CONCENTRIC ANALGESICS

OFFICIAL TITLE:

An Open-Label Study of Intraoperative CA-008 Administration in Subjects Undergoing Bunionectomy

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Clinical Trial Protocol

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02 May 2019

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Version 1.0: 08 March 2019

An Open-Label Study of Intraoperative CA-008 Administration in Subjects Undergoing Bunionectomy

Investigational Product: CA-008 by Injection/Instillation

IND: 129-114

Concentric Analgesics, Inc.

SIGNATURE PAGE

Approved by:

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02 May 2019
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1. KEY PERSONNEL CONTACT INFORMATION

Sponsor	**Concentric Analgesics, Inc. (Concentric)**
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TABLE OF CHANGES

Changes from Protocol version 3.0 to 4.0	Rationale
Addition of two more cohorts of 9 subjects each	To explore CA-008 dosing in different standard of care settings and to evaluate Exparel in a similar setting
Numerous text changes to accommodate the addition of the two cohorts and to provide Exparel instructions	To provide clarity in protocol instructions with the addition of two cohorts, remove redundant text and improve clarity of language

Changes from Protocol version 2.0 to 3.0	Rationale
Addition of stopping rules per Memo to File (MTF) dated 20 March 2019	Per FDA request to continue use of stopping rule.
Modification of Mayo block instructions prior to start of cohort 2 per MTF 26 March: • Previous instructions: A Mayo block using bupivacaine HCl 0.25% 30 mL prior to surgery and lidocaine HCl 1.5% 12 mL at the end of surgery • New instructions: A Mayo block prior to surgery 30 mL of a mixture of bupivacaine HCL 0.5% 15 mL combined with lidocaine HCl 2% 15 mL resulting in bupivacaine 0.25% (75 mg) and lidocaine 1% (300 mg).	To provide adequate time for the Mayo block to set up and avoid a second infiltration post-surgery, lidocaine was added to the block at the outset and not used later on after CA-008 dosing.
Use of monitored anesthesia care (as defined by ASA) rather than the term “sedation”.	To avoid confusion over anesthesia conduct.
Minor changes were made to remove confusing language or make text more readable.	Reduce confusion or the potential for misinterpretation

2. PROTOCOL SYNOPSIS

Sponsor:	Concentric Analgesics, Inc. (Concentric) 101 California St., Suite 1210 San Francisco, CA 94111
CRO:	Lotus Clinical Research (Lotus) 100 W. California Blvd., Unit 25 Pasadena CA 91105
Protocol Number:	CA-PS-205
IND#:	129-114
Study Title:	An Open-Label Study of Intraoperative CA-008 Administration in Subjects Undergoing Bunionectomy
Investigational Product:	CA-008
Planned Study Center(s):	1 US site
Indication:	Acute postsurgical pain
Sample Size:	N = 36 (9 per treatment cohort)
Population:	Adults ages 18 to 65 years, inclusive, who are planning to undergo an elective unilateral Bunionectomy (BUNX) and otherwise meet eligibility criteria may be considered for enrollment into the study.
Study Duration:	Up to 76 days: Screening period from 45 days prior to surgery (D-45) to D29±2 Study Completion Visit. Unscheduled visits or visits after D29 may be necessary to assess ongoing safety issues or to follow an event to resolution or to establishment of a new baseline. Note that D0 is the day of surgery and $T0h_{NRS}$ is the time of admission to the post-anesthesia care unit (PACU).
Study Design:	This is a Phase 2, single-center, open-label study of 3 cohorts of 9 subjects each evaluating a single dose of CA-008 4.2 mg administered during an elective unilateral transpositional first metatarsal osteotomy for the correction of hallux valgus deformity (bunionectomy or BUNX) under monitored anesthesia care (MAC) and Mayo field block with or without a supplemental popliteal block with bupivacaine hydrochloride (HCl) and lidocaine HCl. Additionally, a 4th cohort of 9 subjects will receive Exparel® (bupivacaine liposome injectable suspension; Pacira Pharmaceuticals, Inc.) under monitored anesthesia care (MAC) and Mayo field block with bupivacaine HCl and lidocaine HCl.

	The study will be conducted in two parts: • Inpatient period which continues to $T72h_{NRS}$ • Outpatient period which begins on discharge from the inpatient unit through follow up visits to D29±2 after surgery (cohorts 1-3) or to D8±1 (cohort 4)
Study Objectives:	**Primary Objective:** To evaluate different standard of care anesthetic regimens on CA-008 administration in subjects undergoing an elective BUNX. **Secondary Objective** To confirm the safety and efficacy of CA-008 with different standard of care anesthetic regimens in subjects undergoing an elective BUNX. **Exploratory Objective** To evaluate Exparel's performance in subjects undergoing an elective BUNX under a standard of care anesthetic regimen.
CA-008 Dosing Schedule and Administration (Cohorts 1-3):	CA-008 (4.2 mg in 14 mL) will be injected/instilled intraoperatively into the soft tissues and osteotomy surgical site as follows: • Instill 2 mL at cut bone sites • Prior to capsule closure, infiltrate the deep soft tissue and area proximal to the capsule with a total of 9 mL (approximately 2.25 mL into each quadrant circumferentially) • Close the capsule, but using a small gauge catheter (or needle) infiltrate 2 mL into the closed capsule space • Prior to closure of the subcutaneous tissues and skin, instill 1 mL to coat all exposed surfaces
Exparel Dosing (Cohort 4)	Exparel 106 mg (8 mL of the 133 mg/10 mL suspension) will be infiltrated intraoperatively into the soft tissues and osteotomy surgical site prior to closure as follows: • Infiltrate 7 mL into the tissues surrounding the osteotomy • Infiltrate 1 mL into the subcutaneous tissues See Exparel full prescribing information for detailed administration instructions: https://www.exparel.com/hcp/prescriptioninformation.pdf (as revised 11/2018; Pacira Pharmaceuticals, Inc.).
Anesthesia and Intraoperative Analgesia:	The surgery is to be performed under MAC anesthesia (Appendix 17.H) supplemented with one of two different standard of care regimens to produce surgical anesthesia. In both regimens, intraoperative analgesia will include IV ketorolac 30 mg and IV acetaminophen 1 g at the onset of anesthesia. At least 100 mcg of IV fentanyl should be administered onset of anesthesia and an additional 50 mcg near the end of surgery if not contraindicated for any safety issue. The anesthesiologist is free to administer additional IV fentanyl doses per anesthesia discretion. The systemic anesthesia medication doses detailed in the current protocol (including but not limited to fentanyl, ketorolac and acetaminophen) are suggested guidelines to be

	followed by the anesthesiologist caring for the subject. The actual doses given are at the discretion of the anesthesiologist based on the clinical status of the subject. With respect to non-analgesic medications, the anesthesiologist is free to use clinical discretion on the choice and dose.
Popliteal and Mayo Block Instructions	For the Mayo block, inject just distal to the base of the 1st metatarsal to provide coverage of each quadrant paying particular attention to the space between the 1st and 2nd metatarsals). In the 1st cohort of 9 subjects, prior to surgical incision (except as noted), perform the following local anesthetic nerve blocks: • A popliteal block performed under ultrasound guidance using bupivacaine HCl 0.25% 30 mL (75 mg) • A Mayo block using bupivacaine HCl 0.25% 30 mL (75 mg) also prior to surgery and lidocaine HCl 1.5% 12 mL at the end of surgery In the 2nd cohort of 9 subjects perform the following: • A Mayo block alone using bupivacaine HCl 0.5% 15 mL combined with lidocaine HCl 2% 15 mL prior to surgery In the 3rd and 4th cohorts of 9 subjects in each perform the following: • A Mayo block alone using bupivacaine HCl 0.5% 10 mL combined with lidocaine HCl 2% 20 mL prior to surgery • CA-008 or Exparel must be injected no sooner than 20 minutes after the Mayo block • Total bupivacaine HCl equivalent dose 176.8 mg: 121.8 mg from Exparel and 55 mg from bupivacaine HCl
Postsurgical Care:	Subjects will be monitored after surgery (through $T72h_{NRS}$ hour) at the trial site as an inpatient. Safety and efficacy evaluations will be performed. Subjects will be required to meet standard pre-specified criteria for discharge from the unit. Subjects will continue to be monitored as an outpatient after discharge for safety and efficacy assessments.
Inpatient Multimodal Analgesia:	After recovery from surgery, subjects in cohorts 1 and 2 will be given: • celecoxib (Celebrex®) 200 mg PO bid each day while an inpatient, and • acetaminophen 1 g PO (2 doses on the day of surgery starting at 6±2h after surgery and again at 12±2h after surgery) and t.i.d. each day thereafter while an inpatient After recovery from surgery, subjects in cohorts 3 and 4 will be given no additional non-opioid analgesics. After discharge from the inpatient unit, non-opioid analgesics may be recommended by the Principal Investigator for subject use as needed.
Rescue Medication during the Inpatient	The following rescue medication is available to subjects and may be administered for any moderate to severe breakthrough pain at any time during the inpatient period: • During the PACU stay (90 minutes, if possible, to ensure that pain is well controlled), administer IV fentanyl 25-50 mcg **q5-10 min** *prn* moderate (≥ 4) or severe pain (≥ 7) as reported by subjects using the 0 to 10 numerical rating scale

Period:	of current pain intensity (NRS) • After PACU discharge to T24h, administer PO oxycodone 5 mg for moderate or 10 mg for severe pain *prn* **q2h** • After 24h, administer PO oxycodone 5 mg for moderate or 10 mg for severe pain *prn* **q4h** Subjects will be encouraged to rescue only for moderate-to-severe pain scores, however rescue may be requested at any time and medication will be provided when requested per protocol timing. Documentation of time of rescue medication request or administration should be based on $T0h_{NRS}$ (defined as the time of PACU admission).
Analgesia during Outpatient Period:	Once discharged from the inpatient unit, all study participants will be instructed to take a combination of OTC analgesics (NSAID and acetaminophen) at an appropriate dose per Investigator medical judgment to manage any residual or breakthrough postsurgical pain (note that these medications will not be provided by the sponsor): • NSAID (e.g., ibuprofen 400 - 600 mg prn up to qid [Advil® or Motrin®] or naproxen 220 mg prn up to tid [Aleve®]) or other options per Investigator discretion and • Acetaminophen 1-2 tablets (325 mg or 500 mg) prn but no more than 1g for a single dose and doses may not be taken more frequently than q4h with a daily maximum acetaminophen dose of 3g. If a subject is still requiring opioid rescue in the 6h prior to discharge from the inpatient unit, then at discharge prescribe no more than 9 tablets (1 PO tid prn) of oxycodone 5 mg for the initial outpatient period. Document this prescription and number of tablets prescribed, and if any repeat prescription is required per investigator discretion, document the date of such prescription and number of tablets prescribed. Persistent pain or pain exacerbations during the outpatient period may suggest the need for an unscheduled in-person visit to assess the surgical site. If such a situation occurs, the Investigator should use clinical discretion on adequacy of analgesic treatment, but to capture this event as an adverse event (AE) and document any required treatments.
Stopping Rules:	Enrollment in the study will be paused for evaluation of specific TEAEs after CA-008 dosing (stopping rules will not be enforced during cohort 4): • If one or more subjects experience any grade 4 (or higher) related TEAE (see table below) or • If 2 or more subjects experience the same grade 3 related TEAE (see table below)

Category	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Abnormal Wound Healing: Infection Dehiscence Necrosis	Mild symptoms; clinical or diagnostic observations only; intervention not indicated. No interference with age-appropriate instrumental ADL	Minimal, local or noninvasive intervention indicated; May require local wound care or medical intervention (e.g., dressings or topical medications)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting ADLs. May require IV antibiotics, antifungals, or antivirals or radiologic intervention.	Life-threatening consequences; urgent intervention indicated
ECG/Cardiac issues Vital Signs Labs	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Focused Neurosensory Testing (performed by trained Investigator)	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms requiring medical intervention; limiting self-care ADL	Life-threatening and urgent intervention indicated

Inclusion Criteria:

In order to participate, subjects must meet all inclusion criteria:

1. In the medical judgment of the investigator, be a reasonably healthy adult aged 18 - 65 years old, inclusive, and American Society of Anesthesiology (ASA) physical Class 1, 2 or 3 (Appendix17.A).
2. Plan to undergo an elective primary unilateral first metatarsal Bunionectomy repair, without collateral procedure or additional surgeries, to be performed under monitored anesthesia care (MAC) with a local block.
3. If a male, unless he has a same sex partner, be either sterile (surgically **or** biologically) or commit to an acceptable method of birth control while participating in the study. The site personnel will provide instructions on what is an acceptable method.
4. If a female of child-bearing potential (FCBP), must meet **all** of the following:
    a. Not be pregnant (FCBP must have a negative serum pregnancy test at screening and negative urine pregnancy test before surgery);
    b. No plan to become pregnant or to breast feed during the study; and
    c. Be surgically sterile or at least one year post-menopausal, have a monogamous partner who is surgically sterile, have a same sex partner or (**one** of the following must apply)
        i. is practicing double-barrier contraception
        ii. is practicing abstinence (must agree to use double-barrier contraception in the event of sexual activity)
        iii. is using an insertable, injectable, transdermal or combination oral contraceptive approved by the FDA for at least 2 months prior to screening and commits to the use of an acceptable form of birth control while participating in the study.
5. Have a body mass index ≤ 36 kg/m^2.
6. Be willing and able to sign the informed consent form (ICF) approved by an Institutional Review Board (IRB).
7. Be willing and able to complete study procedures and pain scales and to

	communicate meaningfully in English with study personnel and return for outpatient follow up visits as required.
Exclusion Criteria:	**If any of the following exclusion criteria apply, subjects may not participate in the study:** 1. In the opinion of the Investigator, a. have a concurrent painful condition, other than bunion-related pain, that may require analgesic treatment during the study period or may confound post-surgical pain assessments. b. have active skin disease or other clinically significant abnormality at the anticipated site of surgery that could interfere with the planned surgery. 2. Have a known allergy to chili peppers, capsaicin or the components of CA-008, acetaminophen, bupivacaine HCl, Exparel, fentanyl, ketorolac, lidocaine or oxycodone. 3. As determined by the investigator (with input from the study's medical monitor if requested by the investigator), have a history or clinical manifestation of significant medical, neuropsychiatric or other condition, including an existing arrhythmia, left bundle branch block, myocardial infarction within the prior 6 months, clinically significant abnormal ECG or clinical laboratory test value, that could preclude or impair study participation or interfere with study assessments. 4. The following are considered disallowed medications: a. Be tolerant to opioids defined as those who have been receiving or have received chronic opioid therapy greater than 15 mg of oral morphine equivalents (Table 4) per day for greater than 4 out of 7 days per week over a one-month period within **6** months screening. b. Within 1 day prior to surgery and throughout the inpatient period, be taking any capsaicin-containing products, such as dietary supplements or over-the-counter (OTC) preparations, including topical formulations, and prescription medications. c. Within the 7 days prior to surgery, be taking any central nervous system (CNS) active analgesic adjunct medication, such as anticonvulsants, antidepressants (such as SNRIs, SSRIs, and tricyclic antidepressants), benzodiazepines, sedative-hypnotics, clonidine and other central alpha-2 agents (e.g., tizanidine), ketamine or muscle relaxants. [Note that SNRIs = Serotonin and norepinephrine reuptake inhibitors and SSRI = Selective serotonin reuptake inhibitors.] i. These drugs are permitted if prescribed for non-pain indications and the dose has been stable for at least 30 days prior to surgery. Note that the dose must remain stable throughout the study. ii. If the subject is taking centrally- and/or peripherally-acting analgesic medications, such as acetaminophen, NSAIDs, tramadol or opioids, FOR bunion-related pain, the subject may participate in the study if 4(a) above is not applicable and the subject is willing to discontinue these medications 3 days prior to surgery.

