REC-17-023

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo- and Active-Controlled, Evaluation of the Efficacy and Safety of DEX-IN following Painful Outpatient Procedures

NCT03348423

Study Protocol

05 September 2017

CLINICAL STUDY PROTOCOL

Compound Name:	Dexmedetomidine intranasal spray (DEX-IN)
Protocol Number:	REC-17-023
Protocol Title:	A Phase 2, Multicenter, Randomized, Double-Blind, Placebo- and Active-Controlled, Evaluation of the Efficacy and Safety of DEX-IN following Painful Outpatient Procedures
Date of Protocol:	05 September 2017
Study Designated Physician:	Stewart McCallum, MD 490 Lapp Rd Malvern, PA 19355 Telephone: 484-395-2411 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: _____

_____

_____

SYNOPSIS (PAGE 1 OF 5)

Name of Sponsor/Company: Recro Pharma, Inc.	**Protocol Number:** REC-17-023
Name of Study Drugs: DEX-IN (Dexmedetomidine Intranasal Spray)	**Protocol Title:** A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-and Active-Controlled, Evaluation of the Efficacy and Safety of DEX-IN following Painful Outpatient Procedures
Name of Active Ingredient: Dexmedetomidine HCl	**Phase of Development:** 2

Objective: The primary objective of this study is to evaluate the analgesic efficacy of DEX-IN compared with placebo and active control (fentanyl), in subjects undergoing painful outpatient and office based procedures.

Secondary objectives of this study will include:

- To evaluate the anxiolytic effects of DEX-IN
- To determine the safety and tolerability of DEX-IN as evaluated with vital sign collection, and incidence of Adverse Events (AEs) and Serious AEs (SAEs).

Methodology:

This is a Phase 2, randomized, multicenter, double-blind, placebo- and active-controlled evaluation of the efficacy and safety of DEX-IN in adult subjects undergoing painful outpatient and office based procedures. The study will enroll up to 250 subjects across up to 5 study cohorts, with approximately 50-75 subjects per cohort. Each study cohort will include subjects undergoing a specific painful procedure which may include, but is not limited to, cosmetic procedures (face peel, liposuction/liposculpture, sclerotherapy, etc.), dental procedures, biopsy procedures (prostate, colposcopy, etc.), or other procedures. The procedures to be evaluated in this study will be selected on an ongoing basis.

Subjects planned to undergo a selected procedure, age 18 to 65 years inclusive, will be screened for participation at up to 5 study centers in the United States. Screening will occur within 28 days before study drug administration. After signing the informed consent, demographics and medical history, physical examination, clinical laboratory testing, 12-lead electrocardiogram (ECG), pregnancy testing, and vital sign measurements will be completed during the screening visit.

On the day of the procedure (Day 1), eligible subjects will be randomized to treatment (1:1:1) with DEX-IN 50 µg, intravenous (IV) fentanyl 50 µg, or placebo. Subjects will be administered a study dose in a double dummy fashion, that is, each subject will receive an intranasal (IN) dose (DEX-IN or placebo) approximately 1 hour prior, and an IV injection (fentanyl or placebo) approximately 15 minutes prior to the start of the procedure. The end of the study procedure will be defined as Hour 0. Study assessments of pain and anxiety will be completed at various intervals starting 1 hour before the procedure through Hour 4 following the end of the procedure.

Subjects will be eligible to be discharged home following completion of the Hour 4 assessments at the discretion of the investigator. Subjects may remain beyond Hour 4 at the study center based on their physical status. A follow-up telephone contact will be scheduled for Day 7±2 to assess any subsequent safety events.

Efficacy assessments will include assessment of pain intensity, anxiety intensity, and subject satisfaction with pain experienced during the procedure. Safety assessments will include monitoring of AEs and SAEs, and vital sign measurements.

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Name of Sponsor/Company: Recro Pharma, Inc.	**Protocol Number:** REC-17-023
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Name of Active Ingredient: Dexmedetomidine HCl	**Phase of Development:** 2
Number of subjects to be enrolled: It is planned to enroll up to 250 subjects (approximately 50-75 subjects per cohort in up to 5 study cohorts)	
Number of study sites: Up to 5	
Study country location: United States	

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

1. Voluntarily provide written informed consent.
2. Male or female 18 to 65 years of age at screening, inclusive.
3. Be planned to undergo an office-based or outpatient procedure including, but not limited to, cosmetic procedures, dental procedures, biopsy procedures, or other outpatient and office based procedure, to be performed within the criteria defined in the procedure specific cohort manual.
4. Be naïve to the planned procedure, i.e. no repeated or revision procedures.
5. Be classified as American Society of Anesthesiology (ASA) physical status category 1 or 2.
6. Female subjects are eligible only if all of the following apply:
    - Not pregnant (female subjects of child bearing potential [FOCBP] must have a negative serum pregnancy test at screening and negative urine pregnancy test before procedure);
    - Not lactating;
    - Not planning/attempting to become pregnant during the study;
    - Commits to the use of a highly effective contraceptive method (e.g. abstinence, intrauterine device [IUD], hormonal [estrogen/progestin] contraceptives, or double barrier method) for at least 1 menstrual cycle prior to study enrollment through the Day 7 follow-up; or be menopausal defined as 12 months of amenorrhea in the absence of other biological or physiological causes; or post-menopausal for at least 1 year; or be surgically sterile (documented hysterectomy, bilateral tubal ligation, or bilateral oophorectomy).
7. Male subjects must be surgically sterile (biologically or surgically) or commit to the use of a highly effective contraception method (e.g., abstinence or double barrier method) with female partner(s) from Screening through the Day 7 follow-up.
8. Have a body mass index $\leq$35.0 kg/m^2 at screening

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Name of Active Ingredient: Dexmedetomidine HCl	**Phase of Development:** 2

Criteria for inclusion (continued):

9. Be able to understand the study procedures, comply with all study procedures, and agree to participate in the study program.

