OFFICIAL TITLE:

A Phase 1/Single Ascending Dose (SAD) Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of a Single Intraoperative Administration of CA-008 in Subjects Undergoing Unilateral Transpositional First Metatarsal Osteotomy for the Correction of Hallux Valgus Deformity

NCT NUMBER:

NCT03307837

DOCUMENT DATE:

30 Jan 2018

Clinical Trial Protocol CA-PS-2017-101

A Phase 1/Single Ascending Dose (SAD) Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of a Single Intraoperative Administration of CA-008 in Subjects Undergoing Unilateral Transpositional First Metatarsal Osteotomy for the Correction of Hallux Valgus Deformity

Investigational Product: Subcutaneous Injectable CA-008

IND: 129-114

Version: 3.0
Amendment: 2
Amendment 2 Date: 30-Jan-2018
Amendment 1 Date: 12-Oct-2017
Original Protocol 07-Sep-2017

Concentric Analgesics, Inc.

Amendment 2 changes from Amendment 1 include:

The main objective of Amendment 2 of the study protocol, CA-PS-2017-101, is the addition of a 5th cohort, allowing for exploration of a higher dose level than previously defined.

With the goal of finding the maximum tolerated dose (concentration and volume) a decision was made to add another cohort to this study. This decision was made following review of all previous cohorts, with the finding that these previous dosed cohorts were safe and well tolerated without any dose limiting side effect or toxicity at a regional or systemic level. Subjects in Cohorts 1-4 were all reviewed by the DMC and the decision to study a higher dose was supported by the DMC.

In order to increase the dose, a decision was made to maintain the concentration and increase the total volume. The maximum recommended volume for this surgical condition was a total of 9ml infiltrated and a total of 5 ml instilled. With this recommendation from, it was decided that one additional cohort would be studied, with no plan for study of any cohorts beyond this planned cohort 5. This cohort #5 (study of a total dose of 4.2mg of CA-008), now represents the study of the highest possible dose for this post-surgical condition based on a) maximum concentration 0.3mg/mL, and b) maximum recommended volume for infiltration and instillation. As such, no further dose escalation is expected for this study.

Amendment 2 changes from Amendment 1 include:

- Addition of NCT number to synopsis (previously TBD)
- Addition of Cohort 5 and associated updates required:
  - Increase in total enrollment by 8 subjects
  - Addition of new dose level and details surrounding dosing technique
  - Addition of rationale for addition of cohort 5
- Addition of Capsaicin-glucuronide in the PK analysis, as previously detailed in the PK Manual

Amendment 1 changes from the original protocol include:

- Use of ice as method of post-surgical analgesia removed throughout
- Updates to clinical laboratory tests
- Updates to allowable inpatient and outpatient medications
- X-ray of Surgical Site added at Screening and on Day 29/Early Termination (ET)
- Relationship to Study Drug (causality) definitions added
- Updates to the exclusion section to remove duplicative requirements and further enhance subject safety
- Addition of Audio-Visual Recording section
- Draw time and date remove from details captured on cryogenic storage (PK) tubes
- Removal of 15-minute wait time between completion of NPRS pain score and taking rescue medication
- Addition of 10-minute rest period prior to administration of NPRS
- Clarification regarding intra-operative administration of study drug
- Updates regarding management of subjects requiring analgesic relief beyond what is allowed per protocol
- Addition of Vital Signs and Labs to the 'Category' column in Table 2: Study Stopping Rules
- Addition of Appendix K: Physical / Neurological Examination of the Foot and Great Toe and associated details regarding the Neurosensory Exam
- Administrative changes to:
    - Update of title page and headers throughout

SIGNATURE PAGE

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30-Jan-18

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1. SPONSOR AND KEY PERSONNEL CONTACT INFORMATION

Role in Study	Name	Contact Information
Study Sponsor	Concentric Analgesics, Inc. John Donovan, MD Chief Executive Officer Carole Hodge, PhD Clinical Operations Director Rob Allen, MD Chief Medical Officer	 John@concentricanalgesics.com 415-676-8940 Carole@concentricanalgesics.com 858-442-9884 Rob@concentricanalgesics.com 610-393-1303
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2. PROTOCOL SYNOPSIS

Sponsor:	Concentric Analgesics, Inc.
Protocol Number:	CA-PS-2017-101
NCT:	03307837
Study Title:	A Phase 1/Single Ascending Dose (SAD) Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of a Single Intraoperative Administration of CA-008 in Subjects Undergoing Unilateral Transpositional First Metatarsal Osteotomy for the Correction of Hallux Valgus Deformity
Investigational Product:	CA-008 infiltrated into the surgical site at various concentrations (Cohorts 1-4 doses in a 10 mL volume of administration; Cohort 5 dose in a 14 mL volume of administration)
Comparator Product(s):	Saline (10 mL for Cohorts 1-4, 14 mL for Cohort 5)
Indication:	Bunionectomy
Planned Study Center:	1 study center
Phase of Development:	Phase 1
Study Design:	This is a single-center, randomized, double-blind, placebo-controlled, single ascending dose, sequential-group Phase 1 study. The study will be conducted utilizing a cohort design, with sequential groups of 8 subjects. Within each dose cohort, 6 subjects will be randomized to active, and 2 will be randomized to placebo. The initial cohort will receive the lowest planned dose of CA-008, and sequential cohorts will receive escalating doses of CA-008 in a fixed volume of administration. There will be at least a 6-day period between cohorts, in order to ensure a minimum of 3 days to review safety data from the last subject in a cohort and to allow the meeting of the Data Monitoring Committee (DMC) to review the safety data from the entire cohort prior to a making decision for dose escalation. Dose escalation rules will be protocol defined. Subjects will be undergoing unilateral transpositional first metatarsal osteotomy for the correction of hallux valgus deformity (bunionectomy). In accordance with standard of care, subjects will receive regional

	anesthesia (MAYO block) with 0.5% bupivacaine. Prior to wound closure, 10 mL (Cohorts 1-4) or 14mL (Cohort 5) of study drug will be injected into the soft tissues and periosteum of the surgical site. After the surgery, subjects will be monitored for 48 hours at the trial site. Safety and efficacy evaluations will be performed as described herein. Subjects will be required to meet certain pre-specified criteria prior to discharge.
Number of Subjects:	Up to 40 enrolled subjects (Up to 5 groups of 8 subjects per group)
Population:	Subjects (male or female; aged 18 - 65 years old) who are planning to undergo bunionectomy, and who meet all inclusion and exclusion criteria, may be considered for enrollment in this study.
Dosing Schedule:	Single administration per subject, via wound infiltration, prior to wound closure.

Route of Administration:	Administration of the study drug into the surgical site: A total of 10 mL (for Cohorts 1-4) and a total of 14 mL (for Cohort 5) of the investigative product will be administered into the surgical site as follows:
	• At time of closure of capsule:
	  ○ Infiltration of deep soft tissue and capsule with a total of:
	  ▪ 6 mL volume for Cohorts 1-4
	  ▪ 9 mL volume for Cohort 5
	  ○ Instillation at cut bone with a total of 2 mL volume for all cohorts
	• Following closure of the capsule and prior to closure of the skin and subcutaneous layer:
	  ○ Instillation of wound with 2 mL volume for Cohorts 1-4, and with a 3 mL for Cohort 5
	  ▪ For Cohorts 1-4 study drug is applied to all exposed surfaces prior to subcutaneous and skin closure
	  ▪ For cohort 5, 2 mL of study drug will be instilled into the space under closed capsule and 1 mL of study drug applied to all exposed surfaces prior to subcutaneous and skin closure

Surgical Procedures:	<u>Surgical Anesthesia:</u> Light to moderate sedation which will include propofol, midazolam and/or fentanyl. Regional anesthesia (MAYO Block) utilizing 0.5% bupivacaine (up to 30 cc total). MAYO block should be done proximal to the surgical site and should not involve the immediate area of the planned surgical

	incision. The area starting 1-inch lateral/medial/proximal/distal of the incision site and surrounding tissue that may be affected by the infiltration of the Investigational Product (IP) will subsequently be referred to as the "surgical site."
Dose Groups:	• CA -008, 0.5 mg in 10 mL of saline (50 µg/mL) • CA-008, 1.0 mg in 10 mL of saline (100 µg/mL) • CA-008, 2.0 mg in 10 mL of saline (200 µg/mL) • CA-008, 3.0 mg in 10 mL of saline (300 µg/mL) • CA-008, 4.2 mg in 14mL of saline (300 ug/mL) Note: Weights of CA-008 are provided for the free base, without counterions. Within each cohort of 8 subjects, 6 will be randomized to active treatment, and 2 will be randomized to placebo.
Duration of Treatment and Study Duration:	• Screening period - up to 28 days • Surgery – Day 1 • In-Clinic – through Day 3 (48 hours) • In-Clinic – Day 8 Visit • In-Clinic – Day 15 Visit • Follow-up visit – Day 29 Visit (includes the in-clinic days) • Follow-up visit: Day 36 Visit (Visit is only required to assess wound healing *if* wound is not considered healed by Day 29). If the wound is considered healed at Day 29, Day 36 is not required. Assumptions: • Up to five cohorts of 8 subjects each. • The first cohort will employ sentinel dosing, whereby the first 4 subjects in the first cohort will be dosed initially, before the remaining 4 subjects are dosed. • If the available safety assessments for the first 4 subjects are acceptable through the first 24 hours, then the second group of 4 subjects will be dosed. • Subsequent cohorts will not include sentinel dosing.

	• There must be a minimum of 6 days between the dosing of each cohort to allow for the review of all available safety assessments. • This cycle will repeat until all planned cohorts are completed, or the study is stopped due to safety considerations (as detailed below).
Visit Schedule:	A. Screening. Subjects will undergo a screening visit up to 28 days prior to surgery; All screening assessments (including ICF) must be completed at least 1 day prior to surgery. B. Study Unit Admission. Day 1 Prior to surgery, subjects will be enrolled and randomized, and baseline evaluations will be performed prior to surgery. C. Day 1 Surgery. Subjects will undergo bunionectomy procedure, and study drug will be infiltrated prior to wound closure. Time 0 will be defined as the time of completion of drug administration. D. Day 1 Post-surgery through 48 hours post-surgery. Subject will remain at the Study Unit site for monitoring and PK assessments. E. Day 2 Safety follow-up and PK assessments F. Day 3 Safety follow-up, PK assessments, and discharge from Study Unit G. Day 8 Clinic visit for study assessments H. Day 15 Clinic visit for study assessments I. Day 29 Clinic visit for study assessments J. Day 36 Clinic visit for wound healing evaluation and Surgical Site assessment (only for subjects who will need a follow up visit after Day 29) Note: For subjects who terminate early, an early termination (ET) visit will be required. Safety and subject-reported outcome assessments will be performed at the ET visit.
Postsurgical Analgesia:	Day 1 (Hours 0 – 24): • If needed for management of NPRS score of 4 or higher, oxycodone 5 mg PO q 2 hours prn. Day 2 (Hours 25 – 48): • If needed for management of NPRS score of 4 or higher, oxycodone 5 mg PO q 2 hours prn.

	Day 3 – Day 15: • Over-the-counter standard of care analgesics may be used for management of pain. • If needed for management of NPRS score of 4 or higher, oxycodone 5 – 15 mg PO q 4 - 6 hours prn. Day 15 (post-visit) – Day 29/ET: • Over-the-counter standard of care analgesics should be used for management of pain.
Study Objectives:	
Primary:	To evaluate the safety and tolerability of a single intraoperative administration of CA-008 in subjects undergoing bunionectomy. To evaluate the pharmacokinetics of a single intraoperative administration of CA-008.
Secondary:	To evaluate the efficacy of CA-008 in the management of acute postoperative pain in subjects undergoing bunionectomy.
Evaluated Parameters/Outcome Measures:	
Primary:	**Safety:** 1. Adverse events, physical examination (PE), vital signs, electrocardiogram, Surgical Site assessments, neurosensory testing (neurosensory assessments at site of incision and the skin surrounding the incision and neurosensory monitoring will be performed at 24 and 48 hours post-infiltration, and at follow up clinic visits), clinical labs (standard hematology, clinical chemistry/coagulation, urinalysis), concomitant medications. **Pharmacokinetics:** 2. Plasma samples to measure appropriate analyte concentrations will be collected from all subjects. The PK time points will be adequate to determine the PK profiles of the following analytes: • CA-008 • CA-101 • Capsaicin • Capsaicin-glucuronide The time points for collection are at baseline (before dosing), and at 5 minutes, 15 minutes, 30 minutes, 45 minutes, and 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, and 48 hours after dosing.

