CONCENTRIC ANALGESICS

OFFICIAL TITLE:

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

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Clinical Trial Protocol

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

Investigational Product: CA-008 by Injection/Instillation

IND: 129114

Concentric Analgesics, Inc.

SIGNATURE PAGE

Approved by:

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Jan. 28, 2019

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Date

28 Jan 2019

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Date

1. KEY PERSONNEL CONTACT INFORMATION

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TABLE OF CHANGES: Protocol V 1.3 (05 NOV 2018) to V2.0 (17 JAN 2019)

After a review of the 1st cohort results, it was decided that an additional two cohorts be added and to remove references to the second stage (parallel design portion) of the study. The parallel design study will be conducted under a new protocol with new numbering identifier with the design features to be determined after the results from all three cohorts are evaluated. Additional changes were made to reduce confusion and augment the standard of care treatment for all subjects.

Location of material changes	V 1.3	V 2.0
Synopsis, Sponsor p 8		Address change
Synopsis: Sample Size p 7/Overall Study Design p 7/ Study Objectives p 8/Dose Groups p 8 §6.1 Study Objectives p 43 §7.1 Overall Study Design and Plan p 44 §8.1.1 Number of Participants p46 §9.1.2 Study Treatment Description p 50 §10.1.3 Surgery Day 0 p 55 Universal changes throughout to reflect these changes.	Only one cohort was anticipated prior to a parallel design stage.	Added cohorts #2 and #3 including 18 subjects each with 2:1 randomization to active or standard of care alone, respectively (100 mL of study treatment), and possible a 4th cohort with the dose TBD (but between 5 and 15 mg). Removed stage 2 from this protocol. Study treatment administration instructions remain the same as in cohort #1.
Synopsis: Anesthesia p13 §10.1.2.2 Surgery Day 0 p 55	Ropivacaine 0.5% 30 mL for the TAP block with no additional local anesthetic.	Prior to the surgery, perform the TAP block as a single injection of 0.25% bupivacaine hydrochloride (HCl) 60 mL (150 mg). Replaced ropivacaine dosage guidance with Marcaine's.
Synopsis: Intraoperative Analgesia p8/Inpatient Analgesia p 8/Rescue Medication During the Inpatient Stay p9/Analgesia during the Outpatien Period p 9/Primary Efficacy Endpoint p 16/Key Secondary Efficacy Endpoints p 16 §9.2.1 Intraoperative and Early Postoperative Analgesia p 51 §9.2.2 Inpatient Rescue Medications p 51	IV hydromorphone 2mg during surgery (modified to weight based dosing). IV fentanyl 100 – 300 mcg intraoperatively per anesthesia discretion Confusion as to PO or IV choice during the early postoperative period	Modified intraoperative and immediate postoperative analgesia regimen to remove potential confusion and improve pain control. Within 30 min of anesthesia induction give the subject IV hydromorphone 0.02 mg/kg. During the surgery, ensure that each subject has received at least 100 mcg of IV fentanyl with adjustments above this dose per anesthesiologist discretion. Within 15 min of the end of surgery, give the subject IV hydromorphone 0.007 mg/kg. Within 15 min of the end of surgery, administer IV acetaminophen 1 g After surgery and during the PACU stay use only IV fentanyl 25-50 mcg q5 min prn moderate-to-severe pain (≥ 4 NRS), then from PACU discharge through T12h, use IV hydromorphone 0.2 to 0.5 mg q10-15 min prn, from T12-T24h, PO oxycodone 5 or 10 mg for pain q2h prn, and after T24h, PO oxycodone 5 or 10 mg for pain q4h prn. After discharge from the inpatient unit recommend PO acetaminophen and ibuprofen as directed.
PK endpoints p17/footnote 15 to Table 1 Schedule of Assessments §10.1.4 Inpatient Phase p 57	PK sampling stopped at T24h	Added 3 additional PK sampling times at T30, T36 and T48h to cover increased study treatment doses.
Synopsis: Inclusion Criteria p 10; Exclusion Criteria p 11 §8.2.1 Inclusion Criteria p 47 §8.2.2 Exclusion Criteria p 48	English only	Added Spanish to inclusion criteria (note this will not apply until the IRB approves the Spanish language ICF and related documents) Added bupivacaine and hydromorphone to exclusion criteria and removed ropivacaine
§5.3 Previous Human Experience p29-41		Added safety results from Phase 2 bunionectomy study (CA-pS-201) and the preliminary unblinded 1st cohort data from the current abdominoplasty study to introductory section.

TABLE OF CHANGES V. 1.2 TO 1.3

After a review of the top line results from the bunionectomy study (CA-PS-201), it was decided that the concentration used in this study should be 0.05 mg/mL for a total dose of 5.0 mg which is slightly higher than the 4.2 mg dose, the highest dose used in the Phase 2 bunionectomy study (CA-PS-201) and the Phase 1b study (CA-PS-2017-101). Note that the safety profile in these two bunionectomy studies were similar in that all active doses were well tolerated without an apparent dose response to adverse events.

Location of change	Change	New text
• Synopsis, Study Objectives • Synopsis, Dose Groups • Synopsis, Primary Efficacy Endpoint for the Pilot Stage • Section 6, Study Objectives • Section 7.1, Overall Study Design and Plan • Section 9.1.2, Study Treatment Description • Section 10.1.3, Surgery Phase: Administration of Study Medication into the Surgery Site	Increase in CA-008 concentration and dose: concentration will be increased from 0.025 mg/mL to 0.05 mg/mL or a total dose from 2.5 mg to 5.0 mg	Universal change of CA-008 dose from 2.5 mg (100 mL of a 0.025 mg/mL concentration) to 5.0 mg (100 mL of a 0.05 mg/mL concentration).

TABLE OF CHANGES V. 1.1 TO 1.2

After a meeting with the reconstructive surgeons participating in the study which could not be scheduled until after the site initiation visit, the request to increase the volume of study treatment to 100 mL was made to ensure sufficient volume for the full abdominoplasty particularly in subjects with larger body habitus.

Location of change	Change	New text
• Synopsis, Study Objectives • Synopsis, Dose Groups • Synopsis, Primary Efficacy Endpoint for the Pilot Stage • Section 6, Study Objectives • Section 7.1, Overall Study Design and Plan • Section 9.1.2, Study Treatment Description • Section 10.1.3, Surgery Phase: Administration of Study Medication into the Surgery Site	Increase in study treatment volume to 100 mL (2.5 mg CA-008 for active)	Universal change of CA-008 dose from 1.875 mg (75 mL) to 2.5 mg (100 mL). Note that the concentration will remain the same: 0.025 mg/mL. Additionally, note that this dose and concentration is below that used in both bunionectomy studies (CA-PS-2017-101 and CA-PS-201)

TABLE OF CHANGES V. 1.0 TO 1.1

Minor administrative changes were requested at the site kick-off meeting to remove inconsistencies, provide clarity or reduce the chance for confusion.

Location of change	Change	New text
P8: Synopsis: Analgesa during the Outpatient Period p41: Section 9.2.3 Outpatient Analgesic Medications	Modified instructions for acetaminophen dosing during outpatient period per site request	If needed for pain management, acetaminophen up to 1000 mg prn tid/qid (3g daily maximum limit)…
P40: Section 9.2.2 Inpatient Rescue Medications	Corrected mistake in frequency of oxycodone rescue after 24h	PO oxycodone 5 mg q4h prn moderate pain (NRS $\geq$ 4 and $\leq$ 6) or 10 mg q4h prn severe pain (NRS $\geq$ 7) for T24 to T96h
P55: Section 10.3.14 Urine Drug Screen and Alcohol Test	Removed the second paragraph which is inconsistent with the eligibility criteria: 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 investigator.	n/a

2. PROTOCOL SYNOPSIS

Sponsor:	Concentric Analgesics, Inc. (Concentric) 101 California St., Suite 1210 San Francisco, CA 94111
CRO:	Lotus Clinical Research (Lotus) 100 W. California Blvd., Unit 25 Pasadena CA 91105
Protocol Number:	CA-PS-204
IND#	129114
Study Title:	A Phase 2, Randomized, Double-blind, Placebo-Controlled Efficacy, Pharmacokinetics and Safety Study of CA-008 in Subjects Undergoing Complete Abdominoplasty
Study Treatment	• CA-008, the investigational product • Placebo to match
Planned Study Center(s):	1 US site
Indication:	Acute postsurgical pain
Sample Size:	• Cohort #1: total N=18 (randomized 1:1 active or placebo) • Cohort #2: total N=18 (randomized 2:1 active or placebo) • Cohort #3: total N=18 (randomized 2:1 active or placebo) • Optional 4th cohort with a total N=24 randomized 1:1 to CA-008 or placebo
Population:	Adults ages 18 to 65 years, inclusive, who are planning to undergo an elective complete (full) abdominoplasty (C-ABD) and otherwise meet eligibility criteria may be considered for enrollment into the study.
Study Duration:	Approximately 76 days per subject from screening to the day 29 (D29) visit (however this could be longer to follow any AE to resolution or establishment of a new baseline)
Overall Study Design:	This is a Phase 2, single-center, randomized, double-blind, placebo-controlled, parallel design study evaluating up to 4 exploratory cohorts, each with a single dose of CA-008 or placebo. For each subject, the study will be conducted in two parts: • Inpatient period starts with admission to Post-anesthesia care unit (PACU) and continues to 96h (T96h) after completion of study treatment injection (T0). • Outpatient period begins on discharge from the inpatient unit through various follow visits to D29±2 (W4) after surgery. Note that additional

	follow up visits may occur at any time or even after D29/W4 to follow adverse events (AEs) to resolution or establishment of a new baseline.
Study Objectives:	**Primary Objective:** To evaluate the efficacy of a single intraoperative administration of CA-008 vs. placebo in subjects undergoing an elective C-ABD. **Secondary Objectives:** • To evaluate the safety and tolerability of a single intraoperative administration of CA-008 vs. vehicle placebo in subjects undergoing an elective C-ABD. • To evaluate the PK profile of a single intraoperative administration of CA-008 vs. vehicle placebo in subjects undergoing an elective C-ABD. • To evaluate the opioid-sparing effect of CA-008 vs. placebo in terms of consumption and time to cessation.
Study Treatment Dosing Schedule:	Study treatment is to be administered intraoperatively as a single administration via "surgical site" infiltration prior to wound closure. "Surgical site" is defined as the area extending approximately 2-3 cm in all directions (lateral/medial/proximal/distal/deep) from the incision site and surrounding tissues.
Anesthesia:	The surgery is to be performed under general anesthesia supplemented by a transverse abdominis plane (TAP) block and local surgical site infiltration. Prior to the surgery, perform the TAP block as a single injection of 0.25% bupivacaine hydrochloride (HCl) 60 mL (150 mg).
Dose Groups:	• Cohort #1: total N=18 randomized 1:1 CA-008 5 mg or placebo • Cohort #2: total N=18 randomized 2:1 CA-008 10 mg or placebo • Cohort #3: total N=18 randomized 2:1 CA-008 15 mg or placebo • Optional 4th cohort with a total N=24 randomized 1:1 to CA-008 or placebo at a dose between 5 mg and 15 mg as determined based upon results from cohorts #1-3 The volume for each cohort is 100 mL of CA-008 or placebo vehicle.
Injection of Study Treatment:	Prior to wound closure, study treatment will be infiltrated uniformly throughout the soft tissues around surgical sites with particular attention to the rectus fascia. A 25 g (or larger) 3.5" spinal needle may be useful for the infiltration process. Note that T0 is the time that the study treatment injection is completed.
Allowed Substitutions:	Note that if any standard of care drugs are unavailable, for example due to stock outages, available clinically equivalent alternatives may be substituted, particularly for the protocol-specified analgesic drugs for intraoperative or

	postoperative inpatient analgesia, after approval of the medical monitor who should notify Sponsor of said substitution.
Intraoperative Analgesia:	Within 30 min of anesthesia induction give the subject IV hydromorphone 0.02 mg/kg. During the surgery, ensure that each subject has received at least 100 mcg of IV fentanyl with adjustments above this dose per anesthesiologist discretion. Within 15 min of the end of surgery, administer IV acetaminophen 1g (Ofirmev® full prescribing information at http://ofirmev.com/) and IV hydromorphone 0.007 mg/kg.
Inpatient Analgesia:	No non-opioid analgesics are to be administered after transfer to the PACU during the inpatient phase (through T96h).
Postsurgical Care:	After surgery, subjects will be monitored in the post-anesthesia care unit (PACU) during which time efficacy asssessments can begin once the subject is awake. Document PACU entrance and discharge times. After discharge from the PACU, subjects are followed through T96h as an inpatient. Safety and efficacy evaluations will be performed and blood drawn and urine collected for pharmacokinetic (PK) assessments. Subjects will be required to meet standard criteria for discharge to outpatient status. Subjects will continue to be monitored as an outpatient after discharge through D29/W4 for various safety and efficacy assessments, and later if necessary for safety follow up.
Rescue Medication During the Inpatient Stay:	During the PACU stay, the subject may be administered IV fentanyl 25-50 mcg q5 min *prn* for moderate-to-severe pain (≥ 4) as reported by subjects using the 0 to 10 numerical rating scale of current pain intensity (NRS). From the time of PACU discharge through T12h administer IV hydromorphone 0.2 to 0.5 mg q10-15 min prn for NRS ≥ 4 as reported by subjects. After T12h, administer PO oxycodone 5 mg q2h *prn* moderate pain (NRS ≥ 4 and ≤ 6) or 10 mg q2h *prn* severe pain (NRS ≥ 7). After T24, administer PO oxycodone 5 mg q4h *prn* moderate pain (NRS ≥ 4 and ≤ 6) or 10 mg q4h *prn* severe pain (NRS ≥ 7) Subjects will be encouraged to rescue only for moderate-to-severe pain scores (NRS ≥ 4), however rescue may be requested at any time and medication will be provided when requested.
Analgesia during the Outpatient Period:	Once discharged from the inpatient unit, all study participants will be instructed to take a combination of over-the-counter (OTC) analgesics at an appropriate dose per medical judgment to manage any residual or breakthrough postsurgical pain.

	If a subject is still requiring opioid rescue in the 12h prior to discharge from the inpatient unit (i.e., from T84h on regardless of whether discharge is delayed), then prescribe no more than 9 tablets of oxycodone 5 mg (1 PO tid prn) per investigator discretion for the initial outpatient period. If needed for pain management, acetaminophen up to 1000 mg prn tid/qid (3g daily maximum limit) and ibuprofen 400-600 mg prn tid/qid will be recommended for subjects to self-administer (note that these medications will not be provided by the Sponsor). Persistent pain or pain exacerbations during the outpatient period may suggest the need for an unscheduled in-person visit to assess the surgical site. If such a situation occurs, the Investigator should use clinical discretion on adequacy of analgesic treatment, but to capture this event as an adverse event (AE) and document any required treatments.
Inclusion Criteria:	**In order to participate, subjects must meet all inclusion criteria:** 1. Plan to undergo an elective complete abdominoplasty (C-ABD), without collateral procedure or additional surgeries. 2. In the medical judgment of the investigator, be a reasonably healthy adult aged 18 - 65 years old, inclusive, and American Society of Anesthesiology (ASA) physical Class 1 or 2 at the time of randomization (Section 17.1 Appendix A). 3. If a male, unless he has a same sex partner, be either sterile (surgically **or** biologically) or commit to an acceptable method of birth control while participating in the study. The site personnel will provide instructions on what is an acceptable method. 4. If a female, must meet **all** of the following: a. Females of child-bearing potential (FCBP) must have a negative serum pregnancy test at screening and negative urine pregnancy test before surgery; b. No plan to become pregnant or to breast feed during the study; and c. Be surgically sterile or at least one year post-menopausal, have a monogamous partner who is surgically sterile, have a same sex partner or (**one** of the following must apply) i. is practicing double-barrier contraception ii. is practicing abstinence (must agree to use double-barrier contraception in the event of sexual activity) iii. is using an insertable, injectable, transdermal or combination oral contraceptive approved by the FDA for at least 2 months prior to screening and commits to the use of an acceptable form of birth control while participating in the study.

