CLINICAL TRIAL PROTOCOL

A Phase 2 Multicenter, Randomized, Double-Blind, Multiple-Dose, Parallel-Group, Placebo-Controlled Study of Fentanyl Sublingual Spray for the Treatment of Moderate to Severe Post-Operative Pain

Protocol Number:	INS002-16-092/ NCT02915978
Protocol Amendment 1 Date:	21 Dec 2016
Protocol Version:	2.0
Investigational Product:	Fentanyl Sublingual Spray
IND Number:	121254
Sponsor:	Insys Development Company, Inc. 1333 South Spectrum Blvd, Suite 100 Chandler, AZ 85286
Principal Investigator:	
Medical Monitor:	[redacted], MD Insys Development Company, Inc. [redacted] Phone: [redacted] Fax: [redacted]

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.

SUMMARY OF CHANGES

Rationale for Amendment

The reasons for this protocol amendment are:

1. To add IND number to protocol title page.
2. To update protocol signature page.
3. To clarify screening window.
4. To clarify that regional anesthesia is established using the Popliteal Sciatic Nerve Block.
5. To clarify pulse oximetry time points.
6. To remove study subject drug administration.
7. To add pulse oximetry inclusion/exclusion criteria.
8. To add post-operative vomiting inclusion/exclusion criteria.
9. To update the oxygen saturations percent cutoff for removal of subjects from therapy.
10. To add an oral cavity exam prior to first dose.
11. To add a pulse oximetry measurement at screening.
12. To clarify actions taken for Serious Adverse Reactions.
13. To update the table for hypoxia assessments.
14. To remove Buprenorphine from the Naloxone Administration guidelines.
15. To update rescue medication for post-operative nausea and/or emesis guidelines.

Changes in Protocol Version 2.0

1. Protocol title page had IND number 121254 added.
2. Protocol approval page had [redacted] removed.
3. In the synopsis and section 3.1, overall study design, the protocol incorrectly indicates that the screening period is Days -28 to 1. The protocol should list the screening period as Days -28 to -1.
4. In the synopsis and section 3.1, Overall Study Design, the protocol incorrectly indicates that regional anesthesia is established using the Mayo Block. Regional anesthesia will be established using the Popliteal Sciatic Nerve Block.
5. In the synopsis and section 3.1, Overall Study Design, the protocol incorrectly indicates that pulse oximetry will be recorded at 30 and 60 minutes after Time 0. These pulse oximetry time points have been removed. Pulse oximetry will be recorded before first dose of study drug and 90 minutes and 12, 24, and 48 hours after Time 0.
6. In section 3.1, Overall Study Design, the protocol incorrectly indicates that study drug will be administered by study subject. The following sentences have been removed from the protocol, "Study drug will be administered by study subjects according to the directions provided by study staff."

7. In section 3.2.2, Exclusion Criteria, the following exclusion criteria has been added, "Oxygen saturation (SpO_2) below 95% at screening."
8. In section 3.2.2., Exclusion Criteria, the following exclusion criteria has been added, "Has a history of presences of postoperative vomiting (CTCAE guidelines for vomiting) grade 2 or higher, as a result of surgery and/or anesthesia."
9. In section 3.3, Removal of Subjects from Therapy or Assessment, the protocol requires a subject to discontinues if he or she experiences hypoxia with oxygen saturation $\leq 92\%$ on repeat measurements over 3 minutes, despite stimulation and receiving oxygen 2-4 L/min via nasal cannula. The threshold for oxygen saturation has been updated to $\leq 90\%$ for removal of subject.
10. In section 6.2.2, Physical and Oral Examination, and section 7.3.2, Post-randomization, an oral cavity exam has been added prior to first dose of study drug.
11. In section 6.2.3, Vital Signs, section 7.1, Screening (Day -28 to Day -1), and Table 2, Schedule of Assessments, a pulse oximetry reading has been added to screening.
12. In section 6.2.6.5, Actions Taken, the title has been updated to "Actions Taken for SAE".
13. In Appendix 3, Hypoxia Assessment (Proposed Guidance), the threshold for oxygen saturation has been updated from 92% to 90% for hypoxia level 1, 2, and 3. "Clinical hypoxia will be documented throughout the study in the source documents and in the CRFs," has been removed; and "If oxygen is administered, the oxygen treatment should be documented as a concomitant medication," has been added.
14. In Appendix 4, Naloxone Administration (Proposed Guidance), the protocol incorrectly refers to Buprenorphine instead of Fentanyl. Step 2 and 3 have been updated to "Additional doses may be necessary and depends on the Fentanyl dose and the correct naloxone dose window" and "Because respiratory depression from Fentanyl 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."
15. In Appendix 5, Rescue Medication for Post-Operative Nausea and/or Emesis (PONV, Proposed Guidance), step 2-7 have been updated.
    2. If symptoms are persistent, then a second dose of ondansetron 2mg IV may be administered in 15-60 minutes
    3. If PONV continues to be a problem, an additional dose of ondansetron 2mg IV can be given after an additional 15-60 minutes. Do not administer more than 8 mg of ondansetron within an 8-hour period.
    4. If vomiting persists at least 60 minutes following 8 mg IV ondansetron within an 8-hour period (i.e., patient is refractory to ondansetron) metoclopromide (Reglan®) may be administered for further treatment of persistent PONV.
    5. Metoclopromide (Reglan®), 10-20 mg IM may be administered q4-6hr (max daily dose: 40 mg).
    6. If PONV is not adequately controlled with metoclopromide, subject will be discontinued from the study.

PI should call Medical Monitor to discuss subjects with refractory PONV/emesis.

PROTOCOL APPROVAL PAGE

A Phase 2 Multicenter, Randomized, Double-Blind, Multiple-Dose, Parallel-Group, Placebo-Controlled Study of Fentanyl Sublingual Spray for the Treatment of Moderate to Severe Post-Operative Pain

Protocol Approved By:

[redacted]

Insys Development Company, Inc.

[redacted]

Date: 22 Dec 2016

[redacted], MD

[redacted]

Insys Development Company, Inc.

[redacted]

Date: 22 Dec 2016

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
Insys Development Company, Inc.

Name of Investigational Product:
Fentanyl Sublingual Spray

Name of Active Ingredient:
Fentanyl

Title of Study:
A Phase 2 Multicenter, Randomized, Double-Blind, Multiple-Dose, Parallel-Group, Placebo-Controlled Study of Fentanyl Sublingual Spray for the Treatment of Moderate to Severe Post-Operative Pain

Indication: Moderate to severe post-operative pain

Objectives:

Primary:

To evaluate analgesic efficacy of Fentanyl Sublingual Spray compared with placebo in subjects with postoperative pain after a bunionectomy.

Secondary:

- To evaluate the safety of Fentanyl Sublingual Spray compared with placebo in subjects with moderate to severe postoperative pain after a bunionectomy.
- To evaluate the time to onset of analgesia for Fentanyl Sublingual Spray.
- To evaluate the time to rescue medication following administration of Fentanyl Sublingual Spray.

Methodology:

This is a Phase 2, multicenter, randomized, double blind, multiple dose, parallel group, and placebo controlled study to evaluate the safety and efficacy of up to 2 dosing regimens of Fentanyl Sublingual Spray (100 µg every 4 hours [q4h] or 200 µg q4h) and/or matching placebo in subjects with moderate to severe postoperative pain after a bunionectomy.

The study will comprise 4 periods: Screening Period (Days -28 to -1), Surgical Period (Day 0), Treatment Period (48 hours; Days 1 to 3), and Follow-up Period (Day 7 ± 2 days).

Subjects will be admitted to the study site on the morning of the scheduled surgery (Day 0), will remain at the study site until Postoperative Day 3 (a total of 3 nights at the study site), and will return for the Follow up Visit on Day 7 ± 2 day (5 to 9 days after surgery).

During the 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. Eligible subjects will complete all screening procedures within 28 days before the surgery (Days-28 to -1)

On Day 0, regional anesthesia will be established using a Popliteal Sciatic Nerve block, using standardized techniques, after which subjects will undergo primary, unilateral, first metatarsal bunionectomy with osteotomy and internal fixation. When the regional anesthetic wears off and the

subjects request pain medication, they will be asked to rate their pain intensity using an 11-point (0-10) Numeric Rating Scale (NRS). During the 9-hour period after discontinuation of the anesthetic block, subjects who experience a pain intensity rating of ≥4 on the NRS are eligible to be enrolled in the study. Pulse oximetry will be monitored continuously after the procedure as a safety measure.

During the Treatment Period, approximately 45 subjects will be randomly assigned to 1 of 3 treatment groups: Fentanyl Sublingual Spray 100 µg q4h, 200 µg q4h, or matching placebo.

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 the NRS assessment before study drug administration is defined as Baseline; the time of administration of the first dose of study drug is defined as Time 0. Study drug will be provided by blinded study personnel in a predefined manner to ensure adequate blinding and appropriate dosing regimens for the active drug and placebo. Study drug will be administered by study subjects according to the directions provided by study staff. Subjects should not have anything orally except room-temperature water within 15 minutes of each dose. The Treatment Period will continue through 48 hours after Time 0. Pulse oximetry will be continuously monitored and SpO_2 data will be recorded at select time points including baseline before first dose of study drug and 90 minutes and 12, 24, and 48 hours after Time 0. Additional ECGs will be performed at 90 minutes, 12 hours, 24 hours, and 48 hours after Time 0.

Ibuprofen 400 mg will be allowed orally every 4 to 6 hours as needed for rescue medication after study drug treatment has begun. If subjects are unable to tolerate 400 mg ibuprofen or if there is insufficient pain relief, 30 mg of ketorolac tromethamine (i.e., Toradol®) may be administered intravenously or intramuscularly every 6 to 8 hours as needed for pain. The total daily (24 hour) dosage of ibuprofen medication should not exceed 2400 mg and ketorolac should not exceed 90 mg.

During the Treatment Period subjects will be allowed to use assigned study medication for primary rescue medication no more frequently than 4 hours from previous study medication dose and no more than 6 times in a 24-hour period. Subjects will be encouraged to wait for at least 1 hour after the first dose of study drug before receiving rescue medication to allow time for the study drug to exert its pharmacologic effect.

During the Treatment Period, subjects whose pain 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 will be managed according to usual standard of care at the investigator's discretion.

Pain will be assessed on an 11-point Numeric Rating Scale (NRS) at Baseline before Time 0. Thereafter, subjects will rate their pain intensity (NRS) and pain relief (on a 5-point categorical scale) and record their assessments in an inpatient subject diary at scheduled times during the 48-hour period after Time 0 (at 2.5, 5, 15, 30, and 45 minutes, and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24, 32, 40, and 48 hours) and immediately before each use of rescue analgesia during the Treatment Period. Time to perceptible pain relief and meaningful pain relief will be evaluated using the 2 stopwatch method (after the first dose only). Time to each rescue medication from the prior IP dose will be evaluated. Subjects will complete a subject's global evaluation of the study drug at the end of the Treatment Period (Day 3) before discharge from the study site.

