REC-15-017

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Evaluation of the Safety of N1539 Following Major Surgery

NCT02720692

Clinical Study Protocol – Amendment 003

13 July 2016

CLINICAL STUDY PROTOCOL

Compound Name:	Injectable NanoCrystal Colloidal Dispersion Meloxicam (N1539)
Protocol Number:	REC-15-017 – Amendment 003
Protocol Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Evaluation of the Safety of N1539 Following Major Surgery
Date of Protocol:	13 July 2016
Study Designated Physician:	Stewart McCallum, MD 490 Lapp Rd Malvern, PA 19355 Telephone: 484-395-2411 Mobile: 610-888-3984 Fax: 484-395-2471 Email: smccallum@recropharma.com
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INVESTIGATOR'S AGREEMENT

By signing below I confirm that I have read this protocol and agree

- to assume responsibility for the proper conduct of the study at this site
- to conduct the study according to the procedures described in this protocol and any future amendments
- not to implement any deviation from, or changes to, the protocol without agreement of the sponsor and written approval from the Institutional Review Board or Independent Ethics Committee, except where necessary to eliminate an immediate hazard to subject(s)
- that I am aware of and will comply with all applicable regulations and guidelines

_____ _____

Principal Investigator's Signature **Date**

_____

Principal Investigator's Name (Print)

_____

Principal Investigator's Title (Print)

Site Address: _____

_____

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SYNOPSIS (PAGE 1 OF 7)

Name of Sponsor/Company: Recro Pharma, Inc.	**Protocol Number:** REC-15-017
Name of Study Drugs: Injectable NanoCrystal Colloidal Dispersion (NCD) Meloxicam (N1539)	**Protocol Title:** A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Evaluation of the Safety of N1539 Following Major Surgery
Name of Active Ingredient: Meloxicam	**Phase of Development:** 3

Objective: The primary objective of this study is to evaluate the safety and tolerability of N1539 compared with placebo, as evaluated with physical examination, vital signs, clinical laboratory tests, ECGs, wound evaluation, postoperative opioid consumption, and incidence of Adverse Events (AEs) and Serious AEs (SAEs).

Methodology:

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter, evaluation of the safety of N1539 in adult subjects undergoing major surgery. The study will enroll approximately 700 subjects.

Adult subjects, age 18 to 80 years inclusive, requiring major surgery that is expected to result in inpatient hospitalization for at least 24-48 hours, will be screened for participation at 30-40 study sites in North America, Australia, and New Zealand. Screening will occur within 28 days before study drug administration. After signing the informed consent, medical history, physical examination, baseline laboratory testing, 12-lead electrocardiogram (ECG), pregnancy testing, and vital sign measurements will be completed during the screening visit.

Study enrollment will include a cohort of approximately 30-40 subjects meeting criteria as high risk subjects, defined as age > 65 years with a glomerular filtration rate (GFR) of 60-89 mL/min/1.73 m^2, as calculated using the Modification of Diet in Renal Disease (MDRD) equation (Appendix E).

On the day of surgery (Day 1), subjects will undergo surgical procedure. Following surgery, subjects will be evaluated to ensure their eligibility for randomization within six hours after surgery. Eligible subjects will be randomized and treated with study drug for at least two study doses and will stay at the study center for at least 24-48 hours after treatment initiation or so long as inpatient care is clinically appropriate. Subjects may be discharged from the study center based on their clinical status, with safety assessments performed at the earlier of 1 day (24 hours) following their last study dose (LSD+1) or at time of discharge.

All treated subjects will be followed through 28 days following LSD. All subjects will return to the study center to complete end of study assessments 7 days post-LSD (LSD+7), with a telephone safety follow-up 28 days post-LSD (LSD+28).

Safety assessments will include monitoring of AEs, clinical laboratory tests, opioid consumption, vital sign measurements, wound evaluation, and ECGs.

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Name of Sponsor/Company: Recro Pharma, Inc.	**Protocol Number:** REC-15-017
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Name of Active Ingredient: Meloxicam	**Phase of Development:** 3

The following summarizes key activities for each phase of this study: 1) Pretreatment Phase, 2) Treatment Phase, 3) Follow-up.

1. **Pretreatment Phase:**
   a. Screening Period (Day -28 to Day -1): Subjects will be consented and screened.
   b. Day of Surgery (Day 1):
      1) Pre-surgery: Subjects will be admitted to the site and reassessed for eligibility for the study. Pre-surgery activities will be conducted.
      2) Surgery: Eligible subjects will undergo surgery using an appropriate anesthetic regimen according to the type of surgery.
      3) Postoperative Period: Following surgery, subjects will be evaluated for eligibility for treatment.
   c. Randomization Qualification (Day 1): Subjects will be eligible for randomization and study dosing if/when they meet all of the postoperative randomization criteria within six hours after surgery (Section 4.3).
2. **Treatment Phase (Hour 0 through Discharge)**

   Once the subject meets postoperative randomization eligibility criteria, they will be randomized in a 3:1 ratio to IV treatment with N1539 30 mg or placebo, administered every 24 hours (±1 hour).

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Name of Active Ingredient: Meloxicam	**Phase of Development:** 3

The time of first dose of study drug (Dose 1) will be recorded as Hour 0. Subjects will be administered a study dose according to their randomization every 24 hours (from Hour 0) so long as IV analgesia is clinically appropriate or until they receive a maximum of 7 study doses. A final study dose may be administered up to 4 hours early in subjects who are scheduled to be discharged. When inpatient care is no longer required, subjects may receive additional study doses under continued supervision of the investigator in an appropriate setting. Subjects who do not receive a study dose for >28 hours following their previous study dose should be considered off treatment, and should not receive further study dosing. Subjects may continue to receive standard of care analgesics per the discretion of the investigator, except for medications which may interact with meloxicam or interfere with the objectives of the study, as defined in Section 5.12.

Subjects will undergo safety assessments at the earlier of LSD+1 day or at the time of discharge prior to leaving the study center.

3. **Follow-up:**

Subjects will be provided routine standard of care for pain management after discharge from the study center. All subjects will be asked to return to the study center at LSD+7 days to complete end of study assessments. Subjects will complete a final safety assessment by telephone at LSD+28 days.

Number of subjects to be enrolled: It is planned to enroll approximately 700 subjects; 175 subjects to be randomized to placebo, and 525 subjects to be randomized to N1539 30 mg.

Study enrollment will include a cohort of approximately 30-40 subjects meeting criteria as high risk subjects, defined as age > 65 years with a GFR of 60-89 mL/min/1.73 m^2 (using MDRD equation).

Number of study sites: 30-40

Study country location: United States, Canada, Australia, and New Zealand

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Name of Active Ingredient: Meloxicam	**Phase of Development:** 3

Criteria for inclusion: Subjects must meet all of the following criteria to be considered eligible to participate in the study:

1. Voluntarily provide written informed consent.
2. Male or female 18 to 80 years of age, inclusive.
3. Be planned to undergo major elective surgery, and be expected to require intravenous analgesia, remain in an inpatient setting for at least 24-48 hours, and are expected to receive at least two study doses.
4. Female subjects are eligible only if all of the following apply:
    - Not pregnant (female subjects of child bearing potential must have a negative serum pregnancy test at screening and negative urine pregnancy test before surgery);
    - Not breastfeeding;
    - Not planning to become pregnant during the study through telephone follow-up (LSD+28 days);
    - Commits to the use of an acceptable form of birth control for the duration of the study through telephone follow-up (LSD+28 days): OR
        - Be unable to become pregnant due to postmenopausal status or sterility of male partner while in a monogamous relationship; OR
        - Be in a monogamous relationship with a same sex partner with no intention of becoming pregnant through any means
5. Have a body mass index $\leq$40 kg/m^2
6. Be able to understand the study procedures, comply with all study procedures, and agree to participate in the study program.
7. For oncology cases all of the following criteria must be met:
    - Have a histologically confirmed diagnosis of a primary solid tumor, affecting any one of the following organs: breast, skin, colon, prostate, uterus, ovaries, urethra, penis, or vulva; AND
    - Based on clinical, laboratory, radiologic, pathologic, and surgical findings, the tumor is confined to the primary organ, without evidence of local, regional or distal spread; AND
    - Have a performance status such that they are able to carry on normal activities of daily life without limitations

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Name of Sponsor/Company: Recro Pharma, Inc.	**Protocol Number:** REC-15-017
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Name of Active Ingredient: Meloxicam	**Phase of Development:** 3

Criteria for exclusion: Subjects who meet any of the following criteria will be excluded from participating in the study:

1. Have a known allergy or hypersensitivity to meloxicam or any excipient of N1539, aspirin, or other non-steroidal anti-inflammatory drugs (NSAIDs).
2. Be scheduled to undergo cranial surgery, open heart procedure, any type of coronary artery bypass graft, organ transplant, or any other surgical procedure in which NSAIDs are contraindicated.
3. Planned or actual admission to the intensive care unit at any time during study participation.
4. Have an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) of > 2X the upper limit of normal (ULN), alkaline phosphatase (AP) >1.5X ULN, or total bilirubin > 1.2X ULN, a prothrombin time (PT) > 20% above ULN, or any laboratory abnormality that would place the subject at increased risk for study participation according to the judgment of the investigator at screening and/or prior to surgery.
5. Have a history of myocardial infarction within the preceding 12 months
6. Have history of HIV, or hepatitis B or C at screening.
7. Have, as determined by the investigator or the sponsor's medical monitor, a history or clinical manifestations of significant renal (GFR<60 mL/min/1.73 m^2), hepatic, cardiovascular, metabolic, neurologic, psychiatric, respiratory, or other condition that would preclude participation.
8. Have active or recent (within 6 months) gastrointestinal ulceration or bleeding
9. Have a known bleeding disorder which may be worsened with the administration of a NSAID.
10. Have evidence of a clinically significant 12 lead ECG abnormality according to the judgment of the investigator.
11. Have a history of alcohol abuse (regularly drinks > 4 units of alcohol per day; 8 oz. beer, 3 oz. wine, 1 oz. spirits) or prescription/illicit drug abuse within the previous 5 years.
12. Have positive results on the urine drug screen for cocaine or PCP, or alcohol breath test at screening, and/or prior to surgery.

