JJCA Statistical Analysis Plan (2)

I6F-MC-JJCA: A Phase 1 Study of LY3039478 in Patients with Advanced or Metastatic Cancer

NCT01695005

Approval Date: 16-Feb-2017

1. Statistical Analysis Plan: I6F-MC-JJCA: A Phase 1 Study of LY3039478 in Patients with Advanced or Metastatic Cancer

LY3039478

This Phase 1 study is a multicenter, nonrandomized, open-label, dose-escalation/cohort-expansion study of oral LY3039478 in patients with advanced or metastatic cancer.

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Protocol I6F-MC-JJCA
Phase 1

Statistical Analysis Plan Version 2 electronically signed and approved by Lilly on date provided below.

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3. Revision History

This is version 2 of the Statistical Analysis Plan (SAP), which was approved prior to database lock.

This SAP includes the definitions of the analysis populations, the pharmacokinetic (PK), the pharmacodynamic (PD), efficacy and safety endpoints, the tables, figures and listings (TFLs) for the analysis. It is based on the Protocol Amendment (e) approved by Lilly on 8 July 2016

Version 1 of the SAP was approved based on the Study Protocol approved by Lilly on 15th May 2012. Updates to the SAP are necessary given the additional study parts and study objectives added to the study during protocol amendments (a), (b), (c), (d) and (e).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 Clinical Research Physician (CRP), PK/PD Scientist and Statistician. 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.

4. Study Objectives

4.1. Primary Objective

Part A: The primary objective of this study is to determine a recommended Phase 2 dose of LY3039478 that may be safely administered to patients with advanced or metastatic cancer.

Parts B, C, D, and E: The primary objectives are to confirm the recommended Phase 2 dose of LY3039478 that may be safely administered to patients with specific tumor types and to document antitumor activity.

Part F: The primary objective is to determine a recommended Phase 2 dose of LY3039478 thatmay be safely administered to patients according to 2 alternative dosing schedules withco-administration of prednisone and to document antitumor activity.

4.2. Secondary Objectives

The secondary objectives of this study are:

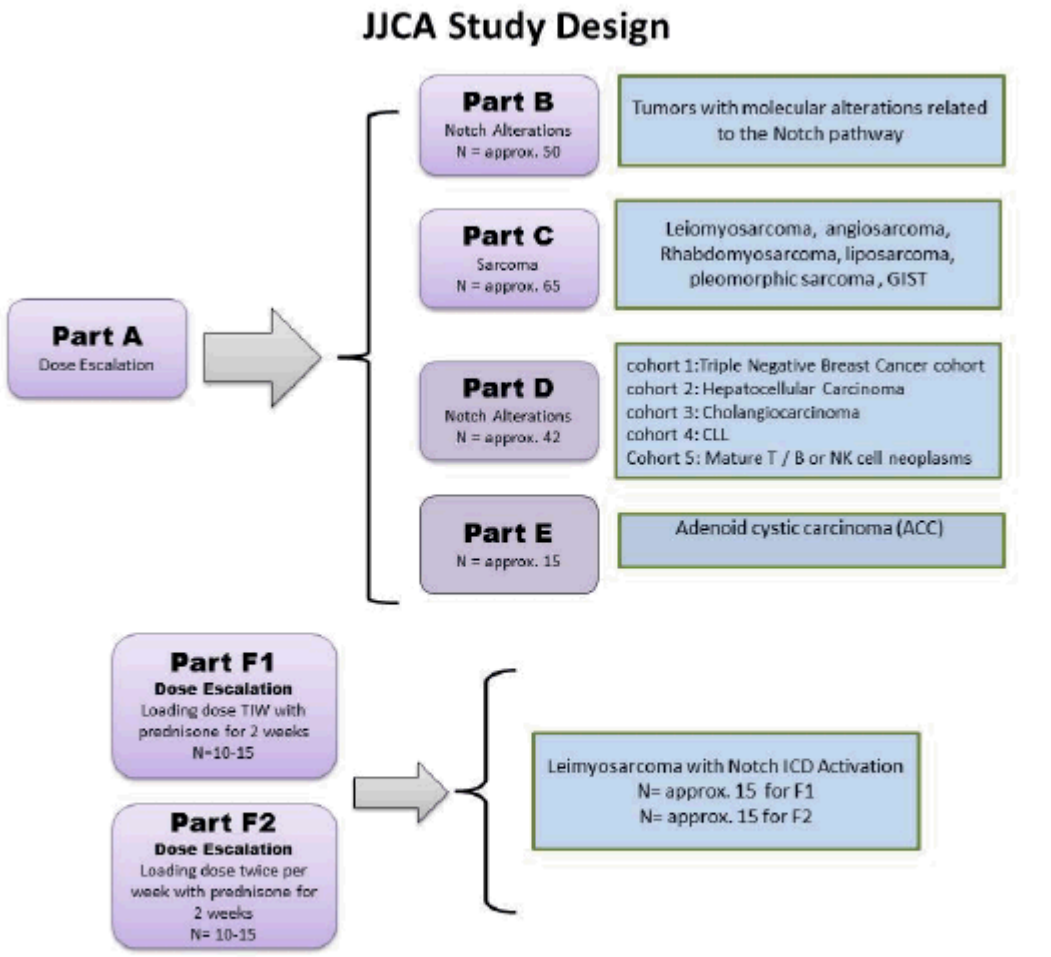
- to characterize the safety and toxicity profile of LY3039478 as assessed by National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0.
- to estimate the pharmacokinetic (PK) parameters of LY3039478.
- Part A: to document any antitumor activity observed with LY3039478
- Parts B, C, D, E and F: to assess duration of response, progression-free survival (PFS) and overall survival (OS)

