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

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STATISTICAL ANALYSIS PLAN FOR FINAL PILOT STAGE

A Phase 2, Randomized, Double-blind, Placebo-controlled Efficacy, Pharmacokinetics and Safety Study of CA-008 in Subjects Undergoing Total Knee Arthroplasty

Protocol Number: CA-PS-203

Protocol Version 3.2 (19FEB2019)

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LIST OF IN-TEXT TABLES AND FIGURES

LIST OF ABBREVIATIONS (COMMONLY USED)

ADaM	Analysis Data Model
ADLs	Actives of Daily Living
AE	Adverse Event
ANOVA	Analysis of variance
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
CDER	Center for Drug Evaluation and Research
CP	Completer
CRF	Case Report Form
CRO	Clinical Research Organization
CSR	Clinical Study Report
ECG	Electrocardiogram
ET	Early Termination
FDA	Food and Drug Administration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IGE	Investigator Global Evaluation
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MED	morphine equivalent dose
NRS	Numerical Rating Scale for Pain Intensity
OC	Opioid Consumption in morphine equivalent dose
OF	Opioid-Free days
PACU	Post-Anesthesia Care Unit
PE	Physical Examination

PGE	Patient Global Evaluation
PK	Pharmacokinetic
PT	Preferred Term
QOL	Quality of Life
SAE	Serious Adverse Event/Experience
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Standard Data Table Model
SOC	System Organ Class
SRC	Safety Review Committee
TKA	Total Knee Arthroplasty
TEAE	Treatment Emergent Adverse Event
WHO	World Health Organization
WOCF	Worst Observation Carried Forward

1. PURPOSE OF THE ANALYSES

This statistical analysis plan (SAP) is based on protocol number CA-PS-203 Version 3.2 (19FEB2019) from Concentric Analgesics, Inc. This SAP will focus on analyses that will be performed on data collected during the pilot stage of the study. A final SAP was planned to be created and signed off that would provide the full description of the analyses that will be performed for the Pilot Stage and the data collected in Stage 2, however, after enrollment of the 3rd Cohort of the Pilot Stage, the sponsor decided to not proceed with Stage 2. Therefore no additional SAP will be created, and no additional analyses are planned.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonization (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials, the most recent ICH E3 Guideline and the Guidance for Industry: Structure and Content of Clinical Study and the most recent FDA draft Guidance for Industry - Analgesic Indications: Developing Drug and Biological Products, dated February 2014.

This SAP describes the data collected during the pilot stage that will be analyzed and the efficacy assessments that will be evaluated for the analysis of Pilot stage. This SAP provides details of the specific statistical methods that will be used for that analysis.

2. PROTOCOL SUMMARY

2.1 Study Objectives

2.1.1 Pilot Stage of the Study

2.1.1.1 Primary Objective

- To evaluate the efficacy of a single intraoperative administration of CA-008 vs. placebo in subjects undergoing an elective total knee arthroplasty (TKA).

2.1.1.2 Secondary Objective

- To evaluate the safety and tolerability of a single intraoperative administration of CA-008 vs. placebo in subjects undergoing an elective TKA.

- To evaluate the Pharmacokinetic (PK) profile of a single intraoperative administration of CA-008 in subjects undergoing an elective TKA.
- To evaluate the opioid-sparing effect of CA-008 vs. placebo.

2.1.2 Second Stage of the Study

To be updated in Final SAP.

2.2 Overall Study Design and Plan

This is a Phase 2, multi-center, randomized, double-blind, placebo-controlled, parallel design study evaluating, in a pilot stage of the study involving 3 exploratory cohorts, each with a single dose of CA-008 vs. placebo injected/instilled during an elective TKA.

After an interim unblinded analysis of the pilot stage results from Cohort #1, and review of those Cohort 1 topline results (the subject of a previously executed Interim SAP), a protocol amendment was performed to add two additional exploratory cohorts: Cohort #2 CA-008 10 mg vs. placebo and Cohort #3 CA-008 15 mg vs. placebo (with each cohort enrolling n=18 randomized 2:1, respectively) with a volume of 100 mL.