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Name of Active Ingredient: Meloxicam	**Phase of Development:** 3

Criteria for Exclusion (cont):

13. Unable to discontinue medications, that have not been at a stable dose for at least 14 days prior to the scheduled surgical procedure, within 5 half-lives of the specific prior medication (or, if half-life is not known, within 48 hours) before dosing with study medication**.**
14. Be unable to discontinue herbal medications at least 7 days prior to surgery through LSD+1/discharge, including but not limited to: gingko biloba, garlic, ginger, ginseng, hawthorn, fish oil (omega-3-fatty acid), dong quai, feverfew, vitamin E
15. Be receiving lithium or a combination of furosemide with either an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker
16. Be currently receiving treatment with oral meloxicam (Mobic®) or another NSAID within 7 days prior to surgery.
17. Have received any investigational product within 30 days before dosing with study medication.
18. Have previously received N1539 in clinical trials, or had major surgery in the last 3 months that could interfere with study assessments.
19. Have undergone or be expected to undergo radiation therapy, chemotherapy, or other biological therapy for cancer treatment, within 60 days prior to screening, through the LSD+28 visit.

Post-Operative Randomization Criteria:

Administration of Dose 1 should be completed within six hours of the end of surgery in subjects who meet the following criteria:

1. Be able to achieve hemostasis and surgical incision closure, prior to Operating Room discharge.
2. The surgical procedure did not require use of > 2 units of packed red blood cells or platelets.
3. The surgical procedure from incision to closure was not longer than 12 hours.
4. Subject is expected to have sufficient pain such that parenteral analgesia is clinically appropriate
5. The subject has had no evidence of respiratory insufficiency, clinically significant hypotension, bradycardia, coagulopathy, or any other abnormality, during or following surgery that, in the investigator's opinion, significantly increases the risks of study participation.

Investigational product: N1539 30 mg

Reference therapy: Placebo

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Duration of treatment: Each subject is expected to receive at least two study doses during the treatment phase of the study, with additional doses administered every 24±1 hours from Hour 0 until discharge, until IV analgesia is no longer clinically appropriate, or until they have received 7 study doses. A final study dose may be administered up to 4 hours early in subjects who are scheduled to be discharged. When inpatient care is no longer required, subjects may receive additional study doses under continued supervision of the investigator in an appropriate setting. Subjects who do not receive a study dose for >28 hours following their previous study dose should be considered off treatment, and not receive further study dosing. Subjects will remain in the study center from the day of surgery (Day 1) to at least 24 hours after randomization (Day 2) or when appropriate for discharge. Subjects will be asked to return at LSD+7 days to complete end of study assessments, with a safety follow-up by phone at LSD+28.

Criteria For Evaluation

Safety:

The safety endpoints will include the following:

1) incidence of AEs and SAEs
2) change from baseline in laboratory tests; incidence of abnormal clinical laboratory tests, including routine blood chemistry, hematology, coagulation tests, and urinalysis
3) change from baseline in vital signs; incidence of clinically significant changes in vital signs
4) incidence of clinically significant abnormal ECG findings
5) incidence of abnormal wound healing
6) total opioid consumption during 0-24, 24-48, and 0-48 hours post first dose of study drug

Statistical methods:

Sample size determination: The sample size for this study was selected to support the required total exposure population for N1539.

Study populations:

Intent-to-Treat (ITT) Analysis Set: The ITT set will include all subjects who qualify for treatment following surgery. The ITT subjects may or may not receive treatment.

Safety Analysis Set: The safety analysis set will include all subjects treated with study drug in the study.

Safety analysis: The Medical Dictionary for Regulatory Activities (Version 18 or higher) will be used to classify all AEs with respect to system organ class and preferred term. AEs will be summarized for by treatment group. Changes in vital signs at each post dosing time point will be summarized by treatment group using descriptive statistics without formal statistical tests. The number and proportion of subjects with abnormal ECG findings will be summarized at each time point by treatment group. Safety data may be summarized by surgery type if data warrant.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
BMI	body mass index
BP	Blood Pressure
BPM	Beats per minute
BSA-CF	body-surface-area conversion factor
CFR	(United States) Code of Federal Regulations
ºC	degrees Centigrade
CL	Clearance
eCRF	Electronic case report form
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
ºF	degrees Fahrenheit
FOCBP	Female subject of childbearing potential
G	Gram
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
H	Hour
HCl	Hydrochloride
HR	Heart Rate
HREC	Human Research Ethics Committee
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
Kg	Kilogram
L	Liter
LSD	Last study dose
m^2	square meters
MDRD	Modification of Diet in Renal Disease
Mg	Milligram
Min	Minute

Abbreviation	Definition
mL	Milliliter
mm Hg	millimeters of mercury
NCD	NanoCrystal Colloidal Dispersion
NF	National Formulary
NSAID	Nonsteroidal anti-inflammatory drug
pH	negative log of hydrogen ion concentration
REB	Research Ethics Board
SAR	suspected adverse reaction
SAE	serious adverse event
SBP	Systolic Blood Pressure
SL	Sublingual
SPID	Summed PID
SpO2	peripheral oxygen saturation
SSAR	Serious suspected adverse reaction
SUSAR	Serious unexpected suspected adverse reaction
UDS	Urine Drug Screen
µg	Microgram
µL	Microliter
ULN	Upper limit of normal
US	United States
USP	*United States Pharmacopeia*
VD	Volume of distribution
WBC	white blood cell

1. INTRODUCTION

Since the year 2000, when the Joint Commission revised their standards for the assessment and management of pain, the treatment of pain has taken an increasingly significant position in medical care. Often referred to as the "fifth vital sign", subjects must now be routinely evaluated for pain symptoms so that therapy may be appropriately adjusted.

While this increased focus has brought more attention to the issue of subject comfort and quality of life, our range of tools has remained largely the same. Current medications run the gamut in duration of activity, ranging from acute medications that provide relief for 1-2 hours, to alternative formulations which can provide as much as 72 hours of analgesia. At the same time, these dosage forms commonly rely on a similar set of active ingredients, which often work through the same opioid pathway to provide relief (morphine, oxycodone, fentanyl) (Swarm, 2007). The result, while there is generally not a ceiling on the effect provided by opiate medications, the use of high doses, and multiple opiate medications may lead to an increased occurrence of adverse events, which may force a decision between symptoms and side effects

N1539 was initially developed as an injectable form of meloxicam for the short-term management of moderate to severe acute pain using proprietary NanoCrystal® technology. N1539 was acquired by Recro Pharma, Inc. (Recro) in April 2015, at which time, Recro assumed its development.

Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) of the enolic acid class that possesses anti-inflammatory, analgesic, and antipyretic activities, which are believed to be related to the inhibition of cyclooxygenase (COX) and subsequent reduction in prostaglandin biosynthesis (Turck, 1997; Del Tacca, 2002; Mobic® 2012).

Meloxicam has been marketed for over a decade as the oral agent, Mobic. Mobic tablets and suspension are indicated for the relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis and the relief of the signs and symptoms of pauciarticular or polyarticular course juvenile rheumatoid arthritis in patients 2 years or older.

Meloxicam has a slow onset of action, largely due to poor water solubility, and is not currently approved for the treatment of acute pain. It has a prolonged absorption, with the time of maximum observed plasma concentration (t_{max}) being approximately 5-6 hours following oral administration (Degner, 1997; Turck, 1997), which is consistent with its poor aqueous solubility. By increasing the dissolution rate of the active meloxicam moiety, the proprietary NanoCrystal technology should provide a faster onset of action of meloxicam, thus providing a suitable treatment of acute pain via the intravenous (IV) route

This study is designed to evaluate the safety of dosing with IV N1539 in a range of surgical procedures with subjects experiencing postoperative pain.

See the N1539 Investigator's Brochure for more information about the compound.

2. STUDY OBJECTIVE

The primary objective of this study is to evaluate the safety and tolerability of N1539 as evaluated with physical examination, vital signs, clinical laboratory tests, ECGs, wound evaluation, postoperative opioid consumption, and incidence of Adverse Events (AEs) and Serious AEs (SAEs).

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter, evaluation of the safety of N1539 in adult subjects undergoing major surgery. The study will enroll approximately 700 subjects.

Adult subjects, age 18 to 80 years inclusive, requiring major surgery that is expected to result in inpatient hospitalization for at least 24-48 hours, will be screened for participation at 30-40 study sites in North America, Australia, and New Zealand. Screening will occur within 28 days before study drug administration. After signing the informed consent, medical history, physical examination, baseline laboratory testing, 12-lead electrocardiogram (ECG), pregnancy testing, and vital sign measurements will be completed during the screening visit.

Study enrollment will include a cohort of approximately 30-40 subjects meeting criteria as high risk subjects, defined as age > 65 years with a glomerular filtration rate (GFR) of 60-89 mL/min/1.73 m^2, as calculated using the Modification of Diet in Renal Disease (MDRD) equation (Appendix E).

On the day of surgery (Day 1), subjects will undergo surgical procedure. Following surgery, subjects will be evaluated to ensure their eligibility for randomization within six hours after surgery. Eligible subjects will be randomized and treated with study drug for at least two study doses and will stay at the study center for at least 24-48 hours after treatment initiation or so long as inpatient care is clinically appropriate. Subjects may be discharged from the study center based on their clinical status, with safety assessments performed at the earlier of 1 day (24 hours) following their last study dose (LSD+1) or at time of discharge.

All treated subjects will be followed through 28 days following LSD. All subjects will return to the study center to complete end of study assessments 7 days post-LSD (LSD+7), with a telephone safety follow-up 28 days post-LSD (LSD+28).

Safety assessments will include monitoring of AEs, clinical laboratory tests, opioid consumption, vital sign measurements, wound evaluation, and ECGs.

The following summarizes key activities for each phase of this study: 1) Pretreatment Phase, 2) Treatment Phase, 3) Follow-up.

