Study Protocol
and Statistical Analysis Plan

Study Title:

Effect of ibuprofen on postoperative opiate medication use and shoulder functional outcomes after arthroscopic rotator cuff repair

NCT Number:

NCT02588027

Document Date:

09/22/2015

University of California, San Francisco
PROTOCOL TEMPLATE

Instructions to User:

1. **Sections and text that are in regular font and that have not been highlighted in grey** represent standard language. In general, these sections should be present in your final protocol and the language should not be changed. However, every protocol is unique and changes to standard sections and language may be necessary to meet the needs of your protocol. Please review the language carefully to make sure that it is accurate for your study.
2. **Sections that are highlighted in grey, but that have regular font**, represent sections or information that needs to be customized as applicable to your study, but the language that is present is generally considered to be standard if that section (or procedure) applies to your protocol.
3. **Sections that are highlighted in grey, and where the text is italicized**, represent instructions with some example text. All require complete customization for your study.
4. As you customize each section of the protocol, **remove the highlighting and restore the font to regular (from italics)** to denote that section as having been completed.
5. When your protocol is complete, **review** it to ensure that all highlighting and italics have been removed.

UCSF Orthopaedic Surgery and Sports Medicine
Clinical Research Protocol
NSAID Study

Protocol Number:	
Version Date:	August 28, 2015
Investigational Product:	Ibuprofen
IND Number:	
Development Phase:	
Sponsor:	UCSF Orthopaedic Surgery and Sports Medicine 1500 Owens Street San Francisco, CA
Funding Organization:	
Principal Investigator:	Name: C. Benjamin Ma Telephone: Fax: E-mail: MaBen@ucsf.edu
Medical Monitor:	Name: Telephone: Fax: E-mail:
Coordinating Center:	If applicable

Approval:

Principal Investigator 8/28/15 *Date*

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PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number:

Protocol Title: NSAID Study

Protocol Date: June 28, 2015

Investigator Signature — *Date* 8/28/15

C. Benjamin Ma, Professor in Residence, Chief- Sports Medicine and Shoulder Service

Print Name and Title

Site # N/A

Site Name UCSF

Address *Orthopaedic Institute Box 3004*

1500 Owens St. Ste 170

San Francisco, CA

94143

Phone Number *(415) 353-7987, Study Coordinator*

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LIST OF ABBREVIATIONS

AE	Adverse event
ASES	American Shoulder and Elbow Surgeon score
CFR	Code of Federal Regulations
CRF	Case report form
DASH	Disability Arm, Shoulder and Hand score
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
NSAID	Non-steroidal anti-inflammatory drug
PI	Principal Investigator
SAE	Serious adverse experience
SF-12	12-Item Short Form Health Survey
VAS	Visual Analog Scale

PROTOCOL SYNOPSIS

TITLE	Effect of ibuprofen on postoperative opiate medication use and shoulder functional outcomes after arthroscopic rotator cuff repair
SPONSOR	
FUNDING ORGANIZATION	Orthopaedic Sports Medicine Department
NUMBER OF SITES	One
RATIONALE	There has been an increasing trend in opiate use and prescription for management of pain and associated rise in rate of opiate abuse and complications. Multimodal pain control has been shown to very effective for pain after orthopaedic surgery and can reduced the amount of opiate medication required for adequate pain control. Non-steroidal anti-inflammatory drugs (NSAID) play an important role in multimodal pain control by inhibiting prostaglandin biosynthesis and reducing the release of inflammatory enzymes from the cell. Although NSAID medication have a role in treating pain after an acute sports injury such as an ankle sprain, its role and effects post-operatively after orthopaedic surgeries is controversial. While there are several human studies showing that NSAIDs can inhibit bone fusion after spine surgery, many studies demonstrating the negative effects on bony ingrowth, bone healing, and tendon healing are limited to animal studies. There have been several preclinical studies demonstrating that NSAID medications impair rotator cuff tendon healing after repair. Cohen et al found celecoxib and indomethacin impaired rotator cuff tendon healing in a rat modal with lower failure loads and decrease collagen organization in the treatment group. Another study found that the detrimental effects of systemic ibuprofen was time dependent with worse outcomes if given in the immediate postoperative period. To our knowledge, there no human studies assessing the outcomes of postoperative NSAID use and rotator cuff repair. The purpose of our study is to evaluate the effect of postoperative NSAID use on pain control and shoulder outcomes after arthroscopic rotator cuff tendon repair.
STUDY DESIGN	This is a randomized, double-blind, placebo-controlled study.
PRIMARY OBJECTIVE	Assess postoperative pain scores and opiate consumption in patients prescribed ibuprofen versus placebo for postoperative pain control after arthroscopic rotator cuff repair

