REC-17-024

A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Evaluation of the Safety and Efficacy of Preoperative N1539 In Colorectal Surgery

NCT03323385

Study Protocol – Amendment 002

16 November 2017

CLINICAL STUDY PROTOCOL

Compound Name:	N1539 (Injectable NanoCrystal® Colloidal Dispersion (NCD) Meloxicam)
Protocol Number:	REC-17-024 Amendment 002
Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Evaluation of the Safety and Efficacy of Preoperative N1539 In Colorectal Surgery
Date of Original Protocol:	01 June 2017
Date of Amendment 001:	30 August 2017
Date of Amendment 002:	16 November 2017
Study Designated Physician	Stewart McCallum, MD 490 Lapp Rd Malvern, PA 19355 Mobile: Fax: 484-395-2471 Email: smccallum@recropharma.com
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INVESTIGATOR'S AGREEMENT

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

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

_____ _____

Principal Investigator's Signature **Date**

_____

Principal Investigator's Name (Print)

_____

Principal Investigator's Title (Print)

Site Address: _____

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Name of Sponsor/Company: Recro Pharma, Inc.	**Protocol Number:** REC-17-024
Name of Study Drugs: Injectable NanoCrystal Colloidal Dispersion (NCD) Meloxicam (N1539)	**Protocol Title:** A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Evaluation of the Safety and Efficacy of Preoperative N1539 In Colorectal Surgery
Name of Active Ingredient: Meloxicam	**Phase of Development:** 3b

Objective: The primary objective of this study is to evaluate the safety and tolerability of preoperative dosing of N1539 30 mg in subjects undergoing colorectal surgery, including clinical laboratory tests, wound healing evaluation, incidence of anastomotic leaks, and incidence of Adverse Events (AEs) and Serious AEs (SAEs).

Additional objectives include:

- Evaluation of N1539 treatment impact on overall postoperative recovery course, including total opioid consumption, length of hospital stay, pain control, cost of hospital stay, return of bowel function, mobilization, and satisfaction with pain medication.

Methodology:

This is a Phase 3b, randomized, double-blind, placebo-controlled, multicenter study evaluating the safety and efficacy of preoperative dosing with N1539 30 mg in adult subjects undergoing open or laparoscopic colorectal surgery. The initial study cohort will enroll approximately 50 subjects randomized (1:1) to N1539 30 mg or placebo; additional study cohorts may be enrolled following review of initial study observations.

Adult subjects, age 18 to 80 years inclusive, scheduled to undergo colorectal surgery that is expected to result in inpatient hospitalization for at least 48-72 hours, will be screened for participation at up to 20 study sites in the United States. Screening will occur within 28 days before study drug administration. After signing the informed consent, medical history, physical examination, laboratory testing, 12-lead electrocardiogram (ECG), pregnancy testing, and vital sign measurements will be completed during the screening visit.

Study sites will follow an Enhanced Recovery After Surgery (ERAS) protocol pre-, peri-, and postoperatively (see Appendix C.1). On the day of surgery (DOS; Day 1), subjects will be evaluated to ensure they remain eligible for participation in the study. Subjects with confirmed eligibility will be stratified by incision type (open vs laparoscopic) and randomized to either N1539 30 mg or placebo treatment within 12 hours prior to surgery and will be administered the first dose of study drug approximately 30 minutes prior to the start of surgery (defined as time of first incision). The start time of first dose of study drug administration (Dose 1) will be used to schedule subsequent doses.

Following surgery (end of surgery defined as the time of last suture; referenced as Hour 0), subjects will receive a standardized care regimen per the specified ERAS protocol, including rescue analgesia, mobilization, and diet advancing guidelines (see Appendix C.1). Subjects will continue to receive study drug every 24-hours from Dose 1 so long as IV analgesia is clinically appropriate or until discharge, whichever comes first. Subjects will stay at the study center for at least 48-72 hours after surgery or so long as inpatient care is clinically appropriate. A final dose of study drug may be administered up to 4 hours early in subjects who are scheduled to be discharged. Subjects who do not receive a dose of study drug for > 28 hours following their previous dose of study drug should be considered off treatment, and should not receive further doses of study drug.

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Subjects may be discharged from the study center based on their clinical status, with safety assessments performed at the earlier of 1 day (24 hours) following their last study dose (LSD+1) or at the time of discharge. Subjects will be provided standard of care analgesic regimen for pain management after discharge from the study center.

All treated subjects will be followed through 30 days after discharge. All subjects will return to the study center to complete follow-up visit 1 (FUV-1) at 5-21 days post-discharge, with follow-up visit 2 (FUV-2) completed by telephone 30 days post-discharge.

Safety assessments will include monitoring of AEs, wound healing assessment, vital signs, and clinical laboratory tests.

Assessments of efficacy will include total opioid consumption, pain intensity according to an 11-point numeric pain rating scale (NPRS; 0 - 10) on first ambulation, time to first analgesic rescue, time to return of bowel function (including time to first flatus or bowel sounds, and first bowel movement), time to mobilization (including time to first assisted mobilization out of hospital bed and time to first independent mobilization out of hospital bed), patient global assessment of pain control, brief pain inventory, subject satisfaction, time to hospital discharge (including time to hospital discharge order written and time to actual hospital departure), incidence of nasogastric (NG) tube insertion, length of stay, incidence of hospital readmission post initial discharge, and total cost of hospitalization.

Number of subjects to be enrolled: The initial study cohort is planned to enroll approximately 50 subjects; 25 subjects to be randomized to placebo, and 25 subjects to be randomized to N1539 30 mg. Additional study cohorts may be enrolled following review of initial study observations.

Number of study sites: Up to 20 sites

Study country location: United States

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

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

1. Voluntarily provide written informed consent.
2. Be able to understand the study procedures, comply with all study procedures, and agree to participate in the study program.
3. Male or female 18 to 80 years of age, inclusive.
4. Be planned to undergo primary (no repeat procedures) open or laparoscopic colorectal surgery (laparoscopic expected to require a ≥ 5 cm incision) with bowel resection and/or anastomosis, and be expected to require IV analgesia, remain in an inpatient setting for at least 48-72 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.
6. Female subjects are eligible only if all of the following apply:
   - Not pregnant or planning/attempting to become pregnant during the study (female subjects of child bearing potential [FOCBP] must have a negative urine pregnancy test before surgery);
   - Not lactating;
   - Commits to the use of an acceptable form of birth control for the duration of the study through FUV-2; OR

     Be unable to become pregnant due to bilateral oophorectomy or tubal ligation, postmenopausal status (1-year post last menstrual period) or sterility of male partner while in a monogamous relationship; OR

     Be in a monogamous relationship with a same sex partner with no intention of becoming pregnant through any means.
7. Have a body mass index <40 kg/m^2.
8. For oncology cases, all of the following criteria must be met:
   - Have a histologically confirmed diagnosis of colorectal cancer with a primary solid tumor confined to the primary organ, without evidence of local, regional, or distal spread;
   - Have a performance status such that they can carry on normal activities of daily life without limitations.

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

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

1. Have a known allergy or hypersensitivity to eggs, meloxicam, aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs), or any excipient of N1539 or placebo.
2. Planned surgical procedure from incision to closure is expected to be longer than 10 hours.
3. Planned surgical procedure includes a resection beyond the peritoneal reflection, is related to an acute bout of diverticulitis, or is associated with an emergency procedure.
4. Have a history of myocardial infarction within the preceding 12 months.
5. Have, as determined by the investigator or the sponsor's medical monitor, a history or clinical manifestations of significant renal (GFR<60 mL/min/1.73 m^2), hepatic, cardiovascular, metabolic, neurologic, psychiatric, respiratory, or other condition that would preclude participation.
6. Have a clinically significant abnormal clinical laboratory tests value according to the judgment of the investigator.
7. Have active or recent (within 6 months) gastrointestinal ulceration or bleeding, with exception of events related to an ulcerative colitis diagnosis.
8. Have a known bleeding disorder which may be worsened with the administration of an NSAID.
9. Have evidence of a clinically significant 12 lead ECG abnormality per the judgment of the investigator.
10. Have a recent history of alcohol or prescription/illicit drug abuse.
11. Have received chronic opioid therapy (daily use of opioids for 30 days or longer) or > 5 days with opioid use, within 30 days prior to screening

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

Criteria for exclusion (continued)

12. 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 prior medication (or, if half-life is not known, within 48 hours) before dosing with study medication, with exception of medications utilized for surgical preparation
13. Be unable to discontinue herbal medications/supplements associated with an increased bleeding risk at least 7 days prior to surgery through LSD+1/discharge, including but not limited to: gingko biloba, garlic, ginger, ginseng, hawthorn, fish oil (omega-3-fatty acid), dong quai, feverfew, vitamin E.
14. Be receiving lithium or a combination of furosemide with either an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker
15. Be currently receiving treatment with oral meloxicam (Mobic®) or another NSAID within 48 hours prior to surgery**.**
16. Have received any investigational product within 30 days before dosing with study medication.
17. Have previously received N1539/IV meloxicam
18. Have undergone major surgery in the last 3 months that could interfere with study assessments.
19. Have undergone or be expected to undergo radiation therapy, chemotherapy, or other biological therapy for cancer treatment, within 60 days prior to screening through FUV-2.

