol JPBA Amendments (f) and (g) approved on the 14 December 2012 and 29 August 2013. Protocol JPBA Amendment (f) added a colorectal cohort in the tumor-specific expansion phases. It also allowed expansions up to 45-60 patients in each tumor-specific expansion if approved by the sponsor. Protocol JPBA Amendment (g) added a hormone receptor positive breast cancer cohort.

4. Study Objectives

4.1. Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of LY2835219 when administered orally to patients with advanced cancer.

4.2. Secondary Objectives

The secondary objectives of this study are to:

- Determine the PK of LY2835219
- Evaluate PD and predictive biomarkers
- Document the antitumor activity of LY2835219
- Establish a recommended dose range for Phase 2 studies.

5. Investigational Plan

This study is a multicenter, nonrandomized, open-label, dose-escalation Phase 1 trial of LY2835219 in approximately 100 patients with advanced cancer.

For the original schedule, patients will continue to receive LY2835219 orally every 24 hours. For the new schedule, patients will receive LY2835219 orally every 12 hours for Days 1 through 28 of a 28-day cycle (refer to Figure JPBA.5.1). There are modifications during cycle 1 to enable PK sampling following a single dose and repeated doses.
Patients will be enrolled in cohorts of 3 patients at each planned dose levels (Part A). Patients will receive 2 cycles of LY2835219 unless one or more of the criteria for discontinuation (Protocol JPBA Section 2.3.1) are fulfilled; the follow-up period for post-study evaluation will be 30±7 days from the date of the last dose of study drug received. A patient may receive more than 2 cycles of treatment only if 1) none of the criteria for discontinuation have been fulfilled, and 2) the investigator, in consultation with the Eli Lilly and Company (Lilly) clinical research physician (CRP), determines that the patient is experiencing clinical benefit from treatment.

During dose escalation (Part A), 33 patients were treated across 2 schedules. For the once daily schedule, patients were treated at 50, 100, 150, and 225 mg every 24 hours (Q24H). For the twice daily schedule, patients were treated at 75, 100, 150, 200, and 275 mg every 12 hours (Q12H). A maximum tolerated dose (MTD) for the once daily schedule was not reached whereas the MTD for the twice daily schedule was tentatively established (pending dose confirmation) at 200 mg Q12H. As depicted in Figure JPBA.5.1, the study design consists of a dose escalation phase (Part A) and 6 tumor-specific expansion phases (Parts B, C, D, E, F, and G). The dose escalation phase (Part A), described in Protocol Section 6.2.2, was guided by safety assessments from Days 1 through 28 of Cycle 1 for all patients in the cohort and also by the emerging PK data. Dose escalation occurred until the MTD (defined in Protocol Section 6.2.2.1) was determined for at least 1 schedule.

After the last patient enrolled in the dose escalation phase (Part A) completes Cycle 1, then the 6 tumor-specific expansion phases (Parts B, C, D, E, F, and G) may begin. In each tumor-specific expansion phase, at least 15 and up to 45-60 patients will be treated on the twice daily schedule at a dose no greater than the MTD (200 mg every 12 hours) with administration of LY2835219 on Days 1 through 28 of a 28-day cycle, with modifications during Cycle 1 to enable PK sampling following a single dose and repeated doses.

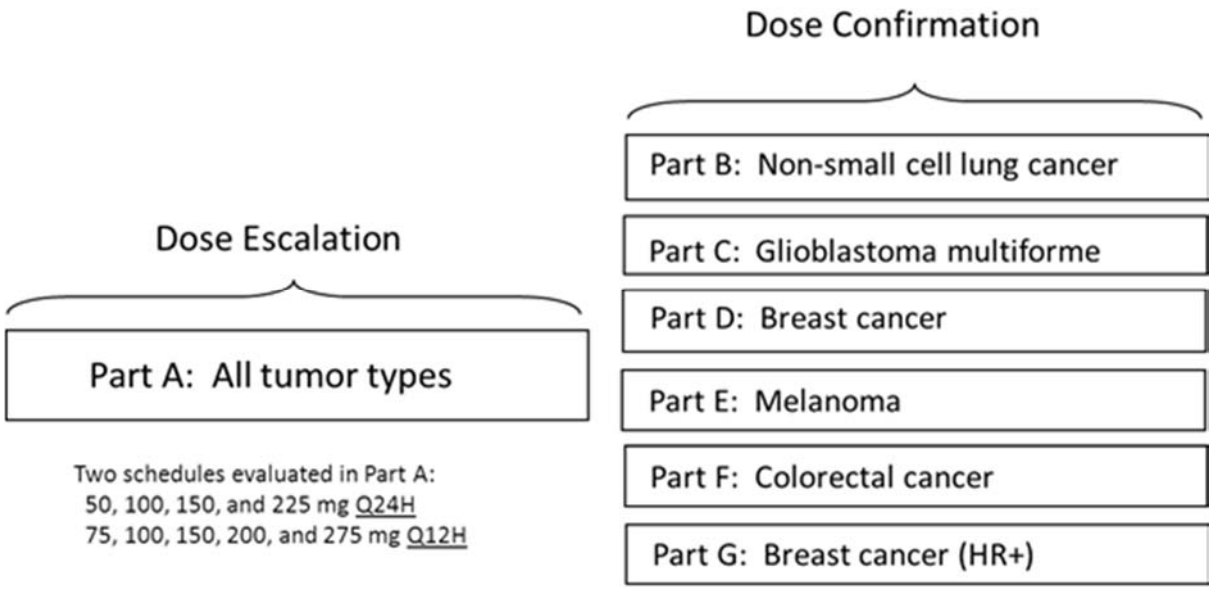

Figure JPBA.5.1. Study design for I3Y-MC-JPBA.