1. **Pretreatment Phase:**
    a. Screening Period (Day -28 to Day -1): Subjects will be consented and screened.
    b. Day of Surgery (Day 1):
        1) Pre-surgery: Subjects will be admitted to the site and reassessed for eligibility for the study. Pre-surgery activities will be conducted.
        2) Surgery: Eligible subjects will undergo surgery using an appropriate anesthetic regimen according to the type of surgery.
        3) Postoperative Period: Following surgery, subjects will be evaluated for eligibility for treatment.

c. Randomization Qualification (Day 1): Subjects will be eligible for randomization and study dosing if/when they meet all of the postoperative randomization criteria within six hours after surgery (Section 4.3).

2. Treatment Phase (Hour 0 through Discharge)

Once the subject meets postoperative randomization eligibility criteria, they will be randomized in a 3:1 ratio to IV treatment with N1539 30 mg or placebo, administered every 24 hours (±1 hour).

The time of first dose of study drug (Dose 1) will be recorded as Hour 0. Subjects will be administered a study dose according to their randomization every 24 hours (from Hour 0) so long as IV analgesia is clinically appropriate or until they receive a maximum of 7 study doses. A final study dose may be administered up to 4 hours early in subjects who are scheduled to be discharged. When inpatient care is no longer required, subjects may receive additional study doses under continued supervision of the investigator in an appropriate setting. Subjects who do not receive a study dose for >28 hours following their previous study dose should be considered off treatment, and not receive further study dosing. Subjects may continue to receive standard of care analgesics per the discretion of the investigator, except for medications which may interact with meloxicam or interfere with the objectives of the study, as defined in Section 5.12.

Subjects will undergo safety assessments at the earlier of LSD+1 day or at the time of discharge prior to leaving the study center.

3. Follow-up:

Subjects will be provided routine standard of care for pain management after discharge from the study center. All subjects will be asked to return to the study center at LSD+7 days to complete end of study assessments. Subjects will complete a final safety assessment by telephone at LSD+28 days.

3.2. Rationale for Study Design and Control Groups

This study will evaluate the safety of repeated dosing with N1539 administered following a range of major surgical procedures. Previous research has demonstrated the safety and efficacy of single and repeated doses of N1539 when administered IV in pharmacokinetic studies and after open and laparoscopic abdominal surgeries. Previous postoperative studies have identified 30 and 60 mg doses of N1539 as efficacious in comparison to placebo and active control groups. However, differences in efficacy between the 30 and 60 mg N1539 dose levels have not been consistently observed. As a result, the 30 mg dose of N1539 has been selected for additional safety and efficacy evaluation.

This study will further explore the safety of dosing with N1539 30 mg IV on a once daily schedule in a population of subjects with pain following major surgery.

4. STUDY POPULATION

4.1. Inclusion Criteria

Subjects must meet all of the following criteria to be considered eligible to participate in the study:

1. Voluntarily provide written informed consent.
2. Male or female 18 to 80 years of age, inclusive.
3. Be planned to undergo major elective surgery, and be expected to require intravenous analgesia, remain in an inpatient setting for at least 24-48 hours, and are expected to receive at least two study doses.
4. Female subjects are eligible only if all of the following apply:
    - Not pregnant (female subject of child bearing potential must have a negative serum pregnancy test at screening and negative urine pregnancy test before surgery);
    - Not breastfeeding;
    - Not planning to become pregnant during the study through telephone follow-up (LSD+28 days);
    - Commit to the use of an acceptable form of birth control for the duration of the study through telephone follow-up (LSD+28 days); OR
        - Be unable to become pregnant due to postmenopausal status or sterility of male partner while in a monogamous relationship; OR
        - Be in a monogamous relationship with a same sex partner with no intention of becoming pregnant through any means
5. Have a body mass index $\leq$40 kg/m^2
6. Be able to understand the study procedures, comply with all study procedures, and agree to participate in the study program.
7. For oncology cases all of the following criteria must be met:
    - Have a histologically confirmed diagnosis of a primary solid tumor, affecting any one of the following organs: breast, skin, colon, prostate, uterus, ovaries, urethra, penis, or vulva; AND
    - Based on clinical, laboratory, radiologic, pathologic, and surgical findings, the tumor is confined to the primary organ, without evidence of local, regional or distal spread at any time during study participation; AND
    - Have a performance status such that they are able to carry on normal activities of daily life without limitations

4.2. Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participating in the study:

1. Have a known allergy or hypersensitivity to meloxicam or any excipient of N1539, aspirin, or other non-steroidal anti-inflammatory drugs (NSAIDs).
2. Be scheduled to undergo cranial surgery, open heart procedure, any type of coronary artery bypass graft, organ transplant, or any other surgical procedure in which NSAIDs are contraindicated.
3. Planned or actual admission to the intensive care unit at any time during study participation
4. Have an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) of > 2X the upper limit of normal (ULN), alkaline phosphatase (AP) >1.5X ULN, or total bilirubin > 1.2X ULN, a prothrombin time (PT) >20% above ULN, or any laboratory abnormality that would place the subject at increased risk for study participation according to the judgment of the investigator at screening and/or prior to surgery.
5. Have a history of myocardial infarction within the preceding 12 months
6. Have history of HIV, or hepatitis B or C at screening.
7. Have, as determined by the investigator or the sponsor's medical monitor, a history or clinical manifestations of significant renal (GFR<60 mL/min/1.73 m^2), hepatic, cardiovascular, metabolic, neurologic, psychiatric, respiratory, or other condition that would preclude participation in the study.
8. Have active or recent (within 6 months) gastrointestinal ulceration or bleeding.
9. Have a known bleeding disorder which may be worsened with the administration of a NSAID.
10. Have evidence of a clinically significant 12 lead ECG abnormality according to the judgment of the investigator.
11. Have a history of alcohol abuse (regularly drinks > 4 units of alcohol per day; 8 oz. beer, 3 oz. wine, 1 oz. spirits) or a history of prescription/illicit drug abuse within the previous 5 years.
12. Have positive results on the urine drug screen for cocaine or PCP, or alcohol breath test at screening, and/or prior to surgery.
13. Unable to discontinue medications, that have not been at a stable dose for at least 14 days prior to the scheduled surgical procedure, within 5 half-lives of the specific prior medication (or, if half-life is not known, within 48 hours) before dosing with study medication
14. Be unable to discontinue herbal medications at least 7 days prior to surgery through LSD+1/discharge, including but not limited to: gingko biloba, garlic, ginger, ginseng, hawthorn, fish oil (omega-3-fatty acid), dong quai, feverfew, vitamin E
15. Be receiving lithium or a combination of furosemide with either an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker.

16. Be currently receiving treatment with oral meloxicam (Mobic®) or another NSAID within 7 days prior to surgery.
17. Have received any investigational product within 30 days before dosing with study medication.
18. Have previously received N1539 in clinical trials, or had major surgery in the last 3 months that could interfere with study assessments.
19. Have undergone or be expected to undergo radiation therapy, chemotherapy, or other biological therapy within 60 days prior to screening, through the LSD+28 visit

4.3. Postoperative Randomization Criteria

Administration of Dose 1 should be completed within six hours of the end of surgery in subjects who meet the following criteria:

1. Be able to achieve hemostasis and surgical incision closure, prior to Operating Room discharge.
2. The surgical procedure did not require use of > 2 units of packed red blood cells or platelets.
3. The surgical procedure from incision to closure was not longer than 12 hours.
4. Subject is expected to have sufficient pain such that parenteral analgesia is clinically appropriate.
5. The subject has had no evidence of respiratory insufficiency, clinically significant hypotension, bradycardia, coagulopathy, or any other abnormality, during or following surgery that, in the investigator's opinion, significantly increases the risks of study participation.

4.4. Discontinuation of Subjects

4.4.1. Procedures for Withdrawal

A subject may be discontinued from the study by the investigator or the sponsor at any time if either determines that it is not in the subject's best interest to continue participation. Subjects who withdraw consent to continue treatment should be encouraged to complete the discharge assessments prior to leaving the study center. Subjects will be encouraged to return for the LSD+7 visit and to agree to be followed through 28 days after receiving study medication. The date the subject is withdrawn and the primary reason for discontinuation will be recorded in the subject's electronic case report form (eCRF).

4.4.2. Replacement of Subjects

Discontinued subjects will not be replaced in the study. However, the study will enroll an adequate number of subjects to meet the target size of 700 subjects in the safety population for evaluation.

4.5. Lifestyle Guidelines

4.5.1. Confinement

Prior to the surgical procedure (Day 1), subjects will arrive at the study site in sufficient time to prepare for the procedure and confirm eligibility to participate in the study. Following the surgical procedure, qualifying subjects will be randomized and should initiate dosing with study drug on the day of surgery (Day 1) within six hours after surgery. Subjects may continue to receive study drug every 24 hours so long as IV analgesia is clinically appropriate or until they receive a maximum of 7 study doses. When inpatient care is no longer required, subjects may receive additional study doses under continued supervision of the investigator in an appropriate setting. Subjects may be discharged from the study center when appropriate based on clinical status.

Subjects will follow standard postoperative care instructions after discharge.

4.5.2. Diet

Subjects must not consume any poppy seeds within 48 hours prior to confinement, or any alcohol within 24 hours before or during the inpatient period.

5. TREATMENTS

5.1. Surgical Procedure and Perioperative Care

On Day 1, day of surgery, subjects will undergo major elective surgery, which may include, but is not limited to, open or laparoscopic abdominal or gynecological surgeries, or total hip or knee replacement.

Disallowed surgical procedures for inclusion in this study include cranial surgeries, open heart procedures, any type of coronary artery bypass, organ transplant, and/or any other surgical procedure in which NSAIDs are contraindicated.

Surgeries should be completed using an appropriate anesthesia and analgesic regimen according to the clinical practice of the surgeon based on the surgery type. Disallowed medications are described in Section 5.12.

Venous thromboembolism prophylaxis before and after surgery will be administered according to standard practice for the surgical procedure based on the patients individual needs, and at the discretion of the investigator and surgeon, taking into consideration known drug interactions and contraindications with NSAIDs.

