Concentric Analgesics, Inc.

Protocol Name: CA-PS-209

Protocol Title: A Three-Part, Phase 1/2, Randomized, Double-blind, Placebo Controlled, Adaptive Safety, Pharmacokinetics, and Preliminary Efficacy Study of CA-008 (Vocacapsaicin) in Patients Undergoing Ventral Hernia Repair

Investigational Product: CA-008 by Injection/Instillation

IND: 129114

NCT: 04774328

Study Protocol, version dated 15 March 2021

CLINICAL TRIAL PROTOCOL

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Original Protocol Date: 27 July 2020

Amendment 1 Date: 13 January 2021

Amendment 2 Date: 15 March 2021

CONFIDENTIAL

SIGNATURE PAGE

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1 KEY PERSONNEL CONTACT INFORMATION

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Summary of Changes for protocol CA-PS-209 Version 1.0 to 2.0

Substantive Changes

Not Applicable

Other Changes:

Clarifications and Additions:

- Updated study title for consistency (Synopsis)
- Updated Overall Study Design – Part B dose of CA-008 will be decreased to 24 mg delivered as 80 mL of a 0.3 mg/mL solution (Synopsis and Section 7.1)
- Updated Primary Study Objectives for Part B to reflect dose and dose volume change (Synopsis and Section 6.1)
- Updated Secondary Study Objectives for Part B to reflect dose change (Synopsis and Section 6.2)
- Updated Inclusion Criteria #1 to reduce maximum length of ventral hernia allowed for enrollment into study (Synopsis and Section 8.2.1)
- Updated Dose Groups – Parts B and C for study drug volumes and delivery (Synopsis and Section 9.1.2)
- Updated Preoperative, Anesthesia and Perioperative Care to clarify dosing for bupivacaine in Parts A, B and C (Synopsis, Sections 9.2.1, and 10.1.2.2)
- Clarified Sample Size Stratification - Part C (Synopsis and Section 13.1)
- Updated Dose Escalation - Part B to reflect dose change (Section 7.3)Updated Study Treatment Description to reflect dose change (Section 9.1.2)Updated Injection of Study Treatment – Parts B and C to reflect decreased volume of 80 ml and volume of amount administered to each site (Synopsis)
- Updated Surgery Phase: Administration of Study Medication into the Surgical Site – Parts B and C to reflect decreased volume of 80 ml and volume amount administered to each site (Synopsis and Section 10.1.3)
- Updated Investigator Protocol Agreement Page to remove version number
- Clarified Pharmacokinetic Endpoints to reflect that the analysis will be found in the analysis plan (Synopsis and Section 10.3.20)

Administrative:

- Corrected minor grammatical errors throughout protocol
- Updated study contact personnel and information

Summary of Changes from CA-PS-209 original protocol to V1.0

Substantive Changes:

1. Bupivacaine dose

Rationale: Clarified local anesthetic techniques so that the total dose of bupivacaine hydrochloride will not exceed 175 mg (Synopsis, Sections 9.2, and 10.1.2.2)

2. CA-008 dose

Rationale: Previous animal models and clinical trial studies, along with the characterization of the pharmacology, PK, and toxicology profiles and the anticipated benefits and potential risks support the dosage for CA-008 (Section 5.5.1)

Other Changes:

Clarifications and Additions:

- Updated sample size for Parts A, B, and C (Synopsis and Section 13.1)
- Clarification of study population for primary ventral hernia repair (Synopsis and Section 8.1)
- Made laparoscopic assistance optional for all Parts (Synopsis and Sections 8.2.1, and 10.1.3)
- Updated Overall Study Design - Part A dose is CA-008 15 mg and Part B dose of CA-008 will be increased to 30 mg if the formal safety from Part A is favorable (Synopsis and Section 7.1)
- Clarified Primary Study Objectives for Parts A and B (Synopsis and Section 6.1)
- Updated Secondary Study Objectives for Parts A and B to evaluate the PK profile for both Parts and the ECG QT interval for Part B (Synopsis and Section 6.2)
- Clarification Parts A, B, and C Dose Groups - study drug volumes and delivery (Synopsis and Section 9.1.2)
- Specified the injection of Study Treatment for all Parts (Synopsis and Section 10.1.3)
- Clarified language regarding intraoperative IV fluid volume (Synopsis and Section 9.2.2)
- Clarification of Inclusion Criteria # 2 regarding TAP block (Synopsis and Section 8.2.1)
- Clarification of antibiotic use (Exclusion # 5c). (Synopsis, Sections 8.2.2 and 9.5)
- Updated Vital Signs to include O_2 saturation [SpO_2] (Synopsis and Section 10.4.1)
- Clarification of Exploratory efficacy endpoints (Synopsis and Section 10.4.3.5)
- Clarification of Pharmacokinetic endpoints (Synopsis and Section 10.3.20)
- Updated Stopping Rules to apply to any grade 3 TEAE (Synopsis and Section 7.4)

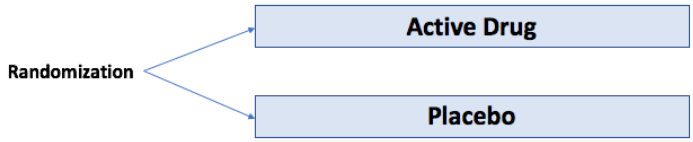
- Added independent medical monitor to team to review relevant data for dose escalation or cohort expansion (Synopsis, Sections 7.3, 7.4, and 13.3)
- Updated the timing of the Pharmacokinetic draws (Synopsis, Schedule of Assessments and Section 10.3.20)
- Updated text for tests of statistical significance (Section 13.3)
- Updated definition of PKT0 to "Pre-IP Dose" (Synopsis, Schedule of Assessments, Section 10.1.4, Section 10.3.20 and Section 13.4.5)
- Added details to the ongoing clinical trials (Table 9, Section 5.3)
- Corrected language that patients must abstain from THC-containing products for 7 days prior to surgery (Section 10.3.13)
- Modification of Intent-to-treat (MITT) Population to consist of all patients who received any dose of study treatment (Synopsis and Section 13.2)
- Corrected the location of the neurosensory examination form (Section 17.12)
- Updated Schedule of Assessments – vital signs, Holter monitor, and PK blood sample timepoints (Table 1)

Administrative:

- Corrected minor grammatical errors throughout protocol
- Updated study contact personnel and information

2 PROTOCOL SYNOPSIS

Sponsor:	Concentric Analgesics, Inc. (Concentric) 101 California Street, Suite 1210 San Francisco, CA 94111
CRO:	Lotus Clinical Research, LLC
Protocol Number:	CA-PS-209
IND#	129114
Study Title:	A Three-Part, Phase 1/2, Randomized, Double-blind, Placebo-Controlled, Pharmacokinetics, Adaptive Safety and Preliminary Efficacy Study of CA-008 (Vocacapsaicin) in Patients Undergoing Ventral Hernia Repair
Study Treatment	CA-008 (also known as vocacapsaicin) and placebo
Planned Study Center(s):	Part A and Part B: 1 US site Part C: Up to 5 US sites
Indication:	Acute postsurgical pain
Background Information:	CA-008 is a prodrug of the analgesic capsaicin being developed to reduce postsurgical pain and reduce the need for opioids. The drug is delivered into the surgical site during the operative procedure. An open laparotomy procedure using an abdominal incision through all abdominal layers to repair a ventral hernia is a standard surgical model for the evaluation of experimental anesthetic and analgesic therapies.
Sample Size:	The total number of patients to be enrolled in Parts A and B together will not exceed ~48. **Part A** – Open-label, feasibility and safety assessment: N = At least 8 with an acceptable range of up to N=16 **Part B** – Double-blind, placebo-controlled pilot: Expected N = 24 with an acceptable range of up to N = 32 (randomized 1:1 active to placebo). **Part C** – Double-blind, placebo-controlled efficacy: In Part C, a total of up to N = ~100 patients will be randomized 1:1 active:placebo in 2 parallel arms to bring the total number of patients enrolled in the study to up to ~150.
Population:	Adults 18 to 80 years of age, inclusive, who are planning to undergo an elective open laparotomy for ventral hernia repair (VHR), with retromuscular, preperitoneal mesh repair (i.e., Rives-Stoppa technique or equivalent), with or without laparoscopic assistance, and who otherwise meet eligibility criteria may

	be considered for enrollment into the study.
Study Duration:	Approximately 90 days per patient from screening to Day 29 (D29) + 2 days (however, this could be longer to follow any adverse event [AE] to resolution or to establishment of a new baseline).
Overall Study Design:	This is a three-part, Phase 1/2, randomized, double-blind, placebo-controlled, pharmacokinetics (PK), and adaptive safety study of CA-008 in patients undergoing VHR. In Part A, CA-008 15 mg will be administered in an open-label exploration of different delivery techniques. The objective is to determine the safety, feasibility, PK and appropriateness of administration of a single dose of CA-008 infiltrated/instilled during surgery in patients undergoing VHR. It is expected that 8-12 patients will be enrolled in Part A, but it may be up to 16 patients so that at least 8 patients receive the optimal delivery technique which will allow a formal safety assessment of the 15 mg dose of study drug. In Part B, if the formal safety assessment from Part A of CA-008 15 mg is favorable, then the active study drug dose will be increased. The single dose selected for Part B is 24 mg, based on the experience in Part A, delivered as 80 mL of a 0.3 mg/mL solution. Using the general delivery technique identified in Part A, this dose, concentration and volume will be assessed compared to a placebo in a pilot, double-blind, randomized, parallel-group design (see Figure). The objective of Part B is to determine preliminarily the tolerability of planned study drug administration as well as the pain profile of the placebo control group. It is expected that approximately 24 patients (up to 32) will be enrolled in Part B. The results of Part B will be unblinded for analysis prior to the initiation of Part C.  In Part C, the active dose level of CA-008 from Part B will be evaluated compared to placebo in a larger randomized, double-blind, parallel-group design to evaluate efficacy and safety. It is expected that ~100 patients will be enrolled in Part C to bring the total number of patients enrolled in the study to up to ~150. For each patient, the study will be conducted in two periods: • Inpatient period which continues from check-in on D1 until discharge (4 days or 96 hours [h] following surgery [T96 ± 4 h], [D5]). Discharge may be delayed, if needed, for medical reasons. • Outpatient period which begins on discharge from the inpatient unit through follow up visits to D29 + 2 days. Note that additional follow up

	visits may occur at any time or even after D29 to follow AEs to resolution or to establish a new baseline. During the inpatient period, patients will undergo VHR including study drug treatment (CA-008 or placebo) followed by serial assessments of safety, PK, and drug effect, in particular focusing on reported pain and need for analgesia. During the outpatient period, patients will have serial assessments of safety and drug effect.
Study Objectives:	**Part A:** **Primary Objective:** • Evaluate the safety, tolerability and feasibility of a single intraoperative administration of CA-008 15 mg in patients undergoing an elective VHR. **Secondary Objectives:** • Evaluate the PK profile of a single intraoperative administration of CA-008 15 mg in patients undergoing an elective VHR. **Part B:** **Primary Objective:** • Evaluate the safety, tolerability and feasibility of a single intraoperative administration of a fixed dose of CA-008, 24 mg in patients undergoing an elective VHR. **Secondary Objectives:** • Determine the pain profile of patients undergoing an elective VHR. • Determine the appropriateness of progression to Part C. • Assessment of opioid consumption. • Evaluate the PK profile of a single intraoperative administration of CA-008 24 mg in patients undergoing an elective VHR. • Explore the relationship between CA-008 and its metabolite plasma concentrations and electrocardiogram (ECG) QT interval using a concentration-QT (cQT) analysis. **Part C:** **Primary Objective:** • Evaluate the efficacy of CA-008 on reported pain in patients undergoing an elective VHR during a specified post-operative time interval. **Secondary Objectives:** • Evaluate the efficacy of CA-008 on reported pain in patients undergoing an elective VHR during additional specified post-operative time intervals. • Evaluate the effect of CA-008 on opioid consumption.

	• Evaluate the effect of CA-008 on patient-reported outcomes (PROs). • Evaluate, preliminarily, the effect of CA-008 on performance-based outcome measures (PBOMs). • Evaluate the safety and tolerability of CA-008 or placebo in patients undergoing an elective VHR.
Study Treatment Dosing Schedule:	Study treatment is to be administered intraoperatively as a single administration via infiltration/instillation into the "surgical site" prior to wound closure. In general, the intent is to deliver local anesthetic into the surgical site "on the way in" (upon adequate exposure of and prior to incision/dissection of target tissues). Conversely, study drug (active or placebo) delivery to the same and other areas will be administered by infiltration (injected) and/or instillation/irrigation (dripped) to the surgical site "on the way out" (prior to and at the time of surgical closure). The "surgical site" is defined as the area extending approximately at least 2-3 cm in all directions (lateral/medial/proximal/distal/deep) from the margins of substantially all tissue traumatized by the surgical procedure, i.e., all tissue dissected, cut, electrocauterized (bovied), sutured or tacked, including both deep and superficial areas. The surgical site will include the full area of surgical mesh placement.
Dose Groups:	In Part A, CA-008 15 mg (50 ml of a 0.3 mg/mL solution) will be delivered and used to explore the optimal technique of delivery, i.e., location and volumes of delivery to the different areas and layers of the surgical procedure. The dose of CA-008 delivered in Part A will not exceed 15 mg. In Parts B and C, CA-008 at a fixed dose of 24 mg (80 mL of a 0.3 mg/mL concentration) or blinded placebo will be delivered using the general technique identified in Part A.
Injection of Study Treatment:	Note: Intent is to distribute study drug by infiltration (injected) and/or instillation/irrigation (dripped/spread) into/onto substantially all areas in the "surgical site." "Surgical site" is defined as the area extending approximately at least 2−3 cm in all directions (lateral/medial/proximal/distal/deep) from the incision site and will include all deep and superficial tissue traumatized by the surgical procedure, i.e., tissue that has been dissected, cut, electrocauterized (bovied), sutured, tacked areas and surrounding tissues and includes the full area of surgical mesh. The surgical site includes those areas accessed directly via the surgical incision and also via laparoscopic access. Note: The technique for all tissue infiltration described below should include multiple microinjections. The needle may be inserted deeply at first and as the needle is withdrawn, the study drug can be injected slowly along the needle

	track. The intent is to distribute the study drug widely in the surgical site where transient receptor potential cation channel, subfamily V (vanilloid) member 1 (TRPV1) receptor targets are located, to act as a conduction block in intact nerves and not in a single, deep depot injection. Substantially all tissue traumatized by the surgical procedure should be exposed to study drug. If laparoscopic assistance is used, study drug will also be delivered to the site of the laparoscopic incisions requiring surgical closure. The general technique to be used is to allocate the total study drug volume to the different tissue layers as follows: • Deep midline/peritoneal layer – approximately up to 25% of the total volume • Mesh/fascia layer – at least approximately 50% of the total volume • Anterior layer – approximately up to 25% of the total volume If laparoscopy is utilized, then a few milliliters of study drug intended for the anterior later will be infiltrated into the laparoscopy ports. Part A: The initial total study drug volume administered per patient will be 50 mL delivered during the surgical procedure in divided aliquots. Modifications to the total study drug dose, volume, drug concentration, and allocation for subsequent patients may occur based on information from prior patients. • Deep midline/peritoneal layer –10 mL • Mesh/fascia layer –30 mL • Anterior layer – 10 mL Parts B and C: The allocation will be as follows, equating to a total study drug volume of 80 mL (details follow in the protocol): • Deep midline/peritoneal layer – approximately 10 mL • Mesh/fascia layer –approximately 60 mL • Anterior layer – approximately 10 mL (up to 5 mL of this volume may be delivered to the laparoscopy port(s))
Preoperative, Anesthesia and Perioperative Care:	At check-in (pre-operatively), at least 1-2 hours before surgery: • Celecoxib 200 mg orally (PO) • Acetaminophen 1000 mg PO After these medications have been administered, no additional non-opioid analgesics are to be administered during the inpatient phase (through T96).

	The surgery will be performed under general anesthesia: • Inhaled anesthetic or propofol infusion with or without nitrous oxide (N2O). • Adequate optional premedication typically with midazolam (up to 5 mg), fentanyl (up to 100 mcg), more can be given if indicated • Supplemental anesthesia and sedation will be per institutional guidelines • Intra-operative titration of intravenous (IV) fentanyl, including during emergence, will be per institutional guidelines. In addition, patients will receive bupivacaine hydrochloride (BupiHCl) 175 mg delivered as follows: • Prior to start of surgery under ultrasound guidance: o BupiHCl 0.25%, 30 mL (75 mg) diluted with 10 mL of normal saline to a volume of 40 mL delivered as a rectus block with 20 mL on each side. Note: In Part A, the adequacy of the anesthetic regimen is part of the assessment of the technique feasibility. If patients report excessive pain during the immediate post-operative period, a TAP block may be added for subsequent patients but the total dose of bupivacaine will not exceed 175 mg. • Immediately before/after surgical incision: o PART A: BupiHCl 0.25%, 40 mL (100 mg), may be diluted in up to 110 mL of normal saline to a total volume of not more than 150 mL: Infiltration of abdominal wall, anterior rectus abdominis sheath, posterior rectus abdominis sheath, other fascia, peritoneum (including circumferential areas of intended mesh placement) o PARTS B and C: BupiHCl 0.25%, 40 mL (100 mg), to be diluted in 40 mL of normal saline to a total volume of 80 mL: Infiltration of abdominal wall, anterior rectus abdominis sheath, posterior rectus abdominis sheath, other fascia, peritoneum (including circumferential areas of intended mesh placement) Standard supplemental anesthetic and perioperative care will be provided per institutional guidelines. This will typically include (but not be limited to) steps to ensure preservation of intraoperative normothermia (including the use of preoperative and intraoperative forced-air warming) and deep venous thrombosis prophylaxis.
Intraoperative Analgesia and Care:	Patients will receive general anesthesia and bilateral rectus blocks (see Section 9.2.1 Preoperative, Anesthesia and Perioperative Care). During surgery, ensure that patients receive the following:

	• 3–500 mL IV fluid, more can be given if indicated • Ondansetron 4 mg IV Note: Ondansetron should not be given to patients in Part B undergoing 24 hours of 12-lead Holter monitoring to assess the effects of study drug on the QT interval. Within 15 minutes prior to the end of surgery, administer the following: • IV hydromorphone, 0.5 mg • Note: IV morphine 2.0 mg can be used if IV hydromorphone is not available Patients who develop clinically significant hemodynamic instability or other anesthesia complication prior to study drug administration should not receive study drug; in Parts A and B, these patients will be replaced. Replacement patients will be assigned the same treatment as the original patient. A 'replacement' randomization list matching that of the main list will be created to facilitate this process.

Rescue Medication during the Inpatient Period:	Patients will be encouraged to use rescue medication only for moderate-to-severe pain (NRS ≥ 4); however, rescue medication may be requested at any time (i.e., even when NRS < 4) and medication will be provided when requested. Conversely, patients may refuse rescue medication even when the NRS is ≥ 4. Time intervals for all rescue medication use are guidelines that can be modified by Investigator discretion.
	• From the time of post-anesthesia care unit (PACU) discharge through T12:
	  o Administer IV hydromorphone 0.5 mg, Q15 minutes PRN for pain of NRS ≥ 4.
	  o Note: IV morphine 2.0 mg can be used if IV hydromorphone is not available
	• After T12–48:
	  o Administer PO oxycodone 10 mg, Q 4 hours (h) PRN for pain NRS ≥ 4.
	  o Only PO oxycodone may be used as rescue. If a patient still requires IV opioid rescue after T12, then the patient will revert to IV opioid analgesia management per institutional guidelines. These patients will still also be followed for NRS, safety, and all other assessments.
	• After T48–96:
	  o Administer PO oxycodone 5 mg, Q 4 h PRN pain NRS 5–10.
	  o Only PO oxycodone may be used as rescue. If a patient still requires IV opioid rescue after T12, then the patient will revert to IV opioid analgesia management per institutional guidelines. These patients

	will still also be followed for NRS, safety, and all other assessments. An NRS pain score should be recorded prior to any dose of rescue medication NRS scores recorded for PRN pain medication will not replace the recording of scheduled NRS scores. However, if PRN rescue medication has recently been administered and persistent pain is reported in a scheduled NRS record prior to rescue medication taking effect, a second dose of rescue medication should not be administered.
Postsurgical Care:	After surgery, patients will be transferred to the post-anesthesia care unit (PACU) where patients will be monitored for at least 90 minutes during which time pain assessments can begin once the patient is awake. T0 is the time of admission into the PACU (as recorded in notes by the PACU nurse). The time of extubation will be recorded, if applicable. Patients will use the 0 to 10 numerical rating scale (NRS) to report their current pain intensity multiple times per day during the remainder of the inpatient part of the study. Scheduled times for serial pain assessments are outlined in the protocol. Rescue medication will always only be administered upon request, i.e., independent of the currently reported pain score. That is, an NRS pain score alone does not trigger rescue medication administration. If the patient reports pain spontaneously and requests analgesia at an unscheduled time (i.e., PRN), an NRS should be used to record the pain present at that time. This unscheduled NRS must be recorded just prior to administration of any PRN analgesia, i.e., within 5 minutes prior to any PRN IV analgesic treatment and within 15 minutes prior to any PRN oral analgesic treatment. NRS scores for PRN pain medication will not replace the recording of scheduled NRS scores. Medication for moderate to severe pain (NRS ≥ 4) will be administered upon request as follows: • From T0 to T25 minutes: o IV fentanyl 50 mcg, every (Q) 5 minutes for pain NRS ≥ 4 • From T26 minutes to PACU discharge: o IV hydromorphone 0.5 mg, Q 10 minutes for pain NRS ≥ 4 o Note: IV morphine 2.0 mg can be used if IV hydromorphone is not available After discharge from the PACU, patients are followed through T96 (± 4 h) as inpatients in the inpatient unit where safety and activity/efficacy evaluations will be performed. Patients will be required to meet standard criteria for discharge to outpatient status. Patients will continue to be monitored as outpatients after discharge from the inpatient unit through D29 + 2 days for various safety and efficacy assessments, and later if necessary, for safety follow up.

Analgesia during the Outpatient Period:	Following discharge from the hospital through the D15 visit, pain will be managed with the following regimen only:
	• Scheduled medication:
	  o Celecoxib, 100 mg PO twice daily (BID) (unless contraindicated)
	• Rescue medications (for pain as needed):
	  o Acetaminophen, 500-650 mg PO Q 6 h for mild pain (i.e., NRS < 4) (unless contraindicated)
	  o Oxycodone, 5 mg – 1 or 2 tablets PO Q 4–6 h for moderate-severe pain (i.e., NRS ≥ 4). Discharge patient with a prescription for 20 tablets. Use of this rescue medication [time, dose] must be recorded in the diary. Pre-rescue medication NRS for opioids will also be recorded in the diary.
	Note:
	• Instruct patients to use acetaminophen as the initial option for treating pain up to a total daily dose of 4,000 mg.
	Document the number of opioid tablets prescribed and document any additional prescriptions required if the patient's pain continues to be an issue requiring additional opioid medication.
	Following D15, pain will be managed per institutional guidelines and standards of care. Pain medication use will be recorded as a concomitant medication from D15 through D29.
	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 visit occurs, the Investigator should use clinical discretion regarding the adequacy of analgesic treatment, capture this occurrence as an AE, and document any required treatments

Inclusion Criteria:	**In order to participate, patients must meet all inclusion criteria:** 1. Plan to undergo an elective, primary, open laparotomy with VHR, with retromuscular, preperitoneal synthetic (polypropylene) mesh placement, with midline fascial reconstruction (i.e., Rives-Stoppa technique or equivalent) and with optional laparoscopic assistance under general anesthesia with sedation, without collateral procedure or additional surgeries. Ventral hernia should not be longer than ~6 cm in length. 2. Appropriate candidate for TAP block, including no contraindications, no anatomical constraints. Note: TAP block may replace or supplement rectus sheath block if rectus sheath block inadequate. 3. Adults 18–80 years of age, inclusive. 4. American Society of Anesthesiology (ASA) physical Class 1, 2, or 3 at the time of randomization (Section 17.2, Appendix B). 5. If a male, 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. 6. 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 (as documented by history and appropriate follicle stimulating hormone [FSH] level), 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. 7. Have a body mass index ≤ 40 kg/m^2. 8. Be willing and able to sign the informed consent form (ICF) approved by an Institutional Review Board (IRB). 9. Be willing and able to complete study procedures and pain scales and to return for outpatient follow up visits as required. 10. Be willing and able to avoid foods containing capsaicin for 24 hours prior to surgery.
Exclusion Criteria:	**If any of the following exclusion criteria apply, a patient may not participate in the study:** 1. In the opinion of the Investigator, the patient has: a. a concurrent chronic painful condition (i.e., daily pain) that may require analgesic treatment during the study period or may confound postsurgical pain assessments; b. active skin disease or other clinically significant abnormality at the anticipated site of surgery that could interfere with the planned surgery. 2. The patient has taken opioids more than twice per week in any week within 6 months of screening or has used any opioids during the 2 weeks prior to surgery. 3. The patient has a known allergy (or contraindication) to any of the following: chili peppers, capsaicin or the components of CA-008, propofol, bupivacaine hydrochloride (HCl), midazolam, inhaled anesthetic, nitrous

	oxide, ondansetron, acetaminophen, fentanyl, hydromorphone, morphine, oxycodone, or celecoxib. 4. As determined by the Investigator (with input from the study's medical monitor if requested by the Investigator), the patient has 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. 5. Use of the following disallowed medications: a. Within 1 day prior to surgery and throughout the inpatient period, taking or using any capsaicin-containing products, such as dietary supplements or over the counter (OTC) preparations, including topical formulations, and prescription medications. b. Within the 7 days prior to surgery, taking any central nervous system active agent as an analgesic adjunct medication, such as anticonvulsants (e.g., gabapentin), 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. i. These drugs are permitted if prescribed for non-pain indications and the dose has been stable for at least 30 days prior to surgery. Note that the dose must remain stable throughout the study. ii. If the patient is taking centrally- and/or peripherally acting analgesic medications, such as acetaminophen, nonsteroidal anti-inflammatory drug (NSAIDs), or pregabalin, the patient may participate in the study if the patient is willing to discontinue these medications 3 days prior to surgery. Note that (a) baby aspirin (81 mg/day) for cardiovascular prophylaxis or (b) regular or enteric-coated aspirin (up to 325 mg given up to twice daily) for venous thrombo-embolism prophylaxis is allowed during the study. c. Within the 7 days prior to the planned surgery taking (a) antiarrhythmics (except beta-blockers and digoxin); (b) warfarin or other anticoagulants (see exception above); (c) lithium; (d) aminoglycosides or other antibiotics for an infection (except for ophthalmic use); or (e) medical (or other) regular marijuana use. d. Within the 14 days prior to surgery, 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).

	e. Taking 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. 6. In the opinion of the Investigator, within the past year, the patient has 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). 7. The patient has a disqualifying positive urine drug screen or alcohol breath/saliva test during screening or check-in (See Section 10.3.14). 8. The patient has previously participated in a clinical study with CA-008. 9. The patient has participated in another clinical trial or used an investigational product within 30 days or 5 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 Day Prior to Surgery**: Patients undergo screening during this period. All screening assessments (including ICF) must be completed at least 1 day prior to surgery. • **Site Unit Admission D1**: Day of surgery, patients will be randomized, and baseline evaluations will be performed prior to surgery. Day 1 includes the day before surgery if check-in occurs at that time. • **Surgery D1**: VHR procedure is performed; study treatment is administered prior to wound closure. PK sample collection is to be done per protocol-specified time points through 48 h following the first study treatment instillation. • **Post-surgery T0 to T96**: T0 is the time of admission into the PACU (as recorded in notes by the PACU nurse). Patient remains in the PACU and then in the inpatient unit for study assessments. Discharge to outpatient status after T96 (± 4 h) [D5] assessments with follow up instructions, particularly on diary completion. • **Follow Up D8 +1 day**: clinic visit for study assessments. • **Follow Up D15 +2 days:** clinic visit for study assessments. • **Follow Up D29 +2 days:** clinic visit for study assessments and study completion visit, unless additional follow up for wound healing is needed. • **If needed, Unscheduled Visits or Follow Up after D29:** Clinic visit as needed for any ongoing safety issue occurring between scheduled visits or continuing after the D29 visit. • **Early Termination (ET):** For patients who terminate early, an ET visit will be required.

