Concentric Analgesics, Inc.

Protocol Name: CA-PS-209

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

Investigational Product: CA-008 by Injection/Instillation

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Statistical Analysis Plan, dated 14 May 2021

STATISTICAL ANALYSIS PLAN

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

Protocol Number: CA-PS-209

Protocol Version Amendment 2 (15MAR2021)

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LIST OF ABBREVIATIONS

AC	Analgesic Consumption
ADaM	Analysis Data Model
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
cQT	Plasma Concentration–QT
CRO	Clinical Research Organization
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ET	Early Termination
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IV	Intravenous
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

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(s)
PO	Per Os (oral)
PP	Per Protocol
PRO	Patient-Reported Outcome
PROMIS	Patient Reported Outcomes Measurement Information System
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Standard Data Tabulation Model
SE	Standard Error
SOC	System Organ Class
SPI	Sum of Pain Intensity
TEAE	Treatment Emergent Adverse Event
TFLs	Tables, Figures, and Listings
TUG	Timed Up and Go
VHR	Ventral Hernia Repair
WHO	World Health Organization
wLOCF	Windowed Last Observation Carried Forward
WOCF	Worst Observation Carried Forward

1. PURPOSE OF THE ANALYSES

This statistical analysis plan (SAP) is based on protocol number CA-PS-209 Amendment 2 (15MAR2021) from Concentric Analgesics, Inc.

The purpose of this statistical analysis plan is to provide details on study populations, how variables will be derived, how missing data will be handled, and the statistical methodologies to be used to analyze the safety and efficacy data from the study. The document may evolve over time, for example, to reflect the requirements of protocol amendments or regulatory requests. 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-209.

2. PROTOCOL SUMMARY

This is a three-part, phase 1/2, randomized, double-blind, placebo-controlled, adaptive safety, pharmacokinetics (PK), and preliminary efficacy study of CA-008 in patients undergoing ventral hernia repair (VHR). Part A is an open-label exploration of different delivery techniques of the study drug. Part B is a randomized, double-blind, placebo-controlled pilot study and Part C is a larger randomized, double-blind, placebo-controlled efficacy study.

2.1 Study Objectives

2.1.1 Part A of the Study

2.1.1.1 Primary Objective

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

2.1.1.2 Secondary Objective

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

2.1.2 Part B of the Study

2.1.2.1 Primary Objective

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

2.1.2.2 Secondary Objectives

- Determine the pain profile of patients undergoing an elective VHR.
- Determine the appropriateness of progression to Part C.
- Assessment of opioid consumption.
- Evaluate the PK profile of a single intraoperative administration of CA-008 24 mg in patients undergoing an elective VHR.

- Explore the relationship between CA-008 and its metabolite plasma concentrations and electrocardiogram (ECG) QT interval (time from the start of the Q wave to the end of the T wave) using a concentration-QT (cQT) analysis.

2.1.3 Part C of the Study

2.1.3.1 Primary Objective

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

2.1.3.2 Secondary Objectives

- Evaluate the efficacy of CA-008 on reported pain in patients undergoing an elective VHR during additional specified post-operative time intervals.
- Evaluate the effect of CA-008 on opioid consumption.
- Evaluate the effect of CA-008 on patient-reported outcomes (PROs).
- Evaluate, preliminarily, the effect of CA-008 on performance-based outcome measures (PBOMs).
- Evaluate the safety and tolerability of CA-008 or placebo in patients undergoing an elective VHR.

2.2 Overall Study Design and Plan

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

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

- An inpatient period which continues from check-in on Day 1 (D1) until discharge (4 days or 96 hours [h] following surgery [T96 ± 4 h], [D5]). Discharge may be delayed, if needed, for medical reasons.
- An 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 Adverse Events (AEs) to resolution or to establish a new baseline.

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

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

In Part A, it is expected that 8-12 patients will be enrolled, but it may be up to 16 patients. CA-008 will be administered at a dose of 15 mg (delivered as a 50 mL solution at a concentration of 0.3 mg/mL) in an open-label exploration of different delivery techniques. In Part B, the active study drug dose will be increased to 24 mg, delivered as 80 mL of a 0.3 mg/mL solution, and tested vs placebo in a pilot phase. It is expected that approximately 24 patients (up to 32) will be enrolled in Part B.

The results of Part B will be unblinded for analysis prior to the initiation of Part C.

Cohort expansion decisions will be made by the Sponsor's medical monitor, the CRO's medical monitor, a designated Principal Investigator (PI), and an independent medical monitor.

Cohort expansion decisions will be based on review of at least the following safety data:

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

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

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

Adults aged 18 to 80 years of age, inclusive, who are planning to undergo an elective primary, open VHR, with retromuscular, preperitoneal mesh repair (i.e., Rives Stoppa technique or equivalent), with or without laparoscopic assistance, and who otherwise meet eligibility criteria described in Sections 8.2.1 and 8.2.2 of the study protocol, may be considered for enrollment into the study.

2.2.3 Treatment Regimens

Part A:

CA-008 will be administered at a dose of 15 mg (delivered as a 50 mL solution at a concentration of 0.3 mg/mL) in an open-label exploration of different delivery techniques.

Cohort #1: CA-008 15 mg

Part B:

In Part B, the active study drug dose will be increased to 24 mg (delivered as an 80 mL solution at a concentration of 0.3 mg/mL) and tested versus placebo in a pilot phase.

Cohort #1: CA-008 24 mg

Cohort #2: Placebo

Part C:

In Part C, 24 mg CA-008 will be evaluated compared to placebo.

Cohort #1: CA-008 24 mg

Cohort #2: Placebo

Note: Treatment group for each study part will be labelled as **"CA-008 XX mg"** and/or "Placebo" in TLFs. In addition, the study part will be labeled clearly in output header (or output title).