5.2. Administration of Study Medication

Unblinded study personnel will prepare and administer all doses of study drug according to the treatment schedule. All study doses will be administered as an IV bolus over 15-30 seconds. If infusion over 15-30 seconds is not tolerated, the bolus may be administered over up to 2 minutes; stop and start time of IV push should be recorded in the subject's eCRF. Because the appearance of N1539 does not match the appearance of placebo, drug administration will be done in an appropriately blinded fashion so that the subjects, and other blinded study staff, will not be aware of the treatment administered.

Each subject is expected to receive at least two study doses during the treatment phase of the study, with additional doses administered every 24±1 hours from Hour 0 until discharge, until IV analgesia is no longer clinically appropriate, or until they have received 7 study doses. A final study dose may be administered up to 4 hours early in subjects who are scheduled to be discharged. When inpatient care is no longer required, subjects may receive additional study doses under continued supervision of the investigator in an appropriate setting.

The time of first administered study dose will be considered Hour 0.

5.3. Identity of Study Medication

N1539 will contain 30 mg meloxicam in each 1 mL of solution, as well as excipients including: povidone, sodium deoxycholate (deoxycholic acid), sucrose, and water for injection.

Placebo will include: dextrose and water for injection.

5.4. Method of Assigning Subjects to Treatment Groups

A computer generated block randomization scheme will be prepared prior to study initiation. Subjects will be randomly assigned to treatment with N1539 30 mg or placebo in a 3:1 assignment ratio according to the randomization scheme. Randomization will be stratified by risk status (high risk [age > 65 years with GFR 60-89 mL/min/1.73 m^2] vs. other) and surgery type (orthopedic vs. other surgeries), non-high risk subjects will further be stratified by study center. All study doses administered will be according to the original assignment.

5.5. Selection of Doses

Doses of N1539 have been selected following review of safety, efficacy and pharmacokinetic data from five previous clinical studies. Clinical studies have evaluated doses of N1539 ranging from 5 to 60 mg. Study N1539-02 demonstrated the analgesic efficacy of a single dose of N1539 at 15, 30 and 60 mg administered following third molar extraction. All three dose levels of N1539 resulted in a $SPID_{24}$ value that was statistically superior to placebo. The $SPID_{24}$ value for the 60 mg dose of N1539 was also statistically significantly greater than that of the 15 or 30 mg doses of N1539. In a subsequent study of 460 female subjects undergoing open abdominal hysterectomy (Study N1539-04), subjects were randomized to N1539 doses of 5, 7.5, 15, 30, or 60 mg, as well as an active control arm (morphine) or placebo. All N1539 dose levels showed statistically significant improvement compared to placebo in $SPID_{24}$ results. However, in this study, the LS mean $SPID_{24}$ value for the 30 mg N1539 was numerically greater than that of the 60 mg dose. A third study of N1539 was conducted in subject undergoing laparoscopic abdominal surgery with doses of 7.5 or 15 mg every 12 hours, or 30 mg once daily, compared to placebo (Study N1539-05). This study was discontinued early and efficacy analyses were not completed. All study doses were well tolerated in these studies, and there was no evidence of any dose related safety concerns.

The current study has been planned to evaluate the safety of the 30 mg dose level of N1539 in a range of postoperative subjects.

5.6. Selection of Timing of Dose

Qualified subjects will be administered study doses every 24 hours for a minimum of 2 study doses, and up to a maximum of 7 doses. This interval has been evaluated to maintain consistent levels of analgesia. The 24-hour dosing interval has been selected based on the pain relief and pharmacokinetic profile of N1539 established in previous clinical studies. The exact start and stop time each dose is administered will be recorded in the subject's eCRF.

5.7. Blinding and Unblinding of Study Medications

All doses administered in this study will be administered by an unblinded staff member. Study doses will be prepared by the designated unblinded and appropriately qualified member(s) of the healthcare team at the research center, for administration according to the subject's randomization sequence.

The study blind may be broken only if the safety of a subject is at risk and the treatment plan for that subject depends on which study medication he or she received. Unless the subject is at

immediate risk, the investigator must make diligent attempts to contact the sponsor before unblinding the subject's data.

If a subject's data are unblinded without the prior knowledge of the sponsor, the investigator must notify the sponsor as soon as possible and no later than the next business morning. All circumstances surrounding a premature unblinding must be clearly documented.

5.8. Treatment Compliance

Unblinded study personnel will administer each dose of study medication. The exact date and time each dose is administered will be recorded in the subject's eCRF.

5.9. Drug Accountability

The investigator (or designee) will sign for the study medications when they are received. The study medication must be handled and stored as described and dispensed only to those subjects formally entered into the study.

At the completion of the study, and after reconciliation of all delivery and usage records, any unused study medication supplied by the sponsor will be returned to the sponsor (or designee) or destroyed per written instructions from the sponsor.

5.10. Packaging, Labeling, and Storage

Study medication will be provided in non-blinded, study labeled packaging for preparation by an unblinded study pharmacist for use in this study.

N1539 will be provided in 1 mL, single use vials containing 30 mg meloxicam per vial.

Placebo will be provided in 1 mL, single use vials.

Directions for preparation of study medication will be provided as pharmacy instructions prior to initiation of the study.

Study medication should be stored at the study site at 20° to 25°C (68° to 77°F), although a range of 15ºC to 30ºC (59ºF to 86ºF) will be permitted. Study medication should be protected from light.

All study medication at the study site(s) should be stored in a locked area with restricted access. A temperature log or chart should be maintained to monitor the environment at the study site.

5.11. Prior and Concomitant Medications

All medications and other treatments taken by subjects within 5 days before dosing and during the study will be recorded in the eCRF.

All medications that have not been at a stable dose for at least 14 days prior to the scheduled surgical procedure will be prohibited within five half-lives of the specific prior medication (or, if half-life is unknown, within 48 hours) before the surgical procedure.

5.12. Prohibited Medications

The following medications or drug classes will be prohibited during the treatment phase of the study:

- Any NSAIDs (ketorolac, ibuprofen)

5.13. Concomitant Interventions and Procedures

All interventions or procedures, whether diagnostic or therapeutic, will be recorded in the eCRF, along with time, date, and reason for the intervention or procedure. If an intervention or procedure is implemented to treat an AE, the event must be recorded as an AE, along with all relevant information.

5.14. Rescue Medication

During the treatment phase, pain symptoms that are not adequately controlled by dosing with study drug, may be treated according to the standard practice of the investigator except for use of NSAIDs. All doses of analgesic medications should be recorded in the subject's eCRF.

Once discharged, subjects may utilize analgesics according to the standard practice of the investigator.

6. STUDY PROCEDURES

A schedule of study procedures for overall study assessments and day-of-dosing assessments is provided in Appendix A.

Study procedures should be completed within a window of ±15 minutes unless otherwise stated.

6.1. Demographic Assessments

6.1.1. Demographics

Demographics information will be collected during screening visit including age, sex, ethnicity, race, weight, height, and BMI. The type of surgery required will also be collected.

6.1.2. Medical History

The investigator or designee will document each subject's medical history during the screening visit. Medical history will be updated on Day 1 when the subject reports for surgery, and the subject will be reviewed to confirm that they continue to meet the required study inclusion and exclusion criteria.

6.1.3. Physical Examination

The investigator or designee will perform a physical examination (HEENT, cardiovascular, respiratory, gastrointestinal, neurological, dermatologic, and musculoskeletal systems) during the screening visit, at LSD+1/prior to discharge, and at the follow-up visit (LSD+7 days). Body weight and height will be measured, and BMI will be calculated during the screening visit only.

The study Investigator may perform a physical examination (the extent of which is determined by the study investigator) at any time during the study if indicated by change in a subject's medical history or condition.

6.2. Safety Assessments Description

6.2.1. Clinical Laboratory Tests

During the screening visit, on Day 1 during check-in (if greater than 14 days since screening labs or if screening labs were not performed at the central laboratory), Hour 48 ± 4 hours, at LSD+1/prior to discharge (if prior to Hour 48, or to be repeated in subjects who receive ≥ 4 doses), and at the follow-up visit (LSD+7 days), subjects will have blood and urine samples collected for routine clinical laboratory testing as follows:

- hematology: complete blood count consisting of white blood cell (WBC) and red blood cell count, platelet count, hemoglobin, hematocrit, and differential counts (total neutrophils, eosinophils, basophils, lymphocytes, and monocytes)
- clinical chemistry tests: urea, glucose, creatinine, sodium, potassium, chloride, bicarbonate, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, direct bilirubin, gamma-glutamyltransferase, lactate dehydrogenase,

calcium, total protein, magnesium, phosphate, albumin, cholesterol, triglycerides, and uric acid

- urinalysis: pH, protein, specific gravity, glucose, ketones, blood, white blood cell esterase, nitrites, and urobilinogen; microscopic examination will be performed only if dip stick is positive for blood or leukocytes unless otherwise specified
- coagulation tests: prothrombin time, activated partial thromboplastin time, international normalized ratio

Additional urine or blood samples will be collected and tested as follows:

- urine drug screen (UDS) and alcohol breath test at the screening visit, and during admission to the study center on Day 1. Urine drug screen will include screening of (at minimum): cocaine and phencyclidine (PCP).
- serum pregnancy testing at the screening visit, and urine pregnancy testing at check-in on Day 1 for FOCBP.

Screening laboratory results, and Day 1 urine drug and urine pregnancy results, will be used for assessing eligibility for randomization. Clinical laboratory tests done on Day 1 prior to surgery will be used as baseline reference and not for assessing study randomization eligibility.

6.2.2. Vital Sign Measurements

Resting vital signs will include resting blood pressure, resting pulse, and peripheral oxygen saturation (SpO2). Resting tests must be obtained after resting (seated/supine) for ≥ 5 minutes.

At screening and on Day 1 prior to surgery, resting vital signs will be collected. Vital signs will also be collected prior to the first two study doses, at LSD+1/prior to discharge, and at the follow-up visit (LSD+7 days). Predose vital signs will be collected within 15 minutes prior to dosing.

Actual times will be recorded for all events, and any deviation outside the specified ranges must be clearly documented in the subject's study records.