	5. Have a body mass index ≤ 35 kg/m^2. 6. Be willing and able to sign the informed consent form (ICF) approved by an Institutional Review Board (IRB). 7. Be willing and able to complete study procedures and pain scales and to communicate meaningfully in English or Spanish with study personnel and return for outpatient follow up visits as required.
Exclusion Criteria:	**If any of the following exclusion criteria apply, subjects may not participate in the study:** 1. In the opinion of the Investigator, a. have a concurrent painful condition that may require analgesic treatment during the study period or may confound post-surgical pain assessments. b. have active skin disease or other clinically significant abnormality at the anticipated site of surgery that could interfere with the planned surgery. 2. Have a known allergy to chili peppers, capsaicin or the components of CA-008, acetaminophen, bupivacaine, fentanyl, hydromorphone or oxycodone. 3. As determined by the investigator (with input from the study's Medical Monitor if requested by the investigator), have a history or clinical manifestation of significant medical, neuropsychiatric or other condition, including a clinically significant existing arrhythmia, left bundle branch block or abnormal ECG, myocardial infarction or coronary arterial bypass graft surgery within the prior 12 months, significant abnormal clinical laboratory test value, or known bleeding abnormality that could preclude or impair study participation or interfere with study assessments. 4. The following are considered disallowed medications: a. Be tolerant to opioids defined as those who have been receiving or have received chronic opioid therapy greater than 15 mg of oral morphine equivalents (Table 9) per day for greater than 3 out of 7 days per week over a one-month period within 6 months of screening. b. Within 1 day prior to surgery and throughout the inpatient period, be taking or using any capsaicin-containing products, such as dietary supplements or over-the-counter (OTC) preparations, including topical formulations, and prescription medications. c. Within the 7 days prior to surgery, be taking any central nervous system (CNS) active agent as an analgesic adjunct medication, such as anticonvulsants, antidepressants (such as SNRIs, SSRIs,

	and tricyclic antidepressants), benzodiazepines, sedative-hypnotics, clonidine and other central alpha-2 agents (e.g., tizanidine), ketamine or muscle relaxants. [Note that SNRIs = Serotonin and norepinephrine reuptake inhibitors and SSRI = Selective serotonin reuptake inhibitors.] i. These drugs are permitted if prescribed for non-pain indications and the dose has been stable for at least 30 days prior to surgery. Note that the dose must remain stable throughout the study. ii. The use of benzodiazepines and the non-benzodiazepines (eszopiclone, ramelteon, zaleplon and zolpidem) are permitted to treat insomnia during the postoperative period. d. Within the 7 days prior to the planned surgery and throughout the study, be taking antiarrhythmics except beta-blockers, digoxin, warfarin (see exception below), lithium, or aminoglycosides or other antibiotics for an infection (except for ophthalmic use or for treatment or prophylaxis of postoperative surgical site infections). e. Within the 14 days prior to surgery, be taking parenteral or oral corticosteroids (steroid inhaler for allergy or asthma treatment, topical steroid for a non-clinically significant skin condition not involving the area of surgery or ophthalmic steroids are permissible). f. Be on an antianginal, antihypertensive agent or diabetic regimen at a dose that has not been stable for at least 30 days or which is not expected to remain stable while participating in the study. 5. In the opinion of the Investigator, within the past year have a history of illicit drug use or prescription medicine or alcohol abuse (regularly drinks > 4 units of alcohol per day; where a unit = 8 oz. beer, 3 oz. wine or 1 oz. spirits). 6. Have positive results on the alcohol breath/saliva 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. Note that for those subjects who test positive for tetrahydrocannabinol (THC), if they are willing to abstain from use or consumption of THC-containing products from 3 days prior to surgery to the day 8 visit, they may be allowed to participate in the study.

	7. Willing and able to avoid foods containing capsaicin for 24 hours prior to surgery/ PK blood draws. 8. Have previously participated in a clinical study with CA-008. 9. Have participated in another clinical trial or used an investigational product within 30 days or five half-lives (whichever is longer) prior to the planned surgery, or is scheduled to receive an investigational product other than CA-008 while participating in the study.
Visit Schedule:	• **Screening D-45 to D-1**: Subjects undergo screening during this period. All screening assessments (including informed consent form [ICF]) must be completed at least 1 day prior to surgery. • **Site Unit Admission D0**: Day of surgery, subjects will be randomized and baseline evaluations will be performed prior to surgery. • **Surgery D0**: C-ABD procedure is performed; study treatment is injected prior to wound closure with T0 defined as the time of study treatment completion of administration. PK assessments are to be done per protocol-specified time points through T24h. • **Post-surgery T0 to T96h**: Subject remains at the Site Facility for study assessments and PK blood draws. Discharge after T96±4h assessments with follow up instructions, particularly on diary completion. • **Follow Up D8±1 (W1)**: clinic visit for study assessments • **Follow Up D15±2 (W2):** clinic visit for study assessments • **Follow Up D29±2 (W4):** clinic visit for study assessments and study completion visit, unless follow up for wound healing is needed • **If needed, Unscheduled visits or Follow Up after D29±2:** Clinic visit as needed for any ongoing safety issue occurring between scheduled visits or continuing after the D29 visit • **Early Termination (ET):** For subjects who terminate early, an ET visit will be required if the subject is agreeable. Safety and subject-reported outcome assessments will be performed. If the subject does not wish to participate in these assessments, he/she should be asked to at least return for a wound check.
Monitored Parameters:	• Treatment-emergent AEs (TEAEs) • Medical history (MHx) • Physical examination (PE) findings, particularly neurosensory findings at the site of incision and the skin proximal and distal to the incision • Surgical site assessment for wound healing • Neurosensory testing near the surgical site • Clinical laboratory testing (standard chemistry, CBC, coagulation, urinalysis), drug and alcohol testing, pregnancy testing • Electrocardiograms (ECGs)

	• Blood draws for pharmacokinetics (PK) • NRS scores at rest and on rising from a recumbent to sitting position (arising) using a 0 to 10 numeric rating scale for pain intensity • Presence of rebound pain at the surgical site • Total postsurgical opioid consumption converted to an oral morphine equivalent dose (MED) • Patient global evaluation (PGE) of satisfaction with study treatment • Investigator global evaluation (IGE) satisfaction with study treatment (performed by any qualified investigator)
Safety Parameter Assessment Times:	• Incidence of spontaneous reported TEAEs or SAEs from T0 through D29/W4 or later if necessary: o TEAEs are defined as AEs occurring post T0 o AEs recorded from the time the informed consent form (ICF) is signed up to D0/T0 will be recorded in medical history. • PE: full PE at screening (without a breast, genital or rectal examination). Interim targeted PE on D-1 or D0 prior to surgery (to be conducted on D0 if not done on D-1), T96h, and as an outpatient on D8/W1, D15/W2, and D29/W4 (later if necessary). • Vital signs (heart rate [HR], blood pressure [BP], respiratory rate [RR]) at screening, D0 prior to surgery, post-surgery T1, T2, T4, T6, T12, and T24h, and every 8 hours thereafter until T96h, and as an outpatient on D8/W1, D15/W2, and D29/W4 or later if necessary. Assess temperature on D-1 or D0 prior to surgery. Daily temps can be recorded along with vital signs per site SOPs at 1, 2, 4, 6, 12, 24, and every 8 hours thereafter until discharge from the inpatient facility (if awake at the time of assessment between hours of midnight and 6 a.m.). • Surgical site assessments at T96h (prior to discharge from the unit) and then as an outpatient on D8/W1, D15/W2, and D29/W4 (later if necessary). If there are skin reactions atypical for the type of surgery, e.g., more than expected erythema, drainage, bruising or hematoma, induration, swelling or other skin changes, they should be documented as AEs, graded for severity and followed regularly until resolution or establishment of a new baseline. • Neurosensory testing near the incision (compared to a control site just distal to the costal margin) will be performed at Screening visit, T96h (prior to discharge from the unit) and then as an outpatient on D8/W1, D15/W2, and D29/W4. o Numbness at or near the incision need not be considered a neurologic AE since this could occur because of tissue trauma and inflammation from the surgery. o Sensory deficits or clinically significant persistent sensory change beyond the area immediately proximal/distal to the incision at time of discharge, such as allodynia or hyperalgesia,

	must be designated as a neurologic AE. Subjects will be followed until there is a return to baseline or establishment of a new baseline. • Query subjects as to whether they have experienced any rebound or worsening pain at the surgical site at D8, 15 and 29. • ECGs, standard clinical labs at screening and post-surgery as specified in the Schedule of Assessments and outlined below The Investigator is responsible for determining if out of range laboratory values are clinically significant or not. All clinically significant values will be recorded in the eCRF and followed until resolution. o ECG at screening and T24±2 h o Hematology/Coagulation at screening and T96±4h: hemoglobin, hematocrit, white blood cell count with differential, red blood cell count, platelet count, activated partial thromboplastin time (aPTT) and prothrombin time (PT) or international normalization ratio (INR). o Blood Chemistry at screening and T96±4h to include at least the following: Alanine aminotransferase (ALT; SGPT) and Aspartate aminotransferase (AST; SGOT), total bilirubin (TBili), gamma-glutamyl transferase (GGT), albumin, blood urea nitrogen (BUN), creatinine, alkaline phosphatase (ALK), sodium, potassium, calcium, chloride and glucose. o Serum and urine pregnancy test for FCBP: βhCG test at screening and urine test usually to be done within 24 hours prior to surgery. o Urinalysis at screening and T96±4h: including macroscopic analysis and, if indicated, microscopic analysis.
Efficacy Parameter Assessment Times:	1. NRS scores will be assessed as follows: • During the inpatient stay, NRS at rest beginning with the PACU admission may be assessed once the subject is awake. If the subject is able to provide responses, obtain NRS scores at 0.5, 1, 2, 4, 6, 8, 12, 16, 20, 24, and every 4 hours (if awake at time of assessment) until discharge from the inpatient unit. Time windows: for T0.5 to T2 (±5 min) and from T4 onward (±15 min). • Pain scores may be skipped between the hours of midnight and 6 a.m., but the subject may not miss two consecutive assessments. • An additional NRS assessment must be obtained prior to rescue medication request (±15 min). The T12, T24, T48, T72 and T96h assessments must be completed even if the subject is asleep at these times.

	• During the inpatient stay, starting on postoperative day 1 perform the following each morning: on arising at 0800h (±2h) and each evening at 2000h (±2h) document the NRS on arising from a recumbent position to a sitting or standing position. Actual assessment times must be documented. If however these twice daily assessments coincide with timed assessments of NRS at rest, then the time assessment at rest is used in place of the twice daily assessments. Resting pain scores are performed on the schedule noted above in the first bullet. • During the outpatient period, instruct the patient to document, if possible, their NRS scores twice daily at 0800h (±4h) and 2000h (±4h) at rest and on arising from a recumbent position to a sitting or standing position at T96. W1. W2. Amd W4. Note that the actual time of these assessments must be documented in the diary whenever possible. Instruct the patient to: o Obtain the morning NRS assessment prior to taking any pain medication or 2 (±15min) hours after taking any pain medication o Obtain the evening NRS assessment 2 (±15min) hours after taking any pain medication 2. Total opioid consumption (OC) and daily opioid (rescue medication) consumption in MEDs will be recorded during the inpatient period. • Document subject days in which no rescue medication or analgesic consumption is required (opioid free, OF) during the inpatient and outpatient period. • Document daily use of OTC analgesics (and oxycodone if prescribed) during the outpatient period. • Document the fraction of subjects who rescue at T6, T12, T24, T48, T72 and T96h • Document any prescriptions for opioids provided to the subject prior to discharge to outpatient status and the number of tablets prescribed. Also document any new such prescriptions. 3. Patient Global Evaluation (PGE) at T96±4h prior to discharge, D8/W1, D15/W2 and D29/W4 clinic visits. 4. Investigator Global Evaluation (IGE) at T96±4h prior to discharge, D8/W1, D15/W2 and D29/W4 clinic visits.
Primary Efficacy Endpoint:	Time-specific mean NRS pain intensity scores at T96h for CA-008 (100 mL volume) 0.05 mg/mL (5.0 mg) vs. vehicle placebo (100 mL volume).
Key Secondary Efficacy Endpoints:	For the CA-008 vs. vehicle placebo comparison:

	• Weighted sum of pain intensity (SPI) assessments = Area Under the Curve (AUC) of the NRS current pain intensity scores from T0 to 96h at rest ($AUC_{0 \text{ to } 96h}$). • Time to opioid cessation or freedom (T_{OF}) • Percentage of subjects who do not require opioids (i.e., opioid free; OF) from T24 to T96: $OF_{24 \text{ to } 96h}$
Other Endpoints:	For each CA-008 dose vs. placebo comparison: • Using NRS at rest: $AUC_{0 \text{ to } 120h}$, $AUC_{24 \text{ to } 96h}$, $AUC_{0 \text{ to } W1}$ • $AUC_{0 \text{ to } 96h \text{ (arising)}}$, $AUC_{0 \text{ to } W1 \text{ (arising)}}$, • Time-specific mean NRS at T48, T72, T96, T120, T144 and T168h • $OC_{24 \text{ to } 96h}$ • $OF_{24 \text{ to } 96h}$, $OF_{96h \text{ to } W1}$ and $OF_{96h \text{ to } W2}$ • The fraction of subjects who rescue at T48, T72 and T96h • Analgesic consumption from T96h to W1 ($AC_{96h \text{ to } W1}$) and $AC_{96h \text{ to } W2}$ • PGE comparing the %age of subjects reporting "poor" + "fair" vs. "good" + "excellent" responses, and the %age reporting each category of response at T96h, D8/W1, D15/W2 and D29/W4 • IGE comparing the %age of those reporting "poor" + "fair" vs. "good" + "excellent" responses, and the %age reporting each category at T96h, D8/W1, D15/W2 and D29/W4. Note that the IGE may be performed by any investigator or sub-investigator.
PK Endpoints:	The time points for whole blood collection will be at baseline (from checkin and up to 30 min before the start of surgery), and T5min, T10 min, T15min, T30min, T45min, and T1, T1.5, T2, T2.5, T3, T4, T6, T8, T12, T16, T24, T30, T36 and T48h for a total of 20 samples) with T0 = end of study treatment administration. Actual sampling times will be used to calculate plasma-derived PK parameters. The PK will be documented in the PK Analysis Plan document. Additionally, immediately post surgery begin a 24h urine collection to assess urinary CA-101 excretion to be collected in two aliquots: after surgery to T6h and T6h to T24h.
Stopping Rules:	Study enrollment will be paused if subjects experience intolerable at least possibly related TEAEs, as defined: • 1 or more subjects with any grade 4 "related" TEAE in any of the categories shown in the table below • 2 or more subjects with the same grade 3 "related" TEAE in any of the categories shown in the table below Refer to the in-text table below for descriptions of AE grading.

	<table><tr><th>Category</th><th>Mild (Grade 1)</th><th>Moderate (Grade 2)</th><th>Severe (Grade 3)</th><th>Potentially Life Threatening (Grade 4)</th></tr><tr><td>Abnormal Wound Healing: Infection Dehiscence Necrosis</td><td>Mild symptoms; clinical or diagnostic observations only; intervention not indicated. No interference with age-appropriate instrumental ADL</td><td>Minimal, local or noninvasive intervention indicated; May require local wound care or medical intervention (e.g., dressings or topical medications)</td><td>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.</td><td>Life-threatening consequences; urgent intervention indicated</td></tr><tr><td>ECG/Cardiac issues Vital Signs Labs</td><td>Asymptomatic, intervention not indicated</td><td>Non-urgent medical intervention indicated</td><td>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated</td><td>Life-threatening consequences; urgent intervention indicated</td></tr><tr><td>Focused Neurosensory Testing (performed by trained Investigator)</td><td>Mild symptoms</td><td>Moderate symptoms; limiting instrumental ADL</td><td>Severe symptoms requiring medical intervention; limiting self-care ADL</td><td>Life-threatening and urgent intervention indicated</td></tr></table> Should a stopping rule be triggered, an external independent Safety Review Committee (SRC) will review the data to determine whether or not it is appropriate to continue with enrollment. The SRC Charter details the membership, roles and responsibilities of the SRC.
Sample Size Justification:	Given the uncertainty in estimating a sample size for C-ABD surgery, the data from the current study will be used to determine the sample size for a subsequent parallel design study selecting one or more optimal doses of CA-008 vs. placebo in the setting of standard of care for abdominoplasty.
Study Populations:	The following three analysis populations are planned for this study: • The Safety Population will include all subjects who received any part of a dose of study treatment. • The PK Population will include all subjects who receive a full dose of study treatment and complete all PK assessments. • The intent-to-treat (ITT) population will include all subjects as randomized to study treatment. The modified intent-to-treat (mITT) Population will include all subjects who receive a full dose of study treatment and complete the first 3 pain assessments (through T2h). • Study completers (Study Completers) will include all subjects who receive a full dose of study treatment and complete the entire study period through D29±2/W4. Subjects who elect to discontinue study participation (early termination or ET) after randomization but prior to receiving study treatment will be replaced.