4.3. Exploratory Objectives

The exploratory objectives of this study are:

- to explore renal clearance of LY3039478 and PK of LY3039478 metabolites in plasma and urine.
- to explore predictive biomarkers related to LY3039478
- to explore pharmacodynamic (PD) effects of LY3039478 on biomarkers indicative of Notch activity (NICD by immunohistochemistry [IHC] or an alternative validated method) including cytokeratin 18 or Rules Based Medicine (RBM)
- to explore the utility of positron emission tomography (PET) scan to assess treatment effect with LY3039478
- to explore the utility of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) to assess treatment effect with LY3039478

4.4. Study Design



Abbreviations: approx = approximately; CLL= Chronic lymphocytic leukemia; GIST = gastrointestinal stromal tumors; ICD = intercellular domain; NK= natural killer; TIW = 3 times per week.

5. A Priori Statistical Methods

5.1. Endpoint Definitions

5.1.1. Safety Endpoints

All patients who receive at least 1 dose of LY3039478 will be evaluated for safety and toxicity. Safety measures that will be used in the study include adverse event (AE), dose limiting toxicity (DLT), clinical laboratory test results, vital signs and electrocardiograms (ECG). All AEs will be classified and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.

Dose Limiting Toxicity:

Dose limiting toxicity (DLT) is defined as an AE during Cycle 1 that is related to the study drug(s) and fulfills any 1 of the following criterion using the NCI CTCAE v 4.0:

- ≥ CTCAE Grade 3 non-hematological toxicity. Exceptions will be made for:
    - Nausea, vomiting, or constipation that lasts < 72 hours and can be controlled with treatment
        - electrolyte disturbance that can be controlled with treatment
        - Diarrhea CTCAE Grade 3 for <5 days and that can be controlled with standard treatment
    - Transient (<7 days) Grade 3 elevations of ALT and/or AST, that are not accompanied by a Grade 2 bilirubin increase are considered an exception to the DLT criteria, unless there is a clear alternative cause(e.g. worsening bilary obstruction) if agreed by the study investigator and Lilly clinical research physician (CRP)/clinical research scientist (CRS)
- CTCAE Grade 4 hematological toxicity of >5 days duration
- Any febrile neutropenia
- Grade 3 thrombocytopenia with bleeding or Grade 4 thrombocytopenia
- Any other significant toxicity deemed by the primary investigator and Lilly clinical research personnel to be dose limiting (for example, any toxicity that is possibly related to the study medication that requires the withdrawal of the patient from the study during Cycle 1)

Maximum Tolerated Dose:

For the purpose of this study, the maximum tolerated dose (MTD) is defined as the highest dose that has less than 33% probability of causing a DLT during Cycle 1.