Investigational product: N1539 30 mg

Reference therapy: Placebo

Duration of treatment: Each subject is expected to receive at least two doses of study drug during the treatment phase of the study, with the first dose (Dose 1) administered approximately 30 minutes prior to surgery start and additional doses administered every 24±1 hours from Dose 1 until discharge or until IV analgesia is no longer clinically appropriate, whichever comes first. A final dose of study drug may be administered up to 4 hours early in subjects who are scheduled to be discharged. Subjects who do not receive a dose of study drug for > 28 hours following their previous dose of study drug should be considered off treatment, and not receive further study dosing. Subjects will be asked to return for FUV-1 to complete end of study assessments, with a safety follow-up by phone at FUV-2.

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Criteria For Evaluation

Safety:

The safety endpoints will include the following:

1. Incidence of treatment-emergent AEs and SAEs (including AEs of interest and opioid related AEs)
2. Incidence of anastomotic leaks
3. Change from baseline in laboratory tests; incidence of abnormal clinical laboratory tests
4. Change from baseline in vital signs
5. Assessment of surgical wound healing

Efficacy: The efficacy endpoints will be:

1. Total opioid consumption.
2. Time to hospital discharge order written
3. Pain intensity on first ambulation
4. Time to actual hospital departure
5. Time to first rescue analgesia use
6. Time to return of bowel function, including time to first bowel sound or first flatus, and time to first bowel movement
7. Time to mobilization, including time to first assisted mobilization out of hospital bed and first independent mobilization out of hospital bed
8. Patient Global Assessment (PGA) of pain control
9. Brief Pain Inventory
10. Subject assessment of satisfaction with pain medication
11. Hospital length of stay (LOS)
12. Incidence of postoperative NG tube insertion
13. Incidence of hospital readmission
14. Total cost of hospitalization

Exploratory endpoints include:

1. Change in inflammatory markers

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Statistical methods:

Sample size determination: The initial sample size of 50 subjects was selected empirically without a formal power calculation.

An unblinded data review will be performed after approximately 40-50 subjects are enrolled and have completed study assessments through initial hospital discharge. An independent statistician will perform the analysis. Details will be discussed in the analysis plan to be prepared for this study.

Following enrollment and review of this initial cohort, if study data warrant, additional subject cohorts may be enrolled to further evaluate safety in this setting, or may explore other endpoints.

Study populations:

Intent-to-Treat (ITT) Analysis Set: The ITT set will include all eligible subjects who were randomized. The ITT subjects may or may not receive randomized treatment and may or may not have the scheduled surgery.

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

Efficacy Analysis Set: The efficacy analysis set will include all subjects in the safety analysis set who underwent the scheduled surgery and had NG tube removed prior to Hour 24.

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 for by treatment group. Changes in vital signs and clinical laboratory tests at each post dosing time point will be summarized by treatment group using descriptive statistics without formal statistical tests. The number and proportion of subjects with abnormal wound healing observations will be summarized at each time point by treatment group.

Efficacy analysis: Efficacy parameters will be summarized for each study treatment. Difference between the groups will be evaluated using analysis of covariance (ANCOVA) models that include main effect of treatment and investigational sites for all continuous variables; Cox proportional hazards analysis will be used to evaluate treatment effect in time to event parameters; and the Cochran-Mantel-Haenszel analysis controlling for investigational sites will be used to assess the differences in groups for the categorical parameters.

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ARTICLE I. CONTENTS

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ANCOVA	Analysis of covariance
BMI	body mass index
BP	Blood Pressure
BPI	Brief Pain Inventory
BPM	Beats per minute
CFR	(United States) Code of Federal Regulations
ºC	degrees Centigrade
CL	Clearance
CMH	Cochran-Mantel-Haenszel
eCRF	Electronic case report form
CRP	C-reactive protein
DBP	Diastolic Blood Pressure
DOS	Day of surgery
Dose 1	Start time of first dose of study drug injection
ECG	Electrocardiogram
ERAS	Enhanced recovery after surgery
FOCBP	Female of Childbearing Potential
FUV-1	Follow-up visit 1
FUV-2	Follow-up visit 2
GCP	Good Clinical Practice
H	Hour
HCl	Hydrochloride
Hour 0	Time of end of surgery (i.e., time of last suture)
HR	Heart Rate
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IP	Investigational Product
ITT	Intend-to-treat
IV	Intravenous
Kg	Kilogram

Abbreviation	Definition
L	Liter
LSD	Last study dose
m^2	square meters
Mg	Milligram
Min	Minute
mITT	Modified intend-to-treat
mL	Milliliter
mm Hg	millimeters of mercury
N1539	Injectable NanoCrystal® Colloidal Dispersion (NCD) Meloxicam
NCD	NanoCrystal Colloidal Dispersion
NF	National Formulary
NG	Nasogastric
NPRS	Numeric Pain Rating Scale
NSAID	Nonsteroidal anti-inflammatory drug
OOB	Out of bed
PGA	Patient Global Assessment
pH	negative log of hydrogen ion concentration
PI	Pain Intensity
PID	Pain Intensity Difference
PK	Pharmacokinetic
POD (PODx)	Postoperative Day (Postoperative day x)
PRN	As needed
Q1H	Every hour
Q4H	Every 4 hours
Q8H	Every 8 hours
Q24H	Every 24 hours
SAR	suspected adverse reaction
SAE	serious adverse event
SBP	Systolic Blood Pressure
SpO2	peripheral oxygen saturation
SSAR	Serious suspected adverse reaction
SUSAR	Serious unexpected suspected adverse reaction
UDS	Urine Drug Screen

Abbreviation	Definition
µL	Microliter
ULN	Upper limit of normal
US	United States
USP	*United States Pharmacopeia*
VD	Volume of distribution
WBC	white blood cell

1. INTRODUCTION

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

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

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

Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) of the enolic acid class that possesses anti-inflammatory, analgesic, and antipyretic activities, which are believed to be related to the inhibition of cyclooxygenase (COX) and subsequent reduction in prostaglandin biosynthesis (Turck, 1997; Del Tacca, 2002; Mobic 2016).

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

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

Prior evaluations of N1539 have included postoperative dosing, before and after the onset of pain symptoms. While administration of N1539 postoperatively has been well tolerated with a favorable safety and efficacy profile. It is unknown whether any differences in surgical outcome or hospitalization course may be evident following preoperative dosing, where the use of N1539 could further reduce the requirement for opioid analgesia. This study is designed to evaluate the safety and efficacy of preoperative dosing with N1539 in subjects undergoing open or laparoscopic colorectal surgery, prior to expanding into larger subject enrollment.

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

2. STUDY OBJECTIVE

The primary objective of this study is to evaluate the safety and tolerability of preoperative dosing of N1539 30 mg in subjects undergoing colorectal surgery, including clinical laboratory tests, wound healing evaluation, incidence of anastomotic leaks, and incidence of Adverse Events (AEs) and Serious AEs (SAEs).