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

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

Study Period	**Screening**	**Inpatient** **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		
Admission to PACU				$T0_{nrs}$									
Surgical Site assessment								X[8]	X[8]	X[8]	X[8]	X[8]	X[8]
Neurosensory Exam	X							X[9]	X[9]	X[9]	X[9]	X[9]	X[9]
Blood draw for laboratory tests	X[10]							X[10]					
Rescue Medication consumption Recording				X	X	X	X	X	X	X			X
Concomitant Medication Assessment	X	X		X	X	X	X	X	X	X	X		X
Adverse Event Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X
NRS pain assessments				X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	X[11]			X[11]
Patient home diary record (NRS)								X[12]	X[12]	X[12]			X[12,19]
Electronic Diary (review, distribution and/or collection)								X[13]	X[13]	X[13]			X[13]
Patient home diary (analgesic consumption)								X	X	X			X
Prescription for outpatient opioid rescue if needed								X[14]					
PRO[15]	X					X		X	X	X	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 **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		
PBOMs[16]						X		X	X	X	X		
Blood draw for PK analysis		X[17,18]	X[17]	X[17]	X[17]	X[17]							

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

2 Pain assessment training with test during screening; re-watch video only prior to surgery.

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

4 Vital signs (HR, BP, RR (supine), SpO2) and temperature assessed together after T0 at T1, T2, T6, T12, T24, and every 12 hours thereafter (if awake at time of assessment between the hours of 12:00 AM and 6:00 AM) until discharge from the inpatient unit (may not miss two consecutive assessments). There will be a ± 5-minute window allowed for the collection of vital signs in the first 4 hours after the end of surgery, after which 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.
In a subset of 12 patients per randomized arm at one site in Part C, 12-lead Holter monitors will be placed prior to surgery and record for 24 hours to assess for effects on the QT interval during study drug administration. Note: If the number of patients enrolled in Part B is increased, PK sampling and Holter monitoring as described above may be conducted in Part B instead of Part C.

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, and coagulation) should be performed at Screening and T48 (± 4 hours.

10 During the inpatient stay, NRS at rest beginning with the PACU admission (T0) may be assessed once the patient is awake. Obtain NRS scores T0 plus 1 hour (T1), T0 plus 2 hours (T2), T4, T6, T8, T12, T16, T20, T24, and every 4 hours (if awake at time of assessment) until discharge from the inpatient unit. Time windows: for T1 to T2 (± 5 min) and from T4 onward (± 15 min). Scheduled NRS scores must be recorded regardless of timing of pre-rescue medication NRS scores and administration of rescue medication. The actual time of all NRS scores must be recorded, i.e., not the nominal time. During the inpatient stay, as soon as feasible, evoked NRS twice daily after 3 maneuvers: (a) coughing 3 times, and (b) sitting up from the supine position into a standardized position (both legs dangling on the side of the bed), and (c) ambulation for approximately 10 yards (30 feet). Obtain these NRS scores in the morning at 10:00 AM (± 1 h) and in the afternoon at 4:00 PM (± 1 h). During the inpatient stay, pain scores may be skipped between the hours of midnight and 6:00 AM, but the patient may not

miss two consecutive assessments. The T12, T24, T48, T72, and T96 assessments must be completed even if the patient must be awakened at these times. During the inpatient stay, an additional NRS assessment must be obtained within 5 minutes prior to IV rescue medication administration and within 15 minutes prior to oral rescue medication administration. During the outpatient period, (D8 and D15), instruct the patient to document their NRS scores twice daily at 11:00 AM (± 1 h) and 7:00 PM (± 1 h) (a) at rest, (b) after coughing 3 times, (c) after sitting up from the supine position into a standardized position (both legs dangling on the side of the bed), and (d) during ambulation for approximately 10 yards (30 feet). Note that the actual time of these assessments must be documented in the diary. Instruct the patient to:

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

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

[14] PROs: PROMIS 10 Global (Appendix 15.2) and Activities Assessment Scale (AAS) (Appendix 15.3).PROMIS 10 Global will not be measured at T48.

[15] PBOMs: Sit to Stand Test, Timed Up and Go (TUG) Test.

[16] Collect blood samples for PK. The time points for whole blood collection will be at pre-dose (from check-in and up to 30PKT 0 (Pre-IP Dose, 2-10 minutes before the start of surgery), and at PKT 0 (at prior to the first study treatment instillation), 0.03 h (2 min), 0.083 h (5 min), 0.167 h (10 min), 0.25 h (15 min), 0.33 h (20 min), 0.5 h (30 min), 0.75 h (45 min), and at 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 36 and 2448 hours after the first study treatment instillation (total of 1618 samples)..). There will be a ± 2-minute window allowed for the 10- to-, 15 and 20-minute collections, a ± 5-minute window allowed for collections at 30 minutes through 4 hours, and a ± 15-minute window for collections after 4 hours. In the event of ana SAE or severe TEAE, an unscheduled PK draw will be performed. The actual time of collection will be recorded and used in any analysis. Out-of-window collections will not be considered protocol deviations.

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

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

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

2.2.4 Treatment Group Assignments or Randomization

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

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

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

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

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

Patients who discontinue study participation before or after randomization but prior to receiving study treatment will be replaced. Patients who are withdrawn or elect to withdraw after receiving study treatment will not be replaced. Replacement patients will be assigned the same treatment as the original patient. A ‘replacement’ randomization list matching that of the main list will be created to facilitate this process.

2.2.5 Sample Size Determination

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

For the primary efficacy endpoint of rest NRS $AUC_{0\text{-}96}$, assuming a *t*-test for the difference in the means of 2 independent groups, a sample size of approximately 50 patients per group provides

approximately 80% power to detect a standardized effect size (Cohen's d) of 0.55 at a two-sided level of significance, alpha, of 0.05. Therefore, in Part C, a total of up to 100 patients will be randomized in 2 parallel arms (1:1) with approximately 50 patients in each arm to bring the total number of patients enrolled to approximately 150.

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

3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

General analysis and reporting conventions to be employed for study CA-PS-209 data are described below. If departures from these conventions are appropriate, details will be presented in the relevant sections of this SAP.

Data will be summarized by study part, treatment group, and time point. The total number of patients in the treatment group (N) under the stated population will be displayed in the header of summary tables.

Continuous variables will be summarized by study part, treatment group, and time point (as applicable) using descriptive statistics: the total number of patients with non-missing data within the specific category (n); mean; standard deviation (SD); median; and range (minimum and maximum).