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

1. Have a known allergy to dexmedetomidine or other alpha-2-agonist, any excipient DEX-IN/placebo, fentanyl, or to any medications used in the planned study procedure.
2. Have a clinically significant abnormal clinical laboratory tests value according to the judgment of the investigator.
3. Have, as determined by the investigator or the sponsor's medical monitor, a history or clinical manifestations of significant renal, hepatic, cardiovascular, metabolic, neurologic, psychiatric, or other condition that would preclude participation in the study.
4. Have a history of migraine or frequent headaches, seizures, or are currently taking anticonvulsants.
5. Have another painful physical condition or anxiety related diagnosis that, in the opinion of the investigator, may confound study assessments.
6. Have a history of syncope or other syncopal attacks.
7. Have evidence of a clinically significant 12-lead ECG abnormality according to the judgment of the investigator.
8. Have a history of alcohol abuse or prescription/illicit drug abuse in the last 5 years.
9. Have positive results on the urine drug screen or alcohol breath test indicative of illicit drug or alcohol abuse at screening or at check-in prior to randomization.
10. Have a history or evidence of orthostatic hypotension at screening or at check-in prior to randomization.
11. Have a resting heart rate of < 50 beats per minutes or systolic blood pressure <100 mmHg on evaluation of vital signs at screening or at check-in prior to randomization.
12. Use concurrent therapy that could interfere with the evaluation of efficacy or safety, such as any drugs which in the investigator's opinion may exert significant analgesic or anxiolytic properties or act synergistically with DEX-IN.

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Name of Active Ingredient: Dexmedetomidine HCl	**Phase of Development:** 2

Criteria for exclusion (continued)

13. Be unable to discontinue medications that have not been at a stable dose for at least 14 days prior to the scheduled procedure; medications not at a stable dose to be discontinued approximately 5 half lives of the specific prior medication prior dosing with study medication (or, if half life is not known, approximately 48 hours).
14. Have utilized any intranasal medications within 10 days prior to the procedure.
15. Have signs or a history of significant rhinitis or rhinorrhea (constant or chronic), nasal polyps, mucosal lesions of the nostril, postnasal drip of any etiology (constant or chronic), nasal ulcers, septal perforation or deviation, any nasal surgery, anosmia, nasal piercings, or frequent nosebleeds or other nasal pathology, that in the investigator's opinion is sufficient to interfere with intranasal drug delivery.
16. Have had an upper respiratory tract infection within 14 days of screening or procedure, or at any time during the conduct of the study.
17. Have received any investigational product within 30 days before dosing with study medication.
18. Have previously received DEX-IN in clinical trials

Investigational product: DEX-IN 50 µg (Dexmedetomidine Intranasal Spray) will be supplied by the sponsor, for administration by subjects according to their randomization

Reference therapy: IV fentanyl 50 µg; IV and IN placebo

Duration of treatment: Study drug will be administered in double dummy fashion in order to maintain the study blind. Each subject will receive one IN dose (DEX-IN or Placebo) and one IV injection (Fentanyl or Placebo) during their participation in the study. Subjects will be asked to remain at the study center from a minimum of 1 hour before the study procedure through approximately 4 hours after the procedure on Day 1. Subjects will be asked to complete a follow-up assessment by phone on Day 7±2.

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Criteria for Evaluation

Efficacy: The primary efficacy endpoint will be the mean PI score during the study procedure.

Secondary efficacy endpoints include:

1) Mean PI score at other intervals (start of procedure to Hour 1, start of procedure to Hour 4)
2) Worst pain intensity
3) Mean anxiety score at various intervals.
4) Subject satisfaction with pain during and following the procedure.

Safety:

The safety endpoints will include the following:

1) incidence of AEs and SAEs
2) change from baseline in vital signs; incidence of clinically significant changes in vital signs

Statistical methods:

Sample size determination: The sample size for this study was selected empirically without a power calculation.

Study populations:

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

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 had at least one pain assessment post dosing of study drug.

Efficacy analysis: Efficacy parameters will be summarized within each cohort by treatment group. Where appropriate, data may be pooled from multiple cohorts for additional summary.

Safety analysis: The Medical Dictionary for Regulatory Activities (Version 20 or higher) will be used to classify all AEs with respect to system organ class and preferred term. AEs will be summarized by treatment. Changes in vital signs at each post dosing time point will be summarized by treatment using descriptive statistics without formal statistical tests.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
BMI	body mass index
BP	Blood Pressure
BPM	Beats per minute
BSA-CF	body-surface-area conversion factor
CFR	(United States) Code of Federal Regulations
ºC	degrees Centigrade
CL	Clearance
eCRF	Electronic case report form
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
ºF	degrees Fahrenheit
FOCBP	Female of Childbearing Potential
GCP	Good Clinical Practice
H	Hour
HCl	Hydrochloride
HR	Heart Rate
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IN	Intranasal
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intend-to-treat
IV	Intravenous
Kg	Kilogram
L	Liter
m^2	square meters
Mg	Milligram
Min	Minute
mITT	Modified intend-to-treat
mL	Milliliter
mm Hg	millimeters of mercury

Abbreviation	Definition
NF	National Formulary
Ng	Nanogram
NPRS	Numeric Pain Rating Scale
NRS	Numeric Rating Scale
pH	negative log of hydrogen ion concentration
PI	Pain Intensity
PK	Pharmacokinetic
PRN	As needed
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
µg	Microgram
µL	Microliter
ULN	Upper limit of normal
US	United States
USP	*United States Pharmacopeia*
VD	Volume of distribution
WBC	white blood cell

1. INTRODUCTION

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

While this increased focus has brought more attention to the issue of subject comfort and quality of life, our range of tools has remained largely the same. Current medications run the gamut in duration of activity, ranging from acute medications that provide relief for 1-2 hours, to alternative formulations which can provide as much as 72 hours of analgesia. At the same time, these dosage forms commonly rely on a similar set of active ingredients, which often work through the same opioid pathway to provide relief (morphine, oxycodone, fentanyl).[1] 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.

Dexmedetomidine is a selective α_2-aderenoceptor agonist, with selectivity approximately 10-fold that of clonidine. Dexmedetomidine has an extensive history of safe intravenous use in acute care and surgical settings, utilizing its sedative properties, and is indicated for use under the trade name Precedex®. At lower doses, dexmedetomidine has been observed to provide analgesic[2] and anxiolytic[3] benefits, without risk of respiratory depression.[4]

Following IV dosing, dexmedetomidine undergoes rapid distribution. Dexmedetomidine undergoes extensive hepatic metabolism, with very little unchanged drug detected in the urine and feces. The elimination half-life of dexmedetomidine following IV administration is approximately 2 hours. Due to the primarily hepatic elimination of dexmedetomidine, dose adjustment may be required in subjects with hepatic impairment.

Doses of nasal dexmedetomidine were initially explored by Recro in canine models, with safety in humans supported by clinical studies in the published literature utilizing nasal dexmedetomidine. These published studies have shown dexmedetomidine to be well tolerated in studies in pediatric patients with doses up to 1.5 µg/kg. Subsequent studies conducted by Recro have explored single 17.5 and 35 µg doses, as well as repeated dosing at the 35 µg dose level with 7 doses administered at 6 hour intervals. These doses have been well tolerated both locally and systemically. Further, in a study of healthy subjects undergoing bunionectomy surgery, doses of 25 and 50 µg DEX-IN every 6 hours for a minimum of 8 doses have been evaluated. Dosing with DEX-IN in these studies were generally well tolerated. These studies and their findings are discussed further in the DEX-IN Investigators Brochure.