	iii. The use of benzodiazepines and the non-benzodiazepines (eszopiclone, ramelteon, zaleplon and zolpidem) are permitted to treat insomnia during the postoperative period. d. Within the 7 days prior to the planned surgery and throughout the study, be taking antiarrhythmics except beta-blockers, digoxin, warfarin (see exception below), lithium, or aminoglycosides or other antibiotics for an infection (except for ophthalmic use or for treatment or prophylaxis of postoperative surgical site infections). (Use of warfarin or other agents is allowed, at the investigator's discretion, for DVT prophylaxis after the surgery is completed). e. Within the 14 days prior to surgery, be taking parenteral or oral corticosteroids (steroid inhaler for allergy or asthma treatment, topical steroid for a non-clinically significant skin condition not involving the area of surgery or ophthalmic steroids are permissible). f. Be on an antianginal, antihypertensive agent or diabetic regimen at a dose that has not been stable for at least 30 days or which is not expected to remain stable while participating in the study. 5. In the opinion of the Investigator, within the past year have a history of illicit drug use or prescription medicine or alcohol abuse (regularly drinks > 4 units of alcohol per day; where a unit = 8 oz. beer, 3 oz. wine or 1 oz. spirits). 6. Have positive results on the alcohol test (breath or saliva) indicative of alcohol abuse or urine drug screen indicative of illicit drug use (unless results can be explained by a current prescription or acceptable over-the-counter medication at screening as determined by the investigator) at screening, and/or prior to surgery. a. Note that for those subjects who test positive for tetrahydrocannabinol (THC), if they are willing to abstain from use or consumption of THC-containing products from 3 days prior to surgery to the day 8 visit, they may be allowed to participate in the study. Additionally, it may be permissible for the subject to participate if the results can be explained by a current prescription or acceptable over-the-counter medication as determined by the investigator at screening, and/or prior to surgery. 7. Have previously participated in a clinical study with CA-008. 8. Have participated in another clinical trial or used an investigational product within 30 days or five half-lives (whichever is longer) prior to the planned bunionectomy surgery or is scheduled to receive an investigational product other than CA-008 while participating in the study.
Visit Schedule:	1. **Screening D-45 to D-1**: Subjects undergo screening during this period. All screening assessments (including informed consent form [ICF]) must be completed at least 1 day prior to surgery. If screening occurs prior to D-30, it may be necessary to reverify eligibility and ICF agreement, but only if the facility SOP requires such reverification be performed. 2. **Site Unit Admission D0**: Day of surgery, perform baseline evaluations prior to surgery. 3. **Surgery D0**: BUNX procedure is performed under MAC anesthesia with the

	supplemental blocks and other treatments as described. 4. **Post-surgery to T72h$_{NRS}$**: Subject remains at the Site Unit for study assessments. At discharge provide follow up instructions, particularly on diary completion. 5. **Follow Up D8±1**: clinic visit for study assessments (cohorts 1-3) and study completion visit (cohort 4). 6. **Follow Up D15±2:** clinic visit for study assessments (cohorts 1-3 only) 7. **Follow Up D29±2:** clinic visit for study assessments and study completion visit (cohorts 1-3 only) unless a pending safety event is ongoing and requires follow up 8. **Early Termination (ET):** For subjects who terminate early, an ET visit will be required. Safety and subject-reported outcome assessments will be performed. 9. **Unscheduled visits:** may occur at any time to assess any safety event
Safety Parameters:	• Incidence of spontaneous reported TEAEs or SAEs: o TEAEs are defined as AEs occurring after start of CA-008 or Exparel dosing o AEs/SAEs recorded from the time the informed consent form (ICF) is signed up to D0/T0 will be recorded in medical history. The Investigator must determine whether any such AE/SAE merits a delay in study participation. • Surgical site assessments and neurosensory testing near the incision as an outpatient on D8, D15 and D29 (CA-008) or D8 only (Exparel). o If there are skin reactions atypical for the type of surgery, e.g., more than expected erythema, drainage, bruising or hematoma, induration, swelling or other skin changes, they should be documented as AEs, graded for severity and followed regularly until resolution or establishment of a new baseline. If the local reactions are typical of this type of surgery, it should not be captured as an AE. o Numbness at or near the incision need not be considered a neurologic AE since this could occur because of tissue trauma and inflammation from the surgery. o Sensory deficits or clinically significant persistent sensory change beyond the area proximal to the incision at time of discharge, such as allodynia or hyperalgesia atypical of this type of surgery, must be designated as a neurologic AE. Subjects will be followed until there is full return to baseline for the neurosensory assessment or until there is a determination that it has reached a resolution or establishment of a new baseline. • D15 and D29 visits: assess for presence of rebound pain at the surgical site (cohorts 1-3 only) • Physical examination (PE): complete at screening; interim assessments on D-1 (or D0 prior to surgery if not done on D-1) and during each outpatient visit (D8, D15 and D29) for cohorts 1-3 only; for cohort 4, at screening, interim assessments on D-1 (or D0 prior to surgery if not done on D-1) and D8. • Vital signs (heart rate [HR], blood pressure [BP], respiratory rate [RR]) and temperature at screening, entrance and discharge from the PACU, and during the inpatient period (per site SOP but generally once per shift or every 8h) and during

	each outpatient visit (D8, D15 and D29) for cohorts 1-3 only; and for cohort 4, through D8 only. • X-rays should be obtained during screening, if not already performed in the 6 months prior to screening, and at the D29 visit (cohorts 1-3 only). • Screening clinical laboratory tests o CBC o Blood Chemistry: sodium, potassium, calcium, chloride, creatinine and glucose o Serum and urine pregnancy test for FCBP: βhCG test at screening and urine test usually to be done within 24 hours prior to surgery. • Drug screen
Efficacy Parameters:	1. NRS scores will be assessed as follows: • At T0h (entry to PACU), T1h_{NRS}, 2h_{NRS}, 3h_{NRS}, 4h_{NRS}, 6h_{NRS}, 8h_{NRS} and 12h_{NRS} and every 6h thereafter while an inpatient. • Pain scores may be skipped between the hours of midnight and 6 a.m., but the subject may not miss two consecutive assessments due to sleeping. • The T24h_{NRS} and T48h_{NRS} hour assessments must be completed even if the subject is asleep at these times. • An additional NRS assessment must be obtained within 15 min of the time of rescue medication request but prior to administration of rescue. Note that failure to obtain this assessment will be considered a major protocol deviation. • Starting in the evening of the 1st postoperative day through the D8 visit, NRS assessments twice daily at approximately 0800h (±2h) and each evening prior to bedtime at approximately 2000h (±2h) at rest and with ambulation of approximately 10 yards. Note that the actual time of these assessments must be documented in the diary. 2. Daily and total opioid consumption (OC) in oral morphine dose equivalents (MEDs) will be recorded during the inpatient and outpatient periods.
Safety Endpoints:	The following safety endpoints will be evaluated: • Incidence of TEAEs or treatment-emergent SAEs • Clinically significant changes in surgical site assessments and neurosensory testing • X-ray healing (CA-008 only) • Absence of rebound pain at the surgical site (CA-008 only)
Efficacy Endpoints:	Using NRS scores (at rest and with ambulation), pain intensity over the 72h inpatient stay will be assessed. NRS scores at various time points: T24h_{NRS}, T48h_{NRS} and T72h_{NRS}.
Sample Size Justification:	The currently planned study is a follow-on exploratory study to a prior phase 2 study (CA-PS-201) which showed CA-008 4.2 mg was statistically significantly superior to placebo. This study is being performed to evaluate optimal anesthesia conduct, therefore no sample size estimation was performed.
Study Populations:	The following three analysis populations are planned for this study: • The Safety Population will include all subjects who received any part of a dose of CA-008 or Exparel.

	• Study completers (Study Completers) will include all subjects who receive a full dose of CA-008 or Exparel and complete the entire applicable study period. Subjects who elect to discontinue study participation during the inpatient phase of the study, will be asked to continue with assessments through $T72h_{NRS}$ if they have not elected to withdraw from all aspects of study participation. Subjects who elect to discontinue participation prior to D8 will be considered to have terminated as of the date of their election, however they will be asked to return to the site one time, if willing and at their convenience, to ensure wound healing. All assessments and baseline characteristics will be summarized using the Safety Population.

Table 1. Schedule of Assessments

Assessment	Screening	In Patient				Follow-Up Note: The D15 and 29 visits apply only to cohorts 1-3			Unscheduled Visit	Early Termination
		Prior to Surgery	Surgery	Post-Surgery PACU Stay	Assessments during Inpatient stay to 72h					
Study Day	-45 to -1	0	0	0	1	8±1 day	15±2 days	29±2 days		
Informed Consent	X	X								
Screening Medical and Surgical History	X	X								
Inclusion/Exclusion Criteria	X	X								
Screens for alcohol/drugs of abuse	X	X								
Enroll		X								
Demographics	X									
Subject Pain Assessment Training	X	X								
Surgery			X							
CA-008 administration			X							
Pregnancy Test	X (serum)	X[1] (urine)								
Vital Signs	X	X		X[2]	X[2]	X[2]	X[2]	X[2]		X
Physical Examination[3]	X[3]	X[3]			X[3]	X[3]		X[3]		X
ECG	X									
Surgical Site assessment[4]	X				X[4]	X	X	X	X	X
Neurosensory Exam[4]	X				X[4]	X	X	X	X	X
Clinical laboratory tests[5]	X									
X-ray of surgical site (cohorts 1-3 only)	X							X		X
Concomitant Medication Assessment	X	X		X	X	X	X	X	X	X
Adverse Event Assessment	X	X	X	X	X	X	X	X	X	X
Rebound pain assessment						X	X	X	X	X
NRS pain assessments (inpatient and outpatient)				X[6]	X[6]	X				X
Subject home diary record (NRS)						X[6,7]				X
Paper Diary (review, distribution and/or collection)					X[8,9]	X[8,9,10]				X[10]
Dispense outpatient rescue if needed					X[11]					

1. Within 24 hours of scheduled surgery

2. Vital signs: (HR, BP, RR and temperature) at screening, entrance and discharge from the PACU, and during the inpatient period (per site SOP but generally at least once per shift or every 8h) and during each outpatient visit (D8, D15 and D29 for CA-008 and D8 for Exparel). There will be a ±5-minute window allowed for the collection of vital signs in the first 4 hours after the end of surgery, after which will be a ±15-minute window allowed.
3. A complete medical history and physical examination including all major body systems will be performed at Screening. In addition, at the following times, a targeted reassessment will be performed prior to surgery, at discharge from the inpatient unit to capture changes after Surgery, and on the D29 visit for CA-008 or D8 visit for Exparel. If the subject terminates early, a targeted reassessment should be performed at that time if allowed by the subject. Body weight (kg), in indoor clothing, but without shoes, will be measured at Screening. Height (in cm) will be measured and BMI will be calculated at Screening.
4. Surgical Site assessment and neurosensory testing: only at 72 hours (±2 hours) but prior to discharge from the inpatient unit, and on D8, D15 and D29 for CA-008 or D8 for Exparel, and, if necessary, at any unscheduled or early termination visit.
5. Clinical Laboratory tests at screening
6. NRS pain assessments at T0h (entry to PACU), T1h$_{NRS}$, 2h$_{NRS}$, 3h$_{NRS}$, 4h$_{NRS}$, 6h$_{NRS}$, 8h$_{NRS}$ and 12h$_{NRS}$ and every 6h thereafter while an inpatient (if awake at time of assessment especially between the hours of 00:00 and 06:00) until discharge from the inpatient unit (may not miss two consecutive assessments). The T24h$_{NRS}$ and T48h$_{NRS}$ assessments must be completed even if the subject is asleep at these times. During the inpatient stay, NRS must be obtained at the time of or within 15 min of rescue medication request, regardless of the time of other protocol-specified pain assessments and even if the subject is asleep. There will be a ±5-minute window allowed for the collection of each assessment in the first 4 hours after the end of surgery, after which will be a ±15-minute window allowed.
7. Starting in the evening of the 1st postoperative day through the D8 visit, NRS assessments twice daily at approximately 0800h (±2h) and each evening prior to bedtime at approximately 2000h (±2h) at rest and with ambulation of approximately 10 yards. Note that the actual time of these assessments must be documented in the diary.
8. Review Subject Diary instructions with subject
9. Dispense Subject Diary
10. Collect Subject Diary
11. Dispense no more than 9 tablets per investigator discretion of oxycodone 5 mg tablets. Document prescription and # of tablets prescribed.

