REC-17-025

A Phase 3b, Randomized, Double-Blind, Placebo-Control, Multicenter, Evaluation of the Safety and Efficacy of N1539 Administered Preoperatively in Open Unilateral Total Knee Arthroplasty

NCT03434275

Study Protocol – Amendment 002

24 January 2018

CLINICAL STUDY PROTOCOL

Compound Name:	N1539 (meloxicam) Injection, for intravenous use
Protocol Number:	REC-17-025
Protocol Title:	A Phase 3b, Randomized, Double-Blind, Placebo-Control, Multicenter, Evaluation of the Safety and Efficacy of N1539 Administered Preoperatively in Open Unilateral Total Knee Arthroplasty
Date of Protocol:	29 September 2017
Amendment 001:	17 November 2017
Amendment 002:	24 January 2018
Study Designated Physician:	Stewart McCallum, MD 490 Lapp Rd Malvern, PA 19355 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 (REC-17-025) 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:

PROTOCOL SYNOPSIS

Name of Sponsor/Company: Recro Pharma, Inc.	**Protocol Number:** REC-17-025
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Name of Active Ingredient: Meloxicam	**Phase of Development:** 3b

Objectives: The primary objective of this study is to assess the effect of preoperative administration of N1539 on opioid consumption in subjects undergoing open unilateral total knee arthroplasty compared to placebo.

Secondary objectives are to assess:

- The safety and tolerability of preoperative administration of N1539 compared to placebo
- The effect of preoperative administration of N1539 on postoperative pain compared to placebo
- The effect of preoperative administration of N1539 on healthcare utilization costs compared to placebo.

Methodology: This is a Phase 3b, randomized, double-blind, placebo-controlled, multicenter study in adult subjects undergoing elective open unilateral total knee arthroplasty. The surgical procedure will be conducted in an inpatient hospital setting that is expected to result in a hospital stay of ≥24 hours. Each subject will be screened for eligibility within 28 days before undergoing surgery on Day 1.

Before surgery, approximately 200 eligible subjects will be randomized in a 1:1 ratio to receive either N1539 30 mg or placebo administered as an intravenous (IV) bolus injection in ≤15 seconds.

As part of multimodal pain management, subjects will receive oral acetaminophen 650 mg and oral gabapentin 600 mg 30 to 90 minutes before the scheduled surgical procedure. Subjects will continue to receive acetaminophen 650 mg PO Q8H through last study dose + 1 day (LSD+1). Subjects will also receive an appropriate prophylactic IV antibiotic and tranexamic acid 1 gram IV 30 to 90 minutes before surgery (Appendix B).

Following administration of spinal anesthesia and before the start of surgery (ie, time of first incision), subjects will receive the first dose of study drug according to randomization. All subjects will then undergo the surgical procedure according to the investigator's clinical practice and in accordance with institutional standards.

Just prior to wound closure, bupivacaine HCl 0.5% 30 mL with epinephrine 0.5 mg expanded in a volume of 90 mL normal saline will be injected locally into various areas of the surgical site as described in Section 5.2.3.

At the end of the surgical procedure (Hour 0, defined as the time of last suture, staple, or steri-strip placement) and through hospital discharge, postoperative pain management will be according to the protocol (Section 5.13). Other standard of care procedures associated with the surgical procedure will be carried out according to the investigator's clinical practice and in accordance with institutional standards. Subjects may also receive IV ondansetron 4 mg as needed for postoperative nausea and vomiting (PONV) according to FDA prescribing information.

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Additional doses of study drug will be administered every 24 hours (±1 hour) after the first dose. Dosing will continue until the subject is either discharged from the hospital or until IV study drug analgesia is no longer clinically appropriate.

In addition to study drug, all subjects will have access to IV and/or oral (PO) opioid medication as needed for the management of breakthrough pain starting at Hour 0 and continuing through hospital discharge.

Subjects will remain as inpatients for at least 24 hours or until inpatient care is no longer clinically indicated. Upon discharge, subjects will be provided a standard of care regimen for pain management and for physical therapy as determined by the investigator.

Twenty-four hours and 48 hours after hospital discharge qualified study staff will conduct telephone interviews to assess opioid medication use, pain intensity, physical therapy visits, and utilization of healthcare resources (ie, hospital readmission, use of skilled nursing facilities, unscheduled phone calls and/or office visits related to pain, and emergency room [ER] visits related to pain and/or other medical issues).

Subjects will visit the clinical site between Postoperative Days (PODs) 10 and 14 to be assessed for adverse events, wound healing, and utilization of healthcare resources.

A final telephone interview will be conducted on POD 30 to assess for AEs, opioid use, and utilization of healthcare resources. After the POD 30 telephone interview, subjects will be discharged from the study.

Number of subjects to be enrolled: Approximately 200 subjects will be enrolled (N1539: 100; placebo, 100).

Number of study sites: Up to 20 sites

Study country location: United States

Inclusion criteria: No subject should be assigned to treatment until all eligibility criteria have been satisfied. To qualify for the study a subject must:

1. Voluntarily provide written informed consent.
2. Be able to understand and comply with all study procedures and agree to participate in the study program as outlined in the protocol.
3. Be male or female 35 to 80 years of age, inclusive at the time of consent.
4. Have plans to undergo an elective, primary (no repeat arthroplasties) open unilateral total knee arthroplasty, and be expected to require IV analgesia, remain in an inpatient setting for ≥24 hours, and receive at least two doses of study drug.
5. Be classified as American Society of Anesthesiology (ASA) physical status category 1, 2, or 3 (Appendix D).

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Inclusion criteria (continued):

6. Have a negative pregnancy test at screening and before surgery and be using a highly effective contraception method (ie, abstinence, intrauterine device [IUD], hormonal [estrogen/progestin] contraceptives, or double barrier method) for at least one menstrual cycle prior to screening and for the duration of the study, if female of childbearing potential; or be menopausal defined as 12 months of amenorrhea in the absence of other biological or physiological causes; or post-menopausal for at least 1 year; or be surgically sterile (documented hysterectomy, bilateral tubal ligation, or bilateral oophorectomy).
7. Be surgically sterile (biologically or surgically) or commit to the use of a highly effective contraception method (eg, abstinence or double barrier method) with female partner(s) of childbearing potential from screening through the end of the study, if male.
8. Have a body mass index <40 kg/m^2, inclusive at screening.

Exclusion criteria: A subject will be excluded from study participation if he/she:

1. Has a known allergy or hypersensitivity to eggs, meloxicam, aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs), or any excipient of N1539 or placebo.
2. Has plans for the open unilateral total knee arthroplasty procedure to be performed under general anesthesia (requiring intubation or laryngeal mask airway).
3. Is female and presently nursing a baby or providing breast milk for a baby.
4. Is female and intends to become pregnant during the study.
5. Has a diagnosis of rheumatoid or inflammatory arthritis or systemic disease.
6. Has a history of previous total knee arthroplasty (TKA).
7. Has plans for a concurrent surgical procedure (eg, bilateral TKA).
8. Is undergoing unicompartmental knee replacement or revision TKA.
9. Has a history of myocardial infarction within the 12 months before screening.

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Exclusion criteria (continued):

10. Has, as determined by the investigator or the sponsor's medical monitor, a history or clinical manifestations of significant renal (glomerular filtration rate [GFR]<60 mL/min/1.73 m^2), hepatic, cardiovascular, metabolic, neurologic, psychiatric, respiratory, or other condition that would preclude participation.
11. Has a clinically significant abnormal clinical laboratory test value as determined by the investigator.
12. Has active or recent (within 6 months) gastrointestinal ulceration or bleeding, with exception of events related to an ulcerative colitis diagnosis.
13. Has a known bleeding disorder that may be worsened with the administration of an NSAID.
14. Has evidence of a clinically significant 12-lead ECG abnormality as determined by the investigator.
15. Has a confirmed allergy to opioid medications.
16. Has received chronic opioid therapy (daily use of opioids for 30 days or longer) or > 5 days of opioid use, within 30 days prior to screening.
17. Has used long acting opioid medication within 3 days before the surgical procedure.
18. Is unable to discontinue medications, that have not been at a stable dose for at least 7 days prior to the scheduled surgical procedure, within 5 half-lives of the specific medication (or, if half-life is not known, within 48 hours) before dosing with study drug, with exception of medications utilized for surgical preparation.
19. Is unable to discontinue herbal medications/supplements associated with an increased bleeding risk at least 7 days prior to surgery through hospital discharge, including but not limited to: gingko biloba, garlic, ginger, ginseng, hawthorn, fish oil (omega-3-fatty acid), dong quai, feverfew, vitamin E.
20. Is receiving lithium or a combination of furosemide with either an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker.
21. Is currently receiving treatment with oral meloxicam (Mobic®) or another NSAID within 48 hours prior to surgery.
22. Has received any investigational product within 30 days before dosing with study drug.
23. Has undergone major surgery in the last 3 months that could interfere with study assessments.
24. Has undergone or is expected to undergo radiation therapy, chemotherapy, or other biological therapy for cancer treatment, within 60 days prior to screening through POD 30.

Investigational product: N1539 (meloxicam) Injection 30 mg, for intravenous use

Reference product: Placebo injection for intravenous use

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Duration of treatment: Each subject is expected to receive at least two doses of study drug during their participation in the study. Randomized subjects will receive their first dose of study drug (Dose 1) after administration of spinal anesthesia and prior to the start of surgery (defined as time of first incision). Additional doses of study drug will be administered every 24 hours ± 1 hour from Dose 1 (ie, 24 hours and 48 hours) until hospital discharge or until IV study drug analgesia is no longer clinically appropriate, whichever is first.

A final dose of study drug may be administered up to 4 hours early in subjects who are scheduled to be discharged, at the discretion of the investigator. Subjects who do not receive a dose of study drug for >28 hours following their previous dose should be considered off treatment, and should not receive further study drug.

Efficacy assessments: Efficacy assessments include:

- Pain intensity assessments using an 11-point numeric pain rating scale (NPRS; 0 - 10) where 0=no pain, and 10=the worst pain imaginable, as follows: upon arrival at the PACU, at various scheduled timepoints relative to first dose of study drug, before administration of opioid medication, before and during ambulation, before hospital discharge, 24 hours and 48 hours after discharge, POD 10 to 14, and POD 30
- Patient Global Assessment (PGA) of pain control starting at POD 1 and continuing each day through hospital discharge or last study dose (LSD) +1 day, whichever occurs first.
- Overall Benefit of Analgesia Score Questionnaire (OBAS) starting at POD 1 and continuing each day through hospital discharge or LSD +1, whichever occurs first

Efficacy endpoints: The primary efficacy endpoint is total use of opioid analgesia from Hour 0 through 24 hours.