A second stage of the study was anticipated with that second stage using the doses, sample size and number of CA-008 treatment groups vs. placebo to be determined after an interim analysis of the combined cohort #1 - cohort #3 data in this pilot stage. However, after enrollment of Cohort 3 the sponsor decided to end the study after the pilot stage, and Stage 2 will not be performed..

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

- Inpatient period which continues to 96h (T96h) after completion of study treatment injection (T0).
- Outpatient period which begins on discharge from the inpatient unit through various follow-up visits to day 29 (D29±2) (W4) after surgery or later if necessary for ongoing safety assessment.

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

The protocol-defined visits are presented in Table 2-1:

Table 2-1 Protocol-Specified Visits and Visit Windows

Study Phase	*Visit Time*
Screening	From days -45 to -1
Prior to Surgery/ Surgery	Day 0
In-Patient (Post Surgery)	Hours 0 (post-surgery), 24, 48, 72 and 96
Follow-up	Days 8(±1 day), 15(±2 days), 29(±2 days)

All study assessments are outlined in Table 1 of the Protocol.

2.2.1 Study Stopping Rules

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

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

More details are described in Section 7.3 of the Protocol.

An external independent safety review committee (SRC) will be consulted should a stopping rule be triggered to determine whether it is appropriate to continue with dosing in the study. This committee will be independent of the Sponsor or clinical research organization (CRO) and will in no way be involved with study conduct. The SRC Charter details the membership, roles and responsibilities of the SRC.

Table 2-2 Study Stopping Rules

Category	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Abnormal Wound Healing: Infection Dehiscence Necrosis	Mild symptoms; clinical or diagnostic observations only; intervention not indicated. No interference with age-appropriate instrumental ADL	Minimal, local or noninvasive intervention indicated; May require local wound care or medical intervention (e.g., dressings or topical medications)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting ADLs. May require IV antibiotics, antifungals, or antivirals or radiologic intervention.	Life-threatening consequences; urgent intervention indicated
ECG/Cardiac issues Vital Signs Labs	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Focused Neurosensory Testing (performed by trained Investigator)	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms requiring medical intervention; limiting self-care ADL	Life-threatening and urgent intervention indicated

2.2.2 Study Population

The study population will consist of adults, aged 18-80 years old inclusive, who are undergoing elective TKA and otherwise meet eligibility criteria (as described in the protocol Sections 8.2.1 and 8.2.2) may be considered for enrollment into the study.

2.2.3 Treatment Regimens

Pilot Stage:

Cohort #1: CA-008 5 mg vs. placebo in 100 mL of vehicle

Cohort #2: CA-008 10 mg vs. placebo in 100 mL of vehicle

Cohort #3: CA-008 15 mg vs. placebo in 100 mL of vehicle

2.2.4 Treatment Group Assignments or Randomization

In pilot stage of the study, subjects who meet the enrollment criteria will be randomly allocated to receive either an active drug or placebo in a 1:1 (for Cohort #1) or a 2 active: 1 placebo ratio (for Cohorts #2 or #3). This study will use manual randomization.

Subjects who have provided written informed consent will be assigned a unique number in the screening process. This number will be used to identify the subject throughout the study. Once any subject number or randomization number is assigned, it cannot be reassigned to any other subject. Subjects may be rescreened if the screening window is exceeded due to scheduling issues.

2.2.5 Sample Size Determination

In the pilot stage, 18 subjects will be randomized to either the active medication or placebo in a 1:1 ratio for Cohort #1. For Cohorts #2 and #3, 18 subjects will be randomized with a ratio of 2 Active : 1 Placebo. Subjects who elect to discontinue study participation after randomization but prior to receiving study treatment will be replaced.

3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

This section discusses general policies to be employed in the analysis and reporting of the data from the study. Departures from these general policies may be provided in the specific detailed

sections of this SAP. When this situation occurs, the rules set forth in the specific section take precedence over the general policies.

Cohort 1 active and placebo treatments will be presented separately from cohorts 2 and 3 and placebo treatments will not be pooled across all 3 cohorts. Cohort 2 and 3 will have a pooled placebo group and each active dose will be presented separately in summaries and analyses as appropriate.