6. A Priori Statistical Methods

6.1. Derived Endpoint Definitions

6.1.1. Safety Endpoints

Safety measures that will be recorded in the study include adverse events (AE), dose limiting toxicities (DLT), DLT equivalent toxicity, laboratory test results, vital signs, electrocardiogram (ECG) and Eastern Cooperative Oncology Group (ECOG) performance status. All AEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, CCI NCI CTCAE CCI.

Dose Limiting Toxicity and Equivalent Toxicity

Dose-limiting toxicity is defined as an AE occurring between Day -3 and Day 28 of Cycle 1 for a patient enrolled in Part A that is possibly related to the study drug and fulfills any one of the following criteria:

- Grade 3 or 4 non-hematological toxicity according to the NCI Common Terminology Criteria for Adverse Events (CTCAE CCI except for nausea, vomiting, diarrhea, or electrolyte disturbance.
- Grade 3 or 4 nausea, vomiting, diarrhea, or electrolyte disturbance that persists more than 2 days despite maximal supportive intervention.
- Grade 4 hematological toxicity that persists more than 5 days.
- Grade 3 or 4 thrombocytopenia with bleeding.
- Grade 3 or 4 neutropenia with fever.

Investigators, together with the Lilly CRP, can declare a DLT if a patient is experiencing increasing toxicity during treatment, and it becomes clear that it is not going to be possible to complete the treatment without exposing the patient to excessive risk. In this case, the remaining treatment has to be suspended and a DLT declared. In Part A (Cycle 1 only), AEs mentioned above that are possibly related to study medication are designated a DLT; by contrast, in Part A (Cycle 2 and beyond) and in Parts B, C, D, E F, and G (regardless of cycle), similar events are designated dose-equivalent toxicities.

Maximum Tolerated Dose

Maximum tolerated dose (MTD) is defined as the highest study dose level at which less than 33% of patients experience a DLT during Part A Cycle 1. If DLT (or DLT equivalent-toxicity) occurs in 33% or more of patients within a tumor-specific cohort expansion, then investigators and the Lilly CRP will assess the nature and severity of these toxicities. No additional patients will be accrued until this safety review is completed and a decision is made either to continue at the current dose or to deescalate the dose and define a new dose for the expansion phase.

Biologically Effective Dose

Biologically effective dose (BED) is estimated using the PK and PD data. For the purpose of this study, the BED is defined as the lowest dose that achieves a minimum of 30% to 50% inhibition of CDK4/6 (measured by pRb and topoIIα) in surrogate tissues (hair follicles or skin) at steady state throughout the duration of the treatment.

6.1.2. Efficacy Endpoints

Efficacy assessments will be derived for patients during the Dose Confirmation Phase (Part B, C, D, E, F, and G).

Response (Complete Response [CR] and Partial Response [PR]) and progression (Stable Disease [SD] and Progressive Disease) for tumors will be evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (Eisenhauer et al. 2009), with the notable exception that response and progression for lymphomas will be evaluated using the Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007).

The Best Overall Response is the best response recorded by the investigator from the start of the treatment until the end of treatment taking into account any requirement for confirmation. Any radiological assessment that occurs within seven days of the end of treatment will also be included in this evaluation.

All lesion assessments, whether by physical exam or radiological methods, should be repeated by the same method at least 4 weeks following the initial observation of an objective response to ensure response confirmation. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of not less than 6 to 8 weeks. If a patient is discontinued from the study, repeat radiology may be omitted if there are clear clinical signs of progressive disease.

The Duration of Overall Response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The Duration of Overall CR is measured from the time measurement criteria are first met for CR until the date that recurrent disease is objectively documented.

The Duration of Stable Disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Progression-Free Survival (PFS) time is defined as the time from the date of first day of study drug to the first date of progressive disease (symptomatic or objective) or death due to any cause, whichever occurs first. For patients who are not known to have died or progressed as of the data-inclusion cutoff date, PFS time will be censored at the date of the last objective progression-free disease assessment prior to the date of any subsequent anticancer therapy.

Overall Survival (OS) time is defined as the time from the date of first day of study drug to the date of death from any cause. For patients not known to have died as of the data cut-off date, OS time will be censored at the last contact date the patient was known to be alive prior to the cut-off date.

6.2. Populations for Analysis

Safety analyses will be conducted on all patients who have received at least one dose of LY2835219.

