**OFFICIAL TITLE:**

STATISTICAL ANALYSIS PLAN

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:**

12 Nov 2020

# STATISTICAL ANALYSIS PLAN

## 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

**Protocol Number: CA-PS-208**

Protocol Version Amendment 1 (22APR2020)

SPONSORED BY

Concentric Analgesics, Inc.

PREPARED BY
Lotus Clinical Research®, LLC
100 W California Blvd, Unit 25
Pasadena, CA 91105
626-397-2390 office
info@LotusCR.com
www.LotusCR.com

## DOCUMENT VERSION CONTROL

| Version Number | Date | Comments/Changes |
|---|---|---|
| V1.0 | 21Jun2020 | SAP |
| V2.0 | 07Oct2020 | Update SAP After blinded TLFs review |
| V3.0 | 12Nov2020 | Update the definition of Per-Protocol analysis population prior to DBL/unblinding |

## APPROVALS

Author:

DocuSigned by:
Leonid Zeitlin
Signer Name: Leonid Zeitlin
Signing Reason: I am the author of this document
Signing Time: 13-Nov-20 | 2:10:15 AM PST
0AF02DA317D540269094A6B4BCE6B408

13-Nov-20

Leonid Zeitlin
Biostatistician
Quartesian LLC

Date

Reviewed:

DocuSigned by:
Song Liou
Signer Name: Song Liou
Signing Reason: I have reviewed this document
Signing Time: 12-Nov-20 | 1:54:27 PM PST
85C80776CFA1404FB9C34B43BB0AA100

12-Nov-20

Song Liou
Senior Biostatistician
Lotus Clinical Research®, LLC

Date

Approved:

DocuSigned by:
Sam Teichman
Signer Name: Sam Teichman
Signing Reason: I approve this document
Signing Time: 12-Nov-20 | 1:54:04 PM PST
EA3F6C62DE634E3484AD6BF24BCAA75C

12-Nov-20

Sam Teichman, MD
VP, Head of Clinical Development
Concentric Analgesics, Inc.

Date

DocuSigned by:
Henry C. Foehl
Signer Name: HENRY FOEHL
Signing Reason: I approve this document
Signing Time: 12-Nov-20 | 2:43:44 PM PST
ABAF4AD4E11B4C41909E3B4693085652

12-Nov-20

Henry C. Foehl, PhD
Consultant to Concentric Analgesics, Inc.
Foehl Statistics & Analytics LLC

Date

## TABLE OF CONTENTS

**LIST OF IN-TEXT TABLES**

## LIST OF ABBREVIATIONS

| | |
|---|---|
| AC | Analgesic Consumption |
| ADaM | Analysis Data Model |
| ADL | Actives of Daily Living |
| AE | Adverse Event |
| ANCOVA | Analysis of Covariance |
| ANOVA | Analysis of Variance |
| ATC | Anatomical Therapeutic Chemical |
| AUC | Area Under the Curve |
| BMI | Body Mass Index |
| CI | Confidence Interval |
| CMH | Cochran-Mantel-Haenszel |
| CRO | Clinical Research Organization |
| CSR | Clinical Study Report |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| ET | Early Termination |
| FDA | Food and Drug Administration |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IV | Intravenous |
| KOOS | Knee injury and Osteoarthritis Outcome Score |
| LOCF | Last Observation Carried Forward |
| LOE | Lack of Efficacy |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | Modified Intent-to-treat |
| NRS | Numerical Rating Scale for Pain Intensity |

| | |
|---|---|
| OC | Opioid Consumption in oral morphine equivalents (Sec 7.3.6) |
| OF | Opioid-free |
| OME | Oral Morphine Equivalent |
| PACU | Post-anesthesia Care Unit |
| PBOM | Performance-based Outcome Measure |
| PE | Physical Examination |
| PI | Principal Investigator |
| PK | Pharmacokinetic |
| PO | Per Os (orally) |
| PP | Per Protocol |
| PRO | Patient-reported Outcome |
| PT | Preferred Term |
| QOL | Quality of Life |
| ROM | Range of Motion |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SDTM | Standard Data Table Model |
| SE | Standard Error |
| SOC | System Organ Class |
| TEAE | Treatment Emergent Adverse Event |
| TFLs | Tables, figures, and listings |
| TKA | Total Knee Arthroplasty |
| WHO | World Health Organization |
| wLOCF | Windowed Last Observation Carried Forward |

## 1. PURPOSE OF THE ANALYSES

This statistical analysis plan (SAP) is based on protocol number CA-PS-208 Amendment 1 (22APR2020) from Concentric Analgesics, Inc.

This SAP is written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) Efficacy Guideline E9, Statistical Principles for Clinical Trials, and the most recent ICH Efficacy Guideline E3, Structure and Content of Clinical Study Reports.

Presented in this SAP are the details of the specific statistical methods that will be employed in the summary and analysis of data from study CA-PS-208.

## 2. PROTOCOL SUMMARY

This is a two-part, Phase 1/2 study in patients undergoing total knee arthroplasty (TKA); in each part, patients receive, in randomized, double-blind fashion, administration of a single dose of CA-008 or placebo infiltrated/instilled during surgery. In Part A, 3 exploratory sequential dose-escalation cohorts will be evaluated; in Part B, 2 active dose levels of CA-008 will be evaluated compared to placebo in a parallel-group design.

### 2.1 Study Objectives

#### *2.1.1 Part A of the Study*

2.1.1.1 Primary Objective

- Evaluate the safety and tolerability of a single intraoperative administration of either CA-008 or placebo in patients undergoing an elective TKA.

2.1.1.2 Secondary Objectives

- Evaluate the pharmacokinetic (PK) profile of a single intraoperative administration of CA-008 in patients undergoing an elective TKA.
- Evaluate, preliminarily, the effect of CA-008 with respect to patients' self-reported pain, opioid consumption (OC), patient-reported outcomes (PROs), performance-based outcome measures (PBOMs), and range of motion (ROM).
- Determine the dose(s) for testing in Part B.

#### *2.1.2 Part B of the Study*

2.1.2.1 Primary Objective

- Evaluate, during a specified post-operative time interval, the efficacy of 2 selected doses of CA-008 with respect to self-reported pain in patients undergoing an elective TKA.

2.1.2.2 Secondary Objectives

- Evaluate, during specified additional post-operative time intervals, the efficacy of 3 selected doses of CA-008 with respect to self-reported pain in patients undergoing an elective TKA.
- 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 PBOMs and 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.

### 2.2 Overall Study Design and Plan

In Part A, of this two-part, Phase 1/2 study, 3 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.

During Part A, patients were randomized in a 3:1 ratio, active to placebo. Dose escalation, dose reduction, or cohort expansion decisions were made by the Sponsor's medical monitor, the CRO's medical monitor, and a designated Principal Investigator (PI) after reviewing blinded safety data.

In Part B, 2 active dose levels (36 mg and 60 mg) of CA-008 will be evaluated compared to placebo in a randomized, double-blind, parallel-group design.

For each patient, the study was to 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 undergo TKA and administration of study drug (CA-008 or placebo) followed by serial assessments of safety, PK, and drug effect, in particular focusing on patients' self-reported pain using a numeric rating scale (NRS) for pain intensity and patients' self-expressed need for analgesia. During the outpatient period, serial assessments of safety and drug effect are performed; safety and drug effect assessments focus on patients' self-reported pain and need for analgesia.

Each patient is expected to be in the study for approximately 76 days from screening to the D29 + 2 days visit; this period could be longer to permit following any AE to resolution or the establishment of a new baseline.

As per the protocol, after the 3rd cohort of Part A was enrolled, a safety review was conducted by site investigators, the medical monitor of the CRO, and the sponsor's medical monitor. Part A included 3 cohorts with dose levels 36 mg (0.3 mg/mL), 60 mg (0.5 mg/mL), and 90 mg (0.75 mg/mL) of CA-0008 or placebo.

Also, as per the protocol, a decision was made to progress to Part B of the study. Part B will include 3 parallel, blinded arms: 36 mg of CA-008 (0.3 mg/mL), 60 mg (0.5 mg/mL) of CA-008, and placebo. Up to 201 patients will be randomized to Part B in a 1:1:1 ratio with ~67 patients in each arm. See Section 2.2.5 below for sample size considerations.

### *2.2.1 Study Assessment Schedule*

The Schedule of Assessments is presented in Table 1 below. Note: Time 0 (T0) is further defined for analyses in Section 3.

### *2.2.2 Study Population*

The study population consists of adults, aged 18-80 years old inclusive, who are planning to undergo an elective unilateral TKA and meet the eligibility criteria described in Sections 8.2.1 and 8.2.2 of the study protocol.

### *2.2.3 Treatment Regimens*

Part A:

**Cohort #1:** CA-008 36 mg vs. placebo in 120 mL of vehicle (0.3 mg/mL)
**Cohort #2:** CA-008 60 mg vs. placebo in 120 mL of vehicle (0.5 mg/mL)
**Cohort #3:** CA-008 90 mg vs. placebo in 120 mL of vehicle (0.75 mg/mL)

Part B:

Doses were selected based on safety and tolerability data from Part A and from prior studies of CA-008. The selected doses are:

**Arm #1:** CA-008 36 mg in 120 mL of vehicle (0.3 mg/mL)
**Arm #2:** CA-008 60 mg in 120 mL of vehicle (0.5 mg/mL)
**Arm #3:** Placebo (120 mL of vehicle)

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

| **Study Period** | | **Inpatient** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Screening** | **Day of Surgery** | **Surgery** | **Post-Surgery** | **T24** | **T48** | **T72** | **T96 ± 4 h** | **Follow-Up Clinic Visits** | | | **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 |
| Temperature (oral) | X | X | | X[4] | X[4] | X[4] | X[4] | X[4] | X | X | X | X | X |
| Physical Examination | X[5] | X[5] | | | | | | X[5] | X[5] | X[5] | X[5] | X[5] | X[5] |
| 12-Lead ECG | X | | | | X[6] | | | | | | | | |
| Enroll/Randomize | | X | | | | | | | | | | | |
| Surgery | | | X | | | | | | | | | | |
| Study treatment | | | X | | | | | | | | | | |

| **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**<br>**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 | | |
| Infiltration/instillation | | | | | | | | | | | | | |
| Admission to PACU | | | | $T0_{nrs}$ | | | | | | | | | |
| 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] |
| Patient home diary record (NRS) | | | | | | | | X[11] | X[11] | X[11] | | | X[11] |
| 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] | | | | | |

| **Study Period** | **Screening** | **Inpatient** | | | | | | | **Follow-Up Clinic Visits** | | | **Unscheduled Visit**[1] | **Early Termination**[19] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day**<br>**Assessment** | D -45 to Day Prior to Surgery | **Day of Surgery**<br>D1 (prior to surgery) | **Surgery**<br>D1 | **Post-Surgery**<br>D1 | **T24**<br>D2 | **T48**<br>D3 | **T72**<br>D4 | **T96 ± 4 h**<br>D5 | D8 + 1 day | D15 + 2 days | D29 + 2 days | | |
| if needed | | | | | | | | | | | | | |
| PROMIS 10 Global 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) | | | | | | X | X | X | | | | | |
| 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 96 hours (± 4 hours) after T0, but prior to discharge, and D8, D15, and D29 after T0 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 hours. Height (cm) will be measured and BMI will be calculated at Screening only.

6 Post-Surgery ECG should be performed at 24 hours (± 2 hours) after T0.

7 Surgical Site assessment: 96 hours (± 4 hours after T0 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, 96 hours (± 4 hours, but prior to discharge) and D8, D15, and D29 after T0 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 ($T0_{nrs}$) may be assessed once the patient is awake. If the patient is able to provide responses, obtain NRS scores at $T0_{nrs}$, $T0_{nrs}$ plus 1 hour (T1), $T0_{nrs}$ 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 (± 4 h) and 7:00 PM (± 4 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 prior to taking any pain medication or at least 2 hours after taking any pain medication.
- Obtain the evening NRS assessment at least 2 hours after taking any pain medication.
- 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] If the patient continues to require opioids during the 12 hours prior to discharge (any time from T84 h onward), then write a prescription for no more than 9 tablets of acetaminophen 325 mg/oxycodone 5 mg (Percocet) one or two tablets PO Q 4-6 h PRN per Investigator discretion.