The use of an intranasal dosage form with dexmedetomidine is intended to provide a noninvasive mechanism for rapid drug uptake. This accelerated uptake facilitates a quick pharmacologic response, with potential benefit for patients experiencing acute pain and anxiety symptoms. Dexmedetomidine has the potential to control pain without additional sedation or respiratory depression.

The current study is planned to evaluate the use of single doses of DEX-IN in an office based or outpatient surgery/procedure setting where patients may receive limited or no analgesic medications. Patients undergoing these procedures generally experience a range of pain and anxiety symptoms that may not be well managed under the current standard of care. This study

will utilize a placebo control, as well as an active control arm using IV fentanyl to verify the efficacy of DEX-IN dosing.

2. STUDY OBJECTIVE

The primary objective of this study is to evaluate the analgesic efficacy of DEX-IN compared with placebo and active control (fentanyl), in subjects undergoing painful outpatient and office based procedures.

Secondary objectives of this study will include:

- To evaluate the anxiolytic effects of DEX-IN
- To determine the safety and tolerability of DEX-IN as evaluated with vital sign collection, and incidence of Adverse Events (AEs) and Serious AEs (SAEs).

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a Phase 2, randomized, multicenter, double-blind, placebo- and active-controlled evaluation of the efficacy and safety of DEX-IN in adult subjects undergoing painful outpatient and office based procedures. The study will enroll up to 250 subjects across up to 5 study cohorts, with approximately 50-75 subjects per cohort. Each study cohort will include subjects undergoing a specific painful procedure which may include, but is not limited to, cosmetic procedures (face peel, liposuction/liposculpture, sclerotherapy, etc.), dental procedures, biopsy procedures (prostate, colposcopy, etc.), or other procedures. The procedures to be evaluated in this study will be selected on an ongoing basis.

Subjects requiring a selected procedure, age 18 to 65 years inclusive, will be screened for participation at up to 5 study centers in the United States. Screening will occur within 28 days before study drug administration. After signing the informed consent, demographics and medical history, physical examination, clinical laboratory testing, 12-lead electrocardiogram (ECG), pregnancy testing, and vital sign measurements will be completed during the screening visit.

On the day of the procedure (Day 1), eligible subjects will be randomized to treatment (1:1:1) with DEX-IN 50 µg, intravenous (IV) fentanyl 50 µg, or placebo. Subjects will be administered a study dose in a double dummy fashion, that is, each subject will receive an intranasal (IN) dose (DEX-IN or placebo) approximately 1 hour prior, and an IV injection (fentanyl or placebo) approximately 15 minutes prior to the start of the procedure. The end of the study procedure will be defined as Hour 0. Study assessments of pain and anxiety will be completed at various intervals starting 1 hour before the procedure through Hour 4 following the end of the procedure.

Subjects will be eligible to be discharged home following completion of the Hour 4 assessments at the discretion of the investigator. Subjects may remain beyond Hour 4 at the study center based on their physical status. A follow-up telephone contact will be scheduled for Day 7±2 to assess any subsequent safety events.

Efficacy assessments will include assessment of pain intensity, anxiety intensity, and subject satisfaction with pain experienced during the procedure. Safety assessments will include monitoring of AEs and SAEs, and vital sign measurements.

3.2. Rationale for Study Design and Control Groups

This study will evaluate the efficacy and safety of a known drug substance administered via an alternative route of delivery. Previous research has demonstrated the safety and efficacy of single and repeated doses of dexmedetomidine when administered by the intranasal route in healthy and postoperative (bunionectomy) populations.

This study will explore the analgesic and anxiolytic effects of dosing with DEX-IN in a population of subjects undergoing painful office-based and outpatient procedures. Dosing will occur in a single dose setting prior to the procedure to evaluate the benefits of DEX-IN in reducing the incidence of more severe pain during and following the procedure, as well as reducing anxiety which may further increase satisfaction with the procedure overall. These effects will be compared between DEX-IN and placebo and active controls. Fentanyl IV is

included as an active control arm to act as a positive control for an analgesia signal. Though not an ideal analgesic for use clinically in this setting due to the requirement for IV access, for research purposes, its established analgesic profile will better gauge the efficacy of DEX-IN dosing. In order to maintain the double blind, study drug will be administered in a double dummy fashion so each subject will receive an IN dose (DEX-IN or placebo) and an IV dose (fentanyl or placebo).

4. STUDY POPULATION

4.1. Inclusion Criteria

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

1. Voluntarily provide written informed consent.
2. Male or female 18 to 65 years of age at screening, inclusive.
3. Be planned to undergo an office-based or outpatient procedure including, but not limited to, cosmetic procedures, dental procedures, biopsy procedures, or other outpatient and office based procedure, to be performed within the criteria defined in the procedure specific cohort manual.
4. Be naïve to the planned procedure, i.e. no repeated or revision procedures.
5. Be classified as American Society of Anesthesiology (ASA) physical status category 1 or 2.
6. Female subjects are eligible only if all of the following apply:
    - Not pregnant (female subjects of child bearing potential [FOCBP] must have a negative serum pregnancy test at screening and negative urine pregnancy test before procedure);
    - Not lactating;
    - Not planning/attempting to become pregnant during the study;
    - Commits to the use of a highly effective contraceptive method (e.g. abstinence, intrauterine device [IUD], hormonal [estrogen/progestin] contraceptives, or double barrier method) for at least 1 menstrual cycle prior to study enrollment through the Day 7 follow-up; or be menopausal defined as 12 months of amenorrhea in the absence of other biological or physiological causes; or post-menopausal for at least 1 year; or be surgically sterile (documented hysterectomy, bilateral tubal ligation, or bilateral oophorectomy).
7. Male subjects must be surgically sterile (biologically or surgically) or commit to the use of a highly effective contraception method (e.g., abstinence or double barrier method) with female partner(s) from Screening through the Day 7 follow-up.
8. Have a body mass index $\leq$35.0 kg/m^2 at screening
9. Be able to understand the study procedures, comply with all study procedures, and agree to participate in the study program.