Categorical variables will be summarized by study part, treatment group, and time point (as applicable) using frequency counts (n) which indicate the actual number of patients with a particular value of a variable or event and rate of occurrence (%). Unless specified otherwise, in the analysis of categorical variables, the denominator for percentages will be the total number of patients in the appropriate analysis population and treatment group (N) who have a non-missing value of the categorical variable. Percentages will be calculated as (n/N)*100.

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 study part, treatment group, patient, and time point (as applicable).

The statistic “Missing” will also be evaluated by enumerating the number of missing entries/patients, if any at that visit, and presented as a summary statistic only for the resulting time points. Proportions will be calculated as (n/N).

No preliminary rounding of numeric data values will be performed; rounding will only occur after the completion of an analyses when data or calculation results are formatted for display. 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. Also, the least squares mean, standard error and

its confidence interval, and least squares mean differences 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. *P*-values will be presented to three decimal places; *p*-values less than 0.001 will be presented as < 0.001 and *p*-values greater than 0.999 will be presented as > 0.999.

Statistical testing including *p*-values and confidence intervals (CIs) will be presented as described in each section below. Tests of statistical significance will be 2-sided at the 0.05 level of significance.

Because preliminary assessments of efficacy are the focus of efficacy analyses, no adjustments to the level of significance will be made for multiple comparison tests.

All dates will be displayed in DDMMMYYYY format.

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 the 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 Day 1.

- 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.
- PK/QT Population—consists of all patients with at least one time point with both PK and QT data for use in concentration-QT response modeling. Patients in the PK/QT 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 T12, 24, 48, 72, and 96 and no two consecutive missing assessments among the other time points prior to T96 (± 4 h)/Discharge. Patients in the PP Population will be analyzed as treated.
- Study Completers—consists of all patients who received a full dose of study treatment and 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 and cQT analysis will be performed using the PK Population and PK/QT Population, respectively.

4.2 Disposition of Patients

All patients and the analysis populations for which they qualify for will be presented in the listings. Patients who are screened and who fail screening, 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 treatment group and overall and presented for each study part A, B, and C separately 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 prior to database lock and before the unblinding 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 each study part A, B, or C separately using All Randomized Patients in a data listing and will be summarized by category of deviation and major/minor classification.

NOTE: In March 2020, (updated January 2021) 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 might occur due to the COVID-19 situation. In general, if a study procedure is completed, it might 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 might be considered a protocol deviation. COVID-19 related Protocol deviations be documented, and specific information that explains the basis of missing data including relationship to CoVID-19 must be captured in the CSR. Missing data related to COVID-19 will be treated as non-COVID-19 related missing data. Any causal relationship between the study drug and SAE's in trial participants diagnosed with CoVID-19 must be submitted to the FDA. Sponsors and investigators are required to document how restrictions related to CoVID-19 led to changes in study conduct, duration of those changes, which trial participants were impacted and how they were impacted.

5. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

5.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics (age, sex, race, ethnicity, weight (kg), height (cm), and body mass index (BMI; kg/m^2)) will be summarized separately for each study part by treatment group and overall using the Safety Population. Categorical variables (sex, ethnicity, and race) will be summarized using frequency count and percentage while continuous variables (age, weight, height, and BMI) will be summarized using descriptive statistics: n, mean, SD, median, minimum, and maximum.

Demographic and baseline data will be listed All Randomized Patients.

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 24.0 and summarized for the Safety Population separately by each study part A, B, and C 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. Counts will be presented in descending frequency of SOC term for the overall column unless otherwise specified.

Medical histories will also be presented for the Safety Population 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 by each study part separately. 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 in the Safety Population will be presented separately for each study Part A, B, and C in a summary table by 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. In the following, AUC refers to the area determined by a plot of NRS pain intensity scores versus time over a given time interval.

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 and PROMIS 10 Global questionnaire responses, is discussed in detail in section 7.2.6. 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

There are no efficacy endpoints specified for Part A and Part B. Efficacy Endpoints for Part C are:

7.2.1 Primary Efficacy Endpoint

- Rest NRS AUC from T0 to T96 (rest NRS $AUC_{0\text{-}96}$)

7.2.2 Key Secondary Efficacy Endpoints

- Evoked NRS AUC (three maneuvers) from T0 to T96 (evoked NRS $AUC_{0–96}$)
- Total opioid consumption (OC), in daily oral morphine equivalent (OME) dose, from T0 to T96, and from T0 to D8 ($OC_{0\text{-}96}$ and $OC_{0\text{-}D8}$)
- Patient is opioid-free (OF) after discharge from T96 to D15 ($OF_{96\text{-}D15}$), (patient has discontinued opioid use prior to hospital discharge)
- Rest NRS AUC from T0 to D8 (rest NRS $AUC_{0\text{-}D8}$)
- Evoked NRS AUC (three maneuvers) from T0 to D8 (evoked NRS $AUC_{0\text{-}D8}$)

7.2.3 Exploratory Efficacy Endpoints

- Rest NRS AUC for the indicated time intervals: $AUC_{12\text{-}96}$, $AUC_{0\text{-}48}$, $AUC_{48\text{-}96}$, and $AUC_{0\text{-}D15}$

- Evoked NRS AUC (three maneuvers) for the indicated time intervals: $AUC_{12\text{-}96}$, $AUC_{0\text{-}48}$, $AUC_{48\text{-}96}$, and $AUC_{0\text{-}D15}$
- Rest NRS scores at T48, T72, and T96
- Rest NRS scores daily from D5-D15
- Rest NRS ≤ 3 during T0-T96, T0-48, and T48-96
- Total OC, in daily OME dose, for the indicated time intervals: $OC_{12\text{-}96}$, $OC_{24\text{-}96}$, $OC_{0\text{-}D8}$, and $OC_{0\text{-}D15}$
- Patient is OF for the indicated time intervals: $OF_{0\text{-}96}$, $OF_{0\text{-}D15}$, $OF_{24\text{-}96}$, $OF_{24\text{-}D15}$, $OF_{48\text{-}D15}$, $OF_{72\text{-}D15}$, and $OF_{D8\text{-}D15}$
- Time to cessation of opioid use
- Change in PRO questionnaire scores (PROMIS 10 Global and AAS) from Screening to D8, D15, and D29; and from T96 to D8, D15, and D29
- Change in PBOMs (Sit to Stand, TUG) from T48 (± 4 h), to D5/Discharge, to D8, to D15, and to D29
- Total non-opioid analgesic consumption (AC), i.e., rescue acetaminophen use, for the indicated time intervals: $AC_{96\text{-}D8}$ and $AC_{96\text{-}D15}$

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

7.2.4 NRS Pain Intensity Measurements

At designated times during the study following the administration of study treatment, patients will report or record their pain intensity at the assessment time as follows:

- During the inpatient stay, NRS at rest beginning with the PACU admission may be assessed once the patient is 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), 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 will 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, i.e., scheduled and pre-rescue, will be recorded.

