I6F-MC-JJCD Statistical Analysis Plan Version 1

# A Phase 1b Study of LY3039478 in Combination with Other Anticancer Agents in Patients with Advanced or Metastatic Solid Tumors

NCT02784795

Approval Date: 1-Aug-2016

# 1. Statistical Analysis Plan: I6F-MC-JJCD A Phase 1b Study of LY3039478 in Combination with Other Anticancer Agents in Patients with Advanced or Metastatic Solid Tumors



LY3039478

Study I6F-MC-JJCD (JJCD) is a multicenter, nonrandomized, open-label Phase 1b study consisting of 5 separate, parallel dose escalations in patients with advanced/metastatic cancer from a variety of tumors followed by a dose-confirmation phase in specified tumor types.


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Protocol I6F-MC-JJCD
Phase 1b

Statistical Analysis Plan electronically signed and approved by Lilly on date provided below.

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# 3. Revision History

SAP Version 1 was approved prior to the first visit when a patient receives study drug or any other protocol intervention.

# 4. Study Objectives

## 4.1. Primary Objective

The primary objective of this study is to determine the recommended Phase 2 dose of LY3039478 in individual combinations with other anticancer agents.

## 4.2. Secondary Objectives

The secondary objectives of this study are:

- to characterize the safety and toxicity profile of LY3039478 in combination with other anticancer agents as assessed by National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.0
- to estimate the pharmacokinetic (PK) parameters of LY3039478 in combination with other anticancer agents
- to estimate the PK parameters of taladegib and its active metabolite LSN3185556, and in combination with LY3039478
- to estimate the PK parameters of LY3023414, and in combination with LY3039478
- to estimate the PK parameters of abemaciclib and its metabolites LSN2839567 and LSN3106726, and in combination with LY3039478
- to document any antitumor activity observed with LY3039478 in combination with other anticancer agents
- to assess duration of response and progression-free survival (PFS)

## 4.3. Exploratory Objectives

The exploratory objectives of this study are:

- to explore pharmacodynamic (PD) effects of LY3039478 on biomarkers indicative of Notch activity or other study drugs.
- to explore the utility of positron emission tomography (PET) scan to assess treatment effect with LY3039478 in combination with other anticancer agents
- to explore predictive biomarkers related to induction of cytochrome P450 enzymes, such as cortisol and 6β-hydroxycortisol.
- to evaluate tumor tissue and blood for biomarkers related to the Notch signaling pathway and drug target pathways, mechanism of action of study drug(s) or disease state and their potential association with the objectives of the study.

# 5. Study Design

## 5.1. Summary of Study Design

Study I6F-MC-JJCD (JJCD) is a multicenter, nonrandomized, open-label Phase 1b study consisting of 5 separate, parallel dose escalations in patients with advanced/metastatic cancer from a variety of solid tumors followed by a dose-confirmation phase in specified tumor types (Figure JJCD.5.1).