Monitored Parameters:	• Treatment-emergent AEs (TEAEs)
	• Medical history
	• Physical examination (PE) findings, particularly neurosensory findings at the site of incision and the skin surrounding the incision
	• Surgical site assessment for wound healing, including a digital photograph if the patient has consented
	• Neurosensory testing near the surgical site
	• Clinical laboratory testing (standard chemistry, hematology, coagulation), drug and alcohol testing, pregnancy testing
	• 12-lead ECGs
	• Blood draws for PK
	• NRS scores assessing rest pain and evoked pain (a) after coughing 3 times, (b) after sitting up from the supine position into a standardized position (both legs dangling on the side of the bed) and (c) during ambulation for approximately 10 yards using a 0 to 10 numeric rating scale for pain intensity
	• Patient-reported outcomes:
	  ○ Activity Assessment Scale (AAS),
	  ○ Patient Reported Outcomes Measurement Information System (PROMIS) 10 GLOBAL Health Questionnaire
	• Performance-based outcome measures (PBOMs):
	  ○ Timed Up and Go (TUG) (Section 17.9, Appendix I)
	  ○ Sit to Stand Test (Section 17.8, Appendix H)
	• Total postsurgical opioid consumption converted to an oral morphine equivalent dose (OME)
	• 12-lead Holter monitors will be placed prior to surgery and record for 24 hours to assess for effects on the QT interval and correlation with PK levels (Subset of at least 12 patients per randomized arm in Part B)

Safety Endpoints:	• Incidence of spontaneously reported TEAEs or serious AEs (SAEs) from study medication administration through D29 or later if necessary:
	  ○ TEAEs are defined as AEs occurring post study medication administration
	  ○ AEs recorded from the time the ICF is signed up to study medication administration will be recorded in medical history.
	  ○ Note: An unscheduled PK sample should be collected where feasible during the inpatient phase of the study for all patients as part of the evaluation of any SAE or severe TEAE.

	• PE: Full PE at Screening (without a breast, genital, or rectal examination). Interim targeted PE on D1 prior to surgery (can be done on the day before surgery if check-in occurs then), T96, and as an outpatient on D8, D15 and D29 (later if necessary). • Vital signs (heart rate [HR], blood pressure [BP], respiratory rate [RR], O_2 saturation [SpO_2]) at screening, D1 prior to surgery, post-surgery T1, T2, T6, T12, and T24, and every 12 hours thereafter until T96, and as an outpatient on D8, D15 and D29 or later if necessary. Assess temperature on D1 prior to surgery. Temperature will be recorded daily along with vital signs per site SOPs at 2, 6, 12, 24, and every 12 hours thereafter until discharge from the inpatient facility (if awake at the time of assessment between hours of midnight and 6:00 AM). • Surgical site assessments at T96 prior to discharge from the inpatient unit and then as an outpatient on D8, D15 and D29 (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 will be performed at Screening visit, T96 (prior to discharge from the inpatient unit) and then as an outpatient on D8 and D29. o Numbness at or near, i.e., within 5 cm of the incision need not be considered a neurologic AE since this could occur because of tissue trauma and inflammation from the surgery. Persistent numbness would meet the criteria for an adverse event. o Sensory deficits or clinically significant persistent sensory change beyond the area proximal/distal to the incision at time of discharge, such as allodynia or hyperalgesia, must be designated as a neurologic AE. Patients will be followed until there is a return to baseline or establishment of a new baseline. • 12-lead ECGs, and standard clinical laboratory tests 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. • 12-lead ECG at Screening and T24 (± 2 h) • Clinical laboratory test results o Hematology/Coagulation at Screening and T48 (± 4 h): 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).

	○ Blood chemistry at screening and T48 (± 4 h) to include at least the following: alanine aminotransferase (ALT) and aspartate aminotransferase (AST), total bilirubin (Tot. Bili), gamma-glutamyl transferase (GGT), albumin, blood urea nitrogen (BUN), creatinine, alkaline phosphatase (ALK), sodium, potassium, calcium, chloride, and glucose. ○ Serum and urine pregnancy test for FCBP: βhCG test at screening and urine test usually to be done within 24 hours prior to surgery. ○ Note: Safety laboratory assessments may be collected, as appropriate, as part of the evaluation of a SAE or severe TEAE. • In Part B, for at least 24 patients (i.e., 12 in each blinded, randomized arm), 12-lead Holter monitors will be placed prior to surgery and will record for 24 hours to assess for effects on the QT interval during study drug administration. Serial PK samples should be drawn in patients undergoing Holter ECG assessments.
Activity/Efficacy Parameter Assessments:	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 patient is awake. T0 is the time of admission into the PACU (as recorded in notes by the PACU nurse). Obtain NRS scores T0 plus 1 hour (T1), T0 plus 2 hours (T2), T4, T6, T8, T12, T16, T20, T24, and every 4 hours thereafter (if awake at time of assessment) until discharge from the inpatient unit. Time windows: ± 5 minutes for T1 and T2; ± 15 minutes for T4 onward. Scheduled NRS scores must be recorded regardless of timing of pre-rescue medication NRS scores and administration of rescue medication. The actual time of all NRS scores must be recorded, i.e., not the nominal time. • During the inpatient stay, as soon as feasible, obtain evoked NRS twice daily after 3 maneuvers: (a) coughing 3 times, and (b) sitting up from the supine position into a standardized position (both legs dangling on the side of the bed), and (c) ambulation for approximately 10 yards (30 feet). Obtain these NRS scores in the morning at 10:00 AM (± 1 h) and in the afternoon at 4:00 PM (± 1 h). • During the inpatient stay, pain scores may be skipped between the hours of midnight and 6:00 AM, but the patient may not miss two consecutive assessments. The T12, T24, T48, T72 and T96 assessments must be completed even if the patient must be awakened at these times. • During the inpatient stay, an additional NRS assessment must be obtained within 5 minutes **prior** to IV rescue medication administration and within 15 minutes **prior** to oral rescue medication administration. • During the outpatient period (after T96 and through D15), an additional NRS assessment must be obtained **prior** to oral rescue medication administration. If entered in the electronic diary, the timing of the

	additional NRS assessment will be assumed to be coincident with the use of rescue medication. If not entered in the electronic diary, the additional NRS assessment should be within 15 minutes prior to use of rescue medication to be used for imputation. • During the outpatient period (after T96 and through D15), instruct the patient to document their NRS scores twice daily at 11:00 AM (± 1 h) and 7:00 PM (± 1 h) (a) at rest, (b) after coughing 3 times, (c) after sitting up from the supine position into a standardized position (both legs dangling on the side of the bed), and (d) during ambulation for approximately 10 yards. Note that the actual time of these assessments must be documented in the electronic diary. Instruct the patient to: o Obtain the morning NRS assessments; o Obtain the evening NRS assessments; o Opioid and non-opioid rescue medication (dose, date, time) must be recorded in the diary through D15, including a pre-rescue NRS score. 2. Daily opioid consumption (specific drug, dose, date, time) will be recorded during the inpatient and outpatient periods (through D15) to allow calculation of total opioid consumption (OC) and daily opioid (rescue medication) consumption in OMEs. • Document daily use of opioid analgesia during the outpatient period through D15. • Document each opioid prescription provided to the patient and the number of and type of tablets provided to the patient for site records and reconciliation. 3. PROs: AAS, PROMIS 10 Global at Screening, T48, T96, D8, D15, and D29. 4. PBOMs: Sit to Stand Test, TUG at T48 (± 4 h), D5/Discharge, D8, D15, and D29.
Efficacy Endpoints	Part A: There are no efficacy endpoints for Part A Part B: There are no efficacy endpoints for Part B Part C: Primary efficacy endpoint: • Area under the curve (AUC) of the rest NRS from T0 to T96 ($AUC_{0\text{-}96h}$). AUC is the weighted sum of current pain intensity (SPI) assessments for a specified time interval. Key secondary efficacy endpoints: • Evoked pain NRS (three maneuvers): $AUC_{0–96}$ • Total opioid consumption (in daily OME) = OC from T0 to T96: $OC_{0\text{-}96}$ and from T0 to D8: $OC_{0\text{-}D8}$

	• Percentage of patients who do not require opioids after discharge (i.e., opioid-free or OF) from T96 to D15: $OF_{96\text{-}D15}$ • NRS at rest and evoked NRS (three maneuvers) from T0 to D8: $AUC_{0\text{-}D8}$ Exploratory efficacy endpoints for Part C: • Using rest NRS: $AUC_{12\text{-}96}$, $AUC_{0\text{-}48}$, $AUC_{48\text{-}96}$, and $AUC_{0\text{-}D15}$; • Using evoked (three maneuvers) NRS: $AUC_{12\text{-}96}$, $AUC_{0\text{-}48}$, $AUC_{48\text{-}96}$, and $AUC_{0\text{-}D15}$; • Time-specific mean NRS scores at T48, T72, and T96; • Time-specific mean NRS scores daily from D5-D15; • Proportion of patients with NRS ≤ 3 during T0-T96, T0-48 and T48-96 • $OC_{12\text{-}96}$, $OC_{24\text{-}96}$, $OC_{0\text{-}D8}$, and $OC_{0\text{-}D15}$; • $OF_{0\text{-}96}$, $OF_{0\text{-}D15}$, $OF_{24\text{-}96}$, $OF_{24\text{-}D15}$, $OF_{48\text{-}D15}$, $OF_{72\text{-}D15}$ and $OF_{D8\text{-}D15}$ • Time to cessation of opioid use; • Additional exploratory and sensitivity analyses rest/evoked NRS AUC, OC, and OF during different intervals may be undertaken, e.g., T48-T168, T72-T168; • PRO questionnaire score improvement from Screening to D8, D15, and D29; and from T48 to D8, D15, and D29; • Improvement in PBOMs (Sit to Stand, TUG) from T48 (± 4 h), to D5/Discharge, to D8, to D15, and to D29; PBOM difference between groups at T48, T96, D8, D15 and D29; • Total non-opioid analgesic consumption (AC), i.e., rescue acetaminophen use for the indicated time intervals: AC96-D8 and AC96-D15; • Other endpoints to be defined in the statistical analysis plan (SAP).

Pharmacokinetic Endpoints:	Part A: PK sampling will be performed on at least 8 patients at a single site. Part B: PK sampling will be performed on at least 24 patients receiving blinded study drug, i.e., 12 patients per randomized arm at a single site. All patients undergoing 24-hour Holter ECG recordings should have PK sampling. Part C: No PK sample collection is planned for Part C. The time points for whole blood collection will be at pre-dose pharmacokinetic time PKT 0 (Pre-IP Dose, 2-10 minutes prior to the first study treatment instillation), 0.03 h (2 min), 0.083 h (5 min), 0.167 h (10 min), 0.25 h (15 min), 0.33 h (20 min), 0.5 h (30 min), 0.75 h (45 min), and at 1, 1.5, 2, 4, 8, 12, 16, 24, 36 and 48 hours after the first study treatment instillation (total of 18 samples). Plasma concentration for CA-008, capsaicin and CA-101 at PK sampling times will be summarized using descriptive statistics, including mean, standard deviation, median, minimum and maximum values, and coefficient of variation (CV%). PK parameters include (but are not limited to) maximum observed plasma drug concentration (Cmax), time to maximum plasma drug concentration (Tmax), half-life, and area under the plasma concentration-time curve (PK-AUC). Actual sampling times will be used to calculate plasma-derived PK parameters. The PK analysis plan will be documented in the PK Analysis Plan. A concentration-QT (cQT) analysis (PK/PD) analysis will be performed to assess for drug effect on the QT interval. This analysis will be documented in the Analysis Plan. Note: An unscheduled PK sample should be collected where feasible during the inpatient phase of the study for all patients as part of the evaluation of any SAE or severe TEAE.
Stopping Rules:	Study enrollment will be paused if any patients experience any grade 3 TEAE, in particular in any of the categories shown in Table 19, Section 7.4, in Appendix A (Section 17.1) or found in the toxicity grading scale cited therein. Should a stopping rule be triggered, the Sponsor's medical monitor, the CRO medical monitor, the relevant Principal Investigator and an independent medical monitor will review the relevant data to determine whether or not it is appropriate to resume enrollment with the same or a modified dose, modify the study or stop the study. The independent medical monitor will have the authority to unblind the treatment assignment for the affected patients as part of the safety review. The study will be stopped if a safety signal is detected that indicates an unacceptable risk to study participants.

Sample Size Justification:	In Part A and Part B, no formal statistical hypothesis testing will be performed. The sample size of 8-12 initial patients in Part A, with the potential for expansion, and 24-32 patients in Part B have been selected empirically based on prior clinical trial experience with CA-008 and is considered sufficient for exploration of feasibility, tolerability, PK, preliminary efficacy and safety parameters. In Part C, a total of ~100 patients will be randomized in 2 parallel arms (1:1) with ~50 patients in each arm. Assuming a t-test for the difference in 2 independent means, a sample size of approximately 40 patients per group would provide approximately 80% power to detect a standardized effect size (Cohen's d) of ~0.55 at a one-sided level of significance, alpha, of 0.05 in the primary efficacy endpoint rest NRS AUC0-96. In Part C, randomization may be stratified based on the size of the ventral hernia: for example, < 4 cm vs. ≥ 4 cm. Alternative assumptions concerning the anticipated effect size lead to a different number of patients per group. The total number of patients to be enrolled in the study will not exceed ~150.
Study Populations:	The following 6 analysis populations are planned for this study: • Safety Population consists of all patients who received any part of a dose of study treatment. (Note this must include anyone who terminates early for lack of efficacy). • PK Population consists of all patients who received at least one dose of study treatment and have at least one PK sample. • PK/QT Population for cQT analysis consists of all patients with at least one time point with both PK and QT data. • Modified Intent-to-treat (mITT) Population consists of all patients who received any dose of study treatment • Per Protocol (PP) Population consists of all patients who received a full dose of study treatment and have evaluable NRS pain assessments at T12, 24, 48, 72, and 96 and no two consecutive missing assessments among the other time points prior to T96 (± 4 h)/Discharge • Study Completers consists of all patients who received a full dose of study treatment and completed the entire study period through D29 + 2 days. Patients who discontinue study participation before or after randomization but prior to receiving study treatment will be replaced. Patients who are withdrawn or who elect to withdraw after receiving study treatment will not be replaced. Those who withdraw during the inpatient phase of the study, will be asked to continue with assessments through T96 if they have not elected to withdraw from all aspects of study participation (see Section 10.2). Patients who elect to discontinue participation on or prior to D8 will be considered to have terminated as of the date of their election; however,

	they will be asked to return to the site one time to ensure that adequate wound healing has occurred (see Section 10.2).
Statistical Considerations:	Progression from Part A to Part B will take place after a formal safety assessment has been completed showing that the total study drug dose, volume, allocation, and technique is acceptably safe and feasible. The formal safety assessment will be conducted by the Sponsor's medical monitor, the CRO medical monitor, the relevant Principal Investigator, and an independent medical monitor. Progression from Part B to Part C will take place after an ("interim") analysis of unmonitored, unblinded data from Part B occurs including data through Day 15. This analysis will assess preliminarily the safety and tolerability of the active study drug as well as the duration and severity of postsurgical pain in the control group. In general, descriptive statistics for continuous variables will include n, mean, SD, standard error of mean (SEM), (if appropriate), median, minimum, and maximum. Categorical variables will be described by frequency and percentage. All safety assessments and baseline characteristics will be summarized using the Safety Population. All safety summaries will be grouped by the actual treatment received. Safety and tolerability will be evaluated by examining the occurrence of AEs, including TEAEs. AEs leading to discontinuation from the study, AEs related to study treatment, and AEs by severity will be summarized by treatment group. Actual values 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. Abnormal values will be determined and flagged in the listings. Laboratory shift tables displaying the change (number of patients) 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. Efficacy, PK, and other assessments will be summarized using appropriate descriptive statistics. A detailed methodology for the statistical analyses of the data collected in this study will be documented in an SAP which will be signed prior to the database lock.

Table 1 Schedule of Assessments – Parts A, B and C

Study Period	Screening	Inpatient							Follow-Up Clinic Visits			Unscheduled Visit[1]	Early Termination[19]
		Day of Surgery	Surgery	Post-surgery	T24	T48	T72	T96 ± 4 h					
Study Day	D -45 to Day Prior to Surgery	D1 (prior to surgery)	D1	D1	D2	D3	D4	D5	D8 + 1 day	D15 + 2 days	D29 + 2 days		
Assessment													
Informed Consent	X	X											
Screening Medical and Surgical History	X	X											
Inclusion/ Exclusion Criteria	X	X											
Screens for Alcohol/Drugs of Abuse	X	X											
Demographics	X												
Patient Pain Assessment Training	X[2]	X[2]											
Pregnancy Test (or FSH if post-menopausal)	X[3] (serum)	X[3] (urine)											
Vital Signs (supine)	X	X		X[4]	X[4]	X[4]	X[4]	X[4]	X	X	X	X	X[19]
Temperature (oral)	X	X		X[4]	X[4]	X[4]	X[4]	X[4]	X	X	X	X	X[19]
Physical Examination	X[5]	X[5]						X[5]	X[5]	X[5]	X[5]	X[5]	X[5,19]
12-Lead ECG	X				X[6]								
Enroll/Randomize		X											
12-lead Holter ECG (24h)[7]			X	X	X								
Surgery			X										
Study treatment Infiltration/instillation			X										
Admission to PACU				T0									
Surgical Site Assessment								X[8]	X[8]	X[8]	X[8]	X[8]	X[8]

Study Period	Screening	Inpatient							Follow-Up Clinic Visits			Unscheduled Visit[1]	Early Termination[19]
		Day of Surgery	Surgery	Post-surgery	T24	T48	T72	T96 ± 4 h					
Study Day / **Assessment**	D -45 to Day Prior to Surgery	D1 (prior to surgery)	D1	D1	D2	D3	D4	D5	D8 + 1 day	D15 + 2 days	D29 + 2 days		
Neurosensory Examination	X							X[9]	X[9]	X[9]	X[9]	X[9]	X[9]
Blood Draw for Laboratory Tests	X[10]					X[10]							
Rescue Medication Consumption Recording				X	X	X	X	X	X	X			X
Concomitant Medication Assessment	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
NRS Pain Assessments				X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	X[11]			X[11]
Patient Home Diary Record (NRS)								X[12]	X[12]	X[12]			X[12,19]
Electronic Diary (Review, Distribution and/or Collection)								X[13]	X[13]	X[13]			X[13]
Patient Home Diary (Analgesic Consumption)								X	X	X			X
Prescription for Outpatient Opioid Rescue								X[14]					
PROs[15]	X					X		X	X	X	X		
PBOMs[16]						X		X	X	X	X		X
Blood Draw for PK Analysis		X[17,18]	X[17]	X[17]	X[17]	X[17]							

FOOTNOTES:

[1] Unscheduled visits may occur at any time and assessments are to be completed at the Investigator's discretion.

[2] Pain assessment training with test during screening; re-watch 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 (HR, BP, RR (supine), SpO_2) and temperature assessed together after T0 at T1, T2, T6, T12, T24, and every 12 hours thereafter (if awake at time of assessment between the hours of 12:00 AM and 6:00 AM) 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 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, and a physical examination to capture changes after Surgery, at T96 (± 4 hours), but prior to discharge from the inpatient unit, and D8, D15, and D29 or if the patient terminates early, at that time if allowed. Body weight (kg), in indoor clothing, but without shoes, will be measured at Screening and at T96. Height (cm) will be measured, and body mass index (BMI) will be calculated at Screening only.

[6] Post-surgery ECG should be performed at T24 (± 2 hours).

[7] In a subset of 12 patients per randomized arm at one site in Part C, 12-lead Holter monitors will be placed prior to surgery and record for 24 hours to assess for effects on the QT interval during study drug administration. Note: If the number of patients enrolled in Part B is increased, PK sampling and Holter monitoring as described above may be conducted in Part B instead of Part C.

[8] Surgical site assessment: T96 (± 4 hours, but prior to discharge from the inpatient unit) and D8, 15, and 29.

[9] Neurosensory examination of the area proximal to the surgical incision approximately 3 cm from the incision at Screening visit, T96 (± 4 hours, but prior to discharge from the inpatient unit) and D8, D15, and D29 or if the patient terminates early, at that time if allowed.

[10] Clinical laboratory tests (chemistry, hematology, and coagulation) should be performed at Screening and T48 (± 4 hours.

[11] During the inpatient stay, NRS at rest beginning with the PACU admission (T0) may be assessed once the patient is awake. Obtain NRS scores T0 plus 1 hour (T1), T0 plus 2 hours (T2), T4, T6, T8, T12, T16, T20, T24, and every 4 hours (if awake at time of assessment) until discharge from the inpatient unit. Time windows: for T1 to T2 (± 5 min) and from T4 onward (± 15 min). Scheduled NRS scores must be recorded regardless of timing of pre-rescue medication NRS scores and administration of rescue medication. The actual time of all NRS scores must be recorded, i.e., not the nominal time. During the inpatient stay, as soon as feasible, evoked NRS twice daily after 3 maneuvers: (a) coughing 3 times, and (b) sitting up from the supine position into a standardized position (both legs dangling on the side of the bed), and (c) ambulation for approximately 10 yards (30 feet). Obtain these NRS scores in the morning at 10:00 AM (± 1 h) and in the afternoon at 4:00 PM (± 1 h). During the inpatient stay, pain scores may be skipped between the hours of midnight and 6:00 AM, but the patient may not miss two consecutive assessments. The T12, T24, T48, T72, and T96 assessments must be completed even if the patient must be awakened at these times. During the inpatient stay, an additional NRS assessment must be obtained within 5 minutes prior to IV rescue medication administration and within 15 minutes prior to oral rescue medication administration. During the outpatient period, (D8 and D15), instruct the patient to document their NRS scores twice daily at 11:00 AM (± 1 h) and 7:00 PM (± 1 h) (a) at rest, (b) after coughing 3 times, (c) after sitting up from the supine position into a standardized position (both legs dangling on the side of the bed), and (d) during ambulation for approximately 10 yards (30 feet). Note that the actual time of these assessments must be documented in the diary. Instruct the patient to:

a. Obtain the morning NRS assessment.

b. Obtain the evening NRS assessment.

c. Opioid and non-opioid rescue medication must be recorded in the diary through D15, including a pre-rescue NRS score.

[12] The patient is expected to document NRS pain scores at rest and on ambulation 2 ×/day through D15 (at the times and qualifications noted above).

[13] The diary and instructions are provided to the patient prior to discharge (T96). At each subsequent visit, review Patient Diary instructions with patient and collect the patient's NRS scores and other study-related assessments.

[14] Patients will be given a prescription for 20 tablets of oxycodone 5 mg one or two tablets PO Q 4–6 h PRN for moderate-severe pain (i.e., NRS 5–10).

[15] PROs: PROMIS 10 Global (17.6 Appendix F) and Activities Assessment Scale (AAS) (17.7 Appendix G)

[16] PBOMs: Sit to Stand Test (17.8 Appendix H), Timed Up and Go (TUG) Test (17.9 Appendix I).

[17] Collect blood samples for PK. The time points for whole blood collection will be at PKT 0 (Pre-IP Dose, 2-10 minutes prior to the first study treatment instillation), 0.03 h (2 min), 0.083 h (5 min), 0.167 h (10 min), 0.25 h (15 min), 0.33 h (20 min), 0.5 h (30 min), 0.75 h (45 min), and at 1, 1.5, 2, 4, 8, 12, 16, 24, 36 and 48 hours after the first study treatment instillation (total of 18 samples). There will be a ± 2-minute window allowed for the 10-, 15 and 20-minute collections, a ± 5-minute window allowed for collections at 30 minutes through 4 hours, and a ± 15-minute window for collections after 4 hours. In the event of a SAE or severe TEAE, an unscheduled PK draw will be performed. The actual time of collection will be recorded and used in any analysis. Out-of-window collections will not be considered protocol deviations.

[18] Patients must abstain from foods containing capsaicin for T24 prior to surgery.

[19] If the patient terminates early, complete all procedures listed, as appropriate. The following assessments are done only if the Early Termination occurs prior to the D15 visit: Patients home diary review, vital signs, and targeted physical examination.

Abbreviations: AAS = Activities Assessment Scale; AE = adverse event(s); ECG = electrocardiogram; FSH = follicle stimulating hormone; NRS = numeric rating scale of pain intensity; PACU = post-anesthesia care unit; PBOM = performance-based outcome measure; PK = pharmacokinetic(s); PKT = pharmacokinetic time; PO = orally (per os); PRN = as needed; PRO = patient-reported outcome; PROMIS = Patient Reported Outcomes Measurement Information System; T0 = time of admission into the PACU; TUG = Timed Up and Go.

