UCSF Helen Diller Family Comprehensive Cancer Center

NCT# 02950480

Breast capsular contracture following post-mastectomy reconstruction in women treated with the leukotriene inhibitor zafirlukast: A Phase II Trial

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Protocol Signature Page

Protocol No.: 15754 Version Date: 06/13/2018

1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Committee on Human Research (CHR), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable CHR requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. I agree to maintain adequate and accurate records in accordance with CHR policies, Federal, state and local laws and regulations.

UCSF Principal Investigator / Study Chair

_____
Printed Name

_____ _____
Signature Date

Principal Investigator Site

_____ _____
Printed Name

_____ _____
Signature Date

Abstract

Title: Breast capsular contracture following post-mastectomy reconstruction in women treated with the leukotriene inhibitor zafirlukast

Patient population: Patients who will be undergoing mastectomy with immediate tissue-expander reconstruction

Background

Primary objective:

a) Compare capsular thickness by gross and microscopic measurement at the time of expander-implant exchange in those treated with zafirlukast (20 mg PO BID) compared with standard of care

Secondary objectives:

a) Perform histologic analysis of the capsule specimens to compare overall fibrosis and collagen deposition between the zafirlukast and standard of care groups

Exploratory objectives:

a) The capsule tissue that is removed at the time of expander-implant exchange will be fixed and histologically assessed for the presence of fibroblasts and myofibroblasts.

Study design:

We propose a 2-arm, 90 patient (45 per cohort) trial in patients who will be undergoing mastectomy with immediate tissue-expander reconstruction to determine whether treatment with zafirlukast (20 mg PO BID) can reduce or prevent the development of capsular contracture. All patients undergoing mastectomy with immediate tissue-expander placement will be approached in clinic at the time of their initial consultation with the plastic surgeon and enrolled in the trial at this point. Approximately 60 women undergo mastectomy with tissue-expander reconstruction at our institution per year, thus enrollment will occur over a two-year period.

Number of patients:

90 total: 45 per cohort factoring in a 10% attrition rate

Duration of therapy:

In the absence of treatment delays due to adverse events, treatment may continue until tissue expansion is complete or until:

- Illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patients decides to withdraw from the study
- Significant patient non-compliance with protocol
- General or specific changes in the patients' condition render the patient unacceptable for further treatment in the judgment of the investigator.

Duration of follow up:

Patients are routinely followed for two years after undergoing implant-based reconstruction. In this study, we will initially see patients periodically for research visits until tissue expansion has been completed. After implant exchange, we will see patients every 2 weeks for the first month, and every month for the subsequent 4 months. We will then see them every 6 months for the remainder of the two years. Those patients who are removed from treatment will be followed as per our standard of care, which is monthly for the first six months and then every six months for two years. Serious adverse events will be collected for 30 days after the end of treatment, or until death, whichever occurs first. Patients removed from the study for unacceptable treatment-related adverse event(s) will be followed until resolution or stabilization of all treatment-related adverse events to Grade 1 or baseline.

Study drugs:

Zafirlukast 20mg PO BID

Safety assessments:

Safety will be assessed by reviewing adverse events (AEs), laboratory evaluations, physical examination, and spontaneous report. Each patient will be assessed periodically for the development of any toxicity. All AEs and serious AEs (SAEs) will be documented and reported. We will also pay particular attention to adverse events of clinical interest specific to zafirlukast.

Unique aspects of this study:

This is the first study to prospectively investigate the potential of zafirlukast to slow or prevent capsular contracture from occurring.

List of Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CHR	Committee on Human Research (UCSF IRB)
CR	complete response
CRC	Clinical Research Coordinator
CRF	case report form
CSF	cerebral spinal fluid
CT	computerized tomography
CTCEA	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
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
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HGB	Hemoglobin
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization
IND	investigational new drug application
IP	investigational product
IRB	Institutional Review Board
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
IV	Intravenous
LDH	lactate dehydrogenase
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute

List of Abbreviations

NHL	non-Hodgkin's lymphoma
ORR	overall response rate
PD	disease progression
PK	Pharmacokinetics
PO	Per os (by mouth, orally)
PR	partial response
PRC	Protocol Review Committee (UCSF)
QOL	Quality of Life
RBC	red blood cell (count)
SD	stable disease
SD	standard deviation
ULN	upper limit of normal
WBC	white blood cell (count)

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1 INTRODUCTION

1.1 Background on Indication

The majority of women who undergo mastectomy for breast cancer will choose expander-implant reconstruction. Unfortunately, breast implants are frequently complicated by the development of

capsular contracture[1]. Contracture formation is an excessive foreign body reaction that results in a tight and hard fibrous capsule around the implant. This causes distortion of the breast, displacement of the implant, and in more severe cases, pain and limited range of motion. Reported rates in the literature of women affected by this condition range from 3 to 50%[2-4]. However, these percentages likely under-represent the actual number of women affected as this complication may develop long after a patient is regularly evaluated by the plastic surgeon.

