CONCENTRIC ANALGESICS

OFFICIAL TITLE:

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

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STATISTICAL ANALYSIS PLAN

A Phase 2, Randomized, Double-blind, Placebo-controlled Safety,

Pharmacokinetics and Efficacy Study of CA-008 in Subjects Undergoing

Bunionectomy

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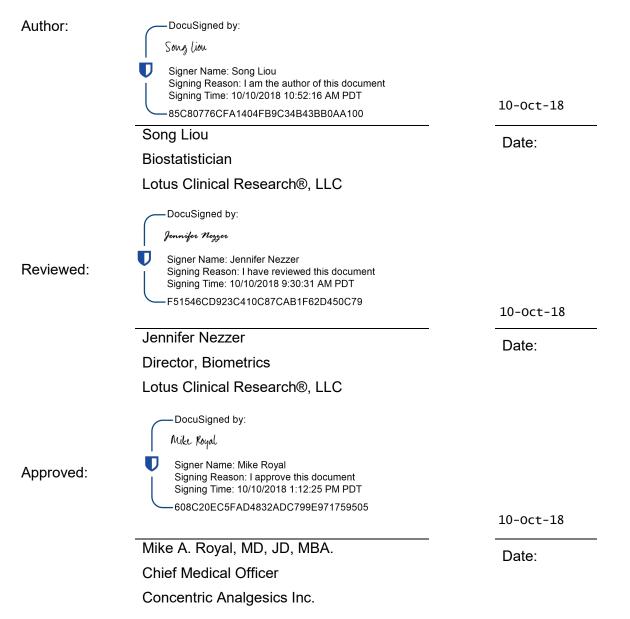Protocol Version 1.2 (06JUN2018)

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V1.0	11SEP2018	Final SAP
V2.0	09OCT2018	Add the sensitivity analysis of imputing early drop out using median value for selected efficacy endpoints

APPROVALS

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LIST OF IN-TEXT TABLES AND FIGURES

LIST OF ABBREVIATIONS (COMMONLY USED)

AC	Analgesic Consumption
ADaM	Analysis Data Model
AE	Adverse Event
ANOVA	Analysis of variance
ASA	American Society of Anesthesiologists
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
BUNX	Bunionectomy
CDER	Center for Drug Evaluation and Research
CMH	Cochran Mantel Haenszel Test
CP	Completer
CRF	Case Report Form
CSR	Clinical Study Report
ECG	Electrocardiogram
ET	Early Termination
FDA	Food and Drug Administration
HCl	Hydrochloride
HCU	Health care utilization
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IGE	Investigator Global Evaluation
LOCF	Last Observation Carried Forward
LOE	Lack of Efficacy
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
PE	Physical Exam
PGE	Patient Global Evaluation
PK	Pharmacokinetic
PT	Preferred Term
SAE	Serious Adverse Event/Experience
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Standard Data Table Model
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TTFR	Time to First use of Rescue medication
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-201 Version 1.2 (06JUN2018) from Concentric Analgesics, Inc. The SAP will be signed off before the final database lock. The SAP contains detailed information to aid in the performance of the statistical analysis and reporting of the study data for use in the final clinical study report (CSR). 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 that will be analyzed and the subject characteristics, safety, and efficacy assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. If additional analyses are performed after database lock and unblinding to supplement the planned analyses described in this SAP, they will be clearly identified as post-hoc in the CSR.

2   PROTOCOL SUMMARY

2.1   Study Objectives

2.1.1   Primary Objective

- To evaluate the efficacy of a single intraoperative administration of CA-008 vs placebo in subjects undergoing an elective bunionectomy (BUNX).

2.1.2   Secondary Objectives

- To evaluate the safety and tolerability of a single intraoperative administration of CA-008 vs. placebo in subjects undergoing an elective BUNX.
- To evaluate the PK profile of a single intraoperative administration of CA-008 vs. placebo in subjects undergoing an elective BUNX.
- To explore the efficacy of various doses of CA-008 administered intraoperatively in subjects undergoing an elective BUNX.