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term
AC	Analgesic consumption
ADaM	Analysis Data Model
AE	Adverse event
ALK	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ASA	American Society of Anesthesiologists
AST	Aspartate aminotransferase
AUC	Area Under the Curve
$AUC_{0-\infty}$	Area Under the Curve from time 0 to infinity
AUC_{0-last}	Area Under the Curve from time 0 to the last PK sample collection time
BID	Bis in die (twice daily)
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CA-008	Investigational product
CA-101	Cyclic urea
CFR	Code of Federal Regulations
cm	Centimeter
C_{max}	Maximum observed plasma drug concentration
CRF / eCRF	Case Report Form (may include electronic data capture systems or paper forms)
CRO	Contract research organization
CS	Clinically significant
D# or D-#	Day # (study days after surgery), Day # prior to surgery
ECG	Electrocardiogram
EDC	Electronic data capture
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
h or hrs	Hour(s)
HCl	Hydrochloride
HR	Heart rate

Abbreviation	Term
ICF	Informed consent form
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
LOCF	Last pain score carried forward
m	Meter
mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minutes
mITT	Modified Intent-to-treat
mL	Milliliter
ms	Millisecond
NCS	Not clinically significant
NRS	Numeric Rating Scale of Pain Intensity
OC	Opioid consumption
OF	Opioid free
OME	Oral morphine equivalent
OTC	Over the counter
PACU	Post-anesthesia care unit
PBOM	Performance-based outcome measure
PDS	Polydioxanone sutures
PE	Physical examination
PI	Principal Investigator
PKT	Pharmacokinetic time
PK	Pharmacokinetic(s)
PO	Per os (oral)
PRN	Pro re nata (as needed)
PRO	Patient-reported outcome
PROMIS	Patient Reported Outcomes Measurement Information System
PT	Prothrombin time
Q	Every
RBC	Red blood cell

Abbreviation	Term
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SNRIs	Serotonin-norepinephrine reuptake inhibitors
SPI	Sum of pain intensity
SpO_2	Oxygen saturation
SSRIs	Selective serotonin reuptake inhibitors
T#	Time in hours since arrival in the PACU (T0 equals time of admission into the PACU)
TEAEs	Treatment emergent adverse event(s)
THC	Tetrahydrocannabinol
TKA	Total knee arthroplasty
T_{max}	Time to maximum plasma drug concentration
Tot. Bili	Total bilirubin
TRPV1	Transient receptor potential subfamily V (vanilloid) member 1
TUG	Timed Up and Go
ULN	Upper limit of normal
US	United States
VHR	Ventral hernia repair
W#	Week # visit after surgery
wLOCF	Last prior pain score carried forward for a specified period (window)
WOCF	Worst prior pain score carried forward

5 INTRODUCTION

5.1 Background

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

Capsaicin exposure to TRPV-1-expressing nociceptor peripheral terminals results in initial excitation of the nociceptor followed by a functional desensitization which continues for some time after removal of capsaicin from the site. 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 postsurgical 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 simple administration technique 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.

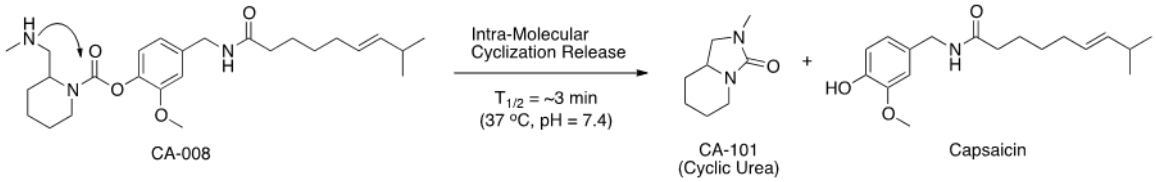
In order to work around the solubility limitations of capsaicin, the highly water-soluble capsaicin pro-drug CA-008 was developed for local infiltration. It avoids the physicochemical limitations of capsaicin while providing greater target engagement which theoretically would produce superior local analgesia, 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 postsurgical 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 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 Good Laboratory Practice (GLP) safety studies and the pharmacokinetic (PK) profile for various doses have been determined in multiple clinical trials conducted to date.

In Concentric GLP toxicological Study CA-NC-008-TOX-019-CR, single-dose subcutaneous administration of CA-008 HCl was well-tolerated when administered to male and female anesthetized dogs at dose levels up to 3.24 mg/kg CA-008 HCl (3.00 mg/kg CA-008 free base). Test article was formulated in 0.5 mM citrate, 0.4 mg/mL mannitol in saline for injection, with a final pH of approximately 3.7 to 3.8. This study supports clinical doses up to 100 mg of CA-008 (free base), with concentrations up to 2.00 mg/mL CA-008 (free base).

Concentric Study CA-NC-008-WH-005-MP evaluated the effect of CA-008 on wound healing of a hernia defect surgically repaired with mesh. In the study, CA-008 was administered alone or in combination with bupivacaine or ropivacaine by wound infiltration to a hernia defect repaired with mesh, in male and female Yucatan minipigs. The dose of CA-008 HCl administered to each animal was 15 mg of CA-008 HCl/animal, which was equivalent to~0.375 mg/kg. The Human Equivalent Dose (HED) was ~ 20 mg/60 kg human and the concentration used in the study was ~0.87 mg/mL free base (16 mL). A 9-cm

circular Prolene Mesh (polypropylene) patch was placed into the hernia site, flattened, and attached to the muscle using 8 simple interrupted sutures of 2-0 Prolene. The hernia (muscle) was closed with 2-0 Prolene in a simple interrupted pattern. The subcutaneous tissue layer was closed with 2-0 polydioxanone sutures (PDS) in a continuous pattern. The subcuticular tissue layer was closed with 4-0 PDS in a continuous pattern. The skin was then closed with skin glue and the closed incisions were covered with Ioban. There were no unscheduled sacrifices, no related macroscopic findings at Days 30 and 57 and no histological findings at Day 30 and Day 57 that could be directly attributed to local wound infiltration of CA-008 HCl.

Overall, treatment with CA-008 did not affect wound healing of a hernia defect surgically repaired with mesh. Furthermore, pre-treatment of the wound area with ropivacaine or bupivacaine prior to treatment with CA-008 did not impact the hernia wound healing process.

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 over-the-counter (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 Adverse Events in Prior Clinical Studies

A first-in-human study (Study CA-PS-2017-101) evaluated the safety and tolerability of CA-008 in 40 patients undergoing a unilateral transpositional first metatarsal osteotomy for correction of hallux valgus deformity, more commonly known as a bunionectomy. This study also evaluated PK and preliminary efficacy assessment of CA-008 to inform future studies in our clinical development plan. This study evaluated 5 different doses of CA-008 (0.5 mg, 1 mg, 2 mg, 3 mg and 4.2 mg). The safety, efficacy and PK results for the Phase 1 bunionectomy study are shown in the current Investigators' Brochure.

A Phase 2 bunionectomy study (CA-PS-201) was completed with 147 patients enrolled and randomized to one of 3 active doses: 0.05 mg/mL (0.7 mg, N = 36), 0.15 mg/mL (2.1 mg, N = 36) and 0.3 mg/mL (4.2 mg, N = 37) vs. placebo (N = 38) in a 1:1:1:1 randomization, respectively. The highest dose of 4.2 mg was statistically significantly superior to placebo for the primary efficacy endpoint of Pain $AUC_{0\text{-}96}$ ($p = 0.005$) and key secondary efficacy endpoints: Pain AUC 0 to Week 1 ($AUC_{0\text{-}W1}$) ($p = 0.036$); mean opioid consumption (reduced by 50%, $p < 0.002$); and percent of patients who were opioid free (OF) from 0-96 hours (26% vs. 5% for placebo; $p = 0.039$).

In CA-PS-201, low but measurable levels of CA-008 were documented in the systemic circulation for a few hours following study drug instillation with a T_{max} of ~15 minutes. CA-008 was safe and well-tolerated at all doses. There were no treatment-emergent adverse events (TEAE) leading to patient discontinuation and no pattern of TEAEs that suggested a

drug-related safety concern. There were no serious adverse events (SAEs) reported. Table 2 and Table 3 show the summary of safety for the study based upon summary tables and patient listings.

Table 2 Overall 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 System Organ Class / Preferred Term (CA-PS-201)

No. of Subjects		CA-008			Placebo (Standard of care alone) N = 37 n (%)
System Organ Class Preferred Term	Total N = 147 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 = 38 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 pectoris	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 haematoma	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)

No. of Subjects	Total N = 147 n (%)	CA-008			Placebo (Standard of care alone) N = 37 n (%)
System Organ Class Preferred Term		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 = 38 n (%)	
Diarrhoea	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)
Paraesthesia 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 administration site conditions	20 (13.6)	6 (16.7)	3 (8.3)	5 (13.2)	6 (16.2)
Administration site warmth	2 (1.4)	1 (2.8)	0	1 (2.6)	0
Application site pain	1 (0.7)	0	0	0	1 (2.7)
Application site rash	1 (0.7)	0	0	1 (2.6)	0
Chills	1 (0.7)	0	0	0	1 (2.7)
Feeling hot	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
Infusion site oedema	6 (4.1)	3 (8.3)	0	1 (2.6)	2 (5.4)
Infusion site pain	3 (2.0)	1 (2.8)	1 (2.8)	0	1 (2.7)
Oedema peripheral	2 (1.4)	0	0	2 (5.3)	0
Pain	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
Postoperative 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	1 (0.7)	0	0	0	1 (2.7)
Incision site haematoma	2 (1.4)	1 (2.8)	1 (2.8)	0	0
Scar	1 (0.7)	1 (2.8)	0	0	0
Wound	1 (0.7)	0	0	1 (2.6)	0
Wound dehiscence	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	3 (2.0)	0	0	3 (7.9)	0
Aspartate aminotransferase increased	3 (2.0)	0	0	3 (7.9)	0
Blood glucose increased	1 (0.7)	0	1 (2.8)	0	0

No. of Subjects	Total N = 147 n (%)	CA-008			Placebo (Standard of care alone) N = 37 n (%)
System Organ Class Preferred Term		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 = 38 n (%)	
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 disorders	17 (11.6)	7 (19.4)	5 (13.9)	4 (10.5)	1 (2.7)
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	2 (1.4)	2 (5.6)	0	0	0
Muscle spasms	3 (2.0)	0	3 (8.3)	0	0
Muscle twitching	1 (0.7)	1 (2.8)	0	0	0
Musculoskeletal pain	1 (0.7)	0	0	1 (2.6)	0
Musculoskeletal stiffness	1 (0.7)	0	1 (2.8)	0	0
Neck pain	1 (0.7)	0	0	1 (2.6)	0
Pain in extremity	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)
Hyperaesthesia	2 (1.4)	1 (2.8)	0	1 (2.6)	0
Hypoaesthesia	2 (1.4)	0	1 (2.8)	1 (2.6)	0
Paraesthesia	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 haemorrhage	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

No. of Subjects System Organ Class Preferred Term	Total N = 147 n (%)	CA-008 0.7 mg (0.05 mg/mL) N = 36 n (%)	CA-008 2.1 mg (0.15 mg/mL) N = 36 n (%)	CA-008 4.2 mg (0.3 mg/mL) N = 38 n (%)	Placebo (Standard of care alone) N = 37 n (%)
Rhinorrhoea	1 (0.7)	0	0	1 (2.6)	0
Skin and subcutaneous tissue disorders	13 (8.8)	2 (5.6)	4 (11.1)	1 (2.6)	6 (16.2)
Dermatitis	1 (0.7)	0	1 (2.8)	0	0
Dry skin	1 (0.7)	0	0	1 (2.6)	0
Hyperhidrosis	4 (2.7)	2 (5.6)	0	0	2 (5.4)
Petechiae	1 (0.7)	0	1 (2.8)	0	0
Pruritus	3 (2.0)	0	1 (2.8)	0	2 (5.4)
Rash	2 (1.4)	0	0	0	2 (5.4)
Rash erythematous	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	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

A Phase 2, single-ascending dose study was completed in patients undergoing total abdominoplasty (CA-PS-204). A total of 54 patients received one of three active doses of CA-008: 5 mg as 0.05 mg/mL (N = 9), 10 mg as 0.1 mg/mL (N = 13), 15 mg as 0.15 mg/mL (N = 12) or placebo (N = 20). All doses of CA-008 were safe and well-tolerated (Table 4 and Table 5). Four SAEs occurred in 4 patients and all were considered unrelated to study drug: post-procedural hemorrhage in two patients, spontaneous abortion in one patient, and deep venous thrombosis in one patient (Table 6). No effect on pain relief was detected due to the small sample size and low doses of study drug administered.

Table 4 Overall Summary of TEAEs – (CA-PS-204)

	Total Events / Number (No.) of Subjects with Any Event, n (%)					
		Cohort 1		Cohorts 2 and 3		
	Total (N = 54)	CA-008 5 mg (N = 9)	Placebo (N = 9)	CA-008 10 mg (N = 12)	CA-008 15 mg (N = 12)	Pooled Placebo (N = 12)
No. of TEAEs /	135/	28/	28/	23/	32/	24/
No. of Subjects with any TEAE[1]	49 (90.7%)	9 (100.0%)	8 (88.9%)	11 (91.7%)	10 (83.3%)	11 (91.7%)
No. of Treatment Related AEs/	21/	2/	5/	8/	4/	2/
No. of Subjects with Any Related TEAE[2]	16 (29.6%)	2 (22.2%)	2 (22.2%)	7 (58.3%)	3 (25.0%)	2 (16.7%)
No. of Severe TEAEs/	7/	2/	0/	2/	2/	1/
No. of Subjects with Any Severe TEAE	7 (13.0%)	2 (22.2%)	0	2 (16.7%)	2 (16.7%)	1 (8.3%)
No. of SAEs/	4/	2/	0/	1/	1/	0/
No. of Subjects with Any SAE	4 (7.4%)	2 (22.2%)	0	1 (8.3%)	1 (8.3%)	0
No. of TEAEs Leading to Discontinuation/	2/	0/	0/	1/	1/	0/
No. of Subjects with TEAEs Leading to Discontinuation	2 (3.7%)	0	0	1 (8.3%)	1 (8.3%)	0

Abbreviations: AE = adverse events; N = total number of subjects; SAE = serious adverse event; TEAE = treatment-emergent adverse event

[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 as probably or possibly related to study drug.

Source: Table 14.3.1

Table 5 Summary of TEAEs by MedDRA System Organ Class / Preferred Term (CA-PS-204)

	Number of subjects with at least 1 TEAE, n (%)					
		Cohort 1		Cohorts 2 and 3		
System Organ Class Preferred Term	Total (N = 54)	CA-008 5 mg (N = 9)	Placebo (N = 9)	CA-008 10 mg (N = 12)	CA-008 15 mg (N = 12)	Pooled Placebo (N = 12)
Subjects with at least TEAE	49 (90.7)	9 (100.0)	8 (88.9)	11 (91.7)	10 (83.3)	11 (91.7)
Gastrointestinal disorders	33 (61.1)	6 (66.7)	8 (88.9)	6 (50.0)	6 (50.0)	7 (58.3)
Constipation	12 (22.2)	3 (33.3)	2 (22.2)	1 (8.3)	2 (16.7)	4 (33.3)
Diarrhoea	1 (1.9)	0	0	0	1 (8.3)	0
Dyspepsia	1 (1.9)	0	0	0	0	1 (8.3)
Lip oedema	1 (1.9)	0	0	0	1 (8.3)	0
Nausea	27 (50.0)	5 (55.6)	8 (88.9)	6 (50.0)	5 (41.7)	3 (25.0)
Toothache	1 (1.9)	0	0	1 (8.3)	0	0
Vomiting	4 (7.4)	0	2 (22.2)	0	2 (16.7)	0

System Organ Class Preferred Term	Number of subjects with at least 1 TEAE, n (%)					
		Cohort 1		Cohorts 2 and 3		
	Total (N = 54)	CA-008 5 mg (N = 9)	Placebo (N = 9)	CA-008 10 mg (N = 12)	CA-008 15 mg (N = 12)	Pooled Placebo (N = 12)
Musculoskeletal and connective tissue disorders	21 (38.9)	3 (33.3)	4 (44.4)	4 (33.3)	5 (41.7)	5 (41.7)
Back pain	19 (35.2)	3 (33.3)	4 (44.4)	3 (25.0)	4 (33.3)	5 (41.7)
Musculoskeletal chest pain	1 (1.9)	0	0	1 (8.3)	0	0
Musculoskeletal pain	1 (1.9)	0	0	0	1 (8.3)	0
Nervous system disorders	12 (22.2)	4 (44.4)	1 (11.1)	1 (8.3)	2 (16.7)	4 (33.3)
Dizziness	1 (1.9)	0	0	0	0	1 (8.3)
Headache	10 (18.5)	4 (44.4)	1 (11.1)	1 (8.3)	2 (16.7)	2 (16.7)
Sciatica	1 (1.9)	0	0	0	0	1 (8.3)
Injury, poisoning and procedural complications	10 (18.5)	1 (11.1)	1 (11.1)	2 (16.7)	4 (33.3)	2 (16.7)
Abdominal wound dehiscence	1 (1.9)	0	0	0	1 (8.3)	0
Airway complication of anaesthesia	1 (1.9)	0	0	1 (8.3)	0	0
Arthropod bite	1 (1.9)	0	0	1 (8.3)	0	0
Flap necrosis	2 (3.7)	0	0	0	1 (8.3)	1 (8.3)
Incision site pruritus	1 (1.9)	0	0	0	1 (8.3)	0
Post procedural haematoma	1 (1.9)	0	0	0	0	1 (8.3)
Post procedural haemorrhage	2 (3.7)	0	0	1 (8.3)	1 (8.3)	0
Seroma	1 (1.9)	1 (11.1)	0	0	0	0
Wound dehiscence	1 (1.9)	0	1 (11.1)	0	0	0
Respiratory, thoracic and mediastinal disorders	8 (14.8)	1 (11.1)	1 (11.1)	1 (8.3)	3 (25.0)	2 (16.7)
Cough	2 (3.7)	0	0	0	2 (16.7)	0
Epistaxis	1 (1.9)	0	0	0	0	1 (8.3)
Hypoxia	4 (7.4)	1 (11.1)	1 (11.1)	1 (8.3)	0	1 (8.3)
Oropharyngeal pain	1 (1.9)	0	0	1 (8.3)	0	0
Respiratory tract congestion	1 (1.9)	0	0	0	1 (8.3)	0
Skin and subcutaneous tissue disorders	8 (14.8)	2 (22.2)	1 (11.1)	2 (16.7)	3 (25.0)	0
Dermatitis contact	1 (1.9)	0	0	0	1 (8.3)	0
Pruritus	3 (5.6)	0	1 (11.1)	1 (8.3)	1 (8.3)	0
Pruritus generalised	2 (3.7)	1 (11.1)	0	1 (8.3)	0	0
Rash	2 (3.7)	1 (11.1)	0	0	1 (8.3)	0
Rash macular	1 (1.9)	0	0	0	1 (8.3)	0

Abbreviations: AE = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; n = number of subjects reporting an event; PT = preferred term; SAE = serious adverse event; SOC = System Organ Class; TEAE = treatment-emergent adverse event

Source: Table 14.3.1.1

Table 6 Summary of Serious Adverse Events – (CA-PS-204)

System Organ Class Preferred Term	Subjects with at least 1 SAE, n (%)					
		Cohort 1		Cohorts 2 and 3		
	Total (N = 54)	CA-008 5 mg (N = 9)	Placebo (N = 9)	CA-008 10 mg (N = 12)	CA-008 15 mg (N = 12)	Pooled Placebo (N = 12)
Subjects with at least 1 SAE	4 (7.4)	2 (22.2)	0	1 (8.3)	1 (8.3)	0
Injury, poisoning and procedural complications	2 (3.7)	0	0	1 (8.3)	1 (8.3)	0
Post procedural haemorrhage	2 (3.7)	0	0	1 (8.3)	1 (8.3)	0
Pregnancy, puerperium and perinatal conditions	1 (1.9)	1 (11.1)	0	0	0	0
Abortion spontaneous	1 (1.9)	1 (11.1)	0	0	0	0
Vascular disorders	1 (1.9)	1 (11.1)	0	0	0	0
Deep vein thrombosis	1 (1.9)	1 (11.1)	0	0	0	0

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; n = number of subjects reporting an event; PT = preferred term; SAE = serious adverse event; SOC = System Organ Class; TEAE = treatment-emergent adverse event

Source: Table 14.3.1.3

A Phase 2, single-ascending dose study was completed in patients undergoing total knee arthroplasty (TKA) (CA-PS-203). A total of 54 patients received one of three active doses of CA-008: 5 mg as 0.05 mg/mL (N = 9), 10 mg as 0.1 mg/mL (N = 13), 15 mg as 0.15 mg/mL (N = 12) or placebo (N = 20). All doses of CA-008 were safe and well-tolerated (Table 7 and Table 9). Four SAEs occurred in 3 patients and all were considered unrelated to study drug: perforated ulcer in one patient, cerebrovascular accident and seizure in one patient, and deep venous thrombosis in one patient (Table 8). No effect on pain relief was detected due to the small sample size and low doses of study drug administered.

Table 7 Overall Summary of TEAEs – (CA-PS-203)

	Total Events / N of Subjects with Any Event, n (%)					
		Cohort 1		Cohorts 2 and 3		
	Total N = 54	CA-008 5 mg N = 9	Placebo N = 9	CA-008 10 mg N = 13	CA-008 15 mg N = 12	Pooled Placebo N = 11
No. of TEAEs /	172/	35/	28/	36/	46/	27/
No. of Subjects with any TEAE[1]	45 (83.3)	7 (77.8)	7 (77.8)	12 (92.3)	10 (83.3)	9 (81.8)
N of Treatment Related AEs/	11/	1/	3/	1/	1/	5/
N of Subjects with Any Related TEAE[2]	8 (14.8)	1 (11.1)	3 (33.3)	1 (7.7)	1 (8.3)	2 (18.2)
N of Severe TEAEs/	1/	0/	0/	0/	0/	1/
N of Subjects with Any Severe TEAE	1 (1.9)	0	0	0	0	1 (9.1)
N of SAEs/	4/	1/	0/	0/	2/	1/
N of Subjects with Any SAE	3 (5.6)	1 (11.1)	0	0	1 (8.3)	1 (9.1)
N of TEAEs Leading to Discontinuation/	2/	0/	0/	0/	2/	0/
N of Subjects with TEAEs Leading to Discontinuation	1 (1.9%)	0	0	0	1 (8.3)	0

[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 to probably or possibly related.

Source: Table 14.3.1

Table 8 Summary of Serious Adverse Events – (CA-PS-203)

	Total Events / N of Subjects with Any Event, n (%)					
		Cohort 1		Cohorts 2 and 3		
System Organ Class Preferred Term	Total N = 54	CA-008 5 mg N = 9	Placebo N = 9	CA-008 10 mg N = 13	CA-008 15 mg N = 12	Pooled Placebo N = 11
No. of Subjects with any SAE	3 (5.6)	1 (11.1)	0	0	1 (8.3)	1 (9.1)
General disorders and administration site conditions	1 (1.9)	0	0	0	0	1 (9.1)
Perforated ulcer	1 (1.9)	0	0	0	0	1 (9.1)
Nervous system disorders	1 (1.9)	0	0	0	1 (8.3)	0
Cerebrovascular accident	1 (1.9)	0	0	0	1 (8.3)	0
Seizure	1 (1.9)	0	0	0	1 (8.3)	0
Vascular disorders	1 (1.9)	1 (11.1)	0	0	0	0
Deep vein thrombosis	1 (1.9)	1 (11.1)	0	0	0	0

Source: Table 14.3.1.3

Table 9 Summary of TEAEs by MedDRA SOC/PT (CA-PS-203)

System Organ Class Preferred Term	Total Events / N of Subjects with Any Event, n (%)					
		Cohort 1		Cohorts 2 and 3		
	Total N = 54	CA-008 5 mg N = 9	Placebo N = 9	CA-008 10 mg N = 13	CA-008 15 mg N = 12	Pooled Placebo N = 11
No. of Subjects with any TEAE	45 (83.3)	7 (77.8)	7 (77.8)	12 (92.3)	10 (83.3)	9 (81.8)
Cardiac disorders	16 (29.6)	5 (55.6)	0	2 (15.4)	3 (25.0)	6 (54.5)
Sinus tachycardia	16 (29.6)	5 (55.6)	0	2 (15.4)	3 (25.0)	6 (54.5)
Gastrointestinal disorders	30 (55.6)	5 (55.6)	5 (55.6)	8 (61.5)	8 (66.7)	4 (36.4)
Abdominal distension	1 (1.9)	0	1 (11.1)	0	0	0
Constipation	8 (14.8)	2 (22.2)	3 (33.3)	0	3 (25.0)	0
Dyspepsia	2 (3.7)	0	0	2 (15.4)	0	0
Nausea	27 (50.0)	5 (55.6)	5 (55.6)	8 (61.5)	5 (41.7)	4 (36.4)
Vomiting	12 (22.2)	1 (11.1)	0	4 (30.8)	5 (41.7)	2 (18.2)
General disorders and administration site conditions	17 (31.5)	4 (44.4)	3 (33.3)	4 (30.8)	2 (16.7)	4 (36.4)
Application site pain	2 (3.7)	0	2 (22.2)	0	0	0
Instillation site induration	1 (1.9)	1 (11.1)	0	0	0	0
Oedema peripheral	3 (5.6)	1 (11.1)	0	0	1 (8.3)	1 (9.1)
Perforated ulcer	1 (1.9)	0	0	0	0	1 (9.1)
Peripheral swelling	1 (1.9)	0	0	0	0	1 (9.1)
Pyrexia	12 (22.2)	3 (33.3)	2 (22.2)	4 (30.8)	2 (16.7)	1 (9.1)
Infections and infestations	4 (7.4)	2 (22.2)	1 (11.1)	0	1 (8.3)	0
Respiratory tract infection	1 (1.9)	1 (11.1)	0	0	0	0
Upper respiratory tract infection	1 (1.9)	0	1 (11.1)	0	0	0
Urinary tract infection	3 (5.6)	1 (11.1)	1 (11.1)	0	1 (8.3)	0
Injury, poisoning and procedural complications	13 (24.1)	2 (22.2)	3 (33.3)	2 (15.4)	3 (25.0)	3 (27.3)
Contusion	3 (5.6)	1 (11.1)	0	0	2 (16.7)	0
Deep vein thrombosis postoperative	1 (1.9)	0	0	1 (7.7)	0	0
Incision site vesicles	1 (1.9)	0	0	0	0	1 (9.1)
Lumbar vertebral fracture	1 (1.9)	0	0	0	1 (8.3)	0
Post procedural haematoma	4 (7.4)	1 (11.1)	2 (22.2)	0	0	1 (9.1)
Post procedural haemorrhage	2 (3.7)	1 (11.1)	0	0	0	1 (9.1)
Post procedural oedema	3 (5.6)	1 (11.1)	1 (11.1)	1 (7.7)	0	0
Postoperative wound complication	3 (5.6)	1 (11.1)	1 (11.1)	0	1 (8.3)	0
Procedural pain	2 (3.7)	0	0	0	1 (8.3)	1 (9.1)
Wound secretion	1 (1.9)	1 (11.1)	0	0	0	0
Investigations	1 (1.9)	0	0	0	1 (8.3)	0
Electrocardiogram QT prolonged	1 (1.9)	0	0	0	1 (8.3)	0

System Organ Class Preferred Term	Total Events / N of Subjects with Any Event, n (%)					
		Cohort 1		Cohorts 2 and 3		
	Total N = 54	CA-008 5 mg N = 9	Placebo N = 9	CA-008 10 mg N = 13	CA-008 15 mg N = 12	Pooled Placebo N = 11
Musculoskeletal and connective tissue disorders	9 (16.7)	1 (11.1)	1 (11.1)	3 (23.1)	2 (16.7)	2 (18.2)
Arthralgia	4 (7.4)	0	1 (11.1)	1 (7.7)	1 (8.3)	1 (9.1)
Back pain	1 (1.9)	0	0	0	0	1 (9.1)
Groin pain	3 (5.6)	1 (11.1)	0	2 (15.4)	0	0
Pain in extremity	1 (1.9)	0	0	0	1 (8.3)	0
Nervous system disorders	7 (13.0)	2 (22.2)	1 (11.1)	2 (15.4)	2 (16.7)	0
Allodynia	1 (1.9)	0	1 (11.1)	0	0	0
Cerebrovascular accident	1 (1.9)	0	0	0	1 (8.3)	0
Dizziness	4 (7.4)	1 (11.1)	0	1 (7.7)	2 (16.7)	0
Dysarthria	1 (1.9)	0	0	0	1 (8.3)	0
Headache	1 (1.9)	1 (11.1)	0	0	0	0
Paraesthesia	1 (1.9)	1 (11.1)	0	0	0	0
Seizure	1 (1.9)	0	0	0	1 (8.3)	0
Tremor	1 (1.9)	0	0	1 (7.7)	0	0
Psychiatric disorders	1 (1.9)	0	0	1 (7.7)	0	0
Anxiety	1 (1.9)	0	0	1 (7.7)	0	0
Renal and urinary disorders	2 (3.7)	0	1 (11.1)	0	1 (8.3)	0
Pollakiuria	1 (1.9)	0	1 (11.1)	0	0	0
Urinary retention	1 (1.9)	0	0	0	1 (8.3)	0
Respiratory, thoracic and mediastinal disorders	2 (3.7)	0	0	1 (7.7)	1 (8.3)	0
Hiccups	1 (1.9)	0	0	1 (7.7)	0	0
Respiratory depression	1 (1.9)	0	0	0	1 (8.3)	0
Skin and subcutaneous tissue disorders	9 (16.7)	0	3 (33.3)	2 (15.4)	3 (25.0)	1 (9.1)
Blister	1 (1.9)	0	0	0	1 (8.3)	0
Erythema	1 (1.9)	0	0	0	0	1 (9.1)
Hyperhidrosis	1 (1.9)	0	1 (11.1)	0	0	0
Pruritus	2 (3.7)	0	1 (11.1)	1 (7.7)	0	0
Pruritus generalised	3 (5.6)	0	1 (11.1)	0	2 (16.7)	0
Rash	2 (3.7)	0	1 (11.1)	1 (7.7)	0	0
Surgical and medical procedures	1 (1.9)	0	0	0	0	1 (9.1)
Post procedural drainage	1 (1.9)	0	0	0	0	1 (9.1)
Vascular disorders	15 (27.8)	2 (22.2)	2 (22.2)	4 (30.8)	5 (41.7)	2 (18.2)
Deep vein thrombosis	1 (1.9)	1 (11.1)	0	0	0	0
Hot flush	1 (1.9)	0	1 (11.1)	0	0	0
Hypertension	8 (14.8)	0	0	2 (15.4)	4 (33.3)	2 (18.2)
Hypotension	6 (11.1)	1 (11.1)	1 (11.1)	2 (15.4)	2 (16.7)	0

Source: Table 14.3.1.1

A two-part, Phase 1/2, randomized, double-blind, placebo-controlled study has been completed (final report pending) in subjects undergoing elective primary unilateral TKA (CA-PS-208).