Pharmacokinetic analyses will be conducted on patients who have received at least one dose of the LY2835219 and have sufficient samples collected to allow the estimation of LY2835219 PK parameters.

Pharmacodynamic analyses will be conducted on patients who have undergone PD assessments.

Pharmacokinetic/Pharmacodynamic analyses will be conducted on the population of the PK analyses.

Efficacy analyses will be conducted on patients who have received at least one dose of LY2835219.

6.3. Statistical Methods

6.3.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly.

CCI [redacted]

Additional exploratory analyses may be conducted by Lilly as documented in a post-hoc section of this SAP.

The interpretation of the study results will be the responsibility of the investigator with the Lilly Clinical Research Physician (CRP), pharmacokineticist, statistician and clinical development associate. The Lilly CRP and statistician will also be responsible for the appropriate conduct of an internal review process for both the final study report and any study-related material to be authorized for publication by Lilly.

Approximately 200 patients will be enrolled in this multicenter open-label Phase 1 study with dose escalation CCI [redacted] followed by dose confirmation in 6 tumor types. During dose escalation (Part A), patients will be enrolled into sequential cohorts; the total number of patients in a specific cohort will be determined based on the occurrence of DLTs (2-6 patients per cohort) at that dose level. In each tumor-specific expansion cohort, at least 15 and up to 45-60 patients will be treated on the twice daily schedule at a dose no greater than the MTD (200 mg every 12 hours) with administration of LY2835219 on Days 1 through 28 of a 28-day cycle, with modifications during Cycle 1 to enable PK sampling following a single dose and repeated doses.

The analyses for this study will be descriptive; no p-values will be calculated. Data analyses will be provided by cohort and for all study patients combined wherever appropriate. For continuous variables, summary statistics will include number of patients, mean, median, standard deviation, standard error, minimum, and maximum. Categorical endpoints will be

summarized using number of patients, frequency, percentages, and their standard errors. Missing data will not be imputed.

Additional exploratory analyses of the data may be conducted if deemed appropriate.

Dose Escalation Phase (Part A)

All data will be summarized by cohort (and all patients combined when appropriate), unless stated otherwise.

Dose Confirmation Phase (Part B, C, D, E, F, and G)

All data will be summarized by tumor-specific cohort:

- Part B: Non-small cell lung cancer of any subtype that is advanced and/or metastatic
- Part C: Glioblastoma multiforme (GBM) that has progressed or recurred after radiotherapy and/or chemotherapy
- Part D: Breast cancer that is advanced and/or metastatic
- Part E: Melanoma that is advanced and/or metastatic
- Part F: Colorectal cancer that is advanced and/or metastatic
- Part G: Breast cancer that is advanced and/or metastatic and hormone receptor positive.

The following data handling conventions (Table JPBA 6.1) will be used in the analysis:

Table JPBA 6.1. Data Handling Conventions

Term	Definition or Rule
Entered	Patients entered into the trial as those who sign the informed consent document directly or through their legally acceptable representatives.
Enrolled	Patients who are enrolled in the trial are those who have been assigned to a treatment.
On therapy	Patients who have received at least one dose of LY2835219.
Phase	This study has 2 phases: Dose Escalation Phase (Part A) and Dose Confirmation Phase (Part B, C, D, E F, and G).
Study day	• There is no study day 0. Day -1 is the day before the day 1 of cycle 1 of each phase. • Day -3 of cycle 1 of Dose Escalation Phase is the first dose of LY2835219.
Cycle day	• There is no cycle day 0. Cycle day -1 is the day before the cycle day 1 of cycle 1 of each phase. • Day -3 of cycle 1 is the first dose of LY2835219 in each phase. Day 1 of cycle 2 and beyond is the first dose of LY2835219 within cycle for each phase.
Treatment Day	Treatment Day relative to first day of the study (Cycle 1 Day -3).
Baseline	For change from baseline analyses, baseline value is defined as the last reported measure on or before the first dose date (prior to the dose administration), unless otherwise specified. For change from baseline within a cycle, baseline value is defined as the measure prior to the first dose of that cycle, unless otherwise specified.

The following are the General Reporting Requirements for the non-PK analyses (Table JPBA.6.2).

Table JPBA.6.2. General Reporting Requirements for the Non-PK Analyses

<table>
<tr><th>Variable</th><th>Requirements</th></tr>
<tr><td>Categorical variables</td><td>Report the formatted values</td></tr>
<tr><td>Statistical summary / Percentage</td><td>(if applicable) Round to the nearest tenths. For example, 45.6</td></tr>
<tr><td>Age</td><td>Round to the nearest tenths. For example, 49.3</td></tr>
<tr><td>Date</td><td>Report date in SAS date9 format (DDMMMYYYY). For example, 11NOV2009</td></tr>
<tr><td>Laboratory results units</td><td>Report in SI units (International System of Units).</td></tr>
<tr><td>Laboratory values</td><td>• Report values up to a maximum of four significant digits.
• No non-significant zeros for values less than four digits.
• Use scientific notation to report values beyond the 1000th or 1/1000th.
Example:
<table>
<tr><th>Actual Lab Values</th><th>Reported Lab Values</th></tr>
<tr><td>0.11123</td><td>0.1112</td></tr>
<tr><td>1.2034</td><td>1.203</td></tr>
<tr><td>1.2</td><td>1.2</td></tr>
<tr><td>10.234</td><td>10.23</td></tr>
<tr><td>102.345</td><td>102.3</td></tr>
<tr><td>1000.34</td><td>1000</td></tr>
<tr><td>12034</td><td>1.203E+4</td></tr>
<tr><td>0.000001</td><td>1.E-6</td></tr>
</table></td></tr>
</table>