Radiation therapy increases the likelihood of capsular contracture[1-3,5,6]. Women who have been irradiated face contracture rates upwards of 20%[7-9]. Unfortunately, many women who require mastectomy and implant reconstruction for breast cancer had radiation in the past or will require radiation therapy in the future, thus putting them at greater risk for this complication.

The treatment of capsular contracture is primarily surgical, requiring removal of the implant, excision of the capsule, and replacement of the implant. However, excision of the capsule and implant replacement does not guarantee contracture will not recur, and many women face repeated operations.

Recent research has focused on methods to decrease capsule formation[10-13]. These include: altering the properties of implants[14-16], coating the implants[17], fat grafting the capsule[18], inserting acellular dermal matrix[19,20], treating with anti-estrogens[21] and treating with leukotriene receptor antagonists (LTAs)[22,23]. The goal of many of these interventions is to actually prevent capsular contracture from even occurring.

1.2 Background on the Compounds

1.2.1 Zafirlukast

Zafirlukast is a synthetic, selective peptide leukotriene receptor antagonist (LTRA), with the chemical name 4-(5-cyclopentyloxycarbonylamino-1-methyl-indol-3-ylmethyl)-3-methoxy-N-o-tolylsulfonylbenzamide. It is a selective and competitive receptor antagonist of leukotriene D4 and E4 (LTD4 and LTE4), components of slow-reacting substance of anaphylaxis (SRSA). Cysteinyl leukotriene production and receptor occupation have been correlated with the pathophysiology of asthma, including airway edema, smooth muscle constriction, and altered cellular activity associated with the inflammatory process, which contribute to the signs and symptoms of asthma. Patients with asthma were found in one study to be 25-100 times more sensitive to the bronchoconstricting activity of inhaled LTD4 than non-asthmatic subjects. *In vitro* studies demonstrated that zafirlukast antagonized the contractile activity of three leukotrienes (LTC4, LTD4 and LTE4) in conducting airway smooth muscle from laboratory animals and humans. Zafirlukast prevented intradermal LTD4-induced increases in cutaneous vascular permeability and inhibited inhaled LTD4-induced influx of eosinophils into animal lungs. Inhalational challenge studies in sensitized sheep showed that zafirlukast suppressed the airway responses to antigen; this included both the early-and late-phase response and the nonspecific hyper-responsiveness. In humans, zafirlukast inhibited bronchoconstriction caused by several kinds of inhalational challenges. Pretreatment with single oral doses of zafirlukast inhibited the bronchoconstriction caused by sulfur dioxide and cold air in patients with asthma. Pretreatment with single doses of zafirlukast attenuated the early-and late-phase reaction caused by inhalation of various antigens such as grass, cat dander, ragweed, and mixed antigens in patients with asthma. Zafirlukast also attenuated the increase in bronchial hyper-responsiveness to inhaled histamine that followed inhaled allergen challenge.

1.3 Rationale for the Proposed Study

The development of capsular contracture is multifactorial[24-26]with histologic studies demonstrating the primary role of inflammatory cells in this process. Peptide growth factors and inflammatory cytokines are reactivated by the presence of an implant, leading to a persistent sub-acute

inflammatory response ultimately resulting in capsular contracture[27-29]. As inflammation is induced as part of normal healing, as well as by the ongoing presence of an implant, pharmacologic inhibition of inflammation is an appealing target in preventing capsular contracture from developing. The control of inflammation has been an underlying factor in successful treatment[26,30].

Cysteinyl leukotrienes play a role in the activation and up-regulation of capsular contracture mechanisms[31-33]. Grella et al. demonstrated that in women with severe capsular contracture (Baker grade III/IV) there was marked up-regulation of cysLTR mRNA and protein compared to women with implants who did not develop capsular contracture[32]. Treatment with leukotriene receptor antagonists thereby presents a novel mechanism in the potential prevention of capsular contracture. Zafirlukast specifically inhibits LTC4, LTD4 and LTE4 and has a presumed suppressive effect on myofibroblasts. Several studies have looked at the effects of leukotriene inhibitor administration on capsular contracture in animal models, and found decreased capsule formation following treatment[22,34]. Histologic analysis of capsules in rats treated with zafirlukast demonstrated thinner capsules with decreased collagen fibers[34,35] .