Part A was an exploratory, sequential, dose-escalation phase in which three doses of CA-008 were evaluated versus placebo for safety, tolerability, and PK. Each cohort in Part A had 8 subjects randomized 3:1 to active drug or placebo. Subjects received placebo or CA-008 in a 120 mL volume, delivered as 36 mg (0.3 mg/mL), 60 mg (0.5 mg/mL) and 90 mg (0.75 mg/mL).

Two dose levels of CA-008 were chosen in Part B of the study, based on the most effective dose (0.3 mg/mL) in a prior positive bunionectomy postsurgical pain study (Study CA-PS-201). CA-008 was evaluated at doses of 36 mg (delivered as 0.3 mg/mL) and a higher dose of 60 mg (delivered as 0.5 mg/mL) compared to placebo in a multicenter randomized, double-blind, parallel-group design with a 1:1:1 ratio.

A total of 193 subjects (mean age 62.3 years) were enrolled in the combined Parts A and B of the study, with 61 in the combined 36 mg dose group, 62 in the combined 60 mg dose group, 6 in the 90 mg dose group, and 64 in the combined placebo group. Results from Part A remained blinded until the end of the study and were therefore included with Part B for efficacy and safety analyses. Subjects who received 90 mg CA-008 in Part A were included in the safety analyses only.

All doses of CA-008 (36 mg, 60 mg, 90 mg) were well tolerated. Overall, of the 193 subjects enrolled and randomized, 184 (95.3%) reported 624 TEAEs (Table 10). Most TEAEs were unrelated (96.9%) and all but 7 (3.6%) were mild or moderate in severity. There were no stopping-rule pauses during the study to investigate any specific TEAE. No deaths occurred during the study or the follow-up period and there were no TEAEs causing early termination from the study.

No meaningful differences were present across treatment groups for the overall summary of TEAEs (Table 10).

Related TEAEs were uncommon during the study and no pattern was observed across treatment groups. AEs probably or possibly related to study drug were reported for 2 subjects in the CA-008 36 mg group (mild pyrexia); 2 subjects in the CA-008 60 mg group (mild pyrexia and mild calf pain) and 2 subjects in the placebo group (mild incision site drainage and mild pruritus). All related AEs resolved, typically within a few days after surgery.

The frequency of subjects with the TEAE of pyrexia was greater in all active treatment groups (16% to 33%) compared to the placebo group (6%) without a clear dose-response (Table 11). All cases in all groups except for one patient that received placebo were considered mild in severity. The AE of pyrexia typically occurred 12-48 hours following surgery and represented transient low-grade fever (~99-100°F) without any associated abnormal clinical signs or symptoms suggesting a safety concern. During the 12-48 hours following surgery, the mean temperature of the groups receiving active drug appeared to be about 0.1-0.2°C higher than the placebo-treated group (Post hoc Figure 14.3.3).

The frequency of patients with the TEAE of tachycardia showed an apparent dose-response across all groups treated with active drug with the frequency in the 36 mg group (22%) comparable to that in the placebo group (18%), representing a difference of one patient (Table 11). Tachycardia occurred in 17 (27.9%) subjects in the 60 mg group and in 3 (50.0%) subjects in the 90 mg group. All cases in all groups were considered mild in severity. The AE of tachycardia typically occurred 1-2 days following surgery, lasted 1-2 days and resolved without intervention. Tachycardia was not associated with any other abnormal clinical signs or symptoms or other AEs suggesting a safety concern.

The frequency of patients with the TEAE of drug ineffective was higher in the group that received placebo (10%) than in the groups that received 36 or 60 mg of active drug (5%; Table 11).

Five SAEs occurred during the study (Table 10); however, none of these events were related to study drug. In the CA-008 36 mg group, there was one event each of myocardial infarction and knee postoperative haematoma; in the CA-008 60 mg group one subject had an allergic reaction to lisinopril; and in the placebo group, there was one event each of pulmonary embolus and post procedural haematoma.

There were no meaningful differences across the treatment groups for assessments of wound healing of the surgical site or neurosensory evaluations.

Table 10 Summary of Treatment-Emergent Adverse Events (for Study CA-PS-208)

No. of Subjects	Total (N = 193)n (%)	CA-008			Placebo N = 37 n (%)
		36 mg N = 60 n (%)	60 mg N = 61 n (%)	90 mg N = 6 n (%)	
Number of TEAEs	624	194	199	24	207
Number (%) of subjects with at least one AE[1]	184 (95.3%)	54 (90.0%)	58 (95.1%)	6 (100.0%)	66 (100.0%)
Number of treatment related AEs	6	2	2	0	2
Number (%) of subjects with at least one treatment related TEAE[2]	6 (3.1%)	2 (3.3%)	2 (3.3%)	0	2 (3.0%)
Number of severe AEs[3]	7	2	2	1	2
Number (%) of subjects with severe, life-threatening or fatal TEAEs	7 (3.6%)	2 (3.3%)	2 (3.3%)	1 (16.7%)	2 (3.0%)
Number of SAEs	5	2	1	0	2
Number (%) of subjects with at least one SAE	5 (2.6%)	2 (3.3%)	1 (1.6%)	0	2 (3.0%)
Number of TEAEs leading to discontinuation	0	0	0	0	0
Number (%) of subjects with TEAEs leading to discontinuation	0	0	0	0	0

Abbreviations: AE = adverse event; SAE = serious adverse event; TEAE = treatment emergent adverse event.

Note: 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 1 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.

[3] No life-threatening or fatal TEAEs occurred.

Source: Study CA-PS-208 Table 14.3.1.1; Listing 16.2.7.1.

Table 11 Summary of Treatment Emergent Adverse Events Occurring in ≥10% Subjects by System Organ Class and Preferred Term for Study CA-PS-208

System Organ Class Preferred Term	Total (N = 193) n (%)	CA-008 36 mg N = 60 n (%)	CA-008 60 mg N = 61 n (%)	CA-008 90 mg N = 6 n (%)	Placebo N = 66 n (%)
Number of subjects with at least one TEAE[1]	184 (95.3%)	54 (90.0%)	58 (95.1%)	6 (100.0%)	66 (100.0%)
Gastrointestinal disorders	138 (71.5%)	39 (65.0%)	45 (73.8%)	6 (100.0%)	48 (72.7%)
Abdominal pain	1 (0.5%)	0	1 (1.6%)	0	0
Constipation	95 (49.2%)	29 (48.3%)	32 (52.5%)	4 (66.7%)	30 (45.5%)
Diarrhoea	1 (0.5%)	0	1 (1.6%)	0	0
Dyspepsia	1 (0.5%)	1 (1.7%)	0	0	0
Flatulence	1 (0.5%)	0	1 (1.6%)	0	0
Lip Swelling	1 (0.5%)	0	1 (1.6%)	0	0
Nausea	93 (48.2%)	24 (40.0%)	28 (45.9%)	5 (83.3%)	36 (54.5%)
Vomiting	36 (18.7%)	9 (15.0%)	11 (18.0%)	1 (16.7%)	15 (22.7%)
Cardiac disorders	58 (30.1%)	17 (28.3%)	20 (32.8%)	3 (50.0%)	18 (27.3%)
Atrial fibrillation	1 (0.5%)	0	0	0	1 (1.5%)
Bradycardia	12 (6.2%)	3 (5.0%)	4 (6.6%)	0	5 (7.6%)
Myocardial infarction	1 (0.5%)	1 (1.7%)	0	0	0
Supraventricular tachycardia	1 (0.5%)	0	1 (1.6%)	0	0
Tachycardia	45 (23.3%)	13 (21.7%)	17 (27.9%)	3 (50.0%)	12 (18.2%)
General disorders and administrative site conditions	47 (24.4%)	18 (30.0%)	15 (24.6%)	3 (50.0%)	11 (16.7%)
Chills	2 (1.0%)	1 (1.7%)	1 (1.6%)	0	0
Drug ineffective	14 (7.3%)	3 (5.0%)	3 (4.9%)	1 (16.7%)	7 (10.6%)
Infusion site pruritus	1 (0.5%)	0	0	0	1 (1.5%)
Injection site bruising	1 (0.5%)	1 (1.7%)	0	0	0
Injection site pain	1 (0.5%)	0	1 (1.6%)	0	0

System Organ Class Preferred Term	Total (N = 193) n (%)	CA-008 36 mg N = 60 n (%)	CA-008 60 mg N = 61 n (%)	CA-008 90 mg N = 6 n (%)	Placebo N = 66 n (%)
Injection site swelling	1 (0.5%)	0	1 (1.6%)	0	0
Non-cardiac chest pain	1 (0.5%)	0	1 (1.6%)	0	0
Oedema peripheral	1 (0.5%)	0	0	0	1 (1.5%)
Peripheral swelling	7 (3.6%)	5 (8.3%)	1 (1.6%)	0	1 (1.5%)
Pyrexia	28 (14.5%)	12 (20.0%)	10 (16.4%)	2 (33.3%)	4 (6.1%)
Nervous system disorders	41 (21.2%)	15 (25.0%)	11 (18.0%)	2 (33.3%)	13 (19.7%)
Dizziness	19 (9.8%)	8 (13.3%)	2 (3.3%)	2 (33.3%)	7 (10.6%)
Headache	17 (8.8%)	5 (8.3%)	7 (11.5%)	0	5 (7.6%)
Hypoaesthesia	4 (2.1%)	1 (1.7%)	2 (3.3%)	0	1 (1.5%)
Sinus headache	1 (0.5%)	1 (1.7%)	0	0	0
Tremor	1 (0.5%)	1 (1.7%)	0	0	0
Skin and subcutaneous tissue disorders	37 (19.2%)	10 (16.7%)	10 (16.4%)	2 (33.3%)	15 (22.7%)
Blister	2 (1.0%)	1 (1.7%)	0	0	1 (1.5%)
Ecchymosis	1 (0.5%)	1 (1.7%)	0	0	0
Erythema	1 (0.5%)	1 (1.7%)	0	0	0
Pruritus	29 (15.0%)	7 (11.7%)	9 (14.8%)	2 (33.3%)	11 (16.7%)
Rash	5 (2.6%)	0	2 (3.3%)	0	3 (4.5%)
Skin induration	1 (0.5%)	0	0	0	1 (1.5%)
Urticaria	1 (0.5%)	0	1 (1.6%)	0	0
Musculoskeletal and connective tissue disorder	27 (14.0%)	10 (16.7%)	8 (13.1%)	1 (16.7%)	8 (12.1%)
Arthralgia	4 (2.1%)	0	1 (1.6%)	0	3 (4.5%)
Back pain	2 (1.0%)	1 (1.7%)	1 (1.6%)	0	0
Groin pain	2 (1.0%)	1 (1.7%)	1 (1.6%)	0	0
Intervertebral disc protrusion	1 (0.5%)	1 (1.7%)	0	0	0

System Organ Class Preferred Term	Total (N = 193) n (%)	CA-008 36 mg N = 60 n (%)	CA-008 60 mg N = 61 n (%)	CA-008 90 mg N = 6 n (%)	Placebo N = 66 n (%)
Joint stiffness	1 (0.5%)	0	1 (1.6%)	0	0
Muscle spasms	3 (1.6%)	1 (1.7%)	1 (1.6%)	0	1 (1.5%)0
Musculoskeletal pain	1 (0.5%)	0	1 (1.6%)	0	0
Musculoskeletal stiffness	1 (0.5%)	1 (1.7%)	0	0	0
Myalgia	1 (0.5%)	0	0	0	1 (1.5%)
Pain in extremity	16 (8.3%)	5 (8.3%)	5 (8.2%)	1 (16.7%)	5 (7.6%)
Respiratory, thoracic and mediastinal disorders	21 (10.9%)	6 (10.0%)	8 (13.1%)	1 (16.7%)	6 (9.1%)
Bradypnoea	1 (0.5%)	0	1 (1.6%)	0	0
Cough	1 (0.5%)	0	0	0	1 (1.5%)
Dyspnoea	1 (0.7%)	0	0	0	1 (1.5%)
Hypoxia	12 (6.2%)	4 (6.7%)	4 (6.6%)	1 (16.7%)	3 (4.5%)
Oropharyngeal pain	5 (2.6%)	2 (3.3%)	3 (4.9%)	0	0
Pulmonary embolism	1 (0.7%)	0	0	0	1 (1.5%)
Vascular disorders	21 (10.9%)	7 (11.7%)	6 (9.8%)	0	8 (12.1%)
Deep vein thrombosis	1 (0.5%)	0	0	0	1 (1.5%)
Diastolic hypotension	3 (1.6%)	2 (3.3%)	0	0	1 (1.5%)
Haematoma	3 (1.6%)	0	2 (3.3%)	0	1 (1.5%)
Hypertension	12 (6.2%)	3 (5.0%)	5 (8.2%)	0	4 (6.1%)
Hypotension	3 (1.6%)	2 (3.3%)	0	0	1 (1.5%)

Source: Study CA-PS-208 Table 14.3.1.2

5.3.2 Pharmacokinetic Exposures in Prior Clinical Studies

Rich pharmacokinetic data has been collected at defined timepoints following the completion of CA-008 instillation or infiltration in each of the previous studies. Due to the inherent low levels of pH-labile prodrug expected systemically and limits of detection, the CA-008 parameters are less well defined in the studies with lower CA-008 doses. Generally, CA-008 has a rapid T_{max} (< 0.25 hr) following the end of infusion. The capsaicin and CA-101 T_{max} occur between approximately 0.2 to 1.5 hours after the end of administration. In preliminary results from CS-PS-208 (TKA) clinical study, CA-008 had a half-life of less than 0.2 hours in most cases. Topically applied capsaicin has an elimination half-life of 1.64 hours (Babbar *et al.*, 2009). The $t_{1/2}$ for capsaicin ranges from approximately 0.5 to 1.5 hours. CA-101 mean $t_{1/2}$ ranges from approximately 1.5 to 2 hours (Table 12, Table 13, Table 14).

CA-PS-201 (BUN) (CA-008 doses between 0.7 and 4.2 mg): When dose normalized, C_{max} appeared to be dose proportional based on visual comparison of the box plots for CA-008, capsaicin and CA-101. CA-008 AUC_{0-t} appeared to be dose proportional while CA-101 and capsaicin AUC_{0-t} appeared to be slightly greater than dose proportional. Note a similar trend was observed in the bunionectomy study, CA-PS-2017-101 (CA-008 doses between 0.5 and 4.2 mg [Table 13, Table 14]).

CA-PS-203 (TKA) (CA-008 doses between 5 and 15 mg): CA-008 C_{max} and AUC_{0-tt} were low and not significantly different across dose groups. Capsaicin and CA-101 exposures appeared to be dose proportional based on visualization of the box plot between 5 and 15 mg, but the 10 mg dose group appeared to have greater variability (Table 13).

CA-PS-204 (ABD) (CA-008 doses between 5 to 15 mg): Proportionality of CA-008 was difficult to determine due to many time points having values below the limits of quantitation. CA-101 C_{max} increased proportionally with dose. AUC_{0-t} for capsaicin and CA-101 appeared to be dose proportional, given the intercohort variability (Table 13).

CA-PS-208 (TKA): (CA-008 doses between 36 and 90 mg): When normalized to dose, CA-008 exposure at 90 mg was disproportionally higher than 36 and 60 mg. CA-101 and capsaicin exposure increased with increasing dose. When normalized to dose, C_{max} and AUC_{0-t} were approximately consistent at 36 and 90 mg, with the 60 mg mean C_{max} and AUC_{0-t} to dose ratios less than expected (Table 14).

Table 12 Summary of PK Parameters by Dose Cohort for Study CA-PS-2017-101 (BUN) and CA-PS-201 (BUN): 0.5 to 4.2 mg

Study	Dose		CA-008				Capsaicin				CA-101			
		Statistics	t_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (hr•ng/mL)	$t_{1/2}$ (hr)	t_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (hr•ng/mL)	$t_{1/2}$ (hr)	t_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (hr•ng/mL)	$t_{1/2}$ (hr)
CA-PS-2017-101 (BUN)	0.5 mg	N	3	3	0	0	6	6	6	3	6	6	6	1
		Mean	–	0.0668	NC	NC	–	0.370	0.566	0.685	–	0.850	1.69	2.57
		SD	–	0.06	NC	NC	–	0.133	0.312	0.248	–	0.305	1.80	NC
		CV%	–	89.7	NC	NC	–	35.9	55.2	36.2	–	35.9	107	NC
	1 mg	N	3	3	2	0	6	6	6	1	6	6	6	1
		Mean	–	0.142	0.0524	NC	–	0.374	0.666	0.703	–	1.07	2.79	1.96
		SD	–	0.0997	0.0362	NC	–	0.193	0.294	NC	–	0.256	1.24	NC
		CV%	–	69.9	69	NC	–	51.5	44.2	NC	–	24	44.6	NC
	2 mg	N	5	5	3	0	6	6	6	4	6	6	6	3
		Mean	–	0.155	0.0395	NC	–	1.05	1.46	1.07	–	2.19	5.4	1.26
		SD	–	0.0586	0.00936	NC	–	0.532	0.722	0.765	–	0.445	1.65	0.514
		CV%	–	37.8	23.7	NC	–	50.5	49.4	71.1	–	20.4	30.6	40.7
	3 mg	N	6	6	5	0	6	6	6	5	6	6	6	3
		Mean	–	0.247	0.0925	NC	–	1.52	2.68	0.743	–	4.26	9.53	1.10
		SD	–	0.337	0.116	NC	–	0.504	0.828	0.201	–	0.502	1.95	0.286
		CV%	–	136	125	NC	–	33.1	30.9	27.1	–	11.8	20.4	26.1
	4.2 mg	N	6	6	6	1	6	6	6	4	6	6	6	5
		Mean	–	0.572	0.260	0.167	–	2.42	4.07	0.843	–	8.91	46.7	2.41
		SD	–	0.407	0.176	NC	–	1.82	1.74	0.355	–	5.66	69.4	2.23
		CV%	–	71.2	67.6	NC	–	75.4	42.9	42.2	–	63.6	149	92.4
CA-PS-201 (BUN)	0.7 mg	N	12	12	10	0	12	12	12	9	12	12	12	7
		Mean	NC	0.108	0.0272	NC	NC	0.723	0.734	0.760	NC	1.06	1.73	1.82
		SD	NC	0.100	0.0169	NC	NC	0.405	0.285	0.474	NC	0.442	0.955	0.709
		CV%	NC	92.5	62	NC	NC	56.1	38.8	62.3	NC	41.6	57.1	39
	2.1 mg	N	13	13	13	1	13	13	13	13	13	13	13	12
		Mean	NC	0.216	0.0653	0.248	NC	2.59	3.32	1.53	NC	2.95	7.73	1.82
		SD	NC	0.171	0.0521	NC	NC	1.62	1.60	0.777	NC	1.04	3.50	1.08
		CV%	NC	79.2	79.8	NC	NC	62.6	48.1	50.8	NC	35.4	45.3	59.4

Study	Dose		CA-008				Capsaicin				CA-101			
		Statistics	t_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (hr•ng/mL)	$t_{1/2}$ (hr)	t_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (hr•ng/mL)	$t_{1/2}$ (hr)	t_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (hr•ng/mL)	$t_{1/2}$ (hr)
	4.2 mg	N	14	14	14	4	14	14	14	13	14	14	14	11
		Mean	NC	0.502	0.149	0.185	NC	4.87	7.02	1.38	NC	6.52	18.9	1.58
		SD	NC	0.414	0.125	0.0367	NC	2.43	2.48	0.505	NC	2.22	6.64	0.534
		CV%	NC	82.3	84.3	19.8	NC	49.9	35.3	36.5	NC	34	35.1	33.9

Table 13 Summary of PK Parameters by Dose Cohort for Study CA-PS-203 (TKA) and CA-PS-204 (ABD): 5 to 15 mg

Dose	Statistics	CA-008				Capsaicin				CA-101			
		T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (hr•ng/mL)	$t_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (hr•ng/mL)	$t_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (hr•ng/mL)	$t_{1/2}$ (hr)
CA-PS-203 (TKA)													
5 mg	N	-	9	9	-	9	9	9	9	9	9	9	8
	Mean	-	0.524	0.0660	-	NR	9.09	6.46	0.878	NR	9.65	22.5	1.91
	SD	-	0.475	0.113	-	NR	5.54	3.54	0.466	NR	2.89	8.51	0.613
	Min	-	0.108	0.00483	-	0.17	1.82	3.16	0.492	0.50	5.8	10.2	1.30
	Median	-	0.424	0.0156	-	0.23	7.90	5.28	0.709	0.73	8.89	23.6	1.82
	Max	-	1.40	0.337	-	0.50	18.6	12.8	1.93	2.0	15.6	38.5	3.29
10 mg	N	-	13	12	-	13	13	13	13	13	13	13	13
	Mean	-	1.63	0.345	-	NR	23.9	18.8	1.46	NR	29.8	80.6	1.92
	SD	-	1.80	0.310	-	NR	14.5	8.83	0.620	NR	15.1	35.4	0.485
	Min	-	0	0.0347	-	0.22	3.12	2.80	0.812	0.28	19	40.0	1.20
	Median	-	1.11	0.243	-	0.32	20.7	18.3	1.19	0.50	26.7	73.9	1.84
	Max	-	6.08	0.970	-	0.83	48.5	35.1	3.02	1.4	68.1	170	3.15
15 mg	N	12	12	12	2	12	12	12	12	12	12	12	12
	Mean	-	0.569	0.116	-	NR	21.0	20.9	1.61	NR	28.8	75.5	1.96

Dose	Statistics	CA-008				Capsaicin				CA-101			
		T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (hr•ng/mL)	$t_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (hr•ng/mL)	$t_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (hr•ng/mL)	$t_{1/2}$ (hr)
	SD	-	0.492	0.0985	-	NR	13.5	10.6	0.586	NR	9.16	28.2	0.654
	Min	-	0.0594	0.0104	-	0.050	4.27	6.60	0.594	0.13	15.7	41.9	1.12
	Median	NR	0.378	0.111	NR	0.39	20.6	20.7	1.51	0.57	28.2	66.4	1.75
	Max	NR	1.66	0.292	NR	1.0	50.1	35.9	2.62	1.0	44.6	129	3.25
CA-PS-204 (ABD)													
5 mg	N	-	9	9	-	9	9	9	9	9	9	8	8
	Mean	-	2.60	0.321	-	0.21	14.1	10.5	0.951	0.40	19.3	47.6	1.12
	SD	-	1.25	0.193	-	0.13	4.78	3.98	0.261	0.27	8.26	11.8	0.210
	Min	-	0.0313	0.00809	-	0.083	8.35	6.16	0.577	0	0	36.4	0.826
	Median	-	2.96	0.286	-	0.17	14.2	9.06	0.938	0.47	19.9	43.9	1.14
	Max	-	3.84	0.629	-	0.52	21.9	18.0	1.50	0.77	31.1	67.4	1.39
10 mg	N	-	12	12	-	12	12	12	12	12	12	12	11
	Mean	-	5.62	0.619	-	0.19	28.0	22.0	1.23	0.65	46.8	136	1.71
	SD	-	4.10	0.532	-	0.12	13.5	9.49	0.356	0.78	10.7	121	1.11
	Min	-	1.97	0.210	-	0.067	12.7	12.3	0.600	0.17	28.0	54.5	0.880
	Median	-	3.66	0.328	-	0.18	26.4	18.4	1.32	0.50	47.6	97.9	1.26
	Max	-	15.0	1.82	-	0.5	53.8	41.2	1.82	3.0	68.9	489	4.64
15 mg	N	12	12	12	7	12	12	12	12	12	12	12	12
	Mean	0.11	6.00	0.773	0.111	0.17	43.3	32.9	1.57	0.32	65.2	147	1.24
	SD	0.034	3.81	0.493	0.0328	0.068	16.5	8.78	0.551	0.14	24.5	113	0.415
	Min	0.067	1.04	0.139	0.0777	0.067	20.2	19.6	0.628	0.10	47.6	71.9	0.752
	Median	0.1	5.79	0.793	0.103	0.17	42.4	32.8	1.59	0.26	58.7	121	1.14
	Max	0.18	11.7	1.68	0.177	0.28	77.5	49.8	2.55	0.52	140	501	2.41

Table 14 Summary of PK Parameters by Dose Cohort for Study CA-PS-208: 36 to 90 mg

Dose	Statistic	CA-008				Capsaicin				CA-101			
		Tmax (h)	Cmax (ng/mL)	AUC_{0-t} (h*ng/mL)	Half-life (h)	Tmax (h)	Cmax (ng/mL)	AUC_{0-t} (h*ng/mL)	Half-life (h)	Tmax (h)	Cmax (ng/mL)	AUC_{0-t} (h*ng/mL)	Half-life (h)
36 mg	N	15	15	15	2	15	15	15	15	15	15	15	15
	Mean	0.42	3.64	0.937	0.148	0.54	51.4	62.8	2.65	1.0	68.9	220	1.73
	SD	0.25	4.58	1.28	0.0761	0.21	32.7	27.6	0.947	0.60	29	68	0.337
	CV%	58.9	125.8	137	51.5	42.8	63.6	43.9	35.7	59.9	42.1	30.9	19.5
60 mg	N	14	14	14	7	14	14	14	14	14	14	14	14
	Mean	0.26	5.99	1.47	0.514*	0.54	59.1	91	2.52	0.91	86.1	281	1.94
	SD	0.12	8.65	2.54	0.598	0.36	27.3	42.1	1.04	0.44	38.1	105	0.498
	CV%	46.5	144.5	172.2	116.3	66.1	46.2	46.3	41.4	48.9	44.3	37.4	25.6
90 mg	N	6	6	6	5	6	6	6	6	6	6	6	6
	Mean	0.22	15.8	4.56	0.145	0.37	108	183	3.67	1.0	170	489	1.44
	SD	0.039	12.3	3.77	0.0288	0.17	63	91.3	1.7	0.44	45.6	209	0.196
	CV%	18.2	78.1	82.7	19.9	47.2	58.5	49.9	46.2	41.7	26.9	42.7	13.6

*two subjects had low but persistent CA-008 past 0.5 hours, resulting in a longer half-life calculation than most subjects.

