

Clinical Trial Protocol

A Phase 2, Randomized, Open Label, Multiple-Dose, Comparator, Parallel-Group, Safety and Tolerance Study of Buprenorphine Sublingual Spray (0.5 mg TID) versus Standard of Care Post-Operative Narcotic Therapy for the Treatment of Post-Operative Pain

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Investigational Product: Buprenorphine Sublingual Spray

IND Number: 120,673

Sponsor: Insys Development Company, Inc.

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Confidentiality Statement

This study will be performed in compliance with Good Clinical Practices (GCP) and applicable regulatory requirements. The confidential information in this document is provided to you as an investigator, potential investigator or consultant for review by you, your staff and applicable Independent Ethics Committee (IEC) or Institutional Review Board (IRB). It is understood that the information will not be disclosed to others without written authorization from Insys Development Company, Inc., except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

A. PROTOCOL APPROVAL PAGE

A Phase 2, Randomized, Open Label, Multiple-Dose, Comparator, Parallel-Group, Safety and Tolerance Study of Buprenorphine Sublingual Spray (0.5 mg TID) versus Standard of Care Post-Operative Narcotic Therapy for the Treatment of Post-Operative Pain

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Date: 4 Aug 2017

B. PROTOCOL SYNOPSIS

Name of Sponsor/Company: Insys Development Company, Inc.	
Name of Investigational Product: Buprenorphine Sublingual Spray	
Name of Active Ingredient: Buprenorphine	
Title of Study: A Phase 2, Randomized, Open Label, Multiple-Dose, Comparator, Parallel-Group, Safety and Tolerance Study of Buprenorphine Sublingual Spray (0.5 mg TID) versus Standard of Care Post-Operative Narcotic Therapy for the Treatment of Post-Operative Pain	
Study center(s): 2	
Studied period (years): Estimated date first patient enrolled: Q3 2017 Estimated date last patient completed: Q4 2017	Phase of development: Phase 2
<p>Objectives:</p> <p>Primary:</p> <p>To evaluate the safety and tolerability based on the incidence of adverse experiences of Buprenorphine Sublingual Spray (0.5 mg three times daily [TID]) compared with standard post-operative narcotic therapy in subjects with postoperative pain. Standard post-operative narcotic therapy is defined as Morphine Intravenous Injection (IV) (4 mg TID) followed by Oxycodone Hydrochloride Tablet (10 mg TID).</p>	
<p>Methodology:</p> <p>This is a Phase 2, randomized (stratified according to surgery and postoperative nausea and vomiting risk factors), open label, multiple-dose, comparator controlled, parallel-group, study to evaluate the safety and tolerability of Buprenorphine Sublingual Spray (0.5 mg TID) versus standard postoperative narcotic therapy in subjects with postoperative pain. Standard postoperative narcotic therapy is defined as Morphine IV (4 mg TID) for 24 hours followed by Oxycodone Hydrochloride Tablet (10 mg TID).</p> <p>The study will comprise four periods: Screening Period (Days -28 to -1), Surgical Period (Day 1), Treatment Period (Days 1 to 4 Inpatient / Days 4 to 7 Outpatient), and Follow-up Period (Day 8, +2 day window).</p> <p>Subjects will be admitted to the study site on the morning of the scheduled surgery (Day 1), will remain at the study site until Postoperative Day 4 (a total of 3 nights at the study site) then be evaluated to participate in the outpatient setting and meet criteria in order to proceed to the outpatient treatment period Days 4 to 7, and will return to the clinic for the Follow-up Visit on Day 8 (+2 day window).</p> <p>Screening Period: Subjects who meet all inclusion and no exclusion criteria will be eligible for enrollment. After providing written Informed Consent, subjects will undergo study specific screening procedures, including a review of inclusion and exclusion, demographics, medical history, concomitant medication use, assessment of postoperative nausea and</p>	

vomiting (PONV) risk factors, physical and oral cavity examination, baseline laboratory testing, alcohol breath test, urine drug screening, HIV and hepatitis screening, 12-lead electrocardiogram (ECG), and pregnancy testing. Eligible subjects will complete all screening procedures within 28 days before the surgery (Days -28 to -1).

Surgical Period: On Day 1, anesthesia will be established using standardized techniques, as appropriate, for each surgical procedure. The surgical procedures will be bunionectomy, breast augmentation, and abdominoplasty. For nausea prophylaxis, all subjects will receive a uniform standard of care regimen which includes the following: 10 mg of dexamethasone at induction and 8 mg of ondansetron near the end of surgery. Vitals, pulse oximetry, and ECG measurements will be taken. Concomitant medications and Adverse Events will be recorded.

Post surgery and prior to randomization, subjects may be treated with intravenous morphine and or fentanyl for post-surgical analgesia (dose and frequency per the discretion of the investigator).

Treatment Period: Within 4 hours after surgery, subjects who meet the post-surgical eligibility requirements will be randomized to treatment (see [Post-surgical Eligibility Requirements](#)).

After meeting post-surgical eligibility requirements and subsequently being randomized to treatment, subjects may receive their first dose of investigational drug any time between 0-4 hours after surgery. The first dose does not need to be immediately administered after meeting post-surgical eligibility requirements.

During the Treatment Period, approximately 100 subjects will be randomly assigned to 1 of 2 treatment groups: Buprenorphine Sublingual Spray 0.5 mg TID, or standard of care postoperative narcotic therapy. Randomization will be stratified according to surgical procedure and baseline PONV risk factors. Vitals, pulse oximetry, and ECG measurements will be taken. Concomitant medications and Adverse Events will be recorded.

Pulse oximetry will be monitored continuously after surgery as a safety measure. An electrocardiogram (ECG) will be conducted after surgery but before the first dose of the study drug and serve as a baseline for comparison to subsequent tracings. The time of administration of the first dose of study drug will be defined as Time 0. During confinement, study drug will be administered by site staff to ensure appropriate dosing of study medication. Subjects should not have anything orally except room-temperature water within 15 minutes of each dose. The inpatient Treatment Period will continue through 72 hours after Time 0. Additional ECGs will be performed at 90 minutes, 12 hours, 24 hours, 48 hours and 72 hours after Time 0.

Rescue for inadequate analgesic response:

During confinement to the study center during the first 72 hours (Days 1-4), subjects requiring rescue medication for pain will be provided with acetaminophen 1000 mg every six hours and/or ketorolac 30 mg every six hours, as needed. On outpatient days 4-7, ketorolac will not be available to study subjects (because it is intravenous). Therefore, subjects will be

provided with acetaminophen, and will be advised to take acetaminophen 1000 mg every six hours as needed for rescue analgesia.

Rescue for postoperative nausea: During confinement to the study center during the first 72 hours (Day 1-4), subjects requiring rescue medication for nausea will be provided with Zofran 4 mg IV per the discretion of the clinician. On outpatient days 4-7 subjects will be provided Zofran ODT (oral dissolvable tablet) to be taken as needed for postoperative nausea.

Subjects whose pain or nausea cannot be adequately managed (in the investigator's opinion) by a combination of study drug and rescue medication or who develop unacceptable side effects during the study will be discontinued from further study participation. Their pain or nausea will be managed according to usual standard of care at the investigator's discretion.

Site staff will train subjects on how to self-administer study drug. Investigators will determine if patients are able to proceed with the outpatient treatment period. Before discharge from the study site on Day 4, site personnel will dispense rescue medication and will train subjects on how to administer the study drug, educate patients on the signs and symptoms of Adverse Events, and observe subjects self-administer medication. After discharge, study drug will be administered by subjects at home according to the directions provided by study staff. Study personnel will dispense outpatient diary, study drug, rescue pain and nausea medication. Subjects will also be instructed to return the outpatient diary to study personnel at the Follow up Visit 8 + 2 days after surgery.

Follow-up Visit on Day 8 (+2 day window): Subjects will be instructed to return any unused outpatient study drug to study personnel. Vitals, pulse oximetry, and ECG will be measured. Concomitant medications and Adverse Events will be recorded.

Subject outpatient diary will be collected and reviewed by study staff.

Number of patients (planned): Approximately 100 subjects (50 subjects assigned to Buprenorphine Sublingual Spray and 50 subjects assigned to standard post-operative pain management) will be enrolled.

Diagnosis and main criteria for inclusion:

Subjects must meet all of the following criteria and post-surgical eligibility criteria to be considered eligible to participate in the study.

Criteria for Inclusion:

1. Is able to speak and understand the language in which the study is being conducted, is able to understand and comply with the procedures and study requirements, and has voluntarily signed and dated an informed consent form approved by an Institutional Review Board before the conduct of any study procedure.
2. Is a male or female ≥ 18 and ≤ 65 years of age.
3. Scheduled for elective bunionectomy, breast augmentation (in women only), or abdominoplasty.

4. Is classified using the American Society of Anesthesiologists Physical Status Classification System as P1 to P2.
5. If female, is either not of childbearing potential (defined as postmenopausal for at least 1 year or surgically sterile [bilateral tubal ligation, bilateral oophorectomy, or hysterectomy]) or practicing one of the following medically acceptable methods of birth control:
 - a. Hormonal methods such as oral, implantable, injectable, vaginal ring, or transdermal contraceptives for a minimum of 1 full cycle (based on the subject's usual menstrual cycle period) before study drug administration;
 - b. Total abstinence from sexual intercourse since the last menses before study drug administration;
 - c. Intrauterine device; OR
 - d. Double-barrier method (condoms, sponge, or diaphragm with spermicidal jellies or cream).
6. Has a body weight ≥ 45 kg and a body mass index (BMI) ≤ 40 kg/m².
7. Is willing and able to comply with study requirements (including diet, alcohol, and smoking restrictions), complete evaluations and diary, remain at the study site for ≥ 72 hours, and return for follow up Day 8 + 2 days after surgery.

Criteria for exclusion:

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

1. Has a known history of allergic reaction or clinically significant intolerance to acetaminophen, aspirin, opioids, or any nonsteroidal anti-inflammatory drugs (NSAIDs); history of NSAID-induced bronchospasm (subjects with the triad of asthma, nasal polyps, and chronic rhinitis are at greater risk for bronchospasm and should be considered carefully); or hypersensitivity, allergy, or significant reaction to sulfa (including sulfonamide) medicines, ingredients of the study drug, or any other drugs used in the study, including anesthetics and antibiotics that may be required on the day of surgery.
2. Has experienced any surgical complications or other issues that, in the investigator's opinion, could compromise the subject's safety if he or she continues into randomized treatment or could confound the results of the study.
3. Has a known or suspected history of alcoholism or drug abuse or misuse within 2 years of Screening or evidence of opioid tolerance or physical dependence before dosing with the study drug.
4. Has any clinically significant unstable cardiac, respiratory, neurological, immunological, hematological, or renal disease, or any other condition that, in the investigator's opinion, could compromise the subject's welfare, ability to communicate with the study staff, or otherwise contraindicate study participation.
5. Has long QT Syndrome, a family history of long QT Syndrome, or is taking Class IA or Class III antiarrhythmic medications.

