CONCENTRIC ANALGESICS

OFFICIAL TITLE:

A Phase 2, Randomized, Double-blind, Placebo-controlled Safety, Pharmacokinetics and Efficacy Study of CA-008 in Subjects Undergoing Bunionectomy

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Clinical Trial Protocol

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A Phase 2, Randomized, Double-blind, Placebo-controlled Safety, Pharmacokinetics and Efficacy Study of CA-008 in Subjects Undergoing Bunionectomy

Investigational Product: CA-008 by Injection/Instillation

IND: 129-114

Concentric Analgesics, Inc.

SIGNATURE PAGE

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1. KEY PERSONNEL CONTACT INFORMATION

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2. TABLE OF CHANGES PROTOCOL VERSION 1.1 TO VERSION 1.2

In lieu of an Administrative Protocol Clarification Letter to respond to requests from the various participating sites' additional questions, it was elected to proceed with this administrative amendment to provide improved readability and clarity to ensure proper conduct of the study.

Material change made (page #s are for Protocol V1.1)	**Rationale**
P7, P40 (Section 8.1.3), P53 (Section 10.2.1): Multimodal analgesia – reduced the number of doses of ketorolac and acetaminophen allowed by the protocol from 3 to 1	Prior to receipt of the final data from the Phase 1 bunionectomy study, there was a concern that the Mayo block alone would not be sufficient to control pain sufficiently in the immediate hours after surgery before the onset of benefit from the active product. However, this turned out not to be the case, and to reduce any confounding from the use of additional doses of systemic analgesics on the primary endpoint after the Mayo block wore off, it was elected to make this change.
Note that all other changes are administrative in nature and do not materially affect the conduct of the study.	
Administrative changes made	**Rationale/Clarification**
P3: added additional names and contact information for Lotus Project Mgr and Aspire IRB	n/a
P8 (Synopsis), P42 (Section 8.1.4): clarification on outpatient multimodal analgesia dosing and timing of the 12h period before discharge triggering the potential need for a 2-day oxycodone prescription for pain control	Rescue analgesia as an outpatient should be p.r.n. whether for ibuprofen or acetaminophen. If the subject requires opioid rescue in the period after T84h regardless of the time of discharge this triggers the need for a prescription for oxycodone. Refills are per investigator discretion.
P11 (Synopsis), P49: clarification of Exclusion criterion 4d to allow antibiotics for treatment if necessary after surgery to treat an AE; 4e refers to steroid inhaler for allergy treatment	If the investigator feels that antibiotics are appropriate treatment for an AE this should be done and should not automatically trigger an ET. Antibiotic prophylaxis is allowed is routinely performed per site standard of care. Language was added to include the use of steroid inhaler for treatment of asthma as well.
P11 (Exclusion 6.a), P49 (Exclusion 6.a), P61 (Section 11.5.2): clarification on positive drug screen	There is the potential for confusion with Exclusion 6.a and language on P61: *"If any of these tests are positive (note exception for THC below* [referring to Exclusion criterion 6.a]*), the subject will not be allowed further participation."* Added explanatory note to this exclusion criterion. 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.
P13 (Synopsis), P58 (Section 11.4.1): clarification on guidelines for "ambulation"	In the immediate postoperative period, partial weightbearing on transfers to/from bed/wheelchair may be all that is appropriate for "ambulation". Once closer to discharge from the inpatient facility and during the outpatient period, subjects should be instructed to walk about 10 yards to assess pain with "ambulation".
P14(Synopsis), P20 (Schedule of Events): clarification on timing of specific protocol assessments	The physical examination, neurosensory examination and surgical site assessment need not be collected at 24h after study treatment injection. Clinical laboratory tests should be collected at screening and 96h.

	Urinalysis is performed only at screening and 96h. No need for repeat screening labs on day 0 (surgery day) unless it was not performed during screening. Daily temps can be recorded along with vital signs per site SOPs at 1, 2, 4, 6, 12, 24, and every 8 h thereafter until discharge from the inpatient facility (if awake at the time of assessment between hours of midnight and 6 a.m.)
P14 (Synopsis): clarification on time windows	Lab collection window for 24h and 96h are ±30 min. Neurosensory examination at 96h is ±4 h, but prior to discharge from the inpatient facility.
P14 (Synopsis): clarification on coagulation tests	These tests are not required.
P20 (Schedule of Events), P62 (Section 11.5.6): clarification on subject weights	Weight assessments are not needed on day 15 and 29, or day 36 if this visit is necessary.
P38 (Section 8.1); regarding timing of enrollment of PK subjects	Removed language regarding a "smooth startup"
P39 (Section 8.1.2), 44 (Section 8.1.8): clarification on vital signs	Site is to collect temperature, BP, HR and RR.
P42 (Section 8.1.4): clarification on topical ice and cooling packs	Use of topical cooling is not allowed during the inpatient stay but is allowed for treatment of areas remote from the surgery site. It may be used as an outpatient on the surgical site but subjects should be instructed to report this as a concomitant treatment that may be in response to an AE.
P52 (Section 10.1.2): clarification on IP preparation	Any language on preparation has been removed and the investigator is referred to the Pharmacy Manual to avoid potential conflicting language.
P57 (Section 11.4.1): clarification on medical history documentation	Only medical history deemed pertinent to the study by the investigator need be assessed for clinical significance.
P57 (Section 11.1.5): clarification on contraceptives to prevent pregnancy	Under double-barrier methods, the protocol specifies that this is a "male condom in addition to a diaphragm of a contraceptive sponge." Spermicidal contraceptives are acceptable as part of a double-barrier contraceptive program (i.e., spermicidal jellies, foams or gels) in any combination per discretion of the investigator. When considering male inclusion, they should be qualified by Inclusion #3.
P59 (Section 11.1.4): clarification on rescue usage documentation after discharge	Rescue consumption should be recorded through the day 15 visit when diaries are collected.
P59 (Section 11.1.3): clarification on who may perform the IGE	The IGE assessment may be performed by any of the investigators listed on the 1572.
P61 (Section 11.5.5): clarification on timing of ECGs	ECGs are required only at screening and 24h.
P62 (Section 11.5.7): clarification on frequency of follow up for AEs	Regarding the sentence "…they will be evaluated and graded for severity regularly until resolution." The word "regularly" in this context should be clarified to mean as deemed per standard of care by the investigator. Contact the medical monitor for any questions and guidance for follow-up if this occurs.
P63 (Section 11.5.9): clarification on serious AEs and AEs deemed possibly related	P63, "Serious AEs and AEs that have been designated as possible related to study treatment will be followed until resolution or stabilization."

	To clarify, AEs that are either possibly or probably related should be followed.
P64 (Section 11.6.3.1): clarification on PK draw instructions	The language on handling of PK samples has been removed and the investigator is instructed to refer to the Clinical Laboratory Manual.
P81 (Section 15.1.3): clarification on documentation of ICF process	Protocol language: *"the time that informed consent is obtained must be documented;"* however the ICF time will not be required per the IRB-approved ICF template.
P44 (Section 8.1.7), P45 (Section 8.1.9), Table 1 Schedule of Events	Requirement for x-rays of the operated foot was inadvertently left off and should be included in the D29 visit (and if not done on D29, perform x-rays on D36 visit) and the Schedule of Events Table
Throughout the Protocol, clarification on timing of NRS assessments and impact of subject sleeping and use of rescue.	Rewritten for clarity
P10, 48: clarification on exclusion criterion 3 regarding arrhythmia	The word "significant" at the beginning of the exclusion criterion applies to arrhythmia and is subject to clinical discretion.
P61 (Section 11.5.8): clarification on location and timing of neurosensory testing	Language in the protocol states that *"The exam will involve the dorsal aspect of the great toe, midway between the nail fold and the distal interphalangeal joint;"* however, the assessment and of the foot should focus on the area *proximal* to the surgical site, i.e. the area over the dorsum of the foot near the great toe. Additional language removed regarding changes within 3 days of end of surgery (EOS).
P71 (Section 12.1.3.1.)Serious Adverse Event Reporting: Added CRO medical Monitor information for Jon L. Ruckle, MD, CPI	CRO Medical Monitor and 24/7 Emergency contact information needed

3. PROTOCOL SYNOPSIS

Sponsor:	Concentric Analgesics, Inc. (Concentric) One Ferry Building, Suite 255 San Francisco, CA 94111
CRO:	Lotus Clinical Research (Lotus) 100 W. California Blvd., Unit 25 Pasadena CA 91105
Protocol Number:	CA-PS-201
IND#	129-114
Study Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled Safety, Pharmacokinetics and Efficacy Study of CA-008 in Subjects Undergoing Bunionectomy
Study Treatment:	CA-008, the investigational product (IP), and matching placebo vehicle are collectively referred to as study treatment
Planned Study Center(s):	≈ 3 US sites
Indication:	Acute postsurgical pain
Sample Size:	N ≈ 144 (target ≈ 36 subjects per treatment arm)
Population:	Adults ages 18 to 75 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 83 days: Screening period from 45 days prior to surgery (D-45) to D29±2 (week 4 or W4) Study Completion Visit, and if necessary to assess any ongoing safety issues, a D36±2 Safety Follow-Up Visit. Note that D0 is the day of surgery and study treatment administration.
Study Design:	This is a Phase 2, multi-center, randomized, double-blind, placebo-controlled, parallel design study evaluating a single dose of one of three CA-008 dose groups vs. placebo injected during an elective BUNX under light to moderate sedation supplemented by a Mayo block with bupivacaine hydrochloride (HCl) and a multimodal analgesia regimen, including ketorolac and acetaminophen, and access to rescue medication (oxycodone). The study will be conducted in two parts: • Inpatient period which continues to 96h after completion of study treatment injection (T0) or T96h. • Outpatient period which begins on discharge from the inpatient unit

	through various follow up visits to D29±2 (W4) after surgery, or if necessary for ongoing safety assessments, to D36±2 (W5).
Study Objectives:	**Primary Objective:** • To evaluate the efficacy of a single intraoperative administration of CA-008 vs placebo in subjects undergoing an elective BUNX. **Secondary Objectives** • To evaluate the safety and tolerability of a single intraoperative administration of CA-008 vs. placebo in subjects undergoing an elective BUNX. • To evaluate the PK profile of a single intraoperative administration of CA-008 vs. placebo in subjects undergoing an elective BUNX. • To explore the efficacy of various doses of CA-008 administered intraoperatively in subjects undergoing an elective BUNX. **Exploratory Objectives** Pharmacoeconomic benefits from administration of CA-008 vs. placebo in subjects undergoing an elective BUNX.
Study Treatment Dosing Schedule:	Study treatment is to be administered intraoperatively as a single administration via "surgical site" infiltration / instillation prior to wound closure.
"Surgical Site":	"Surgical site" is defined as the area extending approximately 2-3 cm in all directions (lateral/medial/proximal/distal) from the incision site and surrounding tissues which may be affected by the infiltration of the Investigational Product (IP).
Anesthesia:	The surgery will be performed under light to moderate sedation (what constitutes this level of sedation and the additional anesthetic medications used per discretion of the anesthesiologist) and a Mayo block to produce surgical anesthesia and postoperative analgesia. After administering light to moderate sedation, but prior to surgery, perform a Mayo block by infiltrating 0.5% bupivacaine hydrochloride (up to 30 mL total volume, 150 mg) proximal to the planned surgical incision. The Mayo block should be performed 15-30 minutes prior to study treatment dosing.
Injection of Study Treatment:	Prior to wound closure, study treatment will be injected/instilled into the soft tissues and osteotomy surgical sites with a total volume of 14 mL of study treatment as follows: • CA-008: 3 doses: 0.7, 2.1 and 4.2 mg in 14 mL volume (concentrations: 0.05, 0.15, 0.3 mg/mL) • Placebo: CA-008 vehicle using the same 14 mL volume