5.3.3 Estimated Exposures in VHR/Soft Tissue

In the current study, a dose of 15 and 30 mg CA-008 may be explored initially.

The projected PK data for a 15 mg dose (50 mL of 0.3 mg/ml solution) of CA-008 in patients undergoing ventral hernia repair (CA-PS-209) is expected to be similar to the PK profile for a 15 mg dose of CA-008 in patients undergoing abdominoplasty (CA-PS-204). There are no reasons to expect the safety profile of a 15 mg dose in these two similar surgeries to be different, and the safety profile of the 15 mg dose was indistinguishable from placebo in CA-PS-204. As such, the Sponsor considers a starting dose of 15 mg of CA-008 in CA-PS-209 to be safe and appropriate with escalation to up to 30 mg (0.3 mg/ml in 100 mL).

Table 15 includes the 15 mg exposure observed in CA-PS-203 (TKA), the 36-90 mg exposure in observed in CA-PS-208 (TKA; part A and B, preliminary data), and the 15 mg exposure observed in an abdominoplasty study, CA-PS-204 (ABD). The table also includes exposures predicted in CA-PS-209 (VHR) at 15 and 30 mg.

It is assumed that a 15 mg dose of CA-008 in CA-PS-209 will lead to exposures similar to that observed in the abdominoplasty surgery, CA-PS-204. Both are soft tissue surgeries and both locations are similarly vascularized. To fully characterize the absorption phase in CA-PS-209, unlike in CA-PS-204, PK will be collected during dosing. This may impact the determination of T_{max} and C_{max}. To predict exposure at 30 mg, dose proportionality from 15 mg to 30 mg was assumed for CA-008 and CA-101. Capsaicin exposures were also independently modeled from PS-204 data PK. A two-compartment model with linear elimination and zero-order absorption adequately fit the observed capsaicin concentrations in women undergoing abdominoplasty. A Monte-Carlo simulation (via R) was performed for delivery of 30 mg CA-008 in a total of 1000 virtual healthy subjects per dose level.

As shown in Table 15, a dose of 15 mg is expected to produce exposures to CA-008, CA-101 and capsaicin that are less than exposures from the 60 mg dose in CA-PS-208 (TKA), a dose shown to be safe. A dose of 30 mg is expected to produce exposures to CA-008, CA-101 and capsaicin that are less than exposures from the 90 mg dose in CA-PS-208 (TKA), a dose shown preliminarily to be safe. The 30 mg dose will not be administered unless the safety assessment of the 15 mg dose is supportive.

Table 15 Supporting exposure data for administration of CA-008 up to 36 mg (0.3 mg/ml) in CA-PS-209

Concentric Study	Type of Study	Dose (mg/kg)	CA-008 C_{max} (ng/mL)	CA-008 AUC_{0-t} (ng*h/mL)	CA-101 C_{max} (ng/mL)	CA-101 AUC_{0-t} (ng*h/mL)	Cap C_{max} (ng/mL)	Cap AUC_{0-t} (ng*h/mL)
Previous Human Exposure								
15 mg CA-PS-203	TKA	15 mg	0.569 (±0.492, %CV 86.4)[a]	0.116 (±0.985, %CV 84.7)[a]	28.8 (±9.16, %CV 31.9)	75.5 (±28.2, %CV 37.4)	21 (±13.5, %CV 64.2)	20.9 (±10.6, %CV 50.8)
15 mg CA-PS-204	ABD	15 mg	6 (±3.81, %CV 63.6)	0.773 (±0.493, %CV 63.8)	65.2 (±24.5, %CV 37.7)	147 (±113, %CV 77.1)	43.3 (±16.5, %CV 38.2)	32.9 (±8.78, %CV 26.7)
36 mg CA-PS-208	TKA	36 mg	3.64 (±4.58, %CV 125.8)	0.937 (±1.28, %CV 137.0)	68.9 (±29.0, %CV 42.1)	220 (±68.0, %CV 30.9)	51.4 (±32.7, %CV 63.6)	62.8 (±27.6, %CV 43.9)
60 mg CA-PS-208	TKA	60 mg	5.99 (±8.65, %CV 144.5)	1.47 (±2.54, %CV 172.2)	86.1 (±38.1, %CV 44.3)	281 (±105, %CV 37.4)	59.1 (±27.3, %CV 46.2)	91.0 (±42.1, %CV 46.3)
90 mg CA-PS-208	TKA	90 mg	15.8 (±12.3, %CV 78.1)	4.56 (±3.77, %CV 82.7)	170 (±45.6, %CV 26.9)	489 (±209, %CV 42.7)	108 (±63.0, %CV 58.5)	183 (±91.3, %CV 49.9)
Predicted Human Exposure in CA-PS-209 (VHR)								
15 mg soft tissue (Same as CA-PS-204)	VHR / Soft tissue	15 mg	6 (±3.81, %CV 63.6)[b]	0.77 (±0.493, %CV 63.8)[b]	65.2 (±24.5, %CV 37.7)[b]	147 (±113, %CV 77.1)[b]	43.3 (±16.5, %CV 38.2)[b]	32.9 (±8.78, %CV 26.7)[b]
30 mg soft tissue, projected	VHR /Soft tissue	30 mg	12[c]	1.55[c]	130[c]	294[c]	96.8 (±29.4, %CV 30.4)[d]	96.3 (±24, %CV 24.9)[d]

[a] Many subjects had ≤ 3 quantifiable CA-008 time points thus there may be some error in the reporting of Cmax and AUC_{0-t}.

[b] Same as PS-204

[c] Exposure in soft tissues scaled from CA-PS-204: 15 mg $Cmax_{CA-PS-204}$ x 2 or $AUC_{0-t\_CA-PS-204}$ x 2

[d] Exposure modeled and simulated: a population PK analysis of capsaicin was performed based on data collected in CA-PS-204. A two-compartment model with linear elimination and zero-order absorption adequately fit the observed concentrations in female undergoing abdominoplasty. Monte-Carlo simulations (via R) were performed for an infiltration of 30 and 60 mg CA-008 in a total of 1000 virtual healthy subjects per dose level. Rich capsaicin concentrations were simulated after a single dose up to 24 hours to derive the following: Cmax, AUC_{0-t} (mean, SD, %CV)

Table 16 Exposure from PS-208 vs. Predicted Exposures in Soft Tissue

Proposed Soft Tissue Dose	CA-008 C_{max} ratio[a]	CA-008 AUC_{0-t} ratio[a]	CA-101 C_{max} ratio[a]	CA-101 AUC_{0-t} ratio[a]	Capsaicin C_{max} ratio[a]	Capsaicin AUC_{0-t} ratio[a]
Observed 60 mg exposure in CA-PS-208 (TKA) / predicted exposure in VHR						
15 mg	1.0	1.9	1.3	1.9	1.3	2.6
30 mg	0.5	0.9	0.7	1.0	0.6	0.9
Observed 90 mg exposure in CA-PS-208 (TKA)/ / predicted exposure in VHR						
15 mg	2.6	5.9	2.6	3.3	2.5	5.6
30 mg	1.3	2.9	1.3	1.7	1.1	1.9

Cells in grey indicate exposure in soft tissue is predicted to be less than that at 60 or 90 mg in CA-PS-208

[a] Table 15 was used to calculate the ratio.

5.3.4 Preclinical Supporting Data

Preclinical NOAEL exposures are presented in Table 17 along with human equivalent dose (HED). Two pivotal GLP toxicology studies are presented: dog study CA-NC-008-TOX-019-CR and rat study CA-NC-008-TOX-0179-CR. Another GLP rat study CA-NC-008-RT-003-CO is also presented. It is a repeat dose EFD study and thus has slightly higher rat exposures, though it is acknowledged that this study is not a general toxicology study with histology. On a dose basis, the GLP dog single dose toxicology study (CA-NC-008-TOX-019-CR) supports human dosing up to 100 mg in a 60 kg human.

Table 17 Nonclinical Exposures and HED in Dog and Rat following SC administration of CA-008

Concentric Study	Type of Study	Species	Dose Frequency	NOAEL Dose (mg/kg) CA-008 HCl	CA-008 Cmax (ng/mL)	CA-008 AUC_{0-t} (ng*h/mL)	CA-101 Cmax (ng/mL)	CA101 AUC_{0-t} (ng*h/mL)	Cap Cmax (ng/mL)	Cap AUC_{0-t} (ng*h/mL)	Free base HED (mg) (60kg human)
CA-NC-008-TOX-019-CR	Single dose toxicology GLP	Dog	Single	3.24	208	78	313	359	230	467	100
CA-NC-008-TOX-017-CR	Single dose toxicology GLP	Rat	Single	1.9 (Toxicology Group) /1.5 (TK group)	8.5#	5.9#	490	1020	134	109	17/13.5
CA-NC-008-RT-003-CO	Reproductive Toxicology (repeat dose) GLP	Rat	Daily (23-29 days)	M/F = ND Mating, fertility = 3	26#	12#	685	1883	220	206	26.9

Except in CA-NC-008-RT-003-CO, male and female exposures were averaged.

#Due to limited time points, the C_{max} may be under reported.

M = Males

F= Females

ND – NOAEL not determined for maternal and paternal animals due to injection site reactions after repeat dosing

To ensure preclinical exposures provide at least a 2x margin over expected clinical exposure in CA-PS-209, Table 18 presents the ratio of the NOAEL C_{max} and AUC_{0-t} observed in the dog and rat to the predicted exposure in human following administration to soft tissue. In the pivotal dog study CA-NC-008-TOX-019-CR, dog exposures to CA-008, capsaicin and CA-101 are expected to be equal to or exceed twice that predicted in CA-PS-209 at 15 and 30 mg, except for CA-101 at 30 mg. The pivotal rat study CA-NC-008-TOX-017-CR was dosed to 1.9 mg/kg (HED of 8.5 mg) and exposures in this study are expected 2-fold above that expected at 15 mg in CA-PS-209 (VHR), except the CA-008 C_{max}. It is possible the CA-008 C_{max} was missed in the rat studies due to the first time point being at 10 minutes post subcutaneous dose, as well as the toxicokinetic (TK) groups in this study were dosed at approximately 1.3-fold below that of the toxicology groups. Based on time-concentration curves in rat, dog and human, the rat appears to allow the conversion from CA-008 to capsaicin and CA-101 faster than humans and dogs, though in all cases, the elimination phase appears steep. The pivotal rat study is also expected to be 2-fold above that of 30 mg in CA-PS-209, except the CA-008 C_{max} and capsaicin exposure. While it lacks the full evaluation of a general toxicology study, a rat GLP FEED study (CA-NC-008-RT-003-CO) is also presented in Table 18. It has a higher dose and exposure than CA-NC-008-TOX-017-CR and are likely to be equal to or exceed twice that observed in humans following soft tissue administration up to 30 mg.

Table 18 Preclinical Exposure: Predicted Exposures in CA-PS-209 (VHR) Ratio

Proposed Dose	CA-008 C_{max} Ratio[a]	CA-008 AUC_{0-t} ratio[a]	CA-101 C_{max} ratio[a]	CA-101 AUC_{0-t} ratio[a]	Capsaicin C_{max} Ratio[a]	Capsaicin AUC_{0-t} Ratio[a]
CA-NC-008-TOX-019-CR NOAEL Exposure in Dog 3.24 mg/kg / Predicted exposure in VHR						
15	35	101	4.8	2.4	5.3	14
30	17	50	2.4	1.2	2.4	4.8
CA-NC-008-TOX-017-CR NOAEL Single Dose Rat (1.9 or 1.5 mg/kg, Tox or TK group respectively / Predicted exposure in VHR						
15	1.4[b,c]	7.7	7.5	6.9	3.1	3.3
30	0.74[b,c]	3.8	3.8	3.5	1.4	1.1
CA-NC-008-RT-003-CO mating and fertility NOAEL Repeat Dose Rat (3 mg/kg) / Predicted exposure in VHR						
15	4.3	16	11	13	5.1	6.3
30	2.2	7.7	5.3	6.4	2.3	2.1

Grey indicates exposure in preclinical studies are ≥ 2X expected human exposure in CA-PS-209 (VHR)

[a] Table 15 and Table 17 were used to calculate ratios.

[b] In most cases, Tmax was at the first time point, so it is possible the true Tmax following s.c. injection was likely missed, thus exposure may be underestimated.

[c] The Tk group was dosed at 1.5 mg/kg rather than the 1.9 mg/kg used in the main toxicology group so exposures presented may be under reported by a factor of approximately 1.3.

[d] Maternal and paternal NOAEL could not be determined due injection site reactions associated with repeat dosing.

5.4 Study Rationale

CA-008 is being investigated as a potential therapy for treatment of pain following surgery. Ventral hernia repair (VHR) is a standard surgical model for the assessment of postsurgical pain.

5.5 Dose Rationale

5.5.1 Selection of Doses

The preliminary safety of CA-008 was established in relevant animal models and supported by two clinical studies of bunionectomy (CA-PS-2017-101 and CA-PS-201) with doses up to 4.2 mg (concentration 0.3 mg/mL) and clinical studies after TKA (CA-PS-203, CA-PS-208) and total abdominoplasty (CA-PS-204) with doses up to 90 mg (concentration 0.75 mg/mL) (Section 5.3), as well as knowledge from prior human studies with an injectable formulation of capsaicin. Taken together, the characterization of the pharmacology, PK, and toxicology profiles and the anticipated benefits as well as the potential risks are considered appropriate to support the intended initial dose in Part A of 15 mg CA-008 (concentration of 0.3 mg/mL), and if well-tolerated, potentially followed in Parts B and C by a higher, fixed dose of between 15-30 mg (concentration of 0.3 mg/mL) in this study of acute postsurgical pain following VHR. The selection of the dose for Parts B and C will be based on the experience in Part A.

To predict exposure at 30 mg, dose proportionality from 15 mg to 30 mg was assumed for CA-008 and CA-101. Capsaicin exposures were also independently modeled from CA-PS-204 (ABD) PK data. A two-compartment model with linear elimination and zero-order absorption adequately fit the observed capsaicin concentrations in women undergoing abdominoplasty. Monte-Carlo simulations (via R) were performed for delivery of 30 mg CA-008 in a total of 1000 virtual healthy subjects per dose level (Section 5.3.2). The predicted exposures in this study following administration of 30 mg or less are expected to be within a range that has been shown to be acceptably safe in preclinical and prior clinical studies.

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 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 of the surgical site should sufficiently address any transient pain that results from TRPV1 agonism. Administration of CA-008 during the wound closure process is ideal for delivering therapy to the surgical site, thus optimizing target engagement. Study treatment is to be administered intraoperatively as a single administration via infiltration/instillation into the "surgical site" prior to wound closure. 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 generated.

6 STUDY OBJECTIVES

6.1 Primary Objectives

For Part A:

- Evaluate the safety, tolerability, and feasibility of a single intraoperative administration of CA-008 15 mg in patients undergoing an elective VHR.

For Part B:

- Evaluate the safety, tolerability and feasibility of a single intraoperative administration of a fixed dose of CA-008, 24 mg in patients undergoing an elective VHR.

For Part C:

- Evaluate the efficacy of CA-008 on reported pain in patients undergoing an elective VHR during a specified post-operative time interval.

6.2 Secondary Objectives

For Part A:

- Evaluate the PK profile of a single intraoperative administration of CA-008 15 mg in patients undergoing an elective VHR.

For Part B:

- Determine the pain profile of patients undergoing an elective VHR.
- Determine the appropriateness of progression to Part C.
- Assessment of opioid consumption.
- Evaluate the PK profile of a single intraoperative administration of a fixed dose of CA-008, 24 mg in patients undergoing an elective VHR.
- Explore the relationship between CA-008 and its metabolite plasma concentrations and electrocardiogram (ECG) QT interval using a concentration-QT (cQT) analysis.

For Part C:

- Evaluate the efficacy of CA-008 on reported pain in patients undergoing an elective VHR during additional specified post-operative time intervals.
- Evaluate the effect of CA-008 on opioid consumption.
- Evaluate the effect of CA-008 on patient-reported outcomes (PROs).

- Evaluate, preliminarily, the effect of CA-008 on performance-based outcome measures (PBOMs).
- Evaluate the safety and tolerability of CA-008 or placebo in patients undergoing an elective VHR.

7 INVESTIGATIONAL PLAN

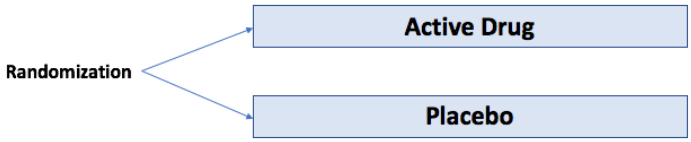
7.1 Overall Study Design and Plan

This is a three-part, Phase 1/2, randomized, double-blind, placebo-controlled, adaptive safety, PK and preliminary efficacy study of CA-008 in patients undergoing VHR.

In Part A, CA-008 15 mg will be administered in an open-label exploration of different delivery techniques. The objective of Part A is to determine the safety, feasibility, PK, and appropriateness of administration of a single dose of CA-008 infiltrated/instilled during surgery in patients undergoing VHR. It is expected that 8 to 12 patients will be enrolled in Part A but it may be up to 16 patients, so that at least 8 patients receive the optimal delivery technique which will allow a formal safety assessment of the 15 mg dose of study drug.

In Part B, if the formal safety assessment from Part A of CA-008 15 mg is favorable, then the active study drug dose will be increased to a fixed dose of 24 mg. Using the general delivery technique identified in Part A, this dose, concentration, and volume will be assessed compared to a placebo in a pilot, double-blind, randomized, parallel-group design. The objective of Part B is to determine preliminarily the tolerability of planned study drug administration as well as the pain profile of the placebo control group. It is expected that approximately 24 patients (up to 32) patients will be enrolled in Part B (see Figure 1). The results of Part B will be unblinded for analysis prior to the initiation of Part C.

Figure 1 Study Design



In Part C, the active dose level of CA-008 from Part B will be evaluated compared to placebo in a larger randomized, double-blind, parallel-group design to evaluate efficacy and safety. It is expected that ~100 patients will be enrolled in Part C to bring the total number of patients enrolled in the study to up to ~150.

In Parts A, B and C for each patient, the study will be conducted in two periods:

- Inpatient period which continues from check-in on Day 1 (D1) until discharge (4 days or 96 hours [h] following surgery [T96 ± 4 h], [D5]). Discharge may be delayed, if needed, for medical reasons.
- Outpatient period which begins on discharge from the inpatient unit through follow up visits to D29 + 2 days. Note that additional follow up visits may occur at any time or even after D29 to follow AEs to resolution or to establish a new baseline.

During the inpatient period, patients will undergo VHR including study drug treatment (CA-008 or placebo) followed by serial assessments of safety, PK, and drug effect, in particular focusing on reported pain and need for analgesia. During the outpatient period, patients will have serial assessments of safety and drug effect.

7.2 Duration of Participation

Approximately 90 days per patient from screening to Day 29 (D29) + 2 days (however, this could be longer to follow any AE to resolution or to establishment of a new baseline).

7.3 Dose Escalation and Cohort Expansion

In Part A, it is expected that 8-12 patients will be enrolled but it may be up to 16 patients. CA-008 will be administered at a dose of 15 mg (delivered as a 50 mL solution at a concentration of 0.3 mg/mL) in an open-label exploration of different delivery techniques.

In Part B, the active study drug dose will be increased to a fixed dose of 24 mg and tested vs placebo in a pilot phase. It is expected that approximately 24 patients (up to 32) will be enrolled in Part B. The results of Part B will be unblinded for analysis prior to the initiation of Part C.

In general, dose escalation in Part B will be permitted if there have been no adverse effects on wound healing and no intolerable systemic side effects during Part A. Dose escalation, or cohort expansion decisions will be made by the Sponsor's medical monitor, the CRO's medical monitor, a relevant Principal Investigator (PI) and an independent medical monitor. This will be based on review of at least the following safety data:

- Inpatient (i.e., through 96 h) safety and tolerability data from all 8–12 initial patients, including vital signs, physical examination (PE), neurosensory examination, surgery site assessment, laboratory assessments, and AEs;
- D8 ambulatory visit safety and tolerability data from at least 4 of the initial 8 patients in the current cohort, including vital signs, PE, neurosensory examination, surgery site assessment, and AEs.

In Part C, the active dose level of CA-008 from Part B will be evaluated compared to placebo in a larger randomized, double-blind, parallel-group design to evaluate efficacy and safety. It is expected that ~100 patients will be enrolled in Part C to bring the total number of patients enrolled in the study to up to ~150.

7.4 Study Stopping Rules

Study enrollment will be paused if any patient experience any grade 3 TEAE, in particular in any of the categories shown in Table 19, in Appendix A (Section 17.1) or found in the toxicity grading scale cited therein.

Should a stopping rule be triggered, the Sponsor's medical monitor, the CRO medical monitor, the relevant Principal Investigator, and an independent medical monitor will review the relevant data to determine whether or not it is appropriate to resume enrollment with the same or a modified dose, modify the study or stop the study.

The independent medical monitor will have the authority to unblind the treatment assignment for the affected patients as part of the safety review.

The study will be stopped if a safety signal is detected that indicates an unacceptable risk to study participants.

Table 19 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 intravenous (IV) antibiotics, antifungals, or antivirals or radiologic intervention.	Life-threatening consequences; urgent intervention indicated
ECG/Cardiac issues Vital Signs Labs	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Focused Neurosensory Testing (performed by trained Investigator)	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms requiring medical intervention; limiting self-care ADL	Life-threatening and urgent intervention indicated

8 SELECTION OF STUDY POPULATION

8.1 Study Population

The study population consists of adults 18 to 80 years of age, inclusive, who are planning to undergo an elective, primary, open VHR, with retromuscular, preperitoneal mesh repair (i.e., Rives-Stoppa technique or equivalent), with or without laparoscopic assistance, and who otherwise meet eligibility criteria may be considered for enrollment into the study.

8.1.1 Number of Participants

- **Part A** – Open-label, feasibility and safety assessment:
  - N = At least 8 with an acceptable range of up to 16
- **Part B** – Double-blind, placebo-controlled pilot:
  - Expected N = 24 with an acceptable range of up to N = 32 (randomized 1:1 active to placebo)
- **Part C** – Double-blind, placebo-controlled efficacy:
  - In Part C, a total of up to N= ~100 patients will be randomized in a 1:1 ratio to active or placebo to bring the total number of patients enrolled in the study to up to ~150.

8.2 Eligibility Criteria

8.2.1 Inclusion Criteria

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

1. Plan to undergo an elective, primary, open laparotomy with VHR, with retromuscular, preperitoneal synthetic (polypropylene) mesh placement, with midline fascial reconstruction (i.e., Rives-Stoppa technique or equivalent) and with optional laparoscopic assistance under general anesthesia with sedation, without collateral procedure or additional surgeries. Ventral hernia should not be longer than ~6 cm in length.
2. Appropriate candidate for TAP block, including no contraindications, no anatomical constraints. Note: TAP block may replace or supplement rectus sheath block if rectus sheath block is inadequate.
3. Adults 18–80 years of age, inclusive.
4. American Society of Anesthesiology (ASA) physical Class 1, 2, or 3 at the time of randomization (Section 17.2, Appendix B).
5. If a male, 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.
6. 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 (as documented by history and appropriate follicle stimulating hormone [FSH] level), 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 Food and Drug Administration (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.

7. Have a body mass index ≤ 40 kg/m^2.
8. Be willing and able to sign the informed consent form (ICF) approved by an Institutional Review Board (IRB).
9. Be willing and able to complete study procedures and pain scales and to return for outpatient follow up visits as required.
10. Be willing and able to avoid foods containing capsaicin for 24 hours prior to surgery.