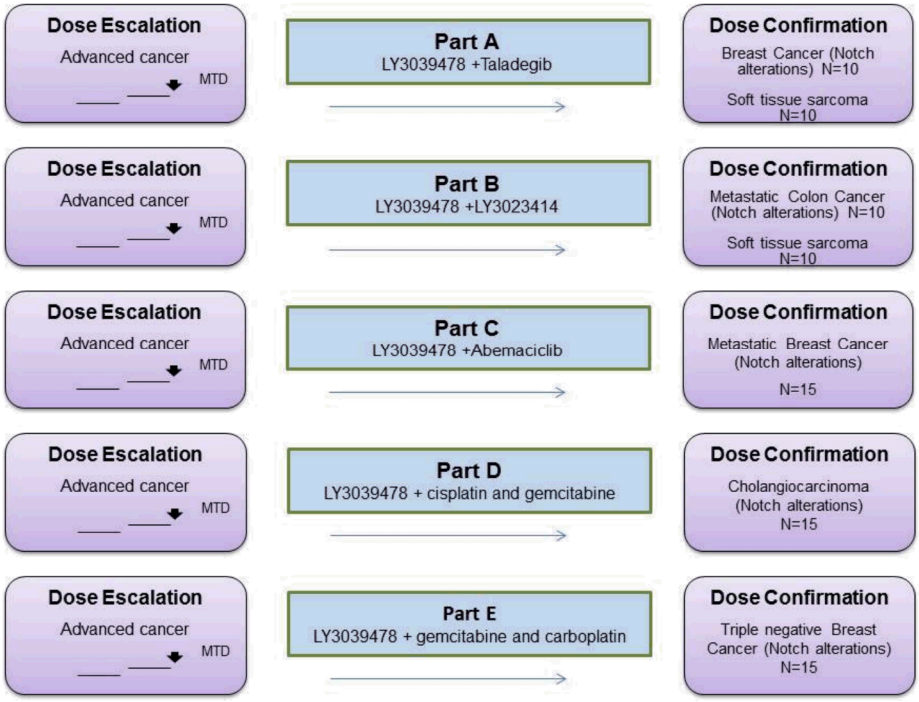


**Figure JJCD.5.1. Illustration of study design for Protocol I6F-MC-JJCD.**

# 6. A Priori Statistical Methods

## 6.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company.

The interpretation of the study results will be the responsibility of the investigator with the Lilly CRP or CRS, pharmacokineticist, and statistician. The CRP or CRS and statistician will also be responsible for the appropriate conduct of an internal review for both the final study report and any study-related material to be authorized by Lilly for publication.

Unless otherwise stated, all data summaries and figures will be split by assigned treatment arm and part (escalation/confirmation). Treatment arm will specify the 2 combination treatments and corresponding dose levels of each. Listings will include the full database of data in 1 output file. Summaries and figures will be presented as separate output files for each study part A-E.

All data will be listed for all enrolled patients, including derived data, by study part, treatment arm, cycle and time point where appropriate, unless stated otherwise in the following text or in the table shells.

Sponsor standard TFLs and supporting programs and software (e.g. TAFFY) will be utilized for all analyses where a suitable standard exists. Data derivations in this SAP are defined based upon current sponsor reporting standards at the time of writing, and may be updated at the time of analysis in order to maintain accordance with the most current sponsor standards at that time.

In general, continuous variables will be presented using the mean, standard deviation (SD), coefficient of variation, median, minimum, maximum and number of patients with an observation (n). For categorical variables, the population size (N), the number of patients with events (n) and the percentage of patients with events are usually reported.

The following data handling conventions will be used in the analysis.

| Term | Definition or Rule |
|---|---|
| Relative Study Day | If assessment is on or after date of first dose then<br>(date of assessment) – (date of first study drug dose) +1 |
| | If assessment precedes first dose of drug then<br>(date of assessment) – (date of first study drug dose) |
| | There is no study day 0. Study day 1 is the date of first dose and study day -1 is the day before the first dose. |
| Cycle Day | If assessment is on or after date of first dose in cycle then<br>(date of assessment) – (date of first study drug dose in cycle) +1 |
| | There is no cycle day 0. Cycle day 1 is the date of first dose in that cycle. |
| 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. |
| Entered | Patients who have signed the informed consent document directly. |
| Enrolled | Patients who have been assigned to study treatment |
| Safety analysis set | Patients who have been enrolled and received at least one dose of any study drug. |
| Screen Failures | Patients who have signed informed consent, do not meet eligibility criteria and are not enrolled. |

## 6.2. Adjustments for Covariates

Given the small sample size for each tumor type and treatment, no formal analysis investigating the impact of covariates is planned. If data warrant, exploratory analyses may incorporate patient disease characteristics in evaluation of time to disease progression.

## 6.3. Handling of Dropouts or Missing Data

Missing data, except for dates, will not be imputed. They will be kept as missing in the data analyses, except for dates when used in calculations of relative study day, for which sponsor reporting standards will be utilized for imputation rules, defined as: Missing start days will be replaced with 1 and missing day/month with 01 JAN. Missing end days will be replaced with the last day of the month, and missing day/month with 31 DEC. The imputation rule may be updated at the time of study reporting if necessary to maintain accordance with most recent sponsor standards. Partial dates should be reported in all listings and not the imputed date.

Analyses of response will include all patients with measureable disease. Analyses of change in tumor size will include only patients with measureable disease and evaluable target lesion measures at baseline and at least one post-treatment visit.