- During the inpatient stay, as soon as was feasible, evoked NRS scores will be obtained twice daily after: (a) coughing 3 times; (b) sitting up from the supine position into a standardized position (both legs dangling on the side of the bed); and (c) ambulation for approximately 10 yards (30 feet). These NRS scores will be obtained in the morning at 10:00 AM (± 1 h) and in the afternoon at 4:00 PM (± 1 h).
- During the inpatient stay, pain scores may be skipped between the hours of 12:00 AM and 6:00 AM, but the patient was not to have missed two consecutive assessments. The T12, T24, T48, T72, and T96 assessments will be completed even if the patient had to be awakened at those times.
- During the inpatient stay, an additional NRS assessment will be obtained within 5 minutes prior to IV rescue medication administration and within 15 minutes prior to oral rescue medication administration.
- During the outpatient period (after T96 and through D15), an additional NRS assessment must be obtained prior to oral rescue medication administration. If entered in the electronic diary, the timing of the additional NRS assessment will be assumed to be coincident with the use of rescue medication. If not entered in the electronic diary, the additional NRS assessment should be within 15 minutes prior to use of rescue medication to be used for imputation.
- During the outpatient period (after T96, and through D15), patients will be instructed to document their NRS scores twice daily at 11:00 AM (± 1 h) and 7:00 PM (± 1 h) (a) at rest, (b) after coughing 3 times, (c) after sitting up from the supine position into a standardized position (both legs dangling on the side of the bed), and (d) during ambulation for approximately 10 yards. Note that the actual time of these assessments will be documented in the electronic diary. Patients will be instructed to:
    - obtain the morning NRS assessments
    - obtain the evening NRS assessments
    - record opioid and non-opioid rescue medication use (dose, date, time, and pre-rescue NRS score) in the diary through D15.

7.2.5 Handling of NRS Pain Intensity 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;
- 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 T12 (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 pain intensity 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 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 will also to be recorded as the pre-rescue NRS assessment.
- If a patient requested rescue medication within a wLOCF imputation time window, and additional rescue medication was 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 recorded in the rescue medication page in 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; hence, 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.

7.2.6 Imputation of Missing Data for Efficacy Assessments

For the primary analysis of the primary efficacy 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 score for scheduled rest NRS assessments after the date of discontinuation will be imputed using the worst rest NRS score recorded during the 24-hour period prior to the patient's date of discontinuation; similarly, for all scheduled evoked NRS scores after the date of discontinuation. If no rest NRS assessments exist prior to the patient's date of discontinuation, all AUC calculations based on rest NRS scores for that patient will be set to missing; similarly, if no evoked NRS assessments exist on or prior to the date of discontinuation, all AUC calculations based on evoked NRS scores will be set to missing.

Note that the replacement via imputation of a censored post-rescue NRS assessment (as described in section 7.2.5) must be performed prior to the selection of imputed values as described in this section.

7.2.7 NRS AUC Calculation

AUC calculations will be done using the standard trapezoidal rule:

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

Where NRS_i = NRS at time *i, n* is the number of assessments 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.

The NRS is an 11-point scale with anchors 0 (no pain) and 10 (worst pain imaginable). 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 $\mathrm{AUC}_{0\text{-}96}$, all uncensored NRS scores recorded from 12 hours minus 15 minutes to 96 hours plus 15 minutes relative to $\mathrm{T0}_{\mathrm{nrs}}$ (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 time points) 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 present, 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.

7.2.8 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 formula below will be used to convert daily rescue medication dose into daily OME dose:

Total OME units per day = Rescue medication use #1 [(rescue medication strength per unit) × (number of units per day) × (OME conversion factor)] +
Rescue medication use #2 [(rescue medication strength per unit) × (number of units per day) × (OME conversion factor)] + etc.

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 Day 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: $T0_{nrs}$ to T96, $T0_{nrs}$ to D8, T12 to T96, T48 to d8, T72 to D8, T24 to T96, $T0_{nrs}$ to D8, and $T0_{nrs}$ to D15.

7.2.9 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 $AC_{96\text{-}D15}$.

7.2.10 Performance-based Outcome Measures (PBOMs)

PBOMs will be assessed at T48 (D3), T96 (D5), D8, 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 is recorded.
- Timed Up and Go (TUG) test: the time in seconds the patient takes to perform the test is recoded.

7.2.11 PROMIS 10 Global Health Questionnaire

The Patient-reported Outcomes Measurement Information System 10 (PROMIS 10) Global Health survey is a 10-item questionnaire for use in the assessment of health-related quality of life; instrument scores can be contrasted with normative scores (*t*-scores) for the US population. The PROMIS 10 consists of 5 domains: physical function, fatigue, pain, emotional distress, and social health; responses are recorded on a 5-point scale. The PROMIS 10 questionnaire, version 1.1, is to be administered at Screening, T96 (D5), D8, D15, and D29. Global Physical Health and Global Mental Health subscale scores will be calculated. Details of the scoring algorithm are provided in Appendix 15.2.