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LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
aPTT	Activated partial thromboplastin time
ASA	American Society of Anesthesiologists
AST	Aspartate aminotransferase
AUC	Area Under the Curve
BID	Bis in die (twice daily)
BLQ	Below limit of quantitation
BP	Blood Pressure
BUNX	Bunionectomy
CA-008	Investigational product
CA-101	Cyclic urea
CFR	Code of Federal Regulations
CK	Creatine kinase
CL	Clearance
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CRF	Case Report Form (may include electronic data capture systems or paper forms)
CRO	Contract research organization
CS	Clinically significant
CSA	Clinical Study Agreement
D# or D-#	Day # (study days after surgery), Day # prior to surgery
DBP	Diastolic Blood Pressure
DIP	Distal interphalangeal
DMC	Data Monitoring Committee
DVT	Deep Venous Thrombosis
ECG	Electrocardiogram
EDC	Electronic data capture
ET	Early Termination
FCBP	Female of child bearing potential
FDA	Food and Drug Administration
FIH	First-In-Human
FSH	Follicle Stimulating Hormone
G	Gram
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase

Abbreviation	Term
GLP	Good Laboratory Practice
h, H or HRS	Hours
HCl	Hydrochloride
HED	Human Equivalent Dose
HEENT	Head, Eye, Ear, Nose and Throat
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Institutional Ethics Committee
IGE	Investigator Global Evaluation
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantitation
LOE	Lack of efficacy
mcg or µ	Microgram
MAC	Monitored anesthesia care
MED	Morphine equivalent dose
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
min	Minutes
mL	Milliliter
NCS	Not clinically significant
NOAEL	No Observed Adverse Effect Level
NRS	Numeric Rating Scale of Pain Intensity
NSAID	Nonsteroidal anti-inflammatory drug
OC	Opioid consumption in morphine equivalent dose
OF	Opioid-free days
OTC	Over-the-counter
PACU	Post-anesthesia care unit
PE	Physical examination
PGE	Patient Global Evaluation
PHN	Postherpetic neuralgia
PI	Principal Investigator
PO	Per oram (oral)
PRN	Pro re nata (as needed)
PT	Prothrombin time
QID	Quater in die (four times daily)
RBC	Red blood cell

Abbreviation	Term
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SOC	System Organ Class
SNRIs	Serotonin-norepinephrine reuptake inhibitors
SSRIs	Selective serotonin reuptake inhibitors
T#	Time in hours after T0
$t_{½}$	Elimination half-life
TEAEs	Treatment emergent adverse event[s]
TID	Ter in die (three times daily)
T_{max}	Time to maximum plasma concentration
TRPV1	Transient receptor potential vanilloid-1
TTFR	Time to first rescue
UDS	Urine drug screen[ing]
US	United States
V	Volume of distribution
W#	Week # visit after surgery
WHO	World Health Organization

5. INTRODUCTION

5.1. Background

Concentric Analgesics, Inc. (Concentric) is developing CA-008 to provide long-lasting pain relief of post-surgical pain following a single local administration (for 96h and beyond). CA-008 is a prodrug of trans-capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide), the substance in chili peppers that produces the sensation of spiciness. Capsaicin is a transient receptor potential cation channel, subfamily V (vanilloid), member 1 (TRPV1) agonist. TRPV1 is a ligand-gated, nonselective, cation channel preferentially expressed most densely in C-fiber nociceptors and to a lesser extent on Aδ–fiber nociceptors (Babbar 2009, Caterina 2001). TRPV1 responds to noxious stimuli including capsaicin, heat, and extracellular acidification, and integrates simultaneous exposures to these stimuli (Suresh 2010, Surh 1995, Tominaga 1998).

Capsaicin exposure to TRPV-1-expressing nociceptor peripheral terminals results in initial excitation of the nociceptor followed by a functional desensitization which continues for some time after removal of capsaicin from the site. Capsaicin, however, is virtually insoluble in aqueous media or local anesthetic solutions which means that capsaicin formulations tend to be quite hydrophobic and viscous making them hard to inject and less likely to permeate surgical site tissues. To work around the solubility limitations of capsaicin, the highly water-soluble capsaicin pro-drug CA-008 was developed for local infiltration. It avoids the physicochemical limitations of capsaicin while providing greater target engagement which theoretically would produce superior local analgesia, particularly after surgical trauma. Based upon this mechanism of action, local delivery of a TRPV1 agonist throughout the tissues around the surgical site prior to wound closure to maximize target engagement should result in a meaningful reduction of post-surgical pain over several days to weeks. This improved long-term pain relief has the ability to augment current multimodal analgesia or enhanced recovery programs which may help to avoid the need for supplemental opioid use after surgery.

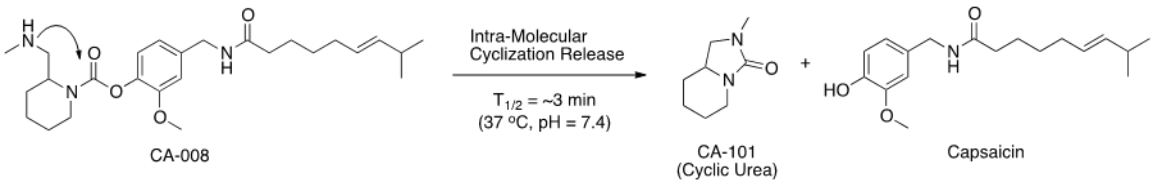
While no capsaicin products have been approved for injection or instillation into a wound site in the US, several companies have or had clinical development programs for such products. Centrexion Therapeutics has an active development program (CTNX-4975) for intraarticular injection of capsaicin in a polyethylene glycol solution for chronic knee osteoarthritis (currently in Phase 3) and Morton's neuroma (see http://centrexion.com/our-pipeline/).

5.2. CA-008 Product Introduction

The active moiety of CA-008, capsaicin, has certain attractive properties for treatment of post-operative pain from a pharmaceutical perspective. CA-008 is water soluble and easy to inject through a 25 g needle or larger. It readily penetrates surgical site tissues where it releases capsaicin through a non-enzymatic pH-driven process. Local administration of CA-008 at or

near the source of pain either topically, by infiltration or by instillation into a surgical site results in low systemic levels of capsaicin.

CA-008 provides an aqueous formulation that could be simply infiltrated in the wound site to achieve local capsaicin release to produce a maximal effect. The free base form of CA-008 rapidly breaks down at physiological pH to yield capsaicin and a cyclic urea, as shown in the scheme below:



CA-008 was specifically selected for development due to its short half-life (<5 min) at neutral pH. In Tris buffer at pH 7.4 and 37°C, it completely breaks apart to capsaicin and CA-101 as the sole degradants.

The cyclic urea (CA-101) formed has not been previously evaluated for biological activity. While not a known compound in the clinical literature, its safety was evaluated in all nonclinical studies with CA-008 and it was shown to be inactive. The toxicokinetic profiles for CA-008, CA-101, and capsaicin were determined in GLP safety studies and the PK profile for various doses were determined in a Phase 1 ascending dose safety study and a Phase 2 parallel design study in patients undergoing bunionectomy.

5.3. Previous Human experience

There is substantial clinical support for the potential safety of capsaicin, the active molecule released by CA-008 in vivo. In addition to consumption in hot spicy foods (chili peppers), capsaicin is an approved product for dermal applications for OTC and prescription use (Qutenza; 8% patch for management of neuropathic pain associated with post herpetic neuralgia), is frequently used intradermally in experimental pain models, and has been studied clinically for wound instillation for postsurgical analgesia (Anesiva; Adlea; capsaicin for instillation).

Additionally, a first-in-human study (Study CA-PS-2017-101) evaluated the safety and tolerability of CA-008 (dose ranges 0.5 mg to 4.2 mg) in 40 subjects (6 at each CA-008 dose for a total of 30 and 10 receiving placebo) undergoing a unilateral transpositional first metatarsal osteotomy for correction of hallux valgus deformity, more commonly known as a bunionectomy. A follow-on Phase 2 bunionectomy study (CA-PS-201) was completed with 147 subjects enrolled and randomized to one of 3 active doses: 0.7 mg (N=36), 2.1 mg (N=36) and 4.2 mg (N=38) vs. placebo (N=37). The highest dose of 4.2 mg was well tolerated and was statistically significantly superior to placebo for the primary efficacy endpoint of AUC 0-96h (p=0.005) and key secondary efficacy endpoints: AUC 0 to week 1 (p=0.036); mean opioid consumption

(reduced by 50%, p<0.002); and percent of subjects who were opioid free from 0 to 96h (26% vs. 5% for placebo; p=0.039). There was a single SAE (delayed cellulitis) in the placebo group.

5.4. Study and Dose Rationale

5.4.1. Study Rationale

CA-008 is being investigated as a potential therapy for treatment of pain following surgery.

5.4.2. Selection of Doses

The safety of CA-008 was established in relevant animal models and supported by two studies after bunionectomy (CA-PS-2017-101 and CA-PS-201) as well as the first dosing cohorts (CA-008 5 mg dose) in complete abdominoplasty and total knee arthroplasty. These studies are considered sufficient to support the intended use of CA-008 in this study.

5.4.3. Selection and Timing of Dose

CA-008 is a pH labile prodrug of capsaicin that rapidly releases capsaicin after administration into tissue. Decision for single administration at the time of surgery is based on capsaicin's mechanism of action. Capsaicin exposure results in initial excitation followed by a functional desensitization of TRPV-1-expressing nociceptors which continues for some time after removal of capsaicin from the site. Administration while the patient is under anesthesia for the procedure supplemented by a regional local anesthetic block or local anesthetic infiltration addresses the pain that results from TRPV1 agonism. Administration of CA-008 during the closure process is ideal for delivering therapy to the surgical site, thus optimizing target engagement. During closure, the surgical tissue is exposed and visible which allows for complete and adequate delivery of CA-008 to the potential areas where noxious pain is being generated.

6. STUDY OBJECTIVES

6.1. Primary Objective

The primary objective of the study is to evaluate different standard of care anesthetic regimens on CA-008 administration in subjects undergoing an elective BUNX.

6.2. Secondary Objective

The secondary objective of the study is to confirm the safety and efficacy of CA-008 with different standard of care anesthetic regimens in subjects undergoing an elective BUNX.

6.3. Exploratory Objective

The exploratory objective of the study is to evaluate Exparel's performance in subjects undergoing an elective BUNX under a standard of care anesthetic regimen.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design and Plan

This is a Phase 2, single-center, open-label study evaluating a single dose of CA-008 4.2 mg or Exparel administered during an elective unilateral transpositional first metatarsal osteotomy for the correction of hallux valgus deformity (bunionectomy or BUNX) under MAC and Mayo field block with or without a supplemental popliteal block with bupivacaine HCl.

The study will be conducted in two parts:

- Inpatient period which continues to $T72_{NRS}$ hour
- Outpatient period which begins on discharge from the inpatient unit through various follow up visits to D29±2 (cohorts 1-3) or D8±1 (cohort 4) after surgery

7.2. Screening Phase (Day -45 [D-45] to D-1 or D0):

Subjects requiring bunionectomy between the ages of 18 and 65 years, inclusive, will be screened for participation at the study site within 45 days of surgery. The following assessments will be completed:

- Informed Consent
- Eligibility for study participation (Inclusion / Exclusion criteria)
- Demographics
- Medical and surgical history
- Prior/current medications
- Complete physical examination (PE) including vital signs (resting blood pressure, resting pulse and respiration rate) (Appendix 17.G). Tests must be obtained after resting (seated/reclined) for ≥ 5 minutes.
- ECG
- Ensure that an x-ray of the bunion to be operated on has been obtained (cohorts 1-3 only)
- Screening clinical laboratory tests
- Urine Drug Screening (UDS) and alcohol breath test (or other appropriate test)
- Serum Pregnancy test (FCBP)
- Subject pain assessment training
- Adverse Event (AE) Assessment

7.3. D-1 or D0: Prior to surgery (baseline) up to the end of surgery

7.3.1. Prior to Surgery

Subjects who meet the selection criteria at the Screening Visit and are eligible to participate in the study will be required to return to the study center within 45 days of screening. The site may elect to admit the subject to the inpatient unit the evening prior to surgery (D-1) or the day of surgery (D0). The following assessments will be performed:

- Confirm informed consent and eligibility for study participation
- Interim medical and surgical history
- Prior medications
- Interim PE and vital signs as before (include temperature assessment)
- Planned Surgical Site Assessment including neurosensory exam of the Foot / Great toe (bilateral)
- Screening clinical laboratory tests
- Urine Drug Screening (UDS) and alcohol breath test
- Urine Pregnancy test (FCBP)
- AE Assessment

7.3.2. Planned Anesthesia and Regional Blocks

The surgery is to be performed under MAC supplemented with one of two different standard of care regimens to produce surgical anesthesia: popliteal + Mayo block OR Mayo block alone. For the Mayo block, the surgeon should inject just distal to the base of the 1st metatarsal to provide coverage of each quadrant paying particular attention to the space between the 1st and 2nd metatarsals). In each cohort, intraoperative analgesia will include IV ketorolac 30 mg and IV acetaminophen 1 g at the onset of anesthesia.

The systemic anesthesia medication doses (including but not limited to fentanyl, ketorolac and acetaminophen) are suggested guidelines to be followed by the anesthesiologist caring for the subject. The actual doses given are at the discretion of the anesthesiologist based on the clinical status of the subject. With respect to non-analgesic medications, the anesthesiologist is free to use clinical discretion on the choice and dose.

In the 1st cohort of 9 subjects, prior to surgical incision (except as noted), perform the following local anesthetic blocks:

- A popliteal block performed under ultrasound guidance using bupivacaine HCl 0.25% (30 mL volume) with an assessment of the adequacy of the block
- A Mayo block using bupivacaine HCl 0.25% 30 mL (75 mg) prior to surgery and lidocaine HCl 1.5% 12 mL at the end of surgery.

