

Clinical Protocol 101-99

An Extension Study to Investigate the Safety and Durability of Clinical Activity of CAL-101 in Patients with Hematologic Malignancies

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1 LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
FDA	US Food and Drug Administration
IRB	institutional review board
MedDRA	Medical Dictionary for Regulatory Activities
PI3K	phosphatidylinositol 3-kinase
SAE	serious adverse event
TEAE	treatment-emergent adverse event

2 INTRODUCTION

2.1 Background

Calistoga Pharmaceuticals, Inc. (Sponsor) is developing CAL-101, an oral small molecule inhibitor of the p110 δ isoform of phosphatidylinositol 3-kinase (PI3K), for the treatment of hematologic malignancies.

Class I PI3Ks are a family of intracellular lipid kinases that are essential components of migratory, proliferative, survival and differentiation pathways in many cell types. Activating mutations in PI3K as well as functional loss of PTEN, the phosphatase that opposes the enzymatic activity of PI3K, occur frequently in human cancer and provide a rationale for targeting this signaling pathway as a potential therapy. PI3K p110 δ , the therapeutic target of CAL-101, shows an expression pattern that is largely restricted to cells of hematopoietic origin. Mice deficient in p110 δ have no gross abnormalities, are fertile and live a normal life span without an increased susceptibility to infections. An essential role of PI3K signaling in the proliferation and survival of hematopoietic cancer cells has been demonstrated for several myeloid and B-cell malignancies. PI3K p110 δ is uniformly expressed in primary patient cells in acute myeloid leukemia, chronic lymphocytic leukemia and multiple myeloma as well as leukemia, lymphoma and myeloma cell lines. Many of these malignant cells or cell lines had constitutive activation of the PI3K pathway as indicated by AKT phosphorylation. Preclinical studies showed that in vitro CAL-101 treatment of a variety of malignant cells or cell lines results in inhibition of AKT phosphorylation and induction of apoptosis.

CAL-101 is a potent and selective small molecule inhibitor of the p110 δ isoform of PI3K. It has been studied in normal healthy subjects, patients with allergic rhinitis and patients with hematologic malignancies.

2.2 Potential Risks

Standard acute and 28-day nonclinical systemic toxicity studies were conducted in rats and dogs. These toxicity studies demonstrated no-observed-adverse-effect-levels of 50 mg/kg/day in the 28-day rat study and 5 mg/kg/day in the 28-day dog study. Lymphoid depletion in lymphoid tissues was observed in both species and is consistent with the expected pharmacological activity of PI3K p110 δ inhibition. Target organs for toxicity included bone marrow in the rat, with changes of myeloid hyperplasia and decreased erythropoietic precursors, and liver in the dog, with elevated serum transaminases and hepatocellular necrosis.

In the Phase 1 study of CAL-101 in patients with relapsed or refractory hematologic malignancies, a dose limiting toxicity of reversible increases in ALT/AST was observed. Hematological toxicity was infrequent and not clearly associated with CAL-101 dosing.

2.3 Study Rationale

This extension study provides the opportunity for patients with hematologic malignancies who complete a prior CAL-101 study protocol to continue CAL-101 treatment as long as the patient is deriving clinical benefit.

3 OBJECTIVES

3.1 Primary Objective

The primary objectives of this study are:

- To investigate the long-term safety of CAL-101 in patients with hematologic malignancies
- To determine the duration of clinical benefit of CAL-101 in patients with hematologic malignancies

3.2 Endpoints

Primary Endpoints

- Safety will be assessed using toxicity grading of adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0
- Progression free survival

4 INVESTIGATIONAL PLAN

4.1 Summary of Study Design

This is a long-term safety extension study of CAL-101 in patients with hematologic malignancies who complete other CAL-101 studies. Patients will be followed according to the standard of care as appropriate for their type of cancer. The dose of CAL-101 will generally be the same as the dose that was administered at the end of the prior study, but may be titrated up to improve clinical response or down for toxicity. Patients may receive other anti-cancer therapy. Patients will be withdrawn from the study if they develop progressive disease, unacceptable toxicity related to CAL-101, or if they no longer derive clinical benefit in the opinion of the investigator.

5 STUDY POPULATION

- Patients with hematologic malignancies completing a prior CAL-101 study with a clinical benefit are eligible

5.1 Removal of Patients from Therapy

A patient may be withdrawn from the study under the following circumstances:

- The patient wishes to withdraw consent to participate in the study
- The patient wishes to discontinue study drug treatment for any reason
- The patient experiences a toxicity that necessitates discontinuing study drug treatment permanently
- The patient has progressive disease or is no longer deriving clinical benefit
- The investigator or Sponsor decides to discontinue treatment for medical reasons or due to the patient's noncompliance with the protocol
- The Sponsor discontinues the study

The reason for withdrawal should be recorded in the CRF.

