OFFICIAL TITLE:

A Two-Part, Phase 1/2, Randomized, Double-blind, Placebo-controlled, Adaptive Safety, Pharmacokinetics, and Preliminary Efficacy Study of CA-008 in Patients Undergoing Total Knee Arthroplasty

NCT NUMBER:

NCT04203537

DOCUMENT DATE:

22 April 2020 Amendment 1

Clinical Trial Protocol

A Two-Part, Phase 1/2, Randomized, Double-blind, Placebo-Controlled, Adaptive Safety, Pharmacokinetics, and Preliminary Efficacy Study of CA-008 in Patients Undergoing Total Knee Arthroplasty

Investigational Product: CA-008 by Injection/Instillation

IND: 129114

Concentric Analgesics, Inc.

Original Protocol Date: 12 November 2019
Amendment 1 Date: 22 April 2020

SIGNATURE PAGE

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1. KEY PERSONNEL CONTACT INFORMATION

Sponsor	**Concentric Analgesics, Inc. (Concentric)**
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Summary of Changes from CA-PS-208 protocol v1.0 to v2.0

Substantive changes:

1. Inclusion criterion #7 (Synopsis and Section 8.2.1):

Expanded eligible body mass index from ≤ 36 kg/m^2 to body mass index ≤ 42 kg/m^2

Rationale: Patients requiring total knee arthroplasty are often overweight or obese. Obesity is not a contraindication to treatment with this locally-acting analgesic

2. Clarified and added detail on study drug administration based on cases completed to date and surgeon input (Section 10.1.3)

Rationale: As per protocol Section 10.1.3, "Modifications to the total study drug dose, volume, drug concentration, and allocation for subsequent patients may occur based on information from prior patients." No changes were made to total dose, volume or concentration. Additional detail and instruction were provided for the locations of study drug delivery based on input and experience from Part A of the study and surgeon input.

Other changes:

Clarifications and Additions:

- Removed background information that is no longer verifiable (Section 5.1)
- Added information on recently completed toxicological study (Section 5.2)
- Reworded study objectives for clarity (Synopsis, Section 6.1.1 and Section 6.1.2)
- Clarified Exclusion Criterion #3 (Synopsis and Section 8.2.2) concerning allergy or contraindication to study components
- Clarified Exclusion Criterion #5 (Synopsis and Section 8.2.2) concerning maximum acceptable prophylactic dose of aspirin
- Clarified Exclusion Criterion #7 (Synopsis, Section 8.2.2 and Section 10.3.16) to define more clearly a disqualifying positive urine drug screen
- Resolved ambiguities of timing of certain drug administration. The original protocol has two different instructions due to a typo. All patients enrolled have received the correct dosing. (Synopsis and Section 9.2.1 10.1.3)
- Clarified protocol deviation criterion for rescue medication use (Section 9.2.2)
- Clarified timing of pre-rescue NRS in relation to rescue medication (Section 9.2.3)
- Clarified that all opioid rescue medication is to be included in total opioid consumption (Section 9.2.3)
- Added detail on type of local anesthetic to be used (Synopsis and Section 10.1.2.2)
- Added detail on post-incision local anesthetic delivery (Section 10.1.2.2)
- Noted that tourniquet use is as per institutional guidelines and is not required (Section 10.1.2.2)
- Clarified definition of surgical site (Section 10.1.3)
- Clarified timing of study assessments (Section 10.1.4)

- Clarified appropriate staff who can perform assessment (Synopsis and Section 10.1.4)
- Revised description of complete physical examination to match standard being used in CRF (Section 10.3.19)
- Clarified definition of post-menopausal FSH level (Section 10.3.5)
- Added clarity on NRS pain score recording to specify knee surgical site (Synopsis, Section 10.3.8 and Appendix F)
- Clarified requirement for knee X-ray study procedure (Synopsis and Section 10.4.1)
- Clarified definition of non-opioid analgesic consumption endpoint (Synopsis and Section 10.4.3.2)
- Corrected the definition of mITT population (Synopsis and Section 13.2)
- Added definition of major protocol deviation (Section 13.4.2)
- Corrected formula for Area Under the Curve (AUC) (Section 13.4.6)
- Added information on exploratory efficacy analyses from the SAP (Section 13.4.6)

Administrative:

- Updated study contact personnel and information
- Corrected typographical errors in directions for study drug administration (Synopsis and Section 10.1.3)
- Added reference to Statistical Analysis Plan for detail on statistical considerations and exploratory efficacy endpoints (Synopsis, Section 10.4.3.2 and Section 13.1)

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-208
IND#	129114
Study Title:	A Two-Part, Phase 1/2, Randomized, Double-blind, Placebo-Controlled, Adaptive Safety, Pharmacokinetics, and Preliminary Efficacy Study of CA-008 in Patients Undergoing Total Knee Arthroplasty
Study Treatment	CA-008 and placebo
Planned Study Center(s):	Part A: 1 US site Part B: Up to 3 US sites
Indication:	Acute postsurgical pain
Sample Size:	Part A: • Cohort #1: total N = 8 (randomized 3:1 active to placebo), no more than 4 patients dosed per week • Cohort #2: total N = 8 (randomized 3:1 active to placebo), no more than 4 patients dosed per week After review of cohort study data, a cohort may be expanded to N = 16. One (1) or 2 additional cohorts may be added with N = 8 or 16 in each cohort, using the same 3:1 randomization ratio. The total sample size in Part A is thus 16-64 patients. Part B: In Part B, a total of 150-300 patients will be randomized in 3-4 parallel arms (with 50-100 patients in each arm). The number of patients to be enrolled in Part B will not exceed 300.
Population:	Adults 18 to 80 years of age, inclusive, who are planning to undergo an elective unilateral total knee arthroplasty (replacement) (TKA) and who otherwise meet eligibility criteria may be considered for enrollment into the study.
Study Duration:	Approximately 76 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 two-part, Phase 1/2, randomized, double-blind, placebo-controlled study. In Part A, 2 or more exploratory sequential dose-escalation cohorts will be evaluated, each with administration of a single dose of CA-008 or placebo infiltrated/instilled

	during surgery in patients undergoing TKA. In Part B, 2 or 3 active dose levels of CA-008 will be evaluated compared to placebo in a randomized, double-blind, parallel-group design. 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]). • 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 TKA including study drug treatment (CA-008 or placebo) followed by serial assessments of safety, pharmacokinetic (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. Safety and drug effect assessments will focus on reported pain and need for analgesia.
Study Objectives:	**Part A:** **Primary Objective:** • Evaluate the safety and tolerability of a single intraoperative administration of either CA-008 or placebo in patients undergoing an elective TKA. **Secondary Objectives:** • Evaluate the PK profile of a single intraoperative administration of CA-008 in patients undergoing an elective TKA. • Evaluate, preliminarily, the activity of CA-008 on reported pain, opioid consumption, and patient-reported outcomes (PROs). • Determine the dose(s) for testing in Part B. **Part B:** **Primary Objective:** • Evaluate, during a specified post-operative time interval, the efficacy of 2 or 3 selected doses of CA-008 on reported pain in patients undergoing an elective TKA. **Secondary Objectives:** • Evaluate the efficacy of 2 or 3 selected doses of CA-008 on reported pain in patients undergoing an elective TKA during additional specified post-operative time intervals. • Evaluate the effect of CA-008 on opioid consumption. • Evaluate the effect of CA-008 on PROs. • Evaluate, preliminarily, the effect of CA-008 on performance-based outcome measures (PBOMs), including knee range of motion (ROM). • Evaluate the safety and tolerability of CA-008 or placebo in patients

	undergoing an elective TKA. • Evaluate the PK profile of a single intraoperative administration of CA-008 in patients undergoing an elective TKA.
Study Treatment Dosing Schedule:	Study treatment is to be administered intraoperatively as a single administration via "surgical site" infiltration/instillation prior to wound closure. "Surgical site" is defined as the area extending approximately 5 cm in all directions (lateral/medial/proximal/distal/deep) from the incision and osteotomy sites and surrounding tissues.
Anesthesia and Perioperative Care:	The surgery will be performed under spinal anesthesia (isobaric bupivacaine 0.5%, [preservative-free] 12-15 mg and fentanyl 25 mcg) with adequate supplemental sedation, typically with midazolam (up to 5 mg), fentanyl (up to 100 mcg) and propofol infusion, but anesthesia and sedation will be per institutional guidelines. If the patient appears to have an inadequate level of anesthesia from the spinal anesthetic ("failed spinal anesthetic"), the patient should receive a general anesthetic with either an inhaled anesthetic or propofol infusion with or without nitrous oxide (N_20). In addition, patients will receive ropivacaine hydrochloride (RopiHCl) delivered as follows: • Prior to start of surgery under ultrasound guidance: o Femoral nerve block: RopiHCl 0.5%, 12 mL (60 mg) o IPACK infiltration: RopiHCl 0.2%, 20 mL (40 mg) • Immediately after surgical incision: o Periarticular infiltration: RopiHCl 0.2%, 50 mL (100 mg). The total RopiHCl should not exceed 200 mg. See Section 17.5, Appendix E for guidance on RopiHCl dosing. Note: **IPACK = I**nterspace between the **P**opliteal **A**rtery and the **C**apsule of the posterior **K**nee between the femoral condyles) Standard 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.

Dose Groups:	**Part A:** 1. Sequential Cohort #1: total N = 8 patients randomized 3:1 CA-008 36 mg in 120 mL (0.3 mg/mL) or placebo 120 mL 2. Sequential Cohort #2: total N = 8 patients randomized 3:1 CA-008 60 mg in 120 mL (0.5 mg/mL) or placebo 120 mL 3. Additional sequential cohorts may receive doses between 15-90 mg or placebo using the same 3:1 randomization ratio **Part B:** 4. The doses of active drug to be administered in Part B will be in the range of 15-90 mg and will not exceed the maximum dose administered safely in Part A. Doses will be selected based on safety and tolerability data from Part A and from prior studies of CA-008.
Injection of Study Treatment:	The initial total study drug volume administered per patient will be 120 mL. This initial 120 mL of study treatment administered per patient in the first study cohort will be delivered during the surgical procedure in 3 divided aliquots. The initial allocation will be: (a) a total of 15 mL into the cut surfaces divided into aliquots following each osteotomy; (b) 30 mL prior to hardware placement; (c) 60 mL after hardware placement and (d) 15 mL following closure of the joint capsule. Modifications to the total study drug dose, volume, drug concentration, and allocation for subsequent patients may occur based on information from prior patients.
Intraoperative Analgesia:	Within 15 minutes prior to the end of surgery, administer the following: • IV hydromorphone, 1 mg • IV ketorolac, 30 mg Dose adjustments may be made per surgeon's/anesthesiologist's discretion to accommodate the patient's age and health status. • IV acetaminophen, 1g After these have been administered, no additional non-opioid analgesics are to be administered during the inpatient phase (through T96). If a patient had an inadequate level of anesthesia from the spinal anesthetic and received a general anesthetic, the patient should receive IV hydromorphone, 1 mg, within 30 minutes of anesthesia induction and up to 1 mg of IV hydromorphone within 15 minutes of end of surgery. Patients who develop clinically significant hemodynamic instability or other anesthesia complication prior to study drug administration should not receive study drug; in Part A, 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.
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).
	
	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 below. Rescue medication will be administered at these times only upon request based on the currently reported pain score.
	
	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 $\geq$ 4) will be administered upon request as follows:
	
	• From T0 to T25 minutes:
	  o IV fentanyl 50 mcg, Q 5 minutes for pain NRS $\geq$ 4
	• From T26 minutes to PACU discharge:
	  o IV hydromorphone 0.5 mg, Q 10 minutes for pain NRS $\geq$ 4
	
	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.

Rescue Medication during the Inpatient Period:	• From the time of PACU discharge through T24:
	  o Administer IV hydromorphone 0.5 mg, Q15 minutes PRN pain NRS $\geq$ 4.
	• After T24:
	  o Administer PO oxycodone 10 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 T24, then the patient will revert to IV analgesia management per institutional guidelines. These patients will still also be followed for NRS, safety, and other assessments.
	
	Patients will be encouraged to use rescue medication only for moderate-to-severe pain (NRS 5-10); however, rescue with oxycodone, 10 mg PO may be requested at any time (i.e., even when NRS < 5) and medication will be provided when requested.
	
	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.

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:
	  ○ 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 < 5) (unless contraindicated)
	  ○ Acetaminophen, 325 mg/Oxycodone, 5 mg (Percocet) – 1 or 2 tablets PO Q 4-6 h for moderate-severe pain (i.e., NRS 5-10). 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.
	
	Document the number of 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.

