Protocol I6F-MC-JJCB (a)

A Phase 1b/Randomized Phase 2 Study to Evaluate LY3039478 in Combination with Dexamethasone in T-ALL/T-LBL Patients

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Approved Date: 04-Jun-2015

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LY3039478

A Phase 1b/randomized Phase 2 study to evaluate LY3039478 in combination with dexamethasone in patients with T-ALL/T-LBL.

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Protocol Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 04-Jun-2015 GMT

2. Synopsis

Clinical Protocol Synopsis: Study I6F-MC-JJCB(a)

<table>
<tr><td colspan="2">Name of Investigational Product: LY3039478</td></tr>
<tr><td colspan="2">Title of Study: A Phase 1b/Randomized Phase 2 Study to Evaluate LY3039478 in Combination with Dexamethasone in T-ALL/T-LBL Patients</td></tr>
<tr><td>Number of Planned Patients: 86 to 92 total patients
Entered:
Enrolled/Randomized:
Phase 1: Part A 13 to 16 patients; Part B 13 to 16 patients
Phase 2: 60 patients</td><td>Phase of Development: 1b / 2</td></tr>
<tr><td colspan="2">Length of Study: approximately 60 months
Planned first patient visit: May 2015
Planned last patient visit, excluding the continued access: May 2020
Planned interim analysis: At end of Phase 1 and during Phase 2, every 12 months and once 30 patients are randomized and have completed the CR determination.</td></tr>
<tr><td colspan="2">Objectives:
The primary objective is as follows:
• Phase 1: to determine the recommended dose of LY3039478 in combination with dexamethasone in adult patients with relapsed/refractory T-cell acute lymphoblastic leukemia (T-ALL) or T-cell lymphoblastic lymphoma (T-LBL) (Part A) and pediatric patients (Part B)
• Phase 2: to determine if the overall remission rate (ORR) (CR plus CR with incomplete blood count recovery [CRi]) in adult patients with relapsed/refractory T-ALL/T-LBL treated with LY3039478 in combination with dexamethasone exceeds that of those patients treated with placebo in combination with dexamethasone
The secondary objectives are as follows:
• Phase 1:
o to characterize the safety and toxicity profile of LY3039478 in combination with dexamethasone as assessed by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.0
o to assess the pharmacokinetic (PK) parameters of LY3039478 in combination with dexamethasone therapy
o to document efficacy based on Cheson criteria for leukemia and modified response criteria for malignant lymphoma
o to evaluate gene mutation (eg, NOTCH-1/FBXW7/RAS/PTEN) status with efficacy
• Phase 2:
o to compare the ORR plus partial remission (PR) and PR alone for both arms
o to assess the remission rate for patients receiving LY3039478 in combination with dexamethasone after failure of placebo in combination with dexamethasone
o to assess duration of remission (DoR) (= CR and Cri and PR)
o to assess relapse-free survival (RFS), event-free survival (EFS), and overall survival (OS)
o to compare the safety and toxicity profile of LY3039478 in combination with dexamethasone to dexamethasone and placebo as assessed by NCI CTCAE v 4.0
o to assess the pharmacokinetic (PK) parameters of LY3039478 and dexamethasone in combination therapy
o to assess patient quality of life using the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu)
o to evaluate gene mutation (eg, NOTCH-1/FBXW7/RAS/PTEN) status with efficacy</td></tr>
</table>

The exploratory objectives are as follows:

- to assess clinical utility of the NICD immunohistochemistry (IHC) assay as a potential companion diagnostic for LY3039478
- to evaluate biomarkers in tumor tissue, blood, plasma, and cerebrospinal fluid (CSF), which may include, but not be limited to, NICD enzyme-linked immunosorbent assay (ELISA) (or an alternative validated method), gene expression, relevant to the study disease or safety, efficacy, and mechanism of action of LY3039478 and dexamethasone
- to explore pharmacodynamic (PD) effects of LY3039478 on biomarkers indicative of Notch activity
- to evaluate the CSF exposure of LY3039478

Study Design: Study I6F-MC-JJCB is a multicenter study consisting of a nonrandomized, open-label, dose-escalation Phase 1 study followed by a randomized, double-blind, Phase 2 study in patients with relapsed or refractory T-ALL/T-LBL. The Phase 1 portion of the study will consist of 2 different patient populations, an adult (Part A) and a pediatric (Part B), and will define the recommended dose of LY3039478 in combination with dexamethasone in each of these populations. The decision to proceed with the pediatric dose exploration (Part B) will be made after safety analysis of the adult cohort. The randomized Phase 2 study will be a double-blinded, multicenter evaluation to determine if the ORR (CR and CRi) rate in adult patients with relapsed/refractory T-ALL/T-LBL treated with LY3039478 in combination with dexamethasone exceeds that of those patients treated with placebo in combination with dexamethasone.

Diagnosis and Main Criteria for Inclusion and Exclusions: Patients must have T-ALL or T-LBL. T-ALL is defined ≥25% of blasts in the bone marrow and expression of at least 2 of the following cell surface antigens: CD1a, CD2, CD3 (surface or cytoplasmic), CD4, CD5, CD7, and/or CD8. If the only T cell markers present are CD4 and CD7, the leukemia cells must also lack the myeloid markers CD33 and/or CD13. Patients with initial refractory disease should have received at least 2 multi-agent chemotherapy induction regimens. Patients in first or second relapse must have been refractory to at least 1 multi-agent chemotherapy reinduction regimen. They must have had at least 60 days between prior hematopoietic stem cell transplant and first dose of study drug, have adequate performance status and organ function, be ≥16 years old for the adult cohort (Phase 1, Part A) and 2 to <16 years old for the pediatric cohort (Phase 1, Part B), and have a life expectancy of 2 months.

Patients may be excluded if they are currently enrolled in another ongoing clinical trial with investigational products, have recently discontinued (within less than 2 weeks) prior anticancer therapy, have a serious concomitant illness, have an uncontrolled or active infection <7 days prior to administration of study drug, have current or recurrent (within 3 months) gastrointestinal disease, have conditions requiring chronic systemic glucocorticoid use, have active graft versus host disease, have active leukemic involvement of the central nervous system, or have a second primary or prior malignancy that would affect the interpretation of study results.

Test Product, Dosage, and Mode of Administration: LY3039478, dose range 25 to 200 mg, given orally as capsules 3 times per week during a 28-day cycle.

Placebo will be given orally as capsules 3 times per week during a 28-day cycle.

Planned Duration of Treatment: Patients will receive 2 cycles (28 days each) of LY3039478 unless 1 or more of the criteria for discontinuation are fulfilled. A patient may receive >2 cycles of treatment only if: 1) none of the criteria for discontinuation have been fulfilled, and 2) the investigator determines that the patient is experiencing clinical benefit from treatment.

Short-term follow-up period (postdiscontinuation): 30 days.

Long-term follow-up (postdiscontinuation): until death.

Reference Therapy, Dose, and Mode of Administration: Dexamethasone will be administered at a dose of 24 mg on Day 1 through Day 5 every other week to the adult patients and 10 mg/m^2 twice a day (BID) to the pediatric patients.

Criteria for Evaluation:

Efficacy:

- ORR
- CR rate
- proportion of patients achieving a CRi
- proportion of patients achieving a PR
- DoR
- OS
- RFS
- EFS

Safety: Safety will be evaluated based on recorded adverse events (AEs), physical examinations, vital sign measurements, electrocardiograms, and clinical laboratory assessments. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events and clinical laboratory values will be graded using NCI CTCAE v4.0.

Health Outcomes: Patient health-related quality of life including physical, social/family, emotional and functional well-being will be assessed using the self-administered FACT-Leu questionnaire at the beginning of each visit only in the Phase 2 portion of the study.

Pharmacokinetics: Blood and CSF samples will be used to determine the concentrations of LY3039478. CSF concentrations of LY3039478, and plasma concentrations of LY3039478 and dexamethasone will be quantified using validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) assays. The remaining plasma samples collected for PK evaluation may be used for exploratory studies to assess the metabolism of LY3039478, which may involve sample pooling.

Pharmacodynamics/Tailoring Biomarkers: Blood, CSF, EDTA plasma, tissue, and bone marrow samples will be collected. Samples will be tested for markers of Notch and related pathway activation including, but not limited to, protein expression and activation by IHC and ELISA, and gene expression by quantitative polymerase chain reaction (PCR) analysis to evaluate their association with the observed clinical outcomes to LY3039478.

Statistical Methods:

Statistical:

In the Phase 1 portion of the study, approximately 13 to 16 patients will be enrolled into each of the adult (Part A) and pediatric (Part B) cohorts sequentially and without randomization to dose. The total sample size per cohort will be determined by DLTs.

In the Phase 2 portion of the study, approximately 60 evaluable patients will be randomized to the 2 treatment arms in a 2:1 ratio (40 randomized to LY3039478 and dexamethasone and 20 randomized to placebo and dexamethasone).

Efficacy analyses will be based on the intention-to-treat (ITT) analysis set. This population is defined as all patients randomized to study treatment. Patients will be grouped according to dose level cohort or randomized treatment. A secondary analysis of the primary efficacy endpoint based upon the per-protocol set (PPS) of patients may be performed if there are significant numbers of patients with major protocol deviations (≥10% of total patient population). The PPS is defined as those patients in the ITT set who are compliant with the study protocol.

Safety analyses will be based on the safety population, defined as all enrolled patients receiving at least 1 dose of any study drug. Patients will be grouped according to treatment received in Cycle 1.

PD and/or tailoring biomarker analyses will be based on the subset of patients from the above populations from whom a valid assay result (according to laboratory guideline) has been obtained.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. All tests of interactions will be conducted at a 2-sided alpha level of 0.1, and all confidence intervals (CIs) will be given at a 2-sided 95% level, unless otherwise stated.

Efficacy:

No formal efficacy analysis is planned for the Phase 1 portion of this trial. However, any response data will be listed and tabulated. In the Phase 2 portion, the primary efficacy endpoint of ORR (CR plus CRi) and its exact 95%

CI will be estimated for each treatment arm. The proportion in each treatment arm will be compared using Fisher's exact test. All randomized patients, according to the ITT principle, will be included in the analysis of this endpoint. The secondary efficacy endpoints of proportion of patients achieving an ORR plus PR, and PR, and their exact 95% CIs will be estimated for each treatment arm and compared by 2-sided Chi-squared test or Fisher's exact test between 2 arms. For the secondary efficacy endpoints OS, RFS, and EFS, the Kaplan-Meier method will be used to estimate the survival curves as well as survival rates at various prespecified time points (12 months for OS, 6 and 12 months for RFS and EFS) for each treatment arm. The secondary efficacy endpoint DoR is subject to competing risk of death without relapse; therefore, the cumulative incidence of relapse will be used. In the calculation, patients who did not have the event will be considered right-censored observations. All randomized patients, according to the ITT principle, will be included in the analysis of these endpoints. The comparison of the survival curves between treatment groups will be conducted by a log-rank test.

Safety: Safety analyses will include listings and/or summaries of the following:

- adverse events (AEs) and treatment-emergent adverse events (TEAEs),
- drug exposure,
- dose adjustments,
- laboratory measures,
- reasons for death, and
- hospitalizations and transfusions.

Health Outcomes: FACT-Leu results will be summarized descriptively by cycle, including number of completed questionnaires, scores for each scale and subscale, and changes from baseline.

Pharmacokinetics: PK analyses will be conducted on patients who receive at least 1 dose of the study drug and have samples collected. PK parameter estimates for LY3039478 and dexamethasone, where possible, will be calculated by standard noncompartmental methods of analysis.

Pharmacodynamics/Tailoring Biomarkers: Biomarker data from all patients undergoing biomarker assessments will be analyzed using descriptive statistics.

Interim Analyses: An interim analysis including safety, PK, and PD data will be conducted prior to proceeding to the Phase 2 portion of the study. All relevant data will be reviewed to confirm the estimation of the MTD. The decision to proceed to Phase 2 will be made following discussions between the investigators and Lilly clinical research personnel and documented in writing. In the Phase 2 portion, safety interim analyses are planned every 12 months, and at the planned futility interim analysis, when response data from 30 patients has been obtained. There are no prespecified rules for stopping the trial due to safety concerns. The assessment committee members will review unblinded safety data at each interim analysis to determine whether there are sufficient safety concerns to justify the termination of study treatment and/or enrollment.

One futility interim analysis is planned in Phase 2 once 30 patients are randomized and have completed the CR status determination. The assessment committee may recommend stopping the trial for futility if the observed ORR (CR plus CRi) rate difference is <0.05 for the treatment arm compared to the control arm.

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A Phase 1b/Randomized Phase 2 Study to Evaluate LY3039478 in Combination with Dexamethasone in T-ALL/T-LBL Patients

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4. Abbreviations and Definitions

Term	Definition
AE	adverse event Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and risks involved in participating in a study (required by some institutional review boards [IRBs]).
AST	aspartate aminotransferase
AUC	area under the plasma drug concentration versus time curve
$AUC_{(0-\infty)}$	area under the concentration-time curve from time zero to infinity
$AUC_{[0\text{-}tlast]}$	area under the plasma concentration-time curve from time zero to last measurable plasma concentration
AUC_T	area under the concentration-time curve over 1 dosing interval at steady state
audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
BID	twice per day
blinding/masking	A procedure in which 1 or more parties to the trial are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received.
BSA	body surface area
CI	confidence interval

CLL	chronic lymphocytic leukemia
C_{max}	maximum observed concentration
CNS	central nervous system
collection database	A computer database where clinical trial data are entered and validated.
companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
continued access period	The period between study completion and end of trial during which patients on study therapy who continue to experience clinical benefit may continue to receive study therapy until 1 of the criteria for discontinuation is met.
CR	complete remission
CrCl	creatinine clearance
CRF/eCRF	case report form/electronic case report form Sometimes referred to as clinical report form: A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRi	complete remission with incomplete blood count recovery
CRP	clinical research physician Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CSF	cerebrospinal fluid
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCSI	Development Core Safety Information (of Investigator's Brochure)
DDI	drug-drug interaction
DLET	dose-limiting equivalent toxicity
DLT	dose-limiting toxicity

DoR	duration of remission
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylenediaminetetraacetic acid
EFS	event-free survival
ELISA	enzyme-linked immunosorbent assay
end of trial	End of trial is the date of the last visit or last scheduled procedure for the last patient.
Enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB/IRB	ethical review board/institutional review board A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical trial are protected.
ESA	erythropoiesis-stimulating agent
F	oral absorption
FACT-Leu	Functional Assessment of Cancer Therapy-Leukemia
FHD	first-in-human dose
GCP	good clinical practice
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
GnRH	gonadotropin-releasing hormone
GSI	γ-secretase inhibitors
HD	heterodimerization domain
hERG	human ether-à-go-go-related gene
HNSTD	highest non–severely toxic dose
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form

ICH	International Conference on Harmonisation
IHC	immunohistochemistry
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical trial data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product (IP)	A pharmaceutical form of an active ingredient substance or placebo being tested, or used as a reference, in a clinical trial. Investigational product (IP) includes a product with a marketing authorization when: 1. used or assembled (formulated or packaged) in a way different from the authorized form, 2. used for an unauthorized indication, or 3. used to gain further information about the authorized form.
investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
ITT	intention-to-treat The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IVTI	in vivo target inhibition
IWG	International Working Group
IWRS	interactive web-response system
LBL	lymphoblastic lymphoma
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the clinical study.
Lilly Safety System	Global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system.
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MRI	magnetic resonance imaging

MTD	maximum tolerated dose
N1ICD	NOTCH-1 intracellular domain
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NICD	Notch intracellular domain
NOAEL	no-observed-adverse-effect level
ORR	overall remission rate
OS	overall survival
patient	a study participant who has the disease or condition for which the investigational product is targeted.
PD	pharmacodynamic(s)
PEST	proline, glutamate, serine, and threonine
PET-CT	positron emission tomography-computed tomography
PK	pharmacokinetic(s)
PPS	per-protocol set The set of data generated by the subset of patients who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model.
PR	partial remission
PT	preferred term
QTc	corrected QT interval
randomize	the process of assigning patients to an experimental group on a random basis
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
RFS	relapse-free survival
re-screen	to screen a patient who was previously declared a screen failure for the same study
SAE	serious adverse event
SAP	Statistical Analysis Plan

screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, diagnostic psychological tests, x-rays, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
screen failure	patient who does not meet 1 or more criteria required for participation in a trial
SCT	stem cell transplantation
SD	stable disease
SOC	system organ class
study completion	This study will be considered complete after the final analysis of overall survival is performed.
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	elimination half-life
T-ALL	T-cell acute lymphoblastic leukemia
TEAE	treatment-emergent adverse event Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
TEC_{50}	threshold plasma concentration of the compound required to inhibit cleavage by 50%
TED_{50}	threshold dose concentration of the compound required to inhibit cleavage by 50%
TIW	3 times per week
T-LBL	T-cell lymphoblastic lymphoma
TLS	tumor lysis syndrome
t_{max}	time of maximal plasma concentration
TPO	third-party organization
ULN	upper limit of normal

A Phase 1b/Randomized Phase 2 Study to Evaluate LY3039478 in Combination with Dexamethasone in T-ALL/T-LBL Patients

5. Introduction

5.1. Rationale and Justification for the Study

5.1.1. T-Cell Acute Lymphoblastic Leukemia/T-Cell Lymphoblastic Lymphoma

Acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) are heterogeneous clonal disorders of hematopoiesis characterized by aberrant proliferation and/or mutation of hematopoietic progenitor cells (blasts). In T-cell ALL (T-ALL) and T-cell LBL (T-LBL), the neoplasm is characterized by malignant expansion of immature lymphoblasts committed to the T-cell lineage. T-ALL and T-LBL are widely thought of as the same disease type differing only by the amount of involvement in the bone marrow. Infiltration above 25% is considered T-ALL and below 25% is T-LBL (Hoelzer and Gökbuget 2009). They are a heterogeneous group of diseases with regard to immunophenotyping, cytogenetics molecular genetic abnormalities, and clinical features including response to therapy.

Although ALL is relatively more common in children, it can also affect adults. T-ALL and T-LBL account for approximately 12% to 15% of childhood and 25% of adult ALL cases. Molecular subtypes of T-ALL with Notch mutations are found in about 50% to 60% of children and adults with T-ALL (Armstrong and Look 2005; Graux et al. 2006; Hoelzer and Gökbuget 2009).

Treatment for T-LBL has moved from traditional lymphoma protocols to treatments designed for ALL (Hoelzer and Gökbuget 2009). Treatment results in newly diagnosed adult patients with ALL have improved in the past decade with an increase of complete remission (CR) rates to between 85% and 90% and overall survival (OS) rates to between 40% and 50% with the developments of intensified and targeted chemotherapies and stem cell transplantation (SCT) (Gökbuget and Hoelzer 2009). The 5-year overall survival of T-ALL has improved to between 48% and 56% (Hoelzer et al. 2009; Marks et al. 2009). T-ALL represents one of the most favorable subgroups of adult ALL. Mortality rates of T-ALL patients have significantly decreased over the last decades because of advances in the treatment of this aggressive subset of ALL. The 5-year OS rates are approximately 35% to 40% in adults and 75% to 85% for children and adolescents (Goldberg et al. 2003; Demarest et al. 2011). Despite the progress in the treatment results of newly diagnosed T-ALL or T-LBL, approximately half of these patients relapse within the first 2 years or fail to achieve a CR and have an extremely poor prognosis. Response rates of 50% are achievable among relapsed or refractory T-ALL/T-LBL patients treated with high or intermediate doses of cytarabine-based combination therapy, but remissions are of short duration.

Given the historically poor clinical outcomes for the majority of patients with relapsed T-ALL/T-LBL, there is a clear need for new treatment options.

5.1.2. Notch Signaling and LY3039478

The Notch pathway is a highly conserved signaling system that plays an important role in development in several tissues and organs and in tissue homeostasis. Notch mutations are well characterized and implicated in hematological malignancies such as T-ALL. Notch signaling is activated when the Notch family receptor transmembrane proteins (NOTCH -1 -4) bind to the membrane-bound ligands on neighboring cells. Upon ligand binding the Notch receptor undergoes a series of proteolytic cleavage steps. The final step results in the release of the Notch intracellular domain (NICD). Notch signaling regulates hematopoietic stem cell maintenance and plays a critical role in T-cell development (Maillard et al. 2005). An oncogenic role for Notch was first reported as the result of a chromosomal translocation occurring in a patient with T-cell leukemia (Grabher et al. 2006). Overexpression of NICD in hematopoietic progenitor cells of mice recapitulated this phenomenon, as they developed T-cell leukemia similar to humans. Furthermore, treatment of these cells with the γ-secretase inhibitor prevented their cell growth.

NOTCH-1 signaling plays a prominent role in the pathogenesis of T-ALL/T-LBL (Aster et al. 2011; Tosello and Ferrando 2013). The first identification of activating NOTCH-1 mutations in over 60% of T-ALLs (Weng et al. 2004) was subsequently confirmed in other series including T-LBL (Park et al. 2009). NOTCH-1 mutations localized in the heterodimerization (HD) domain found in 20% of T-ALLs result in ligand-independent activation of the receptor, while mutations of the proline, glutamate, serine, and threonine (PEST) domain present in 15% of T-ALLs cause increased NOTCH-1 intracellular domain (N1ICD) stability and aberrantly prolonged NOTCH-1 activation (Weng et al. 2004). Finally, 20% of T-ALL cases show activation of NOTCH-1 via mutations in the FBXW7 gene and result in increased N1ICD protein stability (Malyukova et al. 2007; O'Neil et al. 2007; Thompson et al. 2007). Mechanistically, FBXW7 mutations are related to NOTCH-1 PEST mutations. Notably, in about 25% of T-ALL cases HD mutations are associated with PEST or FBXW7 mutations which results in a dual NOTCH-1 activation that combines ligand-independent activation and prolonged ICN1 stability (Weng et al. 2004).