6. Has a history or current diagnosis of a significant psychiatric disorder that, in the investigator's opinion, would affect the subject's ability to comply with the study requirements.
7. Has tested positive either on the urine drug screen or on the alcohol Breathalyzer test. Subjects who test positive at Screening only and can produce a prescription in their name from their physician for the medication producing the positive test may be considered for study enrollment at the investigator's discretion. However, they must test negative on the day of the surgery.
8. Has a history of a clinically significant (in the investigator's opinion) gastrointestinal (GI) event within 6 months before Screening or has any history of peptic or gastric ulcers or GI bleeding.
9. Has an active infection, mucositis, cold sores, viral lesions, local irritation, or in the investigator's opinion has significant periodontal disease of the oral cavity. In addition, recent (within 1 year) piercing of the tongue or anywhere in the oral cavity.
10. Has a surgical or medical condition of the GI or renal system that, in the investigator's opinion, might significantly alter the absorption, distribution, or excretion of any drug substance.
11. Is considered by the investigator, for any reason (including, but not limited to, the risks described as precautions, warnings, and contraindications in the current version of the investigator's brochure for Buprenorphine Sublingual Spray), to be an unsuitable candidate to receive the study drug.
12. Is receiving systemic chemotherapy, has an active malignancy of any type, or has been diagnosed with cancer within 5 years before Screening (excluding squamous or basal cell carcinoma of the skin).
13. Is currently receiving anticoagulants (eg, heparin or warfarin). Low-dose aspirin for cardioprotection is allowed.
14. Has used drugs known to be a strong inhibitor or inducer of CYP3A4 within 1 weeks before surgery.
15. Has received a course of systemic corticosteroids (either oral or parenteral) within 1 months before Screening (inhaled nasal steroids and topical corticosteroids are allowed).
16. Has a history of chronic use (defined as daily use for >2 weeks) of NSAIDs, opiates, or glucocorticoids (except inhaled nasal steroids and topical corticosteroids) within 1 month before study drug administration. Aspirin at a daily dose of ≤ 325 mg is allowed for cardiovascular prophylaxis if the subject has been on a stable dose regimen for ≥ 30 days before Screening and has not experienced any relevant medical problem.
17. Has a significant renal or hepatic disease, as indicated by clinical laboratory assessment (results $\geq 3 \times$ the upper limit of normal [ULN] for any liver function test, including aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase, or creatinine $\geq 1.5 \times$ ULN).
18. Has any clinically significant laboratory or 12-lead electrocardiogram finding at Screening that in the investigator's opinion contraindicates study participation.

19. Has screening systolic blood pressure ≥ 160 mmHg and diastolic blood pressure > 100 mmHg (may be repeated one additional time after 5 minutes rest to verify). The investigator may, at his discretion, choose to exclude subjects with hypertensive levels lower than these if he deems it in the best interest of the subject.
20. Has a history of sleep apnea or other obstructive airway disease.
21. Has a history of nausea and vomiting with buprenorphine products.
22. Has significant difficulties swallowing capsules or is unable to tolerate oral medication.
23. Previously participated in another clinical study of Buprenorphine Sublingual Spray or received any investigational drug or device or investigational therapy within 30 days before Screening.

Post-surgical eligibility requirements:

The subject will be assessed for the following postoperative eligibility criteria.

1. Subjects must be awake, breathing spontaneously without significant respiratory depression.
2. Subjects must not be actively vomiting or complaining of severe nausea.
3. Subjects must be able to answer questions and follow commands.
4. Subjects must not have surgical complications that could compromise safety of the subject or confound the results of the study.

Investigational product, dosage and mode of administration:

Buprenorphine Sublingual Spray, 0.5 mg manufactured for and supplied by Insys Development Company, Inc.

Duration of treatment:

The estimated duration of the study for each subject is approximately 5 weeks, which includes a Screening Period (Days -28 to -1), a Surgical Period (Day 1), a Treatment Period (Inpatient Days 1 to 4 / Outpatient Days 4 to 7), and a post-treatment Follow up Visit at the clinic (Day 8, + 2 day window).

Reference therapy, dosage and mode of administration:

Morphine IV, 4 mg TID for 24 hrs, followed by Oxycodone Hydrochloride Tablet, 10 mg TID

Criteria for safety evaluation:**Primary Safety Endpoint**

- Incidence of Treatment Emergent Adverse Events (TEAEs)

Secondary Safety Endpoints:

- Proportion of subjects using rescue medication for nausea
- Time to first use of rescue medication for nausea following each dose of the investigational product (IP)
- Total use of rescue medication for nausea over 0 to 8 hours, 0 to 24 hours, over 0 to 48 hours, over 0-72 hours and 0-7 days
- Pulse oximetry recorded prior to study drug administration
- ECGs at 90 minutes, 12, 24, 48 and 72 hours
- Oral Examinations

Statistical methods:**Sample Size Determination**

No formal sample size estimate has been completed. However, a sample size of 50 subjects per treatment group is considered sufficient to demonstrate that the incidence of nausea and vomiting associated with buprenorphine is consistent with that of standard post-operative narcotic therapy.

Analysis Populations

Statistical analysis will be done on the safety population, which will include all subjects who are treated with the study drug. The safety population is the population for all safety assessments.

Safety Analyses

Data listings will be provided for protocol specified safety data. The Medical Dictionary for Regulatory Activities (MedDRA; Version 19.0 or higher) will be used to classify all AEs with respect to system organ class and preferred term. Adverse event summaries will include only TEAEs, which will be summarized for each treatment group.

Statistical analyses will be performed using SAS[®]

Clinical laboratory and vital signs results and changes from baseline will be summarized at each time point.

Incidence of abnormal ECG and PE findings will be summarized by treatment group. Any clinically significant findings will be recorded as AEs.

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D. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation or Specialist Term	Explanation
AE	Adverse Event
BMI	Body Mass Index
CRF	Case Report Form
ECG	Electrocardiogram
ET	Early Termination
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IRB	Institutional Review Board
IB	Investigator's Brochure
IP	Investigational Product
IV	Intravenous
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
PCP	Primary Care Provider
PI	Principal Investigator The investigator who leads the study conduct at an individual study center. Every study center has a principal investigator.
PONV	Post-Operative Nausea and Vomiting
Mg	Milligram
mL	Milliliter
NSAIDS	Nonsteroidal Anti-inflammatory Drugs
ODT	Oral Dissolvable Tablet
Oz	Ounce
SpO2	Peripheral Capillary Oxygen Saturation
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SPID	Sum of Pain Intensity Difference

Abbreviation or Specialist Term	Explanation
TID	3 times a day
TEAEs	Treatment Emergence Adverse Events
PE	Physical Examination

1. INTRODUCTION

1.1. Background

The majority of patients who undergo surgical procedures are likely to experience post-operative pain. Furthermore, 75% of those patients report the pain as moderate, severe or extreme (1). These patients require effective postoperative pain control in order to provide comfort, earlier mobilization, faster recovery, and decreased likelihood of post-operative complications.

Traditionally, acute post-operative pain management has relied on opioid medications to target central mechanisms involved in the perception of pain. Opioids bind to receptors in the central nervous system and peripheral tissues and modulate the effect of the nociceptors. They can be administered via oral, transdermal, parenteral, neuraxial, and rectal routes. Morphine is the standard choice for opiates and is widely used for acute post-operative pain. However, morphine has significant amount of first-pass metabolism in the liver with only around 40 to 50% of the amount absorbed actually reaching the nervous system (2). Most of the morphine is processed in the kidneys and eliminated from the body in urine. Oxycodone, another opioid agonist, is being widely used to alleviate moderate-to-severe pain but even then its bioavailability is 67–80% (3).

It would be beneficial to manage patients' post-operative pain effectively with opioids through a route that by-passes liver metabolism and is feasible in the ambulatory setting. An option would be the sublingual route which allows drug to diffuse to the blood through the tissues under the tongue and avoiding the first pass effect by the liver.

Buprenorphine is currently approved by the FDA to be administered as a transdermal patch or a buccal film to treat chronic pain. Buprenorphine binds to mu-receptors with high affinity but less intrinsic activity compared to full opioid agonists. Because of its partial agonist features, the efficacy and adverse effects of buprenorphine are thought to plateau at higher doses. Past research suggests that buprenorphine may show a respiratory depression “ceiling effect” where analgesic efficacy continues to escalate at higher doses, but respiratory depression does not. Dahan et al. (4) found that when tested over a dose range, buprenorphine demonstrated a ceiling effect for respiratory depression but not for analgesia. In a separate study, Dahan et al. (5) found that the ceiling effect shown for buprenorphine-induced respiratory depression was not demonstrated for the full μ -agonist opioid fentanyl. In addition, buprenorphine dissociates from the mu-receptor very slowly, which likely accounts for its longer duration of action than morphine, and its low level of manifested physical dependence. Actions at kappa-receptors, where buprenorphine is an antagonist, are believed to produce alterations in the perception of pain and the emotional response to pain.

It is postulated that using buprenorphine for acute pain relief through the sublingual spray route may have multiple benefits over full opioids such as less constipation, milder withdrawal and less abuse potential, better efficacy in older population, and treatment in a broad range of pain types. In addition, its use through sublingual is advantageous over oral administration such that the effect is more direct and faster (6).

The proposed study will evaluate the safety with the administration of buprenorphine delivered as a sublingual spray for post-operative pain.

1.2. Clinical Experience

The drug being investigated in this study is the sublingual preparation spray of buprenorphine. Buprenorphine has been shown to be safe and effective in its currently marketed oral forms: tablet (Subutex®) and buccal film (Belbuca™) (www.accesseddata.fda.gov). Subutex® sublingual tablets have been studied in 1834 patients and Belbuca™ has been evaluated in three 12-week double-blind, placebo-controlled clinical trials in opioid-naïve and opioid-experienced patients with moderate-to-severe chronic low back pain. Two of the 3 studies showed efficacy in lower back pain.

Buprenorphine Sublingual Spray has been studied in a Phase 3, multicenter, randomized, double-blind, multiple-dose, parallel-group, placebo-controlled study (Study INS005-15-062) to evaluate the safety and efficacy of 3 dosing regimens (0.5 mg, 0.25 mg, or 0.125 mg 3 times daily [TID]) in subjects with moderate to severe pain after bunionectomy). In summary, the study demonstrated that the Buprenorphine Sublingual Spray given TID at doses of 0.125 mg, 0.25 mg, or 0.5 mg had significantly higher efficacy than a placebo spray over 48 hours after the start of dosing as measured using the primary endpoint of SPID-48 score in subjects with acute pain following bunionectomy surgery. Overall, all doses of Buprenorphine Sublingual Spray evaluated in this study were safe and generally well tolerated.

1.3. Dose Selection Rationale

In study INS005-15-062, Buprenorphine Sublingual Spray 0.5 mg TID demonstrated the largest reduction in pain as assessed by SPID-48 and was statistically significant to placebo ($p < 0.0001$). The 0.25 mg tid and 0.125 mg tid doses also demonstrated statistically significant reductions in SPID-48 ($p = 0.0108$ and $p = 0.0120$, respectively). Because all treatments were generally well tolerated, the 0.5 mg TID dose is being studied.

1.4. Summary of Potential Risks and Benefits

There are no anticipated benefits of participation.

The potential risks of study participation include those associated with exposure to Buprenorphine Sublingual Spray and the risks of medical evaluation, including venipuncture. Adverse Events common with buprenorphine are constipation, dizziness, headache, nausea, sweating, and vomiting. Severe side effects that may occur with buprenorphine include rash, hives, itching, difficulty breathing, tightness in the chest, swelling of the mouth, face, lips, or tongue, anxiety or nervousness, dark urine, fast or irregular heartbeat, mental or mood changes, pale stools, pain, redness, or swelling at the injection site, slow or shallow breathing, unusual weakness, vision changes, yellowing of eyes or skin. Safety monitoring will occur during the in-clinic period of the study. All subjects will be actively monitored with pulse-oximetry (SpO₂) and ECG after surgery.

A summary of the pharmaceutical properties and known potential risks of Buprenorphine Sublingual Spray is provided in the current version of the investigator's brochure. The

investigator must become familiar with all sections of the investigator's brochure and the prescribing information before the start of the study.

1.5. Primary Objective

To evaluate the safety and tolerability based on the incidence of adverse experiences of Buprenorphine Sublingual Spray (0.5 TID) compared with standard post-operative narcotic therapy in subjects with postoperative pain. Standard post-operative narcotic therapy is defined as Morphine Intravenous Injection (IV) (4 mg TID) followed by Oxycodone Hydrochloride Tablet (10 mg TID).