There are descriptive studies of patients treated with LTAs as an off-label use for capsular contracture[36-40]. Women who have developed capsular contracture who are subsequently treated with standard dosing of LTAs show decreased capsule contracture based on clinical assessment[36,38,40]. However, there have been no studies to date evaluating the biology behind this observation in humans. Based on an evidence-based analysis by Cheng et al., further prospective randomized studies are needed to determine the efficacy and safety of leukotriene inhibitors as a potential treatment of capsular contracture[19]. No studies are prospectively investigating the potential of zafirlukast to slow or prevent capsular contracture from occurring.

2 OBJECTIVES OF THE STUDY

2.1 Primary objective

- Compare capsular thickness by gross and microscopic measurement at the time of expander-implant exchange in those treated with zafirlukast (20 mg PO BID) compared with standard of care

2.2 Secondary objectives

- Perform histologic analysis of the capsule specimens to compare overall fibrosis and collagen deposition between the zafirlukast and standard of care groups

2.3 Exploratory objectives

- The capsule tissue that is removed at the time of expander-implant exchange will be fixed and histologically assessed for the presence of fibroblasts and myofibroblasts.

3 STUDY DESIGN

3.1 Characteristics

We propose a 2-arm, 90 patient (45 per cohort) trial in patients who will be undergoing mastectomy with immediate tissue-expander reconstruction to determine whether treatment with zafirlukast (20mg PO BID) can reduce or prevent the development of capsular contracture. All patients undergoing mastectomy with immediate tissue-expander placement will be approached

in clinic at the time of their initial consultation with the plastic surgeon and enrolled in the trial at this point. Approximately 60 women undergo mastectomy with tissue-expander reconstruction at our institution per year, thus enrollment will occur over a two-year period.

Patients will be block randomized 1:1 into two cohorts: treatment with zafirlukast and the standard of care, or standard of care alone. Patients will begin treatment with zafirlukast on post-operative day one (+/- 5 days) following placement of tissue expander(s) after the participant is determined safe from a surgical recovery standpoint. They will be continued on the standard dosing (20mg PO twice per day) of zafirlukast through expander fill. Last dose of Zafirlukast will be administered the day prior to expander implant exchange procedure. Patients will be seen every 1 to 2 weeks for expander fill, and will be assessed clinically (refer to section 6.2 for research visits). The treating physician will determine the frequency of visits based on each patient's expander need.

During expander-implant exchange, three representative sections of the expander capsule will be collected: medial, lateral and anterior capsule specimens. These specimens will be bisected; half will be sent to pathology and half will be collected by the Munster lab. Gross and microscopic determination of capsule thickness will be performed by the pathology department. The Munster lab will fix and stain the tissues to look for the presence of collagen, level of fibrosis, and number of myofibroblasts. Fibrosis level and collagen presence will be determined by performing immunohistochemistry with a Trichrome stain of the tissues, as well as Western blot analysis with Collagen-1. Myofibroblasts will be detected using immunohistochemistry with commercially available antibodies.

3.2 Number of Subjects

90 total: 45 per cohort factoring in a 10% attrition rate

3.3 Eligibility Criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

3.3.1 Inclusion Criteria

1. Patients who are scheduled to undergo therapeutic or prophylactic mastectomy with immediate placement of tissue expanders and have a strong family history or hereditary cancer
2. Age ≥ 18 years
3. Zafirlukast is pregnancy category B. There are no adequate and well-controlled trials in pregnant women. Therefore, the effects of zafirlukast on the developing human fetus are unknown. For this reason, women of child-bearing potential must agree to use adequate contraception: 2 methods of birth control, prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately.
4. Ability to understand a written informed consent document, and the willingness to sign it
5. At least 4 weeks post-completion of chemotherapy
6. Adequate organ function within 14 days start of study start:
    a. Absolute neutrophil count (ANC) ≥ 1.5 X 10^9/L
    b. Hemoglobin (Hgb) ≥9g/dL
    c. Platelets (plt) ≥ 100 x 10^9/L
    d. Potassium within normal range, or correctable with supplements;

e. AST and ALT ≤2.5 x Upper Limit Normal (ULN) or ≤5.0 x ULN if liver tumor is present
f. Serum total bilirubin ≤ 1.5 x ULN
g. Serum creatinine ≤ 1.5 x ULN, or 24-hr clearance ≥ 60ml/min

3.3.2 Exclusion Criteria

1. Any significant medical condition, laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study
2. Currently on a leukotriene inhibitor or used within the past 6 months
3. Prior chest wall radiation
4. Pregnant or breastfeeding
5. Hepatic impairment as defined by:
   - AST(SGOT) > 2.5X institutional ULN and ALT(SGPT) > 2.5X institutional ULN
6. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

4 STUDY DRUGS

4.1 Description, Supply and Storage of Investigational Drugs

Classification

Zafirlukast is a synthetic, selective peptide leukotriene receptor antagonist (LTRA).