In the 2nd cohort of 9 subjects, prior to surgical incision, perform the following:

- A Mayo block using a combination of bupivacaine HCl 0.5% 15 mL and lidocaine HCl 2% 15 mL prior to surgery.

In the 3rd and 4th cohorts of 9 subjects in each, prior to surgical incision, perform the following:

- A Mayo block using a combination of bupivacaine HCl 0.5% 10 mL and lidocaine HCl 2% 20 mL prior to surgery.
- Note that CA-008 or Exparel administration should be no sooner than 20 minutes after the Mayo block.
- In cohort 4, total bupivacaine HCl equivalent dose 176.8 mg: 121.8 mg from Exparel and 55 mg from bupivacaine HCl

After the surgery, patients will be monitored in the PACU to ensure recovery from the anesthesia. Note that $T0h_{NRS}$ is the time of entry to the PACU. Subjects will be monitored for 72 hours in an inpatient unit during which time safety and efficacy evaluations will be performed. Subjects will be required to meet certain pre-specified criteria prior to discharge.

7.3.3. Administration of CA-008

Prior to wound closure, CA-008 will be injected/instilled into the soft tissues and osteotomy surgical site with a total volume of 14 mL of CA-008 as follows:

- Instill 2 mL at cut bone sites
- Prior to capsule closure, infiltrate the deep soft tissue and area proximal to the capsule with a total of 9 mL (approximately 2.25 mL into each quadrant circumferentially)
- Close the capsule, but using a small gauge catheter infiltrate 2 mL into the closed capsule space
- Prior to closure of the subcutaneous tissues and skin, instill 1 mL to coat all exposed surfaces of the wound

7.3.4. Administration of Exparel

Exparel 106 mg (8 mL of the 133 mg/10 mL suspension) will be infiltrated intraoperatively into the soft tissues and osteotomy surgical site prior to closure as follows:

- Infiltrate 7 mL into the tissues surrounding the osteotomy
- Infiltrate 1 mL into the subcutaneous tissues

Note that Exparel administration should not begin until 20 minutes after the Mayo block. See Exparel full prescribing information for detailed administration instructions: https://www.exparel.com/hcp/prescriptioninformation.pdf (as revised 11/2018; Pacira Pharmaceuticals, Inc.).

7.4. Postoperative Multimodal Analgesia

For cohorts 1 and 2, after recovery from surgery, subjects will be given:

- celecoxib (Celebrex®) 200 mg PO bid each day while an inpatient, and
- acetaminophen 1 g PO (2 doses on the day of surgery starting at 6±2h after surgery and again at 12±2h after surgery) and t.i.d. thereafter each day while an inpatient

For cohorts 3 and 4, other than the non-opioids administered during surgery, no additional non-opioids are to be given to subjects until discharged to outpatient status at which time the Investigator is free to recommend the appropriate non-opioid analgesic combination for *prn* use.

No other non-opioid analgesics are to be administered during the inpatient phase except as specified in the protocol.

7.5. Postoperative Rescue Medication

Additionally, the following rescue medication may be administered for any moderate to severe breakthrough pain during the inpatient period:

- During the PACU stay (90 minutes, if possible, to ensure that pain is well controlled), administer IV fentanyl 25-50 mcg q5-10 min prn moderate (≥ 4) or severe pain (≥ 7) as reported by subjects using the 0 to 10 numerical rating scale of current pain intensity (NRS)
- From time of PACU discharge to $T24h_{NRS}$ hours, PO oxycodone 5 mg for moderate or 10 mg for severe pain prn q2h
- After $T24h_{NRS}$ hour to discharge from the inpatient unit, PO oxycodone 5 mg for moderate or 10 mg for severe pain prn q4h

Subjects will be encouraged to rescue only for moderate pain scores (≥ 4), however rescue may be requested at any time and medication will be provided when requested per protocol timing.

7.6. Postoperative Care While an Inpatient

After surgery, subjects will be monitored as an inpatient until discharged. Safety and efficacy evaluations will be performed. Subjects will be required to meet standard pre-specified criteria for discharge from the unit.

The schedule of assessments are as follows:

- Perform NRS assessments of current pain intensity (Appendix 17.B):
  - During the inpatient stay, at $T0h_{NRS}$ (entrance to PACU), $1h_{NRS}$, $2h_{NRS}$, $3h_{NRS}$, $4h_{NRS}$, $6h_{NRS}$, $8h_{NRS}$ and $12h_{NRS}$ and every 6 hours (if awake at time of assessment) until discharge from the inpatient unit (may not miss two consecutive assessments.
  - Pain scores may be skipped between the hours of midnight and 6 a.m., but the subject may not miss two consecutive assessments due to sleeping.

- The $T24h_{NRS}$ and $T48h_{NRS}$ assessments must be completed even if the subject is asleep at these times.
- NRS must be completed within 15 minutes after rescue request but prior to use of pain rescue medication.
- Starting in the evening of the 1st postoperative day through the D8 visit, NRS assessments twice daily at approximately 0800h (±2h) and each evening prior to bedtime at approximately 2000h (±2h) at rest and with ambulation of approximately 10 yards. Note that the actual time of these assessments must be documented in the diary.
- There will be a ±5 minute window allowed for the collection of each assessment in the first 4 hours after the end of surgery after which will be a ±15 minute window allowed while an inpatient.

- Vital signs: (HR, BP, RR and temperature) at screening, entrance and discharge from the PACU, and during the inpatient period (per site SOP but generally at least once per shift or every 8h). There will be a ±5-minute window allowed for the collection of vital signs in the first 4 hours after the end of surgery, after which will be a ±15-minute window allowed.
- Perform interim PE: surgical site assessment (Appendix 17.D and Appendix 17.E) and neurosensory testing (Appendix 17.F) of the foot proximal to the surgical site with contralateral comparison: prior to discharge from the inpatient unit.
- Document concomitant medication use including doses and times taken
- Document AEs

After completing the assessments through $T72_{NRS}$ hours after surgery and prior to discharge from the inpatient unit, review with the subject the use of a diary for at-home use to record pain assessments and medication use (including pain medication) at home. Finally, instruct subjects to return to the study center on D8±1 for a follow-up assessment.

Once discharged from the inpatient unit, all study participants will be instructed to take a combination of OTC analgesics (NSAID and acetaminophen) at an appropriate dose per medical judgment to manage any residual or breakthrough postsurgical pain through D29/W4.

Outpatient period:

- If needed for pain management, over-the-counter (OTC) analgesics administered PO, e.g.,
  - NSAID (e.g., ibuprofen 200 mg to 400 mg prn qid [Advil® or Motrin®] or naproxen 220 mg prn tid [Aleve®]) or other options per investigator discretion **and**
  - Acetaminophen 1-2 500 mg tablets (up to 1 g) tid or 650 mg qid (3g daily limit)
- If a subject is still requiring opioid rescue in the 6h prior to discharge from the inpatient unit then at discharge prescribe no more than 9 tablets (1 PO tid prn) of oxycodone 5 mg for the initial outpatient period. Document this prescription and number of tablets

prescribed, and if any repeat prescription is required per investigator discretion, document the date of such prescription and number of tablets prescribed

7.7. Outpatient Phase: D8±1 Visit

In their diary, subjects will assess their current pain intensity at rest and after ambulation each morning (08:00 ±2 hours), and each evening (20:00 ±2 hours) using the NRS. The morning NRS assessment should be obtained prior to taking any pain medication. Subjects will also record any medication they take (dose and time) whether to treat their pain or for any other reasons.

Persistent pain or pain exacerbations during this period may suggest the need for an unscheduled in-person visit to assess the surgical site. If such a situation occurs, the Investigator should use clinical discretion on adequacy of analgesic treatment, but to capture this event as an adverse event (AE) and document any required treatments.

For cohort 4, the D8 visit is the study completion visit.

Subjects will return to the study center on D8±1 for the following assessments:

- Subject home diary review, then collect subject home diary
- Document pain intensity (NRS) at rest and after ambulation each day since discharge from the inpatient unit
- Perform surgical site assessment and neurosensory exam of the foot proximal to the surgical site with contralateral comparison
- Document concomitant medication use including doses and times taken for analgesic medications
- Document concomitant treatment use including topical ice pack or cooling treatments
- Record AE Assessment
- Query the subject as to the presence of any rebound pain (increased pain at the surgery site) (Appendix 17.C)

7.8. Outpatient Phase: D15±2 Visit (Cohort 1-3 only)

Persistent pain or pain exacerbations during this period may suggest the need for an unscheduled in-person visit to assess the surgical site. If such a situation occurs, the Investigator should use clinical discretion on adequacy of analgesic treatment, but to capture this event as an adverse event (AE) and document any required treatments.

Subjects will return to the study center on D15±1 for the following assessments:

- Perform surgical site assessment and neurosensory exam of the foot proximal to the surgical site with contralateral comparison
- Document concomitant medication use including doses and times taken for analgesic medications

- Document concomitant treatment use including topical ice pack or cooling treatments
- Record AE Assessment
- Query the subject as to the presence of any rebound pain (increased pain at the surgery site)

7.9. Outpatient Phase: D29±2 Visit (Cohort 1-3 only) / Early Termination

Subjects will return to the study center on D29±2, or if applicable at premature study discontinuation (early termination or ET), for the following assessments:

- Subject home diary review (NRS scores at rest and after ambulation each day since the last visit and pain medication usage, *if* ET is ≤ Day 8)
- Perform surgical site assessment and neurosensory exam of the foot proximal to the surgical site with contralateral comparison
- Interim PE and vital signs (if early termination prior to Day 8 visit).
- Document concomitant medication use including doses and times taken for analgesic medications
- Document concomitant treatment use
- Record AE Assessment
- Query the subject as to the presence of any rebound pain (increased pain at the surgery site)

7.10. Outpatient Phase: Unscheduled Visits

Unscheduled visits may be scheduled at any time if warranted due to the subject's complaints or condition per investigator discretion. Assessments performed at Unscheduled Visits will be at the discretion of the investigator. If these visits occur prior to D29±2, perform the following:

- Perform surgical site assessment and neurosensory exam of the foot proximal to the surgical site with contralateral comparison
- Document concomitant medication use including doses and times taken for analgesic medications
- Document concomitant treatment use
- Record AE Assessment
- Query the subject as to the presence of any rebound pain (increased pain at the surgery site)

8. SELECTION OF STUDY POPULATION

8.1. Inclusion Criteria

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

1. In the medical judgment of the investigator, be a reasonably healthy adult aged 18 - 65 years old, inclusive, and American Society of Anesthesiology (ASA) physical Class 1, 2 or 3 (Appendix 17A).
2. Plan to undergo an elective primary unilateral first metatarsal bunionectomy repair, without collateral procedure or additional surgeries, to be performed under monitored anesthesia care (MAC) (Appendix 17.H) with a local block.
3. If a male, unless he has a same sex partner, be either sterile (surgically **or** biologically) or commit to an acceptable method of birth control while participating in the study. The site personnel will provide instructions on what is an acceptable method.
4. If a female of child-bearing potential (FCBP), must meet **all** of the following:
    a. Not be pregnant (FCBP must have a negative serum pregnancy test at screening and negative urine pregnancy test before surgery);
    b. No plan to become pregnant or to breast feed during the study; and
    c. Be surgically sterile or at least one year post-menopausal, have a monogamous partner who is surgically sterile, have a same sex partner or (**one** of the following must apply)
        i. is practicing double-barrier contraception
        ii. is practicing abstinence (must agree to use double-barrier contraception in the event of sexual activity)
        iii. is using an insertable, injectable, transdermal or combination oral contraceptive approved by the FDA for at least 2 months prior to screening and commits to the use of an acceptable form of birth control while participating in the study.
5. Have a body mass index ≤ 36 kg/m^2.
6. Be willing and able to sign the informed consent form (ICF) approved by an Institutional Review Board (IRB).
7. Be willing and able to complete study procedures and pain scales and to communicate meaningfully in English with study personnel and return for outpatient follow up visits as required.

8.2. Exclusion Criteria

Subjects will not be eligible to participate in this study if any one of the following exclusion criteria is met:

1. In the opinion of the Investigator,
    a. have a concurrent painful condition, other than bunion-related pain, that may require analgesic treatment during the study period or may confound post-surgical pain assessments.
    b. have active skin disease or other clinically significant abnormality at the anticipated site of surgery that could interfere with the planned surgery.
2. Have a known allergy to chili peppers, capsaicin or the components of CA-008, acetaminophen, bupivacaine HCl, Exparel, fentanyl, ketorolac, lidocaine or oxycodone.
3. As determined by the investigator (with input from the study's medical monitor if requested by the investigator), have a history or clinical manifestation of significant medical, neuropsychiatric or other condition, including a clinically significant abnormal clinical laboratory test value, that could preclude or impair study participation or interfere with study assessments.
4. The following are considered disallowed medications:
    a. Be tolerant to opioids defined as those who have been receiving or have received chronic opioid therapy greater than 15 mg of oral morphine equivalents (Table 4) per day for greater than 4 out of 7 days per week over a one-month period within **6** months screening.
    b. Within 1 day prior to surgery and throughout the inpatient period, be taking any capsaicin-containing products, such as dietary supplements or over-the-counter (OTC) preparations, including topical formulations, and prescription medications.
    c. Within the 7 days prior to surgery, be taking any central nervous system (CNS) active analgesic adjunct medication, such as anticonvulsants, antidepressants (such as SNRIs, SSRIs, and tricyclic antidepressants), benzodiazepines, sedative-hypnotics, clonidine and other central alpha-2 agents (e.g., tizanidine), ketamine or muscle relaxants. [Note that SNRIs = Serotonin and norepinephrine reuptake inhibitors and SSRI = Selective serotonin reuptake inhibitors.]
        i. These drugs are permitted if prescribed for non-pain indications and the dose has been stable for at least 30 days prior to surgery. Note that the dose must remain stable throughout the study.

ii. If the subject is taking centrally- and/or peripherally-acting analgesic medications, such as acetaminophen, NSAIDs, tramadol or opioids, FOR bunion-related pain, the subject may participate in the study if 4(a) above is not applicable and the subject is willing to discontinue these medications 3 days prior to surgery.

iii. The use of benzodiazepines and the non-benzodiazepines (eszopiclone, ramelteon, zaleplon and zolpidem) are permitted to treat insomnia during the postoperative period.

d. Within the 7 days prior to the planned surgery and throughout the study, be taking antiarrhythmics except beta-blockers, digoxin, warfarin (see exception below), lithium, or aminoglycosides or other antibiotics for an infection (except for ophthalmic use or for treatment or prophylaxis of postoperative surgical site infections). (Use of warfarin or other agents is allowed, at the investigator's discretion, for DVT prophylaxis after the surgery is completed).

e. Within the 14 days prior to surgery, be taking parenteral or oral corticosteroids (steroid inhaler for allergy or asthma treatment, topical steroid for a non-clinically significant skin condition not involving the area of surgery or ophthalmic steroids are permissible).

f. Be on an antianginal, antihypertensive agent or diabetic regimen at a dose that has not been stable for at least 30 days or which is not expected to remain stable while participating in the study.