Associations between mutation status and outcome have been inconsistent (summarized in Aster et al. 2011 and Tosello and Ferrando 2013). While a few series have suggested that NOTCH-1 mutations are associated with worse outcomes, most have shown no association or a trend towards more favorable responses.

As discussed in Tosello and Ferrando (2013), treatment of T-ALL cell lines with γ-secretase inhibitors (GSI) resulted in decreased levels of intracellular NOTCH-1, as well as transcriptional down regulation of NOTCH-1-target genes in T-ALL (Palomero et al. 2006b). In addition, compound E, a specific and highly active GSI, blocked NOTCH-1 signaling and induced cell cycle arrest, resulting in decreased proliferation of T-ALL cell lines (Weng et al. 2004; Palomero et al. 2006a). Finally, treatment of mouse models of T-ALL with GSIs resulted in apparent

antileukemic effects in vivo (Cullion et al. 2009; Tatarek et al. 2011). Still, to date, only 1 clinical trial using GSIs in T-ALL has been reported (Deangelo et al. 2006). This Phase 1 study tested MK-0752, an oral GSI developed as monotherapy, in 7 patients with T-ALL. One patient with NOTCH-1 mutated T-ALL achieved a 45% reduction in a mediastinal mass after 28 days of treatment. Most patients in the study showed dose-limiting on-target gastrointestinal (GI) toxicity.

The use of parenteral intermittent dosing schedules has been proposed as a possible approach to ameliorate the toxic effects of GSIs.

The use of GSIs in animal models inhibited NOTCH signaling, reversed glucocorticoid resistance in T-ALL, and abrogated gastrointestinal (GI) toxicity (Real and Ferrando 2009; Real et al. 2009; Wei et al. 2010; Samon et al. 2012). The synergistic effects of GSI and glucocorticoids and the enteroprotective effects of dexamethasone against GSI-induced gut toxicity warrant the design of clinical trials testing the safety and efficacy of this drug combination in T-ALL (Cullion et al. 2009; Tammam et al. 2009; Wei et al. 2010).

LY3039478 is a novel small molecule that is a potent inhibitor of N1ICD cleavage with a half-maximal inhibitory concentration (IC_{50}) of approximately 1 nM in most of the tumor cell lines tested.

LY3039478 potently inhibits mutant Notch receptor activity. In a xenograft tumor model, LY3039478 inhibited N1ICD cleavage and expression of Notch-regulated genes in the tumor microenvironment. The inhibition of Notch cleavage also resulted in the induction of apoptosis in a Notch-dependent xenograft model.

LY3039478 as a Notch inhibitor may provide benefits in patients with T-ALL and T-LBL.

Study I6F-MC-JJCB (JJCB) is a Phase 1b/Phase 2 clinical trial designed to evaluate LY3039478 in combination with dexamethasone in T-ALL/T-LBL adult and pediatric patients.

5.1.3. Mechanism of Action and Nonclinical Activity

LY3039478 is a potent Notch inhibitor with an IC_{50} of $\leq$1 nM in the majority of cancer cell lines tested for its ability to inhibit NOTCH-1 cleavage (Bender et al. 2013). Several different tumor cell lines representing solid tumors (n = 10) and leukemia (n = 7) were used to assess the in vitro activity of LY3039478 for Notch cleavage inhibition in the context of a whole cell. Cell lines representing malignancies of colon, pancreas, ovary, breast, skin, brain, and leukemia, including T-ALL and chronic lymphocytic leukemia (CLL), were included in this evaluation.

In order to understand the pharmacokinetic (PK)/pharmacodynamic (PD) relationship and to guide the dosing regimen for the efficacy study, key in vivo target inhibition (IVTI) studies involving dose response and time course were carried out following a single oral administration of LY3039478 in Balb/C mice. LY3039478 potently inhibits Notch cleavage and downstream Notch signaling in lung and skin of Balb/C mice in a dose-dependent manner with a threshold dose concentration of the compound required to inhibit cleavage by 50% (TED_{50}) value for N1ICD inhibition of 0.8 and 0.9 mg/kg, respectively, and threshold plasma concentration of the

compound required to inhibit cleavage by 50% (TEC_{50}) value of 6.2 and 6.6 ng/mL, respectively. LY3039478 inhibits Notch signaling as early as 4 hours in A2780 xenograft tumor.

Based on PK properties of the molecule and similar PD effect on N1ICD levels between 3 and 10 mg/kg from the dose response study, a series of schedule and dose optimization studies were conducted. Doses of 7 to 10 mg/kg administered on an intermittent schedule of every other day produced optimal efficacy while balancing on-target GI toxicity. Furthermore, coadministration of dexamethasone with LY3039478 significantly decreased body-weight loss and GI toxicity without negatively impacting anti-tumor activity of LY3039478. LY3039478 also inhibited NOTCH-1 cleavage and downstream signaling as measured by analysis of Notch-regulated gene expression within the tumor microenvironment. Furthermore, dexamethasone did not interfere with the LY3039478 mediated inhibition of Notch signaling as measured by NICD cleavage and gene expression of Notch regulated genes (HeyL, Hey1, and Hes1). These data provide a sound scientific justification for combining LY3039478 with dexamethasone in the treatment of cancer while reducing GI toxicity.

Additionally, LY3039478 inhibited Notch signaling in the tumor and produced antitumor activity in patient-derived human tumor models (EL1989 adenocarcinoma of colon, EL1986 adenocarcinoma of colon, EL1997 triple negative invasive ductal carcinoma of breast, and EL2056 glioblastoma) and cell line-derived xenograft tumors (A2780 ovarian carcinoma, U-87 MG glioblastoma, HCT-116 colon carcinoma, SW480 colon carcinoma, and K562 chronic myelogenous leukemia).

In T-ALL cell lines, LY3039478 was used to treat CUTLL1 cells (cells harboring a chromosomal rearrangement resulting in expression of a N-terminal truncated membrane bound form of NOTCH-1) and CCRF-CEM cells (cells harboring an activating mutation in heterodimerization domain of NOTCH-1 and a mutation in FBXW7, a negative regulator of NOTCH-1). LY3039478 treatment decreased activated NOTCH-1 protein levels in a dose-dependent manner with about 75% inhibition at 10 nM and about 90% N1ICD clearance at 100 nM.

Four models of patient-derived T-ALL lymphoblasts were treated in vitro with LY3039478. The results of these experiments showed a reduction of cell viability in 2 models.

5.1.4. Nonclinical Pharmacokinetics/Pharmacodynamics

Preliminary nonclinical PK of LY3039478 was characterized in mice, rats, and dogs. Oral absorption (F) was extensive and rapid (F = 65% to 67%; time of maximal plasma concentration [t_{max}] = 0.25 to 0.4 hour). Elimination half-life ($t_{1/2}$) of 2 to 6 hours was consistent with desired washout between 3 times per week (TIW) doses. LY3039478 was well distributed into tissues (volume of distribution = 1.4 to 4.9 L/kg) with preferential tumor partitioning (tumor/plasma = 3.4 to 33) and unbound brain concentrations 22- to 118-fold in excess of the Notch IC_{50}. In 1-month rat and dog toxicokinetic studies (TIW dosing), LY3039478 exposure increased in proportion to dose, with no apparent sex differences or time-dependent changes in exposure (eg, accumulation). LY3039478 was extensively cleared by urinary excretion of parent compound, and by hydrolysis of the amide bond connecting the azepine ring to the aliphatic side

chain. No drug-drug interaction (DDI) perpetrator potential was identified: LY3039478 was not an inhibitor or inducer of key cytochrome P450s (CYPs) or transporters. LY3039478 clearance mechanisms, urinary excretion of parent and amide hydrolysis, are consistent with low DDI potential.

A PK/PD model was developed to relate the LY3039478 plasma concentration to the level of in vivo NOTCH-1 cleavage (IVTI) in mouse lung, as a surrogate marker for tumor. A precursor-dependent indirect-response model with a rebound was used to describe the relationship between plasma concentrations and NOTCH-1 cleavage. The model identified a maximal inhibition of the NOTCH-1 signal of 98%, and the estimated IC_{50} was 1.8 ng/mL. The model adequately characterized the observed rebound above baseline levels in NOTCH-1 that occurred between 12 and 24 hours, with a recovery to baseline by 36 to 48 hours. A tumor-growth kinetics model was also developed based on tumor sizes in mice bearing A2780 xenografts. This model supported an understanding of the relationship between LY3039478 exposure and tumor growth delay.

5.1.5. LY3039478 Nonclinical Toxicity

LY3039478 was evaluated in nonclinical toxicology studies of up to 1 month in duration using TIW (eg, Monday, Wednesday, and Friday) oral dosing in rats and dogs to characterize the toxicity (see compound's Investigator's Brochure [IB] for more details).

Based on results from nonclinical studies, the primary target organ is the GI tract. The intestinal toxicity in rat and dog 1-month toxicology studies was characterized by fecal abnormalities and histologic changes described as a mucoid enteropathy with increases in the size and/or number of goblet cells within the mucosal epithelial enterocytes. Mucoid enteropathy is a known target mediated toxicity of Notch inhibitors (Milano et al. 2004). Although the enteropathy contributed to the mortality in rats at the highest dose, the intestinal toxicity was almost completely reversed following a 3-week reversibility period in the 1-month rat study.

In the 1-month rat toxicology study, mortality was observed on Days 20, 21, and/or 22 in 2 male and 2 female main-study rats and in 2 female toxicokinetic rats at 6 mg/kg/dose. A mucoid enteropathy of the small and large intestines characterized by increases in the size and/or number of goblet cells within the mucosal epithelial enterocytes was observed at all doses. This change was sometimes accompanied by blunting of villi, subacute/chronic inflammation, and increased mucus in the intestinal lumen. The mucoid enteropathy was considered to be adverse at ≥3 mg/kg/dose in males and females due to the increased severity (mild to moderate) at these dose levels. Decreased number of ovarian follicles were observed in all female rats (≥1 mg/kg/dose) and were considered adverse to fertility but not to the overall health of the female rat. Additional non adverse histology findings included bone growth plate thickening of the femur and sternum and single-cell necrosis of epithelia in the pancreas, exorbital lacrimal glands, and mandibular salivary glands. The mucoid enteropathy, decreased ovarian follicles, and all other toxicities were reversible or partially reversible following a 3-week recovery period in rats. The maximum tolerated dose (MTD) and highest non-severely toxic dose (HNSTD) was

considered to be 3 mg/kg/dose based on mortality observed at the high dose of 6 mg/kg. Additional details and findings from this study are presented in the compound's IB.

No mortality was observed in the 1-month dog toxicity study. Substantial decreases in body weight and food consumption occurred early in the study at 0.3 and 1 mg/kg/dose and resulted in supplemental food being offered to all dogs at these dose levels. Clinical signs were limited to fecal changes including soft, watery, mucoid, and discolored feces in dogs administered 0.3 and 1 mg/kg/dose. Fecal changes at 0.1 mg/kg/dose were less frequent and less severe than at higher doses. These changes were consistent with the dose-dependent mucoid enteropathy that was evident histologically in the small and large intestines at all doses and was considered to be adverse at ≥0.3 mg/kg/dose based on the presence of concurrent mucosal degeneration/necrosis at these mid and high doses. Generalized lymphoid depletion occurred in multiple tissues including the thymus, spleen, mesenteric lymph nodes, and/or gut-associated lymphoid tissue. Hypercellularity of the bone marrow (femur and sternum) at 1 mg/kg/dose correlated with hematology findings including increased total leukocytes, likely associated with inflammation in the large and small intestines. Increased thickness of the hypertrophy zone was also evident in cartilage of the rib and sternum at 1 mg/kg/dose, which was similar but more subtle than the finding in the rat. The MTD and HNSTD in this dog study was 1 mg/kg, the highest dose tested. Additional details and findings from this study are presented in the compound's IB.

Thrombocytopenia was identified as a DLT in a few Phase 1 patients (see Section 5.1.6) however no effects on platelets were noted in the 1-month rat or dog toxicology studies.

Based on in vitro hERG results, there is no expected risk for QT prolongation by hERG inhibition. In the 1-month dog study, no test article-related effects were observed in any of the electrocardiogram (ECG) parameters (heart rate, RR interval, PR interval, QRS duration, QT interval, and corrected QT [QTc] interval). No evidence of mutagenicity was observed in a bacterial mutagenicity (Ames) assay. In additional in vitro assays, LY3039478 was classified as a nonirritant and demonstrated no phototoxic potential.

In conclusion, nonclinical toxicology studies in rats and dogs dosed TIW for 1 month have characterized the target tissues for toxicity that may be clinically relevant. Data indicate that the intestinal tract is the primary target organ for LY3039478 toxicity. The mucoid enteropathy and all other toxicities were reversible or partially reversible following a 3-week recovery period in rats. The observed human AUC exposure at the previously tested starting dose of 2.5 mg (98.4 ng hr/mL) was 7.9-fold and 26.5-fold lower than AUC at the HNSTD in rats and dogs, respectively. Although exposure multiples are <1 at higher clinical doses, the dose-limiting enteropathy in nonclinical studies was monitorable and/or reversible.

5.1.6. Clinical Experience with LY3039478

As of April 2014, validated data from 39 patients in the first-in-human dose (FHD) Study I6F-MC-JJCA (JJCA) treated with LY3039478 in doses ranging from 2.5 mg to 60 mg are available. As of November 2014, LY3039478 doses of up to 100 mg have been explored. The MTD has been determined to be 75 mg.

Dose-limiting toxicities (DLTs) observed at dose levels of 20 mg, 30 mg, and 60 mg LY3039478 were thrombocytopenia Grade 4 in 1 patient in each dose group. Dose limiting toxicities at 100 mg included Grade 3 nausea (not manageable by medical treatment) and Grade 3 asthenia. In addition, 1 patient at 100 mg experienced Grade 2 colitis.

The most common adverse events (AEs) (>5% of patients) assessed as possibly related to study drug by the investigator included vomiting (41.0%); diarrhea (30.8%); asthenia, nausea, and hypophosphatemia (28.2%, each); decreased appetite (17.9%); hair color changes (15.4%); weight decreased (12.8%); thrombocytopenia, mucosal inflammation, alanine aminotransferase (ALT) increased, dry skin, and skin fissures (10.3% each); stomatitis and aspartate aminotransferase (AST) increased (7.7%, each); eyelash discoloration, dyspepsia, lipase increased, and dysgeusia (5.1%, each).

No Grade 5 Common Terminology Criteria for Adverse Events (CTCAE) events that were possibly related to study drug were reported. Grade 4 events possibly related to study drug included thrombocytopenia (3 patients, 7.7%) and increased lipase (1 patient, 2.6%). Grade 3 events possibly related to study drug included hypophosphatemia (5 patients, 12.8%) and colitis, asthenia, weight loss, and anorexia (1 patient each, 2.6%).

More information about the known and expected benefits, risks and reasonably anticipated AEs of LY3039478 can be found in the compound's IB. Information on AEs expected to be related to the investigational product can be found in Section 7 (Development Core Safety Information [DCSI]) of the IB. Information on serious adverse events (SAEs) expected in the study population independent of drug exposure and assessed by the sponsor in aggregate, periodically during the course of the study, can be found in Section 6 (Effects in Humans) of the IB.

5.2. Rationale for Selection of Dose/Schedule and Design Discussion

The Phase 1 (Part A) portion of Study JJCB will assess escalating doses of LY3039478 when administered TIW in combination with 24 mg of dexamethasone given on Days 1 through 5 every other week. The TIW schedule for LY3039478 was selected based on the nonclinical toxicology and PK/PD data modeling and was explored in the FHD study, Study JJCA. The dose range to be explored in JJCB showed a decrease of a-beta as a PD marker in plasma (80%) and at least 50% inhibition of Notch target genes HES1, NRARP, and CCND1 in Study JJCA. The starting dose of 50 mg is below the MTD of 75 mg defined in Study JJCA as single-agent therapy. The administration schedule and fixed dose of 24 mg of dexamethasone have been chosen based on the current standard of care treatment of T-ALL/T-LBL. It is hypothesized that the combination of LY3039478 with dexamethasone will provide an active therapy option for adult patients with relapsed/refractory T-ALL/T-LBL disease.

The Phase 1 (Part B) portion of Study JJCB will assess escalation doses of LY3039478 when administered TIW in combination with dexamethasone in pediatric patients age 2 to <16 years. The starting dose for LY3039478 will be 80% of the initial dose administered to adults provided that no DLT is observed in the initial adult cohort and follows regulatory guidance as common practice. In addition, the administered dose of LY3039478 for pediatric patients will be calculated by body surface area (BSA). LY3039478 will be administered TIW. The

dexamethasone dose will be 10 mg/m² twice per day (BID) on Days 1 through 5 every other week.

The randomized Phase 2 portion of the study will assess LY3039478 at a dose defined in Phase 1 (Part A) given TIW in combination with dexamethasone versus placebo given TIW in combination with dexamethasone. Dexamethasone will be administered at a fixed dose of 24 mg on Days 1 through 5 every other week.

Treatment with corticosteroids, such as dexamethasone, is part of the standard of care regimen for patients with ALL and LBL (Estey et al. 2008). Besides being a therapy against leukemic blasts by direct apoptotic effects and overcoming cytotoxic resistance, corticosteroids play a role in the supportive therapy of ALL. Dexamethasone can also provide protection against central nervous system (CNS) relapse of ALL. Even at relapse, most ALL patients retain sensitivity to dexamethasone. Patients with relapsed/refractory ALL progress quickly and require effective therapy, yet there is no established standard of care for relapsed T-ALL/T-LBL therapy. This study will combine dexamethasone with the active drug, LY3039478, to test efficacy. In addition, dexamethasone in combination with Notch inhibitors overcomes glucocorticoids resistance and mitigates GI toxicity.

5.3. Rationale for Amendment (a)

This study was amended at the request of the Food and Drug Administration (FDA) to clarify the criteria for DLTs (Section 9.2.2) and to change the PK sampling. In addition, CSF sampling was simplified based on new data; the CSF sampling has been reduced to one draw. PK analysis for dexamethasone during the Phase 1 portion of the study was added and one additional time point for determination of plasma concentrations of LY3039478 and dexamethasone was added during the Phase 2 portion of the study (Attachment 3).

6. Objectives

6.1. Primary Objective

The primary objective are as follows:

- Phase 1: to determine the recommended dose of LY3039478 in combination with dexamethasone in
  - adults patients with relapsed/refractory T-ALL/T-LBL (Part A)
  - pediatric patients (Part B)
- Phase 2: to determine if the overall remission rate (ORR) (CR plus CR with incomplete blood count recovery [CRi]) in adult patients with relapsed/refractory T-ALL/T-LBL treated with LY3039478 in combination with dexamethasone exceeds that of those patients treated with placebo in combination with dexamethasone

6.2. Secondary Objectives

The secondary objectives of the study are as follows:

- Phase 1:
  - to characterize the safety and toxicity profile of LY3039478 in combination with dexamethasone as assessed by National Cancer Institute (NCI) CTCAE v 4.0
  - to assess the PK parameters of LY3039478 in combination with dexamethasone therapy
  - to document efficacy based on Cheson criteria for leukemia and malignant lymphoma
  - to evaluate gene mutation (eg, NOTCH1/FBXW7/RAS/PTEN) status with efficacy
- Phase 2:
  - to compare the ORR plus partial remission (PR) and PR alone for both arms
  - to assess the remission rate for patients receiving LY3039478 in combination with dexamethasone after failure of placebo in combination with dexamethasone
  - to assess duration of remission (DoR) = (CR, CRi, and PR)
  - to assess relapse-free survival (RFS), event-free survival (EFS), and OS
  - to compare the safety and toxicity profile of LY3039478 in combination with dexamethasone to dexamethasone and placebo as assessed by NCI CTCAE v 4.0
  - to assess the PK parameters of LY3039478 and dexamethasone in combination therapy
  - to assess patient quality of life using the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu)
  - to evaluate gene mutation (eg, NOTCH-1/FBXW7/RAS/PTEN) status with efficacy

6.3. Exploratory Objectives

The exploratory objectives of the study are as follows:

- to assess clinical utility of the NICD immunohistochemistry (IHC) assay as a potential companion diagnostic for LY3039478
- to evaluate biomarkers in tumor tissue, blood, plasma and cerebrospinal fluid (CSF), which may include, but not be limited to, NICD enzyme-linked immunosorbent assay (ELISA) (or an alternative validated method), gene expression, relevant to the study disease or safety, efficacy, and mechanism of action of LY3039478 and dexamethasone
- to explore PD effects of LY3039478 on biomarkers indicative of Notch activity
- to evaluate the CSF exposure of LY3039478

7. Study Population

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened. Individuals may be re-screened up to 2 times. Each time re-screening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number. Note that repeating laboratory tests during the 28-day screening period does not constitute rescreening.

Prospective approval of protocol deviations to recruitment and enrollment criteria (also known as protocol waivers or exemptions) is not permitted.

7.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet **all** of the following criteria during screening prior to first dose of study drug.