Inclusion Criteria:	I**n order to participate, patients must meet all inclusion criteria:** 1. Plan to undergo an elective primary unilateral TKA under spinal anesthesia with sedation, without collateral procedure or additional surgeries. 2. Appropriate candidate for spinal anesthesia, including no contraindications, no anatomical constraints. 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 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 ≤ 42 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 painful condition, other than pain in the knee to be replaced, that may require analgesic treatment during the study period or may confound post-surgical pain assessments; b. moderate to severe chronic neuropathic pain or signs of central sensitization; c. active skin disease or other clinically significant abnormality at the anticipated site of surgery that could interfere with the planned surgery. 2. The patient is tolerant to opioids (opioid-tolerant) defined as someone who has been receiving or has received chronic opioid therapy (use within the 2 weeks prior to surgery and duration of use > 4 weeks) greater than 15 mg of oral morphine equivalents per day for greater than 3 out of 7 days per week over a one-month period within 6 months of screening. 3. The patient has a known allergy (or contraindication) to any of the following: chili peppers, capsaicin or the components of CA-008, ropivacaine hydrochloride (HCl), ketorolac, 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

electrocardiogram (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 (CNS) active agent as an analgesic adjunct medication, such as anticonvulsants, antidepressants (such as SNRIs, SSRIs, and tricyclic antidepressants), benzodiazepines, sedative-hypnotics, clonidine and other central alpha-2 agents (e.g., tizanidine), ketamine, or muscle relaxants.
      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, NSAIDs, tramadol, or opioids, **for knee-related pain**, the patient may participate in the study if not opioid-tolerant (defined above) and 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 and throughout the study, taking (a) antiarrhythmics (except beta-blockers and digoxin); (b) warfarin or other anticoagulants (see exception below); (c) lithium; or (d) aminoglycosides or other antibiotics for an infection (except for ophthalmic 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 10.3.16). 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:	1. **Screening D −45 to Day Prior to Surgery**: Patients undergo screening during this period. All screening assessments (including informed consent form [ICF]) must be completed at least 1 day prior to surgery. 2. **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. 3. **Surgery D1**: TKA procedure is performed; study treatment is administered prior to wound closure. PK sample collection is to be done per protocol-specified time points through 24 h following the last study treatment instillation. 4. **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) assessments with follow up instructions, particularly on diary completion. 5. **Follow Up D8 + 1 day**: clinic visit for study assessments. 6. **Follow Up D15 + 2 days:** clinic visit for study assessments. 7. **Follow Up D29 + 2 days:** clinic visit for study assessments and study completion visit, unless additional follow up for wound healing is needed. 8. **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. 9. **Early Termination (ET):** For patients who terminate early, an ET visit will be required.
Monitored Parameters:	• Treatment-emergent AEs (TEAEs) • Medical history (MHx) • Physical examination (PE) findings, particularly neurosensory findings at the site of incision and the skin proximal and distal to the incision • Surgical site assessment for wound healing, including a digital photograph if the patient has consented • Neurosensory testing near the surgical site • Clinical laboratory testing (standard chemistry, CBC, coagulation, urinalysis), drug and alcohol testing, pregnancy testing

	• X-ray of the knee, only if any evidence of abnormalities in bone healing
	• 12-lead ECGs
	• Blood draws for pharmacokinetics (PK)
	• NRS scores assessing rest pain and evoked pain at the knee surgical site after physical therapy or transfers to/from bed or wheelchair (inpatient) or ambulation for approximately 10 yards (inpatient or outpatient) using a 0 to 10 numeric rating scale for pain intensity
	• Presence of worsening (rebound) pain at the surgical site
	• Knee injury and Osteoarthritis Outcome Score (KOOS)
	• Knee Range of Motion (ROM) (using goniometry: active flexion and extension, passive flexion and extension) (Section 17.10, Appendix J)
	• Ability to walk > 100 ft (> 30 m) with only the aid of a walker during twice-daily inpatient physical therapy sessions (or assessed by site staff)
	• Performance-based functional outcome measures (PBOMs):
	  ○ Timed Up and Go (TUG) (Section 17.13, Appendix M)
	  ○ Sit to Stand Test (Section 17.11, Appendix K)
	  ○ Walking Speed Test (Section 17.12, Appendix L)
	• Total postsurgical opioid consumption converted to an oral morphine equivalent dose (OME)
	• Patient Reported Outcomes Measurement Information System (PROMIS) 10 Global Health questionnaire, V1.1 (Section 17.9, Appendix I)

Safety Endpoints:	1. 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: A PK sample should be collected during the in-patient phase of the study as part of the evaluation of any SAE or severe TEAE.
	2. 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).
	3. Vital signs (heart rate [HR], blood pressure [BP], respiratory rate [RR]) at screening, D1 prior to surgery, post-surgery T2, T6, T12, and T24, and every 8 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 8 hours thereafter until discharge from the inpatient facility (if awake at the time of assessment between hours of midnight and 6:00 AM).

	4. 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. 5. Neurosensory testing near the incision (compared to a similar site on the opposite leg) will be performed at Screening visit, T96 (prior to discharge from the inpatient unit) and then as an outpatient on D8, D15, and D29. o Numbness at or near the incision need not be considered a neurologic AE since this could occur because of tissue trauma and inflammation from the surgery. o Sensory deficits or clinically significant persistent sensory change beyond the area proximal/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. 6. X-ray of the operated knee at D29 and later only if any evidence of abnormalities in bone healing until resolution or stabilization 7. Query patients as to whether they have experienced any worsening (rebound) pain at the surgical site at D8, D15, and D29. 8. 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. o 12-lead ECG at screening and T24 (± 2 h) o Hematology/Coagulation at screening and T96 (± 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). o Blood Chemistry at screening and T96 (± 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. o Serum and urine pregnancy test for FCBP: βhCG test at screening and urine test usually to be done within 24 hours prior to surgery. o Urinalysis at screening and T96 (± 4 h): including macroscopic analysis and, if indicated, microscopic analysis. o Note: Safety laboratory assessments may be collected, as appropriate, as part of the evaluation of an SAE or severe TEAE.

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). If the patient is able to provide responses, obtain NRS scores at T0 plus 1 hour (T1), T0 plus 2 hours (T2, etc.), 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, evoked NRS twice daily after physical therapy (most preferred) or ambulation for approximately 10 yards (preferred) or transfers to/from bed or wheelchair. Obtain these NRS scores after morning physical therapy or ambulation at 10:00 AM (± 1 h) and after afternoon physical therapy or ambulation 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), instruct the patient to document their NRS scores twice daily at 11:00 AM (± 1 h) and 7:00 PM (± 1 h) at rest and during ambulation (e.g., with the use of a walker or a cane) for approximately 10 yards. Note that the actual time of these assessments must be documented in the diary. Instruct the patient to: o Obtain the morning NRS assessment; o Obtain the evening NRS assessment; 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. 1. Document each opioid prescription provided to the patient and the number of and type of tablets provided to the patient. 3. Ability to walk > 100 ft (> 30 m) with only the aid of a walker during twice-daily inpatient physical therapy sessions (or assessed by site staff) on D3, D4, and D5 to allow assessment of discharge readiness. 4. KOOS survey at Screening, T96, D8, D15, and D29.

	5. PROMIS 10 Global Health questionnaire at Screening, D15, and D29. 6. Knee ROM at Screening, T48 (± 4 h), T96 (± 4 h)/Discharge, D8, D15, and D29. 7. PBOMs: (Sit to Stand Test, Walking Speed Test, TUG) at T96 (± 4 h)/Discharge, D15, and D29.
Efficacy Endpoints	Part A: There are no efficacy endpoints for Part A Part B: Primary efficacy endpoint: • Area under the curve (AUC) of the rest NRS from T12 to T96 (AUC_{12-96}). AUC is the weighted sum of current pain intensity (SPI) assessments for a specified time interval. Key secondary efficacy endpoints: • Evoked pain NRS: $AUC_{12–96}$ • Percentage of patients who do not require opioids (i.e., opioid-free or OF) from T24 to T96: OF_{24-96} • Total opioid consumption (in daily OME) = OC from T12 to T96: OC_{12-96} • NRS at rest and evoked NRS from T12 to D8: AUC_{12-D8} Exploratory efficacy endpoints for Part B: • Using rest NRS: AUC_{0-24}, AUC_{0-96}, AUC_{6-96}, AUC_{24-96}, AUC_{96-D8}, and AUC_{96-D15}; • Using evoked NRS: $AUC_{0-96\ (ambulation)}$, $AUC_{0-D8\ (ambulation)}$, $AUC_{24-D8(ambulation)}$, and $AUC_{96-D15\ (ambulation)}$; • Time-specific mean NRS scores at T48, T72, T96, T120, T144, and T168; • OC_{0-96}, OC_{24-48}, OC_{24-72}, OC_{24-96}, OC_{24-D8}, and OC_{24-D15}; • OF_{0-96}, OF_{24-D15}, OF_{96-D8}, and OF_{96-D15}; • Additional exploratory and sensitivity analyses rest/evoked NRS AUC, OC, and OF during different intervals may be undertaken: • Knee ROM: mean and proportion of patients with > 90° and proportion of patients with > 115° active flexion at T48 (± 4 h), T96 (± 4 h)/Discharge, D8, D15, and D29. • KOOS improvement from Screening to D8, D15, and D29; and from T96 to D8, D15, and D29; • Improvement in PBOMs (Sit to Stand, Walking Speed Test, TUG) at T96 (± 4 h)/Discharge, D15, and D29; • The proportion of patients who rescue T0-T6, T6-T12, T12-T24, T24-T48, T48-T72, and T72-T96; • Total non-opioid analgesic consumption (AC), ie, rescue acetaminophen use for the indicated time intervals: AC_{96-D8} and AC_{96-D15}; • PROMIS 10 Global Health questionnaire score improvement from Screening to D15 and to D29; • Number and percentage patients with an AE of lack of efficacy (LOE) during the inpatient period: LOE_{0-96}.

	• Discharge readiness at T48 (± 4 h), T72 (± 4 h), and T96 (± 4 h)/Discharge as assessed by the earliest presence of all three of the following: (i) Adequate analgesia (defined as median rest NRS < 4 during an 8-hour period); (ii) independence from intravenous opioids during an 8-hour period; and (iii) ability to ambulate > 100 ft (> 30 m) with only the aid of a walker during a physical therapy session. Note: Details on additional or alternative exploratory efficacy endpoints are provided in the study Statistical Analysis Plan (SAP). The SAP will supersede the protocol with respect to the analyses specified, although the primary and key secondary efficacy endpoints described in the protocol will remain unchanged.
PK Endpoints:	Part A: PK sample collection will be performed on all patients. The time points for whole blood collection will be at pre-dose (from check-in and up to 30 minutes before the start of surgery), and at pharmacokinetic time (PKT) 0.167 h (10 min), 0.25 h (15 min), 0.5 h (30 min), 0.75 h (45 min), and at 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours after the last study treatment instillation (total of 15 samples). Part B: PK sample collection will be performed at one site. The time points for whole blood collection will be at pre-dose (from check-in and up to 30 minutes before the start of surgery), and at PKT 0.167 h (10 min), 0.25 h (15 min), 0.5 h (30 min), 0.75 h (45 min), and at 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours after the last study treatment instillation (total of 15 samples). At least 12 of the 15 samples should be collected in each of these patients. The number of patients will depend on the number of dose levels being tested, but approximately15 patients per dose level are planned. Actual sampling times will be used to calculate plasma-derived PK parameters. 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, SD, median, minimum and maximum values, coefficient of variation (CV%), and geometric mean and geometric coefficient of variation (geoCV%). 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 ($AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$). The PK will be documented in the PK Analysis Plan. Note: A PK sample should be collected during the in-patient phase of the study as part of the evaluation of any SAE or severe TEAE.
Stopping Rules:	Study enrollment will be paused if patients experience intolerable “related” TEAEs, as outlined below. 1 or more patients with any grade 4 “related” TEAE in any of the categories shown in Table 7, Section 7.4 2 or more patients with the same grade 3 “related” TEAE in any of the categories

	shown in Table 7, Section 7.4 2 or more patients with the same grade 3 or 4 "related" TEAE shown in Appendix A (Section 17.1) or found in the in the toxicity grading scale cited therein. "Related" includes possibly, probably, and definitely related causality assessments. In Part A, should a stopping rule be triggered, the Sponsor's medical monitor, the CRO medical monitor, and the relevant Principal Investigator (PI) will review the blinded data to determine whether or not it is appropriate to resume enrollment with the same or a modified dose. Unblinding of an individual treatment assignment may be required to complete this safety assessment. In Part B, should a stopping rule be triggered, the Sponsor's medical monitor, the CRO medical monitor, the relevant PI, and an independent medical monitor will review the blinded data to determine whether or not it is appropriate to resume enrollment, 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, no formal statistical hypothesis testing will be performed. The sample size of 8 initial patients per dose level, with the potential for expansion to 16 patients, has been selected based on prior clinical trial experience with CA-008 and is considered sufficient for exploration of tolerability and safety parameters, establishment of a PK profile, and preliminary assessment of the efficacy of CA-008 in postoperative analgesia. In Part B, a total of 150-300 patients will be randomized in 3-4 parallel arms with 50-100 patients in each arm. The number of patients to be enrolled in Part B will not exceed 300. Assuming a *t*-test for the difference in 2 independent means, a sample size of approximately 50 patients per group would provide approximately 85% power to detect an effect size (Cohen's *d*) of 0.6 at a two-sided level of significance, alpha, of 0.05 in the primary efficacy endpoint NRS $AUC_{12\text{-}96}$. Enrollment is currently planned at 55 patients per arm to allow for patients whose data are not eligible for inclusion in the final analysis. In this scenario, it is anticipated that, in Part B, 3 active dose levels – 60 mg, 36 mg, and 15 mg – are to be tested versus placebo, yielding 4 trial arms and a resulting total sample size of 220 patients. Alternative assumptions concerning the anticipated effect size lead to a different number of patients per group. The actual doses, number of active arms (2 or 3), and sample size to be tested in Part B will be determined at the end of Part A based on information in the protocol and Statistical Analysis Plan.
Study Populations:	The following 5 analysis populations are planned for this study: 1 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). [2] PK Population consists of all patients who received a full dose of study treatment and completed at least one PK assessment. [3] Modified Intent-to-treat (mITT) Population consists of all patients who received any dose of study treatment. [4] 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 [5] 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:	In general, descriptive statistics for continuous variables will include n, mean, standard deviation (SD), standard error of mean (SEM), (if appropriate), median, minimum, and maximum. Categorical variables will be described by number 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. Data from all patients receiving 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. 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 a statistical analysis plan (SAP) which will be signed prior to the database lock.

Table 1. Schedule of Assessments – Part A and Part B

Study Period		Inpatient							Follow-Up Clinic Visits				
	Screening	Day of Surgery	Surgery	Post-Surgery	T24	T48	T72	T96 ± 4 h				Unscheduled Visit[1]	Early Termination[19]
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		
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											
Surgery			X										
Study treatment Infiltration/instillation			X										
Admission to PACU				T0									
Surgical Site assessment								X[7]	X[7]	X[7]	X[7]	X[7]	X[7]
Neurosensory Exam	X							X[8]	X[8]	X[8]	X[8]	X[8]	X[8]
Blood draw for laboratory tests	X[9]							X[9]					
Urine sample for urinalysis	X[9]							X[9]					
Rescue Medication consumption				X	X	X	X	X	X	X			X
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[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]			X[10]

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		
Patient home diary record (NRS)								X[11]	X[11]	X[11]			X[11,19]
Paper/Electronic Diary (review, distribution and/or collection)								X[12]	X[12]	X[12,13]			X[13]
Patient home diary (analgesic consumption)								X	X	X[13]			X
Prescription for outpatient opioid rescue								X[14]					
PROMIS 10 Global Health questionnaire	X									X	X		
KOOS Survey	X							X	X	X	X		X
Knee ROM	X					X		X	X	X	X		X
Ability to walk > 100 ft (> 30 m)						BID	BID	BID					
PBOMs[15]								X		X	X		
Blood draw for PK analysis		X[16,17]		X[16]	X[16]								
Worsening (rebound) pain									X[18]	X[18]	X[18]		X[18]
Knee x-ray											X[20]		X[20]

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 and temperature assessed together after T0 at 2, 6, 12, 24, and every 8 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 for vital signs and temperatures there will be a ± 15-minute window allowed.

5 A complete medical history and physical examination including all major body systems will be performed at Screening. In addition, at the following times, an interim medical history and targeted physical examination will be performed prior to surgery, 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 Surgical Site assessment: T96 (± 4 hours, but prior to discharge from the inpatient unit) and D8, 15, and 29.