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

No preliminary rounding will be performed; rounding will only occur after the analysis. To round, consider the digit to the right of the last significant digit: if <5, then round down; if ≥5, then round up. Means and medians will be presented with one more decimal place than the precision of the data. Standard deviations will be presented with two more decimal places than the precision of the data. Percentages will be presented with one decimal place. A percentage of 100% will be reported as 100%. Minimums and maximums will be presented with the same precision as the original data.

All analyses will be performed using the SAS System® version 9.3 or higher. For interim analyses, no SDTM or ADaM data will be generated and data will be analyzed as described in the Interim SAP.

For Final TLFs after Pilot Stage, the domain (Study data tabulation Model [SDTM]) and analysis (Analysis Data Model [ADaM]) data sets will be taken as input to the SAS programs that generate the report-ready tables, figures and listings. The submission ready SDTM and ADaM data sets will be provided to the sponsor along with display deliveries.

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

- Time 0 (T0) is the time of completion of study drug administration.
- Time P (TP) is the time of discharge from the post-anesthesia care unit (PACU)

- Day of surgery is defined as Day 0 (D0).
- Assessment visit times are defined by D0 and/or T0.
- Baseline value is defined as the last valid measurement prior to the dosing of study treatment.
- Change from baseline is defined as post-baseline value minus baseline value.
- The date/time of early termination will be the date/time that the subject confirms they no longer want to participate in the study, regardless of whether they decide to withdraw from all or only some study procedures and regardless of if they return for to the site for assessment of wound healing.
- The number of days in the study is computed as: [Date of study completion or withdrawal minus the date of study drug administration] + 1.
- Values that compromise interpretation will not be used in summaries (e.g., values that were obtained post-dose will not be summarized as pre-dose values).

4. SUBJECT POPULATIONS

4.1 Analysis Populations

For the analysis of pilot stage, two analysis populations are defined as follows:

- **Safety** Population will include all randomized subjects who received any amount of study drug. Subjects will be analyzed by treatment group according to the actual treatment received, i.e., “as treated”.
- **PK** Population will include all subjects who receive a full dose of study treatment and complete all PK assessments. Subjects will be analyzed by treatment group according to the actual treatment received, i.e., “as treated”.

Analysis population will be determined before the unblinding.

All efficacy and safety analyses will be performed using Safety population for Pilot Stage. PK analyses will be performed using PK population.

4.2 Disposition of Subjects

All subjects and the populations for which they qualify will be listed. Subjects who are screened and who fail screening or withdraw consent prior to randomization or are randomized but not treated will be listed and summarized in the disposition summary table. Subjects who are randomized, subject inclusion into each study population, subjects who are treated, subjects who complete follow-up as well as subjects who withdraw early from the study and the reason for withdrawal will be summarized by treatment group and overall in the subject disposition summary table.

4.3 Protocol Deviations

Deviations are categorized as informed consent procedures, inclusion/exclusion criteria, study medication, prohibited medications, study procedures, study drug assignment/treatment, visit or assessment time window, missed visit or assessment and/or other. All protocol deviations will be captured on case report forms (CRFs) and/or documented in site specific logs throughout the study. Deviations will be categorized and classified as major or minor by the project team and the medical monitor after database lock but before unbinding and will be discussed in the CSR. The number of subjects with protocol deviations, both minor and major, will be presented in a data listing and will be summarized by type of deviation and major/minor classification for the ITT population.

5. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

5.1 Demographics and Baseline Characteristics

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

5.2 Medical/Surgical History

The complete medical and surgical history will include histories of acute, chronic, or infectious disease; surgical or oncologic histories; and any reported conditions affecting major body systems. Subject’s medical history will be evaluated by an Investigator for clinical significance. Medical and Surgical history, as collected at screening, will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 to determine system organ class (SOC) and

preferred term (PT). Medical histories will be presented in a by-subject listing. Any events that occur prior to the study procedure will be categorized as medical history.