2.1.3   Exploratory Objectives

- Pharmacoeconomic benefits from administration of CA-008 vs. placebo in subjects undergoing an elective BUNX (Addressed outside this SAP).

2.2   Overall Study Design and Plan

This is a Phase 2, multi-center, randomized, double-blind, placebo-controlled, parallel design study evaluating a single dose of one of three CA-008 dose groups vs. placebo injected during an elective BUNX under light to moderate sedation supplemented by a Mayo block with bupivacaine hydrochloride (HCl) and a multimodal analgesia regimen, including ketorolac and acetaminophen, and access to rescue medication (oxycodone).

During the screening phase, subjects requiring bunionectomy between the ages of 18 and 75 years, inclusive, will been screened at the study site in the United States within 45 days of surgery/study treatment administration. Subjects who meet the selection criteria and are eligible to participate in the study will be required to return to the study center for surgery.

The study will be conducted in two parts:

- Inpatient period which continues to 96h after completion of study treatment injection (T0) or T96h.
- Outpatient period which begins on discharge from the inpatient unit through various follow up visits to D29±2 (W4) after surgery, or if necessary for ongoing safety assessments, to D36±2 (W5).

Subjects will be undergoing unilateral transpositional first metatarsal osteotomy for the correction of hallux valgus deformity (bunionectomy or BUNX). The surgery is to be performed under light to moderate sedation anesthesia (what constitutes this level of sedation and the additional anesthetic medications used per discretion of the anesthesiologist). In accordance with standard of care, light to moderate sedation will be supplemented with a Mayo block to produce surgical anesthesia and postoperative analgesia. After administering light to moderate sedation, but prior to surgery, perform a Mayo block by infiltrating 0.5% bupivacaine hydrochloride (up to 30 mL total volume, 150 mg) at least 3 cm proximal to the "surgical site". The Mayo block should be performed at 15-30 minutes prior to study treatment dosing. "Surgical site" is defined as the area extending approximately 2-3 cm in all directions (lateral/medial/proximal/distal) from the incision site and surrounding tissues which may be affected by the infiltration of study treatment.

After the surgery, subjects will be monitored for 96 hours in an inpatient unit. Safety and efficacy evaluations will be performed. After the first week of enrollment, subjects may be enrolled for the pharmacokinetic (PK) portion of the study and have samples drawn prior to CA-008 injection and at various time points over 24h after surgery until the target of 48 PK subjects (12 per treatment group) are enrolled and complete PK assessments. In the event that a subject cannot complete their PK assessments the Unblinded Randomization Contact will provide a replacement randomization number for the site. Subjects will be required to meet certain pre-specified criteria prior to discharge. After completing the assessments through T96h hours after study treatment administration and prior to discharge from the inpatient unit, the site will review with the subject the use of a diary for at-home use to record pain assessments and medication use (including pain medication) at home.

In their outpatient diary, subjects will assess their current pain intensity at rest and after ambulation each morning (08:00 ±3 hours), and each evening (20:00 ±3 hours) using the NRS.

The dose and time of any medication the subject takes, whether to treat their pain or for any other reasons, will also be recorded. Subjects are instructed to return to the study center on D8±1, D15±2 (W2) D29±2 (W4), and D36±2 (W5) for follow-up assessments. Unscheduled visits may be scheduled at any time if warranted due to the subject's complaints or condition per investigator discretion. Assessments performed at Unscheduled Visits will be at the discretion of the investigator.

A subject is free to withdraw his/her consent and discontinue participation in the study at any time for any reason. Subjects who elect to discontinue study participation during the inpatient phase of the study, will be asked to continue with assessments through T96h if they have not elected to withdraw from all aspects of study participation. Subjects who elect to discontinue participation after discharge from the inpatient unit but prior to D8 (W1) will be considered to have terminated as of the date of their election, however they will be asked to return to the site to reassess the surgical site for wound healing.