8 Neurosensory Exam 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.

[9] Clinical Laboratory tests (chemistry, hematology, coagulation and urinalysis) should be performed at screening and prior to discharge from the inpatient unit (Lab collection window for T96 is ± 4 hours).

[10] During the inpatient stay, NRS at rest beginning with the PACU admission (T0) may be assessed once the patient is awake. If the patient is able to provide responses, obtain NRS scores T0 plus 1 hour (T1), T0 plus 2 hours (T2, etc.), 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, evoked NRS twice daily after physical therapy (most preferred) or ambulation for approximately 10 yards (preferred) or transfers to/from bed or wheelchair. Obtain these NRS scores after morning physical therapy or ambulation at 10:00 AM (± 1 h) and after afternoon physical therapy or ambulation 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), instruct the patient to document their NRS scores twice daily at 11:00 AM (± 1 h) and 7:00 PM (± 1 h) at rest and during ambulation (e.g., with the use of a walker or a cane) for approximately 10 yards. Note that the actual time of these assessments must be documented in the diary. Instruct the patient to:

- Obtain the morning NRS assessment;
- Obtain the evening NRS assessment;
- Opioid and non-opioid rescue medication (dose, date, time) must be recorded in the diary through D15, including a pre-rescue NRS score.

[11] 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).

[12] 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.

[13] Collect Patient Diary Data.

[14] Patients will be given a prescription for 20 tablets of acetaminophen 325 mg/oxycodone 5 mg (Percocet) one or two tablets PO Q 4-6 h PRN moderate-severe pain (i.e., NRS 5 – 10).

[15] PBOMs: Sit to Stand Test, Walking Speed Test, TUG.

[16] Collect blood samples for PK. The time points for whole blood collection will be at pre-dose (from check-in and up to 30 minutes before the start of surgery), and at PKT 0.167 (10 min), 0.25 (15 min), 0.5 (30 min), 0.75 (45 min), and at 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and T24 after last study treatment instillation (total of 15 samples). There will be a ± 2-minute window allowed for the 10- to 15-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 an AE, an unscheduled PK draw will be performed.

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

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

[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.

[20] X-ray of the operated knee on D29 and later only if any evidence of abnormal bone healing until resolution or stabilization. Also perform this at early termination if patient gives consent.

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LIST OF TABLES

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
CBC	Complete blood count
CFR	Code of Federal Regulations
cm	Centimeter
C_{max}	Maximum observed plasma drug concentration
CNS	Central nervous system
CRF / eCRF	Case Report Form (may include electronic data capture systems or paper forms)
CRO	Contract research organization
CS	Clinically significant
CSA	Clinical Study Agreement
CV%	Coefficient of variation
D# or D-#	Day # (study days after surgery), Day # prior to surgery
DVT	Deep Venous Thrombosis
ECG	Electrocardiogram
EDC	Electronic data capture
ET	Early Termination
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
FIH	First-In-Human

Abbreviation	Term
FSH	Follicle stimulating hormone
G	Gram
GCP	Good Clinical Practice
geoCV%	Geometric coefficient of variation
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
h or HRS	Hour(s)
HCl	Hydrochloride
HCU	Health care utilization
HEENT	Head, Eye, Ear, Nose and Throat
HR	Heart rate
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Institutional Ethics Committee
INR	International Normalized Ratio
IPACK	Interspace between the Popliteal Artery and the Capsule of the posterior Knee
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
KOOS	Knee Injury and Osteoarthritis Outcome Score
LOCF	Last pain score carried forward
LOE	Lack of efficacy
m	Meter
mcg or µ	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MHx	Medical history
min	Minutes
mITT	Modified Intent-to-treat
mL	Milliliter
ms	Millisecond
NCS	Not clinically significant
NIH	National Institute of Health
NRS	Numeric Rating Scale of Pain Intensity
NSAID	Nonsteroidal anti-inflammatory drug
OC	Opioid consumption in morphine equivalent dose

Abbreviation	Term
OF	Opioid free
OME	Oral morphine equivalent
OTC	Over-the-counter
PACU	Post-anesthesia care unit
PBOM	Performance-based functional outcome measure
PE	Physical examination
PHN	Postherpetic neuralgia
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
QID	Quater in die (four times daily)
RBC	Red blood cell
RopiHCl	Ropivacaine hydrochloride
ROM	Range of motion
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDTM	Study data tabulation model
SEM	Standard error of mean
SNRIs	Serotonin-norepinephrine reuptake inhibitors
SOC	System Organ Class
SPI	Sum of pain intensity
SSRIs	Selective serotonin reuptake inhibitors
T#	Time in hours since arrival in the PACU (T0 equals time of admission into the PACU)
$t_{½}$	Elimination half-life
TEAEs	Treatment emergent adverse event[s]
THC	Tetrahydrocannabinol
TID	Ter in die (three times daily)
TKA	Total knee arthroplasty
TKR	Total knee replacement

Abbreviation	Term
T_{max}	Time to maximum plasma drug concentration
Tot. Bili	Total bilirubin
TRPV1	Transient receptor potential vanilloid-1
TUG	Timed Up and Go
UDS	Urine drug screen[ing]
ULN	Upper limit of normal
US	United States
V	Volume of distribution
W#	Week # visit after surgery
wLOCF	windowed last pain score carried forward
WOCF	worst prior pain score carried forward

5. INTRODUCTION

5.1. Background

Concentric Analgesics, Inc. (Concentric) is developing CA-008 to provide long-lasting pain relief of post-surgical pain following a single local administration (for T96 and beyond). CA-008 is a prodrug of trans-capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide), the substance in chili peppers that produces the sensation of spiciness. Capsaicin is a transient receptor potential cation channel, subfamily V (vanilloid), member 1 (TRPV1) agonist. TRPV1 is a ligand-gated, nonselective, cation channel preferentially expressed most densely in C-fiber nociceptors and to a lesser extent on Aδ–fiber nociceptors (Babbar 2009, Caterina 2001). TRPV1 responds to noxious stimuli including capsaicin, heat, and extracellular acidification, and integrates simultaneous exposures to these stimuli (Suresh 2010, Surh 1995, Tominaga 1998).

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

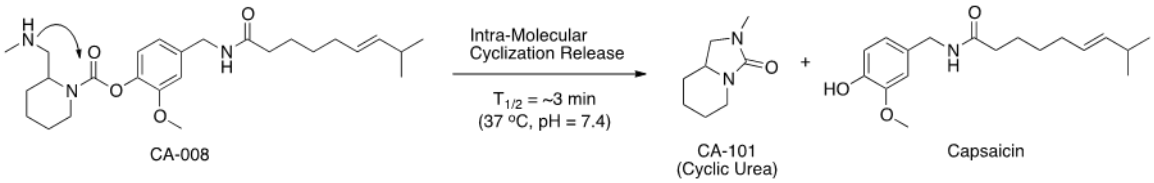
In order to work around the solubility limitations of capsaicin, the highly water-soluble capsaicin pro-drug CA-008 was developed for local infiltration. It avoids the physicochemical limitations of capsaicin while providing greater target engagement which theoretically would produce superior local analgesia, 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 post-surgical pain over several days to weeks. This improved long-term pain relief has the ability to augment current multimodal analgesia or enhanced recovery programs which may help to avoid the need for supplemental opioid use after surgery.

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

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 GLP safety studies and the PK profile for various doses have been determined in multiple clinical trials conducted to date.

In Concentric GLP toxicological study no. 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; Human Equivalent Dose [HED] of approximately 100 mg for a 60 kg patient). 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).

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).

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 pharmacokinetic (PK) and preliminary efficacy assessment of CA-008 to inform future studies in our clinical development plan. This study was originally designed to look at 4 different doses of CA-008 (0.5 mg, 1 mg, 2 mg, and 3 mg), however based upon the relatively benign adverse event (AE) profile, the Data Management Committee gave the go-ahead for a 5th cohort (4.2 mg) to be added. The safety, efficacy and PK results for the Phase 1 bunionectomy study are shown in the current Investigators' Brochure.

Additionally, a follow-on Phase 2 bunionectomy study (CA-PS-201) was completed with 147 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. Based upon topline results, 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 (26% vs. 5% for placebo; $p = 0.039$).

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 SOC/PT (CA-PS-201)

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

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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
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

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

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 (%)
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
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

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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 (%)

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

1. A TEAE is defined as any new AE or an existing AE that worsens in severity during or after study drug administration. At each level of summarization (SOC or PT), subjects who experienced more than one TEAE were only counted once. All adverse events were coded using MedDRA, Version 21.0. Percentages are based on the number of subjects in the Safety Population. Many of the preferred terms chosen by investigators were vague and, in these cases, the verbatim terms are noted below for these.
2. "Administration site warmth": Two cases with the verbatim terms "warm feeling on surgical foot" and "warmth top of surgical foot".
3. "Application site pain": One case with the verbatim term "burning sensation at L foot surgical site"
4. "Application site rash": One case with the verbatim term "rash on both arms from tape"
5. "Feeling hot": Six cases with the following verbatim terms:
   a. "feeling hot" from 32h to 33h post study treatment
   b. "generalized warm feeling all over body" from days 5-11 post study treatment
   c. "warm sensation lower torso" from 17.6h to 96.6h post study treatment
   d. "warmth at neck area" from 0.9h to 1.2h post study treatment
   e. "feeling hot" from 18.7h-24.4h post study treatment
   f. "feeling hot" from 51.9h-54.4h post study treatment
6. "Infusion site edema": Six cases with the following verbatim terms:
   a. "edema at left hand IV site
   b. "edema – left arm proximal to AC IV site"
   c. "edema distal to left hand IV site"
   d. "edema at left forearm IV site"
   e. "edema on right hand at IV site"
   f. "edema left wrist at IV site"
7. "Infusion site pain": Three cases with the following verbatim terms:
   a. "soreness at left hand IV site"
   b. "stinging sensation at IV site upon attempting to flush"
   c. "pain left wrist at IV site"
8. "Edema peripheral": Two cases with the verbatim terms "right forearm edema proximal to IV site" and "moderate edema right foot"
9. "Pain": Four cases with the following verbatim terms:
   a. "stinging sensation on the dorsal aspect of the left foot" (the operated foot: one event on day 11 and one on day 13)
   b. "intermittent generalized body aches"
   c. "increased pain in right foot after putting pressure on toes"
   d. "worsening of post operative pain"
10. "Incision site erythema": one case with the verbatim term "erythema – dorsum right foot over 3-4 metatarsal retention incision" noted on days 10-14
11. "Incision site hematoma": two cases with the verbatim terms "superficial hematoma at surgical site" noted on days 10-17 post study treatment, and "superficial hematoma at incision" on days 9-16 post study treatment.
12. "Scar": One case with the verbatim term "full thickness fibrotic tissue proximal to the surgical site". The PI at this site noted that the individual who was performing surgical site assessments did not characterize findings as "typical" for the surgery and therefore not an AE or "atypical" and thus an AE.
13. "Wound": One case with the verbatim term "full thickness open wound at incision" noted on day 29 post study treatment and treated with wound debridement and resolved by day 58.
14. "Wound dehiscence": Each site was instructed to capture "atypical" findings at the surgical site as an AE with "atypical" being a finding different than what is normally seen with this type of surgery. All wound dehiscence cases were identified at site 102. The PI at this site noted that the individual who was performing surgical site assessments did not characterize findings as typical for the surgery (therefore not an AE) or atypical and thus designated as an AE, but instead captured all findings as an AE. Once the PI realized this, the individual was removed from study assessments. Unfortunately, this occurred after database lock and could not be adjusted. The PI noted that in retrospect the cases were mild in severity and most were likely typical for the type of surgery (examples 1-2 mm of wound puckering, a stitch showing or similar minor issues).
15. "ALT or AST increased": As can be seen, these 3 cases of each were captured in the CA-008 4.2 mg group. At site 102, 2 of the transaminase elevations were captured as related AEs. Subject 102-060 had "mild" increases in ALT 147 (4.6 X ULN) and AST 88 (2.2 X ULN) at the T96h assessment. They resolved without treatment and returned to normal by day 16. Subject 102-068 had "severe" increase in ALT 170 (5.3 X ULN) and "moderate" increase in AST 140 (3.5 X ULN). They resolved without treatment and returned to normal by day 15. While these were the only 2 related AEs captured for transaminases, Subject102-053 had mild and unlikely related elevations ALT/AST were 51 (1.6X ULN)/41 (1.03X ULN) at T96h and an Alk Phos elevation 142 (1.2X ULN). Additionally, there were 3 cases in the CA-008 0.7 mg group, 2 in the 2.1 mg group, 2 other cases in the 4.2 mg group, and 3 cases in the placebo group (one of which was a 9X increase from baseline value), respectively, that were normal at baseline and because elevated at T96h, but not captured as TEAEs. Additionally, there were 2, 3 and 2 cases, respectively, in the CA-008 0.7, 2.1 and 4.2 mg groups, where the transaminases were elevated at screening, but became normal at T96h.
16. "Limb discomfort": Two cases with the verbatim terms "pressure on plantar aspect of left foot" and "discomfort on dorsal aspect of left foot" (the operated foot in each case).
17. "Muscle spasm": Three cases with the following verbatim terms:
   a. "bilateral leg cramps"
   b. "muscle spams in neck and upper back"
   c. "muscle spams in left side of hip"
   d. "cramping in left calf"
18. "Muscle twitching": One case with the verbatim term "left shoulder twitching"
19. "Musculoskeletal pain": One case with the verbatim term "pain, right buttocks"
20. "Musculoskeletal stiffness": One case with the verbatim term "stiff neck"
21. "Pain in extremity": Four cases with the following verbatim terms:
   a. "pain on top of left foot"
   b. "left foot pain"
   c. "right heel pain"
   d. "severe pain in right surgical foot".
22. "Hyperhidrosis": Four cases with the following verbatim terms:
   a. "diaphoresis" from 19.7h to 19.8h post study treatment
   b. "diaphoresis" from 12.7h to 87.7h post study treatment
   c. "intermittent diaphoresis" from 7.2h to 33.3h post study treatment
   d. "intermittent diaphoresis" from 51.9h to 54.4h post study treatment
23. "Pruritus": Three cases with the following verbatim terms:

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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 (%)

a. "pruritus dorsal aspect of left foot" from 78.3h to 96.3h post study treatment
b. "right foot pruritis [sic]" from 39.9h to 40.9h post study treatment
c. "pruritis [sic] on left hand from 20.3h to 90.3h post study treatment

24. "Rash": Two cases with the verbatim terms "rash (back)" and "rash of left hand"
25. "Rash erythematous": One case with the following verbatim term: "erythematic rash on foot"
26. "Hot flush": One case with the verbatim term "hot flash" from 19.1h to 23.9h post study treatment

Source: Table 14.3.1.2

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 4 and Table 6). 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 5). 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-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 5. 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 6. 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
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

Table 6. 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
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

An additional Phase 2, single-ascending dose study was completed in patients undergoing complete 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. 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. No effect on pain relief was detected due to the small sample size and low doses of study drug administered.