2. STUDY OBJECTIVES

2.1. Primary Objective

To evaluate the safety and tolerability based on the incidence of adverse experiences of Buprenorphine Sublingual Spray (0.5 TID) compared with standard post-operative narcotic therapy in subjects with postoperative pain. Standard post-operative narcotic therapy is defined as Morphine Intravenous Injection (IV) (4 mg TID) followed by Oxycodone Hydrochloride Tablet (10 mg TID).

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a Phase 2, randomized (stratified according to surgery and postoperative nausea and vomiting risk factors), open label, multiple-dose, comparator controlled, parallel-group, study to evaluate the safety and tolerability of Buprenorphine Sublingual Spray (0.5 mg TID) versus standard postoperative narcotic therapy in subjects with postoperative pain. Standard postoperative narcotic therapy is defined as Morphine IV (4 mg TID) for 24 hours followed by Oxycodone Hydrochloride Tablet (10 mg TID).

The study will be composed of four periods: Screening Period (Day -28 to -1), Surgical Period (Day 1), Treatment Period (Inpatient Days 1 to 4 / Outpatient Days 4 to 7), and Follow-up Period (Day 8, +2 day window).

Screening Period (Day -28 to -1): Subjects who meet all inclusion and no exclusion criteria will be eligible for enrollment. After providing written Informed Consent, subjects will undergo study specific screening procedures as outlined in Appendix 4: Schedule of Events.

3.1.1. Surgical Period (Day 1):

Subjects will be admitted to the study site on the morning of the scheduled surgery on Day 1. Anesthesia will be established using standardized techniques, as appropriate, for each surgical procedure. Surgical procedures will be bunionectomy, breast augmentation, and abdominoplasty. For nausea prophylaxis, all subjects will receive a uniform standard of care regimen including:

10 mg of dexamethasone at induction and 8 mg of ondansetron near the end of surgery. Vitals, pulse oximetry, and ECG measurements will be recorded as outlined in the Appendix 4: Schedule of Events. Concomitant medications and Adverse Events will be recorded as outlined in Appendix 4: Schedule of Events.

3.1.2. Treatment Period (Inpatient Days 1 to 4 / Outpatient Days 4 to 7):

Within 4 hours after surgery, subjects who meet post-surgical eligibility criteria will be assigned to 1 of 2 treatment groups: Buprenorphine Sublingual Spray 0.5 mg TID or standard of care postoperative narcotic therapy defined as Morphine 4 mg TID for 24 hours followed by Oxycodone 10 mg TID. Randomization will be stratified according to surgical procedure and baseline PONV risk factors. The first dose of investigational drug may be received any time between 0-4 hours after surgery and should be administered either in the surgical recovery room or in the clinical research unit and does not need to be immediately administered after meeting post-surgical eligibility requirements. The time of administration of the first dose of study drug will be defined as Time 0 and the inpatient Treatment Period will continue through 72 hours after Time 0 as per Appendix 4: Schedule of Events.

Subjects will be admitted to the study site on the morning of the scheduled surgery (Day 1), will remain at the study site until Postoperative Day 4 (a total of 3 nights at the study site) then be evaluated to participate in the outpatient setting and must meet eligibility criteria in order to proceed to the outpatient treatment period Days 4 to 7.

3.1.3. Follow-up (Day 8):

Subjects will be instructed to return unused outpatient study drug and diary to study personnel at the Follow-up Visit on Day 8 (+2 day window). For additional assessments refer to Appendix 4: Schedule of Events.

3.2. Subject Selection

All subjects must satisfy the following criteria and post-surgical eligibility criteria to be considered eligible for the study.

3.2.1. Inclusion Criteria

1. Is able to speak and understand the language in which the study is being conducted, is able to understand and comply with the procedures and study requirements, and has voluntarily signed and dated an informed consent form approved by an Institutional Review Board before the conduct of any study procedure.
2. Is a male or female ≥ 18 and ≤ 65 years of age.
3. Scheduled for elective bunionectomy, breast augmentation (in women only), or abdominoplasty.
4. Is classified using the American Society of Anesthesiologists Physical Status Classification System as P1 to P2.
5. If female, is either not of childbearing potential (defined as postmenopausal for at least 1 year or surgically sterile [bilateral tubal ligation, bilateral oophorectomy, or

hysterectomy]) or practicing one of the following medically acceptable methods of birth control:

- a. Hormonal methods such as oral, implantable, injectable, vaginal ring, or transdermal contraceptives for a minimum of 1 full cycle (based on the subject's usual menstrual cycle period) before study drug administration;
 - b. Total abstinence from sexual intercourse since the last menses before study drug administration;
 - c. Intrauterine device; OR
 - d. Double-barrier method (condoms, sponge, or diaphragm with spermicidal jellies or cream).
6. Has a body weight ≥ 45 kg and a body mass index (BMI) ≤ 40 kg/m².
 7. Is willing and able to comply with study requirements (including diet, alcohol, and smoking restrictions), complete evaluations and diary, remain at the study site for ≥ 72 hours, and return for follow up 8 + 2 days after surgery.

3.2.2. Exclusion Criteria

Subjects will be excluded for any of the following:

1. Has a known history of allergic reaction or clinically significant intolerance to acetaminophen, aspirin, opioids, or any nonsteroidal anti-inflammatory drugs (NSAIDs); history of NSAID-induced bronchospasm (subjects with the triad of asthma, nasal polyps, and chronic rhinitis are at greater risk for bronchospasm and should be considered carefully); or hypersensitivity, allergy, or significant reaction to sulfa (including sulfonamide) medicines, ingredients of the study drug, or any other drugs used in the study, including anesthetics and antibiotics that may be required on the day of surgery.
2. Has experienced any surgical complications or other issues that, in the investigator's opinion, could compromise the subject's safety if he or she continues into randomized treatment or could confound the results of the study.
3. Has a known or suspected history of alcoholism or drug abuse or misuse within 2 years of Screening or evidence of opioid tolerance or physical dependence before dosing with the study drug.
4. Has any clinically significant unstable cardiac, respiratory, neurological, immunological, hematological, or renal disease, or any other condition that, in the investigator's opinion, could compromise the subject's welfare, ability to communicate with the study staff, or otherwise contraindicate study participation.
5. Has long QT Syndrome, a family history of long QT Syndrome, or is taking Class IA or Class III antiarrhythmic medications.
6. Has a history or current diagnosis of a significant psychiatric disorder that, in the investigator's opinion, would affect the subject's ability to comply with the study requirements.

7. Has tested positive either on the urine drug screen or on the alcohol Breathalyzer test. Subjects who test positive at Screening only and can produce a prescription in their name from their physician for the medication producing the positive test may be considered for study enrollment at the investigator's discretion. However, they must test negative on the day of the surgery.
8. Has a history of a clinically significant (in the investigator's opinion) gastrointestinal (GI) event within 6 months before Screening or has any history of peptic or gastric ulcers or GI bleeding.
9. Has an active infection, mucositis, cold sores, viral lesions, local irritation, or in the investigator's opinion has significant periodontal disease of the oral cavity. In addition, recent (within 1 year) piercing of the tongue or anywhere in the oral cavity.
10. Has a surgical or medical condition of the GI or renal system that, in the investigator's opinion, might significantly alter the absorption, distribution, or excretion of any drug substance.
11. Is considered by the investigator, for any reason (including, but not limited to, the risks described as precautions, warnings, and contraindications in the current version of the investigator's brochure for Buprenorphine Sublingual Spray), to be an unsuitable candidate to receive the study drug.
12. Is receiving systemic chemotherapy, has an active malignancy of any type, or has been diagnosed with cancer within 5 years before Screening (excluding squamous or basal cell carcinoma of the skin).
13. Is currently receiving anticoagulants (eg, heparin or warfarin). Low-dose aspirin for cardioprotection is allowed.
14. Has used drugs known to be a strong inhibitor or inducer of CYP3A4 within 1 weeks before surgery.
15. Has received a course of systemic corticosteroids (either oral or parenteral) within 1 months before Screening (inhaled nasal steroids and topical corticosteroids are allowed).
16. Has a history of chronic use (defined as daily use for >2 weeks) of NSAIDs, opiates, or glucocorticoids (except inhaled nasal steroids and topical corticosteroids) within 1 month before study drug administration. Aspirin at a daily dose of ≤ 325 mg is allowed for cardiovascular prophylaxis if the subject has been on a stable dose regimen for ≥ 30 days before Screening and has not experienced any relevant medical problem.
17. Has a significant renal or hepatic disease, as indicated by clinical laboratory assessment (results $\geq 3 \times$ the upper limit of normal [ULN] for any liver function test, including aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase, or creatinine $\geq 1.5 \times$ ULN).
18. Has any clinically significant laboratory or 12-lead electrocardiogram finding at Screening that in the investigator's opinion contraindicates study participation.
19. Has screening systolic blood pressure ≥ 160 mmHg and diastolic blood pressure > 100 mmHg (may be repeated one additional time after 5 minutes rest to verify). The

investigator may, at his discretion, choose to exclude subjects with hypertensive levels lower than these if he deems it in the best interest of the subject.

20. Has a history of sleep apnea or other obstructive airway disease.
21. Has a history of nausea and vomiting with buprenorphine products.
22. Has significant difficulties swallowing capsules or is unable to tolerate oral medication.
23. Previously participated in another clinical study of Buprenorphine Sublingual Spray or received any investigational drug or device or investigational therapy within 30 days before Screening.

3.2.3. Post-surgical eligibility requirements:

The subject will be assessed for the following postoperative eligibility criteria:

1. Subjects must be awake, breathing spontaneously without significant respiratory depression.
2. Subjects must not be actively vomiting or complaining of severe nausea.
3. Subjects must be able to answer questions and follow commands.
4. Subjects must not have surgical complications that could compromise safety of the subject or confound the results of the study.

3.3. Removal of Subjects from Therapy or Assessment

Subjects are free to terminate their participation in the study at any time and for any reason. Likewise, a subject may be terminated from the study by the Investigator if the Investigator determines that it is not the subject's best interest to continue participation. The Investigator has the right to withdraw subjects from the study at any time for an effect that is intolerable or otherwise unacceptable to the subjects, for intolerable or unacceptable AEs, intercurrent illness, noncompliance with study procedures, administrative reasons, or in the investigator's opinion to protect the patient's best interest. Subjects may be considered terminated if they state an intention to terminate, or fail to comply or return for assessments/ visits, or become lost to follow up for any other reason. If early termination occurs for any reason, the Investigator must determine the primary reason for a subject's early termination from the study and this information must be recorded in the subject's eCRF. Subjects will be required to return on Day 7 if early termination occurs and they do not withdraw consent.

Subjects whose pain or nausea cannot be adequately managed in the Investigator's opinion by a combination of study drug and rescue medication will be discontinued from further study participation. Their pain or nausea will be managed according to usual standard of care at the Investigator's discretion. In addition, subjects who develop unacceptable side effects during the study will be discontinued from further study participation.

The Investigator must document early or other termination for randomization and drug reconciliation purposes.

3.4. Dose Adjustment Criteria

There will be no dose adjustments for IP and the reference drugs.

4. TREATMENTS

4.1. Treatments Administered

Eligible subjects meeting all study entry criteria will be randomly allocated in a 1:1 ratio to one of the following treatments: Buprenorphine Sublingual Spray (1 x 0.5 mg TID; total of 21 doses); or reference drugs Morphine Intravenous Injection (1 x 4 mg TID for 24 hours; total of 3 doses) followed by Oxycodone Hydrochloride Tablet (1 x 10 mg TID; total of 18 doses).

4.2. Identity of Investigational Product

The drug is formulated as a sublingual spray. The product is a clear solution filled into a glass vial, stoppered and assembled within a unit-dose sublingual spray pump. Priming is not required. Each spray pump delivers 0.5 mg of buprenorphine.

4.3. Method of Assigning Subjects to Treatment Groups

Up to 100 subjects will be dosed in this study. The sample size is not based on statistical considerations. The number of subjects planned for enrollment is considered sufficient to achieve the study objectives.