DLT-Equivalent Toxicity:

A DLT-equivalent toxicity is defined as an AE occurring between Day 1 and Day 28 of any cycle (other than Cycle 1) for a patient enrolled in Part A or in any cycle (including Cycle 1) for a patient enrolled in Parts B that would have met the criteria for DLT if it had occurred during Cycle 1 for a patient enrolled in Part A.

Treatment emergent adverse events:

A treatment emergent adverse event (TEAE) is defined as (i) any AE with a new LLT MedDRA term relative to baseline, or (ii) any AE with a LLT MedDRA term (or CTCAE term) present at baseline that has an increased severity (CTCAE grade) compared to baseline for this MedDRA term

5.1.2. Efficacy Endpoints

This phase 1 trial has not been designed to assess comparative efficacy; however, antitumor or disease modifying activity is a secondary objective and as such response data will be summarized, listed and exploratory analyses may be performed.

Change in tumor size (CTS) 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 with soft tissue sarcoma or hepatocellular carcinoma (HCC) by using Choi response criteria, per protocol amendment (c). 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.

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 systemic 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.

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), Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007) ,the RANO criteria for glioblastoma (Wen et al. 2010)] or the Guidelines from the National Cancer Institute

Working Group for CLL [Hallek et al. 2008]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 or hepatocellular carcinoma (HCC) enrolled from protocol amendment (c), 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 have been demonstrated to be a more sensitive prognostic marker for time to progression and disease specific survival in gastrointestinal stromal tumor (GIST) (Benjamin et al. 2007; Choi et al. 2007). Best Choi ORR will be determined from a sequence of response using a similar method to that described for RECIST best response.

PET Metabolic Response: For Part E, Part F, Part C patients with sarcoma (leiomyosarcoma, GIST, liposarcoma, and angiosarcoma), and Part D patients with mature T cell, B cell, or NK cell neoplasms enrolled under amendment (d), PET maximum standardized uptake values (SUVmax) will also 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 ORR and is defined only for responders. 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.

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

5.2. Analysis Sets

Patients **entered** into the trial are those who sign the informed consent document.

Patients **enrolled** in the trial are those who have been assigned to a treatment. All patients who received at least one dose of any study drug will be referred to as a **patient on therapy**.

Safety and efficacy analyses will be performed on all patients who received at least one dose of study drug (patients on therapy).

The **PK analysis set** will include all patients who received at least one dose of study drug and had sufficient samples collected to estimate PK parameters.

The **PD analysis set** will include all patients who received at least one dose of study drug and had at least one PD endpoint measurement.

The numbers of patients who do not qualify for analysis, who die, or who discontinue before treatment begins, will be reported.

5.3. Statistical Methods

5.3.1. Interim Analyses

In line with Section 10.3 of the Protocol no formal interim analyses are planned for this study.

During Part A, however, patient safety will be assessed prior to each dose escalation to ensure nothing precludes administration of larger doses to future study patients. In addition to reviewing AEs and laboratory measurements, PK/PD profiles of LY3039478 will be reviewed per cohort. Based on these interim results, modifications (eg, reductions in dose increment) to the dose-escalation strategy or other design elements may be made to ensure patient safety. The study investigators and the Lilly CRP will make the determination regarding dose escalation based upon their review of the safety/tolerability data and the PK data from the previous cohorts.