Additional objectives include:

- Evaluation of N1539 treatment impact on overall postoperative recovery course, including total opioid consumption, length of hospital stay, pain control, cost of hospital stay, return of bowel function, mobilization, and satisfaction with pain medication.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a Phase 3b, randomized, double-blind, placebo-controlled, multicenter study evaluating the safety and efficacy of preoperative dosing with N1539 30 mg in adult subjects undergoing open or laparoscopic colorectal surgery. The initial study cohort will enroll approximately 50 subjects randomized (1:1) to N1539 30 mg or placebo; additional study cohorts may be enrolled following review of initial study observations.

Adult subjects, age 18 to 80 years inclusive, scheduled to undergo colorectal surgery that is expected to result in inpatient hospitalization for at least 48-72 hours, will be screened for participation at up to 20 study sites in the United States. Screening will occur within 28 days before study drug administration. After signing the informed consent, medical history, physical examination, laboratory testing, 12-lead electrocardiogram (ECG), pregnancy testing, and vital sign measurements will be completed during the screening visit.

Study sites will follow an Enhanced Recovery After Surgery (ERAS) protocol pre-, peri-, and postoperatively (see Appendix C.1). On the day of surgery (DOS; Day 1), subjects will be evaluated to ensure they remain eligible for participation in the study. Subjects with confirmed eligibility will be stratified by incision type (open vs laparoscopic) and randomized to either N1539 30 mg or placebo treatment within 12 hours prior to surgery and will be administered the first dose of study drug approximately 30 minutes prior to the start of surgery (defined as time of first incision). The start time of first dose of study drug administration (Dose 1) will be used to schedule subsequent doses.

Following surgery (end of surgery defined as the time of last suture; referenced as Hour 0), subjects will receive a standardized care regimen per the specified ERAS protocol, including rescue analgesia, mobilization, and diet advancing guidelines (see Appendix C.1). Subjects will continue to receive study drug every 24-hours from Dose 1 so long as IV analgesia is clinically appropriate or until discharge, whichever comes first. Subjects will stay at the study center for at least 48-72 hours after surgery or so long as inpatient care is clinically appropriate. A final dose of study drug may be administered up to 4 hours early in subjects who are scheduled to be discharged. Subjects who do not receive a dose of study drug for > 28 hours following their previous dose of study drug should be considered off treatment, and should not receive further doses of study drug.

Subjects may be discharged from the study center based on their clinical status, with safety assessments performed at the earlier of 1 day (24 hours) following their last study dose (LSD+1) or at the time of discharge. Subjects will be provided standard of care analgesic regimen for pain management after discharge from the study center.

All treated subjects will be followed through 30 days after discharge. All subjects will return to the study center to complete follow-up visit 1 (FUV-1) at 5-21 days post-discharge, with follow-up visit 2 (FUV-2) completed by telephone 30 days post-discharge.

Safety assessments will include monitoring of AEs, wound healing assessment, vital signs, and clinical laboratory tests.

Assessments of efficacy will include total opioid consumption, pain intensity according to an 11-point numeric pain rating scale (NPRS; 0 - 10) on first ambulation, time to first analgesic rescue, time to return of bowel function (including time to first flatus or bowel sounds, and first bowel movement), time to mobilization (including time to first assisted mobilization out of hospital bed and time to first independent mobilization out of hospital bed), patient global assessment of pain control, brief pain inventory, subject satisfaction, time to hospital discharge (including time to hospital discharge order written and time to actual hospital departure), incidence of nasogastric (NG) tube insertion, length of stay, incidence of hospital readmission post initial discharge, and total cost of hospitalization.

3.2. Rationale for Study Design and Control Groups

This study will evaluate the safety and efficacy of repeated dosing with N1539 with the first dose of N1539 administered prior to colorectal surgery. Previous research has demonstrated the safety and efficacy of single and repeated doses of N1539 administered after surgery in a range of postoperative populations, including open hysterectomy, bunionectomy, and abdominoplasty, along with a range of major surgeries including orthopedic and abdominal surgeries.

This study will further explore the safety and efficacy of N1539 when administered preoperatively on a once daily schedule, in a population of subjects undergoing colorectal surgery. Preoperative dosing is anticipated to reduce the need for postoperative opioid analgesics, thereby improving the postoperative recovery course as evidenced by length of stay, return of bowel function, and pain control satisfaction. However, it is unknown whether preoperative dosing may have other consequences on the safety of treated subjects. The inclusion of a placebo control group will support the comparison of safety results observed in N1539 treated subjects.

As the first preoperative evaluation of N1539, this study will initially enroll a limited cohort of approximately 50 subjects. Following review of observations in the initial cohort, additional cohorts may be enrolled in this study to further evaluate the safety of N1539 in this setting, or to evaluate other endpoints. Appropriate IRB approval will be obtained before enrolling additional cohorts in this study beyond the proposed initial cohort.

4. STUDY POPULATION

4.1. Inclusion Criteria

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

1. Voluntarily provide written informed consent.
2. Be able to understand the study procedures, comply with all study procedures, and agree to participate in the study program.
3. Male or female 18 to 80 years of age, inclusive.
4. Be planned to undergo primary (no repeat procedures) open or laparoscopic colorectal surgery (laparoscopic expected to require a ≥ 5 cm incision) with bowel resection and/or anastomosis, and be expected to require IV analgesia, remain in an inpatient setting for at least 48-72 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.
6. Female subjects are eligible only if all of the following apply:
    - Not pregnant or planning/attempting to become pregnant during the study (female subjects of child bearing potential [FOCBP] must have a negative urine pregnancy test before surgery);
    - Not lactating;
    - Commits to the use of an acceptable form of birth control for the duration of the study through FUV-2; OR

      Be unable to become pregnant due to bilateral oophorectomy or tubal ligation, postmenopausal status (1-year post last menstrual period), or sterility of male partner while in a monogamous relationship; OR

      Be in a monogamous relationship with a same sex partner with no intention of becoming pregnant through any means.
7. Have a body mass index <40 kg/m^2.
8. For oncology cases, all of the following criteria must be met:
    - Have a histologically confirmed diagnosis of colorectal cancer with a primary solid tumor confined to the primary organ, without evidence of local, regional, or distal spread;
    - Have a performance status such that they can carry on normal activities of daily life without limitations.

4.2. Exclusion Criteria

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

1. Have a known allergy or hypersensitivity to eggs, meloxicam, aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs), or any excipient of N1539 or placebo.
2. Planned surgical procedure from incision to closure is expected to be longer than 10 hours.
3. Planned surgical procedure includes a resection beyond the peritoneal reflection, is related to an acute bout of diverticulitis, or is associated with an emergency procedure.
4. Have a history of myocardial infarction within the preceding 12 months.
5. Have, as determined by the investigator or the sponsor's medical monitor, a history or clinical manifestations of significant renal (GFR<60 mL/min/1.73 m^2), hepatic, cardiovascular, metabolic, neurologic, psychiatric, respiratory, or other condition that would preclude participation.
6. Have a clinically significant abnormal clinical laboratory tests value according to the judgment of the investigator.
7. Have active or recent (within 6 months) gastrointestinal ulceration or bleeding, with exception of events related to an ulcerative colitis diagnosis.
8. Have a known bleeding disorder which may be worsened with the administration of an NSAID.
9. Have evidence of a clinically significant 12 lead ECG abnormality per the judgment of the investigator.
10. Have a recent history of alcohol or prescription/illicit drug abuse.
11. Have received chronic opioid therapy (daily use of opioids for 30 days or longer) or > 5 days with opioid use, within 30 days prior to screening.
12. 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 prior medication (or, if half-life is not known, within 48 hours) before dosing with study medication, with exception of medications utilized for surgical preparation.
13. Be unable to discontinue herbal medications/supplements associated with an increased bleeding risk at least 7 days prior to surgery through LSD+1/discharge, including but not limited to: gingko biloba, garlic, ginger, ginseng, hawthorn, fish oil (omega-3-fatty acid), dong quai, feverfew, vitamin E.
14. Be receiving lithium or a combination of furosemide with either an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker.
15. Be currently receiving treatment with oral meloxicam (Mobic®) or another NSAID within 48 hours prior to surgery.
16. Have received any investigational product within 30 days before dosing with study medication.
17. Have previously received N1539/IV meloxicam.
18. Have undergone major surgery in the last 3 months that could interfere with study assessments.

19. Have undergone or be expected to undergo radiation therapy, chemotherapy, or other biological therapy for cancer treatment, within 60 days prior to screening through FUV-2.