Randomized treatment will be assigned utilizing a computer generated randomization scheme. Patients will be randomly assigned to treatment administered in a 1:1 assignment ratio according to the randomization scheme. All study doses administered will be according to IWRS to ensure that study personnel will not be aware of the next subject's treatment assignment until the decision to randomize that subject has been made. Randomization will be stratified by surgical procedure and baseline PONV risk factors. Patients with PONV risk factors of 0-2 will be stratified as low risk and 3-4 as high risk.

4.4. Selection and Timing of Dose for Each Subject

The buprenorphine dose was chosen based on a Phase 3 trial which showed that Buprenorphine 0.5 mg Sublingual Spray TID is effective in reducing moderate-to-severe pain after bunionectomy compared to placebo and is generally well tolerated. The reference drugs morphine 4 mg TID for 24 hours followed by oxycodone 10 mg TID was chosen because the regimen is accepted as standard postoperative narcotic therapy.

4.5. Blinding

This is an open-label study without treatment blinding.

4.6. Treatment Compliance

All subjects will receive IP at the study site under the surveillance of appropriate study personnel during Inpatient Treatment Days 1 to 4. Subjects will receive IP to take home on Outpatient Treatment Days 4 to 7 and will be instructed how to correctly dose with IP at home. The IP lot number(s) will be recorded in the subject's chart/source documents. Exposure (total dose of study drug) for the Inpatient, Outpatient and overall treatment periods will be recorded.

During Inpatient Treatment, any rescue medication administered to the subject will be recorded in the subject's source.

4.7. Permitted and Prohibited Therapies

4.7.1. Permitted Therapies

Prescription medications that in the opinion of the investigator will not potentially interact with buprenorphine, morphine, oxycodone, or interfere with its respiratory effects may be permitted during the course of the study.

4.7.2. Prohibited Therapies

The following therapies are prohibited:

- Anticoagulants (e.g., heparin or warfarin). Aspirin at a daily dose of ≤ 325 mg is allowed for cardiovascular prophylaxis if the subject has been on a stable dose regimen for ≥ 30 days before Screening and has not experienced any relevant medical problem.
- Drugs known to be a strong inhibitor or inducer of CYP3A4 within 1 week before surgery.
- Systemic corticosteroids (either oral or parenteral) within 1 month before Screening (inhaled nasal steroids and topical corticosteroids are allowed).
- Chronic use (defined as daily use for >2 weeks) of NSAIDs, opiates, or glucocorticoids (except inhaled nasal steroids and topical corticosteroids) within 1 months before study drug administration.
- Agents that could affect the analgesic response (such as central alpha agents [clonidine and tizanidine], neuroleptic agents, and other antipsychotic agents) within 2 weeks before Screening. Selective serotonin reuptake inhibitors and selective noradrenergic reuptake inhibitors are allowed if the subject has been on a stable dose for at least 8 weeks before Screening and does not anticipate a dose change during the course of the study.

Subjects receiving excluded therapies will be ineligible for study enrollment or for continuation in the study.

Subjects should not have anything orally except room-temperature water within 15 minutes of each dose.

4.8. Rescue Medication

Rescue for inadequate analgesic response during confinement to the study center during the first 72 hours for pain will be acetaminophen 1000 mg every six hours and/or ketorolac 30 mg every six hours, as needed. On outpatient days 4-7 subjects will be provided with acetaminophen, and will be advised to take acetaminophen 1000 mg every six hours as needed for rescue analgesia.

Rescue for postoperative nausea during confinement to the study center during the first 72 hours will be Zofran 4 mg IV per the discretion of the clinician. On outpatient days 4-7, subjects will be administered Zofran ODT (oral dissolvable tablet) to be taken as needed.

The rescue medication and specific reason for use will need to be captured in the subject outpatient diaries.

5. STUDY DRUG MATERIALS AND MANAGEMENT

5.1. Labeling and Packaging

5.1.1. Labeling

The labels for the investigational product will contain all information according to regulatory requirements.

5.1.2. Packaging

The test product is formulated as a sublingual spray. Buprenorphine sublingual spray is a clear solution filled into a glass vial that is stoppered and assembled within a unit-dose sublingual spray pump. Priming is not required. Each spray pump delivers 0.5 mg of buprenorphine.

Morphine will be supplied in clear glass snap-ampules (1 mL) containing 4 mg of morphine.

Oxycodone Hydrochloride Tablet will be supplied as uncoated tablet containing 10 mg of oxycodone hydrochloride.

5.2. Dispensing and Storage

The study treatments will be shipped to site upon receipt of appropriate Drug Enforcement Administration (DEA) documentation. Upon receipt of the study drug, the supplies will be inventoried and stored in an environmentally controlled and secure, limited access area.

Buprenorphine Sublingual Spray will be stored at a temperature of 20 -25 degrees °C (inclusive).

5.3. Drug Supply and Accountability

Insys Development Company, Inc. will supply sufficient quantities of Buprenorphine Sublingual Spray, Morphine IV, Oxycodone Hydrochloride Tablets, Acetaminophen, Ketorolac, Naloxone Zofran IV, and Zofran ODT to complete the study.

The investigator must maintain adequate records showing the receipt, dispensing, return, or other disposition of the IP, including the date, quantity, lot number, and identification of subjects (subject number and initials) who received the IP. The investigator will not supply the IP to any person except those named as sub-investigators on Form FDA 1572, designated study personnel, and subjects in this study. The Investigator will not dispense the IP from any study sites other than those listed on Form FDA 1572. The IP may not be relabeled or reassigned for use by other subjects. If any of the IP is not dispensed; is lost, stolen, spilled, unusable, or is received in a damaged container, this information must be documented and reported to Insys Development Company and appropriate regulatory agencies, as required.

On the last study visit day, subjects will return any unused study drug.

Upon completion of the study, all unused IP and other study materials are to be reconciled and returned to Insys Development Company (or designee) as per Insys Development Company's written instructions. Reconciliation forms will be provided and must be included with all return.

To prevent theft or diversion, study drug must be stored in a securely locked, substantially constructed cabinet or enclosure appropriate for a Schedule II drug. Any actual or suspected theft, diversion, or loss of study drug must be immediately reported to the principal investigator

at the study center and DEA license holder to ensure federal reporting requirements and sponsor notification requirements are met.

Specific instructions as to how to handle the study drug, including storage, during the outpatient treatment period will be provided to the patients in the written informed consent form/opioid agreement, which the patient must sign to qualify for the study. The informed consent form/written opioid agreement will provide information about the medication the patient may be taking for pain management (Buprenorphine 0.5 mg sublingual spray) and to assure that the patient can comply with all state and federal regulations concerning the medical use of controlled substances. The patient will be responsible for keeping the assigned study drug in a safe and secure place, such as a locked cabinet or safe. The patient will be expected to protect the assigned study drug from loss or theft. Stolen study drug should be reported to the police and to the study physician immediately. If the assigned study drug is lost, misplaced, or stolen, the study investigator may choose not to replace the study drug and may terminate the patient from the study.

6. STUDY ASSESSMENTS

6.1. Efficacy Assessments

No efficacy assessments will be measured.

6.2. Safety Assessments

Safety variables will include physical and oral cavity examinations, vital signs, pulse-oximetry, clinical laboratory testing, electrocardiogram collection (ECG), concomitant medications, and adverse event assessments.

6.2.1. Demographics and Medical History

Each potential study participant will have the following assessments by the Investigator or designee during the Screening Period, within 28 days prior to study start: demographic data, including sex, age, race, ethnicity, body weight (kg), height (cm), and body mass index (BMI [kg/m^2]), medical and surgical history, medications history, and concomitant medications.

Height/weight and BMI will also be recorded. BMI will be calculated using the following NIH website: https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi-m.htm

6.2.2. Physical Examinations

A physical examination (excluding the genitourinary examination) will be performed as per Appendix 4: Schedule of Events. Systems include HEENT, cardiovascular, respiratory, gastrointestinal, neurological, dermatologic, and musculoskeletal systems.

6.2.3. Oral Cavity Examinations

Oral cavity examination will be performed at the time-points specified in Appendix 4: Schedule of Events. The oral examination at Screening will exclude subjects with any active infection, mucositis, cold sores, viral lesions, local irritation, or periodontal disease of the oral cavity. In addition, subjects with recent (within 1 year) piercing of the tongue or anywhere in the oral

cavity will be excluded. If there is a recent history of significant dental disease, the investigator may decide to exclude the subject. All other oral examinations will check for mucositis and local irritation.

6.2.4. Post-Operative Nausea and Vomiting (PONV) Risk Factor Assessment

PONV risk will be assessed at screening to assess the likelihood of nausea and vomiting after surgery using the Apfel scale (7)

6.2.4.1. Table 1: (PONV) Risk Factor Assessment

Risk Factors	Points
Post-operative Opioids (if planned)	1
Non Smoker	1
Female Gender	1
History of postoperative nausea and vomiting / Motion Sickness	1
Risk score = sum	0...4

Score	Probability of Postoperative Vomiting and Nausea (%)
0	10
1	21
2	39
3	61
4	79

Assessment will be collected in the source documentation and entered into IWRS for randomization. Patients with PONV risk factors of 0-2 will be classified as low risk and 3-4 as high risk.

6.2.5. Vital Signs

Vitals signs will be measured at time-points specified by Appendix 4: Schedule of Events. Vital signs will be taken after the subject has been sitting/reclined position for 5 minutes. Vital signs will also be measured before ET if a subject discontinues. Vital signs will include blood

pressure, heart rate, respiration rate, oral body temperature. Assessments will be repeated based on the Investigator's discretion.

6.2.6. Pulse Oximetry

Pulse oximetry will be measured continuously for safety and recorded at selected times as specified by the time point in Appendix 4: Schedule of Events. Pulse oximetry will be taken after the subject has been sitting/reclined position for 5 minutes.

6.2.7. Electrocardiograms

A standard 12-lead ECG will be performed at the time-points specified in Appendix 4: Schedule of Events. The 12-lead ECG will be collected after the subject has been supine for 5 minutes. All ECG recordings will be identified with the subject number, initials, date, and time of the recording. The ECG will be evaluated for any clinically relevant cardiovascular conditions, defined as any clinically significant abnormalities identified by the reader related to coronary artery disease, coronary spasm, abnormal heart rhythm, hypertrophic cardiomyopathy, heart failure, rheumatic heart disease, or myocarditis.

6.2.8. Clinical Laboratory Assessments

Clinical laboratory tests will be performed as per Appendix 4: Schedule of Events. Pregnancy tests and urine drug screens will be performed at Screening and before surgery. Samples for the following laboratory tests will be collected:

6.2.8.1. Hematology

Hemoglobin, hematocrit, red blood cell count, red blood cell indices, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count (or estimate), and white blood cell count including differential.

6.2.8.2. Serum Chemistry

Albumin, total bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, cholesterol, glucose, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase, uric acid, creatinine with calculated creatinine clearance (Cockcroft-Gault method).

6.2.8.3. Urinalysis

pH, specific gravity, blood, glucose, protein, and ketones.

6.2.8.4. Pregnancy Screen

For women of childbearing potential only; a serum test at Screening and a urine test before surgery.

6.2.8.5. Urine Drug Screen

Urine drug screen will be performed to test for amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, and tetrahydrocannabinol.

6.2.8.6. Alcohol Breathalyzer

An alcohol breathalyzer test will be performed as per Appendix 4: Schedule of Events.

6.2.8.7. Virus Serology

Virus serology will be completed to test for Hepatitis B surface antigen, antibodies to hepatitis C, and antibodies to HIV at the screening visit.

6.2.9. Adverse Events and Serious Adverse Events

6.2.9.1. Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a subject administered a pharmaceutical product during the course of a clinical investigation. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not thought to be related to the investigational product.