[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 24 hours 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 24 hours 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.

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

### *2.2.4 Treatment Group Assignments or Randomization*

In Part A of the study, 3 exploratory, sequential, dose-escalation cohorts were evaluated. For each cohort, patients meeting the enrollment criteria were randomly allocated to receive either active drug or placebo in a 3:1 ratio using a block size of 4. Eight patients were randomized in each cohort with no more than 4 patients dosed per week. The total sample size in Part A was 24 patients.

In Part B, a block randomization for each site is used with a block size of 9 patients.

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

### *2.2.5 Sample Size Determination*

In Part A, no formal statistical hypothesis testing will be performed. The sample size of 8 initial patients per dose level was selected based on prior clinical trial experience with CA-008 and 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, assuming a *t*-test for the difference in 2 independent means, a sample of 62 patients per group would provide approximately 80% power to detect a treatment difference equivalent to an effect size (Cohen's *d*) of 0.45 at a 1-sided level of significance, alpha, of 0.05 in the primary efficacy endpoint, which is the area under the NRS versus time curve, NRS $AUC_{12\text{-}96}$. Because this is a proof-of-concept study, in which a decrease in mean NRS $AUC_{12\text{-}96}$ for active treatment compared to placebo is postulated, a 1-sided test is specified for the sample size estimate.

Assuming that for each of the 3 study arms (36 mg, 60 mg, and placebo) in the final primary endpoint efficacy analysis, an additional 5 patients per study arm should be enrolled to account for dropouts or unevaluable patients, the target sample size per study arm in Part B is 67 patients, resulting in a total target sample size for the final efficacy analysis of 201 patients.

Since it is intended that data for Part A will remain blinded until Part B is unblinded, data collected for both Part A and Part B patients will be pooled for final analyses as appropriate. Anticipating that pooling of Part A and Part B data will occur for the final efficacy analysis, and that the data for 6 patients from each of cohorts 1 and 2 of Part A that received active drug and

6 patients overall from cohorts 1, 2 and 3 that received placebo will be available for pooling, the target enrollment for Part B may be reduced to 183 patients, if warranted.

## 3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

General analysis and reporting conventions to be employed for study CA-PS-208 data are described below. If departures from these conventions are appropriate, details will be presented in the relevant sections of this SAP.

Continuous variables will be summarized by treatment group and time point (as applicable) using descriptive statistics: number of patients (n); mean; standard deviation (SD); median; and range (minimum and maximum). Categorical variables will be summarized by treatment group and time point (as applicable) using frequency counts (n) and rates of occurrence (%). Changes from baseline for continuous variables will be presented as their corresponding continuous measures for post-baseline visits as applicable. All study data will be listed by treatment group, patient, and time point (as applicable).

Unless specified otherwise, in the analysis of categorical variables, the denominator for percentages will be the number of patients in the appropriate analysis population and treatment group who have a non-missing value of the categorical variable.

No preliminary rounding of numeric data values will be performed; rounding will only occur after the completion of an analysis when data or calculation results are to be displayed. Means and medians will be presented to one more decimal place than the number of decimal places recorded in the data. Standard deviations will be presented to two more decimal places than the number of decimal places recorded in the data. Percentages will be presented to one decimal place. A percentage of 100 calculated to any number of decimal places will be reported as 100%; a percentage of 0 calculated to any number of decimal places will be reported as 0. Minimums and maximums will be presented with the same number of decimal places as the original data.

Statistical testing including *p*-values and confidence intervals (CIs) will be presented as described in each section below. Tests of statistical significance will be 1-sided or 2-sided at the 0.05 level of significance depending on the endpoint being tested, as specified below. In particular, a 1-sided test of significance is specified for the primary analysis of the primary endpoint, NRS $AUC_{12\text{-}96}$, because this is a proof-of-concept study in which a decrease in mean NRS $AUC_{12\text{-}96}$ for active treatment compared to placebo is postulated.

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.

All analyses will be performed using SAS® version 9.3 or higher. The domain (Study data tabulation Model [SDTM]) and analysis (Analysis Data Model [ADaM]) data sets will be source of input to the SAS programs that generate the submission-ready tables, figures, and listings (TFLs). Submission-ready SDTM and ADaM data sets, define files, reviewer's guide, and Open CDISC reports will be provided to the sponsor in addition to the TFLs.

The following conventions will be used in the study analysis as needed for calculations:

- Time 0 for safety assessments (T0) is the start time of study drug administration.
- Time 0 for efficacy assessments ($T0_{nrs}$) is the time of admission into the post-anesthesia care unit (PACU).
- Time 0 for PK assessments ($T0_{pk}$) is the stop time of study drug administration.
- Day of surgery/study drug administration is defined as Day 1.
- Elapsed assessment visit times are defined by time elapsed from the corresponding Time 0 (T0, $T0_{nrs,}$ or $T0_{pk}$) or D1.
- The baseline value of any parameter is defined as the most recent valid measurement of that parameter prior to the beginning of Time 0 (T0, $T0_{nrs,}$ or $T0_{pk}$).
- 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 24 or more hours, and as hours for AEs lasting less than 24 hours.

# 4. ANALYSIS POPULATIONS

## 4.1 Analysis Populations

The following analysis populations will be used in this study:

- Safety Population—consists of all patients who received any part of a dose of study treatment. Patients in the Safety Population will be analyzed as treated.
- PK Population—consists of all patients who received a full dose of study treatment and completed at least one PK assessment. Patients in the PK Population will be analyzed as treated.
- Modified Intent-to-treat (mITT) Population—consists of all patients who were randomized and received any dose of study treatment. Patients in the mITT Population will be analyzed as randomized.
- Per Protocol (PP) Population—consists of all patients who received a full dose of study treatment and have evaluable NRS pain assessments at the T12, T24, T48, T72, and T96 timepoints and no two consecutive missing assessments among the other scheduled timepoints prior to T96. Missing scheduled assessments after the T96 timepoint will not exclude patients from the PP population. Patients included in the PP Population must not have any major protocol deviations. Patients in the PP Population will be analyzed as treated.
- Study Completers—consists of all patients in the mITT population who completed the entire study period through D29 + 2 days, whether or not they have complete sets of NRS scores.

Analysis populations will be determined before the study data are unblinded for analysis.

Efficacy analyses will be performed using the mITT and PP populations as detailed below. Safety analyses will be performed using the Safety population. PK analyses will be performed using the PK population.

## 4.2 Disposition of Patients

All patients and the analysis populations for which they qualify for inclusion will be presented in the listings. Patients who are screened and who fail screening or withdraw consent prior to randomization or are randomized but not treated will be presented in a listing and included in

the patient disposition summary table. Patients who are randomized, patients who are included in each study population, patients who are treated, patients who complete the study, and patients who withdraw early from the study and the reason for withdrawal, will be included by study part and by treatment group and overall in the patient disposition summary table.

### 4.3 Protocol Deviations

Deviations from the study protocol will be categorized as deviations from protocol-specified requirements regarding: informed consent procedures; inclusion/exclusion criteria; study medication; prohibited medications; study procedures; study drug assignment/treatment; visit or assessment time windows; missed visits or assessments; and, other. All protocol deviations will be captured on the electronic case report forms (eCRFs) and/or documented in site specific logs throughout the study. Deviations will be categorized as described above and classified as major or minor by the Sponsor and the medical monitor after database lock but before the unbinding of study data for analysis. Major protocol deviations will be discussed in the clinical study report (CSR). 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 patient's rights, safety, or well-being. The number of patients with protocol deviations, both minor and major, will be presented for the Safety population in a data listing and will be summarized by category of deviation and major/minor classification.

NOTE: In March 2020, the FDA issued guidance on the conduct of clinical trials during the COVID-19 pandemic to assure the safety of trial participants and to maintain study compliance with GCP. The FDA provided information on alternative methods to complete serial, non-invasive study assessments that allow compliance with local shelter-in-place considerations, e.g., phone contact or virtual visit using video chat/conferencing.

Unavoidable protocol deviations involving study procedure scheduling delays, early or missed visits and missing information will result due to the COVID-19 situation. In general, if a study procedure is completed, it will not be considered a protocol deviation, even if it is completed remotely, out-of-window, or using alternative methods. If a procedure cannot be completed and results in missing data, it will be considered a protocol deviation.

# 5. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

## 5.1 Demographics and Baseline Characteristics

Demographic variables include age, sex, race, and ethnicity. Baseline characteristics include height (cm), weight (kg), and body mass index (BMI; $kg/m^2$). Demographic variables and baseline characteristics will be summarized overall and by treatment group for the Safety population.

## 5.2 Medical History

Medical history will include acute, chronic, or infectious disease history; surgical or oncologic history; and any reported conditions affecting major body systems. Medical events that occur prior to the study procedure (i.e., initiation of any surgery or anesthesia-related procedure) will be categorized as medical history. All findings in a patient's medical history will be evaluated by the Investigator for their potential effect on a patient's eligibility for study participation. Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 and presented for the Safety population in a summary table of the number and percentage of occurrences, within treatment groups and overall, by System Organ Class (SOC) and Preferred Term (PT). Patients will only be counted once for each SOC and PT.

Medical histories will also be presented in a by-patient listing.

## 6. MEASUREMENTS OF TREATMENT EXPOSURE AND COMPLIANCE

Because study medication is administered as a single dose at the study center by trained study personnel, patient compliance with respect to study medication administration will not be calculated. A by-patient listing of study drug administration and exposure data will be provided. Individual instances of incomplete or problematic study medication delivery will be noted as protocol deviations.

Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for the volume (mL) of study drug administered will be presented for the Safety population in a summary table by treatment group, overall active treatment group, and overall.

# 7. EFFICACY EVALUATION

The analysis of the primary endpoint and key secondary endpoints will be performed for the mITT and PP populations. The analysis of the exploratory efficacy endpoints will be performed for the mITT population only.

## 7.1 Handling of Dropouts or Missing Data

Imputation of missing data, where appropriate, will be performed as indicated in this SAP for a given analysis; in particular, imputation of missing NRS scores is discussed in detail in section 7.3.3. Any spurious or erroneous data will be queried and followed up until satisfactorily resolved; if not resolvable, the data will be set to missing. Study procedures have been designed to minimize opportunities for data not to be captured as planned, hence missing data will be considered to be missing at random.

## 7.2 Efficacy Endpoints

### *7.2.1 Primary Efficacy Endpoint*

- Rest NRS AUC from T12 to T96: $AUC_{12\text{-}96}$

### *7.2.2 Key Secondary Efficacy Endpoints*

- Evoked NRS AUC from T12 to T96: $AUC_{12\text{-}96\ (ambulation)}$
- Patient does not require opioids, i.e., patient is opioid-free (OF), from T24 to T96: $OF_{24\text{-}96}$
- Total opioid consumption (OC), in oral morphine equivalent (OME) dose, from T12 to T96: $OC_{12\text{-}96}$
- Rest NRS AUC from T12 to D8: $AUC_{12\text{-}D8}$
- Evoked NRS AUC from T12 to D8: $AUC_{12\text{-}D8\ (ambulation)}$

### *7.2.3 Exploratory Efficacy Endpoints*

- Rest NRS AUC for the indicated time intervals: $AUC_{0\text{-}24}$, $AUC_{0\text{-}96}$, $AUC_{6\text{-}96}$, $AUC_{24\text{-}96}$, $AUC_{96\text{-}D8}$, and $AUC_{96\text{-}D15}$
- Evoked NRS AUC for the indicated time intervals: $AUC_{0\text{-}96\ (ambulation)}$, $AUC_{0\text{-}D8\ (ambulation)}$, $AUC_{24\text{-}D8\ (ambulation)}$, and $AUC_{96\text{-}D15\ (ambulation)}$
- Rest NRS scores at T48, T72, T96, T120, T144, and T168
- Total opioid consumption (OC), in oral morphine equivalent (OME) dose, for the indicated time intervals: $OC_{0\text{-}96}$, $OC_{24\text{-}48}$, $OC_{24\text{-}72}$, $OC_{24\text{-}96}$, $OC_{24\text{-}D8}$, and $OC_{24\text{-}D15}$