6.3.2. Patient Disposition

All patients who discontinue from the treatment will be identified and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given. This information will be listed and summarized for the end of Pre-study and end of study. All patients entered in the study will be accounted for in the summary of disposition by study phase. The number of patients who do not qualify for analysis, who die, or who discontinue before treatment begins will be specified. A patient will be considered to have received a cycle of treatment if they received any of the required treatments in that cycle. Follow-up disposition information will also be listed.

All clinically relevant protocol deviations will be listed by pre-determined categories (for example, inclusion/exclusion criteria, non-compliance with protocol procedures, drug dosage/intervention, use of excluded treatments, informed consent/assent process, continuing after meeting withdrawal criteria, or other).

Patient disposition will be summarized and listed for all enrolled patients.

6.3.3. Demographics and Baseline Characteristics

6.3.3.1. Demographics and Baseline Characteristics

Patient demographic and baseline characteristics will be listed for all patients on therapy. At a minimum, patient demographics (sex, age, and race), baseline disease characteristics (Basis for diagnosis, initial pathological diagnosis, stage at initial diagnosis, baseline ECOG performance status, height, weight and derived body mass index [BMI]) will be listed and summarized by cohort/treatment group and overall by study phase.

In addition, alcohol and tobacco consumption habits will be listed for all patients on therapy.

6.3.3.2. Historical Illness and Prior Therapies

Historical illnesses are clinically relevant events in the past that ended before the pre-study visit. Historical illnesses will be coded according to the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary and listed for all patients on therapy by cohort and study phase.

Pre-existing conditions are existing clinically relevant events that started prior to the study. The conditions will be graded using the CTCAE[CCI] and it will be presented in the AE listings.

Prior therapies are procedures completed before the pre-study visit and include any therapy administered prior to the first dose of the study drug. The therapies, including radiotherapy, surgery, systemic and topical, will be listed for each study phase and summarized for patients on therapy by cohort and overall in each study phase.

Post-treatment therapies will be listed for all patients on therapy.

6.3.3.3. Concomitant Medication

All medications will be coded to the generic preferred name according to the current World Health Organization (WHO) drug dictionary.

All concomitant medications will be listed and summarized using the preferred name for all patients on therapy by cohort.

6.3.4. Study Drug Exposure

LY2835219 will be supplied as 25-mg and 150-mg capsules in 28-count bottles for oral administration by Eli Lilly and Company.

Clinical trial (CT) lot numbers will be listed for all patients on therapy.

Study drug data will be listed for all patients on therapy. At least the data on LY2835219 will include dose level assignment, administration date and time, actual dose administered, number of capsules taken and responses to the patient compliance CRF question.

A summary of LY2835219 drug exposure will be presented. Within this table, the maximum number of completed cycles of study drug per patient will be summarized. A completed cycle is any cycle for which the patient was compliant with study drug as defined in Protocol Section 6.6.

A summary of LY2835219 dose administration, detailing the number of doses given as planned, increased, reduced, omitted and cycle delays will be presented by cohort and cycle.

LY2835219 drug intensity will be listed and summarized by cycle and overall for all patients on therapy by cohort.

Drug Intensity (DI) is defined as follows:

$$DI(\%) = \left(\frac{Actual\_cumulative\_dose\_taken}{Planned\_cumulative\_dose} \right) * 100$$

6.3.5. Safety Analyses

6.3.5.1. Dose Limiting Toxicity and Maximum Tolerated Dose Estimation

Dose limiting toxicities, for Part A cycle 1, and DLT-equivalent toxicity, for all cycles except Part A cycle 1, will be listed and summarized for all patients on therapy by cohort.

To guide dose selection and to find the MTD, a logistic regression model will be fitted to the data to establish the relationship between the dose and the probability of experiencing a DLT. The model-based MTD estimate, defined as the highest dose level at which no more than 33% of patients experience a DLT during cycle 1, will be estimated from the model together with its confidence limits.

6.3.5.2. Adverse Events

Pre-existing conditions are events that occur prior to the first dose of study drug. Pre-existing conditions are collected on the AE page and will be included in the AE listing.

Adverse events will be classified into 3 periods: On therapy (AE starts after the first dose), Follow-up (AE starts after the last dose) and more than 30 days (AE starts after 30 days of the last dose). The incidence of AEs will be summarized by cohort and period, taking into account CTCAE grade, relationship, seriousness, and cycle. Events will be summarized by CTCAE code (category and term) and, when necessary, MedDRA terms.