6.2.3. 12-Lead Electrocardiogram (ECG)

A 12-lead ECG will be completed for all subjects at screening, at check-in on Day 1 (if screening ECG was done >14 days prior to Day 1), at LSD+1/prior to discharge, at the follow-up visit (LSD+7 days), and at time of early discontinuation. At the Screening Visit, 12-lead ECG will be used to exclude subjects with a clinically significant abnormal ECG.

The findings (i.e., classification as "normal", "abnormal not clinically significant" or "abnormal clinically significant") will be recorded in the subject's eCRF. No interval measurements will be collected, and the ECG tracings will not be collected for Data Management.

6.2.4. Wound Evaluation

Surgical wound healing will be evaluated by the investigator at LSD+1/prior to discharge, and at the follow-up visit (LSD+7 days).

Wound evaluation will be performed at LSD+1/prior to discharge and at the follow-up visit (LSD+7 days) to determine whether healing is following a normal course in the opinion of the investigator. The investigator will evaluate the healing of the wound using an 11-point scale (0-10) where a score of 0 is "Completely unsatisfied", and a score of 10 is "Completely satisfied".

At the LSD+7 visit, the surgical wound healing status, and incidence of hematoma formation, will be evaluated according to the criteria defined in Appendix C.1.

6.3. Assessments by Visit

6.3.1. Screening Visit

Subjects meeting the eligibility criteria listed in Section 4 may be enrolled in the study after the nature and purpose of the protocol have been explained to them, and they have voluntarily granted written informed consent to participate. All subjects will have a screening evaluation within 28 days before surgery (Day 1). After informed consent is obtained, the following procedures will be performed at the screening visit for all subjects:

- Review of inclusion/exclusion criteria eligibility (Section 4.1 and Section 4.2)
- Demographics and medical history (Section 6.1.2)
- Physical examination including height, weight and BMI (Section 6.1.3)
- Measurement of resting vital signs (Section 6.2.2)
- 12-lead ECG (Section 6.2.3)
- Clinical laboratory tests (Section 6.2.1)
- Drug and alcohol screen (Section 6.2.1)
- Serum pregnancy test (FOCBP only; Section 6.2.1)

6.3.2. Day 1 (Check-In)

The following assessments will be conducted on the day of admission (Day 1, prior to surgery) for all subjects:

- Medical history update (Section 6.1.2)
- Measurement of resting vital signs (Section 6.2.2)
- 12-lead ECG (if screening ECG was >14 days prior to Day 1) (Section 6.2.3)
- Clinical laboratory tests (required if greater than 14 days since screening labs or if screening labs were not performed at the central laboratory; Section 6.2.1)
- Drug and alcohol screen (Section 6.2.1)
- Urine pregnancy test (FOCBP only; Section 6.2.1)

Subjects who continue to meet eligibility criteria will undergo surgical procedure per Section 5.1.

6.3.3. Day 1 (Randomization)

The following assessments will be conducted on Day 1 following surgery, prior to administration of Dose 1 (Hour 0) for all subjects while confined at the study clinic:

- Qualification, if subject meets eligibility criteria (Section 4.3)
- Measurement of resting vital signs before Dose 1 (Section 6.2.2)

6.3.4. Treatment Phase - Day 1 to Discharge (Up to Day 7)

The following assessments/procedures will be conducted during the treatment phase on Day 1 through discharge beginning with administration of the first study dose (Dose 1; Hour 0) for all subjects while confined at the study clinic:

- Study drug administration
- Clinical laboratory tests (Hour 48 ± 4 hours; Section 6.2.1)
- Measurement of resting vital signs (Section 6.2.2)
- Monitoring of AEs and concomitant medication (Section 7)

6.3.5. LSD+1 Day / Discharge

The following assessments will be conducted for all subjects at the earlier of LSD+1 day, or prior to discharge from the study center (including early termination):

- Physical examination (Section 6.1.3)
- Clinical laboratory tests (to be repeated in subjects who receive ≥ 4 doses; Section 6.2.1)
- Measurement of resting vital signs (Section 6.2.2)
- 12-lead ECG (Section 6.2.3)
- Wound evaluation (Section 6.2.4)
- Monitoring of AEs and concomitant medication (Section 7)

6.3.6. Follow-Up Visit (LSD+7 Days ± 2)

The following procedures will be conducted for all subjects during the follow-up visit.

- Physical examination (Section 6.1.3)
- Clinical laboratory tests (Section 6.2.1)
- 12-lead ECG (Section 6.2.3)
- Measurement of vital signs (Section 6.2.2)
- Wound evaluation (Section 6.2.4)
- Monitoring of AEs and concomitant medications (Section 7)

6.3.7. Follow-Up Telephone Contact (LSD+28 Days ± 4)

The following procedures will be conducted during the follow-up telephone contact:

- Monitoring of AEs and concomitant medications (Section 7)

6.4. Appropriateness of Assessments

Safety measures used in this study are standard for clinical trials of investigational medications.

6.5. Clinical Stopping Rules

This study will be discontinued if it is determined that there is a significant safety risk posed towards study subjects. Potential safety risks will be evaluated continuously throughout the course of enrollment in the study.

7. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND SERIOUS SUSPECTED ADVERSE REACTIONS

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE, SAE, or Serious Suspected Adverse Reaction (SSAR) as provided in this protocol. During the study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

7.1. Definition of an Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE may be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study medication, whether or not considered causally associated with the use of the study medication. Any abnormal laboratory value deemed clinically significant by the investigator, regardless of causal relationship, must be reported as an AE beginning after administration of study medication.

Examples of an AE include the following:

- significant or unexpected worsening or exacerbation of the condition or indication under study
- exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency or intensity of the condition (e.g., abnormal physical examination finding)
- signs, symptoms, or clinical sequelae of a suspected interaction
- signs, symptoms, or clinical sequelae of a suspected overdose of the study medication or a concurrent medication (overdose per se should not be reported as an AE or SAE, unless nonserious or serious sequelae occur)

The following examples are not considered AEs:

- medical or surgical procedure (e.g., endoscopy, appendectomy), although the condition that leads to the procedure is an AE
- anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) (including laboratory values) present or detected at the start of the study that do not worsen
- the disease or disorder being studied, or expected progression, signs, or symptoms of the disease or disorder being studied, unless they become more severe or occur with a greater frequency than expected for the subject's condition

All AEs, whether volunteered, elicited, or noted on physical examination, and regardless of causality or seriousness, will be assessed and recorded in the eCRF beginning after administration of study medication through 28 days after the last study dose. SAEs will be assessed and recorded after administration of study medication through 28 days after the last study dose (see Sections 7.2 and 7.3).

7.2. Definition of a Serious Adverse Event

An SAE is defined as any event that meets the following criteria:

- It results in death or is life-threatening (i.e., presents an immediate risk of death from the event as it occurred). (This criterion is not intended to include an AE that, had it occurred in a more severe form, might have caused death.)
- It results in persistent or substantial disability or incapacitation. (This criterion is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, diarrhea, or sprained ankle.)
- It results in hospitalization.
- It results in prolongation of an existing hospitalization.
- It is a congenital anomaly or birth defect.
- It requires medical or surgical intervention to prevent any of the above outcomes.

Medical and scientific judgment should be exercised in determining whether an AE is serious when considering important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent any of the other outcomes listed. Examples of such medical events that may also be considered serious include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline does not meet the definition of an SAE.

Social or convenience admission to a hospital or prolongation of a hospitalization for social or convenience reasons not associated with the occurrence of an AE does not meet the definition of an SAE.

7.2.1. Serious Adverse Events That Occur After Study Completion

If an investigator becomes aware of an SAE or death that occurs in a subject more than 30 days after the subject receives study medication and that investigator considers the event to be related to the study medication, the investigator is obligated to report the SAE to the sponsor.

7.3. Definition of a Suspected Adverse Reaction (SAR)

A SAR is defined as any adverse event for which there is a reasonable possibility that the adverse event was caused by the study drug. For the purposes of IND safety reporting, 'reasonable possibility' means 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 adverse reaction, which means any adverse event caused by a drug.

7.4. Definition of a Serious Suspected Adverse Reaction (SSAR)

A SSAR is any Suspected Adverse Reaction (SAR) that is determined to be serious, based on the outcomes of a SAE described in Section 7.2; i.e. death, life-threatening, causes or prolongs

inpatient hospitalization, causes a persistent of significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital abnormality/birth defect.

7.5. Recording and Evaluating Adverse Events and Serious Adverse Events

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, or other clinical information. In such cases, the diagnosis, not the individual signs or symptoms, should be documented as the AE or SAE.

7.5.1. Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study, using his or her clinical judgment. The intensity of each AE and SAE recorded in the eCRF should be assigned to one of the following categories:

- mild: an event that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities
- moderate: an event that is sufficiently discomforting to interfere with normal everyday activities
- severe: an event that prevents normal everyday activities

An AE that is assessed as severe should not be confused with an SAE. *Severity* is a term used to describe the intensity of a specific event, and both AEs and SAEs can be assessed as severe. The event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as *serious,* which is based on the subject's or event's outcome or on action criteria usually associated with events that pose a threat to a subject's life or functioning (see Section 7.2).

7.5.2. Assessment of Causality

The investigator is obligated to use his or her clinical judgment to assess the relationship between the study medication and the occurrence of each AE or SAE. The investigator will assess the relationship to the study medication by using the following criteria:

- **Definitely Related**: An AE has a strong temporal relationship to the study drug. The AE is most likely explained by study drug. Dechallenge and rechallenge (if possible) are positive. The AE is consistent with a known response to the study drug. Another etiology is unlikely or significantly less likely.
- **Probably Related**: An AE has a strong temporal relationship to the study drug. The AE is more likely explained by study drug than by another cause. Dechallenge (if performed) is positive.
- **Possibly Related**: An AE has a reasonable temporal relationship to study drug. The AE could have been due to another equally likely cause. Dechallenge is positive.
- **Not Related**: The subject did not receive the study drug **OR** the AE has no temporal relationship to study drug **OR** the AE has a much more likely alternate etiology **OR** the AE is due to an underlying or concurrent illness or effect of another drug.