6 TREATMENTS

6.1 Treatments Administered

The Sponsor will provide CAL-101 drug product to study sites.

6.2 Study Drug Supplies

6.2.1 Packaging and Labeling

CAL-101 (capsules) will be supplied in bottles. A label containing the following information will be affixed to the bottle:

- Sponsor name and address
- Protocol identifier
- Description of contents of package, including dose strength
- Caution statement
- Storage conditions
- Manufacture date
- Lot number
- "Keep out of Reach of Children" statement

6.2.2 Preparation and Administration

CAL-101 drug product of various dose strengths will be provided to the patient to be taken home. The study site personnel will be instructed by the Sponsor as to the appropriate dose strengths and number of capsules to configure the dose level to be administered. The study drug should be taken with water, according to the frequency specified. For twice a day dosing, the evening dose should be taken approximately 12 hours after the morning dose. Dosing is unaffected by food intake.

6.2.3 Storage and Handling

CAL-101 capsules will be provided in sealed bottles. The bottles should be stored at room temperature.

6.2.4 Study Drug Accountability

The movement of all study drug and associated supplies should be documented from the time of receipt at the site through patient dispensing and return. All supplies, including partially used or empty bottles, should be tracked. Drug accountability logs will be provided by the Sponsor and should contain the identification of the patient to whom the drug was dispensed and the date and quantity of the drug dispensed. The study drug supply should be retrieved from patients at the end of the dosing interval and the number

of remaining drug product recorded. All study drug bottles should be retained at the site until inventoried by the Sponsor's representative. Instructions for disposition of study drug will be provided to the site by the Sponsor.

6.3 Blinding

The study is unblinded.

6.4 Concomitant Therapy

6.4.1 Allowed Concomitant Therapy

Concomitant treatment as deemed medically necessary by the investigator is allowed, including anti-cancer therapy. Only anti-cancer concomitant medications will be recorded in the CRF.

6.4.2 Dose Adjustment for Concomitant Therapy

Medications that are potent inhibitors or inducers of CYP3A4 (Appendix 12.1) are expected to affect the blood levels of CAL-101, which is a substrate of CYP3A4. Concomitant treatment with a CYP3A4 inhibitor is expected to increase plasma concentrations of CAL-101 and decrease with a CYP3A4 inducer. If concomitant treatment is medically necessary then a dose adjustment of CAL-101 should be considered, i.e., a lower dose with a CYP3A4 inhibitor and a higher dose with a CYP3A4 inducer. The dose adjustment should be discussed with the Sponsor prior to implementation.

6.5 Treatment Compliance

Subject compliance with study drug dosing will be assessed by return of unused study drug by site personnel. The number of drug product dispensed, days of therapy, and number of drug product returned will be recorded.

6.6 Dose Adjustment

The CAL-101 dose may be increased to improve the clinical response, generally in 50 mg increments. Dose reduction may be considered if severe toxicities occur that may be related to study drug. If a grade 4 hematological toxicity or a grade ≥ 3 non-hematological toxicity occur that is considered to be related to study drug then dosing should be stopped until the toxicity resolves to grade ≤ 2 . The patient may restart CAL-101 at the same dose or at a reduced dose, generally in 50 mg decrements. Any planned dose changes should be discussed with the Sponsor prior to implementation.

7 VISIT SCHEDULE

7.1 Enrollment Visit

Patients will sign the informed consent document prior to undergoing any study procedures.

The following information will be collected:

- Demographics
- Hematologic malignancy diagnosis
- Prior CAL-101 study protocol number
- Clinical response status at completion of prior CAL-101 study
- Dose of CAL-101 at completion of prior CAL-101 study
- Date of Last Patient Visit of prior CAL-101 study (may be the same date as enrollment to this study)
- Recording of grade 3 or higher adverse events, all SAEs and anti-cancer concomitant medications

The patient will be dispensed a 2-month supply of study drug.

7.2 Treatment

While on study, the patient will return every 2 months for the following procedures:

- Recording of grade 3 or higher adverse events, all SAEs and anti-cancer concomitant medications
- Return of used drug supply and dispensing of 2-months of new drug supply

7.3 Clinical Evaluation

While on study, the patient will be followed for disease status according to standard of care. Any change in the clinical response status should be recorded.