8.2.2 Exclusion Criteria

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

1. In the opinion of the Investigator, the patient has:
    a. a concurrent chronic painful condition (i.e., daily pain) that may require analgesic treatment during the study period or may confound postsurgical pain assessments;
    b. active skin disease or other clinically significant abnormality at the anticipated site of surgery that could interfere with the planned surgery.
2. The patient has taken opioids more than twice per week in any week within 6 months of screening or has used any opioids during the 2 weeks prior to surgery.
3. The patient has a known allergy (or contraindication) to any of the following: chili peppers, capsaicin or the components of CA-008, propofol, bupivacaine hydrochloride (HCl), midazolam, inhaled anesthetic, nitrous oxide, ondansetron, acetaminophen, fentanyl, hydromorphone, morphine, oxycodone, or celecoxib.
4. As determined by the Investigator (with input from the study's medical monitor if requested by the Investigator), the patient has 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.

5. Use of the following disallowed medications:
    a. Within 1 day prior to surgery and throughout the inpatient period, taking or using any capsaicin-containing products, such as dietary supplements or OTC preparations, including topical formulations, and prescription medications.
    b. Within the 7 days prior to surgery, taking any central nervous system active agent as an analgesic adjunct medication, such as anticonvulsants (e.g., gabapentin), 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.
        i. These drugs are permitted if prescribed for non-pain indications and the dose has been stable for at least 30 days prior to surgery. Note that the dose must remain stable throughout the study.
        ii. If the patient is taking centrally- and/or peripherally-acting analgesic medications, such as acetaminophen, nonsteroidal anti-inflammatory drug (NSAIDs), or pregabalin the patient may participate in the study if the patient is willing to discontinue these medications 3 days prior to surgery. Note that (a) baby aspirin (81 mg/day) for cardiovascular prophylaxis or (b) regular or enteric-coated aspirin (up to 325 mg given up to twice daily) for venous thrombo-embolism prophylaxis is allowed during the study.
    c. Within the 7 days prior to the planned surgery taking (a) antiarrhythmics (except beta-blockers and digoxin); (b) warfarin or other anticoagulants (see exception above); (c) lithium; (d) aminoglycosides or other antibiotics for an infection (except for ophthalmic use); or (e) medical (or other) regular marijuana use.
    d. Within the 14 days prior to surgery, 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).
    e. Taking 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.
6. In the opinion of the Investigator, within the past year, the patient has 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).

7. The patient has a disqualifying positive urine drug screen or alcohol breath/saliva test during screening or check-in (See Section 10.3.14).
8. The patient has previously participated in a clinical study with CA-008.
9. The patient has participated in another clinical trial or used an investigational product within 30 days or 5 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

CA-008 for injection, 15 mg per vial, is a white lyophilized powder. On the day of use the appropriate number of vials will be reconstituted in sterile saline.

The placebo comparator is identical in appearance to the reconstituted CA-008 solution.

In Part A, CA-008 will be delivered at a dose of 15 mg (50 mL of a 0.3 mg/mL solution) and used to explore the optimal technique of delivery i.e., location and volumes of delivery to the different areas and layers of the surgical procedure. The dose of CA-008 delivered in Part A will not exceed 15 mg.

In Parts B and C, CA-008 at a fixed dose of 24 mg (80 mL of a 0.3 mg/mL concentration) or blinded placebo will be delivered using the general technique identified in Part A.

An unblinded pharmacist or designee may use unblinded vials identified as to contents to prepare the study treatment solutions. The anesthesia and surgical team and study site personnel will be blinded as to study treatment; details will be presented in the Unblinding Plan and/or the Pharmacy Manual.

9.1.3 Study Treatment Storage

Study treatments will be stored at 5°C (2°C to 8°C) until the day of surgery. All study treatments 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. All unused supplies will be checked against the drug accountability

records during the study and/or at the end of the study. Unused supplies will be returned to the Sponsor's drug supply vendor at the end of the trial.

Only eligible patients 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 patients.

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.

9.2 Other Interventions

9.2.1 Preoperative, Anesthesia and Perioperative Care

At check-in (pre-operatively), at least 1-2 hours before surgery:

Celecoxib 200 mg orally (PO)

Acetaminophen 1000 mg PO

After these medications have been administered, no additional non-opioid analgesics are to be administered during the inpatient phase (through T96).

The surgery will be performed under general anesthesia:

Inhaled anesthetic or propofol infusion with or without nitrous oxide (N_2O).

Adequate optional premedication typically with midazolam (up to 5 mg) fentanyl (up to 100 mcg); more can be given if indicated.

Supplemental anesthesia and sedation will be per institutional guidelines.

Intra-operative titration of intravenous (IV) fentanyl, including during emergence, will be per institutional guidelines.

In addition, patients will receive bupivacaine hydrochloride (BupiHCl) 175 mg delivered as follows:

Prior to start of surgery under ultrasound guidance:

- Bupivacaine 0.25%, 30 mL (75 mg) diluted with 10 mL of normal saline to a volume of 40 mL delivered as a rectus block with 20 mL on each side.

  Note: In Part A, the adequacy of the anesthetic regimen is part of the assessment of the technique feasibility. If patients report excessive pain during the immediate

postoperative period, a TAP block may be added or may replace the rectus sheath block in subsequent patients, but the total dose of bupivacaine will not exceed 175 mg.

Immediately before/after surgical incision:

- PART A: BupiHCl 0.25%, 40 mL (100 mg), may be diluted in up to 110 mL of normal saline to a total volume of not more than 150 mL: Infiltration of abdominal wall, anterior rectus abdominis sheath, posterior rectus abdominis sheath, other fascia, peritoneum (including circumferential areas of intended mesh placement)
- Parts B and C: Bupivacaine 0.25%, 40 mL (100 mg), which should be diluted in 40 mL of normal saline to a total volume of 80 mL: Infiltration of abdominal wall, anterior rectus abdominis sheath, posterior rectus abdominis sheath, other fascia, peritoneum (including circumferential areas of intended mesh placement), and laparoscopy ports.

Standard supplemental anesthetic and perioperative care will be provided per institutional guidelines. This will typically include (but not be limited to) steps to ensure preservation of intraoperative normothermia (including the use of preoperative and intraoperative forced-air warming) and deep venous thrombosis prophylaxis.

9.2.2 Intraoperative Analgesia and Care

Patients will receive general anesthesia and bilateral rectus blocks (see Section 9.2.1).

During surgery, ensure that patients receive the following:

3–500 mL intravenous (IV) fluid; more can be given if indicated

Ondansetron 4 mg IV

Note: Ondansetron should not be given to patients in Part B undergoing 24 hours of 12-lead Holter monitoring to assess the effects of study drug on the QT interval.

Within 15 minutes prior to the end of surgery, administer the following:

Intravenous (IV) hydromorphone, 0.5 mg

Note: IV morphine 2.0 mg can be used if IV hydromorphone is not available

Patients who develop clinically significant hemodynamic instability or other anesthesia complication prior to study drug administration should not receive study drug; in Parts A and B, these patients will be replaced. Replacement patients will be assigned the same treatment as the original patient. A ‘replacement’ randomization list matching that of the main list will be created to facilitate this process.

9.2.3 Inpatient Rescue Medications

Patients will be encouraged to use rescue medication only for moderate-to-severe pain (numeric rating scale [NRS] ≥ 4); however, rescue medication may be requested at any time (i.e., even when NRS < 4) and medication will be provided when requested. Conversely, patients may refuse rescue medication even when the NRS is ≥ 4. Time intervals for all rescue medication use are guidelines that can be modified by Investigator discretion.

From the time of post-anesthesia care unit (PACU) discharge through T12:

- Administer IV hydromorphone 0.5 mg, Q15 minutes as needed (PRN) for pain NRS ≥ 4.
- Note: IV morphine 2.0 mg can be used if IV hydromorphone is not available

After T12–48:

- Administer PO oxycodone 10 mg, Q 4 h PRN pain NRS ≥ 4.
- Only PO oxycodone may be used as rescue. If a patient still requires IV opioid rescue after T12, then the patient will revert to IV opioid analgesia management per institutional guidelines. These patients will still also be followed for NRS, safety, and all other assessments.

After T48–96:

- Administer PO oxycodone 5 mg, Q 4 h PRN pain NRS 5–10.
- Only PO oxycodone may be used as rescue. If a patient still requires IV opioid rescue after T12, then the patient will revert to IV analgesia management per institutional guidelines. These patients will still be followed for NRS, safety, and all other assessments.

NRS scores recorded for PRN pain medication will not replace the recording of scheduled NRS scores. However, if PRN rescue medication has recently been administered and persistent pain is reported in a scheduled NRS record prior to rescue medication taking effect, a second dose of rescue medication should not be administered.

9.2.4 Postsurgical Care

After surgery, patients will be transferred to the post-anesthesia care unit (PACU) where patients will be monitored for at least 90 minutes during which time pain assessments can begin once the patient is awake. T0 is the time of admission into the PACU (as recorded in notes by the PACU nurse). The time of extubation will be recorded, if applicable.

Patients will use the 0 to 10 numerical rating scale (NRS) to report their current pain intensity multiple times per day during the remainder of the inpatient part of the study. Scheduled times for serial pain assessments are outlined in the Schedule of Assessments (Table 1). Rescue medication will always only be administered upon request i.e., independent of the currently reported pain score. That is, an NRS pain score alone does not trigger rescue medication administration.

If the patient reports pain spontaneously and requests analgesia at an unscheduled time (i.e., PRN), an NRS should be used to record the pain present at that time. This unscheduled NRS must be recorded just prior to administration of any PRN analgesia, i.e., within 5 minutes prior to any PRN IV analgesic treatment and within 15 minutes prior to any PRN oral analgesic treatment. NRS scores for PRN pain medication will not replace the recording of scheduled NRS scores.

Medication for moderate to severe pain (NRS ≥ 4) will be administered upon request as follows:

From T0 to T25 minutes:

- IV fentanyl 50 mcg, every (Q) 5 minutes for pain NRS ≥ 4

From T26 minutes to PACU discharge:

- IV hydromorphone 0.5 mg, Q 10 minutes for pain NRS ≥ 4
- Note: IV morphine 2.0 mg can be used if IV hydromorphone is not available

After discharge from the PACU, patients are followed through T96 (± 4 h) as inpatients in the inpatient unit where safety and activity/efficacy evaluations will be performed. Patients will be required to meet standard criteria for discharge to outpatient status. Patients will continue to be monitored as outpatients after discharge from the inpatient unit through D29 + 2 days for various safety and efficacy assessments, and later if necessary, for safety follow up.

9.2.5 Outpatient Analgesic Medications

Following discharge from the hospital through the D15 visit, pain will be managed with the following regimen only:

Scheduled medication:

- Celecoxib, 100 mg PO BID (unless contraindicated)

Rescue medications (for pain as needed):

- Acetaminophen, 650 mg PO Q 6 h for mild pain (i.e., NRS < 4) (unless contraindicated)
- Oxycodone, 5 mg – 1 or 2 tablets PO Q 4–6 h for moderate-severe pain (i.e., NRS ≥ 4). Discharge patient with 20 tablets. Use of this rescue medication [time, dose] must be recorded in the diary. Pre-rescue medication NRS for opioids will also be recorded in the diary.

Note:

Instruct patients to use acetaminophen as the initial option for treating pain up to a total daily dose of 4,000 mg.

Document the number of opioid tablets prescribed and also document any additional prescriptions required if the patient's pain continues to be an issue requiring additional opioid medication.

Following D15, pain will be managed per institutional guidelines and standards of care. Pain medication use will be recorded as a concomitant medication from D15 through D29.

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 visit occurs, the Investigator should use clinical discretion regarding the adequacy of analgesic treatment, capture this occurrence as an AE, and document any required treatments.

9.3 Method of Assigning Patients to Treatment Groups

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

Patients who have provided written informed consent will be assigned a unique number in the screening process. This number will be used to identify the patient throughout the study.

Patients in Parts B and C will be randomized in a ratio of 1:1, active to placebo, in a blocked randomization of 4 patients, so that successive groups of patients will include 2 patients receiving active drug and 2 patients receiving placebo.

Treatment assignments will be determined by a computer-generated randomization schedule. Once any patient number or randomization number is assigned, it cannot be reassigned to any other patient.

Patients 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 for Part B and Part C will be double-blinded during the study. The patient, investigational site personnel except for the unblinded pharmacist, Sponsor, and Sponsor designees directly involved in the conduct and/or monitoring of this study will not be aware of patients' treatment group assignments. Note that the placebo is identical in appearance to CA-008 once reconstituted.

Under normal circumstances, unless consistent with the protocol, 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 patient'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 assignment is prematurely unblinded, the reason, date and time of the unblinding, and the individual who broke the blind must be documented.

It is assumed that the need to unblind a study patient's treatment assignment will occur in the setting of a 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, OTC, or herbal therapies, used by the patient will be documented for the 30 days prior to screening (prior medications), during screening, and throughout the study (concomitant medications). The Investigator will determine if the prior/concomitant medication(s) affect the patient's eligibility to participate or continue to participate in the study.

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

Within the 7 days prior to the planned surgery, antibiotics for an infection are permitted for ophthalmic use or for treatment or prophylaxis of post-operative surgical site infections. At the Investigator's discretion, agents intended for deep venous thrombosis (DVT) prophylaxis after the surgery are allowed.

On a case-by-case basis, the Investigator is permitted to allow the use of some concomitant medications, for example to treat an AE, if the Investigator determines that the medication will not affect the patient'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, 9.2, 9.5, and 10.1.2 the patient 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:

Patients will be asked to abstain from consuming more than 1 (women) or 2 drinks (men) per day of alcohol

Patients will be asked to abstain from illicit drug use or non-medical use of therapeutic drugs (See Section 10.3.13)

Patients will be asked to abstain from taking prohibited medications

9.7 Treatment Compliance

Because all study medication is being administered by study personnel, no patient compliance procedures are necessary. Potential diversion of controlled opioid medication 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 Prior to Surgery):

Patients will be screened for participation at the study within 45 days of surgery/study drug administration. The following will be completed at least 1 day prior to surgery:

Informed consent;

Inclusion/exclusion criteria evaluation;

Demographics;

Medical and surgical history;

Prior/current medications;

Complete PE (without a breast, genital, or rectal examination), including height and weight;

Vital signs - heart rate (HR), blood pressure (BP), respiratory rate (RR), O_2 saturation (SpO_2) in the supine position, and temperature (oral) (Section 17.3, Appendix C);

Baseline neurosensory exam;

Clinical laboratory tests (Section 17.4, Appendix D):

- Hematology/Coagulation: hemoglobin, hematocrit, white blood cell count with differential, red blood cell (RBC) count, platelet count, activated partial thromboplastin time (aPTT), and prothrombin time (PT) or international normalization ratio (INR).
- Blood Chemistry: including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (Tot. Bili), gamma-glutamyl transferase (GGT), albumin, blood urea nitrogen (BUN), creatinine, alkaline phosphatase (ALK), sodium, potassium, calcium, chloride, and glucose.

Urine drug screening;

Alcohol breath/saliva test;

Serum pregnancy test (FCBP), if applicable, (unless post-menopausal status confirmed by FSH);

12-lead ECG;

Patient reported outcomes (PROs; Section 10.3.9 and Section 10.3.10)

- Patient Reported Outcomes Measurement Information System (PROMIS) 10 Global Health questionnaire (Section 17.6, Appendix F)

- Activity Assessment Scale (AAS) (Section 17.7, Appendix G)

Patient pain assessment training;

AE assessment (record any current conditions as medical history);

10.1.2 Surgery Phase: Admission to Unit for Surgery (Baseline) to End of Surgery

10.1.2.1 Admission to Site Unit (D1) Prior to Surgery

Patients 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 for surgery within 45 days of screening. The following will be performed on D1 prior to surgery:

Confirm informed consent;

Review of inclusion/exclusion criteria;

Review medical and surgical history since screening;

Review prior and current concomitant medications;

Interim targeted PE

Urine pregnancy test (FCBP), if applicable, (unless post-menopausal status confirmed by FSH), usually to be done within 24 hours prior to surgery;

Urine drug screen;

Alcohol breath/saliva test;

Patient pain assessment training, patient to watch pain training video;

Blood draws for PK analyses (See Section 10.1.4 for timing);

Vital signs - HR, BP, RR (supine), and temperature (oral);

Randomize the patient to treatment after confirmation of patient's continued eligibility;

AE assessment (record any current conditions as medical history);

Patients will be asked to abstain from foods containing capsaicin for 24 hours prior to their surgery.

10.1.2.2 Anesthesia and Surgery (D1)

The surgery will be performed under general anesthesia:

Inhaled anesthetic or propofol infusion with or without nitrous oxide (N_2O).

Adequate optional premedication typically with midazolam (up to 5 mg) and fentanyl (up to 100 mcg).

Supplemental anesthesia and sedation will be per institutional guidelines.

Intra-operative titration of intravenous (IV) fentanyl, including during emergence, will be per institutional guidelines.

12-lead Holter monitors will be placed prior to surgery and record for 24 hours to assess for effects on the QT interval in a subset of patients in Part B.

In addition, patients will receive bupivacaine 175 mg delivered as follows:

Prior to start of surgery under ultrasound guidance:

- Bupivacaine 0.25%, 30 mL (75 mg) diluted with 10 mL of normal saline to a volume of 40 mL delivered a rectus block with 20 mL on each side.

  Note: In Part A, the adequacy of the anesthetic regimen is part of the assessment of the technique feasibility. If patients report excessive pain during the immediate postoperative period, a TAP block may be added or may replace the rectus sheath block, but the total dose of bupivacaine will not exceed 175 mg.

Immediately before/after surgical incision:

- PART A: BupiHCl 0.25%, 40 mL (100 mg), may be diluted in up to 110 mL of normal saline to a total volume of not more than 150 mL: Infiltration of abdominal wall, anterior rectus abdominis sheath, posterior rectus abdominis sheath, other fascia, peritoneum (including circumferential areas of intended mesh placement)
- PARTS B and C: BupiHCl 0.25%, 40 mL (100 mg), which should be diluted in 40 mL of normal saline to a total volume of 80 mL: Infiltration of abdominal wall, anterior rectus abdominis sheath, posterior rectus abdominis sheath, other fascia, peritoneum (including circumferential areas of intended mesh placement)

Standard supplemental anesthetic and perioperative care will be provided per institutional guidelines. This will typically include (but not be limited to) steps to ensure preservation of intraoperative normothermia (including the use of preoperative and intraoperative forced-air warming) and deep venous thrombosis prophylaxis.

10.1.3 Surgery Phase: Administration of Study Medication into the Surgical Site

Study treatment is to be administered intraoperatively as a single administration via infiltration/instillation into the “surgical site” prior to wound closure.

In general, the intent is to deliver local anesthetic into the surgical site “on the way in” (upon adequate exposure of and prior to incision/dissection of target tissues). Conversely, study drug (active or placebo) delivery to the same and other areas will be administered by infiltration (injected) and/or instillation/irrigation (dripped) to the surgical site “on the way out” (prior to and at the time of surgical closure).

The "surgical site" is defined as the area extending approximately at least 2–3 cm in all directions (lateral/medial/proximal/distal/deep) from the margins of substantially all tissue traumatized by the surgical procedure, i.e., all tissue dissected, cut, electrocauterized (bovied), sutured or tacked, including both deep and superficial areas. The surgical site will include the full area of surgical mesh placement.

If laparoscopic assistance is used, study drug may also be delivered to the site of the laparoscopic incisions requiring surgical closure.

Note: The technique for all tissue infiltration described below should include multiple microinjections. The needle may be inserted deeply at first and as the needle is withdrawn, the study drug can be injected slowly along the needle track. The objective is to distribute the study drug widely in the surgical site where TRPV1 receptor targets are located and not in a single, deep depot injection to act as a conduction block in intact nerves. The intent is that all tissue traumatized by the surgical procedure should be exposed to study drug.

Note: If after the surgery is underway, it becomes evident that the surgical mesh must be placed intra-peritoneally (i.e., IPOM technique), then the patient will not receive study drug. In Parts B and C, this patient would be considered randomized but not treated.

The total study drug volume administered per patient will be 50 mL in Part A and 80 mL in Parts B and C, delivered during the surgical procedure in divided aliquots. Modifications to the delivery technique for subsequent patients may occur based on information from prior patients. In fact, the purpose of Part A is to optimize the delivery technique and allocation of study drug for use in Parts B and C.

Study drug will be delivered to (a) the midline deep, peritoneum layer which includes the closure of the peritoneal sac, (b) the mesh layer which includes both the dorsal and ventral aspects of the space created by the surgeon to accommodate placement of the surgical mesh, whether this space is anterior or posterior to the posterior rectus fascia and (c) the anterior fascia layer which includes the closure of the anterior rectus fascia and linea alba. In addition, a small amount of study drug will be delivered to laparoscopic portals requiring suture closure.

The initial allocation and general approach to dosing will be as follows, though minor modifications are permissible based on surgeon judgment and experience with earlier patients in the trial:

Deep midline/peritoneal layer – up to approximately 25% of the total volume:

Infiltrate or instill 10 mL (Part A) or approximately 10 mL (Parts B and C), approximately half the volume per side, into the deep midline area where closure of the peritoneal sac has been completed, along with the posterior rectus sheath if not separated from (peeled off) the peritoneum. Use multiple, micro-injections to distribute study drug widely along the closure. Ensure that all dissected, resected and sutured areas of the peritoneum (and posterior rectus sheath) are exposed to study drug.

Note: Laparoscopic visualization can be used to ensure that induration of the peritoneum confirms targeted delivery of study drug.

Mesh/fascia layer – at least approximately 50% of the total volume:

The mesh layer includes the space created by dissection for placement of the surgical mesh. It can be in-between the peritoneum and the posterior rectus fascia or in-between the posterior rectus fascia and the rectus abdominis muscle. In either case, the intent is to deliver sufficient study drug to both the posterior (dorsal) and anterior (ventral) aspects of the space created for the mesh, including all tissues that will be in contact with the mesh after placement as well as the perimeter area around the mesh itself.

The following is a general description of the delivery of study drug to the mesh/fascia layer and is a guide for the surgeon. The actual delivery technique may vary based on the individual patient anatomy encountered by the surgeon.

Part A:

Using micro-injections, infiltrate ~10 mL (Part A) into the posterior surface of the mesh layer space where the mesh will be placed on both sides of the midline peritoneal closure. Ensure that any areas where mesh fixation with sutures or tacks are to be placed are exposed to study drug.

Instill (drip/irrigate) ~5 mL (Part A) onto the posterior surface of the mesh layer space where the mesh will be placed. Instill about half the volume (~2.5 mL) at first using a finger to spread it around to the entire area followed 2–3 minutes later by the remaining volume (~2.5 mL).

Using micro-injections, infiltrate ~7.5 mL (Part A) into the circumferential perimeter, i.e., edges, of the mesh space, e.g., where the peritoneum and posterior rectus fascia remain attached.

An additional ~7.5 mL (Part A) should be delivered to the anterior surface of the mesh layer space where the mesh will be placed on both sides of the intended midline closure. If the mesh space is in-between the peritoneum and posterior rectus fascia, then this volume should be delivered to the posterior rectus fascia by micro-injections. If the mesh space is in-between the rectus abdominis muscle and the posterior rectus fascia, then this volume should be delivered by instillation using a finger to spread it around to the entire area. Instill about half this volume at first using a finger to spread it around to the entire area followed 2-3 minutes later by the remaining half.

Part B:

Using micro-injections, and instillation (drip/irrigation) wherever appropriate and feasible to ensure maximum exposure, infiltrate ~30 mL into each side of the mesh/fascia layer. Depending on the placement of the mesh, this should include (a) the posterior surface of the mesh layer (preperitoneal/fascia layer), (b) the circumferential perimeter of the mesh space, i.e., edges of the mesh space, e.g., where the peritoneum and posterior rectus fascia remain

attached, (c) any areas of mesh fixation with sutures or tacks and (d) the anterior surface of the mesh layer space (retromuscular/fascia layer).

Anterior layer – up to approximately 25% of the total volume:

Infiltrate 10 mL (Part A) or approximately 10 mL (Parts B and C) into the primary closure of the anterior rectus sheath and linea alba, divide equally on each side.

Laparoscopy ports – Up to 5 mL:

If a laparoscopy port(s) will require a suture closure, then infiltrate ~2–5 mL from the anterior layer allocation into the deeper tissues of the port (1-2 mL per port) prior to closure using study drug from the volume allocated to the anterior layer.

Minor modifications to study drug dosing will be described in the study Pharmacy Manual and patient-specific dosing memos but the general approach will not change substantively.

10.1.4 Postsurgery: T0 (Admission into the PACU) to T96 (Discharge)

Following surgery, patients will be transferred to the PACU where they will undergo an assessment of safety and efficacy over the next 90 minutes. After discharge from the PACU, patients are followed through T96 (± 4 h) as inpatients in the inpatient unit where safety and activity/efficacy evaluations will be performed. T0 is the time of admission into the PACU (as recorded in notes by the PACU nurse).

The schedule of assessments is as follows:

If the patient reports pain spontaneously and requests analgesia at an unscheduled time (i.e., PRN), an NRS should be used to record the pain present at that time. This unscheduled NRS must be recorded just prior to administration of any PRN analgesia, i.e., within 5 minutes prior to any PRN IV analgesic treatment and within 15 minutes prior to any PRN oral analgesic treatment. NRS scores for PRN pain medication will not replace the recording of scheduled NRS scores.

Medication for moderate to severe pain (NRS ≥ 4) will be administered upon request as follows:

- From T0 to T25 minutes:
  - IV fentanyl 50 mcg, Q 5 minutes for pain NRS ≥ 4
- From T26 minutes to PACU discharge:
  - IV hydromorphone 0.5 mg, Q 10 minutes for pain NRS ≥ 4
  - Note: IV morphine 2.0 mg can be used if IV hydromorphone is not available

Pain intensity (assessed with NRS):

- During the inpatient stay, NRS at rest beginning with the PACU admission (T0) may be assessed once the patient is awake. Obtain NRS scores at T0 plus 1 hour (T1), T0 plus 2 hours (T2), T4, T6, T8, T12, T16, T20, T24, and every 4 hours

thereafter (if awake at time of assessment) until discharge from the inpatient unit. Time windows: ± 5 minutes for T1 and T2; ± 15 minutes for T4 onward. Scheduled NRS scores must be recorded regardless of timing of pre-rescue medication NRS scores and administration of rescue medication. The actual time of all NRS scores, i.e., scheduled and pre-rescue, must be recorded, i.e., not the nominal time.

- During the inpatient stay, as soon as feasible, obtain evoked NRS twice daily after 3 maneuvers: (a) coughing 3 times, and (b) sitting up from the supine position into a standardized position (both legs dangling on the side of the bed), and (c) ambulation for approximately 10 yards (30 feet). Obtain these NRS scores in the morning at 10:00 AM (± 1 h) and in the afternoon at 4:00 PM (± 1 h).
- During the inpatient stay, pain scores may be skipped between the hours of midnight and 6:00 AM, but the patient may not miss two consecutive assessments. The T12, T24, T48, T72, and T96 assessments must be completed even if the patient must be awakened at these times.