	Subjects who elect to ET after receiving study treatment will not be replaced, however those who ET during the inpatient phase of the study, will be asked to continue with assessments through T96h if they have not elected to withdraw from all aspects of study participation. Subjects who elect to discontinue participation prior to D8 (W1) will be considered to have terminated as of the date of their election, however they will be asked to return to the site one time, if willing and at their convenience, to ensure wound healing.
Statistical Considerations:	All safety assessments and baseline characteristics will be summarized using the Safety Population. Efficacy analyses will be performed using the mITT population. PK analyses will be performed using the PK population. All summaries will be grouped by the actual treatment received. Subjects receiving vehicle placebo 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 study treatment 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. While the study is not specifically designed to detect a significant difference in efficacy between CA-008 and placebo, efficacy analyses will be performed as secondary endpoints.

Table 1. Schedule of Assessments

Assessment	Screening	In Patient							Follow-Up			Unscheduled Visit[1]	Early Termination[19]
		Prior to Surgery	Surgery	Post-Surgery	24h	48h	72h	96h					
Study Day	-45 to -1	0	0	0	1	2	3	4	8±1 days	15±2 days	29±2 days		
Informed Consent	X	X											
Screening Medical and Surgical History	X	X											
Inclusion/Exclusion Criteria	X	X											
Screens for alcohol/drugs of abuse	X	X											
Enroll/Randomize		X											
Demographics	X												
Subject Pain Assessment Training	X[2]	X[2]											
Surgery			X										
Study treatment Infiltration/instillation			X										
Pregnancy Test	X[3] (serum)	X[3] (urine)											
Vital Signs	X	X		X[4]	X[4]	X[4]	X[4]	X[4]	X	X	X	X	X
Temperature	X	X		X[4]	X[4]	X[4]	X[4]	X[4]	X	X	X	X	X
Physical Examination	X[5]	X[5]						X[5]	X[5]	X[5]	X[5]	X[5]	X[5]
12-Lead ECG	X				X[6]								
Surgical Site assessment						X[7]		X[7]	X[7]	X[7]	X[7]	X[7]	X[7]
Neurosensory Exam	X					X[8]		X[8]	X[8]	X[8]	X[8]	X[8]	X[8]
Blood draw for laboratory tests	X[9]							X[9]					
Urine sample for urinalysis	X[9]							X[9]					
Rescue Medication consumption				X	X	X	X	X	X	X		X	X
Concomitant Medication Assessment	X	X		X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X
Rebound Pain Assesmment									X[18]	X[18]	X[18]	X[18]	X[18]
NRS pain assessments				X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]		X[10]	X[10]

Assessment	Screening	In Patient							Follow-Up			Unscheduled Visit[1]	Early Termination[19]
		Prior to Surgery	Surgery	Post-Surgery	24h	48h	72h	96h					
Study Day	-45 to -1	0	0	0	1	2	3	4	8±1 days	15±2 days	29±2 days		
Subject home diary record (NRS)								X[11]	X[11]	X[11]		X[11]	X[11]
Paper Diary (review, distribution and/or collection)								X[12]	X[12,13]	X[12,13]		X[12,13]	X[13]
Subject home diary (analgesic consumption)								X	X	X		X	X
Prescription for outpatient opioid rescue if needed								X[14]					
PGE assessment								X	X	X	X	X	X
IGE assessment								X	X	X	X	X	X
Blood draw for PK analysis		X[16]		X[15, 16]	X[15, 16]								
24h Urine Collection				X[16, 17]	X[16, 17]								
Rebound pain									X[18]	X[18]	X[18]	X[18]	X[18]

1 Unscheduled visit after Day 29 may occur if insufficient wound healing is assessed by the Investigator at the Day 29 visit or to follow up any ongoing AE to resolution or establishment of a new baseline. For unscheduled visits prior to Day 15, collect efficacy assessments, including NRS scores and diary logs.

2 Pain assessment training with test during screening; rewatch video only prior to surgery.

3 Note pregnancy tests are for FCBP; urine pregnancy test is to be performed within 24 hours of scheduled surgery.

4 Vital signs and temperature assessed together at 1, 2, 4, 6, 12, 24 and every 8 hours thereafter (if awake at time of assessment between the hours of 00:00 and 06:00) until discharge from the inpatient unit (may not miss two consecutive assessments). There will be a ±5-minute window allowed for the collection of vital signs in the first 4 hours after the end of surgery, after which for vital signs and temperatures there will be a ±15-minute window allowed.

5 A complete medical history and physical examination including all major body systems will be performed at Screening. In addition, at the following times, an interim medical history and targeted physical examination will be performed prior to surgery (if not done on D-1), and to capture changes after Surgery, at 96 hours (± 4 hours) after the administration of study medication, but prior to discharge, and Day 8, Day 15 and Day 29 after the administration of study medication or if the subject terminates early, at that time if allowed. Body weight (kg), in indoor clothing, but without shoes, will be measured at Screening and at 96 hours. Height (in cm) will be measured and BMI will be calculated at Screening only.

6 Post-Surgery ECG should be performed at 24 hours (±2 hours) after study medication administration.

7 Surgical Site assessment: 48 hours (±2 hours) and 96 hours (±4 hours after study medication administration but prior to discharge from the inpatient unit) and Day 8, 15 and 29.

8 Neurosensory Exam of the area proximal to the surgical incision approximately 3 cm from the incision at Screening visit, 48 hours (±2 hours), 96 hours (±4 hours, but prior to discharge) and Day 8, Day 15 and Day 29 after the administration of study medication or if the subject terminates early, at that time if allowed.

9 Clinical Laboratory tests (chemistry, hematology, coagulation and urinalysis) should be performed at screening and prior to discharge from the inpatient unit (Lab collection window for 96h is ±4h hours).

10 NRS pain assessments during the inpatient stay, NRS at rest assessments start in the PACU once the subject is awake at 0.5, 1, 2, 4, 6, 8, 12, 16, 20, 24, and every 4 hours (if awake at time of assessment) until discharge from the inpatient unit. Pain scores may be skipped between the hours of midnight and 6 a.m., but the subject may not miss two consecutive assessments. Also assess

NRS at the time of rescue request (±15 min). The T12, T24, T48, T72 and T96h assessments must be completed even if the subject is asleep at these times. There will be a ±5-minute window allowed for the collection of each assessment in the first 2 hours after PACU admission, after which will be a ±15-minute window allowed. During the inpatient period document the NRS at rest and on arising from a recumbent position twice daily at 0800h (±2h) and 2000h (±2h) with the actual time of these assessments documented. These twice daily scores are performed independently of pain scores at rest during the inpatient period. If however these twice daily assessments coincide with timed assessments of NRS at rest, then the time assessment at rest is used in place of the twice daily assessments. During the outpatient period, instruct the subject to document, if possible, their NRS scores twice daily at 0800h (±4h) and 2000h (±4h) at rest and on arising from T96 through D15 (not through D29). Note that the actual time of these assessments must be documented in the diary. Instruct the subject to:

- Obtain the morning NRS assessment prior to taking any pain medication or 2 (±15-min) hours after taking any pain medication.
- Obtain the evening NRS assessment 2 (±15-min) hours after taking any pain medication.

If an early termination is elected before Day 15, collect efficacy assessments, including NRS scores and diary logs.

[11] The subject is expected to document NRS pain scores at rest and on arising from recumbency to sitting or standing 2x/day through Day 15 (at the times and qualifications noted above).

[12] The diary and instructions are provided to the subject prior to discharge (T96h). At each subsequent visit, review Subject Diary instructions with subject and collect their NRS scores and other study-related assessments.

[13] Collect Subject Diary Data

[14] If the subject is continuing to require opioids during the 12 hours prior to discharge (any time from T84h onward), then write a prescription for no more than 9 tablets of oxycodone 5 mg tablets for use tid prn per investigator discretion.

[15] Collect blood samples for PK. The time points for whole blood collection will be at baseline (from Check-in and up to 30 min prior to surgery), and T5min, T10 min, T15min, T30min, T45min, and T1, T1.5, T2, T2.5, T3, T4, T6, T8, T12, T16, T24, T30, T36 and T48h for a total of 20 samples) where T0 = end of study treatment administration. There will be a ±2-minute window allowed for the 5 to 15-minute collections, a ±5-minute window allowed for collections T30 min through T4h, and a ±15-minute window for collections after T4 hours.

[16] Subjects must abstain from foods containing capsaicin for 24 hours prior to all PK blood draws.

[17] Collect the subject's urine for 24 hours after surgery in two aliquots: post surgery to T6h and T6h to T24h.

[18] Assess for presence of rebound pain at the surgical site (yes/no response).

[19] If the subject terminates early and is willing to come in to complete all safety and efficacy assessments then complete all procedures listed. If unwilling to come in for all such assessments, at least attempt to bring the subject in for a surgical site assessment,

3. TABLE OF CONTENTS

LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation	Term
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
H or HRS	Hours
HCl	Hydrochloride
HCU	Health care utilization
HED	Human Equivalent Dose
HEENT	Head, Eye, Ear, Nose and Throat
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Institutional Ethics Committee
IGE	Investigator Global Evaluation
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantitation
LOE	Lack of efficacy
mcg or µ	Microgram
MED	Morphine equivalent dose
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
min	Minutes
mL	Milliliter
NCS	Not clinically significant
NOAEL	No Observed Adverse Effect Level
NRS	Numeric Rating Scale of Pain Intensity
NSAID	Nonsteroidal anti-inflammatory drug
OC	Opioid consumption in morphine equivalent dose
OF	Opioid-free days
OTC	Over-the-counter
PACU	Post-anesthesia care unit
PE	Physical examination
PGE	Patient Global Evaluation
PHN	Postherpetic neuralgia
PI	Principal Investigator
PK	Pharmacokinetic[s]

Abbreviation	Term
PO	Per oram (oral)
PRN	Pro re nata (as needed)
PT	Prothrombin time
QID	Quater in die (four times daily)
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SOC	System Organ Class
SNRIs	Serotonin-norepinephrine reuptake inhibitors
SRC	Safety Review Committee
SSRIs	Selective serotonin reuptake inhibitors
T#	Time in hours after completion of study medication dosing (T0)
$t_{½}$	Elimination half-life
TEAEs	Treatment emergent adverse event[s]
TID	Ter in die (three times daily)
T_{max}	Time to maximum plasma concentration
TRPV1	Transient receptor potential vanilloid-1
TTFR	Time to first rescue
UDS	Urine drug screen[ing]
US	United States
V	Volume of distribution
W#	Week # visit after surgery
WHO	World Health Organization

5. INTRODUCTION

5.1. Background

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

Capsaicin exposure to TRPV-1-expressing nociceptor peripheral terminals results in initial excitation of the nociceptor followed by a functional desensitization which continues for some time after removal of capsaicin from the site. Capsaicin, however, is virtually insoluble in aqueous media or local anesthetic solutions which means that capsaicin formulations tend to be quite hydrophobic and viscous making them hard to inject and less likely to permeate surgical site tissues. Anesiva, which had been developing capsaicin for the management of post-surgical pain and osteoarthritis, solubilized capsaicin in polyethylene glycol 300 (Hartrick 2011). The product was instilled into the open surgical site and after waiting for 5 minutes, was removed via surgical suction. This route of administration while simple and perhaps convenient, limited exposure of capsaicin only to the exposed surfaces of cut tissue and bone with little to no ability to penetrate into the affected soft tissues.

To work around the solubility limitations of capsaicin, the highly water soluble capsaicin pro-drug CA-008 was developed for local infiltration. It avoids the physicochemical limitations of capsaicin while providing greater target engagement which theoretically would produce superior local analgesia, particularly after surgical trauma. Based upon this mechanism of action, local delivery of a TRPV1 agonist throughout the tissues around the surgical site prior to wound closure to maximize target engagement should result in a meaningful reduction of post-surgical pain over several days to weeks. This improved long-term pain relief has the ability to augment current multimodal analgesia or enhanced recovery programs which may help to avoid the need for supplemental opioid use after surgery.

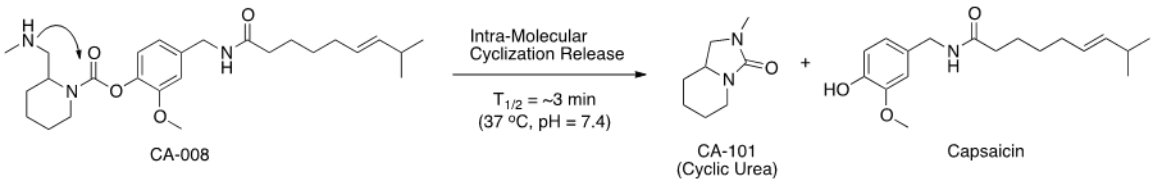
While no capsaicin products have been approved for injection or instillation into a wound site in the US, several companies have or had clinical development programs for such products. Centrexion Therapeutics has an active development program (CTNX-4975) for intraarticular injection of capsaicin for chronic osteoarthritis and Morton's neuroma (see

http://centrexion.com/our-pipeline/). Note that Centrexion is using the Anesiva highly viscous polyethylene glycol formulation for its intraarticular knee joint injections.

5.2. CA-008 Product Introduction

The active moiety of CA-008, capsaicin, has certain attractive properties for treatment of post-operative pain from a pharmaceutical perspective. CA-008 is water soluble and easy to inject through a 25 g needle or larger. It readily penetrates surgical site tissues where it releases capsaicin through a non-enzymatic pH-driven process. Local administration of CA-008 at or near the source of pain either topically, by infiltration or by instillation into a surgical site results in low systemic levels of capsaicin.

CA-008 was created to improve delivery of capsaicin without having to account for its poor solubility profile in tissues. CA-008 provides an aqueous formulation that could be simply infiltrated in the wound site to achieve local capsaicin release to produce a maximal effect. The free base form of CA-008 rapidly breaks down at physiological pH to yield capsaicin and a cyclic urea, as shown in the scheme below:



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

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

5.3. Previous Human experience

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

5.3.1. Study CA-PS-201 (Bunionectomy)

A first-in-human study (Study CA-PS-2017-101) evaluated the safety and tolerability of CA-008 in subjects undergoing a unilateral transpositional first metatarsal osteotomy for correction of hallux valgus deformity, more commonly known as a bunionectomy. This study also evaluated pharmacokinetic (PK) and preliminary efficacy assessment of CA-008 to inform future studies in our clinical development plan. This study was originally designed to look at 4 different doses of CA-008 (0.5 mg, 1 mg, 2 mg, and 3 mg), however based upon the relatively benign adverse event (AE) profile, the Data Management Committee gave the go-ahead for a 5th cohort (4.2 mg) to be added. The safety, efficacy and PK results for the Phase 1 bunionectomy study are shown in the current Investigators' Brochure.

Additionally, a follow-on Phase 2 bunionectomy study (CA-PS-201) was completed with 147 subjects enrolled and randomized to one of 3 active doses: 0.05 mg/mL (0.7 mg), 0.15 mg/mL (2.1 mg) and 0.3 mg/mL (4.2 mg) vs. placebo in a 1:1:1:1 randomization, respectively. The results are still being compiled at the time of this protocol amendment. Based upon topline results, the highest dose of 4.2 mg was statistically significantly superior to placebo for the primary efficacy endpoint of AUC 0-96h ($p=0.005$) and key secondary efficacy endpoints: AUC 0 to week 1 ($p=0.036$); mean opioid consumption (reduced by 50%, $p<0.002$); and percent of subjects who were opioid free from 0 to 96h (26% vs. 5% for placebo; $p=0.039$). The following Tables 2-7 show the summary of safety for the study based upon summary tables and subject listings. Note that in Table 3, the Summary of TEAEs by MedDRA SOC/PT, there were a number of preferred terms that were somewhat vague, so these are accompanied by footnotes detailing the verbatim terms to provide background context.

Table 2. Summary of Adverse Events (CA-PS-201)

No. of Subjects TEAEs.	Total (N=147)	CA-008			Placebo (Standard of care alone) N=38 n (%)
		0.7 mg (0.05 mg/mL) N=36 n (%)	2.1 mg (0.15 mg/mL) N=36 n (%)	4.2 mg (0.3 mg/mL) N=37 n (%)	
No. of TEAEs	287	69	82	76	60
No. of Subjects with any TEAE[1]	106 (72.1%)	27 (75.0%)	28 (77.8%)	26 (68.4%)	25 (67.6%)
No. of "Related" AEs	43	8	11	14	10
No. of Subjects with any "Related" TEAE	28 (19.1%)	8 7 (19.4%)	11 7 (19.4%)	14 7 (18.4%)	10 7 (18.9%)
No. of "Severe" AEs	7	3	2	2	0
No. of Subjects with any "Severe" TEAE	6 (4.1%)	2 (5.6%)	2 (5.6%)	2 (5.3%)	0
No. of SAEs	1	0	0	0	1
No. of Subjects with any SAE	1 (0.7%)	0	0	0	1 (2.7%)
No. of TEAEs leading to discontinuation	0	0	0	0	0
No. of Subjects with TEAEs leading to discontinuation	0	0	0	0	0

Note: TEAE = treatment emergent adverse events; serious TEAEs (SAEs) = serious adverse event
Events with missing severity were imputed as severe. Events with missing relationship were imputed as probably related. Percentages are based on subjects in the Safety Population. For subject counts, if a subject experienced one or more events, they were counted only once.
[1] A TEAE is defined as any new AE or an existing AE that worsens in severity during or after study drug administration.
[2] Treatment related TEAEs are defined as TEAEs with relationship of "probably" or "possibly" related.