If the CTCAE category is not in the database, it will have to be programmed by assigning the category to the range of Lilly determined codes associated with the terms in each category.

MedDRA versions may be upgraded as frequently as twice in a year. Therefore, different MedDRA versions will be used in the database of this trial, based on when the AE information is received. However, the data will be summarized and listed in preferred terms (PTs) of the most current version of MedDRA at the time of reporting. Safety information collected with previous versions of MedDRA will be updated at the PT and system organ class (SOC) level to the most current version in the locked database. The version used in any report will be documented.

Appendix 2 lists outputs to be generated. Adverse events, treatment-emergent adverse events (TEAEs), deaths and serious adverse events (SAEs) will be listed and summarised. Summaries for patients on therapy by cohort will include:

- Listing of Patients who Discontinued due to Adverse Events or Death
- Listing of Deaths Reported
- Listing of Serious Adverse Events
- Listing of Pre-existing Conditions and Adverse Events
- Summary of Pre-existing Conditions – Preferred Term by Decreasing Frequency within System Organ Class
- Summary of Adverse Events – Preferred Term by Decreasing Frequency within System Organ Class (regardless of relatedness to study drug)
- Summary of Study Drug Related Adverse Events – Preferred Term by Decreasing Frequency within System Organ Class
- Summary of Maximum Laboratory Investigator Determined CTC Adverse Events Grade Post-baseline – Regardless of Study Drug Relatness
- Summary of Maximum Laboratory Investigator Determined CTC Adverse Events Grade Post-baseline – Possibly Drug Related
- Summary of Treatment Emergent Adverse Events by MedDRA System Organ Class and Preferred Term
- Summary of Treatment Emergent Adverse Events by Relation to Study Drug

6.3.5.3. Laboratory Parameters

Relevant hematology and chemistry laboratory values will be graded according to CTCAE CCI The grades will be included on the listing and summarized by the maximum grade at each cycle within each cohort (and over the entire study) for all patients on therapy.

Abnormal laboratory results will be listed for all patients on therapy by cohort and cycle. International System of Units will be presented in all outputs.

6.3.5.4. Deaths

All deaths recorded in this study will be included as part of the complete AE listing and listed separately. A summary of deaths for all patients on therapy by cohort will be provided if there are a sufficient number of death events and it deems useful.

6.3.5.5. Vital Signs

Vital sign data including blood pressure (BP), pulse rate, temperature (T), respiratory rate, height and weight will be listed and summarized for all patients on therapy by cohort.

6.3.5.6. Electrocardiograms

An ECG will be recorded once pre-study as the baseline ECG. On Day -3, an ECG will be recorded once at pre-dose and once between 2 hours and 4 hours post-dose. On both Day -2 and Day -1, an ECG will be recorded once pre-dose. On Day 15, an ECG will be recorded at the same time points as Day -3.

All ECG data will be listed and summarized in absolute and change from baseline values for all patients on therapy by cohort. QTc will be calculated by Bazett's and Fridericia's QT correction formulas.

6.3.5.7. Transfusion Data

Transfusion data will be listed for all patients on therapy by cohort.

6.3.5.8. X-Ray Data

Chest x-ray data will be listed for all patients on therapy by cohort.

6.3.5.9. Patient Summaries

One-page patient summaries will be created by Lilly.

6.3.6. Pharmacokinetic Analyses

Pharmacokinetic (PK) parameter estimates for LY2835219 will be computed by standard noncompartmental methods of analysis using CCI Professional Edition on a computer that meets or exceeds the minimum requirements for this program. The version of any software used for the analysis will be documented and the program will meet Lilly requirements of software validation. It is possible that other validated equivalent PK software programs may be utilized if appropriate, warranted, and approved by Lilly Global PK management.

The maximum concentration (C_{max}), area under the concentration-time curve (AUC(0-72), AUC(0-24), AUC(0-12) and AUC(0-inf), half-life ($T_{1/2}$), volume of distribution (V_d), clearance (CL), and other relevant parameters that can be calculated from the data will be reported from the non-compartmental analyses (NCA), in which details are described in a PK NCA plan, for the following time periods in both phases where appropriate (Table JPBA.6.3):

Table JPBA.6.3. Time Periods Included in Non-Compartmental Analysis Plan

Cycle	Day	Profile
1	-3 to 1	72 hour profile of LY2835219 following a single dose.
1	27	24 hour profile of LY2835219 following a multiple doses.
2 and beyond		No Pharmacokinetic sampling.

6.3.6.1. Pharmacokinetic Parameters

Pharmacokinetic parameters will be listed and summarized using descriptive statistics. The patients and data-points to be included in the PK population will be defined and documented by the Pharmacokineticist in a separate report.

Least square estimates of geometric means and their corresponding 90% confidence intervals (CI) will be provided by dose, together with the dose-normalized ratio of geometric means and CI.

6.3.6.2. Plasma Concentration Data

The plasma concentration data and it metabolites (if determined) will be listed.