Secondary endpoints include:

- Sum of pain intensity from the time of first dose of study drug through 24 hours (SPI_{24})
- Percentage of subjects who are opioid free from Hour 0 through 24 hours
- Time to first use of IV or oral opioid analgesia

Other efficacy endpoints include:

- Total use of opioid analgesia from first dose of study drug through 24 hours (before 2nd dose of study drug)
- Total use of opioid analgesia from Hour 0 through 48 hours
- Total use of opioid analgesia from Hour 0 through hospital discharge
- Total use of opioid analgesia from hospital discharge through 24-hour telephone interview

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Efficacy endpoints (continued):

- Total use of opioid analgesia from the 24-hour telephone interview through the 48-hour telephone interview
- Percentage of subjects that are opioid free from Hour 0 through 48 hours
- Percentage of subjects that are opioid free from Hour 0 through hospital discharge
- Percentage of subjects who used any opioid medication after hospital discharge through POD 30.
- Time to first IV opioid medication defined as the time from Hour 0 until time of first use of IV opioid medication
- Time to first oral opioid rescue medication defined as the time from Hour 0 until time of first use of oral opioid medication
- Pain intensity during first assisted ambulation
- Pain intensity during first unassisted ambulation
- SPI from time of first dose of study drug through first assisted ambulation
- SPI from time of first dose of study drug through first unassisted ambulation
- SPI from time of first dose of study drug through 48 hours
- SPI from time of first dose of study drug through hospital discharge or LSD+1, whichever comes first
- Time to first assisted ambulation defined as the time from Hour 0 until time when first assisted ambulation occurs
- Time to first unassisted ambulation defined as the time from Hour 0 until time when first unassisted ambulation occurs
- Subject overall evaluation of pain control on 5-point categorical scale on each postoperative day, starting on POD 1 and continuing through hospital discharge or LSD+1, whichever occurs first.
- The OBAS total score and opioid distress dimension subscore on each postoperative day, starting on POD 1 and continuing through hospital discharge or LSD+1, whichever occurs first
- Pain intensity at the following follow-up time points: 24 hours and 48 hours post discharge, and POD 10-14, and POD 30

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Safety Assessments: Safety will be assessed throughout the study through the recording of adverse events, vital signs, clinical laboratory testing, and the evaluation of wound healing.

Safety endpoints include:

- Incidence of treatment-emergent adverse events (TEAEs)
- Incidence of potentially clinically significant abnormal clinical laboratory values
- Investigator satisfaction with wound healing before hospital discharge and during the follow-up visit (POD 10 to 14).

Healthcare Utilization Assessments:

Health economic outcomes assessments include:

- Hospital length of stay
- Total cost of hospitalization
- Incidence of hospital readmissions
- Postsurgical physical therapy visits
- Use of skilled nursing facility
- Use of other health services following hospital discharge (ie, unscheduled phone calls related to pain, unscheduled visits related to pain, and visits to the emergency department related to pain).

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Healthcare Utilization endpoints include:

- Length of hospital stay defined as days from hospital admission until the hospital discharge order is written.
- Total cost of hospitalization (taken from the UB-04/hospital claims form)
- Duration of time in the PACU (time in through time out of PACU)
- Percentage of subjects with hospital readmission through POD 30
- Total number of postsurgical physical therapy visits through POD 30
- Percentage of subjects who required a skilled nursing facility from hospital discharge through POD 30
- Total time spent in skilled nursing facility from hospital discharge through POD 30
- Percentage of subjects who made a phone call related to postsurgical pain from hospital discharge through POD 30
- Total number of phone calls per subject related to postsurgical pain from hospital discharge through POD 30
- Percentage of subjects who had an unscheduled visit related to postsurgical pain from hospital discharge through POD 30
- Total number of unscheduled visits per subject related to postsurgical pain from hospital discharge through POD 30
- Percentage of subjects who had an emergency room visit for postsurgical pain from hospital discharge through POD 30
- Total number of visits to the emergency room per subject for postsurgical pain from hospital discharge through POD 30

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Sample Size: The sample size for this study (100 subjects per group) will have at least 90% power to detect the difference between N1539 30 mg versus placebo in total opioid consumption based on the results observed in a Phase 3 safety study that evaluated all major surgeries. The study results suggested that the total opioid consumption was lower in subjects treated with N1539 30 mg compared to placebo, and that the observed effect size in total opioids consumption measured by IV morphine equivalent dose (IVMED, mg) ranged from 0.5 to 0.7 in this subgroup.

Study populations:

Intent-to-Treat Population (ITT): The ITT population will include all subjects who qualify for the study and are randomized for treatment prior to surgery. ITT subjects may or may not receive randomized treatment.

Safety population: The safety population will consist of all subjects who receive at least one injection of study drug. All safety evaluations will be based on the safety population.

The efficacy population (ie, modified intent-to-treat [mITT]): The efficacy population will consist of all subjects who receive at least one injection of study drug and have the scheduled surgery. All efficacy evaluations will be based on the efficacy population.

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Statistical Methods:

Efficacy analysis: Efficacy endpoints will be tabulated by treatment groups and time points as appropriate; descriptive statistics will be provided, including sample size, mean, standard deviation, median, minimum and maximum for continuous variables, or frequency (number of subjects and percentage) distribution of each category for categorical variables.

Treatment effect will be evaluated using Analysis of Covariance (ANCOVA) for opioid consumption related endpoints, pain intensity related endpoints, and OBAS related endpoints; the ANCOVA model will include treatment effect and investigational sites as a covariate. Difference in LS means will be compared between the treatment groups.

Kaplan-Meier survival analysis will be carried out for time to event endpoints, including survival curves, 25%, 50% and 75% tiles estimates and corresponding 95% confidence intervals (CI), and log-rank test. Cox proportional hazards analysis will also be performed for time to event endpoints; the model will include the treatment effect and the investigational sites; hazards ratio and corresponding 95% CI will be presented.

Treatment effect on PGA scores will be evaluated based on proportion of subjects rated their pain control as good, very good, or excellent using CMH test controlling for analysis center. CMH test will apply to other category variables, such as proportion of subjects who took any opioids or who were opioid free at various time periods.

Safety analysis: The Medical Dictionary for Regulatory Activities (Version 20 or higher) will be used to classify all AEs with respect to system organ class and preferred term. AEs will be summarized by treatment group. Clinical laboratory parameters collected after the first dose of study drug will be evaluated by comparing to baseline; subjects with potentially clinically significant changes from baseline in clinical laboratory parameters will be identified and tabulated by treatment group. The number and proportion of subjects with abnormal wound healing observations will be summarized by treatment group.

Healthcare Utilization analysis: A separate SAP will be constructed for analysis of Health Care Utilization and total costs as recorded on the UB 04. This SAP will detail the objectives, methods for conducting the relevant analyses, and the format for presentation of the findings. Subject cohorts of interest will be defined and the variables to be measured as well as the steps in data processing and analyses will also be presented.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition of Term
AE	Adverse event
ASA	American Society of Anesthesiology
AUC	Area under the concentration-time curve
BMI	Body mass index
BP	Blood Pressure
BPM	Beats per minute
CFR	(United States) Code of Federal Regulations
ºC	degrees Centigrade
CL	Clearance
C_{max}	Maximum observed drug concentration
eCRF	Electronic case report form
ER	Emergency room
DBP	Diastolic Blood Pressure
DOS	Day of surgery
Dose 1	Start time of first dose of study drug via IV bolus injection
ECG	Electrocardiogram
GCP	Good Clinical Practice
H	Hour
HCl	Hydrochloride
Hour 0	Time of end of surgery (ie, time of last suture, staple, or steri-strip placement)
HR	Heart Rate
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IP	Investigational Product
IR	Immediate release
ITT	Intend-to-treat
IUD	Intrauterine device
IV	Intravenous
Kg	Kilogram

Abbreviation	Definition of Term
L	Liter
LSD	Last study dose
LSD +1	Last study dose plus 1 day
m^2	Square meters
Mg	Milligram
Min	Minute
mITT	Modified intent-to-treat
mL	Milliliter
mmHg	Millimeters of mercury
N1539	N1539 (meloxicam) Injection, for intravenous use
NCD	NanoCrystal Colloidal Dispersion
NF	National Formulary
NPRS	Numeric Pain Rating Scale
NSAID	Nonsteroidal anti-inflammatory drug
OBAS	Overall Benefit of Analgesia Score Questionnaire
PGA	Patient Global Assessment
pH	Negative log of hydrogen ion concentration
PI	Pain Intensity
PK	Pharmacokinetic
POD (PODx)	Postoperative Day (Postoperative day x)
PONV	Postoperative nausea and vomiting
Q2H	Every 2 hours
Q4H	Every 4 hours
Q24H	Every 24 hours
SAR	Suspected adverse reaction
SAE	Serious adverse event
SBP	Systolic blood pressure
SPI	Sum of pain intensity
SSAR	Serious suspected adverse reaction
SUSAR	Serious unexpected suspected adverse reaction
TEAE	Treatment-emergent adverse event
TKA	Total knee arthroplasty
Tmax	Time to maximum observed drug concentration

Abbreviation	Definition of Term
µL	Microliter
ULN	Upper limit of normal
US	United States
USP	*United States Pharmacopeia*

1. INTRODUCTION

1.1. N1539 (meloxicam) Injection, for Intravenous Use

Meloxicam, a non-steroidal anti-inflammatory (NSAID) of the enolic acid class, was first approved for oral use in the United States in 2000 and has a well-established safety profile in commercial use as an effective treatment for osteoarthritis and rheumatoid arthritis.

Meloxicam administered orally 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}) approximately 5-6 hours following oral administration (Degner 1997; Turck 1997a), which is consistent with its poor aqueous solubility. By increasing the dissolution rate of the active meloxicam moiety using the proprietary NanoCrystal technology, N1539 administered by (intravenous) IV bolus injection has been shown to have a rapid onset of action.

In the N1539 clinical studies, meloxicam exposure was consistently greater after administration of N1539 via IV bolus injection compared to oral administration of Mobic at equivalent doses. As expected, N1539 administered as an IV bolus injection resulted in substantially higher maximum observed concentration (C_{max}) and earlier time to maximum concentration (T_{max}) compared with oral administration of Mobic at equivalent doses over a range of 15 to 60 mg. Eight to 12 hours after administration of equivalent doses of IV and oral meloxicam, plasma concentration-time curves were similar. The C_{max} and area under the concentration-time curve (AUC) for N1539 administered IV were similar across studies.

Ad hoc analyses from the Phase 1 studies demonstrated that a single dose of N1539 30 mg administered by IV bolus injection resulted in a slightly more than 2-fold higher AUC_{∞} and 4.65-fold higher C_{max} relative to a single dose of Mobic 15 mg, the highest FDA approved dose, administered orally. Importantly meloxicam plasma concentrations were sustained for 24 hours after N1539 IV administration making N1539 suitable for once a day dosing.