Mechanism of Action

Zafirlukast is a selective and competitive receptor antagonist of leukotriene D4 and E4 (LTD4 and LTE4), components of slow-reacting substance of anaphylaxis (SRSA). Cysteinyl leukotriene production and receptor occupation have been correlated with the pathophysiology of asthma, including airway edema, smooth muscle constriction, and altered cellular activity associated with the inflammatory process, which contribute to the signs and symptoms of asthma. Patients with asthma were found in one study to be 25- 100 times more sensitive to the bronchoconstricting activity of inhaled LTD4 than non-asthmatic subjects.

In vitro studies demonstrated that zafirlukast antagonized the contractile activity of three leukotrienes (LTC4, LTD4 and LTE4) in conducting airway smooth muscle from laboratory animals and humans. Zafirlukast prevented intradermal LTD4-induced increases in cutaneous vascular permeability and inhibited inhaled LTD4-induced influx of eosinophils into animal lungs. Inhalational challenge studies in sensitized sheep showed that zafirlukast suppressed the airway responses to antigen; this included both the early- and late-phase response and the nonspecific hyper-responsiveness.

In humans, zafirlukast inhibited bronchoconstriction caused by several kinds of inhalational challenges. Pretreatment with single oral doses of zafirlukast inhibited the bronchoconstriction caused by sulfur dioxide and cold air in patients with asthma. Pretreatment with single doses of zafirlukast attenuated the early- and late-phase reaction caused by inhalation of various antigens such as grass, cat dander, ragweed, and mixed antigens in patients with asthma. Zafirlukast also attenuated the increase in bronchial hyper-responsiveness to inhaled histamine that followed inhaled allergen challenge.

Storage

Store at controlled room temperature, 20-25°C (68-77°F). See Investigator Brochure. Protect from light and moisture. Dispense in the original airtight container.

Method of Administration
Because food can reduce the bioavailability of zafirlukast, it should be taken at least 1 hour before or 2 hours after meals.

Patient Care Implications:

Patients should be told that a rare side effect of zafirlukast is hepatic dysfunction, and to contact their physician immediately if they experience symptoms of hepatic dysfunction (e.g. right upper quadrant abdominal pain, nausea, fatigue, lethargy, pruritus, jaundice, flu-like symptoms, and anorexia). Liver failure resulting in liver transplantation and death has occurred in patients taking zafirlukast.

4.1.1 Investigational Drug Zafirlukast

Zafirlukast is available in the following doses for oral administration.

20mg PO twice per day
Complete and updated adverse event information is available in the Investigational Drug Brochure and product package insert.

4.2 Drug Accountability

The Investigational Pharmacist will manage drug accountability records.

4.3 Drug Ordering

UCSF will provide the study drug directly to the patient

4.4 Packaging and Labeling of Study Drugs

Drugs will be packaged and labeled per UCSF institutional standards, adhering to applicable local and federal laws.

5 TREATMENT PLAN

5.1 Dose Modifications and Dosing Delays

Zafirlukast will be administered in 20mg tablets as a single dose. Although zafirlukast is available as a 10mg tablet as well, there will be no dose modification. Should a patient be unable to tolerate the standard dose of 20mg, she will be removed from this study. Zafirlukast should be stopped prior to expander implant exchange

5.2 Monitoring and Toxicity Management

Each patient receiving zafirlukast will be evaluable for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical findings, and spontaneous reports of adverse events reported to the investigator by patients.

6 STUDY PROCEDURES AND ASSESSMENTS

The study-specific assessments are detailed in this section and outlined in Table 6 Schedule of Study Procedures and Assessments. Screening assessments must be performed from day -28 to day 1, prior to the scheduled mastectomy and tissue-expander placement. Treatment or visit delays for public holidays or weather conditions, patient's personal reasons or per PI discretion

that do not compromise safety do not constitute a protocol violation. Treatment delays may not exceed 3 weeks, unless discussed with the study team for patients with documented benefit.

6.1 Screening Assessments

Must be performed from day -28 to day 1, prior to the scheduled mastectomy and tissue-expander placement:

- Medical history
- Physical examination (including height and weight)
- Vital signs (blood pressure, pulse rate, respiratory rate, temperature)
- Con-Med review
- CBC with differential
- Serum biochemical panel including creatinine, fasting glucose, potassium, sodium, chloride, bicarbonate, ALT/AST, total bilirubin
- Blood or urine pregnancy test

6.2 Assessments and procedures during treatment

Once the patient is confirmed to be eligible based on screening assessments, the following study assessments will be performed. See Table 6 for summary. Cohort A participants will begin treatment with zafirlukast on post-operative day one (+/- 5 days) following placement of tissue expander(s) after the participant is determined safe from a surgical recovery standpoint. Cohort A participants will take zafirlukast twice per day until the patient has completed expansion of the tissue expander. Zafirlukast should be stopped prior to expander implant exchange. Patients will be randomized on the day of surgery by a study personnel other than the surgeon. The surgeon and patient will be informed of the assigned cohort immediately post-surgery.