Table 3. Summary of TEAEs by MedDRA SOC/PT (CA-PS-201)

No. of Subjects TEAEs.	Total (N=147)	CA-008			Placebo (Standard of care alone) N=38 n (%)
		0.7 mg (0.05 mg/mL) N=36 n (%)	2.1 mg (0.15 mg/mL) N=36 n (%)	4.2 mg (0.3 mg/mL) N=37 n (%)	
No. of TEAEs	287	69	82	76	60
No. of Subjects with any TEAE[1]	106 (72.1%)	27 (75.0%)	28 (77.8%)	26 (68.4%)	25 (67.6%)
Cardiac disorders	6 (4.1%)	1 (2.8%)	2 (5.6%)	3 (7.9%)	0
Angina	1 (0.7%)	1 (2.8%)	0	0	0
Bradycardia	2 (1.4%)	0	1 (2.8%)	1 (2.6%)	0
Sinus tachycardia	1 (0.7%)	0	1 (2.8%)	0	0
Tachycardia	2 (1.4%)	0	0	2 (5.3%)	0
Eye disorders	1 (0.7%)	0	1 (2.8%)	0	0
Eye hematoma	1 (0.7%)	0	1 (2.8%)	0	0
Gastrointestinal disorders	41 (27.9%)	8 (22.2%)	10 (27.8%)	10 (26.3%)	13 (35.1%)
Abdominal pain	1 (0.7%)	0	0	0	1 (2.7%)
Abdominal pain upper	1 (0.7%)	1 (2.8%)	0	0	0
Constipation	10 (6.8%)	3 (8.3%)	2 (5.6%)	1 (2.6%)	4 (10.8%)
Diarrhea	1 (0.7%)	0	1 (2.8%)	0	0
Dyspepsia	1 (0.7%)	0	1 (2.8%)	0	0
Flatulence	1 (0.7%)	0	0	1 (2.6%)	0
Nausea	29 (19.7%)	6 (16.7%)	7 (19.4%)	7 (18.4%)	9 (24.3%)
Paresthesia oral	1 (0.7%)	0	0	0	1 (2.7%)
Stomatitis	1 (0.7%)	1 (2.8%)	0	0	0
Vomiting	12 (8.2%)	1 (2.8%)	4 (11.1%)	3 (7.9%)	4 (10.8%)
General disorders and administrative site conditions	20 (13.6%)	6 (16.7%)	3 (8.3%)	5 (13.2%)	6 (16.2%)
Administrative site warmth[2]	2 (1.4%)	1 (2.8%)	0	1 (2.6%)	0
Application site pain[3]	1 (0.7%)	0	0	0	1 (2.7%)
Application site rash[4]	1 (0.7%)	0	0	1 (2.6%)	0
Chills	1 (0.7%)	0	0	0	1 (2.7%)
Feeling hot[5]	6 (4.1%)	1 (2.8%)	2 (5.6%)	1 (2.6%)	2 (5.4%)
Impaired healing	1 (0.7%)	1 (2.8%)	0	0	0

Table 3 (Cont.). Summary of TEAEs by MedDRA SOC/PT (CA-PS-201)

Infusion site edema[6]	6 (4.1%)	3 (8.3%)	0	1 (2.6%)	2 (5.4%)
Infusion site pain[7]	3 (2.0%)	1 (2.8%)	1 (2.8%)	0	1 (2.7%)
Edema peripheral[8]	2 (1.4%)	0	0	2 (5.3%)	0
Pain[9]	4 (2.7%)	1 (2.8%)	1 (2.8%)	1 (2.6%)	1 (2.7%)
Infections and infestations	9 (6.1%)	0	5 (13.9%)	3 (7.9%)	1 (2.7%)
Cellulitis	3 (2.0%)	0	1 (2.8%)	1 (2.6%)	1 (2.7%)
Pharyngitis	1 (0.7%)	0	1 (2.8%)	0	0
Post procedural cellulitis	1 (0.7%)	0	1 (2.8%)	0	0
Post procedural infection	1 (0.7%)	0	1 (2.8%)	0	0
Post procedural wound infection	3 (2.0%)	0	1 (2.8%)	1 (2.6%)	1 (2.7%)
Tooth infection	1 (0.7%)	0	0	1 (2.6%)	0
Injury, poisoning and procedural complications	18 (12.2%)	3 (8.3%)	5 (13.9%)	3 (7.9%)	7 (18.9%)
Foot fracture	1 (0.7%)	0	0	0	1 (2.7%)
Incision site erythema[10]	1 (0.7%)	0	0	0	1 (2.7%)
Incision site hematoma[11]	2 (1.4%)	1 (2.8%)	1 (2.8%)	0	0
Scar[12]	1 (0.7%)	11 (2.8%)	0	0	0
Wound[13]	1 (0.7%)	0	0	1 (2.6%)	0
Wound dehiscence[14]	15 (10.2%)	2 (5.6%)	5 (13.9%)	3 (7.9%)	5 (13.5%)
Investigations	7 (4.8%)	2 (5.6%)	2 (5.6%)	3 (7.9%)	0
Alanine aminotransferase increased[15]	3 (2.0%)	0	0	3 (7.9%)	0
Aspartate aminotransferase increased[15]	3 (2.0%)	0	0	3 (7.9%)	0
Blood glucose increased	1 (0.7%)	0	1 (2.8%)	0	0
Blood pressure increased	2 (1.4%)	2 (5.6%)	0	0	0
Body temperature increased	1 (0.7%)	0	1 (2.8%)	0	0
Gamma-glutamyltransferase increased	1 (0.7%)	0	0	1 (2.6%)	0
Metabolism and nutrition disorders	3 (2.0%)	0	1 (2.8%)	2 (5.3%)	0
Decreased appetite	3 (2.0%)	0	1 (2.8%)	2 (5.3%)	0
Musculoskeletal and connective tissue disorder	17 (11.6%)	7 (19.4%)	5 (13.9%)	4 (10.5%)	1 (2.7%)

Table 3 (Cont.). Summary of TEAEs by MedDRA SOC/PT (CA-PS-201)

Arthralgia	2 (1.4%)	1 (2.8%)	1 (2.8%)	0	0
Back pain	4 (2.7%)	2 (5.6%)	0	2 (5.3%)	0
Joint stiffness	1 (0.7%)	0	1 (2.8%)	0	0
Limb discomfort[16]	2 (1.4%)	2 (5.6%)	0	0	0
Muscle spasms[17]	3 (2.0%)	0	3 (8.3%)	0	0
Muscle twitching[18]	1 (0.7%)	1 (2.8%)	0	0	0
Musculoskeletal pain[19]	1 (0.7%)	0	0	1 (2.6%)	0
Musculoskeletal stiffness[20]	1 (0.7%)	0	1 (2.8%)	0	0
Neck pain	1 (0.7%)	0	0	1 (2.6%)	0
Pain in extremity[21]	4 (2.7%)	1 (2.8%)	0	2 (5.3%)	1 (2.7%)
Nervous system disorders	53 (36.1%)	17 (47.2%)	14 (38.9%)	14 (36.8%)	8 (21.6%)
Burning sensation	4 (2.7%)	2 (5.6%)	0	2 (5.3%)	0
Dizziness	12 (8.2%)	4 (11.1%)	5 (13.9%)	1 (2.6%)	2 (5.4%)
Headache	28 (19.0%)	7 (19.4%)	8 (22.2%)	7 (18.4%)	6 (16.2%)
Hyperesthesia	2 (1.4%)	1 (2.8%)	0	1 (2.6%)	0
Hypoesthesia	2 (1.4%)	0	1 (2.8%)	1 (2.6%)	0
Paresthesia	3 (2.0%)	1 (2.8%)	0	1 (2.6%)	1 (2.7%)
Presyncope	1 (0.7%)	1 (2.8%)	0	0	0
Somnolence	6 (4.1%)	2 (5.6%)	0	2 (5.3%)	2 (5.4%)
Syncope	1 (0.7%)	0	1 (2.8%)	0	0
Psychiatric disorders	1 (0.7%)	0	0	0	1 (2.7%)
Depressed mood	1 (0.7%)	0	0	0	1 (2.7%)
Renal and urinary disorders	4 (2.7%)	0	4 (11.1%)	0	0
Polyuria	4 (2.7%)	0	4 (11.1%)	0	0
Urge incontinence	1 (0.7%)	0	1 (2.8%)	0	0
Reproductive system and breast disorders	1 (0.7%)	0	0	1 (2.6%)	0
Vaginal hemorrhage	1 (0.7%)	0	0	1 (2.6%)	0
Respiratory, thoracic and mediastinal disorders	6 (4.1%)	3 (8.3%)	0	3 (7.9%)	0
Dysphonia	1 (0.7%)	1 (2.8%)	0	0	0
Hypoxia	4 (2.7%)	2 (5.6%)	0	2 (5.3%)	0
Rhinorrhea	1 (0.7%)	0	0	1 (2.6%)	0
Skin and subcutaneous	13 (8.8%)	2 (5.6%)	4 (11.1%)	1 (2.6%)	6 (16.2%)

Table 3 (Cont.). Summary of TEAEs by MedDRA SOC/PT (CA-PS-201)

tissue disorders					
Dermatitis	1 (0.7%)	0	1 (2.8%)	0	0
Dry skin	1 (0.7%)	0	0	1 (2.6%)	0
Hyperhidrosis[22]	4 (2.7%)	2 (5.6%)	0	0	2 (5.4%)
Petechiae	1 (0.7%)	0	1 (2.8%)	0	0
Pruritus[23]	3 (2.0%)	0	1 (2.8%)	0	2 (5.4%)
Rash[24]	2 (1.4%)	0	0	0	2 (5.4%)
Rash erythematous[25]	1 (0.7%)	0	1 (2.8%)	0	0
Skin maceration	3 (2.0%)	0	1 (2.8%)	0	2 (5.4%)
Surgical and medical procedures	1 (0.7%)	1 (2.8%)	0	0	0
Wound drainage	1 (0.7%)	1 (2.8%)	0	0	0
Vascular disorders	9 (6.1%)	2 (5.6%)	3 (8.3%)	4 (10.5%)	0
Deep vein thrombosis	1 (0.7%)	0	1 (2.8%)	0	0
Diastolic hypotension	1 (0.7%)	1 (2.8%)	0	0	0
Hot flush[26]	2 (1.4%)	0	0	2 (5.3%)	0
Hypertension	2 (1.4%)	0	0	2 (5.3%)	0
Hypotension	2 (1.4%)	0	2 (5.6%)	0	0
Thrombophlebitis	1 (0.7%)	1 (2.8%)	0	0	0

Abbreviations: Related = possibly or probably related; TEAE = treatment emergent adverse event, SOC = System Organ Class, PT = Preferred Term.

1. A TEAE is defined as any new AE or an existing AE that worsens in severity during or after study drug administration. At each level of summarization (SOC or PT), subjects who experienced more than one TEAE were only counted once. All adverse events were coded using MedDRA, Version 21.0. Percentages are based on the number of subjects in the Safety Population. Many of the preferred terms chosen by investigators were vague and, in these cases, the verbatim terms are noted below for these.
2. "Administration site warmth": Two cases with the verbatim terms "warm feeling on surgical foot" and "warmth top of surgical foot".
3. "Application site pain": One case with the verbatim term "burning sensation at L foot surgical site"
4. "Application site rash": One case with the verbatim term "rash on both arms from tape"
5. "Feeling hot": Six cases with the following verbatim terms:
   a. "feeling hot" from 32h to 33h post study treatment
   b. "generalized warm feeling all over body" from days 5-11 post study treatment
   c. "warm sensation lower torso" from 17.6h to 96.6h post study treatment
   d. "warmth at neck area" from 0.9h to 1.2h post study treatment
   e. "feeling hot" from 18.7h-24.4h post study treatment
   f. "feeling hot" from 51.9h-54.4h post study treatment
6. "Infusion site edema": Six cases with the following verbatim terms:
   a. "edema at left hand IV site
   b. "edema – left arm proximal to AC IV site"
   c. "edema distal to left hand IV site"
   d. "edema at left forearm IV site"
   e. "edema on right hand at IV site"
   f. "edema left wrist at IV site"
7. "Infusion site pain": Three cases with the following verbatim terms:
   a. "soreness at left hand IV site"

Table 3 (Cont.). Summary of TEAEs by MedDRA SOC/PT (CA-PS-201)

b. "stinging sensation at IV site upon attempting to flush"
c. "pain left wrist at IV site"

8. "Edema peripheral": Two cases with the verbatim terms "right forearm edema proximal to IV site" and "moderate edema right foot"
9. "Pain": Four cases with the following verbatim terms:
   a. "stinging sensation on the dorsal aspect of the left foot" (the operated foot: one event on day 11 and one on day 13)
   b. "intermittent generalized body aches"
   c. "increased pain in right foot after putting pressure on toes"
   d. "worsening of post operative pain"
10. "Incision site erythema": one case with the verbatim term "erythema – dorsum right foot over 3-4 metatarsal retention incision" noted on days 10-14
11. "Incision site hematoma": two cases with the verbatim terms "superficial hematoma at surgical site" noted on days 10-17 post study treatment, and "superficial hematoma at incision" on days 9-16 post study treatment.
12. "Scar": One case with the verbatim term "full thickness fibrotic tissue proximal to the surgical site". The PI at this site noted that the individual who was performing surgical site assessments did not characterize findings as "typical" for the surgery and therefore not an AE or "atypical" and thus an AE.
13. "Wound": One case with the verbatim term "full thickness open wound at incision" noted on day 29 post study treatment and treated with wound debridement and resolved by day 58.
14. "Wound dehiscence": Each site was instructed to capture "atypical" findings at the surgical site as an AE with "atypical" being a finding different than what is normally seen with this type of surgery. All wound dehiscence cases were identified at site 102. The PI at this site noted that the individual who was performing surgical site assessments did not characterize findings as typical for the surgery (therefore not an AE) or atypical and thus designated as an AE, but instead captured all findings as an AE. Once the PI realized this, the individual was removed from study assessments. Unfortunately, this occurred after database lock and could not be adjusted. The PI noted that in retrospect the cases were mild in severity and most were likely typical for the type of surgery (examples 1-2 mm of wound puckering, a stitch showing or similar minor issues).
15. "ALT or AST increased": As can be seen, these 3 cases of each were captured in the CA-008 4.2 mg group. At site 102, 2 of the transaminase elevations were captured as related AEs. Subject 102-060 had "mild" increases in ALT 147 (4.6 X ULN) and AST 88 (2.2 X ULN) at the T96h assessment. They resolved without treatment and returned to normal by day 16. Subject 102-068 had "severe" increase in ALT 170 (5.3 X ULN) and "moderate" increase in AST 140 (3.5 X ULN). They resolved without treatment and returned to normal by day 15. While these were the only 2 related AEs captured for transaminases, Subject102-053 had mild and unlikely related elevations ALT/AST were 51 (1.6X ULN)/41 (1.03X ULN) at T96h and an Alk Phos elevation 142 (1.2X ULN). Additionally, there were 3 cases in the CA-008 0.7 mg group, 2 in the 2.1 mg group, 2 other cases in the 4.2 mg group, and 3 cases in the placebo group (one of which was a 9X increase from baseline value), respectively, that were normal at baseline and because elevated at T96h, but not captured as TEAEs. Additionally, there were 2, 3 and 2 cases, respectively, in the CA-008 0.7, 2.1 and 4.2 mg groups, where the transaminases were elevated at screening, but became normal at T96h.
16. "Limb discomfort": Two cases with the verbatim terms "pressure on plantar aspect of left foot" and "discomfort on dorsal aspect of left foot" (the operated foot in each case).
17. "Muscle spasm": Three cases with the following verbatim terms:
   a. "bilateral leg cramps"
   b. "muscle spams in neck and upper back"
   c. "muscle spams in left side of hip"
   d. "cramping in left calf"
18. "Muscle twitching": One case with the verbatim term "left shoulder twitching"
19. "Musculoskeletal pain": One case with the verbatim term "pain, right buttocks"
20. "Musculoskeletal stiffness": One case with the verbatim term "stiff neck"
21. "Pain in extremity": Four cases with the following verbatim terms:
   a. "pain on top of left foot"
   b. "left foot pain"
   c. "right heel pain"
   d. "severe pain in right surgical foot".
22. "Hyperhidrosis": Four cases with the following verbatim terms:
   a. "diaphoresis" from 19.7h to 19.8h post study treatment
   b. "diaphoresis" from 12.7h to 87.7h post study treatment
   c. "intermittent diaphoresis" from 7.2h to 33.3h post study treatment
   d. "intermittent diaphoresis" from 51.9h to 54.4h post study treatment
23. "Pruritus": Three cases with the following verbatim terms:
   a. "pruritus dorsal aspect of left foot" from 78.3h to 96.3h post study treatment
   b. "right foot pruritis [sic]" from 39.9h to 40.9h post study treatment
   c. "pruritis [sic] on left hand from 20.3h to 90.3h post study treatment
24. "Rash": Two cases with the verbatim terms "rash (back)" and "rash of left hand"
25. "Rash erythematous": One case with the following verbatim term: "erythematic rash on foot"
26. "Hot flush": One case with the verbatim term "hot flash" from 19.1h to 23.9h post study treatment