[1] Have acute T-cell lymphoblastic leukemia (T-ALL) or T-cell lymphoblastic lymphoma (T-LBL).

T-ALL is defined by ≥25% of blasts in the bone marrow and expression of at least 2 of the following cell surface antigens:

- CD1a, CD2, CD3 (surface or cytoplasmic) CD4, CD5, CD7, and/or CD8.

If the only T-cell markers present are CD4 and CD7, the leukemia cells must also lack the myeloid markers CD33 and/or CD13.

[2] T-ALL or T-LBL patients with relapsed/refractory disease. Patients with initial refractory disease should have received at least 2 multi-agent chemotherapy induction regimens. Patients in first or second relapse must have been refractory to at least 1 multi-agent chemotherapy reinduction regimen.

[3] Have had at least 60 days between prior hematopoietic SCT and first dose of study drug.

[4] Have a performance status of 0 to 2 on the Eastern Cooperative Oncology Group (ECOG) scale (see Attachment 5) for adults.

[5] Lansky score >50% for patients <16 years old.

[6] Have adequate organ function:

- hepatic: bilirubin ≤1.5 × the upper limit of normal (ULN) and ALT and AST ≤3 × ULN. For patients with liver involvement, ALT and AST ≤5 × ULN
- renal: calculated creatinine clearance ≥45 mL/min or a serum creatinine based on age/gender (Attachment 6)

[7] Are at least:

- Adult Phase 1 Part A and Phase 2: ≥16 years old at the time of screening.
- Pediatric Phase 1 Part B: 2 to <16 years old.

[8a] *Men and women with reproductive potential:* Must agree to use a reliable method of birth control during the study and for 3 months following the last dose of study drug(s) or country requirements, whichever is longer.

[8b] *Females with childbearing potential:* Have had a negative serum pregnancy test ≤7 days before the first dose of study drug and also must not be breastfeeding.

[9] Have an estimated life expectancy of at least 2 months and in the judgment of the investigator, will be able to complete at least 2 cycles of treatment.

[10] Have given written informed consent/assent prior to any study-specific procedures.

All patients and/or their parents or legally authorized representatives must sign a written ICF. Assent, when appropriate, will be obtained according to institutional guidelines.

[11] Are able to swallow capsules and tablets.

7.2. Exclusion Criteria

Potential study patients may not be included in the study if **any** of the following apply during screening.

[12] Are currently enrolled in a clinical trial involving an investigational product or nonapproved use of a drug or device (other than the study drug/device used in this study), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

[13] Have discontinued prior anticancer therapy less than 2 weeks prior to starting therapy or 5 half-lives (whichever is longer) with the following exceptions:

- glucocorticoids administered as antileukemic treatment should be discontinued at least 5 days prior to starting therapy
- mercaptopurine may be dosed up to 5 days prior to first dose of LY3039478
- Vinca alkaloids may be dosed up to 7 days prior to first dose of LY3039478
- intrathecal chemotherapy may be dosed up to 7 days prior to first dose of LY3039478

- At the discretion of the investigator, hormone-sensitive prostate cancer patients who are in remission and stable on gonadotropin-releasing hormone (GnRH) agonist therapy and breast cancer patients who are stable on antiestrogen therapy (for example, an aromatase inhibitor) may have that treatment continued while they are enrolled in this study.

[14] Have previously completed or withdrawn from this study or any other study investigating LY3039478 or other Notch inhibitors. (This exclusion criterion does not apply to patients who are re-screened prior to enrollment/randomization.)

[15] Have a serious concomitant systemic disorder that, in the opinion of the investigator, would compromise the patient's ability to adhere to the protocol.

[16] Have evidence of uncontrolled, active infection <7 days prior to administration of study medication.

[17] Have current or recent (within 3 months of study drug administration) GI disease with chronic or intermittent diarrhea, or disorders that increase the risk of diarrhea, such as inflammatory bowel disease. Nonchronic conditions (eg, infectious diarrhea) that are completely resolved for at least 1 week prior to starting study treatment are not exclusionary.

[18] Have conditions requiring chronic systemic (not inhaled) glucocorticoid use, such as autoimmune disease or severe asthma. Low doses of corticosteroids are permitted.

[19] Have active (symptomatic or requiring current medical treatment) graft versus host disease.

[20] Have active leukemic involvement of the CNS as shown by spinal fluid cytology or imaging. A lumbar puncture is not required unless CNS involvement is clinically suspected. Patients with signs or symptoms of leukemic meningitis or a history of leukemic meningitis must have a blast-free cerebrospinal fluid within 14 days of the first day of study treatment.

[21] Have a second primary malignancy or prior malignancy that, in the judgment of the investigator and following consultation with Lilly, may affect the interpretation of results. Patients with carcinoma in situ of any origin and patients with prior malignancies who are in remission and whose likelihood of recurrence is very low, as judged by the Lilly clinical research physician (CRP), are eligible for this study. The Lilly CRP will approve enrollment of patients with prior malignancies in remission before these patients are enrolled.

7.3. Discontinuations

7.3.1. Discontinuation of Patients

The criteria for enrollment must be followed explicitly. If a patient who did not meet enrollment criteria and was inadvertently enrolled is identified, either by the Sponsor or investigator, a discussion must occur between the Lilly CRP and the investigator to determine if the patient may continue in the study. The investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without treatment with study drug. In addition, patients will be discontinued from the study drug in the following circumstances:

- enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- investigator decision
  - the investigator decides that the patient should be discontinued from the study or study drugs
  - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study drug occurs prior to introduction of the new agent
- patient decision
  - the patient or the patient's designee (for example, parents or legal guardian) requests to be withdrawn from the study or study drug(s)
- sponsor decision
  - Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice
- the patient is significantly noncompliant with study procedures and/or treatment
- unacceptable toxicity
- treatment failure in T-LBL or PD in T-ALL patients as described in Sections 10.1.3.1 and 10.1.3.2.

The reason for and date of discontinuation will be collected for all patients. All patients who received study drug will have procedures performed as shown in the Study Schedule (Attachment 1).

7.3.2. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ethical review board (ERB) of the study site judges it necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).

7.3.3. Discontinuation of the Study

The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

8. Investigational Plan

8.1. Summary of Study Design

Study JJCB is a multicenter study consisting of a nonrandomized, open-label, dose-escalation Phase 1 study followed by a randomized, double-blind, Phase 2 study in patients with relapsed or refractory T-ALL/T-LBL. The Phase 1 portion of the study will consist of 2 different patient populations, an adult (Part A) and a pediatric (Part B), and will define the recommended dose of LY3039478 in combination with dexamethasone in each of these populations. The randomized Phase 2 study will be a double-blinded, multicenter evaluation to determine if the CR and CRi (CR with incomplete blood count recovery) rate in adult patients with relapsed/refractory T-ALL/T-LBL treated with LY3039478 in combination with dexamethasone exceeds that of those patients treated with placebo in combination with dexamethasone. Figure JJCB.8.1 illustrates the study design.

Eligible adult patients will receive LY3039478 administered orally TIW and dexamethasone administered 24 mg orally Days 1 to 5 every other week. In Part B (pediatric patients), dexamethasone is administered at 10 mg/m^2 BID, orally, Days 1 through 5 every other week. A cycle is defined as 28 days of treatment (4 weeks).

The Phase 1 portion will start with the adult cohort (Part A). The decision to proceed with the pediatric dose exploration (Part B) will be made after safety analysis of the adult cohort.

The dose escalation, described in Section 9.2.1, will be guided primarily by safety assessments from Days 1 through 28 of Cycle 1 for patients in all cohorts. Dose escalation will occur until the MTD (defined in Section 9.2.2) is determined. Patients will be enrolled in Part A with the first dose level of 50 mg LY3039478, TIW. Table JJCB.9.2 outlines the proposed dose-escalation scheme. Dose levels will be determined based on the review of the safety, PK, and PD data from the previous doses. Additional dose levels (to a maximum of 200 mg TIW) may be explored if necessary. No dose escalation will occur beyond MTD. In Parts A and B, the sample size is estimated to be approximately 13 to 16 patients in each part depending on the relationship between exposure and toxicity as well as the relationship between exposure and pharmacological effects.

After the last patient on Part A has completed Cycle 1 and the recommended dose for the Phase 2 portion is determined, the randomized, Phase 2 portion will begin following an interim review of the data as outlined in Section 12.2.14. The patient population in the Phase 2 portion of the study will be identical to the patient population assessed in Part A.

In the Phase 2 portion, 60 patients will be randomized in a 2:1 ratio to receive either LY3039478 in combination with dexamethasone administered 24 mg orally on Days 1 to 5 every other week or placebo in combination with dexamethasone administered 24 mg orally on Days 1 to 5 every other week. Placebo or LY3039478 will be administered orally TIW at the recommended dose from Part A. Patients will receive treatment until progression or meeting discontinuation criteria (Section 7.3).

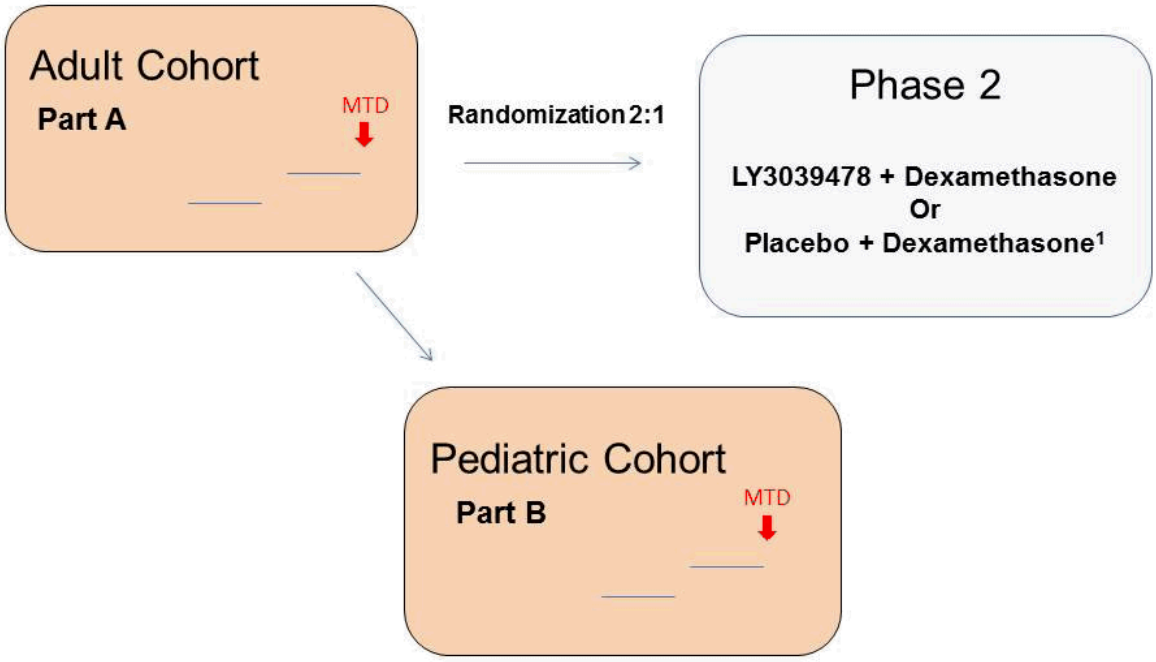
Patients discontinuing the study for treatment failure as defined in Section 7.3.1 will be unblinded after discontinuation. A crossover to LY3039478 in combination with dexamethasone will be allowed for patients who were receiving placebo in combination with dexamethasone.

A futility interim analysis will be performed in the Phase 2 portion of the study when 30 patients have completed the CR status determination. The analysis will assess the safety profile, verify that the chosen regimen is clinically feasible, and determine if the futility criteria have been met. See Section 12.2.14 for additional information on this futility interim analysis.

An internal assessment committee consisting of (at minimum) a Lilly Medical Director, a Lilly CRP not associated with the study, a PK scientist, and a statistician will examine the interim results and make recommendations about the trial.

The total sample size for this study is estimated to be approximately 86 to 92 patients.

There is no fixed duration of treatment; patients will remain on study until they fulfill 1 of the criteria for study discontinuation (Section 7.3). Refer to Attachment 1 for the Study Schedule.



[1] Phase 2 patients who discontinue the study due to relapse/refractory disease or treatment failure may crossover to treatment with LY3039478 + Dexamethasone.

Abbreviation: MTD = maximum tolerated dose.

Figure JJCB.8.1. Illustration of study design.

8.2. Discussion of Design and Control

A randomized, controlled design is being used in the Phase 2 portion of the study. Randomization minimizes systematic bias in the selection and assignment of patients to study therapy and provides justification for inferential statistical methods to be used on data from this study. Using an appropriate concurrent control arm enables direct statistical estimation of benefits and harms due to study therapy and minimizes bias in the assessment and interpretation of observed treatment effects. To further reduce the potential for bias and improve the power of the analyses, patients will be stratified for differences in factors thought to be associated with clinical outcomes.

Investigational treatment administration in this study is double-blind. Patients, study personnel at investigational sites, and study personnel at Lilly do not have immediate access to treatment assignments for any patients. This design feature minimizes potential bias due to knowledge of treatment assignments during the study.

8.3. Study Periods, Study Completion, and End of Trial

Terms used to describe the periods during the study are defined below:

- **baseline:** begins when the ICF is signed and ends at the first study treatment (or at discontinuation, if no treatment is given)
- **study period:** begins at the first study treatment and ends at study completion. The study period does not include the continued access period.
    - **study treatment period:** begins at the first study treatment and ends when the patient and the investigator agree that the patient will no longer continue study treatment. The date of this agreement is to be reported on the case report form (CRF) as the Date of Discontinuation from study treatment..
    - **postdiscontinuation follow-up period:** begins the day after the patient and the investigator agree that the patient will no longer continue study treatment.
        - ***short-term follow-up:*** begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days.
        - ***long-term follow-up:*** begins the day after short-term follow-up is completed and continues until the patient's death or overall study completion.
- **continued access period:** begins after study completion and ends at the end of trial. During the continued access period, patients on study therapy who continue to experience clinical benefit may continue to receive study therapy until 1 of the criteria for discontinuation is met. The continued access period includes continued access follow-up.
    - **continued access follow-up:** begins 1 day after the patient and the investigator agree that the patient will no longer continue treatment in the extension period and lasts approximately 30 ± 6 days
- **study completion:** begins following the final analysis/evaluation of OS, as determined by Lilly. Investigators will continue to follow the Study Schedule for all patients until notified by Lilly that study completion has occurred.
- **end of trial:** occurs after study completion and after the last patient has discontinued study treatment and completed continued access period follow-up (if applicable).

Upon determination of treatment failure or study completion, investigators and patients may be unblinded to study treatment assignment. Patients with relapsed or refractory disease who were receiving placebo in combination with dexamethasone may crossover to LY3039478 in combination with dexamethasone and follow the "study period" treatment schedule.

8.3.1. Continued Access Period

The continued access period will apply to this study only if at least 1 patient is still on LY3039478 when study completion occurs.

Patients receiving LY3039478 and experiencing ongoing clinical benefit and no undue risks may continue to receive LY3039478 in the continued access period until 1 of the criteria for

discontinuation is met (Section 7.3). Lilly will notify investigators when the continued access period begins.

Patients who are in short-term follow-up when the continued access period begins will continue in short term follow-up until the [30-day] short-term follow-up visit is completed. Long-term follow-up does not apply.

Patients who are in long term follow-up when the continued access period begins will be discontinued from long-term follow-up.

During the continued access period, all AEs, SAEs, and LY3039478 exposure will be reported on the CRF. Serious adverse events will also be reported to Lilly Global Patient Safety (see Section 10.3.1). In the event that an SAE occurs, Lilly may request additional information (such as local laboratory results, concomitant medications, and hospitalizations) in order to evaluate the reported SAE.

Investigators will perform any other standard procedures and tests needed to treat and evaluate patients; however, the choice and timing of the tests will be at the investigator's discretion. Lilly will not routinely collect the results of these assessments.

9. Treatment

9.1. Materials and Supplies

All clinical trial materials will be labeled according to the country's regulatory requirements.

LY3039478 will be supplied as 25- and 50-mg capsules in bottles for oral consumption for adult patients and 10-mg capsules in bottles for oral consumption for pediatric patients. LY3039478 capsules should be stored at room temperature within the temperature range stated on the label. Investigators should instruct patients or parents to store the capsules at home in the original container and to keep out of the reach of children. Capsules should not be opened, crushed, or dissolved.

Placebo will be supplied as capsules in bottles (consisting of inactive ingredients) for oral administration. Packaging, storage information, and instructions will match LY3039478.

Dexamethasone will be supplied as an oral tablet in several potencies including a 4-, 6-, or 8-mg dose size or as an oral solution in several potencies including 0.5 mg per 5 mL or 2 mg per 5 mL for pediatric patients. It should be used and stored in accordance with the package insert or as indicated on the label.

9.2. Treatments Administered

The following treatments will be administered in this study:

Phase 1:

Part A – Adults:

- LY3039478 dosed according to the dose-escalation scheme, oral TIW, Table JJCB.9.2
- dexamethasone: 24 mg, oral, Days 1 through 5 every other week

Part B – Pediatric:

- The starting dose of LY3039478 will be determined by the adult portion of the study and will be 80% of the dose administered to adults and calculated on a BSA, oral TIW, dose escalation following similar scheme for adults (Table JJCB.9.2). Doses calculated based on BSA will be rounded to the nearest 10-mg capsule.
- dexamethasone: 10 mg/m^2 BID, oral, Days 1 through 5 every other week

Phase 2:

- LY3039478 or placebo: at or below the MTD defined from Phase 1, Part A, oral TIW
- dexamethasone: 24 mg, oral, Days 1 through 5 every other week

Table JJCB.9.1 shows the treatment regimens.

Table JJCB.9.1. Treatment Regimens/Dosing Schedule

	Regimen	Period/Cycle	Dose
Phase 1 Part A	LY3039478	Treatment/28-day cycle	Escalating doses TIW PO (see Table 9.2)
	Dexamethasone	Treatment/28-day cycle	24 mg Days 1-5 PO every other week
Phase 1 Part B	LY3039478	Treatment/28-day cycle	Escalating doses (mg/m^2) TIW PO (80% dose from Part A)
	Dexamethasone	Treatment/28-day cycle	10 mg/m^2 BID Days 1-5 PO every other week
Phase 2	LY3039478 or Placebo	Treatment/28-day cycle	At or below MTD dose TIW PO
	Dexamethasone	Treatment/28-day cycle	24 mg Days 1-5 PO every other week

Abbreviations: BID = twice per day; PO = orally; TIW = 3 times per week.

LY3039478 or placebo will be administered orally TIW during both the dose-escalation phase and the Phase 2 following 1 of these schedules (decision at investigator's discretion):

- Monday, Wednesday, and Friday every week, for a 28-day cycle
- Tuesday, Thursday, and Saturday every week, for a 28-day cycle
- Wednesday, Friday, and Sunday every week, for a 28-day cycle
- Thursday, Saturday, and Monday every week, for a 28-day cycle

LY3039478 or placebo will be taken once per day on days of administration prior to a meal (recommendation is within 30 minutes) on an empty stomach. During all cycles, study drug should be taken at approximately the same time on the dosing days. If a patient misses or vomits a dose, that dose should be omitted.

Dexamethasone will be taken approximately 30 minutes after LY3039478 or placebo and together with a meal. Pediatric patients (Part B) will take dexamethasone BID approximately 12 hours apart.

The patient, caregiver, or clinic personnel will record time and amount of each dose in the patient diary on days of PK assessment (Attachment 3) during Cycle 1 and Cycle 2, and study monitors will cross-reference clinic records at the site to verify accuracy. For cycles 3 and beyond first and last dose date and amount of both drugs for each individual cycle will be documented. Clinic personnel will instruct patients to pay particularly close attention to record this information accurately.

For Cycle 2 and beyond, a delay of $\leq$7 days in the start of a cycle (Dose 1) for justifiable reasons (for example, inclement weather, holidays, or weekends) other than toxicity will be permitted and does not constitute a protocol violation.

For Cycle 2 and beyond, a delay of ≤21 days in the start of a cycle (Dose 1) to allow for recovery from toxicity will be permitted and does not constitute a protocol violation (refer to Section 9.4.2).

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the drugs and planned duration of each individual's treatment to the patient/site personnel/legal representative
- verifying that instructions are followed properly
- maintaining accurate records of study drug dispensing and collection
- returning all unused medication to Lilly or its designee at the end of the study

In some cases, sites may destroy the material if, during the investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose clinical trial materials.

Patients will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study drug so that the situation can be assessed.

9.2.1. Dose-Escalation Phase

Dose escalation will be driven by safety using a modified 3+3 scheme, with incorporation of model-based dose escalation (Neuenschwander et al. 2008) to assist in estimation of DLT rate at recommended dose level.

A model-based method that incorporates prior expectations about the dose-toxicity curve and controls for over-dosing probability will be applied to the data at the end of each cohort, which will provide quantitative guidance to the investigators and Lilly CRP to help determine the next dose level. Prior expectations about the dose-toxicity curve will be based on observed DLT rates in Study JJCA. After incorporation of observed DLT rates in this study, the posterior probability of a DLT at each dose level will be categorized to 4 bands:

- under-dosing: the probability of a DLT at a given dose level in (0, 0.20)
- targeted toxicity: the probability of a DLT at a given dose level in (0.20, 0.35)
- excessive toxicity: the probability of a DLT at a given dose level in (0.35, 0.60)
- unacceptable toxicity: the probability of a DLT at a given dose level in (0.60, 1.00)

The model aims to recommend a dose which maximizes the probability of targeted toxicity, while controlling the probability of excessive or unacceptable toxicity to less than 25%. The maximum increment of escalation will be no more than 100%. The exact increment will be determined by the investigators and Lilly CRP and may be less than the model prediction or <100%.