Vital signs - HR, BP, RR (supine), SpO_2 and temperature (oral) - are assessed together postsurgery at T1, T2, T6, T12, and T24, and every 12 hours thereafter until T96. Assessments between the hours of 12:00 AM and 6:00 AM may be skipped if the patient is sleeping; however, two consecutive assessments may not be skipped. The allowable window is ± 5 minutes for the first 4 hours postsurgery, and ± 15 minutes for all other times.

Targeted PE: T96 (± 4 h) and prior to discharge from the inpatient unit.

12-lead ECG: T24 (± 2 h).

Surgical site assessment: T96 (± 4 h) prior to discharge from the inpatient unit (Section 17.10, Appendix J). If the Investigator determines 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 (Section 17.11, Appendix K). A digital photograph of the wound site should be taken if the patient has consented.

Neurosensory testing of the surgical area near the incision will be performed at T96 (± 4 h) prior to discharge from the inpatient unit.

- 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.
- Sensory deficits or clinically significant persistent sensory change beyond the area proximal/distal to the incision at time of discharge, such as allodynia or hyperalgesia, must be designated as a neurologic AE. Patients will be followed until there is a return to baseline or establishment of a new baseline.

Clinical laboratory tests T48 (± 4 h):

- Hematology/Coagulation: hemoglobin, hematocrit, white blood cell count with differential, RBC count, platelet count, aPTT, and PT or INR.

- Blood Chemistry: including ALT, AST, Tot. Bili, GGT, albumin, BUN, creatinine, ALK, sodium, potassium, calcium, chloride, and glucose.

Blood draw for PK analysis postsurgery and at T24. The time points for whole blood collection will be at pre-dose at pharmacokinetic time (PKT) 0 (Pre-IP dose, 2–10 minutes prior to the first study treatment instillation), 0.03 h (2 min), 0.083 h (5 min), 0.167 h (10 min), 0.25 h (15 min), 0.33 h (20 min), 0.5 h (30 min), 0.75 h (45 min), and at 1, 1.5, 2, 4, 8, 12, 16, 24, 36 and 48 hours after the first PK study treatment instillation (total of 18 samples). In the event of a SAE or severe TEAE, an unscheduled PK draw will be performed whenever feasible. The actual time of collection will be recorded and used in any analysis. Out-of-window collections will not be considered protocol deviations.

Record rescue medication consumption and concomitant medications throughout the inpatient period.

Record AEs throughout the inpatient period (Section 17.1, Appendix A may be useful to the Investigator for assessing systemic [general] AEs).

PBOMs at T48 and at T96 (± 4 h) (Section 10.3.10):

- Sit to Stand Test (also known as 30-Second Chair Stand) Assessment (Section 17.8, Appendix H);
- Timed Up and Go (TUG) Test (Section 17.9, Appendix I).

PROs at T48 and at T96 (± 4 h) (Section 10.3.9 and Section 10.3.10):

- PROMIS 10 Global Health questionnaire (Section 17.6, Appendix F)
- Activity Assessment Scale (AAS) (Section 17.7, Appendix G)

After completing the assessments through T96, the diary for at-home use will be reviewed and patients will be discharged from the study center with the diary to record pain assessments and pain medication at home. Patients will be provided routine standard of care for pain management after discharge from the study center.

Patients will be given a prescription for 20 tablets of oxycodone 5 mg one or two tablets PO Q 4–6 h PRN for moderate-severe pain (i.e., NRS 5–10).

Patients will be instructed to return to the study center on D8 (+ 1 day) for follow-up assessments.

10.1.5 Outpatient Phase: T96 (after Discharge) through D15

After discharge at T96 (± 4 h) and through D15, patients will assess their pain intensity in their diary.

Instruct patients to document their NRS scores twice daily at 11:00 AM (± 1 h) and 7:00 PM (± 1 h) (a) at rest, (b) after coughing 3 times, (c) after sitting up from the supine position into a standardized position (both legs dangling on the side of the bed), and (d) during ambulation

for approximately 10 yards. Note that the actual time of these assessments must be documented in the diary. Instruct patients to:

- Obtain the morning NRS assessment;
- Obtain the evening NRS assessment;

Opioid and non-opioid rescue medication (dose, date, time) must be recorded through D15, including a pre-rescue NRS score. If entered in the electronic diary, the timing of the additional NRS assessment will be assumed to be coincident with the use of rescue medication. If not entered in the electronic diary, the additional NRS assessment should be within 15 minutes prior to use of rescue medication to be used for imputation.

Patients will return to the study center on D8 (+ 1 day) and Day 15 (+ 2 days) for the following assessments:

Patient home diary review (pain intensity [NRS score] and pain medication; Section 10.3.8);

Vital signs - HR, BP, RR (supine), SpO_2 and temperature (oral);

Targeted PE;

Surgical site assessment (Section 17.10, Appendix J): If the Investigator determines 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 (Section 17.11, Appendix K). A digital photograph of the wound site should be taken if the patient has consented;

Neurosensory testing of the surgical area near the incision. This evaluation will include the details described in Section 17.12, Appendix L:

- 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 the surgery.
- Sensory deficits or clinically significant persistent sensory change beyond the area proximal/distal to the incision at time of discharge, such as allodynia or hyperalgesia, must be designated as a neurologic AE. Patients will be followed until there is a 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.

PBOMs (Section 10.3.10);

- Sit to Stand Test (also known as 30-Second Chair Stand) Assessment (Section 17.8, Appendix H);
- TUG Test (Section 17.9, Appendix I).

PROs: (Section 10.3.9and Section 10.3.10):

- PROMIS 10 Global Health questionnaire (Section 17.6, Appendix F)
- Activity Assessment Scale (AAS) (Section 17.7, Appendix G)

Concomitant medication use/concomitant treatments;

AE assessment.

10.1.6 Outpatient Phase: D29

Patients will return to the study center on D29 (+ 2 days), or at the time of discontinuation, for the following assessments:

Vital signs - HR, BP, RR (supine), SpO_2 and temperature (oral);

Targeted PE;

Surgical site assessment (Section 17.10 Appendix J): If the Investigator determines 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 (Section 17.11, Appendix K). A digital photograph of the wound site should be taken if the patient has consented;

Neurosensory testing of the surgical area near the incision. This evaluation will include the details described in Section 17.12, Appendix L:

- 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 the surgery.
- Sensory deficits or clinically significant persistent sensory change beyond the area proximal/distal to the incision at time of discharge, such as allodynia or hyperalgesia, must be designated as a neurologic AE. Patients will be followed until there is a 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.

PBOMs: (Section 10.3.10):

- Sit to Stand Test Assessment (Section 17.8, Appendix H);
- TUG Test (Section 17.9, Appendix I).

PROs: (Section 10.3.9 and Section 10.3.10):

- PROMIS 10 Global Health questionnaire (Section 17.6, Appendix F)
- Activity Assessment Scale (AAS) (Section 17.7, Appendix G)

Concomitant medication use/concomitant treatments;

AE assessment.

10.1.7 Early Termination

If prior to D15 visit, patients will return for the following assessments:

Patient home diary review (pain intensity [NRS] and pain medication) (Section 10.3.8);

Vital signs - HR, BP, RR (supine), SpO_2 and temperature (oral);

Targeted PE;

Surgical site assessment (if the Investigator determines there are atypical wound healing or visible abnormal findings, a digital photograph of the wound site should be taken if the patient has consented; Section 17.10, Appendix J);

Neurosensory testing of the surgical area (Section 10.3.18);

PBOMs;

Concomitant medication use/concomitant treatments;

AE assessment.

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

Surgical site assessment (if the Investigator determines there are atypical wound healing or visible abnormal findings, a digital photograph of the wound site should be taken if the patient has consented; Section 17.10, Appendix J);

Neurosensory testing of the surgical area (Section 10.3.18);

PBOMs (Section 10.3.10),

Concomitant medication use/concomitant treatments;

AE assessment.

If after D29 visit, the Investigator has clinical discretion as to what assessments are to be completed 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 photograph of the wound site should be taken if the patient has consented; Section 17.10, Appendix J);

Neurosensory testing of the surgical area (Section 10.3.18);

Concomitant medication use/concomitant treatments;

AE assessment.

10.1.8 Unscheduled Visit

Unscheduled visits may occur at any time and assessments are to be completed at the Investigator's discretion based on the reason for the visit and entered into the electronic data capture (EDC). At a minimum, the following should be performed:

Vital signs - HR, BP, RR (supine), SpO_2 and temperature (oral);

Targeted PE;

Surgical site assessment: If the Investigator determines there are atypical wound healing or visible abnormal findings, a digital photograph of the wound site should be taken if the patient has consented; Section 17.10, Appendix J);

Neurosensory testing of the surgical area (Section 10.3.18);

AE assessment.

10.2 Patient Completion and Withdrawal

10.2.1 Patient Completion

A patient is considered to have completed the study once all end-of-study assessments are completed at D29 (+ 2 days), or at the last visit upon early termination of the study.

10.2.2 Patient Withdrawal

If a patient still requires IV opioid rescue after T12, then the patient will revert to IV analgesia management per institutional standard-of-care but will continue serial NRS, activity/efficacy and safety assessments. These patients will still be evaluated for pain and safety assessments as described in the Statistical Analysis Plan.

A patient is free to withdraw his/her consent and discontinue participation in the study at any time for any reason. A patient's participation must therefore be terminated immediately upon his/her request, and the reason(s) for discontinuation appropriately documented. Patients who elect to discontinue participation prior to D8 will be considered to have terminated as of the date of their election however, they will be asked to return to the site one time to ensure that adequate wound healing has occurred

The degree to which a patient withdraws can vary, and efforts will be made to collect important safety data whenever feasible and if the patient agrees. Patients can:

Withdraw from activity/efficacy assessments but agree to participate in all study safety assessments;

Withdraw from activity/efficacy assessments but agree to participate in limited study safety assessments;

Withdraw from study activity/efficacy and safety assessments. In this case, patients should still return for a surgical follow-up assessment of wound healing.

A patient 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);
- Patient is lost to follow-up;
- Patient treatment allocation is unblinded (i.e., individual code break; Section 9.4);
- Death of patient.

A patient may also be discontinued from the study, at the discretion of the Investigator and/or Sponsor, for any of the following reasons:

- Patient 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 patient to continue;
- Administrative reasons (e.g., termination of enrollment or study).

The Investigator must maintain a record of all patients who discontinue from the study prior to completion; the reason(s) for study discontinuation will be documented. If a patient 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 patient is not obligated to provide such a reason.

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 patient by the Investigator or designated study personnel. The patient must voluntarily provide written informed consent on an IRB-approved ICF, prior to performing any study-related procedures. The patient's source records must document that the consent process has been completed and that written informed consent has been obtained from the patient prior to the initiation of any study-specific procedures. Documentation that the patient 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 patient should also be included in the medical records or clinical chart.

10.3.2 Demographics

The following demographic data 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 impact on study eligibility.

10.3.4 Medication History

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

10.3.5 Contraceptive Requirements

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

Female patients 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 patient 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 with an FSH > 40 mIU/mL (or FSH above the relevant laboratory value for post-menopausal status) confirmed during screening.

Male patients, unless in a relationship with 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 study participation.

10.3.6 Patient Pain Assessment Training

Patients 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, patients 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 pain imaginable) (Section 17.5, Appendix E).

Patients will report or record the intensity of their current pain at designated times during the study after administration of study treatment. Patients should be at rest for at least 5–10 minutes prior to completing NRS resting assessment.

During the inpatient stay, NRS at rest beginning with the PACU admission may be assessed once the patient is awake. T0 is the time of admission into the PACU (as recorded in notes by the PACU nurse). Obtain NRS scores at T0 plus 1 hour (T1), T0 plus 2 hours (T2), T4, T6, T8, T12, T16, T20, T24, and every 4 hours thereafter (if awake at time of assessment) until discharge from the inpatient unit. Time windows: ± 5 minutes for T1 and T2; ± 15 minutes for T4 onward. Scheduled NRS scores must be recorded regardless of timing of pre-rescue medication NRS scores and administration of rescue medication. The actual time of all NRS scores, i.e., scheduled and pre-rescue, must be recorded, i.e., not the nominal time.

During the inpatient stay, as soon as feasible, obtain evoked NRS twice daily after: (a) coughing 3 times, and (b) sitting up from the supine position into a standardized position (both legs dangling on the side of the bed), and (c) ambulation for approximately 10 yards (30 feet). Obtain these NRS scores in the morning at 10:00 AM (± 1 h) and in the afternoon at 4:00 PM (± 1 h).

During the inpatient stay, pain scores may be skipped between the hours of 12:00 AM (midnight) and 6:00 AM, but the patient may not miss two consecutive assessments. The T12, T24, T48, T72, and T96 assessments must be completed even if the patient must be awakened at these times.

During the inpatient stay, an additional NRS assessment must be obtained within 5 minutes prior to IV rescue medication administration and within 15 minutes prior to oral rescue medication administration.

During the outpatient period (after T96 and through D15), instruct the patient to document their NRS scores twice daily at 11:00 AM (± 1 h) and 7:00 PM (± 1 h) (a) at rest, (b) after coughing 3 times, (c) after sitting up from the supine position into a standardized position (both legs dangling on the side of the bed), and (d) during ambulation for approximately 10 yards. Note that the actual time of these assessments must be documented in the electronic diary. Instruct the patient to:

- Obtain the morning NRS assessments;
- Obtain the evening NRS assessments;
- Opioid and non-opioid rescue medication (dose, date, time) must be recorded in the diary through D15, including a pre-rescue NRS score. If entered in the electronic diary, the timing of the additional NRS assessment will be assumed to be coincident with the use of rescue medication. If not entered in the electronic diary, the additional NRS assessment should be within 15 minutes prior to use of rescue medication to be used for imputation.

10.3.9 Patient-Reported Outcomes

Patients will complete the PROs at Screening, T48, T96, D8, D15, and D29. These questionnaires include:

PROMIS 10 Global Health questionnaire (Section 17.6, Appendix F)

Activity Assessment Scale (Section 17.7, Appendix G)

10.3.10 Performance-Based Outcome Measures (PBOMs)

Patients will undergo PBOMs at T48, T96 (± 4 h)/Discharge, D8, D15, and D29. These measures include:

Sit to Stand Test Assessment (Section 17.8, Appendix H);

TUG Test (Section 17.9, Appendix I).

10.3.11 Rescue Medications

The details of rescue analgesic medication (specific drugs, doses, dates, and times) will be recorded during the inpatient period beginning from the end of surgery through the outpatient period to D15 (+ 2 days) visit or to the Early Termination Visit, if applicable. Patients will be instructed on the proper use and timing of rescue medication.

The statistician will use a standard conversion table to calculate the oral morphine equivalent (OME) dose of various opioids (see the Statistical Analysis Plan [SAP] for further details).

Total opioid consumption (OC) and daily opioid (rescue medication) consumption in OMEs will be calculated during the inpatient period and up to the D15 visit.

Document daily use of OTC analgesics (and oxycodone if prescribed) during the outpatient period through D15.

Document each opioid prescription provided to the patient and the number of and type of tablets provided to the patient for site records and reconciliation.

10.3.12 Clinical Laboratory Assessments

All protocol-specified laboratory tests on blood samples will be collected, processed, shipped, and analyzed according to instructions from a selected central laboratory. The laboratory 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 laboratory reports expeditiously to document appropriate safety monitoring of study patients. The Investigator should sign and date each laboratory report concurrent with her or his review. The Investigator should exercise medical and scientific judgment in deciding whether abnormal laboratory values are clinically significant or not and should indicate the clinical significance

of each abnormal/flagged value by noting "NCS" (not clinically significant) or "CS" (clinically significant). All clinically significant values will be recorded in the eCRF and followed until resolution. 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, and chemistry assessments are listed in Table 20.

Table 20 Clinical Laboratory Assessments

Hematology	**Chemistry**
Hematocrit Hemoglobin Red blood cell (RBC) count Total and differential (absolute) white blood cell count Platelet count	Sodium Potassium Calcium Chloride Glucose Creatinine Blood urea nitrogen (BUN) Albumin Total bilirubin (Tot. Bili) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Gamma-glutamyl transferase (GGT) Alkaline phosphatase (ALK)
Coagulation	
Activated partial thromboplastin time (aPTT) Prothrombin time (PT) / International normalized ratio (INR)	
Endocrinology Follicle stimulating hormone (FSH), as appropriate	

The clinical laboratory tests will be completed per the Schedule of Assessments (Table 1). In addition to the clinical laboratory tests, a serum pregnancy test (β-hCG) will be performed at the Screening Visit and a urine pregnancy test will be performed prior to surgery for females of childbearing potential.

ALT or AST > 3 × upper limit of normal (ULN), Tot. Bili > 2 × ULN, and ALK > 2 × ULN will be considered an AE, as well as any other changes deemed clinically significant by the Investigator.

10.3.13 Urine Drug Screen and Alcohol Test

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

The drug and alcohol screens will be performed in-house at the inpatient unit. If any of these tests are positive, except as indicated below, the patient will not be allowed further participation in the trial. However, a positive test may be repeated at the discretion of the Investigator.

In the case of a urine drug screen at screening that is positive for THC, if the patient is willing to abstain from use or consumption of THC-containing products from 7 days prior to surgery until the Day 15 visit, they may be allowed to participate in the study. In this case, a urine drug screen positive for THC at check-in will not exclude the patient.

If other positive urine drug screen results can be explained by a current prescription or acceptable OTC medication (that does not otherwise exclude the patient as determined by the Investigator), then the patient may continue to participate in the study.

10.3.14 Vital Signs

Vital signs (supine) will consist of HR, BP, RR, SpO_2 and temperature (oral) following a rest period. Vital signs will be assessed per the Schedule Assessments (Table 1). One missed assessment between 12:00 AM and 6:00 AM will not be considered a protocol deviation. Two missed assessments of vital signs in a row is a protocol deviation. The allowable window is ± 5 minutes for the first 4 hours postsurgery, and ± 15 minutes for all other times.

10.3.15 Electrocardiogram

10.3.15.1 12-Lead Electrocardiogram

All 12-lead ECGs will be performed per the Schedule of Assessments (Table 1) after the patient 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 QTcF, clinically significant prolongation of QTcF should be > 450 ms for male patients and > 470 ms for female patients or an increase of QTcF of 30 ms or greater (compared to the pre surgical ECG), as well as any other changes deemed by the Investigator as significant. Clinically significant changes in ECG will be considered an AE.

10.3.15.2 12-lead Holter Monitor

12-lead Holter monitors will be placed prior to surgery and record for 24 hours to assess for effects on the QT interval and correlation with PK levels in a subset of at least 12 patients per randomized arm in Part B.

10.3.16 Physical Examination

A complete PE including all major body systems (general appearance, head, eye, ear, nose, throat (HEENT), neck, neurologic, cardiovascular, lungs, abdomen, skin, extremities, lymph

nodes, and musculoskeletal systems but without a breast, genital or rectal examination) 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 (see Table 1).

Body weight (kg), in indoor clothing, but without shoes, will be measured at Screening and at T96. Height in centimeters (cm) will be measured, and body mass index (BMI) will be calculated at Screening only. BMI shall be calculated as kg/m^2. The site should use the National Institute of Health (NIH) website BMI calculator (available at: http://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi-m.htm).

10.3.17 Surgical Site Assessment

The surgical site should be assessed per the Schedule of Assessments (Table 1) 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 (010) where a score of 0 is "Completely unsatisfied," and a score of 10 is "Completely satisfied" (Section 17.10, Appendix J). Assessments will also be performed at each of the follow-up visits or at the time of early discontinuation. Insufficient wound healing that is clinically significant should be recorded as an AE. A follow-up visit will be scheduled after the D29 visit if the Investigator observes insufficient wound or bone healing or to ensure resolution of an ongoing AE.

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 17.11, Appendix K).

10.3.18 Neurosensory Testing

Neurosensory testing of the skin surrounding the incision (will be conducted per the Schedule of Assessments (Table 1). This evaluation will include the details described in Section 17.12, Appendix L.

> 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. Patients 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.

10.3.19 Assessment of Adverse Events

All SAEs will be documented and followed from the time the patient has signed the ICF until D29 + 2 days after the completion of surgery or later, as necessary. All SAEs and non-serious AEs will be documented and followed from the time of administration of study treatment until D29 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 patient's medical record, unless related to a study-related procedure (such as phlebotomy), in which case it will be recorded as a non-treatment emergent AE. SAEs 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.

10.3.20 Pharmacokinetic Assessments and Samples

Details for the collection and processing of blood samples for measurement of PK (CA-008, capsaicin, and CA-101) are outlined in the Laboratory Manual.

Part A:

PK sampling will be performed on at least 8 patients at a single site.

Part B:

PK sampling will be performed on at least 24 patients receiving blinded study drug, i.e., 12 patients per randomized arm at a single site. All patients undergoing 24-hour Holter ECG recordings should have PK sampling.

There will be no PK sample collection in Part B (unless Holter monitoring is done).

Part C:

No PK sample collection is planned for Part C.

The time points for whole blood collection will be pre-dose at PKT 0 (Pre-IP Dose, 2–10 minutes prior to the first study treatment instillation), 0.03 h (2 min), 0.083 h (5 min), 0.167 h (10 min), 0.25 h (15 min), 0.33 h (20 min), 0.5 h (30 min), 0.75 h (45 min), and at 1, 1.5, 2, 4, 8, 12, 16, 24, 36 and 48 hours after the first study treatment instillation (total of 18 samples).

The PK analysis plan will be documented in the PK Analysis Plan.,

A cQT analysis (PK/PD) analysis will be performed to assess for drug effect on the QT interval. This analysis will be documented in an Analysis Plan.

Note: An unscheduled PK sample should be collected where feasible during the inpatient phase of the study for all patients as part of the evaluation of any SAE or severe TEAE.

10.4 Safety, Tolerability, Pharmacokinetic, and Efficacy Endpoints

10.4.1 Safety Endpoints

Safety endpoints include the following:

Incidence of spontaneously reported TEAEs or serious AEs (SAEs) from study medication administration through D29 or later if necessary:

- TEAEs are defined as AEs occurring post study medication administration
- AEs recorded from the time the ICF is signed up to study medication administration will be recorded in medical history.
- Note: An unscheduled PK sample should be collected where feasible during the inpatient phase of the study for all patients as part of the evaluation of any SAE or severe TEAE.

PE: full PE at Screening (without a breast, genital, or rectal examination). Interim targeted PE on D1 prior to surgery (can be done on the day before surgery if check-in occurs then), T96, and as an outpatient on D8, D15 and D29 (later if necessary).

Vital signs (HR, BP, RR], O_2 saturation [SpO_2]) at screening, D1 prior to surgery, postsurgery T1, T2, T6, T12, and T24, and every 12 hours thereafter until T96 (see Section 10.3.14), and as an outpatient on D8, D15 and D29 or later if necessary. Assess temperature on D1 prior to surgery. Temperature will be recorded daily along with vital signs per site SOPs at 2, 6, 12, 24, and every 12 hours thereafter until discharge from the inpatient facility (if awake at the time of assessment between hours of midnight and 6:00 AM).

Surgical site assessments at T96 prior to discharge from the inpatient unit and then as an outpatient on D8, D15 and D29 (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 will be performed at Screening visit, T96 (prior to discharge from the inpatient unit) and then as an outpatient on D8 and D29.

- Numbness at or near, i.e., within 5 cm of the incision need not be considered a neurologic AE since this could occur because of tissue trauma and inflammation from the surgery. Persistent numbness would meet the criteria for an AE.
- Sensory deficits or clinically significant persistent sensory change beyond the area proximal/distal to the incision at time of discharge, such as allodynia or hyperalgesia, must be designated as a neurologic AE. Patients will be followed until there is a return to baseline or establishment of a new baseline.

12-lead ECGs, and standard clinical laboratory tests at Screening and postsurgery as specified in the Schedule of Assessments (Table 1)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.

12-lead ECG at Screening and T24 (± 2 h)

Clinical laboratory test results

Hematology/Coagulation at Screening and T48 (± 4 h): hemoglobin, hematocrit, white blood cell count with differential, RBC count, platelet count, aPTT, and PT or INR.

- Blood chemistry at screening and T48 (± 4 h) to include at least the following: ALT and AST, Tot Bili, GGT, albumin, BUN, creatinine, ALK, sodium, potassium, calcium, chloride, and glucose.
- Serum and urine pregnancy test for FCBP: βhCG test at screening and urine test usually to be done within 24 hours prior to surgery.
- Note: Safety laboratory assessments may be collected, as appropriate, as part of the evaluation of a SAE or severe TEAE.

In Part B, for at least 24 patients (i.e., 12 in each blinded, randomized arm), 12-lead Holter monitors will be placed prior to surgery and record for 24 hours to assess for effects on the QT interval during study drug administration. Serial PK samples must be drawn in patients undergoing Holter ECG assessments.

10.4.2 Pharmacokinetic Endpoints

Full details of PK will be described in a separate PK Analysis Plan. The time points for whole blood collection are outlined in the Schedule of Assessments (Table 1) and Section 10.3.20.

Plasma concentration for CA-008 and key metabolite(s) (including capsaicin and CA-101) at PK sampling times will be summarized using descriptive statistics, including mean, standard deviation (SD), median, minimum and maximum values, and coefficient of variation (CV%). PK parameters include (but are not limited to) maximum observed plasma drug concentration (C_{max}), time to maximum plasma drug concentration (T_{max}), half-life, and area under the plasma concentration-time curve (PK-AUC). Actual sampling times will be used to calculate plasma-derived PK parameters.

For the cQT analysis, QTc intervals will be matched with plasma concentrations for CA-008, capsaicin, and CA-101 and analyzed to describe the relationship between concentration and QTc using nonlinear mixed effects modeling. Methodologic details and results will be reported separately.

10.4.3 Efficacy Endpoints

10.4.3.1 Primary Efficacy Endpoints for Part A

There are no efficacy endpoints for Part A.

10.4.3.2 Primary Efficacy Endpoints for Part B

There are no efficacy endpoints for Part B.

10.4.3.3 Primary Efficacy Endpoints for Part C

Area under the curve (AUC) of the rest NRS from T0 to T96 (AUC_{0-96}) AUC is the weighted sum of current pain intensity (SPI) assessments for a specified time interval.

10.4.3.4 Key Secondary Efficacy Endpoints for Part C

Evoked pain NRS (three maneuvers): $AUC_{0–96}$

Total opioid consumption (in daily OME) = OC from T0 to T96: OC_{0-96} and from T0 to D8: OC_{0-D8}

Percentage of patients who do not require opioids after discharge (i.e., opioid-free or OF) from T96 to D15: OF_{96-D15}

NRS at rest and evoked NRS (three maneuvers) from T0 to D8: AUC_{0-D8}

10.4.3.5 Exploratory Endpoints for Part C

Using rest NRS: AUC_{12-96}, AUC_{0-48}, AUC_{48-96}, and AUC_{0-D15};

Using evoked (three maneuvers) NRS: AUC_{12-96}, AUC_{0-48}, AUC_{48-96}, and AUC_{0-D15};

Time-specific mean NRS scores at T48, T72, and T96;

Time-specific mean NRS scores daily from D5-D15;

Proportion of patients with NRS ≤ 3 during T0-T96 , T0-48 and T48-96

OC_{12-96}, OC_{24-96}, OC_{0-D8}, and OC_{0-D15};

OF_{0-96}, OF_{0-D15}, OF_{24-96}, OF_{24-D15}, OF_{48-D15}, OF_{72-D15} and OF_{D8-D15}.