In addition, an interim review will be conducted prior to proceeding to Part B including safety, PK, and PD. All relevant data will be reviewed to confirm the estimation of the MTD. The decision to proceed to Part B will be made following discussions between the investigators and Lilly clinical research personnel.

5.3.2. Dose Escalation Method

In this study, dose escalation will be driven by safety using the 3+3 method as outlined in Section 7.7.2 of the Protocol.

Model-based analyses that incorporate prior expectations about the dose-toxicity curve will also be fitted to the data at the end of each cohort, which may be used by the investigators and Lilly CRP to help determine the next dose level. Dose escalation will take into account PK and PD information when available. The aim will be to identify a range of possible future doses, the associated estimated DLT rates and the estimated MTD.

The modeling approach is outlined in Appendix 1.

5.3.3. General Considerations

All patients who have received at least 1 dose of study drug will be evaluated for safety, efficacy, and PD endpoints.

All data summaries, figures and listings will be split by assigned dose level. All data will be listed for all enrolled subjects, including derived data, by study part, assigned dose level, cohort, patient number, cycle and time point where appropriate, unless stated otherwise in the following text or in the table shells. Data will be presented as received from the designated data management group.

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 events, the number of subjects with events (n) and the percentage of subjects with events are usually reported. General reporting requirements will be outlined in the accompanying TFL template document.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

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 (date of assessment) – (date of first study drug dose) +1
	If assessment precedes first dose of drug then (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 (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. 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.
Entered	Patients who have signed the informed consent document directly.
Enrolled	Patients who have been assigned to study treatment.
Patients on therapy	Patients who have been assigned to study treatment and have received at least one dose of study treatment.
Screen Failures	Patients who have signed informed consent, but? do not meet eligibility criteria and are not enrolled.

5.3.4. Handling of 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. Missing days will be replaced with 15 and missing day/month with 01 JULY. Partial dates should be reported in all listings and not the imputed date.

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.

5.3.5. 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, enrolled in the study, and treated and the number and percentage of patients completing the study, or discontinuing from study treatment and study (overall and by reason for discontinuation, if known). All patients entered in the study will be included in the summary. Reason for discontinuation from both study treatment and study will be listed by the pre-determined categories. If reason for discontinuation is due to AE or death, the associated AE or cause of death will be reported.

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).

5.3.6. Patient Demographics and Baseline Disease Characteristics

5.3.6.1. Demographics and Baseline Disease Characteristics

Patient demographic and baseline disease characteristics will be listed for all patients on therapy and summarized by cohort/treatment group and overall by study part.

Patient demographics will include sex, race, age, height and weight. Baseline disease characteristics will include basis for diagnosis, initial pathological diagnosis and ECOG performance status.

Special instructions regarding presentation of race: patient may select more than one of the values for Race in the electronic case report form (eCRF). Derive Race to ‘Multiple’ if more than one race is selected. Otherwise, race equals the single race selected. For example, if a patient selects both ‘White’ and ‘Asian’ then RACE = ‘Multiple’. However, if a patient select only ‘Asian’ then RACE = ‘Asian’.

5.3.6.2. Historical Illnesses and Pre-existing Conditions

Historical illnesses are clinically relevant events in the past that ended before the screening visit. Historical illnesses (using preferred term from the most current version of the Medical Dictionary for Regulatory Activities [MedDRA]) will be listed for all patients on therapy.

Pre-existing conditions are existing clinically relevant events that started prior to signing the inform consent document. These conditions will be graded using NCI CTCAE v4.0 terms and will be part of the AE listing. Pre-existing conditions will be summarized separately for all patients on therapy.

5.3.6.3. Prior and Post Discontinuation Therapies

Prior therapies, including systemic therapy and radiotherapy will be listed for all patients on therapy. Any prior surgeries will also be listed. These data will be summarized for all patients on therapy.

Any post-treatment therapies following discontinuation will also be listed.

5.3.7. Concomitant Medications

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 for all patients on therapy.