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 to dexmedetomidine or other alpha-2-agonist, any excipient DEX-IN/placebo, fentanyl, or to any medications used in the planned study procedure.
2. Have a clinically significant abnormal clinical laboratory tests value according to the judgment of the investigator.
3. Have, as determined by the investigator or the sponsor's medical monitor, a history or clinical manifestations of significant renal, hepatic, cardiovascular, metabolic, neurologic, psychiatric, or other condition that would preclude participation in the study.
4. Have a history of migraine or frequent headaches, seizures, or are currently taking anticonvulsants.
5. Have another painful physical condition or anxiety related diagnosis that, in the opinion of the investigator, may confound study assessments.
6. Have a history of syncope or other syncopal attacks.
7. Have evidence of a clinically significant 12 lead ECG abnormality according to the judgment of the investigator.
8. Have a history of alcohol abuse or prescription/illicit drug abuse in the last 5 years.
9. Have positive results on the urine drug screen or alcohol breath test indicative of illicit drug or alcohol abuse at screening or at check-in prior to randomization.
10. Have a history or evidence of orthostatic hypotension at screening or at check-in prior to randomization.
11. Have a resting heart rate of < 50 beats per minutes or systolic blood pressure <100 mmHg on evaluation of vital signs at screening or at check-in prior to randomization.
12. Use concurrent therapy that could interfere with the evaluation of efficacy or safety, such as any drugs which in the investigator's opinion may exert significant analgesic or anxiolytic properties or act synergistically with DEX-IN.
13. Be unable to discontinue medications that have not been at a stable dose for at least 14 days prior to the scheduled procedure; medications not at a stable dose to be discontinued approximately 5 half-lives of the specific prior medication prior dosing with study medication (or, if half-life is not known, approximately 48 hours).
14. Have utilized any intranasal medications within 10 days prior to the procedure.
15. Have signs or a history of significant rhinitis or rhinorrhea (constant or chronic), nasal polyps, mucosal lesions of the nostril, postnasal drip of any etiology (constant or chronic), nasal ulcers, septal perforation or deviation, any nasal surgery, anosmia, nasal piercings, or frequent nosebleeds or other nasal pathology, that in the investigator's opinion is sufficient to interfere with intranasal drug delivery.
16. Have had an upper respiratory tract infection within 14 days of screening or procedure, or at any time during the conduct of the study.
17. Have received any investigational product within 30 days before dosing with study medication.

18. Have previously received DEX-IN in clinical trials.

4.3. Discontinuation of Subjects

4.3.1. Procedures for Withdrawal

A subject may be discontinued from the study by the investigator or the sponsor at any time if either determines that it is not in the subject's best interest to continue participation. Subjects who receive the study dose and withdraw from the study should be encouraged to complete the Hour 4 assessments prior to discharge. Subjects will be encouraged to complete the Day 7±2 follow-up contact. 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 this study.

4.4. Lifestyle Guidelines

4.4.1. Confinement

Prior to the procedure (Day 1), subjects will arrive at the study center in sufficient time to prepare for the procedure, confirm eligibility to participate in the study, and begin study assessments approximately 1 hour prior to the procedure. Following the procedure, subjects will complete study assessments through approximately 4 hours post-procedure.

4.4.2. Diet

Subjects should not consume any poppy seeds within 48 hours prior to arrival at the study center, or any alcohol or xanthines (i.e. tea, coffee, caffeine or cola drinks or chocolate) containing foods or beverages within 24 hours before or during the study procedure visit.

5. TREATMENTS

5.1. Office Based/Outpatient Procedure

On Day 1, subjects will undergo a painful office based or outpatient procedure according to their enrolled cohort. Procedures may include, but are not limited to, cosmetic procedures (face peel, liposuction/liposculpture, sclerotherapy, etc.), dental procedures, biopsy procedures (prostate, colposcopy, etc.), and other outpatient and office based procedures.

Prior to enrolling any subjects for a study cohort, the procedure to be performed in that cohort will be defined and a procedure specific cohort manual will be prepared to provide additional operational details. Details provided in the procedure specific cohort manual may include, but are not limited to, duration of the procedure, materials and techniques to be utilized, number and types of samples to be collected or sites to be treated, etc. The procedure specific cohort manual will be distributed to all investigators who will be eligible to enroll subjects in that cohort for review and training.

5.2. Administration of Study Medication

Blinded study personnel will administer all doses of study drug according to the randomization. In order to maintain the study blind, study drug will be administered in a double-dummy fashion and each subject will receive a single IN dose (DEX-IN or placebo) approximately 1 hour prior to the scheduled procedure, and a single IV dose (fentanyl or placebo) approximately 15 minutes prior to the scheduled procedure. Study doses will be administered according to the study randomized treatment assignment with IV and IN doses administered as described in Table 1.

Table 1: Summary of Study Treatment Doses

Randomized Treatment Group	**IN Dose** 1 Hour Prior to Procedure	**IV Dose** 15 Minutes Prior to Procedure
DEX-IN	DEX-IN 50 µg	Placebo
Fentanyl	Placebo	Fentanyl 50 µg
Placebo	Placebo	Placebo

The exact time of administration of the IN and IV dose will be documented in the subject eCRF. Study IN doses will be administered by the subject as a single spray into the right or left nostril. Study IV doses will be administered by study staff as a slow IV push over approximately 1-2 minutes.

Prior to IN administration, the nostrils should be cleared by blowing into a tissue. A single dose (i.e., a single spray) will be administered into one nostril with the untreated nostril covered with a finger. The subject's head should be held in an upright or semi upright position with the spray applicator inserted approximately ½-inch into the treated nostril. The subject should inhale gently through the treated nostril as the device is squeezed and the dose is delivered. The subject should inhale normally through the nose and exhale through the mouth for 10-20 seconds while maintaining the head upright after dosing.

5.3. Identity of Study Medication

5.3.1. IN Dosing

DEX-IN will contain 50 µg dexmedetomidine in each 100 µL of solution (DEX-IN.02 formulation), as well as excipients including: citric acid, sodium citrate, sodium chloride, phenylethyl alcohol, disodium EDTA, and purified water. DEX-IN doses are calibrated to deliver 50 µg (100 µL) with each dose actuation

Placebo solution will contain citric acid, sodium citrate, sodium chloride, phenylethyl alcohol, disodium EDTA, and purified water. Placebo doses are calibrated to deliver 100 µL with each dose actuation

Doses of DEX-IN/placebo will utilize a unit dose spray device containing the appropriate volume of study drug to deliver the assigned dose for administration into the nostril.

5.3.2. IV Dosing

Fentanyl IV doses will be administered using fentanyl citrate injection USP 50 µg/mL to be sourced locally by the clinical site(s). Each IV fentanyl dose will be administered as 50 µg (1 mL) via slow IV push.

