**Phase I Protocol Template**

|  |  |
| --- | --- |
| **Template Version Date** | **July 23, 2019** |
| Replaces Version Date | April 23, 2019 |

General Instructions for using the HDFCCC protocol template

* Guidance for completing the template is included within the document:
	+ *Blue italic text:* Instructions for completing the protocol sections. **As you fill in the template, please delete all blue italic text.**
	+ <<Red text>>: Placeholders to fill in study-specific information. Please add the appropriate information and format to plain black protocol text when completed.
	+ Black text: “Boilerplate” HDFCCC protocol language.
* Please use the built-in styles for section headings and protocol text (located in the ‘Home’ tab). Appropriate use of these styles allows for automatic updates to the Table of Contents.

 

* Please delete this instructions page from the protocol document.

Instructions for merging an existing protocol or sponsor protocol template with the HDFCCC template

Investigators who have drafted a study protocol or are using a sponsor template must incorporate the following sections of this template into the existing/sponsor protocol document:

* HDFCCC Cover Page
* HDFCCC logo, protocol version date, and CC# on every page
* [Protocol Signature Page](#_Protocol_Signature_Page) (multi-center studies must include the signature page for [UCSF and participating sites](#_Protocol_Signature_Page_1))
* [Study Objectives](#_Study_Objectives) – Provide distinct endpoint(s) and time frame(s) for measuring each objective, per [ClinicalTrials.gov requirements](https://prsinfo.clinicaltrials.gov/ProtocolDetailedReviewItems.pdf)
* [Inclusion and Recruitment of Women and Minorities](#_Inclusion_and_Recruitment)
* [Primary Completion](#_Primary_Completion)
* [Study Completion](#_Study_Completion)
* [Participant Registration](#_Participant_Registration)
* [Schedule of Procedures and Assessments](#_Schedule_of_Procedures)
* [Definitions of Adverse Events](#_Definitions_of_Adverse)
* [Recording of Adverse Events](#_Recording_of_Adverse)
* [Follow-up of Adverse Events](#_Follow-up_of_Adverse)
* [Adverse Events Monitoring](#_Adverse_Events_Monitoring)
* [Expedited Reporting](#_Expedited_Reporting)
* [Study Management](#_Study_Management)
* [Protection of Human Subjects (for multicenter studies)](#_Protection_of_Human)
* [Data and Safety Monitoring Plan](http://cancer.ucsf.edu/itr/sm_files/UCSF%20HDFCCC%20DSMP2017.pdf)

Study Title

Protocol Number: CC #

Investigational Product(s):

Version Number:

Version Date:

IND Number:

NCT Number:

Principal Investigator (Sponsor-Investigator)

PI Name

University of California San Francisco

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San Francisco, CA 94

Telephone: 415-

E-mail:

Statistician

**Revision History**

|  |  |
| --- | --- |
| Version        | Date  |

# Protocol Signature Page

**Protocol No.:**       **Version Date:**

1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Institutional Review Board (IRB), and Data and Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with Good Clinical Practices (ICH-GCP) and the applicable IRB, ethical, federal, state, and local regulatory requirements.
3. I certify that I, and the study staff, have received the required training to conduct this research protocol.
4. I agree to maintain adequate and accurate records in accordance with IRB policies, federal, state and local laws and regulations.

|  |  |  |
| --- | --- | --- |
| **UCSF Principal Investigator**  |  |  |
| Printed Name |  |  |
| Signature |  | Date |

# Protocol Signature Page – Participating Sites

***For multicenter trials – delete this page if the study will be conducted at UCSF only***

**Protocol No.:**       **Version Date:**

Participating Site(s)

|  |  |
| --- | --- |
| **Principal Investigator Name:**  **Institution Name:****Address:** **Telephone:**  **E-mail:**  | **Principal Investigator Name:**  **Institution Name:****Address:** **Telephone:** **E-mail:**  |

I have read this protocol and agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP) and the applicable IRB, ethical, federal, state, and local regulatory requirements.

|  |  |  |
| --- | --- | --- |
| **Principal Investigator** |  | **Site** |
| Printed Name |  | Institution Name |
| Signature |  | Date |

# Abstract

|  |  |
| --- | --- |
| Title | *Cross-reference Study Title* |
| Study Description | *Provide a short description of the protocol and study design, including a brief statement of the study hypothesis. This should be only a few sentences in length.* |
| Phase of Study | Phase 1 |
| Investigational Products | *Cross-reference* [*Section 4*](#_Investigational_Products) |
| Study population | *Specify gender, age, demographic group, general health status, and geographic location limiters.* |
| Primary Objective | *Cross-reference* [*Section 2.2*](#_Primary_Objective_and) |
| Secondary Objectives | *Cross-reference* [*Section 2.3*](#_Secondary_Objective(s)_and) |
| Sample Size | *State planned number of participants to be treated/enrolled in the investigational portion of the study. This can be a range with minimum and maximum projections, depending on protocol design. Information provided here should be consistent with* [*Section 3.2*](#_Number_of_Participants)*.* |
| Duration of Study Treatment | Participants may continue study treatment for << # / time frame / maximum treatment duration: weeks, months, years >> from the time of initiating treatment.  |
| Duration of Follow up | *Cross-reference* [*Section 3.5*](#_Duration_of_Follow) |
| Unique Aspects of this Study | *Optional, for example: “This is the first study to evaluate the safety and efficacy of XXX in patients with XXX.”* |

| List of Abbreviations |
| --- |
| AE | adverse event |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| BUN | blood urea nitrogen |
| CBC | complete blood cell (count) |
| CNS | central nervous system |
| CR | complete response |
| CRF | case report form |
| CT | computerized tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTMS | Clinical Trial Management System |
| DFS | disease-free survival |
| DLT | dose limiting toxicity |
| DSMC | Data and Safety Monitoring Committee |
| DSMP | Data and Safety Monitoring Plan |
| ECG/EKG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| FDA | Food and Drug Administration |
| FDG | Fluorodeoxyglucose |
| FLC | free light chain |
| GCP | Good Clinical Practice |
| GFR | glomerular filtration rate |
| HBeAg | hepatitis B “e” antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HDFCCC | Helen Diller Family Comprehensive Cancer Center |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | human immunodeficiency virus |
| ICF | informed consent form |
| ICH | International Conference on Harmonization |
| IDS | Investigational Drug Services (UCSF) |
| IND | investigational new drug application |
| IP | investigational product |
| IRB | Institutional Review Board |
| IV | intravenous |
| LDH | lactate dehydrogenase |
| MRI | magnetic resonance imaging |
| MTD | maximum tolerated dose |
| NCI | National Cancer Institute |
| ORR | overall response rate |
| PD | disease progression |
| PK | pharmacokinetics |
| PO | *Per os* (by mouth, orally) |
| PR | partial response |
| PRC | Protocol Review Committee (UCSF) |
| SD | stable disease |
| SGOT | serum glutamic oxaloacetic transaminase |
| SGPT | serum glutamic pyruvic transaminase |

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# Introduction

## Background on Indication

*State the problem or question (e.g., describe the population, disease, current standard of care, if one exists, and limitations of knowledge or available therapy).*

## Background on the Investigational Product(s) and Associated Known Toxicities

*This section should include:*

* *A summary of mechanism of action for each investigational agent.*
* *A summary of findings from nonclinical in vitro or in vivo studies that have potential clinical significance*
* *A summary of relevant clinical research and any history of human use or exposure to the investigational product(s), including*
	+ *Use in other countries*
	+ *Pharmacokinetics*
	+ *Major route of elimination*
	+ *Metabolism of the agent(s) in humans*
	+ *Potential drug interactions*

## Rationale for the Proposed Study

*Why is the study being done? What is the intent of the research? This section should connect the disease background with the investigational product(s) under evaluation and provide a brief overview of the study.*

* *Provide background rationale for evaluating this intervention in this disease.*
* *Survey current treatment options for patient population and review of clinical outcomes for these treatments.*
* *Indicate why this information is valuable and how it advances knowledge.*
* *Identify possible risks and benefits; how risks will be mitigated in the study, and why potential benefits outweigh the risks.*

## Rationale for the Dose Selection/Regimen

*Provide a justification for the route of administration, planned maximum dosage, and regimen, including starting dose and dos-escalation scheme of the investigational product(s).*

## Correlative Studies

*If applicable:*

* *Provide background information on each planned correlative study including the biological rationale and hypothesis as well as the relevant preclinical and clinical data (if available). Correlative studies should align with Exploratory (Correlative) objectives listed in Section 2.4*
* *For additional information, see FDA’s Guidance* [*Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories*](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073162.pdf) *and CTEP’s* [*Guidelines for Correlative Studies in Clinical Trials*](http://ctep.cancer.gov/protocolDevelopment/templates_applications.htm)*.*

*If this trial includes no correlative studies, this section can be removed.*

# Study Objectives

## Hypothesis

We hypothesize that <<study specific prediction about what the study will demonstrate>>.