A separate listing of transfusions will be created.

If concomitant medication use is due to an AE, the associated AE will be listed. The Anatomical Therapeutic Chemical (ATC) level to be used in the summary will be defined in the separate document of Table Shells.

5.3.8. Efficacy Analyses

Tumor markers and disease progression data will be listed for all patients on therapy.

Reported lesion data (target/ non-target or measurable/ nonmeasurable) and investigator assessment of response (where available), will be listed for all patients on therapy.

The following efficacy endpoints, detailed in Section 5.1.2 will be listed for all patients and summarized as appropriate:

- Overall response rate and Choi response rate (where applicable). Where data warrant, patients will be grouped by mutation and/or amplificaction and by tumor type. Logistic regression analyses may also be utilized to estimate the ORR for each grouping of patients, provided a sufficient number of CR or PR are observed to warrant modelling (>10%). Further exploratory analyses may utilize a Bayesian hierarchical model in order to explore response rates across each tumor type
- Time to event endpoints including PFS, OS, duration of response, and duration of stable disease, PFS and OS will be summarized descriptively using the Kaplan-Meier method
- Change in tumor size and change in tumor density: A waterfall plot of change in tumor size and change in tumor density will be produced. All patients with at least one target lesion measurement will be represented in the plot. If data warrant, statistical analyses may be conducted utilizing analysis of covariance models with potential covariates

including baseline measurements, mutations/amplification group, tumor type, ECOG status and other covariates as deemed appropriate.

5.3.9. Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic (PK), Pharmacodynamic (PD) and predictive biomarker analyses are described in a separate analysis plan.

Pharmacokinetic analyses will be conducted on patients who have received at least 1 dose of the study drug and have had samples collected. The Lilly pharmacokineticist will perform the PK analyses per the separate PK/PD analysis plan and provide PK parameters for the analysis described below.

Providing that the data allow (i.e. PK parameters are available for more than two dose levels), the PK parameter estimates (Cmax and AUC(0-∞), AUC(0-t_{last}), $AUC_{\tau,ss}$) for LY3039478 will be evaluated statistically to delineate the effects of dose proportionality with the method as described in Smith et al (2000).

The degree of dose proportionality will be assessed by fitting the power model to the applicable AUCs outlined above and Cmax versus dose. The data will be analyzed with PROC MIXED using the maximum likelihood estimation method. The power model is defined below:

LOG(RESPONSE) = LOG(DOSE) + RANDOM ERROR

Response in this equation means AUC or Cmax.

The ratio of dose-normalized geometric means over the entire dose range will be tested and its 90% confidence interval will be presented. In addition, the estimated slope for total dose against the PK parameter and its 90% confidence interval together with the least squares geometric means for each dose level tested will be produced. Different fold-ranges of doses will be chosen to provide estimates of ratios of dose-normalized geometric means after a single dose, depending on the actual range of doses tested in the study.

In the event that the power model is not a good representation of the data over the entire dose range tested, alternative models may be investigated.

5.3.9.1. Biomarker Analyses

Biomarker/PD effects will be investigated graphically to explore patterns of change over time and how the patterns differ among arms or exposure. Further analysis (eg, by linear mixed model) may be performed to characterize the relationship. To identify and assess biomarkers for potential tailoring purposes, associations between baseline biomarker measures and clinical outcomes may be analyzed using appropriate single-marker or multimarker analysis approaches

5.3.10. Safety Analyses

5.3.10.1. Study Drug Exposure

All study drug information and dose level assignment will be listed for all patients on therapy.

The total number of cycles completed and number days on treatment by dose for each patient will be listed. In addition, a Napoleon plot of the treatment duration and dose received by patient and cohort will be produced.

A summary of drug exposure will be presented. Within this table, the number of completed cycles of study drug by dose level will be summarized.