Research Visits (+/- 1 week)

- Physical examination (including height and weight)
- Vital signs (blood pressure, pulse rate, respiratory rate, temperature)
- Con-Med and AE review
- CBC with differential and platelet count
- Serum biochemical panel including creatinine, fasting glucose, potassium, sodium, chloride, bicarbonate
- Liver function tests: alkaline phosphatase, ALT/AST, total bilirubin (only for Cohort A)

Expander-Implant Exchange

- Tissue specimen collection

End of Treatment (*14 days (+/- 3 days) of expander-implant exchange*)

- Medical history, physical examination (including height and weight), vital signs (blood pressure, pulse rate, respiratory rate, temperature)
- CBC with differential and platelet count
- Serum biochemical panel including creatinine, fasting glucose, potassium, sodium, chloride, bicarbonate
- Liver funtion tests: alkaline phosphatase, ALT/AST, total bilirubin (only for Cohort A)
- Con-Med and AE review

Follow up

Patients are followed for two years after implant reconstruction. After implant exchange we will see patients every 2 weeks for the first month, every month for the subsequent 4 months, and, every 6 months for the remainder of the two years. For those patients are removed from the treatment, they will be followed as per our standard of care which is monthly for the first six months and then every six months for a total of two years.

- Physical examination (including height and weight), vital signs (blood pressure, pulse rate, respiratory rate, temperature)

Table 6. Schedule of Study Procedures and Assessments

Period/ Procedure	Screening[9]	Treatment period (+/- 1 week)					Expander-implant exchange	End of Treatment	Follow up visits[5]
Study Day/Visit Day	Days -28 to Day 1	Mastectomy and Tissue-expander placement (week 0)	Day 15-21 (wk 2)	Day 29-35 (wk 5)	Day 71-77 (wk 11)	Day 113-119 (wk 17)[8]			
Informed Consent	x								
Baseline Conditions[1]	x								
Tissue Specimen Collection							x		
Zafirlukast[6]		x							
Medical History	x							x	
Vital Signs	x		x	x	x	x		x	x
Physical Exam	x		x	x	x	x		x	x
Con-med and AE review[7]	x							x	
CBC w/diff[2]	x		x	x	x	x		x	
Chemistry[3]	x		x	x	x	x		x	
Liver Function Tests[4]	x			x				x	
Pregnancy Test (HCG)	x								

1. Baseline conditions assessment per DSMC policy.
2. Including CBC with differential and platelet count.
3. Including creatinine, fasting glucose, potassium, sodium, chloride, bicarbonate.
4. Including alkaline phosphatase, ALT/AST, total bilirubin. For Cohort A only on week 5 and EOT. Alkaline phosphatase is not required for screening.
5. Patients are followed for two years after implant reconstruction. After implant exchange we will see patients every 2 weeks for the first month, every month for the subsequent 4 months, and, every 6 months for the remainder of the two years. For those patients are removed from treatment, they will be followed as per our standard of care which is monthly for the first six months and then every six months for a total of two years.
6. 20mg PO twice per day from Day 1 to Treatment Termination for Cohort A only. Treatment may continue until tissue expansion is complete. Zafirlukast should be stopped prior to expander implant exchange.
7. Con-med and AE review begins 28 days prior to treatment and continues 30 days after treatment termination.
8. As needed .
9. Screening procedures must be completed prior to mastectomy and tissue-expander placement.

6.3 Randomization Procedures

This study is an open-label randomized trial; therefore the investigator and subject will know the treatment administered. Patients will be randomized by a study personnel other than the surgeon. The surgeon and patient will be notified of the patient's cohort immediately post-surgery. Two arms will be tested, with each independent assessment. Patients will be block randomized to either treatment with zafirlukast or the standard of care. Enrollment will continue until 90 patients (45 per cohort) have been enrolled.

6.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until tissue expansion is complete or until:

- Illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patients decides to withdraw from the study
- Significant patient non-compliance with protocol
- General or specific changes in the patients' condition render the patient unacceptable for further treatment in the judgment of the investigator.

Patients are routinely followed for two years after undergoing implant based reconstruction. In this study we will initially see patients periodically for research visits until tissue expansion has been completed. After implant exchange we will see patients every 2 weeks for the first month, and every month for the subsequent 4 months. We will then see them every 6 months for the remainder of the two years. Those patients who are removed from treatment will be followed as per our standard of care, which is monthly for the first six months and then every six months for two years. Serious adverse events will be collected for 30 days after the end of treatment, or until death, whichever occurs first. Patients removed from treatment for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related adverse events to Grade 1 or baseline.