Secondary:	1. Pain as assessed by a standard 11-point (0–10) NPRS at post-infiltration time points of 15, 30, 45 min, 1, 2, 4, 8, 12 hours, then every 4 hours (if awake at time of assessment) until discharge or ET. Subjects will report pain twice daily through Day 15 or early termination (method of reporting – Subject Diary). 2. Use of postoperative analgesic therapy/treatments and NPRS scores prior to use of the analgesics will be collected during the study period through Day 15 or early termination (by site staff during in-patient stay, and via Subject Diary during outpatient portion).
Endpoints: *Primary (Safety):*	1. Incidence and severity of abnormalities in physical / neurosensory examination, vital signs, ECG, Surgical Site assessments, or clinical labs. 2. Incidence and severity of adverse events and serious adverse events.
Secondary (efficacy):	1. Area-under-the-curve (AUC) over various time points using NPRS score (0–10), with adjustment for use of analgesic therapy/medication. 2. Mean average daily NPRS score of 2 daily diary assessments. 3. Mean daily opioid consumption (in morphine equivalents). 4. Proportion of patients who drop out of the study due to inadequate analgesia from Day 1 to 15. 5. Brief Pain Inventory-short form (BPI-SF) scores at the Day 8 (Week 1), Day 15 (Week 2) and Day 29 (Week 4) or ET clinic visits. 6. Patient Global Evaluation (PGE) at the Day 8 (Week 1), Day 15 (Week 2) and Day 29 (Week 4) clinic visits. 7. Investigator Global Evaluation (IGE) at the Day 8 (Week 1), Day 15 (Week 2) and Day 29 (Week 4) clinic visits.
Eligibility: *Inclusion Criteria:*	1. Male or female aged 18 - 65 years old, inclusive. 2. Planning to undergo a primary unilateral first metatarsal bunionectomy repair, without collateral procedures. 3. Be American Society of Anesthesiology (ASA) physical Class 1 or 2. Appendix J 4. In good health and capable of undergoing a bunionectomy under regional anesthesia. 5. No additional planned surgeries other than a bunionectomy during the

	course of the study. 6. Male subjects must be either sterile (surgically or biologically), or commit to an acceptable method of birth control while participating in the study. 7. Female subjects are eligible only if all of the following apply: a. Not pregnant (female subject of child bearing potential must have a negative serum pregnancy tests at screening and negative urine pregnancy test before surgery); b. Not lactating; c. Not planning to become pregnant during the study; d. Be surgically sterile; or at least two years post-menopausal; or have a monogamous partner who is surgically sterile; or is practicing double-barrier contraception; or practicing abstinence (must agree to use double-barrier contraception in the event of sexual activity); or using an insertable, injectable, transdermal, or combination oral contraceptive approved by the FDA for greater than 2 months prior to screening visits and commits to the use of an acceptable form of birth control for the duration of the study and for 30 days from completion of the study. 8. Have a body mass index ≤ 35 kg/m^2. 9. Willing and able to sign the informed consent form (ICF) approved by the Institutional Review Board (IRB). 10. Willing and able to complete the study procedures and pain scales, and to communicate meaningfully in English with study personnel.
Exclusion Criteria:	1. Subjects with a history of hypertension, cardiovascular disease or a history of cerebrovascular events. 2. Subjects with concurrent painful conditions that may require analgesic treatment during the study period, or, in the opinion of the Investigator, may confound post-operative pain assessments. 3. Have been receiving or have received chronic opioid therapy defined as greater than 15 morphine equivalents units per day for greater than 3 out of 7 days per week over a one-month period within 12 months of study treatment initiation.

	4. Have a known allergy or intolerance to the following medications or related substances: capsaicin, chili peppers, propofol, bupivacaine, benzodiazepines, midazolam, oxycodone, fentanyl or ondansetron. 5. Have a clinically significant abnormal clinical laboratory test value that places the subject at an undue risk according to the judgment of the investigator. 6. Have, as determined by the investigator or the study's medical monitor, a history or clinical manifestations of significant renal, hepatic, cardiovascular, metabolic, neurologic, psychiatric, or other condition that would preclude participation in the study. 7. Use concurrent therapy that could interfere with the evaluation of efficacy or safety, such as any drugs which, in the investigator's opinion, may exert significant analgesic properties or act synergistically with CA-008. 8. Use of disallowed pain medications within 2 days prior to Day 1 (NSAIDs, COX-2 inhibitors, tramadol, ketamine, clonidine, gabapentin, pregabalin, or cannabinoids). 9. Use of central nervous system (CNS) active drugs such as benzodiazepines, tricyclic antidepressants, SNRIs, or SSRIs for pain within seven days prior to Day 1. These drugs are permitted for non-pain indications if the dose has been stable for at least 30 days prior to Day 1 and is planned to remain stable throughout the study. The use of lorazepam and other sleep medications, except those containing analgesic properties, is permitted. 10. Have evidence of a clinically significant 12-lead ECG abnormality according to the judgment of the investigator, including QTcF >450 for men and >470 for women. 11. Use of dietary supplements or over-the-counter (OTC) medications containing significant amounts of capsaicin within 1 day prior to Day 1, and throughout the hospitalization period. 12. Subjects with active cutaneous disease, or other disease, at the anticipated site of surgery. 13. History of peripheral vascular disease, sickle cell disease, vascular grafts, or vasospastic disorders. 14. Use of parenteral or oral corticosteroid(s) within 14 days prior to Day 1.

	15. Known bleeding disorder or is taking agents affecting coagulation preoperatively. Deep venous thrombosis (DVT) prophylaxis of the surgeon's choice is permitted postoperatively. 16. A medical condition that in the investigator's opinion could adversely impact the subject's participation or safety, conduct of the study, or interfere with the pain assessments. 17. Diabetes mellitus. 18. Use of 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 throughout the study. 19. Use of digoxin, warfarin (see exception below), lithium, theophylline preparations, aminoglycosides, and all antiarrhythmics except beta-blockers, and use of anticonvulsants except benzodiazepines within 7 days prior to Day 1 and throughout the study. (Use of warfarin is allowed, at the investigator's discretion, for DVT prophylaxis after the surgery). 20. History of illicit drug use, or prescription medicine or alcohol abuse (regularly drinks > 4 units of alcohol per day; 8 oz. beer, 3 oz. wine, 1 oz. spirits) within the past 2 years, in the opinion of the Investigator. 21. Have positive results on the alcohol breath test 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. 22. 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. 23. Previously participated in a clinical study with CA-008 or capsaicin. 24. Subjects with peripheral neuropathies which would potentially confound the planned neurosensory testing. 25. Subjects who donated blood or plasma within the 30 days prior to screening.
Monitored Parameters:	
Safety:	• ECG • Clinical laboratory tests (standard hematology, clinical

	chemistry/coagulation, urinalysis) (at screening, Day 1 pretreatment, and Day 1 post-treatment): All routine samples will be analyzed by a clinical laboratory. The clinical laboratories tests are as follows: ○ Hematology: hemoglobin, hematocrit, white blood cell count with differential, red blood cell count, platelet count, activated partial thromboplastin time (aPTT), prothrombin time (PT), and international normalization ratio. ○ Blood Chemistry/Coagulation: Alanine aminotransferase (ALT; SGPT) and Aspartate aminotransferase (AST; SGOT), total bilirubin, direct bilirubin, gamma-glutamyl transferase (GGT), blood urea nitrogen (BUN), creatinine, alkaline phosphatase, lactate dehydrogenase (LDH), sodium, potassium, calcium, chloride, albumin, uric acid, and glucose. ○ Serum and urine pregnancy test: βhCG test for female subjects of child bearing potential, usually to be done within 24 hours prior to study intervention. The results must be available prior to administration of study drug. ○ Urinalysis: Urinalysis will include macroscopic analysis and microscopic analysis only when indicated by dipstick. Analyses will include: color, turbidity, specific gravity, pH, glucose, protein, ketones, urobilinogen, bilirubin, blood nitrite, and leukocyte esterase. • 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. Once resolved, the appropriate AE/SAE eCRF page(s) will be updated. • Surgical Site assessments (screening, baseline (Day 1, pre-treatment), 24 and 48 hours after study drug administration, and at every follow-up visit). If there are skin reactions, for example, erythema, pain, pruritus, bruising, swelling, bruising or other skin changes, they will be evaluated and graded for severity regularly until resolution.
Efficacy:	• Pain as assessed by a standard 11-point (0–10) NPRS at post-infiltration time points of 15, 30, 45 min, 1, 2, 4, 8, 12 hours, then every 4 hours (if awake at time of assessment) until discharge or ET. After discharge, subjects will report pain twice daily through Day 15 or early termination (method of reporting - Subject Diary) • Use of postoperative rescue medication and NPRS pain scores prior to

	use of the rescue therapy/medication will be collected through Day 15 or early termination (by site staff during the inpatient stay, and via Subject Diary during the outpatient portion).
AE Considerations:	The following is a partial list of additional AE considerations for the protocol, based on FDA comments: • Vital signs-based adverse event definitions will be pre-specified in the protocol. • Any sensory deficits or clinically significant persistent sensory change 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 is most likely going to be a permanent change and, consequently, classified as an adverse event. • Numbness at or near the incision need not be considered a neurologic AE since this could occur as a result of tissue trauma and inflammation from the surgery. • If a subject develops cardiac adverse events (chest pain, change in heart rate, shortness of breath or diaphoresis) a 12-lead ECG must be performed and read by a qualified physician.
Study Stopping Rules:	Dose escalation, or continuation of dosing, will not occur if subjects in a cohort experience intolerable treatment related AEs on active drug, as defined below: • 1 or more treatment-related AE of grade 4 or higher (per Table 2, Appendix G or Appendix H); • 2 or more treatment-related AEs of grade 3 or higher (per Table 2, Appendix G or Appendix H)
Sample Size Justification:	Sample size is appropriate for Phase 1 dose ranging safety study.
Data Analysis Plan:	Two analysis populations will be defined as follows: • Safety Population will include all subjects who received at least one dose of study drug. • PK Population: will include all subjects who received a full dose of study drug and have sufficient concentration-time profiles for estimation of PK parameters. All safety assessments and baseline characteristics will be summarized using the Safety Population. PK analyses will be performed using the PK population. All summaries will be grouped by the actual treatment received. Placebo subjects will be combined for summaries.

	Safety and tolerability will be evaluated by examining the occurrence of AEs, including Treatment-Emergent AEs. AEs leading to discontinuation from the study, AEs related to the study dose, and AE severity will be summarized by treatment group. Actual and change from baseline in clinical laboratory measures, vital signs, and ECGs will also be assessed and summarized by treatment group. These data will be summarized using descriptive statistics including n, mean, SD, SEM (if appropriate), median, minimum and maximum. Abnormal values will be determined and flagged in the listings. Laboratory shift tables displaying the change (number of subjects) relative to the normal range from baseline to each study visit will also be presented by treatment for each test. The Investigator should exercise medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. The study is not designed to detect a significant difference in analgesia between the two treatment groups. All secondary efficacy endpoints (e.g., NPRS scores), will be summarized over time by treatment using descriptive statistics including confidence intervals as appropriate.
Data Monitoring Committee (DMC):	Safety data will be reviewed by a DMC after the final dosing within each cohort to determine appropriate dose escalation in the next planned cohort.