SECONDARY OBJECTIVES	Assess functional shoulder outcome scores and repair integrity in patients prescribed ibuprofen versus placebo for postoperative pain control after arthroscopic rotator cuff repair. Evaluate the effect of post-operative NSAID use on pain scores, opiate use, functional shoulder outcomes, and repair integrity after arthroscopic rotator cuff repair.
NUMBER OF SUBJECTS	90
SUBJECT SELECTION CRITERIA	Inclusion Criteria: -Patients 18 years or older -Patients that undergo arthroscopic rotator cuff repair only Exclusion Criteria: - Patients less than 18 years of age, pregnant, are incarcerated - Patients who are unable to and not willing to comply with the study protocol and follow-up visits - Patients with a history of prior rotator cuff repair - Patients with rotator cuff tears that require open repair - Patients with contraindications to taking ibuprofen postoperatively such as an allergy to ibuprofen, history of gastroenterology bleed, or renal dysfunction.
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Ibuprofen 400mg Ibuprofen will be taken by mouth three times a day for two weeks after surgery.
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	Placebo Placebo will be taken by mouth three times a day for two weeks after surgery.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be on study for up to 2 year **Screening:** 1-2 days **Treatment:** 2 weeks **Follow-up:** 1 week, 6 weeks, 3 months, 6 months, 1 year, and 2 years; each visit lasting about 15 minutes) The total duration of the study is expected to be 3 years. One year for subject recruitment and 2 years for final subject follow-up.

CONCOMMITANT MEDICATIONS	Allowed: hydrocodone/acetaminophen, colace, ondansetron, senna, other medically required medications not related to pain control Prohibited: over the counter or prescribed ibuprofen, naproxen, diclofenac, additional tylenol, other opiate medications unless approved by study physicians
EFFICACY EVALUATIONS	
PRIMARY ENDPOINT	• VAS pain scores
SECONDARY ENDPOINTS	• Number of opiate pills used • ASES survey • DASH survey • SF-12 health survey • Shoulder range of motion • Rotator cuff repair integrity, assessed by ultrasound
OTHER EVALUATIONS	
SAFETY EVALUATIONS	Incidence of adverse events
PLANNED INTERIM ANALYSES	When approximately 50% of patients have completed the study through the 6 week visit, an interim analysis will be conducted by the investigators. Serious adverse events will be monitored by the committee on an ongoing basis throughout the study.
STATISTICS **Primary Analysis Plan**	This will be a randomized controlled trial, powered to primary outcomes of VAS pain scores at 6 weeks after surgery. Secondary outcomes will be opiate medication use, shoulder range of motion, ASES (American Shoulder and Elbow Society) score. DASH (Disability of Arm, Shoulder, and Hand) score, and repair integrity. As described previously, we will have two cohorts: 1) ibuprofen and 2) placebo. Means and standard deviations will be calculated. Categorical data will be analyzed using Fisher exact test or a chi-square test when appropriate. Continuous variables will be analyzed using student test. Statistical significance will be set at a p-value < 0.05. If necessary we will also do a multivariate analysis to look for possible confounding factors such as age, sex, weight, smoking status, etc.