5.3 Prior and Concomitant Medications

Prior medications/therapies are those that stop prior to the start of the study drug administration. Any medication/therapy that stops at or after this time or on going is considered concomitant medication/therapy. Prior and concomitant medications are collected for the 45 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 1, 2018. The number and percentage of subjects who take concomitant medications will be summarized by drug class and preferred term, overall and by treatment group, for the safety population. All medications and non-medical therapies captured in CRFs will appear in data listings.

6. MEASUREMENTS OF TREATMENT EXPOSURE AND COMPLIANCE

Because study medication is administered as a single dose at the study center by trained study personnel, compliance with respect to study medication will not be calculated. A listing of study drug administration and exposure data will be provided.

After completing the assessments through 96 hours after study medication administration, the diary for at-home use will be distributed to the subject to collect pain intensity (twice daily on NRS) and pain medication through Day 15. Compliance with home diary use will be evaluated based on post-discharge home diary records. Compliance for each subject will be based on the number of days the subject participated in the outpatient study period, defined as:

$$\text{Compliance (\%)} = \frac{\textit{(N of non-missing NRS recorded on Diary)}}{\textit{(N of Expected NRS from diary)}} \textit{ X 100}$$

Where the N of expected NRS records in the diary for each subject is calculated as 2 times the number of days the subject participated in the outpatient portion of the study. The number of days of participation will be calculated as the date of the Day 15 visit or the date of the last study visit (whichever is earlier) minus the date of discharge. NRS recorded prior to a rescue use will not be included in this calculation of compliance. For example, Subject A was discharged on Day 4, if

this subject discontinues the study on Day 13, then the expected N of NRS records on diary will be 18 (2 * (13-4)). Assuming Subject A had 10 NRS available from his/her diary, then compliance for this subject would be 55.6% ((10/18) *100). However, if subject A had discontinued the study on Day 10 (prior to Day 13), then the expected N of NRS for this subject would be 12 (2 * (10-4)) and compliance would be 83.3% ((10/12) *100). A summary of compliance will be provided overall and by treatment group. Compliance with recording an NRS prior to rescue in the diary will be calculated as the number of NRS recorded prior to taking rescue medications divided by the number of rescue medication uses recorded.

7. EFFICACY EVALUATION

7.1 Handling of Dropouts or Missing Data

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

- Subjects are required to consent to continuous data collection even after discontinuation of study medication;
- Data collection will continue after subjects take rescue medication.

With the procedures above, it is expected that missing data will be minimal. Missing at random is expected to be a reasonable assumption for this study.

For the endpoints of NRS (at rest and/or after ambulation) in this study, NRS values will be imputed in the following manner:

First, when rescue medication is used, any NRS measured at rest within following window is considered invalid :

- 30 minutes for IV fentanyl
- 2 hours for IV hydromorphone
- 4 hours for PO opioids.

The last NRS prior to the use of any rescue medication will be used to impute subsequent NRS at rest scores for the subsequent protocol-specified time points for measurement of pain intensity through an appropriated time window (as specified above) after the time of the dosing of the rescue medication. Note: if a pre-rescue NRS assessment occurs at the same time as a scheduled assessment, the schedule NRS will be assumed to happen first, and then the pre-

rescue NRS will be assumed to occur. If an NRS assessment occurs at the same time as the time of taking a rescue medication, the NRS will be assumed to be a Pre-rescue medication result. If the NRS time is the same as the end of time window after taking the rescue medication (end of imputation period), then NRS will be considered as occurring before the 4 hours assessment and will be imputed. For example, if a rescue dose (IV morphine) is taken at 1pm, all protocol-scheduled NRS will be imputed with the appropriate NRS value up to and including through 5pm (a 4-hour window). If multiple doses of rescue medication are taken within a 4-hour period, the pre-rescue NRS for the first rescue use will be carried forward continuously until 4 hours past the last use of rescue falling within the continuous window. For example, if rescue is used at Hour 2.3 and Hour 5.1, the pre-rescue NRS at Hour 2.3 will be carried forward till Hour 9.1 (5.1 +4). NRS scores taken after ambulation will be based on reported values and the pre-rescue 4-hour imputation rule will not be used. The scores after ambulation are collected every 12 hours and no ambulation NRS score is collected prior to taking rescue medication.