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), 36(±2 days)[1]

[1] Day 36 visit will occur if insufficient wound healing is assessed by the investigator at the Day 29 visit.

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

2.2.1   Study Population

The study population will consist of approximately 144 subjects (36 per treatment group) between the ages of 18 and 75 years who are planning to undergo an elective unilateral BUNX and otherwise meet eligibility criteria (as described in the protocol Sections 10.1 and 10.2) may be considered for enrollment into the study.

2.2.2   Treatment Regimens

Study Material

The proposed doses of CA-008 to be evaluated in this study are:

- CA-008, 0.7 mg in 14mL of saline (0.05 mg/mL)
- CA-008, 2.1 mg in 14mL of saline (0.15 mg/mL)
- CA-008, 4.2 mg in 14mL of saline (0.30 mg/mL)

Comparator Group

- The placebo will use the same 14mL volume.

2.2.3   Treatment Group Assignments or Randomization

The study will be conducted in a randomized, double-blinded and placebo-controlled manner. The study includes 4 treatment groups (3 active and 1 placebo group). Subjects who meet the enrollment criteria will be randomly allocated in a 1:1:1:1 ratio to receive either active drug or placebo. Randomization will be accomplished manually on the day of surgery.

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. Prior to randomization, subjects must meet all inclusion and not meet any exclusion criteria (as described in Sections 10.1 and 10.2). Once any subject number or randomization number is assigned, it cannot be reassigned to any other subject.

2.2.4   Sample Size Determination

In the previously completed Phase 1 ascending dose safety study in bunionectomy (CA-008 vs. placebo), the mean difference between CA-008 (all dose groups combined) and placebo for the area under the curve (AUC) from 24 to 96 hours was -120. The standard deviation (SD) estimates for the six treatment arms in this study ranged from 70 to 190 with a median SD of 108. For the primary endpoint (AUC0 to 96h), the true treatment difference between the 4.2 mg CA-008 group and the placebo group is assumed to be equal to -100 and the assumed true SD is equal to 130. For these assumptions, and based on the use of a two-sided, two-sample comparison of means at the alpha=0.05 level of significance, a sample size of 36 subjects per arm will provide 90% power. Thus, the target sample size is 144 subjects.

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.

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. 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. 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 throughout the study analysis:

- Time 0 (T0) is the time of completion of study drug administration.
- 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.
- Duration of an AE will be computed in days for AEs lasting longer than 24 hours, and as hours for AEs lasting less than 24 hours. Duration in hours will be calculated as the stop date/time of the event minus the start date/time. Duration in days will be calculated by using stop date minus the start date +1 if AE occurs on or after taking study medication. If AE occurs prior to the study medication, then the duration will be calculated by using stop date minus the start date; If reported as ongoing at the time of database lock, the duration will be calculated using the date of the last visit or the last date of any AE for the subject in the database, whichever is later. Missing dates will be imputed as described in Table 8-1.
- 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.
- If duplicate values are obtained at a given visit (e.g., repeated vital sign measurements), the last value will be used unless it is noted that the measurement was in error for that value. 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

Six analysis populations are defined as follows:

- **Intent-to-treat (ITT)** population: all subjects who are randomized. Subjects will be analyzed according to the treatment they were randomized to.
- **Modified intent-to-treat (mITT)** population: all subjects who receive a full dose of study treatment and complete the first 3 pain assessments (through T2h). Subjects will be analyzed according to the treatment they were randomized to.
- **In patient study completer (Inpatient CP):** all subjects who receive a full dose of study treatment and complete the inpatient assessment period (through T96h). Subjects will be analyzed according to the treatment they were randomized to.
- **Study Completers (CP):** all subjects who receive a full dose of study treatment and complete the entire study period through D29±2/W4. Subjects will be analyzed according to the treatment they were randomized to.
- **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".
- **Pharmacokinetic (PK)** population: All randomized participants who received a full dose of study drug and complete all PK assessments through the first 6 hours (T6h) time point. Note, subjects who fail to complete these PK assessments will be replaced.