Rationale for Number of Subjects	A sample size calculation was based VAS pain scores. We assumed an alpha error of 0.05 and applied an allocation ratio of 1. A sample size of thirty-five participants was calculated to provide 80% power to detect a minimally important clinical difference of 1.4 points in VAS pain scores and a standard deviation of two based on the literature. To allow for patients who wish to drop out as well as those who become lost to follow-up, the total enrollment goal will be 90.

1 BACKGROUND

Non-steroidal anti-inflammatory drugs (NSAID), such as ibuprofen, play an important role in pain control by inhibiting prostaglandin biosynthesis and reducing the release of inflammatory enzymes from the cell. Although NSAID medication have a role in treating pain after an acute sports injury such as an ankle sprain, its role and effects post-operatively after orthopaedic surgeries is controversial. While there are several human studies showing that NSAID medications can inhibit bone fusion after spine surgery, many studies demonstrating the negative effects on bony ingrowth, bone healing, and tendon healing are limited to animal studies.

1.1 Overview of Non-Clinical Studies

There have been several preclinical studies demonstrating that NSAID medications impair rotator cuff tendon healing after repair. Cohen et al found celecoxib and indomethacin impaired rotator cuff tendon healing in a rat modal with lower failure loads and decrease collagen organization in the treatment group. Another study found that the detrimental effects of systemic ibuprofen were time dependent with worse outcomes if given in the immediate postoperative period.

1.2 Overview of Clinical Studies

To our knowledge, there no human studies assessing the use of postoperative ibuprofen on outcomes after rotator cuff repair. One case control study by Rouhani et al showed that preoperative COX2 inhibitors resulted in better pain control, reduced sides effects from opiate medication, decreased sleep disturbance and faster recovery after arthroscopic rotator cuff repair. Other studies have shown that the addition of an anti-inflammatory medication to a multimodal pain control regimen can provide effective pain control and reduced requirement for opiate medications; however this has been limited to inpatient joint replacement patients and few have looked the effectiveness in an outpatient, arthroscopic shoulder surgery population.

2 STUDY RATIONALE

In general, there is little information in the literature about the clinical effects of anti-inflammatory medications after rotator cuff repair. To our knowledge, there are no randomized human studies assessing the effect of anti-inflammatory medications use postoperatively on outcomes after rotator cuff repair. There have been several animal studies showing negative effects rotator cuff healing with anti-inflammatory medications in both a dose and time dependent manner however this has not been evaluated in human studies. This study will help provide more information on the effects of ibuprofen on rotator cuff repair outcomes.

2.1 Risk / Benefit Assessment

The risks of the side effects from ibuprofen are standard risks for any patient taking this FDA approved, over-the-counter medication. Patients are instructed to take the medication with food to minimize the GI side effects. They will also be given a prescription for an anti-emetic medication and stool softeners.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is to assess postoperative pain scores and opiate consumption in patients prescribed ibuprofen versus placebo for postoperative pain control after arthroscopic rotator cuff repair over the two week treatment period.

3.2 Secondary Objectives

The secondary objectives include assessing functional shoulder outcome scores and repair integrity in patients prescribed ibuprofen versus placebo for postoperative pain control after arthroscopic rotator cuff repair.

4 STUDY DESIGN

4.1 Study Overview

This is a single center, double-blinded, placebo-controlled, randomized trial. Ninety subjects are planned. Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study. Patients will be randomized into two cohorts:

1) Ibuprofen 400mg by mouth three times daily for 2 weeks. Patients will also receive the standard opiate medication (hydrocodone/acetaminophen 10mg/325mg) for the orthopaedic clinic for postoperative pain control.

2) Placebo tablet by mouth three times daily for 2 weeks. Patients will also receive the standard opiate medication (hydrocodone/acetaminophen 10mg/325mg) for the orthopaedic clinic for postoperative pain control.

Evaluations will be taken at baseline and postoperative clinic visits at 1 week, 6 weeks, 3 months, 6 months, 1 year, and 2 years. Total duration of subject participation will be one year. Total duration of the study is expected to be 3 years.