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 withdraw consent to continue treatment should be encouraged to complete the discharge assessments prior to leaving the study center. Subjects will be encouraged to return for FUV-1 and to agree to be followed through FUV-2. The date the subject is withdrawn and the primary reason for discontinuation will be recorded in the subject's electronic case report form (eCRF).

4.3.2. Replacement of Subjects

Discontinued subjects will not be replaced in the study. However, the study will enroll an adequate number of subjects to meet the target size of 50 subjects in the safety population for evaluation.

4.4. Lifestyle Guidelines

4.4.1. Confinement

Prior to the surgical procedure (Day 1), subjects will arrive at the study site in sufficient time to prepare for the procedure and confirm eligibility to participate in the study. Prior to the surgical procedure, qualifying subjects will be stratified and randomized and should receive the first dose of study drug approximately 30 minutes prior to surgery. Subjects may continue to receive study drug every 24 hours so long as IV analgesia is clinically appropriate or until time of discharge, whichever comes first. Subjects may be discharged from the study center when appropriate based on clinical status.

Subjects will follow a standardized postoperative care regimen during their hospitalization as defined in the study ERAS (Appendix C.1)

4.4.2. Diet

Subjects will be diet restricted before and after surgery as defined in the study ERAS (Appendix C.1).

5. TREATMENTS

5.1. Surgical Procedure and Perioperative Care

On Day 1, day of surgery, subjects will undergo colorectal surgery. Disallowed surgical procedures for inclusion in this study include repeat procedures or re-resections, resections beyond the peritoneal reflection, surgeries associated with acute bouts of diverticulitis, and surgeries associated with an emergency procedure.

Surgeries should be completed using an appropriate anesthesia and analgesic regimen per the clinical practice of the surgeon within the guidelines of the study ERAS (Appendix C.1). Disallowed medications are described in Section 5.12.

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

Time of surgery start (time of first incision) and end of surgery (time of last suture; Hour 0) will be captured in the eCRF.

5.2. Administration of Study Medication

Appropriately qualified study personnel will prepare all doses of study drug according to the treatment schedule, for administration in this study. Additional details on study dose preparation and administration will be provided in the study specific pharmacy manual.

All doses of study drug will be administered as an IV bolus over approximately 15 seconds. Start time of IV push should be recorded in the subject's eCRF.

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) approximately 30 minutes prior to the start of surgery. Additional doses of study drug will be administered every 24±1 hours from Dose 1 until discharge or until IV 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.

5.3. Identity of Study Medication

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

Placebo will 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. A block randomization will be generated stratified by center and planned incision type (open vs.

laparoscopic). 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

Doses of N1539 have been selected following review of safety, efficacy and pharmacokinetic data from 11 previous clinical studies. Clinical studies have evaluated doses of N1539 ranging from 5 to 180 mg. Findings in the Phase 2 program for N1539 supported the use of a 30 mg dose administered via IV push once daily (every 24 hours). These findings were verified in two well controlled Phase 3 studies of N1539 30 mg administered to subjects with moderate to severe pain following bunionectomy and abdominoplasty surgeries. Both studies demonstrated a significant effect of N1539 30 mg for pain reduction compared with placebo. The safety of N1539 30 mg has been further evaluated in a 721 subject, placebo controlled postoperative safety study where dosing with N1539 30 mg was observed to have a similar safety profile with placebo.

The current study has been planned to evaluate the safety and efficacy of preoperative dosing with N1539 30 mg in a repeated dose setting compared with placebo.

5.6. Selection of Timing of Dose

Randomized subjects will be administered doses of study drug every 24 hours. This interval has been demonstrated to maintain analgesia throughout the dosing interval in a range of Phase 2 and 3 clinical studies. The 24-hour dosing interval has been selected based on the pain relief and pharmacokinetic profile of N1539 established in previous clinical studies. Administration of the first dose of study drug prior to the surgical procedure will be evaluated to determine its effect on postoperative outcomes. The start time each dose is administered will be recorded in the subject's eCRF.

5.7. Blinding and Unblinding of Study Medications

All doses of study drug will be prepared by an appropriately qualified member(s) of the healthcare team at the research center, for administration 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 medication he or she received. Unless the subject is at immediate risk, the investigator must make diligent attempts to contact the sponsor before unblinding the subject's data.

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

5.8. Treatment Compliance

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

5.9. Drug Accountability

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

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

5.10. Packaging, Labeling, and Storage

Study medication will be provided in 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 medication will be provided as pharmacy instructions prior to initiation of the study.

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

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

5.11. Prior and Concomitant Medications

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

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

5.12. Prohibited Medications

The following medications or drug classes **will be prohibited** during the study:

- Any NSAIDs other than study drug (ketorolac, ibuprofen, diclofenac, etc.) are prohibited from 48 hours prior to surgery through LSD+1
- Non-opioid analgesics (other than ERAS specific post procedure acetaminophen) are prohibited from the end of surgery through LSD+1. (see Appendix C.1)
- Alvimopan
- Short or long acting local anesthetic agents infiltrated into the incision or port sites.
- Other analgesic agents not expressly permitted in the ERAS protocol (see Appendix C.1).

5.13. Concomitant Interventions and Procedures

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

5.14. Rescue Medication

During the study, inpatient and following discharge, pain symptoms that are not adequately controlled by dosing with study drug, may be treated with IV and PO opioids according to the standardized regimen defined in the study ERAS (Appendix C.1).

6. STUDY PROCEDURES

The timing of study procedures are to be performed relative to Hour 0, end of surgery, defined as completion of surgical closure.

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

6.1. Demographic and Efficacy Assessment

6.1.1. Demographics

Demographics information will be collected during screening visit including age, sex, ethnicity, race, weight, height, and BMI.

6.1.2. Medical History

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

6.1.3. Physical Examination

The investigator or designee will perform a physical examination (HEENT, cardiovascular, respiratory, gastrointestinal, neurological, dermatologic, and musculoskeletal systems) during the screening visit, at check-in on Day 1, and at LSD+1. Physical examination results collected within 7 days prior to the screening visit may be utilized to evaluate subject eligibility at screening. Body weight and height will be measured, and BMI will be calculated during the screening visit only.

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

6.1.4. Surgical Information

Information on the surgical procedure, including time of start and end of surgery, time into and out of recovery room, planned and actual incision type (open, laparoscopic, or laparoscopic converted to open), incision length, and any surgical complications will be recorded in the subject eCRF. Surgery procedures will be grouped into surgery types for the purpose of analysis.

6.1.5. Concomitant Medications and Opioid Use

All medications utilized during the study will be captured as concomitant medications. Opioid analgesics used from Hour 0 to discharge will be the primary efficacy endpoint and the dose of each opioid medication will be converted into their IV morphine equivalent dose (IVMED) for the total opioid consumption analysis. Hence, each opioid medication used from Hour 0 to discharge will be captured separately in the eCRF.

Following discharge, subjects will be questioned regarding continued use of opioid analgesics during the FUV-1 and FUV-2 visits.

6.1.6. Pain Intensity (PI) on Ambulation

PI will be assessed by the study subject for their current pain according to an 11-point numeric pain rating scale (NPRS; 0 - 10) where 0 equates to no pain, and 10 equates to the worst pain imaginable, as described in Appendix C.2.

PI will be assessed within 15 minutes prior to first ambulation. Subjects will also utilize the NPRS to assess their worst pain intensity experienced during their first ambulation.

6.1.7. Cost of Hospitalization

Cost of hospitalization will be determined using UB-04 and/or similar hospital claim forms used for billing purposes. Cost of hospitalization will be determined from the billing codes and/or procedure codes for all hospital care from the time of hospital admission until discharge.

When available, hospital costs resulting from hospital readmissions during the follow-up period should be collected.

6.1.8. Time to Events

Following surgery, subjects will be questioned regarding the occurrence of first flatus and bowel movements, and study staff will be asked to document the first observed bowel sounds. The times that these events first occur following the end of surgery (Hour 0) will be recorded.

Time to rescue analgesia use will be determined from the first recorded time of opioid analgesic use in the subject's medical record, beginning after surgery.

Times to event pertaining to hospital discharge will include time that hospital discharge order was written or when discharge readiness was recorded in the subject chart, and actual departure time of hospital.