- Patient does not require opioids, i.e., patient is opioid-free (OF), for the indicated time intervals: $OF_{0-96}$, $OF_{24-96}$, $OF_{24-D15}$, $OF_{96-D8}$, and $OF_{96-D15}$
- Time to cessation of opioid use
- Knee ROM at T48 (± 4 h), T96 (± 4 h)/Discharge, D8, D15, and D29: active and passive flexion; active and passive extension
- Change in KOOS score from Screening to D8, D15, and D29
- Change in KOOS score from T96 to D8, D15, and D29
- PBOM scores (Sit to Stand, Walking Speed Test, TUG) at T96 (± 4 h)/Discharge, D15, and D29
- Patient required rescue medication for the indicated time intervals: $T0_{nrs}$ -T6, T6-T12, T12-T24, T24-T48, T48-T72, and T72-T96
- Total non-opioid analgesic consumption (AC), i.e., rescue acetaminophen use for the indicated time intervals: $AC_{96-D8}$ and $AC_{96-D15}$
- Change in PROMIS 10 Global Health questionnaire score from Screening to D15 and D29
- Patient experienced an AE of lack of efficacy (LOE) during the inpatient period: $LOE_{0-96}$
- Discharge readiness at T24 (± 4 h), T48 (± 4 h), T72 (± 4 h), and T96 (± 4 h)/Discharge
- Time to first occurrence of discharge readiness

## 7.3 Derivation of Efficacy Endpoints

### *7.3.1 NRS Measurements*

At designated times during the study following the administration of study treatment, patients were to have reported or recorded their pain intensity at the time of assessment as follows:

- During the inpatient stay, beginning at PACU admission, NRS at was to have been assessed once the patient was awake. $T0_{nrs}$ is the time of admission into the PACU. If the patient was able to provide responses, NRS scores were to be obtained at $T0_{nrs}$ plus 1 hour (T1), $T0_{nrs}$ plus 2 hours (T2, etc.), T4, T6, T8, T12, T16, T20, T24, and every 4 hours thereafter (if the patient was awake at the scheduled 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 were to be recorded regardless of

timing of pre-rescue medication NRS scores and administration of rescue medication. The actual time, not the nominal time, of all NRS scores was to be recorded.

- During the inpatient stay, evoked NRS twice daily was to be recorded after physical therapy (most preferred) or ambulation for approximately 10 yards (preferred) or transfers to/from bed or wheelchair. These NRS scores were to be obtained 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 have been skipped between the hours of 12:00 AM and 6:00 AM, but the patient was not to have missed two consecutive assessments. The T12, T24, T48, T72, and T96 assessments were to have been completed even if the patient had to be awakened at those times.
- During the inpatient stay, an additional NRS assessment was to have been 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), patients were to be instructed 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 was to have been documented in the diary whenever possible. Patients were also to have been instructed to record pre-rescue NRS scores.

### *7.3.2 Handling of NRS Scores Post Rescue Medication Use*

When rescue medication was used, any scheduled rest NRS assessment is censored if the assessment was taken within:

- 30 minutes after the start of IV fentanyl;
- 2 hours after the start of IV hydromorphone (from T0-T24);
- 4 hours after the administration of PO opioids.

If other opioid rescue medications are used, other censoring intervals will be documented, e.g., 3 hours after the start of IV morphine. In the special case of the use of IV hydromorphone after T24 (defined as an adverse event of lack of efficacy), scheduled rest NRS assessments will be censored for 8 hours after the start of dosing. Censored NRS assessments will be replaced by imputed values in summaries, derivations, and analyses as described below.

For patients who take rescue medication a 'windowed' last NRS score carried forward (wLOCF) will be used in the calculation of the rest NRS AUC. Specifically, the most recent NRS score obtained prior to the administration of rescue medication, whether that score is the pre-rescue NRS assessment or a scheduled NRS assessment, will be used to impute an NRS score to replace the censored values (whether extant or missing) of all scheduled rest NRS assessments occurring during the censoring window, i.e., all scheduled rest NRS assessments for 30 minutes following rescue use when IV fentanyl is used, for 2 hours when IV hydromorphone is used, and for 4 hours when PO oxycodone is used.

If a patient requested rescue medication at the time of a scheduled rest NRS assessment, the scheduled rest NRS assessment was also to be recorded as the pre-rescue NRS assessment.

If a patient requests rescue medication within a wLOCF imputation time window, and additional rescue medication is administered prior to the end of that time window, the imputation window clock resets to 0 at the time of administration of the newly requested rescue medication and the imputation time window associated with that rescue medication begins; censored values during this new censoring window will be imputed using the pre-rescue NRS score obtained in response to the latest request for rescue medication or the most recent imputed NRS value if the pre-rescue NRS score is missing.

In case a rescue medication administration time is not recoded in the rescue medication eCRF, but the time of the most recent pre-rescue NRS assessment occurring prior to the administration of rescue medication is recorded, that time shall be assumed to be the rescue medication administration time. Conversely, if the most recent pre-rescue NRS assessment is recorded in the rescue medication eCRF, but the time is missing, the time will be assumed to be the time the rescue medication was administered. Note, for the outpatient period, the time of pre-rescue NRS assessments is not captured in the diary. The time of the pre-rescue NRS assessment will be assumed to be the time when the rescue medication was administered.

If a patient's pre-rescue NRS assessment is missing, then the mean of the patient's non-missing pre-rescue NRS scores occurring prior to the missing score will be used to impute values for censored NRS scores during the ensuing wLOCF imputation time window. If the patient has no non-missing pre-rescue NRS scores prior to the missing score, then the mean value of all study patients' pre-rescue NRS scores occurring within the first 48 hours of entry into the PACU will be used to impute values for censored NRS scores during the ensuing wLOCF imputation time window.

Evoked NRS assessments occur twice daily at 10:00 AM (± 1 h) and 4:00 PM (± 1 h). If an evoked NRS assessment is scheduled to occur during a wLOCF imputation time window, the evoked NRS score will not be censored and will not be replaced with an imputed value.

### *7.3.3 Imputation of Missing NRS Scores*

For the primary analysis of the primary endpoint, intermittent missing NRS assessment scores (due to a patient sleeping, etc.) will not be imputed and AUCs will be calculated using the available NRS assessments, unless the missing NRS assessment is a rest NRS assessment occurring during a rescue medication imputation period, in which case the imputed value will be used.

For a patient who dropped out of the study prior to D15 (the last day when NRS assessments were to be collected), the following algorithm will be used to impute NRS assessment scores for use in NRS AUC calculations that include time points after the patient's date of discontinuation:

- The score for scheduled rest NRS assessments after the date of discontinuation will be imputed using the most recent rest NRS score recorded prior to the patient's date of discontinuation, i.e., LOCF. If no rest NRS assessments exist prior to the patient's date of discontinuation, all AUC calculations for that patient will be set to missing.
- The score for scheduled evoked NRS assessments after the date of discontinuation will be imputed using the most recent evoked NRS score recorded on or prior to the patient's date of discontinuation. If no evoked NRS assessments exist on or prior to the date of discontinuation, the AUC calculation will be set to missing.

Note that the replacement via imputation of a censored post-rescue NRS assessment (as described in section 7.3.2) must be performed prior to the selection of imputed values as described in this section.

### *7.3.4 NRS AUC*

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 $\mathrm{NRS}_i = \mathrm{NRS}$ at time $i$, $n$ is the number of hours between $T_1$ and $T_2$, and $(t_i - t_{i-1})$ is the time difference in hours between actual collection time $i$ and actual collection time $i-1$.

NRS assessment scores, whether rest or evoked, from all available eCRFs, including "Pain Intensity Assessment (NRS)," "Morning/Night Pain Intensity Assessment (NRS)—Inpatient," "Morning/Night Pain Intensity Assessment (NRS)—Outpatient," and "Rescue Medications" will be used in AUC calculations as appropriate for a specific computation. For an AUC covering a particular time interval, e.g., from time $T_{n1}$ to time $T_{n2}$, all uncensored NRS assessments recorded from the start of the protocol-allowed window for time $T_{n1}$, up to the end of the protocol-allowed window for time $T_{n2}$, will be used; censored values will be replaced as described in sections 7.3.2. For example, for $AUC_{12\text{-}96}$, all uncensored NRS scores recorded from 12 hours minus 15 minutes to 96 hours plus 15 minutes relative to $T0_{nrs}$ (time of admission to the PACU) will be used.

If the first NRS assessment, or the last NRS assessment, for the time interval specified for an AUC calculation is not recorded (i.e., no assessments occurred within the protocol-specified windows for these timepoints) then, if the score from an adjacent scheduled NRS assessment of the same type (rest or evoked) is recorded, the recorded score at the adjacent time will be used to impute the missing NRS score; if both an earlier and a later adjacent score are extant, then the higher of these two scores will be used for imputing the missing score. If the first two or last two consecutively scheduled NRS scores of the same type (rest or evoked) for the time interval specified for an AUC calculation are not recorded, then the AUC calculation will be set to missing.

### *7.3.5 Total Opioid Consumption*

Opioids taken as rescue medication will be converted into oral morphine equivalents (OME) using the conversion factors in Nielsen 2016. Opioid use is recorded on the rescue medication eCRF from the end of surgery through T96/Discharge and following discharge either in the electronic or paper diary until the Day 15 (D15) visit or the Early Termination (ET) visit. Following discharge to outpatient status, opioid use recorded in the patient paper diary is transferred to the eCRF at subsequent clinic visits and electronic diary data is integrated into the study database directly.

The total opioid consumption (OC) for each patient will be calculated as the sum of the OMEs of all of the medications taken during a specified interval. For example, if a patient takes 5 OME of hydromorphone on Day 1, 5 OME of hydromorphone and 10 OME of oxycodone on Day 2, then

the total OC for Day 1 is 5 OME, and the total OC for Day 2 is 15 OME; the total OC for Days 1 and 2 is 20 OME. Patients that take no opioids in a day will have a total OC of zero for that day.

Total OC will be determined for the following time periods: T12 to T96, $T0_{hrs}$ to T96, T24 to T48, T24 to T72, T24 to T96, T24 to D8, and T24 to D15.

### *7.3.6 Total Non-opioid Analgesic Consumption*

Non-opioid analgesic use is recorded similarly to opioid rescue medication use (Section 7.3.5). Total non-opioid analgesic consumption (AC), i.e., total milligrams of rescue acetaminophen (including the acetaminophen component of Percocet) taken during the specified time intervals by each patient will be calculated for the following time periods: $AC_{96\text{-}D8}$ and $AC_{96\text{-}D15}$.

### *7.3.7 Knee Range of Motion (ROM)*

Knee ROM will be assessed at Screening, T48, T96, D8, D15, and D29. Angles of maximum knee flexion and extension will be recorded under passive motion (staff will flex or extend the knee joint to the end of the range of motion) and active motion (patient will flex or extend the knee joint to the end of the range of motion).

### *7.3.8 KOOS Questionnaire*

The KOOS questionnaire will be administered at Screening, T96 (D5), D8, D15, and D29. The following subscale scores will be calculated: 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). Details of the scoring algorithm are provided in Appendix 15.1.

### *7.3.9 Performance-based Outcome Measures (PBOMs).*

PBOMs will be assessed at T96 (D5), D15, and D29. The following data will be collected:

- Sit to Stand test: the number of times the patient is able to stand up and sit back down again in 30 seconds will be recorded.
- Walking Speed Test: the walking speed (m/sec) over a distance of 5 meters will be recorded
- Timed Up and Go (TUG) test: the time in seconds the patient took to perform the test will be recoded.

*7.3.10 PROMIS 10 Global Health Questionnaire Score*

The PROMIS 10 questionnaire, version 1.1, was to be administered at Screening, D15, and D29. Global Physical Health and Global Mental Health scores will be calculated. Details of the scoring algorithm are provided in Appendix 15.2.

*7.3.11 AE of Lack of Efficacy*

An AE of lack of efficacy will be defined as any AE coded using the Medical Dictionary for Regulatory Activities (MedDRA) with a preferred term (PT) of "drug ineffective." Patients who require IV opioid rescue medication after T24 will be considered to have an AE of lack of efficacy but will continue in the study.