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

The primary endpoint will be VAS pain scores at 6 weeks postoperatively

5.2 Secondary Efficacy Endpoints

- Number of opiate pills used will help assess if the addition of ibuprofen can reduce the requirement of opiate medications for pain control
- ASES survey will assess patient reported outcomes about the use of their operative arm
- DASH survey will assess patient reported outcomes about the use of their operative arm
- SF-12 health survey will assess the patients overall health status
- Shoulder range of motion

- Rotator cuff repair integrity will be assessed by ultrasound study

5.3 Safety Evaluations

- Incidence of adverse events

6 SUBJECT SELECTION

6.1 Study Population

Subjects with a diagnosis of rotator cuff tear requiring arthroscopic repair that meet the inclusion and exclusion criteria will be eligible for participation in this study.

6.2 Inclusion Criteria

1. Male or female ≥ 18 years of age
2. Documentation of a rotator cuff tear diagnosis as evidenced by one or more clinical features consistent with one or more of the following criteria:

- Require arthroscopic rotator cuff repair only

3. Written informed consent (and assent when applicable) obtained from subject or subject's legal representative and ability for subject to comply with the requirements of the study.

6.3 Exclusion Criteria

1. Patients less than 18 years of age, pregnant, are incarcerated. Women who are not post-menopause are screened for pregnancy preoperatively with a urine test per our UCSF Orthopaedic Institute preoperative guidelines.
2. Patients who are unable to and not willing to comply with the study protocol and follow-up visits
3. Patients with a history of prior rotator cuff repair
4. Patients with rotator cuff tears that require open repair
5. Patients with an allergy to ibuprofen or anti-inflammatory medications
6. Patients with a medical chart record or those who report a history of upper gastroenterology bleed or gastic ulcers
7. Patients with a medical chart diagnosis or those who report a history of renal insufficiency or chronic kidney disease.
8. Patients who are currently on warfarin, enoxaparin, heparin, or a factor Xa inhibiting anti-coagulation medication

7 CONCURRENT MEDICATIONS

All subjects should be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies.

7.1 Allowed Medications and Treatments

Standard therapy for rotator cuff repair is allowed except for treatments noted in the exclusion criteria described above and as noted in the prohibited medications section below.

Prohibited Medications and Treatments

The following medications are prohibited during the study and administration will be considered a protocol violation.

- Over the counter or prescribed ibuprofen, naproxen, diclofenac, or other anti-inflammatory medications
- Opiate medications not prescribed by study physicians

8 STUDY TREATMENTS

8.1 Method of Assigning Subjects to Treatment Groups

Up to 85 eligible patients will be randomly assigned to ibuprofen or placebo treatment groups in a 1:1 ratio using a SAS-based computer-generated randomization scheme developed by the study data management provider. The investigator or designee will complete a randomization worksheet (at Visit 1).

8.2 Blinding

Due to the objectives of the study, the identity of test and control treatments will not be known to investigators or patients. The following study procedures will be in place to ensure double-blind administration of study treatments.

- Access to the randomization code will be strictly controlled.
- Packaging and labeling of test and control treatments will be identical to maintain the blind.

The study blind will be broken on completion of the clinical study and after the study database has been locked.

During the study, the blind may be broken **only** in emergencies when knowledge of the patient's treatment group is necessary for further patient management. When possible, the Investigator should discuss the emergency with the prior to unblinding.

8.3 Formulation of Test and Control Products

8.3.1 Formulation of Test Product

Ibuprofen tablets will be packaged in capsules by the UCSF Clinical Research Pharmacy.

8.3.2 Formulation of Control Product

A placebo capsule will be provided by the UCSF Clinical Research Pharmacy.

8.3.3 Packaging and Labeling

Study drug and placebo will be supplied in bottles containing 42 capsules by the UCSF Clinical Research Pharmacy.