5.4. Study Rationale

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

5.5. Dose Rationale

5.5.1. Selection of Doses

The safety of CA-008 was established in relevant animal models and supported by two clinical studies after 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 total knee arthroplasty (CA-PS-203) and total abdominoplasty (CA-PS-204) with doses up to 15 mg (concentration 0.15 mg/mL), as well as knowledge from prior human studies with an injectable formulation of capsaicin. Taken together, the characterization of the pharmacology, pharmacokinetics, and toxicology profiles and the anticipated benefits as well as the potential risks are considered appropriate to support the intended initial dose of 36 mg CA-008 (concentration 0.3 mg/mL), and if well-tolerated, followed by 60 mg (concentration 0.5 mg/mL) in this total knee arthroplasty study.

5.5.2. Selection and Timing of Dose

CA-008 is a pH labile prodrug of capsaicin that rapidly releases capsaicin after administration into tissue. Decision for single administration at the time of surgery is based on capsaicin's mechanism of action. Capsaicin exposure results in initial excitation followed by a functional desensitization of TRPV-1-expressing nociceptors which continues for some time after removal 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. 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 and tolerability of a single intraoperative administration of CA-008 or placebo in patients undergoing an elective TKA.

For Part B:

- Evaluate, during a specified post-operative time interval, the efficacy of 2 or 3 selected doses of CA-008 on reported pain in patients undergoing an elective TKA.

6.2. Secondary Objectives

For Part A:

- Evaluate the PK profile of a single intraoperative administration of CA-008 in patients undergoing an elective TKA.
- Evaluate, preliminarily, the activity of CA-008 on reported pain, opioid consumption, and PROs (PBOMs and ROM).
- Determine of the dose(s) for testing in Part B.

For Part B:

- Evaluate, during additional specified post-operative time intervals, the efficacy of 2 or 3 selected doses of CA-008 on reported pain in patients undergoing an elective TKA.
- 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), including knee range of motion (ROM).
- Evaluate the safety and tolerability of CA-008 or placebo in patients undergoing an elective TKA.
- Evaluate the PK profile of a single intraoperative administration of CA-008 in patients undergoing an elective TKA.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design and Plan

This is a two-part, Phase 1/2, randomized, double-blind, placebo-controlled study. In Part A, 2 or more exploratory sequential dose-escalation cohorts will be evaluated, each with administration of a single dose of CA-008 or placebo infiltrated/instilled during surgery in patients undergoing TKA.

In Part B, 2 or 3 active dose levels of CA-008 will be evaluated compared to placebo in a randomized, double-blind, parallel-group design.

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]).
- 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 TKA 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. Safety and drug effect assessments will focus on reported pain and need for analgesia.

7.2. Duration of Participation

Each patient is expected to be in the study approximately 76 days from screening to D29 + 2 days visit (however, this could be longer to follow any AE for resolution or establishment of a new baseline).

7.3. Dose Escalation and Cohort Expansion

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

- In-patient (i.e., through 96 h) safety and tolerability data from all 8 initial patients in a current cohort, including vital signs, physical examination, neurosensory examination, surgery site assessment, laboratory assessments, and adverse events;

- D8 ambulatory visit safety and tolerability data from at least 4 of the initial 8 patients in the current cohort, including vital signs, physical examination, neurosensory examination, surgery site assessment, and adverse events;
- D15 ambulatory visit safety and tolerability data from all patients in any previously completed cohort, including vital signs, physical examination, neurosensory examination, surgery site assessment, and adverse events.

Also, please note that cohorts in Part A will be randomized 3:1 active to placebo in a blocked randomization of 4 patients so that the first 4 patients will include 3 patients receiving active drug and 1 patient receiving placebo.

7.4. Study Stopping Rules

Study enrollment will be paused if patients experience intolerable "related" TEAEs, (shown in Table 7) as defined below:

- 1 or more patients with any grade 4 "related" TEAE in any of the categories
- 2 or more patients with the same grade 3 "related" TEAE in any of the categories
- 2 or more patients with the same grade 3 or 4 "related" TEAE shown in Section 17.1, Appendix A or found in the in the toxicity grading scale cited therein.

"Related" includes possibly, probably, and definitely related causality assessments.

Refer to Table 7 below for descriptions/definitions of AE severity grading.

In Part A, should a stopping rule be triggered, the Sponsor's medical monitor, the CRO medical monitor, and the relevant PI will review the blinded data to determine whether or not it is appropriate to resume enrollment with the same or a modified dose. Unblinding of an individual treatment assignment may be required to complete this safety assessment.

In Part B, should a stopping rule be triggered, the Sponsor's medical monitor, the CRO medical monitor, the relevant PI, and an independent medical monitor will review the blinded data to determine whether or not it is appropriate to resume enrollment, 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 7. 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, 18-80 years of age inclusive, who are planning to undergo an elective unilateral TKA.

8.1.1. Number of Participants

Part A:

- Cohort #1: N = 8 (randomized 3:1 CA-008 to placebo), no more than 4 patients dosed per week
- Cohort #2: N = 8 (randomized 3:1 CA-008 to placebo), no more than 4 patients dosed per week

After review of cohort study data, a cohort may be expanded to N = 16. One (1) or 2 additional cohorts may be added with N = 8 or 16, in each cohort, using the same 3:1 randomization ratio. The total sample size in Part A is thus 16-64 patients.

Part B:

In Part B, a total of 150-300 patients will be randomized in 3-4 parallel arms (with 50-100 patients in each arm). The number of patients to be enrolled in Part B will not exceed 300.

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 unilateral TKA under spinal anesthesia with sedation, without collateral procedure or additional surgeries;
2. Appropriate candidate for spinal anesthesia, including no contraindications, no anatomical constraints;
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 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 ≤ 42 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 painful condition, other than pain in the knee to be replaced, that may require analgesic treatment during the study period or may confound post-surgical pain assessments;
    b. moderate to severe chronic neuropathic pain or signs of central sensitization;
    c. active skin disease or other clinically significant abnormality at the anticipated site of surgery that could interfere with the planned surgery.
2. The patient is tolerant to opioids (opioid-tolerant) defined as someone who has been receiving or has received chronic opioid therapy (use within the 2 weeks prior to surgery and duration of use > 4 weeks) greater than 15 mg of oral morphine equivalents per day for greater than 3 out of 7 days per week over a one-month period within 6 months of screening.
3. The patient has a known allergy (or contraindication) to any of the following: chili peppers, capsaicin or the components of CA-008, ropivacaine HCl, ketorolac, 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:
    - 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;
    - Within the 7 days prior to surgery, taking any central nervous system (CNS) active agent as an analgesic adjunct medication, such as anticonvulsants, antidepressants (such as SNRIs, SSRIs, and tricyclic antidepressants), benzodiazepines, sedative-hypnotics, clonidine and other central alpha-2 agents (e.g., tizanidine), ketamine, or muscle relaxants;
        - 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.
        - If the patient is taking centrally- and/or peripherally-acting analgesic medications, such as acetaminophen, NSAIDs, tramadol, or opioids, **for knee-related pain**, the patient may participate in the study if not opioid-tolerant (defined above) and 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.
    - Within the 7 days prior to the planned surgery and throughout the study, taking (a) antiarrhythmic drugs (except beta-blockers and digoxin); (b) warfarin or other anticoagulants (see exception below); (c) lithium; or (d) aminoglycosides or other antibiotics for an infection (except for ophthalmic use);
    - 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);
    - 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;
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 to a total volume of 120 mL.

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

The proposed initial doses of CA-008 to be evaluated in Part A are:

- Cohort #1: CA-008 36 mg in 120 mL (0.3 mg/mL) or placebo in 120 mL
- Cohort #2: CA-008 60 mg in 120 mL (0.5 mg/mL) or placebo in 120 mL
- Additional sequential cohorts may receive doses between 15-90 mg or placebo
- Modifications to the total study drug dose, volume, drug concentration, and allocation for subsequent patients may occur based on information from prior patients.

The doses of CA-008 to be administered in Part B will be in the range of 15-90 mg and will not exceed the maximum dose administered safely in Part A. Doses will be selected based on safety and tolerability data from Part A and from prior studies of CA-008.

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. Inpatient Analgesia

During the surgery, ensure that each patient has received at least 100 mcg of intravenous (IV) fentanyl with adjustments above this dose per anesthesiologist's discretion.

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

- IV hydromorphone, 1 mg
- IV ketorolac, 30 mg (for example, ketorolac full prescribing information is available at: http://www.sagentpharma.com/wpcproduct/ketorolac-tromethamine-injection-usp/ [Sagent Pharmaceuticals 2018]). Dose adjustments may be made per surgeon/anesthesiologist discretion to accommodate the patient's age and health status.
- IV acetaminophen, 1 g (Ofirmev®, Mallinckrodt Pharmaceuticals 2018) full prescribing information at http://ofirmev.com/.

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

If a patient had an inadequate level of anesthesia from the spinal anesthetic and received a general anesthetic, the patient should receive IV hydromorphone, 1 mg, within 30 minutes of anesthesia induction and up to 1 mg of IV hydromorphone within 15 minutes of the end of surgery.

Patients who develop clinically significant hemodynamic instability or other anesthesia complication prior to study drug administration should not receive study drug; in Part A, 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.

9.2.2. Inpatient Rescue Medications

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).

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 below. Rescue medication will be administered at these times only upon request based on the currently reported pain score.

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

After discharge from the PACU, patients are followed through T96 ($\pm$ 4 h) as inpatients in the inpatient unit where safety and activity/efficacy evaluations will be performed.

From the time of PACU discharge through T24:

- Administer IV hydromorphone, 0.5 mg Q15 minutes PRN pain NRS ≥ 4 as reported by patients.

After T24:

- Administer PO oxycodone, 10 mg Q4 h PRN pain NRS 5-10.
- Only PO oxycodone may be used as rescue. If a patient still requires IV opioid rescue after T24, then the patient will revert to IV analgesia management per institutional guidelines. These patients will still also be followed for NRS, safety, and other assessments.

Patients will be encouraged to use rescue medication only for moderate-to-severe pain scores

(NRS 5-10); however, rescue with oxycodone 10 mg PO may be requested at any time (i.e., even when NRS < 5) and medication will be provided when requested.

Note: Since rescue medication may be taken at any time, it will not be considered a protocol deviation during the inpatient or outpatient periods if a patient takes a rescue medication more frequently than the protocol prescribing interval, eg, if oxycodone is prescribed as 10 mg PO Q4h PRN pain, it is not a protocol deviation if a dose is taken fewer than 4 hours following a prior dose. This will be recorded in the rescue medication list and/or in the diary.

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 prior to rescue medication taking effect, a second dose of rescue medication should not be administered.

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.

9.2.3. 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 Q6 hours for mild pain (i.e., NRS < 5) (unless contraindicated)
    - Acetaminophen 325 mg/Oxycodone 5 mg (Percocet) – 1 or 2 tablets PO Q 4-6 h for moderate-severe pain (i.e., NRS 5-10). 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. The timing of the pre-rescue NRS will be assumed to be the same as the timing of the pre-rescue medication.

Note:

- Instruct patients to use acetaminophen as the initial option for treating pain.
- If opioids other than oxycodone are taken for rescue medication, eg, hydrocodone, they will be recorded in the diary and included in the total amount of opioid rescue medication.

Document the number of 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.

The use of these and/or other medications to treat pain will be documented in the patient diary through the D15 visit.

Note: All medications taken during the outpatient period through the D29 visit will be documented as concomitant medications.

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 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 each cohort in Part A will be randomized in a ratio of 3:1, active to placebo, in a blocked randomization of 4 patients so that the first 4 patients will include 3 patients receiving active drug and 1 patient receiving placebo. After review of cohort study data, a cohort may be expanded to N = 16. One (1) or 2 additional cohorts may be added with N = 8 or 16, using the same 3:1 randomization ratio.

In Part B, a blocked randomization for each site will be used with a block size that is three times the number of study arms, e.g., if there are 4 treatment arms, the block size will be 12 patients.

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 will be double-blinded during the study. The patient, investigational site personnel with the exception of 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.

Under normal circumstances, the blind will not be broken until all participants have completed treatment. In case of emergency, and only if the information is required by the Investigator to ensure 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 an SAE, and therefore, all procedures for the reporting of a SAE must be followed.

9.5. Prior and Concomitant Therapy

All non-study medications, including prescription, 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, and throughout the study, 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 is 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:

1. Consuming any alcohol
2. Smoking or vaping (nicotine-containing or other substances)
3. Illicit drug use or non-medical use of therapeutic drugs not allowed by the protocol

4. 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
- 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 assessments 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 physical examination (PE) (without a breast, genital, or rectal examination), including height and weight;
- Vital signs - heart rate (HR), blood pressure (BP), respiratory rate (RR) 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 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.
    - Urinalysis: including macroscopic analysis and, if indicated, microscopic analysis.
- Urine drug screening (UDS);
- Alcohol breath/saliva test;
- Serum pregnancy test (FCBP), βhCG test at screening, if applicable;

- FSH (if post-menopausal only);
- 12-lead electrocardiogram (ECG);
- KOOS survey (Section 10.3.10);
- Patient Reported Outcomes Measurement Information System (PROMIS) 10 Global Health questionnaire (Section 10.3.11);
- Knee Range of Motion (ROM) (Section 10.3.12);
- Patient pain assessment training;
- 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. 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 with inspection of the planned area of surgery;
- Urine pregnancy test (FCBP), if applicable, (unless post-menopausal status confirmed by FSH), usually to be done within 24 hours prior to surgery;
- UDS;
- Alcohol breath/saliva test;
- Blood draws for PK analyses;
- Vital signs - HR, BP, RR (supine), and temperature (oral);
- Patient to watch pain training video;
- Randomize the patient to treatment after confirmation of patient's continued eligibility;
- AE assessment (record any current conditions as medical history).

10.1.2.2. Anesthesia and Surgery (D1)

The surgery will be performed under spinal anesthesia (isobaric bupivacaine [preservative-free] 0.5% 12-15 mg, and fentanyl 25 mcg) with adequate supplemental sedation, typically with

midazolam (up to 5 mg), fentanyl (up to 100 mcg), and propofol infusion, but anesthesia and sedation will be per institutional guidelines.