Intermittent missing pain scores at rest or after ambulation (due to subject sleeping, etc.) will not be imputed, and AUC will be calculated based on non-missing values. For subjects who drop out of the study early, scheduled assessments will first be imputed using the worst prior pain score carried forward (WOCF).

7.2 Assessment Time Windows

For calculations of all AUC endpoints and use of opioid endpoints, the actual dates/times of the assessments will be used in calculations. Thus, while the NRS are intended to be collected at the pre-defined protocol scheduled time points (e.g., Hour 0.5, 1, 2, etc.), it is recognized that operationally the scores are collected as close to the target times as possible but there is some flexibility in terms of the actual times the scores are collected. Thus, to account for this inherent aspect of data collection, the ACTUAL TIMES will be used for the calculation of the AUC. The actual times will be based relative to the time of completion of study drug administration.

Safety assessment summaries will be based on the nominal protocol-specified assessment times.

7.3 Efficacy Endpoints for Pilot Stage

7.3.1 Primary Efficacy Endpoint

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

7.3.2 Key Secondary Efficacy Endpoints

Following are key secondary endpoints (in descending order of importance):

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

7.4 Analysis Methods

7.4.1 NRS Measurements

The NRS is an 11-point scale with anchors 0 (no pain) and 10 (worst possible pain). NRS will be assessed as follows:

- During the inpatient stay, NRS at rest beginning with the PACU admission may be assessed once the subject is awake. If the subject is able to provide responses, obtain NRS scores at T0.5, 1, 2, 4, 6, 8, 12, 16, 20, 24, and every 4 hours (if awake at time of assessment) until discharge from the inpatient unit. Time windows: for T0.5 to T2 (±5 min) and from T4 onward (±15 min).
- Pain scores may be skipped between the hours of midnight and 6 a.m., but the subject may not miss two consecutive assessments.
- An additional NRS assessment must be obtained prior to rescue medication request (±15 min). The T12, T24, T48, T72 and T96h assessments must be completed even if the subject is asleep at these times.
- During the inpatient stay, starting on postoperative day 1 (after T24) perform the following each morning at 0800h (±2h) and each evening at 2000h (±2h) document the NRS at rest and after physical therapy or transfers to/from bed or wheelchair (inpatient) or ambulation for approximately 10 yards (inpatient or outpatient). Actual assessment times must be documented. If, however these twice daily assessments coincide with timed assessments of NRS at rest, then the time assessment at rest is used in place of the twice daily

assessments. Resting pain scores are performed on the schedule noted above in the first bullet.

- During the outpatient period (after T96h through W2), instruct the patient to document, if possible, their NRS scores twice daily at 0800h (±4h) and 2000h (±4h) at rest and on ambulation (e.g. with the use of a walker or a cane) for approximately 10 yards. Note that the actual time of these assessments must be documented in the diary whenever possible. Instruct the patient to:
- Obtain the morning NRS assessment prior to taking any pain medication or 2 (±15min) hours after taking any pain medication.
- Obtain the evening NRS assessment 2 (±15min) hours after taking any pain medication.

7.4.2 Mean Pain Intensity Scores at T96h (Primary Efficacy Endpoint)

Missing NRS at 96 hours will be handled as discussed in Section 7.1.

Mean NRS scores at 96 hours will be analyzed using a 1-factor (treatment) analysis of variance (ANOVA) model with treatment as the main effect. Descriptive summaries will be presented for each treatment group. Similar ANOVA analyses will also be performed at each time point without imputation for early drop out. In addition, the pain intensity score at Hour 96 and at each time point will be analyzed using Wilcoxon sum-rank test for sensitivity.

7.4.3 AUC 0-96h at Rest (Secondary Efficacy Endpoint)

AUC calculations will be done using the standard trapezoidal rule

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

Where: NRS_i = NRS at rest at time I, and ($T_{i+1} - T_i$) is the Time difference in hours between time i and time i+1.