Placebo IV doses will utilize normal saline, 0.9% sodium chloride injection USP, to be sourced locally by the clinical site(s). Each IV placebo dose will be administered as 1 mL via slow IV push.

5.4. Method of Assigning Subjects to Treatment Groups

A computer generated randomization scheme will be prepared prior to study initiation for each procedure cohort. Subjects will be randomly assigned to treatment with DEX-IN, IV fentanyl, or placebo in a 1:1:1 assignment ratio according to the randomization scheme.

5.5. Selection of Doses

Doses of dexmedetomidine have been selected following review of pharmacokinetic data in man and canine. Study REC-10-007 evaluated three doses of DEX-IN (17.5 µg in one nostril, or 35 µg in one nostril or divided between nostrils) in healthy human volunteers. This study found all doses to be well tolerated, with the most rapid and extensive absorption seen with a single 100 µL volume dose, containing 35 µg dexmedetomidine, administered into a single nostril. This dose achieved plasma concentrations that were observed to produce analgesia in a previous study of dexmedetomidine administered by the sublingual route.

Upon subsequent evaluation in a repeated dose study in the U.S. (Study REC-11-008), this 35 µg dose yielded mean observed plasma concentrations below those seen in REC-10-007. Based on this observation, the formulation of DEX-IN was modified to contain 50 µg dexmedetomidine base equivalent per 100 µL. This was explored in a single dose study of efficacy, safety and pharmacokinetics in a group of subjects with chronic low back pain (REC-11-010). This study utilized doses of 25 and 50 µg per actuation and demonstrated significant efficacy at the 50 µg dose level.

Based on these data, DEX-IN doses of 35 and 50 µg per actuation were evaluated in two studies of moderate to severe postoperative pain in subjects undergoing bunionectomy (REC-13-012 and REC-14-013). Data from these studies demonstrated efficacy of the 50 µg dose in subjects with more moderate pain severity, while consistent efficacy was not seen with the 35 µg dose level. Therefore a dose of 50 µg has been selected for evaluation in this study.

The fentanyl dose was selected to provide analgesia for pain of moderate severity lasting for a period of less than 4 hours without causing excessive adverse and prolonged effects, based on the fentanyl prescribing information.

5.6. Selection of Timing of Dose

Randomized subjects will receive IN study dosing approximately 1 hour prior to the initiation of the study procedure. This pre-procedural dosing will enable peak plasma concentrations to be achieved prior to the procedure for improved pain control, while providing pre-procedural relief of anxiety symptoms due to the rapid uptake seen with IN administration of dexmedetomidine. IV dosing will be performed at 15 minutes prior to the start of the study procedure due to the rapid onset and short duration of effect for IV fentanyl.

The time of IN and IV dose administrations will be recorded in the subject's eCRF.

5.7. Blinding and Unblinding of Study Medications

Study doses will be prepared by an incompletely unblinded study pharmacist; blinded to IN treatment assignment, unblinded to IV treatment assignment.

All doses administered in this study will be under double-blind conditions; both the subject and the investigator/site staff will be blinded to the treatment assignment. That is, the study drug will be administered in a double-dummy fashion and each subject will receive a single IN dose (DEX-IN or placebo) and a single IV dose (fentanyl or placebo).

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. If knowledge of the treatment assignment is absolutely necessary for the management of a subject's safety, the blind may be broken by removing the blind card provided for the assigned randomization number. 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

Study subjects will receive a single IN and a single IV study dose during their participation in the study. All study doses will be observed by (IN) or administered by (IV) study personnel while the subject is at the study center. 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

Intranasal study medication will be provided in single use, unit-dose, blind labeled nasal spray devices. DEX-IN solution will contain a dexmedetomidine base equivalent of 50 µg/100 µL. Study medication labeling will include the study number.

Intravenous study medication (fentanyl and placebo [normal saline]) will be sourced locally by the study center(s).

Sealed randomization envelopes will be provided and should be stored in a locked area with controlled access until required to break the blind in the event of an emergent condition in a treated subject.

DEX-IN and IN placebo should be stored at the study site at 25ºC (77ºF), although a range of 15ºC to 30ºC (59ºF to 86ºF) will be permitted.

IV fentanyl and placebo (saline) should be stored according to the conditions defined within the product labeling.

All study medication at the study site(s) should be stored in a locked area with restricted access. As a schedule 2 (CII) medication, additional inventory and dispensing records should be maintained for fentanyl according the practice of the study center and appropriate federal and local regulatory requirements. A temperature log or chart should be maintained to monitor the environment at the study site.

5.11. Prior and Concomitant Medications

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

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

5.12. Prohibited Medications

The following medications or drug classes will be prohibited on the day of the procedure:

- Any anxiolytics (benzodiazepines, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, or other antidepressants)
- Any analgesics (NSAIDs, opioids, etc.).

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.

6. STUDY PROCEDURES

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 the procedure, and the subject's eligibility will be reviewed to confirm that they continue to meet the required study 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 and at check-in (Day 1) to the study site prior to randomization.

The 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. Pain Intensity (PI)

PI will be assessed by the study subject for their current pain according to an 11-point numeric pain rating scale (NPRS; 0 - 10); see Appendix C.1.

PI will be assessed 1 hour (within 5 minutes prior to IN dosing), 15 minutes (within 5 minutes prior to IV dosing), and 5 minutes before the start of the procedure. PI assessment during and following the procedure will be determined based on the procedure type selected for the study cohort. The schedule of PI assessments will be defined in the procedure specific cohort manual, prior to enrollment of subjects in the cohort.

6.1.5. Worst Pain Intensity

Subjects will also assess their worst pain intensity during the procedure and in the post-procedure period using the 11-point NPRS; see Appendix C.1. The worst pain during the procedure will be collected at Hour 0 (end of procedure); at that time subjects will be asked to rate their worst pain experienced during the procedure. At Hour 4, prior to discharge, subjects will be asked to rate their worst pain experienced in the time since the end of the procedure.

Assessments to be completed within 15 minutes of the scheduled time point.

6.1.6. Anxiety Assessment

6.1.6.1. Numeric Rating Scale (NRS)

Anxiety will be assessed by the study subject for their current level of anxiety using an 11-point numeric rating scale (NRS); see Appendix C.2.

Anxiety will be assessed using the NRS 1 hour (within 5 minutes prior to IN dosing), 15 minutes (within 5 minutes prior to IV dosing), 5 minutes before the start of the procedure, and immediately prior to the start of the procedure (within 1 minute). Anxiety assessment during and following the procedure will be determined based on the procedure type selected for the study cohort. The schedule of anxiety assessments will be defined in the procedure specific cohort manual, prior to enrollment of subjects in the cohort.