In the clinical program for N1539 for the management of moderate to severe acute pain, a total of 2075 subjects were evaluated for safety in 11 clinical studies: 109 subjects were healthy volunteers who were enrolled in the four Phase 1 studies and 1966 were postoperative subjects who were enrolled in the seven Phase 2/3 efficacy and safety studies.

In clinical studies, subjects who received N1539 by IV bolus injection had a rapid onset of pain relief. Improvement in pain intensity scores was observed as early has 10 minutes after N1539 dosing and the treatment effect was sustained over the 24-hour dosing interval. The reduction in pain intensity after treatment with N1539 30 mg was associated with less opioid rescue medication utilization.

The safety data from the 1045 subjects who received two or more doses of N1539 postoperatively including the 743 who received two or more doses at the commercial

dose of 30 mg support N1539 administered IV once daily as a safe treatment for the management of moderate to severe pain in adults. The safety data demonstrate that N1539 30 mg has a safety profile similar to approved drugs in this NSAID class.

1.2. Total Knee Arthroplasty

Total knee arthroplasty, also known as total knee replacement, is one of the most commonly performed orthopedic procedures. As of 2010, total knee replacements were becoming increasingly common with over 600,000 performed annually in the United States (UpToDate®). Among older patients in the United States, the per capita number of primary total knee replacements doubled from 1991 to 2010 (from 31 to 62 per 10,000 Medicare enrollees annually) (Cram 2012) and this number is expected to grow by 673 percent to 3.48 million procedures by 2030 (Kurtz 2007). A variety of pathologic conditions affecting the knee can be treated with total knee replacement, leading to pain relief, to restoration of function, and to mobility.

Severe postoperative pain, which remains one of the main problems after total knee arthroplasty, can negatively affect postoperative recovery. Over the last 10 years, surgeons have prescribed IV patient-controlled analgesia, femoral nerve block, and continuous epidural infusions for 24 and 48 hours with and without a femoral block (Maheshwari 2009). Unfortunately, these techniques have been found to have shortcomings, not the least of which has been suboptimal pain control and unwanted side effects (Maheshwari 2009).

Improvements in pain management techniques in the last decade have had a major impact on the practice of total hip and knee arthroplasty; however, a gold standard has not been established. Although there are a number of treatment options for postoperative pain, there appears to be a shift towards multimodal approaches using systemic, local, and regional analgesia to minimize opioid consumption and to avoid opioid-related side effects (Maheshwari 2009).

In a double-blind, randomized study by Motififard et al, (2017) a multimodal pain management regimen that included injections of bupivacaine, morphine, and the NSAID ketorolac was shown to provide postoperative pain relief and resulted in less opioid consumption and better early rehabilitation 48 hours after total knee arthroplasty compared to a control group that received epinephrine only.

This study is designed to evaluate the effect of N1539 administered preoperatively and postoperatively as part of a multimodal pain management plan. It is expected that N1539 administered as an IV bolus injection before and after surgery will reduce the requirement for opioid analgesia and will improve the rehabilitation course in subjects undergoing total knee arthroplasty.

2. STUDY OBJECTIVE

The primary objective of this study is to assess the effect of preoperative administration of N1539 on opioid consumption in subjects undergoing open unilateral total knee arthroplasty compared to placebo.

Secondary objectives are to assess:

- The safety and tolerability of preoperative administration of N1539 compared to placebo
- The effect of preoperative administration of N1539 on postoperative pain compared to placebo
- The effect of preoperative administration of N1539 on healthcare utilization costs compared to placebo.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a Phase 3b, randomized, double-blind, placebo-controlled, multicenter study in adult subjects undergoing elective open unilateral total knee arthroplasty. The surgical procedure will be conducted in an inpatient hospital setting that is expected to result in a hospital stay of ≥24 hours. Each subject will be screened for eligibility within 28 days before undergoing surgery on Day 1.

Before surgery, approximately 200 eligible subjects will be randomized in a 1:1 ratio to receive either N1539 30 mg or placebo administered as an intravenous (IV) bolus injection in ≤15 seconds.

As part of multimodal pain management, subjects will receive oral acetaminophen 650 mg and oral gabapentin 600 mg 30 to 90 minutes before the scheduled surgical procedure. Subjects will continue to receive acetaminophen 650 mg PO Q8H through last study dose + 1 day (LSD+1). Subjects will also receive an appropriate prophylactic IV antibiotic and tranexamic acid 1 gram IV 30 to 90 minutes before surgery (Appendix B).

Following administration of spinal anesthesia and before the start of surgery (ie, time of first incision), subjects will receive the first dose of study drug according to randomization. All subjects will then undergo the surgical procedure according to the investigator's clinical practice and in accordance with institutional standards.

Just prior to wound closure, bupivacaine HCl 0.5% 30 mL with epinephrine 0.5 mg expanded in a volume of 90 mL normal saline will be injected locally into various areas of the surgical site as described in Section 5.2.3.

At the end of the surgical procedure (Hour 0, defined as the time of last suture, staple, or steri-strip placement) and through hospital discharge, postoperative pain management will be according to the protocol (Section 5.13). Other standard of care procedures associated with the surgical procedure will be carried out according to the investigator's clinical practice and in accordance with institutional standards. Subjects may also receive IV ondansetron 4 mg as needed for PONV according to FDA prescribing information.

Additional doses of study drug will be administered every 24 hours (±1 hour) after the first dose. Dosing will continue until the subject is either discharged from the hospital or until IV study drug analgesia is no longer clinically appropriate.

In addition to study drug, all subjects will have access to IV and/or oral (PO) opioid medication as needed for the management of breakthrough pain starting at Hour 0 and continuing through hospital discharge.

Subjects will remain as inpatients for at least 24 hours or until inpatient care is no longer clinically indicated. Upon discharge, subjects will be provided a standard of care regimen for pain management and for physical therapy as determined by the investigator.

Twenty-four hours and 48 hours after hospital discharge qualified study staff will conduct telephone interviews to assess opioid medication use, pain intensity, physical therapy visits, and utilization of healthcare resources (ie, hospital readmission, use of skilled nursing facilities, unscheduled phone calls and/or office visits related to pain, and emergency room [ER] visits related to pain and/or other medical issues).

Subjects will visit the clinical site between Postoperative Days (PODs) 10 and 14 to be assessed for adverse events, wound healing, and utilization of healthcare resources.

A final telephone interview will be conducted on POD 30 to assess for AEs, opioid use, and utilization of healthcare resources. After the POD 30 telephone interview, subjects will be discharged from the study.

3.2. Rationale for Study Design and Control Groups

The double-blind, placebo-controlled study design for N1539 30 mg administered preoperatively and followed by once daily dosing in a population of subjects undergoing open unilateral total knee arthroplasty is intended to avoid potential bias from subject or investigator knowledge of assigned treatment that could confound the interpretation of the efficacy and safety findings.

4. STUDY POPULATION

4.1. Inclusion Criteria

No subject should be assigned to treatment until all eligibility criteria have been satisfied. To qualify for the study a subject must:

1. Voluntarily provide written informed consent.
2. Be able to understand and comply with all study procedures and agree to participate in the study program as outlined in the protocol.
3. Be male or female 35 to 80 years of age, inclusive at the time of consent.
4. Have plans to undergo an elective, primary (no repeat arthroplasties) open unilateral total knee arthroplasty, and be expected to require IV analgesia, remain in an inpatient setting for ≥24 hours, and receive at least two doses of study drug.
5. Be classified as American Society of Anesthesiology (ASA) physical status category 1, 2, or 3 (Appendix D).
6. Have a negative pregnancy test at screening and before surgery and be using a highly effective contraception method (ie, abstinence, intrauterine device [IUD], hormonal [estrogen/progestin] contraceptives, or double barrier method) for at least one menstrual cycle prior to screening and for the duration of the study, if female of childbearing potential; or be menopausal defined as 12 months of amenorrhea in the absence of other biological or physiological causes; or post-menopausal for at least 1 year; or be surgically sterile (documented hysterectomy, bilateral tubal ligation, or bilateral oophorectomy).
7. Be surgically sterile (biologically or surgically) or commit to the use of a highly effective contraception method (eg, abstinence or double barrier method) with female partner(s) of childbearing potential from screening through the end of the study, if male.
8. Have a body mass index <40 kg/m^2, inclusive at screening.

4.2. Exclusion Criteria

A subject will be excluded from study participation if he/she:

1. Has a known allergy or hypersensitivity to eggs, meloxicam, aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs), or any excipient of N1539 or placebo.
2. Has plans for the open unilateral total knee arthroplasty procedure to be performed under general anesthesia (requiring intubation or laryngeal mask airway).
3. Is female and presently nursing a baby or providing breast milk for a baby.
4. Is female and intends to become pregnant during the study.
5. Has a diagnosis of rheumatoid or inflammatory arthritis or systemic disease.

6. Has a history of previous total knee arthroplasty (TKA).
7. Has plans for a concurrent surgical procedure (eg, bilateral TKA).
8. Is undergoing unicompartmental knee replacement or revision TKA
9. Has a history of myocardial infarction within the 12 months before screening.
10. Has, as determined by the investigator or the sponsor's medical monitor, a history or clinical manifestations of significant renal (glomerular filtration rate [GFR]<60 mL/min/1.73 m^2), hepatic, cardiovascular, metabolic, neurologic, psychiatric, respiratory, or other condition that would preclude participation.
11. Has a clinically significant abnormal clinical laboratory test value as determined by the investigator.
12. Has active or recent (within 6 months) gastrointestinal ulceration or bleeding, with exception of events related to an ulcerative colitis diagnosis.
13. Has a known bleeding disorder that may be worsened with the administration of an NSAID.
14. Has evidence of a clinically significant 12-lead ECG abnormality as determined by the investigator.
15. Has a confirmed allergy to opioid medications.
16. Has received chronic opioid therapy (daily use of opioids for 30 days or longer) or > 5 days of opioid use, within 30 days prior to screening.
17. Has used long acting opioid medication within 3 days before the surgical procedure.
18. Is unable to discontinue medications, that have not been at a stable dose for at least 7 days prior to the scheduled surgical procedure, within 5 half-lives of the specific medication (or, if half-life is not known, within 48 hours) before dosing with study drug, with exception of medications utilized for surgical preparation.
19. Is unable to discontinue herbal medications/supplements associated with an increased bleeding risk at least 7 days prior to surgery through hospital discharge, including but not limited to: gingko biloba, garlic, ginger, ginseng, hawthorn, fish oil (omega-3-fatty acid), dong quai, feverfew, vitamin E.
20. Is receiving lithium or a combination of furosemide with either an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker.
21. Is currently receiving treatment with oral meloxicam (Mobic®) or another NSAID within 48 hours prior to surgery.
22. Has received any investigational product within 30 days before dosing with study drug.
23. Has undergone major surgery in the last 3 months that could interfere with study assessments.

24. Has undergone or is expected to undergo radiation therapy, chemotherapy, or other biological therapy for cancer treatment, within 60 days prior to screening through POD 30.