For time-to-event endpoints, the method for handling missing data will be censoring. Patients that withdrew from the study without progression will be censored at the date of the last tumor assessment. Additional sensitivity analyses may be conducted applying different censoring rules if data warrant and will follow sponsor defined standards.

## 6.4. Multicenter Studies

Given the small number of patients for each tumor type and treatment, patients across all sites will be grouped together for analysis purposes.

## 6.5. Multiple Comparisons/Multiplicity

No formal hypothesis testing is planned for this study; thus, there will be no adjustments for multiplicity.

## 6.6. Use of an “Efficacy Subset” of Patients

Analyses of disposition will use all patients entered in to the study. All other analyses for this study, including efficacy analyses, will utilize the safety analysis set, defined as all enrolled patients who have received at least one dose of any study drug. Analyses will be reported according to patients assigned treatment.

## 6.7. Patient Disposition

A detailed description of patient disposition will be provided. It will include a summary of the number and percentage of patients entered into the study, and treated as well as number and percentage of patients completing the study, or discontinuing (overall and by reason for discontinuation of LY3039478). Patients are permitted per protocol to discontinue one of their assigned study drugs and remain in the study receiving LY3039478 alone, or one ore more of

their assigned combination therapies without LY3039478. Treatment discontinuation information for each unique study drug will be reported in listings.

A list of deaths and reasons for death will be provided. Reasons for death will also be summarized by treatment arm, including the specific AE preferred term if reason for death is AE.

A listing of primary reasons for study treatment and study discontinuation will also be provided according to each treatment.

## 6.8. Patient Characteristics

Patient demographics including age, sex, screening height, weight and body mass index, race, ethnicity, and country will be reported using descriptive statistics. The summary will include the number of patients for each treatment group and the total across treatment groups.

The following baseline disease characteristics will be summarized by treatment arm: ECOG performance status, disease stage, histopathological diagnosis grade, initial pathological diagnosis and basis of initial pathological diagnosis.

For sarcomas, the French or FNCLCC (French Federation Nationale des Centres de Lutte Contre le Cancer) grading system will be used for this study, and consists of the following parameters:

- Tumor differentiation, score =1, 2 or 3
- Mitotic count, score = 1, 2 or 3
- Tumor necrosis, score = 0, 1 or 2

Histological grade is then derived as grade 1 (total score 2-3), grade 2 (total score 4-5), grade 3 (total score 6-8). Further information is available at: https://www.iarc.fr/en/publications/pdfs-online/pat-gen/bb5/bb5-classifsofttissue.pdf

The Nottingham combined histologic grade is the preferred system for the NCCN Guidelines for treating breast cancer, and consists of the following parameters:

- Glandular (Acinar)/Tubular differentiation, score =1, 2 or 3
- Nuclear pleomorphism, score =1, 2 or 3
- Mitotic count, score =1, 2 or 3

Grade is then derived as grade 1 (total score 3-5), grade 2 (total score 6-7), grade 3 (total score 8-9). Further information is available at: http://pathology.jhu.edu/breast/grade.php

For dose confirmation cohorts in sarcoma and breast cancer, the scoring information for the FNCLCC and Nottingham tumor grading systems will be listed. Any post-treatment tumor biopsies obtained will also have the scoring system information listed. Further exploratory analyses will be conducted where data warrant, for example, correlation of tumor response to tumor differentiation, mitotic count and tumor necrosis scores. The intent of such exploratory analyses is to generate hypotheses relating to the potential activity of LY3039478 and identification of patients most likely to respond to LY3039478.

Other patient characteristics will be summarized as deemed appropriate.

## 6.9. Treatment Compliance

Treatment compliance will be summarized for each oral treatment separately (LY3039478, Taladegib, LY3023414, Abemaciclib). Treatment compliance will not be calculated for anticancer treatments administered intravenously (Gemcitabine, Cisplatin and Carboplatin). Treatment compliance information for oral study drug will be collected through pill counts at each visit, and the number of tablets taken relative to the number expected to be taken will be summarized.

The patient must take ≥75% of the intended doses to be deemed compliant with study drug administration. Similarly, a patient will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication.

Percent compliance is calculated from dispensed and returned capsules as:

100 x (actual drug taken (mg) / total drug (mg) prescribed)

where total drug prescribed is the drug assigned excluding dose omissions and accounting for dose adjustments.