	Study treatment will be injected/instilled into the surgical site as follows: • Instill 2 mL at cut bone sites prior to fixation • 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 Note that T0 is the time that the study treatment injection/instillation is completed.
Postoperative Multimodal Analgesia Regimen during the Inpatient Period:	In addition to the Mayo block noted above, a multimodal analgesia regimen will include the following during the immediate postoperative period: • Ketorolac 30 mg IV (a non-steroidal anti-inflammatory drug (NSAID) to be administered intraoperatively before end of surgery (EOS). Per investigator discretion, adjust the ketorolac dose as necessary for subject age and medical condition. • Acetaminophen 1000 mg IV to be administered intraoperatively before EOS. After the above have been administered, no additional NSAIDs or acetaminophen are to be administered during the inpatient phase of the study through T96h.
Postsurgical Care:	Subjects will be monitored for 96 hours after completion of study treatment (through T96h) at the trial site as an inpatient. Safety and efficacy evaluations will be performed, and blood drawn for pharmacokinetic (PK) assessments in a portion of enrolled subjects. 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 through D29/W4 for various safety and efficacy assessments, and if necessary for safety follow up, D36/W5 or longer if needed to establish a new baseline for an AE.
Rescue Medication during the Inpatient Period:	Additionally, the following rescue medication are available to subjects and may be administered for any moderate to severe breakthrough pain at any time during the inpatient period: • PO oxycodone 5 mg prn q2h in the first 12 hours after surgery for moderate or severe pain (≥ 4) as reported by subjects using the 0 to 10 numerical rating scale of current pain intensity (NRS) • PO oxycodone 5 mg prn q4h from 12 to 96 hours after surgery for

	moderate or severe pain (NRS ≥ 4) 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.
Multimodal Analgesia and Rescue Medication 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 medical judgment to manage any residual or breakthrough postsurgical pain through D29/W4. Administration of rescue medication should be based on T0. Outpatient period: D4 through D29/W4, if needed for pain management, the following oral over-the-counter (OTC) analgesics will be recommended for subjects to self-administer (note that these medications will not be provided by the sponsor): • NSAID (e.g., ibuprofen 200 – 400 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 1-2 500 mg tablets prn up to tid or 650 mg prn up to qid (3g daily maximum limit) If a subject is still requiring opioid rescue in the 12h prior to discharge from the inpatient unit (i.e., from T84h on regardless of whether discharge is delayed), then prescribe no more than 6 tablets (1 PO tid prn) of oxycodone 5 mg for the initial outpatient period with the number of tablets dispensed and refills as needed per investigator discretion. 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.
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 - 75 years old, inclusive, and American Society of Anesthesiology (ASA) physical Class 1, 2 or 3 at the time of randomization (Appendix 1A). 2. Plan to undergo an elective primary unilateral first metatarsal Bunionectomy repair, without collateral procedure or additional surgeries, to be performed under light to moderate sedation with regional anesthesia.

	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 ≤ 40 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. For the portion of subjects who will participate in the PK analyses, be willing to undergo 17 blood draws for PK assessments at various time points during the surgery and the following 24 hours.
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, bupivacaine HCl, ketorolac, acetaminophen 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 5) 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, subjects will be randomized and baseline evaluations will be performed prior to surgery. 3. **Surgery D0**: BUNX procedure is performed under light to moderate sedation (what constitutes this level of sedation and the additional anesthetic medications used per discretion of the anesthesiologist) and Mayo block; study treatment is injected/instilled prior to wound closure with T0 defined as the time of study treatment completion of administration. If a subject is to participate in the PK study, assessments are to be done per protocol-specified time points through T24h. 4. **Post-surgery T0 to T96h**: Subject remains at the Site Unit for study assessments and PK blood draws. Discharge after T96h assessments with follow up instructions, particularly on diary completion. 5. **Follow Up D8±1 (W1)**: clinic visit for study assessments 6. **Follow Up D15±2 (W2):** clinic visit for study assessments 7. **Follow Up D29±2 (W4):** clinic visit for study assessments and study completion visit, unless follow up for wound healing is needed 8. **If needed follow Up D36±2:** Clinic visit as needed for any ongoing safety issue continuing after the D29 visit 9. **Early Termination (ET):** For subjects who terminate early, an ET visit will be required. Safety and subject-reported outcome assessments will be performed.
Monitored Parameters:	• Treatment-emergent AEs (TEAEs) • Medical history • Clinical laboratory testing, drug and alcohol testing, pregnancy testing • ECGs • X-rays of the surgical site • Surgical wound healing assessments.

	• Physical examination findings • Neurosensory testing of the lower extremity and foot proximal to the surgical incision with contralateral comparison for a control • Blood draws for PK assessments for participating subjects • Pain intensity scores to be assessed at rest and with "ambulation" (standing or walking on transfers to/from bathroom or frank ambulation (for approximately 10 yards) after discharge) • Total postsurgical opioid consumption converted to an oral morphine equivalent dose (MED) • Total OTC analgesic or prescription analgesic consumption • Time to first rescue medication use • Patient global assessment of satisfaction with study treatment • Investigator global satisfaction with overall analgesia performance, and discharge readiness. • Postsurgical health economic outcome assessments
Efficacy Parameter Assessment Times:	1. NRS scores will be assessed as follows: • During the inpatient stay, at T0.5, 1, 2, 4, 6, 8, 12, 16, 20, 24, and every 4 hours (if awake at time of assessment and if no rescue opioid had been administered in the past 4 hours) until discharge from the inpatient unit. • Pain scores may be skipped between the hours of midnight and 6 a.m., but the subject may not miss two consecutive assessments. • An additional NRS assessment must be obtained 4 hours (±15 min) after every rescue dose even if this time point occurs between midnight and 6 a.m. The T12, T24, T48, T72 and T96h assessments must be completed even if the subject is asleep at these times. • During the inpatient stay, starting on postoperative day 1 (after T24): each morning on arising at approximately 0800h (±2h) and each evening prior to bedtime at approximately 2000h (±2h) document the NRS score with partial (e.g., transfers to or from bed or wheelchair) or full ambulation of approximately 10 yards (must document time of assessment). Actual assessment times must be documented. • During the outpatient period, twice daily at approximately 0800h (±3h) and 2000h (±3h) document the NRS score at rest and with ambulation of approximately 10 yards. Note that the actual time of these assessments must be documented in the diary. 2. Total opioid consumption (OC) and daily opioid (rescue medication) consumption in MEDs will be recorded during the inpatient period.

	• Document subject days in which no rescue medication or analgesic consumption is required (opioid free, OF) during the inpatient and outpatient period. • Document daily use of OTC analgesics (and oxycodone if prescribed) during the outpatient period. • Document time to first use of rescue medication (TTFR) after T0 ($TTFR_{after\ T0}$) and first use after 24h ($TTFR_{after\ T24h}$). 3. Patient Global Evaluation (PGE) at T96h prior to discharge, W1, W2 and W4 clinic visits. 4. Investigator Global Evaluation (IGE) at T96h prior to discharge, W1, W2 and W4 clinic visits. 5. Healthcare utilization (HCU) costs defined as an overall summary of costs related to prescription medications, additional visits related to post discharge treatments, particularly for pain crises, and other related outpatient or inpatient treatments D29/W4 or if necessary D36/W5 visits
Safety Parameter Assessment Times:	• Incidence of spontaneous reported TEAEs or SAEs from T0 through D29/W4 or if necessary D36/W5: o TEAEs are defined as AEs occurring post T0 o AEs recorded from the time the informed consent form (ICF) is signed up to D0/T0 will be recorded in medical history. • Surgical site wound status assessments at T96h (prior to discharge from the unit) and then as an outpatient on D8/W1, D15/W2, and D29/W4 or if necessary D36/W5. 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. • Physical examination (PE): complete at screening; interim assessments on D-1 (or D0 prior to surgery if not done on D-1), T96h, and as an outpatient on D8/W1, D15/W2, and D29/W4 or if necessary D36/W5 • Vital signs (heart rate [HR], blood pressure [BP], respiratory rate [RR]) at screening, and T24h, T96h, and as an outpatient on D8/W1, D15/W2, and D29/W4 or if necessary D36/W5. Assess temperature on D-1 or D0 prior to surgery. Daily temps can be recorded along with vital signs per site SOPs at 1, 2, 4, 6, 12, 24, and every 8 h thereafter until discharge from the inpatient facility (if awake at the time of assessment between hours of midnight and 6 a.m.). • Neurosensory testing at site of incision and the skin surrounding the incision will be performed at T96h (prior to discharge from the unit) and then as an outpatient on D8/W1, D15/W2, and D29/W4. 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, 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. • ECGs, standard clinical labs at screening and T96h post-treatment [except as noted for pregnancy test]. The Investigator is responsible for determining if out of range laboratory values are clinically significant or not. All clinically significant values will be recorded in the eCRF and followed until resolution. o ECG at screening and T24h ±2 hr o Hematology at screening and T96h: hemoglobin, hematocrit, white blood cell count with differential, red blood cell count, platelet count, o Blood Chemistry at screening and T96h: Alanine aminotransferase (ALT; SGPT) and Aspartate aminotransferase (AST; SGOT), total bilirubin (TBili), gamma-glutamyl transferase (GGT), blood urea nitrogen (BUN), creatinine, alkaline phosphatase (ALK), lactate dehydrogenase (LDH), sodium, potassium, calcium, chloride 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. o Urinalysis at screening and T96h: including macroscopic analysis and, if indicated, microscopic analysis.
Primary Endpoint:	Weighted sum of pain intensity (SPI) assessments = Area Under the Curve (AUC) of the NRS current pain intensity scores from T0 to 96h at rest ($AUC_{0\ to\ 96h}$).
Key Secondary Endpoints:	The key secondary endpoints are: • Percentage of subjects who do not require opioids or are opioid free (OF) from T0 to T96: $OF_{0\ to\ 96h}$ • Total opioid consumption (in daily oral morphine equivalents) = OC from T0 to T96h: $OC_{0\ to\ 96h}$ • Using NRS at rest: $AUC_{0\ to\ W1}$
Other Endpoints:	• $AUC_{0\ to\ 24h}$, $AUC_{0\ to\ 120h}$, $AUC_{0\ to\ W1\ (walking)}$, $AUC_{0\ to\ W2}$, $AUC_{0\ to\ W2\ (walking)}$, $AUC_{12\ to\ 24h}$, $AUC_{24\ to\ 48h}$, $AUC_{24\ to\ 72h}$, $AUC_{24\ to\ 96h}$, $AUC_{96h\ to\ 120h}$, $AUC_{96h\ to\ W1}$, $AUC_{24h\ to\ W1(walking)}$, $AUC_{96h\ to\ W2}$, $AUC_{96h\ to\ W2(walking)}$ • $OC_{24\ to\ 48h}$, $OC_{24\ to\ 72h}$, $OC_{24\ to\ 96h}$

	• $OF_{24\ to\ 96h}$, $OF_{96h\ to\ W1}$ and $OF_{96h\ to\ W2}$ • $TTFR_{after\ T0}$ and $TTFR_{after\ T24h}$ • Analgesic consumption from T96h to W1 ($AC_{96h\ to\ W1}$) and $AC_{96h\ to\ W2}$ • PGE comparing the %age of subjects reporting "poor" + "fair" vs. "good" + "excellent" responses, and the %age reporting each category of response at W1, W2 and W4 • IGE comparing the %age of those reporting "poor" + "fair" vs. "good" + "excellent" responses, and the %age reporting each category at W1, W2 and W4 • Number and %age subjects with an AE of lack of efficacy (LOE) during the inpatient period: $LOE_{0\ to\ 96h}$ • $HCU_{96h\ to\ W2}$ and $HCU_{96h\ to\ W4}$
Safety Endpoints:	The following safety endpoints will be evaluated: • Incidence of TEAEs or treatment-emergent SAEs from D0/T0 through D29: Note that all AEs will be recorded from the time the informed consent form (ICF) is signed through D29 (or D36 as applicable). TEAEs are defined as AEs occurring post T0 (end of study treatment infiltration). • Surgical site assessment / wound evaluations to assess for atypical skin reactions, e.g., erythema, pain, pruritus, bruising, swelling, bruising or other skin changes, should be evaluated and graded for severity and followed regularly until resolution or a stable baseline is achieved. • Physical examination (PE) of the lower extremities and vital signs, including neurosensory testing of both lower extremities o Note that any observed or reported sensory deficit or clinically significant persistent sensory change remote from the immediate surgical site, such as allodynia or hyperalgesia, must be designated as a neurologic AE. Subjects should be followed until resolution or a stable baseline is achieved. o Numbness proximal to the incision need not be considered a neurologic AE since this could occur because of tissue trauma and inflammation from the surgery. • ECG changes from screening to T24h post-treatment • Clinically significant clinical labs changes from screening
Pharmacokinetics:	Approximately 1/3rd of enrolled subjects at each site will participate in the PK study (48 in total; 12 in each treatment group). The PK population will include all subjects who have sufficient concentration-time profiles for estimation of PK parameters. Based upon the PK results from the Phase 1 bunionectomy ascending dose safety study, the time points for whole blood collection will be at baseline (within the 30 min before the start of study treatment dosing), and T5min, T10 min, T15min,