4.3. Discontinuation of Subjects

4.3.1. 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 receive at least one dose of study drug and are subsequently withdrawn from the study should be encouraged to complete the discharge assessments prior to leaving the study. Subjects will be encouraged to return for the POD 10 to 14 follow-up visit and to be followed through POD 30 telephone interview. The date the subject is withdrawn and the primary reason for discontinuation will be recorded.

4.3.2. Replacement of Subjects

Discontinued subjects will not be replaced in this study. However, the study will enroll an adequate number of subjects to meet the target size of approximately 200 subjects for evaluation in the safety population.

4.4. Lifestyle Guidelines

4.4.1. Confinement

Each subject will arrive at the study site on Day 1 with sufficient time to be prepared for the surgical procedure and for the investigator or qualified designee to confirm continued eligibility to participate in the study.

Subjects are expected to remain in the hospital for a minimum of 24 hours and will be discharged when appropriate based on clinical status. Subjects may be discharged to home or to a skilled nursing facility as determined by the investigator or qualified designee.

4.4.2. Diet

Prior to the surgical procedure, subjects will be allowed nothing by mouth starting at a time designated by the investigator. Following surgery, subjects will be encouraged to progress to a regular diet as tolerated and as determined by the investigator.

5. TREATMENTS

5.1. Venous Thromboembolism Prophylaxis

Venous thromboembolism prophylaxis before and after surgery will be administered according to standard practice, based on the subject's individual needs, at the discretion of the investigator and surgeon, and taking into consideration the American College of Chest Physicians (ACCP) (http://journal.chestnet.org/article/S0012-3692(12)60114-7/fulltext#cesec390) and American Academy of Orthopaedic Surgeons (AAOS) https://www.aaos.org/research/guidelines/VTE/VTE_full_guideline.pdfguidelines for orthopedic surgery.

5.2. Perioperative Drug Administration

On the day of surgery (Day 1), eligible subjects will receive perioperative medications as shown in Table 1. All subjects will undergo open unilateral total knee arthroplasty according to institutional standards. Surgery start (first incision) and surgery end (last suture, staple, or steri-strip placement [Hour 0]) times will be recorded.

Table 1: Perioperative Medications

30 to 90 Minutes Prior to Start of Surgical Procedure	Prior to Start of Surgical Procedure	Prior to Wound Closure	End of Surgical Procedure (ie, Hour 0)
Administer: Acetaminophen 650 mg PO Gabapentin 600 mg PO Tranexamic acid 1gram IV[a] Prophylactic IV antibiotic	Following administration of intrathecal anesthesia (ie, 7.5 to 15 mg bupivacaine HCl (Section 5.2.1) and before the start of surgery; Administer **1st dose** of study drug by IV bolus injection in ≤15 seconds according to randomization (Section 5.2.4)	Administer local infiltration of bupivacaine HCl 0.5% 30 mL with epinephrine 0.5 mg expanded in a volume of 90 mL normal saline (Section 5.2.3)	Follow a standardized care regime based on the surgeon's clinical practice and according to institutional standards Acetaminophen 650 mg Q8H PO through LSD+1 Subjects may receive IV ondansetron 4 mg as needed for postoperative nausea and vomiting (PONV) according to FDA prescribing information.
Surgery start (first incision) Surgery end (last suture, staple, or steri-strip placement [Hour 0]) a A second dose of tranexamic acid may be given approximately 3 hours after the first at the discretion of the surgeon.			

5.2.1. Intrathecal Anesthesia

Before the start of surgery, 7.5 mg to 15 mg of bupivacaine HCl will be administered intrathecally. The time intrathecal anesthesia is administered will be recorded.

The following are prohibited:

- Femoral and adductor canal blocks
- Other regional neuraxial blocks not specified by protocol
- Recent or planned cryoneurolysis

5.2.2. Intraoperative Medications

Fentanyl and morphine or other morphine derivatives may be administered intraoperatively (during the course of the surgical procedure); however, dosing with fentanyl (and morphine or other morphine derivatives) is to be avoided within the 30 minutes prior to the anticipated conclusion of the surgical procedure (Section 5.12.1).

Anxiolytics, sedatives, and other medications (except for analgesic agents) that are used for subject well-being during the intraoperative period may be administered according to the investigator's clinical practice and in accordance with institutional standards.

The time and dose of any medication administered during the intraoperative period will be recorded.

5.2.3. Local Infiltrate

Expand 30 mL of bupivacaine HCl 0.5% + epinephrine (0.5 mg) in a volume of 90 mL normal saline. Draw up the expanded bupivacaine into six 20 mL syringes each with a 22-gauge needle.

Just prior to wound closure, inject approximately 1 mL of the local infiltrate per needle stick into each of the following areas. The tissue in each area should visibly expand with minimal leakage.

- Prior to final implant placement:
  - Posterior capsule (8-10 sticks medial and 8-10 sticks lateral)
  - Femur (medial and lateral periosteum, posterior periosteum suprapatellar/quadriceps tendon—20 sticks)
  - Tibia—fat pad (5 sticks); pes anserinus, medial collateral ligament, and gutter (15 sticks)
  - Circumferential periosteum (15-20 sticks)
- After final implant placement:
  - Midline quadriceps tendon (10 sticks)
  - Retinaculum, medial gutter, femoral to tibia (10 sticks)
  - Lateral gutter, femoral to tibial (10 sticks)
  - Subcutaneous/closure (10 sticks)

5.2.4. Study Drug Administration

Appropriately qualified study personnel will prepare all doses of study drug according to subject randomization. All doses of study drug will be administered as an IV bolus injection in ≤15 seconds. Start time of IV push should be recorded. Additional details on study drug preparation and administration will be provided in the study specific pharmacy manual.

Each subject is expected to receive at least two doses of study drug during their participation in the study. Randomized subjects will receive their first dose of study drug (Dose 1) after administration of spinal anesthesia and prior to the start of surgery (defined as time of first incision). Additional doses of study drug will be administered every 24 hours ± 1 hour from Dose 1 (ie, 24 hours and 48 hours) until hospital discharge or until IV study drug analgesia is no longer clinically appropriate, whichever is first.

The investigator may administer a final dose of study drug up to 4 hours ahead of schedule in subjects who are to be discharged. Subjects who do not receive a dose of study drug for more than 28 hours following their previous dose will be considered off treatment, and will not receive further doses of study drug.

5.3. Identity of Study Drug

N1539 (meloxicam) Injection for intravenous use 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 injection for intravenous use will contain: soybean oil, egg yolk phospholipids, glycerin, fluorescein sodium, sodium folate, edetate disodium, benzyl alcohol, polysorbate 80, dextrose and water for injection. Hydrochloric acid and/or sodium hydroxide may be used for pH adjustment.

5.4. Method of Assigning Subjects to Treatment Groups

A computer-generated randomization scheme will be prepared prior to study initiation. Eligible subjects will be randomized in a 1:1 ratio to IV treatment with N1539 30 mg or placebo according to the randomization scheme. A block randomization will be generated stratified by center. Investigators and site staff will not be aware of the size of the block. All doses of study drug administered will be according to the original assignment.

5.5. Selection of Doses

The proposed commercial dose of N1539 30 mg administered once daily by IV bolus injection and matching placebo have been chosen for this study.

Based on the findings from multiple adequate and well-controlled Phase 2 and 3 studies, along with supportive PK/PD modeling, N1539 30 mg administered once daily by IV bolus injection has been shown to be safe and effective in the management of moderate to severe pain.

5.6. Selection of Timing of Dose

In the Phase 2 and 3 registration studies, N1539 was administered once daily by IV bolus injection in the postoperative period to manage (reduce) moderate to severe pain.

This study is designed to explore the efficacy and safety of N1539 30 mg administered preoperatively and followed by once daily dosing in a population of subjects undergoing open unilateral total knee arthroplasty. It is expected that preoperative administration of N1539 30 mg followed by once daily dosing will reduce the need for postoperative opioid analgesics and will result in an improved postoperative recovery course, a shorter length of hospital stay, and higher degree of subject satisfaction with pain control.

5.7. Blinding and Unbinding of Study Drug

All doses of study drug will be prepared by an appropriately qualified member(s) of the healthcare team at the research center according to the subject's randomization.

Doses of study drug will be administered by staff members who will be blinded to the treatment assignment.

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 drug 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

Blinded study personnel will administer each dose of study drug. 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 drugs when they are received. The study drug 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 drug 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 drug will be provided in study labeled packaging for preparation for use in this study.

N1539 will be provided in single use vials containing 30 mg per mL.

Placebo will be provided in single use vials.

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

Study drug 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 drug should be protected from light.

All study drug 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 administration of the first dose of study drug and during the study through POD 30 will be recorded in the eCRF.

All medications that have not been at a stable dose for at least 7 days prior to the scheduled surgical procedure on Day 1 will be prohibited within five half-lives of the specific medication (or, if half-life is unknown, within 48 hours) before the surgical procedure, with exception of medications utilized in the preparation of the subject for surgery.

5.12. Concomitant Interventions and Procedures

All interventions or procedures, whether diagnostic or therapeutic, will be recorded through POD 30, 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.

5.13. Opioid Medication

5.13.1. Intraoperative

Fentanyl and morphine or other morphine derivatives may be administered intraoperatively (during the course of the surgical procedure); however, dosing with fentanyl (and morphine or other morphine derivatives) is to be avoided within the 30 minutes prior to the anticipated conclusion of the surgical procedure. The time and dose of fentanyl (and morphine or other morphine derivatives) administered will be recorded.

Other opioid analgesics are not to be administered pre- or intraoperatively, as this may confound or influence the subjects' demand for opioid analgesia during the postoperative period (Hour 0 through hospital discharge).

5.13.2. Inpatient

Starting at Hour 0 and continuing through hospital discharge, pain intensity that is not adequately controlled with study drug may be treated with IV and/or PO opioids as

follows. Conversion from IV to oral analgesia should be made once subjects are tolerating liquid intake.

- Morphine 1 to 4 mg IV every 10 minutes for the first hour and then 1 to 8 mg IV Q1H PRN
- oxycodone immediate release (IR) 5 mg PO Q4H (maximum of 10 mg Q4H PRN)

No other analgesic agents except for study drug, the opioids designated above, acetaminophen, and aspirin for venous thromboembolism prophylaxis at the discretion of the investigator and according to institutional standards are permitted (Section 5.14).

5.13.3. Follow-up

Opioid medication usage for the management of postsurgical pain will be assessed at the following time points during the follow-up period:

- Telephone interview 24 hours after hospital discharge (Section 6.3.5)
- Telephone interview 48 hours after hospital discharge (Section 6.3.5)
- Postoperative clinical visit (POD 10 to 14) (Section 6.4.5)
- Telephone interview on POD 30 (Section 6.3.5)

5.14. Non-Opioid Analgesics

All subjects will receive 650 mg of acetaminophen Q8H PO as tolerated until LSD+1.