Source: Post-text Table TBD (Subject Listing TBD)

Table 4. Summary of Related TEAEs by MedDRA SOC/PT

No. of Subjects TEAEs	Total (N=147)	CA-008			Placebo (Standard of care alone) N=38 N (%)
		0.7 mg (0.05 mg/mL) N=36 N (%)	2.1 mg (0.15 mg/mL) N=36 N (%)	4.2 mg (0.3 mg/mL) N=37 N (%)	
No. of Subjects with any related TEAE[1]	28 (19.0%)	7 (19.4%)	7 (19.4%)	7 (18.4%)	7 (18.9%)
Gastrointestinal disorders	3 (2.0%)	0	1 (2.8%)	0	2 (5.4%)
Nausea	2 (1.4%)	0	1 (2.8%)	0	1 (2.7%)
Paresthesia oral	1 (0.7%)	0	0	0	1 (2.7%)
Vomiting	1 (0.7%)	0	1 (2.8%)	0	0
General disorders and administrative site conditions	3 (2.0%)	2 (5.6%)	0	0	1 (2.7%)
Administrative site warmth[2]	1 (0.7%)	1 (2.8%)	0	0	0
Impaired healing	1 (0.7%)	1 (2.8%)	0	0	0
Pain[3]	1 (0.7%)	0	0	0	1 (2.7%)
Infections and infestations	2 (1.4%)	0	1 (2.8%)	1 (2.6%)	0
Cellulitis	1 (0.7%)	0	0	1 (2.6%)	0
Post procedural cellulitis	1 (0.7%)	0	1 (2.8%)	0	0
Injury, poisoning and procedural complications	5 (3.4%)	1 (2.8%)	0	0	4 (10.8%)
Incision site erythema[4]	1 (0.7%)	0	0	0	1 (2.7%)
Scar[5]	1 (0.7%)	1 (2.8%)	0	0	0
Wound dehiscence[6]	3 (2.0%)	0	0	0	3 (8.1%)
Investigations	2 (1.4%)	0	0	2 (5.3%)	0
Alanine aminotransferase increased[7]	2 (1.4%)	0	0	2 (5.3%)	0
Aspartate aminotransferase increased[7]	2 (1.4%)	0	0	2 (5.3%)	0

Table 4 (Cont.). Summary of Related TEAEs by MedDRA SOC/PT

Musculoskeletal and connective tissue disorder	1 (0.7%)	1 (2.8%)	0	0	0
Limb discomfort[8]	1 (0.7%)	1 (2.8%)	0	0	0
Nervous system disorders	11 (7.5%)	3 (8.3%)	2 (5.6%)	5 (13.2%)	1 (2.7%)
Burning sensation	4 (2.7%)	2 (5.6%)	0	2 (5.3%)	0
Headache	4 (2.7%)	1 (2.8%)	1 (2.8%)	2 (5.3%)	0
Hypoesthesia	2 (1.4%)	0	1 (2.8%)	1 (2.6%)	0
Paresthesia	1 (0.7%)	0	0	0	1 (2.7%)
Renal and urinary disorders	3 (2.0%)	0	3 (8.3%)	0	0
Polyuria	3 (2.0%)	0	3 (8.3%)	0	0
Urge incontinence	1 (0.7%)	0	1 (2.8%)	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.7%)	0	0	1 (2.6%)	0
Rhinorrhea	1 (0.7%)	0	0	1 (2.6%)	0
Skin and subcutaneous tissue disorders	1 (0.7%)	0	0	0	1 (2.7%)
Pruritus[9]	1 (0.7%)	0	0	0	1 (2.7%)
Skin maceration	1 (0.7%)	0	0	0	1 (2.7%)
Vascular disorders	1 (0.7%)	0	0	1 (2.6%)	0
Hot flush[10]	1 (0.7%)	0	0	1 (2.6%)	0

Abbreviations: Related = possibly or probably related; TEAE = treatment emergent adverse event, SOC = System Organ Class, PT = Preferred Term.

1. A TEAE is defined as any new AE or an existing AE that worsens in severity during or after study drug administration. At each level of summarization (SOC or PT), subjects who experienced more than one TEAE were only counted once. All adverse events were coded using MedDRA, Version 21.0. Percentages are based on the number of subjects in the Safety Population.
2. "Administration site warmth": One case with the verbatim term "warm feeling on surgical foot" which lasted 3.5h – 15.9h post study treatment
3. "Pain": One case with the verbatim term "worsening of post operative pain" required medication and physical therapy
4. "Incision site erythema": One case with the verbatim term "erythema – dorsum right foot over 3-4 metatarsal retention incision" noted on days 10-14
5. "Scar": One case with the verbatim term "full thickness fibrotic tissue proximal to the surgical site". The PI at this site noted that the individual who was performing surgical site assessments did not characterize findings as "typical" for the surgery and therefore not an AE or "atypical" and thus an AE.
6. "Wound dehiscence": Each site was instructed to capture "atypical" findings at the surgical site as an AE with "atypical" being a finding different than what is normally seen with this type of surgery. All wound dehiscence cases were identified at site 102. The PI at this site noted that the individual who was performing surgical site assessments did not characterize findings as typical for the surgery (therefore not an AE) or atypical and thus designated as an AE, but instead captured all findings as an AE. Once the PI realized this, the individual was removed from study assessments. Unfortunately, this occurred after database lock and could not be adjusted. The PI noted that in retrospect the cases were mild in severity and most were likely typical for the type of surgery (examples 1-2 mm of wound puckering, a stitch showing or similar minor issues).
7. "ALT or AST increased": As can be seen, these 3 cases of each were captured in the CA-008 4.2 mg group. At site 102, 2 of the transaminase elevations were captured as related AEs. Subject 102-060 had "mild" increases in ALT 147 (4.6 X ULN) and AST 88 (2.2 X ULN) at the T96h assessment. They resolved without treatment and returned to normal by day 16. Subject 102-068 had "severe" increase in ALT 170 (5.3 X ULN) and "moderate" increase in AST 140 (3.5 X ULN). They resolved without treatment and returned to normal by day 15. While these were the only 2 related AEs captured for transaminases, Subject102-053 had mild and unlikely related elevations ALT/AST were 51 (1.6X ULN)/41 (1.03X ULN) at T96h and an Alk Phos elevation 142 (1.2X ULN). Additionally, there were 3 cases in the CA-008 0.7 mg group, 2 in the 2.1 mg group, 2 other cases in the 4.2 mg group, and 3 cases in the placebo group (one of which was a 9X increase from baseline value), respectively, that were normal at baseline and because elevated at T96h, but not captured as TEAEs. Additionally, there were 2, 3 and 2 cases, respectively, in the CA-008 0.7, 2.1 and 4.2 mg groups, where the transaminases were elevated at screening, but became normal at T96h.
8. "Limb discomfort": while it was the preferred term chosen, the verbatim description was "discomfort on dorsal aspect of left foot" (the operated foot).
9. "Pruritus": One case with the following verbatim term: "right foot pruritis [sic]" from 39.9h to 40.9h post study treatment
10. "Hot flush": One case with the verbatim term "hot flash" from 19.1h to 23.9h post study treatment

Table 5. Summary of Related TEAEs by Frequency

No. of Subjects	Total (N=147)	CA-008			Placebo (Standard of care alone) N (%)
		0.7 mg (0.05 mg/mL) N (%)	2.1 mg (0.15 mg/mL) N (%)	4.2 mg (0.3 mg/mL) N (%)	
No. of TEAEs	287	69	82	76	60
No. of Subjects with any TEAE[1]	106 (72.1%)	27 (75.0%)	28 (77.8%)	26 (68.4%)	25 (67.6%)
No. of "Related" AEs	43	8	11	14	10
No. of Subjects with any "Related" TEAE	28 (19.1%)	7 (19.4%)	7 (19.4%)	7 (18.4%)	7 (18.9%)
Burning sensation	4 (2.7%)	2 (5.6%)	0	2 (5.3%)	0
Headache	4 (2.7%)	1 (2.8%)	1 (2.8%)	2 (5.3%)	0
Polyuria	3 (2.0%)	0	3 (8.3%)	0	0
Wound dehiscence	3 (2.0%)	0	0	0	3 (8.1%)
Alanine transaminase increase	2 (1.4%)	0	0	2 (5.3%)	0
Aspartate transaminase increase	2 (1.4%)	0	0	2 (5.3%)	0
Hypoesthesia	2 (1.4%)	0	1 (2.8%)	1 (2.6%)	0
Nausea	2 (1.4%)	0	1 (2.8%)	0	1 (2.7%)
Administration site warmth	1 (0.7%)	1 (2.8%)	0	0	0
Cellulitis	1 (0.7%)	0	0	1 (2.6%)	0
Hot flush	1 (0.7%)	0	0	1 (2.6%)	0
Impaired healing	1 (0.7%)	1 (2.8%)	0	0	0
Incision site erythema	1 (0.7%)	0	0	0	1 (2.7%)
Limb discomfort	1 (0.7%)	1 (2.8%)	0	0	0
Pain	1 (0.7%)	0	0	0	1 (2.7%)
Paresthesia	1 (0.7%)	0	0	0	1 (2.7%)
Paresthesia oral	1 (0.7%)	0	0	0	1 (2.7%)
Pruritus	1 (0.7%)	0	0	0	1 (2.7%)
Rhinorrhea	1 (0.7%)	0	0	1 (2.6%)	0
Scar	1 (0.7%)	1 (2.8%)	0	0	0
Skin maceration	1 (0.7%)	0	0	0	1 (2.7%)
Urge incontinence	1 (0.7%)	0	1 (2.8%)	0	0
Vomiting	1 (0.7%)	0	1 (2.8%)	0	0

Abbreviations: Related = possibly or probably related; TEAE = treatment emergent adverse event, SOC = System Organ Class, PT = Preferred Term.
[1]A TEAE is defined as any new AE or an existing AE that worsens in severity during or after study drug administration. At each level of summarization (SOC or PT), subjects who experienced more than one TEAE were only counted once. All adverse events were coded using MedDRA, Version 21.0. Percentages are based on the number of subjects in the Safety Population.

Table 6. Summary of Related Local TEAEs by Frequency

No. of Subjects	Total (N=147)	CA-008			Placebo (Standard of care alone) N (%)
		0.7 mg (0.05 mg/mL) N (%)	2.1 mg (0.15 mg/mL) N (%)	4.2 mg (0.3 mg/mL) N (%)	
No. of TEAEs	287	69	82	76	60
No. of Subjects with any TEAE[1]	106 (72.1%)	27 (75.0%)	28 (77.8%)	26 (68.4%)	25 (67.6%)
No. of "Related" AEs	43	8	11	14	10
No. of Subjects with any "Related" TEAE	28 (19.1%)	7 (19.4%)	7 (19.4%)	7 (18.4%)	7 (18.9%)
Burning sensation	4 (2.7%)	2 (5.6%)	0	2 (5.3%)	0
Wound dehiscence	3 (2.0%)	0	0	0	3 (8.1%)
Hypoesthesia	2 (1.4%)	0	1 (2.8%)	1 (2.6%)	0
Administration site warmth	1 (0.7%)	1 (2.8%)	0	0	0
Cellulitis	1 (0.7%)	0	0	1 (2.6%)	0
Impaired healing	1 (0.7%)	1 (2.8%)	0	0	0
Incision site erythema	1 (0.7%)	0	0	0	1 (2.7%)
Limb discomfort	1 (0.7%)	1 (2.8%)	0	0	0
Pain	1 (0.7%)	0	0	0	1 (2.7%)
Paresthesia	1 (0.7%)	0	0	0	1 (2.7%)
Scar	1 (0.7%)	1 (2.8%)	0	0	0
Skin maceration	1 (0.7%)	0	0	0	1 (2.7%)

Abbreviations: Related = possibly or probably related; TEAE = treatment emergent adverse event, SOC = System Organ Class, PT = Preferred Term.
[1]A TEAE is defined as any new AE or an existing AE that worsens in severity during or after study drug administration. At each level of summarization (SOC or PT), subjects who experienced more than one TEAE were only counted once. All adverse events were coded using MedDRA, Version 21.0. Percentages are based on the number of subjects in the Safety Population.

Table 7. Summary of Severe TEAEs by Frequency

No. of Subjects	Total (N=147)	CA-008			Placebo (Standard of care alone) N (%)
		0.7 mg (0.05 mg/mL) N (%)	2.1 mg (0.15 mg/mL) N (%)	4.2 mg (0.3 mg/mL) N (%)	
No. of TEAEs	287	69	82	76	60
No. of Subjects with any TEAE[1]	106 (72.1%)	27 (75.0%)	28 (77.8%)	26 (68.4%)	25 (67.6%)
Burning sensation	2 (1.4%)	1 (2.8%)	0	1 (2.6%)	0
Alanine aminotransferase increased	1 (0.7%)	0	0	1 (2.6%)	0
Deep vein thrombosis	1 (0.7%)	0	1 (2.8%)	0	0
Dizziness	1 (0.7%)	1 (2.8%)	0	0	0
Hyperhidrosis	1 (0.7%)	1 (2.8%)	0	0	0
Sinus tachycardia	1 (0.7%)	0	1 (2.8%)	0	0

Abbreviations: Related = possibly or probably related; TEAE = treatment emergent adverse event, SOC = System Organ Class, PT = Preferred Term.
[1]A TEAE is defined as any new AE or an existing AE that worsens in severity during or after study drug administration. At each level of summarization (SOC or PT), subjects who experienced more than one TEAE were only counted once. All adverse events were coded using MedDRA, Version 21.0. Percentages are based on the number of subjects in the Safety Population.

5.3.2. Study CA-PS-204 (Abdominoplasty)

Preliminary unblinded safety data was made available with an interim data snapshot after the first cohort (5 mg) was completed. For this cohort, 18 subjects were randomized 1:1 to receive 100 mL infiltration of either 5 mg CA-008 or placebo vehicle in the setting of standard of care treatments including a a general anesthetic supplemented with a transverse abdominis plane (TAP) block, intraoperative IV opioids and intraoperative IV acetaminophen.

There were 8/9 subjects in each treatment group who experienced TEAEs: 28 in the placebo group and 26 in the CA-008 group. There was one SAE of a deep venous thrombosis in the active group which occurred on day 10 after surgery and was deemed unrelated and moderate in severity. There were no severe events. Most TEAEs were moderate in severity: 20/28 in the placebo group and 20/26 in the active group. Most TEAEs were deemed unrelated. There were 5/28 possibly related events in the placebo group (all nausea events) and 2/26 possible related in the active group (one each of pruritus – mild and nausea – moderate). The most frequent TEAEs in descending order were:

- Placebo: nausea – 14; low back pain – 5; vomiting, constipation and hypoxia at 2 each and the rest single events
- CA-008: nausea – 9; headache – 5; low back pain – 3; constipation – 3; and the rest were single events

5.4. Study Rationale

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

5.5. Dose Rationale

5.5.1. Selection of Doses

The safety of CA-008 was established in relevant animal models and supported by two studies after bunionectomy (CA-PS-2017-101 and CA-PS-201) and knowledge from prior human studies with an injectable formulation of capsaicin. Taken together, the characterization of the pharmacology, pharmacokinetics, and toxicology profiles are considered sufficient to support the intended use of CA-008 in this study.

5.5.2. Selection and Timing of Dose

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

6. STUDY OBJECTIVES

6.1. Pilot Stage of the Study

6.1.1. Primary Objective

- To evaluate the efficacy of a single intraoperative administration of CA-008 vs. vehicle placebo (100 mL volume) in subjects undergoing an elective C-ABD.