Subjects will be monitored throughout the study for AEs. Monitoring for treatment-emergent AEs will begin as soon as the subject is dosed. All AEs must be followed until they are resolved or stabilized, or until all attempts to determine resolution of the event are exhausted. The investigator should use their discretion in ordering additional tests as necessary to monitor the progress of such events.

Adverse Events reported prior to dose administration will be recorded as part of the subject's medical history.

An AE may be:

- A new illness, not documented in the subject's medical history;
- Worsening of a concomitant illness;
- An effect of the study medication; it could be an abnormal laboratory value, as well as a significant shift from baseline within normal range which the qualified investigator or medical qualified designate considers to be clinically important;
- A combination of two or more of these factors.

Surgical procedures themselves are not AEs. They are therapeutic measures for conditions that required surgery. The condition for which the surgery is required is an AE, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not AEs, if the condition(s) was (were) known before the start of study treatment. In the latter case, the condition should be reported as medical history.

6.2.9.2. Classification of Adverse Events

Adverse Events are to be recorded on the AE page of the subject's case report form (CRF). Severity will be graded according to the following definitions:

- Mild: The subject experiences awareness of symptoms but these are easily tolerated or managed without specific treatment.

- Moderate: The subject experiences discomfort enough to cause interference with usual activity, and/or the condition requires specific treatment.
- Severe: The subject is incapacitated with inability to work or do usual activity, and/or the event requires significant treatment measures.

Action taken will be categorized as none, study drug discontinued, dose modified, required concomitant medication, required procedure, or other.

Event outcome at resolution or time of last follow-up will recorded as event resolved, resolved with sequelae, ongoing, or death.

6.2.9.3. Causality/Drug Relationship Assessment

The relationship of the event to the study drug should be determined by the investigator according to the following criteria:

- Definitely related: The event follows a reasonable temporal sequence from the time of drug administration that cannot be explained, follows a known or expected response pattern to the study drug, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by other factors such as the subject's clinical condition, intercurrent illness, or concomitant drug.
- Probably related: The event follows a reasonable temporal sequence from the time of drug administration, and/or follows a known response pattern to the study drug, and cannot be reasonably explained by other factors such as the subject's clinical condition, intercurrent illness, or concomitant drugs.
- Possibly related: The event follows a reasonable temporal sequence from the time of drug administration, and/or follows a known response pattern to the study drug, but could have been produced by other factors such as the subject's clinical condition, intercurrent illness, or concomitant drugs.
- Unlikely related: The event follows little or no temporal sequence from the time of drug administration that makes a causal relationship improbable and/or other factors such as the subject's clinical condition, intercurrent illness, or concomitant drugs is a more likely alternative.
- Not related: The event is most likely produced by other factors such as the subject's clinical condition, intercurrent illness, or concomitant drugs, and does not follow a known response pattern to the study drug, or the temporal relationship of the event to study drug administration makes a causal relationship unlikely.

6.2.9.4. Definition of Serious Adverse Events

A serious AE (SAE) is any AE that fulfills any of the following criteria, as per 21 CFR 312.32:

- Results in death;
- Is life-threatening;
- Requires in-patient hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect;
- Is medically significant or requires intervention to prevent one of the outcomes listed above.

Serious AEs will be captured from the time of consent through the end of the study.

6.2.9.5. Actions Taken for Serious Adverse Events

Actions taken may consist of:

- None: No action taken
- Treatment: Standard of care measures instituted
- Drug withdrawn: Study medication was permanently discontinued because of the AE
- Unknown: Not known, not observed, not recorded, or refused

6.2.9.6. Outcome at the Time of Last Observation for Serious Adverse Events

The outcome at the time of last observation will be classified as:

- Recovered/resolved
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Death
- Unknown

6.2.9.7. Adverse Event Recording and Reporting

Adverse Events will be recorded throughout the study in the source documents and in the CRFs. The investigator will rate AEs for seriousness, intensity, causality, action taken, and outcome as described in the previous section.

Expedited reporting is required for serious unexpected adverse drug reactions. Fatal or life-threatening unexpected drug reactions must be reported by the Sponsor to regulatory agencies no more than 7 days after the Sponsor's first knowledge of the reaction; followed by a complete report as possible within 8 additional days. Unexpected drug reactions must be reported no later than 15 days after the Sponsor's first knowledge of the reaction. In order to comply with these requirements, the investigator or delegate must inform the Sponsor immediately upon occurrence of any SAE. The site will complete the SAE Report Form as thoroughly as possible and email/fax it to Insys Development Company within 24 hours of the investigator's first knowledge of the event.

Sponsor contact information is listed below:

[REDACTED]

[REDACTED]

Insys Development Company Development Company, Inc.

Email: [REDACTED]

Telephone: [REDACTED]

These SAE reports must contain the following information:

- A. Study name/number
- B. Study drug
- C. Investigator details (name, phone, fax, e-mail)
- D. Subject number
- E. Subject initials
- F. Subject demographics
- G. Clinical event
 - 1) Description
 - 2) Date of onset
 - 3) Treatment (drug, dose, dosage form)
 - 4) Adverse event relationship to study drug
 - 5) Action taken regarding study drug in direct relationship to the AE
- H. If the AE was fatal or life-threatening
- I. Cause of death (whether or not the death was related to study drug)
- J. Autopsy findings (if available)

The Sponsor or its representative will be responsible for notification to regulatory agencies.

6.2.9.8. Adverse Event Follow-Up

All non-serious AEs that are not related or unlikely to be related to study treatment will be followed until the end of study participation. All SAEs or AEs that are considered as possibly, probably, or definitely related to treatment will be followed until resolution or stabilization.

6.2.9.9. Special Considerations

Pregnancy

All women of childbearing potential who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation. Women should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted before IP administration on every woman of childbearing potential. A woman who is found to be pregnant at the Screening Visit will be excluded from the study and considered to be a screening failure.

If a subject becomes pregnant, the investigator must report the pregnancy within 24 hours of learning of the pregnancy. The investigator should contact the designated individual(s) who receive SAE notification and record information related to the pregnancy on the designated form.

The investigator is responsible for following the pregnancy until delivery or termination. These findings must be reported on the designated form and forwarded to the designated individual(s). The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly.

Subjects who become pregnant during the course of the study will be followed to collect data on lactating women and health of the child (for births) or until termination of the pregnancy.

7. STUDY PROCEDURES

The assessments and procedures that will be conducted during this study are summarized in Appendix 4: Schedule of Events

7.1. Screening (Day -28 to -1)

The subject must be screened prior to enrollment in the study. The following procedures will be performed at screening:

- Obtain written informed consent
- Review inclusion/exclusion criteria
- Collect demographic information, including height/weight, BMI
- Record medical and surgical history
- Perform a physical examination
- Perform oral cavity exam
- Measure resting vital signs (blood pressure [BP], heart rate [HR], respiratory rate [RR], temperature)
- Measure pulse oximetry
- Perform 12-lead electrocardiogram (ECG)

- Perform serum pregnancy test on women of child-producing potential
- Collect hematology, chemistry, and urinalysis samples
- Collect serology sample
- Perform urine drug screen and alcohol breath test
- Record concomitant medications and concomitant therapies, including current therapies taken 30 days prior to Screening (e.g. prescription and non-prescription medications)
- Record Adverse Events
- PONV risk assessment
- X-ray and podiatric examination (applies only to subjects receiving bunionectomy)
- ASA classification

7.2. Surgical Period (Day 1)

7.2.1. Pre-surgery/Morning of Surgery

Subjects will be admitted to the study site on the morning of the scheduled surgery (Day 1). The following procedures will be performed prior to surgery:

- Collect medical/surgical history (changes since screening)
- Review inclusion/exclusion criteria
- Perform a physical examination
- Perform oral cavity exam
- Measure vital signs (resting blood pressure, heart rate, respiratory rate, and oral body temperature)
- Perform a urine pregnancy test on women of child-producing potential
- Perform urine drug screen and alcohol breath test
- Collect concomitant medications and concomitant therapies
- Collect Adverse Events

7.2.2. Surgery and Standardized Anesthesia

Subjects who continue to meet all study entry criteria will undergo a surgical procedure (bunionectomy, breast augmentation, or abdominoplasty). Anesthesia will be established using standardized techniques. Surgical and Anesthesia protocol is summarized in Appendix 1: Surgical and Anesthesia Protocols. For nausea prophylaxis, all subjects will receive a uniform standard of care regimen which includes the following: 10 mg of dexamethasone at induction and 8 mg of ondansetron near the end of surgery. Subjects may be treated with intravenous morphine and or fentanyl for post-surgical analgesia (dose and frequency per the discretion of the investigator). Pulse oximetry will be monitored continuously after the procedure as a safety measure.

7.3. Treatment Period (Inpatient; Day 1-4)

7.3.1. Pre-Dose

Upon completion of surgery on Day 1, subjects who request pain medication within 4 hours after surgery will be assessed for post-surgical eligibility requirements. Subjects who meet all post-surgical eligibility criteria 4 hours after surgery are able to be enrolled in the study. Subjects who do not meet all entry criteria within 4 hours after surgery will not be eligible for enrollment and will receive routine post-operative care at the investigator's discretion.

Prior to dosing on Day 1, the following assessments will be performed:

- Perform 12-lead ECG
- Randomize the subject via IWRS
- Measure vital signs (resting blood pressure, heart rate, respiratory rate, and oral body temperature)
- Perform an oral cavity exam
- Collect Adverse Events
- Collect Concomitant medications and procedures

7.3.2. Drug Administration (Day 1; Time 0)

Upon completion of all pre-dose procedures on Day 1, the following assessments will be performed:

- First Dose of Study Medication administered within 4 hours of end of surgery.
- Collect Adverse Events.
- Collect concomitant medications and procedures.
- Heart rate and respiration rate will be taken at study drug administration/Time 0.

7.3.3. Inpatient Treatment Period (Day 1-4; Time 0-72)

In the inpatient treatment period (Day 1-4; Time 0-72), the following assessment will be performed:

- Heart rate and respiration rate will be taken 1 hour (\pm 10 minutes) after the first dose of study drug on Day 1, then every 2 hours (\pm 10 minutes) after Time 0.
- Blood pressure will be taken every 4 hours (\pm 10 minutes) after the first dose of study drug on Day 1 (Time 0).
- ECG will be measured at 90 minutes, 12, 24, 48 and 72 hours (\pm 10 minutes) after the first dose of study drug on Day 1 (Time 0).
- Pulse Oximetry will be continuously monitored after surgery for safety; pulse oximetry will be recorded at screening and at selected times (\pm 10 minutes), including baseline before Time 0 (prior to first dose) and at 90 minutes and 12, 24, 48, 72 hours after Time 0, and at Follow-up Visit/ET.

- Collect concomitant medications and procedures.
- Study Medication Administration will be administered every 8 hours after the First dose of study drug (Treatment Days 1 – 4).
- Oral cavity exam will be performed at 90 minutes, 12, 24, 48 and 72 hours (\pm 10 minutes) after the first dose of study drug on Day 1 (Time 0).
- Physical examination will be performed at 72 hours (\pm 4 hours).
- Collect Adverse Events.

7.3.4. Discharge From Research Site (Day 4)

Subjects will remain at the study site until all inpatient treatment procedures are completed on Day 4 (a total of 3 nights at the study site). Then the subjects will be evaluated by the investigator in order to participate in the outpatient treatment period Days 4 to 7. Prior to discharge on Day 4, the following assessments will be performed:

- Investigator to assess patients ability to continue in the outpatient treatment
 - If subjects are eligible to participate in the outpatient phase:
 - Study staff to provide outpatient dosing instructions
 - Study staff to observe subject administration of study drug dosing
 - Study staff to dispense outpatient study drug
 - Study staff to dispense rescue pain medication and nausea medications
 - Study staff to instruct subject on guidance for rescue pain medication and nausea medication
 - Study staff to provide completion instructions and dispense Outpatient Diary
 - Discharge subject from research site
 - If subjects are not eligible to participate in the outpatient phase:
 - Discharge subject from research site
- Collect Adverse Events.
- Collect concomitant medications and procedures.