* *The hypothesis should be an educated, well-defined, and testable prediction about what will happen in the study. The hypothesis should be coupled with the primary objective.*

## Primary Objective and Endpoint(s)

* *The primary objective is the main question. This objective generally drives statistical planning for the trial (e.g., calculation of the sample size to provide the appropriate power for statistical testing).*
	+ *Generally, there should be just one primary endpoint that will provide a clinically relevant, valid, and reliable measure of the primary objective.*
	+ *Examples of Primary Objectives are included below. Please add/remove/modify as applicable to the study.*
* *Each endpoint should specify:*
	+ *One measurement*
	+ *How it’s being measured*
	+ *Time frame for the measurement (this should be included in the ‘Time Frame’ column of the table.*
* *HDFCCC recommends that PIs state objectives and endpoints to align with ClinicalTrials.gov registration and reporting requirements.*
	+ *For more information, see Outcome Measures:* [*https://prsinfo.clinicaltrials.gov/ProtocolDetailedReviewItems.pdf*](https://prsinfo.clinicaltrials.gov/ProtocolDetailedReviewItems.pdf)
* *FDA guidance on use of multiple endpoints in clinical trials is available here:* [*https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm536750.pdf*](https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm536750.pdf)

| **Primary Objective** | **Endpoint(s)** | **Time Frame** |
| --- | --- | --- |
| 1. To determine the safety and tolerability of <<investigational product(s)>>.
 | * Proportion of participants with Adverse Events, as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 5.0
 | <<e.g. from initiation of study treatment until discontinuation of treatment. >> |
| 1. To determine the maximum tolerated dose (MTD) for <<investigational product(s)>>.
 | * MTD, defined as the dose at which fewer than one-third of participants experience a dose limiting toxicity (DLT).
 |  |
| 1. To assess the feasibility of <<type/intervention of pilot study>>.
 | * <<measurement for determining if the study is considered feasible. (E.g., proportion of participants with delayed surgery due to study-related AEs, proportion of participants who complete X cycles of study treatment>>
 |  |

## Secondary Objective(s) and Endpoint(s)

* *The secondary objective(s) are goals that will provide further information on the use of the study treatment. Secondary objectives can provide supportive information about the study intervention’s effect on the primary endpoint or demonstrate additional effects on the disease or condition.*
	+ *Examples of Secondary Objectives are included below. Please add/remove/modify as applicable to the study.*
* *Each endpoint should specify:*
	+ *One measurement*
	+ *How it’s being measured*
	+ *Time frame for the measurement (this should be included in the ‘Time Frame’ column of the table.*
* *HDFCCC recommends that PIs state objectives and endpoints to align with ClinicalTrials.gov registration and reporting requirements.*
	+ *For more information, see Outcome Measures:* [*https://prsinfo.clinicaltrials.gov/ProtocolDetailedReviewItems.pdf*](https://prsinfo.clinicaltrials.gov/ProtocolDetailedReviewItems.pdf)
* *FDA guidance on use of multiple endpoints in clinical trials is available here:* [*https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm536750.pdf*](https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm536750.pdf)
* *Pharmacokinetic outcome measures (e.g., Cmax, AUC) rely on multiple measurements over time, so these Time Frames may include multiple time points describing the intervals at which data are collected (e.g., “1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, and 96 hours post-dose”).*

| **Secondary Objective** | **Endpoint(s)** | **Time Frame** |
| --- | --- | --- |
| 1. To describe the pharmacokinetics associated with << investigational product(s)>>
 | * Pharmacokinetic (PK) assessments for << investigational product(s) >>
 |  |
| 1. To describe the efficacy of << investigational product(s) >> in patients with << tumor/disease type, etc. >>
 | * <<measurement (e.g. ORR)>>
* <<measurement>>
 |  |

## Exploratory (Correlative) Objectives

* *Exploratory objectives aim to explore other effects for new hypotheses or clinically important events that are expected to occur too infrequently to show a treatment effect.*
* *Each endpoint should specify:*
	+ *One measurement*
	+ *How it’s being measured*
	+ *Time frame for the measurement (this should be included in the ‘Time Frame’ column of the table.*
* *FDA guidance on use of multiple endpoints in clinical trials is available here:* [*https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm536750.pdf*](https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm536750.pdf)
* *HDFCCC recommends that PIs state objectives and endpoints to align with ClinicalTrials.gov registration and reporting requirements.*
	+ *For more information, see Outcome Measures:* [*https://prsinfo.clinicaltrials.gov/ProtocolDetailedReviewItems.pdf*](https://prsinfo.clinicaltrials.gov/ProtocolDetailedReviewItems.pdf)

| **Exploratory Objective** | **Endpoint(s)** |
| --- | --- |
|  |  |
|  |  |
|  |  |

# Study Design

## Characteristics

*This section should include the following information:*

* *Phase of the trial*
* *A description of the type/design of trial to be conducted (e.g., randomized, placebo-controlled, double-blinded, parallel design, open-label, dose escalation, dose-ranging, adaptive, cluster randomized, group sequential, multi-regional, superiority or non-inferiority design)*
* *A description of methods to be used to minimize bias*
* *Dose escalation or dose-ranging information should not be detailed here, this information is contained in Section 5*
* *The number of study groups/arms and study intervention duration*
* *Indicate if single site or multi-site*
* *Name of study intervention(s)*
* *Note if interim analysis is planned and refer to details in Section 9.4.6, Planned Interim Analysis*
* *Note if the study includes any stratifications and if so, identify the stratification planned (e.g. sex, race/ethnicity, age, dose) and refer to details in Section 9.4.7, Sub-Group Analyses*

## Sample Size

* *State the target number of participants to be treated under the study/ enrolled in the investigational portion of the study (sample size for primary objective).*
	+ *If the study includes multiple arms/cohorts, specify sample size needed for each arm/cohort (provide ranges with minimum and maximum projections, if applicable to study design)*
* *Also state the total number of participants to be consented for the study in order to reach sample size needed- take into account:*
	+ *Screening failures*
	+ *Withdrawals*
* *If participants are to be replaced, this should also be included in this section. For example:* Participants who do not <<criteria for replacement>> will not be evaluable and will be replaced.

## Eligibility Criteria

*The eligibility criteria included in this template are based on:*

* *The recommendations of the American Society of Clinical Oncology and Friends of Cancer Research for broadening eligibility criteria to make clinical trials more representative:* [*http://ascopubs.org/doi/full/10.1200/JCO.2017.73.7916*](http://ascopubs.org/doi/full/10.1200/JCO.2017.73.7916)
* *NCI clinical trial protocol template:* [*https://ctep.cancer.gov/protocolDevelopment/templates\_applications.htm*](https://ctep.cancer.gov/protocolDevelopment/templates_applications.htm)
* *NIH-FDA clinical trial protocol template:* [*https://grants.nih.gov/policy/clinical-trials/protocol-template.htm*](https://grants.nih.gov/policy/clinical-trials/protocol-template.htm)

### Inclusion Criteria

1. Participants must have histologically or cytologically confirmed << indication or study disease >>.
2. <<Measure of lesions OR criteria for diseases other than solid tumors>>
3. <<Allowable type and amount of prior therapy>>
4. Age ≥18 years
* [*FDA Guidance for Industry - Cancer Clinical Trial Eligibility Criteria: Minimum Age for Pediatric Patients*](https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM633138.pdf?utm_campaign=SBIA%3A%20FDA%20Announces%20a%20Series%20of%20Draft%20Guidances%20Regarding%20Cancer%20Clinical&utm_medium=email&utm_source=Eloqua)
* *Note: Pediatric-specific cohorts should be included in early-phase trials when there is strong scientific rationale for likelihood of benefit, based on molecular pathways or histology as well as preclinical data.*
	+ *Investigators and their industry collaborators are encouraged to discuss the inclusion of pediatric participants in the investigational product development plan early in the development process and determine when it is relevant to study the product in pediatric cancers.*
	+ *For studies that plan to include participants younger than age 18, a pediatric oncologist coinvestigator must be involved with the study.*
* *State reason for age restriction. If applicable, the following text can be used.*