6.1.2. Secondary Objectives

- To evaluate the safety and tolerability of a single intraoperative administration of CA-008 vs. vehicle placebo in subjects undergoing an elective C-ABD.
- To evaluate the PK profile of a single intraoperative administration of CA-008 vs. vehicle placebo in subjects undergoing an elective C-ABD.
- To evaluate the opioid-sparing effect of CA-08 vs. placebo in subjects undergoing an elective C-ABD in terms of consumption and time to cessation.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design and Plan

This is a Phase 2, single-center, randomized, double-blind, placebo-controlled, parallel design study consisting of three exploratory cohorts of 18 subjects each: a single dose of CA-008 at 5.0 mg, 10 mg or 15 mg vs. placebo each in 100 mL of vehicle, randomized 1:1 in the first cohort and 2:1, respectively, in cohorts 2 and 3, and an optional 4th cohort may be enrolled with a total N=24 randomized 1:1 to CA-008 or placebo at a dose between 5 mg and 15 mg as determined based upon results from cohorts #1-3.

For each subject, the postoperative assessments will be conducted in two parts:

- Inpatient period which starts with completion of study treatment injection (T0) and continues through 96h (T96h).
- Outpatient period which begins on discharge from the inpatient unit through various follow up visits to day 29 (D29) or week 4 (W4) after surgery, or later if necessary for ongoing safety assessments. Note that additional follow up visits could occur after D29/W4 to follow adverse events (AEs) to resolution or establishment of a new baseline.

7.2. Study Stopping Rules

Study enrollment will be paused if subjects experience intolerable at least possibly related TEAEs, as defined:

- 1 or more subjects with any grade 4 “related” TEAE in any of the categories shown in the table below
- 2 or more subjects with the same grade 3 “related” TEAE in any of the categories shown in the table below

Refer to Table 8 below for descriptions/definitions of AE severity grading. Additional guidance on descriptions of AE grading may be found in Appendices I-K (Sections 17.9, 17.10 and 0).

An external independent Safety Review Committee (SRC) will be consulted should a stopping rule be triggered to determine whether or not it is appropriate to continue with dosing in the study. This committee will be independent of the Sponsor or CRO and will in no way be involved with study conduct. The SRC Charter details the membership, roles and responsibilities of the SRC.

Table 8: 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

7.3. Duration of Participation

Each subject is expected to be in the study up to 76 days (screening through end-of-study visit).

8. SELECTION OF STUDY POPULATION

8.1. Study Population

The study population consists of reasonably healthy men and women, aged 18-65 years old inclusive, who are undergoing elective C-ABD.

8.1.1. Number of Participants

- Cohort #1: N=18 randomized 1:1, CA-008 vs. placebo
- Cohort #2: N=18 randomized 2:1, CA-008 vs. placebo, respectively
- Cohort #3: N=18 randomized 2:1, CA-008 vs. placebo, respectively
- Optional 4th cohort with a total N=24 randomized 1:1 to CA-008 or placebo at a dose between 5 mg and 15 mg as determined based upon results from cohorts #1-3

8.2. Eligibility Criteria

8.2.1. Inclusion Criteria

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

1. Plan to undergo an elective complete abdominoplasty (C-ABD) without collateral procedure or additional surgeries.
2. In the medical judgment of the investigator, be a reasonably healthy adult aged 18 - 65 years old, inclusive, and American Society of Anesthesiology (ASA) physical Class 1 or 2 at the time of randomization (Section 17.1 Appendix A).
3. If a male, unless he has a same sex partner, be either sterile (surgically **or** biologically) or commit to an acceptable method of birth control while participating in the study. The site personnel will provide instructions on what is an acceptable method.
4. If a female, must meet **all** of the following:
    a. A female of child-bearing potential (FCBP) must have a negative serum pregnancy test at screening and negative urine pregnancy test before surgery;
    b. No plan to become pregnant or to breast feed during the study; and
    c. Be surgically sterile or at least one year post-menopausal, have a monogamous partner who is surgically sterile, have a same sex partner or (**one** of the following must apply)
        i. is practicing double-barrier contraception
        ii. is practicing abstinence (must agree to use double-barrier contraception in the

event of sexual activity)

iii. is using an insertable, injectable, transdermal or combination oral contraceptive approved by the FDA for at least 2 months prior to screening and commits to the use of an acceptable form of birth control while participating in the study.

5. Have a body mass index ≤ 35 kg/m^2.
6. Be willing and able to sign the informed consent form (ICF) approved by an Institutional Review Board (IRB).
7. Be willing and able to complete study procedures and pain scales and to communicate meaningfully in English or Spanish with study personnel and return for outpatient follow up visits as required.

8.2.2. Exclusion Criteria

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

1. In the opinion of the Investigator,
    a. have a concurrent painful condition that may require analgesic treatment during the study period or may confound post-surgical pain assessments.
    b. have active skin disease or other clinically significant abnormality at the anticipated site of surgery that could interfere with the planned surgery.
2. Have a known allergy to chili peppers, capsaicin or the components of CA-008, acetaminophen, bupivacaine, fentanyl, hydromorphone or oxycodone.
3. As determined by the investigator (with input from the study's medical monitor if requested by the investigator), have a history or clinical manifestation of significant medical, neuropsychiatric or other condition, including a clinically significant existing arrhythmia, left bundle branch block or abnormal ECG, myocardial infarction or coronary arterial bypass graft surgery within the prior 12 months, significant abnormal clinical laboratory test value, or known bleeding abnormality that could preclude or impair study participation or interfere with study assessments.
4. The following are considered disallowed medications:
    a. Be tolerant to opioids defined as those who have been receiving or have received chronic opioid therapy greater than 15 mg of oral morphine equivalents (Table 9) per day for greater than 3 out of 7 days per week over a one-month period within 6 months of screening.

b. Within 1 day prior to surgery and throughout the inpatient period, be taking any capsaicin-containing products, such as dietary supplements or over-the-counter (OTC) preparations, including topical formulations, and prescription medications.

c. Within the 7 days prior to surgery, be taking any central nervous system (CNS) active agent as an analgesic adjunct medication, such as anticonvulsants, antidepressants (such as SNRIs, SSRIs, and tricyclic antidepressants), benzodiazepines, sedative-hypnotics, clonidine and other central alpha-2 agents (e.g., tizanidine), ketamine or muscle relaxants. [Note that SNRIs = Serotonin and norepinephrine reuptake inhibitors and SSRI = Selective serotonin reuptake inhibitors.]

   i. These drugs are permitted if prescribed for non-pain indications and the dose has been stable for at least 30 days prior to surgery. Note that the dose must remain stable throughout the study.

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

d. Within the 7 days prior to the planned surgery and throughout the study, be taking antiarrhythmics except beta-blockers, digoxin, warfarin (see exception below), lithium, or aminoglycosides or other antibiotics for an infection (except for ophthalmic use or for treatment or prophylaxis of postoperative surgical site infections).

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

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

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

6. Have positive results on the alcohol 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. Note that for those subjects who test positive for tetrahydrocannabinol (THC), if they are willing to abstain from use or consumption of THC-containing products from 3 days prior to surgery to the day 8 visit, they may be allowed to participate in the study.

7. Willing and able to avoid foods containing capsaicin for 24 hours prior to surgery and PK blood draws.
8. Have previously participated in a clinical study with CA-008.
9. Have participated in another clinical trial or used an investigational product within 30 days or five half-lives (whichever is longer) prior to the planned surgery, or is scheduled to receive an investigational product other than CA-008 while participating in the study.

9. STUDY TREATMENTS

9.1. Study Treatment

Complete details of study drug packaging, storage, dispensation, preparation and tracking are provided in the pharmacy manual.

9.1.1. CA-008 HCl Description

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

9.1.2. Study Treatment Description

The active drug product will be provided as CA-008 frozen concentrate solution for injection in a 1.0 mL vial with doses calculated as the freebase.

The placebo comparator is identical in appearance.

The proposed dose of CA-008 to be evaluated in the study are:

- Cohort #1: CA-008 5 mg vs. placebo in 100 mL of vehicle
- Cohort #2: CA-008 10 mg vs. placebo in 100 mL of vehicle
- Cohort #3: CA-008 15 mg vs. placebo in 100 mL of vehicle
- Optional 4th cohort with a total N=24 randomized 1:1 to CA-008 or placebo at a dose between 5 mg and 15 mg as determined based upon results from cohorts #1-3

At time of use, the concentrate will be completely reconstituted in saline and used for treatment (see the Pharmacy Manual). All study treatment vials are unblinded and the dose (for CA-008) or placebo will be identified on the vial label. The pharmacist reconstituting the study treatment for administration is unblinded, however the surgeon and other site participants are blinded.

9.1.3. Study Treatment Storage

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

9.1.4. Study Treatment Accountability

All study treatment will be transported, received, stored, and handled strictly in accordance with the container or product label, the instructions provided to the research site, and applicable regulations. Detailed drug accountability records must be maintained, including the dates shipments are received, the quantity of material received, the dates dispensed and the running inventory. The unused quantities will be returned to the Sponsor's drug supply vendor at the end of the trial. All unused supplies will be checked against the drug accountability records during the study and/or at the end of the study. The Investigator or designee must maintain an inventory record of all dispensed rescue medications to subjects. Additional details are provided in the Pharmacy Manual.

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

9.1.5. Control of Study Treatment and Rescue Medication

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

9.2. Other Interventions

Note that if any standard of care drugs are unavailable, for example due to stock outages, available clinically equivalent alternatives may be substituted, particularly for the protocol-specified drugs in Section 9.2.1 and 9.2.2, after approval of the medical monitor who should notify Sponsor of said substitution.

9.2.1. Intraoperative and Early Postoperative Analgesia

Within 30 min of anesthesia induction give the subject IV hydromorphone 0.02 mg/kg and IV acetaminophen 1 g (Ofirmev®, Mallinckrodt Pharmaceuticals 2018) full prescribing information at http://ofirmev.com/.

During the surgery, ensure that each subject has received at least 100 mcg of IV fentanyl with adjustments above this dose per anesthesiologist discretion.

Within 15 min of the end of surgery, give the subject IV hydromorphone 0.007 mg/kg.

9.2.1. Inpatient Rescue Medications

After surgery, subjects will be monitored in the post-anesthesia care unit (PACU) during which time efficacy asssessments can begin once the subject is awake. During the PACU stay administer the subject IV fentanyl 25-50 mcg q5 min *prn* for moderate-to-severe pain (≥ 4) as reported by subjects using the 0 to 10 numerical rating scale of current pain intensity (NRS). After discharge from the PACU, subjects are followed through T96h as an inpatient.

From the time of discharge from the PACU through T12h administer IV hydromorphone 0.2 to 0.5 mg q10-15 min prn for NRS ≥ 4 as reported by subjects.

After T12h, administer PO oxycodone 5 mg q2h prn moderate pain (NRS ≥ 4 and ≤ 6) or 10 mg q2h prn severe pain (NRS ≥ 7).

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

9.2.2. Outpatient Analgesic Medications

Once discharged from the inpatient unit, all study participants will be instructed to take a combination of over-the-counter (OTC) analgesics at an appropriate dose per medical judgment to manage any residual or breakthrough postsurgical pain.

If needed for pain management, acetaminophen up to 1000 mg prn tid /qid (3g daily maximum limit) will be recommended for subjects to self-administer (note that this medications will not be provided by the Sponsor).

If a subject is still requiring opioid rescue in the 12h prior to discharge from the inpatient unit (i.e., from T84h on regardless of whether discharge is delayed), then prescribe no more than 9 tablets of oxycodone 5 mg (1 PO tid prn) per investigator discretion for the initial outpatient period.

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

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.

In the Pilot Stage, 18 subjects will be randomized to either the active medication or placebo in a 1:1 ratio. Subsequently, the number of active treatment groups and sample size will be determined after the interim unblinded analysis of topline data from the Pilot Stage.

Once any subject number or randomization number is assigned, it cannot be reassigned to any other subject. This study will use manual randomization.

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

9.4. Blinding

In order to reduce the potential for bias in the study, treatment group assignments will be double-blinded during the study. Aside from the unblinded pharmacist who reconstitutes the study treatment for administration by the surgeon, the subject, surgeon and all other study participants, including the Sponsor, directly involved in the conduct and/or monitoring of this study will not be aware of the treatment group assignments. Note that the placebo is identical in appearance to CA-008.

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.

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.

9.5. 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.

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. Wherever possible, the Investigator should obtain approval from the Medical Monitor prior to administering the medication.

9.6. Study Restrictions

In addition to the criteria described in Sections 8.2, 9.5, and 10.1.2 the subject must agree to abide by the following study restrictions:

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

- consuming any alcohol
- smoking or vaping (nicotine-containing or other substances)
- illicit drug use or non-medical use of therapeutic drugs not allowed by the protocol
- any foods containing capsaicin for 24 hours prior to PK blood draws

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

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

9.7. 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. CONDUCT OF THE STUDY

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

10.1. Study Visits

10.1.1. Screening Phase (Day -45 to Day -1):

Subjects will be screened for participation at the study within 45 days of surgery/study drug administration. The following assessments will be completed:

- Informed Consent
- Inclusion / Exclusion evaluation
- Demographics
- Medical and surgical history
- Prior/current medications
- Complete Physical Exam (PE), including height and weight
- Vital signs including temperature (Section 17.10 Appendix J)
- Baseline neurosensory exam
- Clinical laboratory tests (chemistry/coagulation, hematology, and urinalysis) (Section 17.9 Appendix I)
- Urine Drug Screening (UDS)
- Alcohol breath/saliva test
- Serum Pregnancy test (FCBP), if applicable
- 12-Lead Electrocardiograms (ECG)
- Subject pain assessment training
- Adverse Event (AE) assessment (record any current conditions as medical history)

10.1.2. Surgery Phase: Day -1 Prior to surgery (baseline) up to the end of surgery Day 0

10.1.2.1. Prior to Surgery (D-1 to D0)

Subjects who meet the selection criteria at the Screening Visit and are eligible to participate in the study will be required to return to the study center within 45 days of screening. The following assessments will be performed:

- Confirm informed consent
- Review of Inclusion / Exclusion

- Review of medical and surgical history since screening (any changes to health should be added to medical history)
- Review of prior and current concomitant medications
- Interim targeted PE with inspection of the planned area of surgery (if not done at Screening visit)
- Urine Pregnancy test (FCBP) if applicable
- UDS
- Alcohol breath/saliva test
- Blood draw for PK analysis
- Vital signs and temperature
- Subject pain training review (watch video)
- AE assessment
- Randomize to treatment after confirmation of continued eligibility

10.1.2.2. Surgery Day 0

The surgery is to be performed under general anesthesia supplemented by a transverse abdominis plane (TAP) block with bupivacaine hydrochloride (BupiHCl). Note that the regimen for the general anesthetic is left to the anesthesiologists' discretion. Prior to the surgery, perform the TAP block as a single injection of 0.25% bupivacaine hydrochloride (HCl) 60 mL (150 mg). Refer to Section 17.12 Appendix L for bupivacaine dosage recommendations. The volume windows for the bupivacaine injection is ± 2 mL.

During the surgery, ensure that each subject has received at least 100 mcg of IV fentanyl with adjustments above this dose per anesthesiologist discretion.

Upon completion of surgery, subjects will be observed for 96-hours in the clinic. AEs will be assessed during the surgery.

10.1.3. Surgery Phase: Administration of Study Medication Into the Surgical Site

The "surgical site" is defined as the area extending approximately 2-3 cm in all directions (lateral/medial/proximal/distal/deep) from the incision and surrounding tissues which may be affected by the infiltration of the study drug. Study treatment is to be administered intraoperatively as a single administration via "surgical site" infiltration prior to wound closure. A total of 100 mL of study treatment will be infiltrated into the deep peri-incisional subcutaneous tissues and rectus fascia within the exposed incision surfaces.