7.4. Treatment Period (Outpatient; Day 4-7)

During the outpatient section of the study, subjects should not drive, operate heavy machinery, climb ladders, drink alcohol or take any other narcotics. Subjects will be instructed to call the research site prior to any additional dosing if they experience dizziness, lightheaded, sleepy, confused, slurred speech.

The following assessments will be performed during this period:

- Self-administration of study medication
- Recording of study doses in the outpatient diary
- Recording of Adverse Events in the outpatient diary
- Recording concomitant medications and procedures in the outpatient diary

7.5. Follow-up Period/End of Study/Early Termination (Day 8, + 2 day window)

Subjects will be instructed to return all outpatient study drug, rescue pain and nausea medication, and diaries to study personnel at the Follow-up Visit on Day 8 (+ 2 day window). The following assessments will be performed:

- Resting vital signs (blood pressure [BP], heart rate [HR], respiratory rate [RR], temperature)
- Measure pulse oximetry
- Perform a physical examination
- Collect hematology, chemistry, and urinalysis samples
- Perform 12-lead ECG
- Perform oral cavity exam
- Concomitant medications and procedures
- Assess and record AEs that have occurred since the last evaluation
- Collect and review outpatient diary if applicable
- Perform drug accountability and reconciliation
- Discharge subject from study

8. STATISTICS

8.1. Efficacy Endpoints

No efficacy endpoints will be assessed.

8.2. Safety Endpoints

The primary safety endpoints are the incidence of TEAEs.

The secondary safety endpoints are as follows:

- Proportion of subjects using rescue medication for nausea
- Time to first use of rescue medication for nausea following each dose of the investigational product (IP)
- Total use of rescue medication for nausea over 0 to 8 hours, 0 to 24 hours, over 0 to 48 hours, over 0-72 hours and 0-7 days
- Pulse oximetry recorded prior to study drug administration
- ECGs at 90 minutes, 12, 24, 48 and 72 hours
- Oral examinations

8.3. Sample Size Determination

No formal sample size estimate has been completed. However, a sample size of 50 subjects per treatment group is expected considered sufficient to demonstrate that the incidence of nausea and

vomiting associated with buprenorphine is similar consistent with to that of standard post-operative narcotic therapy.

8.4. Analysis Populations

Statistical analysis will be done on the safety population, which will include all subjects who are treated with the study drug. The safety population is the population for all safety assessments.

8.5. Statistical Analyses

No formal statistical hypothesis testing will be performed for this safety study.

Summary statistics will be provided for all safety variables by treatment group. For continuous variables, these statistics will typically include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, these statistics will typically include the number and percentage of subjects in each category. A Statistical Analysis Plan that describes the details of the analyses to be conducted will be finalized prior to database lock.

8.5.1. Disposition and Demographics

8.5.1.1. Disposition and Withdrawals

The numbers of subjects randomized, completing, and withdrawing, along with reasons for withdrawal, will be tabulated overall and by treatment group. The number of subjects in each analysis population will be reported.

8.5.1.2. Protocol Deviations

Protocol deviations will be identified and classified as minor or major and summarized by treatment group.

8.5.1.3. Demographics and Other Baseline Characteristics

These analyses will be conducted for the safety populations.

Demographic and baseline characteristics (including age, gender, race, weight, height, BMI, surgical procedure, surgery duration and PONV risk factor) will be summarized by treatment group and for the overall population by descriptive statistics. No formal statistical analyses will be performed.

Medical history will be listed.

Prior and concomitant medications will be classified by using the World Health Organization Drug Dictionary Anatomical Therapeutic Chemical classes and preferred terms and summarized by treatment group

8.5.2. Exposure and Compliance

The exposure to study medication during the treatment periods will be summarized by descriptive statistics. As the dose administration during the inpatient period is under the control of the study sites, compliance during that time will not be an issue. Compliance of the subject during the outpatient portion of the study will also be summarized.

8.5.3. Safety Analyses

Safety analyses will be conducted using data from the safety population. No formal inferential analyses will be conducted for safety variables. Data listings will be provided for protocol-specified safety data.

8.5.3.1. Adverse Events

The Medical Dictionary for Regulatory Activities (Version 19.0 or higher) will be used to classify all AEs. Adverse event summaries will include only TEAEs, which will be summarized for each treatment group.

The number and percentage of subjects with AEs will be displayed for each treatment group by system organ class and preferred term. Summaries of AEs by severity and relationship to the IP will also be provided. Serious Adverse Events and AEs resulting in discontinuation will be summarized separately in a similar manner. Subject listings of AEs and SAEs will be produced.

8.5.3.2. Vital Signs

Vital signs results and changes from baseline will be summarized at each time point.

8.5.3.3. ECGs and Physical Exam

Any abnormal ECG or Physical Exam finding at each time point will be summarized. Clinically significant abnormalities in ECGs or PE will be recorded as AEs.

9. STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel prior to the study, periodic monitoring visits, and meticulous data management.

9.1. Sponsor and Investigator Responsibilities

9.1.1. Sponsor Responsibilities

The sponsor, and/or sponsor's representative is obligated to conduct the study in accordance with strict ethical principles. The sponsor reserves the right to withdraw a subject from the study, to terminate participation of a study site at any time, and/or to discontinue the study.

The sponsor, or sponsor's representative, agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study according to the study protocol.

9.1.2. Investigator Responsibilities

By signing the Investigator's Agreement, the investigator indicates that she/he has carefully read the protocol, fully understands the requirements, and agrees to conduct the study in accordance with the procedures and requirements described in this protocol.

The investigator also agrees to conduct this study in accordance with all laws, regulations, and guidelines of the pertinent regulatory authorities, including and in accordance with the April

1996 International Conference on Harmonisation (ICH) Guidance for Industry E6 Good Clinical Practice (GCP) and in agreement with the 1996 Version of the Declaration of Helsinki. While delegation of certain aspects of the study to sub-investigators and study coordinators is appropriate, the investigator will remain personally accountable for closely overseeing the study and for ensuring compliance with the protocol and all applicable regulations and guidelines. The investigator is responsible for maintaining a list of all persons that have been delegated study-related responsibilities (e.g., sub-investigators and study coordinators) and their specific study-related duties.

Investigators should ensure that all persons who have been delegated study-related responsibilities are adequately qualified and informed about the protocol, IPs, and their specific duties within the context of the study. Investigators are responsible for providing Medtronic with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study will be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

9.2. Site Initiation

Study personnel may not screen or enroll subjects into the study until after receiving notification from the sponsor or sponsor's representative that the study can be initiated at the study site. The study site will not be authorized for study initiation until:

- The study site has received the appropriate institutional review board (IRB) approval for the protocol and the appropriate informed consent form (ICF).
- All regulatory documents have been submitted to and approved by the sponsor or sponsor's representative.
- The study site has a clinical trial agreement in place.
- Study site personnel, including the investigator, have participated in a study initiation meeting.

9.3. Screen Failures

Subjects who fail inclusion and/or exclusion criteria may not be rescreened for the study. Screen failures for scheduling issues may be rescreened at the investigators discretion.

9.4. Study Documents

All documentation and material provided by the sponsor, or sponsor's representative for this study are to be retained in a secure location and treated as confidential material.

9.4.1. Investigator's Regulatory Documents

The regulatory documents must be received from the investigator and reviewed and approved by the sponsor or sponsor's representative before the study site can initiate the study and before the sponsor, or sponsor's representative, will authorize shipment of investigational product (IP) to the study site. Copies of the investigator's regulatory documents must be retained at the study

site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the IB, CRF/electronic case report form (eCRF) completion guidelines, copies of regulatory references, copies of IRB correspondence, and IP accountability records should also be retained as part of the investigator's regulatory documents. It is the investigator's responsibility to ensure that copies of all required regulatory documents are organized, current, and available for inspection.

9.4.2. Case Report Forms

By signing the Investigator's Agreement, the investigator agrees to maintain accurate CRFs/eCRFs and source documentation as part of the case histories for all subjects who sign an ICF.

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor, or sponsor's representative, will provide the necessary training on the use of the specific CRFs/eCRF system used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, CRF/eCRF data for individual subject visits should be completed as soon as possible after the visit. All requested information must be entered in the CRF/electronic data capture (EDC) system according to the completion guidelines provided by the sponsor, or sponsor's representative.

9.4.3. Source Documents

All information recorded in the CRF/EDC system must be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

During the study, select CRF/eCRF data may be used as original data collection tools as long as a description of this documentation process is maintained in the investigator's study files.

Clinical laboratory data required by the protocol will be electronically transferred from the central laboratory to the sponsor or the sponsor's representative. A paper copy of the laboratory results will be provided to the study site and should be retained with each subject's source data.

The investigator will provide direct access to source data and documents for trial-related monitoring, audits, IEC/IRB review, and regulatory requirements.

9.5. Study Termination

The study may be terminated at the sponsor's discretion at any time and for any reason. Study sites may be asked to have all subjects currently participating in the study complete all of the assessments for the Follow-up visit

In the event of study discontinuation, study sites may be asked to have all subjects currently participating in the study complete all of the assessments for the Early Termination Visit.

9.6. Study Site Closure

At the end of the study, all study sites will be closed. The sponsor or sponsor's representative may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines
- Inadequate subject enrollment

9.6.1. Record Retention

The investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including, but not limited to, those defined by GCP as essential until the following occur:

- At least 2 years after the last marketing authorization for the Investigational Product has been approved or the sponsor has discontinued its research with the Investigational Product, or
- At least 2 years have elapsed since the formal discontinuation of clinical development of the Investigational Product

These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

9.6.2. Laboratory Sample Retention

Laboratory samples may be used for purposes related to this research. The samples will be stored until the sponsor has determined that specimens are no longer needed and the decision has been made that none of the samples needs to be reanalyzed. In addition, identifiable samples can be destroyed at any time at the request of the subject.

10. QUALITY CONTROL AND QUALITY ASSURANCE

The sponsor or its designee will implement and maintain quality control and quality assurance procedures with written standard operating procedures to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements. This trial will be conducted in accordance with the provisions of the Declaration of Helsinki (October 1996) and all revisions thereof, and in accordance with the FDA CFR 312.50 and 312.56, and with the ICH guidelines on GCP (CPMP/ICH/135/95).

10.1. Changes To The Protocol

Only Insys Development Company may modify the protocol. Amendments to the protocol will be made only after consultation and agreement between the sponsor and the investigator. The only exception is when the investigator assesses a subject's safety will be compromised without immediate action. In these circumstances, immediate approval of the chairman of the IEC/IRB must be sought, and the investigator should inform the sponsor and the full IEC/IRB within 5 working days after the emergency occurred. All amendments that have an impact on subject risk

or the study objectives, or require revision of the informed consent form, must receive approval from the IEC/IRB prior to their implementation.

10.2. Monitoring

The sponsor or sponsor's representative will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associate(s) (CRA[s]) will visit the investigator and study site at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRA(s) and other authorized sponsor/contract research organization (CRO) personnel access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff.

10.3. Data Review Meeting

The sponsor will review all data reported in CRFs of all subjects before database lock. The data review meeting determines whether or not all enrolled subjects can be included in the analysis population according to the specified definition of analysis populations and evaluates whether or not medical decisions of the Investigator were appropriate for important data affecting the safety and efficacy endpoint.

10.4. Protocol Violations

The Investigator will conduct the study in compliance with the protocol approved by the IRB. Modifications to the protocol should not be performed without agreement of both the Investigator and the sponsor. Changes to the protocol will require written IRB approval prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects.