In addition, PK concentration data will be analyzed using nonlinear mixed effect modeling (as implemented in nonlinear mixed effects model [CCI]) to define the PK parameters by the Pharmacokineticist.

CCI


CCI

6.3.8. Pharmacokinetic/Pharmacodynamic Analyses

For exploratory purpose, all patients' plasma concentration of LY2835219 data will be pooled together and analyses by means of a compartmental approach using CCI to determine the compartmental PK parameters and between- and within-patient variability. Covariates analysis will be performed. The effect of patient factors and covariate data distribution will be assessed once a structural and statistical model has been established. This population PK model will be used to develop a PK/PD model where the levels of p-Rb and topoIIa in hair follicles are the primary PD measure. Additional PK/PD models may be developed using other PD measures. This analysis is described more in detail in a separate population PK analysis plan.

The results from these analyses may be used to support dose selection for Phase 2 studies. Based on the nonclinical PK/PD model, the BED range is predicted to be between 150 mg and 300 mg, so the PK and PD data will be used for estimating the BED.

6.3.9. Efficacy

Efficacy assessments will be derived for patients during Dose Confirmation Phase (Parts B, C, D, E, F, and G).

Eastern Cooperative Oncology Group performance status (PS) will be listed and summarized for patients on therapy by cohort and cycle.

Reported lesion data (target or non-target) and investigator evaluation will be listed for patients on therapy.

Tumor markers will be listed for patients on therapy.

The best overall response, duration of overall response, duration of overall CR and duration of SD will be listed for patients on therapy. If appropriate, the efficacy endpoints, including Overall Response Rate, Disease Control Rate, Duration of Overall Response, Duration of

Overall CR, Duration of Stable Disease, PFS, and OS, will be summarized for Parts B, C, D, E F, and G.

The Overall Response Rate is defined as the proportion of patients who exhibits a confirmed CR or PR relative to baseline as defined by RECIST Version 1.1 (Eisenhauer et al. 2009). A responder is defined as any patient who exhibits a confirmed CR or PR relative to baseline assessment.

Disease Control Rate is defined as the proportion of patients in the analysis population who exhibit a SD or confirmed CR or PR relative to baseline during the study. Response is defined by RECIST Version 1.1 (Eisenhauer et al. 2009).

Overall Response Rate and Disease Control Rate with their respective 95% CI will be estimated using the Clopper-Pearson method. For time to event endpoints, including Duration of Overall Response, Duration of Overall CR, Duration of Stable Disease, PFS, and OS, the survival curve will be estimated by the Kaplan-Meier method (Kaplan and Meier 1958). Quartiles and rates at time points of every 3 months, together with the 95% CIs, will be provided.

6.3.10. Additional Reports to Support Annual Reporting

The following reports are needed as requested for annual reporting purposes.

Investigator Brochure (IB):

- Listing of Serious Adverse Events
- List of Deaths Reported
- Summary of Patient Disposition
- List of Primary Reason for Treatment Discontinuation
- Summary of Adverse Events – Preferred Term by Decreasing Frequency (regardless of relatedness to study drug)
- Summary of Study Drug Related Adverse Events Preferred Term by Decreasing Frequency within System Organ Class
- Summary of Maximum Laboratory Investigator Determined CTC Adverse Events Grade Post Baseline - Regardless of Study Drug Relatedness
- Summary of Maximum Laboratory Investigator Determined CTC Adverse Events Grade Post Baseline - Possibly Drug Related
- Summary of Dose Limiting Toxicities
- Summary of Treatment Emergent Adverse Events by MedDRA System Organ Class and Preferred Term
- Summary of Treatment Emergent Adverse Events by Relation to Study Drug
- List of Dose Limiting Toxicities
- List of Abnormal Laboratory Results and Calculated CTCAE Grade - Hematology
- List of Abnormal Laboratory Results and Calculated CTCAE Grade – Chemistry
- List of Laboratory Hematology
- List of Laboratory Chemistry
- Summary of Concomitant Therapy
- Summary of ECG Data
- List of ECG Data
- List of Systemic Therapies

- List of Tumor Markers
- List of Dose Level Assignment
- Summary of Reported Prior Therapies
- Summary of Pre-existing Conditions - Preferred Term by Decreasing Frequency within System Organ Class

Annual Report:

- Summary of Patient Demographic
- Summary of Baseline Disease Characteristics
- Listing of Patients who Discontinued due to Adverse Events or Death

6.3.11. Additional Reports to Support the Clinical Trial Registry

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

Summary of adverse events (AEs), provided as a dataset which will be converted to an XML file. Adverse events, serious adverse events (SAEs) and 'Other' AEs will be summarized by treatment arm and by MedDRA PT.

- An AE is considered 'Serious' whether or not it is a TEAE.
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each SAE and 'Other' AE, for each PT and treatment arm, the following will be provided:
  - the number of patients at risk of an event
  - the number of patients who experienced each event
  - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients in every treatment arm may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- Adverse event reporting will be consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

A participant flow will also be produced. This participant flow will describe how many patients in each study part completed the study, and for those who did not, the frequency of each reason for not completing.