Mobilization will be attempted per the postoperative schedule defined in the ERAS (Appendix C.1:). Study staff will be asked to document the time of first successful postoperative mobilizations in the subject eCRF, including first assisted mobilization out of hospital bed, and first independent mobilization out of hospital bed.

6.1.9. Patient Global Assessment (PGA) of Pain Control

Subjects will be asked to evaluate their pain control during the preceding period according to the following scale: 0-poor, 1-fair, 2-good, 3-very good, or 4-excellent" (See Appendix C.3).

The PGA of pain control will be completed at Hour 24 (± 2 hours) from Hour 0, every 24 hours (± 2 hours) thereafter until LSD+1 (Hour 48, Hour 72, etc.), and at LSD+1 (± 2 hours).

6.1.10. Brief Pain Inventory

The Brief Pain Inventory (BPI; short form; Appendix C.5) will be completed by all subjects to evaluate their pain control and functioning.

The BPI assessment will be completed at screening, Hour 24 (± 2 hours) from Hour 0, every 24 hours thereafter (± 2 hours) until LSD+1, and at LSD+1 (± 2 hours).

6.1.11. Subject Satisfaction with Postoperative Pain Medication

Subjects will report their satisfaction with the medication they received to manage their postoperative pain according to a 7-point Likert scale including categories of: completely dissatisfied (1), mostly dissatisfied (2), somewhat dissatisfied (3), neither satisfied to dissatisfied (4), somewhat satisfied (5), mostly satisfied 6), and completely satisfied (7) (see Appendix C.4).

The subject assessment of satisfaction will be assessed at LSD+1.

6.1.12. Postoperative NG Tube Insertion

All NG tubes inserted pre- or perioperatively should be removed at or before Hour 24. Any NG tube inserted postoperatively will be recorded in the eCRF, along with time of insertion where appropriate.

6.1.13. Hospital Readmission

Following discharge, subjects will be asked to report any hospital readmissions to the study staff. Subjects will be questioned regarding any hospital readmissions during FUV-2.

6.2. Safety Assessments Description

6.2.1. Clinical Laboratory Tests

During the screening visit, on Day 1 during check-in, and at LSD+1, subjects will have blood and urine samples collected for routine clinical laboratory testing. Screening laboratory tests 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. Laboratory tests on Day 1 and at LSD+1 should be performed at the central laboratory. Laboratory tests to be performed include:

- hematology: platelet count, hemoglobin, and hematocrit
- clinical chemistry tests: urea, glucose, creatinine, sodium, potassium, chloride, bicarbonate, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, direct bilirubin, and gamma-glutamyltransferase
- coagulation tests: prothrombin time, activated partial thromboplastin time, international normalized ratio

Additional urine samples will be collected and tested as follows:

- urine pregnancy testing at check-in on Day 1 for FOCBP.

Additional blood samples will be collected from a cohort of subjects for exploratory analysis of inflammatory markers; participation in this cohort will be optional. Blood samples will be collected at check-in prior to surgery on Day 1, and once daily thereafter (POD1, POD2, etc.; may be collected at any time on the stated POD) until LSD+1, for analysis of inflammatory markers including, but not limited to: c-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), interleukin (IL) 1B, IL-4, IL-6, IL-8, IL-10, and IL-18.

Screening laboratory results, and Day 1 urine pregnancy results, will be used for assessing eligibility for randomization.

6.2.2. Vital Sign Measurements

Resting vital signs will include blood pressure, pulse, and peripheral oxygen saturation (SpO2), should be collected at the screening visit, at check-in prior to surgery on Day 1, and at LSD+1. Resting tests must be obtained after resting (seated/supine) for ≥ 5 minutes. Historic vital signs results collected within 7 days prior to the screening visit may be utilized for subject eligibility evaluation at screening visit.

Additional vital signs may be collected during the study according to standard practice and clinical status. Any clinically significant changes in vital signs after study drug treatment should be captured as AEs at the discretion of the investigator.

6.2.3. 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.

6.2.4. Wound Evaluation

Surgical wound healing will be evaluated by the investigator at time of discharge and at FUV-1 to determine whether healing is following a normal course in the opinion of the investigator. The investigator will evaluate the healing of the wound using an 11-point scale (0-10) where a score of 0 is “Completely unsatisfied”, and a score of 10 is “Completely satisfied”.

6.2.5. Anastomotic Leaks

Following the end of surgery, subjects will be monitored for any occurrence of anastomotic leaks. Any incidence of anastomotic leaks will be reported in the eCRF.

6.3. Assessments by Visit

6.3.1. Screening Visit

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

- Review of inclusion/exclusion criteria eligibility (Section 4.1 and Section 4.2)
- Demographics and medical history (Section 6.1.1 and Section 6.1.2)
- Physical examination including height, weight and BMI (may utilize historical results collected within 7 days prior to screening visit; Section 6.1.3)
- Measurement of resting vital signs (may utilize historical results collected within 7 days prior to screening visit; Section 6.2.2)
- 12-lead ECG (may utilize historical results collected within 7 days prior to screening visit; Section 6.2.3)
- Clinical laboratory tests (may utilize historical results collected within 7 days prior to screening visit; Section 6.2.1)
- Brief Pain Inventory (Section 6.1.10)

6.3.2. Day 1 - Check-In

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

- Medical history update (Section 6.1.2)
- Physical examination (Section 6.1.3)
- Clinical laboratory tests (Section 6.2.1)
- Urine pregnancy test (FOCBP only; Section 6.2.1)
- Inflammatory marker sample collection (Section 6.2.1)
- Measurement of resting vital signs (Section 6.2.2)

Subjects who continue to meet eligibility criteria will be randomized and undergo surgery per Section 5.1.

6.3.3. Day 1 - Randomization and Surgery

The following assessments will be conducted on Day 1 prior to surgery:

- Randomization to treatment within 12 hours prior to surgery (Section 5.4)
- Study drug administration per randomization assignment approximately 30 minutes prior to start of surgery (Section 5.2)

- Undergo surgery per Section 5.1.

6.3.4. Inpatient Treatment

The following assessments will be conducted during inpatient treatment from Hour 0, end of surgery (time of last suture), until LSD+1:

- Study drug administration per randomization; time of Dose 1 will be used to schedule subsequent doses (Section 5.2)
- PI assessment on first ambulation (Section 6.1.6)
- Monitoring of rescue analgesia usage (Section 6.1.5)
- Monitoring of bowel function (Section 6.1.8)
- Monitoring of mobilization (Section 6.1.8)
- PGA of pain control (collected Q24H until LSD+1 Section 6.1.9)
- Brief Pain Inventory (collected Q24H until LSD+1 Section 6.1.10)
- Monitoring of AEs (Section 7)
- Monitoring of all concomitant medications (Section 6.1.5)
- Inflammatory marker sample collection (once daily until LSD+1; Section 6.2.1)

6.3.5. LSD+1

The following assessments will be conducted for all subjects 24 hours (± 2 hours) following the last study dose (LSD+1); if a subject is ready for discharge less than 24 hours following the last study dose, LSD+1 procedures should be performed prior to discharge:

- Physical examination (Section 6.1.3)
- PGA of pain control (Section 6.1.9)
- Brief Pain Inventory (Section 6.1.10)
- Subject satisfaction with postoperative pain medication (Section 6.1.11)
- Clinical laboratory tests (Section 6.2.1)
- Measurement of resting vital signs (Section 6.2.2)
- Monitoring of AEs and concomitant medications (Section 7)

6.3.6. Discharge

The following assessments will be conducted for all subjects within 4 hours prior to discharge:

- Time hospital discharge order was written and time of actual departure from hospital (Section 6.1.8)
- Wound evaluation (Section 6.2.4)
- Monitoring of AEs and concomitant medications (Section 7)

6.3.7. Follow-Up Visit 1 (FUV-1)

The following procedures will be conducted for all subjects during FUV-1, conducted 5-21 days post-LSD.

- Wound evaluation (Section 6.2.4)
- Monitoring of AEs and concomitant medications (Section 7)

6.3.8. Follow-Up Visit 2 (FUV-2)

The following procedures will be conducted for all subjects during FUV-2, conducted by telephone contact 30±4 days post-LSD:

- Monitoring for hospital readmission (Section 6.1.13)
- Monitoring of AEs and concomitant medications (Section 7)

6.4. Appropriateness of Assessments

The efficacy measures utilized in this study are appropriate to support the objectives of the study. The timing of assessments is intended to evaluate efficacy throughout the dosing interval.