Table 1 Schedule of Assessments

Assessment	Screening	In Patient					Discharge through EOS	Follow-Up				ET[2]
		Prior to Surgery	Surgery	Post-Surgery	24 hr	48 hr						
Study Day	-28 to -1	1	1	1	2	3		8 ±1 day	15 ±2 days	29 ±2 days	36 ±2 days[1]	
Informed Consent	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	X										
Surgery			X									
Infiltration			X									
Safety Evaluations												
Pregnancy Test	X (serum)	X[3] (urine)										
Vital Signs	X	X		X[4]	X[4]	X[4]		X	X	X		X
Physical Exam[5]	X[5]	X[5]		X[5]	X[5]	X[5]				X[5]		X
12-Lead ECG	X			X[6]								
Surgical Site assessment	X	X			X[7]	X[7]		X	X	X	X	X
Neurosensory Exam	X	X			X[8]	X[8]		X	X	X	X	X
Blood draw for hematology and serum chemistry/coagulation	X	X		X[9]								
Urine sample for urinalysis	X	X		X[9]								
X-ray of Surgical Site	X									X		X
Concomitant Medication Assessment	X	X		X	X	X		X	X	X	X	X
Adverse Event Assessment	X	X	X	X	X	X		X	X	X	X	X
Efficacy Evaluations												
NPRS pain assessments				X[10]	X[10]	X[10]		X	X	X		X
Subject home diary record (NPRS)						X	X[11]	X[11]	X[11]			X
Subject home diary (pain medication)						X		X[14]	X[14]			X

Assessment	Screening	In Patient					Discharge through EOS	Follow-Up				ET[2]
		Prior to Surgery	Surgery	Post-Surgery	24 hr	48 hr						
Study Day	-28 to -1	1	1	1	2	3		8 ±1 day	15 ±2 days	29 ±2 days	36 ±2 days[1]	
Paper Diary (review, distribution and collection)				X[12, 13]					X[14]			X
Supplemental Pain Medication dispensing				X								X
BPI-SF assessment								X	X	X		X
PGE assessment								X	X	X		X
IGE assessment								X	X	X		X
Pharmacokinetics												
Blood draw for PK analysis		X		X[15]	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. Early Termination (ET); Subjects who discontinue participation, or who are discontinued after Day 3 but prior to Day 29.
3. Within 24 hours of scheduled surgery
4. Vital signs: 0.5, 1, 1.5, 2, 4, 6, 8,10 and 12 hours after study drug administration, and then every 4 hours until discharge. Vital sign assessments between 00:00 and 06:00 may be skipped if the subject is sleeping; however, consecutive assessments may not be skipped, and the Hour 12, Hour 24, and Hour 48 assessments must be completed even if the subject is asleep. 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.
5. A complete physical examination including all major body systems will be performed at Screening, prior to Surgery, and at the Day 29 Follow-Up visit. In addition, at the following times, an abbreviated review of systems will be performed to capture changes since Surgery: 1 hour (±30 minutes), 24 hours (± 2 hours), and 48 hours (± 4 hours) after the administration of study medication. Body weight (kg), in indoor clothing, but without shoes, will be measured at Screening, at 48 hours, and on Day 29, or at the time of discontinuation. Height (in cm) will be measured and BMI will be calculated at Screening only.
6. Post-Surgery ECG should be performed at 1.5 hours (±0.5 hour) after administration of study medication.
7. Surgical Site assessment: 24 hours (±2 hours) and 48 hours (±4 hours) after study drug administration.
8. Neurosensory Exam of the Foot / Great toe (bilateral): 24 hours (±2 hours) and 48 hours (±4 hours) after study drug administration.
9. Clinical Laboratory tests (chemistry/coagulation, hematology and urinalysis) should be performed at 1.5 hours (±0.5 hour) after administration of study medication
10. NPRS pain assessments at: 0.25, 0.5, 0.75, 1, 2, 4, 8, 12 hours, then every 4 hours (if awake at time of assessment) until discharge or ET, and prior to supplemental pain therapy or medication. NPRS assessments between 00:00 and 06:00 may be skipped if the subject is sleeping; however, consecutive assessments may not be skipped, and the Hour 12, Hour 24, and Hour 48 assessments must be completed even if the subject is asleep. There will be a ±5 minute window allowed for the collection of each pain intensity assessment in the first 4 hours after the end of surgery, after which will be a ±15 minute window allowed.
11. 2x/day through Day 15
12. Review Subject Diary instructions with subject
13. Dispense Subject Diary
14. Collect Subject Diary

15. Collect blood samples. The time points for collection are at baseline (before dosing), and at 5 minutes, 15 minutes, 30 minutes, 45 minutes, and 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, and 48 hours after dosing. There will be a ±2 minute window allowed for the 5 and 15 minute collections, a ±5 minute window allowed for collections through 4 hours, and a ±15 minute window for collections through 48 hours.

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4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area Under the Curve
BP	Blood Pressure
BPI-SF	Brief Pain Inventory-Short Form
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CK	Creatine kinase
CL	Clearance
Cmax	Maximum plasma concentration
CNS	Central nervous system
CRF	Case Report Form (may include electronic data capture systems or paper forms)
CS	Clinically significant
CSA	Clinical Study Agreement
DBP	Diastolic Blood Pressure
DIP	Distal interphalangeal
DMC	Data Monitoring Committee
DVT	Deep Venous Thrombosis
ECG	Electrocardiogram
EDC	Electronic data capture
ET	Early Termination
FDA	Food and Drug Administration
FIH	First-In-Human
FSH	Follicle Stimulating Hormone
G	Gram
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
HED	Human Equivalent Dose
HEENT	Head, Eye, Ear, Nose and Throat
HRS	Hours
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
MedDRA	Medical Dictionary of Regulatory Activities
Mg	Milligram

Abbreviation	Term
mL	Milliliter
NCS	Not clinically significant
NOAEL	No Observed Adverse Effect Level
NPRS	Numeric Pain Rating Scale
OTC	Over-the-counter
PGE	Patient Global Evaluation
PHN	Postherpetic Neuralgia
PI	Principal Investigator
PK	Pharmacokinetic
PRN	As needed
PT	Prothrombin time
QID	Four times a day
RBC	Red blood cell
SAE	Serious adverse event
SAD	Single Ascending Dose
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SOC	System Organ Class
SNRIs	Serotonin-norepinephrine reuptake inhibitors
SSRIs	Selective serotonin reuptake inhibitors
TEAEs	Treatment emergent adverse events
TID	Three times a day
T1/2	Half-life
Tmax	Time to maximum plasma concentration
TRPV1	Transient receptor potential vanilloid-1
Ug	microgram
US	United States
V	Volume of distribution
WHO	World Health Organization

5. INTRODUCTION

5.1. Background

Concentric Analgesics, Inc. 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), a transient receptor potential cation channel, subfamily V, 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 (Caterina and Julius, 2001). TRPV1 responds to noxious stimuli including capsaicin, heat, and extracellular acidification, and integrates simultaneous exposures to these stimuli (Tominaga et al., 1998). Capsaicin exposure results in initial excitation followed by a functional desensitization of TRPV-1-expressing nociceptors which continues for some time after removal of capsaicin from the site. 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 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.

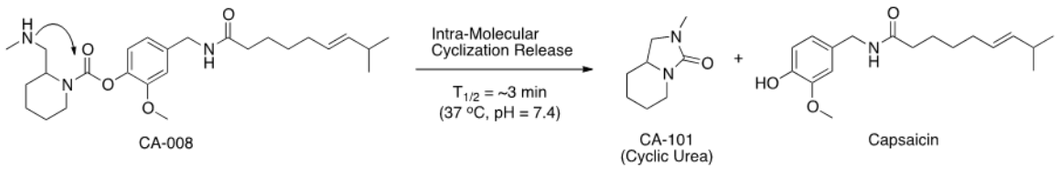
Capsaicin formulations in relatively low concentrations (0.025 to 0.25%) are marketed as over-the-counter products under a tentative final monograph for external analgesics (proposed in the Federal Register 8 Feb 1983; vol 48, No. 27; proposed for 21 CFR 348.12). These formulations include topical ointments, nasal sprays (Sinol-M®) and dermal patches to relieve pain. For example, the Qutenza® (capsaicin) 8% dermal patch (Acorda Therapeutics) was recently approved in the US for the management of neuropathic pain associated with postherpetic neuralgia (PHN). 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 for intraarticular injection for chronic osteoarthritis. Anesiva, Inc. previously had an early stage program for intraarticular injection for osteoarthritis as well as a late-stage program evaluating capsaicin instillation during surgery for the management of post-surgical pain.

5.1.1. 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. Local administration to the source of pain either topically, by infiltration or by instillation into a surgical site results in low systemic levels of capsaicin. Systemic capsaicin is heavily protein-bound, with levels rapidly diminishing to non-detectable levels (e.g., systemic capsaicin from Qutenza is 93% protein bound, present in maximum levels of 17.8 ng/mL immediately following patch administration, and is undetectable within 3 hours after patch removal; FDA Summary Basis for Regulatory Action, page 6). Based on capsaicin's mechanism of action, the duration of pain relief extends well beyond the relatively limited time of exposure.

Capsaicin, however, is virtually insoluble in aqueous media or local anesthetic solutions. Anesiva, which had been developing capsaicin for the management of post-surgical pain and osteoarthritis, solubilized capsaicin in polyethylene glycol (Hartrick et al., 2011). The product was instilled in the 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 surfaces of cut tissue and bone.

CA-008 was created to improve upon the solubility profile of capsaicin and allow for an aqueous formulation that could be simply infiltrated in the wound site to achieve a maximal effect. The free base form of this molecule rapidly cyclizes at physiological pH to yield capsaicin and a cyclic urea, shown in the scheme below:



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

The cyclic urea formed, CA-101, has not been previously evaluated for biological activity and it was shown to be inactive. While not a known compound in the literature, its safety was inherently evaluated in all nonclinical studies with CA-008. The toxicokinetic profiles for CA-008, CA-101, and capsaicin were determined in GLP safety studies.

The synthesis of CA-008 is relatively straightforward, and can be achieved in three synthetic steps from capsaicin starting material.

The current form of CA-008 is a hydrochloride salt (HCl) in a crystalline powder. The HCl salt was chosen to provide a counter ion commonly used in injectable pharmaceutical products, and significant aqueous solubility (>50 mg/mL in deionized water).

5.1.2. 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 et al., 2012) and clinical studies (Savage et al., 2009; Pollak et al., 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). Activation of TRPV1 receptor with an agonist such as capsaicin immediately results in hyperalgesia, erythema, and localized burning sensation. Subsequently, exposure of the receptor to capsaicin leads to a functional desensitization that results in less response to both spontaneous and evoked painful stimuli. This desensitization leads to a sustained analgesia for a long period of time. Given its rapid conversion to capsaicin, a similar profile would be expected following the administration of CA-008 alone.

It is anticipated that CA-008 will be used with a standard of care multimodal analgesia (systemic medications +/- local anesthetic administered by regional block or local infiltration) to manage pain for the first 24 hours after which the TRPV1 agonism may provide adequate pain relief. Alternatively, CA-008 may be used with co-administration of other standard of care local anesthetics to improve analgesia in the initial hours after surgery. Concentric is initially planning to confirm the efficacy of CA-008 as a monotherapy in combination with standard of care systemic analgesic therapy or peripheral nerve blocks for treatment of post-surgical pain for periods of up to 96 hours.

5.1.3. Management of Acute Post-Operative Pain

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 (Chou et al., 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 et al., 2003; Gan TJ et al., 2014). Evidence suggests that less than half of patients who undergo surgery report adequate post-surgical pain relief (Apfelbaum et al., 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 (Kehlet et al., 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 et al., 2012), and there is no ideal way to provide continuous, effective pain relief beyond 12 -18 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, especially due to known safety issues such as respiratory depression, gastrointestinal dysfunction, and abuse. 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 et al., 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 with local anesthetics such as bupivacaine are attractive as a component of multi-modal 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 is highly effective, but limited due to its typically short duration of action.

Liposomal bupivacaine (Exparel®) is approved for single-dose infiltration into the surgical site to produce post-surgical analgesia and is part of the current pain management approach for appropriate surgical procedures.

5.1.4. Clinical burden and unmet need of current standard of care

Opioids are often used to treat short and long-term pain or other indications, but have both 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 2013 there were 21,932 drug overdose deaths from prescription opioid analgesics, not including illicit drug use, and this number has increased significantly over time with increased use of opioid products to treat pain. During the past decade, prescription opioid use became more prevalent in the United States. The death rate due to overdose of opioid analgesics increased considerably. Each day according to statistics, 120 persons die from overdose in the United States and another 6,748 are treated in emergency departments for opioid misuse or abuse of drugs (1). Of these overdose cases, in 2013, 35,663 (81.1%) of the deaths caused by opioid overdose were a result of accidental overdose and unintentional. Pediatric cases (children 18 or younger) account for approximately 50,000 cases of opioid overdose a year and as many as 10,000 deaths.