5. In the opinion of the Investigator, within the past year have a history of illicit drug use or prescription medicine or alcohol abuse (regularly drinks > 4 units of alcohol per day; where a unit = 8 oz. beer, 3 oz. wine or 1 oz. spirits).

6. Have positive results on the alcohol test (breath or saliva) indicative of alcohol abuse or urine drug screen indicative of illicit drug use (unless results can be explained by a current prescription or acceptable over-the-counter medication at screening as determined by the investigator) at screening, and/or prior to surgery.

    a. Note that for those subjects who test positive for tetrahydrocannabinol (THC), if they are willing to abstain from use or consumption of THC-containing products from 3 days prior to surgery to the day 8 visit, they may be allowed to participate in the study. Additionally, it may be permissible for the subject to participate if the results can be explained by a current prescription or acceptable over-the-counter medication as determined by the investigator at screening, and/or prior to surgery.

7. Have previously participated in a clinical study with CA-008.

8. Have participated in another clinical trial or used an investigational product within 30 days or five half-lives (whichever is longer) prior to the planned bunionectomy surgery or is scheduled to receive an investigational product other than CA-008 while participating in the study.

8.3. Study Stopping Rules

Enrollment in the study will be paused for evaluation of specific TEAEs (cohorts 1-3 only):

- If one or more subjects experience any grade 4 (or higher) related TEAE (Table 2) or
- If 2 or more subjects experience the same grade 3 related TEAE (Table 2)

Table 2. Stopping Rule Triggers

Category	*Mild (Grade 1)*	*Moderate (Grade 2)*	*Severe (Grade 3)*	*Potentially Life Threatening (Grade 4)*
Abnormal Wound Healing: Infection Dehiscence Necrosis	*Mild symptoms; clinical or diagnostic observations only; intervention not indicated. No interference with age-appropriate instrumental ADL*	*Minimal, local or noninvasive intervention indicated; May require local wound care or medical intervention (e.g., dressings or topical medications)*	*Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting ADLs. May require IV antibiotics, antifungals, or antivirals or radiologic intervention.*	*Life-threatening consequences; urgent intervention indicated*
ECG/Cardiac issues Vital Signs Labs	*Asymptomatic, intervention not indicated*	*Non-urgent medical intervention indicated*	*Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated*	*Life-threatening consequences; urgent intervention indicated*
Focused Neurosensory Testing (performed by trained Investigator)	*Mild symptoms*	*Moderate symptoms; limiting instrumental ADL*	*Severe symptoms requiring medical intervention; limiting self-care ADL*	*Life-threatening and urgent intervention indicated*

Should a trigger occur, the principal investigator, CRO medical monitor and the Sponsor medical monitor will meet to determine whether to unblind study treatment for the subject and determine whether to continue study enrollment.

8.4. Removal of Subjects from Therapy or Assessment

A subject is free to withdraw consent and discontinue participation in the study at any time for any reason. A subject's participation must therefore be terminated immediately upon his/her request, and the reason(s) for discontinuation appropriately documented.

A subject may be discontinued from the study for any of the following reasons:

- Safety reasons, including AEs or significant concomitant illness, injury, or urgent surgeries/procedures that would, in the judgment of the investigator, affect assessments of clinical status to a significant extent, require discontinuation of CA-008, or both
- At the request of the Sponsor, regulatory agency, or Institutional Review Board (IRB)
- Subject is lost to follow-up
- Death of subject
- A subject may also be discontinued from the study, at the discretion of the investigator and/or Sponsor, for any of the following reasons:
- Subject refuses or is unable to adhere to the study protocol
- Major protocol violation
- Pregnancy
- Use of unacceptable concomitant medication(s)
- It is not considered in the best interest of the subject to continue
- Administrative reasons (e.g., termination of enrollment or study)

The Investigator must maintain a record of all subjects who discontinue from the study prior to completion; the reason(s) for study discontinuation will be documented. If a subject chooses to withdraw from the study, the Investigator should make a reasonable attempt to obtain and record the reason(s) for withdrawal in as much detail as possible, although the subject is not obligated to provide such a reason.

If a subject is discontinued while at the clinical site, the early termination procedures should be performed prior to discharge from the clinical site. The investigator should ask the subject to participate in follow-up procedures, provided that the subject has not withdrawn consent for such procedures. If the subject refuses to complete early termination/follow-up procedures or continued data collection, this information will be recorded.

8.5. Study Restrictions

In addition to the criteria described in Section 8.1 and Section 8.2, the subject must agree to abide by the following study restrictions:

Abstain from the following during the inpatient portion of the study:

- consuming any alcohol
- smoking or vaping (nicotine-containing or other substances)
- illicit drug use or non-medical use of therapeutic drugs not allowed by the protocol

Abstain from the following during the outpatient portion of the study:

- illicit drug use or non-medical use of therapeutic drugs not allowed by the protocol
- prohibited medications described in Section 9.5

9. STUDY TREATMENT

9.1. CA-008

9.1.1. Description

CA-008, provided as the hydrochloride salt is a white solid, highly soluble in water. It degrades rapidly to capsaicin at neutral pH but is stable for several days at room temperature in aqueous solution at pH~3. Capsaicin is known to be irritating to mucous membranes when aerosolized and is a skin irritant.

The active drug product will be provided as CA-008 Solution for Injection, 1.0 mL in a 5 mL clear sterile vial, ***with the dose per vial calculated as the freebase***. Inactive ingredients are mannitol, citrate buffer and water.

At time of use, the concentrate will be completely constituted with sterile saline and only a portion of the solution will be used for treatment (see the Pharmacy Manual for details on reconstitution). For clarity, CA-008 and treatment solution is shown in Table 3.

Table 3. CA-008

CA-008	Solution for Injection, 1.0 mL per vial
Drug Product as provided	15 mg
	Each cohort
Concentration upon reconstitution with saline	0.30 mg/mL
Dose in 14 mL of solution	4.2 mg

9.1.2. Storage

CA-008s will be shipped to sites and stored at -20°C (-15°C to -30°C) until the day of surgery. All CA-008 should be stored in a secured area and in accordance with the product labeling and all applicable laws, regulations, and local/institutional requirements. A description of storage conditions for all investigational products will be provided in the Pharmacy Manual.

9.1.3. Accountability

All CA-008 will be transported, received, stored, and handled strictly in accordance with the container or product label, the instructions provided to the research site, and applicable regulations. Detailed drug accountability records must be maintained, including the dates shipments are received, the quantity of material received, the dates dispensed and the running inventory. The unused quantities will be returned to the Sponsor's drug supply vendor at the end

of the trial. All unused supplies will be checked against the drug accountability records during the study and/or at the end of the study. The Investigator or designee must maintain an inventory record of all dispensed rescue medications to subjects. Additional details are provided in the Pharmacy Manual.

Only eligible subjects participating in the study will receive the CA-008. Only authorized research site staff may supply, prepare or administer the CA-008s. Once dispensed, CA-008 may not be relabeled or reassigned for use by other subjects.

9.1.4. Control of CA-008 and Rescue Medication

Mishandling, potential theft, significant loss of clinical supplies, including CA-008s, multimodal analgesia medications and rescue medications at the site, or other suspected diversion must be reported to the Sponsor or designee within 24 hours of first knowledge of the issue. If diversion is confirmed or suspected (e.g., excessive use of rescue medications), the study staff will be required to complete a clinical supply documentation form, including information related to situations in which a subject sold drug or gave drug to a friend or relative, there is a discrepancy in drug accountability and suspected diversion, or a subject had drug stolen, or if there was diversion or theft by site staff or others.

9.2. Exparel

The site has responsibility for procuring sufficient Exparel supplies for cohort 4 administration and will be reimbursed for this purchase.

9.3. Method of Assigning Subjects to Treatment Groups

Subjects who have provided written informed consent will be assigned a unique number in the screening process. This number will be used to identify the subject throughout the study. Once any subject number is assigned, it cannot be reassigned to any other subject. There will be 4 treatment cohorts exploring different anesthesia regimens. For cohorts 1-3, the site will be provided with sufficient CA-008 supplies. Subjects may be rescreened if the screening window is exceeded due to scheduling issues.

9.4. Blinding

This is an open-label study without blinding.

9.5. Prior and Concomitant Therapy

All concomitant medications, including prescription, over-the-counter, or herbal therapies, used by the subject will be reviewed for eligibility and documented for the 30 days prior to Screening and throughout the study. Allowed rescue medication is described in Section 7.5.

The Investigator is permitted to use clinical discretion for required concomitant medications to treat any AE.

9.6. Treatment Compliance

Because all CA-008, Exparel or rescue medication is being administered by study personnel, no compliance procedures are necessary. Diversion will be monitored and recorded through rescue medication accountability. Any suspected or confirmed diversion will be documented and reported.

10. STUDY PROCEDURES AND ASSESSMENTS

All study assessments will be performed at the visits and timepoints outlined in the Schedule of Assessments (Table 1); the following sections outline the details and procedures associated with the assessments.

10.1. Demographics and Other Baseline Characteristics

10.1.1. Informed Consent

The nature of the study and its risks and benefits will be explained to the subject by the Investigator or designated study personnel. The subject must voluntarily provide written informed consent on an ethics-approved informed consent form (ICF), prior to performing any study-related procedures. The subject's source records must document that the consent process has been completed and that written informed consent has been obtained from the subject prior to the initiation of any study-specific procedures. Documentation that the subject was given adequate time to ask the Investigator (or designee) questions about their participation in the study and that a signed and dated copy of the ICF was provided to the subject should also be included in the medical records or clinical chart.

10.1.2. Demographics

The following demographics will be recorded: age (birthdate), sex, race, and ethnicity.

10.1.3. Medical and Surgical History

The complete medical and surgical history will include histories of acute, chronic, or infectious disease; surgical or oncologic histories; and any reported conditions affecting major body systems. All findings on medical history will be evaluated by the Investigator for clinical significance.

10.1.4. Medication History

All medications (prescription and non-prescription, herbal medications/natural health products, or investigational drugs) taken by the subjects during the 30 days prior to Screening will be recorded in the source documentation as medication history.

10.1.5. Contraceptive Requirements

Female subjects of childbearing potential must be using and willing to continue using medically acceptable contraception during the study unless they have a same sex partner. Examples of medically acceptable forms of contraception include true abstinence, hormonal contraceptives (combined oral pill, patch or vaginal ring, intrauterine device or system, progestin implant or injection), bilateral tubal ligation, or double-barrier methods (i.e., male condom in addition to a diaphragm or a contraceptive sponge).

Female subjects of non-childbearing potential are not required to use contraception or undergo pregnancy tests; however, they must be surgically sterile (hysterectomy and/or bilateral oophorectomy or salpingo-oophorectomy, as determined by subject medical history) or congenitally sterile or must be post-menopausal. Post-menopausal is defined as being amenorrheic for at least one year without another cause.

Male subjects, unless in a relationship with a same sex partner or a female partner who is of non-childbearing potential (see above), must either be sterile (surgically **or** biologically) or commit to using double-barrier methods (i.e., male condom in addition to a diaphragm or a contraceptive sponge) during the study.

10.2. Eligibility Review

Subjects must meet all inclusion and not meet any exclusion criteria as outlined in Section 8.1 and Section 8.2. The Investigator or designee must document that the subjects met each individual criterion via a signed note or eligibility and inclusion/exclusion checklist during Screening and at D0 prior to surgery. Signatures on these documents must be dated on or before the day of surgery.

10.3. Subject Pain Assessment Training

Subjects will undergo study participation education on pain assessments and written testing procedures according to the Schedule of Assessments.

10.4. Efficacy Assessments

10.4.1. Numerical Rating Scale (NRS) for Pain Intensity

The NRS is an 11-point scale with anchors 0 (no pain) and 10 (worst possible pain). Subjects will report or record the intensity of their current pain at designated times during the study after administration of CA-008.

10.4.2. Rescue Medications

The details of rescue medication (doses and times) will be recorded beginning from the end of surgery through 14 days after the end of surgery (D15 visit) or to Early Termination Visit if applicable. Subjects will be instructed on the proper use and timing of rescue medication. Use Table 4 to calculate the morphine equivalent dose (MED) of various opioids.

Table 4. Equianalgesic Conversion Table

Opioid (Doses in mg)	Conversion Factor to IV morphine	Conversion Factor to PO morphine
IV Fentanyl	100	
IV Hydromorphone	6	
IV Morphine	1	6*
PO Hydrocodone		1
PO Morphine		1
PO Oxycodone		1.5
PO Tramadol		0.1

For any IV opioid, we will use a 2-step process to calculate its oral (PO) morphine equivalent dose (MED).

1. Convert its IV dose to IV morphine MED by multiplying by the conversion factor for IV equivalence.
2. Once the IV morphine MED is calculated, convert to the PO morphine MED using the conversion factor for PO equivalence.

For any PO opioid, use the conversion factor to calculate the PO MED.