Subjects may withdraw consent at any time for any reason, or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

6.5 Long Term/Survival Follow-up Procedures

Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 2 will be followed until the resolution of the AE to Grade 1 or baseline.

6.6 Survival Follow-up

6.6.1 Discontinuation of Therapy

The Investigator will withdraw a patient whenever continued participation is no longer in the patient's best interests. Reasons for withdrawing a patient include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a patient's request to end participation, or simply significant uncertainty on the part of the Investigator that continued participation is prudent. There may also be administrative reasons to terminate participation, such as concern about a patient's compliance with the prescribed treatment regimen.

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.

6.7 Usage of Concurrent/Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and Events of Clinical Interest (ECI) as defined in Section 8.

6.8 Dietary Restrictions

There are no dietary restrictions within this trial.

6.9 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Anti-cancer systemic chemotherapy or biological therapy

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

<u>Potential Drug Interactions:</u>
The following drug interaction studies have been conducted with zafirlukast

- Co-administration of multiple doses of zafirlukast (160 mg/day) to steady-state with a single 25 mg dose of warfarin (a substrate of CYP2C9) resulted in a significant increase in the mean AUC (+63%) and half-life (+36%) of S-warfarin. The mean prothrombin time increased by approximately 35%. The pharmacokinetics of zafirlukast were unaffected by co-administration with warfarin.

- Co-administration of zafirlukast (80 mg/day) at steady-state with a single dose of a liquid theophylline preparation (6 mg/kg) in 13 asthmatic patients, 18 to 44 years of age, resulted in decreased mean plasma concentrations of zafirlukast by approximately 30%, but no effect on plasma theophylline concentrations was observed.

- Co-administration of zafirlukast (20 mg/day) or placebo at steady-state with a single dose of sustained release theophylline preparation (16 mg/kg) in 16 healthy boys and girls (6 through 11 years of age) resulted in no significant differences in the pharmacokinetic parameters of theophylline.

- Co-administration of zafirlukast dosed at 40 mg twice daily in a single-blind, parallel-group, 3-week study in 39 healthy female subjects taking oral contraceptives, resulted in no significant effect on ethinyl estradiol plasma concentrations or contraceptive efficacy.

- Co-administration of zafirlukast (40 mg/day) with aspirin (650 mg four times daily) resulted in mean increased plasma concentrations of zafirlukast by approximately 45%.

- Co-administration of a single dose of zafirlukast (40 mg) with erythromycin (500 mg three times daily for 5 days) to steady-state in 11 asthmatic patients resulted in decreased mean plasma concentrations of zafirlukast by approximately 40% due to a decrease in zafirlukast bioavailability.

- Co-administration of zafirlukast with fluconazole, a moderate CYP2C9 inhibitor, resulted in increased plasma levels of zafirlukast, by approximately 58% (90% CI:28, 95). The clinical significance of this interaction is unknown. Zafirlukast exposure is likely to be increased by other moderate and strong CYP2C9 inhibitors. Co-administration of zafirlukast with itraconazole, a strong CYP3A4 inhibitor, caused no change in plasma levels of zafirlukast.

6.10 Contraception

Zafirlukast may have adverse effects on a fetus in utero. Furthermore, it is not known if zafirlukast has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study.

7.0 CORRELATIVE STUDIES

Collection of tissue specimen

At the time expander-implant exchange, a portion of the capsule is normally excised as part of the standard of care. For research purposes, we will collect and study several small pieces of capsular tissue excised at the time of surgery. The tissue collected will be used to determine if zafirlukast can reduce the thickness and scarring of the capsule tissue compared to standard of care.

Handling of specimen

Tissue samples will be fixed in 10% neutral-buffered formalin and embedded in paraffin for further analysis.

Shipping of specimen

Specimen will be processed by the surgical pathology department laboratory affiliated with UCSF.

8 ADVERSE EVENTS

8.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs and more frequently if clinically indicated. Adverse experiences will be assessed, graded and recorded throughout the study and during the follow-up period by the treating physician. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

8.2 Definition of 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.

8.3 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.

8.3.1 Suspected

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.

8.3.2 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 patients exposed to drugs in the ACE inhibitor 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.

8.3.3 Serious

An adverse event or suspected adverse reaction is considered serious if, in the view of the study PI, 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 patient or subject 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.

8.3.4 Life-threatening

An adverse event or suspected adverse reaction is considered life-threatening if, in the view of either the study Principal Investigator, its occurrence places the patient or subject 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.

8.4 Evaluation of an Adverse Event

All grade 3 and above adverse events will be entered into OnCore®, whether or not the event is believed to be associated with use of the study drug.