## 6.10. Concomitant Therapy

All medications will be coded to the generic preferred name according to the current World Health Organization (WHO) drug dictionary. All concomitant medications listings will include both the term reported in CRF and the WHO dictionary term and if concomitant medication use is due to an adverse event (AE), the associated AE will also be listed.

Prior anti-cancer systemic therapy, radiotherapy and surgery will be summarized by treatment arm and indication, as described in Section 6.11.2. Summaries will include the reason, type of therapy, number of prior regimens and drug name. Prior therapies will also be listed, including the patients response to prior therapy.

Anti-cancer systemic therapy, radiotherapy or surgery that occurs post discontinuation of study treatment is captured separately from concomitant medication as the existence of such therapies can lead to censoring of time to event endpoints. Patients that received post discontinuation therapies will be listed and summarized by treatment arm and indication , as described in Section 6.11.2.

## 6.11. Efficacy Analyses

This phase 1 trial has not been designed to formally assess efficacy. However, antitumor activity and PFS are secondary objectives and will be summarized and listed. Further exploratory analyses may be performed.

### *6.11.1. Efficacy Definitions*

The following definitions for efficacy endpoints will be used:

**Overall response rate (ORR)** is the proportion of patients who achieved a complete response (CR) or partial response (PR) out of all patients. Depending on the histology, tumor responses

will be measured and recorded using the appropriate guidelines [RECIST 1.1 (Eisenhauer et al. 2009), RANO criteria for glioblastoma (Wen et al. 2010)]. To confirm objective responses, all lesions should be radiologically assessed, and the same radiologic method used for the initial response determination should be repeated at least 4 weeks following the initial observation of an objective response, using the sample method that was used at baseline. If a patient is discontinued from the study, repeat radiology assessments may be omitted if clear clinical signs of progressive disease are present.

**Best response** is determined from a sequence of responses assessed. Two objective status determinations of CR before progression are required for a best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR.

**Choi Response:** For patients with soft tissue sarcoma, ORR defined using the Choi criteria (Choi et al. 2007) will be considered for response evaluation in addition to RECIST criteria. Modified response criteria incorporating changes in tumor density in addition to tumor size has been demonstrated to be a more sensitive prognostic marker for time to progression and disease specific survival in GIST sarcomas (Benjamin et al. 2007; Choi et al. 2007). Best Choi ORR will be determined in a similar method to the RECIST best response.

**PET Metabolic Response:** PET imaging is optional in this study. For patients undergoing PET imaging, PET maximum standardized uptake values (SUVmax) will be analyzed, and metabolic responses defined using PET response criteria of the European Organisation for Research and Treatment of Cancer (Young et al. 1999).

**Duration of Response** will be calculated for patients with CR or PR. It is measured from the date of first evidence of a confirmed response to the date of first progression of disease or the date of death due to any cause, whichever is earlier. For each patient who is not known to have died or to have had a progression of disease as of the data-inclusion cut-off date, duration of response will be censored at the date of last objective response assessment prior to the date of any subsequent systemic anticancer therapy (if applicable).

**Duration of Stable Disease** will be calculated only for patients with best response of stable disease. It is measured from the date of start of treatment to the date of first progression of disease or the date of death due to any cause, whichever is earlier. For each patient who is not known to have died or to have had a progression of disease as of the data-inclusion cut-off date, duration of stable disease will be censored at the date of last objective response assessment prior to the date of any subsequent systemic anticancer therapy.

**Change in tumor size** will be assessed in each patient with measurable disease using radiographic imaging. Tumor size is the sum of the tumor measurements for target lesions at each tumor evaluation. Change in tumor size is defined as the percent change in tumor size from the baseline evaluation to the minimum post-dose evaluation. Other definitions of CTS may be explored (including specific time points, and AUC formulations).

**Change in tumor density** will be assessed in each patient assessed using Choi response criteria. Tumor density is the mean of the tumor density measurements (HU) for target lesions at each tumor evaluation. Change in tumor density is defined as the percent change in tumor density from the baseline evaluation to the minimum post-dose evaluation. Other definitions of CTS may be explored (including specific time points, and AUC formulations).