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

6.5. Clinical Stopping Rules

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

7. ADVERSE EVENTS 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

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 details. A separate SAP will also be prepared for the planned interim analysis for this study.

8.1. Determination of Sample Size

The initial sample size of 50 subjects was selected empirically without a formal power calculation.

An unblinded data review will be performed after approximately 40-50 subjects are enrolled and have completed study assessments through initial hospital discharge. An independent statistician will perform analysis. Details will be discussed in the analysis plan to be prepared for this study.

Following enrollment and review of this initial cohort, if study data warrant, additional cohorts may be enrolled to further evaluate safety in this setting, or may to explore other endpoints.

8.2. Study Endpoints

8.2.1. Safety Endpoints

The safety endpoints will include the following:

1. Incidence of treatment-emergent AEs and SAEs (including AEs of interest and opioid related AEs)
2. Incidence of anastomotic leaks
3. Change from baseline in laboratory tests; incidence of abnormal clinical laboratory tests
4. Change from baseline in vital signs
5. Assessment of surgical wound healing

8.2.2. Efficacy Endpoints

The efficacy endpoints will include:

1. Total opioid consumption
2. Time to hospital discharge order written
3. Pain intensity on first ambulation
4. Time to actual hospital departure
5. Time to first rescue analgesia use
6. Time to return of bowel function, including time to first bowel sounds or first flatus, and time to first bowel movement
7. Time to mobilization, including time to first assisted mobilization out of hospital bed and time to first independent mobilization out of hospital bed
8. PGA of pain control

9. Brief Pain Inventory
10. Subject assessment of satisfaction with pain medication
11. Hospital length of stay (LOS)
12. Incidence of postoperative NG tube insertion
13. Incidence of hospital readmission.
14. Total cost of hospitalization

Exploratory endpoints include:

1. Change in inflammatory markers

8.3. General Considerations for Statistical Analysis

8.3.1. Analysis Datasets

Intent-to-Treat (ITT) Analysis Set: The ITT set will include all eligible subjects who were randomized. The ITT subjects may or may not receive randomized treatment and may or may not have the scheduled surgery.

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

Efficacy analysis set will include all safety analysis set subjects who had the scheduled surgery. Subjects whose surgery was cancelled, whose surgery was changed will be excluded from the efficacy analysis, or who required NG tube use (placed perioperatively) beyond Hour 24. Efficacy analysis set will be the primary population for efficacy evaluation, but additional sensitivity analysis may be performed based on the ITT analysis set.

8.3.2. Test Hypothesis and *P* Value Justification

Each efficacy analysis will be performed to assess the differences between the 2 treatment groups; difference will be derived by 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 tests at the 0.05 level of significance.

Nominal p-value will be reported as is.

Details for study-wise Type 1 error control, including interim analyses, final co-primary efficacy endpoints analyses, and final secondary efficacy endpoints, will be discussed in the formal SAP.

8.3.3. Procedures for Handling Missing Data

Unless indicated otherwise (see Section 8.3.5), no imputation will be done for missing data. However, AEs with missing severity assessments will be tabulated as “severe,” and AEs with missing relationship assessments will be tabulated as “related” for the purpose of analysis; and the missing data will be presented in data listing as is.

8.3.4. Definitions for Assessment Windows

For the purpose of data analysis, *baseline* measures for a given parameter will be the last measurements taken before the subject receives the first dose of study medication. End of Study Visit will be the last follow-up (FUV-2) to be conducted 30 ± 4 days post-discharge.

8.3.5. Derived Variables

Detailed rules to be used to derive various efficacy parameters will be documented in the statistical analysis plan, including method to compute time to events and censoring rules for time to event endpoints, imputation of partial/incomplete time of analgesic medications start and/or stop times, and computing scores for BPI at domain and sub-dimension level.

8.4. Study Population Summaries

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

8.4.1. Disposition

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

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

8.4.2. Demographics and Surgical Characteristics

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

Surgery characteristics will include surgery information, such as surgery description and surgery duration (hr).

8.4.3. Protocol Deviations

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

8.4.4. Treatment Compliance

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

8.4.5. Prior and Concomitant Medications

All prior and concomitant medications will be tabulated for the overall study population. Prior and concomitant medications will be coded to the therapeutic drug classes and generic drug

names using the World Health Organization (WHO) Drug classifications version 1Q2017 or higher.

8.5. Efficacy Analysis

8.5.1. Total Opioid Consumption

All concomitant medications will be coded according to WHO Drug library. Opioid medications will be identified per ATC level 2 and level 3. The dose from each identified opioid record will then be converted to IV Morphine Equivalent Dose (IVMED) in mg; examples of IVMED of some commonly used analgesics are provided in Table 1.

All analgesic medications will be mapped to the following time periods based on the start date/time and stop date/time: Hour 0 to discharge, Hour 0-24, Hour 0-48, Hour 24-48, Hour 0-72, and Hour 48-72.

Total opioid consumptions in IVMED (mg) per subject will be determined for each interval. A summary table will be prepared to provide group descriptive statistics, including sample size, mean, standard deviation, minimum, median, and maximum. Difference between treatment groups will be evaluated using an ANCOVA model that will include main effect of treatment and investigational site. Nominal p-values will be reported as is.

Table 1: IV Morphine Equivalent Dose (mg) For Commonly Used Analgesics

Generic Opioid Name	1 Unit	Route	IV MED (mg)
Morphine	mg	IV	1
Morphine	mg	PO	0.333
Methadone	mg	IV	1
Methadone	mg	PO	0.333
Nalbuphine	mg	IV	1
Nalbuphine	mg	PO	0.333
Buprenorphine	mg	IV	25
Fentanyl	µg (mcg)	IV	0.1
Sufentanil	µg (mcg)	IV	1.00
Alfentanil	µg (mcg)	IV	0.02
Hydromorphone	mg	IV	6.67
Hydromorphone	mg	PO	1.3
Codeine	mg	PO	0.05
Meperidine	mg	PO	0.025
Pentazocine	mg	PO	0.1
Oxycodone	mg	PO	0.5
Hydrocodone	mg	PO	0.3

8.5.2. PI on First Ambulation

NPRS scores will be summarized by assessment time point. The difference between groups will be analyzed by ANCOVA model that include the main effect of treatment and investigational sites. Least-squares means (LSmeans) and standard error (SE) of the LSmeans will be calculated; difference in LSmeans between groups, corresponding 95% CI, and p-value from 2-sample t-test will be derived.

8.5.3. Time to Event Endpoints

There are 7 time to event endpoints to be reported in this study, all events will be calculated as the elapsed time relative to the recorded end of surgery (Hour 0):

1) Time to hospital discharge order written
2) Time to actual hospital discharge
3) Time to first dose of rescue analgesia
4) Time to first flatus or bowel sounds
5) Time to first bowel movement
6) Time to first assisted mobilization
7) Time to first independent mobilization

Time to event endpoints will be derived for each subject. Subjects without the event will be censored at time of last evaluation during inpatient treatment phase. Differences between the groups in time to event endpoints will be analyzed using the Cox proportional hazards analysis model that include the main effects of treatment and investigational sites; proportion of subjects censored will be presented and the time to event percentiles (25%, 50%, and 75% tiles) will be estimated. The data will be graphically display using a Kaplan-Meier (KM) survival curve by treatment group.

8.5.4. Length of Stay (LOS)

Length of stay will be defined as days from the date of admission to the date of actual hospital discharge. LOS will be tabulated with descriptive statistics by treatment groups and difference between the groups in the LOS will be evaluated using ANCOVA model that include main effect of treatment and investigational sites.

8.5.5. PGA of Pain Control

The number and percent of subjects in each global pain control category (0-poor, 1-fair, 2-good, 3-very good, or 4-excellent) will be tabulated by treatment group. The difference between the groups in global pain control will be evaluated based on proportion of subjects rating their pain control as good, very good, or excellent using the CMH test controlling for investigational site.