If the patient appears to have an inadequate level of anesthesia from the spinal anesthetic ("failed spinal anesthetic"), the patient should receive a general anesthetic with either an inhaled anesthetic or propofol infusion with or without nitrous oxide (N_20).

In addition, patients will receive ropivacaine hydrochloride (RopiHCl) delivered as follows:

- Prior to start of surgery under ultrasound guidance:
    - Femoral nerve block: RopiHCl 0.5%, 12 mL (60 mg)
    - IPACK infiltration: RopiHCl 0.2%, 20 mL (40 mg)

And

- Immediately after surgical incision:
    - Periarticular infiltration: RopiHCl 0.2%, 50 mL (100 mg)
    - Periarticular infiltration is to be performed using a 22-gauge needle as follows:
    - After the surgical incision and prior to the arthrotomy, infiltrate 25 mL of RopiHCl into the tissue adjacent to and along the planned arthrotomy incision site.
    - After the arthrotomy and after the initial dissection but prior to bony resection/cuts, infiltrate 25 mL of RopiHCl into the residual soft tissue envelope of the distal femur and proximal tibia that has been surgically debrided (eg, the fat pad, subperiosteal dissection, synovium, etc).

Note regarding periarticular infiltration: 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 of target tissues). Conversely, study drug (active or placebo) will be administered to target tissues "on the way out" (at the time of device implantation and surgical closure).

The total RopiHCl should not exceed 200 mg. See Section 17.5, Appendix E for guidance on RopiHCl dosing.

Note: **IPACK = I**nterspace between the **P**opliteal **A**rtery and the **C**apsule of the posterior **K**nee between the femoral condyles)

Standard 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.

As per institutional guidelines, a pneumatic tourniquet is inflated prior to incision and deflated at the conclusion of the surgery. The time of tourniquet placement and removal will be documented.

For failed spinal anesthetic (either inability to place or inadequate level), patient may receive general anesthesia that includes additional intraoperative analgesics as described in Section 9.2.1.

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

The initial total study drug volume administered per patient will be 120 mL. This initial 120 mL of study treatment administered per patient in the first study cohort will be delivered during the surgical procedure in 4 divided aliquots. The initial allocation will be:

(a) a total of 15 mL onto the cut surfaces following each osteotomy;

(b) 30 mL prior to hardware placement;

(c) 60 mL following hardware placement; and

(d) 15 mL following closure of the joint capsule.

Modifications to the total study drug dose, volume, drug concentration, and allocation for subsequent patients may occur based on information from prior patients. Minor variability may occur due to implementation by different surgeons and to anatomical differences.

Study treatment is to be administered intraoperatively as a single administration via "surgical site" infiltration/instillation prior to wound closure. The "surgical site" is defined as the area extending approximately 5 cm in all directions (lateral/medial/proximal/distal/deep) from the incision and osteotomy sites and surrounding tissues. The "surgical site" will include all tissue traumatized by the surgical procedure, ie, tissue that has been dissected, cut, electrocauterized (bovied), or sutured, etc.

Record start and end time of study treatment instillation. Syringe numbers correspond to instructions provided in the pharmacy manual.

A total volume of 15 mL will be instilled on cut bone surfaces. Study treatment will be instilled on the cut surfaces (cortical and cancellous bone) immediately after each osteotomy using a syringe with a soft catheter (eg, Angiocath). The initial allocation of volume of study treatment for each osteotomy site will be:

Syringe #1: Femur bone: Instill ~8 mL in two aliquots separated by >1-2 minutes

Syringe #2: Tibia bone: Instill ~5 mL in two aliquots separated by >1-2 minutes

Syringe #3: Patella bone: Instill ~2 mL in two aliquots separated by >1-2 minutes

Note: Instillation of study treatment at each osteotomy site to be divided into two equal portions with administration separated by >1-2 minutes (e.g., for femur, instill 4 mL, repeat after >1–2 minutes).

Note: The technique for all tissue infiltration described below should include multiple, small-volume micro-injections along the course of each needle track. The intent is to distribute the study drug widely across the nerve endings in the surgical site where TRPV1 receptor targets are

located not in isolated deep depot injections along nerves. Study drug is designed for field block rather than conduction block

Prior to hardware placement, 30 mL of study treatment will be infiltrated using a control syringe with a 22-gauge needle as follows:

Infiltrate periosteum of distal femur:

Syringe #4: Femoral periosteum area (20 mL):

These three infiltration sites are optimally accessed with the syringe held in front of the joint and the needle angled proximally (cephalad). The injections can be made from within the joint.

- Infiltrate ~7-8 mL into periosteum of lateral half of distal femur (lateral femoral periosteum) AND

- Infiltrate ~7-8 mL into periosteum of medial half of distal femur (medial femoral periosteum) AND

- Infiltrate ~5 mL into the meniscectomy site and along the remnant edge of the coronary (meniscotibial) ligament

Note: Use multiple small-volume injections delivered slowly. Infiltration should cause a wheal to form under the periosteal tissue and there should be minimal extravasation of the injection fluid into the joint.

Syringe #5: Posterior capsule area (10 mL):

- Infiltrate 10 mL into the posterior aspect of the capsule

Note: Use multiple small injections across the back of the knee. Do not plunge into the midline or laterally near the peroneal nerve.

After the implants have been placed, with the leg in full extension, 60 mL of study treatment will be infiltrated as follows (working from top to bottom, clockwise or using another standardized method per surgeon discretion):

Syringe #6: Distal femur area: Infiltrate ~15 mL into the deep tissue of the distal femur, i.e., capsule and other soft tissue that can be associated with postoperative pain

Infiltrate a total of ~30 mL divided equally into the medial and lateral gutter areas ensuring coverage of the periosteal borders

Infiltrate a total of ~30 mL divided equally into the medial and lateral gutter areas ensuring coverage of the periosteal borders:

Syringe #7: Medial gutter area (15 mL)

Syringe #8: Lateral gutter area (15 mL)

Note: The gutter area is to include (a) any tissue that has been traumatized by the surgery, i.e., that has been cut, sutured, electrocauterized (bovied), dissected, etc, and (b) the deeper contiguous tissues that have not been directly traumatized by the surgical procedure.

Syringe #9: Peripatellar area: Infiltrate ~5 mL around the peripatellar region

Syringe #10: Tibial tubercle area: Infiltrate ~10 mL divided equally medial and lateral to the tibial tubercle

Note: Syringes #7-10 are intended to include any tissue that has been traumatized by the surgery. This would include the arthrotomy "edges," retinaculum, etc.

Note: Place the needle to the desired depth and inject as the needle is being withdrawn. Aspirate when needed or in areas of concern. Aim to deliver as much of the liquid into the tissue as possible.

Following closure of the joint capsule,

Syringe #11: Intra-Articular ("Capsule"): Instill ~15 mL "intra-articularly" (lateral approach) and move the joint through full range of motion.

10.1.4. Post-surgery: T0 (Admission into the PACU) to D5 (Discharge)

Following surgery, patients will be transferred to the PACU where they will undergo an assessment of safety and efficacy over the next 96 (± 4) hours. T0 is the time of admission into the PACU (as recorded in notes by the PACU nurse). The schedule of assessments is as follows:

- Patients with inadequately controlled pain may request rescue at any time during T0 to D5; however, patients will be encouraged to receive rescue medication only with an NRS ≥ 4.
- Pain intensity (assessed with NRS):
    - 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). If the patient is able to provide responses, obtain NRS scores at T0 plus 1 hour (T1), T0 plus 2 hours (T2, etc.), 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, evoked NRS twice daily after physical therapy (most preferred) or ambulation for approximately 10 yards (preferred) or transfers to/from bed or wheelchair. Obtain these NRS scores after morning physical

therapy or ambulation at 10:00 AM (± 1 h) and after afternoon physical therapy or ambulation 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.

- Vital signs - HR, BP, RR (supine), and temperature (oral) - are assessed together post-surgery at T2, T6, T12, and T24, and every 8 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 post-surgery, and ± 15 minutes for all other times.
- Targeted PE: T96 (± 4 h) (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. 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 17.15, Appendix O). A digital photograph of the wound site should be taken (Section 17.14, Appendix N).
- Neurosensory testing of the surgical area near the incision (compared to a similar site on the opposite leg): 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.
- KOOS Survey: T96 (± 4 h) prior to discharge from the inpatient unit (Section 10.3.10).
- Knee ROM at T48 (± 4 h) and Discharge (T96) (Section 10.3.12).
- Ability to walk >100 ft (> 30 m) with only the aid of a walker during twice-daily inpatient physical therapy sessions (or assessed by site staff) on D3, D4, and D5 to allow assessment of discharge readiness.

- Performance-based functional outcome measures (PBOMs) at T96 (± 4 h) (Section 10.3.13):
    1. Sit to Stand Test (also known as 30-Second Chair Stand) Assessment (Section 17.11, Appendix K);
    2. Walking Speed Test (Section 17.12, Appendix L);
    3. TUG Test (Section 17.13, Appendix M).
- Clinical laboratory tests T96 (± 4 h) prior to discharge from the inpatient unit:
    - Hematology/Coagulation: hemoglobin, hematocrit, white blood cell count with differential, red blood cell 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.
    - Urinalysis: including macroscopic analysis and, if indicated, microscopic analysis.
- Blood draw for PK analysis: The time points for whole blood collection will be at pre-dose (from check-in and up to 30 minutes before the start of surgery), and pharmacokinetic time (PKT) 0.167 h (10 min), 0.25 h (15 min), 0.5 h (30 min), 0.75 h (45 min), and at 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours after the last study treatment instillation (total of 15 samples). In the event of an AE, an unscheduled PK draw will be performed.
- Total post-surgical opioid consumption converted to an oral morphine equivalent dose (OME).
- 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).

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 acetaminophen 325 mg/oxycodone 5 mg (Percocet) one or two tablets PO Q 4-6 h PRN moderate-severe pain (i.e., NRS 5 – 10). Document the number of tablets prescribed and also document any additional prescriptions required if the patient's pain continues to be an issue requiring additional opioid medication.

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

10.1.5. Outpatient Phase: D5 (after Discharge) through D8

After discharge at T96 (± 4 h) and through D8, 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) at rest and during ambulation (e.g., with the use of a walker or a cane) 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.

Patients will return to the study center on D8 (+ 1 day) for the following assessments:

- Patient home diary review (pain intensity [NRS score] and pain medication);
- Vital signs - HR, BP, RR (supine), and temperature (oral);
- Targeted PE;
- Surgical site assessment: 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 17.15, Appendix O). A digital photograph of the wound site should be taken (Section 17.14, Appendix N);
- Neurosensory testing of the surgical area near the incision (compared to a similar site on the opposite leg):
    - 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.
- Query the patient as to whether they have experienced any worsening (rebound) pain at the surgical site (Section 10.3.9);
- KOOS Survey on D8 (+ 1 day) (Section 10.3.10);
- Knee ROM (D8) (Section 10.3.12);
- Concomitant medication use/concomitant treatments;
- AE assessment.

10.1.6. Outpatient Phase: D9 through D15

From D9 through D15, patients will assess their pain intensity in their diary.

- Instruct the patient to document their NRS scores twice daily at 11:00 AM (± 1 h) and 7:00 PM (± 1 h) at rest and during ambulation (e.g., with the use of a walker or a cane) for approximately 10 yards. Note that the actual time of these assessments must be documented in the diary whenever possible. Instruct the patient 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.

Patients will return to the study center on D15 (+ 2 days) for the following assessments:

- Patient home diary review (pain intensity [NRS score] and pain medication) and collection (Section 10.3.8);
- Vital signs - HR, BP, RR - (supine), and temperature (oral);
- Targeted PE;
- Surgical Site assessment: 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 17.15, Appendix O). A digital photograph of the wound site should be taken (Section 17.14, Appendix N);
- Neurosensory testing of the surgical area near the incision (compared to a similar site on the opposite leg):
    a. 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.
    b. 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.
- Query the patient as to whether they have experienced any worsening (rebound) pain at the surgical site (Section 10.3.9);
- KOOS Survey (Section 10.3.10);
- PROMIS 10 Global Health questionnaire (Section 10.3.11);
- Knee ROM (Section 10.3.12);
- PBOMs: (Section 10.3.13):
    1. Sit to Stand Test Assessment (Section 17.11, Appendix K);
    2. Walking Speed Test (Section 17.12, Appendix L);

3. TUG Test (Section 17.13, Appendix M).

- Concomitant medication use/concomitant treatments;
- AE assessment.

10.1.7. 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), and temperature (oral);
- Targeted PE;
- Surgical site assessment: 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 17.15, Appendix O). A digital photograph of the wound site should be taken (Section 17.14, Appendix N);
- Neurosensory testing of the surgical area near the incision (compared to a similar site on the opposite leg):
    - 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.
- Query the patient as to whether they have experienced any worsening (rebound) pain at the surgical site (Section 10.3.9);
- KOOS survey (Section 10.3.10);
- PROMIS 10 Global Health questionnaire (Section 10.3.11);
- Knee ROM (Section 10.3.12);
- PBOMs: (Section 10.3.13):

    4. Sit to Stand Test Assessment (Section 17.11, Appendix K);
    5. Walking Speed Test (Section 17.12, Appendix L);
    6. TUG Test (Section 17.13, Appendix M).

- X-ray of the operated knee (and later if any evidence of abnormalities in bone healing until resolution or stabilization);
- Concomitant medication use/concomitant treatments;
- AE assessment.

10.1.8. 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), and temperature (oral);
- Targeted physical examination;
- 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) (Section 17.14, Appendix N);
- Neurosensory testing of the surgical area (Section 10.3.21);
- Query the patient as to whether they have experienced any worsening (rebound) pain at the surgical site (Section 10.3.9);
- KOOS survey (Section 10.3.10);
- PROMIS 10 Global Health questionnaire (Section 10.3.11)
- 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) (Section 17.14, Appendix N);
- Neurosensory testing of the surgical area (Section 10.3.21);
- Query the patient as to whether they have experienced any worsening (rebound) pain at the surgical site (Section 10.3.9);
- KOOS survey (Section 10.3.10);
- PROMIS 10 Global Health questionnaire (Section 10.3.11);
- 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) (Section 17.14, Appendix N);
- Neurosensory testing of the surgical area (Section 10.3.21);
- Query the patient as to whether they have experienced any worsening (rebound) pain at the surgical site (Section 10.3.9);
- KOOS survey (Section 10.3.10);

- PROMIS 10 Global Health questionnaire (Section 10.3.11);
- X-ray of the operated knee to ensure proper healing. Follow patient until resolution or stabilization;
- Concomitant medication use/concomitant treatments;
- AE assessment.