Because no dosing or adverse event data are currently available on the use of <<investigational product(s)>> in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

1. ECOG performance status <2 (Karnofsky >60% (see Appendix 1)
2. Demonstrates adequate organ function as defined below:

|  |
| --- |
| Adequate bone marrow function: |
| absolute neutrophil count | ≥1,500/mcL |
| platelets | ≥100,000/mcL |
| Adequate hepatic function: |
| total bilirubin | within normal institutional limits, unless elevated due to Gilbert’s syndrome and direct bilirubin is within normal limits |
| AST(SGOT) | ≤3 X institutional upper limit of normal |
| ALT(SGPT) | ≤3 X institutional upper limit of normal |
| Adequate renal function: |
| creatinine | ≤ 1.5 x within institutional upper limit of normal |
| ORcreatinine clearance  | GFR ≥ 60 mL/min/1.73 m2,calculated using the Cockcroft-Gault equation, unless data exists supporting safe use at lower kidney function values, no lower than 30 mL/min/1.73 m2  |

* *Note: Investigators can refer to the following FDA guidance for setting organ function requirements:* [*FDA Guidance for Industry - Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies*](https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM633137.pdf?utm_campaign=SBIA%3A%20FDA%20Announces%20a%20Series%20of%20Draft%20Guidances%20Regarding%20Cancer%20Clinical&utm_medium=email&utm_source=Eloqua)
1. Ability to understand a written informed consent document, and the willingness to sign it
2. Human immunodeficiency virus (HIV)-infected individuals on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.
* [*FDA Guidance for Industry - Cancer Clinical Trial Eligibility Criteria: Patients with HIV, Hepatitis B Virus, or Hepatitis C Virus Infections*](https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM633136.pdf?utm_campaign=SBIA%3A%20FDA%20Announces%20a%20Series%20of%20Draft%20Guidances%20Regarding%20Cancer%20Clinical&utm_medium=email&utm_source=Eloqua)
* *Note: HIV-related eligibility criteria should be straightforward and focus on: - Current and past CD4 and T-cell counts - History (if any) of AIDS-defining conditions - Status of HIV treatment Individuals with HIV infection should be treated using the same standards as other individuals with co-morbidities. Antiretroviral therapy should be considered a concomitant medication.*
1. For participants with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.
2. Individuals with a history of hepatitis C virus (HCV) infection must have been treated and cured. For individuals with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.
3. Individuals with treated brain metastases are eligible if follow-up brain imaging after central nervous system (CNS)-directed therapy shows no evidence of progression.
* [*FDA Guidance for Industry - Cancer Clinical Trial Eligibility Criteria: Brain Metastases*](https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM633132.pdf?utm_campaign=SBIA%3A%20FDA%20Announces%20a%20Series%20of%20Draft%20Guidances%20Regarding%20Cancer%20Clinical&utm_medium=email&utm_source=Eloqua)
* *Note: In specific trials, it may be necessary to add a time factor regarding the follow-up brain imaging, but this should be as lenient as medically indicated.*
1. Individuals with new or progressive brain metastases (active brain metastases) or leptomeningeal disease are eligible if the treating physician determines that immediate CNS specific treatment is not required and is unlikely to be required during the first cycle of therapy.
* *Note: Individuals with active brain metastases should be included early in clinical development when there is strong scientific rationale for likelihood of benefit based on molecular pathways or histology as well as preclinical data. - For drugs/modalities with less robust preclinical information on potential CNS activity, inclusion of participants with active brain metastases should still be considered, particularly if brain metastases are common in the intended-use population.*
1. Individuals with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.
* [*FDA Guidance for Industry - Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies*](https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM633137.pdf?utm_campaign=SBIA%3A%20FDA%20Announces%20a%20Series%20of%20Draft%20Guidances%20Regarding%20Cancer%20Clinical&utm_medium=email&utm_source=Eloqua)
1. The effects of << investigational product(s) >> on the developing human fetus are unknown. For this reason and because << class(es) of investigational product(s)>> used in this trial are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception: << specify which method is adequate for this study: hormonal or barrier method of birth control; abstinence, etc. >> for the duration of study participation and for <<## months/weeks>> after last administration of study treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and << # >> months/weeks>> after last administration of study treatment.

1. <<Any other applicable inclusion criteria>>

### Exclusion Criteria

1. Has received systemic anti-cancer therapies within 3 weeks of first dose, radiation within 2 weeks, antibody therapy within 4 weeks. Concomitant administration of LHRH analogues for prostate cancer and somatostatin analogues for neuroendocrine tumors are allowed as per standard of care.
* *Note: consider shorter interval for kinase inhibitors or other short half-life drugs*
1. Has not recovered from adverse events due to prior anti-cancer therapy to ≤ grade 1 or baseline (other than alopecia).
2. Is currently receiving any other investigational agents.
3. Has participated in a study of an investigational product and received study treatment or used an investigational device within <<XX weeks>> of the first dose of treatment.
4. <<Exclusion requirements due to co-morbid disease or concurrent illness>>
5. Hypersensitivity to <<study product(s)>> or any of its excipients.
6. <<Criteria relating to concomitant medications>>
7. Pregnant women are excluded from this study because << investigational product(s) is/are <<class(es) of investigational product(s)>> with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with << investigational product(s) >>, breastfeeding should be discontinued if the mother is treated with << investigational product(s) >>.
8. <<Any other applicable exclusion criteria>>

## Inclusion and Recruitment of Women and Minorities

Individuals of any sex/gender, race, or ethnicity may participate.

* *If inclusion of women or minority groups is not appropriate for the trial design please alter the statement above and provide a clear rationale and justification in the context of the scientific goals of the study. Cost to recruit certain groups is not considered an acceptable justification for limiting the inclusion of those groups, unless substantial scientific data pertinent to the population already exists. For more information, see* [*NIH Policy and Guidelines on The Inclusion of Women and Minorities as Subjects in Clinical Research*](https://grants.nih.gov/grants/funding/women_min/guidelines.htm)*.*
* *Please include specifics about the sex/gender, race, and ethnicity of the study’s target population as applicable.*

The study recruitment strategy aims to achieve representation of minority groups that reflects the demographics of the affected population in the catchment area.

* *The study must include a recruitment strategy consistent with the guidelines set forth by the* [*NIH Revitalization Act of 1993, Public Law 103-43*](https://www.nap.edu/read/2304/chapter/12)*. This requires consideration of outreach programs to conduct or support recruitment of women and members of minority groups as participants and design of the clinical trial to include a valid analysis plan of whether variables being studied in the trial affect women or minority groups. These recruitment programs should aim to achieve representation of minority groups that reflects the demographics of the affected population in the catchment area.*
* *Please include specifics about the study’s recruitment strategy as applicable.*

## Duration of Treatment

In the absence of treatment delays due to adverse events, treatment may continue for << # cycles/time frame >> or until:

* Disease progression which requires discontinuation of the study treatment;
* Inter-current illness that prevents further administration of treatment;
* Unacceptable adverse event(s);
* Participant decides to withdraw from the study;
* Significant participant non-compliance with protocol;
* If the participant meets an exclusion criterion (either newly developed or not previously; or, recognized) that precludes further study participation
* General or specific changes in the participant’s condition render the participant unacceptable for further treatment in the judgment of the investigator.

## Duration of Follow Up

Participants will be followed for <<## days (minimum of 30 days)>> after last treatment or removal from study, or until death, whichever occurs first. Participants removed from study for unacceptable treatment or study related adverse event(s) will be followed until resolution or stabilization (as determined by the investigator) or until initiation of new anti-cancer therapy, whichever occurs first.

* *Add long-term follow up, if applicable. Please note, the FDA requires up to fifteen years of long-term follow up for gene therapy agents. See:* <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM610797.pdf>

## Randomization Procedures

* *Describe the randomization process and any stratification factors. If this is a non-randomized study, please remove this section.*

## Primary Completion

The expected primary completion is <<## months/years>> after the study opens to accrual.

* *The estimated primary completion date is the date that the last study participant will be examined or receive an intervention so that data collection for the primary outcome measure/endpoint is complete.*
* *In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection will be completed for all of the primary outcomes.*
* *For more information see:* [*https://clinicaltrials.gov/ct2/help/glossary/primary-completion-date*](https://clinicaltrials.gov/ct2/help/glossary/primary-completion-date)

## Study Completion

The expected study completion date is <<## months/years>> after the study opens to accrual.