8.5.6. Brief Pain Inventory

Responses to each BPI parameter will be tabulated at each time point by treatment group, including score for each question (referred to as the item score), score for each domain (referred to as the domain score), and score for each subdomain (referred to as the sub-dimension score), change from baseline in item score, domain score, and sub-dimension score (Cleeland 2009). Differences between the treatment groups in domain score, sub-dimension score, and item score, as well as change from baseline in scores will be analyzed by ANCOVA model that includes treatment and investigational sites, and baseline score as a covariate.

8.5.7. Subject Satisfaction for Postoperative Pain Medication

Subjects will be categorized as dissatisfied (completely dissatisfied [1], mostly dissatisfied [2], or somewhat dissatisfied [3]), neither satisfied or dissatisfied (4), or satisfied (somewhat satisfied [5], mostly satisfied [6], or completely satisfied [7]) with postoperative pain medication. The number and percent of subjects in each category will be tabulated by treatment group. The difference between the groups in satisfaction with postoperative pain medication will be

evaluated based on proportion of subjects rating their satisfaction as dissatisfied (ratings of 1, 2, and 3), neither (rating 4), or satisfied (ratings of 5, 6, and 7) using the CMH test controlling for investigational site.

8.5.8. Incidence of Postoperative NG Tube Insertion

The proportion of subjects requiring postoperative NG tube insertion will be summarized by treatment group. Differences between the groups will be evaluated using CMH test controlling for investigational site or Fisher's exact test.

8.5.9. Incidence of Hospital Readmission

The incidence of all-cause hospital readmission will be reported during or prior to FUV-2. Hospital readmission will be summarized as the proportion of subjects with at least one readmission within the follow-up period by treatment group. If data permits causality of hospital readmission will also be examined. Differences between the groups will be examined using Fisher's exact test.

8.5.10. Cost of Hospitalization

Cost of hospitalization will be calculated using UB-04 and/or similar hospital claim forms used for billing purposes. Cost of hospitalization will be the cost of all hospital care from the charge of hospital admission until discharge. When available, hospital costs resulting from hospital readmissions during the follow-up period should be collected.

Cost of hospitalization will be summarized by treatment group for the primary admission, and for all related readmissions if data are available.

8.5.11. Exploratory Analysis: Inflammatory Markers

Inflammatory markers will be analyzed for each collected sample.

8.5.12. Subgroup Analyses for Efficacy

Subgroups to be analyzed for efficacy may include: race, gender, age, and surgery type. The analysis within a subgroup will follow the same analysis approach for the overall. The subgroup analysis will focus on the primary efficacy endpoint total opioid use from Hour 0 to discharge; subgroup analysis on secondary efficacy endpoint will be performed if data warrants. Potential covariates (such as incision type, surgery duration, and incision length) will be evaluated if data permits.

8.6. Safety and Tolerability Evaluations

8.6.1. Extent of Exposure

Evaluation of the extent of exposure for the treatment period will be assessed via number of doses taken prior to discharge. A summary of the number of subjects receiving increasing numbers of doses of study drug will be prepared.

8.6.2. 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.

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

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

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

8.6.3. Opioid Related AEs

A summary of opioid related AEs will be generated for events including, but not limited to: somnolence, respiratory depression, hypoventilation, hypoxia, dry mouth, nausea, vomiting, constipation, sedation, confusion, pruritus, urinary retention, and postoperative ileus.

A separate summary of opioid related SAEs may be generated if data warrant.

8.6.4. AEs of Interest

A summary of AEs of interest will be generated including: cardiovascular events, thrombotic events, bleeding-related events, renal events, hepatobiliary events, injection site related events, and wound healing related events.

A separate summary of SAEs of interest may be generated if data warrant.

8.6.5. Incidence of Anastomotic Leaks

The incidence of anastomotic leaks will be summarized by the proportion of subjects experiencing the event in each treatment group.

8.6.6. Clinical Laboratory Tests

Laboratory values will be collected at screening, Day 1 during check-in, and at LSD+1/discharge; locally performed screening laboratory results will not be included in the study database or summaries and listings. Observed values at each time point, and change from baseline will be summarized by treatment group without formal statistical testing

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

8.6.7. Vital Sign Measurements

Resting vital sign values will be summarized by treatment group without formal statistical testing. Incidence of clinically important changes from baseline will be identified and tabulated if data permits.

8.6.8. Wound Evaluation

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

8.6.9. Subgroup Analyses for Safety Endpoints

Subgroups to be analyzed for safety may include: race, gender, age, and surgery type. The subgroup analysis will focus on the incidence of adverse event; subgroup analysis on other safety endpoints will be performed if data warrants.

9. STUDY ADMINISTRATION

9.1. Regulatory and Ethical Considerations

9.1.1. Regulatory Authority Approval

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

9.1.2. Ethical Conduct of the Study and Ethics Approval

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

9.1.2.1. Ethics Committees

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

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. 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. The investigator must promptly forward to the sponsor copies of the IRB or IEC approval of the amended informed consent form or other information and the approved amended informed consent form or other information. IRB or IEC approval of the consent forms must be obtained in addition to the approval given for the clinical study. Regulatory review and approval may be required in some countries before IRB or IEC approval can be sought.

9.1.2.2. General Considerations

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

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

Recro Pharma, Inc. is the sponsor of study REC-17-024. The sponsor is responsible for all of the following:

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

9.1.3. Informed Consent

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

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

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

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

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

If a subject (or legally authorized representative) cannot read, a short form approved by the IRB or IEC may be used. Only the short form itself is to be signed by the subject or the

representative. However, the witness shall sign both the short form and a copy of the summary, and the person obtaining the consent shall sign the copy of the summary in accordance with 21 CFR 50.27 (b2).

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

9.1.4. Investigator Reporting Requirements

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

9.2. Study Monitoring

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

9.3. Quality Assurance

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

9.4. Study and Site Closure

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

- discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study

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

9.5. Records Retention

9.5.1. Health Insurance Portability and Accountability Act of 1996

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

9.5.2. Financial Disclosure

Financial disclosure is required for this study.

9.5.3. Access to Original Records

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

9.5.4. Archiving of Study-Related Documents

Records related to this clinical study must be retained either for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The sponsor will notify the investigator as to when these documents no longer need to be retained for this use.

9.6. Provision of Study Results and Information to Investigators

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

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

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

9.7. Information Disclosure and Inventions

9.7.1. Ownership

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

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

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

9.7.2. Confidentiality

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

9.7.3. Publication

For multicenter studies, the first publication or disclosure of study results shall be a complete, joint, multicenter publication or disclosure coordinated by Recro Pharma, Inc. Thereafter, any secondary publications will reference the original publication(s). If no multicenter publication is submitted for publication within 18 months of study database hard lock, then the site shall be free to disclose its own results, subject to sponsor rights under Section 9.7.1.

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

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

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

9.7.4. Data Management

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

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

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

9.7.5. Data Security

Access to the data will be strictly controlled.

9.8. Subject Tracking

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

10. REFERENCES

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APPENDIX A: OVERVIEW OF STUDY SCHEDULE

	Screening (Day -21 to Day -1)	Treatment Period Day 1 - Day of Last Study Dose (LSD)			End of Treatment (LSD+1[a])	Hospital Discharge	Follow-Up Visit 1 (5-21 days post-discharge)	Follow-Up Visit 2 (30 ± 4 days post-discharge)
		Prior to Surgery	Surgery (End of Surgery=Hour 0)	Hour 24 & Q24Hr after Hour 0 Until LSD (Including LSD)				
Informed Consent	X							
Eligibility Assessment	X	X						
Demographics and Medical History	X	X						
Physical Examination	X[c]	X			X			
Pregnancy Test (FOCBP only)		X[urine]						
Clinical Laboratory Tests[b]	X[c]	X			X			
Inflammatory Markers		X		X - Once Daily	X			
Vital Signs[d]	X	X			X			
12 Lead ECG	X[c]							
Surgical Procedure			X					
Study Drug Administration			X[e]	Q24 from Dose 1				
PI Assessment				On first ambulation[f]				
Monitoring Bowel Function				X	X			
PGA of Pain Control				X	X			
BPI Assessment	X			X	X			
Subject Satisfaction					X			
Wound Evaluation						X	X	
Incidence of Readmission								X
Prior and Concomitant Medication	←	←	←	←	X	→	→	→
Adverse Event Monitoring		←	←	←	X	→	→	→

a If a subject is prepared for discharge less than 24 hours following the last study dose, LSD+1 procedures should be completed prior to discharge.
b Laboratory tests will be performed locally at screening and centrally at Day 1 prior to surgery and LSD+1.
c Historic results collected within 7 days prior to screening may be utilized for eligibility assessment purposes
d Vital signs (VS) include: resting blood pressure, resting pulse, and SpO2. Tests must be obtained after resting (seated/supine) for ≥ 5 minutes.
e Dose 1 is to be administered approximately 30 minutes prior to first incision. Subsequent doses may be administered every 24±1 hours from Dose 1.
f PI will be assessed within 15 minutes prior to first ambulation, and for the worst pain experienced during first ambulation.