The Investigator or sub-investigator should document any deviation from the protocol and the reason. If the Investigator performs a deviation from the protocol or a change of the protocol to eliminate an immediate hazard(s) to subjects, the record should be immediately submitted to the sponsor, the CRO, and the IRB by the Investigator and the IRB will provide expedited review and approval. After the Investigator has obtained approval of the IRB, the Investigator should obtain written permission of the CRO and written agreement of the sponsor.

When deviation from the protocol is required to eliminate immediate hazard(s) to subjects, the Investigator will contact the sponsor, if circumstances permit, to discuss the planned course of action. Any deviations from the protocol must be fully documented in the CRF and source documentation.

10.5. Quality Assurance Audit

This study will be subject to audit by the sponsor, CRO, or designee.

The sponsor or sponsor's representative may conduct audits on a selection of study sites, requiring access to subject notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with CRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify sponsor or sponsor's representative immediately.

11. REGULATORY AND ETHICAL CONSIDERATIONS

11.1. Regulatory Authority Approval

The investigator will ensure that the protocol and consent form are reviewed and approved by the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) prior to the start of any study procedures. The IEC/IRB will be appropriately constituted and will perform its functions in accordance with Food and Drug Administration (FDA) regulations, International Conference on Harmonization (ICH) good clinical practice (GCP) guidelines, and local requirements as applicable.

In addition, the IRB will approve all protocol amendments (except for logistical or administrative changes), written informed consent documents and document updates, subject recruitment procedures, written information to be provided to the subjects, available safety information, information about payment and compensation available to subjects, the investigator's curriculum vitae and/or other evidence of qualifications, and any other documents requested by the IRB/IEC and regulatory authority, as applicable.

11.2. Ethical Conduct of the Study

The study will be conducted in accordance with the Declaration of Helsinki and GCP according to ICH guidelines. Specifically, the study will be conducted under a protocol reviewed by an IRB or IEC; the study will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each subject will give his or her written, informed consent before any protocol-driven tests or evaluations are performed.

11.3. Statement of Investigator/Delegation of Authority

As a condition for conducting the clinical investigation, the Principal Investigator will sign the FDA Form 1572, Statement of Investigator (21 Code of Federal Regulations [CFR] Part 312).

The Principal Investigator will ensure that all persons assisting with the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions. The qualified investigator will maintain a list of sub-investigator and other appropriately qualified persons to whom to delegate significant trial-related duties. Should the qualified investigator delegate the supervision of the investigational product administration to a designated person, this individual must have the appropriate medical qualifications to effectively conduct or supervise any potential resuscitation procedures.

11.4. Subject Informed Consent

The investigator or his/her designee will inform the subject of all aspects pertaining to their participation in the study. The process for obtaining subject informed consent will be in accordance with all applicable regulatory requirements (e.g., CFR Part 50 and ICH E6 Section 4.8). The investigator or his/her designee and the subject must both sign and date the informed consent document (ICD) before the subject can participate in the study. The subject will receive a copy of the signed and dated form, and the original will be retained in the site's study records. The decision to participate in the study that is made by the subject is entirely voluntary. The

investigator or his/her designee must emphasize to the subject that consent for study participation may be withdrawn at any time without penalty or loss of benefits to which the subject is otherwise entitled. If the ICD is amended during the study the investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICD by the IRB, and use of the amended form, including the necessity of re-consenting ongoing subjects.

11.5. Investigator Reporting Requirements

In accordance with applicable local regulatory requirements, the investigator may be obligated to provide periodic safety updates on the conduct of the study at his/her site and notification of study closure to the IRB. Such periodic safety updates and notifications are the responsibility of the investigator and not of Insys Development Company or its delegate.

12. DATA HANDLING AND RECORD KEEPING

12.1. Data Management

The sponsor or sponsor's representative will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and the CRO's SOPs. A comprehensive Data Management Plan will be developed including a data management overview, database contents, annotated CRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data.

12.2. Case Report Forms and Source Documents



The CRFs will be supplied by [REDACTED]. The complete CRFs will be reviewed, signed, and dated by the qualified investigator and a copy returned to the Sponsor with the final report.

Source documents are defined as original documents, data, and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media and/or X-rays.

12.3. Documentation and Retention of Essential Documents

All documents pertaining to the study, including a copy of the approved protocol, copy of the informed consent document, completed CRFs, source documents, drug accountability and retention records, and other study related documents will be retained in the permanent archives of the study site. These will be available for inspection at any time by the Sponsor or the FDA. Per 21 CFR 312, record retention for this study is required for a period of two years following the date on which this study agent is approved by the FDA for the marketing purposes that were the subject of this investigation; or, if no application is to be filed or if the application is not

approved for such indication, until two years following the date on which the entire study is completed, terminated, or discontinued, and the FDA is notified.

The investigator will provide direct access to source data and documents for trial-related monitoring, audits, IEC/IRB review, and regulatory requirements.

12.4. Financial Disclosure

These issues will be addressed in a separate agreement between the sponsor and the Investigator.

The US FDA Financial Disclosure by Clinical Investigators (21 Code of Federal Regulations [CFR] 54) regulations require sponsors to obtain certain financial information from investigators participating in covered clinical studies; each investigator and sub-investigator is required to provide the required financial information and to promptly update Insys Development Company, Inc., with any relevant changes to their financial information throughout the course of the clinical study and for up to 1 year after its completion. This rule applies to all investigators and sub-investigators participating in covered clinical studies to be submitted to the FDA in support of an application for market approval.

13. ADDRESSES

Sponsor

Name: Insys Development Company, Inc.
Address: 1333 South Spectrum Blvd., Suite 100
Chandler, AZ 85286



Phone: [REDACTED]

Fax: [REDACTED]

Clinical Research Organization

Name: [REDACTED]
Address: [REDACTED]
[REDACTED]

Phone: [REDACTED]

Drug Safety

Name: Insys Development Company, Inc.
Address: 1333 South Spectrum Blvd., Suite 100
Chandler, AZ 85286

Phone: [REDACTED]

Drug Safety: [REDACTED]

Packaging

Name: [REDACTED]

Address: [REDACTED]
[REDACTED]
[REDACTED]

Manufacturing

Name: Insys Manufacturing
Address: 2700 Oakmont Dr.
Round Rock, TX 78665

Central Lab

Name: [REDACTED]

Address: [REDACTED]
[REDACTED]
[REDACTED]

Report Writing

Name: [REDACTED]

Address: [REDACTED]
[REDACTED]
[REDACTED]

14. USE OF INFORMATION AND PUBLICATION POLICY

14.1. Use Of Information

All information concerning Buprenorphine Sublingual Spray 0.5 mg and Insys Development Company' operations, such as Insys Development Company' patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by Insys Development Company and not previously published, is considered confidential information.

This confidential information shall remain the sole property of Insys Development Company, shall not be disclosed to others without the written consent of Insys Development Company, and shall not be used except in the performance of this study.

The investigator will maintain a confidential subject identification code list of all subjects enrolled in the study (by name and subject number). This list will be maintained at the site, and will not be retrieved by Insys Development Company.

14.2. Publication Policy

Insys Development Company, Inc. will retain ownership of all data. All proposed publications based on this study will be subject to the sponsor's approval requirements.

15. REFERENCES

- 1) Apfelbaum JL, Chen C, Mehta SS, Gan TJ: Postoperative pain experience: Results from a national survey suggest postoperative pain continues to be undermanaged. *Anesth Analg* 97:534-540, 2003.
- 2) Kelly DJ, Ahmad M, Brull SJ. Preemptive analgesia I: physiological pathways and pharmacological modalities. *Can J Anaesth*. 2001; 48:1000.1.
- 3) Dahan A, Yassen A, Romberg R, Sarton E, Teppema L, Olofsen E, Danhof M; Buprenorphine induces ceiling in respiratory depression but not in analgesia. *Br J Anaesth* 2006; 96 (5): 627-632.
- 4) Dahan A, Yassen A, Bijl H, Romberg R, Sarton E, Teppema L, Olofsen E, Danhof M; Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats. *Br J Anaesth* 2005; 94 (6): 825-834.
- 5) Garimella,V , Cellini C. Postoperative pain control. *Clin Colon Rectal Surg*. 2013 Sep; 26(3): 191–196.
- 6) Moradi M, Esmaili S, Shoar S, et al. Use of oxycodone in pain management. *Anesthesiology and Pain Medicine*. 2012 March; 1(4): 262-264.
- 7) Apfel, C. C., et al. (1999). A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. *Anesthesiology*. 91(3): 693-700.

16. INVESTIGATOR SIGNATURE PAGE

TITLE: A Phase 2, Randomized, Open Label, Multiple-Dose, Comparator Controlled, Parallel-Group, Safety and Tolerance Study of Buprenorphine Sublingual Spray (0.5 mg TID) versus Standard of Care Post-Operative Narcotic Therapy for the Treatment of Post-Operative Pain

PROTOCOL NUMBER: INS005-17-111

PHASE OF STUDY: Phase 2

PROTOCOL DATE: Version 1.0, 28 July 2017

STUDY SPONSOR: Insys Development Company, Inc.
1333 South Spectrum Blvd, Suite 100
Chandler, AZ 85286

PRINCIPAL INVESTIGATOR COMMITMENT:

I, the undersigned Principal Investigator, submit this statement of commitment as evidence that I understand my responsibilities pursuant to the Code of Federal Regulations (21 CFR § 312.60 through § 312.70, 21 CFR § 11, 50, 54, 56) and ICH E6 Good Clinical Practice guidelines, as well as with any and all applicable federal, state and/or local laws and regulations, and agree to conduct the study in accordance with the protocol referenced herein.

Principal Investigator Printed Name

Principal Investigator Signature

Date

17. APPENDICES

17.1. Appendix 1: Surgical and Anesthesia Protocols

Below are surgical and anesthetic protocols for the allowed surgical procedures in this protocol. The anesthetic regimens listed for each surgical model are a guide that should be followed to minimize interpatient variability to the greatest extent possible. However, it is understood that hemodynamic fluctuations and other intraoperative events may necessitate some deviation from this standard regimen and that is acceptable.

Bunionectomy

Subjects will undergo primary unilateral first metatarsal bunionectomy with no other collateral procedures. The use of midazolam, fentanyl, nitrous oxide and propofol are allowed with doses at discretion of anesthesia. A small dose of lidocaine (up to 5 mL of 1% lidocaine without epinephrine) may be administered prior to medications to reduce peripheral vein irritation. A standard Mayo block will be established using 2% lidocaine (plain), not to exceed 24 mL. For nausea prophylaxis, all subjects will receive a uniform standard of care regimen which includes the following: 10 mg of dexamethasone at induction and 8 mg of ondansetron near the end of surgery. Airway management is at the discretion of anesthesia (typically LMA vs MAC). The bunionectomy procedure time should not exceed 90 minutes. No Popliteal nerve block should be used. Post surgically and prior to randomization, subjects may be treated with intravenous morphine and or fentanyl for post-surgical analgesia (dose and frequency per the discretion of the investigator).

Breast Augmentation

Subjects will undergo a bilateral submuscular augmentation mammoplasty via an inframammary approach under general anesthesia utilizing saline implants not to exceed 500cc each. Ancillary procedures (liposuction, breast reduction, breast lift, abdominoplasty etc.) are prohibited. Midazolam, Fentanyl, Sevoflurane, nitrous oxide and propofol are allowed with doses at discretion of anesthesia. A small dose of lidocaine (up to 5 mL of 1% lidocaine without epinephrine) may be administered prior to medications to reduce peripheral vein irritation. For nausea prophylaxis, all subjects will receive a uniform standard of care regimen which includes the following: 10 mg of dexamethasone at induction and 8 mg of ondansetron near the end of surgery. LMA without muscle relaxation is preferred for all subjects however ET intubation may be performed if deemed necessary. Post surgically and prior to randomization, subjects may be treated with intravenous morphine and or fentanyl for post-surgical analgesia (dose and frequency per the discretion of the investigator).