If a subject discontinues the study prematurely, pain intensity, pain relief, and the subject's global satisfaction with study treatment should be assessed and recorded immediately before discontinuation.

Before discharge from the study site on Day 3, study personnel will dispense a prescription for outpatient pain medication (if not already dispensed) and subjects will be given an outpatient subject diary in which they will be instructed to record concomitant medications taken and adverse events (AEs) experienced after discharge. Subjects will also be instructed to return the outpatient subject diary to study personnel at the Follow-up Visit on Day 7 ± 2 days (5 to 9 days after surgery).
Number of subjects (planned): Approximately 45 subjects (15 subjects per treatment group) will be enrolled.
Diagnosis and main criteria for inclusion: Eligible study subjects will be male or female, between 18 and 65 years of age inclusive, who have undergone primary, unilateral, distal first metatarsal bunionectomy (osteotomy and internal fixation) with no additional collateral procedures, and experienced a pain intensity rating of ≥4 on an 11-point (0-10) NRS during the 9-hour period after discontinuation of the regional anesthetic block.

Investigational product, dosage and mode of administration:

Fentanyl SL Spray 100 µg or 200 µg, manufactured for and supplied by Insys Development Company, Inc.

Duration of treatment:

The estimated duration of the study for each subject is approximately 6 weeks, which includes a Screening Period (Days -28 to -1), a Surgical Period (Day 0), a Treatment Period (48 hours; Days 1 to 3), and a post-treatment Follow up Visit (Day 7 ± 2 days). Subjects will be confined for approximately 72 hours at the study site for the Surgical and Treatment Periods.

Reference therapy, dosages and modes of administration:

Matching placebo.

Criteria for evaluation:

Efficacy

Primary efficacy endpoint:

- NRS summed pain intensity difference (NRS SPID) (calculated as a time-weighted average) over 0 to 48 hours (NRS SPID-48) after Time 0.

Secondary efficacy endpoints:

- NRS pain intensity difference (NRS PID) at each scheduled time point after Time 0
- NRS pain intensity score at each scheduled time point
- NRS SPID over 0 to 4 hours (NRS SPID-4), over 0 to 8 hours (NRS SPID-8), and over 0 to 24 hours (NRS SPID-24) after Time 0
- Total pain relief (TOTPAR) over 0 to 4 hours (TOTPAR-4), over 0 to 8 hours (TOTPAR-8), over 0 to 24 hours (TOTPAR-24), and over 0 to 48 hours (TOTPAR-48) after Time 0
- Time to onset of analgesia (measured as time to perceptible pain relief confirmed by meaningful pain relief using the 2-stopwatch method)
- Pain relief score on a 5-point categorical scale at each scheduled time point after Time 0
- Peak pain relief
- Time to peak pain relief
- Time to first perceptible pain relief
- Time to meaningful pain relief
- Proportion of subjects using rescue medication
- Time to first use of rescue medication (duration of analgesia) following each dose of the investigational product (IP)
- Total use of rescue analgesia over 0 to 24 hours and over 0 to 48 hours
- Subject's global evaluation of study drug

Safety

The safety endpoints are the incidence of treatment-emergent adverse events (TEAEs), physical and oral examination findings, and changes in vital signs, pulse oximetry, and ECG measurements.

Statistical Methods:

Sample Size Determination

A sample size of 15 subjects per treatment group will provide ≥80% power to detect a minimal standardized effect size of 0.5 between the 100 µg q4h, 200 µg q4h active treatment arms, and placebo in NRS SPID-48 using a 3-group analysis of covariance (ANCOVA) with baseline NRS score as the covariate with a 0.05 two-sided significance level (EAST v6) assuming a common standard deviation of 100 for SPID-48.

Analysis Populations

Statistical analysis will be done on the following populations:

- The intent to treat (ITT) population will consist of all subjects who are randomized. The ITT population is the primary population for the efficacy analysis.
- The per protocol (PP) population will consist of all ITT subjects who receive at least 1 dose of study drug, who remain in the study for at least 48 hours of treatment, and who do not incur a major protocol violation that would challenge the validity of their data. This population will be used to evaluate the sensitivity of the primary efficacy analysis.
- The safety population will include all subjects who are treated with the study drug. The safety population is the population for all safety assessments.

Efficacy Analyses

An analysis of covariance (ANCOVA) will first be assessed among the SPID-48 measurements of the three treatment groups. If the F statistic is significant with a $p < 0.05$, then a post-hoc analysis of the treatment groups will be performed. The least square (LS) mean, standard error (SE), and 95% confidence interval (CI) for each treatment group will be estimated. In addition, the mean (LS mean) difference between each treatment and placebo, SE, p-value, and the associated 95% CI will be computed.

Sensitivity analyses to explore the impact of missing data and use of rescue will also be performed for the primary analysis. Specifics of the sensitivity analyses will be described in a detailed Statistical Analysis Plan (SAP).

The secondary endpoints NRS SPID-4, NRS SPID-8, NRS SPID-24, TOTPAR-4, TOTPAR-8, TOTPAR-24, TOTPAR-48, time to use of rescue analgesia, and total use of rescue analgesia will be analyzed similarly to the primary endpoint. The NRS pain intensity and the pain relief scores at each time point will also be summarized descriptively. Time to event endpoints (time to onset of analgesia, time to peak pain relief, time to perceptible relief, time to meaningful relief, and time to first rescue medication) will be analyzed using Kaplan-Meier methods. Peak pain relief score, proportion of subjects using rescue medication, and the subject's global evaluation will be analyzed using chi-square, Fishers exact, or logistic regression techniques as appropriate. No formal statistical inferences will be made on any secondary endpoints. Details of statistical analyses will be described in a SAP that will be finalized before database lock and unblinding.

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.

For vital sign measurements, descriptive statistics will be provided at each scheduled time point for each treatment group. Changes from Baseline for vital signs will be calculated for each subject, and descriptive statistics will be provided on changes in vital signs from Baseline for each treatment group at each scheduled time point after Baseline. No formal statistical tests will be performed.

Statistical analyses will be performed using and SAS® (Version 9.3 or higher, SAS Institute Inc.).

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
AE	adverse event
ANCOVA	analysis of covariance
BID	twice daily
BMI	body mass index
CFR	Code of Federal Regulations
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
ECG	electrocardiogram
eCRF	electronic case report form
ED50	median effective dose
EDC	electronic data capture
ET	early termination
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IM	intramuscular
IP	investigational product
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
PID	pain intensity difference
PK	pharmacokinetic(s)
PP	per-protocol
QTc	QT interval corrected for heart rate

Abbreviation or Specialist Term	Explanation
AE	adverse event
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SL	sublingual
SOP	standard operating procedure
SPID	summed pain intensity difference
SPID-4	summed pain intensity scores (calculated as a time-weighted average) over 1 to 4 hours
SPID-8	summed pain intensity scores (calculated as a time-weighted average) over 1 to 8 hours
SPID-24	summed pain intensity scores (calculated as a time-weighted average) over 1 to 24 hours
SPID-48	summed pain intensity scores (calculated as a time-weighted average) over 1 to 48 hours
t_{max}	Time to maximum plasma concentration observed
TEAE	treatment-emergent adverse event
TID	3 times daily
TOTPAR	total pain relief
TOTPAR-4	total pain relief over 0 to 4 hours
TOTPAR-8	total pain relief over 0 to 8 hours
TOTPAR-24	total pain relief over 0 to 24 hours
TOTPAR-48	total pain relief over 0 to 48 hours
ULN	upper limit of normal
US	United States

1. INTRODUCTION

1.1. Background

Pain is typically experienced when the free nerve endings of pain receptors are subject to noxious mechanical, thermal, or chemical stimuli. These pain receptors can transmit signals along afferent neurons to the spinal cord and then to the brain. When a person feels pain, any one or more of a number of problems can be associated with this sensation including, but not limited to, reduced function, reduced mobility, complication of sleep patterns, and decreased quality of life.

The causes of pain include, but are not limited to, inflammation, injury, disease, muscle stress, and damage that can result from surgery or an adverse physical, chemical, or thermal event. When a tissue is damaged, a host of endogenous pain inducing substances (eg, bradykinin and histamine) can be released from the injured tissue. The pain inducing substances can bind to receptors on the sensory nerve terminals and thereby initiate afferent pain signals. After activation of the primary sensory afferent neurons, the projection neurons in the spinal cord may be activated. These neurons carry the signal via the spinothalamic tract to higher parts of the central nervous system.

Surgical correction of bunions, an enlargement and deformation of the first metatarsal joint, are performed through a procedure called bunionectomy. A model for assessing analgesic efficacy and safety for the acute postoperative pain following this procedure has been developed and widely used.[1, 2, 3, 4, 5] The pain relief outcomes with this model can also be generalized to other surgical procedures as well as for acute pain, in general. The model has many ideal characteristics. Because bunionectomy patients are generally healthy and compliant, their postoperative pain is predictable and sustained at moderate to severe levels for several days after surgery.[1, 2, 5] This allows assessment of multiple doses of the drug being studied when necessary. In addition, the surgical and anesthetic procedures are standardized, homogeneous, and suitable for clinic settings. [1, 2, 5] Use of regional anesthesia during and after surgery also allows randomization of subjects with minimal use of adjunctive opioid pain medicine that could confound tolerability assessments.

Fentanyl, a synthetic phenylpiperidine derivative, is a μ-opioid receptor agonist. Fentanyl has been marketed in several dosage forms for over 35 years, producing a long record of safety and efficacy in the treatment of pain. Fentanyl was synthesized as a replacement of morphine in 1960. It is approximately 100 times more potent than morphine.[6,7] SUBLIMAZE® (fentanyl injection) has been used peri-operatively in hospitals since its approval; however, because of its potency and availability as an IV injection it has also been used in the ED and pre-hospital setting as a pain reliever for a variety of indications.[8-10] Since fentanyl obtained its initial Food and Drug Administration (FDA) approval in the United States in 1968, other delivery forms of fentanyl have been studied and approved for use in patients with a variety of painful conditions. DURAGESIC® (fentanyl transdermal patch) is used frequently in chronic pain conditions[11] and has also been studied for acute pain conditions.[12] Additionally, a class of products collectively known as transmucosal immediate release fentanyl (TIRFs) has been approved since 1988 for use in patients who are opioid tolerant and have breakthrough pain related to cancer.[13] One such TIRF, SUBSYS® (fentanyl sublingual spray) by INSYS, was approved for use in the United States in January 2012.[14] A distinguishing characteristic of this potent, short acting opioid

fentanyl given via sublingual spray is that it has demonstrated pharmacokinetic (PK) parameters similar to those of IV fentanyl, showing a rapid increase in plasma concentrations and significant blood levels as early as 5 minutes after administration. In a 3-way crossover PK study, the mean percent bioavailability of 400 μg fentanyl sublingual spray was 76%, which is closer to that of 100 μg IV fentanyl than to 400 μg oral transmucosal fentanyl citrate (51%).[15] In the pivotal efficacy study in the treatment of breakthrough pain in opioid-tolerant patients with cancer, compared with placebo, fentanyl sublingual spray showed statistically significant improvements in the primary efficacy measure, the mean Summed Pain Intensity Difference (SPID), at 30 minutes. Additionally, significant difference in pain relief measured in a variety of validated pain scales was observed as early as 5 minutes and was maintained at all other time points through 60 minutes.[16]

Because of the unique PK profile of fentanyl sublingual spray and its rapid onset for pain relief, it has been postulated that it might have use for acute or postoperative pain. Specifically, it may well be a less invasive, viable alternative to IV opioids for patients with conditions that cause significant pain but without other potential medical needs that would otherwise warrant placing IV access.[16] The bunionectomy model is a well-established model for the study of effective treatments for acute moderate to severe pain.