7.2.12 Activities Assessment Scale

The Activities Assessment Scale (AAS) is a postoperative functional activity scale validated in men who underwent hernia surgery. The AAS includes 13 items covering a broad sample of sedentary (e.g., lying in bed), movement-related (e.g., walking outdoors), and graded-intensity physical activities (extending from housekeeping to various forms of exercise to construction work). The preoperative scale references the impact of the hernia itself, and the postoperative version assesses the effects of the hernia repair on functioning. The time frame for all questions is the previous 24 hours. Five categories ranging from “no difficulty” to “not able to do it” will be used for responses. A “did not do it for other reasons” category is included but is not scored. The AAS scores are then numerically transformed to produce a range extending from 0 to 100, with higher values indicating better functional ability. The final version of the Activities Assessment Scale with both preoperative and postoperative instructions is presented in the Appendix 15.3.

The AAS will be completed when patients complete the PROs at screening, T48 (D3), T96 (D5), D8, D15, and D29.

7.3 Analysis Methods

7.3.1 General Considerations

Per the study design, progression from Part A to Part B will take place after an empirical assessment has been completed showing that the total study drug dose, volume, allocation (of volume administered at locations within the surgical site), and technique is feasible. Progression from Part B to Part C will take place after an UNBLINDED analysis of unmonitored data from Part B occurs including data through Day 15. The final data analysis for Part C will be performed after all patients in Part C have either completed or have been discontinued from the study, all data cleaning has been completed, and the study database has been locked. Part C 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 and displayed by each Study Part.

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, key secondary efficacy endpoint analyses and exploratory endpoint analyses is 0.05 (two-sided).

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

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

7.3.2 Pooling of Data

No data pooling from different study parts will be done in this study but may be explored. Please refer to Section 10 of the SAP (Other Analyses).

7.3.3 Primary Efficacy Endpoint

7.3.3.1 Primary Efficacy Endpoint Hypothesis

The null hypothesis associated with the primary efficacy endpoint is that the mean rest NRS AUC_{0-96} does not differ between active treatment and placebo, tested against the alternative hypothesis that the mean rest NRS AUC_{0-96} is different for active treatment compared to placebo.

7.3.3.2 Primary Analysis of the Primary Efficacy Endpoint

The primary analysis of the primary efficacy endpoint will be performed for the mITT Population using a analysis of variance (ANOVA) model with treatment group as main effect and hernia size may be included as an additional covariate.

The analysis result will be reported as the Estimates (LS means, 95% CI) and standard error (SE) from the model for each treatment group. The difference in LS means for treatment group vs. placebo for rest NRS AUC_{0-96}, 95% CI, and SE for the difference along with two-sided *p*-values will also be presented. Primary analysis of the primary efficacy endpoint will be repeated for PP Population.

For the ANOVA of rest NRS AUC_{0-96} values, the Shapiro-Wilk test will be used to check normality of residuals, and Levene's test will be used to check homogeneity of variances. If assumptions of normality are violated, then the primary analysis may be repeated after suitable transformation of the data or the analysis may be replaced with the non-parametric analysis Kruskal-Wallis test.

7.3.3.3 Primary Efficacy Endpoint Sensitivity Analyses

In order to assess the sensitivity of the primary analysis of the primary efficacy endpoint to the censoring and imputation scheme specified for calculating the primary endpoint rest NRS AUC_{0-96} value following rescue medication administration, the primary analysis of the primary efficacy endpoint will be repeated in the mITT Population and PP Population in two ways:

- No post rescue medication administration censoring and imputation is performed; the rest NRS AUC_{0-96} calculation will employ all scheduled rest NRS scores and pre-rescue rest NRS scores available in the interval T0 to T96.
- No post rescue medication administration censoring and imputation is performed; the rest NRS AUC_{0-96} calculation will employ all available scheduled rest NRS scores only. Pre-rescue rest NRS scores will not be considered for AUC_{0-96} calculation.

7.3.3.4 Exploratory Analyses of the Primary Efficacy 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_{0-96} 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_{0-96} 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.

Should the ANCOVA assumptions of normality of rest NRS AUC_{0-96} values, residuals, or homogeneity of variances be significantly violated and the relationship between the dependent variable and the covariate is not linear, then the primary analysis may be performed using Rank ANCOVA.

The exploratory analyses for the primary endpoint will be performed using mITT Population.

7.3.3.5 Primary Efficacy Endpoint Reporting

The primary efficacy endpoint analysis results will be presented in a summary for part B and C respectively and analysis table for part C. The number of patients (n) included in the analysis, mean (SD) of rest NRS AUC_{0-96}, LS mean of rest NRS AUC_{0-96} and its standard error (SE) will be presented for all treatment groups. The difference in LS mean from placebo, the 95% confidence interval (CI) for the difference in LS means, and the corresponding *p*-value for the difference will

be presented by treatment group using ANOVA and ANCOVA as described in the Section 7.4.3.2 and Section 7.4.3.4 respectively.

The output of the Kruskal-Wallis test 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 OME) over all treatment groups 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 patient 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 patient 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 values due to early drop out are imputed using WOCF as specified in Section 7.2.6.
- A plot of mean scheduled rest NRS scores by nominal time point, where in calculating the mean, no post rescue medication administration censoring and imputation is performed and missing NRS scores post drop out are imputed using WOCF as specified in Section 7.2.6.
- 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 and the regions corresponding to rest NRS $AUC_{0\text{-}96}$ 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 imputation) 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.

7.3.4 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 efficacy endpoint Section 7.4.3.2 for both mITT and PP Population respectively (as appropriate).

7.3.4.1 Other AUC Endpoints and Total Opioid Consumption Endpoints Reporting

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

Figures will be provided displaying plots similar 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 OME values for each treatment group in a bar chart will be provided. A similar figure for total non-opioid analgesic consumption will also be provided.

7.3.5 Time to Cessation of Opioid Use

Time to cessation of opioid use (in hours from $T0_{nrs}$ to the last recorded use of opioid analgesics through D15) will be analyzed via a log-rank test. A Kaplan-Meier plot will be provided by treatment group. Median time to cessation and the 95% confidence interval of the median times to cessation will be presented, if estimable.

In this time to event analyses, patients with ongoing opioids up to Day 15 or discontinuing from the study prior to Day 15 with ongoing opioid use will be censored at Day 15 or the day of last follow up, respectively.

This endpoint will be analyzed for mITT Population and will be repeated for the PP Population.