*7.3.12 Discharge Readiness*

Each patient's data will be assessed for the 8-hour intervals that end daily at 7:00 a.m., 3:00 p.m., and 11:00 p.m., starting at 7:00 a.m. the morning after entry into the PACU ($T0_{nrs}$) through T96 (± 4 h)/Discharge. The elapsed time from $T0_{nrs}$ to the end time of any of the above specified 8-hour periods during which all three of the following criteria are simultaneously present in that 8-hour time period (i.e., a satisfied criterion's presence in a prior 8-hour time period does not count, with the exception noted below), will be designated as a time point at which a patient is ready for discharge:

- adequate analgesia, defined as median rest NRS < 4 (where rest NRS refers to recorded, not imputed, rest NRS scores within the 8-hour period);
- independence from intravenous opioids;
- ability to ambulate > 100 ft (> 30 m) with only the aid of a walker during a physical therapy session.

Note: Because daily physical therapy sessions are scheduled at 10:00 AM (± 1 h) and 4:00 PM (± 1 h), the 'ability to ambulate' discharge criterion may not be fully evaluable during the 11:00 PM to 7:00 AM 8-hour time periods. For the 7:00 a.m. assessment of discharge readiness, the evaluation of the ability to ambulate from the prior 8-hr period (i.e., the period from 3:00 p.m. until 11:00 p.m. on the day before) will be used.

## 7.4 Analysis Methods

*7.4.1 General Considerations*

The final data analysis will be performed after all patients have either completed or have been

discontinued from the study, all data cleaning has been completed, and the study database has been locked. 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 specified in this SAP will be detailed in the clinical study report.

All data collected in the clinical database will be included in the data listings.

Statistical testing including *p*-values and confidence intervals (CIs) will be presented as described in each section below. The Type I error rate (alpha) for the primary analysis of the primary efficacy endpoint, primary endpoint sensitivity analyses, and key secondary efficacy endpoint analyses is 0.05 (one-sided). For all other analyses, the Type I error rate is two-sided at the 0.05 level of significance. Where appropriate, a significance level in the interval $0.05 < p < 0.10$ will be considered as evidence of a trend.

For this proof-of-concept study, no adjustment of the level of significance will be made for multiple testing.

Because the 90 mg treatment group occurred only in Part A, and includes only 6 patients who received active treatment, inferential analyses for the 90 mg group will not be undertaken; only descriptive statistics will be provided for the 90 mg treatment group.

See Section 13 for example SAS code for the analyses described in the following subsections.

### *7.4.2 Pooling of Data*

The efficacy and safety data from Parts A and B of study CA-PS-208 will be pooled by treatment group, for the placebo, 30 mg, and 60 mg treatment groups, prior to performing analyses.

### *7.4.3 Primary Efficacy Endpoint*

#### 7.4.3.1 Primary Efficacy Endpoint Hypothesis

The null hypothesis associated with the primary efficacy endpoint is that the mean rest NRS $AUC_{12\text{-}96}$ does not differ between active treatment and placebo, tested against the alternative hypothesis that the mean rest NRS $AUC_{12\text{-}96}$ is smaller for at least one active treatment compared to placebo.

#### 7.4.3.2 Primary Analysis of the Primary Efficacy Endpoint

The primary analysis of the primary efficacy endpoint will be performed for the mITT Population using a one-way analysis of variance (ANOVA) with a fixed effect for treatment. The analysis result will be reported as the difference in Least Squares (LS) means, active minus placebo, for rest NRS $AUC_{12\text{-}96}$, with the 90% confidence interval for the difference and the corresponding statistical *p*-value for the one-sided significance test.

Should the ANOVA assumptions of normality of rest NRS $AUC_{12\text{-}96}$ values, normality of residuals, or homogeneity of variances be significantly violated, the primary analysis may be repeated after suitable transformation of the data or the analysis may be replaced with a non-parametric analysis.

#### 7.4.3.3 Primary Efficacy Endpoint Sensitivity Analyses

In order to assess the sensitivity of the primary analysis of the primary endpoint to the censoring and imputation scheme specified for calculating the primary endpoint rest NRS $AUC_{12\text{-}96}$ value following rescue medication administration, the primary analysis of the primary endpoint will be repeated in the mITT population in two ways:

- No post rescue medication administration censoring and imputation is performed; the rest NRS $AUC_{12\text{-}96}$ calculation will employ all scheduled rest NRS scores and pre-rescue rest NRS scores available in the interval $T_{12}$ to $T_{96}$.
- No post rescue medication administration censoring and imputation is performed; the rest NRS $AUC_{12\text{-}96}$ calculation will employ all available scheduled rest NRS scores only.

#### 7.4.3.4 Exploratory Analyses of the Primary Endpoint

For the primary efficacy endpoint, two exploratory analyses will be performed as to explore different methods of accounting for the effect of rescue medication use in the primary analysis. Censoring of rest NRS scores post rescue medication use as described in Section 7.3.2 will not be included in these analyses.

- Silverman Rank Analysis: Rank patients in the combined treatment groups according to their NRS $AUC_{12\text{-}96}$ values; when ties occur, assign each of the tied observations the average of the ranks the tied observations would have if there were no ties. Perform the above steps for total opioid use OME values. Each rest NRS $AUC_{12\text{-}96}$ rank and each total opioid use OME rank will be expressed as a percentage difference from the mean rank for that variable in the overall study population and plotted. The integrated ranks of

the active treatment and placebo groups will be compared using the Kruskal-Wallis test (non-parametric ANOVA). (See Silverman 1993.)

- Analysis of Covariance (ANCOVA): The primary analysis of the primary efficacy endpoint will be revised with the addition of the patient's Total Opioid Consumption as a covariate in the model as well as the treatment by Total Opioid Consumption interaction. The interaction term will be omitted from the model if not significant at the 0.1 level.

7.4.3.5 Primary Efficacy Endpoint-related Tables, Figures, and Listings

The primary endpoint analysis results will be presented in a summary and analysis table. The number of patients (n) included in the analysis, mean (SD) of rest NRS $AUC_{12\text{-}96}$, LS mean of rest NRS $AUC_{12\text{-}96}$ and its standard error (SE) will be presented for all treatment groups. The difference in LS mean from placebo for the 36 mg and 60 mg treatment groups, the 90% confidence interval (CI) for the difference in LS means, and the corresponding *p*-value for the difference will be presented by treatment group (36 mg and 60 mg). Contrasts generated for the primary endpoint analysis for tests of active combined (36 mg and 60 mg groups combined) versus placebo and the 60 mg group versus the 36 mg group will also be presented.

The output of the Kruskal-Wallis ANOVA for the Silverman rank analysis will be presented in a summary and analysis table. A plot of the Silverman analysis summed percentage differences (for rest NRS and total opioid consumption OEM) over all treatment groups (placebo, 36 mg, and 60 mg) versus mean overall rank will be presented in a figure.

NRS values by time point, and computed AUC values by type, will be presented in patient listings by treatment group. Imputed NRS values will be flagged in the listing.

. In order to visualize the effect of censoring scheduled rest NRS scores due to the administration of rescue medication, three figures will be provided:

- A plot of mean scheduled rest NRS scores by nominal time point, where in calculating the mean, wherever a subject has a scheduled rest NRS score falling within a censoring interval due to the administration of rescue medication, the observed rest NRS score is replaced by the imputed score for that subject at that nominal time point (i.e., the wLOCF value is imputed at that nominal time point), and the mean is then calculated over all such NRS scores for each nominal time point. Missing due to early drop out are not imputed.

- A plot of mean scheduled rest NRS scores by nominal time point, where in calculating the mean post-dropout results are imputed with LOCF, but post-rescue results are not imputed.
- A plot of the mean observed scheduled rest NRS scores with no imputation due to rescue medication use or post-dropout.

Each figure will display the plot of NRS score by time for each treatment group (placebo, 36 mg, and 60 mg) and the regions corresponding to rest NRS AUC12-96 will be indicated on the plot. These figures will be provided for both the mITT and PP populations. The corresponding table with descriptive summaries at each time point will also be produced for each figure.

Similar figures (with or without post-dropout LOCF imputations) and the corresponding tables will be created for evoked NRS.

Plots of NRS values over time may be displayed in figures, by patient, as warranted.

### *7.4.4 Other AUC Endpoints, Total Opioid Consumption, and Total Non-opioid Analgesic Consumption Endpoints*

Other AUC-based endpoints, total opioid consumption endpoints, and total non-opioid analgesic consumption endpoints will be analyzed using the same ANOVA approach employed in the primary analysis of the primary endpoint.

#### 7.4.4.1 Other AUC Endpoints and Total Opioid Consumption Endpoints and Related TFLs

ANOVA output for other AUC-based endpoints, total opioid consumption endpoints, and total non-opioid analgesic consumption endpoints will be presented in tables analogous to those presented for the primary endpoint analysis.

Figures will be provided displaying plots analogous to those specified for the primary endpoint for mean rest NRS values and mean evoked NRS values; regions corresponding to AUC for the relevant time periods will be indicated on the plots.

A figure displaying total opioid consumption OEM values for each treatment group (placebo, 36 mg, and 60 mg) in a bar chart will be provided. A similar figure for total non-opioid analgesic consumption will also be provided.

### *7.4.5 Time to Cessation of Opioid Use*

The time in hours from $T0_{nrs}$ to the last recorded use of opioid analgesics through D15 will be analyzed using time to event analysis. The mean and median time to cessation of opioid use and their 95% CIs will be presented by treatment group (placebo, 36 mg, and 60 mg) with log-rank *p*-values for the difference in cessation time estimates between treatment groups (36 mg and 60 mg) and placebo. Plots of time to cessation of opioid use will also be provided, by treatment group.

### *7.4.6 Percentage of Patients Who Are Opioid-free*

The number and percentage of patients who are opioid-free (yes/no) from $T0_{nrs}$ to T96 ($OF_{0-96}$), will be presented in an analysis table, by treatment group (placebo, 36 mg, and 60 mg), excluding the 90 mg treatment group. A Cochran-Mantel-Haenszel (CMH) test will be used to test the null hypothesis of no difference between each active treatment group and placebo in the proportion of opioid-free patients in the mITT population from $T0_{nrs}$ to T96; the analysis will be repeated for the following time intervals: $OF_{24-D15}$, $OF_{96-D8}$, and $OF_{96-D15}$. Each of the OF analyses will be repeated for the PP population. For $OF_{24-96}$ (one of the key secondary endpoints), one-sided Fisher's exact test will be used instead of the two-sided CMH test.

Treatment versus placebo odds ratios with 95% CI, the difference in proportions (active treatment minus placebo) with 95% CI, and CMH *p*-values for the comparisons of active treatment versus placebo will be presented in the analysis table.

### *7.4.7 Time-specific Mean Rest NRS Scores*

The mean rest NRS scores at T48, T72, T96, T120, T144, and T168 will be summarized descriptively by time point and treatment group and presented in a summary table.

For this analysis, post-rescue assessments will be imputed as described in section 7.3.2. However, post-dropout missing NRS scores (described in section 7.3.3) will not be imputed.

The difference in mean rest NRS scores between treatment groups at T48, T72, T96, T120, T144, and T168 will be will be analyzed in the mITT population using a linear mixed-effects model repeated measures ANOVA with fixed effects for treatment, time point, and the interaction of treatment and time point. The Kenward-Roger method for computing the denominator degrees of freedom will be used. An unstructured covariance matrix will be assumed; if convergence issues are experienced with this matrix type, then Toeplitz, first-order auto-regressive, and compound symmetry types will be tried in order and the first matrix to

result in successful convergence will be used. Least Squares (LS) means, with 95% confidence intervals and the corresponding statistical *p*-value, will be presented for each time point for the difference between each active treatment group (36 mg and 60 mg) and placebo. The analysis will be repeated for the PP population.

In addition, a plot of mean NRS scores versus nominal time point, by treatment group, will be presented in a figure.

*7.4.8 Knee Range of Motion (ROM)*

Knee ROM scores collected at Screening, T48, T96, D8, D15, and D29, and their changes from Screening, will be summarized descriptively at each nominal time point, by treatment group; changes from T48 to T96, D8, D15, and D29 will also be summarized.

The change from baseline and change from T48 in each (both passive and active flexion or extension) ROM score will be analyzed in the mITT population using a linear mixed-effects model with fixed effects for treatment, time point, baseline value as covariate, and the interaction of treatment and time point. The Kenward-Roger method for computing the denominator degrees of freedom will be used and the covariance structure will be selected in the same way as described in section 7.4.7. For each treatment group (placebo, 36 mg, and 60 mg), the change from baseline mean (SD), LS mean (SE), and difference in LS mean from placebo with 95% CI and the corresponding statistical *p*-value, will be presented for each time point and treatment group; the analysis will be repeated for the PP population.