1.2. Nonclinical Experience

The pharmacologic effects of fentanyl are mediated primarily via agonist activity at the μ_1- (high affinity) and μ_2- (low affinity) opioid receptors. Fentanyl binding in the CNS occurs in the following sites in sequentially decreasing order: midbrain and striatum, hypothalamus, cerebral cortex, hippocampus, brainstem, spinal cord, and cerebellum.

Fentanyl analgesia, associated with decreased somatic and cardiovascular responses to pain, has been demonstrated in numerous preclinical studies, with considerable variability in the resulting median effective dose (ED_{50}) and effective plasma concentrations across species. The median effective SC fentanyl doses in the mouse acetic acid–induced writhing test, tail immersion test, phenylquinone writhing test, formalin-induced hind paw pain test, and tailclamp test were 11.5, 94, 34, 50 and 80 μg/kg, respectively. In the tail-clamp test, the onset of fentanyl analgesia was approximately 4 minutes, peak analgesic effect occurred at 10 to 15 minutes, and duration of action was approximately 30 minutes. In the rat, the fentanyl ED_{50} in the tail pressure and anti-bradykinin tests were 20 and 8 μg/kg SC, respectively. Intravenous fentanyl (ED_{50}, 11.35 μg/kg) antagonized the response to tooth pulp stimulation in rabbits for approximately 26 minutes[17].

Maximal analgesia was achieved in dogs at a plasma fentanyl concentration of ~30 ng/mL,[18] and in rhesus monkeys at 43.4 ng/mL.[19] In the monkey, significant respiratory and analgesic effects were observed at plasma fentanyl concentrations as low as 3 ng/mL.[19] Compared with other opioid analgesics (i.e., buprenorphine, codeine, hydrocodone, morphine, and oxycodone), fentanyl had the largest ratio of analgesic potency versus the ED_{50} for adverse effects.[20]

1.3. Clinical Experience

Insys Development Company, Inc. has studied the pharmacokinetics, efficacy, safety, and tolerability of fentanyl sublingual spray in 7 clinical studies (5 pharmacokinetic, and 2 efficacy and safety studies). Overall, in the clinical trial program for the 7 completed trials, 98 healthy adult volunteers and 377 adults with cancer were exposed to fentanyl sublingual spray. In

addition, two trials in opioid naïve subjects have recently been completed. Study INS-15-049 was a Phase 1, open-label, randomized, single ascending dose study in 50 opioid naïve subjects at a single study center designed to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of a single dose of fentanyl sublingual spray or fentanyl citrate IV. Study INS002-15-050 was a Phase 1, multiple ascending dose study (INS002-15-050) in 96 opioid naïve subjects at one study site designed to assess the pharmacokinetics (PK), pharmacodynamics (PD), safety, and tolerability of multiples doses of SUBSYS® (fentanyl sublingual spray) or fentanyl citrate IV.

In FNY-P4-270, fentanyl sublingual spray doses of 100 μg, 400 μg, and 800 μg were associated with well-defined, mainly proportional pharmacokinetics. INS-06-003 characterized the pharmacokinetic profile and comparative bioavailability of fentanyl administered by 3 routes: intravenously (100 μg) and via 2 transmucosal delivery systems - OTFC (a lozenge containing 400 μg of fentanyl) and fentanyl sublingual spray 400 μg.[15] INS-06-004 determined the pharmacokinetics of 5 different doses (100, 200, 400, 600, and 800 μg) of fentanyl sublingual spray and investigated the impact of temperature (cold or hot beverage) and pH (oral bicarbonate or carbonate) in the oral cavity on the bioavailability of fentanyl sublingual spray.[21] INS-09-011 assessed the effect of oral mucositis on the absorption and distribution of fentanyl when administered as a sublingual spray in patients with cancer pain. No serious AEs were reported during these 4 pharmacokinetic studies. Another pharmacokinetic study, INS-13-019, compared the bioavailability of fentanyl sublingual spray versus IM fentanyl citrate. INS-05-001, a phase 3 study, demonstrated that fentanyl sublingual spray was well tolerated and efficacious in reducing breakthrough cancer pain, with a rapid onset of action.[16] Long-term safety (90 days) of fentanyl sublingual spray in the management of patients with breakthrough cancer pain was assessed in INS-06-007.

In INS002-15-049, pharmacokinetic analyses showed that mean concentrations and mean exposure parameters of fentanyl increased with increasing doses of fentanyl sublingual spray ranging from 100 to 800 μg. Mean maximum plasma concentrations were reached between 0.27 and 0.60 hours post-dose for fentanyl sublingual spray. Single dose administration of fentanyl sublingual spray at doses ranging from 100 to 800 μg was generally well tolerated in opioid naïve subjects. No SAEs were observed in the study. The most frequently reported AEs were consistent with the safety profile of fentanyl when administered in other forms, and included somnolence, nausea, and vomiting. There were no clinically relevant differences among treatment groups in AEs reported during this clinical trial. The analysis of the results of INS002-15-050 is currently ongoing.

In INS002-15-050, multiple ascending doses were studied and demonstrated that most doses were well-tolerated and that doses up to 400 μg every 4 hours were safe and well-tolerated.

1.4. Dose Selection Rationale

For this study, the total daily doses of 600 μg and 1200 μg fentanyl were selected for this trial based on the observations from the multi-dose study to be well within the margin of safety. These doses are supported by nonclinical pharmacodynamics, pharmacokinetic, efficacy, and safety studies, and the results of the completed Insys Phase 1 studies (INS002-15-049 and INS002-15-050).

1.5. Summary of Potential Risks and Benefits

Fentanyl has a well-known safety profile. Risks for study participants include those associated with the following:

- Fentanyl has side effects similar to other opioids, including vomiting, nausea, constipation, dyspnea, and somnolence.
- The bunionectomy procedure itself may include bleeding, infection, and neurologic injury.

The potential risks of study participation include those associated with exposure to Fentanyl Sublingual Spray and the risks of medical evaluation, including venipuncture. A summary of the pharmaceutical properties and known potential risks of Fentanyl Sublingual Spray is provided in the current version of the investigator's brochure (IB). The investigator must become familiar with all sections of the Fentanyl Sublingual Spray IB before the start of the study.

The potential benefits of study participation are the subjects undergoing bunionectomy may experience a reduction in postoperative pain as a result of treatment with Fentanyl Sublingual Spray and will understand that they are contributing to the scientific knowledge that may lead to expansion of the treatment options for patients with postoperative pain. No other benefits of participation are anticipated.

2. STUDY OBJECTIVES

2.1. Primary Objective

- To evaluate analgesic efficacy of Fentanyl Sublingual Spray compared with placebo in subjects with postoperative pain after a bunionectomy.

2.2. Secondary Objectives

- To evaluate the safety of Fentanyl Sublingual Spray compared with placebo in subjects with moderate to severe postoperative pain after a bunionectomy.
- To evaluate the time to onset of analgesia for Fentanyl Sublingual Spray.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a Phase 2 multicenter, randomized, double blind, multiple dose, parallel group, and placebo controlled study to evaluate the safety and efficacy of up to 2 dosing regimens of Fentanyl Sublingual Spray (100 µg q4h or 200 µg q4h) and/or matching placebo in subjects with moderate to severe postoperative pain after a bunionectomy.

The study will comprise 4 periods: Screening Period (Days -28 to -1), Surgical Period (Day 0), Treatment Period (48 hours; Days 1 to 3), and Follow-up Period (Day 7 ± 2 days). The study design is represented schematically in Figure 1.

Subjects will be admitted to the study site on the morning of the scheduled surgery (Day 0), will remain at the study site until Postoperative Day 3 (a total of 3 nights at the study site), and will return for the Follow up Visit on Day 7 ± 2 days (5 to 9 days after surgery).

During the 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. Eligible subjects will complete all screening procedures within 28 days before the surgery (Days -28 to -1)

On Day 0, regional anesthesia will be established using a Popliteal Sciatic Nerve Block, using standardized techniques, after which subjects will undergo primary, unilateral, first metatarsal bunionectomy with osteotomy and internal fixation. When the regional anesthetic wears off and the subjects request pain medication, they will be asked to rate their pain intensity using an 11-point (0-10) Numeric Rating Scale (NRS). During the 9-hour period after discontinuation of the anesthetic block, subjects who experience a pain intensity rating of ≥4 on the NRS are eligible to be enrolled in the study. Pulse oximetry will be monitored continuously after the procedure as a safety measure.

During the Treatment Period, approximately 45 subjects will be randomly assigned to 1 of 3 treatment groups: Fentanyl Sublingual Spray 100 µg q4h, 200 µg q4h, or matching placebo.

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 the NRS assessment before study drug administration is defined as Baseline; the time of administration of the first dose of study drug is defined as Time 0. Study drug will be provided by blinded study personnel in a predefined manner to ensure adequate blinding and appropriate dosing regimens for the active drug and placebo. Subjects should not have anything orally except room-temperature water within 15 minutes of each dose. The Treatment Period will continue through 48 hours after Time 0. Pulse oximetry will be continuously monitored and SpO_2 data will be recorded at select time points including baseline before first dose of study drug and 90 minutes and 12, 24, and 48 hours after Time 0. Additional ECGs will be performed at 90 minutes, 12 hours, 24 hours, and 48 hours after Time 0.

Ibuprofen 400 mg will be allowed orally every 4 to 6 hours as needed for rescue medication after study drug treatment has begun. If subjects are unable to tolerate 400 mg ibuprofen or if there is insufficient pain relief, 30 mg of ketorolac tromethamine (i.e., Toradol®) may be administered intravenously or intramuscularly every 6 to 8 hours as needed for pain. The total daily (24 hour)

dosage of ibuprofen medication should not exceed 2400 mg and ketorolac should not exceed 90 mg.

During the Treatment Period, subjects will be allowed to use assigned study medication for primary rescue medication no more frequently than 4 hours from previous study medication dose and no more than 6 times in a 24-hour period. Subjects will be encouraged to wait for at least 1 hour after the first dose of study drug before receiving rescue medication to allow time for the study drug to exert its pharmacologic effect.