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.

In addition, accidental or intentional overdose is a life-threatening situation in which severe respiratory depression can result in respiratory and cardiac arrest. Those most at risk of opioid overdose are typically chronic users of opioids for chronic pain or those persons who become addicted to opioids either after initial legitimate use or from illicit use. Risk increases when being treated with rotating opioid medication regimens, which may not allow for complete tolerance to develop to any one opioid. The risk of opioid overdose is also increased with persons discharged from emergency medical care after opioid intoxication or poisoning, and with persons who combine legitimate use of opioids with illicit use.

As outlined above in Section 5.1.3 local anesthetics are effective in reducing post-surgical pain and the need for opioids, but have limitations. Significantly pain relief is short term ranging from 6 to up to 24 hours. Repeat administration of local analgesics are also limited due to increasing toxicity and side effects. Thus, while currently available local anesthetics are effective and appropriate for post-surgical treatment to manage pain for the first 24 hours after surgery, there is an unmet need for safe non-opioid analgesics that would provide pain relief for a period from 24 to 96 hours post-surgery.

5.1.5. Previous Human experience

CA-008 has not been previously studied in humans. There is, however, clinical support for the potential safety and efficacy of capsaicin, the parent molecule released by CA-008 in vivo. 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) and has been studied clinically for wound instillation for postsurgical analgesia (Anesiva; Adlea; capsaicin for instillation).

5.2. Study Rationale

CA-008 is being investigated as a potential therapy for treatment of pain following surgery. In the rat paw incisional model for post-surgical pain, CA-008 and bupivacaine (243 mg in 0.25% bupivacaine and 1:200,000 epinephrine) administered by intraplantar injection demonstrated efficacy on days 1-2. A full battery of toxicology (with toxicokinetic analyses) and safety pharmacology studies have been conducted in two species, rat and beagle dog. In all of these studies, CA-008 was administered as a single dose by subcutaneous administration. CA-008 was well-tolerated in both species with no adverse effects. Additionally, the effect of CA-008 in wound healing was investigated in a rat osteotomy model (a single dose of CA-008 instilled on the femoral bone fracture) and in a pig wound healing model (a single dose of CA-008 administered by wound infiltration). CA-008 had no adverse effects on bone/wound healing in both studies. No repeat dose studies have been conducted so far.

This first-in-human study will evaluate the safety and tolerability of CA-008 in subjects undergoing Unilateral Transpositional First Metatarsal Osteotomy for the Correction of Hallux Valgus Deformity, also termed Bunionectomy. This study will allow for pharmacokinetic and pharmacodynamic (safety and preliminary efficacy) assessment of CA-008 in this study population in order to inform future clinical / surgical studies in our clinical development plan. CA-008 is administered (injected and instilled) directly into the postoperative wound during the surgery, and this study will also be looking at regional safety i.e. wound healing in a double-blinded manner, utilizing study subjects in each dose cohorts that will receive either active or placebo treatment. An independent DMC will be charged with evaluating the safety of each study dose, and will monitor / guide the planned dose escalation within the study.

This study was originally designed to look at four different doses of CA-008, and based on the overall safety and tolerability profile we expected to be able to select one or more doses for our planned phase 2 bunionectomy study. This study was also intended to inform us about the potential regional safety and PK/PD profiles to be expected when CA-008 is used in the treatment of pain associated with other surgeries. The goal from the beginning was to find the maximum tolerated and safe dose (volume/concentration) of CA-008.

At this point, we have studied the first four cohorts and there have been no safety and tolerability concerns identified. After discussion and presentation with the DMC, it was determined that it was safe to proceed to study a higher dose in Cohort 5.

It should be noted, that the planned assessments and study of cohort 5 will be the same as that implemented in the study for the previous 4 cohorts. This final cohort will also be presented to the DMC for final review / safety evaluation.

6. STUDY OBJECTIVES

6.1. Primary Objectives

The primary objectives of the study are:

- To evaluate the safety and tolerability of a single intraoperative administration of CA-008 in subjects undergoing bunionectomy.
- To evaluate the pharmacokinetics of a single intraoperative administration of CA-008.

6.2. Secondary Objectives

The secondary objective of the study is to evaluate the efficacy of CA-008 in the management of acute postoperative pain in subjects undergoing bunionectomy.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design and Plan

This is a single-center, randomized, double-blind, placebo-controlled, single ascending dose, sequential-group Phase 1 study.

The study will be conducted utilizing a cohort design, with sequential groups of 8 subjects. Within each dose cohort, 6 subjects will be randomized to active, and 2 will be randomized to placebo. The initial cohort will receive the lowest planned dose of CA-008, and sequential cohorts will receive escalating doses of CA-008 in a fixed volume of administration. There will be at least a 6-day period between dosing the last subject in a cohort and the first subject in the subsequent cohort, to evaluate safety prior to dose escalation (i.e., dosing in a given cohort may only proceed after all subjects in the previous cohort are discharged). Dose escalation rules will be protocol defined.

Subjects will be undergoing unilateral transpositional first metatarsal osteotomy for the correction of hallux valgus deformity (bunionectomy). In accordance with standard of care, subjects will receive regional anesthesia (MAYO Block) utilizing 0.5% bupivacaine (up to 30 cc total). Prior to wound closure, 10 mL (for Cohorts 1-4) and 14 mL (for Cohort 5) of study drug will be injected into the soft tissues and periosteum of the surgical site.

After the surgery, subjects will be monitored for 48 hours at the trial site. Safety and efficacy evaluations will be performed as described herein. Subjects will be required to meet certain pre-specified criteria prior to discharge.

7.1.1. Screening Phase (Day -28 to Day -1):

Subjects requiring bunionectomy between the ages of 18 and 65 years, inclusive, will be screened for participation at the study site in the United States within 28 days of surgery/study drug administration. The following assessments will be completed:

- Informed Consent
- Inclusion / Exclusion
- Demographics
- Medical and surgical history
- Prior/current medications
- Physical Exam (PE)
- X-ray of Surgical Site
- Neurosensory Exam of the Foot / Great toe (bilateral)
- Clinical laboratory tests (chemistry/coagulation, hematology, and urinalysis)
- Urine Drug Screening (UDS)
- Alcohol breath test
- Serum Pregnancy test (FOCBP)
- Surgical Site Assessment
- Vital signs (resting blood pressure, resting pulse, oral temperature and resting respiration rate). Tests must be obtained after resting (seated/reclined) for ≥ 5 minutes.
- 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
- Adverse Event (AE) Assessment

7.1.2. Day 1- Prior to surgery (baseline) up to the end of surgery

7.1.2.1. 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 28 days of screening. The following assessments will be performed:

- Inclusion / Exclusion
- Medical and surgical history
- Prior medications
- PE
- Neurosensory Exam of the Foot / Great toe (bilateral)
- Clinical laboratory tests (chemistry/coagulation, hematology, and urinalysis)
- Urine Pregnancy test (FOCBP)
- Urine Drug Screening (UDS)
- Alcohol breath test
- Blood draw for PK analysis
- Vital signs (resting blood pressure, resting pulse, oral temperature and resting respiration rate). Tests must be obtained after resting (seated/reclined) for ≥ 5 minutes.
- Subject pain assessment training
- Surgical Site Assessment
- AE Assessment
- Randomize to treatment

7.1.2.2. Surgery

Subjects will then undergo primary, unilateral, transpositional first metatarsal osteotomy for correction of hallux valgus deformity. The bunionectomy surgery will be performed under light to moderate sedation which include propofol, fentanyl and/or midazolam. Subjects will receive regional anesthesia (MAYO Block) utilizing 0.5% bupivacaine (up to 30 cc total). The MAYO block should be done proximal to the surgical wound and should not involve the immediate area of the planned surgical incision. Upon completion of surgery, subjects will be observed for 48-hours in the clinic. AEs will be assessed during the surgery.

7.1.3. Audio-Visual Recording

As this is the first in human use of the study drug, CA-008, the Sponsor may wish to observe its intra-operative application by recording a number of the procedures and/or taking still images of the surgical site during the follow-up period. This will allow for review of the video/images at a later date to better understand the surgical injection technique and visual healing of the surgical site, and educate the study team on the procedure.

During the informed consent process, subjects will be asked if they would like to participate in audio-visual recording of their surgery, or allow subsequent photographs to be taken. This is optional, and their response will in no way affect their inclusion in the study. Their response will be included on the ICF.

If a subject agrees to participate, the sponsor may perform intra-operative audio-visual recording which will be focused only in the area where the study drug will be administered. The recording will start prior to the anticipated time of study drug administration and will end after the completion of study drug administration. Additionally, Site staff may take photographs of the surgical site during follow-up visits.

7.1.4. Administration of Study Medication

Administration of the study drug into the surgical site: A total of 10 mL (for Cohorts 1-4) and a total of 14 mL (for Cohort 5) of the investigative product will be administered into the surgical site as follows:

- At time of closure of capsule:
    - Infiltration of deep soft tissue and capsule with a total of:
        - 6 mL volume for Cohorts 1-4
        - 9 mL volume for Cohort 5
    - Instillation at cut bone with a total of 2 mL volume for all Cohorts
- Following closure of the capsule and prior to closure of the skin and subcutaneous layer:
    - Instillation of wound with 2 mL volume for Cohorts 1-4; study drug is applied to all exposed surfaces prior to subcutaneous and skin closure
    - Instillation of wound with 3 mL volume for Cohort 5; 2 mL of study drug will be instilled into the space under closed capsule, and 1 mL of study drug applied to all exposed surfaces prior to subcutaneous and skin closure)

7.1.5. Time 0 will be defined as the time of completion of drug administration.Day 1 (Post-Surgery) to Day 3 (Discharge)

Following surgery, subjects will be transferred to the appropriate recovery unit where they will undergo an assessment of safety and efficacy over the next 48 hours. The schedule of assessments are as follows:

- Pain intensity (assessed with NPRS): at 0.25, 0.5, 0.75, 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 hours after the administration of study medication. Assessments between the hours of 00:00 and 06:00 may be skipped if the subject is sleeping; however, consecutive assessments may not be skipped, and the Hour 12, Hour 24, and Hour 48 assessments must be completed even if the subject is asleep.
- Vital signs: 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 hours after the administration of study medication. Assessments between the hours of 00:00 and 06:00 may be skipped if the subject is sleeping; however, consecutive assessments may not be skipped, and the Hour 12, Hour 24, and Hour 48 assessments must be completed even if the subject is asleep.
- Physical exam: 1.0, 24, and 48 hours after the administration of study medication.
- ECG: 1.5 hours after the administration of study medication.
- Surgical Site assessment: 24 and 48 hours after the administration of study medication.
- Neurosensory Exam of the Foot / Great toe (bilateral): 24 and 48 hours after the administration of study medication.
- Clinical laboratory tests (chemistry/coagulation, hematology, and urinalysis): 1.5 hours after the administration of study medication.
- Blood draw for PK analysis: are at baseline (before dosing), and at 5 minutes, 15 minutes, 30 minutes, 45 minutes, and 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, and 48 hours after dosing.
- Subjects with inadequately controlled pain may request rescue at any time; however, subjects will be encouraged to receive rescue medication only with an NPRS ≥ 4. Additionally, subjects should be encouraged to wait at least 1 hour after completion of surgery (i.e. completion of sutures) before utilizing pain rescue medication, if possible. Pain intensity (NPRS) will also be completed within 15 minutes prior to use of pain rescue medication.
- Concomitant medications.
- All SAEs that occur from the time a subject's informed consent will be captured. All SAEs and non-serious AEs will be documented and followed from the time of administration of study drug. Non-serious AEs that occur between Screening and the study procedure should be considered medical history, and be added to the subject’s medical record.

After completing the assessments through 48 hours after study medication administration, the diary for at-home use will be reviewed and subjects will be discharged from the study center with

diary to record pain assessments and pain medication at home. Subjects will be provided routine standard of care for pain management after discharge from the study center. Subjects will be instructed to return to the study center on Day 8 [±1 day] for follow-up assessments.

7.1.6. Days 3 through 8:

In their diary, subjects will assess their pain intensity once in the morning (08:00 ±4 hours), and once in the evening (20:00 ±4 hours) using the NPRS. Subjects will also record any medication they take to treat their pain, and will capture an additional NPRS within 15 minutes prior to each dose of pain medication.