	T30min, T45min, and T1, T1.5, T2, T2.5, T3, T4, T6, T8, T12, T16, and T24h, for a total of 17 samples). Actual sampling times will be used to calculate plasma bupivacaine-derived PK parameters. The following parameters will be estimated using noncompartmental analysis for CA-008, capsaicin and CA-101: • C_{max}: The maximum measured plasma concentration, obtained directly from the data without interpolation • C_{last}: Last observed (quantifiable) concentration • T_{max}: Time of C_{max} • $t_{½}$: The apparent first-order terminal elimination half-life, calculated as $0.693/\lambda_z$ • T_{lag}: Time delay between drug administration and first measurable (above lower limit of quantitation) concentration • T_{last}: Time of occurrence of C_{last} • λ_z: Terminal first-order elimination rate constant • AUC_{0-t}: Area under the plasma concentration-time curve from time 0 to the last measurable concentration (where time is postdose), calculated by the linear trapezoidal method • $AUC_{0-\infty}$: Area under the plasma concentration-time curve, from time of dosing to infinity. • AUC_{last}: Area under the plasma concentration-time curve, from time of dosing to the time of the last measurable concentration
Sample Size Justification:	In the previously completed Phase 1 ascending dose safety study in bunionectomy (CA-008 vs. placebo), the mean difference between CA-008 (all dose groups combined) and placebo for the $AUC_{24 \text{ to } 96h}$ was -120. The standard deviation (SD) estimates for the six treatment arms in this study ranged from 70 to 190 with a median SD of 108. For the primary endpoint ($AUC_{0 \text{ to } 96h}$), the true treatment difference between the 4.2 mg CA-008 group and the placebo group is assumed to be equal to -100 and the assumed true SD is equal to 130. For these assumptions, and based on the use of a two-sided, two-sample comparison of means at the alpha=0.05 level of significance, a sample size of 36 subjects per arm will provide 90% power. Thus, the planned total sample size is 144 subjects.
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 study treatment. • The PK Population will include all subjects who receive a full dose of study treatment and complete all PK assessments through the T6h timepoint.

	Subjects who fail to complete these PK assessments will be replaced. • The intent-to-treat (ITT) population will include all subjects as randomized to study treatment. The modified intent-to-treat (mITT) Population will include all subjects who receive a full dose of study treatment and complete the first 3 pain assessments (through T2h). • Inpatient study completers (Inpatient Completers) will include all subjects who receive a full dose of study treatment and complete the inpatient assessment period (through T96h). • Study completers (Study Completers) will include all subjects who receive a full dose of study treatment and complete the entire study period through D29±2/W4. Subjects who elect to discontinue study participation during the inpatient phase of the study, will be asked to continue with assessments through T96h if they have not elected to withdraw from all aspects of study participation. Subjects who elect to discontinue participation prior to D8 (W1) 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 safety assessments and baseline characteristics will be summarized using the Safety Population. PK and efficacy analyses will be performed using the PK and mITT Populations, respectively. Additional efficacy analyses will be performed on the ITT, Inpatient Completer and Study Completer Populations. All summaries will be grouped by the actual treatment received. Each active dose cohort will be presented separately, along with a combined active dose group.

4. TABLE 1. SCHEDULE OF ASSESSMENTS

Assessment	**Screening**	**In Patient**							**Follow-Up**				**Unscheduled Visit**	**Early Termination**
		Prior to Surgery	Surgery	Post-Surgery	24h	48h	72h	96h						
Study Day	-45 to -1	0	0	0	1	2	3	4	8±1 days	15±2 days	29±2 days	36±2 days[1]		
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/Randomize		X												
Demographics	X													
Subject Pain Assessment Training	X													
Surgery			X											
Study treatment Infiltration/instillation			X											
Pregnancy Test	X[2] (serum)	X[2] (urine)												
Vital Signs	X	X		X[3]	X[3]	X[3]	X[3]	X[3]	X	X	X			X
Physical Examination[4]	X[4]	X[4]						X[4]	X[4]	X[4]	X[4]			X
12-Lead ECG	X				X[5]									
Surgical Site assessment								X[6]	X	X	X	X	X	X
Neurosensory Exam	X							X[7]	X	X	X	X	X	X
Blood draw for hematology and serum chemistry	X	X[8]						X[8]						
Urine sample for urinalysis	X	X						X[8]						
X-ray of surgical site	X										X			X
Concomitant Medication Assessment	X	X		X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NRS pain assessments				X[9]	X[9]	X[9]	X[9]	X[9]	X	X				X
Subject home diary record (NRS)								X	X[10]	X[10]				X
Paper Diary (review, distribution and/or collection)								X[11,12]	X[11,12]	X[13]				X

Assessment	Screening	In Patient							Follow-Up				Unscheduled Visit	Early Termination
		Prior to Surgery	Surgery	Post-Surgery	24h	48h	72h	96h						
Study Day	-45 to -1	0	0	0	1	2	3	4	8±1 days	15±2 days	29±2 days	36±2 days[1]		
Subject home diary (analgesic consumption)								X	X[13]	X[13]				X
Dispense outpatient opioid rescue if needed								X[14]						
PGE assessment								X	X	X	X			X
IGE assessment								X	X	X	X			X
Blood draw for PK analysis		X		X[15]	X[15]									

1. Day 36 visit will occur if insufficient wound healing is assessed by the Investigator at the Day 29 visit.
2. Note pregnancy tests are for FCBP; urine pregnancy test is to be performed within 24 hours of scheduled surgery
3. Vital signs: 1, 2, 4, 6, 12, 24 and every 8 hours thereafter (if awake at time of assessment between the hours of 00:00 and 06:00) until discharge from the inpatient unit (may not miss two consecutive assessments). 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.
4. A complete medical history and physical examination including all major body systems will be performed at Screening. In addition, at the following times, an interim medical history and targeted physical examination will be performed prior to surgery (if not done on D-1), and to capture changes after Surgery, at 96 hours (within 4 hours of discharge), and Day 8, Day 15 and Day 29 after the administration of study medication or if the subject terminates early, at that time if allowed. Body weight (kg), in indoor clothing, but without shoes, will be measured at Screening, at 96 hours and Day 29, or at the time of discontinuation. Height (in cm) will be measured and BMI will be calculated at Screening only.
5. Post-Surgery ECG should be performed at 24 hours (±2 hours) after study medication administration
6. Surgical Site assessment: 96 hours (±4 hours) after study medication administration but prior to discharge from the inpatient unit
7. Neurosensory Exam of the Foot / Great toe (bilateral): 96 hours after study medication administration but within 4 hours of discharge from the inpatient unit
8. Clinical Laboratory tests (chemistry, hematology, and urinalysis) should be performed at screening (note if not done during screening, then perform prior to surgery) and prior to discharge from the inpatient unit (Lab collection window for 96h is ±30 min)
9. NRS pain assessments during the inpatient stay, at T0.5, 1, 2, 4, 6, 8, 12, 16, 20, 24, and every 4 hours (if awake at time of assessment and if no rescue opioid had been administered in the past 4 hours) until discharge from the inpatient unit. Pain scores may be skipped between the hours of midnight and 6 a.m., but the subject may not miss two consecutive assessments. An additional NRS assessment must be obtained 4 hours (±15 min) after every rescue dose even if this time point occurs between midnight and 6 a.m. The T12, T24, T48, T72 and T96h assessments must be completed even if the subject is asleep at these times. 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.
10. 2x/day through Day 15
11. Review Subject Diary instructions with subject
12. Dispense Subject Diary
13. Collect Subject Diary Data
14. Dispense no more than 6 tablets of oxycodone 5 mg tablets for use tid prn (although # tablets and refills per investigator discretion).
15. Collect blood samples if subject is participating in the PK study. The time points for collection are at baseline (before dosing), and at T5min, T10 min, T15min, T30min, T45min, and T1, T1.5, T2, T2.5, T3, T4, T6, T8, T12, T16, and T24h (a total of 17 samples). There will be a ±2-minute window allowed for the 5 to 15-minute collections, a ±5-minute window allowed for collections T30 min through T4h, and a ±15-minute window for collections after T4 hours.

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6. 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

Abbreviation	Term
FIH	First-In-Human
FCBP	Female of child-bearing potential
FSH	Follicle Stimulating Hormone
G	Gram
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
H or HRS	Hours
HCl	Hydrochloride
HCU	Health care utilization
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
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

Abbreviation	Term
OTC	Over-the-counter
PE	Physical examination
PGE	Patient Global Evaluation
PHN	Postherpetic neuralgia
PI	Principal Investigator
PK	Pharmacokinetic[s]
PO	Per oram (oral)
PRN	Pro re nata (as needed)
PT	Prothrombin time
QID	Quater in die (four times daily)
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SOC	System Organ Class
SNRIs	Serotonin-norepinephrine reuptake inhibitors
SSRIs	Selective serotonin reuptake inhibitors
T#	Time in hours after completion of study medication dosing (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

7. INTRODUCTION

7.1. Background

Concentric Analgesics, Inc. (Concentric) is developing CA-008 to provide up to 96-hour relief of post-surgical pain following a single local administration. 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. Based upon this mechanism of action, it is thought that the local infiltration of a TRPV1 agonist into a surgical site prior to wound closure will result in a meaningful reduction of post-surgical pain that lasts days to weeks. This improved long-term pain relief, particularly in combination with infiltration of local anesthetics, may help reduce the need for supplemental opioid use after surgery. The capsaicin pro-drug CA-008 has been developed for local infiltration to improve upon the physicochemical properties of capsaicin while providing equivalent local analgesia.

Capsaicin formulations in relatively low concentrations (0.025 to 0.25%) are marketed as over-the-counter (OTC) products (e.g., Zostrix®) under a tentative final monograph for external analgesics (proposed in the Federal Register 8 Feb 1983; vol 48, No. 27; proposed for 21 CFR 348.12). These formulations include topical ointments, nasal sprays (Sinol-M®) and dermal patches to relieve pain. For example, the Qutenza® (capsaicin) 8% dermal patch (Acorda Therapeutics) was approved in 2009 in the US for the management of neuropathic pain associated with postherpetic neuralgia (PHN). Note that each Qutenza patch contains 179 mg of capsaicin (640 mcg/cm^2) (Qutenza PI).

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 for chronic osteoarthritis and Morton's neuroma (see http://centrexion.com/our-pipeline/). Anesiva, Inc. previously had an early stage program for intraarticular injection for osteoarthritis as well as a late-stage program (Adlea™) evaluating capsaicin instillation during surgery for the management of post-surgical pain. Capsaicin, however, is virtually insoluble in aqueous media or local anesthetic solutions. Anesiva's

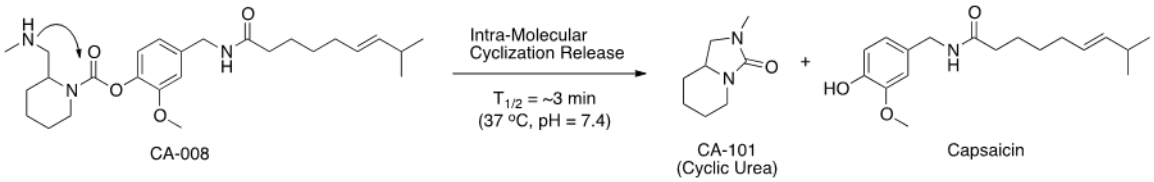
formulation was solubilized capsaicin in polyethylene glycol (Hartrick 2011) and it was instilled in the open surgical site, and after waiting for 5 minutes, was removed via surgical suction. This route of administration was inconvenient and limited exposure of capsaicin to the exposed surfaces of cut tissue and bone.

7.1.1. 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.

Capsaicin, however, is virtually insoluble in aqueous media or local anesthetic solutions which means that capsaicin formulations tend to be quite hydrophobic making them hard to inject and less likely to permeate surgical site tissues resulting in poor target engagement. Anesiva, which had been developing capsaicin for the management of post-surgical pain and osteoarthritis, solubilized capsaicin in polyethylene glycol (Hartrick 2011). The product was instilled into the open surgical site and after waiting for 5 minutes, was removed via surgical suction. This route of administration was inconvenient and limited exposure of capsaicin only to the exposed surfaces of cut tissue and bone.

CA-008 was created to improve delivery of capsaicin without having to account for its poor solubility profile in tissues. 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 CA-101 (Cyclic Urea) Capsaicin

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 and it was shown to be inactive. While not a known compound in the clinical literature, its safety was evaluated in all nonclinical studies with CA-008. The toxicokinetic profiles for CA-008, CA-101, and capsaicin were determined in GLP safety studies and in a Phase 1 ascending dose safety study in patients undergoing bunionectomy.