Aspirin is also allowed for venous thromboembolism prophylaxis at the discretion of the investigator and according to institutional standards (Section 5.1).

5.15. Prohibited Medications/Procedures

The following medications/drug classes or procedures are prohibited:

- All NSAIDs (eg, ketorolac, ibuprofen, diclofenac), other than study drug, starting 48 hours prior to surgery and continuing through last study dose (LSD) +1 day.
- Non-opioid analgesics through LSD+1 except for:
  - acetaminophen (Section 5.14)
  - aspirin if needed for thromboembolism prophylaxis according to the investigator and institutional standards (Section 5.1)
- Femoral and adductor canal blocks and other regional neuraxial blocks not specified by protocol
- Recent or planned cryoneurolysis

Please contact the medical monitor for any questions regarding prohibited medications.

6. STUDY PROCEDURES

The timing of postoperative study procedures will be relative to the end of surgery (ie, Hour 0, defined as placement of the last suture, staple, or steri-strip) except for pain intensity assessments at designated time points, which will be relative to the first dose of study drug. A schedule of study procedures is provided in Appendix A.

6.1. Total Knee Arthroplasty

On Day 1 eligible subjects will undergo unilateral total knee arthroplasty under spinal anesthesia according to the investigator's standard surgical practice. During the surgical procedure, the investigator or qualified designee will record the following:

- Start of surgery (ie, first incision) and end of surgery (ie, placement of the last suture, staple, or steri-strip)
- Was the quadriceps tendon spared during surgery? (yes/no)
- Estimated blood loss (mL)
- Times in and out of the post anesthesia care unit (PACU)
- Post PACU disposition
- Transfusions
- Surgical complications

Preoperative, intraoperative, and postoperative standard of care procedures associated with the surgical procedure and not specifically mentioned in this protocol will be carried out according to the investigator's clinical practice and in accordance with institutional standards.

6.2. Demographic and Efficacy Assessments

6.2.1. Demographics

Demographics information including age, gender, ethnicity, and race will be collected during the screening visit.

6.2.2. Medical History

During the screening period, the investigator or qualified designee will obtain a medical history from each subject that includes relevant diagnoses and/or procedures/therapies with onset/resolutions dates. Medical histories should also include history of tobacco and alcohol use (never, current, former). Medical history will be updated with any relevant information before the surgical procedure on Day 1 to determine the subject's continued eligibility for inclusion in the study.

6.2.3. Physical Examination

The investigator or designee will perform a physical examination by body system during the screening visit, before surgery on Day 1, and during the follow-up visit (POD 10 to 14).

Body weight and height will be measured and body mass index (BMI) will be calculated during the screening visit only.

Physical examination results collected within 7 days prior to the screening visit may be utilized to evaluate subject eligibility at screening.

6.2.4. Physical Therapy Assessments

Within 2 to 4 hours after discharge from the PACU a physical therapy consult will be initiated. Each subject will meet with the physical therapist and a physical therapy rehabilitation plan will be implemented. Follow-up physical therapy assessments will be made at least once daily starting on POD 1 and continuing through hospital discharge.

As part of discharge planning, subjects will meet with the physical therapist to determine an outpatient physical therapy rehabilitation plan.

6.2.5. Ambulation

Within 12 hours after Hour 0 on Day 1, each subject will be assisted out of bed to ambulate with assistance (ie, with the assistance of hospital staff and with or without a walking aid [eg, walker]).

Starting on POD 1, subjects will be encouraged to continue to progress with assisted and unassisted ambulation at least three to four times each day through hospital discharge. Study staff will document the time of each postoperative ambulation through hospital discharge or LSD +1, whichever occurs first, including first assisted ambulation and first independent ambulation.

First assisted ambulation is defined as first time walking with the assistance of hospital staff (with or without a walking aid). First unassisted ambulation is defined as first time walking without the assistance of hospital staff (with or without a walking aid).

Pain intensity will be recorded before and during ambulation as described in Section 6.2.6.

6.2.6. Pain Intensity (PI)

Subjects will be questioned regarding pain intensity using an 11-point numeric pain rating scale (NPRS; 0 - 10) where 0=no pain, and 10=the worst pain imaginable as follows:

- Upon arrival at the PACU
- Timepoints relative to first dose of study drug: 4 hours ± 15 minutes, 6 hours ±15 minutes, 8 hours ± 30 minutes, 10 hours ± 1 hour, 12 hours ± 1 hour, 16 ± 1 hour, 20 hours ± 1 hour, 24 hours ± 1 hour (before study drug

administration, if indicated), 30 hours ± 2 hours, 36 hours ± 2 hours, 42 hours ± 2 hours, and 48 hours ± 2 hours (before study drug administration, if indicated), when the subject is awake

- Immediately before each administration of opioid medication from Hour 0 through hospital discharge or LSD +1, whichever occurs first
- Before and during each ambulation through hospital discharge or LSD +1, whichever occurs first
- Before hospital discharge

Following hospital discharge, subjects will also be questioned regarding pain intensity using the NPRS during each follow-up telephone interview (24 hours and 48 hours after discharge and POD 30) and during the follow-up visit (POD 10 to 14) (Appendix C).

6.2.7. Patient Global Assessment (PGA) of Pain Control

Starting on POD 1 and continuing each day through hospital discharge or LSD+1, whichever occurs first, study staff will ask subjects to respond to the following question:

"Overall, please rate how well your pain has been controlled during the last 24 hours?"

Poor (0)

Fair (1)

Good (2)

Very Good (3)

Excellent (4)

6.2.8. Overall Benefit of Analgesia Score Questionnaire (OBAS)

Starting on POD 1 and continuing each day through hospital discharge or LSD+1, whichever occurs first, study staff will ask subjects to respond to the seven questions contained in the OBAS questionnaire (Table 2).

Table 2: Overall Benefit of Analgesia Score Questionnaire[a]

1. Please rate your current pain at rest on a scale between 0=minimal pain and 4=maximum imaginable pain
2. Please grade any distress and bother from vomiting in the past 24 hours (0=not at all to 4=very much)
3. Please grade any distress and bother from itching in the past 24 hours (0=not at all to 4=very much)
4. Please grade any distress and bother from sweating in the past 24 hours (0=not at all to 4=very much)
5. Please grade any distress and bother from freezing in the past 24 hours (0=not at all to 4=very much)
6. Please grade any distress and bother from dizziness in the past 24 hours (0=not at all to 4=very much)
7. How satisfied are you with your pain treatment during the past 24 hours (0=not at all to 4=very much)

a Lehmann 2010

6.3. Safety Assessments

6.3.1. 12-Lead Electrocardiogram (ECG)

A 12-lead ECG will be completed for all subjects at screening. Historic ECG results collected within 7 days prior to the screening visit may be utilized for evaluation of subject eligibility; 12-lead ECG will be used to exclude subjects with a clinically significant abnormal ECG.

6.3.2. Clinical Laboratory Tests

Routine clinical laboratory testing will be at the time points shown in Table 3. Screening laboratory testing will be performed at a local laboratory. Historic laboratory results collected within 7 days prior to the screening visit may be utilized for subject eligibility evaluation at screening visit. Historical laboratory results must include the full panel for each laboratory test described in Table 3.

Laboratory testing subsequent to screening will be analyzed at a central laboratory. Urine pregnancy testing at screening and before surgery on Day 1 will be done at the clinical site using kits provided by the central laboratory.

Additional clinical laboratory testing may be performed according to the investigator's clinical practice and in accordance with institutional standards.

Table 3: Clinical Laboratory Testing

Hematology	Platelet count, hemoglobin, and hematocrit	Screening Day 1: prior to dosing Before hospital discharge POD 10 to 14, if indicated
Serum chemistry	Urea, glucose, creatinine, sodium, potassium, chloride, bicarbonate, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, direct bilirubin, and gamma-glutamyltransferase	Screening Day 1: prior to dosing Before hospital discharge POD 10 to 14, if indicated
Coagulation	prothrombin time, activated partial thromboplastin time, international normalized ratio	Screening Day 1: prior to dosing Before hospital discharge POD 10 to 14, if indicated
Urine pregnancy[a]	Women of childbearing potential.	Screening Day 1: prior to dosing
a Results must be available before the first dose of study drug on Day 1. Additional clinical laboratory testing may be performed according to the investigator's clinical practice and in accordance with institutional standards.		

Any clinically significant changes in laboratory values after study drug administration on Day 1 should be captured as AEs at the discretion of the investigator.

6.3.3. Vital Sign Measurements

Vital signs including blood pressure, pulse, and respiratory rate will be collected after the subject has rested (seated/supine) for ≥5 minutes during the screening visit and before dosing on Day 1. Vital sign results will be used to determine subject eligibility. Historic vital signs results collected within 7 days prior to the screening visit may be utilized for subject eligibility evaluation at screening visit.

Vital sign assessments during the surgical procedure, while the subject is in the PACU, and during the postoperative period will be at the discretion of the investigator and in accordance with institutional standards.

6.3.4. Wound Healing Assessment

Before hospital discharge and during the follow-up visit (POD 10 to 14), the investigator or qualified designee will rate his/her satisfaction with wound healing using an 11-point scale (0-10) where a score of 0 is "completely unsatisfied", and a score of 10 is "completely satisfied".

6.3.5. Post Discharge Telephone Interviews for Healthcare Utilization

6.3.5.1. 24 Hours and 48 Hours Post Discharge and POD 30

Qualified study staff will conduct telephone interviews 24-hours and 48-hours after hospital discharge and on POD 30. During each phone interview, subjects will be asked

about opioid medication use, pain intensity, physical therapy visits, and utilization of healthcare resources (ie, hospital readmission, use of skilled nursing facilities, unscheduled phone calls and/or office visits related to pain, and emergency room [ER] visits related to pain). Please refer to the Operations Manual for details.

6.3.6. Cost of Hospitalization

Cost of the initial hospitalization will be determined using UB-04 and/or similar hospital claim forms used for billing purposes. Total hospital charges, as recorded on the UB-04/hospital claims forms, will be recorded. In addition, total hospital costs will be determined from the billing codes and/or procedure codes for all hospital care from the time of hospital admission until discharge as reported on the UB-04/hospital claims forms.

6.3.7. End of Study

The end of the study is when the last subject completes the POD 30 telephone interview.

6.4. Assessments by Visit

6.4.1. Screening Period (Day -28 to Day -1)

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 the initial dose of study drug on Day 1.