Subjects will return to the study center on Day 8 [±1 day] for the following assessments:

- Subject home diary review (pain intensity and pain medication)
- Pain Intensity (NPRS)
- Vital signs
- Surgical Site assessment
- Neurosensory Exam of the Foot / Great toe (bilateral)
- Concomitant Medication Use
- AE Assessment
- Brief Pain Inventory-Short Form (BPI-SF)
- Patient Global Evaluation (PGE)
- Investigator Global Evaluation (IGE)

7.1.7. Days 9 through 15:

In their take-home Diary, subjects will assess their pain intensity once in the morning (08:00 ±4 hours), and once in the evening (20:00 ±4 hours) using the NPRS. Subjects will also record any medication they take to treat their pain.

Subjects will return to the study center on Day 15 [±2 days] for the following assessments:

- Subject home diary review (pain intensity and pain medication)
- Pain Intensity (NPRS)
- BPI-SF
- PGE
- IGE
- Vital signs
- Surgical Site assessment
- Neurosensory Exam of the Foot / Great toe (bilateral)
- Concomitant Medication Use
- AE Assessment

7.1.8. Day 29 / Early Termination

Subjects will return to the study center on Day 29 [±2 days], or at the time of discontinuation, for the following assessments:

- Subject home diary review (pain intensity and pain medication, *if* ET is ≤ Day 15)
- Pain Intensity (NPRS)
- BPI-SF
- PGE
- IGE
- PE
- Vital signs
- X-ray of Surgical Site
- Surgical Site assessment (when assessed, if the Investigator observes insufficient wound healing, the subject will be scheduled for a follow-up visit on Day 36. If the wound is considered healed at Day 29, Day 36 is not required.)
- Neurosensory Exam of the Foot / Great toe (bilateral)

- Concomitant Medication Use
- AE Assessment

7.1.9. Day 36 (if required)

If required due to insufficient wound healing noted at Day 29 visit, Subjects will return to the study center on Day 36 [±2 days] for the following assessments:

- Surgical Site assessment
- Neurosensory Exam of the Foot / Great toe (bilateral)
- Concomitant Medication Use
- AE Assessment

7.1.10. Unscheduled Visit

Assessments performed at Unscheduled Visits will be at the discretion of the Investigator.

7.2. Discussion of Study Design

This trial is designed to determine the recommended dose and define the toxicity profile of CA-008.

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 deformities of the first metatarsal and is used as a model to assess adequate duration of acute pain to measure multiple-day efficacy (Singla et al., 2013; Wang et al., 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) 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.

8. SELECTION OF STUDY POPULATION

8.1. Inclusion Criteria

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

1. Male or female aged 18 - 65 years old, inclusive.
2. Planning to undergo a primary unilateral first metatarsal bunionectomy repair, without collateral procedures.
3. Be American Society of Anesthesiology (ASA) physical Class 1 or 2. Appendix J
4. In good health and capable of undergoing a bunionectomy under regional anesthesia.
5. No additional planned surgeries other than a bunionectomy during the course of the study.
6. Male subjects must be either sterile (surgically or biologically), or commit to an acceptable method of birth control while participating in the study.
7. Female subjects are eligible only if all of the following apply:
    a. Not pregnant (female subject of child bearing potential must have a negative serum pregnancy tests at screening and negative urine pregnancy test before surgery);
    b. Not lactating;
    c. Not planning to become pregnant during the study;
    d. Be surgically sterile; or at least two years post-menopausal; or have a monogamous partner who is surgically sterile; or is practicing double-barrier contraception; or practicing abstinence (must agree to use double-barrier contraception in the event of sexual activity); or using an insertable, injectable, transdermal, or combination oral contraceptive approved by the FDA for greater than 2 months prior to screening visits and commits to the use of an acceptable form of birth control for the duration of the study and for 30 days from completion of the study.
8. Have a body mass index ≤ 35 kg/m^2.
9. Willing and able to sign the informed consent form (ICF) approved by the Institutional Review Board (IRB).
10. Willing and able to complete the study procedures and pain scales, and to communicate meaningfully in English with study personnel.

8.2. Exclusion Criteria

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

1. Subjects with a history of hypertension, cardiovascular disease or a history of cerebrovascular events.
2. Subjects with concurrent painful conditions that may require analgesic treatment during the study period, or, in the opinion of the Investigator, may confound post-operative pain assessments.
3. Have been receiving or have received chronic opioid therapy defined as greater than 15 morphine equivalents units per day for greater than 3 out of 7 days per week over a one-month period within 12 months of study treatment initiation.
4. Have a known allergy or intolerance to the following medications or related substances: capsaicin, chili peppers, propofol, bupivacaine, benzodiazepines, midazolam, oxycodone, fentanyl or ondansetron.

5. Have a clinically significant abnormal clinical laboratory test value that places the subject at undue risk according to the judgment of the investigator.
6. Have, as determined by the investigator or the study's medical monitor, a history or clinical manifestations of significant renal, hepatic, cardiovascular, metabolic, neurologic, psychiatric, or other condition that would preclude participation in the study.
7. Use concurrent therapy that could interfere with the evaluation of efficacy or safety, such as any drugs which, in the investigator's opinion, may exert significant analgesic properties or act synergistically with CA-008.
8. Use of disallowed pain medications within 2 days prior to Day 1 (NSAIDs, COX-2 inhibitors, tramadol, ketamine, clonidine, gabapentin, pregabalin, or cannabinoids).
9. Use of central nervous system (CNS) active drugs such as benzodiazepines, tricyclic antidepressants, SNRIs, or SSRIs for pain within seven days prior to Day 1. These drugs are permitted for non-pain indications if the dose has been stable for at least 30 days prior to Day 1 and is planned to remain stable throughout the study. The use of lorazepam and other sleep medications, except those containing analgesic properties, is permitted.
10. Have evidence of a clinically significant 12-lead ECG abnormality according to the judgment of the investigator, including QTcF >450 for men and >470 for women.
11. Use of dietary supplements or over-the-counter (OTC) medications containing significant amounts of capsaicin within 1 day prior to Day 1, and throughout the hospitalization period.
12. Subjects with active cutaneous disease, or other disease, at the anticipated site of surgery.
13. History of peripheral vascular disease, sickle cell disease, vascular grafts, or vasospastic disorders.
14. Use of parenteral or oral corticosteroid(s) within 14 days prior to Day 1.
15. Known bleeding disorder or is taking agents affecting coagulation preoperatively. Deep venous thrombosis (DVT) prophylaxis of the surgeon's choice is permitted postoperatively.
16. A medical condition that in the investigator's opinion could adversely impact the subject's participation or safety, conduct of the study, or interfere with the pain assessments.
17. Diabetes mellitus.
18. Use of 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 throughout the study.
19. Use of digoxin, warfarin (see exception below), lithium, theophylline preparations, aminoglycosides, and all antiarrhythmics except beta-blockers, and use of anticonvulsants except benzodiazepines within 7 days prior to Day 1 and throughout the study. (Use of warfarin is allowed, at the investigator's discretion, for DVT prophylaxis after the surgery).
20. History of illicit drug use, or prescription medicine or alcohol abuse (regularly drinks > 4 units of alcohol per day; 8 oz. beer, 3 oz. wine, 1 oz. spirits) within the past 2 years, in the opinion of the Investigator.
21. Have positive results on the alcohol breath test 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.
22. 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.
23. Previously participated in a clinical study with CA-008 or capsaicin.
24. Subjects with peripheral neuropathies which would potentially confound the planned neurosensory testing.
25. Subjects who donated blood or plasma within the 30 days prior to screening.

8.3. Removal of Subjects from Therapy or Assessment

A subject is free to withdraw his/her 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 drug, 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 9.6)
- 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. In the event that 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.

In the event that a subject is discontinued while at the clinical site, the early termination procedures shown in the Schedule of Assessments (Table 1) should be performed prior to discharge from the clinical site. The Investigator should ask the subject to for the Follow-up procedures, provided that the subject has not withdrawn consent for those procedures. If a subject refuses to complete early termination/Follow-up procedures or continued data collection, this information will be recorded.

8.4. Study Stopping Rules

Dose escalation, or continuation of dosing, will not occur if subjects in a cohort experience intolerable treatment related AEs on active drug, as defined below:

- 1 or more treatment-related AE of grade 4 or higher (per Table 2, Appendix G, or Appendix H);
- 2 or more treatment-related AEs of grade 3 or higher (per Table 2, Appendix G, or Appendix H)

Table 2 Study Stopping Rules

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

8.5. Safety Oversight

A Data Monitoring Committee (DMC) comprised of independent consultants with appropriate medical expertise will regularly monitor all aspects of patient safety throughout this study. The DMC will be responsible for adjudicating all available data in a blinded fashion (which may include: vital signs, ECGs, clinical laboratory tests, Surgical Site assessments, Neurosensory evaluations, incidence of SAE and TEAE) to assess the safety of each dose level of CA-008 prior to escalating to the next dose level. Details regarding the DMC will be included in the DMC Charter.

8.6. Study Restrictions

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

- Subjects will be asked to abstain from consuming more than 1 (women) or 2 drinks (men) per day of alcohol throughout the study.
- Subjects will be asked to abstain from illicit drug use or non-medical use of therapeutic drugs throughout the study.
- Subjects will be asked to abstain from taking prohibited medications described in Section 9.7 throughout the study.

9. TREATMENTS

9.1. Treatment Administration

9.1.1. Study Medication

The proposed doses of CA-008 to be evaluated in this study are:

- CA-008, 0.5 mg in 10 mL of saline (50 µg/mL)
- CA-008, 1.0 mg in 10 mL of saline (100 µg/mL)
- CA-008, 2.0 mg in 10 mL of saline (200 µg/mL)
- CA-008, 3.0 mg in 10 mL of saline (300 µg/mL)
- CA-008, 4.2 mg in 14 mL of saline (300 ug/mL)

In addition, saline for injection, USP will be used.

The study drug is provided as a concentrate that will be diluted just before use in the surgical setting, 1:10 with saline for injection, USP. The study drug will be stored at -20°C (-15°C to -30°C) until the day of surgery. The study drug will be blinded before introduction to surgical setting.

Note: Weights of CA-008 are provided for the free base, without counterions. The drug product uses CA-008 HCl as drug substance, the weights and concentrations of the drug product are shown based on the free base.

9.1.2. Placebo

The placebo will be 10 mL of saline for Cohorts 1-4, and 14 mL of saline for Cohort 5.

The placebo is provided identical to the study drug, and will be "diluted" just before use in the surgical setting, 1:10 with saline for injection, USP. The study drug will be stored at -20°C (-15°C to -30°C) until the day of surgery. The study drug will be blinded before introduction to surgical setting.

9.1.3. Rescue Medications

While in-clinic, subjects will be treated with the prescribed analgesic regimen (oxycodone 5 mg every 2 hours); however, if subjects do not get adequate analgesic relief they will be discontinued from the efficacy portion of the study. At this point, subject's will receive standard of care analgesics (which may or may not include intravenous opioids). Regardless of discontinuation status, subjects will be followed for safety. Discontinuation affects the computation of the analgesic endpoint only. In previous post-operative Day 1 bunionectomy studies, oxycodone 5 mg every 2 hours has provided adequate analgesic relief to >90% of placebo subjects.

Day 1: Hours 0-24

- If needed for management of NPRS score of 4 or higher, oxycodone 5 mg every 2 hours.
- An NPRS should be completed within 15 minutes prior to use of rescue medication.

Day 2: Hours 25-48

- If needed for management of NPRS score of 4 or higher, oxycodone 5 mg every 2 hours.
- Subjects should complete their NPRS within 15 minutes prior to taking rescue medication.

Day 3 - Day 15:

- Over-the-counter standard of care analgesics may be used for management of pain.
- If needed for management of NPRS score of 4 or higher, oxycodone 5 - 15 mg every 4 - 6 hours.
- Subjects should complete their NPRS within 15 minutes prior to taking rescue medication.

Day 15 (post-visit) - Day 29/ET

- Over-the-counter standard of care analgesics may be used for management of pain.

9.2. Identity of Investigational Product(s)

9.2.1. Handling, Storage, and Accountability

All study drug 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.