6.1.6.2. Six Item Spielberger State-Trait Anxiety Inventory (STAI-6)

Anxiety will also be assessed by the subject using the 6-Item Spielberger State-Trait Anxiety Inventory (STAI-6); see Appendix C.2.

Anxiety will be assessed using the STAI-6 at screening, 1 hour (within 5 minutes prior to IN dosing), and 5 minutes before the start of the procedure. Anxiety assessment during and following the procedure will be determined based on the procedure type selected for the study cohort. The schedule of anxiety assessments will be defined in the procedure specific cohort manual, prior to enrollment of subjects in the cohort.

6.1.7. Subject Satisfaction with Pain Experience

Subjects will report their satisfaction with the degree of pain experienced during the procedure and in the post-procedure period according to a 7-point Likert scale including categories of: completely dissatisfied (1), mostly dissatisfied (2), somewhat dissatisfied (3), neither satisfied nor dissatisfied (4), somewhat satisfied (5), mostly satisfied (6), and completely satisfied (7); see Appendix C.3.

The subject assessment of satisfaction will be completed for pain experienced during the procedure at Hour 0, and completed for the pain experienced during the post-procedure period at Hour 4; both assessments to be completed within 15 minute of the scheduled time point.

6.2. Safety Assessments Description

6.2.1. Clinical Laboratory Tests

During the screening visit, subjects will have blood and urine samples collected for routine clinical laboratory testing as follows:

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

total bilirubin, direct bilirubin, gamma-glutamyl transferase, lactate dehydrogenase, calcium, total protein, magnesium, phosphate, albumin, and uric acid

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

- urine drug screen (UDS) and alcohol breath test at the screening visit and at check-in prior to randomization on Day 1. Urine drug screen will include screening of (at minimum): cocaine, opiates, amphetamines, benzodiazepines, and methadone.
- serum pregnancy testing at the screening visit, and urine pregnancy testing prior to randomization on Day 1 for FOCBP.

6.2.2. Vital Sign Measurements

Resting vital signs will include blood pressure, pulse, and peripheral oxygen saturation (SpO_2), and must be obtained after resting (seated/semi-recumbent) for ≥ 5 minutes.

At screening and on Day 1 prior to randomization, resting vital signs will be collected in three determinations approximately 2 minutes apart to ascertain subject's true baseline heart rate and blood pressure values. The average values will be used to determine subject eligibility for participation.

After randomization, subjects will have resting (seated/semi-recumbent) vital signs measured and recorded at the following predefined times: 1 hour (prior to IN dose), 15 minutes (prior to IV dose) and 5 minutes prior to the procedure, at the end of the procedure (Hour 0), and 0.5, 1, 1.5, 2, 3, and 4 hours after the end of the procedure. Vital signs will have a collection window of ± 10 minutes.

Postural vital signs will be determined at screening, on Day 1 prior to randomization for inclusion purposes, within 15 minutes following Hour 0, and at Hour 4 prior to discharge; performed following resting assessments. Postural vital signs will include blood pressure and heart rate – to be taken resting, then after standing for one minute.

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

6.2.3. 12-Lead Electrocardiogram (ECG)

A 12-lead ECG will be completed for all subjects at screening to exclude subjects with a clinically significant abnormal ECG. No ECG data will be collected.

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 the study procedure (Day 1). After informed consent is obtained, the following procedures will be performed at the screening visit for all subjects:

- Review of inclusion/exclusion criteria eligibility (Section 4.1 and Section 4.2)
- Demographics and medical history (Section 6.1.2)
- Physical examination (Section 6.1.3)
- Measurement of vital signs (Section 6.2.2)
- 12-lead ECG (Section 6.2.3)
- Clinical laboratory tests (Section 6.2.1)
- Drug and alcohol screen (Section 6.2.1)
- Serum pregnancy test (FOCBP only; Section 6.2.1)
- Assessment of anxiety (Section 6.1.6)
- Collection of prior and concomitant medications (Section 5.11)

6.3.2. Day 1 (Pre-Procedure)

The following assessments will be conducted on the day of the study procedure (Day 1) for all subjects prior to the start of the procedure:

- Medical history update (Section 6.1.2)
- Physical examination (Section 6.1.3)
- Measurement of vital signs (Section 6.2.2)
- Drug and alcohol screen (Section 6.2.1)
- Urine pregnancy test (FOCBP only; Section 6.2.1)
- Randomized study dosing (Section 5.2)
- Assessment of pain intensity (Section 6.1.4)
- Assessment of anxiety (Section 6.1.6)
- Collection of prior and concomitant medications (Section 5.11)
- Monitoring of AEs (Section 7)

6.3.3. Day 1 (Peri- and Post-Procedure)

The following assessments will be conducted on the Day 1, during and following the study procedure:

- Measurement of vital signs (Section 6.2.2)
- Assessment of pain intensity (Section 6.1.4; according to schedule defined in the procedure specific cohort manual)
- Assessment of worst pain intensity (Section 6.1.5)
- Assessment of anxiety (Section 6.1.6; according to schedule defined in the procedure specific cohort manual)
- Assessment of satisfaction with pain experience (Section 6.1.7)
- Collection of prior and concomitant medications (Section 5.11)
- Monitoring of AEs (Section 7)

6.3.4. Day 7 ± 2 Days

The following procedures will be performed during a telephone contact at Day 7±2 days:

- Collection of prior and concomitant medications (Section 5.11)
- Monitoring of AEs (Section 7)

6.4. Appropriateness of Assessments

The efficacy measures utilized in this study are appropriate to evaluate the study endpoints, and include scales common to studies of acute pain. The timing of assessments is intended to evaluate the efficacy parameters pre-, peri-, and post-procedure.

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

6.5. Clinical Stopping Rules

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

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

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

7.1. Definition of an Adverse Event

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

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

Examples of an AE include the following:

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

The following examples are not considered AEs:

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

All AEs, whether volunteered, elicited, or noted on physical examination, and regardless of causality or seriousness, will be assessed and recorded in the eCRF beginning after administration of study medication through the end of the study.