After informed consent is obtained, the following will be assessed and documented during the screening visit:

1. Review of inclusion/exclusion criteria eligibility (Section 4.1 and Section 4.2)
2. Demographics and medical history (Section 6.2.1 and Section 6.2.2)
3. Review of prior/concomitant medications/procedures (Section 5.11)
4. Physical examination including height, weight and calculation of BMI (Section 6.2.3)
5. 12-lead ECG (Section 6.3.1)
6. Vital sign measurements (Section 6.3.3)
7. Clinical laboratory testing (Section 6.3.2):
    - Hematology, chemistry, and coagulation
    - Urine pregnancy test for women of childbearing potential
8. Serious adverse events (Section 7.2)

6.4.2. Inpatient Period

6.4.2.1. Open Total Knee Arthroplasty (Day 1)

6.4.2.1.1. Preoperative

The following will be assessed and documented preoperatively:

1. Update medical history
2. Concomitant medications/procedures (Section 5.11)
3. Physical examination (Section 6.2.3)
4. Vital sign measurements (Section 6.3.3)
5. Clinical laboratory testing (Section 6.3.2):
    - Hematology, chemistry, and coagulation
    - Urine pregnancy test for women of childbearing potential
6. Establish continued eligibility for treatment
7. Randomization of eligible subjects to treatment (Section 5.4)
8. Administer preoperative medications (Section 5.2)
9. Administer intrathecal anesthesia (Section 5.2.1)
10. Administer study drug according to randomization (Section 5.2.4)
11. Adverse events (Section 7)

6.4.2.1.2. Intraoperative

The following will be assessed and documented intraoperatively:

1. Open unilateral total knee arthroplasty according to the investigator's clinical practice and in accordance with institutional standards (Section 6.1)
2. Concomitant medications/procedures (Section 5.11)
3. Administer local infiltrate prior to wound closure (Section 5.2.3)
4. Adverse events (Section 7)

Surgery start (first incision) and surgery end (last suture, staple, or steri-strip placement [Hour 0]) times, confirmation of quadriceps tendon sparing during surgery, estimated blood loss (mL), transfusions, and surgical complications will be recorded. Upon completion of surgery, subjects may be transported to the post anesthesia care unit (PACU) until they are deemed ready for transport to their hospital room. The times in and out of the PACU and post PACU disposition will be recorded.

6.4.2.2. Postoperative

The following will be assessed during the postoperative period as follows:

1. Concomitant medications/procedures through hospital discharge (Section 5.11)
2. Administration of study drug as needed through hospital discharge (Section 5.2.4)
3. Administration of opioid pain medication as needed through hospital discharge (Section 5.13)
4. Pain intensity through hospital discharge (Section 6.2.6)
5. Physical therapy through hospital discharge (Section 6.2.4)
6. Ambulation through hospital discharge or LSD+1, whichever occurs first (Section 6.2.5)
7. Patient Global Assessment of Pain Control starting on POD 1 through hospital discharge or LSD+1, whichever occurs first (Section 6.2.7)
8. Overall Benefit of Analgesia Score Questionnaire starting on POD 1 through hospital discharge or LSD+1, whichever occurs first (Section 6.2.8)
9. Adverse events through hospital discharge (Section 7)

6.4.3. Hospital Discharge

The following will be assessed before hospital discharge:

1. Concomitant medications/procedures (Section 5.11)
2. Clinical laboratory testing including hematology, chemistry, and coagulation (Section 6.3.2)
3. Administration of study drug at the discretion of the investigator (Section 5.2.4)
4. Administration of opioid pain medication as needed (Section 5.13)
5. Pain intensity:
   - Before administration of opioid pain medication, if still receiving study drug (Section 6.2.6)
   - Before discharge
6. Wound healing assessment (Section 6.3.4)
7. Adverse events (Section 7)

The time hospital discharge order is written and actual departure time from hospital will be recorded. Discharge pain medication prescription(s) and discharge to home or to a skilled nursing facility will be documented.

6.4.4. 24-Hour and 48-Hour Post Discharge Telephone Interviews

Qualified study staff will conduct telephone interviews 24-hours and 48-hours after hospital discharge (refer to Section 6.3.5 for details).

6.4.5. Follow-up Visit (POD 10 to 14)

Subjects will visit the clinical site and the following will be assessed and documented during the follow-up visit:

1. Concomitant medications/procedures (Section 5.11)
2. Physical examination (Section 6.2.3)
3. Clinical laboratory testing including hematology, chemistry, and coagulation, if indicated (Section 6.3.2)
4. Opioid pain medication usage (Section 5.13.3)
5. Pain intensity (Section 6.2.6)
6. Wound healing assessment (Section 6.3.4)
7. Healthcare utilization including physical therapy visits (Section 6.3.5)
8. Adverse events (Section 7)

6.4.6. Postoperative Day 30 Telephone Interview (End of Study)

Qualified study staff will conduct telephone interviews POD 30 (refer to Section 6.3.5 for details). Following this interview subjects will be discharged from the study.

7. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE) 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 drug, whether or not considered causally associated with the use of the study drug. Any abnormal laboratory value deemed clinically significant by the investigator, regardless of causal relationship, must be reported as an AE.

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 (eg, 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 drug 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 (eg, 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, will be assessed and recorded in the eCRF beginning after administration of study drug through end of the study (ie, Day 30).

7.2. Definition of a Serious Adverse Event

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

- Results in death
- Is immediately life-threatening (ie, presents an immediate risk of death from the event as it occurred; this does not include an AE had it occurred in a more serious form may have caused death).
- Results in persistent or significant incapacity or substantial disruption of the ability to perform normal life functions.
- Results in hospitalization.
- Results in prolongation of an existing hospitalization.
- Is a congenital anomaly or birth defect (in the offspring of a subject using the study drug regardless of time to diagnosis).
- Is considered an important medical event.

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 medical or surgical intervention to prevent any of the outcomes listed that define a SAE. 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 a 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 a SAE.

SAEs will be assessed and recorded in the eCRF after the signing of informed consent through the end of the study (ie, Day 30). If an investigator becomes aware of a SAE or death that occurs more than 30 days after the subject receives study drug and the investigator considers the event to be related to the study drug, he/she is obligated to report the SAE to the sponsor.

7.3. 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.

7.3.1. 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 a 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).

7.3.2. Assessment of Causality

The investigator must record the causal relationship of each event in the eCRF, and additionally for SAEs, on the SAE reporting form. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the study drug caused or contributed to an AE.

- Related: There is evidence to suggest a causal relationship between the study drug and the AE.
- Not related: The AE is due to underlying or concurrent illness or effect of another drug or event and is not related to the study drug (eg, has a more likely alternate etiology and / or a temporal relationship does not suggest a causal relationship).

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.

7.3.3. Assessment of Outcome

All AEs and 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(s) by using the following terms:

- Resolved: The event resolved and the subject returned to baseline.
- Resolving: At last observation, the event was improving.

- Resolved with sequelae: The event resolved but the subject is left with residual problems (eg, functional deficits)
- Not resolved: At the last observation, the event was unchanged.
- Unknown: There were no observations after the onset (initial observation or report) of the event, and the status of the event is unknown.
- Death (*Fatal)*: To be selected for the ***one*** AE, which in the judgement of the investigator was the ***primary*** cause of death.

7.4. 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 that are designated as ongoing will be reviewed at subsequent visits or contacts until the event resolves, the condition stabilizes, the event is otherwise explained, or the subject is lost to follow-up. Any additional events that are relevant to the ongoing event will be documented.

The investigator will ensure that follow-up information relevant to SAEs is provided to the sponsor and 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 7.5.

7.5. 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 DRUG, MUST BE REPORTED TO THE SPONSOR IMMEDIATELY (within 24 hours).

COMPLETE THE SAE DETAILS REPORTING FORM AND FORWARD BY EMAIL TO THE FOLLOWING SPONSOR CONTACT:

Medical Safety Recro Pharma, Inc.
Telephone: 484-395-2470
eFax: 484-395-2472
email: AE@recropharma.com

In the initial email, 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.

7.6. Regulatory Reporting Requirements

The investigator must promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 7.5 "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 SAEs 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.

For the purposes of IND safety reporting, expectedness of the SAE will be assessed by the sponsor. A SAE 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.

The sponsor will determine whether the SAE meets regulatory reporting criteria (ie, 7- or 15-day report) in compliance with local and regional law. If so, the sponsor (or the sponsor's representative) will report the event to the appropriate regulatory authorities. The sponsor will report SAEs to the central IRB/EC and the investigator will be report SAE to their local to institutional review board (IRB)/EC. Investigator letters are prepared according to sponsor policy and are forwarded to the investigators as necessary. An investigator letter is prepared for any SAE that is attributable to study drug, 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.

7.7. Special Reporting Situations: Pregnancy

Any subject who becomes pregnant during the study must discontinue further study drug administration and should be followed through delivery or termination of the pregnancy. A subject should be instructed to also notify the investigator immediately if she becomes pregnant within 30 days after receiving study drug. The sponsor must be notified of all pregnancies reported to the investigator (see Section 7.5 for contact information).

Any uncomplicated pregnancy that occurs in a subject during this clinical study will be reported for tracking purposes only. All subject pregnancies that are identified during or after this study, where the estimated date of conception is determined to have occurred within 30 days of receiving study drug need to be reported, followed to conclusion (delivery or termination), and the outcome reported, even if the subject is discontinued from the study. The investigator should report all pregnancies within 24 hours using the Pregnancy Report/Outcome Form, according to the usual timelines and directions for SAE reporting provided in Section 7.5. Monitoring of the pregnancy should continue until conclusion of the pregnancy; and follow-up detailing the outcome of the pregnancy submitted using the Pregnancy Report/Outcome Form.

Pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs.

Any SAEs associated with pregnancy (eg, congenital abnormalities/birth defects/spontaneous miscarriages or any other serious events) must additionally be reported as such using the SAE report form according to the usual timelines and directions for SAE reporting provided in Section 7.5.

8. STATISTICAL METHODOLOGY AND DETERMINATION OF SAMPLE SIZE

The following outlines some of the key elements of the data analysis approach. A formal statistical analysis plan (SAP) will be developed for this study in which statistical models, data derivation methods and rules will be described in detail. A separate statistical analysis plan will be developed for the healthcare utilization endpoints detailed in this study (Section 8.5).

8.1. Determination of Sample Size

The sample size for this study (100 subjects per group) will have at least 90% power to detect the difference between N1539 30 mg versus placebo in total opioid consumption based on the results observed in a Phase 3 safety study that evaluated all major surgeries. The study results suggested that the total opioid consumption was lower in subjects treated with N1539 30 mg compared to placebo, and that the observed effect size in total opioids consumption measured by IV morphine equivalent dose (IVMED, mg) ranged from 0.5 to 0.7 in this subgroup.

8.2. Study Endpoints

8.2.1. Efficacy Endpoints

8.2.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is total use of opioid analgesia from Hour 0 through 24 hours.