During the Treatment Period, subjects whose pain 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 will be managed according to usual standard of care at the investigator's discretion.

Pain will be assessed on an 11-point Numeric Rating Scale (NRS) at Baseline before Time 0. Thereafter, subjects will rate their pain intensity (NRS) and pain relief (on a 5-point categorical scale) and record their assessments in an inpatient subject diary at scheduled times during the 48-hour period after Time 0 (at 2.5, 5, 15, 30, and 45 minutes, and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24, 32, 40, and 48 hours) and immediately before each use of each rescue analgesia during the Treatment Period. Time to perceptible and meaningful pain relief will be evaluated using the 2 stopwatch method (after the first dose only). Subjects will complete a subject's global evaluation of the study drug at the end of the Treatment Period (Day 3) before discharge from the study site.

If a subject discontinues the study prematurely, pain intensity, pain relief, and the subject's global satisfaction with study treatment should be assessed and recorded immediately before discontinuation.

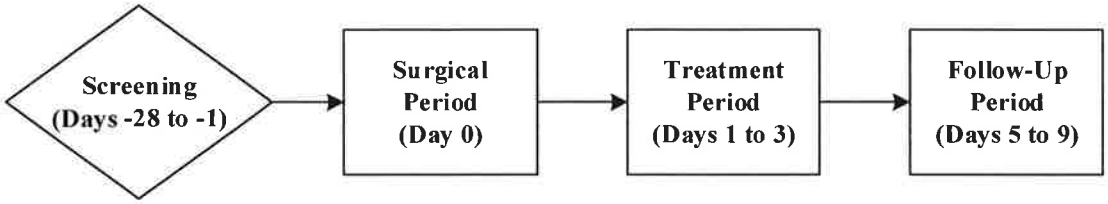
Before discharge from the study site on Day 3, study personnel will dispense a prescription for outpatient pain medication (if not already dispensed) and subjects will be given an outpatient subject diary in which they will be instructed to record concomitant medications taken and adverse events (AEs) experienced after discharge. Subjects will also be instructed to return the outpatient subject diary to study personnel at the Follow up Visit, 7 ± 2 days after surgery.

The planned sequence and maximum duration of the study periods will be as follows:

- Screening Period: up to 28 days
- Surgical Period: Day 0
- Treatment Period: Days 1-3 (up to 9 hours post-surgery plus 48 hours of treatment and inpatient assessments)
- Follow-up: Day 7 ± 2 days (5 to 9 days after surgery) or early withdrawal

Subjects will be confined for approximately 72 hours at the study site for the Surgical and Treatment Periods. The maximum study duration for each subject is approximately 6 weeks

Figure 1: Study Design Schematic



3.2. Subject Selection

3.2.1. Inclusion Criteria

All subjects must satisfy the following criteria to be considered for study participation:

1. Is able to speak and understand the language in which the study is being conducted, is able to understand the procedures and study requirements, and has voluntarily signed and dated an informed consent form approved by an IRB before the conduct of any study procedures;
2. Is a male or female ≥18 and ≤65 years of age;
3. Is classified using the American Society of Anesthesiologists Physical Status Classification System as P1 to P2;
4. Has undergone primary, unilateral, distal first metatarsal bunionectomy (osteotomy and internal fixation) with no additional collateral procedures;
5. Experiences a pain intensity rating of ≥4 on an 11-point (0-10) Numeric Rating Scale (NRS) during the 9-hour period after discontinuation of the anesthetic block;
6. Has a body weight ≥45 kg and a body mass index (BMI) ≤40 kg/m^2;
7. If female and of childbearing potential, is non-lactating and non-pregnant (has negative pregnancy test results at Screening [serum] and on Day 0 before surgery [urine]);
8. 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 1 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
    d. Double-barrier method (condoms, sponge, or diaphragm with spermicidal jellies or cream)

9. Is willing and able to comply with study requirements (including diet, alcohol, and smoking restrictions), complete the pain evaluations, remain at the study site for ≥72 hours, and return for a follow up visit 7 ± 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. Is pregnant or breastfeeding;
5. 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;
6. Has long QT Syndrome, a family history of long QT Syndrome, history of bradyarrhythmias or is taking Class IA or Class III antiarrhythmic medications;
7. Has any ongoing condition, other than one associated with the current primary, unilateral, first metatarsal bunionectomy, that could generate levels of pain sufficient to confound the results of the study (e.g., severe osteoarthritis of the target joint or target extremity, or other painful condition, in the opinion of the investigator, which contraindicates their participation); 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 (e.g., major depression, schizophrenia, or hallucinations);
8. Has tested positive either on the urine drug screen (Screening and/or Day 0) or on the alcohol Breathalyzer test (Day 0). 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;
9. 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;

10. Has an active infection, mucositis, cold sores, viral lesions, local irritation, or periodontal disease of the oral cavity. In addition, has evidence of piercings of the tongue or anywhere in the oral cavity, has a history of oral cavity piercings, or has a history of significant dental disease;
11. 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;
12. 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 Fentanyl Sublingual Spray), to be an unsuitable candidate to receive the study drug;
13. 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);
14. Is currently receiving anticoagulants (e.g., heparin or warfarin). Low-dose aspirin for cardio protection is allowed;
15. Has used drugs with enzyme-inducing properties, such as rifampicin and St. John's Wort, or any drug known to be a strong inhibitor or inducer of CYP3A4 within 3 weeks before surgery;
16. Has received a course of systemic corticosteroids (either oral or parenteral) within 3 months before Screening (inhaled nasal steroids and topical corticosteroids are allowed);
17. Has received or will require any analgesic medication within 5 half-lives (or, if half-life is unknown, within 48 hours) before surgery;
18. 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 6 months 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. (NOTE: Subjects who were prescribed or instructed to use NSAIDs or other analgesics for >2 weeks following a surgical procedure or treatment of temporary acute pain/inflammation secondary to an injury are exempted from this exclusion provided the condition being treated is not chronic and the protocol-mandated washout period is observed);
19. Has been treated with 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 Surgical Period (Day 0).
20. Has used serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) within 2 weeks before Surgical Period (Day 0).

21. Has a significant renal or hepatic disease, as indicated by clinical laboratory assessment (results ≥3 × the upper limit of normal [ULN] for any liver function test, including aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase, or creatinine ≥1.5 × ULN);
22. Has any clinically significant laboratory or 12-lead electrocardiogram finding at Screening that in the investigator's opinion contraindicates study participation;
23. Has screening systolic blood pressure ≥160 mmHg and diastolic blood pressure >100 mmHg (may be repeated 1 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;
24. Oxygen saturation (SpO_2) below 95% at screening;
25. Has a history or presence of postoperative vomiting (CTCAE guidelines for vomiting) grade 2 or higher, as a result of surgery and/or anesthesia. Has a history of sleep apnea, chronic obstructive pulmonary disease and any other obstructive airway disease requiring supplemental oxygen; or
26. Has significant difficulties swallowing capsules or is unable to tolerate oral medication.

3.3. Removal of Subjects from Therapy or Assessment

All subjects will be advised that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. Every reasonable attempt should be made by the investigator to keep subjects in the study. However, subjects must be withdrawn from the study if they withdraw consent to participate. Investigators must attempt to contact subjects who fail to attend scheduled visits by telephone or other means to exclude the possibility of an AE being the cause of withdrawal. Should this be the cause, the AE must be documented, reported, and followed as described in Section 6.2.6.8. The sponsor reserves the right to request the withdrawal of a subject due to protocol violations or other reasons.

The investigator also has the right to withdraw subjects from the study at any time for lack of therapeutic effect that is intolerable or otherwise unacceptable to the subject, for intolerable or unacceptable AEs, intercurrent illness, noncompliance with study procedures, administrative reasons, or in the investigator's opinion, to protect the subject's best interest.

If one of the following events occur during the Treatment Period, the subject will be discontinued from further study participation:

1. Hypoxia with oxygen saturation ≤ 90% on repeat measurements over 3 minutes, despite stimulation and receiving oxygen 2-4 L/min via nasal cannula.
2. Hypoxia or respiratory depression requiring the use of naloxone for reversal.
3. Need for noninvasive respiratory maneuvers (eg, jaw thrust, bag-valve mask for positive pressure ventilation, etc.) to improve or maintain adequate respiratory status (ventilation and/or adequate oxygen saturation) at any point during the study.
4. Hypotension requiring intervention, as follows:
    a. If asymptomatic and <80 mm Hg systolic blood pressure on 3 successive repeat measurements over a 15-minute period.

b. If symptomatic, but >80 mm Hg systolic blood pressure and does not respond to conservative measures such as oral hydration and/or no more than 1 liter of IV fluids (if more than 1 liter of IV fluid is needed and/or if naloxone is administered, the subject will be discontinued from further dosing).

Oxygen saturation will be monitored continuously and the study team will measure all vital signs (blood pressure, heart rate, respiratory rate, and oxygen saturation) at least every 5 minutes until the AE of hypotension or hypoxia as described above is no longer present.

5. If >8 mg i.v. ondansetron is needed within an 8-hour segment and persistent nausea and/or emesis is present.
6. Pain 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.

   Pain will be managed according to usual standard of care at the investigator's discretion.

If a subject is withdrawn before completing the study, the reason for withdrawal and the date of discontinuation will be recorded on the appropriate case report form (CRF). Whenever possible and reasonable, the evaluations that were to be conducted at the completion of the study should be performed at the time of premature discontinuation.

If a subject discontinues the study prematurely, pain intensity, pain relief, and the subject's global satisfaction with study treatment should be assessed and recorded immediately before discontinuation.

Withdrawn subjects will not be replaced. If a substantial number of subjects are withdrawn from the study, then the sponsor will evaluate the need for developing replacement criteria.

3.4. Dose Adjustment Criteria

Dose adjustment is not permitted in this study.

3.5. Stopping Rules

The study may be terminated at the discretion of Insys Development Company, Inc at any time and for any reason.

4. TREATMENTS

4.1. Treatments Administered

Eligible subjects meeting all study entry criteria will be randomly allocated in a 1:1:1 ratio to one of the following treatments containing active or placebo administered up to 6 doses per day as shown in the table below:

Table 1: Study Treatment Regimens

Treatment group	Day 1						Day 2					
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6
100 µg	100 µg	100 µg	100 µg	100 µg	100 µg	100 µg	100 µg	100 µg	100 µg	100 µg	100 µg	100 µg
200 µg	200 µg	200 µg	200 µg	200 µg	200 µg	200 µg	200 µg	200 µg	200 µg	200 µg	200 µg	200 µg
Matching Placebo	P	P	P	P	P	P	P	P	P	P	P	P

4.2. Identity of Investigational Product

The investigational product in this study is Fentanyl Sublingual Spray. Each dose of 100 µg or 200 µg is delivered as a single 100-µL sublingual spray.