Analysis populations will be determined before study unblinding.

The primary and secondary efficacy analyses will be performed using mITT population. Efficacy analyses will also be carried out using ITT, Inpatient CP and/or CP populations for selected endpoints as appropriate. Baseline characteristics will be summarized using ITT population and safety endpoints will be summarized using Safety population. PK summaries will be presented using the 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

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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 American Society of Anesthesiologists (ASA) physical status, target foot (Left/ Right), height, weight (kg), and body mass index (BMI; kg/m^2). Demographics and baseline characteristics will be presented in a by-subject listing and summarized overall and by treatment group using ITT 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 with missing stop dates 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 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:

Compliance (%) =

$$\frac{(N \text{ of non-missing NRS recorded on Diary})}{(N \text{ of Expected NRS from Diary})} \times 100$$

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 dose-escalation 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 the next 4 hours is considered invalid. Therefore, 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 4-hours 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 4 hours 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 is taken at 1pm, all protocol-scheduled NRS will be imputed with the appropriate NRS value up to and including through 5pm. 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.

For subjects who take prohibited medication, NRS results collected after taking the prohibited medication will not be used for AUC calculations but will be imputed according to the methods used for discontinued subjects.

 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 or take prohibited medication prior to Day 15, scheduled assessments will first be imputed using the worst prior pain score carried forward (WOCF).

Two sensitivity analyses will be performed to evaluate the robust of the primary result:

1) AUC will be calculated where assessments after drop out will be imputed using LOCF, using the last scheduled non missing pain score prior to drop out.
2) AUC will be calculated where assessments after dropping out will be imputed using the median score from the remainder of subjects in the group continuing in the study.

For secondary continuous efficacy endpoints, similar methods as the primary analysis will be used. For categorical endpoints, when assessments are imputed for data after a subject discontinues from the study, a WOCF method will be used.

7.2 Assessment Time Windows

For calculations of all AUC endpoints (including the primary endpoint), rate of consumption of rescue and time to first rescue medication endpoints, the <u>actual dates/times of the assessments</u> will be used in calculations. Thus, while the NRS are intended to be collected at the pre-defined protocol scheduled time points (eg, 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 Adjustments for Multiplicity

All efficacy endpoints will be listed in data listings. Unless otherwise indicated, two-sided p values will be reported.

If the outcome of the primary analysis of the primary efficacy endpoint (AUC_{0to96h}) is with a two-sided p-value of <0.05, then key secondary endpoints will be compared between the 4.2 mg CA-008 and placebo. These key secondary endpoints are:

- Percentage of subjects who do not require opioids or are opioid free (OF) from T0 to T96): $OF_{0 \text{ to } 96h}$

- Total opioid consumption (in daily oral morphine equivalents) = OC from T0 to T96h: $OC_{0 \text{ to } 96h}$
- Using NRS at rest: $AUC_{0 \text{ to } W1}$

Each of the above comparisons will be made using a two-sided test at the alpha=0.05 level of significance. Once a p value of >0.05 occurs, all subsequent key secondary endpoints analyses in the hierarchy will be exploratory rather than confirmatory. All other efficacy analyses will be conducted using a significant 2-sided p-value of 0.05, without adjustment for multiplicity.

7.4 Efficacy Endpoints

Efficacy will be evaluated using the numeric rating scale of pain intensity (NRS) scores (at rest and with ambulation), PGE, IGE, Rescue Use and Healthcare utilization. A variety of time-specific summed pain intensity assessments (area under the curve (AUC) for pain intensity) will be calculated using NRS to compare treatment difference between CA-008 and placebo group.

7.4.1 Primary Efficacy Endpoint

- Area under the curve (AUC) of the numeric rating scale of pain intensity (NRS) from 0 to 96 hours at rest ($AUC_{0 \text{ to } 96h}$).