Each dose level will have a minimum of 3 patients enrolled concurrently to it. If 1 patient experiences a DLT, then additional patients can be enrolled to that cohort provided the observed DLT rate dose does not exceed 33%.

Additional patients may be enrolled at a specific dose level to characterize PK/PD, provide that dose level does not exceed the MTD

In case more than 3 patients have been consented concurrently, the additional patients may be treated. The decision about which dose level the patient will be treated at will be made after discussion between the CRP/study team and the investigators. The decision will be documented.

Once the MTD has been identified, a discussion between the sponsor and investigators may occur in order to treat additional patients at intermediate doses below the MTD.

Safety data, in particular AEs, will be the primary criteria to allow for the dose escalation. The dose will be escalated following assessment of toxicity using the standard scoring system, CTCAE v 4.0, established by the NCI. Any AEs related to LY3039478 and/or dexamethasone will be considered as toxicities.

If available at the time of the dose-escalation decision, PK (eg, maximum observed concentration [C_{max}], AUC, and apparent systemic clearance) and PD results will be used as secondary/supporting data for dose escalation. No dose escalation can occur without prior discussion and agreement between the investigator and the Lilly CRP. The decision will be documented in writing. Intrapatient dose escalations are not permitted.

Based on the ongoing safety reviews, modifications to the dose-escalation strategy or other design elements may be made via protocol amendment to ensure patient safety.

Table JJCB.9.2 shows the proposed dose levels for LY3039478 in combination with dexamethasone for the adult cohort. The starting dose level of 50 mg of LY3039478 was defined from Study JJCA and data will be evaluated on an ongoing basis until the MTD is determined. If the starting dose exceeds the MTD, a LY3039478 dose level (-1) may be explored. It should be noted that although an example escalation table is shown in Table JJCB.9.2, alternate doses may be selected. Intermediate dose levels will be explored if deemed necessary after discussion between the sponsor and investigators and taking into account patient safety and PK/PD information.

Table JJCB.9.2. Proposed LY3039478 Dose-Escalation Scheme for the Adult Cohort

Dose Level	LY3039478 Dose (mg)	Dexamethasone Dose (mg)
-1[a]	25	24
1	50	24
2	75	24

[a] Dose level -1 to be used only in the event of dose-limiting toxicities experienced in dose level 1 necessitating a dose de-escalation.

The starting dose for pediatric cohort will be defined upon safety assessment of adult cohort. The starting dose will be 80% of total adult dose. Pediatric patients will be dosed based on BSA. Dose escalation will follow similar scheme to adult cohort.

By nature of being a dose-escalation study, data will be evaluated on an ongoing basis until the MTD is determined, as defined below.

9.2.2. Dose-Limiting Toxicity Determination and Maximum Tolerated Dose Definition

Disease-related myelosuppression is typical in the setting of T-ALL/T-LBL. Therefore, myelosuppression will not be included in the definition of a DLT, unless it fits the criteria outlined below.

A DLT is an AE observed during the first 28-day cycle (when patients receive LY3039478 and dexamethasone) that is determined by the investigator to be at least possibly related to LY3039478 according to CTCAE v 4.0 and fulfills any of the following criteria:

- ≥CTCAE Grade 3 nonhematological toxicity. Exceptions will be made for:
    - Grade 3 nausea, vomiting, or constipation that lasts less than 72 hours and that can be controlled with treatment
    - Grade 3 electrolyte disturbance that can be controlled with treatment and persists less than 5 days
    - Grade 3 hyperglycemia or Grade 4 hyperglycemia without ketoacidosis during and after the end of dexamethasone treatment unless it is not controlled by oral medication or insulin before the start of the next dexamethasone round
    - Grade 3 arterial hypertension during and after the end of dexamethasone treatment unless it is not controlled by oral medication before the start of the next dexamethasone round
    - tumor lysis syndrome (TLS): patients who demonstrate a clinical syndrome consistent with TLS and have transient (<7 days) and manageable Grade 3 abnormalities in serum electrolytes, renal function and/or chemistries (ie, uric acid, potassium, phosphorus, calcium, creatinine, blood urea nitrogen, etc.)
    - Grade 3 diarrhea for <5 days and unless it cannot 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 (eg, worsening biliary obstruction) if agreed by the study investigator and Lilly CRP
- any other significant toxicity deemed by the primary investigator and Lilly clinical research personnel to be dose limiting (eg, any toxicity that is possibly related to the study medication that requires the withdrawal of the patient from the study during Cycle 1)

A dose-limiting equivalent toxicity (DLET) is defined as an AE occurring between Day 1 and Day 28 of any cycle (other than Cycle 1) for a patient enrolled in the Phase 1 portion or in any cycle (including Cycle 1) for a patient enrolled in the Phase 2 portion that would have met the criteria for DLT if it had occurred during Cycle 1 for a patient enrolled in the Phase 1 portion.

MTD is defined as the highest explored dose level for which the probability of DLT does not exceed 33%. For the recommended Phase 2 dose, the rate and nature of AEs observed beyond the first cycle of treatment will be considered.

9.3. Method of Assignment to Treatment

9.3.1. Phase 1

Patients who enter the study during the Phase 1 portion will be assigned to receive LY3039478 and dexamethasone. Prior to enrollment into the study, an eligibility check must be conducted (for every patient) between the investigational site and the Lilly clinical research personnel, to confirm that the patient meets all enrollment criteria. Upon confirmation of eligibility, the sponsor will confirm the dose, cohort, and identification number assignment for each patient. No dose escalations (ie, to the next cohort) can occur without prior discussion and agreement with the responsible Lilly CRP.

9.3.2. Phase 2

Patients who enter the study during the Phase 2 portion will be randomized to receive either LY3039478 in combination with dexamethasone or placebo in combination with dexamethasone. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS).

A dynamic allocation method, introduced by Pocock and Simon (1975) and extended for unequal treatment group sizes by Han et al. (2009), will be adopted to balance patient assignment between treatment arms, using a probability factor of 0.9, based on the following factors:

- age ≤30 years versus >30 years
- T-ALL phenotype versus T-LBL, considered as 6 factors, representing the following 5 phenotypes of T-ALL:

TdT+, variable for all of the following: CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD34

  - Pro-T-ALL: cCD3+, CD7+, CD1a-, CD2-, CD4-, CD8-, CD34+/-
  - Pre-T-ALL: cCD3+, CD7+, CD1a-, CD2+, CD4-, CD8-, CD34+/-
  - Cortical T-ALL: cCD3+, CD7+, CD1a+, CD2+, CD4+, CD8+, CD34-
  - Medullary T-ALL: cCD3+, sCD3+, CD7+, CD1a-, CD2+, CD4+or CD8+, CD34-
  - ETP T-ALL: Lack of CD1a and CD8 expression, weak CD5 expression with less than 75% positive blasts, and expression of 1 or more of the following myeloid or stem cell markers on at least 25% of lymphoblasts: CD117, CD34, HLA-DR, CD13, CD33, CD11b, and/or CD65
- response to last therapy: refractory/relapse within 1 year of last therapy vs. >1 year

The randomization parameter P will be set to 0.9 to maximize the benefit of the allocation procedure, whilst keeping treatment assignments unpredictable.

The IWRS will be used to assign bottles containing double-blind study drug to each patient. Site personnel will confirm that they have located the correct bottles by entering a confirmation number found on the bottles into the IWRS.

9.4. Dose Adjustments and Delays

9.4.1. Dose Adjustments for LY3039478 within a Cycle

No dose adjustments of LY3039478 or placebo will be allowed within a cycle. If a patient treated at a given dose level experiences a DLT or a DLET (as defined in Section 9.2.2), then treatment will be suspended for that patient for the duration of the current cycle. If a toxicity does not meet the criteria for a DLT in Cycle 1 of Phase 1 (or a DLET in Cycle 2 and beyond in Phase 1 or any cycle in Phase 2) but nonetheless requires omission of dose(s) for tolerability, then dosing may resume at the same dose after the toxicity resolves to baseline; however, the dose(s) omitted for tolerability during a cycle will not be replaced.

9.4.2. Dose Adjustments for LY3039478 between Cycles

Before the start of each cycle, nonhematological toxicities (except alopecia and fatigue) must resolve to baseline. The start of LY3039478 may be delayed up to 21 days to allow sufficient time for recovery. Patients experiencing non-transient Grade 4 nonhematological toxicity or not recovering from toxicity within 21 days should be discontinued from the study.

The dose of LY3039478 should be reduced to the dose level administered in the previous cohort for all subsequent cycles of therapy if the investigator determines that it is in the best interest of the patient or if the patient experienced at least 1 of the following events:

- DLT (in Cycle 1 for patients in Phase 1)
- DLET (in Cycle 2 or beyond for patients in Phase 1, or in any cycle for patients in Phase 2)
- omission of more than 7 doses of LY3039478 in a single cycle for tolerability

For patients requiring a dose reduction, re-escalation to the original dose level is not permitted.

A second dose reduction is allowed only for patients treated at adult dose level ≥75 mg or pediatric equivalent (dose may be reduced to 25 mg or pediatric equivalent). Dose reduction by more than 2 dose levels is not permitted; patients requiring dose reduction by more than 2 dose levels should be discontinued from the study.

If a patient experiences a DLET at the second reduced dose level, then the patient will be discontinued from the study. If a patient requires omission of more than 3 doses for tolerability at the reduced dose levels, then treatment may continue if the investigator determines that the patient is receiving clinical benefit.

In the Phase 2 portion of the study, investigators will treat all patients as if the patient is receiving active study drug, LY3039478, and will adjust doses accordingly.

9.4.3. Dose Adjustments – Dexamethasone

Dose adjustments for dexamethasone will be performed in case of toxicities that can't be controlled with appropriate treatment.

Toxicities and dose adjustments should be managed following available or institutional guidelines.

9.5. Blinding

The Phase 1b portion of this study is open-label whereas the Phase 2 portion of this study is double-blind.

To preserve the blinding of the study, a minimum number of sponsor personnel will see the treatment assignments before the study is complete.

Upon determination of relapsed/refractory disease or study completion, investigators and patients may be unblinded to study treatment assignment.

Phase 2 patients who discontinue the study due to relapse/refractory disease or treatment failure (Section 7.3.1) may be unblinded and cross over to treatment with LY3039478 in combination with dexamethasone if they had been randomized to receive placebo in combination with dexamethasone initially.

For this study, the following roles will be permitted to access unblinded data: all members of the assessment committee, plus unblinded statisticians and analysts, data scientists and PK/PD scientist. Access to unblinded data/documents will be controlled by restricting access to the data/documents in Lilly's data and statistical warehouse. Any changes to this unblinding plan may be described in a protocol amendment, the Statistical Analysis Plan (SAP), and/or a separate unblinding plan document. Interim analyses for safety, futility will be conducted, using unblinded data, under the guidance of an assessment committee. See Section 12.2.14 for further details.

9.5.1. Emergency Unblinding

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly CRP prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, Lilly must be notified immediately.

9.5.2. Inadvertent Unblinding

Every effort will be made to blind both the patient and the investigator to the identity of the treatment, but the inadvertent unblinding of a patient may occur. A double-blind study design is known to be imperfect in the oncolytic setting because the potential for individual unblinding exists due to treatment-related signs and symptoms. If an investigator, site personnel performing assessments, or patient is unblinded, the unblinding will not be sufficient cause (in and of itself)

for that patient to be discontinued from study therapy or excluded from any safety or efficacy analyses.

Additionally, there may be ethical reasons to have the patient remain on the study treatment. For patients to continue on study treatment in the event of unblinding, the investigator must obtain specific approval from a Lilly CRP for the patient to continue in the study.

9.6. Concomitant Therapy

Appropriate documentation of all forms of premedications, supportive care, and concomitant medications must be captured at each visit in the CRF. Concomitant medications and supportive care therapies must also be documented at the time of discontinuation and at the 30-day short-term follow-up visit.

No other chemotherapy, other anticancer therapy, immunotherapy, hormonal cancer therapy (except therapy of hormone-sensitive prostate cancer patients who are stable on GnRH agonist therapy and breast cancer patients who are stable on antiestrogen therapy [eg, an aromatase inhibitor]), radiation, surgery for cancer, or experimental medications, including herbal supplements intended to treat the cancer, will be permitted while patients are on study treatment. The need for any form of radiotherapy (including palliative) will be cause for early discontinuation from the study. In addition, any disease relapse requiring other forms of specific antitumor therapy will also necessitate early discontinuation from the study.

Prophylactic intrathecal therapy is allowed for patients with high risk of CNS disease as long as spinal fluid is negative for blasts and no other evidence of active CNS disease.

Patients should receive full supportive care, if necessary. Supportive care is given with the intent to maximize quality of life. Those therapies considered acceptable include, but are not limited to control of infections, treatment of TLS, management of aspariginase toxicity, management of steroid side effects, use of transfusions, use of granulocyte colony-stimulating factor (G-CSF), use of antiemetics, nutritional support, and treatment of pain. Patients will receive supportive care as judged by their treating physician. If it is unclear whether a therapy should be regarded as supportive care, the investigator should consult the Lilly CRP. The use of any supportive care therapy should be reported on the CRFs.

The protocol does not permit the routine use of colony-stimulating factors or erythropoiesis-stimulating agents (ESAs) during treatment. The protocol does not allow the use of products that stimulate thrombopoiesis. Erythropoietic therapy may be considered for treatment of chemotherapy-induced anemia for patients with hemoglobin <10 g/dL after the patients has been counseled about the risks and benefits of ESA use (Smith et al. 2006; Rizzo et al. 2008).

Because recommendations on the use of ESAs are rapidly evolving, investigators should frequently refer to the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology, American Society of Hematology, and/or Centers for Medicare and Medicaid Services websites for the latest guidelines or follow local guidelines.

In the event of diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals, including opioids.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe (Grade 3 or 4) neutropenia, broad-spectrum antibiotics must be prescribed taking into account the local prevalence of infection agents and their probable resistance. Patients with severe diarrhea or any diarrhea associated with severe nausea and vomiting **should be hospitalized** for supportive care including antiemetics, intravenous hydration and correction of electrolyte imbalances. Events that require a patient to be hospitalized are considered SAEs (see Section 10.3.1.1).

Patients experiencing febrile neutropenia, especially with diarrhea or dyspnea, should be managed in a hospital setting according to standard procedures, with the urgent initiation of intravenous antibiotic therapy.

The use of allopurinol should be considered as an adjunct to appropriate use of hydration in prophylaxis of TLS. Evaluation of hydration status and changes in kidney function, serum electrolytes, and uric acid levels may assist in both prophylaxis for and management of acute renal function changes and TLS. When there is concern about the level of disease burden and effects of potential rapid cytoreduction, or if the patient has high baseline uric acid levels, prophylaxis for TLS with allopurinol or another therapeutic substitute may be considered. When used for prophylaxis, allopurinol should be administered orally once daily starting at a minimum the day before the first study drug dose. Allopurinol may be discontinued or dose adjusted during study treatment at the investigator's discretion, for example, based on renal function. If allopurinol is contraindicated, investigators may consider the use of an appropriate therapeutic substitute.

9.7. Treatment Compliance

Patient compliance with study medication will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned capsules. Furthermore, the patient or caregiver will have to complete a diary for Cycles 1 and 2 at time points related to the PK sample schedule as described in Attachment 3. In addition, any Day 1 dosing date in Cycles >2 have to be documented.

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. Any missed doses during a cycle will be omitted and not replaced. In the event of a missed dose, a patient should resume and continue dosing, beginning with the next scheduled dose.

Potential discontinuation of a patient due to study drug noncompliance will be discussed between the investigator and the Lilly CRP before the final determination is made to discontinue the patient. If a patient is discontinued due to study drug noncompliance, the patient may be replaced.

9.7.1. Evaluable Patients Phase 1 Parts A and B

Patients who withdraw from the study before receiving study drug(s) will be replaced and will not be included in the safety or efficacy assessments. Safety analyses will be conducted on all patients who have received at least 1 dose of any study drug, regardless of whether they are deemed evaluable for the assessment of a dose level.

Patients who are not evaluable for PK, but who complete 1 cycle of therapy, may be replaced upon consultation with the investigator(s) and the Lilly CRP to ensure adequate PK data, unless accrual to that cohort has stopped due to a DLT. Patients who are evaluable for PK are defined as patients who have a sufficient number of PK samples to evaluate PK parameters after at least 1 dose of LY3039478.

Patients who are discontinued from the study before completing Cycle 1 will be deemed nonevaluable for assessment of a dose level, unless they experience a DLT prior to withdrawal.

If patients are noncompliant during Cycle 1 due to reasons other than drug-related toxicity, they will be considered nonevaluable.

Nonevaluable patients will be replaced to ensure that 3 patients complete 1 cycle of therapy at each dose level, unless accrual to that cohort has stopped due to a DLT.

9.7.2. Evaluable Patients Phase 2

In the Phase 2 portion of the study, patients will be considered evaluable after randomization as per definition of the intent-to-treat analysis set (Section 12.2.1).

10. Efficacy, Health Outcome/Quality of Life Measures, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Written informed consent must be obtained prior to any study-specific pretreatment evaluations.

Study procedures related to efficacy, safety, health outcome/quality of life measures, sample collection and testing assessments and their timing are described in the sections below and shown in the Study Schedule (Attachment 1).

10.1. Efficacy Measures

10.1.1. Study Assessments

10.1.1.1. Pretreatment (Baseline)

For T-ALL patients, a bone marrow biopsy and/or aspirate will be obtained to locally assess bone marrow cellularity and to determine the percentage of leukemic blasts within 2 weeks and no less than 1 day before the first dose of study drugs. The results of this bone marrow biopsy and/or aspirate will serve as the baseline assessment for efficacy; therefore, the results will not be required to be received before study drug administration. In addition, a computed tomography (CT) or magnetic resonance imaging (MRI) of the thorax and abdomen (including the pelvis) will be performed within 4 weeks and no less than 1 day before the first dose of study drug.

For T-LBL patients, baseline tumor measurements will be performed within 4 weeks and no less than 1 day before the first dose of study drugs. Positron emission tomography-computed tomography (PET-CT) is the preferred method of measurement for FDG-avid lymphomas. A CT, including spiral CT, or MRI of the thorax and abdomen is indicated for non-avid histologies.

For all patients with suspected CNS involvement, a lumbar puncture will be performed within 14 days before the first dose of study drugs. For patients with neurological signs or symptoms at diagnosis, a CT/MRI of the brain and/or affected spinal cord is required within 4 weeks before the first dose of study drugs.

For patients continuing treatment after study completion, efficacy assessments (frequency and type of assessments) will be at the discretion of the investigator and based on the standard of care.

10.1.1.2. During Study Treatment

For T-ALL patients, during the treatment phase of the study, blood samples will be obtained to monitor disease burden weekly according to the Study Schedule (Attachment 1) during Cycle 1 and biweekly thereafter. Additionally, a bone marrow core biopsy and/or aspirate sample will be obtained on Day 28 (-3 days) of Cycle 1. If the morphologic result does not provide a clear response and it is clinically indicated by the investigator, a second bone marrow examination should be repeated 1 week later. For T-ALL and where clinically indicated, the CT/MRI will be repeated on Day 28 (-3 days) of Cycle 1. A response (CR or PR) must be confirmed no less than

28 days from the first evidence of response by bone marrow core biopsy and CT/MRI as indicated. If 2 consecutive bone marrow assessments demonstrate no tumor with adequate cellularity, bone marrow assessments will be discontinued unless there is evidence of relapse. In case of CR by CT/MRI on 2 assessments no less than 28 days apart the interval between assessments may be increased to every 2 months.

In T-LBL patients, the method of assessment used at baseline must be used consistently for tumor assessment and will be repeated every other cycle starting on Day 28 (-3 days) of Cycle 2. For T-LBL patients followed by CT/MRI, response (CR or PR) must be confirmed no less than 28 days from the first evidence of response. Thereafter, a responding patient will be followed every other cycle until objective progression is observed.

10.1.1.3. Posttreatment Discontinuation Follow-Up

Postdiscontinuation follow-up during the study period will be conducted as described in the Study Schedule (Attachment 1).

For T-ALL patients who are in remission, blood samples should be obtained every 1-3 months. After relapse, no blood sample analysis is required. The patient will be followed approximately every 90 days (±14 days) until the patient's death or overall study completion. Bone marrow assessment will be performed at time of treatment discontinuation or in the 30 Day follow-up period only if not assessed in the prior 8 weeks.

For T-LBL patients who discontinue study treatment without objectively measured progressive disease, the investigative sites will continue to monitor patients and periodically evaluate tumor response approximately every 8 weeks by the same method used at baseline and throughout the study until the patient has objective disease progression, or until the final analysis of OS is performed. After the patient has objective disease progression, radiologic tests are no longer required and the patient will be followed approximately every 90 days (±14 days) until the patient's death or overall study completion.

Response (CR or PR) should be confirmed before the initiation of additional anticancer therapy. However, initiation of new therapy should not be delayed solely to confirm response.

After the primary/final analysis of OS, efficacy assessments (frequency and type of assessments) will be at the discretion of the investigator, based on the standard of care.