* *The date the final participant was examined or received an intervention for purposes of final collection of data for the primary and secondary outcome measures and adverse events (for example, last participant’s last visit).*

# Investigational Products

## Description, Supply and Storage of Investigational Products

### <<Investigational Product #1>>

*Most of the information in this section can usually be obtained from the IB or the package insert, or device labeling.*

Classification

Mechanism of Action

Metabolism

Contraindications

Formulation, Appearance, Packaging, and Labeling

<< Investigational Product #1 >> is supplied as << e.g. # capsules/tablets or #/mL solution in a single-use vial>> for <<oral/intravenous>> administration.

* *Describe the formulation, appearance, packaging, and labeling of the investigational product, as supplied.*
* *Include the name of the manufacturer of the investigational product.*

Availability

<<Investigational Product #1>> is being obtained as <<commercial supply OR study supply provided by XXXX>>.

* *If study supply for an FDA-approved product is being used, indicate any differences in manufacturing or appearance from commercial supply of the product.*

Storage and handling

<<Investigational Product #1>> is stored at <<the UCSF investigational pharmacy>>.

* *Describe storage and stability requirements (e.g., protection from light, temperature, humidity) for the study intervention and control product.*
* *For studies in which multi-dose vials are utilized, provide additional information regarding stability and expiration time after initial use (e.g., the seal is broken).*

Side Effects

Complete and updated adverse event information is available in the Investigational Drug Brochure (IB) and/or product package insert.

### <<Investigational Product #2>>

*Most of the information in this section can usually be obtained from the IB or the package insert, or device labeling.*

Classification

Mechanism of Action

Metabolism

Contraindications

Formulation, Appearance, Packaging, and Labeling

<< Investigational Product #2 >> is supplied as << e.g. # capsules/tablets or #/mL solution in a single-use vial>> for <<oral/intravenous>> administration.

* *Describe the formulation, appearance, packaging, and labeling of the investigational product, as supplied.*
* *Include the name of the manufacturer of the investigational product.*

Availability

<< Investigational Product #2 >> is being obtained as <<commercial supply OR study supply provided by XXXXX>>.

* *If study supply for an FDA-approved product is being used, indicate any differences in manufacturing or appearance from commercial supply of the product.*

Storage and handling

<< Investigational Product #2 >> is stored at <<the UCSF investigational pharmacy>>.

* *Describe storage and stability requirements (e.g., protection from light, temperature, humidity) for the study intervention and control product.*
* *For studies in which multi-dose vials are utilized, provide additional information regarding stability and expiration time after initial use (e.g., the seal is broken).*

Side Effects

Complete and updated adverse event information is available in the current IB and/or product package insert.

##  Accountability Records for Investigational Product(s)

UCSF Investigational Drug Services (IDS) will manage drug accountability records for UCSF.

*If this is a multicenter study, also specify management of drug accountability records for participating sites.*

*For example:* Each participating site/institution is responsible for site management of drug accountability records.

## Ordering Investigational Product(s)

UCSF will obtain << investigational product(s) >> directly from <<pharmaceutical company or supplier>>.

* *If the study is using multiple investigational products, indicate if different investigational products are being obtained from different sources.*
* *For multicenter studies, indicate if participating sites order investigational product(s) from UCSF or directly from supplier or other source.*

*For example:* Each participating site will order <<investigational product(s)>> from <<insert supplier, and ordering process if applicable>>.

# Treatment Plan

## Dosage and Administration

Treatment will be administered on an <<inpatient/outpatient>> basis.

* *Describe the regimen (drug, dose, route, and schedule) and state any special precautions or warnings relevant for investigational study drug administration (e.g., incompatibility of the drug with commonly used intravenous solutions, necessity of administering drug with food, how to round a dose of oral drug to available tablet/capsule strengths, premedications etc.), and describe in detail any prophylactic or supportive care regimens required for study drug(s) administration.*
* *See CTEP’s* [*Guidelines for Treatment Regimens, Expression and Nomenclature*](http://ctep.cancer.gov/protocolDevelopment/policies_nomenclature.htm) *for guidance on expressing chemotherapy dosage schedules and treatment regimens.*

* *Provide separate regimen descriptions for different treatment groups of participants.*
* *State how missed (or omitted) doses should be handled.*
* ***Drug diaries:*** *For orally or self-administered drugs, provide a method for assessing compliance with treatment. The use of a diary should also be included in the schedule of procedures and study assessments, In* [*Section 6 Study Procedures and Schedule of Events*](#_Study_Procedures_and)*.*

*For example:* The participant will be requested to maintain a drug diary to document each dose of study drug. The drug diary will be returned to clinic staff at the end of each *<< time frame >>.*

| Table 5.1 Regimen Description |
| --- |
| **Investigational Product** | **Premedication; precautions** | **Dose** | **Route** | **Schedule** | **Cycle Length** |
| <<Agent 1>> | <<E.g. Pre-medicate with << drug >> for << # days/hours>> prior to << Agent 1>> | <<e.g. 100 mg>> | <<e.g. Oral>> | <<e.g. Days 1-3 week 1>> | <<e.g. 4 weeks (28 days) >> |
| <<Agent 2>> | <<E.g. Avoid exposure to cold (food, liquids, air) for 24 hr after each dose>> | <<e.g. 300 mg/m2 >> | <<e.g. Intravenous >> | <<e.g. Days 1-3 week 1>> |
| <<Agent 3>> | <<e.g. Take with food>> | <<e.g. 50 mg tablet>> | <<e.g. Oral>> | <<e.g. Daily, weeks 1 and 2 >> |
| Footnotes |

### Other Investigational Procedures/Modalities

* *Provide a detailed description of any other procedures/modalities (e.g., surgery, radiotherapy, hematopoietic stem cell transplantation) used in the protocol study treatment, if applicable.*

## Dose Escalation Schedule

* *State the starting dose of the investigational agent and describe the dose escalation scheme and treatment regimen. Use exact dose rather than percentages.*
* *Describe the number of participants to be treated at each level and how a decision about dose escalation or expansion of cohort sizes will be made. If there are multiple investigational agents being used in the study, include dose escalation for each investigational agent. Escalation of only one agent at each dose level is recommended.*
* *Utilize table in template as a guideline to describe the dose escalation scheme.*

| Table 5.2 Dose Escalation Schedule |
| --- |
| **Dose Level** | **Dose**  |
|  | **<<Investigational Product 1>>** | **<<Investigational Product 2>>** |
| -1 |  |  |
| 1 |  |  |
| 2 |  |  |
| 3 |  |  |
| \*Footnotes: State exact dose in units (mg/m2, µ/kg, etc.) rather than as a percentage |

* *OPTIONAL: Investigators may choose to add the following statement:*

Intermediate dose levels or alternative dosing schedules may be evaluated based on emerging data.

## Dose Limiting Toxicity (DLT) and Maximum Tolerated Dose (MTD)

Dose escalation will proceed within each cohort according to the following scheme:

| Table 5.3 Dose Escalation Schedule - DLT and MTD |
| --- |
| **Number of Participants with DLT at a Given Dose Level** | **Escalation Decision Rule** |
| 0 out of 3 | Enter 3 participants at the next dose level. |
| 1 out of 3 | Enter at least 3 more participants at this dose level.* If 0 of these 3 additional participants experience DLT (1 of 6), proceed to the next dose level.
* If 1 or more of the 3 additional participants experience DLT (2 of 6), then dose escalation is stopped and this dose is declared the maximal administered dose (highest dose administered). Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
 |
| ≥ 2 out of 3 | Dose escalation will be stopped.This dose level is declared the maximal administered dose.Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose. |
| ≤ 1 out of 6 at highest dose level below the maximal administered dose | This is the maximum tolerated dose (MTD)At least 6 participants must be entered at the MTD/recommended Phase 2 dose. |
| Footnotes |

### Dose Limiting Toxicity

*Provide explicit definitions of the type(s), grade(s), and duration(s) of adverse events that will be considered dose-limiting toxicity (DLT), or provide definitions of other endpoints that will be used to determine dose escalations. Define the DLT determination period (e.g., toxicity during Cycle 1 only).*

*For example:*

A dose limiting toxicity (DLT) will be defined as any of the following events that are considered by the investigator to be at least possibly related to <<investigational products>> and are observed <<specify DLT period, e.g. during the first 28 days of treatment (Cycle 1)>>:

**Hematologic:**

* <<study-specific hematologic DLTs>>
* <<study-specific hematologic DLTs>>

**Non-hematologic:**

* Any non-hematologic grade 3 AE, except for:
	+ << study specific exceptions>>
* Any non-hematologic grade 4 AE, except for:
	+ << study specific exceptions>>

**Study Treatment Interruptions**

* Any AE that results in delay in administration of <<investigational productions>> of more than <<-# days/time period>>
* Any AE that results in missing more than <<#>> doses

Severity of AEs will be graded according to CTCAE Version 5.0.