Even in situations in which minimal information is available for the initial SAE report, it is important that the investigator always make an assessment of causality for every event before transmitting the SAE reporting form and completing the AE eCRF page(s). The causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may change his or her opinion of causality in light of follow-up information and amend the SAE reporting form and AE eCRF page(s) accordingly.

7.5.3. Assessment of Outcome

All SAEs must be followed until they are resolved, the condition stabilizes, the events are otherwise explained, or the subject is lost to follow-up. The investigator will assess the outcome of the event by using the following terms:

- **Resolved**: The event resolved or the subject recovered without sequelae. An event (either serious or nonserious) occurred and had an endpoint, and the subject experienced no restrictions. Examples include stent placement for coronary artery disease (a device implanted is not a sequela), an appendectomy (a scar is not a sequela), a postoperative wound infection, or an upper respiratory tract infection.
- **Resolved with sequelae**: The event has at least one secondary outcome that may result in permanent disability, functional limitation, or both. Such sequelae are usually limited to SAEs. Examples include hip replacement resulting in foot drop (foot drop is not the intended outcome but is a risk of surgery), stroke resulting in paralysis, or emboli formation after a bacterial infection resulting in a renal infarct and loss of renal function.
- **Not resolved**: At the end of the study, a nonserious event either has not changed in intensity or may not have recovered to baseline values, and the outcome is unknown. Examples include headache, low-grade fever, or nausea.
- **Unknown**: The subject has withdrawn from the study prematurely or is lost to follow-up, and the status of the event is unknown.
- **Death**

7.5.4. Assessment of Expectedness

For the purposes of IND safety reporting, adverse events and suspected adverse events should be assessed as being expected or unexpected. An AE or SAR is considered unexpected if it is not listed in the investigator brochure 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.

7.6. Follow-up of Adverse Events and Serious Adverse Events

After the occurrence of an AE or SAE, the investigator is required to follow each subject proactively and provide further information on the subject's condition. All AEs and SAEs documented at a previous visit or contact are designated as ongoing and will be reviewed at subsequent visits or contacts.

SAEs will be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the subject is lost to follow-up. The investigator will ensure that follow-up information provided to the sponsor includes results of any additional laboratory tests or investigations, histopathologic examinations, or consultations with other healthcare professionals that serve to clarify the nature of the event, the cause of the event, or both.

New or updated information will be recorded on the originally completed SAE reporting form and entered into the eCRF pages, with all changes signed and dated by the investigator. The updated SAE reporting form should be resubmitted to the sponsor within the time frames outlined in Section 7.7.

7.7. Prompt Reporting of Serious Adverse Events to the Sponsor

Once the investigator determines that an event meets the protocol definition of an SAE, he or she must notify the sponsor within 24 hours.

ANY SAE OR ANY OUTCOME OF DEATH DUE TO ANY CAUSE, WHICH OCCURS DURING THE COURSE OF THIS STUDY, REGARDLESS OF RELATIONSHIP TO STUDY MEDICATION, MUST BE REPORTED TO THE SPONSOR IMMEDIATELY (within 24 hours).

COMPLETE THE SAE DETAILS REPORTING FORM AND FORWARD BY E-MAIL TO THE FOLLOWING SPONSOR CONTACT:

Medical Safety
Recro Pharma, Inc.

Telephone: 484-395-2470
Fax: 484-395-2471
E-mail: AE@recropharma.com

In the initial e-mail, the investigator must provide to the sponsor the following eCRF pages, completed to the greatest extent possible:

- AE record
- medical history
- prior and concomitant medications

Also, the following documents are to be forwarded: any laboratory results, diagnostic test results, or medical reports relevant to the SAE.

E-mail transmission is the preferred method to transmit SAE information. In rare circumstances and in the absence of e-mail capacity, notification by fax or telephone is acceptable, with a copy of the SAE reporting form sent by overnight mail. Initial notification via telephone does not replace the need for the investigator to complete the SAE reporting form and eCRF pages within the time frames outlined.

If the investigator does not have all information regarding an SAE, he or she must not wait to receive additional information before notifying the sponsor of the event. The form must be updated when additional information is received. Follow-up information received on all SAEs

must be forwarded to the sponsor by using the same procedure and timelines as for an initial report.

7.8. Regulatory Reporting Requirements

The investigator must promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 7.7, "Prompt Reporting of Serious Adverse Events to the Sponsor." The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the appropriate project contact for SAE receipt is essential so that SSARs that are either unexpected or observed with increasing occurrence, be reported and legal obligations and ethical responsibilities regarding the safety of other subjects are met.

Investigator letters are prepared according to sponsor policy and are forwarded to the investigators as necessary. An investigator letter is prepared for any SAR that is attributable to study medication, serious, and unexpected. The purpose of the investigator letter is to fulfill specific regulatory and Good Clinical Practice (GCP) requirements regarding the product under investigation.

The investigator, or responsible person according to local requirements, must comply with requirements related to the reporting of SAEs to the IRB or IEC.

7.9. Precautions

Any subject who becomes pregnant during the study must be discontinued immediately, but should be followed through delivery or termination of the pregnancy. A subject should also notify the investigator if she becomes pregnant within 30 days after receiving study medication. The sponsor must be notified of all pregnancies reported to the investigator (see Section 7.7 for contact information).

8. STATISTICAL METHODOLOGY

8.1. Determination of Sample Size

The sample size for this study was selected to support the total exposure population for N1539.

8.2. Study Endpoints

8.2.1. Safety Endpoints

The safety endpoints will include the following:

1) incidence of AEs and SAEs
2) change from baseline in laboratory tests; incidence of abnormal clinical laboratory tests, including routine blood chemistry, hematology, urinalysis, and coagulation tests
3) change from baseline in vital signs; incidence of clinically significant changes in vital signs
4) incidence of clinically significant abnormal ECG findings
5) incidence of abnormal wound healing
6) total opioid consumption during 0-24, 24-48, and 0-48 hours post first dose of study drug

8.3. General Considerations for Statistical Analysis

8.3.1. Analysis Datasets

Intent-to-Treat (ITT) Analysis Set: The ITT set will include all randomized subjects. The ITT subjects may or may not receive randomized treatment.

Safety Set: The safety set will include all treated subjects and will be used for safety and tolerability assessments.

8.3.2. Test Hypothesis and *P* Value Justification

No formal hypothesis will be evaluated in this safety study; all safety endpoints will be tabulated by treatment groups with descriptive statistics. Inferential statistics may be provided when appropriate.

8.3.3. Procedures for Handling Missing Data

Unless indicated otherwise, no imputation will be done for missing data. However, AEs with missing severity assessments will be tabulated as "severe," and AEs with missing relationship assessments will be tabulated as "related" for the purpose of analysis; and the missing data will be presented in data listing as is.

8.3.4. Definitions for Assessment Windows

For the purpose of data analysis, *baseline* measures for a given period will be the last measurements taken before the subject receives the study medication. End of Study Visit will be the last follow-up telephone call to be conducted on LSD+28 Days ± 4.

8.4. Study Population Summaries

Population summaries will be provided for the safety analysis set included in this study.

8.4.1. Disposition

The summary tables will provide frequency counts for subject disposition (all treated subjects, subjects who completed the study, number and proportion of subjects who discontinued treatment; number and proportion of subjects who discontinued from the study, and reason for discontinuation of study drug treatment and reason for discontinuation of study) by treatment group and study overall.

Disposition in terms of number of subjects excluded from each analysis sets (ITT, safety) will also be provided by randomization strata (surgery type and risk category) and study overall.

8.4.2. Demographics and Surgery Characteristics

The demographic summary will include descriptive statistics for age, sex, race, risk status, weight, height, and BMI by treatment group and by surgery type.

Surgery characteristics include surgery type, surgery duration, time from end of surgery to first dose of study drug.

8.4.3. Protocol Violations

All protocol violations and deviations will be identified. Tabulation may provide if data warrant.

8.4.4. Treatment Compliance

Doses of study medication will be administered by designated unblinded study personnel to study subjects while subjects are confined to the study site. The exact time of administration of study medication will be documented within each subject's eCRF. No formal summary of treatment compliance will be produced.

8.4.5. Prior and Concomitant Medications

All prior and concomitant medications will be tabulated for the overall study population. Prior and concomitant medications will be coded to the therapeutic drug classes and generic drug names using the World Health Organization (WHO) Drug classifications version 1Q2016 or higher.

Total opioids contained in each analgesic will be determined based on total IV morphine equivalent dose for each medication. Total opioid consumption during 0-24, 24-48, and 0-48 hours post first dose of study drug will be determined for each subject and will be tabulated by treatment group.

8.5. Safety and Tolerability Evaluations

8.5.1. Extent of Exposure

A subject may receive up to 7 doses of N1539. For N1539 treatment assigned subjects, the maximum exposure to meloxicam over the treatment period would be 210 mg (30 mg/dose * 7 doses).

Evaluation of the extent of exposure for the treatment period will be assessed via number of doses taken.

8.5.2. Adverse Events

The Medical Dictionary for Regulatory Activities (Version 18 or higher) will be used to classify all AEs with respect to system organ class and preferred term.

Three types of summaries will be produced for the AE summary:

1. an overall summary of AEs: number of subjects with at least one event and number of events for all AEs, and SAEs
2. a summary table of AEs and SAEs by system organ class and preferred term and severity
3. a summary table of AEs and SAEs by preferred terms in descending order of total incidence

AEs will be tabulated by treatment group. AEs that lead to premature discontinuation from the study or to death will be listed separately via data listings.

8.5.3. Clinical Laboratory Tests

Laboratory values will be collected at screening, Day 1 during check-in (baseline; centrally performed screening labs may act as baseline labs if collected within 14 days of Day 1), Hour 48, LSD+1/discharge (if prior to Hour 48, or to be repeated in subjects who receive ≥ 4 doses), and LSD+7 days follow-up visit. Observed values at each time point, and change from baseline will be summarized for the by treatment group without formal statistical testing

Number (%) subjects with abnormal clinical test results relative to the lab normal range at each time point and shift tables may also be prepared if data warrant. Number (%) subjects with clinically significant changes in laboratory test post dosing will also be tabulated.