Fentanyl Sublingual Spray, is a potent opioid analgesic intended for sublingual administration. Fentanyl Sublingual Spray is formulated to be sprayed underneath the tongue to allow for absorption of fentanyl across the sublingual mucosa.

4.3. Method of Assigning Subjects to Treatment Groups

Eligible subjects meeting all study entry criteria will be randomly allocated in a 1:1:1 ratio to 1 of the 3 treatment groups.

The randomization schedule will be computer generated by using a permuted block algorithm and will randomly allocate the investigational produce (IP) to randomization numbers. The randomization numbers will be provided to the drug packager who will prepare blinded drug kits with all twelve (12) doses identified to maintain the drug blinding. The randomization schedule will be prepared by the sponsor or sponsor's representative before the start of the study. No one involved in the study performance will have access to the randomization schedule before official unblinding of treatment assignment. No subject will be randomized into this study more than once.

4.4. Selection and Timing of Dose for Each Subject

This is a randomized study, and treatment assignment is conducted in consecutive order to prevent bias. Randomization will occur on Day 1.

4.5. Blinding and Unblinding Treatment Assignment

All subjects and study personnel involved in the conduct of the study, including data management, will be blinded to treatment assignment with the exception of a specified unblinded statistical programmer from the sponsor or sponsor's representative who will have access to the randomization code. The unblinded study personnel will not otherwise participate in study procedures or data analysis before unblinding of the study data to all study-related personnel.

Study personnel will endeavor to safeguard the integrity of the study blind to minimize bias in the conduct of the study. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment. If a medical emergency occurs and unblinding is required, the site will contact IXRS for drug assignment. Unblinding should be discussed in advance with the sponsor, sponsor's representative, or medical monitor if possible. For emergency unblinding, study personnel will contact the sponsor or sponsor's representative. If the investigator is not able to discuss treatment unblinding in advance, then he or she must notify the sponsor, sponsor's representative, or medical monitor as soon as possible about the unblinding incident without revealing the subject's treatment assignment. The investigator or designee must record the date and reason for study unblinding in the source document for that subject. In all cases that are not emergencies, the investigator must discuss the event with the sponsor, sponsor's representative, and/or medical monitor prior to unblinding the subject's treatment assignment.

If the treatment assignment is unblinded for an individual subject, study personnel will be notified of that subject's treatment assignment without unblinding of the treatment assignments for the remaining subjects in the study. Thus, the overall study blind will not be compromised. If a subject's treatment assignment is unblinded, he or she may or may not be asked to withdraw from the study. The investigator will make this decision after consultation with the sponsor, sponsor's representative, or medical monitor.

4.6. Treatment Compliance

Investigational treatment will be administered at the site under the supervision of site staff. Study compliance with other procedures will be monitored for each subject based on attendance at scheduled visits.

4.7. Permitted and Prohibited Therapies

4.7.1. Permitted Therapies

Prescription medications that in the opinion of the investigator would not potentially interact with fentanyl or interfere with its respiratory effects were permitted during the course of this study.

4.7.2. Prohibited Therapies

The following medications are prohibited during this study:

- Any prescription medication that in the opinion of the investigator could potentially interact with fentanyl or interfere with its respiratory effects within 14 days prior to the first dose of study medication or during the course of this study.
- Enzyme altering drugs such as barbiturates, corticosteroids, phenothiazines, cimetidine, carbamazepine, etc., within 30 days prior to the first dose of study medication or during the course of this study.

Subjects are to abstain from consuming any of the following:

- Alcohol from 24 hours before surgery on Day 0 until 48 hours after treatment and inpatient assessments.
- Caffeine-containing foods and drinks (e.g. coffee, cola, Red Bull, chocolate, etc.) from 24 hours prior to surgery on Day 0 until 48 hours after treatment and inpatient assessments.
- Tobacco products or nicotine-containing products 24 hours before surgery on Day 0 until 48 hours after treatment and inpatient assessments.

4.8. Rescue Medication

Prior to the Treatment Period, ibuprofen 400 mg will be allowed orally every 4 to 6 hours as needed for pain before the regional anesthetic infusion (continuous popliteal sciatic block) is discontinued. If the subject is unable to tolerate 400 mg ibuprofen or if there is insufficient pain relief, then subject may receive supplemental analgesia with a hydrocodone/acetaminophen combination. One to two hydrocodone/acetaminophen 5/325-mg tablets may be administered every 4 to 6 hours as needed for moderate to severe pain, up to a daily limit of 8 to10 tablets. If the subject cannot tolerate the hydrocodone/acetaminophen or if there is insufficient pain relief, then 30 mg ketorolac tromethamine (eg, Toradol®) may be administered intravenously or intramuscularly every 6 to 8 hours as needed for pain. The total daily (24-hour) dosage of ibuprofen medication should not exceed 2400 mg; the total daily dose of acetaminophen should not exceed 3250 mg; the total daily dose of ketorolac should not exceed 90 mg.

During the Treatment Period (after the regional anesthetic infusion is discontinued), ibuprofen 400 mg will be allowed orally every 4 to 6 hours as needed for rescue medication. If subjects are unable to tolerate 400 mg ibuprofen or if there is insufficient pain relief, 30 mg of ketorolac tromethamine (i.e., Toradol®) may be administered intravenously or intramuscularly every 6 to 8 hours as needed for pain. The total daily (24 hour) dosage of ibuprofen medication should not exceed 2400 mg and ketorolac should not exceed 90 mg.

Subjects will be allowed to use assigned study medication for primary rescue medication no more frequently than 4 hours from previous study medication dose and no more than 6 times in a 24-hour period. Subjects will be encouraged to wait for at least 1 hour after the first dose of study drug before receiving rescue medication to allow time for the study drug to exert its pharmacologic effect.

The rescue medication, specific reason for use, andthe time since the last scheduled dose of IP will be captured on the appropriate CRF. Pain intensity assessments will be recorded immediately before each dose of rescue analgesia during the Treatment Period.

4.9. Treatment After the End of Study

After the end of the study, each subject will receive treatment according to standard clinical practice.

5. STUDY DRUG MATERIALS AND MANAGEMENT

5.1. Labeling and Packaging

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

5.1.1. Labeling

Fentanyl Sublingual Spray will be supplied as individual subject kits by the sponsor or the sponsor's representative to the investigational sites. Each clinical kit will be labeled with a subject and product label. The investigator or designee will need to record the kit number and subject identification number on the appropriate accountability logs.

5.1.2. Packaging

Fentanyl Sublingual Spray will be supplied by the sponsor or the sponsor's representative. The investigational product is supplied in a unit dose sublingual spray unit packaged in a vial.

5.2. Dispensing and Storage

Fentanyl Sublingual Spray should be stored at 20° to 25°C (68° to 77°F), with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use. Temperature logs should be kept for the storage area.

All investigational products should be stored in a secure location or in the site pharmacy with limited access. It is the responsibility of the investigator to ensure that the investigational product is only used for subjects enrolled in the study.

The investigational product is intended for single use only.

5.3. Drug Supply and Accountability

The investigator must maintain adequate records showing the receipt, dispensing, return, or other disposition of the IP including the date, quantity, and identification of subjects (subject number and initials) who received the IP. If any of the IP is received in a damaged container, this information must be documented and reported to the sponsor, or sponsor's representative.

All unused investigational kits will be returned to the sponsor, or sponsor's representative, when instructed.

6. STUDY ASSESSMENTS

6.1. Efficacy Assessments

6.1.1. Pain Intensity

Subjects will assess their current pain intensity using an 11-point (0 to 10) Numerical Rating Scale (NRS). Each subject will be instructed to mark the number indicating his or her current pain intensity.

The subject is to record pain intensity (NRS) in the inpatient subject diary at Baseline before the first dose of study drug (Day 1), at Time 0. Thereafter, the subject is to record NRS pain intensity assessments at the following time points during the 48-hour period after Time 0:

- 2.5, 5, 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24, 32, 40 and 48 hours after Time 0, and immediately before each use of rescue analgesia.
- At Early Withdrawal if a subject discontinues prematurely.

6.1.2. Pain Relief

Subjects will assess their current pain relief using a 5-point categorical scale. Each subject will be instructed to mark the number indicating his or her current pain relief.

The subject is to record pain relief (5-point categorical rating scale) in the inpatient subject diary at the following time points during the 48-hour period after Time 0:

- 2.5, 5, 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24, 32, 40 and 48 hours after Time 0, and immediately before each use of rescue analgesia.
- At Early Withdrawal if a subject discontinues prematurely.

6.1.3. Two-Stopwatch Assessment of Pain Relief

Time to perceptible pain relief and meaningful pain relief will be evaluated using the 2 stopwatch method (after the first dose only). The study staff will start 2 stopwatches as soon as the first dose of study drug is administered. Each subject will be instructed to stop the first stopwatch when he or she experiences any perceptible pain relief and the second stopwatch when he or she experiences pain relief that is meaningful to them. Subjects will receive training for this procedure at their screening visit and prior to discontinuation of the regional anesthetic popliteal block.

6.1.4. Subject's Global Evaluation of Study Drug

Subjects will complete a subject's global evaluation of study drug at the end of the treatment period (Day 3) before discharge from the study site or immediately before Early Withdrawal if a subject discontinues prematurely. The subject will be instructed to score his or her global evaluation of the study treatment on a 5-point categorical scale where 0 = poor, 1 = fair, 2 = good, 3 = very good, and 4 = excellent.

6.2. Safety Assessments

Safety assessments include the evaluation of AEs, physical and oral examinations, vital sign measurements, pulse oximetry, and 12-lead ECGs. Clinical laboratory tests will be performed at Screening only.

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 history, medications history, and concomitant medications.

6.2.2. Physical and Oral Examinations

A complete physical examination (excluding the genitourinary examination) will be performed at Screening. An abbreviated physical examination will be performed at the Follow up Visit.

An oral cavity examination will be performed at Screening, on Day 1 prior to and one hour after first dose, and at the Follow up Visit. The oral examination at Screening and prior to first dose 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. The oral examinations on Day 1 one hour after first dose and at the Follow up Visit will check for mucositis and local irritation.

6.2.3. Vital Signs

Vital signs, including blood pressure, heart rate, respiratory rate, and oral body temperature, will be measured after the subject has been in a resting position for 5 minutes. Vital signs will be measured at Screening and before surgery on Day 0. From Day 1 through discharge from the study site, vital signs will be measured immediately before and 1 hour after the first dose of study drug on Day 0, then immediately before and 1 hour after the 24 hour and 40 hour doses, and at 48 hours. Vital signs will also be measured before Early Withdrawal if a subject discontinues.

Height, weight, and BMI will be recorded at Screening.

Pulse oximetry will be measured at Screening and continuously after the procedure for safety, and recorded at the following times: baseline before Time 0, and at 90 minutes and 12, 24, and 48 hours after Time 0 (T_{max}).

6.2.4. Electrocardiograms

A standard 12-lead ECG will be performed after the subject has been supine for at least 3 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. An ECG will be performed after surgery but before the first dose of study drug, and then at 90 minutes and 12, 24, and 48 hours after Time 0.