### Maximum Tolerated Dose

The MTD is the highest dose at which no more than one instance of DLT is observed among 6 participants treated.

## Dose Modifications and Dosing Delays

* *Treatment plans should explicitly identify when treatment (dose) modifications are appropriate. Treatment modifications/dosing delays and the factors predicating treatment modification should be explicit and clear. If dose modifications or treatment delays are anticipated, please provide a dose de-escalation schema.*
* *For combination studies, dose modifications/treatment delays may be presented separately or together, as appropriate. Use of a table format is recommended if applicable.*

| Table 5.4 Dose Modifications and Dosing Delays |
| --- |
| **Dose Level** | **Dose(s) of Investigational Agent(s), Schedule** |
| -2 |  |
| -1 |  |
| 1 |  |
| 2 |  |
| 3 |  |
| <<Footnotes>> |

The following dose modification rules will be used with respect to potential toxicity. Toxicity will be assessed according to the NCI CTCAE version 5.0.

If a participant experiences several adverse events and there are conflicting recommendations, the investigator should use the recommended dose adjustment that reduces the dose to the lowest level.

Table 5.6 Dose Modifications and Dosing Delays Tables for Specific Adverse Events

* *A dose modification table is provided below for the following adverse events: nausea, vomiting, diarrhea, neutropenia, and thrombocytopenia. Please use/modify as appropriate.*
* *A blank dose modification table is provided below for adding study-specific AE dose modifications.*

| **Adverse Events: Nausea, Vomiting, Diarrhea, Neutropenia, thrombocytopenia** |
| --- |
| **Grade of Event** | **Management/Next Dose for << investigational agent >>** | **Management/Next Dose for << investigational agent >>** |
| ≤ Grade 1 | No change in dose | No change in dose |
| Grade 2 | Hold until ≤ Grade 1Resume at same dose level | Hold until ≤ Grade 1Resume at same dose level |
| Grade 3 | Hold\* until < Grade 2Resume at one dose level lower, if indicated\*\* | Hold\* until < Grade 2Resume at one dose level lower, if indicated\*\* |
| Grade 4 | Off protocol therapy | Off protocol therapy |
| \*Participants requiring a delay of > 2 weeks should go off protocol therapy\*\* Participants requiring > two dose reductions should go off protocol therapy |
| **Recommended management:** * Nausea and Vomiting: Antiemetics
* Diarrhea: Loperamide antidiarrheal therapy

Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage 16 mg/24 hours)Adjunct anti-diarrheal therapy is permitted and should be recorded when used* << Neutropenia, thrombocytopenia: Insert any recommended management guidelines >>
 |
|  |

| **Adverse Event:**  |
| --- |
| **Grade of Event** | **Management/Next Dose for << investigational agent >>** | **Management/Next Dose for << investigational agent >>** |
| ≤ Grade 1 |  |  |
| Grade 2 |  |  |
| Grade 3 |  |  |
| Grade 4 |  |  |
| \*Footnote any relevant guidelines regarding how long a delay in therapy is allowed before participants should go off protocol therapy\*\*Footnote any relevant guidelines regarding how many dose reductions are allowed before participants should go off protocol therapy |
| << Insert any recommended management guidelines >> |

## Stopping Rules

* *The dose escalation phase of the study includes ongoing cohort review and decisions made to escalate, enroll more subjects at same dose or de-escalate the dose of investigational product.*
* *In the dose expansion phase, it is recommended to include safety stopping rules. The purpose of these rules is to control the number of participants put at risk, in the event that early experience uncovers important safety problems.*
* *Study stopping rules typically specify a number or frequency of events, such as serious adverse events or deaths, that will result in temporary suspension of enrollment and dosing until the situation can be assessed.*
* *An efficacy stopping rule, such as a Simon-2 stage design, can also be included in the dose expansion phase if desired.*
* *If a multistage design is used, criteria for moving onto subsequent stages of accrual, and for determining if the treatment is promising after the final stage of accrual must be outlined.*

*For example:*

A stopping rule for safety will halt accrual to the study after <<#>> evaluable participants have enrolled. If more than 33% of participants experience dose limiting toxicity <<or ‘unacceptable treatment-related toxicity (defined as XXX)’>>, <<consequence - e.g. study accrual will be temporarily halted and alternative dosing schedule/dose levels will be pursued>>.

# Study Procedures and Schedule of Events

The study-specific procedures and assessments are detailed in this section and outlined in the Study Calendar – Section 6.1.

Screening assessments must be performed within << # >> days prior to the first dose of investigational product, unless otherwise noted. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator.

All on-study visit procedures are allowed **a window of ± << # >> days** unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

## Study Calendar

| **Period/****Procedure** | **Screening** | **Cycle 1** | **Cycle 2 and Future Cycles** | **End of Treatment**  | **Follow-up**  |
| --- | --- | --- | --- | --- | --- |
| **Study Day/Visit Day** | **-#**  | **1(+/- #)** | **8(+/- #)** | **15(+/- #)** | **1(+/- #)** | **8(+/- #)** | **15(+/- #)** | **#(+/- #)** | **Frequency(+/- #)** |
| **Study Treatment/Drug Administration** |  |  |  |  |  |  |  |  |
| << Investigational Product 1 >> |  |  |  |  |  |  |  |  |  |
| << Investigational Product 2 >> |  |  |  |  |  |  |  |  |  |
| **Administrative Procedures** |  |  |  |  |  |  |  |  |
| Informed consent | X |  |  |  |  |  |  |  |  |
| **Clinical Assessments** |  |  |  |  |  |  |  |  |
| Physical exam | X |  |  |  |  |  |  |  |  |
| Medical history | X |  |  |  |  |  |  |  |  |
| Vital signs | X |  |  |  |  |  |  |  |  |
| Concomitant medications | X |  |  |  |  |  |  |  |  |
| AE assessment | X | X | X | X | X | X | X | X | X |
| Disease assessment 1 | X |  |  |  |  |  |  |  |  |
| Performance status | X |  |  |  |  |  |  |  |  |
| Questionnaire | X |  |  |  |  |  |  |  |  |
| Survival/Long-term Follow-up |  |  |  |  |  |  |  |  | X |
| *<< insert as needed >>* |  |  |  |  |  |  |  |  |  |
| **Laboratory Assessments** |  |  |  |  |  |  |  |  |
| Hematology 2 |  |  |  |  |  |  |  |  |  |
| Chemistry 3 |  |  |  |  |  |  |  |  |  |
| Thyroid Function 4 |  |  |  |  |  |  |  |  |  |
| Coagulation 5 |  |  |  |  |  |  |  |  |  |
| Hepatitis 6 |  |  |  |  |  |  |  |  |  |
| PK Testing 7 |  |  |  |  |  |  |  |  |  |
| Urinalysis |  |  |  |  |  |  |  |  |  |
| Tumor Markers 8 |  |  |  |  |  |  |  |  |  |
| Pregnancy test 9 | X |  |  |  |  |  |  |  |  |
| Correlative/research assays10 |  |  |  |  |  |  |  |  |  |
| <<Insert as needed>> |  |  |  |  |  |  |  |  |  |
| **Imaging Procedures** |  |  |  |  |  |  |  |  |
| CT/MRI 11 |  |  |  |  |  |  |  |  |  |
| Cardiac Assessment (ECHO, MUGA) |  |  |  |  |  |  |  |  |  |
| ECG/EKG |  |  |  |  |  |  |  |  |  |
| Bone scan |  |  |  |  |  |  |  |  |  |
| **Tissue Collection/ Biopsy** |  |  |  |  |  |  |  |  |
| Tumor Tissue Collection 12 |  |  |  |  |  |  |  |  |  |

*Insert or re-organize footnotes as needed*

1. <<Specify disease-specific staging criteria (for CRF purposes, e.g.: GU Assessment, BR Disease Eval, AML-MDS Summary, etc.)>>
2. Including CBC with differential and platelet count
3. Including alkaline phosphatase (ALP), ALT/AST, total bilirubin, calcium, phosphorus, (BUN), creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, LDH, fasting lipid panel (LDL, total cholesterol, triglycerides),
4. Including FT4 and TSH
5. Including PT/PTT/INR
6. Including HBsAg, HBsAb, HBcAb, Hep C RN
7. <<Specify PK testing information>>
8. <<Specify non-research specific tumor marker testing performed in the study -CEA, AFP, CA19-9, CA 125, etc. >>
9. For women of child-bearing potential. <<Specify if urine/HCG required/accepted, allowed window, and any applicable details.>>
10. <<Specify what blood tests will be performed for research/correlative purposes. >>
11. <<Specify preferred and/or acceptable imaging (e.g. CT//MRI of chest/abdomen/pelvis. Restaging will occur q x <<X>> cycle)>>
12. <<Specify if archival tissue collection is permissible, whether specimen collection is mandatory or optional, how much tissue will be collected for research testing, types of biopsies that may be performed, any applicable restrictions or procedural/specimen requirements. Complete specimen collection instructions are not needed her– instead “refer to laboratory manual”. Indicate tests to be performed on these specimens>>

## Participant Registration

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All participants consented to the study will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements.