In addition, the number and percentage of patients with > 90° and with > 115° active flexion and passive flexion, and the number and percentage of patients with < 0º, 10° to 0°, 20° to > 10°, and > 20° active extension and passive extension, will be presented in an analysis table by time point and treatment group.

A Cochran-Mantel-Haenszel (CMH) test will be used to test the null hypothesis of no difference between each active treatment group (36 mg and 60 mg) and placebo in the proportion of patients with the given ranges of motion in the mITT population at the specified time points; the analysis will be repeated for the PP population.

Treatment versus placebo odds ratios with 95% CI, the difference in proportions (active treatment minus placebo) with 95% CI, and CMH *p*-values for the comparisons of active treatment versus placebo will be presented in the analysis table.

### *7.4.9 KOOS Questionnaire*

KOOS questionnaire subscale scores calculated for Screening, T96 (D5), D8, D15, and D29, and their changes from Screening, will be summarized descriptively at each nominal time point, by treatment group; changes from T96 (D5) to D8, D15, and D29 will also be summarized. The following subscale scores will be calculated: 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).

The change from Screening to each subsequent time point, and the change from T96 (D5) to each subsequent time point, in each subscale score will be analyzed in the mITT population using a linear mixed-effects model with fixed effects for treatment, time point, the interaction of treatment and time point, and the corresponding baseline value as covariate, similar to the model in section 7.4.8. For each treatment group (placebo, 36 mg, and 60 mg), the change from baseline mean (SD), LS mean (SE), and difference in LS mean from placebo with 95% CI and the corresponding statistical *p*-value, will be presented, by subscale, for each time point and treatment group; the analysis will be repeated for the PP population.

### *7.4.10 Performance-Based Outcome Measure (PBOM).*

The results of PBOM measurements at T96 (± 4 h)/Discharge, D15, and D29 will be summarized descriptively by time point and treatment group and presented in separate summary tables for each of the PBOMs—sit to stand, walking speed, timed up and go (TUG).

The difference in mean PBOM score between treatment groups at T96 (± 4 h)/Discharge, D15, and D29 will be analyzed in the mITT population using a linear mixed-effects model repeated measures ANOVA with fixed effects for treatment, time point, and the interaction of treatment and time point, similar to the model in section 7.4.8. Least Squares (LS) means, with 95% confidence intervals and the corresponding statistical *p*-value, will be presented for each time point for the difference between each active treatment group (36 mg and 60 mg) and placebo. The analysis will be repeated for the PP population.

### *7.4.11 PROMIS 10 Global Health Questionnaire Scores*

The PROMIS 10 questionnaire Global Physical Health and Global Mental Health subscale scores (see Appendix 51.2) at Screening (baseline), D15, and D29 and their changes from baseline will be summarized descriptively by timepoint and treatment group for each subscale.

The change from baseline in each subscale score will be analyzed in the mITT population using a linear mixed-effects model with fixed effects for treatment, time point, the interaction of treatment and time point, and the corresponding baseline value, similar to the model in section 7.4.8. For each treatment group (placebo, 36 mg, and 60 mg), the change from baseline mean (SD), LS mean (SE), and difference in LS mean from placebo with 95% CI and the corresponding statistical *p*-value, will be presented, by subscale, for each time point and treatment group; the analysis will be repeated for the PP population.

*7.4.12 Time to Discharge Readiness*

A time to event analysis will be provided to determine, for each treatment group (placebo, 36 mg, and 60 mg), Kaplan–Meier estimates of the cumulative percentages of patients meeting all three discharge criteria at each time point and subsequent time points, i.e., for each patient, the time point, among T24 (± 4 h), T48 (± 4 h), T72 (± 4 h), and T96 (± 4 h)/Discharge, at which the patient meets all three discharge criteria at that time point and all subsequent time points (meaning no subsequent reversion to *not* ready for discharge status). A time to event plot of cumulative percentage of patients, within each treatment group, versus time will be provided.

*7.4.13 Other Binary Endpoints*

For the following binary endpoints, the number and percentage of patients achieving the endpoint will be presented in an analysis table by timepoint (if applicable) and treatment group (placebo, 36 mg, and 60 mg), excluding the 90 mg treatment group:

- use of rescue medication in time periods $T0_{nrs}$-T6, T6-T12, T12-T24, T24-T48, T48-T72, and T72-T96;
- patient experienced an AE of lack of efficacy (LOE) during the in-patient portion of the study, $LOE_{0\text{-}96}$;
- discharge readiness at T24 (± 4 h), T48 (± 4 h), T72 (± 4 h), and T96 (± 4 h)/Discharge.

For each endpoint, a Cochran-Mantel-Haenszel (CMH) test will be used to test the null hypothesis of no difference between each active treatment group and placebo in the proportion of patients who met the endpoint in the mITT population for the relevant time period, where applicable; the analysis will be repeated for the PP population.

Treatment versus placebo odds ratios with 95% CI, the difference in proportions (active treatment minus placebo) with 95% CI, and CMH *p*-values for the comparisons of active

treatment versus placebo will be presented in the analysis table.

# 8. SAFETY EVALUATION

## 8.1 Overview of Safety Analysis Methods

Analysis of safety will be performed for the Safety population.

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

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.

Safety outcomes include:

- Incidence 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 (if performed)
- Presence of worsening (rebound) pain
- Concomitant medication use/concomitant treatments

## 8.2 Adverse Events

All AEs are documented and followed from the time the patient signed the informed consent form (ICF) until Day 29 or later as necessary. AEs will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA Version

22.1) reporting system. All coding will be reviewed prior to database lock. All recorded AEs will be listed, but only TEAEs will be summarized.

Treatment-emergent AEs are defined as any of the following:

- Non-serious AEs with onset on the date of treatment with the study drug through Day 29 or Early Termination
- Serious AEs with onset on the date of treatment with the study drug through 30 days after Day 29 or 30 days after Early Termination
- AEs that start before the start of treatment but increase in severity or relationship at the time of or following the start of treatment through Day 29 or Early Termination

In case an AE start date is partial, when comparing this date to the date of treatment, the latest possible date consistent with the known portion of the date will be imputed. However, when comparing the start date to the Day 29/Early Termination date, the earliest possible date consistent with the known portion of the date will be imputed.

For evaluation of causal relatedness to treatment, the categories are probably related, possibly related, unlikely related, and not related. For categorization in the summary tables, AEs designated as probably or possibly related will be considered to be related.

For the evaluation of event severity, the criteria are mild, moderate, severe, life-threatening, and fatal.

Safety summaries will include the incidence of treatment emergent adverse events (TEAEs). AEs recorded on the CRF which began prior to treatment with study drug will not be included in the summary tables but will be included in the AE data listings. TEAEs will be evaluated for severity and causality. All TEAE summaries will be based on the number of patients experiencing an event, not the number of AEs experienced. For example, if a patient reports the same AE on three separate occasions that patient will be counted only once for that preferred term. Patients reporting more than one AE in a SOC will be counted only once in the SOC total.

AEs and serious adverse events (SAEs) will be summarized separately and presented by treatment group. The number and percentage of patients experiencing any event, and the number of events, will be presented. Only TEAEs will be included in the summaries. Non-

treatment emergent events will be included in the patient listings and flagged, but they will not be included in the AE summaries.

Summaries classifying AEs according to severity (i.e., mild, moderate, severe, or missing severity) and relationship to study drug (i.e., probably related, possibly related, unlikely related, not related, or relationship is missing) will be presented. If a patient experiences the same AE at more than one severity or with more than one relationship to study drug, the most severe rating or the stronger causal relationship to study drug will be given precedence. Any missing severity, causality, or outcome will not be imputed and will be classified as unknown.

The denominator used for calculation of the safety summary percentages will be the number of patients in the Safety Population in the appropriate group. AEs will be summarized for any exposure to study treatment by treatment group.

### *8.2.1 Adverse Event Summaries*

The following AE summaries will be provided:

- A summary of the number and percentage of patients reporting any TEAE, death, at least one severe TEAE, at least one serious TEAE, at least one TEAE possibly related to study drug, at least one TEAE leading to withdrawal from study drug, by treatment group.
- A summary of the number and percentage of patients reporting a TEAE by treatment group, system organ class, and preferred term.
- A summary of the number and percentage of patients reporting a TEAE by treatment group, system organ class, preferred term, and maximum severity (for each patient and each TEAE, the maximum reported severity recorded will be attributed and used in the summary).
- A summary of the number and percentage of patients reporting a TEAE by treatment group, system organ class, preferred term, and relationship to study drug (the worst relationship to study drug will be attributed and used in the summary).

### *8.2.2 Deaths, Serious Adverse Events, Adverse Events leading to Withdrawal*

The following summaries will be provided:

- A summary of the number and percentage of patients reporting a serious TEAE by treatment group, system organ class, and preferred term.
- A summary of the number and percentage of patients reporting a serious TEAE by treatment group, system organ class, preferred term, and relationship to study drug.
- A summary of the number and percentage of patients reporting a TEAE leading to discontinuation of study drug by treatment group, system organ class, and preferred term.
- A summary of the number and percentage of patients with a SAE outcome of death by treatment group and preferred term.

### 8.3 Clinical Laboratory Test Results

Clinical laboratory tests (chemistry, hematology/coagulation, and urinalysis) will be collected at screening and before discharge from the inpatient unit (T96). All results will be presented in listings by patient and treatment group.

For continuous laboratory parameters, descriptive statistics will be presented for the value at each assessment time and for the changes from baseline by visit and treatment group. Values reported as “< xx” or “> xx” (where xx is a number) will be treated as xx for the purposes of these summaries.

Additionally, clinical laboratory parameters will be categorized as low, normal, or high according to laboratory range specifications. Laboratory shift tables displaying the change (number and percentage of patients) relative to the normal range from baseline to the T96 timepoint will also be presented by treatment group for each test.

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

### 8.4 Drugs of Abuse and Alcohol Screens, Pregnancy Test

Pregnancy tests (for female patients of childbearing potential), urine drug screens, and alcohol (breath or saliva) tests will be performed at screening and on D1 pre-surgery.

Results will be presented in listings by patient. Each test result will be recorded as “negative” or “positive”.

### 8.5 Vital Signs

Vital signs including blood pressure (systolic and diastolic; mmHg), heart rate (beats per minute), respiration rate (breaths per minute), and temperature (°C) will be assessed 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 (a patient 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 a ± 15-minute window is allowed.

Body weight (kg), in indoor clothing, but without shoes, was to be measured at Screening and at T96. Height (cm) was to be measured at screening only. Body mass index (BMI) will be calculated for the Screening visit only.

Vital signs (including weight) and their changes from baseline will be summarized descriptively by timepoint and treatment group.

### 8.6 ECG

ECG will be performed at Screening and 24 hours (± 2 hours) after study medication administration. Overall interpretation (Normal, Abnormal Not Clinically Significant, or Abnormal Clinically Significant) is recorded in the eCRF.

Number and percentage of patients with each interpretation will be summarized by timepoint and treatment group.

### 8.7 Physical Examination

A complete physical examination including all major body systems was to be performed at Screening. In addition, a targeted physical examination was to be performed prior to surgery, then 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 at the time a patient terminates early, if permitted.

Abnormal or clinically significant physical examination results recorded as AEs. Physical examination results will be presented in a listing by patient and treatment group.

### 8.8 Surgical Site Assessments

Surgical sites were to be assessed at 96 hours (prior to discharge from the PACU) and then at the D8, D15, and D29 visits. The investigator was to have evaluated wound healing 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. Any clinically significant wound healing issues are captured as AEs and followed until resolution.

All data will be presented in listings by patient and treatment group. The surgical site assessment score will be summarized descriptively by treatment group and time point

### 8.9 Neurosensory Test

Neurosensory testing near the incision (compared to a similar site on the opposite leg) was to be performed at screening, T96h (prior to discharge from the unit), and then at the D8, D15, and D29 visits.