All study drug should be stored in a secured area and in accordance with the product labeling and all applicable laws, regulations, and local/institutional requirements. The Drug product will need to be stored at -20°C (-15°C to -30°C) in a freezer. A description of storage conditions for all investigational products will be provided in the Pharmacy Manual.

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.

Mishandling, potential theft, significant loss of clinical supplies, including Investigational Product and Rescue Medication 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 product complaint form, including documenting if a subject sold drug or gave drug to a friend or relative, if there was a discrepancy in drug accountability and suspected diversion, if a subject had drug stolen, or if there was diversion or theft by site staff or others.

9.2.2. Dispensing and Administration

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

All study drug will be administered by designated blinded healthcare professional(s).

9.3. 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.

There will be up to 5 cohorts of subjects, each cohort consisting of 8 subjects. Cohorts of subjects will be randomized to either the following active medications or placebo in a 3:1 ratio. The first 4 subjects in cohort one will be dosed initially before the remaining 4 subjects are dosed. Three of these subjects will randomly receive active treatment and 1 will be randomized to placebo. If the safety assessments are acceptable through the first 24 hours, then the second group of 4 subjects will be dosed. Three of these subjects will randomly receive active treatment and 1 will be randomized to placebo.

Once any subject number or randomization number is assigned, it cannot be reassigned to any other subject. This study will use central randomization, as described in Section 10.2.

Subjects may be rescreened if the screening window is exceeded due to scheduling issues.

9.4. Selection of Doses

9.4.1. Dose Rationale

In Good Laboratory Practice (GLP) toxicology studies conducted, the NOAEL was identified as 1.5 mg/kg in the rat and 0.25 mg/kg in the dog. The estimation of the maximum safe starting dose for the first-in-human (FIH) study followed the procedure proposed in the FDA Guidance for Industry document "Estimating the Maximum Safety Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" (FDA, 2005). Using a conversion factor of 6.2 for rat and 1.8 for dog, the human equivalent dose (HED) is:

- Rat HED = 1.5/6.2 = 0.24 mg/kg
- Dog HED = 0.25/1.8 = 0.14 mg/kg

The most relevant and sensitive species was determined to be the dog (HED = 0.14 mg/kg). Using the recommendation of 1/10th of the HED, a safe starting dose for an FIH would be 0.014 mg/kg. In a 60 kg person, this supports a conservative starting dose of 0.84 mg with a maximum dose of 8.4 mg. The clinical dosing is based on CA-008 and not the salt form. Converting the starting dose to the free base results in a conservative starting dose of 0.77 mg with a maximum dose of 7.7 mg.

As presented in Table 3, Concentric will round down to 0.5 mg as a starting dose and dose escalate to up to 3 mg (cohorts of 0.5, 1, 2, and 3 mg). The 0.5 mg starting dose represents a safety margin from 15.4 at the low dose and the 3 mg maximum dose planned represents a safety margin of 2.6 at the high dose. The rationale to dose escalate to a maximum of 3 mg is based on published clinical data with Capsaicin that demonstrates that this dose should achieve a maximal pharmacologic effect while remaining tolerable. Specifically, studies performed by Anesiva using capsaicin for wound instillation in hernia (Aasvang et al., 2008 and 2010) and bunionectomy (Pollak et al., 2009).

Table 3 Human Equivalent Dose and Safety Margins for the CA-008 Starting Dose

NOAEL (mg/kg)	HED (mg/kg)	HED for CA-008 HCl[1] (mg)	HED for free base[1] (mg)	Proposed Human Clinical Dose (mg)	Safety Margin of FIH Dosing
0.25	0.14	8.4	7.7	0.5	15.4
				1	7.7
				2	3.9
				3	2.6
				4.2	1.8

[1] Based on a 60 kg human

Thus, the safety of CA-008 was established in relevant animal models and is partially based on knowledge from prior human studies with Capsaicin. 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 0.5 mg/person and a maximum dose of 4.2 mg/person, has a minimal risk of causing adverse events. Taken together, the characterization of the pharmacology, pharmacokinetics, and toxicology profiles are considered sufficient to support the intended use of CA-008 in the initial Phase 1 study for the treatment of acute post-surgical pain.

9.5. Selection and Timing of Dose

CA-008 is a pH labile prodrug of capsaicin that rapidly releases capsaicin after administration into tissue. Decision for single administration at the time of surgery is based on capsaicin's mechanism of action. Capsaicin exposure results in initial excitation followed by a functional desensitization of TRPV-1-expressing nociceptors which continues for some time after removal of capsaicin from the site. Administration while the patient is under anesthesia for the procedure

addresses the pain that results from TRPV1 agonism. Administration of CA-008 during the closure process is ideal for delivering therapy to the surgical site, thus optimizing target engagement. During closure, the surgical tissue is exposed and visible we can ensure that we have complete and adequate delivery of drug to the potential areas where pain is being generated.

What is unknown is whether CA-008 will behave the same as Capsaicin, however we expect that it will. To this end, administration methods that were followed in previous successful post-surgical pain studies will be applied in this 1st in man study.

9.6. Blinding

In order 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.

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 or 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.

Safety reviews of cohorts of subjects will be performed in a blinded manner unless the data warrant unblinding due to safety concerns. It is assumed that the need to unblind a study subject's treatment assignment will occur in the setting of an SAE, and therefore, all procedures for the reporting of a SAE must be followed (see Section 11.1.3).

9.7. Prior and Concomitant Therapy

All non-study medications, including prescription, over-the-counter, or herbal therapies, used by the subject will be documented for the 30 days prior to Screening and throughout the study. The Investigator will determine if the prior/concomitant medication(s) affect the subject's eligibility to participate or continue to participate in the study. The following concomitant medications and therapies may be permitted during the study:

- Rescue medication, as described in Section 9.1.3

On a case-by-case basis, the Investigator is permitted to allow the use of some concomitant medications, for example, to treat an AE, as long as the Investigator determines that the medication will not affect the subject's safety or study integrity (e.g., topical medications). Wherever possible, the Investigator should obtain approval from the Medical Monitor prior to administering the medication.

9.8. Treatment Compliance

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

10. STUDY PROCEDURES AND ASSESSMENTS

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

10.1. Demographics and Other Baseline Characteristics

10.1.1. Informed Consent

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

10.1.2. Demographics

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

10.1.3. Medical and Surgical History

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

10.1.4. Medication History

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

10.1.5. Contraceptive Requirements

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

Female subjects of non-childbearing potential are not required to use contraception or undergo pregnancy tests; however, they must be surgically sterile (hysterectomy and/or bilateral oophorectomy/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 2 years without another cause.

10.2. Eligibility Review and Randomization

Prior to randomization, subjects must meet all inclusion and not meet any exclusion criteria as outlined in Sections 8.1 and 8.2.

The Investigator or designee must document that the subjects meet each individual criterion via a signed note or eligibility and inclusion/exclusion checklist during Screening and at Day 1 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.

10.3. Subject Pain Assessment Training

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

10.4. Efficacy Assessments

Details regarding primary and secondary endpoints are provided in Section 10.6 (Efficacy Variables); and discussed further in Section 13 (Statistical Analysis). The following sections provide an overview of the efficacy assessments included in the study.

10.4.1. Numerical Pain Rating Scale (NPRS) for Pain Intensity

The NPRS is an 11-point scale with anchors 0 (no pain) and 10 (worst possible pain) (Appendix B; Ferreira-Valente MA et al., 2011; Hjermstad MJ, 2011). Subjects will record the intensity of their current pain at the following times over the initial 48-hour period in a diary: at 0.25, 0.5, 0.75, 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 hours after the administration of study medication and within 15 minutes prior to use of pain medication. Subjects should be at rest for at least 10 minutes prior to completing NPRS assessments. NPRS Assessments between the hours of 00:00 and 06:00 may be skipped if the subject is sleeping; however, consecutive assessments may not be skipped, and the Hour 12, Hour 24, and Hour 48 assessments must be completed even if the subject is asleep. There will be a ±5 minute window allowed for the collection of each pain intensity assessment in the first 4 hours after the end of surgery, after which will be a ±15 minute window allowed.

After discharge and through Day 15, subjects will rate their pain intensity using the NPRS once in the morning (08:00 ±4 hours) and once in the evening (20:00 ±4 hours), and will capture an additional NPRS within approximately 15 min prior to each dose of pain medication. Subjects will also rate their pain intensity using the NPRS at the Day 8, Day 15 and Day 29/Early Termination (ET) visit.

10.4.2. Patient Global Evaluation (PGE)

At the clinic visits on Day 8, Day 15 and Day 29/ET, each subject will be asked to report their satisfaction with the study treatment for pain using a 4-point scale Each subject will be asked the following question: How would you rate the study medication that you have received for pain? Poor (0), Fair (1), Good (2), or Excellent (3). Appendix E

10.4.3. Investigator Global Evaluation (IGE)

At the clinic visits on Day 8, Day 15 and Day 29/ET, the investigator will report their satisfaction with the subject's study treatment for pain using a 4-point scale. A study Investigator will be asked the following question: How would you rate the study medication that the patient received for pain? Poor (0), Fair (1), Good (2), or Excellent (3). Appendix F

10.4.4. Brief Pain Inventory-short form (BPI-SF)

At the clinic visits on Day 8, Day 15 and Day 29/ET, the Brief Pain Inventory- Short Form be assessed. Appendix D

10.4.5. Rescue Medications

The details of rescue medication will be recorded beginning from the end of surgery through 14 days after the end of surgery (Day 15 visit) or to Early Termination Visit. Subjects will be instructed on the proper use and timing of rescue medication.

10.5. Safety Assessments

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

10.5.1. Clinical Laboratory Assessments

All protocol-specified laboratory tests on blood and urine samples will be performed at a selected central laboratory. The lab will generate laboratory reports and forward them to the clinical site in a timely manner. It is the responsibility of the Investigator to review and sign all lab reports expeditiously, in order to document appropriate safety monitoring of study subjects. The Investigator should sign and date each lab report concurrent with her or his review, and should indicate the clinical significance of each abnormal/flagged value by noting “NCS” (not clinically significant) or “CS” (clinically significant), for example. Notations indicating that a value is clinically significant should also include a brief description of the underlying disease or condition that is associated with the value, e.g., “CS/mild anemia.” In general and as determined by the investigator, abnormal, clinically significant laboratory values are expected to be associated with an item recorded in medical history or with an AE.

Blood and urine samples will be collected, processed, and shipped according to instructions from the safety laboratory. Additional laboratory 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. Specific hematology, coagulation, biochemistry, and urinalysis assessments are listed in Table 4.

Table 4 Clinical Laboratory Assessments

<table>
<tr><th>Hematology</th><th>Biochemistry</th><th>Urinalysis</th></tr>
<tr><td>Hematocrit
Hemoglobin
Red blood cell (RBC) count
Total and differential (absolute) white blood cell count
Platelet count</td><td rowspan="3">Sodium
Potassium
Calcium
Chloride
Glucose
Creatinine
Blood urea nitrogen (BUN)
Albumin
Total bilirubin
Direct bilirubin
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Lactic dehydrogenase (LDH)
Gamma-glutamyl transferase (GGT)
Alkaline phosphatase
Uric acid</td><td rowspan="3">Color
Turbidity
pH
Specific gravity
Ketones
Protein
Glucose
Bilirubin
Blood Nitrite
Urobilinogen
Leukocyte esterase
Microscopic examination of sediment, only if urinalysis dipstick results are abnormal</td></tr>
<tr><td>Coagulation</td></tr>
<tr><td>Activated partial thromboplastin time (aPTT)
Prothrombin time (PT)
International normalized ratio (INR)</td></tr>
</table>

The clinical laboratory tests will be completed at Screening, Prior to surgery, and at 1.5 hours (±0.5 hour) after the administration of study medication. 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 ULN / Tot. Bili > 2 X ULN/ Alk Phos. >2X ULN will be considered an adverse event, as well as any other changes deemed clinically significant by the Investigator.

10.5.2. Urine Drug Screen and Alcohol Breath Test

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

The drug and alcohol screens will be performed in-house at the Clinical Unit. If any of these tests are positive, the subject will not be allowed further participation in the trial. However, a positive test may be repeated at the discretion of the PI.

10.5.3. X-Ray

An X-ray of the surgical site will be performed during screening and at Day 29/ET.