- At the time of database lock, the following patients will be considered to have completed the study:
  - any patient enrolled in Part A who completed one cycle of treatment or discontinued due to an adverse event and completed the required safety assessments during follow up
  - any patient enrolled in Parts B, C, D, E, F, or G who was treated until disease progression (objective or symptomatic) or death, or discontinued due to an adverse event and completed the required safety assessments during follow up.

6.3.12. Interim Analyses

The safety data for all patients will be reviewed throughout the study by the study investigators, the Lilly CRP, and Lilly Global Patient Safety (GPS).

6.3.12.1. Analysis by Cohort during Dose Escalation (Part A)

In this dose-finding study, safety data will be analyzed on a cohort by cohort basis throughout the study until the MTD is determined in the dose escalation phase (Part A).

Safety and PK data will be transferred into Lilly at the end of each completed cohort. A set of safety and PK data outputs will be provided to assist the dose escalation decisions, such as listings of study drug administration data, ECG data, concomitant medications, PK data, laboratory data (local and central), adverse events, DLT data, demography and vital signs.

6.3.12.2. Interim Analyses

At the end of the dose escalation phase (Part A), the safety, PK and PD data will be transferred into Lilly for a comprehensive analysis. Data will be reviewed to confirm the MTD prior to initiating the tumor-specific cohort expansions (Parts B, C, D, E F, and G).

Interim analyses will be conducted after approximately 15 to 30 patients have completed 2 cycles in a given tumor-specific expansion. Safety, PK, and PD data will be transferred to Lilly at the completion of dose escalation (Part A). Safety, efficacy, PK, and PD data will be transferred to Lilly at the completion of each tumor specific expansion (Parts B, C, D, E F, and G).

6.4. Individual Table, Figure, and Listing Requirements

The list of tables, listings and figures that will be reported in the study and their shells are detailed in a companion Excel workbook document.

7. References

Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 4.0., NCI, NIH, DHHS. 2009. Publish date: 29 May 2009.

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Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2) 228-247.

Kaplan EL, Meier P. Nonparametric estimation of incomplete observations. *JASA*. 1958;53:457-481.

Smith BP, Vandenhende FR, DeSante KA, Farid NA, Welch PA, Callaghan JT, Forgue ST. Confidence interval criteria for assessment of dose proportionality. *Pharm Res.* 2000;17(10):1278-1283.

Appendix 1. Data Set Requirements

Data set specifications will be detailed in a separate document.

Appendix 2. List of Tables, Listings and Figures

Note: some of these outputs may be combined into single tables/listings (for example, all PK parameters) or expanded to several outputs.

14.1	**Demographic Data**	
14.1-1.1	Summary of Patient Disposition	(all patients)
14.1-2.1	Summary of Patient Demographics	(patients on therapy)
14.1-2.2	Summary of Baseline Disease Characteristics	(patients on therapy)
14.1-2.3	Summary of Historical Illnesses	(patients on therapy)
14.1-2.4	Summary of Reported Prior Therapies	(patients on therapy)
	Study Drug/Compliance	
14.1-3.1	Summary of Study Drug Exposure	(patients on therapy)
14.1-3.2	Summary of Drug Administration	(patients on therapy)
14.1-3.3	Summary Study Drug Intensity – by patient	(patients on therapy)
14.2	**PK/PD/Efficacy Data**	
14.2-1.1	Summary of Maximum Tolerated Dose Estimation	(patients on therapy)
14.2-1.2	Analysis of Maximum Tolerated Dose Estimation	(patients on therapy)
14.2-2.1	Summary of LY2835219 PK parameters	(PK population)
14.2-2.2	Analysis of LY2835219 PK parameters	(PK population)
14.2-2.3	Analysis of Dose Proportionality	(PK population)
14.2-3.x	Summary of [PD endpoint] Data *(Titles to be updated accordingly by endpoint)*	(PD population)
14.2-4.1	Summary of Best Overall Response	(efficacy population)
14.2-4.2	Summary of Time to Events	(efficacy population)
14.3.1	**Adverse Events**	
14.3.1-1.1	Summary of Pre-existing Conditions – Preferred Term by Decreasing Frequency within System Organ Class	(patients on therapy)
14.3.1-1.2	Summary of Adverse Events Preferred Term by Decreasing Frequency within System Organ Class	(patients on therapy)
14.3.1-1.3	Summary of Study Drug Related Adverse Events Preferred Term by Decreasing Frequency within System Organ Class	(patients on therapy)
14.3.1-1.4	Summary of Maximum Laboratory Investigator Determined CTC Adverse Events Grade Post Baseline - Regardless of Study Drug Relatedness	(patients on therapy)
14.3.1-1.5	Summary of Maximum Laboratory Investigator Determined CTC Adverse Events Grade Post Baseline - Possibly Drug Related	(patients on therapy)
14.3.1-1.6	Summary of Dose Limiting Toxicities	(patients on therapy)
14.3.1-1.7	Summary of Maximum Laboratory Investigator Determined CTC Adverse Events Grade Post Baseline - Possibly Drug Related	(patients on therapy)
14.3.1-1.8	Summary of Dose Limiting Toxicities	(patients on therapy)
14.3.1-1.9	Summary of Treatment Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	(patients on therapy)
14.3.1-1.10	Summary of Treatment Emergent Adverse Events by Relation to Study Drug	(patients on therapy)