10.1.9. 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 EDC. At a minimum, the following should be performed:

- Vital signs - HR, BP, RR - (supine), 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 (Section 17.14, Appendix N);
- Neurosensory testing of the surgical area (Section 10.3.21);
- Concomitant medication use/concomitant treatments;
- 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 (or later if necessary), 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 T24, then the patient will be withdrawn from activity/efficacy assessments but continue serial NRS and safety assessments and revert to IV analgesia management per standard-of-care. These patients will still be followed for pain and safety assessments.

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.

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:

1. Withdraw from activity/efficacy assessments but agree to participate in all study safety assessments;
2. Withdraw from activity/efficacy assessments but agree to participate in limited study safety assessments;
3. 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:

4. 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;
5. At the request of the Sponsor, regulatory agency, or Institutional Review Board (IRB);
6. Patient is lost to follow-up;
7. Patient treatment allocation is unblinded (i.e., individual code break; Section 9.4);
8. 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:

9. Patient refuses or is unable to adhere to the study protocol;
10. Major protocol violation;
11. Pregnancy;
12. Use of unacceptable concomitant medication(s);
13. It is not considered in the best interest of the patient to continue;
14. 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 informed consent form (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 confirmed during screening (or FSH above the relevant laboratory value for post-menopausal status).

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 possible pain) (Section 17.6, Appendix F).

Patients will report or record the intensity of their current pain at the knee surgical site 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). If the patient is able to provide responses, obtain NRS scores at T0 plus 1 hour (T1), T0 plus 2 hours (T2, etc.), 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, evoked NRS twice daily after physical therapy (most preferred) or ambulation for approximately 10 yards (preferred) or transfers to/from bed or wheelchair. Obtain these NRS scores after morning physical therapy or ambulation at 10:00 AM (± 1 h) and after afternoon physical therapy or ambulation at 4:00 PM (± 1 h).
- During the inpatient stay, pain scores may be skipped between the hours of 12:00 AM 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) at rest and during ambulation (e.g., with the use of a walker or a cane) for approximately 10 yards. Note that the actual time of these assessments must be documented in the diary whenever possible. Instruct the patient to:
    - Obtain the morning NRS assessment;
    - Obtain the evening NRS assessment;

- Opioid and non-opioid rescue medication (dose, date, time) must be recorded in the diary through D15, including a pre-rescue NRS score.

10.3.9. Worsening (Rebound) Pain at the Surgical Site

Patients will be queried at each outpatient follow up visit as to whether they have noted any worsening pain (rebound pain) at the surgical site since the prior visit report (Section 17.7, Appendix G).

10.3.10. Knee Injury and Osteoarthritis Outcome Score (KOOS)

Patients will complete the KOOS survey at designated times during the study and after administration of study treatment (at Screening, T96, D8, D15, and D29) (Section 17.8, Appendix H). The KOOS survey was developed in the 1990s as an instrument to assess the patient's opinion about their knee and associated problems (see http://www.koos.nu/). Note that for purposes of this study, responses in the KOOS will not be considered or captured as spontaneous AEs.

10.3.11. PROMIS 10 Global Health Questionnaire

Patients will complete the PROMIS 10 Global Health questionnaire at Screening, D15, and D29 (Section 17.9, Appendix I).

10.3.12. Knee Range of Motion (ROM)

Patients will have their Knee ROM tested using a goniometer at Screening, T48 (± 4 h), T96/Discharge, D8, D15, and D29 (Section 17.10, Appendix J).

10.3.13. Performance-Based Objective Measures (PBOMs)

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

1. Sit to Stand Test Assessment (Section 17.11, Appendix K);
2. Walking Speed Test (Section 17.12, Appendix L);
3. TUG Test (Section 17.13, Appendix M).

10.3.14. 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 of OMEs to calculate the oral morphine equivalent 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.

10.3.15. Clinical Laboratory Assessments

All protocol-specified laboratory tests on blood and urine samples will be collected, processed, shipped, and analyzed according to instructions from a selected central laboratory. The 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, biochemistry, and urinalysis assessments are listed in Table 8.

Table 8. Clinical Laboratory Assessments

Hematology	**Chemistry**	**Urinalysis**
Hematocrit Hemoglobin Red blood cell (RBC) count Total and differential (absolute) white blood cell count Platelet count	Sodium Potassium Calcium Chloride Glucose Creatinine BUN Albumin Tot Bili ALT AST GGT Alkaline phosphatase	Color Turbidity pH Specific gravity Ketones Protein Glucose Bilirubin Occult blood / Nitrite Urobilinogen Leukocyte esterase Microscopic examination of sediment, *only if urinalysis dipstick results are abnormal*
Coagulation		
Activated partial thromboplastin time (aPTT) Prothrombin time (PT) / International normalized ratio (INR)		
Endocrinology 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 (βhCG) 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 × ULN, Tot. Bili > 2 × ULN, and Alk Phos > 2 × ULN will be considered an adverse event, as well as any other changes deemed clinically significant by the Investigator.

10.3.16. 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 anti-depressants, 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 3 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 over-the-counter medication (that doesn't otherwise exclude the patient as determined by the investigator), then the patient may continue to participate in the study

10.3.17. Vital Signs

Vital signs (supine) will consist of HR, BP, RR, and temperature (oral) following a rest period. Vital signs will be assessed per the Schedule Assessments (Table 1). One missed scheduled assessment of vital signs will not be considered a protocol deviation. Two missed assessments of vital signs in a row is a protocol deviation.

10.3.18. 12-Lead Electrocardiogram (ECG)

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.

10.3.19. Physical Examination

A complete PE including all major body systems (general appearance, HEENT, neck, neurologic, cardiovascular, lungs, abdomen, skin, extremities, genitourinary, lymph nodes, and musculoskeletal systems) will be performed at Screening. A focused interim or targeted PE will be performed pre-surgery and after surgery during the inpatient and outpatient periods (see Table 1).

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

10.3.20. 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 (0-10) where a

score of 0 is "Completely unsatisfied," and a score of 10 is "Completely satisfied" (Section 17.14, Appendix N). 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. When assessed on D29, if the Investigator observes insufficient wound or bone healing or to ensure an ongoing AE has resolved, the patient will be scheduled for a follow-up visit.

If there are skin reactions atypical for the type of surgery, e.g., more than expected erythema, drainage, bruising or hematoma, induration, swelling, or other skin changes, they should be documented as AEs, graded for severity, and followed regularly until resolution or establishment of a new baseline (the grading guide for atypical wound findings may be useful to the Investigator: Section 17.15, Appendix O).

10.3.21. Neurosensory Testing

Neurosensory testing of the skin surrounding the incision (compared to a similar site on the opposite leg) will be conducted per the Schedule of Assessments (Table 1). This evaluation will include the details described in Section 17.16, Appendix P.

- 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.

10.3.22. Assessment of Adverse Events

All AEs and SAEs will be documented and followed from the time the patient has signed the ICF until D29 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 procedure. Serious AEs and AEs that have been designated as possibly related to study drug will be followed until resolution or stabilization. Further details on AEs, including definitions, elicitation, and reporting are provided in Section 11.

10.3.23. 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 sample collection will be performed on all patients. The time points for whole blood collection will be at pre-dose (from check-in and up to 30 minutes before the start of surgery), and at PKT 0.167 h (10 min), 0.25 h (15 min), 0.5 h (30 min), 0.75 h (45 min), and at 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours after the last study treatment instillation (total of 15 samples).

Part B:

PK sample collection will be performed at one site. The time points for whole blood collection will be at pre-dose (from check-in and up to 30 minutes before the start of surgery), and at PKT 0.167 h (10 min), 0.25 h (15 min), 0.5 h (30 min), 0.75 h (45 min), and at 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours after the last study treatment instillation (total of 15 samples). At least 12 of the 15 samples should be collected in each of these patients. The number of patients will depend on the number of dose levels being tested but approximately 15 patients per dose level are planned.

10.4. Safety, Tolerability, Pharmacokinetic (PK), and Efficacy Endpoints

10.4.1. Safety Endpoints

Safety endpoints include the following:

- Incidence of spontaneously reported TEAEs or SAEs;
- Clinical laboratory test results;
- Vital sign measurements;
- ECG results;
- PE findings;
- Surgical site wound assessment findings;
- Neurosensory testing results;
- Knee x-ray (only if any evidence of abnormalities in bone healing);
- Presence of worsening (rebound) pain;
- Concomitant medication use/concomitant treatments.

10.4.2. Pharmacokinetic (PK) Endpoints

Full details of pharmacokinetics 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).

Part A:

PK sample collection will be performed on all patients. The time points for whole blood collection will be at pre-dose (from check-in and up to 30 minutes before the start of surgery),

and at PKT 0.167 h (10 min), 0.25 h (15 min), 0.5 h (30 min), 0.75 h (45 min), and at 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours after the last study treatment instillation (total of 15 samples).

Part B:

PK sample collection will be performed at one site. The time points for whole blood collection will be at pre-dose (from check-in and up to 30 minutes before the start of surgery), and at PKT 0.167 h (10 min), 0.25 h (15 min), 0.5 h (30 min), 0.75 h (45 min), and at 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours after the last study treatment instillation (total of 15 samples). At least 12 of the 15 samples should be collected in each of these patients. The number of patients will depend on the number of dose levels being tested but approximately 15 patients per dose level are planned.

Actual sampling times will be used to calculate plasma-derived PK parameters.

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, SD, median, minimum and maximum values, and coefficient of variation (CV%), geometric mean and geometric coefficient of variation (geoCV%). PK parameters include (but are not limited to) maximum observed plasma drug concentration (C_{max}), T_{max}, half-life, and areas under the plasma concentration-time curve ($AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$).

Note: A PK sample should be collected during the in-patient phase of the study as part of the evaluation of any SAE or severe TEAE.

10.4.3. Efficacy Endpoints

10.4.3.1. Efficacy Endpoints for Part A

There are no efficacy endpoints for Part A.

10.4.3.2. Efficacy Endpoints for Part B

The primary efficacy endpoint for Part B:

- NRS AUC at rest from T12 to T96 ($AUC_{12\text{-}96}$). NRS AUC is the weighted sum of current pain intensity (SPI) assessments for a specified time interval.

Key secondary efficacy endpoints:

- Evoked pain NRS: AUC_{12-96}
- Percentage of patients who do not require opioids (i.e., opioid-free or OF) from T24 to T96: $OF_{24\text{-}96}$
- Total opioid consumption (in daily OME) = OC from T12 to T96: $OC_{12\text{-}96}$
- NRS at rest and evoked NRS from T12 to D8: $AUC_{12\text{-}D8}$

Exploratory efficacy endpoints for Part B are:

- Using rest NRS: $AUC_{0\text{-}24}$, $AUC_{0\text{-}96}$, $AUC_{6\text{-}96}$, $AUC_{24\text{-}96}$, $AUC_{96\text{-}D8}$, and $AUC_{96\text{-}D15}$;

- Using evoked NRS: $AUC_{0\text{-}96\ (ambulation)}$, $AUC_{0\text{-}D8\ (ambulation)}$, $AUC_{24\text{-}D8\ (ambulation)}$, and $AUC_{96\text{-}D15\ (ambulation)}$;
- Time-specific mean NRS scores at T48, T72, T96, T120, T144, and T168;
- $OC_{0\text{-}96}$, $OC_{24\text{-}48}$, $OC_{24\text{-}72}$, $OC_{24\text{-}96}$, $OC_{24\text{-}D8}$, and $OC_{24\text{-}D15}$;
- $OF_{0\text{-}96}$, $OF_{24\text{-}D15}$, $OF_{96\text{-}D8}$, and $OF_{96\text{-}D15}$;
- Additional exploratory and sensitivity analyses rest/evoked NRS AUC, OC, and OF during different intervals may be undertaken;
- Knee ROM: mean and proportion of patient s with > 90° and proportion of patients with > 115° active flexion at T48 (± 4 h), T96 (± 4 h)/Discharge, D8, D15, and D29;
- KOOS improvement from Screening to D8, D15, and D29; and from T96 to D8, D15, and D29;
- Improvement in PBOMs (Sit to Stand, Walking Speed Test, TUG) at T96 (± 4 h)/Discharge, D15, and D29
- The proportion of patients who rescue T0-T6, T6-T12, T12-T24, T24-T48, T48-T72, and T72-T96;
- Total non-opioid analgesic consumption (AC), ie, rescue acetaminophen use for the specified intervals: $AC_{96\text{-}D8}$ and $AC_{96\text{-}D15}$;
- PROMIS 10 Global Health questionnaire score improvement from Screening to D15 and to D29;
- Number and percentage patients with an AE of lack of efficacy (LOE) during the inpatient period: $LOE_{0\text{-}96}$.
- Discharge readiness at T48 (± 4 h), T72 (± 4 h) and T96 (± 4 h)/Discharge as assessed by the earliest presence of all three of the following: (i) Adequate analgesia (defined as median rest NRS < 4 during an 8-hour period); (ii) independence from intravenous opioids during an 8-hour period; and (iii) ability to ambulate >100 ft (> 30 m) with only the aid of a walker during a physical therapy session.

Note: Details on additional or alternative exploratory efficacy endpoints are provided in the study Statistical Analysis Plan (SAP). The SAP will supersede the protocol with respect to the analyses specified, although the primary and key secondary efficacy endpoints described in the protocol will remain unchanged.

11. ADVERSE EVENTS

11.1. Adverse Events and Serious Adverse Events

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

An AE is any untoward medical occurrence in a 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 adverse event.

11.1.1. Relationship to Study Treatment

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

Causality Category	**Description**
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 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. Serious AEs and AEs that have been designated as possibly related to study treatment will be followed until resolution or stabilization.

11.1.3. Serious Adverse Event (SAE)

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

- Death
- Is life-threatening (at the time of the event)
- Requires 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 an 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 an SAE but must be recorded on the appropriate CRF: study specified hospitalization, short-term administrative hospitalization for procedures, tests or treatments of conditions that would not otherwise constitute an SAE, elective hospitalizations.

11.1.3.1. Serious Adverse Event Reporting

Serious AEs must be reported to the Sponsor or designee within 24 hours of knowledge of the event. All SAEs that occur while a 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 an SAE is as follows:

- All SAEs must be reported immediately (within 24 hours of discovery) by email to the CRO Medical Monitor or designee. Calls related to SAEs should first be directed to the CRO Medical Monitor or designee.
- 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 (or fax, if the database cannot be accessed for any reason) an 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 an SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE and will be followed as such. A spontaneous abortion is considered to be an SAE.