7.4.2 Key Secondary Efficacy Endpoints

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

- Percent of subjects who do not require opioids or are opioid free (OF) from 0 to 96 hours ($OF_{0 \text{ to } 96h}$)
- Total opioid consumption (OC) (in daily oral morphine equivalents) from 0 to 96 hours ($OC_{0 \text{ to } 96h}$)
- AUC of NRS through Week 1 at rest ($AUC_{0 \text{ to } w1}$)

7.4.3 Other Efficacy Endpoints

- AUC of subject's NRS will be examined over various time periods: $AUC_{0 \text{ to } 6h}$, $AUC_{0 \text{ to } 12h}$, $AUC_{0 \text{ to } 24h}$, $AUC_{0 \text{ to } 120h}$, $AUC_{0 \text{ to } w1 \text{ (walking)}}$, $AUC_{0 \text{ to } w2}$, $AUC_{0 \text{ to } w2 \text{ (walking)}}$, $AUC_{12 \text{ to } 24h}$, $AUC_{24 \text{ to } 48h}$, $AUC_{24 \text{ to } 72h}$, $AUC_{24 \text{ to } 96h}$, $AUC_{96 \text{ to } 120h}$, $AUC_{96h \text{ to } w1}$, $AUC_{24h \text{ to } w1 \text{ (walking)}}$, $AUC_{96h \text{ to } w2}$, $AUC_{96h \text{ to } w2 \text{ (walking)}}$.
- Time-specific ("milestone") mean pain intensity NRS at 6, 12, 24, 28, 72, 96, 120, 144, and 168 hours
- Time-specific ("milestone") mean pain intensity NRS by site at 6, 12, 24, 28, 72, 96, 120, 144, and 168 hours
- OC over following time periods: $OC_{24 \text{ to } 48h}$, $OC_{24 \text{ to } 72h}$, $OC_{24 \text{ to } 96h}$.
- OF over following time periods: $OF_{24 \text{ to } 96h}$, $OF_{96h \text{ to } w1}$, $OF_{96h \text{ to } w2}$.
- Time to first use of rescue medication ($TTFR_{after \ T0}$) and first use after 24 hours ($TTFR_{after \ T24h}$). For the analysis of time to use of rescue medication, only OPIOID rescue medication will be considered,
- Analgesic consumption (AC) from T96h to W1 ($AC_{96h \text{ to } W1}$) and $AC_{96h \text{ to } W2}$.
- Patient global evaluation (PGE) comparing the percentage of subjects reporting (poor or fair) versus (good or excellent) responses and the percentage reporting each category of response at W1, W2 and W4.
- Investigator's global evaluation (IGE) comparing the percentage of those reporting (poor or fair) versus (good or excellent) responses and the percentage reporting each category at W1, W2 and W4.
- Number and percentage of subjects who drop out due to an AE or lack of efficacy (LOE) during the inpatient period: $LOE_{24 \text{ to } 96h}$, $LOE_{0 \text{ to } 96h}$.

- Health care utilization after discharge from the inpatient unit: $HCU_{96h\ to\ W2}$ and $HCU_{96h\ to\ W4}$. (Not included in this SAP)

7.5   Analysis Methods

7.5.1   NRS Measurements

The NRS is an 11-point scale with anchors 0 (no pain) and 10 (worst possible pain). Subjects should be at rest for at least 10 minutes prior to completing NRS resting assessments and have ambulated approximately 10 yards within 15 minutes prior to completing NRS ambulation assessments.

During the inpatient stay, NRS pain assessments will be collected at Hours 0.5, 1, 2, 4, 6, 8, 12, 16, 20, 24, and every 4 hours (if awake at time of assessment and if no rescue opioid had been administered in the past 4 hours) until discharge from the inpatient unit. Pain scores may be skipped between the hours of midnight and 6 a.m., but the subject may not miss two consecutive assessments. A pre-rescue NRS will be collected prior to each use of rescue. An additional NRS assessment must be obtained 4 hours (±15 min) after every rescue dose even if this time point occurs between midnight and 6 a.m. Hours 12, 24, 48, 72 and 96 assessments must be completed even if the subject is asleep at these times. Note, a 5-minute window is allowed for the collection of each assessment in the first 4 hours after the end of surgery, after which will be a 15-minute window allowed.