7.3.6 Patients Who Are Opioid-free

The number and percentage of patients who are opioid-free (yes/no) from T24 to D8 (T168), will be presented in an analysis table, by treatment group. A Fisher's exact 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 T24 to D8 (T168); the analysis will be repeated for the following time intervals: $OF_{0\text{-}96}$, $OF_{0\text{-}D15}$, $OF_{24\text{-}96}$, $OF_{24\text{-}D15}$, $OF_{48\text{-}D15}$, $OF_{72\text{-}D15}$, $OF_{96\text{-}D15}$, and $OF_{D8\text{-}D15}$. Each of the OF analyses 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 Fisher's exact test *p*-values for the comparisons of active treatment versus placebo will be presented in the analysis table.

7.3.7 Time-specific Mean Rest NRS Scores

The mean rest NRS scores at T48, T72, and D5(T96), 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 7.3.3. However, post-dropout missing NRS scores (described in section 7.2.6) will not be imputed. In case several NRS scores were collected for the same scheduled time point, the highest score recorded will be used.

The difference in mean rest NRS scores between treatment groups at T48, T72, T96, D5-AM, D5-PM, D6-AM, D6-PM, D7-AM, D7-PM, etc. to D15-AM, D15-PM, 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 *p*-value, will be presented for each time point for

the difference between each active treatment group 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.

For the ANOVA of the difference in mean rest NRS scores between treatment groups, the Shapiro-Wilk test will be used to check normality of residuals and Levene's test will be used to check homogeneity of variances. If the assumptions of normality are violated, then the ANOVA for the difference in mean rest NRS scores may be performed using generalized estimating equations (GEE).

In the GEE approach, mean rest NRS scores will be analyzed as repeated measures over time. The GEE model with normal distribution and Identity link will include treatment group, time point, and interaction between treatment group and time point as fixed effects. To model the covariance structure, the exchangeable covariance matrix will be selected initially; if the exchangeable covariance structure leads to non-convergence, Quasi-Likelihood Information Criterion (QIC) will be used to select the best covariance structure. The adjusted least squares means (LS means) and standard error (SE) from the model will be presented for each active treatment group and placebo. The LS means estimates for the difference of each treatment group versus placebo, SE, 95% CI, and *p*-value will also be provided.

For each analysis, only measurements up to T48, T72, T96, D5-AM, D5-PM, D6-AM, D6-PM, D7-AM, D7-PM, etc. to D15-AM, D15-PM will be included in the model, respectively.

7.3.8 Performance-Based Outcome Measure (PBOM).

The results of PBOM measurements at T48 (± 15 min), 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 and timed up and go (TUG).

The difference in mean PBOM score between treatment groups at T48 (± 15 min), T96 (± 4 h)/Discharge, D8, 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 7.4.7. Least Squares (LS)

means, with 95% confidence intervals and the corresponding *p*-value, will be presented for each time point for the difference between each active treatment group and placebo. The analysis will be repeated for the PP Population.

7.3.9 PROMIS 10 Global Health Questionnaire Scores and AAS

The PROMIS 10 questionnaire Global Physical Health and Global Mental Health subscale scores (see Appendix 15.2) at Screening (baseline), D8, D15, and D29 and their changes from baseline will be summarized descriptively by time point 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 7.4.7. For each treatment group, the change from baseline mean (SD), LS mean (SE), and difference in LS mean from placebo with 95% CI and the corresponding *p*-value, will be presented, by subscale, for each time point and treatment group; the analysis will be repeated for the PP Population.

The above analysis will be repeated for the sensitivity analysis of the PROMIS 10 questionnaire Global Physical Health and Global Mental Health subscale scores when assessments are to be imputed for data after a patient discontinues from the study, using WOCF. The responses to the PROMIS 10 questionnaire items will be listed separately by patient.

The Activities Assessment Scale (see Appendix 15.3) overall AAS score and the Sedentary Activities, Ambulatory Activities, and Work/Exercise Activities subscale scores at Screening (baseline), D8, D15, and D29 and their changes from baseline will be summarized descriptively by time point and treatment group.

The overall AAS score will be calculated as follows:

1) Answers of 1=No difficulty, through 5=Not able to do it, will be summed across questions 1-13. Answers of 6=Did not do it for other reasons, will not be included in the sum.
2) The mean will be calculated by dividing the sum from step 1 by the number of answers contributing to the sum.
3) The mean from step 2 will be multiplied by 13. The result will be the raw score.
4) The raw score will be scaled from 0 to 100 using the following formula:

5) (65 – raw score)/52 x 100. Note: 65 is the maximum raw score, and 52 is the range of possible scores (65-13=52).
6) If more than 6 questions out of 13 did not contribute to the sum in step 1, then the overall AAS score will be set to missing.

Three subscales will be scored using the following steps:

1) Answers of 1=No difficulty, through 5=Not able to do it, will be summed across the questions included in the subscale (see below). Answers of 6=Did not do it for other reasons, will not be included in the sum.
2) The mean will be calculated by dividing the sum from step 1 by the number of answers contributing to the sum.
3) The mean from step 2 will be multiplied by the number of questions in the subscale (3 for the ambulatory subscale, or 4 for the sedentary activities and work/exercise subscales).
4) The raw score will be scaled from 0 to (number of subscale items*100/11) using the following formulas. Note: 11 is the total number of items contributing to the 3 subscales, and the subscales will sum to a maximum of 100 points.
5) 3-item subscale: (15-raw score)/12 x 3x100/11. Note: 15 is the maximum raw score, and 12 is the range of possible scores.
6) 4-item subscale: (20-raw score)/16 x 4x100/11. Note: 20 is the maximum raw score, and 16 is the range of possible scores.

Subscales:

Sedentary Activities subscale: items 1-4 (4 items)

Ambulatory Activities subscale: items 6-8 (3 items)

Work/Exercise Activities subscale: items 10-13 (4 items)

A listing will be provided for AAS scores by patient within treatment group.

7.3.10 Other Binary Endpoints

For the following binary endpoint, the number and percentage of patients achieving the endpoint will be presented in an analysis table by time point (if applicable) and treatment group:

- Patients with NRS ≤ 3 during T0 to T96, T0 to T48, and T48 to T96

A Fisher's exact test will be used to test the null hypothesis of no difference between 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.