APPENDIX B: INVESTIGATOR OBLIGATIONS

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

Debarment

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

Institutional Review Board

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

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

Confidentiality and Safety of Subjects

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

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

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

Study-Related Records

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

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

Accountability of the Investigational Product

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

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

APPENDIX C: STUDY-SPECIFIC INFORMATION

APPENDIX C.1: ENHANCED RECOVERY AFTER SURGERY (ERAS) PROTOCOL

Preoperative

Patient Education:

- Subject education (which may include discussion and a written handout) describing pre-, peri-, and postoperative care and expectations should be provided ahead of surgery.

Diet:

- Encourage hydration 2 days prior to surgery.
- Encourage carbohydrate loading preoperative which may include: ClearFast, Ensure Clear®, clear juices, or Gatorade® up to 2-6 hours prior to surgery (per surgeon/anesthesiologist standard fluids cut off time).

Bowel Prep:

- Clear liquids with mechanical bowel prep as indicated by surgery type.
- Antibiotics as indicated by surgeon.

Motility:

- Use of alvimopan is prohibited.

Analgesia:

- Gabapentin 300 mg PO once, administered approximately 30-90 minutes preoperatively.
- Acetaminophen 650 mg PO or IV once, administered approximately 30-90 minutes preoperatively.
- Study drug IV (per randomization assignment) administered approximately 30 minutes prior to the start of surgery.

Anxiolysis:

- Midazolam 2 mg IV once PRN.

Perioperative

Epidural:

- No epidural medication will be utilized.

Analgesia:

- Perioperative analgesia should be maintained using IV opioids.
- Prohibited perioperative therapies include NSAIDS, ketamine, transverse abdominis plane (TAP) blocks, lidocaine, and/or local instillation.

Nausea prophylaxis:

- Dexamethasone IV up to 4 mg once and ondansetron IV 4 mg once

OR

- Promethazine IV 25 mg once and a scopolamine transdermal patch 0.5 mg

Fluids:

- Target fluids 5-7 mL/kg/hr, as medical condition and intraoperative physiological status permits.

Anesthesia:

- Acceptable agents include nitrous oxide, isoflurane, sevoflurane or desflurane.
- Total intravenous anesthesia is also acceptable.

Neuromuscular blockade (NMB):

- Institution specific standard of care for NMB and reversal agents.

Postoperative

Diet:

- Clear liquids on day of surgery (DOS).
- Advance diet to solids as tolerated starting on postoperative Day 1 (POD1).
- Liquid protein supplements (ex. Boost®, Ensure®) available with each meal.

Ambulation:

- Out of bed (OOB) and ambulating on DOS
- OOB at least 6 hours with ambulation 4 times daily starting on POD1.

Analgesia:

- All subjects will receive 650 mg of acetaminophen Q8H PO as tolerated until 24 hours following the last study dose.
- IV morphine, or morphine patient controlled analgesia (PCA) should be available immediately postoperatively; PCA should be set for 1 mg morphine bolus on patient demand with 6-minute lockout, no basal infusion, which may be supplemented with morphine 1-2 mg IV bolus administered up to Q1H PRN.
- If a PCA is not used, morphine IV boluses may be administered PRN; total morphine dose should not exceed 12 mg/hr.
- Conversion to oral analgesia should be made once subjects are tolerating liquid intake. Oral analgesia regimen must be oxycodone 5mg Q4H PO PRN, with morphine 1-4 mg IV bolus administered up to Q1H available if needed for supplemental analgesia until 24 hours after the last study dose.

Twenty-four hours after the last study dose, patient analgesia will be managed as per site standard of care.

Pyrexia:

- Cooling blankets may be utilized in the event of pyrexia (acetaminophen should not be utilized to manage pyrexia until 24 hours following the last study dose while subject is receiving routine dose of acetaminophen).

Postoperative Nausea and Vomiting:

- Ondansetron 4 mg IV or 8 mg PO PRN (avoid prophylactic use).

Fluids:

- Fluids to be managed per subjects' individual needs.

Motility:

- Gum chewing is prohibited
- Use of Alvimopan is prohibited.

Tubes/Drains:

- Orogastric/nasogastric tubes should be removed in the operating room or on DOS.
- Urinary catheters should be removed on or before POD1.

APPENDIX C.2: PAIN INTENSITY ASSESSMENT

Pain Intensity - Numerical Pain Rating Scale (NPRS)

Pre-Ambulation (within 15 minutes prior to first ambulation):

On a scale of 0-10, please rate your pain by marking an 'X" in the appropriate box that best describes your pain NOW.

☐0	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐9	☐10
No Pain										***worst imaginable pain***

On first ambulation

On a scale of 0-10, please rate your pain by marking an 'X" in the appropriate box that best describes your worst pain during current ambulation.

☐0	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐9	☐10
No Pain										***worst imaginable pain***

APPENDIX C.3: PATIENT GLOBAL ASSESSMENT (PGA) OF PAIN CONTROL

A. The following question will be answered by subjects at Hour 24 from Hour 0 and every 24 hours thereafter until LSD+1:

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

Response to each question will be: (Check (√) one box)

☐ **Poor (0)**

☐ **Fair (1)**

☐ **Good (2)**

☐ **Very Good (3)**

☐ **Excellent (4)**

APPENDIX C.4: SUBJECT SATISFACTION WITH PAIN MEDICATION

The following question will be answered by all subjects at LSD+1:

"Overall, please rate your satisfaction with the pain medication you received following your surgery."

Response to the question will be: (Mark (X) one box)

☐ **Completely Dissatisfied (1)**

☐ **Mostly Dissatisfied (2)**

☐ **Somewhat Dissatisfied (3)**

☐ **Neither Dissatisfied nor satisfied (4)**

☐ **Somewhat Satisfied (5)**

☐ **Mostly Satisfied (6)**

☐ **Completely Satisfied (7)**

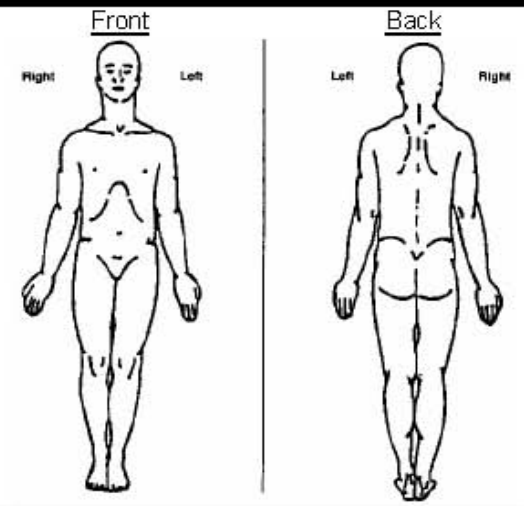
APPENDIX C.5: BRIEF PAIN INVENTORY (BPI) – SHORT FORM

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
☐ No Relief	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

B. Mood

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

C. Walking ability

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

E. Relations with other people

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

F. Sleep

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

G. Enjoyment of life

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

APPENDIX D: AMERICAN SOCIETY OF ANESTHESIOLOGISTS PHYSICAL STATUS CLASSIFICATION SYSTEM

I Normal healthy patient

II Patient with mild systemic disease; no functional limitation – e.g. smoker with well-controlled hypertension

III Patient with severe systemic disease; definite functional impairment – e.g. diabetes and angina with relatively stable disease, but requiring therapy

IV Patient with severe systemic disease that is a constant threat to life – e.g. 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