7.1.2. Capsaicin Metabolism and Clearance

The most common route of human capsaicin exposure is ingestion in spicy foods, like chili peppers. Capsaicin is absorbed by a nonactive process from the stomach and whole intestine (Leelahuta 1983; Kawada 1984), where the total absorption capacity varies between 50 and 90% in different animal studies. Maximum blood concentration is seen about an 1 h after ingestion (Suresh 2010). To a certain extent, capsaicin is absorbed in its intact form, and the amount in the portal blood is measurable by radiolabeling capsaicin (Kawada 1984). A minor part of capsaicin metabolism occurs in the small intestine epithelial cells (Kawada 1984). A study by Chaiyasit and colleagues investigated the human PK profile of 5 g of orally ingested C. frutescens, approximately 26.6 mg of capsaicin or the equivalent of eating 15 habanero peppers (Chaiyasit 2009). Capsaicin could be detected in plasma after 10 min, and the C_{max} was 2.47 ng/ml, T_{max} was 47.1 min, t½ was 24.9 min, and after 90 min, capsaicin could not be detected.

Capsaicin metabolism after oral administration is believed to be similar in the human, rat, and canine microsome. Once absorbed, capsaicin is heavily protein-bound and most is metabolized in the liver. *In vitro* human investigation with hepatic microsomes to investigate involvement of phase 2 metabolisms, showed that capsaicin was rapidly metabolized, producing three major metabolites, 16-hydroxycapsaicin, 17-hydroxycapsaicin, and 16,17-hydroxycapsaicin, whereas vanillin was a minor metabolite (Chanda 2008). This suggests that cytochrome P450 enzymes minimally participate in capsaicin biotransformation in skin compared with their key role in hepatic metabolism.

Animal studies have shown that capsaicin metabolites are eliminated mainly by the kidneys, with a small untransformed proportion excreted in the feces and urine (Leelahuta 1983, Kawada 1984, Surh 1995). It is excreted in both free form and capsaicin glucuronide form. In vivo animal studies have shown that after 48 h, only a small amount (<10%) of an administered dose was found in feces (Leelahuta 1983, Kawada 1984).

7.1.3. Capsaicin PK

Other than by ingestion, most human exposure to capsaicin is from topical administration therapeutically with ointments or patches as noted above or for self-defense or noxious effects with pepper spray. Topical capsaicin in humans is rapidly absorbed through the skin (Hayman 2008). Additionally, capsaicin is often used in basic science studies, such as in experimental pain studies (animal and human), where the main administration method is intradermal or intraplantar injections.

Systemic PK data for topical capsaicin is somewhat limited. In 173 patients with PHN, painful human immunodeficiency virus-associated neuropathy and painful diabetic neuropathy, the highest C_{max} observed in any patient was 17.8 ng/mL (Babbar 2009). Sparse sampling resulted in most patients not having quantifiable levels. Plasma concentrations were fitted adequately using a 1-compartment model with first-order absorption and linear elimination. Capsaicin levels

declined very rapidly, with a mean population elimination half-life of 1.64 hours. Mean area under the curve and C_{max} values after a 60-minute application were 7.42 ng*h/mL and 1.86 ng/mL, respectively. Ninety-minute applications of Qutenza resulted in AUC and C_{max} values approximated 1.78- and 2.15-fold higher than those observed after a 60-minute application. Due to capsaicin's TRPV1 mechanism of action of inducing a prolonged functional depolarization, the duration of pain relief extends well beyond the relatively limited time of its exposure to the target peripheral site.

7.1.4. Background Information on the Use of Capsaicin in Analgesia

While capsaicin is well understood to have long lasting analgesic benefits, it has shown a limited effect in the initial hours following administration in both nonclinical (Dudley-Cash 2012) and clinical studies (Pollak 2009, Savage 2009). In Phase 3 clinical trials conducted by Anesiva, capsaicin instillation demonstrated statistically significant reductions in cumulative pain and opioid use over 48 hours, but failed to show a difference with shorter periods of observation (e.g. pain AUC 4-32 hours) (Hartrick 2011, Pollak 2009). Based upon a post hoc review of these data that periods longer than 48 hours are necessary to demonstrate capsaicin's benefit as the treatment difference increases during this period.

Activation of TRPV1 receptor with an agonist such as capsaicin immediately results in transient hyperalgesia, erythema, and localized burning sensation followed by a functional desensitization that results in reduction in noxious pain stimuli without affecting evoked pain sensations or muscle control. This desensitization can lead a sustained analgesia for a week or longer. Given CA-008's rapid conversion to capsaicin, a similar profile (PK and pharmacodynamic or PD) would be expected following the administration of CA-008 alone.

It is anticipated that CA-008 will be used with standard of care or best practice multimodal analgesia (systemic medications +/- local anesthetic administered by regional block or local infiltration) appropriate for the surgery in question to manage pain for the first 24 hours after which the TRPV1 agonism will provide pain relief. Concentric is planning to confirm the efficacy of CA-008 as monotherapy in combination with standard of care systemic analgesic therapy or proximal regional nerve blocks for treatment of post-surgical pain for periods of up to 96 hours or longer.

7.1.5. Acute Post-Operative Pain Management: the unmet need

A clinical practice guideline on the management of post-surgical pain from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council was published recently in the Journal of Pain (Chaiyasit 2009, Chanda 2008, Chou 2016). This publication presents evidenced-based recommendations for preoperative, intraoperative, and postoperative interventions and pain management strategies. As summarized in this guideline, more than 80% of patients who undergo surgical procedures

experience acute post-surgical pain and approximately 75% of those with post-surgical pain report the severity as moderate, severe, or extreme (Apfelbaum 2003; Gan 2014). Evidence suggests that fewer than half of patients who undergo surgery report adequate post-surgical pain relief (Apfelbaum 2003). Inadequately controlled pain negatively affects quality of life, function, and functional recovery, the risk of post-surgical complications, and the risk of persistent postsurgical pain (Kawada 1984, Kehlet 2006). The publication recommends strategies for the management of post-surgical pain ranging from preoperative education and perioperative pain management planning, multimodal therapies, physical modalities, cognitive-behavioral modalities, systemic pharmacologic therapies, local and/or topical pharmacologic therapies, use of peripheral regional anesthesia, and neuraxial therapies, all depending on the nature of the patient and surgical procedure.

Despite these options, management of pain in patients after surgery remains insufficient (Pogatzki-Zahn 2012), and there is no ideal way to provide continuous, effective pain relief beyond the immediate hours after surgery. Systemic pharmacological therapies remain the mainstay of post-surgical pain relief, with opioids a key component of the arsenal, especially for moderate-to-severe pain. Systemic opioids are effective, but increase cost and morbidity due to known safety issues such as respiratory depression, gastrointestinal dysfunction, and abuse, and produce a heavy societal burden. Non-opioid analgesics including acetaminophen, nonselective NSAIDs and selective COX-2 inhibitors are useful for the treatment of light-to-moderate pain and are part of a balanced multimodal pain treatment (Pogatzki-Zahn 2012). These products also have known safety risks. The use of peripheral regional anesthetic techniques has been shown to be effective as a component of multimodal analgesia for management of post-surgical pain associated with several surgical procedures, including thoracotomy, lower extremity joint surgery, shoulder surgery, cesarean section, hemorrhoid surgery, and circumcision. This approach has limitations including the increased cost and intensively of care and the potential for increased incidence of patient falls.

Site-specific infiltration techniques utilizing a novel mechanism of action are attractive as a component of multimodal analgesia due to the potential for prevention of post-surgical pain, with lower potential safety risks due to the local nature of administration. Treating pain at its source with local anesthetic, e.g., liposomal bupivacaine (Exparel®), while highly effective, is limited due to its typically short duration of action and the potential for unwanted numbness or motor effects.

7.1.6. Clinical burden

Opioids are used to treat short and long-term pain or other indications, but have side effects and the risk of addiction or abuse. Opioid overdose is a major public health problem in the United States (US) and other countries. In the US, opioid overdose contributes to a significant number of accidental deaths among persons that either misuse or abuse illicit and prescription opioids. It was estimated by the Center for Disease Control that in 2016 more than 40,000 deaths from

prescription opioid analgesics (https://www.cdc.gov/drugoverdose/data/index.html), not including illicit drug use, and this number is expected to continue to increase significantly over time unless something can be done.

Common side effects of opioid administration include sedation, dizziness, nausea, vomiting, constipation, physical dependence, tolerance, and respiratory depression. Physical dependence and addiction are clinical concerns that may prevent proper prescribing and in turn inadequate pain management.

7.1.7. 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 be ingested 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).

A first-in-human study (Study CA-PS-2017-101) evaluated the safety and tolerability of CA-008 in subjects undergoing a unilateral transpositional first metatarsal osteotomy for correction of hallux valgus deformity, more commonly known as a bunionectomy. This study also evaluated PK and preliminary efficacy assessment of CA-008 to inform future studies in our clinical development plan. This study was originally designed to look at 4 different doses of CA-008 (0.5 mg, 1 mg, 2 mg, and 3 mg), however based upon the benign adverse event (AE) profile, a 5th cohort (4.2 mg) was added. Based upon the results from this study we selected 3 doses for this phase 2 bunionectomy study.

Of note, is that no dose limiting toxicity or severe or serious AEs were observed in the study. The maximum tolerated dose was not identified. Table 2 shows the preliminary summary of AEs by CA-008 dose and placebo in the study. Table 3 shows the preliminary by-subject listing of TEAEs by CA-008 dose and placebo in the study (note that the TEAEs designated as possibly related are **bolded**). Due to the desire to complete this phase 2 protocol in a timely fashion, these results are based upon an assessment after the last patient completed the study but prior to database lock in the study by an external biostatistician who was not involved in study conduct. The clinical team at Concentric and the CRO site remained blinded until after database lock.

Table 2. Preliminary Summary of Adverse Events (Study CA-PS-2017-101)

	CA-008						Placebo (8)
Doses (n)	**0.5 mg (6)**	**1.0 mg (5)**	**2.0 mg (6)**	**3.0 mg (6)**	**4.2 mg (6)**	**All Active (29)**	
Subjects w/TEAEs N2 (%)	**4 (66.7%)**	**3 (60.0%)**	**2 (33.3%)**	**3 (50.0%)**	**4 (66.7%)**	**16 (55.2%)**	**4 (50.0%)**
TEAEs n	**8**	**4**	**2**	**3**	**5**	**22**	**6**
"Possibly" Related TEAEs n (%)	**2 (25.0%)**	**0 (0.0%)**	**2 (100%)**	**2 (66.7%)**	**2 (40.0%)**	**8 (36.4%)**	**1 (16.7%)**
Mild TEAEs n (%)	**6 (75.0%)**	**2 (50.0%)**	**0 (0.0%)**	**2 (66.7%)**	**3 (60.0%)**	**13 (59.1%)**	**6 (100%)**
Moderate TEAEs n (%)	**2 (25.0%)**	**2 (50.0%)**	**2 (100%)**	**1 (33.3%)**	**2 (40.0%)**	**9 (40.9%)**	**0 (0.0%)**
Severe TEAEs n (%)	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**
SAEs n (%)	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**

Table 3. Subject Listing of Adverse Events (Study CA-PS-2017-101)

TEAEs Cohort #	Subject # Gender (M/F) Age (y)	Group Inj Date Time	Start Date Time	End Date	PT (if documented)	Severity	Relatedness	Action Taken
1	101-001 F 34	0.5 mg 10/31/17 ~1009h	11/1/17 0055h	11.1.17	Nausea	Mild	Unlikely	None
			11/3/17 1530h	11/4/17	Headache	Mild	Unlikely	ConMed
			11/5/17 1300h	11/10/17	Back pain	Mild	Unlikely	ConMed
1	101-004 F 42	Pbo 10/31/17 ~1148h	11/2/17 1300h	11/2/17	Headache	Mild	Unlikely	ConMed
			11/3/17 0900h	12/4/17	Blepharitis (eyelid dermatitis)	Mild	Unlikely	None
			11/2/17 1004h	12/19/17	**Hyperesthesia (R great toe)**	Mild	**Possible**	None
1	110-007 M 51	0.5 mg 10/31/17 ~0815h	11/13/17 0914h	12/6/17	Muscle strain (lumbar strain)	Mild	Unlikely	ConMed
1	101-011 F 49	0.5 mg 11/13/17 ~0821h	11/14/17 0840	11/14/17	Dizziness	Mild	Unlikely	None
			11/20/17 unk	11/28/17	Skin abrasion (wound foot abrasion)	Mild	Unlikely	None
1	101-024 F 19	0.5 mg 11/15/17 ~1139h	11/16/17 0300h	11/16/17	**Nausea**	Moderate	**Possible**	ConMed
			11/16/17 0300h	11/16/17	**Vomiting**	Moderate	**Possible**	ConMed
2	101-026 F 42	Pbo 11/27/17 ~1322h	11/28/17 0950h	11/28/17	Nausea	Mild	Unlikely	ConMed
2	101-028 F 27	1.0 mg 11/28/17 ~0759h	11/29/17 0511h	11/29/17	Syncope (vasovagal)	Mild	Unlikely	ConMed
2	101-033	1.0 mg	12/1/17	12/1/17	Nausea	Moderate	Unlikely	ConMed