10.1.4. Inpatient Phase: Time 0 (Post-Surgery) to Day 4 (Discharge)

Time 0 is defined as the time of completion of study drug administration. Following surgery, subjects will be transferred to the appropriate recovery unit where they will undergo an

assessment of safety and efficacy over the next 96 hours. The schedule of assessments are as follows:

- Subjects with inadequately controlled pain may request rescue at any time; however, subjects will be encouraged to receive rescue medication only with an NRS ≥ 4.
- Pain intensity (assessed with NRS):
  - During the inpatient stay, beginning with the PACU admission and after the subject is awake: assess the NRS at rest at 0.5, 1, 2, 4, 6, 8, 12, 16, 20, and 24 hours, and every 4 hours (if awake at time of assessment) until discharge from the inpatient unit. Time windows: for T0.5 to T2 (±5 min) and from T4 onward (±15 min).
  - Pain scores may be skipped between the hours of midnight and 6 a.m., but the subject may not miss two consecutive assessments. The T12, T24, T48, T72 and T96h assessments must be completed even if the subject is asleep at these times.
  - Pain intensity (NRS) will be completed at the time of rescue medication request (±15 minutes).
  - During the inpatient stay, starting on postoperative day 1: each morning on arising at 0800h (±2h) and each evening at 2000h (±2h) document the NRS at rest and on arising from a recumbent position to a sitting or standing position. Actual assessment times must be documented. These assessments are in addition to the time-specific NRS assessments at rest. If however these twice daily assessments coincide with timed assessments of NRS at rest, then the time assessment at rest is used in place of the twice daily assessments.
- Vital signs (heart rate [HR], blood pressure [BP], respiratory rate [RR]) and temperature are assessed together at screening, D0 prior to surgery, post-surgery at T1, T2, T4, T6, T12, and T24h, and every 8 hours thereafter until T96h, and as an outpatient on D8/W1, D15/W2, and D29/W4 or later if necessary. Assessments between the hours of 00:00 and 06:00 may be skipped if the subject is sleeping; however, two consecutive assessments may not be skipped. The allowable window is ±5 minutes for the first 4 hours post-surgery, and ±15 minutes for all other times.
- Targeted Physical exam: 96 (±4) hours after the administration of study medication (prior to discharge from the unit). Weight is included at the 96 hour assessment.
- ECG: 24 (±2) hours after the administration of study medication.
- Surgical Site assessment: 48 (±2) and 96 (±4) hours after the administration of study medication. If the investigator determines there are atypical wound healing or visible abnormal findings, a digital picture of the wound site should be performed (if subject has consented to digital photography).
- Neurosensory testing of the surgical area: 48 (±2) and 96 (±4) hours after the administration of study medication.
- Clinical laboratory tests: T96h (±4h) prior to discharge from the unit.

- Blood draw for PK analysis: The time points for whole blood collection will be at check-in/ baseline (up to 30 min prior to surgery), and T5min, T10 min, T15min, T30min, T45min, and T1, T1.5, T2, T2.5, T3, T4, T6, T8, T12, T16, T24, T30, T36 and T48h for a total of 20 samples).
- 24h urine collection in two aliquots: end of surgery to T6h and T6h to T24h.
- Subject completes Patient Global Evaluation (PGE) assessment at T96h (±4) prior to discharge
- Investigator completes Investigator Global Evaluation (IGE) assessment at T96 (±4) prior to discharge. Note that the IGE may be performed by any investigator or sub-investigator.
- Record rescue medication consumption and concomitant medications throughout the inpatient period and record any prescriptions for opioids on discharge from the inpatient facility including the opioid prescribed and number of tablets. Also document any additional prescriptions if needed.
- Record AEs throughout the inpatient period (Section 17.11 Appendix K may be useful to the investigator for assessing systemic [general] AEs)

After completing the assessments through T96h, 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.

10.1.5. Outpatient Phase: Days 4 (after discharge) through 8:

In their diary, subjects will assess their pain intensity (at rest and after arising from recumbency) once in the morning (08:00 ±4 hours), and once in the evening (20:00 ±4 hours) using the NRS (these are two separate scores “at rest” and “on arising” obtained twice daily). Subjects will also record any medication they take to treat their pain.

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 assessment (NRS)
- Vital signs including temperature
- Targeted PE
- Surgical Site assessment (If the investigator determines there are atypical wound healing or visible abnormal findings, a digital picture of the wound site should be performed if the subject has consented to such a photo)
- Neurosensory testing of the surgical area
- Query the subject as to any rebound pain
- Concomitant Medication Use/Concomitant Treatments

- Document any prescriptions for opioids provided to the subject and the number of tablets prescribed.
- AE Assessment
- PGE
- IGE

10.1.6. Outpatient Phase: Days 9 through 15:

In their diary, subjects will assess their pain intensity (at rest and after arising from recumbency) once in the morning (08:00 ±4 hours), and once in the evening (20:00 ±4 hours) using the NRS (these are two separate scores "at rest" and "on arising" obtained twice daily). 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 assessment (NRS)
- Vital signs including temperature
- Targeted PE
- Surgical Site assessment (If the investigator determines there are atypical wound healing or visible abnormal findings, a digital picture of the wound site should be performed if the subject has consented to such a photo)
- Neurosensory testing of the surgical area
- Query the subject as to any rebound pain
- Concomitant Medication Use/Concomitant Treatments
- Document any prescriptions for opioids provided to the subject and the number of tablets prescribed.
- AE Assessment
- PGE
- IGE

10.1.7. Outpatient Phase: Day 29

Subjects will record any medication they take to treat their pain. 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 medication)
- Vital signs including temperature
- Targeted PE
- Surgical Site assessment (If the investigator determines there are atypical wound healing or visible abnormal findings, a digital picture of the wound site should be performed if the subject has consented to such a photo)

- Neurosensory testing of the surgical area
- Concomitant Medication Use/Concomitant Treatments
- Document any prescriptions for opioids provided to the subject and the number of tablets prescribed.
- Query the subject as to any rebound pain
- AE Assessment
- PGE
- IGE

10.1.8. Outpatient Phase: Early Termination

Subjects who elect to ET and are willing to perform study completion assessments will return to the study center at a convenient time after discontinuation, for the following assessments:

- Subject home diary review (pain intensity and pain medication)
- Pain Intensity assessment (NRS)
- Vital signs including temperature
- Targeted PE
- Surgical Site assessment (If the investigator determines there are atypical wound healing or visible abnormal findings, a digital picture of the wound site should be performed if the subject has consented to such a photo)
- Neurosensory testing of the surgical area
- Concomitant Medication Use/Concomitant Treatments
- Document any prescriptions for opioids provided to the subject and the number of tablets prescribed.
- Query the subject as to any rebound pain
- AE Assessment
- PGE
- IGE

If the subject has elected an early termination prior to Day 15, collect the information in their take-home Diary: where subjects should have assessed their pain intensity once in the morning (08:00 ±4 hours) at rest and on arising, and once in the evening (20:00 ±4 hours) at rest and on arising using the NRS. Subjects should have also recorded any medication they take to treat their pain. If the subject is unwilling to provide such assessments or perform any of the protocol-specified assessments or even to come in for a face-to-face visit, at least try to have them come in for a wound assessment.

10.1.9. Outpatient Phase: Unscheduled Visit

Note that unscheduled visits will be at the discretion of the Investigator but should include the following if performed prior to D15 visit:

- Subject home diary review (pain intensity and pain medication)
- Pain Intensity assessment (NRS)
- Vital signs including temperature
- Surgical Site assessment (If the investigator determines there are atypical wound healing or visible abnormal findings, a digital picture of the wound site should be performed if the subject has consented to such a photo)
- Targeted Physical Exam
- Neurosensory testing of the surgical area
- Concomitant Medication Use/Concomitant Treatments
- Document any prescriptions for opioids provided to the subject and the number of tablets prescribed.
- Query the subject as to any rebound pain
- AE Assessment

If after D15 visit, subjects will return for the following assessments:

- Surgical Site assessment (If the investigator determines there are atypical wound healing or visible abnormal findings, a digital picture of the wound site should be performed if the subject has consented to such a photo)
- Neurosensory testing of the surgical area
- Concomitant Medication Use/Concomitant Treatments
- Document any prescriptions for opioids provided to the subject and the number of tablets prescribed.
- Query the subject as to any rebound pain
- AE Assessment

If after D29 visit, the investigator has clinical discretion on when subjects should return for follow up and what is performed at the visit. The following are the minimum assessments:

- Surgical Site assessment (If the investigator determines there are atypical wound healing or visible abnormal findings, a digital picture of the wound site should be performed)
- Neurosensory testing of the surgical area
- Concomitant Medication Use/Concomitant Treatments
- Query the subject as to any rebound pain
- AE Assessment

10.2. Subject Completion and Withdrawal

10.2.1. Subject Completion

A subject is considered to have completed the study once all end-of-study assessments are completed at D29 (or later if necessary), or at the last visit upon early termination of the study.

10.2.2. Subject Withdrawal

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 9.4)
- 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.

Subjects who elect to discontinue participation prior to D8 (W1) will be considered to have terminated as of the date of their election, however they will be asked to return to the site one time, if willing and at their convenience, to ensure wound healing. If a subject refuses to complete early termination/Follow-up procedures or continued data collection, this information

will be recorded.

10.3. Study Procedures and Assessments

10.3.1. Informed Consent

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

10.3.2. Demographics

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

10.3.3. 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.

10.3.4. 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.

10.3.5. Contraceptive Requirements

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

Female subjects of non-childbearing potential are not required to use contraception or undergo pregnancy tests; however, they must be surgically sterile (e.g., hysterectomy and/or bilateral oophorectomy or salpingo-oophorectomy, as determined by subject medical history) or

congenitally sterile, or must be post-menopausal. Post-menopausal is defined as being amenorrheic for at least one year without another cause.

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

10.3.6. Subject Pain Assessment Training

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

10.3.7. Digital Photographs of the Surgical Site

During the informed consent process, subjects will be asked if they are willing to allow digital photographs to be taken of the surgical site. This is optional and their response will in no way affect their inclusion in the study. Their response will be included on the ICF.

10.3.8. Numerical Rating Scale for Pain Intensity (NRS)

The NRS is an 11-point scale with anchors 0 (no pain) and 10 (worst possible pain) (Section 17.2 Appendix B).

Subjects will report or record the intensity of their current pain at designated times during the study after administration of study treatment. Subjects should be at rest for at least 5-10 minutes prior to completing NRS resting assessment and have sat or stood up from a recumbent position within the 5-10 minutes prior to completing NRS assessment after this change in position.

10.3.9. Rebound Pain at the Surgical Site

Subjects will be queried at each outpatient follow up visit as to whether they have noted any worsening pain (rebound pain) at the surgical site since the prior visit report (Section 17.3 Appendix C).

10.3.10. Patient Global Evaluation (PGE)

Each subject will be asked to report their satisfaction with the study treatment for pain using a 4-point categorical scale. Each subject will be asked the following question:

“How would you rate the study treatment that you have received for pain? Poor (0), Fair (1), Good (2), or Excellent (3)” (see Section 17.4 Appendix D).

10.3.11. Investigator Global Evaluation (IGE)

The investigator will report their satisfaction with the subject's study treatment for pain using a 4-point scale at designated times during the study after administration of study treatment. A study Investigator will be asked the following question:

"How would you rate the study treatment that the patient received for pain? Poor (0), Fair (1), Good (2), or Excellent (3)" (see Section 17.5 Appendix E).

10.3.12. Rescue Medications

The details of rescue medication (doses and times) will be recorded beginning from the end of surgery through 14 days after the end of surgery (D15 visit) or to Early Termination Visit if applicable. Subjects will be instructed on the proper use and timing of rescue medication. Use Table 9 to calculate the morphine equivalent dose (MED) of various opioids.

Table 9. Equianalgesic Conversion Table

Opioid (Doses in mg)	Conversion Factor
IV Fentanyl	0.3
PO Hydrocodone	1
PO Hydromorphone	4
PO Morphine	1
PO Oxycodone	1.5
PO Tramadol	0.1
Multiply the opioid dose by the conversion factor = oral morphine equivalent dose (MED): e.g., PO oxycodone 5 mg X 1.5 = 7.5 mg MED or IV fentanyl 25 mcg X 0.3 = 7.5 mg MED	

10.3.13. Clinical Laboratory Assessments

All protocol-specified laboratory tests on blood and urine samples will be collected, processed, shipped and analyzed according to instructions from 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.

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 10.

Table 10: 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="4">Sodium
Potassium
Calcium
Chloride
Glucose
Creatinine
Blood urea nitrogen (BUN)
Albumin
Tot Bili
ALT
AST
GGT
LDH
ALK</td><td rowspan="4">Color
Turbidity
pH
Specific gravity
Ketones
Protein
Glucose
Bilirubin
Occult 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 per the Schedule of Assessments. 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 >2X ULN will be considered an adverse event, as well as any other changes deemed clinically significant by the Investigator.

10.3.14. Urine Drug Screen and Alcohol Test

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

10.3.15. Vital Signs

Vital signs will consist of BP, HR, and RR and temperature following a rest period. Vital signs will be assessed per the Schedule Assessments.

10.3.16. 12-Lead Electrocardiogram (ECG)

12-Lead ECGs will be performed per the Schedule of Assessments after the subject has been resting in a recumbent/supine position for at least 5 minutes. The ECG variables will include ventricular heart rate and the PR, QRS, QT and QTcF intervals. 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 (e.g., at Screening) or with an AE (if it occurred post study treatment). Note that for QTc, clinically significant changes in ECG (using QTCf, should be <450 msec for male subjects / < 470 msec for female subjects. Clinically significant changes in ECG are: an increase of QTcF of 30msec or greater, as well as any other changes deemed by the Investigator as significant will be considered an AE.

10.3.17. Physical Examination

A complete PE including all major body systems (HEENT, neurologic, cardiovascular, respiratory, gastrointestinal, dermatologic and musculoskeletal systems) will be performed at Screening. A focused interim or targeted PE will be performed pre-surgery and after surgery during the inpatient and outpatient periods as per Table 1.

Body weight (kg), in indoor clothing, but without shoes, will be measured at Screening and 96 hours. 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 NIH website BMI calculator (available at: http://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi-m.htm.

10.3.18. Surgical Site Assessment

The surgical site should be assessed per the Schedule of Assessments to determine if any site related AEs have occurred. 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.” (Section 17.6 Appendix F). Assessments will also be performed at each of the Follow-up visits or at the time of early discontinuation. When assessed on Day 29, if the Investigator observes insufficient wound or bone healing or to ensure an ongoing AE has resolved, the subject will be scheduled for a follow-up visit.

If there are skin reactions atypical for the type of surgery, e.g., more than expected erythema, drainage, bruising or hematoma, induration, swelling or other skin changes, they should be documented as AEs, graded for severity and followed regularly until resolution or establishment

of a new baseline (the grading guide for atypical wound findings may be useful to the investigator: Section 17.7 Appendix G).

10.3.19. Neurosensory Testing

A Neurosensory testing of the skin surrounding the incision will be conducted per the Schedule of Events. This evaluation will include the details described in Section 17.8 Appendix H. Numbness or other sensory changes at or near the incision need not be considered a neurologic AE since these could occur because of tissue trauma and inflammation from surgery.

Sensory deficits or clinically significant persistent sensory change beyond the area proximal to the incision at time of discharge, such as allodynia or hyperalgesia, must be designated as a neurologic AE. Subjects will be followed until there is full return to baseline for the neurosensory assessment or until there is a determination that it has reached a resolution or establishment of a new baseline

10.3.20. Assessment of Adverse Events

All SAEs and non-serious AEs will be documented and followed from the time of administration of study treatment until Day 29 or until resolution or establishment of a new baseline. AEs that occur between Screening and the surgery should be considered medical history, and be added to the subject's medical record, unless related to a study procedure. 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.

10.3.21. Pharmacokinetic Assessments and Samples

Details for the collection and processing of blood samples for measurement of PK (CA-008, Capsaicin, and CA-101) and urine collections are outlined in the Lab Manual.

10.4. Safety, PK and Efficacy Endpoints

10.4.1. Safety Endpoints

Safety endpoints include the following:

- Incidence of spontaneously reported TEAEs or SAEs
- Clinical laboratory test results
- Vital sign measurements
- ECG results
- PE findings
- Surgical Site wound assessment findings

- Neurosensory testing results
- Presence of rebound pain
- Concomitant Medication Use/Concomitant Treatments

10.4.2. Pharmacokinetic Endpoints

Full details of pharmacokinetic endpoints will be described in a separate PK Analysis Plan. The time points for whole blood collection are outlined in the Schedule of Assessments. Actual sampling times will be used to calculate plasma-derived PK parameters.

10.4.3. Efficacy Endpoints

10.4.3.1. Primary Efficacy Endpoint

Time-specific mean NRS pain intensity scores at T96h for CA-008 vs. placebo.