Treatment versus placebo odds ratios with 95% CI, the difference in proportions (active treatment minus placebo) with 95% CI, and Fisher exact test *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. 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 within each study Part A, B, and C.

No formal statistical comparisons will be performed for safety endpoints.

Safety outcomes include:

- Incidence TEAEs or SAEs
- Clinical laboratory test results
- Vital sign measurements
- 12-lead ECG results
- PE findings
- Surgical site wound assessment findings
- Neurosensory testing results
- 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 24.0) 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 or after the date of treatment with the study drug through Day 29 or Early Termination.
- Serious AEs with onset on or after the date of treatment with the study drug through 30 days after Day 29 or 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, and potentially life-threatening.

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, potentially life-threatening, 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 will be presented by treatment group and by each study Part A, B, and C separately. Each summary will include:

  Number (%) of patients with at least one TEAE
  Number (%) of patients with at least one treatment related TEAE
  Number (%) of patients with at least one severe or potentially life-threatening TEAE
  Number (%) of patients with at least one Serious TEAE
  Number (%) of patients with a TEAE leading to discontinuation from the study
  Number (%) of patients with a TEAE leading to death

- 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 maximum toxicity grade (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 study discontinuation by treatment group, system organ class, and preferred term.
- A summary of the number and percentage of patients reporting a SAE outcome of death by treatment group and preferred term.

All AEs (including non-TEAEs) reported during the study will be present in a by-patient listing. Separate by-patient listings will be generated to present AEs, SAEs, AEs leading to discontinuation from the study, and SAEs leading to death.

8.3 Clinical Laboratory Test Results

Clinical laboratory tests (chemistry, hematology, and coagulation) will be collected at screening and before discharge from the inpatient unit (T48). All results will be presented in listings by patient and treatment group separately for study Part A, Part B, and Part C.

For continuous laboratory parameters, descriptive statistics will be presented for the value at Baseline and Day 3 (T48), and for the changes from baseline to Day 3 (T48), by 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 T48 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), the follicle stimulating hormone (FSH) test, 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 (supine position) including blood pressure (systolic and diastolic; mmHg), heart rate (beats per minute), respiration rate (breaths per minute), SpO_2, and temperature (°C) will be assessed at screening, D1 (pre-surgery) and after T0 at 1, 2, 6, 12, 24, and every 12 hours thereafter (if awake at time of assessment between the hours of 12:00 AM and 6:00 AM) until discharge from the inpatient unit (a patient may not miss two consecutive assessments) and as an outpatient on D8, D15, and D29 or later if necessary. 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) will 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 time point and treatment group.

Vital signs data will be presented in a listing by patient and date and time of assessment for each parameter.

8.6 ECG

12-lead ECG:

12-lead ECG will be performed at Screening and 24 hours (± 2 hours) after study medication administration. ECG parameters and their changes from baseline will be summarized descriptively by treatment group. Overall interpretation (Normal, Abnormal Not Clinically Significant, or Abnormal Clinically Significant) is recorded in the eCRF. The number and percentage of patients with each interpretation will be summarized by time point and treatment group.

12-lead ECG Holter:

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

Details of 12-lead ECG Holter analysis will be described in a separated cQT analysis plan.

8.7 Physical Examination

A complete physical examination including all major body systems will be performed at Screening. In addition, a targeted physical examination will 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 will be recorded as AEs. Physical examination results will be presented in a data listing by patient and treatment group.

8.8 Surgical Site Assessments

Surgical sites will be assessed at 96 hours (prior to discharge from the PACU) and then at the D8, D15, and D29 visits. The investigator will 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.

Assessment results and change from baseline will be summarized descriptively by time point and data will be listed by patient and treatment group.

8.9 Neurosensory Test

Neurosensory testing near the incision (compared to a similar site on the opposite leg) will 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 will 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 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 is ongoing or starts after the start of the study drug administration 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 March, 2020. 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 each study Part A, B & C separately using the Safety Population. All medications and non-medical therapies captured in eCRFs will be presented by patient in listings by treatment group.

8.11 Patient Pain Assessment Training and Surgery Details

Pain assessment training will 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

PK sampling will be performed on at least 8 patients at a single site. PK sampling will be performed on at least 24 patients receiving blinded study drug, i.e., 12 patients per randomized arm at a single site. All patients undergoing 24-hour Holter ECG recordings should have PK sampling.

No PK sample collection is planned for Part C.

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

Unscheduled PK samples will be collected where feasible during the inpatient phase of the study for all patients incurring an SAE or severe TEAE as part of the evaluation of those AEs.

There will be a ± 2-minute window allowed for the 10-, 15-, and 20-minute collections, a ± 5-minute window allowed for collections at 30 minutes through 4 hours, and a ± 15-minute window for collections after 4 hours. In the event of a SAE or severe TEAE, the actual time of collection of any unscheduled PK draw will be recorded for use in any analyses. Out-of-window collections will not be considered protocol deviations.

PK Analysis will be handled by an external vendor.

10. OTHER ANALYSES

Additional analyses involving the pooling treatment groups (from Parts B and C) may be carried out for exploratory purposes.

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.

13. EXAMPLE SAS CODE

Primary endpoint analysis, one-way ANOVA:

```
proc mixed data=auc_data;
  class patient treatment;
  model auc = treatment;
  lsmeans trt / diff cl alpha=0.05;

run;
```

Primary endpoint analysis, ANCOVA:

```
proc mixed data=auc_data;
  class patient treatment;
  model auc = treatment total_OME treatment*total_OME;
  lsmeans trt / diff cl alpha=0.05;


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, choose 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, choose the first structure that converges.

Example SAS code for Fisher's exact test:

```
proc freq data=parameter_data order=data;
  tables treatment*outcome / fisher exact OR;
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

Clinical Trial Protocol CA-PS-209, Amendment Version 2.0 / 15-Mar-2021.

eCRF Version and Date: Specification Version 3.0 and 22-Mar-2021.

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.