*For multicenter studies only:* Each participating site is responsible for OnCore® registration of study participants consented at the site.

## Schedule of Procedures and Assessments

* *UCSF DSMC requires schedule to be listed in this section as well as completion of the Study Calendar.*
* *For clarity, specify Cycle/Day for procedures instead of using “every 3 cycles”*

### Pretreatment Period

#### Screening Assessments

The Screening procedures and assessments must be completed within << #/time frame >> of initiating study treatment.

* Clinical Assessments
	+ Documentation of disease assessment <<Specify disease-specific staging criteria (for CRF purposes, e.g.: GU Assessment, BR Disease Eval, AML-MDS Summary, etc.)>>
	+ Physical examination
	+ Complete medical history
	+ Vital signs
	+ Concomitant medication review
	+ AE assessment
	+ Performance status
	+ Questionnaire <<Specify type of questionnaire and applicable details>>
* Laboratory Assessments
	+ Hematology labs - CBC with differential and platelet count
	+ Blood chemistry assessment, including: Alkaline phosphatase (ALP), aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, lactate dehydrogenase (LDH), fasting lipid panel (low-density lipoprotein [LDL], total cholesterol, triglycerides)
	+ Thyroid function tests - thyroid-stimulating hormone (TSH), free thyroxine (FT4)
	+ Coagulation assessment - including prothrombin time, partial thromboplastin time, international normalized ratio (PT/PTT/INR)
	+ Serum Hepatitis assessment, including Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (HBsAb), Hepatitis B core antibody (HBcAb), Hepatitis C virus RNA
	+ Urinalysis
	+ Tumor marker assessments - <<Specify non-research specific tumor marker testing performed in the study -CEA, AFP, CA19-9, CA 125, etc.>>
	+ Pregnancy Test - For women of child-bearing potential. <<Specify if urine/HCG required/accepted, allowed window, and any applicable details. >>
	+ Research/Correlative Blood Testing <<Specify blood tests that will be performed for research/correlative purposes. >>
* Imaging Procedures
	+ <<CT or MRI>> of << body location(s) >>
	+ Cardiac assessment <<Specify ECHO/MUGA required or acceptable>>
	+ Electrocardiogram (ECG)
	+ Bone scan
* Tumor Tissue Collection
	+ <<Specify if archival tissue collection is permissible, whether specimen collection is mandatory or optional, how much tissue will be collected for research testing, types of biopsies that may be performed, any applicable restrictions or procedural/specimen requirements. Complete specimen collection instructions are not needed her– instead “refer to laboratory manual”. >>
	+ <<Specify tests to be performed>>
* Research Blood Collection
	+ <<Specify tests to be performed. >>

### Treatment Period

#### Study Procedures, Cycle 1, Day 1

#### Study Procedures Cycle << # >>, Day << # >>

### End-of-Treatment Study Procedures

To be completed within 30 days of the last dose of investigational product.

### Post-treatment/Follow-Up

Participants will be followed *<<* frequency >> for up to << time frame >> after discontinuing study treatment. The following procedures will be performed at each Follow Up visit:

### Long Term/Survival Follow-up

After completing the follow-up period, participants will be contacted by telephone every <<frequency>> to assess for survival/anti-cancer therapy status until << e.g. death, withdrawal of consent, or the end of the study, whichever occurs first>>.

* *Add long-term follow up, if applicable. Please note, the FDA requires up to fifteen years of long-term follow up for gene therapy agents. See:* [*https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM610797.pdf*](https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM610797.pdf)
* *Remove this section if no long term/survival follow-up is included in the study design. Example is included below.*

## Correlative Studies

* *Describe any exploratory/correlative/specimen banking aspects of the study (i.e., biomarker studies, sequencing studies, etc.). No need to provide specific specimen collection instructions – use “refer to laboratory manual”.*
* *Studies should be consistent with Exploratory Objectives listed in* [*Section 2.4*](#_Exploratory_(Correlative)_Objective) *and discussed in* [*Section 8.4.4*](#_Exploratory/Correlative_Analysis/As)*.*
* *Information about including correlative studies in a clinical trial is available at “Guidelines for Correlative Studies in Clinical Trials” available on the CTEP Web site (*[*http://ctep.cancer.gov/protocolDevelopment/default.htm#ancillary\_correlatives*](http://ctep.cancer.gov/protocolDevelopment/default.htm%23ancillary_correlatives)*).*

## Use of Concurrent/Concomitant Medications

*State guidelines for use of concomitant medications (e.g. growth factors, steroids, anti-emetics, etc.).*

## Dietary Restrictions

*Describe any food and/or drink restrictions for study participants.*

## Prohibited Medications

*If using template Prohibited Medications List is provided in Appendix 3 of this template, please refer to it here. Otherwise, please state applicable prohibited medications for study participants.*

# Reporting and Documentation of Results

*Response criteria, as per the primary or secondary objectives of the protocol, should be defined or reviewed by the study statistician.*

## Evaluation of Efficacy: Antitumor Effect – Solid Tumors

* *The example text in this section should be used for studies using RECIST v1.1 to evaluate efficacy in solid tumors. Any text that is not applicable to the study should be removed or modified.*
* *If the criteria for solid tumors below are not applicable, the investigator(s) should provide agent- or disease-appropriate criteria with references, and all solid tumor criteria below should be deleted.*
* *Immune RECIST (iRECIST) guidelines for response criteria for use in trials testing immunotherapies developed by the RECIST working group are available at:* [*https://www.sciencedirect.com/science/article/pii/S1470204517300748?via%3Dihub*](https://www.sciencedirect.com/science/article/pii/S1470204517300748?via%3Dihub)

Response and progression in this study will be evaluated using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST v1.1 criteria.

### Definitions

**Evaluable for toxicity**

All participants will be evaluable for toxicity from the time of their first treatment with <<investigational product(s)>>.

**Evaluable for objective response**

Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.)

**Evaluable Non-Target Disease Response**

Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

### Disease Parameters

**Measurable disease**

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.*

**Malignant lymph nodes**

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

**Non-measurable disease (Tumor Markers)**

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

**Target lesions**

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

**Non-target lesions**

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. It is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”). Bone lesions may be measureable if ≥ 1 cm on MRI. Measurements of these lesions are not required, but the presence or absence of each will be noted throughout follow-up.

**Non-measurable disease (Tumor Markers)**

Non-measurable disease is all other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan). Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques are all non-measurable. (e.g. PSA, CA-125, CA19-9, CEA)

### Methods for Evaluation of Measurable Disease

*Please remove any assessments listed below that will not be used/are not applicable to the study. The study protocol should only list assessments relevant to the study.*

All measurements will be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations will be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.

The same method of assessment and the same technique will be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

**Clinical lesions:** Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

**Chest x-ray**: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

**Conventional CT and MRI:** This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

**PET-CT**: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

**Ultrasound**: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

**Endoscopy, Laparoscopy**: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

**Tumor markers**: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

**Cytology, Histology**: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

**Fluorodeoxyglucose (FDG)-PET:** While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
3. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

### Response Criteria

**Evaluation of Target Lesions**

Complete Response (CR)

Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be “0” if there are target nodes). There can be no appearance of new lesions.