8.5.4. Vital Sign Measurements

Resting vital sign values at each time point collected will be summarized by treatment group including change from baseline (predose), without formal statistical testing. Number (%) subjects with clinically significant changes in vital signs post dosing will also be tabulated.

8.5.5. Electrocardiograms

The number and proportion of subjects with clinically significant abnormal ECG findings at each time point collected will be tabulated by treatment group. A data listing will be provided for subjects with changes from normal at baseline to abnormal and clinically significant after baseline.

8.5.6. Wound Evaluation

The investigator assessment scores of satisfaction with wound healing at each time point collected will be summarized by treatment group. Wound healing status and incidence of hematoma formation will be summarized by treatment group.

8.5.7. Subgroup Analyses for Safety Endpoints

Subgroups to be analyzed for safety may include: race, gender, age, surgery type, surgery duration, and/or risk status (high risk vs others).

9. STUDY ADMINISTRATION

9.1. Regulatory and Ethical Considerations

9.1.1. Regulatory Authority Approval

The sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country specific regulatory requirements before any site may initiate the study in that country.

9.1.2. Ethical Conduct of the Study and Ethics Approval

This study will be conducted according to GCP; US 21 Code of Federal Regulations (CFR) Part 50 (Protection of Human Subjects); US 21 CFR Part 56 (IRBs); US 21 CFR Part 54 (Financial Disclosure); International Conference on Harmonization (ICH) Guidance for Industry, E6 GCP: Consolidated Guidance; the Nuremberg Code; and, where applicable Health Canada and the principles of the Declaration of Helsinki (Recommendations guiding Medical Doctors in Biomedical Research Involving Human Subjects), and with the NH&MRC National Statement on Ethical Conduct in Human Research (2007).

9.1.2.1. Ethics Committees

The investigator (or sponsor, where applicable) is responsible for ensuring that this protocol, the site's informed consent form, and any other information that will be presented to potential subjects (e.g., advertisements or information that supports or supplements the informed consent form) are reviewed and approved by the appropriate review board (IRB, REB, HREC, or IEC). The investigator agrees to allow the review board direct access to all relevant documents. The review board must be constituted in accordance with all applicable regulatory requirements. The sponsor will provide the investigator with relevant documents or data needed for review board review and approval of the study. Before investigational products can be shipped to the site, the sponsor must receive copies of the review board approval, the approved informed consent form, and any other information that the review board has approved for presentation to potential subjects.

If the protocol, the informed consent form, or any other information that the review board has approved for presentation to potential subjects is amended during the study, the investigator is responsible for ensuring that the review board reviews and approves, where applicable, these amended documents. The investigator must follow all applicable regulatory requirements pertaining to the use of an amended informed consent form, including obtaining review board approval of the amended form, before new subjects consent to take part in the study using the new version of the form. The investigator must promptly forward to the sponsor copies of the review board approval of the amended informed consent form or other information and the approved amended informed consent form or other information. Review board approval of the consent forms must be obtained in addition to the approval given for the clinical study. Regulatory review and approval may be required in some countries before review board approval can be sought.

9.1.2.2. General Considerations

The ethical standards defined within GCP are intended to ensure the following:

- Human subjects are provided with an adequate understanding of the possible risks of their participation in the study, and they have a free choice to participate or not.
- The study is conducted with diligence and in conformance with the protocol in such a way as to ensure the integrity of the findings.
- The potential benefits of the research justify the risks.

Recro Pharma, Inc. is the sponsor of study REC-15-017. The sponsor is responsible for all of the following:

- selecting qualified investigators
- providing investigators with the information they need to conduct the investigation properly
- ensuring proper monitoring of the investigation
- ensuring that appropriate regulatory agencies and all participating investigators are properly informed of significant new information regarding AEs or risks associated with N1539

9.1.3. Informed Consent

The sponsor will provide investigators with a sample informed consent form for this study. Investigators are encouraged to use the sample form; however, they may adapt the information to suit the needs of their institution, if necessary (although it must reflect the required elements of informed consent specified in 21 CFR Part 50.25). The final informed consent form must be accepted by the sponsor and approved by the IRB or IEC. Investigators must provide the sponsor with an unsigned copy of the final informed consent form before and after it is approved by the IRB or IEC. If any new information becomes available that might affect subjects' willingness to participate in the study, or if any amendments to the protocol require changes to the informed consent form, the sponsor will provide investigators with a revised informed consent form. The IRB or IEC must provide written approval of any revisions to the informed consent form in advance of its use.

Investigators must provide subjects with all the information necessary to make an informed decision about their participation in the study, including the nature and intended purpose of the study, possible benefits, and possible risks.

All information in the informed consent form should be provided in a language (whether written or spoken) that is as nontechnical as practical and that is understandable to the subjects.

Before written informed consent is obtained, the subject should be given ample time and opportunity to inquire about the details of the study. All questions must be answered to the satisfaction of the subject (or his or her legally authorized representative).

Before a subject undergoes procedures specific to the protocol, the informed consent form must be signed and dated by the subject (or his or her legally authorized representative) and any other signatories as required by the IRB or IEC.

If a subject (or legally authorized representative) cannot read, a short form approved by the IRB or IEC may be used. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining the consent shall sign the copy of the summary in accordance with 21 CFR 50.27 (b2).

After all required signatures have been obtained, a copy of the informed consent form should be provided to the subject, and the original must be kept on file at the site and made available for review by the sponsor. Documentation of the informed consent discussion must be noted in the subject's case history.

9.1.4. Investigator Reporting Requirements

The investigator is responsible for completing and maintaining adequate and accurate eCRFs and source documentation. Source documentation constitutes original records (first point of entry, either hard copy or electronic), which may include progress notes, medication administration records, operation reports, laboratory reports, discharge summaries, and so on.

9.2. Study Monitoring

The sponsor is responsible for ensuring the proper conduct of the study with regard to subject protection, ethics, protocol adherence, site procedures, and integrity of the data. At regular intervals during the study, the sponsor's study monitors will contact the study site via visits to the site, telephone calls, and letters in order to review study progress and eCRF completion and to address any concerns or questions regarding the study conduct. During monitoring visits, the following aspects of study conduct will be carefully reviewed: subjects' informed consent documents, subject recruitment procedures, subjects' compliance with the study procedures, source-data verification, drug accountability, use of concomitant therapy by subjects, AE and SAE documentation and reporting, and quality of data.

9.3. Quality Assurance

The sponsor, a regulatory authority, or an IRB representative may visit the study site at any time during the study or after completion of the study to perform audits or inspections. The purpose of a sponsor audit or regulatory inspection is to examine systematically and independently all study-related activities and documents to determine whether these activities were conducted according to the protocol, GCP, ICH guidelines, and any other applicable regulatory requirements. Investigators should contact the sponsor immediately if contacted by a regulatory agency about an inspection at their site.

9.4. Study and Site Closure

If the sponsor, investigator, or officials from regulatory agencies discover conditions arising during the study that indicate that the study should be halted or that the study site should be closed, this action may be taken after appropriate consultation between the sponsor and investigator. Conditions that may warrant termination of the study include, but are not limited to, the following:

- discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study
- submission of knowingly false information from the research facility to the sponsor, study monitor, or regulatory agencies
- failure of the investigator to comply with GCP (e.g., ICH guidelines, regulatory agency guidelines)
- insufficient adherence to protocol requirements or an unacceptably high rate of missing, erroneous, or improperly collected data
- evidence from the blinded data of sufficient technical problems with the study that one could believe with a high degree of certainty that subjects are being exposed to the investigational drug without a realistic expectation of evaluable data
- a decision on the part of the sponsor to suspend or discontinue testing evaluation or development of the product
- failure of the investigator to enroll subjects into the study at an acceptable rate

9.5. Records Retention

9.5.1. Health Insurance Portability and Accountability Act of 1996

The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subjects' health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR Parts 160 and 164 (the Health Insurance Portability and Accountability Act of 1996 privacy regulation) and where applicable in Canada the Privacy Act, Personal Information and Protection and Electronic Documents ACT (PIPEDA) and provincial privacy regulations. The investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with the privacy regulations of the Health Insurance Portability and Accountability Act and in a form satisfactory to the sponsor.

9.5.2. Financial Disclosure

Financial disclosure is required for this study.

9.5.3. Access to Original Records

Regulatory authorities expect that monitors, auditors, and representatives of national and international government regulatory agency bodies have access to original source documentation (see examples in Section 9.1.4) to ensure data integrity. "Original" in this context is defined as the first documentation of an observation and does not differentiate between hard-copy and electronic records.

9.5.4. Archiving of Study-Related Documents

Records related to this clinical study must be retained either for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since

the formal discontinuation of clinical development of the investigational product. The sponsor will notify the investigator as to when these documents no longer need to be retained for this use.

9.6. Provision of Study Results and Information to Investigators

When a clinical study report is completed, the sponsor will provide the major findings of the study to the investigators.

In addition, details of the study treatment assignment will be provided to the investigators to enable them to review the data to determine the outcome of the study for their subjects.

The sponsor may list and summarize the results from coded samples by subject number in the clinical study report. In this event, the investigator and study staff would have access to the research results and would be able to link the results to a particular subject. The investigator and study staff would be directed to hold this information confidentially.

9.7. Information Disclosure and Inventions

9.7.1. Ownership

All information provided by the sponsor and all data and information generated by the site as part of the study (other than a subject's medical records) are the sole property of Recro Pharma, Inc.

All rights, title, and interests in any inventions, know-how, or other intellectual or industrial property rights that are conceived or reduced to practice by site staff during the course of or as a result of the study are the sole property of Recro Pharma, Inc. and are hereby assigned to Recro Pharma, Inc.

If a written contract is executed between Recro Pharma, Inc. and the study site for the conduct of the study and that contract includes ownership provisions inconsistent with this statement, that contract's ownership provisions shall apply rather than this statement.