Two sides of the wound were to be examined: cephalad (upper) and caudad (lower). For each side, the following assessments were to be recorded:

- Visual Examination of the Surgical Site (Normal or Abnormal)
- Light Touch (Normal, Reduced, or Absent)
- Von Frey Stimulation (Normal, Reduced, or Absent)
- Brush Stimulation (Normal, Reduced, Absent, or Pain [Allodynia])

The neurosensory assessment results will be listed and the number and percentage of patients with each response will be summarized by treatment group, time point, wound side (cephalad or caudad), and assessment.

### 8.10 X-ray of the Operated Knee

X-ray of the operated knee was to be performed on Day 29 (or Early Termination, if possible) and later in case of any evidence of abnormal bone healing until resolution or stabilization.

Results of x-ray of the operated knee will not be entered into the study database. The date and time the x-ray was performed will be presented in a listing by patient and treatment group.

### 8.11 Presence of Rebound (or Worsening) Pain

Patients were to report whether they have noted any worsening pain (rebound pain) at the surgical site since the prior visit at visits D8, D15, and D29.

The number and percentage of patients with rebound pain will be presented in a summary table by treatment and time point.

### 8.12 Prior and Concomitant Medications

Prior medications/therapies are those that stop prior to the start of the study drug administration. Any medication/therapy that stops at or after this time or ongoing is considered concomitant medication/therapy. Prior and concomitant medications are collected for the 30 days prior to screening and throughout the study. Prior and concomitant medications will be coded using World Health Organization Drug Dictionary Anatomical Therapeutic Chemical (WHO/ATC) classification index version Sep 1, 2019. The number and percentage of patients who take concomitant medications will be summarized by the drug class (the highest available ATC level) and preferred term, overall and by treatment group for the safety population. All medications and non-medical therapies captured in eCRFs will be presented by patient in listings by treatment group.

### 8.13 Patient Pain Assessment Training and Surgery Details

Pain assessment training was to be provided to patients during screening. Patients were to re-watch the video prior to surgery. Patient pain assessment training and surgery details were to be documented in eCRFs and will be presented by patient in listings by treatment group.

## 9. PHARMACOKINETIC EVALUATION

The time points for pharmacokinetic (PK) whole blood collections were to be at pre-dose (from check-in and up to 30 minutes before the start of surgery), and at pharmacokinetic time (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 24 hours after the last study treatment instillation (total of 15 samples). There was to be a ± 2-minute window allowed for the 10-minute and 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 was to be performed.

Actual sampling times were to be used to calculate plasma-derived PK parameters. Full details of PK endpoints and analyses will be presented in a separate PK Analysis plan.

## 10. OTHER ANALYSES

All additional analyses not included in this SAP, conducted after the study unblinding will be considered exploratory and will be presented and identified separately in the CSR.

## 11. DEVIATIONS FROM THE SAP

Any deviations from the final version of this SAP will be described and justified in the final CSR.

## 12. CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

None noted.

## 13. EXAMPLE SAS CODE

Primary endpoint analysis, one-way ANOVA:

```
proc mixed data=auc_data;
  class patient treatment;
  model auc = treatment;
  lsmeans trt / diff=controlL ('placebo') cl alpha=0.05;
  lsmeans trt / diff cl alpha=0.10;
  estimate '36 and 60 mg vs. Placebo' treatment 0.5 0.5 -1 / cl;
  estimate ’60 vs. 36 mg’ treatment -1 1 0 / cl;
run;
```

Primary endpoint analysis, ANCOVA:

```
proc mixed data=auc_data;
  class patient treatment;
  model auc = treatment total_OME treatment*total_OME;
  lsmeans trt / diff=controlL ('placebo') cl alpha=0.05;
  lsmeans trt / diff cl alpha=0.10;
  estimate '36 and 60 mg vs. Placebo' treatment 0.5 0.5 -1 / cl;
  estimate ’60 vs. 36 mg’ treatment -1 1 0 / cl;
run;
```

Primary endpoint exploratory analysis, non-parametric ANOVA (Silverman rank test):

```
proc npar1way wilcoxon correct=no data=integ_ranks;
  class treatment;
  var int_rank;
run;
```

Example SAS code for ANOVA by time point analyses:

```
proc mixed data=scores;
  class subjid trt time;
  model score = trt time trt*time/ ddfm=kr;
  repeated time / subject = subjid type = UN;
  lsmeans trt*time / diff cl;
run;
```

Note: if the model does not converge with Unstructured covariance matrix (type=UN), then try TOEP, AR(1), and CS, in this order, using the first structure that converges.

Example SAS code for the change from baseline linear mixed-effects model:

```
proc mixed data=parameter_data;
  class patient treatment timepoint;
  model change=baseline treatment timepoint treatment*timepoint / ddfm=kr;
  repeated timepoint / subject = subjid type = UN;
  lsmeans treatment*timepoint / diff cl;
run;
```

Note: if the model does not converge with Unstructured covariance matrix (type=UN), then try TOEP, AR(1), and CS, in this order, using the first structure that converges.

Example SAS code for CMH analysis:

```
proc freq data=parameter_data order=data;
  tables treatment*outcome / cmh exact riskdiff;
  weight count;
  exact riskdiff;
run;
```

Example SAS code for time to event analysis:

```
proc lifetest data=event_data method=KM plots=survival(failure test atrisk);
  time hours*status(0);
  strata treatment;
run;
```

## 14. REFERENCES

US Federal Register. (1998) International Conference on Harmonization; Guidance for Industry: Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration. Federal Register, Vol. 63, No. 179, September 16, 1998, page 49583.

US Federal Register. (1996) International Conference on Harmonization; Guidance for Industry: Structure and Content of Clinical Study Reports. Department of Health and Human Services: Food and Drug Administration. Federal Register Vol. 61, July 17, 1996, page 37320.

Nielsen, Suzanne et al., A synthesis of oral morphine equivalents (OME) for opioid utilisation studies, *Pharmacoepidemiology and Drug Safety* 2016; 25: 733–737

Silverman, David G. et al., Integrated assessment of pain scores and rescue morphine use during studies of analgesic efficacy, *Anesth Analg* 1993;77:168-70

# 15. APPENDICES

## 15.1 Scoring of KOOS Questionnaire

Each item is scored as follows: None = 0, Mild = 1, Moderate = 2, Severe = 3, Extreme = 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 as follows:

Subscale score = 100 – (Mean of subscale items) $\times$ 100/4

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.

## 15.2 Scoring of PROMIS 10 Questionnaire

This study employs PROMIS v1.1 questionnaire that is scored as follows.

1. Recode the response to question 10 (How would you rate your pain on average) as follows:

| Response | Recoded Response |
|---|---|
| 0 | 5 |
| 1, 2, 3 | 4 |
| 4, 5, 6 | 3 |
| 7, 8, 9 | 2 |
| 10 | 1 |

2. Reverse the response to questions 8 (How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?) and 9 (How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?) by subtracting them from 5. This way higher scores for responses always indicate better health.
3. Calculate the Global Physical Health raw score by summing the responses for questions 3, 7, 10, and 9. If not all of these questions are answered, the score will be missing.

4. Calculate the Global Mental Health raw score by summing the responses for 2, 4, 5, and 8. If not all of these questions are answered, the score will be missing.
5. Use the following tables to convert the global raw scores to the T-scores that will be used in analysis:

| **Global Physical Health** | |
|---|---|
| **Raw summed score** | **T-score** |
| 4 | 16.2 |
| 5 | 19.9 |
| 6 | 23.5 |
| 7 | 26.7 |
| 8 | 29.6 |
| 9 | 32.4 |
| 10 | 34.9 |
| 11 | 37.4 |
| 12 | 39.8 |
| 13 | 42.3 |
| 14 | 44.9 |
| 15 | 47.7 |
| 16 | 50.8 |
| 17 | 54.1 |
| 18 | 57.7 |
| 19 | 61.9 |
| 20 | 67.7 |

| **Global Mental Health** | |
|---|---|
| **Raw summed score** | **T-score** |
| 4 | 21.2 |
| 5 | 25.1 |
| 6 | 28.4 |
| 7 | 31.3 |
| 8 | 33.8 |
| 9 | 36.3 |
| 10 | 38.8 |
| 11 | 41.1 |
| 12 | 43.5 |
| 13 | 45.8 |
| 14 | 48.3 |
| 15 | 50.8 |
| 16 | 53.3 |
| 17 | 56.0 |
| 18 | 59.0 |
| 19 | 62.5 |
| 20 | 67.6 |

## 15.3 Planned Tables, Figures, and Listings

### *15.3.1 Tables*

| | | |
|---|---|---|
| Table 14.1.1 | All Patients | Summary of Patient Disposition |
| Table 14.1.2 | Randomized Patients | Summary of Protocol Deviations |
| Table 14.1.3 | Safety Population | Summary of Demographics and Baseline Characteristics |
| Table 14.1.4 | Safety Population | Summary of Concomitant Medications, by ATC Class and Preferred Term |
| Table 14.1.5 | Safety Population | Summary of Medical History, by System Organ Class and Preferred Term |
| Table 14.1.6 | Safety Population | Summary of Study Drug Volume Administered |
| Table 14.2.1.1 | mITT Population | ANOVA Analysis of Rest NRS AUC12-96 (Primary Analysis) |
| Table 14.2.1.2 | PP Population | ANOVA Analysis of Rest NRS AUC12-96 |
| Table 14.2.1.3 | mITT Population | ANOVA Analysis of Rest NRS AUC12-96 – Scheduled Rest |

| | | |
|---|---|---|
| | | NRS and Pre-rescue NRS Scores) (Sensitivity Analysis) |
| Table 14.2.1.4 | mITT Population | ANOVA Analysis of Rest NRS AUC12-96 – Scheduled Rest NRS Scores (Sensitivity Analysis) |
| Table 14.2.1.5 | mITT Population | Rest NRS AUC12-96 and Total Opioid Use, Silverman Rank Analysis (Exploratory Analysis) |
| Table 14.2.1.6 | mITT Population | ANCOVA Analysis of Rest NRS AUC12-96 (Exploratory Analysis) |
| Table 14.2.2.1 | mITT Population | ANOVA Analysis of Rest NRS AUC |
| Table 14.2.2.2 | PP Population | ANOVA Analysis of Rest NRS AUC |
| Table 14.2.2.3 | mITT Population | ANOVA Analysis of Evoked NRS AUC |
| Table 14.2.2.4 | PP Population | ANOVA Analysis of Evoked NRS AUC |
| Table 14.2.3.1 | mITT Population | ANOVA Analysis of Total Opioid Consumption in OME Dose |
| Table 14.2.3.2 | PP Population | ANOVA Analysis of Total Opioid Consumption in OME Dose |
| Table 14.2.4.1 | mITT Population | ANOVA Analysis of Total Non-Opioid Analgesic Consumption in mg |
| Table 14.2.4.2 | PP Population | ANOVA Analysis of Total Non-Opioid Analgesic Consumption in mg |
| Table 14.2.5.1 | mITT Population | Time to Cessation of Opioid Use |
| Table 14.2.5.2 | PP Population | Time to Cessation of Opioid Use |
| Table 14.2.5.3 | mITT Population | Analysis of Percentage of Patients Who Are Opioid Free |
| Table 14.2.5.4 | PP Population | Analysis of Percentage of Patients Who Are Opioid Free |
| Table 14.2.6.1 | mITT Population | Repeated Measures Analysis of Rest NRS Scores, by Time Point |
| Table 14.2.6.2 | PP Population | Repeated Measures Analysis of Rest NRS Scores, by Time Point |
| Table 14.2.7.1.1 | mITT Population | Repeated Measures Analysis of Knee Range of Motion and Change from Baseline |
| Table 14.2.7.1.2 | PP Population | Repeated Measures Analysis of Knee Range of Motion and Change from Baseline |
| Table 14.2.7.2.1 | mITT Population | Repeated Measures Analysis of Knee Range of Motion and Change from T48 |
| Table 14.2.7.2.2 | PP Population | Repeated Measures Analysis of Knee Range of Motion and Change from T48 |
| Table 14.2.7.3.1 | mITT Population | Analysis of Percentage of Patients with Active Flexion > 90° and > 115° |
| Table 14.2.7.3.2 | PP Population | Analysis of Percentage of Patients with Active Flexion > 90° and > 115° |
| Table 14.2.7.4.1 | mITT Population | Categorical Analysis of Knee Extension |
| Table 14.2.7.4.2 | PP Population | Categorical Analysis of Knee Extension |