**Progression-free survival (PFS)** time is defined as the time from the date of study enrollment to the first date of PD (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 cut-off date, PFS time will be censored at the date of the last objective progression-free disease assessment prior to the date of any subsequent systematic anticancer therapy.

**Overall Survival (OS)** is defined as the time from the date of study enrollment 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.

### *6.11.2. Efficacy Analyses*

Reported lesion data (target/ non-target or measurable/ nonmeasurable), investigator assessment of response, duration of response/stable disease, PFS and OS will be listed for all patients. Tumor markers will also be listed.

Efficacy data will be summarized for patients in dose confirmation study parts according to tumor type and treatment. The following groupings will be included in summary tables:

- LY3039478Xmg+TaladegibXmg, breast cancer
- LY3039478Xmg +TaladegibXmg, soft tissue sarcoma
- LY3039478Xmg+LY3023414Xmg, colon cancer
- LY3039478Xmg + LY3023414Xmg, soft tissue sarcoma
- LY3039478Xmg+AbemaciclibXmg, breast cancer
- LY3039478Xmg +Gemcitabine+Cisplatin, cholangiocarinoma
- LY3039478Xmg + Gemcitabine+Carboplatin, triple negative breast cancer

The following efficacy summaries will be provided for the dose confirmation study parts:

- Overall response rate and Choi response rate (where applicable) will be presented with exact 95% CI.
- Time to event endpoints including PFS, OS, and duration of response will be summarized descriptively using the Kaplan-Meier method.
- Change in tumor size, and change in tumor density will be presented using a waterfall plot. All patients with at least one target lesion measurement will be represented in the plot. Statistical analyses, where data warrant, may be conducted for the dose confirmation

study parts utilizing analysis of covariance models with covariates including baseline measurements, combination treatment, tumor type, ECOG status and other covariates as deemed appropriate.

- PET parameters will be listed. Change in SUVmax will be presented using a waterfall plot for patients with evaluable baseline and post-treatment PET imaging data. PET metaolic response will be defined using Young criteria. Exploratory analyses evaluating the correlation of PET parameters to PFS may also be completed.

## 6.12. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

Unless stated otherwise, the Lilly pharmacokineticist will be responsible for the PK and PK/PD analyses.

PK analyses will be conducted on patients who receive at least 1 dose of the study drug and have samples collected. Pharmacokinetic parameter estimates for LY3039478, taladegib and its active metabolite (LSN3185556), LY3023414, abemaciclib and its active metabolites LSN3106726 and LSN2839567, gemcitabine, carboplatin and cisplatin will be calculated by standard noncompartmental methods of analyses where data allow.

The primary parameters for analysis will be maximum concentration ($C_{max}$) and area under the concentration-time curve ($AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$). Other noncompartmental parameters, such as time of half-life ($t_{1/2}$), apparent systemic clearance (CL/F), and apparent volume of distribution (V/F) may be reported. 6β-hydroxycortisol excreted in urine relative to the plasma AUC of cortisol may be analyzed and summarized where appropriate.
Additional exploratory analyses will be performed if warranted by data and other validated PK software programs (for example, NONMEM®) may be used if appropriate and approved by Global Pharmacokinetic management. The version of any software used for the analysis will be documented, and the program will meet the Lilly requirements of software validation.

Pharmacokinetic parameter estimates will be evaluated to delineate effects of the following drug interactions for patients in dose escalation phase only: LY3039478 with taladegib compared to taladegib alone, LY3039478 with LY3023414 compared to alone, and LY3039478 with abemaciclib compared to abemaciclib alone. A single dose of taladegib, LY3023414 or Abemaciclib (for study Part A, B or C respectively) will be given on Day 1 during a 3-day cycle 1 lead-in period and compared to Day 22 of cycle 1 following treatment in combination with LY3039478. Log-transformed $C_{max}$ and AUC estimates will be assessed using mixed effect models with random patient effect, to estimate ratios of geometric means and the corresponding 90% CIs. The Lilly statistician will be responsible for the mixed effect modelling.
Pharmacodynamic data, including plasma Aβ(1-x) from all patients undergoing PD assessments will be analyzed and summarized where appropriate.

## 6.13. Safety Analyses

All safety summaries and analyses will be based upon the safety analysis set. Safety data will be listed and summarized with patient counts and percentages in each treatment arm. Summaries will include actual treatment arm received (e.g. LY3039478Xmg+ TaladegibXmg), total across

different dose combinations for a treatment regimen (e.g Total LY3039478+Taladegib), and total across entire study.