Lilly will continue to collect survival data on all patients but may reduce data collection for other efficacy data. Lilly will notify investigators when this reduced data collection can begin.

10.1.2. Primary Efficacy Measure

For T-ALL patients, assessment of efficacy will be consistent with NCCN guidelines for ALL and Cheson criteria (Cheson et al. 2003). The primary endpoints are defined as follow.

A CR is defined as <5% blasts in an aspirate sample with marrow spicules and with a count of at least 200 nucleated cells, along with peripheral blood levels including platelets $\geq 100 \times 10^9$/L and absolute neutrophil count (ANC) $\geq 1 \times 10^9$/L and without circulating blasts.

A CRi is defined as fulfilling all criteria for CR except for residual neutropenia (<1000/μL) or thrombocytopenia (<100,000/μL). The proportion of patients achieving a CRi is defined as the total number of patients achieving a CRi divided by the total number of patients randomized in that arm.

All previous extramedullary manifestations of disease must be absent (eg, lymphadenopathy, splenomegaly, skin or gum infiltration, testicular masses, CNS involvement). The CR rate is estimated as the total number of patients achieving a CR divided by the total number of patients randomized in that arm.

The ORR (CR and CRi) is the sum of patients achieving a CR and a CRi divided by the total number of patients randomized in that arm.

The Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007) will be used to assess the efficacy of LY3039478 in T-LBL patients followed by CT scan or MRI.

For patients with T-LBL followed by CT/MRI, the criteria for CR is similar to T-ALL and requires the disappearance of all measurable disease, signs, symptoms, and biochemical changes related to the tumor.

For T-LBL patients assessed by PET-CT, the criteria for CR is as follows: complete metabolic response with the lymph nodes or extralymphatic sites having a score or 1, 2, or 3 with or without a residual mass on the 5-point assessment scale with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake. There can be no new lesions and no evidence of FDG-avid disease in the bone marrow.

The PET-CT 5-point assessment scale is as follows: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma (Cheson et al. 2014).

The first assessment of response for T-LBL patients will be performed on Day 28 (±3 days) of Cycle 2. A second assessment must be performed ≥28 days after the first evidence of response (this is only required for patients being followed by CT scan/MRI). Two consecutive objective status determinations of CR before progression are required for a best response of CR by CT scan/MRI.

Best response will be derived to encompass all tumor assessments from baseline until the earliest objective progression or start of new anticancer therapy. Any responses observed after objective progression or the start of new anticancer therapy are excluded from the determination of best response.

The date of first documented objective disease progression must be recorded on the CRF even if it occurs after the patient has started a new therapy.

Lilly or its designee will collect and store all tumor measurement images on all enrolled patients throughout the study. An independent review of imaging scans will be performed by Lilly or its designee.

Minimal residual disease (MRD) will be used to confirm CR/CRi. MRD in T-ALL is defined by the continued presence of leukemic cells below the level of detection by usual methods. Patients who achieved a CR by morphologic assessment alone could still have leukemic cells in the bone marrow. Flow cytometry will be used to assess MRD in bone marrow. The minimal limit of assay sensitivity (to declare MRD negativity) should be $<1 \times 10^{-4}$ (<0.01%). MRD are recommended at the end of the initial induction and additional time points as clinically indicated (Bruggeman et al. 2010). Molecular techniques may be used if necessary.

10.1.3. Secondary Efficacy Measures

The following secondary efficacy measures will be assessed:

Remission rate after failure of placebo plus dexamethasone will be calculated for those patients that cross-over in the Phase 2 part of the trial and receive LY3039478 plus dexamethasone.

OS is defined for all patients in the trial, and measured from the date of study enrollment to the date of death from any cause. OS duration is measured from the date of randomization to the date of death from any cause in the Phase 2 portion of the study. For each patient who is not known to have died as of the data-inclusion cutoff date for a particular analysis, OS will be censored for that analysis at the date of last contact prior to the data inclusion cutoff date (contacts considered in the determination of last contact date include AE date, lesion assessment date, visit date, and last known alive date).

10.1.3.1. T-ALL

For T-ALL: PR rate is defined as a decrease of at least 50% in blast count on the bone marrow aspirate; PR requires all of the hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate. The proportion of patients achieving a PR is defined as the total number of patients achieving a PR divided by the total number of patients randomized in that arm.

DoR (CR and CRi) is measured from the date of CR or CRi by blood count recovery and bone marrow examination, until the date of relapse. It is measured until the date T-ALL relapse is detected. For patients who die without report of relapse, DoR is censored on the date of death, regardless of cause. For a patient with no report of relapse or death by the end of the follow-up data collection, observation is censored at the date of last contact prior to the data inclusion cutoff date.

Relapse-free survival (RFS) is defined as the timeframe before the reappearance of unequivocal leukemia blast cells in the blood or the bone marrow (>5%), in the CNS (positive cytospin examination of CSF) or in any other extramedullary site after a CR.

RFS is defined only for patients who achieve CR, and is measured from the date of attaining the leukemia-free state (as defined in Section 10.1.2) until the date of T-ALL relapse or death from

any cause, whichever occurs first. For a patient who is not known to have relapsed or died by the end of study follow-up, observation of RFS is censored at the date of last contact prior to the data inclusion cutoff date.

Event-free survival (EFS) is defined for all patients and measured from the date of entry on study. It is measured until treatment failure, relapse from CR, or death from any cause, whichever occurs first. For a patient with none of these events before the end of study follow-up, observation of EFS is censored at the date of last contact prior to the data inclusion cutoff date. If the patient does not achieve a CR, EFS is defined as the point of treatment failure or death, whichever comes first.

Refractory disease for T-ALL is defined as failure to achieve CR.

Relapsed disease for T-ALL is defined as the reappearance of the blast in the blood or bone marrow (>5%) or any extramedullary site after achievement of a CR.

Treatment failure for T-ALL is defined by progressive disease, which is an increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease. For T-ALL patients with preexisting mediastinal disease, progressive disease is defined by a greater than 25% increase in the sum of the product of the greatest perpendicular diameters (SDP) of the mediastinal enlargement.

10.1.3.2. T-LBL

For T-LBL followed by CT scan/MRI: PR is defined as a reduction of ≥50% in the sum of the products of the perpendicular diameters of all measurable lesions compared with pretreatment measurements. No new lesions will appear, and no existing lesions will enlarge. Stable disease (SD) is defined as a <50% reduction and no more than a 25% increase in the sum of the products of 2 perpendicular diameters of all measured lesions, and the appearance of no new lesions (Cheson et al. 2007).

Two consecutive determinations of PR before progression, but not qualifying for a CR, are required for a best response of PR for T-LBL patients being followed by CT. Best response of SD is defined as disease that does not meet the criteria for CR, PR, or progressive disease.

For T-LBL followed by PET-CT scan, the criteria for PR is as follows: partial metabolic response and a score of 4 or 5 with reduced uptake compared with baseline and residual masses of any size in the lymph nodes or extralymphatic sites. There can be no new lesions and residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan (Cheson et al. 2014).

DoR for T-LBL is measured from the time when criteria for response (ie, CR or PR) are met, until the first documentation of relapse or progression. For patients who die without report of relapse, DoR is censored on the date of death, regardless of cause. For a patient with no report of relapse or death by the end of the follow-up data collection, observation is censored at the date of last contact prior to the data inclusion cutoff date.

RFS for T-LBL is measured from the time of occurrence of a disease-free state or attainment of a CR to disease recurrence or death as a result of lymphoma or acute toxicity of treatment. For a patient who is not known to have relapsed or died by the end of study follow-up, observation of RFS is censored at the date of last contact prior to the data inclusion cutoff date.

Event-free survival (EFS) is defined for all patients and measured from the date of entry on study. It is measured until treatment failure, relapse from CR, or death from any cause, whichever occurs first. For a patient with none of these events before the end of study follow-up, observation of EFS is censored at the date of last contact prior to the data inclusion cutoff date. If the patient does not achieve a CR, EFS is defined as the point of treatment failure or death, whichever comes first.

Treatment failure for T-LBL is defined in Table JJCB.10.1.

Table JJCB.10.1. Treatment Failure in T-LBL

	PET-CT Based Response	CT/MRI-Based Response
Relapsed disease or progressive disease	• Progressive metabolic disease • Score 4 or 5 with an increase in intensity of uptake from baseline and/or • New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: • LDi >1.5 cm and • Increase by ≥50% from PPD nadir and • An increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm • 1 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline

Abbreviations: CT = computed tomography; FDG = fluorodeoxyglucose; LDi = longest diameter; MRI = magnetic resonance imaging; PET-CT = positron emission tomography-computed tomography; PPD = perpendicular diameter; SDi = shortest diameter.

10.2. Health Outcome/Quality of Life Measures

10.2.1. Patient-Reported Outcomes

Patient health-related quality of life will be measured in the Phase 2 portion of this study using the FACT-Leu, which includes a leukemia-specific module intended to be appropriate for patients with various leukemias (Cella et al. 2012). Attachment 7 contains a reference to the website where this questionnaire may be downloaded. The FACT-Leu includes the 27-item cancer-specific Functional Assessment of Cancer Therapy-Leukemia-General (FACT-G) that assesses physical, social/family, emotional and functional well-being plus a 17-item subscale that assesses additional concerns specific to leukemia. This self-administered questionnaire will be completed by the patient at the beginning of visits (prior to other study procedures, unless there

are patient safety concerns) as described in the Study Schedule (Attachment 1) for patients where the questionnaire has been translated into a language in which the patient is fluent. Scoring will be in accordance with the guidelines suggested by the developers.

10.2.2. Resource Utilization

Investigators will be asked to document the use of best supportive care measures, concomitant medications, transfusions, and disease/adverse event-related hospitalization days. Such assessments are to be taken throughout the Phase 2 portion of the study, through the 30-day short-term follow-up, and during the postdiscontinuation follow-up visit.

10.3. Safety Evaluations

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to the study, or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

The timing of all safety evaluations is shown in the Study Schedule (Attachment 1). Table JJCB.10.2 presents a summary of AE and SAE collection with regard to the type of events to be reported during each period of the study.

Table JJCB.10.2. Adverse Event and Serious Adverse Event Reporting Guidelines

Period	Types of AEs/SAEs to Be Reported
Baseline (pretreatment)	Preexisting conditions All AEs SAEs related to protocol procedures
Study treatment period	All AEs and SAEs
30-day short-term posttreatment discontinuation follow-up	All AEs and SAEs
Long-term posttreatment discontinuation follow-up	All SAEs related to protocol procedures or study drug
Continued access period and follow up	All AEs and SAEs

Abbreviations: AEs = adverse events; SAEs = serious adverse events.

10.3.1. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. A clinical study AE is any untoward medical event associated with the use of a drug in humans, whether or not it is considered related to that drug.

However, leukemia-related hematologic effects should not be reported as AEs. Because Grade 3 or 4 myelosuppression (leukopenia, neutropenia, thrombocytopenia, and anemia) is expected in

the setting of relapsed T-ALL, these cytopenias will not be considered AEs for the purpose of this study, unless the investigator classifies them as AEs based on clinical circumstances.

Lack of drug effect is not an AE in clinical trials, because the purpose of the clinical trial is to establish drug effect.

Any clinically significant findings from ECGs, laboratory values, vital sign measurements, other procedures, and so on that result in a diagnosis should be reported to Lilly or its designee.

Cases of pregnancy that occur during maternal or paternal exposures to study drug should be reported. Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation.

Study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

After the ICF is signed, site personnel will record the occurrence and nature of any AEs and any change in the preexisting condition(s). All AEs related to protocol procedures are reported to Lilly or its designee.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure and study drug via CRF, electronic data entry or other designated data transmission methods.

Patients will be evaluated for AEs at each visit and will be instructed to call their physician to report any AEs between visits.

The NCI CTCAE v4.0 will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. For AEs without matching terminology within the NCI CTCAE v 4.0 criteria, the investigator will be responsible for selecting the appropriate system organ class (SOC) and assessing severity grade based on the intensity of the event.

In addition to collecting the AE verbatim and the CTCAE severity grade, AE verbatim text will also be mapped by Lilly or its designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to Lilly or its designee via CRF, electronic data entry or designated data transmission methods the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

10.3.1.1. Serious Adverse Events

An SAE is any adverse event from this study that results in 1 of the following outcomes:

- death
- a life-threatening experience (ie, immediate risk of dying)
- persistent or significant disability/incapacity

- initial or prolonged inpatient hospitalization
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

SAE collection begins after the patient has signed informed consent and has received study drug. If a patient experiences an SAE after signing informed consent, but prior to receiving study drug, the event will not be reported as serious unless the investigator feels the event may have been caused by a protocol procedure.

Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System.

Study site personnel must alert Lilly or its designee of any **SAE** within 24 hours of investigator awareness of the event via a sponsor-approved method. If study site personnel contact Lilly or its designee by telephone regarding an SAE, study site personnel must also immediately provide official notification on study-specific SAE forms.

This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Planned surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Planned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (eg, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs.

SAEs due to disease relapse or progression, including death, should not be reported unless the investigator deems them to be possibly related to the study drug.

If an investigator becomes aware of an SAE occurring after the patient's participation in the trial has ended, and the investigator believes that the SAE is related to a protocol procedure, LY3039478 or dexamethasone, the investigator should report the SAE to the sponsor, and the SAE will be entered in the Lilly Safety System.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the trial may be found in the IB Section 6.2.1.2.4.

10.3.1.2. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the DCSI of the IB and that the investigator identifies as related to the investigational product or study procedure. United States 21 CFR 312.32, European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and associated detailed guidances.

10.3.2. Electrocardiograms

For each patient, 12-lead digital ECGs will be collected as replicates (usually triplicates) according to the Study Schedule (Attachment 1). Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Consecutive replicate ECGs will be obtained at approximately 1-minute intervals. ECGs may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs (more replicates) than expected at a particular time point is allowed when needed to ensure high quality records.

ECGs will initially be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the patient meets entry criteria at the relevant visit(s) and for immediate patient management, should any clinically relevant findings be identified.

After enrollment, if a clinically significant increase in the QT/QTc interval from baseline or other clinically significant quantitative or qualitative change from baseline is identified, the patient will be assessed by the investigator for symptoms (eg, palpitations, near syncope, syncope) and to determine whether the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation from at least 1 of the replicate ECGs from each time point.

Digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly. The central ECG laboratory will perform a basic quality control (eg, demographics and study details) then store the ECGs in a database. At a future time, the stored ECG data may be overread at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements.

10.3.3. Safety Monitoring

The Lilly CRP will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CRP will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist, and review:

- trends in safety data

- laboratory analytes
- AEs

If a patient experiences elevated ALT >5× ULN and elevated total bilirubin >2× ULN, clinical and laboratory monitoring should be initiated by the investigator. For patients entering the study with ALT >2× ULN, monitoring should be triggered at ALT >2× baseline.

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP regarding collection of specific recommended clinical information and follow-up laboratory tests. See Attachment 4.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the assessment committee (an advisory group for this study formed to protect the integrity of data; refer to Section 12.2.14) can conduct additional analyses of the safety data.

10.3.4. Complaint Handling

Lilly collects product complaints on study drugs used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Complaints related to unblinded comparator drugs or concomitant drugs are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

For blinded studies, all product complaints associated with material packaged, labeled, and released by Lilly or its designee will be reported.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- submit the completed product complaint form within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

10.4. Sample Collection and Testing

Attachment 1 lists the schedule for sample collections in this study.

Attachment 2 lists the specific tests that will be performed for this study and whether these will be performed at a central or local laboratory.

A deviation from the cerebrospinal fluid (CSF) and PK sampling schedule will not be considered a protocol violation.

10.4.1. Samples for Study Qualification and Health Monitoring

Blood, urine, CSF, bone marrow, and tissue samples will be collected to determine whether patients meet inclusion/exclusion criteria, to monitor patient health, and to characterize the malignancy.

From T-ALL patient a bone marrow biopsy will be taken by core needle biopsy. A small amount of archived paraffin tissue block and bone marrow previously obtained will be requested from T-LBL patients. A small amount of archived lymph node tissue or slides with unstained tumor sections are required. For both T-ALL and T-LBL patients, due diligence should be used to make sure that tumor and/or bone marrow specimen (not a normal adjacent or a tumor margin sample) are provided. Pathology notes accompanying archival tissue may also be requested.

Investigators must document their review of each laboratory safety report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

10.4.2. Samples for Pharmacodynamics and/or Biomarkers

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology and/or the molecular subtype of the disease being treated. Therefore, where local regulations and ERBs allow, a blood sample will be collected for pharmacogenetic analysis.

Collection of samples for exploratory biomarker research is also part of this study. Blood, CSF, EDTA plasma, tissue, and bone marrow samples will be collected.

Required samples for biomarker research to be collected from all patients in this study are the following:

- whole blood
- EDTA plasma
- archived bone marrow aspirate/biopsy samples from T-ALL patients
- on study bone marrow aspirate/biopsy samples from T-ALL patients
- archived tumor tissue from T-LBL patients

Optional samples for biomarker research that should be collected from patients in the study where possible are the following:

- on study pretreatment and posttreatment tumor tissue from T-LBL patients
- tumor tissue at time of disease progression or if deemed necessary by the investigator
- CSF (adult patients in Phase 1 only)

Samples will be tested for markers of Notch and related pathway activation including, but not limited to, protein expression and activation by immunohistochemistry and ELISA, and gene expression by quantitative polymerase chain reaction (PCR) analysis to evaluate their association with the observed clinical outcomes to LY3039478, as well as circulating A-beta peptides. Samples will also be tested for miRNA and transcriptome expression.

In the event of an unexpected AE or the observation of unusual response, the pharmacogenetic biomarker samples may be genotyped and analysis may be performed to evaluate a genetic association with response to LY3039478. These investigations may be limited to a focused candidate gene study or, if appropriate, wider analysis of multiple genes and/or regions may be performed to identify regions of the genome associated with the variability observed in drug response. The pharmacogenetic biomarker samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

Other samples may be used for research to develop methods, assays, and/or companion diagnostics related to T-ALL, Notch gene, and Notch gene pathway and related pathways.

Bone marrow or tissue biopsy will be taken by core needle biopsy and/or surgical biopsy.

A small amount of archived bone marrow/tissue or slides with unstained tumor sections are required for biomarker research.

Additionally, the optional tumor biopsies from T-LBL patients will be analyzed at laboratories using assays designated by the sponsor. Sample handling and shipment to the central laboratory will occur per instructions given to the study site.

The samples will be coded with the patient number and stored for up to a maximum 15 years after the last patient visit for the study at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the patient by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study drug.

Samples will be destroyed according to a process consistent with local regulation.

10.4.3. Samples for Drug Concentration Measurements Pharmacokinetics

PK samples will be collected as specified in the Pharmacokinetic Sampling Schedule (Attachment 3).

Venous blood samples of approximately 3 mL each will be collected to determine the plasma concentrations of LY3039478 and dexamethasone. Separate blood samples are not required for LY3039478 and dexamethasone. After harvesting the plasma, samples will be divided into 2 approximately equal portions by site personnel, one for the determination of plasma concentrations of LY3039478, and the other for the determination of plasma concentrations of dexamethasone. Instructions for the collection and handling of blood samples will be provided by the sponsor. A maximum of 5 blood samples may be drawn at additional time points during

the study if warranted and agreed upon between both the investigator and Lilly. CSF samples will be used to determine the concentrations of LY3039478.

CSF concentrations of LY3039478, and plasma concentrations of LY3039478 and dexamethasone will be quantified using validated liquid chromatography-mass spectrometry / mass spectrometry (LC-MS/MS) assays. All bioanalytical samples will be stored in the United States. The remaining plasma samples collected for PK evaluation may be used for exploratory studies to assess the metabolism of LY3039478, which may involve sample pooling. These samples may be retained for a maximum of 2 years following the last patient visit for the study.

11. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate CRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide Lilly, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

11.1. Data Capture System

An electronic data capture system will be used in this trial. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

CRF data collected by the third-party organization (TPO) will be encoded by the TPO and stored electronically in the TPO's database system. Validated data will subsequently be transferred to the Lilly data warehouse, using standard Lilly file transfer processes.

Data managed by a central vendor, such as laboratory test data or ECG data, will be stored electronically in the central vendor's database system. Laboratory data will be transferred from the central vendor to the Lilly generic labs system.

Any data for which the paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary to collect patient-reported outcome measures (eg, a rating scale), a daily dosing schedule, or an event diary.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

Approximately 86 to 92 patients will be enrolled in this multicenter study.

In the Phase 1 portion of the study, the primary objective is to determine the MTD and the recommended dose for Phase 2. Approximately 13 to 16 patients will be enrolled into the adult (Part A), and approximately 13 to 16 patients will be enrolled in the pediatric (Part B) cohorts sequentially and without randomization to dose. The total sample size per cohort will be determined by DLTs.

In the Phase 2 portion of the study, the primary objective of this study is to compare the ORR (CR plus CRi) rate between LY3039478 administered with dexamethasone and placebo administered with dexamethasone, in adult patients with relapsed/refractory T-ALL/T-LBL. Approximately 60 evaluable patients will be randomized to the 2 treatment arms in a 2:1 ratio (40 randomized to LY3039478 and dexamethasone and 20 randomized to placebo and dexamethasone).

Assuming the ORR for the LY3039478 and dexamethasone arm is 40% and the ORR of the placebo and dexamethasone is 5%, the sample size of 60 evaluable patients will give approximately 82% statistical power to detect the difference, using a 2-sided Fisher's test at the significance level of 0.05, with 1 futility interim once the 30th enrolled patient completes the remission status determination (Section 12.2.14).