During the outpatient period (up to Day 15), NRS will assessed twice daily at approximately 08:00 (±3h) and 20:00 (±3h) at rest and with ambulation of approximately 10 yards. The results and the actual time of assessments will be documented in subjects' diary. In addition, the subject will be asked to complete a pre-rescue NRS each time they take rescue.

Mean NRS scores over time (in-patient and diary) will be summarized and graphed over time by treatment. NRS over time by each subject will also be displayed graphically.

7.5.2   AUC Outcomes

All AUC calculations will be done using the standard trapezoidal rule

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

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. A similar calculation of AUC and handling of missing data will be performed for the NRS scores with ambulation and are designated as $AUC_{0-x\ (walking)}$. Both pre-rescue and post-rescue scores will be used in the AUC calculations.

AUC values will be analyzed using a 1-factor (treatment) analysis of variance (ANOVA) model with treatment as the main effect. In addition to the comparisons between each CA-008 group and the placebo group, the test for a linear trend across dose groups will be carried out using the contrast of -1.75, -1.05, 0.35 and 2.45 for placebo, 0.7 mg, 2.1 mg and 4.2 mg group, respectively.

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. Comparisons of individual treated group response may be presented for certain secondary AUC endpoints.

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

The primary analysis of the primary endpoint (($AUC_{0 \text{ to } 96h}$) and secondary AUC endpoints will be based on the mITT population. In addition, the primary and other AUC efficacy endpoints may be analyzed using inpatient CP and/or CP population as appropriate for sensitivity.

7.5.3　Opioid Free (OF) Outcomes

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 (4 levels) 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 ($OF_{0 \text{ to } 96h}$), 24-96 hours ($OF_{24 \text{ to } 96h}$), 96 hours to Week 1 ($OF_{96h \text{ to } w1}$) and 96 hours to Week 2 ($OF_{96h \text{ to } w2}$).

7.5.4　Total Opioid Consumption (in Daily Oral Morphine Equivalents)

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 7-1 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 7-1   Table of Equianalgesic Conversion

Opioid (Doses in mg)	Conversion Factor
Hydrocodone	1
Hydromorphone	4
Morphine	1
Oxycodone	1.5
Tramadol	0.1
Multiply the opioid dose by the conversion factor = morphine equivalent dose (MED): e.g., oxycodone 5 mgX1.5 = 7.5 mg MED	

Total opioid consumption will be calculated overall and for the same periods as the NRS AUC values: 0-96 hours ($OC_{0 \text{ to } 96h}$), 24-48 hours ($OC_{24 \text{ to } 48h}$), 24-72 hours ($OC_{24 \text{ to } 72h}$) and 24-96 hours ($OC_{24 \text{ to } 96h}$). in addition, analgesic consumption (AC) from T96h to W1 (AC96h to W1) and AC96h to W2 will also be summarized. An ANOVA with treatment arm as the main effect will be performed and the same types of comparisons as described in Section 7.4.1 will be presented. A separate summary containing only subjects that have taken at least one dose of rescue will be performed if warranted.

7.5.5   Time to First Use of Rescue Medication

For the analysis of time to use of rescue medication, only OPIOID rescue medication will be included,

The time to first rescue will be measured from Time 0 (time of completion of study drug administration) and 24 hours post-dose. If a subject does not take rescue medication but prematurely discontinues from the study, then for analysis purposes the subject's observation time will be the time of the discontinuation. The observation time will be considered to be a rescue event if the discontinuation was due to LOE, otherwise, it will be considered a censored observation.

The distributions of time to first rescue in each treatment group will be presented graphically using Kaplan-Meier plots.