Each bottle will be labeled with the required FDA warning statement for ibuprofen, the protocol number, a treatment number, the name of the sponsors, and directions for patient use and storage.

8.4 Supply of Study Drug at the Site

The UCSF Clinical Research Pharmacy will ship Study Drug to the investigational sites. The initial study drug shipment will be shipped after site activation (i.e., all required regulatory documentation has been received by the Sponsor and a contract has been executed). Subsequent study drug shipments will be made after site request for resupply.

8.4.1 Dosage/Dosage Regimen

Patient will receive ibuprofen 400mg capsules or placebo capsules to take by mouth three times a day with meals. They will take this as scheduled for the two weeks after surgery.
Dispensing

The research study coordinator will have the authority to dispense the drug to the patients once they have been enrolled in the study.

8.4.2 Administration Instructions

Patients will be provided with thorough instructions on how to take the study medication as well as other routinely prescribed postoperative medications. Below is a sample of the instructions given to patients enrolled in the study:

POST OPERATIVE PAIN MEDICATION INSTRUCTIONS:

Many patients will receive a nerve block to decrease pain after surgery. However, there will be some pain after that nerve block wears off. Please start taking the pain medications prescribed after surgery and **BEFORE** your nerve block wears off as instructed below.

Pain Medication Log Book

You will receive a pain log book with your study medication on the day of surgery to take home with you. We would like you to record when you take pain medications (either the narcotic or study medication) and your pain score on a numeric scale from 0-10 (0 = no pain, 10 = worst pain experienced) at the time the medication was taken. Please fill out this log book every day after surgery until your first post-op visit. You will turn this log book in at your post-op visit.

First 24 hours after surgery

Take the study medication and narcotic on a regularly scheduled basis for the first 24 hours after surgery. A sample schedule is listed below

Hours after surgery	Medication
0	Norco
2	Study Medication

4	Norco
8	Norco
10	Study Medication
12	Norco
16	Norco
18	Study Medication
20	Norco
24	Norco

Day 2 – 6 after surgery

After the first 24 hours, please continue to take the **study medication regularly as scheduled three times a day with meals** until your first post-op visit with your surgeon. You make take the **Norco on an as needed basis** as prescribed if your pain is not sufficiently controlled with the study medication alone.

Please **bring your pain medication bottles (Norco and study medication) to your post-op visit.** Our research staff will count the number of pills taken during the first weeks as part of a data collection for the research study.

Week 1 – 6 after surgery

After your post-op visit, you will continued taking the study medication or placebo to complete a two week course.

Please **bring your pain medication bottles (Norco and study medication) to your 6 week follow-up visit.** Our research staff will count the number of pills taken during this period as part of a data collection for the research study.

Medication refills

Some patient may still experience pain requiring medications several weeks after surgery. Please contact our clinic if you need a refill prescription for the Norco medication. The study medication will **not** be refilled.

8.5 Supply of Study Drug at the Site

The study drug with will shipped to the study site prior to the enrollment of patients into the study. Study drugs will be distributed to the patients on the day of surgery once final inclusion criteria have been finalized.

8.5.1 Storage:

Study drug will be stored by the study site at controlled room temperature, 15 to 30°C (59 to 86°F). If the temperature of study drug storage in the clinic exceeds or falls below this range, this should be reported to the investigator and captured as a deviation. Subjects will be

instructed to store the medication in original packaging at room temperature according to the instructions outlined on the Drug Administration Instructions.

8.6 Study Drug Accountability

An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The number of study drug dispensed and returned by the subject will be recorded on the Investigational Drug Accountability Record. The study monitor will verify these documents throughout the course of the study.

8.7 Measures of Treatment Compliance

Subjects will be asked to keep a patient logbook noting the day and date they take their study drug, pain level and any adverse events. They will be asked to bring their logbook to their first postoperative visit along with all used and unused study drug containers.

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject or subject's legal representative. If appropriate, assent must also be obtained prior to conducting any study-related activities.