7.2. Definition of a Serious Adverse Event

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

  - It results in death or is life-threatening (i.e., presents an immediate risk of death from the event as it occurred). (This criterion is not intended to include an AE that, had it occurred in a more severe form, might have caused death.)
  - It results in persistent or substantial disability or incapacitation. (This criterion is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, diarrhea, or sprained ankle.)
  - It results in hospitalization.
  - It results in prolongation of an existing hospitalization.
- It is a congenital anomaly or birth defect (in the offspring of a subject using the study medication regardless of time to diagnosis).
- It requires medical or surgical intervention to prevent any of the above outcomes.
- It 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 intervention to prevent any of the other outcomes listed. Examples of such medical events that may also be considered serious include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization.

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

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

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

7.3. Definition of a Suspected Adverse Reaction (SAR)

A SAR is defined as any adverse event for which there is a reasonable possibility that the adverse event was caused by the study drug. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

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

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

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

7.5. Recording and Evaluating Adverse Events and Serious Adverse Events

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

7.5.1. Assessment of Intensity

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

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

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

7.5.2. Assessment of Causality

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

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

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

7.5.3. Assessment of Outcome

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

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

7.5.4. Assessment of Expectedness

For the purposes of IND safety reporting, expectedness of the SAE will be assessed by the Sponsor. An AE or SAR is considered unexpected if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

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

Nonserious AEs will be followed after the last scheduled study visit, until an appropriate resolution can be documented.

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

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

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

7.7. Prompt Reporting of Serious Adverse Events to the Sponsor

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

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

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

Medical Safety
Recro Pharma, Inc.

Telephone: 484-395-2470
Fax: 484-395-2472
E-mail: AE@recropharma.com

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

- AE record
- medical history
- prior and concomitant medications

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

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

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

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

7.8. Regulatory Reporting Requirements

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

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

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

7.9. Special Reporting Situations: Pregnancy

Reports of pregnancy exposure in a female subject (maternal exposure) or female partner of male subject (paternal exposure), where the embryo or fetus may have been exposed to investigational product through the placenta or semen will be reported. A subject should be instructed to notify the investigator immediately of a maternal/paternal pregnancy exposure. The sponsor must be notified of all pregnancies reported to the investigator (see Section 7.7 for contact information).

A female subject who becomes pregnant during the study must discontinue further study drug administration.

Any uncomplicated maternal/paternal pregnancy exposures that occurs in a subject or female partner of a male subject during this clinical study will be reported for tracking purposes only. All subject maternal/paternal pregnancy exposures 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 medication 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 7.7. 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.

For purposes of follow-up on a paternal pregnancy exposure, in order to collect information on the pregnancy and outcome of the pregnancy, informed consent will be requested from the male subject and a Pregnant Partner Consent Form completed.

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 (e.g., congenital abnormalities/birth defects/spontaneous miscarriages, ectopic pregnancy 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 7.7.

8. STATISTICAL METHODOLOGY

The following outlines some of the key elements of the data analysis approach. A formal statistical analysis plan will be developed for this study in which statistical models, data derivation methods and rules will be described in details.

8.1. Determination of Sample Size

The sample size for this study was selected empirically without a formal power calculation.

8.2. Study Endpoints

8.2.1. Efficacy Endpoints

Efficacy measures include pain intensity, worst pain intensity, anxiety score, and satisfactory score with pain during and following the procedure. The efficacy measurements will be collected at various time points, including time points prior to, during, and post procedure. The exact time point for each procedure will be determined when the cohort manual is prepared for each cohort.

The primary efficacy endpoint will be the average pain score during the study procedure. The average PI score defined as time weighted PI score, or it is equivocal to say that it is area under the PI score curve divided by the duration of observation. This parameter will be derived for each subject.

Secondary efficacy endpoints include

1) Pain score at each time point
2) Worst pain intensity by time point
3) Anxiety score by time point
4) Subject satisfaction score by time point

8.2.2. Safety Endpoints

The safety endpoints will include the following:

1) incidence of AEs and SAEs
2) change from baseline in vital signs; incidence of clinically significant changes in vital signs

8.3. General Considerations for Statistical Analysis

The following outlines some of the key elements of the data analysis approach. A formal statistical analysis plan will be developed for this study in which statistical models, data derivation methods and rules will be described in detail.

8.3.1. Analysis Datasets

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

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

Efficacy Analysis Set: All subjects in the safety analysis set who had required procedure will be included in the efficacy analysis.

8.3.2. Test Hypothesis and *P* Value Justification

The null hypothesis is that there is no difference between the treatment arms. The alternative hypothesis is that the treatment groups are different.

Differences between DEX-IN, fentanyl, and placebo groups will be evaluated via 2-sided 2-sample t-test at the 0.05 level of significance. Nominal p-values for secondary and exploratory comparisons will be reported without adjustment for multiplicity.

8.3.3. Procedures for Handling Missing Data

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

8.3.4. Definitions for Assessment Windows

For the purpose of data analysis, *baseline* measures for a given period will be the last measurements taken before the subject receives the study medication.

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, subjects who discontinued from the study, and reason for discontinuation) by treatment group and study overall.

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

8.4.2. Demographics and Procedure Characteristics

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

Procedure characteristics will also be tabulated such as procedure type, site, and duration. The exact information collected for each procedure will be defined in the cohort manual to be prepared for each study cohort.

8.4.3. Protocol Deviations

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

8.4.4. Treatment Compliance

All doses of study medication will be administered by, or under the observation of, study personnel while subjects are at the study site. The exact time of administration of study medication will be documented within each subject's eCRF. No formal summary of treatment compliance will be produced.

8.4.5. Prior and Concomitant Medications

All prior and concomitant medications will be tabulated for the overall study population. Prior and concomitant medications will be coded to the therapeutic drug classes and generic drug names using the World Health Organization (WHO) Drug classifications version 1Q2017 or higher.

8.5. Efficacy Analysis

8.5.1. PI Analyses

PI scores will be summarized by treatment at each timepoint within each cohort. Average PI score will be derived for each subject and will be tabulated by treatment group and cohort. Analysis of variance may be used to compare the differences between the treatment groups if data warrants.

8.5.2. Worst Pain Intensity

Worst pain intensity scores will be summarized by treatment at each timepoint within each cohort.

8.5.3. Anxiety Assessment

Anxiety assessment scores will be summarized for the NRS and STAI-6 separately by treatment at each timepoint within each cohort. Mean scores will be calculated for various intervals including: pre-procedure, during the procedure, Hour 0 to Hour 1, Hour 0 to Hour 2, and Hour 0 to Hour 4 after the procedure.

8.5.4. Subject Satisfaction with Pain Experience

Subject satisfaction scores will be summarized by treatment at each timepoint within each cohort.

8.5.5. Subgroup Analyses for Efficacy

Subjects from each cohort will be analyzed separately. Data across cohorts may be pooled for analysis if data warrants. Additional subgroups may be identified if data warrants.