If data warrant, a summary table will present the number of subjects receiving rescue medication, number of censored subjects, median time to first dose of rescue, and 95% confidence intervals of the medians by treatment groups. Individual times to event will be listed. Subjects will be followed at the time of discontinuation if no rescue medication was received prior to discontinuation. For the time to first rescue medication after 24 hours post-dose, subjects will be censored at 24 hours if the subject drop out the study prior to Hour 24.

Time to second rescue will also be explored for subjects who receive the first rescue prior to 60 minutes post-dose. Subjects will be censored at the time of discontinuation if the subject receives only 1 rescue mediation. The observation time will be considered to be a rescue event if the discontinuation was due to LOE, otherwise, it will be considered a censored observation

7.5.6   PGE and IGE

The proportions of subjects in each individual PGE or IGE category will be summarized by treatment group and analyzed using the Cochran-Mantel-Haenszel (CMH) mean score test (using equally spaced scores) at each time point (Weeks 1, 2 or 4) to compare treatments across the 4 levels of outcomes (poor, fair, good, or excellent). In addition, Fisher's exact test will be performed to compare treatments across 2 levels of outcomes (Poor/Fair versus Good/excellent).

Individual PGE and IGE scores will be listed.

7.5.7   Number and Percentage of Subjects Who Drop Out due to AE or Lack of
Efficacy (LOE) During the Inpatient Period

Proportion of subjects who drop out of the study due to AE or LOE during the inpatient periods (24 to 96 ($LOE_{24 \text{ to } 96h}$) and 0 to 96 hours ($LOE_{0 \text{ to } 96h}$)) will be analyzed using Fisher's exact tests. If a subject drops out of the study due to AE or LOE, it is assumed that drop out is pain related. The reasons for discontinuation as documented on the eCRF end of study page will be used to determine the subjects who drop out for AE or LOE. Subjects who drop out of the study prior to 24 hours will be excluded from $LOE_{24 \text{ to } 96h}$ analysis.

A summary table will present the active vs. placebo group proportions, 95% confidence intervals and two-sided Fisher's exact p-values for the difference in proportions between each active group and placebo.

7.5.8   Healthcare Utilization (HCU)

HCU costs defined as an overall summary of costs related to prescription medications will be collected by the sponsor separate from the eCRF and are not covered by this SAP.

7.5.9   Percent of Subjects Taking Rescue / Use of Rescue Medication over Time

Subjects will be counted as having taken rescue on any particular day based on the rescue medication page of the eCRF and the at home rescue diary. If additional medications, other than the study rescue medications, appear on the concomitant medications page and can be identified as having been taken for bunion pain, those medications will also be counted.

The proportion of subjects taking rescue will summarized for each study day through Day 15.

In addition, the proportion of subjects taking any rescue medication during the following periods: 0-96 hours, 24-48 hours, 24-72 hours, 24-96 hours, 96h to Week 1 and 96h to Week 2 and overall will be summarized and will be analyzed using Fisher's exact tests.

Separate summaries for opioid and non-opioid rescue use will be presented if sufficient data are present in the groups.

8   SAFETY EVALUATION

8.1   Overview of Safety Analysis Methods

All safety outcomes will be summarized using the safety population. Safety outcomes include:

- Incidence of treatment emergent adverse events (TEAEs) or treatment emergent serious adverse events (SAEs)
- Surgical site assessment/wound evaluations
- Physical examination (PE) of the lower extremities and vital signs, including neurosensory testing of both lower extremities
- Electrocardiogram (ECG) results
- Clinical laboratory test results

8.2   Adverse Events

Any untoward medical event that occurs after signing the informed consent form (ICF) is considered to be an adverse event (AE). All AEs will be recorded through 29 days (or 36 days as applicable) or ET, after the completion of surgery. SAEs will be recorded until 30 days after the 29 day follow up visit or ET, whichever occurs earlier. Treatment-emergent AEs are defined as AEs that start or worsen in severity after the end of study treatment infiltration (post T0). Verbatim terms used by investigators to identify AEs in the CRFs will be mapped to the appropriate preferred term (PT) and system organ class (SOC) using a standardized coding dictionary (MedDRA Version 21.0). All coding will be reviewed prior to database lock. All recorded AEs will be listed, but only TEAEs will be summarized.