9.7.2. Confidentiality

All information provided by Recro Pharma, Inc. and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the investigator and other site staff. This information and data will not be used by the investigator or other site personnel for any purpose other than conducting the study. These restrictions do not apply to the following: 1) information that becomes publicly available through no fault of the investigator or site staff, 2) information that must be disclosed in confidence to an IEC or IRB solely for the evaluation of the study results, 3) information that must be disclosed in order to provide appropriate medical care to a study subject, or 4) study results that may be published as described in Section 9.7.3. If a written contract for the conduct of the study is executed and that contract includes confidentiality provisions inconsistent with this statement, that contract's confidentiality provisions shall apply rather than this statement.

9.7.3. Publication

For multicenter studies, the first publication or disclosure of study results shall be a complete, joint, multicenter publication or disclosure coordinated by Recro Pharma, Inc. Thereafter, any

secondary publications will reference the original publication(s). If no multicenter publication is submitted for publication within 18 months of study database hard lock, then the site shall be free to disclose its own results, subject to sponsor rights under Section 9.7.1.

Before submitting material for publication, presentation, or use for instructional purposes, or before otherwise disclosing the study results generated by the site (collectively, a "publication"), the investigator shall provide Recro Pharma, Inc. with a copy of the proposed publication and allow Recro Pharma, Inc. a period of at least 90 days to review the proposed publication. Proposed publications shall not include either Recro Pharma, Inc. confidential information (other than the study results) or the personal data (such as name or initials) of any subject.

At Recro Pharma, Inc.'s request, the submission or other disclosure of a proposed publication will be delayed a further 90 days to allow Recro Pharma, Inc. to seek patent or similar protection of any inventions, know-how, or other intellectual or industrial property rights disclosed in the proposed publication.

If a written contract is executed for the conduct of the study and that contract includes publication provisions inconsistent with this statement, that contract's publication provisions shall apply rather than this statement.

9.7.4. Data Management

The investigator (or designee) will enter subject data by using the eCRF defined by Recro Pharma, Inc. Clinical data management will be performed in accordance with applicable Recro Pharma, Inc. standards and data-cleaning procedures. Database freeze will occur when data management quality-control procedures are completed.

In addition, validated laboratory data will be transmitted electronically from the clinical laboratory to Recro Pharma, Inc. or its designee.

The investigator or designee must record all required data using the previously specified data collection method defined by Recro Pharma, Inc. An explanation must be documented for any missing critical data points. The investigator must sign and date a declaration in the eCRF attesting that he or she is responsible for the quality of all data recorded and that the data represent a complete and accurate record of each subject's participation in the study.

9.7.5. Data Security

Access to the data will be strictly controlled.

9.8. Subject Tracking

Drug accountability logs, a subject identification log (to be retained by the investigator only), and a subject enrollment log will be used to track subject participation in the study.

10. REFERENCES

Degner F, Turck D, Pairet M. Pharmacological, pharmacokinetic and clinical profile of meloxicam. *Drugs Today*. 1997;33(10):739-58.

Del Tacca M, Colucci R, Fornai M, Blandizzi C. Efficacy and tolerability of meloxicam, a COX-2 preferential nonsteroidal anti-inflammatory drug. *Clin Drug Invest*. 2002;22(12):799-818.

Mobic (meloxicam) *Prescribing information*. Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT. Revised March 2012.

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Turck D, Busch U, Henizel G, Narjes H. Clinical pharmacokinetics of meloxicam. *Arzneim-Forsch/Drug Res*. 1997;47(I):253-8.

APPENDIX A. OVERVIEW OF STUDY SCHEDULE

Procedure; Dose/Hour	Screening	Inpatient (Day 1 – Discharge)						Follow-Up Visit (LSD+7 days ± 2)	Follow-Up Telephone (LSD+28 days ± 4)
		Prior to Surgery	Surgery	Dose 1 / Hour 0	Dose 2 / Hour 24	Dose 3 / Hour 48	LSD+1 / Discharge		
Informed Consent	X								
Confinement		←	←	←	X	→	→		
Eligibility Assessment	X	X	X[d]						
Demographics and Medical History	X	X							
Physical Examination[e]	X	X					X	X	
Pregnancy Test (FOCBP only)	X[serum]	X[urine]							
Alcohol Breath Test and UDS	X	X							
Clinical Laboratory Tests[a]	X	X[g]				X	X	X	
Vital Signs[b]	X	X		X	X		X	X	
12 Lead ECG	X	X[c]					X	X	
Surgical Procedure			X						
Study Drug Administration				X	X	X	X[f]		
Wound Evaluation							X	X	
Prior and Concomitant Medication	←	←	←	←	X	→	→	→	→
Adverse Event Monitoring				←	←	←	X	→	→

a Laboratory tests will include hematology, chemistry, urinalysis and coagulation tests.
b Vital signs (VS) include: resting blood pressure, resting pulse, and SpO2. Tests must be obtained after resting (seated/reclined) for ≥ 5 minutes.
c 12-lead ECG will be done prior to surgery only if screening ECG was done >14 days before Day 1
d Postoperative randomization criteria will be assessed on the day of surgery (Day 1), prior to treatment.
e BMI, height, and weight will be assessed at the screening visit only.
f Doses may be administered every 24±1 hours for up to 7 days while continued use of IV analgesia is clinically appropriate.
g Day 1 clinical laboratory tests will be required if greater than 14 days have elapsed since screening labs were performed or if screening labs were not performed at the central lab

APPENDIX B. INVESTIGATOR OBLIGATIONS

As an investigator, you are responsible for ensuring that the study is conducted according to the protocol, the signed Statement of Investigator, and all applicable regulations.

Debarment

Individuals ineligible to conduct or be involved with clinical studies, including those ineligible as a result of debarment under the Generic Drug Enforcement Act of 1992, will not be allowed to conduct or work on studies sponsored by Recro Pharma, Inc. You are required to disclose immediately to the sponsor, in writing, if any person involved in the conduct of the study is debarred pursuant to a hearing by FDA under this antifraud law or if any proceeding for debarment is pending or is (to the best of your knowledge) threatened.

Institutional Review Board

You are required to obtain initial and continuing review and approval by an IRB or IEC that complies with the requirements specified in 21 CFR Part 56. Before initiating the trial, you must have written approval from the IRB or IEC for the protocol, informed consent form, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to the subjects. You must submit the Investigator's Brochure and any updates to the IRB or IEC for review. The IRB or IEC must also provide written approval of any amendments to the protocol that affect the conduct of the study and any changes to the informed consent form in advance of use. If the duration of the study is longer than 1 year, reapproval by the IRB or IEC must be obtained on a yearly basis (or at more frequent intervals if required by the IRB or IEC). All IRB or IEC approvals must be forwarded to the sponsor.

You must provide reports of all SAEs from your site to the IRB or IEC. You are also responsible for providing the IRB or IEC with Safety Reports of any SAEs from any other study conducted with the study medication. The latter will be provided to you by the sponsor.

Confidentiality and Safety of Subjects

You are responsible for protecting the rights, safety, and welfare of subjects under your care and for the control of the drug(s) under investigation.

You are responsible for keeping a record of all screened subjects, including full names and last known addresses. All subjects will be identified on the eCRFs by initials and subject numbers. Demographic information including date of birth, sex, and race will also be recorded on the eCRFs. Confidentiality of subject data will be maintained in accordance with local laws.

In addition to your responsibilities for reporting AEs identified during the course of a subject's participation in the study, you must also report any SAEs that occur within 30 days after the last dose of study medication (regardless of relationship to study medication) and any serious adverse drug reactions (SAEs for which you consider that there is a reasonable possibility that the study medication caused the response) that you become aware of at any time (even if the event occurs more than 30 days after the subject's last exposure to study medication). This obligation is in addition to any protocol-specified requirement for reporting AEs occurring after the last dose of study medication. Please refer to Sections 7.7 and 7.8 of this protocol for contact information and SAE reporting requirements.

Study-Related Records

You are required to maintain complete and accurate study documentation in compliance with current GCP standards and all applicable federal, state, and local laws, rules, and regulations related to the conduct of a clinical study.

You are required to make all study documentation promptly available for inspection, review, or audit at your study site upon request by the sponsor, its representatives, or any appropriate regulatory agencies.

Accountability of the Investigational Product

You or your designee (i.e., the pharmacist) is responsible for accountability of the investigational product at the site. You or your designee must maintain records of the product's delivery to the site, inventory at the site, use by each subject, and the return to the sponsor or alternative disposition of any unused product. These records must include dates; quantities; batch, serial, or lot numbers; and expiration dates (if applicable).

You should ensure that the investigational product is used only in accordance with the protocol.

APPENDIX C. STUDY-SPECIFIC INFORMATION

Appendix C.1: Surgical Wound Status Assessment

Parameter	Grade	Description
Erythema	0	None
	1	Very slight (barely perceptible)
	2	Slight (well defined)
	3	Moderate
	4	Severe (beet redness) to slight eschar formation (injuries in depth)
Drainage	0	None
	1	Serous
	2	Serosanguinous
	3	Bloody
	4	Purulent
Edema	0	None
	1	Very slight (barely perceptible)
	2	Slight (edges well defined)
	3	Moderate (raised approximately 1 mm)
	4	Severe (raised >1 mm and beyond area of exposure)
Induration	0	None
	1	Minimal
	2	Mild (spongy tissue)
	3	Moderate (firm, warm)
	4	Severe (hard, red, hot, crepitus)
Hematoma	0	None
	1	Minimal
	2	Mild
	3	Moderate
	4	Severe

APPENDIX D. BMI CALCULATION

Body Mass Index Calculations

Body Mass Index = Weight in kilograms / (height in meters)^2

Meters = inches × 0.0254

Kilograms = pounds × 0.45

Example:

For a man who weighs 165 pounds and is 71 inches tall:

165 lbs × 0.45 = 74.25 kg

71 in. × 0.0254 = 1.8 m

74.25 / (1.8 × 1.8) = 22.92 kg/m^2

APPENDIX E. MDRD CALCULATION

The Modification of Diet in Renal Disease (MDRD) equation is to be used to calculate the estimated GFR, according to the following equation:

GFR (mL/min/1.73 m^2) = 175 x $(SCr)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African American)

SCr = serum creatinine measured with a standardized assay.

Reference: FDA Guidance for Industry (Draft Guidance): Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling; Revision 1, March 2010.