	F 33	11/30/17 ~1040h	0900h					
			12/1/17 1940h	12/1/17	Vomiting	MIld	Unlikely	None
2	101-034 F 43	1.0 mg 11/30/17 ~1127h	12/11/17 0155h	12/11/17	Hypoxia	Moderate	Unlikely	ConMed
3	101-036 F 63	Pbo 12/11/17 ~0853h	12/1/17 2035h	12/1/17	Headache	Mild	Unlikely	None
3	101-040 F 36	2.0 mg 12/11/17 ~0943h	12/18/17 Unk	1/8/18	**Rash (bilateral lower extremity)**	Moderate	**Possible**	ConMed
3	101-042 F 34	2.0 mg 12/12/17 ~0806h	12/14/17 0944h	12/14/17	**Nausea**	Moderate	**Possible**	ConMed
4	101-054 F 26	Pbo 1/15/18 ~0847h	1/15/18 1800h	1/15/18	Dizziness	Mild	Unlikely	None
4	101-055 F 29	3.0 mg 1/8/18 ~1142h	1/9/18 0640h	1/9/18	**Nausea**	Moderate	**Possible**	ConMed
4	101-058 F 34	3.0 mg 1/8/18 ~1416h	1/9/18 1430h	1/10/18	**Headache**	Mild	**Possible**	None
4	101-061 F 59	3.0 mg 1/15/18 ~1035h	1/17/18 0229h	1/17/18	Hypoxia	Mild	Unlikely	ConMed
5	101-068 F 25	4.2 mg 2/12/18 ~1122h	2/12/18 1330h	2/12/18	Nausea	Mild	Unlikely	ConMed
5	101-073 F 44	4.2 mg 2/19/18 ~0729h	2/20/18 0825h	2/27/18	**(wound erythema)**	Mild	**Possibly**	None
			2/19/18 0800h	2/22/18	(constipation)	Moderate	Unlikely	ConMed
5	101-074 F	4.2 mg 2/12/18	2/13/18 0251h	2/13/18	**Hypoxia**	Moderate	**Possibly**	ConMed

	50	~1028h						
5	101-077 F 30	4.2 mg 2/19/18 ~0904h	2/24/18 1730h	2/24/18	Headache	Mild	Unlikely	ConMed

The PK profile was not available at the time of preparation of this protocol, however the preliminary time-concentration values were instructive as to C_{max} and T_{max}. The following preliminary assessments could be made:

- For CA-008, the highest C_{max} value was 1.04 ng/mL and the median T_{max} was 15 minutes. No measurable concentration was identified after 2.5h at the highest dose (4.2 mg) and after 45 min at lower doses. Given the paucity of measurable concentrations at various timepoints in the lower dose cohorts, no assessment of dose proportionality could be made. Note the LLOQ was 0.025 ng/mL.
- For CA-101, the C_{max} value ranged from 3.81 to 19.7 ng/mL with the highest dose and the median T_{max} was 1.5 hours. No apparent dose proportionality was observed. Note the LLOQ was 0.5 ng/mL.
- For capsaicin, the C_{max} value ranged from 0.713 to 5.34 ng/mL with the C_{max} and median T_{max} being highly variable. No apparent dose proportionality was observed. Note the LLOQ was 0.05 ng/mL.

7.2. Study Rationale

CA-008 is being investigated as a potential therapy for treatment of pain following surgery. CA-008 is administered (injected and instilled) directly into the postoperative wound during the surgery. This study is a follow-on placebo-controlled efficacy and safety study which includes assessments of wound healing and a PK study in enrolled subjects.

8. STUDY OBJECTIVES

8.1. Primary Objectives

The primary objective of the study is:

- To evaluate the efficacy of a single intraoperative administration of CA-008 vs. placebo in subjects undergoing an elective bunionectomy (BUNX)

8.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the safety and tolerability of a single intraoperative administration of CA-008 vs. placebo in subjects undergoing an elective BUNX.
- To evaluate the PK profile of a single intraoperative administration of CA-008 vs. placebo in subjects undergoing an elective BUNX.
- To identify the minimally effective and optimal doses of CA-008 to be administered intraoperatively in subjects undergoing an elective BUNX.

9. INVESTIGATIONAL PLAN

9.1. Overall Study Design and Plan

This is a Phase 2, multi-center, randomized, double-blind, placebo-controlled, parallel design study evaluating a single dose of one of three CA-008 dose groups vs. placebo injected during an elective BUNX with a multimodal analgesia regimen including an NSAID and regional Mayo block with bupivacaine. The study will be conducted in two parts:

- Inpatient period which continues to 96h after completion of study treatment injection (T0) or T96h.
- Outpatient period which begins on discharge from the inpatient unit through various follow visits to D29±2 (W4) after surgery, or if necessary for ongoing safety assessments, to D36±2 (W5).

Subjects will be undergoing unilateral transpositional first metatarsal osteotomy for the correction of hallux valgus deformity (bunionectomy or BUNX). The surgery is to be performed under light to moderate sedation anesthesia (what constitutes this level of sedation and the additional anesthetic medications used per discretion of the anesthesiologist). In accordance with standard of care, light to moderate sedation will be supplemented with a Mayo block to produce surgical anesthesia and postoperative analgesia. After administering light to moderate sedation, but prior to surgery, perform a Mayo block by infiltrating 0.5% bupivacaine hydrochloride (up to 30 mL total volume, 150 mg) at least 3 cm proximal to the "surgical site". The Mayo block should be performed at 15-30 minutes prior to study treatment dosing. "Surgical site" is defined as the area extending approximately 2-3 cm in all directions (lateral/medial/proximal/distal) from the incision site and surrounding tissues which may be affected by the infiltration of study treatment.

After the surgery, subjects will be monitored for 96 hours in an inpatient unit. Safety and efficacy evaluations will be performed. After the first week of enrollment, subjects may be enrolled for the pharmacokinetic (PK) portion of the study and have samples drawn prior to CA-008 injection and at various time points over 24h after surgery until the target of 48 PK subjects (12 per treatment group) are enrolled and complete PK assessments. Subjects will be required to meet certain pre-specified criteria prior to discharge.

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

Subjects requiring bunionectomy between the ages of 18 and 75 years, inclusive, will be screened for participation at the study site in the United States within 45 days of surgery/study treatment administration. 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).
- Vital signs and temperature must be obtained after resting (seated/reclined) for ≥ 5 minutes.
- Baseline neurosensory testing
- X-ray of the bunion to be operated on
- Clinical laboratory tests (chemistry and hematology)
- Urine Drug Screening (UDS) and alcohol test (breath or saliva)
- Serum Pregnancy test (FCBP)
- 12-Lead Electrocardiograms (ECGs) will be performed after the subject has been resting in a recumbent/supine position for at least 5 minutes.
- Subject pain assessment training (video and post-test)
- Adverse Event (AE) Assessment

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

9.1.2.1. 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)
- Subject pain assessment training (video only)
- Urine Drug Screening (UDS) and alcohol test (breath or saliva)
- Urine Pregnancy test (FCBP)
- In those subjects participating in the PK study, baseline blood draw for PK analysis prior to surgery (may be done after light to moderate sedation)
- AE Assessment
- Randomize to study treatment

9.1.2.2. Administration of Study treatment

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

- CA-008: 3 doses: 0.7, 2.1 and 4.2 mg in 14 mL volume (concentrations: 0.05, 0.15, 0.3 mg/mL)
- Placebo: CA-008 vehicle (identical to active treatment but without CA-008)

Study treatment will be injected/instilled into the surgical site as follows:

- Instill 2 mL at cut bone sites prior to fixation
- 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

Note that T0 is the time that the study treatment injection/instillation is completed.

9.1.3. Postoperative Multimodal Analgesia and Rescue Medication

Following surgery, subjects will be transferred to the appropriate recovery unit where they will undergo various assessments over the next 96 hours (end of surgery [EOS] to T96h).

In addition to the Mayo block noted above, a multimodal analgesia regimen will include the following during the immediate postoperative period:

- Ketorolac 30 mg IV (a non-steroidal anti-inflammatory drug (NSAID) to be administered intraoperatively before the end of surgery. Per investigator discretion, adjust the dose as necessary for subject age and medical condition.
- Acetaminophen 1000 mg IV to be administered intraoperatively before the end of surgery.

After the non-opioid analgesics noted above have been administered, no additional NSAIDs or acetaminophen are to be administered during the inpatient phase of the study (through T96h).

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

- PO oxycodone 5 mg prn q2h in the first 12 hours after surgery for moderate or severe pain (≥ 4) as reported by subjects using the 0 to 10 numerical rating scale of current pain intensity (NRS)
- PO oxycodone 5 mg prn q4h from 12 to 96 hours after surgery for moderate or severe

pain (NRS ≥ 4)

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.

9.1.4. Postoperative Care Through 96 Hours (T96h)

After surgery, subjects will be monitored for 96 hours (through T96h) at the trial site as an inpatient. Safety and efficacy evaluations will be performed and blood drawn for PK assessments (for the PK study). Subjects will be required to meet standard pre-specified criteria for discharge from the unit. Note that topical ice packs or cooling treatments are prohibited during the inpatient period for use on the foot near the surgical site. Such treatments are allowed to treat conditions remote from the surgical site. After discharge, topical ice packs or cooling treatments may be used over the surgical site or elsewhere.

The schedule of assessments are as follows:

- Perform NRS assessments of current pain intensity:
  - During the inpatient stay, at T0.5, 1, 2, 4, 6, 8, 12, 16, 20, 24, and every 4 hours (if awake at time of assessment and if no rescue opioid had been administered in the past 4 hours) until discharge from the inpatient unit.
  - Pain scores may be skipped between the hours of midnight and 6 a.m., but the subject may not miss two consecutive assessments.
  - An additional NRS assessment must be obtained 4 hours (±15 min) after every rescue dose even if this time point occurs between midnight and 6 a.m. The subject must be awakened if asleep to assess this NRS.
  - The T12, T24, T48, T72 and T96h assessments must be completed even if the subject is asleep at these times.
  - During the inpatient stay, starting on postoperative day 1 (after T24): each morning on arising at approximately 0800h (±2h) and each evening prior to bedtime at approximately 2000h (±2h) document the NRS score with ambulation (partial or full; must document time of assessment). Actual assessment times must be documented.
  - 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.
- Record vital signs: 1, 2, 4, 6, 12, 24 and every 8 hours thereafter (if awake at time of assessment between the hours of 00:00 and 06:00) until discharge from the inpatient unit (may not miss two consecutive assessments). 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. Daily temps can be recorded along with vital signs per site SOPs at 1, 2, 4, 6, 12, 24, and every 8 h thereafter until discharge from the inpatient facility (if awake at the time of assessment between hours of midnight and 6 a.m.).
- Perform interim PE: surgical site assessment and neurosensory exam of the foot proximal to the surgical site with contralateral comparison prior to discharge from the inpatient unit.

- Perform ECG: at 24 (±2) hours after surgery.
- Clinical laboratory tests (chemistry, hematology and urinalysis): at 96 hours prior to discharge from the inpatient unit.
- If the subject is participating in the PK study, obtain whole blood for PK analyses: at baseline (within the 30 min before the start of study treatment dosing), and T5min, T10 min, T15min, T30min, T45min, and T1, T1.5, T2, T2.5, T3, T4, T6, T8, T12, T16, and T24h, for a total of 17 samples).
- Subjects with inadequately controlled pain may request and receive rescue medication at any time; however, subjects will be encouraged to receive rescue only for an NRS ≥ 4. Additionally, subjects should be encouraged to wait at least 1 hour after completion of surgery (EOS) before utilizing pain rescue medication, if possible. NRS must be completed within 15 minutes prior to use of pain rescue medication if the time between rescue request and consumption is prolonged.
- Document the time to first use of rescue medication after T0 (between T0 and T24h) and after T24 (between T24h and T96h).
- Document concomitant medication use including doses and times taken
- All AEs that occur from the time a subject's informed consent but prior to study treatment will be captured in the medical history. All AEs and SAEs will be documented and followed from the time of administration of study treatment and will be considered treatment-emergent AEs (TEAEs).