Partial Response (PR)

At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD)

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

**Evaluation of Non-Target Lesions**

Complete Response (CR)

Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Incomplete Response/Stable Disease (SD)

Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD)

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

**Evaluation of Best Overall Response**

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The participant’s best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 7.1 Response Criteria For Participants with Measurable Disease (*i.e.*, Target Disease)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Target Lesions** | **Non-Target Lesions** | **New Lesions** | **Overall Response** | **Best Overall Response when Confirmation is Required\*** |
| CR | CR | No | CR | ≥4 wks. Confirmation\*\* |
| CR | Non-CR/Non-PD | No | PR | ≥4 wks. Confirmation\*\* |
| CR | Not evaluated | No | PR |
| PR | Non-CR/Non-PD/not evaluated | No | PR |
| SD | Non-CR/Non-PD/not evaluated | No | SD | Documented at least once ≥4 wks. from baseline\*\* |
| PD | Any | Yes or No | PD | no prior SD, PR or CR |
| Any | PD\*\*\* | Yes or No | PD |
| Any | Any | Yes | PD |
| * See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

\*\* Only for non-randomized trials with response as primary endpoint.\*\*\* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “*symptomatic deterioration.”* Every effort should be made to document the objective progression even after discontinuation of treatment. |

Table 7.2 Response Criteria for Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

|  |  |  |
| --- | --- | --- |
| **Non-Target Lesions** | **New Lesions** | **Overall Response** |
| CR | No | CR |
| Non-CR/non-PD | No | Non-CR/non-PD\* |
| Not all evaluated | No | not evaluated |
| Unequivocal PD | Yes or No | PD |
| Any | Yes | PD |
| * ‘Non-CR/non-PD’ is preferred over ‘stable disease’ for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised
 |

**Duration of Response**

Duration of overall response

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

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

Duration of stable disease

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

Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

## Evaluation of Efficacy: Antitumor Effect – Hematologic Tumors

*Insert appropriate criteria for evaluation of response and methods of measurement. Add subsections as needed. References for leukemia, lymphoma and multiple myeloma tumor response measurements are provided below.*

* [*International Working Group response criteria for Acute Myeloid Leukemia*](http://ascopubs.org/doi/10.1200/JCO.2003.04.036)
* [*International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017)*](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5834038/)*:*
* [*International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma*](http://imwg.myeloma.org/international-myeloma-working-group-imwg-uniform-response-criteria-for-multiple-myeloma/)

*Delete this section if it is not applicable.*

## Evaluation of Safety

The safety parameters for this study include all laboratory tests and hematological abnormalities, physical findings, << add other parameters>> and spontaneous reports of adverse events reported to the investigator by participants.

Toxicity will be assessed according to the NCI CTCAE version 5.0. Safety analyses will be performed for all participants who <<insert study criteria for evaluable participants for safety>>.

## Definitions of Adverse Events

* *Standard template language below is approved by the HDFCCC DSMC –* ***this should not be modified unless approved by the DSMC****.*
* *Expedited reporting language for industry partners should be included in Section 7.5.5 per discussion with industry partners. Unless absolutely required by the industry partners, it is not necessary to include their reporting forms in the protocol appendices.*

### Adverse Event

An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. More specifically, an adverse event(can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

### Adverse Reaction

An adverse reaction is defined as any adverse event caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

### Suspected Adverse Reaction

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, “reasonable possibility” indicates that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

### Unexpected

An adverse event or suspected adverse reaction is considered unexpected if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

“Unexpected,” as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse events that would be anticipated to occur as part of the disease process are considered unexpected for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

Some adverse events are listed in the Investigator Brochure as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered unexpected until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some participants exposed to drugs in the angiotensin-converting enzymeinhibitor class and angioedema would be described in the investigator brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered unexpected for reporting purposes.

### Serious

An adverse event or suspected adverse reaction is considered *serious* if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

* Death
* Life-threatening adverse event
* Inpatient hospitalization or prolongation of existing hospitalization
* A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
* Congenital anomaly/birth defect

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

### Life-threatening

An adverse event or suspected adverse reaction is considered life-threatening if, in the view of either the investigator or sponsor, its occurrence places the participant at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

## Recording of Adverse Events

Refer to the Data Safety Monitoring Plan, located in Appendix <<#>>.

## Follow-up of Adverse Events

All participants who experience adverse events will be followed with appropriate medical management until resolved or stabilized, as determined by the investigator, or until the initiation of new anti-cancer therapy, whichever occurs first. For selected adverse events for which administration of the investigational product was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the investigator.

## Adverse Events Monitoring

Refer to the Data Safety Monitoring Plan, located in Appendix <<#>>.

## Expedited Reporting

**Reporting to the Data and Safety Monitoring Committee**

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

**Reporting to Institutional Review Board**

The UCSF PI must report events to the UCSF IRB according to institutional guidelines.

UCSF IRB website for guidance in reporting adverse events: <https://irb.ucsf.edu/adverse-event>

*For multicenter trials add:* The PI at each participating site is responsible for reporting events to the IRB of record according to IRB guidelines.

**Expedited Reporting to the FDA**

* *IND Safety Reporting information is included below. If the study is conducted under an Investigational Device Exemption (IDE), please replace with appropriate FDA safety reporting requirements:* [*https://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/investigationaldeviceexemptionide/ucm046717.htm*](https://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/investigationaldeviceexemptionide/ucm046717.htm)

If the study is being conducted under an IND, the Sponsor (or the Sponsor-Investigator) is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with federal regulations (21 CFR §312.32).

The Sponsor (or Sponsor-Investigator) must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor needs to ensure that the event meets all three definitions:

* Suspected adverse reaction
* Unexpected
* Serious

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator’s initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

**Reporting to Industry Partners**

*Include any reporting requirements for industry partners/collaborators*

# Statistical Considerations and Evaluation of Results

*The statistical section should clearly outline how the data will be evaluated in relation to each objective. A biostatistician should write the information in the sections below.*

*All trials must have a named individual who takes responsibility for the statistical aspects of the study. This person may be a UCSF biostatistician or another member of the study team.*

*Contact the* [*HDFCCC Biostatistics Core*](http://cancer.ucsf.edu/research/cores/biostatistics/) *or the statistician associated with your disease program.*

## Sample Size Considerations

### Sample Size and Power Estimate

* *State the total sample size and all relevant assumptions and calculations. All parameters (e.g., power) used in calculating the sample size should be specified*
* *If the sample size is justified by power, state the null and alternative hypotheses, the significance level and the power, and the method by which it was calculated. Otherwise comment on the expected precision of the estimates to be calculated. If there is substantial uncertainty in the effect size or other aspects of the calculation, provide power for multiple plausible scenarios and explain.*
* *If this is a single-arm (non-randomized) study, justify the historical control rate. Refer to the section that summarizes the literature on which it is based.*
* *If this is a pilot study, state what result would convince you to begin a fully powered study.*
* *A reviewer should be able to duplicate the calculations given the information provided.*

### Randomization

*If the study involves randomization, describe the randomization process. If described previously in the protocol, reference the appropriate section.*

### Stratification Factors

*Identify any stratification planned (e.g. sex, race/ethnicity, age, dose, etc.) and rationale for stratification.*

### Accrual Estimates

*If not mentioned in* [*section 8.1.1*](#_Sample_Size_and) *above, provide an estimate of the number of eligible participants yearly. Describe in detail how the estimate was calculated.*

## Interim Analyses and Stopping Rules

* *If a statistical stopping rule is included in the study design, please refer to that section here.*
* *Specify how the stopping rule will preserve the significance level, coverage of confidence intervals, or other relevant aspects of inference.*

## Analyses Plans

* *In the sections below, describe how each objective (particularly the primary objective) will be addressed by a particular data analysis plan. Provide the details of each data analysis plan for each objective – stating what statistical methods will be used, and under which assumptions. Every objective, every study endpoint should have a plan associated with it.*
* *Confirm that plans analyze the assessments described in* [*Section 6*](#_Study_Procedures_and) *and satisfy the objectives of* [*Section 2*](#_Study_Objectives)*, referring to those sections as appropriate. Describe any plans for descriptive statistics and exploratory data analysis.*

### Analysis Population

*Describe defined subsets of enrolled participants that will be used for different kinds of statistical analysis (e.g. intent to treat population, safety population, PK population, etc.).*

### Primary Analysis (or Analysis of Primary Endpoints)

* *Describe in detail the statistical methods to be used to address the study’s primary objective. Define the participant cohort to be analyzed, state the primary endpoint(s), and explain how the results will be interpreted.*
* *Should be consistent with objective(s) and endpoint(s) listed in* [*Section 2.2*](#_Primary_Objective_and)*.*

### Secondary Analysis (or Analysis of Secondary Endpoints)

* *If secondary endpoints are included in this study, please specify how they will be analyzed. In particular, brief descriptions should be given of analyses of pharmacokinetic, biologic, and correlative laboratory endpoints. If the analysis is inferential and not descriptive, the power for each endpoint to be analyzed should be discussed.*
* *Should be consistent with objective(s) and endpoint(s) listed in* [*Section 2.3*](#_Secondary_Objective(s)_and)*.*

### Exploratory/Correlative Analysis/Assessments

*Should be consistent with objective(s) and endpoint(s) listed in* [*Section 2.4*](#_Exploratory_(Correlative)_Objective) *and information detailed in* [*Section 6.4*](#_Correlative_Studies)*.*

# Study Management

## Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the PI will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to participants before any protocol related procedures are performed on any participants.