The Investigator will assign attribution of the possible association of the event with use of the investigational drug, and this information will be entered into OnCore® using the classification system listed below:

Relationship	Attribution	Description
Unrelated to investigational drug/intervention	Unrelated	The AE is clearly NOT related to the intervention
	Unlikely	The AE is doubtfully related to the intervention
Related to investigational drug/intervention	Possible	The AE may be related to the intervention
	Probable	The AE is likely related to the intervention
	Definite	The AE is clearly related to the intervention

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator according to the CTCAE. When specific adverse events are not listed in the CTCAE they will be graded by the Investigator as none, mild, moderate or severe according to the following grades and definitions:

Grade 0 No AE (or within normal limits)

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2 Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

8.4.1 NCI Common Terminology for Adverse Events (CTCAE)

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

8.5 Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management until resolved. Patients removed from study for unacceptable adverse events will be followed for 30 days or until resolution or stabilization of the adverse event. For selected adverse events for which administration of the investigational drug was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the Investigator.

8.6 Adverse Events Reporting

All adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, as noted above.

The Investigator will assess all adverse events and determine reportability requirements to the UCSF Data and Safety Monitoring Committee (DSMC) and UCSF's Institutional Review Board, the Committee on Human Research (CHR); and, when the study is conducted under an Investigational New Drug Application (IND), to the Food and Drug Administration (FDA) if it meets the FDA reporting criteria.

All adverse events entered into OnCore® will be reviewed by the Helen Diller Family Comprehensive Cancer Center Site Committee on a weekly basis. The Site Committee will review and discuss at each weekly meeting the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

All grade(s) 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

In addition, all suspected adverse reactions considered "serious" entered into OnCore®, will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks.

8.7 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 UCSF Committee on Human Research (Institutional Review Board)

The Principal Investigator must report events meeting the UCSF CHR definition of "Unanticipated Problem" (UP) within 10 business days of his/her awareness of the event.

9.0 STATISTICAL CONSIDERATIONS AND EVALUATION OF RESULTS

Determination of sample size and accrual rate

Sample size calculated to be 82 (41 per arm) based on a two-tailed alpha of 0.05, with a beta of 0.18. With a possible 10% attrition rate, the sample size is increased to 90 (45 per arm). As approximately 60 patients undergo mastectomy with immediate tissue expander placement per year at Mt. Zion, it is expected that roughly 80% of these women will be enrolled in the study.

The determination of sample size is based on the assumption that treatment with the leukotriene inhibitor zafirlukast will decrease capsule thickness in women with tissue expanders at the time of implant exchange. Based on the reported results from literature review, a capsule thickness of >2.4mm would be considered undesirable and <1.2mm would be considered desirable. We assume the capsule thickness is <1.2mm under zafirlukast as the target efficacy of clinical importance for the study population and an efficacy of 50% reduction in capsule contracture between two cohorts would be considered clinically meaningful. Under the t-test with a 2-sided alpha of 5%, we will need 45 evaluable patients in each cohort to have >80% power to detect an

improvement in capsule thickness from average 2.4mm (sd 2mm) to average 1.2mm (sd 2mm), Specifically, the study hypothesis is defined as:

H0: μ1 ≥ μ0 (The capsule thickness of the cohort A is greater than capsule thickness of the cohort B versus

H1: μ1 < μ 0 (The capsule thickness of the cohort A is greater than capsule thickness of the cohort B.

9.1 Analyses Plans

This is an intention to treat analysis. All patients who were randomized will be evaluated.

Data will be summarized using descriptive statistics by study cohorts. For continuous variables, descriptive statistics will include the number of non-missing values, mean, standard deviation, median, minimum and maximum. For categorical variables, descriptive statistics will include counts and percentages per category by study cohorts.

Primary analysis:
The primary objective of the trial is to determine the capsule contracture between the two study cohorts and the primary efficacy outcome in this trial is capsule thickness at the time of expander-implant exchange. Capsule thickness will be determined by averaging thickness from three separate specimens per patient. The capsule thickness will be analyzed by study cohorts, and t-tests and descriptive statistics with mean, standard deviation and 95% confidence intervals will be used for significance. Missing data will not be imputed. An alpha level of 0.05 will be considered significant for the primary endpoint. For exploratory analysis, the primary endpoint of capsule thickness will be presented as mean ± SEM and evaluated using analysis of variance (ANOVA) with factors including study cohort, radiotherapy and length of drug treatment.

Secondary Analysis:
For secondary objectives of the trial, we will determine the level of fibrosis and presence of collagen from the biopsy specimens. The level of fibrosis and the presence of collagen will be analyzed descriptively as continuous levels and as ordinal levels with mean, standard deviation and 95% confidence intervals. The difference in the level of fibrosis and relative presence of collagen between study cohorts will be compared using t-tests for significance.
Similar statistical methods will also be employed to analyze the capsule tissue that is removed at the time of expander-implant exchange to determine the level and presence of collagen, fibroblasts and myofibroblasts.