After completing the assessments through T96h hours after study treatment administration 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. Additionally, obtain the subject's global assessment of satisfaction with study treatment (patient global evaluation or PGE) and the investigator's global evaluation (IGE) prior to discharge. 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: D4 through D29/W4:

- 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) prn tid or 650 mg prn qid (3g daily limit)

- If a subject is still requiring opioid rescue in the 12h prior to discharge (i.e., from T84h on regardless of whether discharge is delayed), prescribe oxycodone 5 mg PO tid prn (medical discretion on dosing and number of tablets dispensed per consideration of subject's age/history and needs, but no more than six tablets should be prescribed and may be taken as needed over the next several days). If additional oxycodone is required, refills are left to investigator discretion.

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.

9.1.5. Outpatient Phase: D8±1 (W1) Visit

Subjects will return to the study center on D8±1 (W1) for the following assessments:

- Subject home diary review
- Document pain intensity (NRS) at rest and after ambulation (approximately 10 yards) each day since discharge from the inpatient unit
- Record vital signs (HR, BP and RR)
- Perform interim PE: 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 (only allowed during outpatient period)
- Record AE Assessment
- Obtain PGE assessment
- Obtain IGE assessment

In their diary, subjects will assess their current pain intensity at rest and after ambulation each morning (08:00 ±3 hours), and each evening (20:00 ±3 hours) using the NRS. The subject should be instructed to perform, if possible, the daily assessments as follows:

- Obtain the morning NRS assessment prior to taking any pain medication or approximately 2 hours after taking any pain medication
- Obtain the evening NRS assessment approximately 2 hours after taking any pain medication

Subjects should be instructed to record any medication they take (dose and time) whether to treat their pain or for any other reasons.

9.1.6. Outpatient Phase: D15±2 (W2) Visit

Subjects will return to the study center on D15±1 (W2) for the following assessments:

- Subject home diary review
- Document pain intensity (NRS) at rest and after ambulation (approximately 10 yards) each day since discharge from the inpatient unit
- Record vital signs (HR, BP and RR)
- Perform interim PE: 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
- Obtain PGE assessment
- Obtain IGE assessment

In their diary, subjects will assess their current pain intensity at rest and after ambulation each morning (08:00 ±3 hours), and each evening (20:00 ±3 hours) using the NRS. The subject should be instructed to perform, if possible, the daily assessments as follows:

- Obtain the morning NRS assessment prior to taking any pain medication or approximately 2 hours after taking any pain medication
- Obtain the evening NRS assessment approximately 2 hours after taking any pain medication

Subjects should be instructed to record any medication they take (dose and time) whether to treat their pain or for any other reasons.

9.1.7. Outpatient Phase: D29±2 (W4) Visit

Subjects will return to the study center on D29±2 (W4) for the following assessments:

- X-ray of the surgical site
- Record vital signs (HR, BP and RR)
- Perform interim physical exam: 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
- Obtain PGE assessment
- Obtain IGE assessment

- When assessed, if the Investigator observes insufficient wound healing or atypical findings on surgical site assessment or to follow up on any unresolved AE, the subject may be scheduled for a follow-up visit on D36±2. If the wound is considered healed at D29, the D36 visit is not required.)

9.1.8. Outpatient Phase: Optional D36±2 (W5) Visit

If required due to any ongoing safety issue, insufficient wound healing or atypical findings on surgical site assessment noted at Day 29 visit or to follow up on an unresolved AE, subjects will return to the study center on D36±2 (W5) for the following assessments:

- Record vital signs (HR, BP and RR)
- Interim PE focusing on the surgical site assessment and neurosensory exam of both feet (proximal to the surgical site)
- Concomitant Medication Use including doses and times taken for analgesic medications
- AE Assessment

9.1.9. Early Termination Visit

If willing, subjects who elect to prematurely discontinue from the study will be requested to come in at their convenience for the following assessments (if subjects are not willing to return for assessments, request that they at least come in to assess the surgical site to ensure adequate wound healing):

- Record vital signs (HR, BP and RR)
- 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

9.1.10. 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 (W4), perform the following:

- Record vital signs (HR, BP and RR)
- Interim PE focusing on the surgical site assessment and neurosensory exam of both feet (proximal to the surgical site)
- Concomitant Medication Use including doses and times taken for analgesic medications

- Concomitant Treatments including topical ice pack or cooling treatments
- AE Assessment

9.2. Discussion of Study Design

This trial is designed to determine the efficacy of study treatment (CA-008 vs. placebo) infiltrated/instilled during surgery in treating postoperative pain after a bunionectomy in the setting of multimodal analgesia in addition to a Mayo block with bupivacaine in the first 24h and to confirm the safety profile observed in the phase 1 study recently completed. For the PK study, additional assessments will be done to further characterize the PK profiles of CA-008, CA-101 and capsaicin.

The current design, post-operative pain following elective primary unilateral first metatarsal bunionectomy surgery with osteotomy, has been used as a model of postoperative pain previously. In this model, the pain is generated from the correction of hallux valgus deformity of the first metatarsal and is used as a model to evaluate the treatment effect on duration of acute pain (multiple-day efficacy) (Singla 2013; Wang 2010).

Randomization will be used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) or other variables are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment as well as to minimize subject and investigator bias. Double-blinded treatments will be used to reduce potential bias of subjects and investigators during data collection and evaluation of clinical endpoints.

10. SELECTION OF STUDY POPULATION

10.1. 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 - 75 years old, inclusive, and American Society of Anesthesiology (ASA) physical Class 1, 2 or 3 at the time of randomization (Appendix 1A).
2. Plan to undergo an elective primary unilateral first metatarsal Bunionectomy repair, without collateral procedure or additional surgeries, to be performed under light to moderate sedation with regional anesthesia.
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 ≤ 40 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. For the portion of subjects who will participate in the PK analyses, be willing to undergo 17 blood draws for PK assessments at various time points during the surgery and the following 24 hours.

10.2. 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, bupivacaine HCl, ketorolac, acetaminophen 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 5) 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 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.

10.3. 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 study treatment, or both
- At the request of the Sponsor, regulatory agency, or Institutional Review Board (IRB)
- Subject is lost to follow-up
- Subject treatment allocation is unblinded (i.e., individual code break; Section 11.5)
- 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.

10.4. Study Restrictions

In addition to the criteria described in Section 10.1 and Section 10.2, 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 11.6

11. STUDY TREATMENTS

11.1. Study Treatment

11.1.1. CA-008 HCl 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.

11.1.2. Study Treatment Description

The active drug product will be provided as CA-008 Solution for Injection 2.5 mg, 7.5 mg and 15 mg/mL, 1.0 mL per vial, calculated as the freebase. Inactive ingredients are mannitol, citrate buffer and water and solution is provided in a 5 mL clear sterile vial.

Placebo comparator identical in appearance will be provided as 1.0 mL per vial. Inactive ingredients are mannitol, citrate buffer and water.

At time of use, the concentrate will be completely constituted with 49 mL of sterile saline and only a portion of the solution will be used for treatment. The Pharmacy Manual includes details on reconstitution and disposal of unneeded solution. For clarity, the drug product and treatment solutions are shown in Table 4.

Table 4. Study Treatments

	Solution for Injection, 1.0 mL per vial		
Drug Product as provided	2.5 mg	7.5 mg	15 mg
Concentration upon constitution with 49 mL saline	0.05 mg/mL	0.15 mg/mL	0.30 mg/mL
Dose in 14 mL of solution	0.7 mg	0.21 mg	0.42 mg

All study treatment vials are blinded and will be identified on the label by vial number.

11.1.3. Study Treatment Storage

Study treatments will be shipped to sites and stored at -20°C (-15°C to -30°C) until the day of surgery. All study treatment 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.

11.1.4. Study Treatment Accountability

All study treatment 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 study treatment. Only authorized research site staff may supply, prepare or administer the study treatments. Once dispensed, study treatment may not be relabeled or reassigned for use by other subjects.

11.1.5. Control of Study Treatment and Rescue Medication

Mishandling, potential theft, significant loss of clinical supplies, including study treatments, 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.

11.2. Other Interventions

11.2.1. Inpatient Multimodal Analgesia

While in-clinic, subjects will be treated with a multimodal analgesic regimen to supplement the Mayo block in the immediate postoperative period. The regimen will include IV ketorolac and IV/PO acetaminophen. Administer the following:

- Ketorolac 30 mg IV (a non-steroidal anti-inflammatory drug (NSAID) to be administered intraoperatively before the end of surgery. Per investigator discretion, adjust the dose as necessary for subject age and medical condition.
- Acetaminophen 1000 mg IV to be administered intraoperatively before the end of surgery. This administration should be based off of T0.

After the above have been administered, no additional NSAIDs or acetaminophen are to be administered during the inpatient phase of the study through T96h.

11.2.2. Inpatient Rescue Medications

Additionally, should the subject have breakthrough or poorly controlled pain at any time from EOS to T96h (the inpatient period), oxycodone rescue medication may be administered for any moderate to severe pain (NRS ≥ 4) (see Section 9.1.3).

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.

11.2.3. Outpatient Analgesic Medications

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: T96h through D29/W4:

- 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®])
    - 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 period beyond the T84 hour timepoint, then prescribe no more than 6 tablet supply of oxycodone 5 mg (for use up to tid prn) to cover the initial outpatient period with actual number of tablets prescribed and refills per investigator discretion and based upon the subject's needs.

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 capture this event as an AE and document any required treatments.

11.3. Method of Assigning Subjects to Treatment Groups

Randomization will be used to avoid bias in the assignment of subjects to treatments, to increase the likelihood that known and unknown subject attributes (e.g., demographics, baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across 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 or randomization number is assigned, it cannot be reassigned to any other subject. The randomization plan is described in Section 12.2.

There will be up to 4 treatment groups of subjects (3 active dose groups and placebo). Each site will be provided with sufficient study treatment supplies for all treatment groups.

Subjects may be rescreened if the screening window is exceeded due to scheduling issues. For other out of screen window situations, Sponsor approval is needed prior to the rescreen visit.

11.4. Selection of Doses

The safety of CA-008 was established in relevant animal models and a prior phase 1 study after bunionectomy. These results support the potential safety of CA-008 with no apparent abnormal findings. Based on these nonclinical studies, a single instillation administration of CA-008 into the surgical site, at an initial dose of 0.7 mg/person and a maximum dose of 4.2 mg/person, has a minimal risk of causing adverse events. This dose range is within the range used in the phase 1 ascending dose safety study in a bunionectomy model and was found to be well tolerated.

Taken together, the characterization of the pharmacology, pharmacokinetics, and toxicology profiles are considered sufficient to support the intended use of CA-008 in the Phase 2 efficacy and safety study for the treatment of acute post-surgical pain after bunionectomy.

11.5. Blinding

To reduce the potential for bias in the study, treatment group assignments will be double-blinded during the study. The subject, investigational site personnel, Sponsor, and Sponsor designees directly involved in the conduct and/or monitoring of this study will not be aware of the treatment group assignments. In the PK study all participating subjects whether randomized to active or placebo will have blood drawn at the specified time points and sent to the bioanalytical laboratory for subsequent processing. As no one at the site is unblinded as to which treatment group any subject is assigned, blinding is preserved within the PK study.

Under normal circumstances, the blind will not be broken until all participants have completed treatment. In case of emergency, and only if the information is required by the Investigator to ensure subject's safety in managing a medical condition, the treatment may be unblinded at the site by using a code break module. The code break module will be provided by the Sponsor's designee. If possible, the Investigator should contact the Sponsor prior to unblinding and after any actions have been taken. Whenever a treatment sequence is prematurely unblinded, the reason, date and time of the unblinding, and the individual who broke the blind must be documented. Individual code breaks will result in withdrawal of the participant from the study.

11.6. Prior and Concomitant Therapy

All non-study treatments, 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 11.2.1.

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

11.7. Treatment Compliance

Because all study treatment 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.

12. 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.

12.1. Demographics and Other Baseline Characteristics

12.1.1. 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.

12.1.2. Demographics

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

12.1.3. 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. Subject's medical history will be evaluated by an Investigator for clinical significance.

12.1.4. 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.

12.1.5. 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 (using investigator discretion, recommend provide guidance as to the appropriate combination of available methods).

Female subjects of non-childbearing potential are not required to use contraception or undergo pregnancy tests; however, they must be surgically sterile (e.g., 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 (using investigator discretion, recommend the appropriate combination of methods, such as male condom, diaphragm, contraceptive sponge, spermicidal contraceptives and other similar methods) during the study.