*Note that for non-tolerant patients, we are using the 6:1 conversion for IV to PO morphine, or in other words, 10 mg IV morphine = 60 mg PO morphine.

10.5. Safety Assessments

Safety monitoring will be performed throughout the study for all subjects. All AEs, regardless of causality or severity, will be recorded on the AE CRF.

10.5.1. Clinical Laboratory Assessments

Appropriate screening labs will be performed at the site's local laboratory. It is the responsibility of the Investigator to review and sign all lab reports expeditiously, and to document appropriate safety monitoring of study subjects. The Investigator should sign and date each lab report concurrent with her or his review and should indicate the clinical significance of each abnormal/flagged value by noting "NCS" (not clinically significant) or "CS" (clinically significant), for example. Notations indicating that a value is clinically significant should also include a brief description of the underlying disease or condition that is associated with the value, e.g., "CS/mild anemia." In general, and as determined by the investigator, abnormal, clinically significant laboratory values are expected to be associated with an item recorded in medical history or with an AE.

Blood samples will be collected, processed, and shipped according to instructions from the local lab. Additional samples may be taken at the discretion of the Investigator if the results of any tests fall outside reference ranges or clinical symptoms necessitate testing to ensure safety and to verify return to normal or to a new baseline. Suggested specific screening assessments are as follows:

- CBC
- Blood Chemistry: sodium, potassium, calcium, chloride, creatinine and glucose
- Serum and urine pregnancy test for FCBP: βhCG test at screening and urine test usually to be done within 24 hours prior to surgery.
- Urinalysis if indicated

10.5.2. Urine Drug Screen and Alcohol Breath Test

Urine drug screen and alcohol breath tests will be completed at screening and pre-procedure. All subjects will be tested for drugs-of-abuse (i.e. amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, tetrahydrocannabinol (THC), methadone, methamphetamine, tricyclic anti-depressants, and oxycodone).

The drug and alcohol screens may be performed in-house at the Clinical Unit. If any of these tests are positive (note exception for THC below), the subject will not be allowed further participation in the trial. A positive test may be repeated at the discretion of the PI. Note that for those subjects who test positive for THC, if they are willing to abstain from use (e.g., inhalational) or consumption of THC-containing products from 3 days prior to surgery to the D8 visit, they may be allowed to participate in the study.

10.5.3. X-Ray

An X-ray of the surgical site will be performed during screening (or verified as previously done) and at D29/ET (cohorts 1-3 only).

10.5.4. Physical Examination

A complete physical examination (PE) including all major body systems (HEENT, neurologic, cardiovascular, respiratory, gastrointestinal, dermatologic and musculoskeletal systems) will be performed at Screening and an interim PEs prior to Surgery. Evaluation of the surgical site and neurosensory testing of both lower extremities should be performed at specific times.

Body weight (kg), in indoor clothing, but without shoes, and height in centimeters (cm) will be measured to calculate BMI at Screening. BMI shall be calculated as kg/m^2. Use the NIH website BMI calculator http://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi-m.htm.

10.5.5. Assessment of Adverse Events

All SAEs will be documented and followed from the time the subject has signed the ICF until D29 (cohorts 1-3) or D8 (cohort 4), and, if necessary, later to follow an AE to resolution or

establishment of a new baseline. All SAEs and non-serious AEs will be documented and followed from the time of administration of until D29 (cohorts 1-3) or D8 (cohort 4). AEs/SAEs that occur between Screening and the study procedure should be considered medical history and be added to the subject's medical record. Serious AEs and AEs that have been designated as possibly related to CA-008 will be followed until resolution or stabilization. Further details on AEs, including definitions, elicitation, and reporting are provided in Section 11.

10.6. Efficacy and Safety Endpoints

10.6.1. Efficacy Endpoints

Using NRS scores (at rest and with ambulation), pain intensity over the 72h inpatient stay will be assessed.

10.6.2. Safety Endpoints

Safety endpoints include the following:

- Incidence of TEAEs and SAEs
- Surgical Site assessment findings
- Neurosensory testing results
- X-ray healing of the surgical site (cohorts 1-3 only)
- Absence of rebound pain at the surgical site (cohorts 1-3 only)

11. ADVERSE EVENTS

11.1. Adverse Events and Serious Adverse Events

The following definitions, developed in accordance with the United States (US) Code of Federal Regulations (CFR) and the International Conference on Harmonization (ICH) Clinical Safety Data Management Guidance for Industry, E2A, will be used to identify AEs in this study.

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or increase in severity of a preexisting abnormality, temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

A "suspected adverse reaction" means any AE for which there is a reasonable possibility that the drug caused the event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.

11.1.1. Relationship to CA-008 or Exparel

A qualified investigator must make the determination of relationship to the investigational product for each AE. The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the CA-008 or Exparel.

Causality Category	Description
Unlikely related	A clinical event, including laboratory test abnormality, with a temporal relationship to CA-008 or Exparel administration which makes a causal relationship improbable or if other drugs, chemicals or underlying disease provide more plausible explanations. While temporal sequence may be an important factor in determining causality: i.e., whether the observed reaction or event began after the CA-008 or Exparel, it may well be that the surgery, anesthesia, a concurrent medical condition or concomitant medications administered during or after surgery were more likely than not to be responsible for the AE. The investigator should use clinical judgment to evaluate the evidence and determine whether there is a reasonable possibility that CA-008 or Exparel actually caused the AE or whether based upon the evidence it is more likely that something else is responsible. If the former, choose "possibly related" and if the latter, "unlikely related."

	For the purpose of this protocol, the term "unlikely related" will be considered an AE not related to CA-008 or Exparel.
Possibly related	A clinical event, including laboratory test abnormality, with a temporal relationship to CA-008 or Exparel administration, which also may be explained by concurrent disease or other drugs or chemicals. In such cases, if the investigator using clinical judgment is unable to rule out a reasonable possibility that CA-008 or Exparel was partly responsible, then choose "possibly related." For the purpose of this protocol, an event that has possible relationship to CA-008 or Exparel will be defined as a "Suspected Adverse Drug Reaction".
Probably related	A clinical event, including laboratory test abnormality, with a temporal relationship to CA-008 or Exparel administration, in which the investigator has determined that the event is unlikely to be attributed to other factors. For the purpose of this protocol, an event that has probable relationship to CA-008 or Exparel will be defined as an "Adverse Drug Reaction".

11.1.2. Adverse Event Reporting

All AEs must be entered on the AE CRF, regardless of causality or severity. AEs include new AEs, worsening baseline conditions, clinically significant laboratory findings, disease-related signs and symptoms that were not present at baseline, and any events or findings that the Investigator feels are clinically significant.

Disease-related signs and symptoms that are present at baseline should not be recorded as AEs unless they worsen in severity or increase in frequency.

Information collected concerning AEs will include the following:

- Name of the event
- Onset date
- Resolution date
- Severity (i.e., mild, moderate, severe or potentially life-threatening)
- Relationship
- Action and outcome
- Seriousness of event

All SAEs will be documented and followed from the time the subject has signed the ICF until D29 visit (cohorts 1-3) or D8 visit (cohort 4) after the completion of surgery. All SAEs and non-

serious AEs will be documented and followed from the time of administration of CA-008 or Exparel until D29 or D8, respectively, or later if necessary. AEs/SAEs that occur between Screening and the administration of study medication should be considered medical history and added to the subject's medical record, unless the AE is due to a study-related procedure (such as phlebotomy), in which case it will be recorded as a non-treatment emergent AE. Serious AEs and AEs that have been designated as possibly related to CA-008/Exparel will be followed until resolution or stabilization.

11.1.3. Serious Adverse Event (SAE)

An SAE or reaction is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- Is life-threatening (at the time of the event)
- Requires subject hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in an offspring)
- An Important medical event that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

For cohorts 1-3, all AEs requiring hospitalization or prolongation of a pre-existing hospitalization should be reported as SAEs unless they occur ≥ 14 days after the Day 29 visit, or 21 days after an early termination AND are not considered to be CA-008-related by the Investigator. For cohort 4, all AEs requiring hospitalization or prolongation of a pre-existing hospitalization should be reported as SAEs unless they occur after the Day 8 visit AND are not considered to be related by the Investigator.

Hospitalizations meeting the following criteria will not be reported as an SAE but must be recorded on the appropriate CRF: study specified hospitalization, short-term administrative hospitalization for procedures, tests or treatments of conditions that would not otherwise constitute an SAE, elective hospitalizations.

11.1.3.1. Serious Adverse Event Reporting

Serious AEs must be reported to the Sponsor or designee within 24 hours of knowledge of the event. All SAEs that occur while a subject is receiving CA-008 and within 14 days following the study completion visit (or 21 days following an ET if applicable) are reportable within 24 hours. During this follow-up period beyond study completion or after an ET, only those SAEs considered to be possibly related to CA-008 or Exparel should be reported within 24 hours.

The procedure for reporting an SAE: All SAEs must be reported immediately (within 24 hours of discovery) by email to the CRO Medical Monitor or designee. Calls related to SAEs should first be directed to the CRO Medical Monitor or designee.

- **CRO Medical Monitor: Jon Ruckle, MD**
- **24/7 Emergency contact: 808-349-9812 / (253) 448-8690**
- **SAE Reporting email: MedicalMonitorCA-PS-205@Lotuscr.com**

- The Sponsor's Medical Monitor is available for questions about safety-related issues:

  Mike A. Royal, MD JD MBA; 858-204-1112 or mike@concentricanalgesics.com.
- The initial report should include all information known at the time of the report (additional information can be reported as discovered). Do not delay the initial reporting in order to obtain resolution or follow-up information.
- The site will enter into the electronic database (or fax, if the database cannot be accessed for any reason) an SAE report, or similar form, that includes the following information, as available:
  - Subject ID
  - Basic demographic information (age, gender, weight)
  - Outcomes attributed to the event (death, life-threatening hospitalization [new or prolonged], disability, congenital anomaly, required medical intervention to prevent permanent impairment/damage, etc.)
  - Onset date and severity of the event
  - Brief description of the event including frequency and severity of symptoms leading to diagnosis
  - List of relevant test results and laboratory data
  - Any other relevant history
  - Whether CA-008 or Exparel was discontinued
  - Investigator's assessment of causality

The CRO Medical Monitor or another representative of the Sponsor may contact the Investigator to request additional information regarding the event or to confirm information. All SAEs will be entered on the AE CRF. The same nomenclature should be used on both the SAE report and the AE CRF. The Investigator is responsible for the complete and timely reporting of all SAEs to the Sponsor (or designee), reporting pertinent follow-up information on the SAE, and notifying the appropriate IRB of the occurrence of and details surrounding the event. In the event there is a question as to whether the AE is serious, the event should be reported.

11.1.4. Severity Grading for AEs

Grading the severity of AEs is per investigator discretion (Section 17.G). Additionally, the following general guideline may be helpful:

- Grade 1 (mild) = asymptomatic or mild symptoms requiring no treatment, only clinical or diagnostic observation
- Grade 2 (moderate) = event or symptoms limit age-appropriate activities of daily living (ADLs) more than is expected from the surgery itself, requiring minimal treatment or local noninvasive intervention indicated.
- Grade 3 (severe) = medically-significant but not immediately life-threatening, significantly limiting of self-care ADLs, requiring of medical treatment and may require hospitalization or prolongation of hospitalization.

11.2. Pregnancy

If a female subject becomes pregnant at any time during the study, the Investigator must notify the CRO Medical Monitor or designee within 48 hours of learning about the pregnancy. The Investigator will be required to follow the subject through the pregnancy term, and report to the CRO Medical Monitor or designee the course of the pregnancy, including perinatal or neonatal outcome. Information on the status of the mother and the child will be forwarded to the CRO Medical Monitor or designee. Any premature termination of the pregnancy will also be reported on this form. Although pregnancy occurring in a clinical study is not considered to be an SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE and will be followed as such. A spontaneous abortion is considered to be an SAE.

12. DATA QUALITY ASSURANCE

This study will be conducted under Good Clinical Practice (GCP) and all applicable regulatory requirements. To ensure compliance, the Sponsor or designee may conduct a quality assurance audit, as outlined in Section 12.2.

Actions to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers; the review of protocol procedures with the Investigator and study personnel prior to study start; the design of suitable source documents with appropriate instructions for use (where applicable); the internal audit of source data according to GCP and internal procedures to ensure their accuracy, completeness, and verifiability; as well as the periodic site monitoring by the Sponsor. The Sponsor or designee will review source documents for accuracy and completeness during on-site monitoring visits and after their return to the Sponsor; any discrepancies will be resolved with the Investigator, as appropriate.

Significant and/or repeated non-compliance will be investigated and remedial action instituted when appropriate. Failure to comply with remedial actions may result in investigational site termination and regulatory authority notification.

12.1. Data Collection

Source documents include, but are not limited to, original documents, data and records such as hospital/medical records (including electronic health records), clinic charts, lab results, participant diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc. This study will use electronic data capture (EDC). At a minimum, all data required by the protocol should have supporting source documentation for entries in the EDC system.

All CRFs will be completed by the site staff prior to review by the Sponsor's monitor or designated representative. The Sponsor's monitor or designated representative will review all source records on-site and compare them to the data collected on the CRF. All entries, corrections, and alterations will be made by the Investigator or other authorized study personnel. All data entries will be verified for accuracy and correctness by independent monitors. The electronic data capture system maintains a full audit trail.

12.2. Study Auditing and Monitoring

Monitoring of the study site (including, but not limited to, reviewing CRFs for accuracy and completeness) will be performed by the Sponsor's designated monitor(s). The extent, nature, and frequency of on-site visits will be based on such considerations as the study objectives and/or

endpoints, the purpose of the study, study design complexity, and enrollment rate. By signing the protocol, the Investigator agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of the Sponsor, a regulatory authority, and/or an IRB may visit the site to perform audits or inspections, including the drug storage area, CA-008 stocks, drug accountability records, participant charts and source documents, and other records related to study conduct. The purpose of the Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether the study-related activities were conducted, and data recorded, analyzed, and accurately reported according to the protocol, the site's standard operating procedures, GCP guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency regarding an inspection.