Primary analysis for ORR will be conducted once the last patient enrolled has completed 3 cycles of treatment, discontinued treatment, started new anticancer therapy or met criteria for objective progression. Patients who are randomized and do not achieve a CR or CRi will be considered as nonresponders in the primary analysis for ORR.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

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

Efficacy analyses will be based on the intention-to-treat (ITT) analysis set. This population is defined as all patients randomized to study treatment. Patients will be grouped according to dose level cohort or randomized treatment. Sensitivity analyses may be conducted (if applicable) excluding patients that are randomized but do not receive treatment, and by actual treatment received.

A secondary analysis of the primary efficacy endpoint based upon the per-protocol set (PPS) of patients may be performed if there are significant numbers of patients with major protocol deviations (≥10% of total patient population). The PPS is defined as those patients in the ITT set who are compliant with the study protocol. Major deviations from the protocol for purposes of this analysis will be detailed in the Statistical Analysis Plan.

Safety analyses will be based on the safety population, defined as all enrolled patients receiving at least 1 dose of any study drug. Patients will be grouped according to treatment received in Cycle 1.

PD and/or tailoring biomarker analyses will be based on the subset of patients from the above populations from whom a valid assay result (according to laboratory guideline) has been obtained.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. All tests of interactions will be conducted at a 2-sided alpha level of 0.1, and all CIs will be given at a 2-sided 95% level, unless otherwise stated.

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.

Before unblinding of the aggregate database, minor modifications or clarifications to the data analysis methods may be described and justified in the statistical analysis plan.

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.

The assumptions for each statistical method will be evaluated. If there is violation of assumptions, alternative statistical methods may be used.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

12.2.2. 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 as well as number and percentage of patients completing the study, or discontinuing (overall and by reason for discontinuation). A summary of all important protocol deviations will be provided.

12.2.3. Patient Characteristics

Patient demographics including age, sex, screening height and weight, and screening body mass index will be reported using descriptive statistics.

Baseline disease characteristics will be summarized by presenting frequency counts and percentages including initial diagnosis (T-ALL or T-LBL), T-ALL subtypes, ECOG performance status, disease status at study entry (refractory or relapse), Notch and FBWX7 mutational status, duration of first remission, number of prior courses of induction therapy, extramedullary disease, and history of CNS leukemia. Other patient characteristics will be summarized as deemed appropriate.

12.2.4. Concomitant Therapy

Concomitant medications will be summarized for the safety population.

12.2.5. Postdiscontinuation Therapy

The numbers and percentages of patients reporting postdiscontinuation therapies will be provided overall, by type of therapy (surgery, radiotherapy, systemic therapy, or stem cell transplant), and by drug name.

In the Phase 2 portion, numbers and percentages of patients randomized to placebo and dexamethasone who following treatment discontinuation receive LY3039478 and dexamethasone with be included in summaries of postdiscontinuation therapies.

12.2.6. Treatment Compliance

The number of dose omissions, reductions, delays, and cycles received and the dose intensity will be summarized for all treated patients per treatment arm. Summarized data will be provided for the period prior to first CR, the period following first CR, and the total treatment period.

Treatment compliance information for 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.

12.2.7. Primary Outcome and Methodology

In the Phase 1 portion, the primary outcome of interest is determining the MTD and recommended dose for Phase 2.

In the Phase 2 portion, the primary efficacy endpoint of ORR (CR plus CRi) rate and its exact 95% confidence interval (CI) will be estimated for each treatment arm. The proportion in each treatment arm will be compared using Fisher's exact test. All randomized patients, according to the ITT principle, will be included in the analysis of this endpoint.

Sensitivity analyses of the primary outcome measure will include a re-randomization test.

12.2.8. Other Analyses of Efficacy

No formal efficacy analysis is planned for the Phase 1 portion of this trial. However, any response data will be listed and tabulated.

In Phase 2, the following secondary efficacy parameters will be summarized for each treatment arm:

- Proportion of patients achieving a ORR or PR
- Proportion of patients achieving a CR, CRi, and PR
- OS
- RFS
- EFS
- DoR

The secondary efficacy endpoints of proportion of patients achieving ORR plus PR, and PR, and their exact 95% CIs will be estimated for each treatment arm and compared by 2-sided Chi-squared test or Fisher's exact test between 2 arms. A Fisher's exact test will be chosen over

a Chi-squared test if in the 2x2 table, any of the expected cell counts are less than 5, or any cell has zero counts.

For the secondary efficacy endpoints OS, RFS, and EFS, the Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the survival curves as well as survival rates at various prespecified time points (12 months for OS, 6 and 12 months for RFS and EFS) for each treatment arm.

The secondary efficacy endpoint DoR is subject to competing risk of death without relapse; therefore, the cumulative incidence of relapse (Gray 1988; Pepe and Mori 1993; Gooley et al. 2001) will be used. In the calculation, patients who did not have the event will be considered right-censored observations. All randomized patients, according to the ITT principle, will be included in the analysis of these endpoints.

The comparison of the survival curves between treatment groups will be conducted by a log-rank test. Exploratory analyses for the comparison of the survival curves between treatment groups may be conducted by a stratified log-rank test with some of the following stratification variables: initial diagnosis (T-ALL phenotype, T-LBL), response to last therapy (refractory or relapsed), age, number of prior therapies (≤2, >2), NOTCH-1/FBXW7/RAS/PTEN status.

The Cox proportional hazard model (Cox 1972) with treatment as a factor will be used to estimate the hazard ratio and corresponding 95% CI with Wald's test p-value after adjusting for the following potential predictive/prognostic variables: initial diagnosis (T-ALL phenotype, T-LBL), response to last therapy (refractory or relapsed), age, number of prior therapies (≤2, >2), NOTCH-1/FBXW7/RAS/PTEN status.

All randomized patients, according to the ITT principle, will be included in the analysis of these endpoints.

For the analysis of time-to-event endpoints, a sensitivity analysis censoring the event time at the date of SCT will be completed to evaluate the potential impact from imbalance in patients receiving transplantation between the study arms.

No missing data will be imputed.

Efficacy data (CR, CRi, PR, and ORR) for patients receiving patients receiving LY3039478 in combination with dexamethasone after failure of placebo in combination with dexamethasone will be tabulated, and further exploratory analyses of efficacy data conducted as warranted.

Additional exploratory analyses may be performed as deemed appropriate.

12.2.9. Pharmacokinetic Analyses

PK analyses will be conducted on patients who receive at least 1 dose of the study drug and have samples collected. PK parameter estimates for plasma LY3039478 and dexamethasone, where possible, will be calculated by standard noncompartmental methods of analysis. The primary parameters for analysis will be C_{max}, area under the plasma concentration-time curve from time zero to last measurable plasma concentration ($AUC_{[0\text{-}tlast]}$), area under the concentration-time

curve from time zero to infinity or over 1 dosing interval at steady state ($AUC_{[0-\infty]}$ or AUC_{τ}). Other noncompartmental parameters, such as $t_{1/2}$, apparent clearance (CL/F), and apparent volume of distribution (V/F) may be reported. CSF LY3039478 concentrations will be summarized. 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 Pharmacokinetics management. The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation.

The PK data will be combined, and analyses may be conducted to determine a relationship between exposure and PD effect (eg, Aβ), data permitting. This model may be used to help reassess the dose cohort escalation as the study progresses. If deemed necessary, PK/PD modeling may be employed to evaluate variability in exposure, pharmacologic effects, and safety parameters.

12.2.10. Pharmacodynamics and Tailoring Analyses

Biomarker data from all patients undergoing biomarker assessments will be analyzed using descriptive statistics. Further exploratory analyses will be detailed in the SAP.

12.2.11. Health Outcome/Quality of Life Analyses

FACT-Leu results will be summarized descriptively by cycle and for postdiscontinuation visits, including number of completed questionnaires, compliance rates, reasons for noncompliance, scores for each scale and subscale, and changes from baseline. Resource utilization with be summarized descriptively by cycle.

12.2.12. Safety Analyses

All safety summaries and analyses will be based upon the safety population as defined in Section 12.2.1. An additional treatment group will be included in analyses representing safety data for patients receiving LY3039478 in combination with dexamethasone after failure of placebo in combination with dexamethasone.

Overall exposure to study drug, the numbers of patients completing each cycle, and the dose intensity will be summarized using descriptive statistics. The number of patients with any dose adjustment will be presented for entire treatment period as well as for each cycle. The number of patients with dose reductions, dose delays, or dose omissions will also be summarized, as will the reasons for dose adjustments.

An overall summary of AEs will be provided for AEs deemed by the investigator to be possibly related to study medication, and repeated for events regardless of study drug causality. Incidence rates of these events will be compared between treatment arms using Fisher's exact test.

A treatment-emergent AE (TEAE) is defined as an event that first occurred or worsened in severity after baseline.

The number of evaluable patients who experienced a TEAE, SAE, AE related to study drug, died, or discontinued from the study due to an AE will be summarized by treatment.

CTCAE v4.0 (or higher) will be used to report AEs by CTCAE terms.

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

MedDRA v16.1 (or higher) will be used when reporting AEs by MedDRA terms. The MedDRA lower level term will be used in the treatment-emergent computation. TEAEs will be summarized by SOC and by decreasing frequency of preferred term (PT) within SOC.

Reasons for death will be summarized separately for on-therapy and within 30 days of last dose of study drug/last visit. Serious adverse events will be summarized by PT.

Hospitalizations and transfusions during the study treatment period or during the 30-day short-term follow-up period will be summarized by treatment group.

12.2.13. Subgroup Analyses

Exploratory subgroup analyses of efficacy endpoints will be performed for stratification or potential prognostic variables (for example, NOTCH-1/FBXW7/RAS/PTEN status, age [≤30, >30 years], initial diagnosis [T-ALL phenotype, T-LBL], ECOG status [0 or 1 vs 2], response to last therapy [refractory or relapsed], number of prior therapies [≤2, >2]).

Other subgroup analyses may be performed as deemed appropriate.

12.2.14. Interim Analyses

The Phase 1 portion is a nonrandomized, open-label study, and no interim analyses are planned until the end of Phase 1. 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 and PD profiles (if available) of LY3039478 will be reviewed per cohort. Based on these interim results, modifications (for example, 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 on their review of the safety/tolerability data and the PK/PD data from the previous cohorts. An interim analysis including safety, PK, and PD data will be conducted prior to proceeding to the Phase 2 portion of the study. All relevant data will be reviewed to confirm the estimation of the MTD. The decision to proceed to Phase 2 will be made following discussions between the investigators and Lilly clinical research personnel and documented in writing.

In the Phase 2 portion, safety interim analyses are planned every 12 months, and at the planned futility interim analysis, when response data from 30 randomized patients have been obtained. There are no prespecified rules for stopping the trial due to safety concerns. The assessment

committee members will review unblinded safety data at each interim analysis to determine whether there are sufficient safety concerns to justify the termination of study treatment and/or enrollment.

One futility interim analysis is planned in Phase 2 once 30 patients are randomized and have completed the CR status determination. The assessment committee may recommend stopping the trial for futility if the observed ORR (CR plus CRi) rate difference is <0.05 for the treatment arm compared to the control arm. Simulations have been conducted in order to understand the operating characteristics of the futility rule and the impact on statistical power is considered minimal. It is not planned to stop the trial early for efficacy, thus there are no adjustments for multiplicity.

A limited number of preidentified individuals may gain access to the limited unblinded data, as specified in the unblinding plan, prior to the interim or final database lock, in order to initiate the final population PK/PD model development processes for interim or final analyses. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded.

Only the assessment committee is authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will receive information about interim results ONLY if they need to know for the safety of their patients.

Unblinding details are specified in the blinding section of the protocol (Section 9.5). If changes to the unblinding plan occurred after protocol approval, they may be described in either a protocol amendment, the unblinding plan section of the SAP, or in separate unblinding plan document.

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

The investigator is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

The ICF will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of study drug.

A legal representative must give informed consent for a child to participate in this study. In addition to informed consent given by the legal representative, the child may be required to give documented assent, if capable.

As used in this protocol, the term "informed consent" includes all consent and assent given by patients or their legal representatives.

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are used at the investigative sites. All ICFs must be compliant with the International Conference on Harmonisation (ICH) guideline on Good Clinical Practice (GCP).

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative sites.

The ERB should include or consult with experts who are knowledgeable in pediatric ethical, clinical, and psychosocial issues.

The study site's ERBs should be provided with the following:

- the current IB or package labeling and updates during the course of the study
- the ICF
- the assent form
- relevant curricula vitae

13.3. Regulatory Considerations

This study will be conducted in accordance with:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- the ICH GCP Guideline (E6)
- the ICH Guideline, Clinical Investigation of Medicinal Products in the Pediatric Population (E11)
- applicable laws and regulations

The investigator or designee will promptly submit the protocol to applicable ERB(s).

Some of the obligations of Lilly will be assigned to a TPO.

An identification code assigned by the investigator to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and/or other trial-related data.

Physicians with a specialty in hematology, hemato-oncology, or pediatric hematology will participate as investigators in this clinical trial.

13.3.1. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

13.3.2. Final Report Signature

The clinical study report coordinating investigator will sign the final clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The investigator with the most enrolled patients will serve as the clinical study report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the clinical study report coordinating investigator.

The Lilly responsible medical officer and statistician will sign/approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

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Attachment 1. Protocol I6F-MC-JJCB Study Schedule

Study Schedule, Protocol I6F-MC-JJCB: Phase 1 and Phase 2 Baseline Assessments

	Relative Day Prior to Day 1 of Cycle 1	≤28	≤14	≤7	Notes
Study Entry	Informed consent	X			Informed consent must be signed prior to performing any protocol procedure.
	Inclusion/exclusion evaluation	X			
	Comprehensive medical history		X		
Physical Exam	Physical exam		X		Including testicular exam for males
	Height/weight		X		
	Vital signs		X		Temperature, blood pressure, pulse rate
	Lansky Performance Status		X		For Phase 1 pediatric patients <16 years
	ECOG Performance Status		X		For adults in Phase 1 and Phase 2
Lab and Diagnostic Tests	Electrocardiogram (ECG)		X		Central ECG required
	Echocardiography	X			Echocardiography or another acceptable alternative method to determine ejection fraction such as MUGA scan
	Hematology			X	Manual differentiation
	Serum chemistry			X	Includes: hsCRP, immunoglobins IgA, IgG, IgM
	Coagulation			X	Prothrombin time (PT/INR), partial thromboplastin time (PTT), fibrinogen, d-dimer, antithrombin (AT)
	HTLV			X	
	Urinalysis			X	
	Serum pregnancy test			X	to be performed on women of child-bearing potential
	Archived bone marrow samples	X			For T-ALL patients only. For example, bone marrow biopsies/clot sections/slides >28 days. Lack of sample will not be considered a protocol deviation.
	Archived tumor tissue or tumor biopsy	X			For T-LBL patients only >28 days prior enrollment
	Immunological phenotyping	X			Peripheral blood and bone marrow Lymphocyte panel according Attachment 2
	Expression analysis	X			Peripheral blood
Disease/Tumor Assessment	CT/MRI of head	X			Only if neurological symptoms are present, to detect meningeal disease, chloromas, or CNS symptoms
	CT/MRI thorax and abdomen	X			For T-ALL patients or T-LBL patients followed by CT/MRI
	PET-CT	X			For T-LBL patients with FDG-avid lymphomas
	Lumbar puncture	X			Only if CNS involvement is suspected – see exclusion. criterion 20
	Bone marrow biopsy and/or aspirate		X		For T-ALL patients only. With approval from Lilly this sample may be obtained earlier than 14 days.
	Tumor biopsy[a]	X			For T-LBL patients
	CTCAE grading (Preexisting conditions)		X		To be reported only after study eligibility is confirmed
	Concomitant medications		X		
	FACT-Leu		X		Phase 2 Only

Abbreviations: CNS = central nervous system; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECOG = Eastern Cooperative Oncology Group; FACT-Leu = Functional Assessment of Cancer Therapy-Leukemia; hsCRP = high-sensitivity C-reactive protein; HTLV= Human T-cell leukemia virus type 1; INR = international normalized ratio; MRI = magnetic resonance imaging; MUGA = multi-gated acquisition scan; PET-CT = positron emission tomography-computed tomography; T-ALL = T-cell acute lymphoblastic leukemia; T-LBL = T-cell lymphoblastic lymphoma.

[a] For patients with T-LBL, a prestudy treatment tumor biopsy/sample is required from tumors that can be biopsied at acceptable clinical risk in the judgment of the investigator. T-LBL patients without accessible tumor for biopsy are eligible.

Study Schedule, Protocol I6F-MC-JJCB: Phase 1

Study Procedures	Cycle 1																			
	Week 1					Week 2					Week 3					Week 4				
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 9	Day 10	Day 11	Day 12	Day 15	Day 16	Day 17	Day 18	Day 19	Day 22	Day 23	Day 24	Day 25	Day 26
LY3039478 therapy[a]	X		X		X	X		X		X	X		X		X	X		X		X
Dexamethasone	X	X	X	X	X						X	X	X	X	X					
Physical exam	X					X					X					X				
Vital signs (temperature, pulse rate, blood pressure)	X					X					X					X				
Weight	X																			
ECOG Performance Status for ≥16 years	X					X					X					X				
Lansky Performance Status for <16 years	X					X					X					X				
CTCAE version 4.0 grading	X					X					X					X				
Concomitant medications	X					X					X					X				
CT/MRI thorax and at least upper abdomen for T-ALL patients[b]																				X
Central ECG[c]	X																			
Hematology[d]	X					X					X					X				
Serum chemistry[d]	X					X					X					X				
ECG chemistry[c, d]	X																			
Coagulation[d]	X					X					X					X				
Blood PK sampling[c]	X					X														
Tumor biopsy (T-LBL), optional[e]																				X
Bone marrow biopsy and/or aspirate[f]																				X

Study Procedures	Cycle 1																			
	Week 1					Week 2					Week 3					Week 4				
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 9	Day 10	Day 11	Day 12	Day 15	Day 16	Day 17	Day 18	Day 19	Day 22	Day 23	Day 24	Day 25	Day 26
Blood PD biomarkers (A beta)[c]	X																			
Blood PD biomarkers[c]	X					X														
Lumbar puncture for T-ALL[c] optional						X														
Pharmacogenetics sample (anytime)	X																			

Abbreviations: CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Group; MRI = magnetic resonance imaging; PD = pharmacodynamic; PK = pharmacokinetic; T-ALL = T-cell acute lymphoblastic leukemia; T-LBL = T-cell lymphoblastic lymphoma.

a LY3039478 is to be administered 3 days per week through each 28-day cycle. If assessments associated with a dose cannot be performed, the assessments may be performed either with the previous dose (if known in advance) or the next dose.

b Per protocol Section 10.1.1. To be done for only those patients who had lesions at the their baseline assessment.

c For complete details, see Attachment 3.

d For central versus local labs refer to Attachment 2.

e Predose any time <28 days prior start of study drug and per protocol Section 10.4.2 postdose as clinically determined by investigator

f Per protocol Section 10.1.1

Study Schedule, Protocol I6F-MC-JJCB: Phase 1 Cycle 2

Study Procedures	Cycle 2- n																			
	Week 1					Week 2					Week 3					Week 4				
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 9	Day 10	Day 11	Day 12	Day 15	Day 16	Day 17	Day 18	Day 19	Day 22	Day 23	Day 24	Day 25	Day 26
LY3039478 therapy[a]	X		X		X	X		X		X	X		X		X	X		X		X
Dexamethasone	X	X	X	X	X						X	X	X	X	X					
Physical exam	X										X									
Vital signs (temperature, pulse rate, blood pressure,)	X										X									
Weight	X																			
ECOG Performance Status ≥16 years	X										X									
Lansky Performance Status <16 years	X										X									
CTCAE version 4.0 grading	X										X									
Concomitant medications	X										X									
CT/MRI thorax and at least upper abdomen for T-ALL patients[b] or T-LBL patients followed by CT/MRI																				X
PET-CT for T-LBL patients																				X
Central ECG[c]	X																			
Hematology[d]	X										X									
Serum chemistry[d]	X										X									
ECG chemistry[c,d]	X																			
Coagulation[d]	X										X									
Blood PK sample[c]	X																			
Tumor biopsy (T-LBL), optional[e]																				X

Study Procedures	Cycle 2- n																			
	Week 1					Week 2					Week 3					Week 4				
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 9	Day 10	Day 11	Day 12	Day 15	Day 16	Day 17	Day 18	Day 19	Day 22	Day 23	Day 24	Day 25	Day 26
Bone marrow biopsy and/or aspirate[f]						X														X
Blood PD biomarkers[c]	X																			

Abbreviations: CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Group; MRI = magnetic resonance imaging; PD = pharmacodynamic; PET-CT = positron emission tomography-computed tomography; PK = pharmacokinetic; T-ALL = T-cell acute lymphoblastic leukemia; T-LBL = T-cell lymphoblastic lymphoma.

a LY3039478 is to be administered 3 days per week through each 28-day cycle. If assessments associated with a dose cannot be performed, the assessments may be performed either with the previous dose (if known in advance) or the next dose.

b Per protocol Section 10.1.1. To be done for only those patients who had lesions at the their baseline assessment.

c For complete details, see Attachment 3.

d For central versus local laboratories refer to Attachment 2.

e Predose any time <28 days prior start of study drug and per protocol Section 10.4.2 postdose as clinically determined by investigator.

f For confirmation of CR and when clinically indicated by investigator; per protocol Section 10.1.1.