| | | |
|---|---|---|
| Table 14.2.8.1.1 | mITT Population | Repeated Measures Analysis of KOOS Questionnaire and Changes from Baseline |
| Table 14.2.8.1.2 | PP Population | Repeated Measures Analysis of KOOS Questionnaire and Changes from Baseline |
| Table 14.2.8.2.1 | mITT Population | Repeated Measures Analysis of KOOS Questionnaire and Changes from T96 |
| Table 14.2.8.2.2 | PP Population | Repeated Measures Analysis of KOOS Questionnaire and Changes from T96 |
| Table 14.2.9.1 | mITT Population | Repeated Measures Analysis of Performance Based Outcome Measures (PBOM) |
| Table 14.2.9.2 | PP Population | Repeated Measures Analysis of Performance Based Outcome Measures (PBOM) |
| Table 14.2.10.1 | mITT Population | Repeated Measures Analysis of PROMIS Questionnaire |
| Table 14.2.10.2 | PP Population | Repeated Measures Analysis of PROMIS Questionnaire |
| Table 14.2.11.1 | mITT Population | Analysis of Percentage of Patients Who Used Opioid Rescue Medications |
| Table 14.2.11.2 | PP Population | Analysis of Percentage of Patients Who Used Opioid Rescue Medications |
| Table 14.2.12.1 | mITT Population | Analysis of Percentage of Patients Who Experienced an AE of Lack of Efficacy During the In-patient Portion of the Study |
| Table 14.2.12.2 | PP Population | Analysis of Percentage of Patients Who Experienced an AE of Lack of Efficacy During the In-patient Portion of the Study |
| Table 14.2.13.1.1 | mITT Population | Analysis of Discharge Readiness [1] |
| Table 14.2.13.1.2 | PP Population | Analysis of Discharge Readiness [1] |
| Table 14.2.13.2.1 | mITT Population | Time to Discharge Readiness [1] |
| Table 14.2.13.2.2 | PP Population | Time to Discharge Readiness [1] |
| Table 14.2.14.1.1 | mITT Population | Rest NRS Scores by Time Point (Primary Analysis - Post-Rescue Medication Imputation and Post-dropout Imputation) |
| Table 14.2.14.1.2 | PP Population | Rest NRS Scores by Time Point (Primary Analysis - Post-Rescue Medication Imputation and Post-dropout Imputation) |
| Table 14.2.14.2.1 | mITT Population | Rest NRS Scores by Time Point (Sensitivity Analysis of Primary Endpoint - Post-Rescue Medication Imputation Only) |
| Table 14.2.14.2.2 | PP Population | Rest NRS Scores by Time Point (Sensitivity Analysis of Primary Endpoint - Post-Rescue Medication Imputation Only) |
| Table 14.2.14.3.1 | mITT Population | Rest NRS Scores by Time Point (Sensitivity Analysis of Primary Endpoint - No Imputations, Observed Scores Only) |
| Table 14.2.14.3.2 | PP Population | Rest NRS Scores by Time Point (Sensitivity Analysis of Primary Endpoint - No Imputations, Observed Scores Only) |
| Table 14.2.14.4.1 | mITT Population | Evoked NRS Scores by Time Point (Post-dropout Imputation) |
| Table 14.2.14.4.2 | PP Population | Evoked NRS Scores by Time Point (Post-dropout Imputation) |

| | | |
|---|---|---|
| Table 14.2.14.5.1 | mITT Population | Evoked NRS Scores by Time Point (No Imputations, Observed Scores Only) |
| Table 14.2.14.5.2 | PP Population | Evoked NRS Scores by Time Point (No Imputations, Observed Scores Only) |
| Table 14.3.1.1 | Safety Population | Overall Summary of Treatment Emergent Adverse Events (TEAEs) |
| Table 14.3.1.2 | Safety Population | Summary of Treatment Emergent Adverse Events, by System Organ Class and Preferred Term |
| Table 14.3.1.3 | Safety Population | Summary of Treatment Related Treatment Emergent Adverse Events (TEAEs), by System Organ Class and Preferred Term |
| Table 14.3.1.4 | Safety Population | Summary of Serious Treatment Emergent Adverse Events (TEAEs), by System Organ Class and Preferred Term |
| Table 14.3.1.5 | Safety Population | Summary of Treatment Emergent Adverse Events (TEAEs) Leading to Study Discontinuation, by System Organ Class and Preferred Term |
| Table 14.3.1.6 | Safety Population | Summary of Treatment Emergent Adverse Events, by System Organ Class, Preferred Term, and Severity |
| Table 14.3.1.7 | Safety Population | Summary of Treatment Emergent Adverse Events, by System Organ Class, Preferred Term, and Relationship to Study Drug |
| Table 14.3.1.8 | Safety Population | Summary of Serious Treatment Emergent Adverse Events, by System Organ Class, Preferred Term, and Relationship to Study Drug |
| Table 14.3.1.9 | Safety Population | Summary of Fatal Serious Adverse Events, by Preferred Term |
| Table 14.3.2.1.1 | Safety Population | Summary of Chemistry Laboratory Tests: Results and Change from Baseline |
| Table 14.3.2.1.2 | Safety Population | Summary of Chemistry Laboratory Tests: Shift from Baseline |
| Table 14.3.2.2.1 | Safety Population | Summary of Coagulation Laboratory Tests: Results and Change from Baseline |
| Table 14.3.2.2.2 | Safety Population | Summary of Coagulation Laboratory Tests: Shift from Baseline |
| Table 14.3.2.3.1 | Safety Population | Summary of Hematology Laboratory Tests: Results and Change from Baseline |
| Table 14.3.2.3.2 | Safety Population | Summary of Hematology Laboratory Tests: Shift from Baseline |
| Table 14.3.2.4.1 | Safety Population | Summary of Urinalysis Laboratory Tests: Results and Change from Baseline |
| Table 14.3.2.4.2 | Safety Population | Summary of Urinalysis Laboratory Tests: Shift from Baseline |
| Table 14.3.3 | Safety Population | Summary of Vital Signs: Results and Change from Baseline |
| Table 14.3.4 | Safety Population | Summary of ECG Overall Interpretation |
| Table 14.3.5 | Safety Population | Summary of Surgical Site Assessment |

| | | |
|---|---|---|
| Table 14.3.6 | Safety Population | Summary of Neurosensory Examination |
| Table 14.3.7 | Safety Population | Summary of Rebound Pain Assessment |

*15.3.2 Figures*

| | | |
|---|---|---|
| Figure 14.2.1.1.1 | mITT Population | Mean Rest NRS Scores Over Time (Primary Analysis - Post-Rescue Medication Imputation and Post-Dropout Imputation), by Treatment Group |
| Figure 14.2.1.1.2 | PP Population | Mean Rest NRS Scores Over Time (Primary Analysis - Post-Rescue Medication Imputation and Post-Dropout Imputation), by Treatment Group |
| Figure 14.2.1.2.1 | mITT Population | Mean Rest NRS Scores Over Time (Sensitivity Analysis of Primary Endpoint - Post-Rescue Medication Imputation Only), by Treatment Group |
| Figure 14.2.1.2.2 | PP Population | Mean Rest NRS Scores Over Time (Sensitivity Analysis of Primary Endpoint - Post-Rescue Medication Imputation Only), by Treatment Group |
| Figure 14.2.1.3.1 | mITT Population | Mean Rest NRS Scores Over Time (Sensitivity Analysis of Primary Endpoint - No Imputation, Observed Scores Only), by Treatment Group |
| Figure 14.2.1.3.2 | PP Population | Mean Rest NRS Scores Over Time (Sensitivity Analysis of Primary Endpoint - No Imputations, Observed Scores Only), by Treatment Group |
| Figure 14.2.1.4.1 | mITT Population | Mean Evoked NRS Scores Over Time (Post-dropout Imputation) , by Treatment Group |
| Figure 14.2.1.4.2 | PP Population | Mean Evoked NRS Scores Over Time ((Post-dropout Imputation), by Treatment Group |
| Figure 14.2.1.5.1 | mITT Population | Mean Evoked NRS Scores Over Time **(**No Imputations, Observed Scores Only), by Treatment Group |
| Figure 14.2.1.5.2 | PP Population | Mean Evoked NRS Scores Over Time **(**No Imputations, Observed Scores Only**)**, by Treatment Group |
| Figure 14.2.1.6 | mITT Population | Silverman Rank Analysis Scores, by Treatment Group |
| Figure 14.2.2.1.1 | mITT Population | Mean Rest NRS AUC, by Treatment Group |
| Figure 14.2.2.1.2 | PP Population | Mean Rest NRS AUC, by Treatment Group |
| Figure 14.2.2.2.1 | mITT Population | Mean Evoked NRS AUC, by Treatment Group |
| Figure 14.2.2.2.2 | PP Population | Mean Evoked NRS AUC, by Treatment Group |
| Figure 14.2.3.1.1 | mITT Population | Total Opioid Consumption in OME Doses, by Treatment Group |
| Figure 14.2.3.1.2 | PP Population | Total Opioid Consumption in OME Doses, by Treatment Group |
| Figure 14.2.3.2.1 | mITT Population | Total Non-opioid Analgesic Consumption (mg), by Treatment Group |
| Figure 14.2.3.2.2 | PP Population | Total Non-opioid Analgesic Consumption (mg), by Treatment |

| | | |
|---|---|---|
| | | Group |
| Figure 14.2.3.3.1 | mITT Population | Time to Cessation of Opioid Use |
| Figure 14.2.3.3.2 | PP Population | Time to Cessation of Opioid Use |
| Figure 14.2.3.4.1 | mITT Population | Cumulative Opioid Use |
| Figure 14.2.3.4.2 | PP Population | Cumulative Opioid Use |
| Figure 14.2.4.1 | mITT Population | Time to Discharge Readiness |
| Figure 14.2.4.2 | PP Population | Time to Discharge Readiness |

### *15.3.3 Listings*

| | | |
|---|---|---|
| Listing 16.2.1.1 | All Patients | Randomization and Study Population |
| Listing 16.2.1.2 | All Patients | Informed Consent and Re-Consent |
| Listing 16.2.1.3 | All Patients | Eligibility |
| Listing 16.2.1.4 | All Patients | Patient Disposition/Early Termination |
| Listing 16.2.2 | All Patients | Protocol Deviations |
| Listing 16.2.4.1 | All Randomized Patients | Demographics and Baseline Characteristics |
| Listing 16.2.4.2 | All Randomized Patients | Medical / Surgical History |
| Listing 16.2.4.3 | All Randomized Patients | Prior and Concomitant Medications |
| Listing 16.2.4.4 | All Randomized Patients | Rescue Medication Administration |
| Listing 16.2.4.5 | All Randomized Patients | Non-Medication Therapies |
| Listing 16.2.4.6 | All Randomized Patients | Surgery |
| Listing 16.2.5 | All Randomized Patients | Study Drug Administration, Pain Assessment Training, and Discharge |
| Listing 16.2.6.1 | All Randomized Patients | Pain Intensity Assessment (Rest NRS) |
| Listing 16.2.6.2 | All Randomized Patients | Pain Intensity Assessment (Evoked NRS) |
| Listing 16.2.6.3 | All Randomized Patients | Primary Endpoint Rest NRS AUC |
| Listing 16.2.6.4 | All Randomized Patients | Secondary and Exploratory Rest NRS AUC Efficacy Endpoints (LOCF) |
| Listing 16.2.6.5 | All Randomized Patients | Evoked NRS AUC Efficacy Endpoints (LOCF) |
| Listing 16.2.6.6 | All Randomized Patients | Total Opioid Consumption (OME Dose) and Non-opioid Analgesic Consumption (mg) Efficacy Endpoints |
| Listing 16.2.6.7 | All Randomized Patients | Opioid-free Efficacy Endpoints |
| Listing 16.2.6.8 | All Randomized Patients | Knee Range of Motion |
| Listing 16.2.6.9.1 | All Randomized Patients | KOOS Questionnaire Scales |
| Listing 16.2.6.9.2 | All Randomized Patients | KOOS Questionnaire Details |

| | | |
|---|---|---|
| Listing 16.2.6.10 | All Randomized Patients | Sit to Stand Test |
| Listing 16.2.6.11 | All Randomized Patients | Walking Speed Test |
| Listing 16.2.6.12 | All Randomized Patients | Timed Up and Go Test |
| Listing 16.2.6.13.1 | All Randomized Patients | PROMIS Questionnaire Scales |
| Listing 16.2.6.13.2 | All Randomized Patients | PROMIS Questionnaire Details |
| Listing 16.2.6.14 | All Randomized Patients | Use of Rescue Medications Efficacy Endpoints |
| Listing 16.2.6.15 | All Randomized Patients | Discharge Readiness |
| Listing 16.2.7.1 | All Randomized Patients | Adverse Events |
| Listing 16.2.7.2 | All Randomized Patients | Serious Adverse Events |
| Listing 16.2.7.3 | All Randomized Patients | Treatment Related Adverse Events |
| Listing 16.2.7.4 | All Randomized Patients | Adverse Events Leading to Study Discontinuation |
| Listing 16.2.8.1 | All Randomized Patients | Chemistry Laboratory Test Results |
| Listing 16.2.8.2 | All Randomized Patients | Coagulation Laboratory Test Results |
| Listing 16.2.8.3 | All Randomized Patients | Hematology Laboratory Test Results |
| Listing 16.2.8.4 | All Randomized Patients | Urinalysis Laboratory Test Results |
| Listing 16.2.8.5 | All Randomized Patients | Alcohol and Urine Drug Screen Tests |
| Listing 16.2.8.6 | All Randomized Patients | Pregnancy Test |
| Listing 16.2.9.1 | All Randomized Patients | Vital Signs |
| Listing 16.2.9.2 | All Randomized Patients | 12-Lead Electrocardiogram |
| Listing 16.2.9.3 | All Randomized Patients | Physical Examination |
| Listing 16.2.9.4 | All Randomized Patients | Surgical Site Assessment and Rebound Pain Assessment |
| Listing 16.2.9.5 | All Randomized Patients | Neurosensory Examination |
| Listing 16.2.9.6 | All Randomized Patients | Knee X-Ray |