Time to cessation of opioid use;

Additional exploratory and sensitivity analyses rest/evoked NRS AUC, OC, and OF during different intervals may be undertaken, e.g., T48-T168, T72-T168;

PRO questionnaire score improvement from Screening to D8, D15, and D29; and from T48 to D8, D15, and D29;

Improvement in PBOMs (Sit to Stand, TUG) from T48 ($\pm$ 4 h), to D5/Discharge, to D8, to D15, and to D29; PBOM difference between groups at T48, T96, D8, D15 and D29;

Total non-opioid analgesic consumption (AC), i.e., rescue acetaminophen use for the indicated time intervals: AC_{96-D8} and AC_{96-D15};

Other endpoints to be defined in the SAP.

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 Harmonisation (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 patient 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.

Since this is a study using a surgical pain model, findings that are "typical" for the surgery should not be captured as an AE. Atypical or worse than typical findings should be captured as AEs.

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 AE.

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
Not Related	Temporal relationship to study treatment administration is missing or implausible, or there is an evident other cause.
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

Causality Category	Description
	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, or severe)

Relationship to study treatment

Action and outcome

Seriousness of event

All SAEs will be documented and followed from the time the patient has signed the ICF until D29 + 2 days after the completion of surgery. All SAEs and non-serious AEs will be documented and followed from the time of administration of study treatment until D29 or later if necessary. AEs that occur between Screening and the administration of study medication should be considered medical history and added to the patient'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. SAEs 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

A 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 patient 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 a SAE when, based upon appropriate medical judgment, the event may jeopardize the patient 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 D29 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 a 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 a 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 patient is receiving study treatment and within 14 days following the study completion visit (or 21 days following an early termination [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 a 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.

The Sponsor's medical monitor is available for questions about safety-related issues or to request waivers to modify post-operative patient care.

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 to obtain resolution or follow-up information.

The site will enter into the electronic database a SAE report, or similar form, that includes the following information, as available:

- Patient 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 17.4, 17.3 and 17.1; Appendices I, J, and K, respectively, 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.

Grade 4 (potentially life-threatening).

11.3 Pregnancy

If a female patient 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 patient 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 a 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 a SAE.

12 DATA QUALITY ASSURANCE

This study will be conducted under Good Clinical Practice (GCP) and all applicable regulatory requirements. In order 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, laboratory results, participant diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc. This study will use EDC. At a minimum, all data required by the protocol should have supporting source documentation for entries in the EDC system.

All eCRFs 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 recorded on the eCRF. 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 EDC system maintains a full audit trail.

12.2 Study Auditing and Monitoring

Monitoring of the study site (including, but not limited to, reviewing eCRFs 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

The statistical methods to be employed in assessing the safety and efficacy of CA-008 in patients undergoing VHR in accordance with this Phase 1/2 study protocol are outlined below. Detailed descriptions of all summaries and analyses to be performed, including all secondary efficacy analyses and all safety analyses, will be provided in a SAP that will be finalized prior to database lock. The SAP will supersede the protocol with respect to the analyses specified.

13.1 Sample Size Justification

In Part A and Part B, no formal statistical hypothesis testing is currently planned. The sample size of 8–12 initial patients in Part A, with the potential for expansion to 16, and 24–32 patients in Part B have been selected empirically based on prior clinical trial experience with CA-008 and is considered sufficient for exploration of feasibility, PK, preliminary efficacy, tolerability and safety parameters.

In Part C, a total of up to ~100 patients will be randomized in 2 parallel arms (1:1) with ~50 patients in each arm to bring the total number of patients enrolled to ~150. Assuming a t-test for the difference in 2 independent means, a sample size of approximately 40 patients per group would provide approximately 80% power to detect a standardized effect size (Cohen's d) of ~0.55 at a one-sided level of significance, alpha, of 0.05 in the primary efficacy endpoint of rest NRS $AUC_{0\text{-}96}$.

In Part C, randomization may be stratified based on the size of the ventral hernia: for example, < 4 cm vs. ≥ 4 cm.

Alternative assumptions concerning the anticipated effect size lead to a different number of patients per group. The total number of patients to be enrolled in the study will not exceed ~150.

13.2 Analysis Populations

The following 6 analysis populations are planned for this study:

Safety Population consists of all patients who received any part of a dose of study treatment. (Note this must include anyone who terminates early for lack of efficacy).

PK Population consists of all patients who received a full dose of study treatment and completed at least one PK assessment.

PK/QT Population for cQT analysis consists of all patients with at least one time point with both PK and QT data.

Modified Intent-to-treat (mITT) Population consists of all patients who received any dose of study treatment. Per Protocol (PP) Population consists of all patients who received a full dose of study treatment and have evaluable NRS pain assessments at least through T96 (± 4 h)/Discharge.

Study Completers consists of all patients who received a full dose of study treatment and completed the entire study period through D29 + 2 days.

Patients who discontinue study participation before or after randomization but prior to receiving study treatment will be replaced.

Patients who are withdrawn or elect to withdraw after receiving study treatment will not be replaced. Those patients who withdraw during the inpatient phase of the study, will be asked to continue with assessments through T96 if they have not elected to withdraw from all aspects of study participation (see Section 10.2). Patients who elect to discontinue participation on or prior to D8 will be considered to have terminated as of the date of their election to discontinue; however, they will be asked to return to the study site one time to ensure that adequate wound healing has occurred (see Section 10.2).

13.3 Planned Analyses

The final data analysis will be performed after all patients have either completed or have been discontinued from the study. Note: If after the surgery is underway, it becomes evident that the surgical mesh must be placed intra-peritoneally (i.e., IPOM technique), then the patient will not receive study drug. In Parts B and C, this patient would be considered randomized but not treated.

The study will be unblinded after patient membership in each of the various analysis populations has been determined at a blinded data review meeting and upon confirmation of database lock.

Any deviations from the analyses presented in the SAP will be detailed in the clinical study report.

Progression from Part A to Part B will take place after a formal safety assessment has been completed showing that the total study drug dose, volume, allocation and technique is acceptably safe and feasible. The formal safety assessment will be conducted by the Sponsor's medical monitor, the CRO medical monitor, the relevant Principal Investigator, and an independent medical monitor.

Progression from Part B to Part C will take place after an ("interim") analysis of unmonitored, unblinded data from Part B occurs including data through Day 15. This analysis will assess preliminarily the safety and tolerability of the active study drug as well as the duration and severity of postsurgical pain in the control group.

Efficacy, PK, and other assessments will be summarized using appropriate descriptive statistics. A detailed methodology for the statistical analyses of the data collected in this study will be documented in the SAP, PK Analysis Plan and cQT Analysis Plan, which will be signed prior to the database lock.

All safety assessments and baseline characteristics will be summarized using the Safety Population. All safety summaries will be grouped by the actual treatment received. Data from all patients receiving vehicle placebo will be combined for summaries.

Safety and tolerability will be evaluated by examining the occurrence of AEs, including TEAEs. AEs leading to discontinuation from the study, AEs related to study treatment, and AEs by severity will be summarized by treatment group.

Actual values 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. Abnormal values will be determined and flagged in the listings. Laboratory shift tables displaying the change (number of patients) 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.

All data recorded in the study database will be included in data listings. Any spurious or erroneous data will be queried and followed up until satisfactorily resolved; if not resolvable, the data will be set to missing.

Summary statistics—number of patients (n), mean, SD, standard error of mean (SEM), (if appropriate), median, minimum, and maximum—will be presented for continuous variables. Frequencies and percentages will be presented for categorical variables. Unless otherwise noted, percentages will be calculated using the total number of patients in the appropriate population and/or subgroup and per treatment group, where applicable. 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, patient, and time point.

Statistical testing including p-values and confidence intervals (CIs) will be presented as described in each section below.

Tests of statistical significance will be 1-sided or 2-sided (as described in the SAP) at the 0.05 level of significance. Because preliminary assessments of efficacy are the focus of efficacy analyses, no adjustments in the level of significance will be made for multiple comparison tests.

13.4 Study Patients and Demographics

13.4.1 Disposition and Withdrawals

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

13.4.2 Protocol Deviations

Protocol deviations will be adjudicated and classified as major or minor during a blinded data review performed by the Sponsor and medical monitor prior to database lock and will be presented in a data listing. Major protocol deviations will be discussed in the Clinical Study Report.

13.4.3 Demographics and Other Baseline Characteristics

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

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

13.4.4 Exposure

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

13.4.5 General Considerations

All analyses will be performed using SAS® version 9.3 or higher. The Clinical Data Interchange Standards Consortium (CDISC) SDTM (Study Data Tabulation Model) domain data sets and the ADaM (Analysis Data Model) analysis data sets employed in generating the tables, figures, and listings (TFLs) specified in the SAP will be provided to the Sponsor along with the generated TFLs. 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 for efficacy measures is the time of admission into the PACU and will be designated by T0.

The timing of PK assessments is based on the time at pre-dose (2-10 minutes prior to the first study treatment instillation) designated PKT = 0.

For safety assessments, TEAEs will be considered those AEs with onset after the beginning of study treatment administration.

Day of surgery/study treatment administration is defined as D1.

Elapsed assessment visit times are defined by time elapsed from T0 or D1.

The baseline value of any parameter is defined as the last valid measurement of that parameter prior to the beginning of study treatment administration.

The change from baseline value of a parameter is defined as the post-baseline value minus the 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. Missing dates will be imputed as described in the SAP.

13.4.6 Analysis of Efficacy Measures

All efficacy endpoints using NRS scores will be summarized over time by cohort and treatment using descriptive statistics including confidence intervals as appropriate.

There are no efficacy endpoints for Part A and Part B.

In Part C, the primary efficacy endpoint is the area under the curve (AUC) for NRS at rest versus time from T0 to T96 ($AUC_{0\text{-}96}$). NRS AUC is the weighted SPI assessments for a specified time interval.

AUC calculations will be done using the standard trapezoidal rule:

$$\mathrm{AUC}_{T_1-T_2} = \sum_{i=1}^{n} \frac{\mathrm{NRS}_{i-1} + \mathrm{NRS}_i}{2}(t_i - t_{i-1})$$

Where NRS_i = NRS at time i, n is the number of minutes between T_1 and T_2, and $(t_i - t_{i-1})$ 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 values will be handled as discussed in the 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.

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

In this study, patients are permitted to take rescue medication for analgesia. It is anticipated that patients randomized to placebo will take rescue medication more often than patients on active treatment. During both inpatient and outpatient portions of the studies, a pre-rescue NRS should be recorded just prior to taking rescue medication, i.e., reflecting the pain level triggering the need for rescue analgesia.

For patients who take rescue medication a windowed last pain score carried forward (wLOCF) will be used in the calculation of the NRS AUC. 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 patient sleeping, etc.) will not be imputed, and AUC will be calculated based on non-missing values.

Sensitivity analyses of the primary efficacy variable using additional methods of imputation for rescue medication may also be performed. Exploratory analyses of the primary efficacy

variable using alternative methods may also be performed, e.g., mixed effects modeling and Silverman Rank Analysis. In addition, exploratory analyses of combined active vs. placebo and high-dose active vs low-dose active may be performed. Information is provided in the SAP.

For secondary continuous efficacy endpoints based on the NRS scores, similar methods as the primary analysis will be used.

13.4.7 Handling of Dropouts or Missing Data

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

Data will be collected regardless of study status or rescue use unless patient withdraws consent or is lost to follow up;

Continue data collection after patients take rescue medication.

With the procedures above, it is expected that the missing data would be minimal and random. Additional sensitivity analyses may be performed to assess the robustness of analysis conclusions, if warranted; details will be presented in the SAP.

For patients who drop out of the study prior to D15 due to lack of efficacy (LOE) or AEs, scheduled assessments may be imputed using worst prior pain score carried forward. For patients who drop out of the study prior to D15, scheduled NRS assessments will first be imputed using the worst prior pain score carried forward (WOCF).

As sensitivity analyses, the NRS AUC may also be calculated where, for each patient, assessments after dropout will be imputed by: (1) using LOCF; (2) using the last scheduled non-missing NRS prior to drop out; (3) the median NRS of the patients continuing in the study who are from the same treatment group as the dropout patients; and (4) without imputation of missing data.

For categorical endpoints, when assessments are to be imputed for data after a patient discontinues from the study, a WOCF method or Worst Case will be used (e.g., for the PROMIS 10 Global, imputed value would be ‘Poor’). Sensitivity analyses using additional methods of imputation may be performed.

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

13.4.8 Analysis of Safety

Analysis of safety will be performed for the Safety population (as defined in Section 13.2).

All safety summaries will be grouped by the actual treatment received. Data from all patients receiving vehicle placebo will be combined for summaries.

Actual values and change from baseline clinical laboratory measures, vital signs, ECGs, PE, surgical site, and neurosensory assessments will be assessed and summarized by treatment group.

No formal statistical comparisons will be performed for safety endpoints.

13.4.8.1 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 D29 or Early Termination, whichever occurs first;

Serious AEs with onset on the date of treatment with the study drug through 30 days after D29 or Early Termination, whichever occurs first;

AEs that start before the start of treatment but increase in severity or relationship at the time of or following the start of treatment through D29 or Early Termination, whichever occurs first.

Safety and tolerability will be evaluated by examining the occurrence of AEs, including TEAEs. AEs leading to discontinuation from the study, AEs related to study treatment, and AEs by the maximum severity will be summarized by treatment group. The number and percentage of patients with TEAEs will be displayed for each treatment group by SOC and preferred term. Additionally, TEAEs will be tabulated for each treatment group by severity and by relationship to the study drug. A listing of SAEs will be provided, if applicable.

13.4.9 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. Laboratory shift tables displaying the change (number of patients) relative to the normal range from baseline to each study visit will also be presented by treatment for each test.

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

13.4.10 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 ECGs. A detailed description of these analyses will be included in the SAP.

The incidence of abnormal ECG findings will be summarized for each visit.

The PK/PD relationship of CA-008, capsaicin and CA-101 will be investigated with respect to Holter evaluation of QT interval. A description of the analysis will be presented in a separate cQT Analysis Plan.

13.4.11 Physical Examination Findings

Physical examination and surgical site examination data will be presented in the listings. Abnormal or clinically significant PE and surgical site examination 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 Patient 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 patient 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 US 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 patient'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 Independent Ethics Committee (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 patient 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 patient 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 PI 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 Three-Part, Phase 1/2, Randomized, Double-blind, Placebo-Controlled, Adaptive Safety, Pharmacokinetics, and Preliminary Efficacy Study of CA-008 in Patients Undergoing Ventral Hernia Repair

Amendment 2

Date: March 15, 2021

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 guidelines.

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

_____ _____

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

16 REFERENCES

1. Babbar S, Marier JF, Mouksassi MS, et al. Pharmacokinetic analysis of capsaicin after topical administration of a high-concentration capsaicin patch to patients with peripheral neuropathic pain. *Ther Drug Monit.* 2009;31:502-10.

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6. Tominaga M, Caterina MJ, Malmberg AB, Rosen TA, Gilbert H, Skinner K, Raumann BE, Basbaum AI, Julius D. The cloned capsaicin receptor integrates multiple pain-producing stimuli. *Neuron* 21, 1998;531-43.

17 APPENDICES

17.1 Appendix A: 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 AEs, 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

17.2 Appendix B: 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

17.3 Appendix C: Toxicity Grading Scale for Clinical Vital Sign Abnormalities

The following guidance is excerpted from the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (November 27, 2017) as a reference. CTCAE v5.0 and prior versions are available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

The grading system can be "useful in defining a particular study's stopping rules (e.g., a certain number of AEs, as defined in the table, may call for stopping the study.)"

Common Terminology Criteria for Adverse Events (CTCAE) v5.0
Publish Date: November 27, 2017

Introduction
The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

SOC
System Organ Class (SOC), the highest level of the MedDRA[1] hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms
An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term).

Grades
Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- **Grade 3** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
- **Grade 4** Life-threatening consequences; urgent intervention indicated.
- **Grade 5** Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a Grade is not available. Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5
Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Definitions
A brief Definition is provided to clarify the meaning of each AE term. A single dash (-) indicates a Definition is not available.

Navigational Notes
A Navigational Note is used to assist the reporter in choosing a correct AE. It may list other AEs that should be considered in addition to or in place of the AE in question. A single dash (-) indicates a Navigational Note has not been defined for the AE term.

Activities of Daily Living (ADL)
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

[1] CTCAE v5.0 incorporates certain elements of the MedDRA terminology. For further details on MedDRA refer to the MedDRA MSSO Web site (https://www.meddra.org/).

These excerpts are from various sections within CTCAE v5.0:

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fever	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)	>39.0 - 40.0 degrees C (102.3 - 104.0 degrees F)	>40.0 degrees C (>104.0 degrees F) for <=24 hrs	>40.0 degrees C (>104.0 degrees F) for >24 hrs	Death
Definition: A disorder characterized by elevation of the body's temperature above the upper limit of normal. **Navigational Note:** -					
Sinus tachycardia	Asymptomatic, intervention not indicated	Symptomatic; non-urgent medical intervention indicated	Urgent medical intervention indicated	-	-
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates in the sinus node. **Navigational Note:** -					
Sinus bradycardia	Asymptomatic, intervention not indicated	Symptomatic, intervention not indicated; change in medication initiated	Symptomatic, intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate less than 60 beats per minute that originates in the sinus node. **Navigational Note:** -					
Hypertension	**Adult:** Systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg; **Pediatric:** Systolic/diastolic BP >90th percentile but< 95th percentile; **Adolescent:** BP ≥120/80 even if < 95th percentile	**Adult:** Systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg if previously WNL; change in baseline medical intervention indicated; recurrent or persistent (>=24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg; monotherapy indicated initiated; **Pediatric and adolescent:** Recurrent or persistent (>=24 hrs) BP >ULN; monotherapy indicated; systolic and /or diastolic BP between the 95th percentile and 5 mmHg above the 99th percentile; **Adolescent:** Systolic between 130-139 or diastolic between 80-89 even if < 95th percentile	**Adult:** Systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated; **Pediatric and adolescent:** Systolic and/or diastolic > 5 mmHg above the 99th percentile	**Adult and Pediatric:** Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	Death
Definition: A disorder characterized by a pathological increase in blood pressure. **Navigational Note:** -					
Hypotension	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated; hospitalization indicated	Life-threatening consequences and urgent intervention indicated	Death
Definition: A disorder characterized by a blood pressure that is below the normal expected for an individual in a given environment. **Navigational Note:** -					
Hypoxia	-	Decreased oxygen saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased oxygen saturation at rest (e.g., pulse oximeter <88% or PaO2 <=55 mm Hg)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a decrease in the level of oxygen in the body. **Navigational Note:** -					

17.4 Appendix D: 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 AEs, 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.

17.5 Appendix E: 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*

Patient Initials: _____

17.6 Appendix F: PROMIS 10 GLOBAL Health Questionnaire

PROMIS v.1.1 - Global

Global Health

Please respond to each item by marking one box per row.

		Excellent	Very good	Good	Fair	Poor
Global01	In general, would you say your health is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global02	In general, would you say your quality of life is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global03	In general, how would you rate your physical health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global04	In general, how would you rate your mental health, including your mood and your ability to think?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global05	In general, how would you rate your satisfaction with your social activities and relationships?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global09	In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.).....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Completely	**Mostly**	**Moderately**	**A little**	**Not at all**
Global06	To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

 Page 1 of 2

PROMIS v.1.1 - Global

PROMIS v.1.1 - Global

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
Global10	How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

		None	Mild	Moderate	Severe	Very severe
Global08	How would you rate your fatigue on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Global07	How would you rate your pain on average?.....	☐ 0 No pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 Worst imaginable pain

17.7 Appendix G: Activities Assessment Scale (AAS)

We want to know how much your hernia or hernia operation has interfered with your ability to perform various activities. Please read the examples in the following table and then circle the number that corresponds to how difficult it was for you to engage in that activity *within the last 24 hours*. Please circle 8 if you were able to perform that activity but did not in fact do so, or if you do not ordinarily engage in that activity.

How much difficulty did you have performing the following activities *in the last 24 hours* as a result of your hernia? [Preoperative Instruction]

How much difficulty did you have performing the following activities *in the last 24 hours* as a result of your hernia operation? [Postoperative Instruction]

Activity	No difficulty	A little difficulty	Some difficulty	A lot of difficulty	Not able to do it	Did not do it for other reasons
Lying in bed	1	2	3	4	5	8
Sitting	1	2	3	4	5	8
Getting in or out of bed or chair	1	2	3	4	5	8
Reaching or stretching	1	2	3	4	5	8
Lifting 3 to 5 pounds	1	2	3	4	5	8
Walking around inside	1	2	3	4	5	8
Climbing up or down stairs	1	2	3	4	5	8
Walking outside or at work	1	2	3	4	5	8
Engaging in sedentary activities, such as typing, talking on the phone, playing cards, watching TV	1	2	3	4	5	8
Engaging in light physical activities, cooking, dusting, clerical work, visiting friends	1	2	3	4	5	8
Engaging in moderate physical activities such as sweeping, washing the car, dancing, playing golf, hiking	1	2	3	4	5	8
Engaging in vigorous physical activities such as construction work, shoveling, playing tennis or basketball, weight lifting	1	2	3	4	5	8
Engaging in sexual intercourse	1	2	3	4	5	8

17.8 Appendix H: Sit to Stand Test (30-Second Chair Stand) Assessment

ASSESSMENT

30-Second Chair Stand

Purpose: To test leg strength and endurance

Equipment: A chair with a straight back without arm rests (seat 17" high), and a stopwatch.

NOTE: Stand next to the patient for safety.

① Instruct the patient:

1. Sit in the middle of the chair.
2. Place your hands on the opposite shoulder crossed, at the wrists.
3. Keep your feet flat on the floor.
4. Keep your back straight, and keep your arms against your chest.
5. On "Go," rise to a full standing position, then sit back down again.
6. Repeat this for 30 seconds.

② On the word "Go," begin timing.

If the patient must use his/her arms to stand, stop the test. Record "0" for the number and score.

③ Count the number of times the patient comes to a full standing position in 30 seconds.

If the patient is over halfway to a standing position when 30 seconds have elapsed, count it as a stand.

④ Record the number of times the patient stands in 30 seconds.

Number: _____ Score: _____

Patient _____

Date _____

Time _____ ☐AM ☐PM

SCORING

Chair Stand Below Average Scores

AGE	MEN	WOMEN
60-64	< 14	< 12
65-69	< 12	< 11
70-74	< 12	< 10
75-79	< 11	< 10
80-84	< 10	< 9
85-89	< 8	< 8
90-94	< 7	< 4

A below average score indicates a risk for falls.

CDC's STEADI tools and resources can help you screen, assess, and intervene to reduce your patient's fall risk. For more information, visit www.cdc.gov/steadi

Centers for Disease Control and Prevention
National Center for Injury Prevention and Control

2017

STEADI Stopping Elderly Accidents, Deaths & Injuries

17.9 Appendix I: TUG Test

ASSESSMENT

Timed Up & Go (TUG)

Purpose: To assess mobility

Equipment: A stopwatch

Directions: Patients wear their regular footwear and can use a walking aid, if needed. Begin by having the patient sit back in a standard arm chair and identify a line 3 meters, or 10 feet away, on the floor.

① Instruct the patient:

NOTE: Always stay by the patient for safety.

When I say "Go," I want you to:

1. Stand up from the chair.
2. Walk to the line on the floor at your normal pace.
3. Turn.
4. Walk back to the chair at your normal pace.
5. Sit down again.

② On the word "Go," begin timing.

③ Stop timing after patient sits back down.

④ Record time.

Time in Seconds: _____

An older adult who takes ≥12 seconds to complete the TUG is at risk for falling.

CDC's STEADI tools and resources can help you screen, assess, and intervene to reduce your patient's fall risk. For more information, visit www.cdc.gov/steadi

Patient _____

Date _____

Time ☐ AM ☐ PM

OBSERVATIONS

Observe the patient's postural stability, gait, stride length, and sway.

Check all that apply:

- ☐ Slow tentative pace
- ☐ Loss of balance
- ☐ Short strides
- ☐ Little or no arm swing
- ☐ Steadying self on walls
- ☐ Shuffling
- ☐ En bloc turning
- ☐ Not using assistive device properly

These changes may signify neurological problems that require further evaluation.

Centers for Disease Control and Prevention
National Center for Injury Prevention and Control

2017

STEADI Stopping Elderly Accidents, Deaths & Injuries

17.10 Appendix J: 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: _____

The assessment of satisfaction with wound healing should be performed with what is typically observed for surgeries of this type in the Investigator's clinical opinion. The surgical wound AE grading scale in Appendix K may be helpful if there is an atypical or abnormal finding.

17.11 Appendix K: 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

17.12 Appendix L: Neurosensory Examination Form

Was the neurosensory exam completed? ___ Yes ___ No

Date of Assessment _____ Time of Assessment ___: ___

Cephalad to Wound	
Visual Exam of the surgical site	___ Normal ___ Abnormal, describe: _____
Light Touch	___ Normal ___Reduced ___Absent
Von Frey Stimulation	___Normal ___ Reduced ___Absent
Brush Stimulation	___ Normal ___ Reduced ___ Absent ___ Pain (Allodynia)

Caudad to Wound	
Visual Exam of the surgical site	___ Normal ___ Abnormal, describe: _____
Light Touch	___ Normal ___Reduced ___ Absent
Von Frey Stimulation	___Normal ___ Reduced ___ Absent
Brush Stimulation	___ Normal ___ Reduced ___ Absent ___ Pain (Allodynia)

Neurosensory testing should be performed in an area approximately 5 cm above and below the surgical incision site compared to the control site. The instructions below may assist the Investigator or designee in performing neurosensory testing.

Visual Examination of Surgical Site: For this examination, report any findings observed during visual inspection of the surgical site.

Light Touch Testing: For this examination, using the tip of your finger or a piece of cotton, briefly touch rather than stroke the patient's skin at the location to be assessed. Ask the patient to close their eyes and indicate when the touch is felt.

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 patient, 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: Performed at the location to be assessed using a foam brush. Note that allodynia testing is best assessed by using the foam brush, and while it may be elicited using von Frey filament testing, document presence of allodynia only with brush stimulation. For **allodynia assessment** the foam brush will be lightly stroked 3 times across the skin in the location to be assessed. Patient 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 patient 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.