9.1 Clinical Assessments

9.1.1 Demographics

Demographic information (date of birth, gender, race) will be recorded at the preoperative visit.

9.1.2 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded at the preoperative visit.

9.1.3 Physical Examination

A complete physical examination will be performed by either the investigator or a subinvestigator who is a physician at Visit 1/preoperative visit. Qualified staff (MD, NP, RN, and PA) may complete the abbreviated physical exam at all other visits. New abnormal physical exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

9.1.4 Patient reported outcome surveys

Patients will be asked to complete health and shoulder specific outcome surveys at each visit. SF-12 and DASH surveys will be completed at the preoperative, one year, and two

year visit. ASES surveys will be completed at the preoperative, 6 weeks, 3 months, 6 months, 1 year, and 2 year visit.

9.1.5 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study drug will be recorded on the case report form (CRF).

9.2 Clinical Imaging Assessments Measurements

9.2.1 Ultrasound

At the one year postoperative visit, patients will also have an ultrasound study of their operative shoulder to assess the rotator cuff repair integrity.

10 EVALUATIONS BY VISIT

10.1 Visit 1 (Preoperative visit)

1. Review the study with the subject (subject's legal representative) and obtain written informed consent and HIPAA authorization and assent, if appropriate.
2. Assign the subject a unique screening number.
3. Record demographics data.
4. Record medical history, including a history of rotator cuff tear, diagnosis date, and prior treatments.
5. Record SF-12, DASH, and ASES survey scores
6. Perform a complete physical examination.
7. Schedule subject for surgery.

10.2 Visit 2 (Day of Surgery)

1. Patients will be randomized and study drug will be dispensed.
2. Patient pain medication logbook will be provided

10.3 Visit 3 (1 week postoperative)

1. Record any Adverse Experiences and/or Review subject diary for adverse experiences and dosing compliance.
2. Record VAS pain score.
3. Perform abbreviated physical examination.
4. Count and record the number of study drug pills and routinely prescribed opiate medication used.

10.4 Visit 4 (6 weeks postoperative)

1. Record any Adverse Experiences.
2. Record VAS pain score.

3. Perform abbreviated physical examination.
4. Count and record the number of study drug pills and routinely prescribed opiate medication used.
5. Record ASES survey scores.

10.5 Visit 5 (3 months postoperative)

1. Record any Adverse Experiences.
2. Record VAS pain score.
3. Perform abbreviated physical examination.
4. Record ASES survey scores.

10.6 Visit 6 (6 months postoperative)

1. Record any Adverse Experiences.
2. Record VAS pain score.
3. Perform abbreviated physical examination.
4. Record ASES survey scores.

10.7 Visit 7 (1 year postoperative)

1. Record any Adverse Experiences.
2. Record VAS pain score.
3. Perform abbreviated physical examination.
4. Record SF-12, DASH, and ASES survey scores.
5. Obtain ultrasound imaging study of operative shoulder.

10.8 Visit 8 (2 year postoperative)

1. Record any Adverse Experiences.
2. Record VAS pain score.
3. Perform abbreviated physical examination.
4. Record SF-12, DASH, and ASES survey scores.

10.9 Early Withdrawal Visit

1. Record any Adverse Experiences.
2. Record VAS pain score.
3. Perform complete physical examination.
4. Record SF-12, DASH, and ASES survey scores.
5. Collect any remaining study drug

11 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

11.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

11.2.1 Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) per UCSF CHR Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

11.3 Medical Monitoring

Insert Medical Monitor Name should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone: (XXX) XXX-XXXX
Pager: (XXX) XXX-XXXX

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Discontinuation of Study Drug

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- Sponsor request for early termination of study
- Positive pregnancy test (females)

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents Refer to Section 10 for early termination procedures.

12.3 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. As noted above, subjects who discontinue study treatment early (i.e., they withdraw prior to Visit 4) should have an early discontinuation visit. Refer to Section 10 for early termination procedures. Subjects who withdraw after

Visit 4 but prior to Visit 8 should be encouraged to come in for a final visit (and the procedures to be followed would include those for their next scheduled visit).