8.2.1.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- Sum of pain intensity from the time of first dose of study drug through 24 hours (SPI_{24})
- Percentage of subjects who are opioid free from Hour 0 through 24 hours
- Time to first use of IV or oral opioid analgesia

8.2.1.3. Other Efficacy Endpoints

Other efficacy endpoints include:

- Total use of opioid analgesia from first dose of study drug through 24 hours (before 2nd dose of study drug)
- Total use of opioid analgesia from Hour 0 through 48 hours
- Total use of opioid analgesia from Hour 0 through hospital discharge
- Total use of opioid analgesia from hospital discharge through 24-hour telephone interview

- Total use of opioid analgesia from the 24-hour telephone interview through the 48-hour telephone interview
- Percentage of subjects that are opioid free from Hour 0 through 48 hours
- Percentage of subjects that are opioid free from Hour 0 through hospital discharge
- Percentage of subjects who used any opioid medication after hospital discharge through POD 30.
- Time to first IV opioid medication defined as the time from Hour 0 until time of first use of IV opioid medication
- Time to first oral opioid rescue medication defined as the time from Hour 0 until time of first use of oral opioid medication
- Pain intensity during first assisted ambulation
- Pain intensity during first unassisted ambulation
- SPI from time of first dose of study drug through first assisted ambulation
- SPI from time of first dose of study drug through first unassisted ambulation
- SPI from time of first dose of study drug through 48 hours
- SPI from time of first dose of study drug through hospital discharge or LSD+1, whichever comes first
- Time to first assisted ambulation defined as the time from Hour 0 until time when first assisted ambulation occurs
- Time to first unassisted ambulation defined as the time from Hour 0 until time when first unassisted ambulation occurs
- Subject overall evaluation of pain control on 5-point categorical scale on each postoperative day, starting on POD 1 and continuing through hospital discharge or LSD+1, whichever occurs first.
- The OBAS total score and opioid distress dimension subscore on each postoperative day, starting on POD 1 and continuing through hospital discharge or LSD+1, whichever occurs first
- Pain intensity at the following follow-up time points: 24 hours and 48 hours post discharge, and POD 10-14, and POD 30

8.2.2. Safety Endpoints

Safety endpoints include:

- Incidence of treatment-emergent adverse events (TEAEs)
- Incidence of potentially clinically significant abnormal clinical laboratory values

- Investigator satisfaction with wound healing before hospital discharge and during the follow-up visit (POD 10 to 14).

8.2.3. Healthcare Utilization Endpoints

Healthcare utilization endpoints include:

- Length of hospital stay defined as days from hospital admission until the hospital discharge order is written
- Total cost of hospitalization (taken from the UB-04/hospital claims form)
- Duration of time in the PACU (time in through time out of PACU)
- Percentage of subjects with hospital readmission through POD 30
- Total number of postsurgical physical therapy visits through POD 30
- Percentage of subjects who required a skilled nursing facility from hospital discharge through POD 30
- Total time spent in skilled nursing facility from hospital discharge through POD 30
- Percentage of subjects who made a phone call related to postsurgical pain from hospital discharge through POD 30
- Total number of unscheduled phone calls related to postsurgical pain from hospital discharge through POD 30
- Percentage of subjects who had an unscheduled visit related to postsurgical pain from hospital discharge through POD 30
- Total number of unscheduled visits related to postsurgical pain from hospital discharge through POD 30
- Percentage of subject who had an emergency room visit for postsurgical pain from hospital discharge through POD 30
- Total number of visits to the emergency room for postsurgical pain from hospital discharge through POD 30

8.1. General Considerations for Statistical Analysis

8.1.1. Analysis Populations

8.1.1.1. Intent-to-Treat (ITT) Population

The ITT population will include all subjects who qualify for the study and are randomized for treatment prior to surgery. ITT subjects may or may not receive randomized treatment.

8.1.1.2. Safety Population

The safety population will consist of all subjects who receive at least one injection of study drug. All safety evaluations will be based on the safety population.

8.1.1.3. Efficacy Population (Modified Intent-to-Treat)

The efficacy population (ie, modified intent-to-treat [mITT]) will consist of all subjects who receive at least one injection of study drug and have the scheduled surgery. All efficacy evaluations will be based on the efficacy population.

8.1.2. Test Hypothesis and *P* Value Justification

Each efficacy analysis will be performed to assess the differences between the 2 treatment groups; N1539 30 mg vs Placebo.

The null hypothesis is that there is not difference between the examined treatment groups. The alternative hypothesis is that the treatment groups are different. Differences between the 2 groups will be evaluated via 2-sided 2-sample t-test at the 0.05 level of significance.

Nominal p-value will be reported as is.

8.1.3. 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.

8.1.4. Definitions for Assessment Windows

For the purpose of data analysis, *baseline* measures will be the last measurements taken before the subject receives the first dose of study drug.

8.1.5. Derived Variables

The study SAP will provide detail description for each endpoint derivation methodology, including censoring rules for each time to events, mapping of opioid dose in IV morphine equivalence dose (mg) for each time period, missing data (time) imputation rules, total pain intensity for each period, OBAS total score and sub-score for opioid distress dimension.

8.2. Study Population Summaries

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

8.2.1. Disposition

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

Disposition in terms of number of subjects excluded from each analysis sets (ITT, safety, and mITT) will also be provided by treatment groups and study overall.

8.2.2. Demographics and Baseline Characteristics

The demographic summary will include descriptive statistics for age, sex, race, weight, height, and BMI for the overall and by treatment group.

Baseline characteristics will include history of tobacco and alcohol use, surgery duration, time from first dose to start of surgery, duration in PACU, and additional surgery related variables (eg, estimated blood lost, number of transfusions).

8.2.3. Protocol Violations

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

8.2.4. Treatment Compliance

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

8.2.5. 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 1Q2017 or higher.

8.3. Efficacy Summaries and Analysis

Efficacy endpoints will be tabulated by treatment groups and time points as appropriate; descriptive statistics will be provided, including sample size, mean, standard deviation, median, minimum and maximum for continuous variables, or frequency (number of subjects and percentage) distribution of each category for categorical variables.

Treatment effect will be evaluated using Analysis of Covariance (ANCOVA) for opioid consumption related endpoints, pain intensity related endpoints, and OBAS related endpoints; the ANCOVA model will include treatment effect and investigational sites as a covariate. Difference in LS means will be compared between the treatment groups.

Kaplan-Meier survival analysis will be carried out for time to event endpoints, including survival curves, 25%, 50% and 75% tiles estimates and corresponding 95% confidence intervals (CI), and log-rank test. Cox proportional hazards analysis will also be performed for time to event endpoints; the model will include the treatment effect and the investigational sites; hazards ratio and corresponding 95% CI will be presented.

Treatment effect on PGA scores will be evaluated based on proportion of subjects rated their pain control as good, very good, or excellent using CMH test controlling for

analysis center. CMH test will apply to other category variables, such as proportion of subjects who took any opioids or who were opioid free at various time periods.

8.4. Safety Summaries

8.4.1. Extent of Exposure

The extent of exposure for the study drug treatment will be assessed via number of doses received.

8.4.2. Adverse Events

The Medical Dictionary for Regulatory Activities (Version 20 or higher) will be used to classify all AEs with respect to system organ class and preferred term. An event is considered treatment emergent if the event onset date/time is on or after the first dose of study drug or if a prior condition is worsened after the first dose of study drug. AEs will be summarized by treatment group. AE summaries will be provided for all treatment emergent AEs, study drug related TEAEs, and serious TEAEs.

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

8.4.3. Subjects with Clinically Significant Laboratory Values

Clinical laboratory parameters collected after the first dose of study drug will be evaluated by comparing to baseline. Subjects with potentially clinically significant changes from baseline in clinical laboratory parameters will be identified and tabulated by treatment group.

8.4.4. Wound Healing

The number and proportion of subjects with abnormal wound healing observations will be summarized by treatment group.

8.5. Healthcare Utilization Summaries

A separate SAP will be constructed for analysis of Health Care Utilization and total costs as recorded on the UB-04. This SAP will detail the objectives, methods for conducting the relevant analyses, and the format for presentation of the findings. Subject cohorts of interest will be defined and the variables to be measured as well as the steps in data processing and analyses will also be presented.

9. STUDY ADMINISTRATION

9.1. Regulatory and Ethical Considerations

9.1.1. Ethical Conduct of the Study

This study will be conducted according to the clinical research guidelines established by FDA Title 21 Code of Federal Regulations (CFR) Parts 50, 54, 56, and 312, ICH GCP and other regulations as applicable.

9.1.1.1. Institutional Review Board/Independent Ethics Committee

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 (eg, advertisements or information that supports or supplements the informed consent form) are reviewed and approved by the appropriate IRB or IEC. If the protocol, the informed consent form, or any other information that the IRB or IEC has approved for presentation to potential subjects is amended during the study, the investigator is responsible for ensuring that the IRB or IEC reviews and approves, where applicable, these amended documents prior to implementation of any changes. The investigator must follow all applicable regulatory requirements pertaining to the use of an amended informed consent form, including obtaining IRB or IEC approval of the amended form, before new subjects consent to take part in the study using the new version of the form.

For study sites with IECs that comply with ICH GCP, but not US FDA 21CFR Part 56, a waiver request will be submitted to the FDA. If granted, the FDA's letter documenting the waiver will be provided to the Investigator.

In addition, the investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC safety procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC and all other applicable regulations

9.1.1.2. Informed Consent

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Template informed consent forms will be provided by the sponsor but may be adapted to meet the needs of the institution. Final consent forms will be IRB/IEC approved and accepted by the sponsor. The subject will be asked to read and review the consent document. The investigator or designee will explain the study to the subject and answer

any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purpose, procedures, and potential risks of the study and of their rights as research subjects. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The subject will sign the informed consent document prior to any procedures being done specifically for the study. Subject must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document and the form signed before the subject undergoes any study-specific procedures. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in the study.

9.1.1.3. Subject Confidentiality

Subjects will be assigned a unique identifier by the sponsor. Any subject records or data that are transferred to the sponsor will contain the identifier; subject names or any information which would make the subject identifiable will not be transferred. The investigator will keep a Master Subject List on which the identifier and full name, address, and telephone number of each subject are listed. The Master Subject List will be stored in a secure location at the site and will not be shared with the sponsor. It is the Investigator's responsibility to inform subjects as part of the informed consent process that representatives of the sponsor, FDA, or other regulatory agencies may review all records that support their participation in the study. The Investigator will comply with all privacy laws to which he/she is subject.

9.1.1.4. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

9.2. Quality Assurance

- All subject data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checks of the data.
- Study monitors will perform ongoing source data verification to confirm that that data entered into the CRF by site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the current approved version of the protocol, ICH GCP, and all applicable regulatory requirements.

9.3. 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 (eg, 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

9.4. Records Retention

9.4.1. 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. No records may be transferred to another location or party without written notification to and approval of the sponsor.

9.5. Information Disclosure

9.5.1. 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 the written contract executed for the conduct of the study. Authorship will be determined by mutual agreement and in line with the International Committee of Medical Journal Editors authorship requirements.

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 120 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.

Where a written contract is executed for the conduct of the study, that contract's publication provisions will supersede the language in this section.