Study Schedule, Protocol I6F-MC-JJCB: Phase 2

Study Procedures	Cycle 1																			
	Week 1					Week 2					Week 3					Week 4				
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 9	Day 10	Day 11	Day 12	Day 15	Day 16	Day 17	Day 18	Day 19	Day 22	Day 23	Day 24	Day 25	Day 26
LY3039478 therapy[a] or Placebo	X		X		X	X		X		X	X		X		X	X		X		X
Dexamethasone	X	X	X	X	X						X	X	X	X	X					
Physical exam	X										X									
Vital signs (temperature, pulse rate, blood pressure)	X										X									
Weight	X																			
ECOG Performance Status	X										X									
CTCAE version 4.0 grading	X										X									
Concomitant medications	X										X									
CT/MRI thorax and at least upper abdomen for T-ALL patients[b]																				X
Central ECG[c]	X																			
Hematology[d]	X										X									
Serum chemistry[d]	X										X									
ECG chemistry[c,d]	X																			
Coagulation[d]	X										X									
Blood PK sampling[c]	X										X									
Tumor biopsy, T-LBL optional[e]																				X
Bone marrow biopsy and/or aspirate[f]																				X
FACT-Leu																				X
Resource utilization																				X

Study Procedures	Cycle 1																			
	Week 1					Week 2					Week 3					Week 4				
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 9	Day 10	Day 11	Day 12	Day 15	Day 16	Day 17	Day 18	Day 19	Day 22	Day 23	Day 24	Day 25	Day 26
Blood PD biomarkers[c]	X																			
Pharmacogentics sample (anytime)	X																			

Abbreviations: CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Group; FACT-Leu = Functional Assessment of Cancer Therapy-Leukemia; MRI = magnetic resonance imaging; PD = pharmacodynamic; PK = pharmacokinetic; T-ALL = T-cell acute lymphoblastic leukemia; T-LBL = T-cell lymphoblastic lymphoma.

[a] LY3039478 is to be administered 3 days per week through each 28-day cycle. If assessments associated with a dose cannot be performed, the assessments may be performed either with the previous dose (if known in advance) or the next dose.

[b] Per protocol Section 10.1.1. To be done for only those patients who had lesions at the their baseline assessment.

[c] For complete details, see Attachment 3.

[d] For central versus local labs refer to Attachment 2.

[e] Optional biopsy postdose, or at time of progression, or as clinically determined by investigator.

[f] Per protocol Section 10.1.1.

Study Procedures	Cycle 2- n																			
	Week 1					Week 2					Week 3					Week 4				
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 9	Day 10	Day 11	Day 12	Day 15	Day 16	Day 17	Day 18	Day 19	Day 22	Day 23	Day 24	Day 25	Day 26
LY3039478 therapy[a] or placebo	X		X		X	X		X		X	X		X		X	X		X		X
Dexamethasone	X	X	X	X	X						X	X	X	X	X					
Physical exam	X										X									
Vital signs (temperature, pulse rate, blood pressure)	X										X									
Weight	X																			
ECOG Performance Status	X										X									
CTCAE version 4.0 Grading	X										X									
Concomitant medications	X										X									
CT/MRI thorax and at least upper abdomen for T-ALL patients[b] or T-LBL patients followed by CT/MRI																				X
PET-CT for T-LBL patients																				X
Central ECG[c]	X																			
Hematology[d]	X										X									
Serum chemistry[d]	X										X									
ECG chemistry[c,d]	X																			
Coagulation[d]	X										X									
Blood PK sample[c]	X																			
Tumor biopsy, (T-LBL), optional[e]																				X
Bone marrow biopsy and/or aspirate[f]																				X
FACT-Leu																				X
Resource utilization																				X

Abbreviations: CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Group; FACT-Leu = Functional Assessment of Cancer Therapy-Leukemia; MRI = magnetic resonance imaging; PD = pharmacodynamic; PET-CT = positron emission tomography-computed tomography; PK = pharmacokinetic; T-ALL = T-cell acute lymphoblastic leukemia; T-LBL = T-cell lymphoblastic lymphoma.

[a] LY3039478 is to be administered 3 days per week through each 28-day cycle. If assessments associated with a dose cannot be performed, the assessments may be performed either with the previous dose (if known in advance) or the next dose.

[b] Per protocol Section 10.1.1. To be done for only those patients who had lesions at the their baseline assessment.

[c] For complete details, see Attachment 3.

[d] For central versus local labs refer to Attachment 2.

[e] Optional biopsy postdose, or at time of progression, or as clinically determined by investigator.

[f] For confirmation of CR and when clinically indicated by investigator (timing as clinically indicated); per protocol Section 10.1.1.

Study Schedule, Protocol I6F-MC-JJCB: Phase 1 and 2 Follow-up Visits

		Initial Follow-up Visit[a] 801	Long-Term Follow-up Visits[b] 8XX	Notes
Physical Exam	Physical exam	X		
	Weight	X		
	Vital signs	X		Temperature, blood pressure, pulse rate
	Performance status	X		
	Hematology with manual differential[c]	X	X	For T-ALL patients who are in remission, CBC and platelets should be obtained every 1-3 months for the first 2 years and then every 3-6 months.
	Coagulation[c]	X		
	Serum chemistry[c]	X		
	CTCAE grading	X	X	
	Concomitant medications	X		
	FACT-Leu	X	X	Phase 2 only and patients in remission
	Resource utilization	X	X	Phase 2 only and patients in remission
Efficacy Measures	Patient survival status	X	X	
	Remission status	X	X	CT/MRI as clinically indiacated every 2 -4 months For T-LBL patients followed by CT/MRI every 2 to 4 month as clinically indicated. For T-LBL patients followed by PET-CT only as clinically indicated.

Abbreviations: CBC = complete blood count; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; FACT-Leu = Functional Assessment of Cancer Therapy-Leukemia; MRI = magnetic resonance imaging; PET = positron emission tomography; T-ALL = T-cell acute lymphoblastic leukemia; T-LBL = T-cell lymphoblastic lymphoma.

a Initial follow-up assessments occur approximately 30 days following the end of treatment.

b Long-term follow-up assessments occur approximately every 60 days following the end of the initial follow-up. Note that follow up for patient AEs does not follow this schedule and is at the discretion of the investigator.

c For central versus local labs refer to Attachment 2.

Study Schedule, Protocol I6F-MC-JJCB: Continued Access

Note: Efficacy assessments will be done at the investigator's discretion based on the standard of care.

Study Procedures	Continued Access Period Only Visit 501-5XX																Continued Access Follow-up[a]
	Week 1					Week 2			Week 3					Week 4			Visit 901
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 10	Day 12	Day 15	Day 16	Day 17	Day 18	Day 19	Day 22	Day 24	Day 26	
LY3039478 therapy	X		X		X	X	X	X	X		X		X	X	X	X	
Dexamethasone	X	X	X	X	X				X	X	X	X	X				
Physical exam	X																X
Vital signs (temperature, pulse rate, blood pressure)	X																X
CTCAE version 4.0 grading	X																X
Hematology[b]	X																
Serum chemistry[b]	X																

Abbreviations: ECOG = eastern cooperative oncology group; CTCAE = Common Terminology Criteria for Adverse Events

[a] Continued access follow-up begins 1 day after the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days ± 6 days.

[b] For central versus local labs refer to Attachment 2.

Attachment 2. Protocol I6F-MC-JJCB Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a,b] with manual differentiation:

Hemoglobin
Hematocrit
Erythrocyte count (RBC)
Mean cell volume (MCV)
Mean cell hemoglobin concentration (MCHC)
Leukocytes (WBC)
Neutrophils, segmented
Neutrophils, bands
Lymphocytes
Monocytes
Eosinophils
Basophils
Metamyelocytes
Myelocytes
Promyelocytes
Blasts
Atypical lymphocytes
Platelets
Nucleated RBCs (NRBC)/100 WBC
Reticulocytes

Urinalysis[a,c]:

Specific gravity
pH
Protein
Glucose
Ketones
Blood
Urine leukocyte esterase

Immunophenotyping Lymphocyte panel in peripheral blood and bone marrow[a]**:**

TdT, CD1a, CD2/3/4/5/7/8/11b/13/33/34/65/117, cCD3, HLA-DR, % of lymphoblasts in bone marrow

Coagulation[b]**:**

D-dimer
PTT
PT/INR
Fibrinogen
Antithrombin

Clinical Chemistry[a,b]:

Serum Concentrations of:

Sodium
Potassium
Phosphorus
Magnesium
Chloride
Total bilirubin
Direct bilirubin
Alkaline phosphatase
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Lactate dehydrogenase (LDH)
Gamma-glutamyl (GGT)
Blood urea nitrogen (BUN) or blood urea
Creatinine
Uric acid
Calcium
Glucose, random
Albumin
Total protein
Lipase

Other:

Immunoglobulins G, A, and M (IgG, IgA, IgM)[b,c]
High-sensitivity C-reactive protein (hsCRP)[b,d]
HTLV[b,c]

Pregnancy Test (females only)[a,c]

Cerebrospinal Fluid[a]

Leukocytes (WBC)
Lymphoblasts

ECG Chemistry[b]

Lipase[e]
Thyroid stimulating hormone (TSH)
Tri-iodothyronine (T3)
Thyroxine (T4)
Albumin[e]
Glucose, random[e]
Calcium[e]

	Sodium[e]
Bone Marrow[a,b,f] with manual differentiation**:**	Potassium[e]
Aspirate	Phosphorus[e]
Core biopsy	Magnesium[e]
	Serum creatinine[e]

Abbreviations: CBC= complete blood count; ECG = electrocardiogram; HTLV= Human T-cell leukemia virus type 1; M/E= myeloid/erythroid; PT/INR = international normalized ratio of prothrombin time; PTT = partial thromboplastin time; RBC = red blood cells; WBC = white blood cells.

a Local or investigator-designated laboratory.
b Assayed by Lilly-designated laboratory.
c Performed at baseline only.
d To be performed with each chemistry panel.
e Test not performed if both chemistry and ECG chemistry required at same time point. See Attachment 3.
f Including Lilly-designated laboratory assessment of minimal residual disease (MRD) to confirm remission status.

Attachment 3. Protocol I6F-MC-JJCB Pharmacokinetic, Pharmacodynamic, CSF and ECG Sampling Schedule

PK, PD, CSF, and ECG Sampling Schedule – Phase 1– Part A (Adult Patients)

PK Sample Number	Cycle	Day	PK Sampling Time for LY3039478[a]	PK Sampling Time for Dexamethasone[a]	CSF Sampling Time for LY3039478[b]	PD Sampling Time for Aβ(1-x)][c]	PD Sampling Time for NICD and Gene Expression Analysis[d,e,f]	ECG and ECG Chemistry
1	1	1	Predose	Predose		Predose	Predose	Predose
2	1	1	1-2h	1-2h		1-2h		
3	1	1	3-4h	3-4h		3-4h		3-4h
4	1	1	6-8h	6-8h		6-8h	6-8h	
5	1	1	24-30h	24-30h		24-30h		24-30h
6	1	8	Predose				Predose	
7	1	8	1-2h		1-4h			
8	1	8	3-4h					
9	1	8	6-8h				6-8h	
10	1	8	24-30h					
11	2	1	Predose					Predose

Abbreviation: CSF = cerebrospinal fluid; ECG = electrocardiogram; NICD = Notch intracellular domain; PD = pharmacodynamic; PK = pharmacokinetic.

[a] Samples of approximately 3 mL of whole blood will be collected for measurement of LY3039478 and dexamethasone on Cycle 1 Day 1 only. On other days, 2 mL of whole blood will be collected for measurement of LY3039478.

[b] Optional and only for Phase 1 adult patients.

[c] Samples of approximately 3 mL of whole blood will be collected.

[d] For the NICD ELISA, approximately 8 mL of whole blood will be collected in sodium citrate CPT tubes.

[e] For the gene expression analysis, approximately 2.5 mL of whole blood will be collected.

[f] NICD collection will be performed at select sites only.

Note: Collection of PD samples, where similar intervals are presented, should be collected the same time as PK samples. Collection of CSF sample should be at the same time as either the 1-2h or 3-4h plasma PK sample.

PK, PD, and ECG Sampling Schedule – Phase 1- Part B (Pediatric Patients)

PK Sample Number	Cycle	Day	PK Sampling Time for LY3039478[a]	PK Sampling Time for Dexamethasone[a]	PD Sampling Time for NICD and Gene Expression Analysis[b]	ECG and ECG Chemistry
1	1	1	Predose	Predose	Predose	Predose
2	1	1	1-3h	1-3h		1-3h
3	1	1	6-8h	6-8h	6-8h	6-8 h
4	1	8	Predose		Predose	Predose
5	1	8	1-3h		3h	

Abbreviation: ECG = electrocardiogram; NICD = Notch intracellular domain; PD = pharmacodynamic; PK = pharmacokinetic.

[a] Samples of approximately 2 mL of whole blood will be collected for measurement of LY3039478 and dexamethasone (where assayed).

[b] NICD collection will be performed at select sites only.

Note: Collection of PD samples, where similar intervals are presented, should be collected the same time as PK samples.

PK, PD, and ECG Sampling Schedule – Phase 2 (Approximately 30 Patients)

PK Sample Number	Cycle	Day	PK Sampling Time for LY3039478/ Placebo[b]	PK Sampling Time for Dexamethasone[b]	PD Sampling Time for NICD and Gene Expression[c]	ECG[a] and ECG Chemistry
1	1	1	Predose	Predose	Predose	Predose
2	1	1	1-3h	1-3h		1-3h
3	1	1	6-8h	6-8h	6-8h	
4	1	15	Predose	Predose		
5	1	15	1-3h	1-3h		
6	1	15	6-8h	6-8h		
7	2	1	Predose			Predose

Abbreviation: ECG = electrocardiogram; NICD = Notch intracellular domain; PD = pharmacodynamic; PK = pharmacokinetic.

a ECG required for all patients.

B Samples of approximately 3 mL of whole blood will be collected for measurement of LY3039478 and dexamethasone in Cycle 1 only. On other days, 2 mL of whole blood will be collected for measurement of LY3039478.

c NICD collection will be performed at select sites only.

Note: Collection of PD samples, where similar intervals are presented, should be collected the same time as PK samples.

Attachment 4. Protocol I6F-MC-JJCB Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow up with patients in consultation with the Lilly clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented[b]	
Lymphocytes	**Hepatic Serologies[a,c]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Anti-smooth muscle antibody[a]**
CPK	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated laboratory.

[b] Neutrophils reported by automated differential hematology instruments include both segmented and band forms. Whenever a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and recorded on the CRF, unless the CRF specifically provides an entry field for bands.

[c] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Attachment 5. Protocol I6F-MC-JJCB Eastern Cooperative Oncology Group, and Lansky Performance Status

ECOG Performance Status

Activity Status	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead.

Source: Oken et al. 1982.

Lansky Performance Status

Play-Performance Scale for Children

Directions for Clinicians

The play-performance scale for children is designed to provide a standardized measure of the performance status of the child with cancer.

Appropriate for use with children:

- With any type of malignancy
- Aged 1 to 16 years
- Inpatients and outpatients
- In active treatment and long-term follow-up

Procedures

The play-performance scale is:

- Rated by parent according to directions on form
- Rated on the basis of the past week
- To be readministered to assess change over time or following treatment

Parent Form

Child's name:

Date of birth: _____/_____/____
mo day yr

Your name:
Relationship Mother: ____
Father: ____
Other: ____

Today's Date: _____

Directions for parents: On this form is a series of descriptions. Each description has a number beside it. Think about your child's play and activity over the past week. Think about both good days and bad days. Average out this period. Now read the descriptions and pick the one that best describes your child's play during the past week. Circle the number beside that *one* description.

100 - Fully active, normal

90 - Minor restrictions in physically strenuous activity

80 - Active, but tires more quickly

70 - Both greater restriction of, and less time spent in, active play

60 - Up and around, but minimal active play; keeps busy with quieter activities

50 - Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities

40 - Mostly in bed; participates in quiet activities

30 - In bed; needs assistance, even for quiet play

20 - Often sleeping; play entirely limited to very passive activities

10 - No play; does not get out of bed

0 - Unresponsive

Attachment 6. Protocol I6F-MC-JJCB Creatinine Clearance and Serum Creatinine Formulas

For adult patients (≥16 Years) Note: This formula is to be used for calculating creatinine clearance (CrCl) from **local laboratory results only.**

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(\mathbf{140 - age^{a}}) \times (\mathbf{wt}) \times \mathbf{0.85}\ (\text{if female}), \text{ or} \times \mathbf{1.0}\ (\text{if male})}{\mathbf{72} \times \mathbf{serum\ creatinine}\ (mg/dL)}$$

For serum creatinine concentration in μmol/L:

$$\text{CrCl (mL/min)} = \frac{(\mathbf{140 - age^{a}}) \times (\mathbf{wt}) \times \mathbf{0.85}\ (\text{if female}), \text{ or} \times \mathbf{1.0}\ (\text{if male})}{\mathbf{0.81} \times \mathbf{serum\ creatinine}\ (\mu mol/L)}$$

[a] age in years, weight (wt) in kilograms.

Reference: Cockcroft and Gault 1976.

-OR-

$$GFR(mL/min/1.73m^2 = 170 \times [PCr]^{-0.999} \times [age]^{-0.176}$$

$$\times [0.762 \text{ if patient is female}] \times [1.18 \text{ if patient is black}]$$

$$\times [SUN]^{-0.17} \times [Alb]^{+0.318}$$

GFR = glomerular filtration rate; PCr = plasma creatinine, mg/dL; SUN = serum urea nitrogen, mg/dL; Alb = serum albumin, g/dL

Source: Murray and Ratain 2003.

Note: This formula is to be used for calculating creatinine clearance from **local laboratory results only. For Pediatric Patients (patients < 16 years of age)**

$$\text{CrCl mL/min} = \frac{(k * Ht)}{Cr_{serum}}$$

Patient	K
Infant (LBW <1 year)	0.33
Infant (term <1 year)	0.45
Child or adolescent girl	0.55
Adolescent boy	0.70

Notes: Height is measured in cm. Serum creatinine is measured in mg/dL. Measured creatinine should be in steady state.

Abbreviations: CrCl = creatinine clearance; Cr_{serum} = serum creatinine; Ht = height; LBW = low birth weight.

Source: Schwartz et al. 1987.

Serum creatinine formula based on age/gender

Age	Maximum Serum Creatinine (mg/dL)	
	Male	**Female**
1 to <2 years	0.6	0.6
2 to <6 years	0.8	0.8
6 to <10 years	1.0	1.0
10 to <13 years	1.2	1.2
13 to <16 years	1.5	1.4
≥16 years	1.7	1.4

The threshold creatinine values in this table were derived from the Schwartz formula for estimating GFR (Schwartz et al. 1987) utilizing child length and stature data published by the Centers for Disease Control and Prevention (CDC).

Attachment 7. Protocol I6F-MC-JJCB FACT-Leu (Version 4) Questionnaire

The FACT-Leu is one in a family of questionnaires available through FACIT and is available to download at the following website:

www.facit.org/FACITOrg/Questionaires

Attachment 8. Protocol JJCB Protocol Amendment I6F-MC-JJCB(a) Summary A Phase 1b/Randomized Phase 2 Study to Evaluate LY3039478 in Combination with Dexamethasone in T-ALL/T-LBL Patients

Overview

Protocol I6F-MC-JJCB, a Phase 1b/Randomized Phase 2 Study to Evaluate LY3039478 in Combination with Dexamethasone in T-ALL/T-LBL patients has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

This study was amended at the request of the Food and Drug Administration (FDA) to clarify the criteria for DLTs (Section 9.2.2) and to change the PK sampling. In addition, CSF sampling was simplified based on new data; the CSF sampling has been reduced to one draw. PK analysis for dexamethasone during the Phase 1 portion of the study was added and one additional time point for the determination of plasma concentrations of LY3039478 and dexamethasone was added during the Phase 2 portion of the study (Attachment 3).

All appropriate section headings have been changed to designate the updated protocol number and other minor editorial changes and formatting corrections were made, but are not necessarily documented below.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

The numbering system used for inclusion and exclusion criteria provides a unique number for each criterion and allows for efficiency in data collection.

In case an amendment to the protocol adds a criterion, that criterion will receive the next available number, regardless of whether it is an inclusion or exclusion criterion.