Missing NRS will be handled as discussed in Section 7.1. AUC values will be analyzed using a 1-factor (treatment) analysis of variance (ANOVA) model with treatment as the main effect.

The AUC analyses will be presented in a summary table with standard summary statistics for each treatment group as well as active vs. placebo mean differences, standard errors, confidence intervals and comparison p-values as appropriate. In addition, $AUC_{0\text{-}96h}$ at rest will be analyzed using Wilcoxon sum-rank test.

The individual NRS and the computed AUC variables will be listed for all individual subjects.

7.4.4 Opioid Free (OF) 0-96h (Secondary Efficacy Endpoint)

Opioid use is recorded on the rescue medication eCRF from the end of surgery through the D15 follow up/Early termination (ET). If additional opioids, other than the study rescue medications, appear on the concomitant medications page and can be identified, those opioids will also be considered.

The percentage of subjects who do not require opioids (are Opioid Free or OF) will be analyzed using a logistic regression with treatment group as the main effect. The analysis will compare the odds ratios of the proportions of OF subjects between each treatment group and the placebo group. A summary of frequencies as well as odds ratio, 95% confidence intervals and p-values will be presented for 0 to 96 hours ($OF_{0 \text{ to } 96h}$).

7.4.5 Total Opioid Consumption (OC) in Daily Oral Morphine equivalents 0-96h (Secondary Efficacy Endpoint)

The amount of opioids taken as rescue will be calculated using the rescue medication page of the eCRF. If additional opioids, other than the study rescue medications, appear on the concomitant medications page and can be identified, those opioids will also be included (in terms of morphine equivalents) in the total consumed. Table 3 will be used to calculate the morphine equivalent dose (MED) for each medication. The total opioid consumption for each day for each subject will be calculated as the sum of the MEDs of all of the medications taken on that day. For example, if a subject takes 5 MED morphine on Day 1 and Day 2, and 10 MED of Oxycodone on Day 2, the total consumption for Day 1 is 5 MED, and the total consumption for Day 2 is 15 MED. Subjects that take no opioids on a day will have a total opioid consumption value of zero for that day.

Table 3 Equianalgesic Conversion Table

Opioid (Doses in mg)	Conversion Factor to IV morphine	Conversion Factor to PO morphine
IV Fentanyl	100	
IV Hydromorphone	6	
IV Morphine	1	6*
PO Hydrocodone		1
PO Morphine		1
PO Oxycodone		1.5
PO Tramadol		0.1

For any IV opioid, we will use a 2-step process to calculate its oral (PO) morphine equivalent dose (MED):

1. Convert its IV dose to IV morphine MED by multiplying by the conversion factor for IV equivalence.
2. Once the IV morphine MED is calculated, convert to the PO morphine MED using the conversion factor for PO equivalence.

For any PO opioid, use the conversion factor to calculate the PO MED.

*Note that for non-tolerant patients, we are using the 6:1 conversion for IV to PO morphine.

Total opioid consumption will be calculated for 0-96 hours ($OC_{0\ to\ 96h}$). An ANOVA with treatment arm as the main effect will be performed. A separate summary containing only subjects that have taken at least one dose of rescue will be performed if warranted.

8. SAFETY EVALUATION

8.1 Overview of Safety Analysis Methods

All safety outcomes will be summarized using the safety population. No formal statistical comparisons will be performed for safety outcomes. Safety outcomes include:

- Incidence of spontaneous reported treatment-emergent adverse events (TEAEs) or serious adverse events (SAEs)
- Physical examination (PE)

- Vital signs
- Surgical site assessments
- Neurosensory testing near the incision
- X-ray of the operated knee
- Rebound or worsening pain
- ECG
- Clinical laboratory test results

8.2 Adverse Events and SAEs

All AEs and SAEs are documented and followed from the time the subject have 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 21.0) 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 the date of treatment with the study drug through Day 29 or Early Termination, whichever occurs first.
- Serious AEs with onset on the date of treatment with the study drug through 30 days after Day 29 or Early Termination, whichever occurs first.
- AEs that start before the start of treatment but increase in severity or relationship at the time of or following the start of treatment through Day 29 or Early Termination, whichever occurs first.