12. DATA QUALITY ASSURANCE

This study will be conducted under Good Clinical Practice (GCP) and all applicable regulatory requirements. 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 electronic data capture (EDC). At a minimum, all data required by the protocol should have supporting source documentation for entries in the EDC system.

All 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 CA-008 in patients undergoing TKA 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 statistical analysis plan (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, no formal statistical hypothesis testing will be performed. The sample size of 8 initial patients per dose level, with the potential for expansion to 16 patients, has been selected based on prior clinical trial experience with CA-008 and is considered sufficient for exploration of tolerability and safety parameters, establishment of a PK profile, and preliminary assessment of the efficacy of CA-008 in postoperative analgesia.

In Part B, a total of 150-300 patients will be randomized in 3-4 parallel arms with 50-100 patients in each arm. The number of patients to be enrolled in Part B will not exceed 300. Assuming a *t*-test for the difference in 2 independent means, a sample size of approximately 50 patients per group would provide approximately 85% power to detect an effect size (Cohen's *d*) of 0.6 at a two-sided level of significance, alpha, of 0.05 in the primary efficacy endpoint NRS $AUC_{12\text{-}96}$. Enrollment is currently planned at 55 patients per arm to allow for patients whose data are not eligible for inclusion in the final analysis. In this scenario, it is anticipated that, in Part B, 3 active dose levels – 60 mg, 36 mg, and 15 mg – are to be tested versus placebo, yielding 4 trial arms and a resulting total sample size of 220 patients. Alternative assumptions concerning the anticipated effect size lead to a different number of patients per group. The actual doses, number of active arms (2 or 3), and sample size to be tested in Part B will be determined at the end of Part A based on information in the protocol and SAP. The SAP will update and supersede the protocol with respect to the sample size, though the total number of patients enrolled will not change.

Note: If activity and efficacy assessments from Part A remain blinded, then the patients enrolled in Part A can be pooled with patients treated with the same dose of active drug or placebo from Part B during the efficacy analysis.

13.2. Analysis Populations

The following 5 analysis populations are planned for this study:

1 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).

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

[3] Modified Intent-to-treat (mITT) Population consists of all patients who received any dose of study treatment.

[4] 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.

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

Note: If activity and efficacy assessments from Part A remain blinded, then the patients enrolled in Part A can be pooled with patients treated with the same dose of active drug or placebo from Part B during the efficacy analysis.

Membership in analysis populations will be determined before treatment assignments are unblinded for planned data analyses.

Patients in Part A 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. 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.

All efficacy data will be summarized and analyzed using the mITT and PP populations unless otherwise noted. Safety data will be summarized using the Safety population.

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, standard deviation (SD), 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 2-sided 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. In general, major protocol deviations are deviations from the study protocol that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. Major protocol deviations will be discussed in the CSR.

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 since the end of the study drug treatment infiltration or instillation.
- Day of surgery/study drug 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.

In Part B, the primary efficacy endpoint is the area under the curve (AUC) for NRS at rest versus time from T12 to T96 ($AUC_{12\text{-}96}$). 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.

Note: If activity and efficacy assessments from Part A remain blinded, then the patients enrolled in Part A can be pooled with patients treated with the same dose of active drug or placebo from Part B during the efficacy analysis.

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 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 placebo will be combined for summaries.

Actual values and change from baseline clinical laboratory measures, vital signs, ECGs, physical examination, 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.

13.4.11. Physical Examination Findings

Physical examination and surgical site examination data will be presented in the listings. Abnormal or clinically significant physical examination 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 United States FDA) may inspect medical records related to the study to check the validity and accuracy of the data gathered in this study. Participant medical records (with participant's initials and/or date of birth) may be copied. Confidentiality of participant records will be maintained except where release of information is required by law.

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

By signing the ICF, the participant consents to the collection, access, use, and disclosure of his or her information as described in the ICF document. If a participant withdraws consent, some of the 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 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 principal Investigator and/or qualified sub-Investigators. However, the Investigator may delegate responsibilities to other investigational site personnel. The Investigator shall delegate tasks only to individuals qualified by education, training and experience to perform the delegated tasks. The Investigator shall have direct oversight of all delegated activities and shall document delegation of responsibilities. The Investigator is responsible for ensuring all delegated staff has been properly trained on the protocol and their assigned study responsibilities. A delegation log identifying all delegated duties and the individual to whom they have been delegated will be maintained at the investigational site.

14.6. Protocol Amendments

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

14.7. Financial Disclosure

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

15. INVESTIGATOR PROTOCOL AGREEMENT PAGE

A Two-Part Phase 1/2, Randomized, Double-blind, Placebo-Controlled, Adaptive Safety, Pharmacokinetics, and Preliminary Efficacy Study of CA-008 in Patients Undergoing Total Knee Arthroplasty

Version: 2.0

Date: 22 April 2020

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

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.
2. Caterina MJ, Julius D. The vanilloid receptor: a molecular gateway to the pain pathway. *Annu Rev Neurosci*. 2001;24:487-517.
3. Hartrick CT, Pestano C, Carlson N, Hartrick S. Capsaicin instillation for post-operative pain following total knee arthroplasty: a preliminary report of a randomized, double-blind, parallel-group, placebo-controlled, multicentre trial. *Clin Drug Investig*. 2011 Dec 1;31(12):877-82.
4. Suresh D, Srinivasan K. Tissue distribution & elimination of capsaicin, piperine & curcumin following oral intake in rats. *Indian J Med Res*. 2010;131:682-91.
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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 adverse events, as defined in the table, may call for stopping the study.)"

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

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

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

17.2. 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 adverse events, 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 adverse events, as defined in the table, may call for stopping the study.)"

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

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

B. Tables for Laboratory Abnormalities

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

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	–
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	–
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	—
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

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

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

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

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

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

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

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

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

17.5. Appendix E: Ropivacaine Dosage Recommendations

Dosage Recommendations

	Conc.		Volume	Dose	Onset	Duration
	mg/mL	(%)	mL	mg	min	hours
SURGICAL ANESTHESIA						
Lumbar Epidural Administration Surgery	5	(0.5%)	15 to 30	75 to 150	15 to 30	2 to 4
	7.5	(0.75%)	15 to 25	113 to 188	10 to 20	3 to 5
	10	(1%)	15 to 20	150 to 200	10 to 20	4 to 6
Lumbar Epidural Administration Cesarean Section	5	(0.5%)	20 to 30	100 to 150	15 to 25	2 to 4
	7.5	(0.75%)	15 to 20	113 to 150	10 to 20	3 to 5
Thoracic Epidural Administration Surgery	5	(0.5%)	5 to 15	25 to 75	10 to 20	n/a*
	7.5	(0.75%)	5 to 15	38 to 113	10 to 20	n/a*
Major Nerve Block† (e.g., brachial plexus block)	5	(0.5%)	35 to 50	175 to 250	15 to 30	5 to 8
	7.5	(0.75%)	10 to 40	75 to 300	10 to 25	6 to 10
Field Block (e.g., minor nerve blocks and infiltration)	5	(0.5%)	1 to 40	5 to 200	1 to 15	2 to 6

17.6. Appendix F: 0 to 10 Numerical Rating Scale of Pain Intensity (NRS)

The NRS score is to be used to rate the pain at the knee surgical site.

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: _____

17.7. Appendix G: Assessment of Worsening (Rebound) Pain at the Surgical Site

Worsening (Rebound) Pain
Ask the patient the following question: "Have you noticed any increase in pain at the surgical site (worsening pain) since your last visit?" **ð yes ð no** **Patient Initials: _____**

Rebound pain may also be characterized as worsening pain at the surgical site.

17.8. Appendix H: Knee Injury and Osteoarthritis Outcome Survey (KOOS)

Knee injury and Osteoarthritis Outcome Score (KOOS), English version LK1.0

KOOS KNEE SURVEY

Today's date: _____/_____/_____ Date of birth: _____/_____/_____

Name: _____

INSTRUCTIONS: This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to perform your usual activities.
Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Symptoms
These questions should be answered thinking of your knee symptoms during the **last week**.

S1. Do you have swelling in your knee?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S3. Does your knee catch or hang up when moving?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S4. Can you straighten your knee fully?

Always	Often	Sometimes	Rarely	Never
☐	☐	☐	☐	☐

S5. Can you bend your knee fully?

Always	Often	Sometimes	Rarely	Never
☐	☐	☐	☐	☐

Stiffness
The following questions concern the amount of joint stiffness you have experienced during the **last week** in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

S6. How severe is your knee joint stiffness after first wakening in the morning?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

S7. How severe is your knee stiffness after sitting, lying or resting **later in the day**?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Pain

P1. How often do you experience knee pain?

Never	Monthly	Weekly	Daily	Always
☐	☐	☐	☐	☐

What amount of knee pain have you experienced the **last week** during the following activities?

P2. Twisting/pivoting on your knee

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P3. Straightening knee fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P4. Bending knee fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P5. Walking on flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P6. Going up or down stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P7. At night while in bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P8. Sitting or lying

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P9. Standing upright

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, daily living

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A1. Descending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A2. Ascending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A3. Rising from sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A4. Standing

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A5. Bending to floor/pick up an object

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A6. Walking on flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A7. Getting in/out of car

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A8. Going shopping

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A9. Putting on socks/stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A10. Rising from bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A11. Taking off socks/stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A12. Lying in bed (turning over, maintaining knee position)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A13. Getting in/out of bath

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A14. Sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A15. Getting on/off toilet

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A17. Light domestic duties (cooking, dusting, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, sports and recreational activities

The following questions concern your physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the **last week** due to your knee.

SP1. Squatting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP2. Running

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP3. Jumping

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP4. Twisting/pivoting on your injured knee

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP5. Kneeling

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Quality of Life

Q1. How often are you aware of your knee problem?

Never	Monthly	Weekly	Daily	Constantly
☐	☐	☐	☐	☐

Q2. Have you modified your life style to avoid potentially damaging activities to your knee?

Not at all	Mildly	Moderately	Severely	Totally
☐	☐	☐	☐	☐

Q3. How much are you troubled with lack of confidence in your knee?

Not at all	Mildly	Moderately	Severely	Extremely
☐	☐	☐	☐	☐

Q4. In general, how much difficulty do you have with your knee?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Thank you very much for completing all the questions in this questionnaire.

KOOS FAQs

Background information

What is the KOOS?

The Knee injury and Osteoarthritis Outcome Score (KOOS) is a patient-reported outcome measurement instrument, developed to assess the patient's opinion about their knee and associated problems. The KOOS evaluates both short-term and long-term consequences of knee injury and also consequences of primary osteoarthritis (OA). It holds 42 items in five separately scored subscales: **KOOS Pain**, **KOOS Symptoms**, Function in daily living (**KOOS ADL**), Function in Sport and Recreation (**KOOS Sport/Rec**), and knee-related Quality of Life (**KOOS QOL**) (Roos and Lohmander 2003).

In which populations can the KOOS be used?

KOOS has been used in patients 13-79 years of age.
KOOS is intended to be used for knee injury that can result in posttraumatic osteoarthritis (OA); i.e. knee ligament injury (ACL, posterior cruciate ligament [PCL], medial collateral ligament [MCL]), meniscal tears, knee cartilage lesions, knee OA, and osteochondritis dissecans, etc.
KOOS is meant to be used over short and long time intervals; to assess changes from week to week induced by treatment (examples include: ligament reconstruction (ACL, PCL, MCL), meniscectomy, microfracture, osteochondral autografts, tibial osteotomy, total knee replacement (TKR), exercise (land-based, aquatic-based), intra-articular sodium hyaluronate injection, pharmacologic therapy, and glucosamine supplementation) or over years due to the primary injury, post traumatic OA or primary OA (Roos and Lohmander 2003).

How was the KOOS developed?

KOOS was developed by Ewa Roos and co-authors in the 1990s as an instrument to assess the patient's opinion about their knee and associated problems. Items were selected based on: (1) the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), version 3.0; (2) a literature review; (3) an expert panel (patients referred to physical therapy for knee injuries, orthopedic surgeons, and physical therapists from Sweden and the US); and, (4) a pilot study of two questionnaires (one for symptoms of ACL injury, one for symptoms of OA) in individuals with posttraumatic OA.

What are the KOOS subscales and what areas of health do they measure?

The KOOS collects data on five knee-specific patient-centered outcomes: (1) **KOOS Pain**; (2) **KOOS Symptoms**: Other symptoms such as swelling, restricted range of motion and mechanical symptoms; (3) **KOOS ADL**: Disability on the level of daily activities; (4) **KOOS Sport/Rec**: Disability on a level physically more demanding than activities of daily living; (5) **KOOS QOL**: Quality of life, mental and social aspects such as awareness and lifestyle changes.

In what settings is the KOOS responsive to change?

KOOS' responsiveness has been reported following surgical procedures including ACL reconstruction, meniscectomy, cartilage repair procedures, tibial osteotomy, total knee replacement as well as physical therapy, nutritional and pharmaceutical interventions. Following orthopedic surgery, including total knee replacement, KOOS QOL is usually as responsive, or more responsive, than KOOS Pain and KOOS ADL (Collins and Roos 2012).

What is the Minimal Detectable Change of the KOOS in different settings?

The minimal detectable change (MDC) is dependent on the test-retest reliability of an instrument. The more reliable a measure is, the smaller the difference that can be detected longitudinally. The test-retest reliability is, in turn, dependent on factors such as patient characteristics and time between assessments.
In studies of patients with knee injury, the MDC ranges for KOOS Pain were 6-6.1, for KOOS Symptoms: 5-8.5, for KOOS ADL: 7-8, for KOOS Sport/Rec: 5.8-12, and for KOOS QOL: 7-7.2 (Collins, Misra et al. 2011).
In one study including patients with knee OA, the MDCs for KOOS Pain were 13.4, for KOOS Symptoms: 15.5, for KOOS ADL: 15.4, for KOOS Sport/Rec: 19.6, and for KOOS QOL: 21.1 (Collins, Misra et al. 2011).

What is the Minimal Clinically Important Change in the KOOS in different settings

The minimal clinically important change (MIC) can be defined as the smallest change score needed for the effect to be considered clinically relevant (de Vet, Ostelo et al. 2007). MIC can be calculated in many different ways using anchor-based and distribution-based methods. Recent publications highlight that there is probably no such thing as one MIC for a specific patient-reported outcome measure, such as the KOOS. Instead MIC seems to be dependent on context factors including patient group, intervention, time to follow-up, etc. Therefore, it is more probable that in the future, a range of MICs will be established for an instrument. Research is ongoing to establish the MIC for the KOOS in many different contexts. Until then, a MIC of 8-10 is considered appropriate for the KOOS (Roos and Lohmander 2003). For performing a sample size calculation, usually an SD of 15 can be used. However, the variation within the group to be studied will depend on the characteristics of the group. Usually elderly or more impaired groups have greater within-group variation than younger or healthier groups.