12.2. Eligibility Review and Randomization

Prior to randomization, subjects must meet all inclusion and not meet any exclusion criteria as outlined in Section 10.1 and Section 10.2.

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 date of randomization on the day of surgery.

Randomization will be accomplished manually.

12.3. Subject Pain Assessment Training

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

12.4. Efficacy Assessments

Details regarding primary and secondary endpoints are provided in Section 12.6 (Efficacy Variables); and discussed further in Section 15 (Statistical Analysis). The following sections provide an overview of the efficacy assessments included in the study.

12.4.1. Numerical Rating Scale for Pain Intensity (NRS)

The NRS is an 11-point scale with anchors 0 (no pain) and 10 (worst possible pain) (Ferreira-Valente 2011, Hjermstad 2011) (see Appendix 1A).

Subjects will report or record the intensity of their current pain at designated times during the study after administration of study treatment (see Section 9.1.4). Subjects should be at rest for at least

10 minutes prior to completing NRS resting assessments and have ambulated approximately 10 yards within 15 minutes prior to completing NRS ambulation assessments.

12.4.2. Patient Global Evaluation (PGE)

At T96h (prior to discharge), and on the D8, D15 and D29/ET visits, each subject will be asked to report their satisfaction with the study treatment for pain using a 4-point categorical scale. Each subject will be asked the following question:

"How would you rate the study treatment that you have received for pain? Poor (0), Fair (1), Good (2), or Excellent (3)" (see Appendix 1C).

12.4.3. Investigator Global Evaluation (IGE)

At T96h (prior to discharge), and on the D8, D15 and D29/ET visits, the principal investigator or designee will report their satisfaction with the subject's study treatment for pain using a 4-point scale. A study Investigator (or authorized designee) will be asked the following question:

"How would you rate the study treatment that the patient received for pain? Poor (0), Fair (1), Good (2), or Excellent (3)" (see Appendix 1D).

12.4.4. Rescue Medications

The details of rescue medication (doses and times) will be recorded beginning from the end of surgery through the D15 visit or to Early Termination Visit if applicable. Subjects will be instructed on the proper use and timing of rescue medication. Use Table 5 to calculate the morphine equivalent dose (MED) of various opioids.

Table 5. Equianalgesic Conversion Table

Opioid (Doses in mg)	Conversion Factor
Hydrocodone	1
Hydromorphone	4
Morphine	1
Oxycodone	1.5
Tramadol	0.1
Multiply the opioid dose by the conversion factor = morphine equivalent dose (MED): e.g., oxycodone 5 mgX1.5 = 7.5 mg MED	

12.5. 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.

12.5.1. Clinical Laboratory Assessments

All protocol-specified laboratory tests on blood and urine samples will be performed at a central laboratory. Blood samples will be collected, processed, and shipped according to instructions from the central laboratory. 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. Required assessments for blood tests are listed in Table 6.

Table 6. Clinical Laboratory Assessments

Hematology	**Chemistry**
Hematocrit Hemoglobin Red blood cell (RBC) count Total and differential (absolute) white blood cell count Platelet count	Sodium Potassium Calcium Chloride Glucose Creatinine Blood urea nitrogen Total bilirubin Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Lactic dehydrogenase (LDH) Gamma-glutamyl transferase (GGT) Alkaline phosphatase

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. The investigator may use Appendix 1H (severity assessments of labs) to assist in the determination of clinical significance.

The clinical laboratory tests will be completed at Screening and at T96h before discharge from the inpatient unit (see). In addition to the clinical laboratory tests, a serum pregnancy test will be performed at the Screening Visit and a urine pregnancy test will be performed prior to surgery for women of childbearing potential. ALT or AST > 3x upper limit normal range (ULN) / Tot. Bili > 3 X ULN/ Alk Phos. >2X ULN will be considered an adverse event, as well as any other changes deemed clinically significant by the Investigator.

12.5.2. Urine Drug Screen and Alcohol Test

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

The drug and alcohol screens may be performed in-house at the Clinical Unit, and the alcohol saliva test may be sent out to a local lab (e.g., LabCorp). If any of these tests are positive, the subject will not be allowed further participation in the trial unless one of the previously noted exceptions is present. A positive test may be repeated at the discretion of the PI.

12.5.3. X-Ray

An X-ray of the surgical site will be performed during screening and at D29/ET.

12.5.4. Vital Signs

Vital signs will consist of blood pressure (BP, mmHg), pulse rate (HR, beats per minute), and respiratory rate (RR, breaths/min) collected while sitting, following a rest period of at least 5 minutes. Vital signs and temperatures will be assessed at various study time points (see Section 9.1.4 through Section 9.1.8).

Vital sign abnormalities are graded in Appendix 1I. If in the opinion of the Investigator the perturbation is considered clinically significant, it will be considered an adverse event.

12.5.5. 12-Lead Electrocardiogram (ECG)

12-Lead ECGs will be performed after the subject has been resting in a recumbent/supine position for at least 5 minutes. The ECG variables will include ventricular heart rate and the PR, QRS, QT and QTcF intervals. The ECGs will be signed and dated by a medically-qualified individual to confirm review of the ECG and verify whether any abnormalities are clinically significant. In general, abnormal, clinically significant ECGs are expected to be associated with an item recorded in medical history or with an AE. ECGs will be assessed at Screening and at T24h (± 2 hour). Clinically significant changes in ECG (i.e., QTcF should be <450 msec / < 470

msec for female / male subjects, respectively; and an increase of QTcF of > 30 msec will be considered an AE.

12.5.6. 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 interim PEs prior to Surgery, and additional interim PEs focused on the surgical site and neurosensory testing of both lower extremities at T96h prior to discharge from the inpatient unit, D8, D15 and D29/ET.

Body weight (kg), in indoor clothing, but without shoes, will be measured at Screening, at T96h prior to discharge from the inpatient unit and ET. Height in centimeters (cm) will be measured, and BMI will be calculated at Screening only. 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.

12.5.7. Surgical Site Assessment

The surgical site should be assessed to determine if any related AEs have occurred. Assessments will be conducted at T96h prior to discharge from the inpatient unit, and on the D8, D15 and D29/ET visits.

At T96h prior to discharge, the investigator will evaluate their satisfaction with the healing of the wound during this Surgical Site assessment using an 11-point scale (0-10) where a score of 0 is "Completely unsatisfied," and a score of 10 is "Completely satisfied." Appendix 1E

Assessments will also be performed at each of the Follow-up visits on Days 8, 15 and 29, or at the time of discontinuation. When assessed on Day 29, if the Investigator observes insufficient wound healing, the subject will be scheduled for a follow-up visit on Day 36. Appendix 1F

If there are atypical skin reactions, for example, erythema, pain, pruritus, bruising, swelling, bruising or other skin changes, they will be evaluated and graded for severity.

12.5.8. Neurosensory Exam

A neurosensory exam of the lower extremity (foot/great toe surgical site with contralateral comparison) will be conducted at screening, at T96h prior to discharge from the inpatient unit, on the D8, D15 and D29/ET (and D36 if necessary) visits. The exam will involve the dorsal aspect of the foot proximal to the great toe.

This evaluation will include the following (details described in Appendix 1G):

- Visual exam of the foot
- Deep Tendon Reflexes (normal, reduced or absent)
- Vibratory sensation (normal, reduced or absent)

- Monofilament Sensation (normal, reduced or absent)
- Allodynia to brush (pain (allodynia), hyperesthesia, normal, reduced or absent)

A persistent atypical sensory change after EOS, such as allodynia or hyperalgesia proximal to the surgical site will be reported as an AE. Numbness at or near the incision need not be considered an AE since this could occur due to tissue trauma and inflammation from surgery.

12.5.9. Assessment of Adverse Events

All SAEs will be documented and followed from the time the subject has signed the ICF until D29 or, if necessary, D36 after the completion of surgery. All SAEs and non-serious AEs will be documented and followed from the time of administration of study treatment until D29 or, if necessary, D36 after the completion of surgery. AEs that occur between Screening and the study procedure should be considered medical history and added to the subject's medical record. AEs that have been designated as possibly or probably related to study treatment will be followed until resolution or stabilization. Further details on AEs, including definitions, elicitation, and reporting are provided in Section 13.

12.6. Efficacy, Safety and PK Endpoints

12.6.1. Efficacy Endpoints

Using NRS scores (at rest and with ambulation) a variety of time-specific summed pain intensity assessments (area under the curve or AUC for pain intensity) will be calculated comparing each CA-008 dosing groups to placebo.

12.6.1.1. Primary Efficacy Endpoint

Weighted sum of pain intensity (SPI) assessments = Area Under the Curve (AUC) of the NRS scores from T0 to T96h at rest ($AUC_{0\ to\ 96h}$).

12.6.1.2. Secondary Efficacy Endpoints

The key secondary endpoints for the comparison of the 4.2 mg CA-008 dose vs. placebo (in descending order of importance):

1. Percentage of subjects who do not require opioids or are opioid free (OF) from T0 to T96): $OF_{0\ to\ 96h}$
2. Total opioid consumption (in daily oral morphine equivalents) = OC from T0 to T96h: $OC_{0\ to\ 96h}$
3. Using NRS at rest: $AUC_{0\ to\ W1}$

12.6.1.3. Other Efficacy Endpoints

- $AUC_{0\ to\ 24h}$, $AUC_{0\ to\ 120h}$, $AUC_{0\ to\ W1\ (walking)}$, $AUC_{12\ to\ 24h}$, $AUC_{24\ to\ 48h}$, $AUC_{24\ to\ 72h}$, $AUC_{24\ to\ 96h}$, $AUC_{96h\ to\ 120h}$, $AUC_{96h\ to\ W1}$, $AUC_{24h\ to\ W1(walking)}$, $AUC_{96h\ to\ W2}$, $AUC_{96h\ to\ W2(walking)}$
- $OC_{24\ to\ 48h}$, $OC_{24\ to\ 72h}$, $OC_{24\ to\ 96h}$

- $OF_{24\ to\ 96h}$, $OF_{96h\ to\ W1}$ and $OF_{96h\ to\ W2}$
- $TTFR_{after\ T0}$ and $TTFR_{after\ T24h}$
- Analgesic consumption of OTC analgesics and if prescribed, oxycodone, from T96h to W1 and T96h to W2
- PGE comparing the %age of subjects reporting "poor" + "fair" vs. "good" + "excellent" responses, and the %age reporting each category of response at W1, W2 and W4
- IGE comparing the %age of those reporting "poor" + "fair" vs. "good" + "excellent" responses, and the %age reporting each category at W1, W2 and W4
- Number and %age Subjects with an AE of lack of efficacy (LOE) during the inpatient period: $LOE_{24\ to\ 96h}$, $LOE_{0\ to\ 96h}$
- $HCU_{96h\ to\ W2}$ and $HCU_{96h\ to\ W4}$

12.6.2. Safety Endpoints

Safety endpoints include the following:

- Incidence of TEAEs and SAEs
- Vital sign measurements
- Physical Exam findings
- Surgical Site assessment findings
- Neurosensory Exam results
- Clinical laboratory test results
- Electrocardiogram (ECG) results
- Concomitant medications

12.6.3. Pharmacokinetic Endpoints

12.6.3.1. PK Sampling and Parameters

Based upon the PK results from the Phase 1 bunionectomy ascending dose safety study, the time points for whole blood collection will be at baseline (within the 30 min before the end of study treatment dosing at T0), and at T5min, T10 min, T15min, T30min, T45min, and T1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24h, for a total of 17 samples or approximately 102 mL). Actual sampling times will be used to calculate plasma bupivacaine-derived PK parameters.

A selected number of subjects will participate in the PK study.

The following parameters will be estimated using noncompartmental analysis for CA-008, capsaicin and CA-101:

- C_{max}: The maximum measured plasma concentration, obtained directly from the data without interpolation

- C_{last}: Last observed (quantifiable) concentration
- T_{max}: Time of C_{max}
- $t_{½}$: The apparent first-order terminal elimination half-life, calculated as $0.693/\lambda_z$
- T_{lag}: Time delay between drug administration and first measurable (above lower limit of quantitation) concentration
- T_{last}: Time of occurrence of C_{last}
- λ_z: Terminal first-order elimination rate constant
- AUC_{0-t}: Area under the plasma concentration-time curve from time 0 to the last measurable concentration (where time is postdose), calculated by the linear trapezoidal method
- $AUC_{0-\infty}$: Area under the plasma concentration-time curve, from time of dosing to infinity.
- AUC_{last}: Percentage of the area extrapolated beyond the last quantifiable plasma concentration

12.6.3.2. Sample Handling:

Handling and labeling requirements after the collection of each PK sample are described in detail in the Clinical Laboratory Manual.