12.4 Replacement of Subjects

Subjects who withdraw from the study treatment will not be replaced.

Subjects who withdraw from the study will not be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject or investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The investigator will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

14 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

14.1 Data Sets Analyzed

All eligible patients who are randomized into the study and receive at least one dose of the study drug (the Safety Population) will be included in the analysis.

14.2 Demographic and Baseline Characteristics

The following demographic variables will also be collected: ethnicity/race, gender, age, hand dominance, medical comorbidities, prior opiate medication use and/or NSAID use, history of cortisone injection, and mechanism of rotator cuff tear.

14.3 Analysis of Primary Endpoint

Means and standard deviations will be calculated. VAS pain score (a continuous variable) will be analyzed using student test. Statistical significance will be set at a p-value < 0.05.

14.4 Analysis of Secondary Endpoints

Means and standard deviations will be calculated. Categorical data will be analyzed using Fisher exact test or a chi-square test when appropriate. Continuous variables will be analyzed using student test. Statistical significance will be set at a p-value < 0.05. If necessary we will also do a multivariate analysis to look for possible confounding factors such as age, gender, etc

Safety and tolerability data will be summarized by treatment group.

Adverse event rates will be coded by body system and MedDra classification term. Adverse events will be tabulated by treatment group and will include the number of patients for whom the event occurred, the rate of occurrence, and the severity and relationship to study drug.

14.5 Interim Analysis

When approximately 50% of patients have completed the study through the 6 week visit, an interim analysis will be conducted by the investigators. Serious adverse events will be monitored by the committee on an ongoing basis throughout the study.

14.6 Sample Size and Randomization

A sample size calculation was based VAS pain scores. We assumed an alpha error of 0.05 and applied an allocation ratio of 1. A sample size of thirty-five participants was calculated to provide 80% power to detect a minimally important clinical difference of 1.4 points in VAS pain scores and a standard deviation of two based on the literature.

To allow for patients who wish to drop out as well as those who become lost to follow-up, the total enrollment goal will be 90.

15 DATA COLLECTION, RETENTION AND MONITORING

15.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) OR paper CRF when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a site number, subject number and initials.

For eCRFs: If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail. *For paper CRFs:* If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

15.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

15.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. *For EDC studies:* Queries are entered, tracked, and resolved through the EDC system directly. *For paper studies:* Query reports (Data Clarification Requests) pertaining to data omissions and discrepancies will be forwarded to the Investigators and study monitors for resolution. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

15.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

15.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

15.6 Monitoring

Monitoring visits will be conducted by representatives of the Sponsor according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

15.7 Subject Confidentiality

In order to maintain subject confidentiality, only a site number, subject number and subject initials will identify all study subjects on CRFs and other documentation submitted to the Sponsor. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

16 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

16.1 Protocol Amendments

Any amendment to the protocol will be written by the investigators. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

16.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the

study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated and prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

16.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

16.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

16.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

APPENDIX 1. EXAMPLE OF SCHEDULE OF STUDY VISITS

	VISIT 1 (Preoperative)[a]	VISIT 2 (Day of Surgery)[a]	VISIT 3 (1 week)[a]	VISIT 4 (6 weeks)[a]	VISIT 5 (3 months)[a]	VISIT 6 (6 months)[a]	VISIT 7 (1 year)[a]	VISIT 8 (2 years)[a]
Informed Consent	X							
Medical History	X							
Complete Physical Exam	X							
Abbreviated Physical Exam		X	X	X	X	X	X	X
Randomization		X						
Dispensing or Administration of Study Drug		X						
Counting of Returned Study Drug			X	X				
Initiate Subject Diary		X						
Subject Diary Review			X					
SF-12 survey	X						X	X
DASH survey	X						X	X
ASES survey	X			X	X	X	X	X
Ultrasound study							X	
Adverse Experiences			X	X				

[a] ±2 days