10. LIST OF REFERENCES

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APPENDIX A: STUDY ASSESSMENTS: PROTOCOL REC-17-025

	Screening	Surgery (Day 1) Through Hospital Discharge or LSD+1, whichever occurs first			Hospital Discharge	Telephone Interview	Follow-up Visit	Telephone Interview
	Day 28 to Day -1	Preoperative	Intraoperative (End of Surgery= Hour 0)	Postoperative Hour 0 Through Hospital Discharge or LSD +1		24 Hours and 48 Hours Post-Discharge	POD 10 to Day 14	POD 30 ± 4 days
Informed consent	X							
Eligibility assessment	X	X						
Demographics and medical history	X	X (update)						
Prior/concomitant medications/procedures	X	X	X	X[a]	X	X	X	X
Physical examination	X	X					X	
12-Lead electrocardiogram	X							
Vital signs	X[b]	X[b]						
Clinical laboratory testing	X (local lab)	X			X		X, if indicated	
Urine pregnancy testing	X	X						
Randomization		X						
Perioperative medications		X[c]	X[d]					
Intrathecal anesthesia (spinal)		X[e]						
Study drug administration		X[f]		Q24H from Dose 1[a,g]	X[g]			
PI assessment				X[h]	X	X	X	X
Opioid pain medication				X[a]	X	X	X	X
Physical therapy				X[a]		X	X	X
Ambulation				X[i]				
PGA of pain control				Each postop day starting with POD 1[i]				
OBAS				Each postop day starting with POD 1[i]				
Wound healing assessment					X		X	
Serious adverse events only	X							
Adverse events		X	X	X[a]	X	X	X	X
Healthcare utilization[j]						X	X	X

IV=intravenous; OBAS=Overall Benefit of Analgesia Score Questionnaire; PGA=Patient Global Assessment; PI=pain intensity; PO=by mouth; POD=postoperative day

a Through hospital discharge.

b Vital signs after the subject has rested (seated/supine) for ≥5 minutes. Results will be used to determine subject eligibility.

c Acetaminophen 650 PO, gabapentin 600 mg PO, tranexamic acid 1 g IV, and prophylactic IV antibiotic 30 to 90 minutes before start of surgical procedure. Subjects will continue to receive acetaminophen 650 mg PO Q8H through LSD+1. Venous thromboembolism prophylaxis before and after surgery according to standard practice, based on the subject's individual needs, at the discretion of the investigator and surgeon, and taking into consideration the ACCP and AAOS guidelines for orthopedic surgery.

d Local infiltrate prior to wound closure.

e Prior to start of surgical procedure.

f Dose 1 is to be administered after spinal anesthesia and before the start of the surgical procedure. Subsequent doses may be administered Q24±1 hours from Dose 1.

g At the discretion of the investigator.

h PI will be assessed upon arrival at the PACU, at various scheduled timepoints relative to first dose of study drug, before each administration of opioid medication (Time 0 through hospital discharge or LSD+1, whichever first), before and during each ambulation (Time 0 through hospital discharge or LSD+1, whichever first), before hospital discharge, 24 hours and 48 hours after discharge, POD 10 to 14, and POD 30 (Section 6.2.6).

i Through hospital discharge or LSD+1, whichever occurs first.

j Hospital readmission, use of skilled nursing facilities, unscheduled phone calls or office visits related to pain, and ER visits related to pain.

APPENDIX B: CLINICAL CARE PROTOCOL MEDICATIONS

Venous Thromboembolism Prophylaxis:

Venous thromboembolism prophylaxis before and after surgery will be administered according to standard practice, based on the subject's individual needs, at the discretion of the investigator and surgeon, and taking into consideration the American College of Chest Physicians (ACCP) and American Academy of Orthopaedic Surgeons (AAOS) guidelines for orthopedic surgery.

Perioperative Concomitant Medications:

- 30 to 90 minutes before surgical procedure administer:
  - Acetaminophen 650 mg by mouth (PO) (administered with sips of water)
  - Gabapentin 600 mg PO (administered with sips of water)
  - Tranexamic acid 1 gram IV (a second dose of tranexamic acid may be given approximately 3 hours after the first, at the discretion of the surgeon).
  - Prophylactic IV antibiotic
- Before the start of the surgical procedure:

Following administration of intrathecal anesthesia (ie, 7.5 mg to 15 mg bupivacaine HCl) and before the start of surgery, **administer 1st dose** of study drug by IV bolus injection in ≤15 seconds according to randomization.

- Intraoperative

Fentanyl and morphine or other morphine derivatives may be administered intraoperatively (during the course of the surgical procedure); however, dosing with fentanyl (and morphine or other morphine derivatives) is to be avoided within the 30 minutes prior to the anticipated conclusion of the surgical procedure. The time and dose of fentanyl (and morphine or other morphine derivatives) administered will be recorded.

Other opioid analgesics are not to be administered pre- or intraoperatively, as this may confound or influence the subjects' demand for opioid analgesia during the postoperative period (Hour 0 through hospital discharge).

Anxiolytics, sedatives, and other medications (except for analgesic agents) that are used for subject well-being during the intraoperative period may be administered according to the investigator's clinical practice and in accordance with institutional standards. The time and dose of any medication administered during the intraoperative period will be recorded.

- Intraoperative: Prior to wound closure administer:

Local infiltration of bupivacaine HCl 0.5% 30 mL with epinephrine 0.5 mg expanded in a volume of 90 mL normal saline and drawn up into six 20 mL syringes each with a 22-gauge needle.

Local infiltrate should be administered so that each needle stick delivers approximately 1 mL of the drug to the intended area. The tissue should visibly expand with minimal leakage. Infiltrate should be injected into the prescribed locations based on the areas of highest nerve density as shown in Table 4.

Table 4: Local Infiltrate Administration

Timing	**Infiltrate Administration Location**	**Number of Needle Sticks[a]**
Prior to final implant placement	Posterior capsule	8-10 sticks medial 8-10 sticks lateral
	Femur (medial and lateral periosteum, posterior periosteum suprapatellar/quadriceps tendon	20 sticks
	Tibia—fat pad	5 sticks
	Pes anserinus, medial collateral ligament, and gutter	15 sticks
	Circumferential periosteum	15-20 sticks
After final implant placement	Midline quadriceps tendon	10 sticks
	Retinaculum, medial gutter, femoral to tibia	10 sticks
	Lateral gutter, femoral to tibial	10 sticks
	Subcutaneous/closure	10 sticks

a Each needle stick delivers approximately 1 mL of the bupivacaine infiltrate.

Postoperative Concomitant Medications:

- Opioid pain medications:

Starting at Hour 0 and continuing through hospital discharge, pain intensity that is not adequately controlled with study drug may be treated with IV and PO opioids as follows. Conversion from IV to oral analgesia should be made once subjects are tolerating liquid intake.

  - Morphine 1 to 4 mg IV every 10 minutes for the first hour and then 1 to 8 mg IV Q1H PRN
  - Oxycodone immediate release (IR) 5 mg PO Q4H (maximum of 10 mg Q4H PRN)

- Acetaminophen:

All subjects will receive 650 mg of acetaminophen Q8H PO as tolerated until 24 hours following the last dose of study drug (LSD+1).

No other analgesic agents except for study drug, the opioids (described above), acetaminophen (through LSD+1), and aspirin for venous thromboembolism prophylaxis according to the investigator and institutional standards (Section 5.1) are permitted.

- Treatment of postoperative nausea and vomiting:

Subjects may receive IV ondansetron 4 mg as needed for postoperative nausea and vomiting (PONV) according to FDA prescribing information.

Study Drug:

Additional doses of study drug will be administered every 24 hours (±1 hour) after the first dose. Dosing will continue until the subject is either discharged from the hospital or until IV study drug analgesia is no longer clinically appropriate. The investigator may administer a final dose of study drug up to 4 hours ahead of schedule in subjects who are to be discharged.

APPENDIX C: NUMBERIC PAIN RATING SCALE (NPRS)

Protocol-Defined Time Points

- Upon arrival at the PACU
- At time points relative to first dose of study drug: 4 hours ± 15 minutes, 6 hours ±15 minutes, 8 hours ± 30 minutes, 10 hours ± 1 hour, 12 hours ± 1 hour, 16 ± 1 hour, 20 hours ± 1 hour, 24 hours ± 1 hour (before study drug administration, if indicated), 30 hours ± 2 hours, 36 hours ± 2 hours, 42 hours ± 2 hours, and 48 hours ± 2 hours (before study drug administration, if indicated), when the subject is awake
- Before hospital discharge

Subjects will be asked: On a scale of 0-10 where 0 is 'no pain' and 10 is the 'worst imaginable pain', please rate your pain NOW.

0 No pain	1	2	3	4	5	6	7	8	9	10 Worst imaginable pain

Opioid Medication Use (Hour 0 through hospital discharge or LSD +1, whichever occurs first)

Immediately before each administration of opioid medication subjects will be asked: On a scale of 0-10 where 0 is 'no pain' and 10 is the 'worst imaginable pain', please rate your pain NOW.

0 No pain	1	2	3	4	5	6	7	8	9	10 Worst imaginable pain

Ambulation (Hour 0 through hospital discharge or LSD +1, whichever occurs first)

Within 15 minutes before each ambulation subjects will be asked:

On a scale of 0-10 where 0 is 'no pain' and 10 is the 'worst imaginable pain', please rate your pain NOW.

0 No pain	1	2	3	4	5	6	7	8	9	10 Worst imaginable pain

After each ambulation, subjects will be asked:

On a scale of 0-10 where 0 is 'no pain' and 10 is the 'worst imaginable pain', please rate your WORST pain during ambulation.

0 No pain	1	2	3	4	5	6	7	8	9	10 Worst imaginable pain

24 Hours and 48 Hours After Discharge and POD 30 Telephone Interviews and During the POD 10 to 14 Visit

At each time point, subjects will be asked:

On a scale of 0-10 where 0 is 'no pain' and 10 is the 'worst imaginable pain', please rate your WORST pain during the past 24 hours.

0 No pain	1	2	3	4	5	6	7	8	9	10 Worst imaginable pain

APPENDIX D: AMERICAN SOCIETY OF ANESTHESIOLOGISTS PHYSICAL STATUS CLASSIFICATION SYSTEM

Classification	Description
I	Normal healthy patient.
II	Patient with mild systemic disease; no functional limitation (eg, smoker with well controlled hypertension).
III	Patient with severe systemic disease; definite functional impairment (eg, diabetes and angina with relatively stable disease, but requiring therapy).
IV	Patient with severe systemic disease that is constant threat to life (eg, diabetes and angina and congestive heart failure; patients with dyspnea on mild exertion and chest pain).
V	Unstable moribund patient who is not expected to survive 24 hours with or without operation.
VI	Brain dead patient whose organs are removed for donation to another.
E	Emergency operation of any type, which is added to any of the above six categories, an in ASA II E.