13. ADVERSE EVENTS

13.1. 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.

13.1.1. Relationship to Study Treatment

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 study treatment.

Causality Category	Description
Unlikely related	A clinical event, including laboratory test abnormality, with a temporal relationship to study treatment 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 study treatment, 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 study treatment 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 study treatment.
Possibly related	A clinical event, including laboratory test abnormality, with a temporal relationship to study treatment 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 study treatment was partly responsible, then choose "possibly related." For the purpose of this protocol, an event that has possible relationship to study treatment will be defined as a "Suspected Adverse Drug Reaction".
Probably related	A clinical event, including laboratory test abnormality, with a temporal relationship to study treatment 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 study treatment will be defined as an "Adverse Drug Reaction".

13.1.2. 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 to study treatment
- Action and outcome
- Seriousness of event

All SAEs will be documented and followed from the time the subject has signed the ICF until 29 (+/- 3 days), or, if necessary, Day 36 after the completion of surgery. All SAEs and non-serious AEs will be documented and followed from the time of administration of study treatment until Day 29 or, if necessary, Day 36 after the completion of surgery. AEs 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. AEs that have been designated as possibly related to study treatment will be followed until resolution or stabilization.

13.1.3. 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.

All AEs requiring hospitalization or prolongation of a pre-existing hospitalization should be reported as SAEs unless they occur greater than 14 days after the Day 29 visit, or 21 days after early termination AND are not considered to be study treatment-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.

13.1.3.1. 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 study treatment 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 study treatment should be reported within 24 hours.

The procedure for reporting an SAE is as follows:

- 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 L. Ruckle, MD, CPI

  24/7 Emergency contact: 808-349-9812

  SAE Reporting email: MedicalMonitorCA-PS-201@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 the study treatment 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.

13.2. 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.

14. 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 14.2.

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.

14.1. 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.

14.2. 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, study treatment 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.

15. STATISTICAL METHODS

15.1. Statistical and Analytical Plans

This section describes the statistical methods to be used to analyze the efficacy and safety. The final analysis 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.

15.2. Sample Size Justification

In the previously completed Phase 1 ascending dose safety study in bunionectomy (CA-008 vs. placebo), the mean difference between CA-008 (all dose groups combined) and placebo for the $AUC_{24\ to\ 96h}$ was -120. The standard deviation (SD) estimates for the six treatment arms in this study ranged from 70 to 190 with a median SD of 108. For the primary endpoint ($AUC_{0\ to\ 96h}$), the true treatment difference between the 4.2 mg CA-008 group and the placebo group is assumed to be equal to -100 and the assumed true SD is equal to 130. For these assumptions, and based on the use of a two-sided, two-sample comparison of means at the alpha=0.05 level of significance, a sample size of 36 subjects per arm will provide 90% power. Thus, the planned total sample size is 144 subjects.

15.3. Analysis Populations

The following three analysis populations are planned for this study:

- The Safety Population will include all subjects who received at least part of a dose of study treatment.
- The PK Population will include all subjects who receive a full dose of study treatment and complete at least all PK assessments through the T6h timepoint. Subjects who fail to complete these PK assessments will be replaced.
- The modified ITT (mITT) Population will include all subjects who receive a full dose of study treatment and complete the first 3 pain assessments (through T2h).

Subjects who elect to discontinue study participation during the inpatient phase of the study, will be asked to continue with assessments through T96h 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 (W1) 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 assessments and baseline characteristics will be summarized using the Safety Population. PK and efficacy analyses will be performed using the PK and mITT Populations, respectively. All summaries will be grouped by the actual treatment received. Each active dose cohort will be presented separately, along with a combined active dose group.

Inpatient Study Completer will be defined as those subjects who complete the assessments through T96h. Outpatient Study Completer will be defined as those subjects who complete the assessments through D29±2 (W4).

Membership in the analysis populations will be determined before unblinding.

15.4. Planned Analyses

Unless otherwise indicated, all testing of statistical significance will be 2-sided, and a difference resulting in a P value of less than or equal to 0.05 will be considered statistically significant. Furthermore, the baseline will be the last assessment before the dosing of study treatment.

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.

15.5. Study Subjects and Demographics

15.5.1. Disposition and Withdrawals

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

15.5.2. 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.

15.5.3. 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.

15.5.4. Exposure

Since this is a single dose study, study treatment administration will be summarized in terms of total exposure by cohort and treatment group.

15.5.5. 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 T0 is the time of completion of study treatment administration.
- Day of surgery is defined as D0
- Assessment visit times are defined by time T0/D0.
- Baseline value is defined as the last valid measurement prior to beginning study treatment 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).

15.6. 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.

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. It is expected subjects randomized to placebo arm will take rescue medication more often. 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 15.6.4.

15.6.1. Primary Efficacy Analysis

The primary efficacy analysis of the primary endpoint ($AUC_{0 \text{ to } 96h}$) will be conducted using an analysis of variance (ANOVA) model with treatment group (four levels) as the main effect. The primary analysis will compare the 4.2 mg CA-008 group to the placebo group using a two-sided test at the alpha=0.05 level of significance.

15.6.2. Key Secondary Efficacy Analyses

If the primary efficacy analysis is statistically significant ($p<0.05$), then comparisons between the 4.2 mg CA-008 group and the placebo group will be made for the following endpoints:

- Percentage of subjects who do not require opioids or are opioid free (OF) from T0 to T96): $OF_{0 \text{ to } 96h}$
- Total opioid consumption (in daily oral morphine equivalents) = OC from T0 to T96h: $OC_{0 \text{ to } 96h}$
- Using NRS at rest: $AUC_{0 \text{ to } W1}$

Each of the above comparisons will be made using a two-sided test at the alpha=0.05 level of significance. However, once a nonsignificant result occurs, then all subsequent analyses in the hierarchy will be exploratory rather than confirmatory.

The percentage of subjects who do not require opioids or are OF will be analyzed using a logistic regression model with treatment group (four levels) as a factor. The other two key secondary endpoints will be analyzed using the same type of ANCOVA model as described for the primary efficacy analysis.

15.6.3. Other Efficacy Analyses

For the primary endpoint and the three key secondary endpoints, comparisons between the 0.7 mg CA-008 group and the placebo group, and between the 2.1 mg CA-008 group and the placebo group will be tested using the same model as used for the primary (key secondary) analysis of the corresponding endpoint.

All other AUC and quantitative endpoints will be analyzed using the same type of ANOVA model as described for the primary analysis. All proportion endpoints will be analyzed using the same type of logistic regression model as described for the first key secondary efficacy analysis.

All other efficacy analyses will be conducted using two-sided tests at the alpha=0.05 level of significance, with no adjustment for multiplicity.

15.6.4. 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 the study treatment;
- 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 4 hours following the rescue use. 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.

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.

15.7. Analysis of Safety

Safety analyses will be conducted using data from the Safety Population (as defined in Section 15.3).

Safety will be assessed through treatment-emergent AEs (TEAEs); hematologic, biochemical, and urinalysis laboratory parameters; vital signs measurements; ECGs; physical exam, surgical site and neurosensory assessments.

No formal statistical comparisons will be performed for safety endpoints.

15.7.1. 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 with the study treatment through Day 29 or Early Termination, whichever occurs first;
- Serious AEs with onset on the date of treatment with the study treatment through 30 days after Day 29 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 Day 29 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 study treatment. A listing of SAEs will be provided if applicable.

15.7.2. Clinical Laboratory Evaluations

For continuous laboratory parameters, descriptive statistics will be presented for the value at each assessment time and for the changes from baseline screening labs by treatment group.

Additionally, clinical laboratory parameters will be categorized as low, normal, or high according to laboratory range specifications and the number and percentage of subjects in each category will be presented in shift tables.

Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges.

15.7.3. Vital Signs and ECG

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from Baseline will be calculated for vital signs and ECG. Detailed description of the analysis will be included in the Study SAP.

The incidence of abnormal ECG findings will be summarized.

15.7.4. Physical Examination Findings

Physical and Surgical Site examination data will be presented in the listings. Abnormal or clinically significant physical exam and surgical site findings will be recorded as AEs.

16. SITE AND INVESTIGATOR RESPONSIBILITIES

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

16.1. Regulatory and Ethical Considerations

16.1.1. 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.

16.1.2. 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.

16.1.3. 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 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.

16.2. 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.

16.3. 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 study treatments, 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.

16.4. 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 study treatment 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 study treatment 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.

16.5. 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.

16.6. 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.

16.7. 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.

17. INVESTIGATOR PROTOCOL AGREEMENT PAGE

A Phase 2, Randomized, Double-blind, Placebo-controlled Safety, Pharmacokinetics and Efficacy Study of CA-008 in subjects Undergoing Bunionectomy

Version: 1.2

Date: 06 June 2018

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)

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1. APPENDICES

APPENDIX A: AMERICAN SOCIETY OF ANESTHESIOLOGISTS PHYSICAL STATUS CLASSIFICATION SYSTEM (ASA CLASS)

I	Normal healthy patient
II	Patient with mild systemic disease; no functional limitation – e.g. smoker with well-controlled hypertension
III	Patient with severe systemic disease; definite functional impairment – e.g. diabetes and angina with relatively stable disease, but requiring therapy
IV	Patient with severe systemic disease that is a constant threat to life – e.g. diabetes and angina and congestive heart failure; patients with dyspnea on mild exertion and chest pain
V	Unstable moriBUNXd patient who is not expected to survive 24 hours with or without operation
VI	Brain dead patient whose organs are removed for donation to another
E	Emergency operation of any type, which is added to any of the above six categories, an in ASA II E

APPENDIX B: 0 TO 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: _____

APPENDIX C: PATIENT GLOBAL EVALUATION [OF SATISFACTION WITH STUDY TREATMENT TREATMENT] (PGE)

Patient Global Evaluation (PGE)
Instructions to Subject: Please respond to the question below. When completed, please initial at the bottom of the page.
How would you rate your satisfaction with the study treatment that you received during surgery for postop pain? **(Mark one box)** ☐ **Excellent (3)** ☐ **Good (2)** ☐ **Fair (1)** ☐ **Poor (0)** **Subject Initials: _____**

APPENDIX D: INVESTIGATOR GLOBAL EVALUATION (IGE)

Investigator Global Evaluation (IGE)
***Instructions to Investigator*:** Please respond to the question below. When completed, please initial at the bottom of the page.
How would you rate the study treatment that this patient received during surgery for pain? **(Mark one box)** ☐ **Excellent (3)** ☐ **Good (2)** ☐ **Fair (1)** ☐ **Poor (0)** **Investigator Initials: _____**

APPENDIX E: 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: _____**

APPENDIX F: SURGICAL WOUND STATUS ASSESSMENT

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

APPENDIX G: NEUROSENSORY EXAMINATION FORM

Subject Number	Subject Initials	Date: __ __/ __ __ __/ 20__ __ (DD-MMM-20YY)	Protocol Number
__ __ __ - __ __ __	__ __ __		CA-PS- 201

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.	Deep Tendon Reflexes:	☐ Normal	☐ Reduced	☐ Absent	☐ Normal	☐ Reduced	☐ Absent
4.	Vibratory Sensation:	☐ Normal	☐ Reduced	☐ Absent	☐ Normal	☐ Reduced	☐ Absent
5.	Monofilament Sensation	☐ Normal	☐ Reduced	☐ Absent	☐ Normal	☐ Reduced	☐ Absent
6.	Allodynia to Brush:	☐ Pain (Allodynia)	☐ Hyperesthesia		☐ Pain (Allodynia)	☐ Hyperesthesia	
		☐ Normal	☐ Reduced	☐ Absent	☐ Normal	☐ Reduced	☐ Absent

APPENDIX H: GUIDANCE FOR INDUSTRY: TOXICITY GRADING SCALE FOR HEALTHY ADULT AND ADOLESCENT VOLUNTEERS ENROLLED IN PREVENTIVE VACCINE CLINICAL TRIALS, TABLE FOR LABORATORY ABNORMALITIES

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUNX mg/dL	23-26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.
***ULN" is the upper limit of the normal range.

APPENDIX I: GUIDANCE FOR INDUSTRY: TOXICITY GRADING SCALE FOR HEALTHY ADULT AND ADOLESCENT VOLUNTEERS ENROLLED IN PREVENTIVE VACCINE CLINICAL TRIALS, TABLE FOR CLINICAL 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.