7.4 End of Study Visit

Patients will be withdrawn from this study if they develop progressive disease, unacceptable toxicity related to CAL-101, or if they no longer derive clinical benefit in the opinion of the investigator. The following procedures will be performed:

Return of used drug supply

- Recording of grade 3 or higher adverse events, all SAEs and anti-cancer concomitant medications
- Recording of the reason for withdrawal

8 STUDY ASSESSMENTS

8.1 Efficacy Measures

The date of disease progression will be captured and the duration of clinical response and progression free survival calculated based on data from the prior CAL-101 study.

8.2 Pharmacokinetic/Pharmacodynamic Measures

Not applicable.

8.3 Safety Evaluations

Safety will be evaluated by assessing all grade 3 or higher adverse events and all SAEs.

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting the Sponsor to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient. The investigator is responsible for appropriate medical care of patients during the study.

Contact information for the Sponsor's Medical Expert for this trial is provided on the cover page.

8.3.1 Adverse Events

8.3.1.1 Definitions of Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. Adverse events may be reported by the patient, discovered by investigator questioning, or detected through physical examination, laboratory test, or other means.

Adverse events include:

- Any sign, medical diagnosis or symptom that occurs between the time the informed consent has been signed and the first administration of study drug.
- Any new undesirable medical experience or an unfavorable and unintended change of an existing condition that occurs during or after treatment, whether or not considered related to study drug.
- Abnormal laboratory findings considered by the investigator to be clinically significant, i.e., those that are unusual for the population being studied or individual patient.

Whenever possible, the investigator should group signs or symptoms that constitute a single diagnosis into a single event term. For example, cough, rhinitis, and sneezing might be grouped together as *upper respiratory tract infection*.

All grade 3 or higher AEs and all SAEs encountered by enrolled patients during the clinical trial from the time the informed consent is signed through the End of Study Visit will be recorded on the AE CRF page(s).

In cases where there is an unanticipated benefit to the patient, study site personnel should record this event in the CRF log.

8.3.1.2 Assessment of the Intensity (Severity) of Adverse Events

The severity of AEs will be graded according to CTCAE v3.0.

8.3.1.3 Assessment of the Relationship of Adverse Events to Study Drug

The investigator (a study physician) will determine the assessment of the causal relationship of the AE to the study drug.

Adverse events that are considered to have a *probable* or *possible* relationship to treatment with study drug will be recorded as *treatment related* in the CRF, while those that are considered to be *unlikely* or *unrelated* to treatment with study drug will be recorded as *not treatment related*.

The following categories should be used in the causality assessment of suspected adverse reactions:

Probable

The AE:

- follows a reasonable temporal sequence from the time of study drug administration; *and/or*
- follows a known response pattern to the study drug; *and*
- was unlikely to have been produced by other factors such as the patient's clinical state, therapeutic intervention or concomitant therapy.

Possible

The AE:

- follows a reasonable temporal sequence from the time of study drug administration; *and/or*
- follows a known response pattern to the study drug; *but*

- could have been produced by other factors such as the patient's clinical state, therapeutic intervention or concomitant therapy.

Unlikely

The AE:

- does not follow a reasonable temporal sequence from the time of study drug administration; *and*
- was most likely produced by other factors such as the patient's clinical state, therapeutic intervention or concomitant therapy.

Unrelated

This category is applicable to those AEs that are judged to be clearly and incontrovertibly due only to extraneous causes (the patient's clinical state, therapeutic intervention or concomitant therapy) and do not meet the criteria for study drug relationship listed under Probable, Possible, or Unlikely.

An AE with causal relationship not initially determined will require follow-up to assign causality.

8.3.1.4 Assessment of the Outcome of Adverse Events

Resolved: The patient has fully recovered from the event with no residual effects observable.

Stabilized: Effects of the event are constant. The likelihood of these effects changing (improving or worsening) is low.

Ongoing: Effects of the event are still present and changing. The event is not considered stabilized or resolved.

Death is an outcome of an event and not an event per se (sudden death or death of unexplainable causes can be reported but follow-up will be required until cause of death is determined).

8.3.2 Serious Adverse Events

8.3.2.1 Immediately Reportable Events

Any AE that is serious (see definition in Section 8.3.2.2) and occurs during the course of the study after the subject has given written informed consent must be reported to the Sponsor's designee within 24 hours of discovery of the event.

8.3.2.2 Serious Adverse Event Definition and Reporting Procedures

A serious AE (SAE) is an AE that suggests a significant hazard or side effect, regardless of the relationship to study drug.