2. Synopsis

Clinical Protocol Synopsis: Study I6F-MC-JJCB(a)

<table>
<tr><td colspan="2">Name of Investigational Product: LY3039478</td></tr>
<tr><td colspan="2">Title of Study: A Phase 1b/Randomized Phase 2 Study to Evaluate LY3039478 in Combination with Dexamethasone in T-ALL/T-LBL Patients</td></tr>
<tr><td>Number of Planned Patients: 86 to 92 total patients
Entered:
Enrolled/Randomized:
Phase 1: Part A 13 to 16 patients; Part B 13 to 16 patients
Phase 2: 60 patients</td><td>Phase of Development: 1b / 2</td></tr>
<tr><td colspan="2">Length of Study: approximately 60 months
Planned first patient visit: May 2015
Planned last patient visit, excluding the continued access: May 2020
Planned interim analysis: At end of Phase 1 and during Phase 2, every 12 months and once 30 patients are randomized and have completed the CR determination.</td></tr>
<tr><td colspan="2">Objectives:
The primary objective is as follows:
• Phase 1: to determine the recommended dose of LY3039478 in combination with dexamethasone in adult patients with relapsed/refractory T-cell acute lymphoblastic leukemia (T-ALL) or T-cell lymphoblastic lymphoma (T-LBL) (Part A) and pediatric patients (Part B)
• Phase 2: to determine if the overall remission rate (ORR) (CR plus CR with incomplete blood count recovery [CRi]) in adult patients with relapsed/refractory T-ALL/T-LBL treated with LY3039478 in combination with dexamethasone exceeds that of those patients treated with placebo in combination with dexamethasone
The secondary objectives are as follows:
• Phase 1:
o to characterize the safety and toxicity profile of LY3039478 in combination with dexamethasone as assessed by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.0
o to assess the pharmacokinetic (PK) parameters of LY3039478 in combination with dexamethasone therapy
o to document efficacy based on Cheson criteria for leukemia and modified response criteria for malignant lymphoma
o to evaluate gene mutation (eg, NOTCH-1/FBXW7/RAS/PTEN) status with efficacy
• Phase 2:
o to compare the ORR plus partial remission (PR) and PR alone for both arms
o to assess the remission rate for patients receiving LY3039478 in combination with dexamethasone after failure of placebo in combination with dexamethasone
o to assess duration of remission (DoR) (= CR and Cri and PR)
o to assess relapse-free survival (RFS), event-free survival (EFS), and overall survival (OS)
o to compare the safety and toxicity profile of LY3039478 in combination with dexamethasone to dexamethasone and placebo as assessed by NCI CTCAE v 4.0
o to assess the pharmacokinetic (PK) parameters of LY3039478 and dexamethasone in combination therapy
o to assess patient quality of life using the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu)
o to evaluate gene mutation (eg, NOTCH-1/FBXW7/RAS/PTEN) status with efficacy</td></tr>
</table>

The exploratory objectives are as follows: • to assess clinical utility of the NICD immunohistochemistry (IHC) assay as a potential companion diagnostic for LY3039478 • to evaluate biomarkers in tumor tissue, blood, plasma, and cerebrospinal fluid (CSF), which may include, but not be limited to, NICD enzyme-linked immunosorbent assay (ELISA) (or an alternative validated method), gene expression, relevant to the study disease or safety, efficacy, and mechanism of action of LY3039478 and dexamethasone • to explore pharmacodynamic (PD) effects of LY3039478 on biomarkers indicative of Notch activity • to evaluate the CSF ~~PK~~ exposure of LY3039478
Study Design: Study I6F-MC-JJCB is a multicenter study consisting of a nonrandomized, open-label, dose-escalation Phase 1 study followed by a randomized, double-blind, Phase 2 study in patients with relapsed or refractory T-ALL/T-LBL. The Phase 1 portion of the study will consist of 2 different patient populations, an adult (Part A) and a pediatric (Part B), and will define the recommended dose of LY3039478 in combination with dexamethasone in each of these populations. The decision to proceed with the pediatric dose exploration (Part B) will be made after safety analysis of the adult cohort. The randomized Phase 2 study will be a double-blinded, multicenter evaluation to determine if the ORR (CR and CRi) rate in adult patients with relapsed/refractory T-ALL/T-LBL treated with LY3039478 in combination with dexamethasone exceeds that of those patients treated with placebo in combination with dexamethasone.
Diagnosis and Main Criteria for Inclusion and Exclusions: Patients must have T-ALL or T-LBL. T-ALL is defined ≥25% of blasts in the bone marrow and expression of at least 2 of the following cell surface antigens: CD1a, CD2, CD3 (surface or cytoplasmic), CD4, CD5, CD7, and/or CD8. If the only T cell markers present are CD4 and CD7, the leukemia cells must also lack the myeloid markers CD33 and/or CD13. Patients with initial refractory disease should have received at least 2 multi-agent chemotherapy induction regimens. Patients in first or second relapse must have been refractory to at least 1 multi-agent chemotherapy reinduction regimen. They must have had at least 60 days between prior hematopoietic stem cell transplant and first dose of study drug, have adequate performance status and organ function, be ≥16 years old for the adult cohort (Phase 1, Part A) and 2 to <16 years old for the pediatric cohort (Phase 1, Part B), and have a life expectancy of 2 months. Patients may be excluded if they are currently enrolled in another ongoing clinical trial with investigational products, have recently discontinued (within less than 2 weeks) prior anticancer therapy, have a serious concomitant illness, have an uncontrolled or active infection <7 days prior to administration of study drug, have current or recurrent (within 3 months) gastrointestinal disease, have conditions requiring chronic systemic glucocorticoid use, have active graft versus host disease, have active leukemic involvement of the central nervous system, or have a second primary or prior malignancy that would affect the interpretation of study results.
Test Product, Dosage, and Mode of Administration: LY3039478, dose range 25 to 200 mg, given orally as capsules 3 times per week during a 28-day cycle. Placebo will be given orally as capsules 3 times per week during a 28-day cycle.
Planned Duration of Treatment: Patients will receive 2 cycles (28 days each) of LY3039478 unless 1 or more of the criteria for discontinuation are fulfilled. A patient may receive >2 cycles of treatment only if: 1) none of the criteria for discontinuation have been fulfilled, and 2) the investigator determines that the patient is experiencing clinical benefit from treatment. Short-term follow-up period (postdiscontinuation): 30 days. Long-term follow-up (postdiscontinuation): until death.
Reference Therapy, Dose, and Mode of Administration: Dexamethasone will be administered at a dose of 24 mg on Day 1 through Day 5 every other week to the adult patients and 10 mg/m^2 twice a day (BID) to the pediatric patients.

Criteria for Evaluation:

Efficacy:

- ORR
- CR rate
- proportion of patients achieving a CRi
- proportion of patients achieving a PR
- DoR
- OS
- RFS
- EFS

Safety: Safety will be evaluated based on recorded adverse events (AEs), physical examinations, vital sign measurements, electrocardiograms, and clinical laboratory assessments. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events and clinical laboratory values will be graded using NCI CTCAE v4.0.

Health Outcomes: Patient health-related quality of life including physical, social/family, emotional and functional well-being will be assessed using the self-administered FACT-Leu questionnaire at the beginning of each visit only in the Phase 2 portion of the study.

Pharmacokinetics: Blood and CSF samples will be used to determine the concentrations of LY3039478. ~~Plasma and~~ CSF concentrations of LY3039478, and plasma concentrations of LY3039478 and dexamethasone will be quantified using validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) assays. The remaining plasma samples collected for PK evaluation may be used for exploratory studies to assess the metabolism of LY3039478, which may involve sample pooling.

Pharmacodynamics/Tailoring Biomarkers: Blood, CSF, EDTA plasma, tissue, and bone marrow samples will be collected. Samples will be tested for markers of Notch and related pathway activation including, but not limited to, protein expression and activation by IHC and ELISA, and gene expression by quantitative polymerase chain reaction (PCR) analysis to evaluate their association with the observed clinical outcomes to LY3039478.

Statistical Methods:

Statistical:

In the Phase 1 portion of the study, approximately 13 to 16 patients will be enrolled into each of the adult (Part A) and pediatric (Part B) cohorts sequentially and without randomization to dose. The total sample size per cohort will be determined by DLTs.

In the Phase 2 portion of the study, approximately 60 evaluable patients will be randomized to the 2 treatment arms in a 2:1 ratio (40 randomized to LY3039478 and dexamethasone and 20 randomized to placebo and dexamethasone).

Efficacy analyses will be based on the intention-to-treat (ITT) analysis set. This population is defined as all patients randomized to study treatment. Patients will be grouped according to dose level cohort or randomized treatment. A secondary analysis of the primary efficacy endpoint based upon the per-protocol set (PPS) of patients may be performed if there are significant numbers of patients with major protocol deviations (≥10% of total patient population). The PPS is defined as those patients in the ITT set who are compliant with the study protocol.

Safety analyses will be based on the safety population, defined as all enrolled patients receiving at least 1 dose of any study drug. Patients will be grouped according to treatment received in Cycle 1.

PD and/or tailoring biomarker analyses will be based on the subset of patients from the above populations from whom a valid assay result (according to laboratory guideline) has been obtained.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. All tests of interactions will be conducted at a 2-sided alpha level of 0.1, and all confidence intervals (CIs) will be given at a 2-sided 95% level, unless otherwise stated.

Efficacy:

No formal efficacy analysis is planned for the Phase 1 portion of this trial. However, any response data will be listed and tabulated. In the Phase 2 portion, the primary efficacy endpoint of ORR (CR plus CRi) and its exact 95%

CI will be estimated for each treatment arm. The proportion in each treatment arm will be compared using Fisher's exact test. All randomized patients, according to the ITT principle, will be included in the analysis of this endpoint. The secondary efficacy endpoints of proportion of patients achieving an ORR plus PR, and PR, and their exact 95% CIs will be estimated for each treatment arm and compared by 2-sided Chi-squared test or Fisher's exact test between 2 arms. For the secondary efficacy endpoints OS, RFS, and EFS, the Kaplan-Meier method will be used to estimate the survival curves as well as survival rates at various prespecified time points (12 months for OS, 6 and 12 months for RFS and EFS) for each treatment arm. The secondary efficacy endpoint DoR is subject to competing risk of death without relapse; therefore, the cumulative incidence of relapse will be used. In the calculation, patients who did not have the event will be considered right-censored observations. All randomized patients, according to the ITT principle, will be included in the analysis of these endpoints. The comparison of the survival curves between treatment groups will be conducted by a log-rank test.

Safety: Safety analyses will include listings and/or summaries of the following:

- adverse events (AEs) and treatment-emergent adverse events (TEAEs),
- drug exposure,
- dose adjustments,
- laboratory measures,
- reasons for death, and
- hospitalizations and transfusions.

Health Outcomes: FACT-Leu results will be summarized descriptively by cycle, including number of completed questionnaires, scores for each scale and subscale, and changes from baseline.

Pharmacokinetics: PK analyses will be conducted on patients who receive at least 1 dose of the study drug and have samples collected. PK parameter estimates for LY3039478 and dexamethasone, where possible, will be calculated by standard noncompartmental methods of analysis.

Pharmacodynamics/Tailoring Biomarkers: Biomarker data from all patients undergoing biomarker assessments will be analyzed using descriptive statistics.

Interim Analyses: An interim analysis including safety, PK, and PD data will be conducted prior to proceeding to the Phase 2 portion of the study. All relevant data will be reviewed to confirm the estimation of the MTD. The decision to proceed to Phase 2 will be made following discussions between the investigators and Lilly clinical research personnel and documented in writing. In the Phase 2 portion, safety interim analyses are planned every 12 months, and at the planned futility interim analysis, when response data from 30 patients has been obtained. There are no prespecified rules for stopping the trial due to safety concerns. The assessment committee members will review unblinded safety data at each interim analysis to determine whether there are sufficient safety concerns to justify the termination of study treatment and/or enrollment.

One futility interim analysis is planned in Phase 2 once 30 patients are randomized and have completed the CR status determination. The assessment committee may recommend stopping the trial for futility if the observed ORR (CR plus CRi) rate difference is <0.05 for the treatment arm compared to the control arm.

5.3 Rationale for Amendment (a)

This study was amended at the request of the Food and Drug Administration (FDA) to clarify the criteria for DLTs (Section 9.2.2), to change the PK sampling, and simplify the CSF sampling. The CSF sampling has been reduced to one draw and PK samples will be split into 2 approximately equal portions: one for the determination of plasma concentrations of LY3039478 and the other for the determination of plasma concentrations of dexamethasone. One additional PK sample is being added to the Phase 2 portion of the study during Cycle 1 at Day 15 during the 6-8 hour post-dose range (Attachment 3).

6.3 Exploratory Objectives

The exploratory objectives of the study are as follows:

- to assess clinical utility of the NICD immunohistochemistry (IHC) assay as a potential companion diagnostic for LY3039478
- to evaluate biomarkers in tumor tissue, blood, plasma and cerebrospinal fluid (CSF), which may include, but not be limited to, NICD enzyme-linked immunosorbent assay (ELISA) (or an alternative validated method), gene expression, relevant to the study disease or safety, efficacy, and mechanism of action of LY3039478 and dexamethasone
- to explore PD effects of LY3039478 on biomarkers indicative of Notch activity
- to evaluate the CSF ~~PK~~ exposure of LY3039478

9.2.2 Dose-Limiting Toxicity Determination and Maximum Tolerated Dose Definition

A DLT is an AE observed during the first 28-day cycle (when patients receive LY3039478 and dexamethasone) that is determined by the investigator to be at least possibly related to LY3039478 according to CTCAE v 4.0 and fulfills any of the following criteria:

- ≥CTCAE Grade 3 nonhematological toxicity. Exceptions will be made for:
  - Grade 3 nausea, vomiting, or constipation that lasts less than 72 hours and that can be controlled with treatment
  - Grade 3 electrolyte disturbance that can be controlled with treatment and persists less than 5 days
  - Grade 3 hyperglycemia or Grade 4 hyperglycemia without ketoacidosis during and after the end of dexamethasone treatment unless it is not controlled by oral medication or insulin before the start of the next dexamethasone round
  - Grade 3 arterial hypertension during and after the end of dexamethasone treatment unless it is not controlled by oral medication before the start of the next dexamethasone round
  - tumor lysis syndrome (TLS): patients who demonstrate a clinical syndrome consistent with TLS and have transient (<7 days) and manageable Grade 3 abnormalities in serum electrolytes, renal function and/or chemistries (ie, uric acid, potassium, phosphorus, calcium, creatinine, blood urea nitrogen, etc.)
  - ~~CTCAE~~ Grade 3 diarrhea for <5 days and unless it cannot 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 (eg, worsening biliary obstruction) if agreed by the study investigator and Lilly CRP
  - ~~hyperglycemia during and after the end of dexamethasone treatment unless it is not controlled by oral medication or insulin before the start of the next dexamethasone round~~
  - ~~arterial hypertension during and after the end of dexamethasone treatment unless it is not controlled by oral medication before the start of the next dexamethasone round~~

- any other significant toxicity deemed by the primary investigator and Lilly clinical research personnel to be dose limiting (eg, any toxicity that is possibly related to the study medication that requires the withdrawal of the patient from the study during Cycle 1)

10.4.3. Samples for Drug Concentration Measurements Pharmacokinetics

PK samples will be collected as specified in the Pharmacokinetic Sampling Schedule (Attachment 3).

~~Blood and CSF~~ Venous blood samples of approximately 3 mL each will be ~~used~~ collected to determine the plasma concentrations of LY3039478 and dexamethasone. Separate blood samples are not required for LY3039478 and dexamethasone. After harvesting the plasma, samples will be divided into 2 approximately equal portions by site personnel, one for the determination of plasma concentrations of LY3039478, and the other for the determination of plasma concentrations of dexamethasone. Instructions for the collection and handling of blood samples will be provided by the sponsor. A maximum of 5 blood samples may be drawn at additional time points during the study if warranted and agreed upon between both the investigator and Lilly. CSF samples will be used to determine the concentrations of LY3039478.

~~Plasma and~~ CSF concentrations of LY3039478, and plasma concentrations of LY3039478 and dexamethasone will be quantified using validated liquid chromatography-mass spectrometry / mass spectrometry (LC-MS/MS) assays. All bioanalytical samples will be stored in the United States. The remaining plasma samples collected for PK evaluation may be used for exploratory studies to assess the metabolism of LY3039478, which may involve sample pooling. These samples may be retained for a maximum of 2 years following the last patient visit for the study.

12.1 Determination of Sample Size

…

Primary analysis for ORR will be conducted once the last patient enrolled has completed 3 cycles of treatment, discontinued treatment, started new anticancer therapy or met criteria for objective progression. Patients who are randomized and do not achieve a CR or CRi will be considered as nonresponders in the primary analysis for ORR.

12.2.8 Other Analyses of Efficacy

No formal efficacy analysis is planned for the Phase 1 portion of this trial. However, any response data will be listed and tabulated.

In Phase 2, the following secondary efficacy parameters will be summarized for each treatment arm:

- Proportion of patients achieving a ORR or PR
- Proportion of patients achieving a CR, CRi, and PR
- OS

- RFS
- EFS
- DoR

…

The Cox proportional hazard model (Cox 1972) with treatment as a factor will be used to estimate the hazard ratio and corresponding ~~90~~ 95% CI with Wald's test p-value after adjusting for the following potential predictive/prognostic variables: initial diagnosis (T-ALL phenotype, T LBL), response to last therapy (refractory or relapsed), age, number of prior therapies (≤2, >2), NOTCH-1/FBXW7/RAS/PTEN status.

…

12.2.9 Pharmacokinetic Analyses

PK analyses will be conducted on patients who receive at least 1 dose of the study drug and have samples collected. PK parameter estimates for plasma ~~and CSF~~ LY3039478 and ~~plasma~~ dexamethasone, where possible, will be calculated by standard noncompartmental methods of analysis. The primary parameters for analysis will be Cmax, area under the plasma concentration-time curve from time zero to last measurable plasma concentration (AUC[0-tlast]), area under the concentration-time curve from time zero to infinity or over 1 dosing interval at steady state (AUC[0-∞] or AUC τ). Other noncompartmental parameters, such as t1/2, apparent clearance (CL/F), and apparent volume of distribution (V/F) may be reported. CSF LY3039478 concentrations will be summarized. 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 Pharmacokinetics management. The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation.

…

PK, PD, CSF and ECG Sampling Schedule – Phase 1– Part A (Adult Patients)

PK Sample Number	Cycle	Day	PK Sampling Time for LY3039478[a]	PK Sampling time for dexamethasone	CSF Sampling Time for LY3039478[b]	PD Sampling Time for Aβ(1-x)][c]	PD Sampling time for NICD and Gene expression Analysis[d,e,f]	ECG and ECG Chemistry
1	1	1	Predose	Predose		Predose	Predose	Predose
2	1	1	1-2h	1-2h		1-2h		
3	1	1	3-4h	3-4h		3-4h		3-4h
4	1	1	6-8h	6-8h		6-8h	6-8h	
5	1	1	24-30h	24-30h		24-30h		24-30h
6	1	8	Predose		~~Predose~~		Predose	
7	1	8	1-2h		1-4h			
8	1	8	3-4h		~~3-4h~~			
9	1	8	6-8h		~~6-8h~~		6-8h	
10	1	8	24-30h		~~24-30h~~			
11	2	1	Predose					Predose

Abbreviation: CSF = cerebrospinal fluid; ECG = electrocardiogram; NICD = Notch intracellular domain; PD = pharmacodynamic; PK = pharmacokinetic.

[a] Samples of approximately ~~2~~ 3 mL of whole blood will be collected for measurement of LY3039478 and dexamethasone on Cycle 1 Day 1 only. On other days, 2mL of whole blood will be collected for measurement of LY3039478.

[b] Optional and only for Phase 1 adult patients.

[c] Samples of approximately 3 mL of whole blood will be collected.

[d] For the NICD ELISA, approximately 8 mL of whole blood will be collected in sodium citrate CPT tubes.

[e] For the gene expression analysis, approximately 2.5 mL of whole blood will be collected.

[f] NICD collection will be performed at select sites only.

Note: Collection of PD samples, where similar intervals are presented, should be collected the same time as PK samples. Collection of CSF sample should be at the same time as either the 1-2h or 3-4h plasma PK sample.

PK, PD, and ECG Sampling Schedule – Phase 1- Part B (Pediatric Patients)

PK Sample Number	Cycle	Day	PK Sampling Time for LY3039478[a]	PK Sampling time for dexamethasone	PD Sampling time for NICD and Gene expression Analysis[b]	ECG and ECG Chemistry
1	1	1	Predose	Predose	Predose	Predose
2	1	1	1-3h	1-3h		1-3h
3	1	1	6-8h	6-8h	6-8h	6-8
4	1	8	Predose		Predose	Predose
5	1	8	1-3h		3h	

Abbreviation: ECG = electrocardiogram; NICD = Notch intracellular domain; PD = pharmacodynamic; PK = pharmacokinetic.

[a] Samples of approximately 2 mL of whole blood will be collected for measurement of LY3039478 and dexamethasone (where assayed).

[b] NICD collection will be performed at select sites only.

Note: Collection of PD samples, where similar intervals are presented, should be collected the same time as PK samples.

PK, PD, and ECG Sampling Schedule – Phase 2 (Approximately 30 Patients)

PK Sample Number	Cycle	Day	PK Sampling Time for LY3039478/ placebo	PK Sampling Time for Dexamethasone[b]	PD Sampling time for NICD and Gene expression[c]	ECG[a] and ECG Chemistry
1	1	1	Predose	Predose	Predose	Predose
2	1	1	1-3h	1-3h		1-3h
3	1	1	6-8h	6-8h	6-8h	
4	1	15	Predose	Predose		
5	1	15	1-3h	1-3h		
6	~~2~~1	15	~~Predose~~ 6-8h	6-8h		~~Predose~~
7	2	1	Predose			Predose

Abbreviation: ECG = electrocardiogram; NICD = Notch intracellular domain; PD = pharmacodynamic; PK = pharmacokinetic.

[a] ECG required for all patients.

[b] Samples of approximately 3 mL of whole blood will be collected for measurement of LY3039478 and dexamethasone in Cycle 1 only. On other days, 2mL of whole blood will be collected for measurement of LY3039478.

[c] NICD collection will be performed at select sites only.

Note: Collection of PD samples, where similar intervals are presented, should be collected the same time as PK samples.

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