8.6. Safety and Tolerability Evaluations

8.6.1. Extent of Exposure

This is a single dose study, therefore the maximum anticipated exposure in any subject will be 50 µg dexmedetomidine for subjects in the DEX-IN treatment group, and 50 µg fentanyl for subjects in the fentanyl treatment group.

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

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

8.6.3. Clinical Laboratory Tests

Laboratory values will be collected at screening and Day 1 for enrollment purposes, no data summary will be prepared.

8.6.4. Vital Sign Measurements

Resting vital sign values and postural vital sign values at each time point collected will be summarized by treatment and time point without formal statistical testing. Potentially clinically significant changes (PCSC) in vital signs will be tabulated by cohort, treatment, and time point. Postural and resting blood pressure measures will be listed side-by-side for subjects with reported orthostatic hypotension. Vital sign listing will be prepared separately for subjects with at least one incidence of PCSC in the study. Time point where the PCSC is observed will be flagged.

PCSC in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) measurements will be defined as follows:

- Hypotension: SBP < 90 mm Hg with a decrease ≥ 20 mm Hg from predose, or a DBP ≤ 50 mm Hg and decrease ≥ 15 mm Hg from predose.
- Hypertension: SBP ≥ 180 mm Hg with an increase of ≥ 20 mm Hg from predose, or a DBP ≥105 and an increase ≥ 15 mm Hg from predose
- Bradycardia: HR ≤ 50 BPM with a decrease ≥15 BPM from predose

- Tachycardia: HR ≥ 120 BPM with an increase ≥15 BPM from predose.

8.6.5. Electrocardiograms

ECGs will be performed at screening for enrollment purposes only, no data summary will be prepared.

8.6.6. Subgroup Analyses for Safety Endpoints

No subgroup analysis is planned for this study.

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-17-023. 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 DEX-IN

9.1.3. Informed Consent

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

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

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

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

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

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

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

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

9.1.4. Investigator Reporting Requirements

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

9.2. Study Monitoring

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

9.3. Quality Assurance

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

9.4. Study and Site Closure

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

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

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

9.5. Records Retention

9.5.1. Health Insurance Portability and Accountability Act of 1996

The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subjects' health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR Parts 160 and 164 (the Health Insurance Portability and Accountability Act of 1996 privacy regulation). 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.

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 will be used to track subject participation in the study.

10. REFERENCES

1. Swarm R. et al. NCCN Clinical Practice Guidelines in Oncology: Adult Cancer Pain. Journal of the National Comprehensive Cancer Network. 2007 Sept; 5(8):726-51.
2. Jaakola ML, Salonen M, Lehtinen R, Scheinen H. The analgesic action of dexmedetomidine – a novel α_2-adrenoceptor agonist – in healthy volunteers. Pain. 1991 Sept; 46(3):281-285.
3. Bhana N, Goa KL, McClellan KJ. Dexmedetomidine. Drugs. 2000 Feb; 59(2):112-118.
4. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The Effects of Increasing Plasma Concentrations of Dexmedetomidine in Humans. Anesthesiology, 2000 Aug; 93(2):382-394.

APPENDIX A. OVERVIEW OF STUDY SCHEDULE

	Screening (Day -28 to -1)	Day 1													Day 7 ± 2 Follow-Up
		Pre-Procedure					Procedure	Post-Procedure							
		Check-In	1 Hr Prior	15 Min Prior	5 Min Prior	Immediately Prior		Hr 0	Hr 0.5	Hr 1	Hr 1.5	Hr 2	Hr 3	Hr 4	
Informed Consent	X														
Eligibility Assessment	X	X[c]													
Demographics and Medical History	X	X[c]													
Physical Examination	X	X[c]													
Pregnancy Test	X[serum]	X[urine, c]													
UDS & Alcohol Breath Test	X	X[c]													
Clinical Laboratory Tests	X														
Resting Vital Signs	X[a]	X[a, c]	X[d]	X[d]	X			X	X	X	X	X	X	X	
Postural Vital Signs	X	X[c]						X						X	
12 Lead ECG	X														
Randomization		X													
IN Study Drug Administration			X												
IV Study Drug Administration				X											
Pain Intensity			X[d]	X[d]	X		X[b]								
Worst Pain Intensity								X						X	
Anxiety - NRS			X[d]	X[d]	X	X	X[b]								
Anxiety – STAI-6	X		X[d]		X		X[b]								
Satisfaction with Pain								X						X	
Adverse Event Monitoring			←				X							→	
Prior and Concomitant Medications		←					X							→	

a At screening and on Day 1 prior to dosing, resting vital signs will be collected in three determinations approximately 2 minutes apart to ascertain subject's true baseline heart rate and blood pressure values. The average values will be used to determine subject eligibility for participation.

b PI and anxiety scores will be assessed according to the schedule defined in the procedure specific cohort manual.

c Assessment to be performed prior to dose randomization

d Assessment to be performed prior to dosing

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

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

APPENDIX C. STUDY-SPECIFIC INFORMATION

Appendix C.1: Pain Assessments - Numeric Pain Rating Scale (NPRS)

Pain Intensity Assessments: On a scale of 0-10, please rate your pain by marking an 'X" in the appropriate box that best describes your pain <u>now</u>.

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

Worst Pain Hour 0: On a scale of 0-10, please rate your pain by marking an 'X" in the appropriate box that best describes <u>the worst pain you experienced during the procedure</u>.

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

Worst Pain Hour 4: On a scale of 0-10, please rate your pain by marking an 'X" in the appropriate box that best describes <u>the worst pain you experienced since the end of the procedure</u>.

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

Appendix C.2: Anxiety Assessment

Anxiety - NRS

On a scale of 0-10, please rate your anxiety by marking an 'X" in the appropriate box that best describes the level of anxiety you are experiencing now.

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

Anxiety – STAI-6

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the most appropriate number to the right of the statement to indicate how you feel right now, at this moment. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	Not at all	**Somewhat**	**Moderately**	**Very much**
1. I feel calm	1	2	3	4
2. I am tense	1	2	3	4
3. I feel upset	1	2	3	4
4. I am relaxed	1	2	3	4
5. I feel content	1	2	3	4
6. I am worried	1	2	3	4

Appendix C.3: Subject Satisfaction with Pain Experience

Hour 0 Assessment:

"Overall, please rate your satisfaction with the degree of pain you experienced during the procedure."

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)**

Hour 4 Assessment:

"Overall, please rate your satisfaction with the degree of pain you experienced following the procedure."

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 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