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 8-1 will be used to impute any missing dates/times:

Table 8-1   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   Surgical Site Assessment/ Wound Evaluation

Surgical site is defined as the area extending approximately 2-3 cm in all directions (lateral/medial/proximal/distal) from the incision site and surrounding tissues which may be affected by the infiltration of the Investigational Product.

At T96h prior to discharge, 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.". Surgical site wound status will be evaluated prior to discharge from the inpatient unit (T96h) and on Days 8, 15, and 29 or if necessary Day 36. Surgical site wound status will be assessed for erythema, drainage, edema, induration, and hematoma using a 5-point scale (0-4) where 0 means none and 4 means severe.

The surgical site and surgical wound assessment results will be listed and will be summarized by treatment and visit.

8.4 Physical Examination

A complete medical history and physical examination including all major body systems will be performed at Screening. In addition, an 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 (within 4 hours of discharge), and Days 8, 15 and 29/ET after the administration of study medication.

Physical examination results will be listed for individual subjects.

8.5 Vital Signs

Vital signs results including blood pressure (systolic and diastolic; mmHg), pulse rate (beats per minute), respiration rate (breaths/min), and body 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.

8.6 Neurosensory Assessment

Neurosensory testing at site of incision and the skin surrounding the incision will be performed at T96h (within 4 hours of discharge) and then as an outpatient on Days 8, 15, and D29/ET or if necessary Day 36.

The neurosensory assessment results will be listed and the number of subjects with normal/abnormal assessments will be summarized descriptively by treatment, target foot and time point.

8.7 ECG Examination

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

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

8.8 Clinical Laboratory Evaluation

Clinical laboratory tests (blood chemistry, hematology and urinalysis) will be collected at screening and before discharge from the inpatient unit (T96h). All results will be listed. For each individual lab test value, 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.

8.9 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".

8.10 Subject Pain Assessment Training and Surgery Details

Patient pain assessment training and surgery details will be documented in CRFs and will be listed for each subject.

9 PHARMACOKINETIC EVALUATION

It is anticipated that approximately 1/3rd of enrolled subjects at each site will participate in the PK study (48 in total; 12 in each treatment group).

Blood draws for PK samples will be collected at baseline (within the 30 minutes before the start of study treatment dosing), and at minutes 5, 10, 15, 30, 45, hours 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 (a total of 17 samples). Actual sampling times will be used to calculate following plasma bupivacaine-derived PK parameters using noncompartmental analysis for CA-008, capsaicin and CA-101:

- C_{max}: The maximum measured plasma concentration, obtained directly from the data without interpolation
- C_{last}: Last observed (quantifiable) concentration
- T_{max}: Time of C_{max}
- $t_{1/2}$: The apparent first-order terminal elimination half-life, calculated as $0.693/\lambda_z$
- T_{lag}: Time delay between drug administration and first measurable (above lower limit of quantitation) concentration
- T_{last}: Time of occurrence of C_{last}
- λ_z: Terminal first-order elimination rate constant
- AUC_{0-t}: Area under the plasma concentration-time curve from time 0 to the last measurable concentration (where time is post dose), calculated by the linear trapezoidal method
- $AUC_{0-\infty}$: Area under the plasma concentration-time curve, from time of dosing to infinity.
- AUC_{last}: Area under the plasma concentration-time curve, from time of dosing to the time of the last measurable concentration

PK concentration data will be listed. There will be a separate PK Analysis Plan that will describe PK analyses.

10   OTHER ANALYSES

Any additional analyses not included in this SAP conducted after database lock will be considered exploratory and identified as Post Hoc in the CSR.

11   INTERIM ANALYSES

There are no planned interim analyses for this study.

12   CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

Any deviations from the statistical plan will be described and a justification given in the CSR.

13   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.

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14 APPENDICES

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