An event is classified as serious if it meets any of the following criteria:

- Results in death.
- Is life threatening. This definition implies that the patient, in the view of the investigator, is at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongs existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly or birth defect. This serious criterion applies if a congenital anomaly/birth defect is diagnosed in a child of a subject who participated in this study and received study drug.
- Other important medical events. Medical and scientific judgment should determine whether an AE should be classified as serious in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or require intervention to prevent one of the outcomes listed in the definition above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependence or abuse.

All SAEs (regardless of suspected causality) should be communicated within 24 hours of discovery of the event to:

Prologue Pharmacovigilance

PPD

Phone number: PPD

Fax number: PPD

SAEs occurring any time after study participation that are considered by the investigator to be possibly related to study drug must also be reported as outlined above.

8.3.2.3 Reporting of Serious Adverse Events to Regulatory Agencies

The Sponsor will determine the SAEs requiring expedited reporting to regulatory agencies. SAEs that qualify for expedited reporting will be reported by the Sponsor or

designee to regulatory agencies. The study site personnel are responsible for reporting these events to their Institutional Review Boards (IRB) in accordance with applicable laws and regulations.

8.3.2.4 Follow-up of Adverse Events

Adverse event information will be collected from the time the subject signs informed consent through the End of Study Visit. AEs should be followed until the event resolves or through the End of Study Visit.

8.3.3 Overdose Reporting

Occurrences of overdose should be reported to the Sponsor for tracking purposes. In this study overdose is defined as a dose greater than the specified dose for the cohort. Instructions for reporting overdose information will be provided by the Sponsor at the time of notification.

9 DATA QUALITY CONTROL AND QUALITY ASSURANCE

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

- Provide instructional material to the study sites, as appropriate.
- Instruct the investigators and study personnel 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, email, telephone, and/or fax.
- Monitor the patient data recorded in the CRF against source documents at the study site.
- Review and evaluate CRF data and use standard computer edits to detect errors in data collection.

The study may be audited by the Sponsor or its representatives and/or regulatory agencies at any time. If contacted by a regulatory agency for an audit, please call the Sponsor's study manager immediately. Contact information for the Sponsor's study manager is included in the investigator file.

10 DATA ANALYSIS METHODS

10.1 Determination of Sample Size

Not applicable.

10.2 Statistical and Analytical Plans

10.2.1 General Considerations

Complete details of the statistical analysis will be provided in the Statistical Analysis Plan. All data summaries will be descriptive in nature. For data summaries involving continuous variables data tables will typically contain the following information: sample size, mean, median, standard deviation, standard error, minimum and maximum. For categorical variables, the following information will typically be presented: sample size and proportion. When required for the statistical analysis of a particular variable, the baseline value will be the last recorded value prior to the administration of the first dose of study treatment.

10.2.1.1 Handling of Missing Data

Analyses will be based upon observed data without imputation.

10.2.1.2 Analysis Populations

All patients receiving at least 1 dose of study drug will be included in the analyses.

10.2.2 Subject Disposition

An accounting of study patients by disposition will be tabulated by indication.

10.2.3 Subject Characteristics

Demographic and other baseline characteristics and anti-cancer concomitant medications will be summarized by indication.

10.2.4 Treatment Compliance

Treatment compliance will be analyzed by comparing the number of doses dispensed, the days of drug therapy, and the number of doses returned.

10.2.5 Efficacy Analyses

The duration of clinical response and progression free survival will be summarized by indication. The data will also be summarized by the use or not of concomitant anti-cancer therapy.

10.2.6 Pharmacokinetic and Pharmacodynamic Analyses

Not applicable.

10.2.7 Safety Analyses

10.2.7.1 Extent of Exposure

Duration of treatment will be summarized.

10.2.7.2 Adverse Events

The incidence of all reported AEs and treatment-related AEs will be tabulated. AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). For incidence reporting, if a patient reported more than one AE that was coded to the same system organ class or preferred term, the patient will be counted only once for that specific system organ class or preferred term. A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in intensity after the administration of study drug.

An overview of AEs, which includes patient incidence of TEAEs, treatment-related AEs, SAEs, deaths, and AEs leading to discontinuation, will be presented. For AEs presented by severity, the worst severity during the study will be presented for each patient. The data will also be summarized by the use or not of concomitant anti-cancer therapy.

The patient incidence of TEAEs will be summarized by system organ class and preferred term. The patient incidence of treatment-related AEs and CTCAE toxicity grade will be summarized by preferred term. The data will also be summarized by the use or not of concomitant anti-cancer therapy.