What is the Patient Acceptable Symptom State of the KOOS in different settings?

The Patient Acceptable Symptom State (PASS) can be defined as the value beyond which the patients can consider them well. The PASS is an absolute value (not a change value) and can be used as a patient centered and clinically relevant treatment target (the proportion of patients reaching a satisfactory state) (Tubach, Ravaud et al. 2005). Similar to the MIC, research is ongoing within this area to establish PASS for KOOS when used in different contexts.

KOOS administration

Who answers the questionnaire?

The KOOS is self-administered and completed by the patient. No interview or phone formats are available.

How long does it take to complete the KOOS?

The KOOS questionnaire takes about 10 minutes to fill out.

How is the KOOS administered?

The KOOS is self-explanatory and can be administered in the waiting room prior to a clinical visit or used in a postal mail survey. KOOS has not been validated for interview administration (Collins, Misra et al. 2011).

KOOS Scores

How is the KOOS scored?

The five patient-relevant subscales of KOOS are scored separately: KOOS Pain (9 items); KOOS Symptoms (7 items); KOOS ADL (17 items); KOOS Sport/Rec (5 items); KOOS QOL (4 items). A Likert scale is used and all items have five possible answer options scored from 0 (No Problems) to 4 (Extreme Problems) and each of the five scores is calculated as the sum of the items included. Scores are transformed to a 0–100 scale, with zero representing extreme knee problems and 100 representing no knee problems as is common in orthopaedic assessment scales and generic measures. Scores between 0 and 100 represent the percentage of total possible score achieved. An aggregate total score is not calculated since it is regarded desirable to analyze and interpret the five dimensions separately. Please find more extensive instructions on score calculations in the scoring section of the KOOS User's Guide.
For statistical purposes, when used as the primary outcome in an RCT, a single score can be constructed. In this case, the five individual subscale scores should be secondary outcomes. Please see reference (Roos, Engelhart et al. 2011) for more information on this procedure.

How are the KOOS scores interpreted?

The score is a percentage score from 0 to 100, with 0 representing extreme problems and 100 representing no problems. This scoring direction, 100 indicating no problems, is common in orthopaedic instruments and generic measures like the SF-36. In measures developed by rheumatologists, like the WOMAC, 100 usually represents the worst possible result.

How should the patient be instructed on scoring activities he/she is not able to perform?

It is important to determine whether or not each subscale is relevant at the time point chosen, considering the specific study population. For example, difficulty with Sport/Rec function may not be relevant to assess 2 weeks post-operatively.
The following guideline for study staff is available:
KOOS Pain and KOOS ADL subscales: If a patient avoids an activity (e.g., twisting/pivoting or going up or down stairs) due to doctor's orders or because the patient has chosen to avoid the activity, the patient should be instructed to choose "(4) Extreme" for those items.
KOOS Sport/Rec subscale: The same as above. Also, if a patient does not normally engage in an activity (e.g., running or jumping), the patient should be instructed to leave the item blank.

How do I handle missing items?

Missing data: If a mark is placed outside a box, the closest box is chosen. If two boxes are marked, that which indicates the more severe problem is chosen.
As long as at least 50% of the subscale items are answered for each subscale, a mean score can be calculated. If more than 50% of the subscale items are omitted, the response is considered invalid and no subscale score should be calculated. For KOOS Pain, this means that 5 items must be answered; for KOOS Symptoms, 4 items; for KOOS ADL, 9 items; for KOOS Sport/Rec, 3 items; and for KOOS QOL, 2 items in order to calculate a subscale score. Subscale scores are independent and can be reported for any number of the individual subscales, i.e. if a particular subscale is not considered valid (for example, KOOS Sport/Rec 2 weeks after total knee replacement), the results from the other subscales can be reported at this time-point.
NB: The excel Scoring sheet available for download does not automatically take the number of missing items into account.

Can a total score be calculated?

An aggregate total score is not calculated since it is regarded desirable to analyze and interpret the five dimensions separately. For statistical purposes, when used as the primary outcome in an RCT, a single score can be constructed. In this case, the five individual subscale scores should be secondary outcomes. For more information on this procedure, see reference (Roos, Engelhart et al. 2011) or the FAQs section on statistics.

How do I present my data?

The results of the five subscales can be plotted as an outcome profile, preferably in a graph with scores from 0-100 on the y-axis and the five subscales on the x-axis (an example is presented in the KOOS User's Guide, under the heading of KOOS Profile). The order of the subscales from left to right should be: KOOS Pain, KOOS Symptoms, KOOS ADL, KOOS Sport/Rec and KOOS QOL. This way profiles can be compared visually across studies. Changing this order makes visual comparison more difficult.

How do I use KOOS as the primary outcome in an RCT?

There are two ways to apply the KOOS as the primary outcome in an RCT. Either way, the primary endpoint should be specified *a priori*. You can either (1) choose the single subscale you consider is the most likely to measure the change from the intervention of interest, or you can (2) create a composite score, referred to as $KOOS_4$ or $KOOS_5$, depending on the number of subscales included in this composite score. Please note that this is very different from calculating a total score! Calculating an average score from subscale scores ensures similar weight from all subscales in the composite score. Calculating a total score is never recommended. In either case, all KOOS subscales should be included as secondary endpoints to enable clinical interpretation of the results.
As examples, since exercise is aimed at improving physical function, it may be appropriate to apply the KOOS ADL subscale as the primary endpoint in an older group of OA patients, and the KOOS Sport/Rec subscale as the primary endpoint in a younger group of knee-injured patients in a trial of an exercise intervention. However, in pharmacological trials, the subscale KOOS Pain may be more appropriate as the primary endpoint since pharmacological agents often are supposed to relieve pain. When two different interventions are included (for example a surgical and a non-surgical) or when the intervention is supposed to affect more than one subscale to a similar degree, a composite score may be most appropriate as the primary outcome. Below, an example is given where $KOOS_4$ was applied. You can also read more about "Single Subscale versus Overall score" and "Multiplicity" in the review by Roos et al (Roos, Engelhart et al. 2011).

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KOOS Scoring 2012

A change in how to manage missing items was introduced in 2012. Previously, 2 missing items were allowed in each subscale. From 2012, at least 50% of the items should be responded to. The differences in subscale level are outlined in the following table:

	Number of items needed for calculation of subscale score (2012 rule for missing items)	Number of items needed for calculation of subscale score (1998 rule for missing items)
Pain	5	7
Symptoms	4	5
ADL	9	15
Sport/Rec	3	3
QOL	2	2

KOOS Scoring instructions

Assign the following scores to the boxes:

None	Mild	Moderate	Severe	Extreme
0	1	2	3	4

Each subscale score is calculated independently. Calculate the mean score of the individual items of each subscale and divide by 4 (the highest possible score for a single answer option). Traditionally in orthopedics, 100 indicates no problems and 0 indicates extreme problems. The normalized score is transformed to meet this standard.

Missing data: If a mark is placed outside a box, the closest box is chosen. If two boxes are marked, that which indicates the more severe problem is chosen.
As long as at least 50% of the subscale items are answered for each subscale, a mean score can be calculated. If more than 50% of the subscale items are omitted, the response is considered invalid and no subscale score should be calculated. For the subscale Pain, this means that 5 items must be answered; for Symptoms, 4 items; for ADL, 9 items; for Sport/Rec, 3 items; and for QOL, 2 items must be answered in order to calculate a subscale score. Subscale scores are independent and can be reported for any number of the individual subscales, i.e. if a particular subscale is not

considered valid (for example, the subscale Sport/Rec 2 weeks after total knee replacement), the results from the other subscale can be reported at this time-point.

KOOS Excel Scoring Files

Excel spreadsheets with formulae to calculate the five subscale scores are available from www.koos.nu. If, for any reason, you prefer to use your own spreadsheets, the Excel formulae are given below. NB: The excel spreadsheet available from koos.nu does not take the number of missing items into account and will return a total subscale score regardless of missing items.

Excel: When the raw data have been entered in the order the items occur in the KOOS questionnaires, these can be copied and pasted directly into an Excel spreadsheet to automatically calculate the five subscore scales. Please note that it has been assumed that the items in the subscale symptoms appear first in the questionnaire.

KOOS Pain:	=100-AVERAGE(I2:Q2)/4*100
KOOS Symptoms:	=100-AVERAGE(B2:H2)/4*100
KOOS ADL:	=100-AVERAGE(R2:AH2)/4*100
KOOS Sport/Rec:	=100-AVERAGE(AI2:AM2)/4*100
KOOS QOL:	=100-AVERAGE(AN2:AQ2)/4*100

KOOS Manual Score Calculation

The slightly updated version of the formulae (presented above and used from August 2012 in the spreadsheets available from www.koos.nu) does not need any manual imputation: Apply the mean of the observed items within the subscale (e.g. KOOS Pain), divide by 4, and multiply by 100; when this number is then subtracted from 100, you have the KOOS subscale estimate for that particular cross-sectional assessment of the individual patient. For manual calculations, please use the formulae provided below for each subscale:

1. PAIN $100 - \frac{\text{Mean Score (P1–P9)}\times 100}{4} = KOOS\ Pain$
2. SYMPTOMS $100 - \frac{\text{Mean Score (S1–S7)}\times 100}{4} = KOOS\ Symptoms$
3. ADL $100 - \frac{\text{Mean Score (A1–A17)}\times 100}{4} = KOOS\ ADL$
4. SPORT/REC $100 - \frac{\text{Mean Score (SP1–SP5)}\times 100}{4} = KOOS\ Sport/Rec$
5. QOL $100 - \frac{\text{Mean Score (Q1–Q4)}\times 100}{4} = KOOS\ QOL$

WOMAC - How to score from the KOOS

Assign scores from 0 to 4 to the boxes as shown above. To get original WOMAC Scores, sum the item scores for each subscale. If you prefer

percentage scores in accordance with the KOOS, use the formula provided below to convert the original WOMAC scores.

Transformed scale = 100 - actual raw score x 100 maximum score

WOMAC subscores	Original score = sum of the following items	Maximum score
Pain	P5-P9	20
Stiffness	S6-S7	8
Function	A1-A17	68

KOOS Profile

To visualize differences in the five different KOOS subscores and change between different administrations of the KOOS (e.g. pre-treatment to post-treatment), KOOS Profiles can be plotted. The example from Nilsdotter et al. [17] shows KOOS profiles prior to and at 3 time points following total knee replacement (TKR).

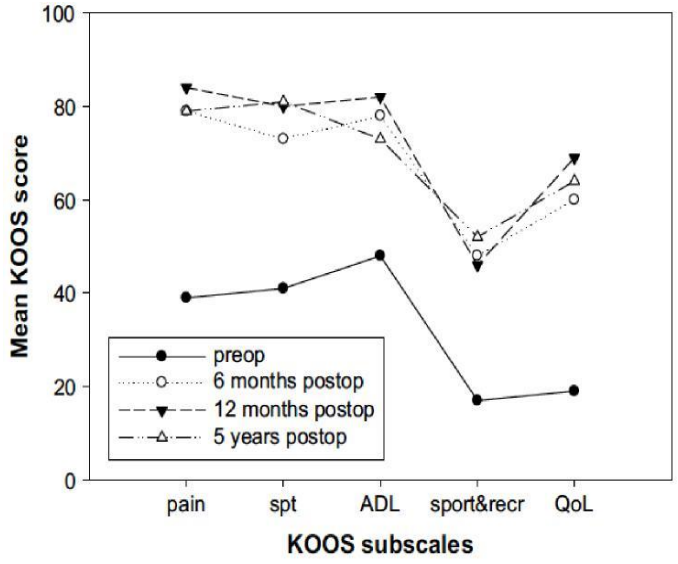

Fig. 1. KOOS profiles prior to and up to 5 years after TKR. Mean KOOS scores ($n = 80$) at the preoperative, 6 months, 12 months and 5 year assessments after TKR.

17.9. Appendix I: 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

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

17.10. Appendix J: Knee ROM Procedure

Goniometry Procedure for Knee Flexion and Extension

- Position joint in zero position and stabilize proximal joint component.
- For passive ROM, staff will move joint to end of range of motion (to assess quality of movement).
- For active ROM, patient will move joint to end of range of motion (to assess quality of movement).
- Determine end-feel at point where measurement will be taken (at the end of available range of motion).
- Identify and palpate bony landmarks.
- Align goniometer with bony landmarks while holding joint at end of range.
- Read the goniometer.
- Record measurement.

17.11. Appendix K: 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.

Patient _____

Date _____

Time _____ ☐AM ☐PM

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: _____

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

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17.12. Appendix L: Walking Speed Test

Walking Speed Test (or Gait Speed)

Test Protocol: Measure and mark a standard distance, e.g. 5 meters (16.4 feet).
Then measure and mark 5 feet before the start, and 5 feet after the end.
Put cones at the starting line and the finish line.

5 feet	**5 Meters (16.4 feet)**	5 feet
← Starting line	← begin timing stop timing →	Finish line →

Gait Speed = distance / time e.g., 5 meters / __ sec.

Instructions: "Walk at a comfortable pace".

Have the person perform 3 repetitions and calculate the average time.

Participant's performance: _____ seconds

Calculated gait speed (distance/time): _____ m/sec

e.g. the person takes 8.5 seconds to walk 5 meters → 5/8.5 = 0.6 m/sec

Quick estimates: 10 sec = 0.5 m/s, 7 sec = 0.7 m/s, 5 sec = 1.0 m/s,
4 sec = 1.25 m/s, 3 sec = 1.7 m/s

Adapted from:
https://geriatrictoolkit.missouri.edu › Gait-Speed

17.13. Appendix M: TUG Test

ASSESSMENT

Timed Up & Go (TUG)

Patient _____

Date _____

Time _____ ☐ AM ☐ PM

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.

NOTE: Always stay by the patient for safety.

① **Instruct the patient:**

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.

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.

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17.14. Appendix N: 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: _____**

In the assessment of satisfaction with wound healing, it should be performed with what is typically observed for surgeries of this type in the Investigator's clinical opinion. The surgical wound adverse event grading scale which follows may be helpful is there is an atypical or abnormal finding.

17.15. Appendix O: 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

17.16. Appendix P: 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 3 to 5 cm above and below the surgical incision site in all 4 quadrants of the leg 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.