Details of the analyses are described in the following sections.

### *6.13.1. Extent of Exposure*

A summary of exposure will be provided for each study drug, including cycle received, cumulative dose and duration of therapy, for all treatment patients per treatment arm and total.

A summary of dose intensity will be provided for each study drug, for all treatment patients per treatment arm and total. Percent dose intensity is calculated as:
100 x (actual cumulative dose taken (mg) / planned cumulative dose (mg))

Note that planned dose is the same as actual dose if there is no dose modification or cycle delays.

A summary of dose adjustments will be provided for each study drug, including dose omissions, dose reductions and cycle delays, and the corresponding reasons for dose adjustment, for all patients per treatment arm and total. If the reason for dose modification is due to an AE, the associated AE will be provided.

A Napoleon plot of treatment duration, treatment received and reason for discontinuation will be provided for each study part.

### *6.13.2. Adverse Events*

A listing of all AEs by patient will be presented. This listing will include patient number, AE (reported term and preferred term [PT]), event start and end dates, CTCAE grade, relationship to study drug/procedure, seriousness, and outcome. A listing of serious AEs (SAEs) will be produced using the similar format.

An overall summary will be provided for AEs. The number and percent of evaluable patients will be summarized by treatment for each category below. The summary will provide counts for all AEs, and AEs related to study treatment.

- Patients with at least one treatment-emergent AE (TEAE)
- Patients with at least one grade 3 or 4 TEAE
- Patients with at least one SAE
- Patients who discontinued due to AE
- Patients who discontinued due to SAE
- Patients who died due to AE on study treatment
- Patients who died due to AE within 30 days of discontinuation from study treatment

**Treatment-emergent adverse events (TEAE)** are defined as follows:

- Any event that first occurred or worsened in severity after baseline, based on the MedDRA LLT term and CTCAE severity grade. This means that any episode of the same

AE with the same grade as at baseline that starts after the first dose of study treatment will not be defined as treatment-emergent, even if now considered drug related.

- Or any pre-existing condition [PEC] (emerged prior to signing the informed consent) or any AE (emerged after signing the informed consent) that was still present prior to the first dose but has increased in severity (CTCAE grade) following the start of study treatment, regardless of causality.

As per Lilly's standard operating procedures, all "related", "probably related," "possibly related," or "does not know" AEs and SAEs will be defined as related to study drug.

MedDRA v16.1 (or higher) will be used when reporting AEs by MedDRA terms. TEAEs will be summarized by System Organ Class [SOC] and by decreasing frequency of PT within SOC.

TEAEs will be summarized by CTCAE grade, including the total for maximum Grade 3 and 4, and Grade 3, 4 and 5. These summaries will be provided for events regardless of study drug causality, and repeated for events deemed by the investigator to be related to study medication.

Medical history and PECs will be listed for each patient.

#### 6.13.2.1. Dose-Limiting Toxicity

Dose-limiting toxicities (DLTs) and DLT-equivalent toxicities will also be listed for all patients on therapy. Dose escalation will be driven for each treatment combination using the 3+3 method.

### *6.13.3. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events*

All deaths in this study, including the reasons for death, will be listed by treatment. The reasons for death will be also summarized separately for on-therapy, within 30 days of last dose of study drug and during the long term follow-up periods.

Serious AEs will be summarized for each treatment by decreasing frequency of PT within SOC. The summary will be provided for events regardless of study drug causality, and repeated for events deemed by the investigator to be related to study medication.

### *6.13.4. Clinical Laboratory Evaluation*

Listings of all laboratory results will be provided (using SI units [International System of Units], when available) by treatment, for hematology, chemistry, urinalysis, ECG chemistry, coagulation and hepatic monitoring. Normal reference ranges, percent of the result outside of range (result divided by lower limit if result is less than lower limit; result divided by higher limit if result is greater than higher limit) and percent change from baseline will also be included. Selected laboratory parameters may be plotted by time.

Laboratory analytes below/above quantifiable levels (data in the database recorded as "<x" and ">x) will be reported as such in listings, and imputed to the lower or upper limit of quantification in any summaries or analyses.