For evaluation of causal relatedness to treatment, the categories are probably related, possibly related or unlikely 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 terms, the criteria are mild, moderate, severe or potentially life-threatening. In addition to a listing of all TEAEs, treatment related TEAEs, serious TEAEs, Deaths, and TEAEs leading to premature discontinuation from the study will be provided.

An overall summary will be prepared giving for each treatment group and overall both the number of TEAEs, and the number of subjects with at least one TEAEs, as well as SAEs, treatment related TEAEs and TEAEs leading to premature discontinuation from study.

The number of subjects with AEs will be summarized for each treatment group by SOC and PT sorted in alphabetically by SOC, and then by PT within SOC. These summaries will be given by treatment in separate tables for each of the following TEAE event sets:

- All events
- Treatment related events
- Serious events
- Events leading to premature discontinuation from study
- Events by maximum severity

If a given subject experiences a TEAE that maps to the same PT/SOC more than once, the subject will be counted only once for the SOC/PT at the greatest severity (i.e., mild, moderate, or severe) and causality (i.e., attribution to study material).

Duration of a TEAE lasting more than 24 hours will be computed in days as the stop date of the event minus the start date plus 1 and will be reported in days. TEAEs lasting less than 24 hours will be computed as stop date/time minus start date/time. If reported as ongoing at the time of database lock, the stop date is defined as the date of the last visit or the last date of any event for the subject in the database, whichever is later.

If a TEAE is considered resolved, but the stop date is missing, the last day of the month will be imputed if the month and year are available. If only the year is available, and the year is the same as the year of the last visit, the stop date will be the latest of the last visit date or latest event for the subject in the database.

If the year of the event is prior to the year of the last treatment, the end day and month will be set to 31 December.

For missing or partial start and stop dates/times, the most conservative imputation will be used (AEs will be assumed to be temporally related to the study medication). Table 4 will be used to impute any missing dates/times:

Table 4 Table of Imputation Rules for Missing AE Start Dates

Missing Date Portion	*Prior to Treatment*	*Same as Treatment Start Date*	*After Treatment Start Date*
Day	*Month and Year < Month and Year of Study treatment:* *Start Day = 1* *Stop Day=last day of the month*	*Month and Year = Month and Year of Study treatment:* *Start Day = Day of first treatment* *Stop Day= last day of the month*	*Month and Year > Month and Year of Study Treatment:* *Start Day = 1* *Stop Day=last day of the month*
Day and Month *Define Day as above, then:*	*Year < Year of first treatment:* *Start Month = July* *Stop Month = Dec*	*Year = Year of study treatment:* *Start Month = Month of study treatment* *Stop Month = Dec*	*Year > Year of study treatment:* *Start Month = January* *Stop Month = Dec*
Day, Month, and Year	*To be conservative, completely missing start dates will be imputed using the date of study treatment, Missing end dates will be imputed using date of last study contact with the subject*		
Time	*Missing start times will be imputed as 00:01* *Missing stop times will be imputed as 23:59*		

After following these imputation rules, if the start date/time is imputed as a date after the end date/time, the start date/time will be set to the end date/time to provide a positive duration for the event incidence.

Missing assessments for AE study medication relationship or severity will be analyzed as related or severe respectively. No other imputation is planned for safety data.

8.3 Physical Examination

A complete medical history and physical examination including all major body systems will be performed at Screening. In addition, a focused interim medical history and targeted physical examination will be performed prior to surgery (if not done on D-1), and to capture changes after Surgery, at 96 hours (± 4 hours) after the administration of study medication, but prior to discharge, and Days 8, 15 and 29/ET after the administration of study medication.

Abnormal or clinically significant physical exam will be recorded as AEs. Physical examination results will be listed for individual subjects.

8.4 Vital Signs

Vital signs results including blood pressure (systolic and diastolic; mmHg), heart rate (beats per minute), respiration rate (breaths/min), and temperature will be listed for individual subjects.