## 16. DOCUMENT HISTORY

| Version # | Summary of Changes | Section Changed | Date |
|---|---|---|---|
| 1.0 | Initial document released | NA | 21Jun2020 |
| 2.0 | • specify treatment group (planned or treatment received) will be analyzed for each analysis population<br>• Add the rule of using the higher score if the same date/time results not covered by the current situation<br>• Remove " ***If additional opioids, other than the study rescue medications, are identified on the concomitant medications eCRF page, those additional medications will also be included in the opioid use calculation***" because CM page will NOT be checked (data cleaning will address the issue)<br>• Add 3 sets of tables/figures to visualize the effect of censoring scheduled rest NRS scores due to the administration of rescue medication<br>• For OF24-96 (one of the key secondary endpoints), one-sided Fisher's exact test will be used instead of the two-sided CMH test<br>• Add a category of $< 0^{o}$, for active extension and passive extension due to negative value | • 4.1<br>• 7.3.2<br>• 7.3.5<br>• 7.4.3.5<br>• 7.4.6<br>• 7.4.8 | 07Oct2020 |
| 3.0 | • Update the definition of Per-Protocol population to include subjects who experienced AE of LOE | • 4.1 | |

## Certificate Of Completion

Envelope Id: BD9C7D2030694B0B86828AE9172DFD77
Status: Completed
Subject: Please DocuSign: CA-PS-208_SAP_v3.0_12Nov2020.pdf
Source Envelope:
Document Pages: 64
Signatures: 4
Certificate Pages: 5
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Enabled
Time Zone: (UTC-08:00) Pacific Time (US & Canada)

Envelope Originator:
Nicole Barnes
100 W California Blvd., Unit 25
Pasadena, CA 91105
nbarnes@lotuscr.com
IP Address: 65.27.233.236

## Record Tracking

Status: Original
11/12/2020 1:46:27 PM
Holder: Nicole Barnes
nbarnes@lotuscr.com
Location: DocuSign

| Signer Events | Signature | Timestamp |
|---|---|---|
| HENRY FOEHL<br>henry.foehl@hcfoehl.com<br>Henry Foehl<br>Security Level: Email, Account Authentication (Required) |  <br>Signature Adoption: Uploaded Signature Image<br>Signature ID:<br>ABAF4AD4-E11B-4C41-909E-3B4693085652<br>Using IP Address: 3.96.184.146<br><br>With Signing Authentication via DocuSign password<br>With Signing Reasons (on each tab):<br>I approve this document | Sent: 11/12/2020 1:51:33 PM<br>Viewed: 11/12/2020 2:41:48 PM<br>Signed: 11/12/2020 2:43:58 PM |
| **Electronic Record and Signature Disclosure:**<br>Accepted: 6/22/2020 10:54:34 AM<br>ID: b2490305-60fd-41f6-bcf7-e1dabb19b9cf | | |
| Leonid Zeitlin<br>Leonid.Zeitlin@quartesian.com<br>Leonid Zeitlin<br>Security Level: Email, Account Authentication (Required) |  <br>Signature Adoption: Pre-selected Style<br>Signature ID:<br>0AF02DA3-17D5-4026-9094-A6B4BCE6B408<br>Using IP Address: 193.138.244.65<br><br>With Signing Authentication via DocuSign password<br>With Signing Reasons (on each tab):<br>I am the author of this document | Sent: 11/12/2020 1:51:32 PM<br>Viewed: 11/13/2020 2:09:41 AM<br>Signed: 11/13/2020 2:10:24 AM |
| **Electronic Record and Signature Disclosure:**<br>Accepted: 4/20/2020 8:49:57 AM<br>ID: 413cc35a-0bc9-4eb8-9097-35830873efd2 | | |

| Signer Events | Signature | Timestamp |
|---|---|---|
| Sam Teichman<br>steichman@concentricanalgesics.com<br>Concentric Analgesics<br>Security Level: Email, Account Authentication (Required) |  <br>Signature Adoption: Pre-selected Style<br>Signature ID:<br>EA3F6C62-DE63-4E34-84AD-6BF24BCAA75C<br>Using IP Address: 69.181.166.132<br><br>With Signing Authentication via DocuSign password<br>With Signing Reasons (on each tab):<br>I approve this document | Sent: 11/12/2020 1:51:33 PM<br>Viewed: 11/12/2020 1:52:54 PM<br>Signed: 11/12/2020 1:54:36 PM |
| **Electronic Record and Signature Disclosure:**<br>Accepted: 11/15/2019 6:09:57 PM<br>ID: 8bdb065a-97c0-403d-aaf5-961e2ac193dd | | |
| Song Liou<br>sliou@lotuscr.com<br>Biostatistician<br>Lotus Clinical Research<br>Security Level: Email, Account Authentication (Required) |  <br>Signature Adoption: Pre-selected Style<br>Signature ID:<br>85C80776-CFA1-404F-B9C3-4B43BB0AA100<br>Using IP Address: 108.56.166.63<br><br>With Signing Authentication via DocuSign password<br>With Signing Reasons (on each tab):<br>I have reviewed this document | Sent: 11/12/2020 1:51:32 PM<br>Viewed: 11/12/2020 1:54:03 PM<br>Signed: 11/12/2020 1:54:32 PM |
| **Electronic Record and Signature Disclosure:**<br>Accepted: 2/16/2018 10:40:34 AM<br>ID: 33003533-520a-46d0-b1ac-311cccf15c53 | | |

| In Person Signer Events | Signature | Timestamp |
|---|---|---|

| Editor Delivery Events | Status | Timestamp |
|---|---|---|

| Agent Delivery Events | Status | Timestamp |
|---|---|---|

| Intermediary Delivery Events | Status | Timestamp |
|---|---|---|

| Certified Delivery Events | Status | Timestamp |
|---|---|---|

| Carbon Copy Events | Status | Timestamp |
|---|---|---|
| Nina Green<br>ngreen@lotuscr.com<br>Project Manager<br>Lotus Clinical Research, LLC-Sub Account<br>Security Level: Email, Account Authentication (Required)<br>**Electronic Record and Signature Disclosure:**<br>Accepted: 12/16/2019 1:58:19 PM<br>ID: 1e97b2f0-14cb-42ed-891b-25a007858d2e | COPIED | Sent: 11/12/2020 1:51:33 PM<br>Viewed: 11/12/2020 5:03:40 PM |

| Witness Events | Signature | Timestamp |
|---|---|---|

| Notary Events | Signature | Timestamp |
|---|---|---|

| Envelope Summary Events | Status | Timestamps |
|---|---|---|

| Envelope Summary Events | Status | Timestamps |
| --- | --- | --- |
| Envelope Sent | Hashed/Encrypted | 11/12/2020 1:51:33 PM |
| Certified Delivered | Security Checked | 11/12/2020 1:54:03 PM |
| Signing Complete | Security Checked | 11/12/2020 1:54:32 PM |
| Completed | Security Checked | 11/13/2020 2:10:24 AM |

| Payment Events | Status | Timestamps |
| --- | --- | --- |

| Electronic Record and Signature Disclosure |
| --- |

## ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

Please read the information below carefully and thoroughly. By checking the "I agree to use Electronic Records and Signatures" box in the DocuSign system, you confirm you can access this information electronically to your satisfaction and agree to these terms and conditions below.

### Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after signing session. If you wish for us to send you paper copies of any such documents from our office to you, please contact your Lotus Lead Project Manager.

### Withdrawing your consent

If you decide to receive documents from us electronically, you may at any time change your mind and tell us thereafter that you want to receive documents only in paper format. If you want to withdraw your consent and receive future documents in paper format, please contact your Lotus Lead Project Manager.

### Consequences of changing your mind

If you elect to receive documents only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the documents to you in paper format, and then wait until we receive back from you and your execution of such paper documents. To indicate to us that you are changing your mind within the DocuSign system, you must withdraw your consent using the DocuSign " Withdraw Consent" form on the signing page of a DocuSign envelope instead of signing it. This will indicate to us that you have withdrawn your consent to receive documents electronically from us and you will no longer be able to use the DocuSign system to receive documents electronically from us or to sign electronically documents from us.

### All documents will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all documents that require your signature during the course of our relationship with you. All documents will be sent to you through your e-mail as recorded in the study-specific Study Contact Sheet. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

### How to contact Lotus Clinical Research, LLC:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically:

### To advise Lotus Clinical Research, LLC of your new e-mail address

To let us know of a change in your e-mail address, you must send an email message to your Lotus Lead Project Manager and in the body of such request you must state: your previous e-mail address, your new e-mail address. We do not require any other information from you to change your email address.

In addition, you must notify DocuSign, Inc. to arrange for your new email address to be reflected

in your DocuSign account by following the process for changing e-mail in the DocuSign system.

**To request paper copies from Lotus Clinical Research, LLC**

To request delivery from us of paper copies of the documents previously provided by us to you electronically, you must send an e-mail to your Lotus Lead Project Manager and in the body of such request you must state your e-mail address, full name, US Postal address, and telephone number.

**To withdraw your consent**

To inform us that you no longer want to receive future documents in electronic format via DocuSign you may:

i. decline to sign a document from within your DocuSign session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;
ii. send an email to your Lotus Lead Project Manager withdrawing consent, and in the body of such request you must state your e-mail, full name, US Postal Address, and telephone number.

**Required hardware and software**

| | |
|---|---|
| Operating Systems: | Windows® 2000, Windows® XP, Windows Vista® Mac OS® X |
| Browsers: | Final release versions of Internet Explorer® 6.0 or above (Windows only); Mozilla Firefox 2.0 or above (Windows and Mac); Safari™ 3.0 or above (Mac only) |
| PDF Reader: | Acrobat® or similar software may be required to view and print PDF files |
| Screen Resolution: | 800 x 600 minimum |
| Enabled Security Settings: | Allow per session cookies |

** These minimum requirements are subject to change. If these requirements change, you will be asked to re-accept the disclosure. Pre-release (e.g. beta) versions of operating systems and browsers are not supported.

**Acknowledging your access and consent to receive materials electronically**

By checking the "I agree to use Electronic Records and Signatures" box in the DocuSign system, you are confirming to us that:

- You can access and read this Electronic CONSENT TO ELECTRONIC RECEIPT OF ELECTRONIC CONSUMER DISCLOSURES document; and

- You can print on paper the disclosure or save or send the disclosure to a place where you can print it, for future reference and access; and

- Until or unless you notify Lotus Clinical Research, LLC, as described above, you consent to receive through electronic means documents that require your signature