10.4.3.2. Key Secondary Efficacy Endpoints

For the CA-008 vs. placebo comparison:

- Weighted sum of pain intensity (SPI) assessments = Area Under the Curve (AUC) of the NRS current pain intensity scores from T0 to 96h at rest ($AUC_{0\ to\ 96h}$).
- Time to opioid cessation or freedom (T_{OF})
- Percentage of subjects who do not require opioids (i.e., opioid free; OF) from T24 to T96: $OF_{24\ to\ 96h}$
- Total opioid consumption (in daily oral morphine equivalents) = OC from T0 to T96h: $OC_{0\ to\ 96h}$

10.4.3.3. Other Endpoints

For the CA-008 vs. placebo comparison:

- Using NRS at rest: $AUC_{0\ to\ 120h}$, $AUC_{24\ to\ 96h}$, $AUC_{0\ to\ W1}$
- $AUC_{0\ to\ 96h\ (arising)}$, $AUC_{0\ to\ W1\ (arising)}$
- Time-specific mean NRS scores at T48, T72, T96, T120, T144 and T168h
- $OC_{24\ to\ 96h}$
- $OF_{24\ to\ 96h}$, $OF_{96h\ to\ W1}$ and $OF_{96h\ to\ W2}$
- The fraction of subjects who rescue at T48, T72 and T96h
- Analgesic consumption from T96h to W1 ($AC_{96h\ to\ W1}$) and $AC_{96h\ to\ W2}$
- PGE comparing the %age of subjects reporting “poor” + “fair” vs. “good” + “excellent” responses, and the %age reporting each category of response at T96h, D8/W1, D15/W2 and D29/W4
- IGE comparing the %age of those reporting “poor” + “fair” vs. “good” + “excellent” responses, and the %age reporting each category at T96h, D8/W1, D15/W2 and D29/W4

11. ADVERSE EVENTS

11.1. Adverse Events and Serious Adverse Events

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

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

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

11.1.1. Relationship to Study Treatment

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

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

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

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 treatment
- Action and outcome
- Seriousness of event

All SAEs will be documented and followed from the time the subject has signed the ICF until D29±2 after the completion of surgery. All SAEs and non-serious AEs will be documented and

followed from the time of administration of study treatment until Day 29 or later if necessary. AEs that occur between Screening and the administration of study medication should be considered medical history and added to the subject's medical record, unless the AE is due to a study-related procedure (such as phlebotomy), in which case it will be recorded as a non-treatment emergent AE. Serious AEs and AEs that have been designated as possibly related to study treatment 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 ≥ 14 days after the Day 29 visit, or 21 days after an early termination AND are not considered to be study treatment-related by the Investigator.

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

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 treatment and within 14 days following the study completion visit (or 21 days following an ET if applicable) are reportable within 24 hours. During this follow-up period beyond study completion or after an ET, only those SAEs considered to be possibly related to study treatment should be reported within 24 hours.

The procedure for reporting an SAE is as follows:

- All SAEs must be reported immediately (within 24 hours of discovery) by email to the CRO Medical Monitor or designee. Calls related to SAEs should first be directed to the CRO Medical Monitor or designee.
    - **CRO Medical Monitor: Jon Ruckle, MD**
    - **24/7 Emergency contact: 808-349-9812 / (253) 448-8690**
    - **SAE Reporting email: MedicalMonitorCA-PS-204@Lotuscr.com**
- The Sponsor's Medical Monitor is available for questions about safety-related issues:

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

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

11.2. Severity Grading for AEs

Grading the severity of AEs is per investigator discretion (the guidance reflected in Sections 17.9, 17.10 and 17.11; Appendices I, J and K may be helpful). Additionally, the following general guideline may be helpful:

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

11.3. Pregnancy

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

12. DATA QUALITY ASSURANCE

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

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

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

12.1. Data Collection

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

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

12.2. Study Auditing and Monitoring

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

endpoints, the purpose of the study, study design complexity, and enrollment rate. By signing the protocol, the Investigator agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of the Sponsor, a regulatory authority, and/or an IRB may visit the site to perform audits or inspections, including the drug storage area, 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. Sample Size Justification

Given the uncertainty in estimating a sample size for C-ABD surgery, the data from the current study will be used to determine the sample size for a subsequent parallel design study selecting one or more optimal doses of CA-008 vs. placebo in the setting of standard of care for abdominoplasty.

13.3. Analysis Populations

The following analysis populations are planned for this study:

- The Safety Population will include all subjects who received any part of a dose of study treatment.
- The PK Population will include all subjects who receive a full dose of study treatment and complete all PK assessments.
- The intent-to-treat (ITT) population will include all subjects as randomized to study treatment.

Membership in analysis populations will be determined before unblinding.

Subjects who elect to discontinue study participation (early termination or ET) after randomization but prior to receiving study treatment will be replaced.

Subjects who elect to ET after receiving study treatment will not be replaced, however those who ET during the inpatient phase of the study, will be asked to continue with assessments through T96h if they have not elected to withdraw from all aspects of study participation.

13.4. Planned Analyses

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

All inferential assessments will be 2-sided tests performed at the 0.05 alpha level unadjusted for multiple comparisons. A hierarchical alpha testing strategy will be utilized to control for the overall experiment-wise alpha. First the primary analysis will be performed at the 0.05 alpha level. If the primary analysis is statistically significant, then a limited number of key secondary analyses will be analyzed in a pre-specified order and analyses will be considered as statistically significant only if the preceding test is statistically significant. The order of the secondary analyses will be specified in the SAP and signed off prior to unblinding.

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

13.5. Study Subjects and Demographics

13.5.1. Disposition and Withdrawals

The numbers of subjects 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.

13.5.2. Protocol Deviations

Major protocol deviations will be classified and documented before database lock and will be discussed in the CSR. All protocol deviations, whether minor or major, will be presented in a data listing.

13.5.3. Demographics and Other Baseline Characteristics

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

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

13.5.4. Exposure

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

13.5.5. General Considerations

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

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

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

The following conventions will be used throughout the study analysis:

- Time T0 is the time of completion of study treatment administration.
- Day of surgery is defined as D0
- Assessment visit times are defined by time T0/D0.
- Baseline value is defined as the last valid measurement prior to beginning study treatment administration.
- Change from baseline is defined as post-baseline value minus baseline value.
- Duration of an AE will be computed in days for AEs lasting longer than 24 hours, and as hours for AEs lasting less than 24 hours. Duration in hours will be calculated as the stop date/time of the event minus the start date/time. Duration in days will be calculated by using stop date minus the start date +1 if AE occur on or after taking study medication. If AE occur prior to the study medication, then the duration will be calculated by using stop date minus the start date. If reported as ongoing at the time of database lock, the duration will be calculated using the date of the last visit or the last date of any AE for the subject in the

database, whichever is later. Missing dates will be imputed as described in the Study's Statistical Analysis Plan (SAP).

- The number of days in the study is computed as: [Date of study completion or withdrawal minus the date of study drug administration (Day 1)] + 1.
- If duplicate values are obtained at a given visit (e.g., repeated vital sign measurements), the last value will be used unless it is noted that the measurement was in error for that value. Values that compromise interpretation will not be used in summaries (e.g., values that were obtained post-dose will not be summarized as pre-dose values).

13.5.6. Analysis of Efficacy Measures

All efficacy endpoints (e.g., NRS scores), will be summarized over time by treatment using descriptive statistics including confidence intervals as appropriate.

AUC calculations will be done using the standard trapezoidal rule

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

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

Missing NRS will be handled as discussed in the Study's SAP.

The AUC analyses will be presented in a summary table with standard summary statistics for each dose cohort and placebo as well as active vs. placebo mean differences, standard errors, confidence intervals and comparison p-values as appropriate. Comparisons of individual dose cohorts for dose response may also be presented for certain secondary AUC endpoints.

The AUC analyses will be presented in a summary table with standard summary statistics for each treatment group mean differences standard errors, confidence intervals and comparison p-values as appropriate.

Mean NRS scores over time (in-clinic and diary) will be graphed over time by treatment group. NRS over time by each subject may also be displayed graphically as warranted. The individual NRS and the computed AUC variables will be listed for all individual subjects.

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

For subjects who take rescue, the pre-rescue pain score will be used to impute scheduled assessments. 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.

13.5.6.1. 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.

For subjects who take rescue medication a windowed last pain score carried forward (wLOCF) will be used. The pre-rescue pain score will be used to impute scheduled assessments for 30 minutes following the rescue use when IV fentanyl is used, 2 hours when IV hydromorphone is used, and 4 hours when PO oxycodone is used. Intermittent missing pain scores (due to subject sleeping, etc.) will not be imputed, and AUC will be calculated based on non-missing values. For subjects who drop out of the study prior to Day 15, scheduled assessments will first be imputed using the worst prior pain score carried forward (WOCF). As sensitivity analyses, the AUC will also be calculated where assessments after drop out will be imputed using LOCF, using the last scheduled non missing pain score prior to drop out, and the median scores for the remainder of the group continuing in the study, without imputation using actual data.

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

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

13.5.7. 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.

13.5.7.1. Adverse Events

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

- Non-serious AEs with onset on the date of treatment with the study 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.

13.5.8. 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.

13.5.9. 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.

13.5.10. 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.

14. SITE AND INVESTIGATOR RESPONSIBILITIES

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

14.1. Regulatory and Ethical Considerations

14.1.1. Ethical Conduct of the Study

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

14.1.2. Ethics Approval

The investigational site's IRB 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 2, Randomized, Double-blind, Placebo-Controlled Efficacy, Pharmacokinetics and Safety Study of CA-008 in Subjects Undergoing Complete Abdominoplasty

Version: 2.0

Date: 28 January 2019

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

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

_____ _____

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

16. REFERENCES

1. Babbar S, Marier J, Mouksassi M et al. Pharmacokinetic Analysis of Capsaicin After Topical Administration of a High-Concentration Capsaicin Patch to Patients With Peripheral Neuropathic Pain. *Ther Drug Monit* 2009; 31(4):502-10.

2. Caterina MJ, Julius D. The vanilloid receptor: a molecular gateway to the pain pathway. Annu Rev Neurosci. 2001 24:487-517

3. Hartrick CT, Pestano C, Carlson N, Hartrick S. Capsaicin instillation for postoperative pain following total knee arthroplasty: a preliminary report of a randomized, double-blind, parallel-group, placebo-controlled, multicentre trial. *Clin Drug Investig* 2011; 31(12):877-82.

4. Suresh D, Srinivasan K. Tissue distribution & elimination of capsaicin, piperine & curcumin following oral intake in rats. Indian J Med Res. 2010;131:682-91.

5. Surh YJ, Lee RC, Park KK et al. Chemoprotective effects of capsaicin and diallyl sulfide against mutagenesis or tumorigenesis by vinyl carbamate and N-nitrosodimethylamine. *Carcinogenesis* 1995; 16:2467-71.

6. Surh YJ, Lee SS. Capsaicin, a double-edged sword: toxicity, metabolism, and cheopreventive potential. *Life Sci* 1995; 56: 1845-55.

7. Tominaga, M., Caterina, M.J., Malmberg, A.B., Rosen, T.A., Gilbert, H., Skinner, K., Raumann, B.E., Basbaum, A.I., Julius, D., 1998. The cloned capsaicin receptor integrates multiple pain-producing stimuli. Neuron 21, 531–543.

17. APPENDICES

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

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

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

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

17.2. Appendix B: 0 to 10 Numerical Rating Scale of Pain Intensity (NRS)

Pain Intensity - Numerical Rating Scale (NRS)

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

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

Subject Initials: _____

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

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

17.4. Appendix D: 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 your satisfaction with the study treatment that you received during surgery for postop pain? **(Mark one box)** ☐ **Excellent (3)** ☐ **Good (2)** ☐ **Fair (1)** ☐ **Poor (0)** **Subject Initials: _____**

17.5. Appendix E: Investigator Global Evaluation of Study Treatment] (IGE)

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

17.6. Appendix F: Surgical Site Assessment

The investigator should grade the level of satisfaction with wound healing using this 0-10 scale with 0=completely unsatisfied and 10=completely satisfied.

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: _____**

17.7. Appendix G: Surgical Wound Adverse Event Grading Guide

The investigator may find the following table to be a useful guide for grading specific AEs using this 4-point categorical scale for common wound complications. The investigator should use clinical discretion in determining whether the particular parameter is atypical or unusual compared to what is expected as a typical healing process.

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

17.8. Appendix H: Neurosensory Examination Form

Subject Number	Subject Initials	Date: __ __/ __ __ __/ 2 0 __ __ (DD-MMM-20YY)	Protocol Number CA-PS-204
___ ___ ___ -___ ___ ___	___ ___ ___		

Instructions to the Investigator: Please assess the surgical wound site (both cephalad [proximal] and caudad [distal] to the site) and answer the questions below. 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 abdominal surgical wound site **using a control site just distal to the costal margin for comparison**

1. Was the Neurosensory Exam completed? ☐ Yes ☐ No

	Cephalad to wound	Caudad to wound	Control site (just distal to costal margin
2. Visual Exam of the surgical site:	☐ Normal ☐ Abnormal, describe: _____	☐ Normal ☐ Abnormal, describe: _____	**Note that allodynia is pain from a normally non painful stimulus.**
3. Von Frey stimulation	☐ Normal ☐ Reduced ☐ Absent ☐ Pain (Allodynia)	☐ Normal ☐ Reduced ☐ Absent ☐ Pain (Allodynia)	
4. Brush stimulation	☐ Normal ☐ Reduced ☐ Absent ☐ Pain (Allodynia)	☐ Normal ☐ Reduced ☐ Absent ☐ Pain (Allodynia)	

If abnormal in comparison to the control site, note if it is reduced or absent and for brush and von Frey hair stimulation, additionally whether there is allodynia.

The sensory testing either slightly cephalad or caudad to the surgical incision is assessed comparing to the control site. Normal means that the stimulation is essentially the same as control.

Neurosensory testing should be performed in an area approximately 3 to 5 cm above and below the surgical incision site in three locations lateral on each side and in the midline. The instructions below may assist the investigator or designee in performing neurosensory testing.

- **Monofilament (von Frey) Testing:** For this examination, the filament should initially be prestressed (4-6 perpendicular applications to the dorsum of the examiner's first finger). The filament is then applied perpendicularly at the location to be assessed and briefly, (<1 second) with even pressure. When the filament bends, the force of 10 grams has been applied. The subject, whose eyes are closed, is asked to respond yes if he / she feels the filament. Eight correct responses out of 10 applications is considered normal: one to seven correct responses indicate reduced sensation and no correct responses translates into absent sensation.
- **Testing for Allodynia:** testing should be performed at the location to be assessed using a foam brush but allodynia may also be a finding during the monofilament testing.

For **allodynia assessment** the foam brush will be lightly stroked 3 times across the skin in the location to be assessed. Subject will be asked to compare sensation to the control site just distal to the costal margin. 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 control area then hyperaesthesia will be reported as present. If subject reports the stimulus as the same as the control area then sensation will be reported as normal. If sensation is less than the control area then sensation will be reported as reduced, and if sensation is not felt as all then it will be reported as absent.

17.9. Appendix I: Toxicity Grading Scale for Clinical Laboratory Abnormalities

The following tables are excerpted from the **Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials**. The grading system can be "useful in defining a particular study's stopping rules (e.g., a certain number of adverse events, as defined in the table, may call for stopping the study.)"

The Guidance may be found in its entirety at:
https://www.fda.gov/downloads/BiologicsBloodVaccines/ucm091977.

For clinical laboratory values not covered in this Guidance, the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (November 27, 2017) may be useful as a reference. CTCAE v5.0 and prior versions are available at
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

B. Tables for Laboratory Abnormalities

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

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	—
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.

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	–
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* 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.

** "ULN" is the upper limit of the normal range.

Urine *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* 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.

17.10. Appendix J: Toxicity Grading Scale for Clinical Vital Sign Abnormalities

The following table is excerpted from the **Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials**. The grading system can be "useful in defining a particular study's stopping rules (e.g., a certain number of adverse events, as defined in the table, may call for stopping the study.)"

The Guidance may be found in its entirety at:
https://www.fda.gov/downloads/BiologicsBloodVaccines/ucm091977.

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.

17.11. Appendix K: Toxicity Grading Scale for Systemic (General) Adverse Events

The following table is excerpted from the **Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials**. The grading system can be "useful in defining a particular study's stopping rules (e.g., a certain number of adverse events, as defined in the table, may call for stopping the study.)"

The Guidance may be found in its entirety at:
https://www.fda.gov/downloads/BiologicsBloodVaccines/ucm091977.

The investigator may find this useful for grading common systemic (general) TEAEs reported after surgery.

Systemic (General)	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

17.12. Appendix L: Bupivacaine (Marcaine) Dosage Recommendations

INDICATIONS AND USAGE

MARCAINE is indicated for the production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures. Only the 0.25% and 0.5% concentrations are indicated for obstetrical anesthesia. (See **WARNINGS**.)

Experience with nonobstetrical surgical procedures in pregnant patients is not sufficient to recommend use of 0.75% concentration of MARCAINE in these patients.

MARCAINE is not recommended for intravenous regional anesthesia (Bier Block). See **WARNINGS**.

The routes of administration and indicated MARCAINE concentrations are:

- local infiltration 0.25%
- peripheral nerve block 0.25% and 0.5%

Maximum dosage limit must be individualized in each case after evaluating the size and physical status of the patient, as well as the usual rate of systemic absorption from a particular injection site. Most experience to date is with single doses of MARCAINE up to 225 mg with epinephrine 1:200,000 and 175 mg without epinephrine; more or less drug may be used depending on individualization of each case.