10.2.7.3 Serious Adverse Events

SAEs will be listed and summarized in a similar manner to AEs as described in Section 10.2.7.2.

11 INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

11.1 Informed Consent

The investigator is responsible for presenting the risks and benefits of study participation to the patient in simple terms using the informed consent document. The investigator will ensure that written informed consent is obtained from each patient by obtaining the appropriate signatures and dates on the informed consent document prior to the performance of protocol evaluations or procedures.

11.2 Ethical Review

The investigator will provide the Sponsor or its designee with documentation of the IRB approval of the protocol and the informed consent document before the study may begin at the investigative site. The name and address of the reviewing IRB are provided in the investigator file.

The investigator will supply the following to the investigative site's IRB:

- Protocol and amendments.
- Informed consent document and updates.
- Any other patient-specific information (e.g., advertisements, website postings).
- Investigator's Brochure and updates.
- Relevant curricula vitae, if required.
- Required safety and SAE reports.
- Any additional submissions required by the site's IRB.

The investigator must provide the following documentation to the Sponsor or its designee:

- The IRB periodic (e.g., quarterly, annual) re-approval of the protocol.
- The IRB approvals of any amendments to the protocol or revisions to the informed consent document.
- The IRB receipt of safety and SAE reports, as appropriate.

11.3 Regulatory Considerations

This study will be conducted in accordance with the protocol and ethical principles stated in the Declaration of Helsinki or the applicable guidelines on good clinical practice, and all applicable federal, state, and local laws, rules, and regulations.

All data recorded in the CRF for patients participating in this study will be transcribed from medical records, though the CRF may serve as the source document in some cases. When the CRF is used as the source, it will be documented in the study file.

After reading the protocol, the investigator will sign the protocol signature page and return it to the Sponsor or its designee.

11.3.1 Investigator Information

The contact information and qualifications of the principal investigator and sub-investigators and name and address of the research facilities are included in the investigator file.

11.3.2 Protocol Amendments and Study Termination

Any investigator-initiated changes to the protocol (with the exception of changes to eliminate an immediate hazard to a study patient) must be approved by the Sponsor prior to seeking approval from the IRB, and prior to implementing. The investigator is responsible for enrolling patients who have met protocol eligibility criteria. Protocol violations must be reported to the Sponsor and the local IRB in accordance with IRB procedures.

The Sponsor may terminate the study at any time. The IRB must be advised in writing of study completion or early termination.

11.4 Study Documentation, Privacy and Records Retention

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the investigator until notified by the Sponsor in writing that retention is no longer necessary.

To protect 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 the Sponsor, applicable regulatory agencies, and applicable IRB with direct access to original source documents.

Records containing subject medical information must be handled in accordance with the requirements of the applicable privacy rules and consistent with the terms of the subject authorization contained in the informed consent document for the study (the Authorization). Care should be taken to ensure that such records are not shared with any person or for any purpose not contemplated by the Authorization. Furthermore, CRFs and other documents to be transferred to Sponsor should be completed in strict accordance

with the instructions provided by Sponsor, including the instructions regarding the coding of patient identities.

No study document should be destroyed without prior written agreement between Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from Sponsor.

11.5 Clinical Trial Agreement

Payments by the Sponsor to investigators and institutions conducting the trial, requirements for investigators' insurance, the publication policy for clinical trial data, and other requirements are specified in the Clinical Trial Agreement.

12 APPENDICES

12.1 Clinically Relevant CYP3A4 Inhibitors and Inducers

CYP3A4 Effect	Medications
Inhibitors	Indinavir Nelfinavir Ritonavir Amiodarone Cimetidine Clarithromycin Diltiazem Erythromycin Fluvoxamine Grapefruit juice Itraconazole Ketoconazole Mibefradil Nefazodone Troleandomycin Verapamil
Inducers	Carbamazepine Phenobarbital Phenytoin Rifabutin Rifampin St. John's wort Troglitazone

13 PROTOCOL SIGNATURES

By signing this protocol, the investigator agrees to conduct the study in accordance with the protocol, generally accepted standards of good clinical practice, and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study. In addition, the investigator agrees to provide the Sponsor with accurate financial information to allow the Sponsor to submit complete and accurate certification and disclosure statements as required by applicable regulations.

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written procedures to ensure that the trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of good clinical practice, and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the study.

Principal Investigator's Signature

Print Name

Date

Site Address and Telephone

Sponsor's Medical Expert's Signature

Print Name

Date