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

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

Martin McCarthy Jr, PhD, Olga Jonasson, MD, FACS, Chih-Hung Chang, PhD, A Simon Pickard, PhD, Anita Giobbie-Hurder, MS, James Gibbs, PhD, Perry Edelman, PhD, Robert Fitzgibbons, MD, FACS, Leigh Neumayer, MD, FACS, Assessment of Patient Functional Status after Surgery. https://www.portalbiocursos.com.br/ohs/data/docs/57/275Assessment_of_Patient_Functional_Status_after_Surgery.pdf

Activity Assessment Scale with Description of Scoring https://cdn-links.lww.com/permalink/aog/b/aog_134_5_2019_09_12_boyd_19-1019_sdc1.pdf

15. APPENDICES

15.1 0 to 10 Numerical Rating Scale of Pain Intensity (NRS)

Pain Intensity - Numerical Rating Scale (NRS)

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

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

Patient Initials: _____

15.2 Scoring of PROMIS 10 Questionnaire

Global Health

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

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

In the past 7 days…

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

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

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

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, 6, 7, 9, and 10. 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 Activities Assessment Scale (AAS)

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

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

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

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

15.4 Sit to Stand Test (30-Second Chair Stand) Assessment

ASSESSMENT

30-Second Chair Stand

Purpose: To test leg strength and endurance

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

NOTE: Stand next to the patient for safety.

① Instruct the patient:

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

② On the word "Go," begin timing.

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

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

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

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

Number: _____ Score: _____

Patient _____

Date _____

Time _____ ☐ AM ☐ PM

SCORING

Chair Stand
Below Average Scores

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

A below average score indicates a risk for falls.

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

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15.5 TUG Test

ASSESSMENT

Timed Up & Go (TUG)

Patient _____

Date _____

Time _____ ☐ AM ☐ PM

Purpose: To assess mobility

Equipment: A stopwatch

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

NOTE: Always stay by the patient for safety.

① Instruct the patient:

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

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

② On the word "Go," begin timing.

③ Stop timing after patient sits back down.

④ Record time.

Time in Seconds: _____

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

OBSERVATIONS

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

Check all that apply:

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

These changes may signify neurological problems that require further evaluation.

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

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15.6 Surgical Site Assessment

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

Post-Operative Surgical Site Assessment

***Instructions to Investigator*:** Please respond to the question below. When completed, please initial at the bottom of the page.

On a scale of 0 to 10, please rate your clinical satisfaction with the wound healing.

£0	£1	£2	£3	£4	£5	£6	£7	£8	£9	£10
Completely unsatisfied									*Completely satisfied*	

Investigator Initials: _____

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

15.7 Planned Tables, Figures, and Listings

15.7.1 Tables

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16. DOCUMENT HISTORY

Version #	Summary of Changes	Section Changed	Date
1.0	Initial document released	NA	14MAY2021

DocuSign

Certificate Of Completion

Envelope Id: E2444B36966A481DA757F35AC5C753CC
Status: Completed
Subject: Please DocuSign: CA-PS-209_SAP_Final_V1.0_14May2021.pdf
Source Envelope:
Document Pages: 78
Signatures: 4
Certificate Pages: 4
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Enabled
Time Zone: (UTC-08:00) Pacific Time (US & Canada)

Envelope Originator:
Isaac Briskin
100 W California Blvd., Unit 25
Pasadena, CA 91105
ibriskin@lotuscr.com
IP Address: 104.176.22.248

Record Tracking

Status: Original
5/17/2021 7:43:10 AM
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Signer Events	Signature	Timestamp
HENRY FOEHL henry.foehl@hcfoehl.com Henry Foehl Security Level: Email, Account Authentication (Required)	 Signature Adoption: Uploaded Signature Image Signature ID: ABAF4AD4-E11B-4C41-909E-3B4693085652 Using IP Address: 69.139.1.91 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 5/17/2021 7:45:38 AM Viewed: 5/17/2021 1:31:35 PM Signed: 5/17/2021 1:33:19 PM
Electronic Record and Signature Disclosure: Accepted: 6/22/2020 10:54:34 AM ID: b2490305-60fd-41f6-bcf7-e1dabb19b9cf		
Isaac Briskin ibriskin@lotuscr.com Biostatistician Lotus Clinical Research, LLC-Sub Account Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 7FCAF097-E1A5-4C38-8210-0027B0ECC2AD Using IP Address: 104.176.22.248 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 5/17/2021 7:45:37 AM Viewed: 5/17/2021 7:46:34 AM Signed: 5/17/2021 7:47:51 AM
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Signer Events	Signature	Timestamp
Sam Teichman steichman@concentricanalgesics.com VP, Clinical Development Concentric Analgesics Security Level: Email, Account Authentication (Required)	Sam Teichman Signature Adoption: Pre-selected Style Signature ID: EA3F6C62-DE63-4E34-84AD-6BF24BCAA75C Using IP Address: 69.181.166.132 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 5/17/2021 7:45:37 AM Viewed: 5/17/2021 1:46:35 PM Signed: 5/18/2021 8:15:27 AM
Electronic Record and Signature Disclosure: Accepted: 11/15/2019 6:09:57 PM ID: 8bdb065a-97c0-403d-aaf5-961e2ac193dd		
Swarupa Changan swarupa.changan@quartesian.com Security Level: Email, Account Authentication (Required)	Swarupa Changan Signature Adoption: Pre-selected Style Signature ID: 7A7B1839-CBD6-499C-8777-6BDE7FF4B95E Using IP Address: 27.7.242.85 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 5/17/2021 7:45:38 AM Viewed: 5/17/2021 8:31:54 AM Signed: 5/20/2021 10:45:00 PM
Electronic Record and Signature Disclosure: Accepted: 5/13/2021 9:46:14 PM ID: 4fa9d933-a45e-4ddf-b8c8-0e277f3195bf		

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

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	5/17/2021 7:45:38 AM
Certified Delivered	Security Checked	5/17/2021 8:31:54 AM
Signing Complete	Security Checked	5/20/2021 10:45:00 PM
Completed	Security Checked	5/20/2021 10:45:00 PM

Payment Events	Status	Timestamps

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