Baseline for vital signs measurements will be defined as the last evaluation before dosing with study medication. Summary statistics, including change from baseline, will be determined for each measure and will be summarized by treatment and time point.

8.5 Surgical Site Assessments and Rebound (or Worsening) Pain Assessments

Surgical sites will be assessed at 96 hours (prior to discharge from the unit) and then as an outpatient on Days 8, 15 and 29. The investigator will evaluate their satisfaction with the healing of the wound during this surgical site assessment using an 11-point scale (0- 10) where a score of 0 is “completely unsatisfied” and a score of 10 is “completely satisfied). In addition, subjects will report whether they have noted any worsening pain (rebound pain; Y/N) at the surgical site since the prior visit at Days 8, 15 and/or 29.

All data will be presented in data listings. Results of surgical site assessments and the number of subjects with rebound pain will be summarized descriptively by treatment and time point.

8.6 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 as an outpatient on Days 8, 15, and 29.

The neurosensory assessment results will be listed and the number of subjects in each response will be summarized descriptively by treatment and time point by wound (cephalad or caudad).

8.7 X-ray of the Operated Knee

X-ray of the operated knee on Day 29 and later if any evidence of abnormal bone healing until resolution or stabilization. Also perform this at early termination if subject gives consent.

Results of x-ray of the operated knee will not be entered in database. Date and time of x-ray performed will be listed.

8.8 ECG

ECG examination will be assessed at screening and 24 hours (±2 hours) after study medication administration.

12-Lead ECGs will be performed after the subject has been resting in a recumbent/supine position for at least 5 minutes. ECGs will be signed and dated by a medically-qualified individual to confirm review of the ECG and verify whether any abnormalities are clinically significant.

Number of subjects with abnormal results will also be summarized by treatment and time point.

8.9 Clinical Laboratory Test Results

Clinical laboratory tests (chemistry, hematology/coagulation and urinalysis) will be collected at screening and before discharge from the inpatient unit (T96h). All results will be listed. For each lab test, the raw value and change from screening will be summarized by treatment.

Each clinical laboratory test will be defined by the clinical laboratory to be “Low”, “Normal”, or “High”, according to the normal reference range from the clinical laboratory.

The number and percentage of subjects who have a shift from within to outside the normal reference range from screening to T96h will be summarized by treatment.

8.10 Drugs of Abuse and Alcohol Screens, Pregnancy Test

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

Results will be listed for individual subjects. Each test result will be defined to be “negative” or “positive”.

8.11 Subject pain Assessment Training and Surgery Details

Pain assessment training will be provided during screening. Subjects will re-watch video prior to surgery. Patient pain assessment training and surgery Details will be documented in CRFs and will be listed for each subject.

9. PHARMACOKINETIC EVALUATION

The time points for PK whole blood collections will be at baseline (from Check-in and up to 30 min prior to surgery), 5, 10, 15, 30, 45 minutes, and at hours 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 30, 36 and 48 (for a total of 20 samples) after the end of study treatment administration.

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

10. OTHER ANALYSES

All additional analyses of Pilot Stage data not included in this SAP, conducted after Pilot stage unblinding will be considered exploratory and will be presented and identified separately in the CSR.

11. INTERIM ANALYSES

An interim unblinded analysis may be performed after the last subject from each pilot stage cohort has completed the D8 visit. Since no Stage 2 data will be collected, final data from the initial Pilot stage will be summarized and no additional SAP or analyses will be performed..

12. REFERENCES

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

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

Guidance for Industry (2014) Analgesic Indications: Developing Drug and Biological Products - Draft Guidance. Department of Health and Human Services: Food and Drug Administration. Center for Drug Evaluation and Research (CDER) February 2014 Clinical/Medical.

13. APPENDICES

13.1 Planned Tables, Figures and Listings

13.1.1 Tables

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13.1.2 Listings

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Listing 16.2.27	PK Population	Pharmacokinetic (PK) Concentration Data

14. DOCUMENT HISTORY

Version #	Summary of Changes	Section Changed	Date
1.0	Initial document released	NA	13MAR2019
2.0	Updated for the final protocol version and date.	Various	24Apr19

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