14.3.2	**Deaths & SAE**	
14.3.2-1.1	List of Serious Adverse Events	(patients on therapy)
14.3.2-1.2	List of Deaths Reported	(all patients)
14.3.4	**Abnormal Lab**	
14.3.4-1.1	List of Abnormal Laboratory Results and Calculated CTCAE Grade - Hematology	(patients on therapy)
14.3.4-1.2	List of Abnormal Laboratory Results and Calculated CTCAE Grade - Chemistry	(patients on therapy)
14.3.4-1.3	List of Abnormal Laboratory Results – Urinalysis	(patients on therapy)
14.3.4-1.3	List of Abnormal Laboratory Results – Additional Safety Parameter	(patients on therapy)
14.3.4-2.x	Summary of [Analyte Name] Data	(patients on therapy)
14.4	**Other Safety**	
14.4-1.1	Summary of Concomitant Therapy	(patients on therapy)
14.4-2.1	Summary of Blood Pressure Data	(patients on therapy)
14.4-2.2	Summary of Other Vital Signs and ECOG Performance Status	(patients on therapy)
14.4-3.1	Summary of ECG Data *(will include QT, QTcB, QTcF as minimum)*	(patients on therapy)
14.4-3.2 (Figure)	Mean ECG Data	(patients on therapy)
16.1.6	**Receiving Test Drugs/Investigational Products From Specific Batches**	
16.1.6-1.1	List of CT Lot Numbers	(patients on therapy)
16.1.7	**Randomization/Dose Assignment**	
16.1.7-1.1	List of Dose Level Assignment	(patients on therapy)
16.2.1	**Discontinued Patients**	
16.2.1-1.1	List of Primary Reason for Treatment Discontinuation	(patients on therapy)
16.2.1-1.2	List of Post Study Follow-up	(patients on therapy)
16.2.2	**Protocol Deviations**	
16.2.2-1.1	List of Major Protocol Deviations	(patients on therapy)
16.2.3	**Patients Excluded from PK/PD/Efficacy Analyses**	
16.2.3-1.1	List of Patients Excluded from PK/PD/Efficacy Analyses	(patients on therapy)
16.2.4	**Demographic Data**	
16.2.4-1.1	List of Patient Demographics and Disease Characteristics at Baseline *(including Pathological Diagnosis)*	(patients on therapy)
16.2.4-1.2	List of Historical Illnesses	(patients on therapy)
16.2.4-1.3	List of Alcohol and Tobacco Consumption	(patients on therapy)
16.2.4-2.1	List of Radiotherapies	(patients on therapy)
16.2.4-2.2	List of Surgeries	(patients on therapy)
16.2.4-2.3	List of Systematic Therapies	(patients on therapy)
16.2.4-2.4	List of Topical Therapies	(patients on therapy)
16.2.5	**Compliance/Drug Concentration Data**	

16.2.5-1.1	List of Study Drug Administration	(patients on therapy)
16.2.5-2.1	List of LY2835219 PK Parameters	(patients on therapy)
16.2.5-3.1	List of LY2835219 PK Concentration	(patients on therapy)
16.2.5-4.1	List of LY2835219 & Metabolite Urine Concentration	(patients on therapy)
16.2.6	**Individual Efficacy/PD Data**	
16.2.6-1.x	List of [PD endpoint] Data *(Titles to be updated accordingly by endpoint)*	(patients on therapy)
16.2.6-2.1	List of Reported Lesions with Measurements and Responses	(patients on therapy)
16.2.6-2.2	List of Tumor Markers	(patients on therapy)
16.2.6-2.3	List of Treatment Cycles	(patients on therapy)
16.2.7	**Adverse Event Data**	
16.2.7-1.1	List of Pre-existing Conditions and Adverse Events	(patients on therapy)
16.2.7-1.2	List of Dose Limiting Toxicities	(patients on therapy)
16.2.8	**Individual Laboratory Data**	
16.2.8-1.1	List of Laboratory Hematology	(patients on therapy)
16.2.8-1.2	List of Laboratory Chemistry	(patients on therapy)
16.2.8-1.3	List of Laboratory Urinalysis	(patients on therapy)
16.2.8-1.4	List of Other Laboratory Data	(patients on therapy)
16.4	**Individual Patient Data Listings**	
16.4-1.1	List of Concomitant Therapy	(patients on therapy)
16.4-2.1	List of Blood Pressure Data	(patients on therapy)
16.4-2.2	List of Other Vital Signs and ECOG Performance Status	(patients on therapy)
16.4-3.1	List of ECG Data	(patients on therapy)
16.4-4.1	List of Transfusions	(patients on therapy)
16.4-5.1	List of X-ray Data	(patients on therapy)

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