10.5.4. Vital Signs

Vital signs will consist of temperature, blood pressure (systolic and diastolic blood pressure, mmHg), pulse rate (beats per minute), and respiratory rate (breaths/min) collected while sitting, following a rest period of at least 5 minutes. Vital signs will be assessed at Screening, Prior to Surgery, and then 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 hours after the administration of study medication. Vital sign assessments between the hours of 00:00 and 06:00 may be skipped if the subject is sleeping; however, consecutive assessments may not be skipped, and the Hour 12, Hour 24, and Hour 48 assessments must be completed even if the subject is asleep. 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.

Vital signs will also be assessed on the Days 8, 15 and 29 Follow-up (or at the time of discontinuation). Elevated BP will be defined as SBP > 150 / DBP >95; depressed SBP will be defined as <90; Elevated HR will be defined as HR > 100 / min). If one or more of these measurements is met, and in the opinion of the Investigator is considered clinically significant, it will be considered an adverse event.

10.5.5. 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, QTcB 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, prior to surgery, and at 1.5 hours (± 0.5 hour) after the administration of study medication. Clinically significant changes in ECG (i.e., QTCf should be <450 msec / < 470 msec for Female / Male subjects respectively; increase of QTCf of 30msec or greater, as well as any other changes as deemed by the Investigator) will be considered an adverse event.

10.5.6. Physical Examination

A complete physical examination including all major body systems (HEENT, neurologic, cardiovascular, respiratory, gastrointestinal, dermatologic and musculoskeletal systems) will be performed at Screening, prior to Surgery, and on the Day 29/ET. In addition, at the following times, an abbreviated review of systems will be performed to capture changes since Surgery: 1 hour (± 30 minutes), 24 hours (± 2 hours), and 48 hours (± 4 hours) after the administration of study medication.

Body weight (kg), in indoor clothing, but without shoes, will be measured at Screening, on Day 3 (48 hours) and Day 29/ET. Height in centimeters (cm) will be measured, and BMI will be calculated at Screening only. BMI shall be calculated as kg/m^2. The site should use the NIH website BMI calculator http://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi-m.htm.

10.5.7. Surgical Site Assessment

Surgical Sites should be assessed to determine if any site related AEs have occurred. Assessments will be conducted at screening, baseline and then at 24 hours (±2 hours) and 48 hours (±4 hours) after the administration of study medication. During the first 48 hours, 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 C

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 I

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

10.5.8. Neurosensory Exam

A Neurosensory Exam of the Foot and Great toe (bilateral) will be conducted at screening, baseline and then at 24 hours (±2 hours) and 48 hours (±4 hours) after the administration of study medication. The exam will involve the dorsal aspect of the great toe, midway between the nail fold and the DIP joint.

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

- 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)
- Hyperalgesia to pin (increased pain (hyperalgesia), hyperesthesia, normal, reduced or absent)

The Neurosensory Exam will also be performed at each of the Follow-up visits on Days 8, 15 and 29, or at the time of discontinuation, and on Day 36, if the visit is needed. Appendix A

A persistent sensory change after 3 days, such as allodynia or hyperalgesia will be reported as an AE. Numbness at or near the incision need not be considered an AE since this could occur as a result of tissue trauma and inflammation from the surgery.

10.5.9. Assessment of Adverse Events

All SAEs will be documented and followed from the time the subject has signed the ICF until Day 29 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 drug until Day 29 or, if necessary, Day 36 after the completion of surgery. AEs that occur between Screening and the study procedure should be considered medical history, and be added to the subject's medical record. Serious AEs and AEs that have been designated as possibly related to study drug will be followed until resolution or stabilization. Further details on AEs, including definitions, elicitation, and reporting are provided in Section 11.

10.5.10. Pharmacokinetic Assessments

The time points for collection are at baseline (before dosing), and at 5 minutes, 15 minutes, 30 minutes, 45 minutes, and 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, and 48 hours after dosing. There will be a ±2 minute window allowed for the 5 and 15 minute collections, a ±5 minute window allowed for collections through 4 hours, and a ±15 minute window for collections through 48 hours.

10.5.11. Processing, Storing, and Shipping of Pharmacokinetic Samples

The time points for bioanalytical samples are the following: Baseline (before dosing), and at 5 minutes, 15 minutes, 30 minutes, 45 minutes, and 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, and

48 hours after dosing. Two bioanalytical samples will be drawn at each specified time point, described below:

10.5.11.1. Samples for quantitation of CA-008, Capsaicin, and CA-101:

This sample will be the first bioanalytical sample drawn at each time point. The blood collection tubes for these samples will be 6 mL, plastic vacutainer tubes with K_2EDTA. The tubes will be pre-loaded with citrate buffer and stored as described in the Clinical Laboratory Manual. Prior to use, the tubes will be placed in wet ice for at least 30 minutes. Sample, with a target blood volume of 6 mL, will be drawn using a catheter set for sterility purposes.

Immediately after the collection of each sample, the collection tube will be gently inverted 8-10 times, and then placed in wet ice. Within 30 minutes of withdrawal, the tubes will be centrifuged at about 1300 x gravity ± (100 x gravity) (e.g. 2500 rpm for 19 cm rotor radius) for 10 minutes at 4°C to separate the cells from the plasma. No aids for separation will be used. Two aliquots of plasma will be transferred from each sample with clean pipettes and placed in two labeled polypropylene cryogenic storage tubes. The plasma samples should contain at least 500 µL in the primary sample and the remaining volume in the secondary sample, with a goal of approximately equal volume in each cryovial in the case that over 1 mL of the plasma is divided. The cryogenic storage tubes will be labelled with the following information: protocol number, randomization number, sample timepoint, subject initials, and biologic matrix to be analyzed (e.g. K_2EDTA plasma). Cap and place the tubes immediately into the freezer or hold on dry ice. Within 60 minutes of the collection time, the storage tubes will be placed into a freezer at approximately -20°C (-15°C to -35°C). They will remain in the freezer until shipped. At a time designated by the sponsor, the samples will be packed with sufficient dry ice to keep them frozen for at least 48 hours and shipped to the bioanalytical facility. On the day prior to shipment, clinical staff will notify (via email) the analytical laboratory of the pending shipment and provide the tracking number information. The address will be provided in the Clinical Laboratory Manual.

These samples will be analyzed for quantitation of CA-008, capsaicin, and CA-101. These samples also will be analyzed for capsaicin-glucuronide metabolite.

10.5.11.2. Samples for exploratory analysis of Capsaicin-glucuronide metabolite:

A separate sample will be drawn second at each time point defined in section 10.5.10 for an exploratory analysis of the metabolite Capsaicin-glucuronide. This method is currently qualified but has not been fully validated and thus will be considered an exploratory PK assessment. The blood collection tubes for these samples will be 4 mL, plastic vacutainer tubes with K_2EDTA. Prior to use, the tubes will be placed in wet ice for at least 30 minutes. Sample, with a target blood volume of 4 mL, will be drawn using standard techniques. The processing and shipping instructions are analogous to those for the samples for quantitation of CA-008, Capsaicin, and CA-101.

Samples previously collected by this approach will not be analyzed for capsaicin-glucuronide (see Section 10.5.11.1), and future patients in the study will not have these samples collected.

10.6. Efficacy and Safety Variables

10.6.1. Safety Endpoints

Safety endpoints include the following:

- Incidence of TEAEs
- Clinical laboratory test results
- Vital sign measurements
- Electrocardiogram (ECG) results
- Physical Exam findings

- Surgical Site assessment findings
- Neurosensory Exam results
- Concomitant medications

10.6.2. Pharmacokinetic Endpoints

Planned pharmacokinetic endpoints will be described in a separate PK Analysis Plan.

10.6.3. Efficacy Endpoints

The following endpoints will be explored for efficacy:

1. Area-under-the-curve (AUC) over various time points using NPRS score (0–10), with adjustment for use of analgesic medication.
2. Mean average daily NPRS score of 2 daily diary assessments (once in the morning (08:00 ±4 hours), and once in the evening (20:00 ±4 hours))
3. Mean daily opioid consumption (in morphine equivalents)
4. Proportion of patients who drop out of the study due to inadequate analgesia from Day 1 to 15.
5. Brief Pain Inventory-short form (BPI-SF) scores at the Day 8 (Week 1), Day 15 (Week 2) and Day 29 (Week 4) clinic visits.
6. Patient Global Evaluation (PGE) and Investigator Global Evaluation (IGE) at the Day 8 (Week 1), Day 15 (Week 2) and Day 29 (Week 4) clinic visits.
7. Investigator Global Evaluation (IGE) at the Day 8 (Week 1), Day 15 (Week 2) and Day 29 (Week 4) clinic visits.

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

11.1. Adverse Events and Serious Adverse Events

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

11.1.1. Relationship to Study Drug

An Investigator who is qualified in medicine 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 investigational product. For purposes of the definitions below, “temporal sequence” is defined as an association between administration of a drug and the observed reaction or event such that the drug was present prior to the reaction or event.

Causality Category	Description
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations. For the purpose of this protocol, the term unlikely will be considered not related to study medication and an “Adverse Event”.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear. For the purpose of this protocol, an event that has possible relationship to study medication will be defined as a “Suspected Adverse Drug Reaction”.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal. For the purpose of this protocol, an event that has probable relationship to study medication will be defined as an “Adverse Drug Reaction”.

11.1.2. Adverse Event Reporting

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

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

Information collected concerning AEs will include the following:

- Name of the event
- Onset date
- Resolution date
- Severity (i.e., mild, moderate, severe or potentially life-threatening)
- Relationship to study drug
- 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 drug until Day 29 or, if necessary, Day 36 after the completion of surgery. AEs that occur between Screening and the study procedure should be considered medical history, and be added to the subject's medical record. Serious AEs and AEs that have been designated as possibly related to study drug will be followed until resolution or stabilization.

11.1.3. Serious Adverse Event (SAE)

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

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

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 drug-related by the Investigator.

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

11.1.3.1. Serious Adverse Event Reporting

Serious AEs must be reported to the Sponsor or designee within 24 hours of knowledge of the event. All SAEs that occur while a subject is receiving study drug and within 14 days following the Follow-up visit (or 21 days following early termination) are reportable within 24 hours. During the follow-up period beyond 14 days from Follow-up (or 21 days following early termination), only those SAEs that are considered to be possibly related to study drug 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 Medical Monitor or designee. Calls related to SAEs should first be directed to the Medical Monitor or designee.

  Medical Monitor: Jon L. Ruckle, MD, CPI

  24/7 Emergency contact: 808-349-9812

  SAE Reporting email: MedicalMonitorCA-PS-2017-101@Lotuscr.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 drug was discontinued
  - Investigator's assessment of causality

The 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/Independent Ethics Committee (IEC) of the occurrence of and details surrounding the event. In the event there is a question as to whether the AE is serious, the event should be reported.

11.2. Pregnancy

In the event that a female subject does become pregnant at any time during the study, the Investigator must notify the 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 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 Medical Monitor or designee. Any premature termination of the pregnancy will also be reported on this form. Although pregnancy occurring in a clinical study is not considered to be an SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE and will be followed as such. A spontaneous abortion is considered to be an SAE.

12. DATA QUALITY ASSURANCE

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

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

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

12.1. Data Collection

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

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

12.2. Study Auditing and Monitoring

Monitoring of the study site (including, but not limited to, reviewing CRFs for accuracy and completeness) will be performed by the Sponsor's designated monitor(s). The extent, nature, and frequency of on-site visits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and enrollment rate. By signing the protocol, the Investigator agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of the Sponsor, a regulatory authority, and/or an IRB may visit the site to perform audits or inspections, including the drug storage area, study drug stocks, drug accountability records, participant charts and source documents, and other records related to study conduct. The purpose of the Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether the study-related activities were conducted, and data recorded, analyzed, and accurately reported according to the protocol, the site's standard operating procedures, GCP guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency regarding an inspection.

13. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

13.1. Statistical and Analytical Plans

The sections of the Statistical Considerations describe the statistical methods to be used to analyze the efficacy and safety. These methods may be revised and updated due to reasons such as regulatory requirements or need for further clarifications. The final analysis will be documented in a formal Statistical Analysis Plan (SAP) that must be finalized before database lock. The SAP will include details on how variables will be derived, how missing data will be handled, and how data will be presented as well as the details on statistical methods to be used for safety and efficacy analyses. The final clinical study report will discuss deviations from the SAP, if any.