Mini-Abdominoplasty

Subjects will undergo a mini-abdominoplasty procedure (defined as a cosmetic surgery involving skin, muscle and adipose tissue, but no relocation of the umbilicus). The approach should be anterior. Surgical drains should be placed per the discretion of the surgeon. The incision should in general be from one ASIS (anterior superior iliac spine) to the other. It is understood that the exact incision length will vary depending on the subject's anatomy and the desired cosmetic outcome. Ancillary procedures (liposuction, breast reduction etc.) are prohibited. Midazolam,

Sevoflurane, nitrous oxide, fentanyl and propofol are allowed with doses at discretion of anesthesia. A small dose of lidocaine (up to 5 mL of 1% lidocaine without epinephrine) may be administered prior to medications to reduce peripheral vein irritation. For nausea prophylaxis, all subjects will receive a uniform standard of care regimen which includes the following: 10 mg of dexamethasone at induction and 8 mg of ondansetron near the end of surgery. LMA without muscle relaxation is preferred for all subjects however ET intubation may be performed if deemed necessary. Post surgically and prior to randomization, subjects may be treated with intravenous morphine and or fentanyl for post-surgical analgesia (dose and frequency per the discretion of the investigator).

17.2. Appendix 2: Naloxone Administration

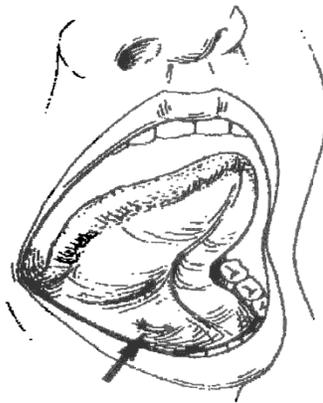
1. Administer at a dose of 0.1 mg to 0.2 mg IV at every 2- to 3- minute's intervals until desired response is achieved.
2. Additional doses may be necessary and depends on the buprenorphine dose and the correct naloxone dose window
3. Because respiratory depression from buprenorphine may last longer than the effects of naloxone boluses or short infusions, continued close supervision of the subject is until vital signs including respiratory rate and oxygen saturation levels stabilize over an extended period of time
4. Naloxone IV is the preferred route of administration (In the event of lost IV access, naloxone may be administered IM and SQ as an alternative)

17.3. Appendix 3: Dosing Instructions

Buprenorphine SL Spray

1. Prior to administration, ask subject to swallow contents of mouth.
2. Ask subject to lift tongue.
3. Bring the unit as close as possible to the mouth.
4. During the treatment period to which the subject is assigned, administer one spray UNDER the tongue at a 45° angle.
5. Subject should be instructed to bring back the tongue to resting position immediately upon administering the product.
6. Instruct the subject NOT to swallow the drug
7. Instruct the subject to avoid swallowing immediately after administering the spray.
8. The subject should hold solution under the tongue for approximately 60 seconds. The medication should not be expectorated or the mouth rinsed.

Drug should be sprayed in area shown by arrow in diagram below:



17.4. Appendix 4: Schedule of Events

Assessments	Screening Period	Surgical Period (Day 1)		Treatment Period (Inpatient; Day 1-4)			Treatment Period (Outpatient; Day 4-7)		Follow-up Period
	Day -28 to -1	Pre-surgery/ Morning of Surgery	Surgery	Pre-Dose	Drug Admin / Time 0	T0 - T72	Discharge from Research Site (Day 4)	Outpatient Treatment (Day 4 – 7)	Day 8/EOS, + 2 day window / ET
Informed Consent	X								
Inclusion/Exclusion	X	X							
Demographics ⁱ	X								
Medical and Surgical History ⁱⁱ	X	X							
ASA Classification ⁱⁱⁱ	X								
PONV Risk Assessment	X								
Physical Exam ^{iv}	X	X				X			X
Clinical laboratory tests (hematology, chemistry, urinalysis, serology) ^v	X								X
12-lead Electrocardiogram ^{vi}	X			X		X			X
Urine Drug Test and Alcohol Breathalyzer Test ^{vii}	X	X							
Pregnancy Test for female subjects ^{viii}	X (Serum)	X (Urine)							
X-ray and podiatric examination ^{ix}	X								
Surgery ^x			X						
Post-Surgical Eligibility				X					
Randomization				X					
Study Medication Administration ^{xi}					X	X	X	X	
Vital Signs ^{xii}	X	X		X	X	X			X
Pulse Oximetry ^{xiii}	X			X		X			X
Oral Cavity Exam ^{xiv}	X	X		X		X			X
Adverse Event Collection ^{xv}	X	X	X	X	X	X	X	X	X
Concomitant Medications ^{xvi}	X	X	X	X	X	X	X	X	X
Investigator Assessment of Outpatient Treatment							X		
Dosing Instructions for Outpatient ^{xvii}							X		
Observe Self-Administration of Study Drug ^{xviii}							X		
Dispense Outpatient Study Drug							X		
Dispense Rescue Pain Medication and Nausea Medications ^{xix}							X		
Staff to instruct subject on guidance for rescue pain medication and nausea medication							X		
Provide completion instructions and Dispense Subject Diary ^{xx}							X		

Assessments	Screening Period	Surgical Period (Day 1)		Treatment Period (Inpatient; Day 1-4)			Treatment Period (Outpatient; Day 4-7)		Follow-up Period
	Day -28 to -1	Pre-surgery/ Morning of Surgery	Surgery	Pre-Dose	Drug Admin / Time 0	T0 - T72	Discharge from Research Site (Day 4)	Outpatient Treatment (Day 4 - 7)	Day 8/EOS, + 2 day window / ET
Recording of study doses in outpatient diary								X	
Collect Outpatient Medication and Review Diary									X
Subjects confinement at research site		X	X	X	X	X			
Discharge subject from the study site							X		
Discharge from study									X

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- ⁱ **Demographics:** Includes Height, weight, and body mass index
- ⁱⁱ **Medical/Surgical History:** Medical history should be reviewed for any changes from Screening
- ⁱⁱⁱ **ASA:** Must be classified using the American Society of Anesthesiologists Physical Status Classification System as P1 to P2.
- ^{iv} **Physical Exam:** A complete physical examination (HEENT, cardiovascular, respiratory, gastrointestinal, neurological, dermatologic, and musculoskeletal systems; excluding the genitourinary examination), includes an examination of the subject's surgical site. A physical exam will be conducted at screening, before surgery on Day 1, 72 hours (± 4 hours) after first dose of study drug (Time 0), and at the Follow-up Visit/ET.
- ^v **Clinical Lab Tests:** Hematology, chemistry (including LFTs) and UA and serology samples will be taken at screening. At the Follow-up Visit/ET, clinical lab testing includes only hematology and chemistry (including LFTs), urinalysis (with microscopic examination if indicated). Assessments will be repeated based on the Investigator's discretion
- ^{vi} **Electrocardiogram:** An ECG will be performed at screening, before the first dose of study drug, and then at 90 minutes (± 10 minutes), and at 12, 24, 48 hours, 72 hours (± 10 minutes) after Time 0. And ECG will also be collected Follow-up Visit/ET.
- ^{vii} **Urine Drug Test & Alcohol Breath Test:** A urine drug screen and alcohol breath test will be collected at Screening and before surgery on Day 1. The test results must be negative for the subject to continue in the study, except in cases where a valid physician's prescription can be verified.
- ^{viii} **Pregnancy Test:** Females of child-bearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test prior to surgery on Day 1.
- ^{ix} **X-ray and podiatry exam:** An x-ray and podiatry exam will only be collected on subject undergo a bunionectomy procedure. Radiographs taken within 6 months before Screening will be acceptable.
- ^x **Surgery:** The surgical procedures will be bunionectomy, breast augmentation, and abdominoplasty. Anesthesia will be established using standardized techniques, as appropriate, for each surgical procedure.
- ^{xi} **Study Medication Administration:** After meeting post-surgical eligibility requirements and subsequently being randomized to treatment, subjects may receive their first dose of study drug any time between 0-4 hours after surgery. The first dose does not need to be immediately administered after meeting post-surgical eligibility requirements. Subjects should not have anything orally except room-temperature water within 15 minutes of each dose. Study Medication Administration after the First dose will be administered every 8 hours (Treatment Days 1 – 7).
- ^{xii} **Vital Signs:** Includes blood pressure, heart rate, respiratory rate, and oral temperature, will be measured after the subject has been in a resting position for 5 minutes. Blood pressure, heart rate, respiratory rate, and oral temperature will be measured at Screening, before surgery on Day 1, and at baseline before Time 0 (prior to first dose). Heart rate and respiratory rate will be measured at study drug administration/Time 0, 1 hour, and every 2 hours (± 10 minutes) after first dose of study drug /Time 0 during the inpatient Treatment Period. Blood pressure will be measured every 4 hours after first dose of study drug /Time 0 during the inpatient Treatment Period. Vital signs will also be measured at Follow-up Visit/ET.
- ^{xiii} **Pulse oximetry:** Will be measured continuously after surgery for safety; pulse oximetry will be recorded at screening and at selected times (± 10 minutes), including baseline before Time 0 (prior to first dose) and at 90 minutes and 12, 24, 48, 72 hours after Time 0, and at Follow-up Visit/ET.
- ^{xiv} **Oral Cavity Exam:** Study staff will perform a sublingual assessment, noting the colour of mucosa and whether inflammation is present. Check for mucositis and local irritation. The oral cavity examinations should be conducted at screening, pre-surgery, before the first dose of study drug, and then at 90 minutes (± 10 minutes), and at 12, 24, 48 hours, 72 hours (± 10 minutes) after Time 0. An oral examination will also be collected at Follow-up Visit/ET. Assessments will be repeated based on the Investigator's discretion.
- ^{xv} **AE Collection:** Serious Adverse Events will be collected from time of consent through 30 days following study participants. Non-serious Adverse Events will be collected from time of first dose of study medication through the end of study participation.
- ^{xvi} **Concomitant Medications:** Study staff will collect concomitant medications taken within 30 days of screening Visit 1 and throughout the study. Subjects will be instructed to record all study drug and concomitant medications taken in addition to adverse events (AEs) experienced after discharge in their take-out outpatient diary.

Subjects will also be instructed to return the outpatient study drug and subject diary to study personnel at the Follow-up Visit on Day 8 (+ 2 day window). See Appendix 3 for Naloxone guidance.

- ^{xvii} **Dosing Instructions for Outpatient:** Study staff will train subjects on how to administer the study drugs **1)** On outpatient Day 4-7 subjects will be provided Buprenorphine 0.5 mg Sublingual Spray TID or reference drugs oxycodone 10 mg TID. **2)** On outpatient Day 4-7 subjects will be provided with acetaminophen, and will be advised to take acetaminophen 1000 mg every six hours as needed for rescue analgesia. **3)** On outpatient Day 4-7, subjects will be administered Zofran ODT (oral dissolvable tablet) to be taken as needed. The rescue medication and specific reason for use will need to be captured in the subject outpatient diaries.
- ^{xviii} **Observe Study Drug Administration:** Site staff will train subjects on how to self-administer study drug. Investigators will determine if patients are able to proceed with the outpatient treatment period. Before discharge from the study site on Day 4, site personnel will dispense rescue medication and will train subjects on how to administer the study drug, educate patients on the signs and symptoms of adverse events, and observe subjects self-administer medication. After discharge, study drug will be administered by subjects at home according to the directions provided by study staff.
- ^{xix} **Outpatient Rescue Pain Medication and Nausea Medication:** Outpatient medication will be dispensed before discharge from the study site on Day 4.
- ^{xx} **Subject Diary:** Study personnel will dispense outpatient diary, study drug, rescue pain and nausea medication. Subjects will also be instructed to return the outpatient diary to study personnel at the Follow up Visit 8 + 2 days after surgery.