A summary of LY3039478 dose adjustments detailing the number of patients with dose reductions and dose omissions will be presented, along with the reason for dose adjustments (e.g. AEs). The number of patients requiring dose omissions for 7 consecutive days or longer, and 14 consecutive days or longer will also be presented by dose level.

A list of dose intensity for LY3039478 by patient will be generated, where dose intensity is given by:

% dose intensity = 100*(actual cumulative dose taken)/ (planned cumulative dose without dose adjustment)

Note that planned dose is the same as actual dose if there is no dose modification. Reasons for dose adjustments will also be summarized. If the reason for dose modification is due to an AE, the associated AE will be provided.

A summary of dose compliance for LY3039478 will be generated, where dose compliance is given by:

% dose compliance = 100*(total amount of drug taken)/ (total amount of drug prescribed, accounting for dose adjustments and omissions)

Patients who are non-compliant (i.e. a dose compliance of <75% or >120%) will be included in the summary.

Additional information on definitions of dose intensity, dose compliance and other exposure parameters are provided in sponsor ADAM standard specifications.

5.3.10.2. Dose Limiting Toxicity

Dose limiting toxicities (DLT) will be listed for all patients on therapy in Part A and Part F dose escalation. DLT-equivalent toxicities will also be listed for all patients on therapy.

A 2 parameter logistic regression model will be fitted to the data from Part A to establish the relationship between the dose and the probability of experiencing a DLT (Appendix 1).The model is defined as

$$\text{Logit}(\Pr[\text{DLT}]) = \alpha + \beta * \text{dose}.$$

Transformation of the dose strength may be considered for the model fit. The probability of experiencing a DLT and its 90% confidence limit will be estimated from the model and plotted. The MTD, defined as the highest dose that has less than 33% probability of causing a DLT during Cycle 1, will be estimated from the model.

5.3.10.3. Adverse Events

Pre-existing conditions are events that are present at screening. Pre-existing conditions recorded on the AEs page will be included in the AE listing.

All observed AEs will be graded using CTCAE version 4.0. Given this, in addition to MedDRA mapping, AEs will also be mapped to CTCAE terms.

The incidence of TEAE will be summarized by dose level and overall by study part, taking into account CTCAE grade, relationship, seriousness, and cycle.

To assess the relationship of the AE to the study drug, the following terminologies are defined (in Protocol Section 8.1.2):

- Related: a direct cause and effect relationship between the study treatment and the AE is likely.
- Possibly related: a cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible.
- Unrelated: without question, the AE is definitely not associated with the study treatment.

As per Lilly's standard operating procedures, all "related," or "possibly related," AEs and SAEs will be defined as related to study drug.

MedDRA mapping is applied to AE data as they are received. MedDRA versions may be upgraded as frequently as twice in a year. Therefore, different MedDRA versions may be used in this trial, based upon when the AE information is received; however, the safety information will be summarized and listed in preferred terms 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 preferred term and system organ class level to the most current version in the locked database. The version used in any reports will be documented.

Specific tables and listings needed include:

- List of DLTs and DLT-equivalent toxicities,
- List of pre-existing conditions and AEs,
- List of SAEs,
- List of deaths,
- Summary of AEs
- Summary of all TEAEs,

- Summary of related TEAEs,

5.3.10.4. Laboratory Parameters

All laboratory results will be reviewed using Spotfire to assess changes over time and differences between cohort/dose levels. Key findings will be summarized in tables and/or illustrated graphically using line plots over time or box plots for example.

Abnormal Laboratory data (including chemisty, hematology, urinalysis and coagulation) will be listed for all patients on therapy. In addition to the Investigator reported AEs, all relevant hematology, chemistry and urinalysis laboratory values will be graded according to CTCAE version 4.0. These calculated grades will be included on the listing and summarized by maximum grade at each cycle (and over the entire study) by dose level and study part. A separate listing for calculated creatinine clearance will be provided.

5.3.10.5. Deaths

All deaths recorded in this study will be included as part of the complete AE listing, where appropriate, and listed separately. A summary of deaths may be presented for all patients on therapy if there are a sufficient number of events for this to be deemed useful.