6.2.5. Clinical Laboratory Assessments

Clinical laboratory tests will be performed at Screening. Pregnancy tests and urine drug screens will be performed at Screening and before surgery. An alcohol breathalyzer test will be performed before surgery. Samples for the following laboratory tests will be collected:

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
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)
Urinalysis	pH, specific gravity, blood, glucose, protein, ketones
Urine & Serum Pregnancy tests	for women of childbearing potential only; a serum test at Screening and a urine test before surgery
Urine Drug Screen	amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, and tetrahydrocannabinol
Alcohol Breathalyzer	alcohol

Blood and urine samples for hematology, serum chemistry, serum pregnancy test, and urinalysis will be sent to a local laboratory for analyses. Urine drug screens and urine pregnancy tests will be conducted at the study sites.

6.2.6. Adverse Events and Serious Adverse Events

Adverse events will be collected from the time the subject signs an informed consent through the Follow-up visit.

6.2.6.1. 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.

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 conditions(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.

Subjects will be monitored throughout the study for AEs. 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 his/her 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.

6.2.6.2. Adverse Reactions from Clinical Trials

The presentation of adverse reactions identified from clinical trials is the major component of the Adverse Reactions section. The Adverse Reactions section must include a listing of all such reactions that occurred at or above a specified rate that is appropriate to the drug's safety database, a separate listing of those adverse reactions that occurred below the specified rate, but for which there is some basis to believe there is a causal relationship between the drug and the event, and, to the extent information is available and relevant, additional detail about the nature, frequency, severity, duration, dose-response, and demographic characteristics of those adverse reactions with significant clinical implications.

The following is the recommended organization of adverse reactions identified from clinical trials.

- Adverse Reaction (21 CFR 201.57(c)(7)): An adverse reaction is an undesirable effect, reasonably associated with the use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event. Adverse reactions may include signs and symptoms, changes in laboratory parameters, and changes in other measures of critical body function, such as vital signs and ECG.
- Adverse Event (or adverse experience): The term adverse event refers to any untoward medical event associated with the use of a drug in humans, whether or not considered drug-related.

- Serious Adverse Reaction: The term serious adverse reaction refers to any reaction occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious adverse reactions when, based upon appropriate medical judgment, they may jeopardize the patient or subject, and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

6.2.6.3. 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.

6.2.6.4. 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 drugs.

- 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.

6.2.6.5. Actions Taken for SAE

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

6.2.6.6. Outcome at the Time of Last Observation

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

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

6.2.6.7. 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

6.2.6.8. Adverse Event Recording and Reporting

Adverse events will be recorded throughout the study in the source documents and in the CRFs.

If known, the diagnosis should be recorded, in preference to the listing of individual signs and symptoms. Adverse event reporting for each subject starts when the subject signs the informed consent and continues at all subsequent visits through the Follow up Visit. Any preexisting conditions that are detected as part of the screening procedures will need to be reported in the medical history and not as an AE.

The investigator will rate AEs for seriousness, intensity, causality, action taken, and outcome as described in the previous sections.

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 as complete a 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 fax it to Insys within 24 hours of the investigators first knowledge of the event.

Sponsor contact information is listed below:

[redacted]

Insys 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.

6.2.6.9. 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.

6.2.6.10. 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 Table 2.

7.1. Screening (Day -28 to Day -1)

The subject will be screened within 28 days before the scheduled surgery. The following procedures will be performed at Screening:

1. Obtain written informed consent.
2. Review inclusion/exclusion criteria.
3. Collect demographic information.
4. Record medical history, including current therapies (eg, prescription and nonprescription medications), and presence of bunion.
5. Perform a physical examination including height, weight, and BMI.
6. Perform an oral cavity examination.
7. Measure vital signs (resting blood pressure, heart rate, respiratory rate, and oral body temperature).
8. Pulse oximetry.
9. Perform clinical laboratory tests (hematology, clinical chemistry, and urinalysis), urine drug screen, and serum pregnancy test (women of childbearing potential only).
10. Perform a 12-lead ECG.
11. Record concomitant medications.
12. Perform podiatric examination and obtain radiograph (a radiograph taken within the previous 6 months will be acceptable).

7.2. Day 0 (Surgery)

Subjects will be admitted to the study site on the morning of the surgery. The following events will occur:

7.2.1. Pre-surgery

1. Collect medical history (changes since screening).
2. Review inclusion/exclusion criteria.
3. Measure vital signs (resting blood pressure, heart rate, respiratory rate, and oral body temperature).
4. Perform a urine pregnancy test and a urine drug screen.
5. Perform an alcohol breathalyzer test.
6. Record concomitant medications.

7. Record AEs.

7.2.2. Surgery and Standardized Regional Anesthesia

Subjects who continue to meet all study entry criteria will undergo a primary, unilateral, first metatarsal bunionectomy with osteotomy and internal fixation under a standardized regimen of regional anesthesia. Regional anesthesia will be established using a popliteal sciatic nerve block, using standardized techniques. The regional anesthesia will be continued postoperatively via a continuous anesthetic infusion (continuous popliteal sciatic block). Subjects may receive supplemental analgesia with ibuprofen and/or an opioid/acetaminophen combination product and/or ketorolac during the continuous infusion period to help control breakthrough pain if the investigator/study site personnel consider the regional anesthetic infusion to offer inadequate pain control or if it becomes nonfunctional. If the regional anesthetic infusion and supplemental analgesia do not control the subject's postoperative pain effectively, then the subject will be discontinued from the study and further treatment will be according to usual standard of care at the investigator's discretion.

Ibuprofen 400 mg will be allowed orally every 4 to 6 hours as needed for pain before the anesthetic infusion (continuous popliteal sciatic block) is discontinued. If the subject is unable to tolerate 400 mg ibuprofen or if there is insufficient pain relief, then subject may receive supplemental analgesia with a hydrocodone/acetaminophen combination. One to two hydrocodone/acetaminophen 5/325-mg tablets may be administered every 4 to 6 hours as needed for moderate to severe pain, up to a daily limit of 8 to10 tablets. If the subject cannot tolerate the hydrocodone/acetaminophen or if there is insufficient pain relief, then 30 mg ketorolac tromethamine (eg, Toradol®) may be administered intravenously or intramuscularly every 6 to 8 hours as needed for pain. The total daily (24-hour) dosage of ibuprofen medication should not exceed 2400 mg; the total daily dose of acetaminophen should not exceed 3250 mg; and the total daily dose of ketorolac should not exceed 90 mg.

7.3. Treatment Period (Days 1-3)

The treatment period comprises Day 1 (Baseline before dosing) and Day 2 and 3 (48 hours after the first dose of study medication).

7.3.1. Pre-randomization

On Day 1, the regional anesthetic infusion will be discontinued at approximately 3:00 AM. Thereafter, when subjects request pain medication, they will be asked to rate their pain intensity using an 11-point (0-10) Numeric Rating Scale (NRS). During the 9-hour period after discontinuation of the anesthetic block, subjects who experience a pain intensity rating of ≥4 on the NRS are eligible to be enrolled in the study. Subjects whose pain intensity ratings do not meet the minimum entry criteria within 9 hours after discontinuation of the regional anesthesia will not be eligible for enrollment and will receive routine postoperative care at the investigator's discretion. Pulse oximetry will be monitored continuously after the procedure as a safety measure.

When a subject's pain meets the pain intensity entry criteria (≥4 on the NRS), he or she will be eligible to begin the Treatment Period and will be randomized.

7.3.2. Post-randomization

1. Measure vital signs (resting blood pressure, heart rate, respiratory rate, and oral body temperature) immediately before and 1 hour after the first dose of study drug on Day 0, then immediately before and 1 hour after the 24-hour and 40-hour doses, and at 48 hours.
2. Perform a 12-lead ECG before the first dose of study drug, and then at 90 minutes and 12, 24, and 48 hours after Time 0.
3. Pulse oximetry will be recorded at selected times, including baseline before Time 0 and at 90 minutes and 12, 24, and 48 hours after Time 0 (Tmax).
4. The subject is to record pain intensity (numerical rating scale) in the inpatient subject diary at Baseline before the first dose of study drug (Day 1). Thereafter, the subject is to record pain intensity and pain relief (5-point categorical scale) assessments at the following time points:
   a. At 2.5, 5, 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24, 32, 40 and 48 hours after Time 0, and immediately before each use of rescue analgesia.
   b. At Early Withdrawal if a subject discontinues prematurely.
5. Administer the first dose of study drug within 9 hours (± 10 minutes) after the anesthetic block has been discontinued when a subject's pain intensity is ≥4 on the 11-point (0 10) NRS. Study drug will be administered from Time 0 through 48 hours within 10-minute windows.
6. Start stopwatches as soon as the first dose of study drug is administered. Stopwatches should be discontinued if the subject has not stopped them by the time of the second IP dose or first use of rescue medication (whichever occurs first).
7. Perform an oral cavity examination prior to and one hour after first dose.
8. Record concomitant medications.
9. Record AEs.
10. Subjects will complete a subject's global evaluation of study drug at the end of the treatment period (Day 3) before discharge from the study site or immediately before ET if a subject discontinues prematurely.
11. Dispense outpatient pain medication and an outpatient subject diary before discharge from the study on Day 3 (approximately 72 hours after completion of surgery).

7.4. Follow-up (Day 7) or Early Withdrawal

Subjects will return to the study site for a Follow-up Visit 7 days after surgery (± 2 days). At this visit, the following procedures will be performed:

1. Perform a physical examination noting changes from Screening.
2. Perform an oral cavity examination.
3. Measure vital signs (resting blood pressure, heart rate, respiratory rate, and oral body temperature).

4. Collect and review diary.
5. Record concomitant medications.
6. Assess and record.

7.5. Interim Visits

Subjects should contact the study site if they experience any problems prior to the Follow-up Visit, and an interim visit will be arranged promptly as needed.