13.2. Analysis Populations

The following three analysis populations are planned for this study:

- Safety Population will include all subjects who received any amount of study drug
- PK Parameter Population: will include all subjects who also have sufficient concentration-time profiles for estimation of PK parameters.

Membership in the analysis populations will be determined before unblinding.

13.3. 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 medication. All p-values will be considered nominal in this dose-finding study and no adjustments for multiplicity will be performed.

Summary statistics will be provided for the variables described in the following sections. For continuous variables, these statistics will typically include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, these statistics will typically include the number and percentage of subjects in each category.

13.4. Study Subjects and Demographics

13.4.1. 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.

13.4.2. Protocol Deviations

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

13.4.3. 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 clinical laboratory tests will be listed.

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

13.4.4. Exposure

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

13.4.5. Analysis of Efficacy Measures

Efficacy variables will be summarized and analyzed.

The primary efficacy parameter is the area-under-the-curve (AUC) for NPRS scores across various time points, with adjustment for use of analgesic therapy/medication. The primary efficacy variable will be analyzed using an ANCOVA model with treatment as the main effect and baseline PI as the covariate. The overall treatment effect will be presented along with specific treatment arm differences and the two-sided 95% confidence intervals of the differences.

In this study, subjects are permitted to take rescue medication for analgesia. It is expected subjects randomized to placebo arm will take rescue medication often. During both inpatient and outpatient portions of the studies, the subjects will be instructed to record NPRS immediately prior (within approximately 15 min) to taking rescue medication.

For subjects who take rescue, the pre-rescue pain score will be used to impute scheduled assessments for 4 hours. 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 due to Lack of Efficacy or Adverse Events, scheduled assessments may be imputed using worst prior pain score carried forward. All other subjects who drop out will have their last pain score carried forward.

Sensitivity analysis of the primary efficacy variable using different methods of imputation for rescue medication may also be performed.

Additional sensitivity analysis with different missing value imputation methods for subjects who drop out of the study may also be performed.

All imputation methods for pain intensity will be documented in the SAP.

13.4.5.1. Handling of Dropouts or 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 medication;
- 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. Missing at random is expected to be a reasonable assumption and the primary analyses are expected to be sufficient for this dose escalation study. Additional sensitivity analyses will be performed to support robust conclusions, if warranted and details are presented in a detailed SAP prior to database lock.

13.4.5.2. Analysis of Secondary Efficacy Endpoints

Time to first rescue (analgesia/nausea) medication will be presented using Kaplan-Meier graphs and analyzed using a log rank test with a model including treatment effect. The median time to rescue medication and 95% confidence interval of the median time for each treatment cohort will be presented.

The percent of days that rescue medication is used will also be analyzed via ANCOVA model including treatment effect as the independent variable. The 95% confidence interval of the treatment differences will be presented.

13.4.6. Analysis of Safety

Safety analyses will be conducted using data from the Safety Population (as defined in Section 13.2).

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.

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

13.4.7. 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 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.

13.4.8. 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 for each visit.

13.4.9. 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.

13.5. Determination of Sample Size

Sample size is appropriate for Phase 1 dose, ranging safety study.

14. STUDY ADMINISTRATION AND INVESTIGATOR RESPONSIBILITIES

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

14.1. Regulatory and Ethical Considerations

14.1.1. Ethical Conduct of the Study

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

14.1.2. Ethics Approval

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

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

14.1.3. Subject Informed Consent

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

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

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

14.2. Privacy and Confidentiality

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

To ensure anonymity and to limit disclosure, participants will be assigned a unique identifier at their first assessment. This identifier will be cross-referenced in the participant's chart. The identifier will not contain any potentially identifiable information. An identifier log will be

maintained, linking each participant's name to the corresponding identifier. This log will be stored at the research site in a secure location.

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

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

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

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

14.3. Study and Site Closure

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

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

14.4. Regulatory Documents and Records Retention

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

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

- A period of 2 years following the final date of approval by the FDA or other regulatory agency of the study drug 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 drug for the purposes that were the subject of the investigation.

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

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

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

14.5. Delegation of Responsibilities and Adequate Resources

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

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

14.6. Protocol Amendments

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

14.7. Financial Disclosure

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

15. INVESTIGATOR PROTOCOL AGREEMENT PAGE

A Phase 1/Single Ascending Dose (SAD) Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of a Single Intraoperative Administration of CA-008 in Subjects Undergoing Unilateral Transpositional First Metatarsal Osteotomy for the Correction of Hallux Valgus Deformity

Version: 3.0

Date: 30-Jan-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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17. APPENDICES

APPENDIX A: NEUROSENSORY EXAMINATION FORM

Subject Number	Subject Initials	Date:	Protocol Number
___ ___ ___ -___ ___ ___	___ ___ ___	__ __/ __ __ __/ 2 0__ __ (DD-MMM-20YY)	CA-PS-2017-101

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 ☐ Normal ☐ Reduced ☐ Absent	☐ Pain (Allodynia) ☐ Hyperesthesia ☐ Normal ☐ Reduced ☐ Absent
7.	Hyperalgesia to Pin:	☐ Increased Pain ☐ Hyperesthesia ☐ Normal ☐ Reduced ☐ Absent	☐ Increased Pain ☐ Hyperesthesia ☐ Normal ☐ Reduced ☐ Absent

APPENDIX B: NUMERICAL PAIN RATING SCALE (NPRS) FOR PAIN INTENSITY

Pain Intensity - Numerical Pain Rating Scale (NPRS)

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: POST-OPERATIVE 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 D: BRIEF PAIN INVENTORY – SHORT FORM (BPI-SF)

Page 1 of 2

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Brief Pain Inventory (Short Form)

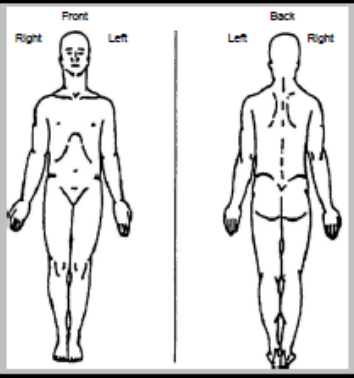
Date: ___/____/____ **Time:** _____

Name: _____ _____ _____
Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

Page 1 of 2

BRIEF PAIN INVENTORY – SHORT FORM (BPI-SF)

(Page 2 of 2)

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Date: ___/____/____ Time:_____

Name: _____ _____ _____
Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0% No Relief 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

B. Mood

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

C. Walking Ability

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

E. Relations with other people

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

F. Sleep

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

G. Enjoyment of life

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

Page 2 of 2

APPENDIX E: PATIENT GLOBAL EVALUATION (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 the study medication that you have received for pain? **(Mark one box)** ☐ **Excellent (3)** ☐ **Good (2)** ☐ **Fair (1)** ☐ **Poor (0)** **Subject Initials: _____**

APPENDIX F: 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 medication that this patient received for pain? **(Mark one box)** ☐ **Excellent (3)** ☐ **Good (2)** ☐ **Fair (1)** ☐ **Poor (0)** **Investigator Initials: _____**

APPENDIX G: 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.

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 BUN 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
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
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
Cholesterol	201 – 210	211 – 225	> 226	---

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 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: 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 J: AMERICAN SOCIETY OF ANESTHESIOLOGISTS PHYSICAL STATUS CLASSIFICATION SYSTEM

I Normal healthy patient

II Patient with mild systemic disease; no functional limitation – e.g. smoker with well-controlled hypertension

III Patient with severe systemic disease; definite functional impairment – e.g. diabetes and angina with relatively stable disease, but requiring therapy

IV Patient with severe systemic disease that is a constant threat to life – e.g. diabetes and angina and congestive heart failure; patients with dyspnea on mild exertion and chest pain

V Unstable moribund patient who is not expected to survive 24 hours with or without operation

VI Brain dead patient whose organs are removed for donation to another

E Emergency operation of any type, which is added to any of the above six categories, an in ASA II E

APPENDIX K: PHYSICAL / NEUROLOGICAL EXAMINATION OF THE FOOT AND GREAT TOE

For all assessments, the foot should be warm.

- **Foot Inspection**: The feet are inspected for evidence of excessively dry skin, callous formation, fissures, frank ulceration or deformities. Deformities include flat feet, hammer toes, overlapping toes, hallux valgus, joint subluxation, prominent metatarsal heads, medial convexity (Charcot foot) and amputation.

- **Vibration Sensation:** Vibration sensation should be performed with the great toe unsupported. Vibration sensation will be tested bilaterally using a 128 Hz tuning fork placed over the dorsum of the great toe on the boney prominence of the DIP joint. Patients, whose eyes are closed, will be asked to indicate when they can no longer sense the vibration from the vibrating tuning fork. In general, the examiner should be able to feel vibration from the hand-held tuning fork for 5 seconds longer on his distal forefinger than a normal subject can at the great toe (e.g. examiner's DIP joint of the first finger versus patient's toe). If the examiner feels vibration for 10 or more seconds on his or her finger, then vibration is considered decreased. A trial should be given when the tuning fork is not vibrating to be certain that the patient is responding to vibration and not pressure or some other clue. Vibration is scored as 1) present if the examiner senses the vibration on his or her finger for < 10 seconds, 2) reduced if sensed for ≥ 10 or 3) absent (no vibration detection.)

- **Deep Tendon Reflexes:** The ankle reflexes will be examined using an appropriate reflex hammer (e.g. Trommer or Queen square). The ankle reflexes should be elicited in the sitting position with the foot dependent and the patient relaxed. For the reflex, the foot should be passively positioned and the foot dorsiflexed slightly to obtain optimal stretch of the muscle. The Achilles tendon should be percussed directly. If the reflex is obtained, it is graded as present. If the reflex is absent, the patient is asked to perform the Jendrassic maneuver (i.e., hooking the fingers together and pulling). Reflexes elicited with the Jendrassic maneuver alone are designated "present with reinforcement." If the reflex is absent, even in the face of the Jendrassic maneuver, the reflex is considered absent.

- **Monofilament Testing:** For this examination, it is important that the patient's foot be supported (i.e., allow the sole of the foot to rest on a flat, warm surface). The filament should initially be prestressed (4-6 perpendicular applications to the dorsum of the examiner's first finger). The filament is then applied to the dorsum of the great toe midway between the nail fold and the DIP joint. Do not hold the toe directly. The filament is applied perpendicularly and briefly, (<1 second) with even pressure. When the filament bends, the force of 10 grams has been applied. The subject, whose eyes are closed, is asked to respond yes if he / she feels the filament. Eight correct responses out of 10

applications is considered normal: one to seven correct responses indicate reduced sensation and no correct responses translates into absent sensation.

- **Testing for Allodynia and Hyperalgesia:** testing should be performed bilaterally with the great toe unsupported. Allodynia will be tested using a foam brush, and hyperalgesia will be tested using a safety pin; both will be applied to the dorsum of the great toe on the boney prominence of the DIP joint.

For **allodynia assessment** the foam brush will be lightly stroked 3 times across the skin over the dorsum of the great toe. Subject will be asked to compare sensation of toe on the surgical side with the toe on the nonsurgical side. If the sensation is described as painful or very unpleasant then allodynia will be reported as present. If sensation is slightly unpleasant or mildly irritating compared to the controlled side then hyperaesthesia will be reported as present. If subject reports the stimulus as the same as the controlled side then sensation will be reported as normal. If sensation is less than the controlled side then sensation will be reported as reduced, and if sensation is not felt as all then it will be reported as absent.

For **hyperalgesia assessment,** a sterile safety pin will be lightly applied 3 times at 1 second intervals over the dorsum of the great toe on the boney prominence of the DIP joint. Subject will be asked to compare sensation of toe on the surgical side with the toe on the nonsurgical side. If the sensation on the side of surgery is described as more painful or very unpleasant in comparison to the sensation on the normal or controlled side then hyperalgesia will be reported as present. If sensation is slightly unpleasant or mildly irritating compared to the controlled side then hyperaesthesia will be reported as present. If subject reports the stimulus as the same as the controlled side then sensation will be reported as normal. If sensation is less than the controlled side then sensation will be reported as reduced, and if sensation is not felt as all then it will be reported as absent.

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