A calculated CTCAE grade using CTCAE v4.0 (or higher) will be provided for all laboratory results, which can be used independently of clinical judgment to determine a CTCAE severity grade. Calculated CTCAE grades will be summarized by treatment and visit.

### *6.13.5. Vital Signs and Other Physical Findings*

Vital signs measurements including height, weight, temperature, blood pressure, pulse, respiratory rate and post-baseline ECOG performance status will be listed and summarized by treatment arm.

### *6.13.6. Electrocardiograms*

Electrocardiogram (ECG) assessment of normality and clinical significance will be listed by treatment group. Quantitative ECG results including PR, QRS, QTcB (Bazett's correction), QTcF (Fridericia's correction) and RR intervals will be provided in patient listings for absolute and change from baseline. In addition, summaries of outlying corrected QT intervals (QTc, QTcB and QTcF) will be provided by treatment. Outlying intervals include absolute values > 450 for males, >470 for females >480 and >500 msec and change from baseline >30 and >60 msec.

Further exploratory analyses may be conducted as warranted.

## 6.14. Subgroup Analyses

Efficacy measures may be summarized descriptively within subgroups of patients. Those may be characterized by the types of Notch pathway alterations. Exploratory analyses may be applied to correlate Notch pathway biomarkers with clinical outcome. If applicable, a subset of potential predictive biomarkers associating with interpretable clinical benefit may be further examined with biological evidence.

## 6.15. Protocol Violations

All clinically relevant protocol deviations will be listed by pre-determined categories (e.g., 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).

## 6.16. Interim Analyses and Data Monitoring

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the sponsor will determine if it is necessary to amend the protocol.

Since this is a dose-finding study, data will be reviewed on a cohort-by-cohort basis during the study, until the MTDs are determined for each treatment arm. The purpose of these cohort-by-cohort reviews is to evaluate the safety data at each dose level and determine if a DLT has been observed that would suggest MTD has been met or exceeded. The investigators and the Lilly study team will make the determination regarding dose escalation based upon their review of the safety and tolerability data as described in this protocol.

Safety and/or PK data will be reviewed during the study if needed for dose escalation, modifications to the dose escalation strategy or other design elements.

After all patients who are deemed evaluable for the assessment of dose levels complete DLT evaluation period or MTD is determined, an interim safety and PK analysis may be conducted for planning next studies.

If it is deemed that enough data are obtained to assess the primary objective and the secondary objectives, a clinical study report might be created before the last patient visit. In this case, all data until the data-cutoff date will be used for the analysis of safety, efficacy, PK and PD biomarkers. All data defined in the protocol will continue to be collected from patients on treatment after the data cut-off date. These data may be reported separately and the analyses on all patients including these data may not be performed.

## 6.17. Annual Report Analyses

The following reports are needed for the Development Safety Update Report (DSUR) at the appropriate annual report timeline for each of the 3 investigational drugs: LY3039478, Taladegib and Abemaciclib :

1. Estimated cumulative patient exposure
2. Cumulative exposure to investigational drug, by demographic characteristics for ongoing unblinded clinical trials and completed clinical trials
3. Exposure information for ongoing clinical trials and clinical trials that completed during the reporting period
4. Listing of patients who died during the DSUR period
5. Discontinuations due to adverse event during the DSUR Period.

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## 6.18. Clinical Trial Registry Analyses

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

Analyses provided for the CTR requirements include the following:

Summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and 'Other' AEs are summarized: by treatment group, 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 term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term

  - the number of events experienced.

- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

Analyses provided for the EudraCT requirements include the following:

- Summary of AEs, provided as a dataset which will be converted to an XML file, in accordance with EudraCT requirements.
- Categorical breakdown of age across the entire study, represented planned and actual number of patients for the following age groups: infants and toddlers (28 days-23 months), children (2-11 years), adolescents (12-17 years), adults (18-64 years, 65-84 years and 85 years and over).

For the purpose of CTR/ EudraCT reporting, patients who have died, or are still in the study but off treatment, at primary DBL will be considered a completer. Those that withdrew consent for all procedures, including follow-up, or were lost to follow up, will be considered as early discontinuers. Patients who remain on treatment will be counted as continuing treatment.

# 7. References

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