Table 2: Schedule of Assessments

	Screening (Days -28 to -1 before surgery)	Surgery Day 0	Treatment Period			Follow-up Day 7 ± 2 days (5 to 9 days after surgery) or Early Withdrawal
			Day 1 (Baseline; before dosing)	Day 1 First dose (Time 0)	Days 2 and 3 Subsequent doses	
Written informed consent	X					
Inclusion/exclusion criteria	X	X				
Demographics	X					
Medical history	X	X[a]				
Physical examination[b]	X					X
Oral examination[c]	X			X		X
Vital signs[d]	X	X	X	X	X	X
Height, weight, and body mass index	X					
Pulse oximetry[e]	X		X	X	X	
12-lead electrocardiogram[f]	X		X	X	X	
Clinical laboratory tests (hematology, chemistry, urinalysis)	X					
Pregnancy test for female subjects[g]	X	X				
Urine drug screen[h]	X	X				
Alcohol breathalyzer test		X				
X-ray and podiatric examination[i]	X					
First metatarsal bunionectomy procedure		X				
Discontinue anesthetic block at approximately 3:00 AM[j]			X			
Assign randomization number			X			
Pain assessments[k]			X	X	X	
Administer study drug[l]				X	X	

	Screening (Days -28 to -1 before surgery)	Surgery Day 0	Treatment Period			Follow-up Day 7 ± 2 days (5 to 9 days after surgery) or Early Withdrawal
			Day 1 (Baseline; before dosing)	Day 1 First dose (Time 0)	Days 2 and 3 Subsequent doses	
Start stopwatches for perceptible and meaningful pain relief[m]				X		
Subject's global evaluation of study drug[n]					X	
Concomitant medications	X	X	X	X	X	X
Adverse events		X	X	X	X	X
Dispense outpatient pain medication and outpatient subject diary[o]					X	
Discharge subject from the study site[p]					X	
Collect and review diary for completion						X

Abbreviations: ET=early termination; NRS=numeric rating scale

a Medical history should be reviewed for any changes since Screening.

b A complete physical examination (excluding the genitourinary examination) will be performed at Screening. An abbreviated physical examination, including an examination of the subject's surgical site, will be performed at the Follow-up Visit.

c The postdose oral examination should be conducted 1 hour (±10 minutes) after dosing.

d Vital signs, including blood pressure, heart rate, respiratory rate, and oral body temperature, will be measured after the subject has been in a resting position for 5 minutes. Vital signs will be measured at Screening and before surgery on Day 0 immediately before and 1 hour (±10 minutes) after the first dose of study drug on Day 0, immediately before and 1 hour (±10 minutes) after the 24-hour and 40-hour doses, and at 48 hours (±10 minutes). Vital signs will also be measured before ET if a subject discontinues.

e Pulse oximetry will be measured at Screening and continuously after the procedure for safety; pulse oximetry will be recorded at selected times (±10 minutes), including baseline before Time 0 and at 90 minutes and 12, 24, and 48 hours after Time 0 (T_{max}).

f An ECG will be performed before the first dose of study drug, and then at 90 minutes (±10 minutes), and at 12, 24, and 48 hours (±10 minutes) after Time 0.

g A serum pregnancy test will be performed at Screening and a urine pregnancy test will be performed before surgery on Day 0. The test results must be negative for the subject to continue in the study.

h A urine drug screen will be collected at Screening and before surgery on Day 0. 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.

i Radiographs taken within 6 months before Screening will be acceptable.

j Immediately after the anesthetic block is discontinued, subjects will be instructed to request pain medication when they experience pain.

k The subject will record pain intensity (numerical rating scale) in the inpatient subject diary at Baseline before the first dose of study drug (Day 1). Thereafter, pain intensity and pain relief (5-point categorical scale) assessments will be recorded at the following time points (± 5 minutes):

- At 2.5, 5, 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24, 32, 40 and 48 hours after Time 0, and immediately before each use of rescue analgesia.
- At Early Withdrawal if a subject discontinues prematurely.

l The first dose of study drug will be administered within 9 hours (±10 minutes) after the anesthetic block has been discontinued when a subject's pain intensity is ≥4 on the 11-point (0-10) NRS. Study drug will be administered from Time 0 through 48 hours within 10-minute windows.

m Start stopwatches as soon as the first dose of study drug is administered. Stopwatches should be discontinued if the subject has not stopped them by the time of the second IP dose or first use of rescue medication (whichever occurs first).

n Subjects will complete a subject's global evaluation of study drug at the end of the Treatment Period (Day 3) before discharge from the study site or immediately before ET if a subject discontinues prematurely.

o Outpatient pain medication and an outpatient subject diary will be dispensed before discharge from the study site on Day 3.

p Subjects will be discharged from the study site on Day 3 (approximately 72 hours after completion of surgery)

8. STATISTICS

8.1. Efficacy Endpoints

8.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the NRS summed pain intensity difference (NRS SPID) (calculated as a time weighted average) over 0 to 48 hours (NRS SPID-48) after Time 0.

8.1.2. Secondary Efficacy Endpoints

The secondary endpoints are the following:

- NRS pain intensity difference (NRS PID) at each scheduled time point after Time 0
- NRS pain intensity score at each scheduled time point
- NRS SPID over 0 to 4 hours (NRS SPID-4), over 0 to 8 hours (NRS SPID-8), and over 0 to 24 hours (NRS SPID-24) after Time 0
- Total pain relief (TOTPAR) over 0 to 4 hours (TOTPAR-4), over 0 to 8 hours (TOTPAR-8), over 0 to 24 hours (TOTPAR-24), and over 0 to 48 hours (TOTPAR-48) after Time 0
- Time to onset of analgesia (measured as time to perceptible pain relief confirmed by meaningful pain relief using the 2-stopwatch method)
- Pain relief score on a 5-point categorical scale at each scheduled time point after Time 0
- Peak pain relief
- Time to peak pain relief
- Time to first perceptible pain relief
- Time to meaningful pain relief
- Proportion of subjects using rescue medication
- Time to first use of rescue medication (duration of analgesia) following each dose of IP
- Total use of rescue analgesia over 0 to 24 hours and over 0 to 48 hours
- Subject's global evaluation of study drug

8.2. Safety Endpoints

The safety endpoints are the incidence of treatment-emergent adverse events (TEAEs), physical and oral examination findings, and changes in vital signs, pulse oximetry, and ECG measurements.

8.3. Sample Size Determination

A sample size of 15 subjects per treatment group will provide ≥80% power to detect a minimal standardized effect size of 0.5 between the 100 µg q4h, 200 µg q4h active treatment arms, and placebo in NRS SPID-48 using a 3-group analysis of covariance (ANCOVA) with baseline NRS score as the covariate with a 0.05 two-sided significance level (EAST v6).

8.4. Analysis Populations

- The intent to treat (ITT) population will consist of all subjects who are randomized. The ITT population is the primary population for the efficacy analysis.
- The per protocol (PP) population will consist of all ITT subjects who receive at least 1 dose of study drug, who remain in the study for at least 48 hours of treatment and who do not incur a major protocol violation that would challenge the validity of their data. This population will be used to evaluate the sensitivity of the primary efficacy analysis.
- The safety population 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

This section presents a summary of the planned statistical analyses. A Statistical Analysis Plan that describes the details of the analyses to be conducted will be finalized prior to database lock.

Summary statistics will be provided for the variables described as follows. 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.

The last observation before study medication administration will be used as the baseline value. The time of the first dose of study medication will be defined as Time 0.

8.5.1. Study Subjects 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 before unblinding.

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, surgery duration, and baseline pain intensity) will be summarized by treatment group and for the

overall population by descriptive statistics. No formal statistical analyses will be performed. Medical history, clinical laboratory test results, and ECG assessments will be listed.

Prior and concomitant medications will be summarized by treatment group and by the number and percentage of subjects taking each medication. They will also be classified by using the World Health Organization Drug Dictionary Anatomical Therapeutic Chemical classes and preferred terms.

8.5.2. Exposure and Compliance

The exposure to study medication will be summarized by descriptive statistics. As the dose administration is under the control of the study sites, compliance will not be an issue.

8.5.3. Efficacy Analyses

8.5.3.1. Primary Efficacy Analysis

An analysis of covariance (ANCOVA) will first be assessed among the SPID-48 measurements of the three treatment groups. If the F statistic is significant with a $p < 0.05$, then a post-hoc analysis of the treatment groups will be performed. The least square (LS) mean, standard error (SE), and 95% confidence interval (CI) for each treatment group will be estimated. In addition, the mean (LS mean) difference between each treatment and placebo, SE, p-value, and the associated 95% CI will be computed.

8.5.3.2. Secondary Efficacy Analysis

The secondary endpoints NRS SPID-4, NRS SPID-8, NRS SPID-24, TOTPAR-4, TOTPAR-8, TOTPAR-24, TOTPAR-48, time to use of rescue analgesia, and total use of rescue analgesia will be analyzed similarly to the primary endpoint. The NRS pain intensity and the pain relief scores at each time point will also be summarized descriptively. Time to event endpoints (time to onset of analgesia, time to peak pain relief, time to perceptible relief, time to meaningful relief, and time to first rescue medication) will be analyzed using Kaplan-Meier methods. Peak pain relief score, average time to use of rescue of analgesia following a dose of IP, proportion of subjects using rescue medication, and the subject's global evaluation will be analyzed using chi-square, Fishers exact, or logistic regression techniques as appropriate. No formal statistical inferences will be made on any secondary endpoints. Details of statistical analyses will be described in the SAP that will be finalized before database lock and unblinding.

8.5.3.3. Sensitivity Analyses

Sensitivity analyses to explore the impact of missing data and use of rescue will be performed for the primary efficacy analysis. Specifics of the sensitivity analyses will be described in the SAP.

8.5.4. Safety and Tolerability Analyses

Safety analyses will be conducted using data from the safety population. The safety endpoints are the incidence of treatment-emergent adverse events (TEAEs), physical and oral examination findings, and changes in vital signs, pulse oximetry, and ECG measurements.

No formal inferential analyses will be conducted for safety variables. Data listings will be provided for protocol-specified safety data.

8.5.4.1. Adverse Events

The Medical Dictionary for Regulatory Activities (Version 17.0 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.

8.5.4.2. Clinical Laboratory Evaluations

Clinical laboratory evaluations are being conducted at Screening for purposes of qualifying subjects for the study and do not represent a safety monitoring tool. Descriptive summaries (mean, SD, median, minimum, and maximum) of actual (absolute) values will be presented for clinical laboratory values for each treatment group.

8.5.4.3. Vital Signs

For vital sign measurements, descriptive statistics will be provided at each scheduled time point for each treatment group. Changes from Baseline for vital signs will be calculated for each subject, and descriptive statistics will be provided on changes in vital signs from Baseline for each treatment group at each scheduled time point after Baseline.

8.5.4.4. Electrocardiograms

The number and percentage of subjects with clinically relevant abnormal ECG findings will be summarized for each treatment group at each time point.

Descriptive summaries of observed values and changes from baseline will be presented for ECG measures of PR interval, QRS interval, QT interval, QT interval corrected for heart rate (QTc) interval (by using Fridericia's QT correction method), and heart rate for each treatment group at each time point.

In addition, the number and percentage of subjects in each treatment group who experienced a change of >30 ms or a change of >60 ms from baseline will be presented.

8.5.4.5. Physical and Oral Examination Findings

The number and percentage of subjects with normal and abnormal findings in the physical and oral examinations at the Follow-up or Early -Withdrawal Visit will be displayed for each treatment group. New and worsening abnormal physical and oral examination findings during the study will be entered as AEs and analyzed within the AE tables.

8.5.5. Interim Analysis

No interim analyses are planned.

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 (Section 11.2). The sponsor reserves the right to withdraw a subject from the study (Section 3.3), to terminate participation of a study site at any time (Section 9.6), and/or to discontinue the study (Section 9.5).

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 (Section 15), 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 (eg, 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 Insys Development Company, Inc. 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.