13. STATISTICAL METHODS

13.1. Statistical and Analytical Plans

This section describes the statistical methods to be used to analyze the efficacy and safety. The final analysis plan will be documented in a formal Statistical Analysis Plan (SAP) that will be finalized before database lock. The SAP will include details on how variables will be derived, how missing data will be handled, and how data will be presented as well as the details on statistical methods to be used for safety and efficacy analyses. The final clinical study report will discuss deviations from the SAP, if any.

13.2. Sample Size Justification

The currently planned study is a follow-on exploratory study to a prior phase 2 study (CA-PS-201) which showed CA-008 4.2 mg was statistically significantly superior to placebo. This study is being performed to evaluate optimal anesthesia conduct, therefore no sample size estimation was performed. It was felt that a comparison of 9 in each treatment cohort would be sufficient to demonstrate the effectiveness of any anesthesia combination.

13.3. Analysis Populations

The following analysis populations are planned for this study:

- The Safety Population will include all subjects who received at least part of a dose of CA-008 or Exparel.
- The Study Completer Population will include all subjects who complete the D29 visit (cohorts 1-3) or D8 visit (cohort 4).

Subjects who elect to discontinue study participation during the inpatient phase of the study, will be asked to continue with assessments through T72h if they have not elected to withdraw from all aspects of study participation. Subjects who elect to discontinue participation after discharge from the inpatient unit but prior to D8 will be considered to have terminated as of the date of their election, however they will be asked to return to the site to reassess the surgical site for wound healing.

All safety and efficacy assessments and baseline characteristics will be summarized using the Safety Population. All summaries will be grouped by the actual treatment received.

13.4. Planned Analyses

Summary statistics will be provided for the variables described in the following sections. 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.

13.5. Study Subjects and Demographics

13.5.1. Disposition and Withdrawals

The numbers of subjects enrolling, 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.

13.5.2. Protocol Deviations

All protocol deviations will be classified and documented before database lock and will be discussed in the CSR. All protocol deviations, both minors and majors, will be presented in a data listing.

13.5.3. Demographics and Other Baseline Characteristics

Demographic and baseline characteristics (including age, sex, race, weight, and height) will be summarized for each treatment group and for the overall population by descriptive statistics. Medical history and screening clinical laboratory tests will be listed.

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

13.5.4. Exposure

Since this is a single dose study, CA-008 or Exparel administration will be summarized by cohort and treatment group.

13.5.5. General Considerations

All continuous study assessments will be summarized by treatment and time point (as applicable) using the descriptive statistics n, mean, SD, median, and range (minimum, and maximum). Categorical assessments will be summarized by treatment and time point (as applicable) using frequency counts and rates of occurrence (%). Changes from baseline for continuous outcomes will be presented as their corresponding continuous measures for post-baseline visits. All study data will be listed by treatment group, subject and time point.

No preliminary rounding will be performed; rounding will only occur after the analysis. Means and medians will be presented with one more decimal place than the precision of the data. Standard deviations will be presented with two more decimal places than the precision of the data. Percentages will be presented with one decimal place. A percentage of 0% or 100% will

be reported as 0% or 100%, respectively. Minimums and maximums will be presented with the same precision as the original data.

All analyses will be performed using the SAS System® version 9.3 or higher. The domain (Study data tabulation Model [SDTM]) and analysis (Analysis Data Model [ADaM]) data sets will be taken as input to the SAS programs that generate the report-ready tables, figures and listings. The submission ready SDTM and ADaM data sets will be provided to the sponsor along with display deliveries. The specifications for the domain data sets and analysis data sets will be provided in a separate document.

The following conventions will be used throughout the study analysis:

- Time $T0h_{NRS}$ is the time of entry to the PACU.
- Day of surgery is defined as D0
- Assessment visit times are defined by time $T0_{NRS}$ /D0.
- Baseline value is defined as the last valid measurement prior to beginning CA-008 administration.
- Change from baseline is defined as post-baseline value minus baseline value.
- Duration of an AE will be computed in days for AEs lasting longer than 24 hours, and as hours for AEs lasting less than 24 hours. Duration in hours will be calculated as the stop date/time of the event minus the start date/time. Duration in days will be calculated by using stop date minus the start date +1 if AE occur on or after taking study medication. If AE occur prior to the study medication, then the duration will be calculated by using stop date minus the start date. If reported as ongoing at the time of database lock, the duration will be calculated using the date of the last visit or the last date of any AE for the subject in the database, whichever is later. Missing dates will be imputed as described in the Study's Statistical Analysis Plan (SAP).
- The number of days in the study is computed as: [Date of study completion or withdrawal minus the date of study drug administration (Day 1)] + 1.
- If duplicate values are obtained at a given visit (e.g., repeated vital sign measurements), the last value will be used unless it is noted that the measurement was in error for that value. Values that compromise interpretation will not be used in summaries (e.g., values that were obtained post-dose will not be summarized as pre-dose values).

13.6. Analysis of Efficacy Measures

All efficacy endpoints (e.g., NRS scores), will be summarized over time by treatment using descriptive statistics including confidence intervals as appropriate. Details may be found it the study statistical analysis plan (SAP)

AUC calculations will be done using the standard trapezoidal rule

$$\text{AUC} = \sum_{i=0}^{x} \left(\frac{NRS_i + NRS_{i+1}}{2}\right) * (T_{i+1} - T_i)$$

Where: NRS_i = NRS at time i, and ($T_{i+1} - T_i$) is the Time difference in minutes between time i and time i+1. A similar calculation and handling of missing data will be performed for the NRS scores with ambulation.

In this study, subjects are permitted to take rescue medication for analgesia. During both inpatient and outpatient portions of the study, the subjects will be instructed to record NRS immediately prior (within approximately 15 min) to taking rescue medication.

Missing NRS will be handled as discussed in the Study's SAP and as briefly outlined in Section 13.6.1.

13.6.1. Handling of Dropouts and Missing Data

All efforts will be made to minimize missing data. These efforts will include the following:

- Subjects are required to consent continuous data collection even after subjects discontinue CA-008 or Exparel;
- Continue data collection after subjects taking rescue medication;
- Establish robust efficacy data collection procedures.

With the procedures above, it is expected that the missing would be minimal.

For subjects who take rescue medication a windowed last pain score carried forward (LOCF) will be used. The pre-rescue pain score will be used to impute scheduled assessments for 30 min after IV fentanyl and 4 hours following PO oxycodone. Intermittent missing pain scores (due to subject sleeping, etc.) will not be imputed, and AUC will be calculated based on non-missing values. For subjects who drop out of the study prior to Day 15, scheduled assessments will first be imputed using the worst prior pain score carried forward (WOCF). As sensitivity analyses, the AUC will also be calculated where assessments after drop out will be imputed using LOCF, using the last scheduled non missing pain score prior to drop out or replacing drop out with the median data from the remainder of subjects in that treatment group.

For secondary continuous efficacy endpoints, similar methods as the primary analysis will be used. For categorical endpoints, when assessments are imputed for data after a subject discontinues from the study, a WOCF method will be used.

Sensitivity analysis of the primary efficacy variable using different methods of imputation for rescue medication may also be performed. Additional sensitivity analysis with different missing value imputation methods for subjects who drop out of the study may also be performed. All imputation methods for pain intensity will be documented in the SAP.

13.7. Analysis of Safety

Safety analyses will be conducted using data from the Safety Population (as defined in Section 13.3).

Safety will be assessed through TEAEs, surgical site and neurosensory assessments.

No formal statistical comparisons will be performed for safety endpoints.

13.7.1. Adverse Events

Adverse events will be coded by system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) reporting system. Treatment-emergent AEs are defined as any of the following:

- Non-serious AEs with onset on the date of treatment through D29 (cohorts 1-3) or D8 (cohort 4) or Early Termination, whichever occurs first;
- Serious AEs with onset on the date of surgery through D29 (cohorts 1-3) or D8 (cohort 4) or Early Termination, whichever occurs first;
- AEs that start before the start of treatment but increase in severity or relationship at the time of or following the start of treatment through D29 (cohorts 1-3) or D8 (cohort 4) or Early Termination, whichever occurs first.

The number and percentage of subjects with TEAEs will be displayed for each treatment group by SOC and preferred term. Additionally, TEAEs will be tabulated for each treatment group by severity and by relationship to the CA-008. A listing of SAEs will be provided if applicable.

13.7.2. Surgical Site and Neurosensory Testing Findings

Surgical site assessments and neurosensory testing data will be presented in the listings. Abnormal or clinically significant findings atypical for the surgery will be recorded as AEs.

14. SITE AND INVESTIGATOR RESPONSIBILITIES

Additional details may be outlined in the Clinical Study Agreement between the sponsor and the investigational site.

14.1. Regulatory and Ethical Considerations

14.1.1. Ethical Conduct of the Study

The Investigator will conduct the study in accordance with GCP and all applicable regulations, including, where applicable, the Declaration of Helsinki. The study will also be carried out in keeping with applicable national and local laws and regulations. This may include an inspection by the Sponsor's representatives and/or regulatory authority's representatives at any time.

14.1.2. Ethics Approval

The investigational site's IRB, if the site is required to use a local IRB as well as the central IRB, must meet all relevant regulatory requirements. The study protocol and ICF will be reviewed by the IRB prior to enrolling participants into the study; written approval from the committee must be received by the sponsor before drug will be released to the Investigator. The Investigator is responsible for submitting all protocol or ICF changes and SAE reports to the IRB according to local procedures. At a minimum, all SAEs requiring an investigational new drug safety report must be immediately reported.

In accordance with applicable regulatory requirements, the Investigator may be obligated to provide periodic safety updates on the conduct of the study at his or her research site and notification of study closure to the IRB. Such periodic safety updates and notifications are the responsibility of the Investigator and not of the Sponsor. The Sponsor will be provided with copies of all notifications sent to the IRB.

All relevant correspondence from the IRB will be forwarded by the respective study site to the Sponsor in a timely fashion.

14.1.3. Subject Informed Consent

The Investigator (or authorized designee) will ensure that the participant (or the participant's legal representative) is given full and adequate oral and written information about the nature, purpose, potential and possible risks and benefits of the study. Each prospective subject will receive an IRB-approved ICF that summarizes the pertinent study information and will be given ample time to read the form and ask questions about the study. All information is to be provided in a language understandable to the participant and must not include any language that waives the participant's legal rights. Prospective participants must also be informed of their right to withdraw consent without prejudice at any time during the study. If the participant chooses to participate, he/she must sign the ICF before any study-related procedures are performed.

Significant changes to the protocol or product safety information may require a revision of the ICF, which must be reviewed and signed by all applicable study participants.

The time that informed consent is obtained must be documented. The Investigator must maintain the original, signed ICF in the participant's source documents. A copy of the signed ICF must be given to the study participant.

14.2. Privacy and Confidentiality

The Investigator is responsible for complying with applicable privacy regulations, per his or her jurisdiction. Only information identified in this protocol will be collected. The information collected will only be used for the purposes identified in this protocol.

To ensure anonymity and to limit disclosure, participants will be assigned a unique identifier at their first assessment. This identifier will be cross-referenced in the participant's chart. The identifier will not contain any potentially identifiable information. An identifier log will be maintained, linking each participant's name to the corresponding identifier. This log will be stored at the research site in a secure location.

The knowledge gained through this study is the property of the Sponsor. The Sponsor, representatives and affiliated companies of the Sponsor, the IRB, and regulatory agencies (such as the United States FDA) may inspect medical records related to the study to check the validity and accuracy of the data gathered in this study. Participant medical records (with participant's initials and/or date of birth) may be copied. Confidentiality of participant records will be maintained except where release of information is required by law.

The results of this study will be reported in such a manner that participants will not be identifiable in any way. Published reports or presentations will refer to grouped data or coded individual data and not to any identifiable individuals. Study reports sent to the Sponsor or drug regulatory agencies will not include participant names.

By signing the ICF, the participant consents to the collection, access, use, and disclosure of his or her information as described in the ICF document. If a participant withdraws consent, some of the subject's information may still be collected, used, and disclosed by those involved in this study, per applicable laws.

By signing this protocol, the Investigator affirms that he or she will maintain in confidence information furnished to him or her by the Sponsor and will divulge such information to his or her respective IRB or IEC under an appropriate understanding of confidentiality with such board. All data will be considered the sole property of the Sponsor. Please refer to the Clinical Study Agreement for details.

14.3. Study and Site Closure

Upon completion of the study, all study data will be provided to the Sponsor following review of site study records for completeness, and data clarifications and resolutions. Accounting, reconciliation, and final disposition of used and unused CA-008s, treatment codes, and emergency code break envelopes will be performed, as applicable.

In addition, the Sponsor reserves the right to temporarily suspend or prematurely discontinue this study at any time and for any reason. If such action is taken, the Sponsor will discuss this with the Investigator (including the reasons for taking such action) at that time. The Sponsor will promptly inform any other investigators and/or institutions conducting the study, if the study is suspended or terminated for safety reasons and will inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the Investigator will inform the IRB promptly and provide the study participants with the reason for the suspension or termination. If the study is prematurely discontinued, all study data will be returned to the Sponsor.

14.4. Regulatory Documents and Records Retention

The Investigator is responsible for creating and/or maintaining all study documentation required by 21 CFR 50, 54, 56 and 312, ICH E6 Section 8, as well as any other documentation defined in the protocol or Clinical Study Agreement. The Investigator must provide key documents to the Sponsor prior to the start of the study. A complete list of required regulatory documents will be supplied by the Sponsor or its representative.

Federal and local regulations require that the Investigator retain a copy of all regulatory documents and records that support the data for this study for whichever of the following is the longest period of time:

- A period of 2 years following the final date of approval by the FDA or other regulatory agency of the CA-008 for the purposes that were the subject of the investigation; or
- A period of 5 years following the date on which the results of the investigation were submitted to the FDA or other regulatory agency in support of, or as part of, an application for a research or marketing permit for the CA-008 for the purposes that were the subject of the investigation.

The Sponsor will notify investigators once one of the above 2 timeframes has been satisfied.