5.3.10.6. Vital Signs

All vital sign results will be reviewed using Spotfire to assess changes over time and differences between cohorts/dose levels. Key findings will be summarized in tables and/or illustrated graphically using line plots over time or box plots for example.

5.3.10.7. Electrocardiograms

ECG results will be reviewed using Spotfire to assess changes over time and differences between cohorts/dose levels. Key findings will be summarized in tables and/or illustrated graphically using line plots over time or box plots for example. The number of patients experiencing a maximum increase from baseline in QTcF interval will be summarised according to the following categories: >30 ms and >60 ms. In addition, the number of patients with QTcF postdose values, according to the following categories: >450 ms, >480 ms and >500 ms, will be summarised.

5.3.10.8. Notch Pathway Alterations

All Notch pathway mutation data collected at screening will be listed for each patient. Exploratory analyses may be performed to investigate associations between Notch pathway mutation data and PK, PD or efficacy measurements as deemed appropriate.

5.3.10.9. PET Scans

European Organization for Research and Treatment of Cancer (EORTC) PET Study Group (Young H, 1999) guidelines will be used to measure tumor response. Exploratory methods may be used too. A waterfall plot of minimum percentage change in SUVmax will be produced. All patients with at least one evaluable lesion by PET scan will be represented in the plot.

Exploratory analyses correlating PET imaging responses with PK, PD or efficacy measurements may be conducted.

5.3.10.10. Nutritional Intake and Consumption Habits

Nutritional intake and consumption habits will be listed for each patient for all patients on therapy.

5.3.10.11. CT Lot Numbers

CT lot numbers will be listed for all patients on therapy.

5.3.11. Protocol Deviations

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). The following protocol deviations relevant to this study have been identified in Table 2.

Table 2. Description of Protocol Deviations

Category	Source	Methods of Identification
Category: Informed Consent		
Informed Consent Not Obtained/Missing/Late	Programmable (clinical database)	Compare all assessment dates to ICD date (except those assessments that may occur before ICD, e.g. disease assessments)
Category: Eligibility		
Participation of a subject(s) that did not meet study inclusion/exclusion criteria	Mixed (Monitoring and clinical database)	Review of the following programmable and relevant protocol inclusion/exclusions criteria: [1], [2], [3], [5], [6], [7], [13], [16],[17], [20], [22]
Discontinuation due to protocol violation during the study	Mixed (Monitoring and clinical database)	Review of reasons for discontinuation
Category: Investigational Product		
Incorrect dosing/treatment	Mixed (Monitoring and clinical database)	Non-Compliance with study treatment (< 75% or >120%)
Category: Treatment Discontinuation		
Patient not withdrawn after meeting protocol discontinuation criteria	Monitoring	NA

Category: Study Procedures		
Excluded concomitant medications	(Monitoring and clinical database)	Study specific definition: a list with all concomitant medication will be generated, and CRP will flag those excluded (the flagged medications will be used in programming to flag important protocol deviations)

Abbreviations: CRP = clinical research physician; ICD = informed consent document.

5.3.12. Annual Reporting

The following reports are needed for the Development Safety Update Report (DSUR):

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.

For guidance on creation of these reports, see the DSUR collaboration site (http://lillynetcollaboration.global.lilly.com/sites/GMRS_GPS/Surv/dsur/default.aspx?PageView=Shared)

5.3.13. Clinical Trial Registry Analyses

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, provided as a dataset which will be converted to an XML file. Both Serious Adverse Events and 'Other' Adverse Events are summarized: by treatment group, by MedDRA preferred term.

- An adverse event is considered 'Serious' whether or not it is a treatment emergent adverse event (TEAE).
- An adverse event is considered in the 'Other' category if it is both a TEAE and is not serious. For each Serious AE 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/subjects 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.

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7. Appendices

Appendix 1. Statistical Modelling Details

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