The PI must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

*If the study involves administration of investigational drugs or biologics, add:*

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the FDA has determined that the study is exempt from IND requirements.

## Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant-facing materials related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF IRB. Prior to obtaining IRB approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

## Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB -approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

## Changes in the Protocol

Once the protocol has been approved by the UCSF IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the PI and approved by PRC and the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to participants, an amendment may be implemented prior to IRB approval. In this circumstance, however, the PI must then notify the IRB according to institutional requirements.

*For multicenter studies add:* The Study Chair and the UCSF study team will be responsible for updating any participating sites.

## Handling and Documentation of Clinical Supplies

*Example language for studies using investigational drugs provided below. If this is a device study, or is not applicable, please modify accordingly.*

The PI <<*for multicenter studies, add:* at each study site>> will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs at the site. The date, quantity and batch or code number of the drug, and the identification of participants to whom the investigational product has been dispensed by participant number and initials will be included.

The PI <<*for multicenter studies, add:* at each study site>> shall not make the investigational drug available to any individuals other than to qualified study participants. Furthermore, the PI <<*for multicenter studies, add:* at each study site>> will not allow the investigational product to be used in any manner other than that specified in this protocol.

## Case Report Forms (CRFs)

The PI and/or designee <<*for multicenter studies, add:* at each study site>> will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. Study personnel <<*for multicenter studies, add:* for each study site>> will complete the CRFs; the PI <<*for multicenter studies, add:* for the study site>> will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the participant’s medical records maintained by study personnel <<*for multicenter studies, add:* at each study site>>. All source documentation should be kept in separate research files for each participant.

In accordance with federal regulations, the PI <<*for multicenter studies, add:* at each study site>> is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

The PI <<*for multicenter studies, add:* at each study site>> will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the <<PI *or, for multicenter studies, use* Study Chair>> and the trial statistician.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies. <<*For multicenter studies where the HDFCCC DSMC is responsible for monitoring, add:* The DSMC performs remote review/monitoring for non-UCSF participating sites. Study personnel at non-UCSF participating sites must upload redacted source documents into the PC console of OnCore prior to scheduled DSMC remote monitoring >>.

## Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered “serious”. The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix <<##>> - Data and Safety Monitoring Plan.

*For multicenter studies only:*

<<*Complete as applicable to the study:* The UCSF Sponsor-Investigator *or* The UCSF Sponsor/IND Holder *or name the UCSF investigator to whom Study Chair responsibilities are delegated to*>> will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites.

## Record Keeping and Record Retention

The PI <<*for multicenter studies, add:* at each study site>> is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The PI <<*for multicenter studies, add:* at each study site>> is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed participant consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the PI <<*for multicenter studies, add:* at each study site>> shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

## Multicenter communication *(for multicenter studies only – remove this section if the study will only be conducted at UCSF)*

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate, at weekly conference calls with the participating sites for Phase I dose escalation studies prior to each cohort escalation and at the completion of each cohort or more frequently as needed to discuss risk assessment. The following issues will be discussed as appropriate:

* Enrollment information
* Cohort updates (i.e. DLTs)
* Adverse events (i.e. new adverse events and updates on unresolved adverse events and new safety information)
* Protocol violations
* Other issues affecting the conduct of the study

## Regulatory Documentation *(for multicenter studies only – remove this section if the study will only be conducted at UCSF)*

Prior to implementing this protocol at UCSF or any participating site, the protocol, informed consent form, and any other information pertaining to participants must be approved by the UCSF IRB. Prior to implementing this protocol at the participating sites, approval of the UCSF IRB approved protocol must be obtained from the participating site’s IRB.

The following documents must be provided to UCSF HDFCCC before the participating site can be initiated and begin enrolling participants:

* Participating Site IRB approval(s) for the protocol, informed consent form, and HIPAA authorization
* Participating Site IRB approved consent form
* Participating Site IRB membership list
* Participating Site IRB’s Federal Wide Assurance number and OHRP Registration number
* Curriculum vitae and medical license for each investigator and consenting professional
* Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
* Participating site laboratory certifications and normals.

Upon receipt of the required documents, UCSF HDFCCC will formally contact the site and grant permission to proceed with enrollment.

# Protection of Human Subjects *(for multicenter studies only – remove this section if the study will only be conducted at UCSF)*

## Protection from Unnecessary Harm

Each clinical site is responsible for protecting all participants involved in human experimentation. This is accomplished through the IRB mechanism and the process of informed consent. The IRB reviews all proposed studies involving human experimentation and ensures that the participant’s rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

## Protection of Privacy

Participants will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the participant’s medical records, and each participant will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

# References

Appendix 1 Performance Status Criteria

|  |  |
| --- | --- |
| **ECOG Performance Status Scale** | **Karnofsky Performance Scale** |
| Grade | Descriptions | Percent | Description |
| 0 | Normal activityFully active, able to carry on all pre-disease performance without restriction | 100 | Normal, no complaints, no evidence of disease |
| 90 | Able to carry on normal activity; minor signs or symptoms of disease |
| 1 | Symptoms, but ambulatoryRestricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work) | 80 | Normal activity with effort; some signs or symptoms of disease |
| 70 | Cares for self, unable to carry on normal activity or to do active work |
| 2 | In bed < 50% of the timeAmbulatory and capable of all self-care, but unable to carry out any work activitiesUp and about more than 50% of waking hours | 60 | Requires occasional assistance, but is able to care for most of his/her needs |
| 50 | Requires considerable assistance and frequent medical care |
| 3 | In bed > 50% of the timeCapable of only limited self-care, confined to bed or chair more than 50% of waking hours | 40 | Disabled, requires special care and assistance |
| 30 | Severely disabled, hospitalization indicatedDeath not imminent |
| 4 | 100% bedriddenCompletely disabledCannot carry on any self-careTotally confined to bed or chair | 20 | Very sick, hospitalization indicatedDeath not imminent |
| 10 | Moribund, fatal processes progressing rapidly |
| 5 | Dead | 0 | Dead |

Appendix 2 Data and Safety Monitoring Plan

*Please insert the appropriate Data and Safety Monitoring Plan (DSMP) template for the study. DSMP templates are located here:*

<http://cancer.ucsf.edu/itr/sm_files/UCSF%20HDFCCC%20DSMP2017.pdf>

Appendix 3 Prohibited Medications List

*Example list is included below, please edit/remove as applicable.*

|  |  |
| --- | --- |
| **Drug** | **Trade name (if applicable)** |
| Aosetron: | lotronex |
| Bosentan: | Tracleer |
| Candesartan: | Atacand |
| Celecoxib: | Celebrex |
| Diclofnac: | Volaren |
| Dronabinol: | Marinol |
| Flubiprofen: | Ansaid |
| Fluvastatin: | Lescol |
| Glimepiride: | Amaryl |
| Ibuprofen: | Advil, Motrin |
| Indomethacin: | Indocin |
| Irbesartan: | Avapro |
| Losartan: | Cozaar |
| Meloxicam: | Mobic |
| Montelukast: | Singulair |
| Maproxen: | Aleve |
| Nateglinide: | Starlix |
| Phenobarbital |
| Phenytoin: | Dilantin |
| Piroxicam: | Feldene |
| Rosiglitazone: | Avandia |
| Rosuvastatin: | Crestor |
| Sulfmethoxazole |
| Tolbutamide |  |
| Torsemide: | Demadex |
| Valsartan: | Diovan |
| Warfarin: | Coumadin |