If the investigation does not result in the submission of the data in support of, or as part of, an application for a research or marketing permit, records must be retained for a period of 2 years following notification by the Sponsor that the entire clinical investigation (not merely the Investigator's portion) is completed, terminated, or discontinued or 2 years following withdrawal

of the Investigational New Drug application/Clinical Trial Authorization or request for marketing approval (New Drug Application/Marketing Authorization Application).

If the Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Study records should not be destroyed without consultation with the Sponsor.

14.5. Delegation of Responsibilities and Adequate Resources

The Investigator should have adequate time to conduct the study properly and should have an adequate number of qualified staff to assist with the conduct of the study.

The term “Investigator” used throughout this protocol refers to the principal investigator and/or qualified sub-investigators. However, the Investigator may delegate responsibilities to other investigational site personnel. The Investigator shall delegate tasks only to individuals qualified by education, training and experience to perform the delegated tasks. The Investigator shall have direct oversight of all delegated activities and shall document delegation of responsibilities. The Investigator is responsible for ensuring all delegated staff has been properly trained on the protocol and their assigned study responsibilities. A delegation log identifying all delegated duties and the individual to whom they have been delegated will be maintained at the investigational site.

14.6. Protocol Amendments

Approval of a protocol amendment by the Investigator’s IRB must be obtained before implementation of the protocol amendment, unless a change is necessary to eliminate an apparent immediate hazard to the participant or when the change involves logistical or administrative aspects of the study. The protocol amendment must be signed and dated by both the Sponsor and the Investigator. The Sponsor or designee will submit protocol amendments to the appropriate regulatory authorities, if required.

14.7. Financial Disclosure

Clinical investigators are required to provide financial disclosure information for the submission of certification or disclosure statements required under 21 CFR § 54. As defined in 21 CFR § 54.2, a clinical investigator is a listed or identified investigator or sub-investigator who is directly involved in the treatment or evaluation of research participants. The term also includes the spouse and each dependent child of the investigator. In addition, investigators must promptly update financial disclosure information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.

15. INVESTIGATOR PROTOCOL AGREEMENT PAGE

An Open-Label Study of Intraoperative CA-008 Administration in Subjects Undergoing Bunionectomy

Version: 4.0

Date: 02 May 2019

I have read this protocol and I agree to conduct the study in accordance with the protocol and with all applicable government regulations and International Conference on Harmonisation/Good Clinical Practice guidances.

Principal Investigator's Name (please print or type) _____

_____ _____

Principal Investigator's Signature Date (DD-MMM-YYYY)

16. REFERENCES

1. Babbar S, Marier JF, Mouksassi MS et al. Pharmacokinetic analysis of capsaicin after topical administration of a high-concentration capsaicin patch to patients with peripheral neuropathic pain. *Ther Drug Monit* 2009; Aug;31(4):502-10. doi: 10.1097/FTD.0b013e3181a8b200.
2. Caterina MJ, Julius D. The vanilloid receptor: a molecular gateway to the pain pathway. Annu Rev Neurosci. 2001 24:487-517.
3. Hartrick CT, Pestano C, Carlson N, Hartrick S. Capsaicin instillation for postoperative pain following total knee arthroplasty: a preliminary report of a randomized, double-blind, parallel-group, placebo-controlled, multicentre trial. Clin Drug Investig. 2011 Dec 1;31(12):877-82.
4. Suresh D and Srinivasan K. Tissue distribution & elimination of capsaicin, piperine & curcumin following oral intake in rats. Indian J Med Res 2010; 131:682– 691.
5. Surh YJ, Ahn SH, Kim KC et al. Metabolism of capsaicinoids: evidence for aliphatic hydroxylation and its pharmacological implications. Life Sci 1995; 56:PL305–PL311.
6. Tominaga M, Caterina MJ, Malmberg AB et al. The cloned capsaicin receptor integrates multiple pain-producing stimuli. Neuron 1998; 21, 531–543.

17. APPENDICES

A. Appendix A: American Society of Anesthesiologists Physical Status Classification System (ASA Class)

	Definition	Examples, including, but not limited to:
ASA I	A normal healthy patient	Healthy, non-smoking, no or minimal alcohol use
ASA II	A patient with mild systemic disease	Mild diseases only without substantive functional limitations. Examples include (but not limited to): current smoker, social alcohol drinker, pregnancy, obesity (30 < BMI < 40), well-controlled DM/HTN, mild lung disease
ASA III	A patient with severe systemic disease	Substantive functional limitations; One or more moderate to severe diseases. Examples include (but not limited to): poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, premature infant PCA < 60 weeks, history (>3 months) of MI, CVA, TIA, or CAD/stents.
ASA IV	A patient with severe systemic disease that is a constant threat to life	Examples include (but not limited to): recent (< 3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis
ASA V	A moribund patient who is not expected to survive without the operation	Examples include (but not limited to): ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes	

*The addition of “E” denotes Emergency surgery: (An emergency is defined as existing when delay in treatment of the patient would lead to a significant increase in the threat to life or body part)

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

B. Appendix B: 0-10 Numerical Rating Scale for Pain Intensity (NRS)

Pain Intensity - Numerical Rating Scale (NRS)

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

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

Subject Initials: _____

C. Appendix C: Assessment of Increased Pain at the Surgical Site (Rebound Pain)

Rebound Pain
Have you noticed any increase in pain at the surgical site (rebound pain) since your last visit? **yes no** **Subject Initials: _____**

D. Appendix D: Surgical Site Assessment

Post-Operative Surgical Site Assessment
Instructions to Investigator**:** Please respond to the question below. When completed, please initial at the bottom of the page.
On a scale of 0 to 10, please rate your clinical satisfaction with the wound healing. ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 ***Completely unsatisfied*** ***Completely satisfied*** **Investigator Initials: _____**

E. Appendix E: Wound Status Assessment Guide

PARAMETER	GRADE	DESCRIPTION
ERYTHEMA	0	NONE
	1	VERY SLIGHT (BARELY PERCEPTIBLE)
	2	SLIGHT (WELL DEFINED)
	3	MODERATE
	4	SEVERE (BEET REDNESS) TO SLIGHT ESCHAR FORMATION (INJURIES IN DEPTH)
DRAINAGE	0	NONE
	1	SEROUS
	2	SEROSANGUINOUS
	3	BLOODY
	4	PURULENT
EDEMA	0	NONE
	1	VERY SLIGHT (BARELY PERCEPTIBLE)
	2	SLIGHT (EDGES WELL DEFINED)
	3	MODERATE (RAISED APPROXIMATELY 1 MM)
	4	SEVERE (RAISED >1 MM AND BEYOND AREA OF EXPOSURE)
INDURATION	0	NONE
	1	MINIMAL
	2	MILD (SPONGY TISSUE)
	3	MODERATE (FIRM, WARM)
	4	SEVERE (HARD, RED, HOT, CREPITUS)
HEMATOMA	0	NONE
	1	MINIMAL
	2	MILD
	3	MODERATE
	4	SEVERE

F. Appendix F: Neurosensory Testing Form

Subject Number	Subject Initials	Date: __ __/ __ __ __/ 20__ __ (DD-MMM-20YY)	Protocol Number CA-PS-205
__ __ __ - __ __ __	__ __ __		

Instructions to the Investigator: Please assess both feet and answer the questions below for each foot. Please enter the time of assessment (in 24H clock format) below and enter your initials.

Time of Assessment: ☐☐ : ☐☐ (H H : M M) ☐ Not Done, Reason:_____ **Investigator Initials**: _____

Neurosensory Examination of the Foot / Great toe (bilateral)

1. Was the Neurosensory Exam of the Foot / Great toe completed? ☐ Yes ☐ No

		LEFT FOOT	RIGHT FOOT
2.	Visual Exam of the foot:	☐ Normal ☐ Abnormal, describe: _____	☐ Normal ☐ Abnormal, describe: _____
3.	Monofilament Sensation	☐ Normal ☐ Reduced ☐ Absent	☐ Normal ☐ Reduced ☐ Absent
4.	Allodynia to Brush:	☐ Pain (Allodynia) ☐ Normal ☐ Reduced ☐ Absent	☐ Pain (Allodynia) ☐ Normal ☐ Reduced ☐ Absent

For all assessments, the foot should be warm.

- **Foot Inspection**: The feet are inspected for evidence of excessively dry skin, callous formation, fissures, frank ulceration or deformities. Deformities include flat feet, hammer toes, overlapping toes, hallux valgus, joint subluxation, prominent metatarsal heads, medial convexity (Charcot foot) and amputation.
- **Monofilament Sensation Testing:** For this examination, it is important that the patient's foot be supported (i.e., allow the sole of the foot to rest on a flat, warm surface). The filament should initially be prestressed (4-6 perpendicular applications to the dorsum of the examiner's first finger). The filament is then applied to the dorsum of the great toe midway between the nail fold and the DIP joint. Do not hold the toe directly. The filament is applied perpendicularly and briefly, (<1 second) with even pressure. When the filament bends, the force of 10 grams has been applied. The subject, whose eyes are closed, is asked to respond yes if he / she feels the filament. Eight correct responses out of 10 applications is considered normal: one to seven correct responses indicate reduced sensation and no correct responses translates into absent sensation.
- **Testing for Allodynia:** testing should be performed bilaterally with the great toe unsupported. Allodynia will be tested using a foam brush applied to the dorsum of the great toe. The foam brush will be lightly stroked 3 times across the skin over the dorsum of the great toe. Subject will be asked to compare sensation of toe on the surgical side with the toe on the nonsurgical side. If the sensation is described as painful or very unpleasant then allodynia will be reported as present. If sensation is not felt at all then it will be reported as absent.

G. Appendix G: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

Table for Vital Sign Abnormalities

Vital Signs *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F) *	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.

** Oral temperature; no recent hot or cold beverages or smoking.

*** When resting heart rate is between 60 - 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

H. Appendix H: Monitored Anesthesia Care

American Society of Anesthesiologists™

Distinguishing Monitored Anesthesia Care ("MAC") From Moderate Sedation/Analgesia (Conscious Sedation)

Committee of Origin: Economics

(Approved by the ASA House of Delegates on October 27, 2004, and last amended on October 17, 2018)

Moderate Sedation/Analgesia (Conscious Sedation; hereinafter known as Moderate Sedation) is a physician service recognized in the CPT procedural coding system. During Moderate Sedation, a physician supervises or personally administers sedative and/or analgesic medications that can allay patient anxiety and limit pain during a diagnostic or therapeutic procedure. During Moderate Sedation the responsible physician typically assumes the dual role of performing the procedure and supervising the sedation. Such drug- induced depression of a patient's level of consciousness to a "moderate" level of sedation, as defined in the Joint Commission (TJC) standards, is intended to facilitate the successful performance of the diagnostic or therapeutic procedure while providing patient comfort and cooperation. Physicians providing moderate sedation must be qualified to recognize "deep" sedation, manage its consequences and adjust the level of sedation to a "moderate" or lesser level. The continual appraisal of the effects of sedative or analgesic medications on the level of consciousness and on cardiac and respiratory function is an integral element of this service.

The American Society of Anesthesiologists has defined Monitored Anesthesia Care (*see Position on Monitored Anesthesia Care, updated on October 17, 2018*). This physician service can be distinguished from Moderate Sedation in several ways. An essential component of MAC is the periprocedural anesthesia assessment and understanding of the patient's coexisting medical conditions and management of the patient's actual or anticipated physiological derangements during a diagnostic or therapeutic procedure. While Monitored Anesthesia Care may include the administration of sedatives and/or analgesics often used for Moderate Sedation, the qualified anesthesia provider of MAC is focused exclusively and continuously on the patient for any attendant airway, hemodynamic and physiologic derangements. Further, the provider of MAC must be prepared and qualified to convert to general anesthesia. The proceduralist providing moderate sedation may have their attention diverted to their primary focus, the procedure. Additionally, a provider's ability to intervene to rescue a patient's airway from any sedation-induced compromise is a prerequisite to the qualifications to provide Monitored Anesthesia Care. By contrast, Moderate Sedation is not expected to induce depths of sedation that would impair the patient's respiratory function or ability to maintain the integrity of his or her airway. These components of Monitored Anesthesia Care are unique aspects of an anesthesia service that are not part of Moderate Sedation.

The administration of sedatives, hypnotics, analgesics, as well as anesthetic drugs commonly used for the induction and maintenance of general anesthesia is often, but not always, a part of Monitored Anesthesia Care. In some patients who may require only minimal sedation, MAC is often indicated because even small doses of these medications could precipitate adverse physiologic responses that would necessitate acute clinical interventions and resuscitation. The attention of the proceduralist

is focused on the completion of the procedure, not physiologic alterations. If a patient's condition and/or a procedural requirement is likely to require sedation to a "deep" level or even to a transient period of general anesthesia, only a practitioner privileged to provide anesthesia services should be allowed to manage the sedation. Due to the strong likelihood that "deep" sedation may, with or without intention, transition to general anesthesia, the skills of an anesthesia provider are necessary to manage the effects of general anesthesia on the patient as well as to return the patient quickly to a state of "deep" or lesser sedation.

Like all anesthesia services, Monitored Anesthesia Care includes an array of post-procedure responsibilities beyond the expectations of practitioners providing Moderate Sedation, including assuring a return to baseline consciousness, relief of pain, management of adverse physiological responses or side effects from medications administered during the procedure, as well as the diagnosis and treatment of co-existing medical problems.

Monitored Anesthesia Care allows for the safe administration of a maximal depth of sedation in excess of that provided during Moderate Sedation. The ability to adjust the sedation level from full consciousness to general anesthesia during the course of a procedure provides maximal flexibility in matching sedation level to patient needs and procedural requirements. In situations where the procedure is more invasive or when the patient is especially fragile, optimizing sedation level is necessary to achieve ideal procedural conditions.

In summary, Monitored Anesthesia Care is a physician service that is clearly distinct from Moderate Sedation due to the expectations and qualifications of the provider who must be able to utilize all anesthesia resources to support life and to provide patient comfort and safety during a diagnostic or therapeutic procedure.