Confounding Factors:
In addition to primary and secondary analysis, we will also determine if there are other confounding factors such as variables in time and length treated with zafirlukast and radiation therapy by using ANOVA models on capsule thickness. Univariate analysis will be done on capsule thickness with all potential factors and selected variables of interest deemed significant will be further analyzed for interaction effect. Capsule thickness will be reported per subgroup of patients to account for time and radiation variables.

Other analysis:
An interim analysis is planned at 1 year to assess treatment efficacy in the treatment group compared to standard of care group.

10.0 STUDY MANAGEMENT

10.1 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 Investigator 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 subjects before any protocol related procedures are performed on any subjects.

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 Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

10.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g., advertisements used to recruit participants) will be reviewed and approved by the UCSF CHR (UCSF Institutional Review Board). Prior to obtaining CHR 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.

10.3 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 CHR-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.

10.4 Changes in the Protocol

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

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to CHR approval. In this circumstance, however, the Investigator must then notify the CHR in writing within five (5) working days after implementation. The Study Chair and the UCSF study team will be responsible for updating any participating sites.

10.5 Handling and Documentation of Clinical Supplies

The UCSF Principal Investigator will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included. The sponsor-investigator will maintain written records of any disposition of the study drug.

The Principal Investigator shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the Principal Investigator will not allow the investigational drug to be used in any manner other than that specified in this protocol.

10.6 Case Report Forms (CRFs)

The Principal Investigator and/or his/her designee 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. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit; the Investigator 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 patient's medical records maintained by UCSF personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator 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.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

The Principal Investigator 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 Study Chair, the Trial Statistician, and the Protocol Project Manager.

10.7 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.

10.8 Record Keeping and Record Retention

The Principal Investigator 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 Principal Investigator 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 (e.g., signed and dated consent forms and medical records, such as 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, CHR correspondence and approval, signed patient 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 investigator 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.

11.0 PROTECTION OF HUMAN SUBJECTS

11.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the CHR mechanism and the process of informed consent. The CHR reviews all proposed studies involving human experimentation and ensures that the subject'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 CHR 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.

11.2 Protection of Privacy

Patients 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 patient's medical records, and each patient 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.

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APPENDIX 1: DATA AND SAFETY MONITORING PLAN FOR A PHASE 2 OR 3 INSTITUTIONAL STUDY

1. Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and subject safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of patient data.
- Review of serious adverse events.
- Auditing every six months (depending on study accrual).
- Minimum of a yearly regulatory audit.

2. Monitoring and Reporting Guidelines

Investigators will conduct continuous review of data and patient safety and discuss each patient's treatment at monthly site committee meetings. These discussions are documented in the site committee meeting minutes. The discussion will include the number of patients, significant toxicities in accordance with the protocol, and observed responses.

All institutional Phase II and III studies are designated with a moderate risk assessment (see Appendix H). The data is audited twice per year with twenty percent of the patients monitored (or at least three patients if the calculated value is less than three).

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

All Grade 3-5 Adverse Events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse Events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) (version 4.03) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to treatment or medical procedure. Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or medical procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or medical procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or medical procedure.

- **Unlikely** – The adverse event is doubtfully related to the investigational agent(s) or medical procedure.
- **Unrelated** – the adverse event is clearly not related to the investigational agent(s) or medical procedure.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

3.2 Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

- Death.
- Life-threatening (i.e. results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Permanent or significant disability/incapacity
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious Adverse Event reporting will be in accordance with the UCSF IRB Regulations and Code of Federal Regulation Title 21 Part 312.32. The SAE will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:

https://irb.ucsf.edu/adverse-event
FDA website for guidance in reporting serious adverse events:

www.fda.gov/Safety/MedWatch/HowToReport/default.htm

Med Watch forms and information:

www.fda.gov/medwatch/getforms.htm

All serious adverse events are entered into OnCore®, as well as submitted to the IRB (per IRB guidelines) via iMedRIS®. The SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and

discussed at DSMC meetings, which take place every six weeks. The date the SAE is sent to all required reporting agencies will be documented in OnCore®.

If the SAE involves a subject death, and is determined to be possibly, probably or definitely related to the investigational drug or any research related procedure, the event must be reported to the DSMC Chair or Vice Chair within 1 business day.

The reporting procedure is by communication via phone or in person with written documentation of the one-on-one communication via e-mail, with a copy of the e-mail to the DSMC Manager.

3.3 Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Principal Investigator will notify the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Investigator stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day via e-mail. and the IRB must be notified within 10 business days via an iRIS Reporting Form.

[redacted]