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 telephone follow-up call.

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 Withdrawal 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. Pharmacokinetic/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

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of the sponsor. The protocol amendment must be signed by the investigator and approved by the IRB before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the study.

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 CRU, 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 CRU 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 must be a properly constituted board or committee operating in accordance with Title 21 Part 56 of the United States of America (US) CFR relating to IRBs and the ICH Guideline for Good Clinical Practice (E6). Clinical supplies cannot be shipped to the principal investigator until the sponsor, or sponsor's representative, has received a copy of the letter or certificate of approval from that investigator's IRB for the protocol and any amendments.

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.

This protocol is written in accordance with:

- The Declaration of Helsinki (1996 Revision).
- Good Clinical Practices as delineated in Title 21 Part 50 of the US CFR, Protection of Human Subjects," Part 54, "Financial Disclosure by Clinical Investigators," and Part 56, "Institutional Review Boards."
- US Health Insurance Portability and Accountability Act regulations.
- ICH Guideline for Good Clinical Practice (E6) and Clinical Safety Data Management (E2A).

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 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 Amarex data management services. 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. USE OF INFORMATION AND PUBLICATION POLICY

13.1. Use of Information

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

This confidential information shall remain the sole property of Insys Development Company, Inc., shall not be disclosed to others without the written consent of Insys Development Company, Inc., 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.

13.2. 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.

14. REFERENCES

1. Desjardins PJ, Shu VS, Recker DP, Verburg KM, Woolf CJ. A single preoperative oral dose of valdecoxib, a new cyclooxygenase 2 specific inhibitor, relieves post oral surgery or bunionectomy pain. *Anesthesiology*. 2002; 97(3): 565-573.
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15. INVESTIGATOR SIGNATURE PAGE

TITLE:	A Phase 2 Multicenter, Randomized, Double-Blind, Multiple-Dose, Parallel-Group, Placebo-Controlled Study of Fentanyl Sublingual Spray for the Treatment of Moderate to Severe Post-Operative Pain
PROTOCOL NUMBER:	INS002-16-092
PHASE OF STUDY:	2
PROTOCOL DATE:	21 Dec 2016
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**

APPENDIX 1. REGULATIONS AND GOOD CLINICAL PRACTICE GUIDELINES

1. Regulations

Refer to the following United States Code of Federal Regulations (CFR):

- Food and Drug Administration (FDA) Regulations 21 CFR, Parts 50.20 – 50.27
- Subpart B – Informed Consent of Human Subjects
- FDA Regulations 21 CFR, Parts 56.107 – 56.115

  Part 56 – Institutional Review Boards

  Subpart B – Organization and Personnel

  Subpart C – IRB Functions and Operations

  Subpart D – Records and Reports
- FDA Regulations 21 CFR, Parts 312.50 – 312.70

  Subpart D – Responsibilities of Sponsors and Investigators

2. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URL:
http://www.ich.org/LOB/media/MEDIA482.pdf

APPENDIX 2. AMERICAN SOCIETY OF ANESTHESIOLOGISTS (ASA) PHYSICAL STATUS CLASSIFICATION SYSTEM

ASA Physical Status 1 - A normal healthy patient

ASA Physical Status 2 - A patient with mild systemic disease

ASA Physical Status 3 - A patient with severe systemic disease

ASA Physical Status 4 - A patient with severe systemic disease that is a constant threat to life

ASA Physical Status 5 - A moribund patient who is not expected to survive without the operation

ASA Physical Status 6 - A declared brain-dead patient whose organs are being removed for donor purposes

These definitions appear in each annual edition of the ASA Relative Value Guide®. There is no additional information that will help you further define these categories.

Source: https://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system

APPENDIX 3. HYPOXIA ASSESSMENT (PROPOSED GUIDANCE)

Hypoxia Level	Condition	Action
1	Hypoxia on Room Air	• Verbal Stimulation/Position Change. • If not able to maintain a saturation of greater than 90% after two verbal interventions, then advance to Level 2.
2	Hypoxia on Oxygen via Nasal Cannula	• Administer oxygen 2-4 L/min via nasal cannula. • If not able to maintain a saturation greater than 90% despite oxygen via NC, then advance to Level 3.
3	Hypoxia on Oxygen via Face Mask	• Change oxygen to facemask delivery. • If not able to maintain a saturation greater than 90% despite oxygen via FM, then advance to Level 4.
4	Hypoxia despite Maximal Oxygen Therapy	Mechanical Intervention (sternal rub, airway management) + Chemical Narcotic Reversal

Note: Proposed process for Hypoxia is a guidance, and will not supersede the investigator's medical judgement and treatment process. If oxygen is administered, the oxygen treatment should be documented as a concomitant medication.

APPENDIX 4. NALOXONE ADMINISTRATION (PROPOSED GUIDANCE)

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 fentanyl dose and the correct naloxone dose window
3. Because respiratory depression from fentanyl 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)

APPENDIX 5. RESCUE MEDICATION FOR POST-OPERATIVE NAUSEA AND/OR EMESIS (PONV, PROPOSED GUIDANCE)

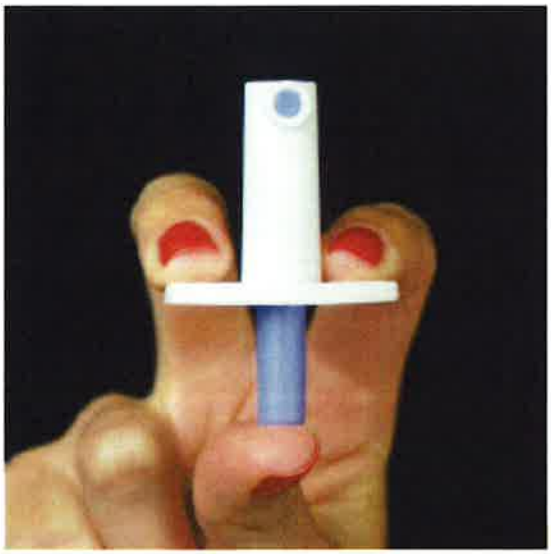
1. Administer initial dose of ondansetron (Zofran®) 4 mg IV if nausea ≥ 5 mins.
2. If symptoms are persistent, then a second dose of ondansetron 2mg IV may be administered in 15-60 minutes
3. If PONV continues to be a problem, an additional dose of ondansetron 2mg IV can be given after an additional 15-60 minutes. Do not administer more than 8 mg of ondansetron within an 8-hour period.
4. If vomiting persists at least 60 minutes following 8 mg IV ondansetron within an 8-hour period (i.e., patient is refractory to ondansetron) metoclopromide (Reglan®) may be administered for further treatment of persistent PONV.
5. Metoclopromide (Reglan®), 10-20 mg IM may be administered q4-6hr (max daily dose: 40 mg).
6. If PONV is not adequately controlled with metoclopromide, subject will be discontinued from the study.
7. PI should call Medical Monitor to discuss subjects with refractory PONV/emesis.

APPENDIX 6. DOSING INSTRUCTIONS

Fentanyl Sublingual Spray

1. A qualified research staff will instruct the subject to swallow any saliva in mouth.
2. Qualified research staff will hold the spray device upright using their index and middle figure and thumb. (See Figure 2)

Figure 2: Qualified Research Staff Holding Spray Device



3. Qualified research staff will point the nozzle into the subject's mouth and under their tongue. (See Figure 3 and Figure4)

Figure 3: Qualified Research Staff Pointing Nozzle into Subject's Mouth

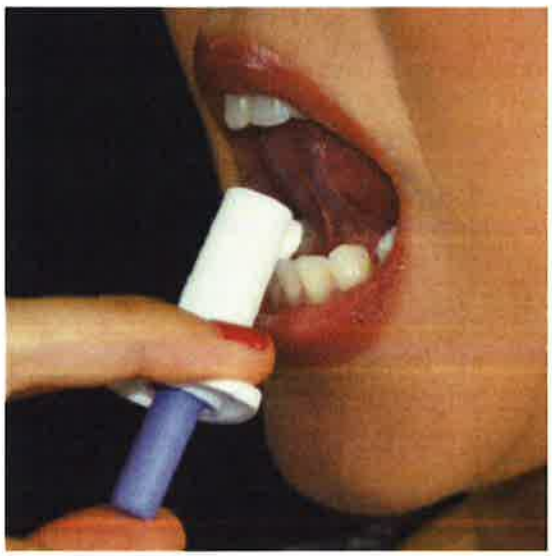
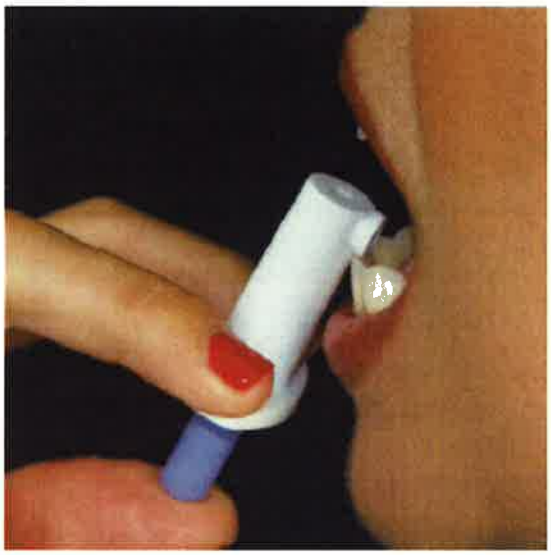
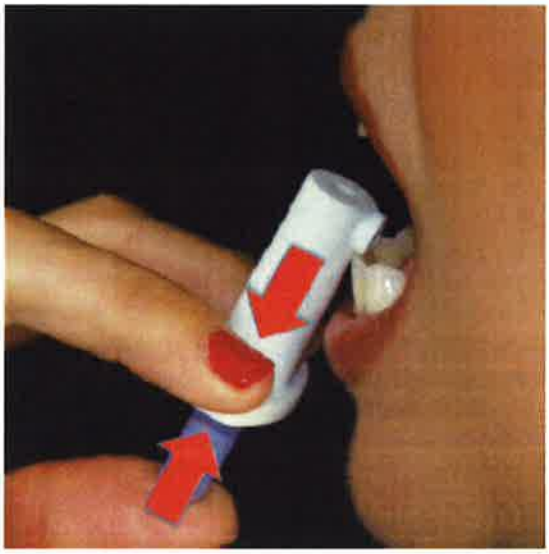


Figure 4: Qualified Research Staff Pointing Nozzle into Subject's Mouth and Under Tongue



4. Qualified research staff will squeeze their fingers and thumb together to spray the device under the subject's tongue. (See Figure 5)

Figure 5: Qualified Research Staff Spraying Device under Subject's Tongue



5. Qualified research staff will instruct the subject to hold the medicine under their tongue for 30-60 seconds. Do not spit out the medicine. Do not rinse your mouth.

6. The spray device will remain locked after use. (See Figure 6)

Figure 6: Spray Device after Use