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STATISTICAL ANALYSIS PLAN

A Phase 1/Single Ascending Dose (SAD) Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of a Single Intraoperative Administration of CA-008 in Subjects Undergoing Unilateral Transpositional First Metatarsal Osteotomy for the Correction of Hallux Valgus Deformity

Protocol Number: CA-PS-2017-101

Protocol Version 3.0 Amendment 2 (30JAN2018)

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TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES 6
LIST OF ABBREVIATIONS (COMMONLY USED) 7
1 PURPOSE OF THE ANALYSES 9
2 PROTOCOL SUMMARY 9
2.1 Study Objectives 9
2.1.1 Primary Objectives 9
2.1.2 Secondary Objective 9
2.2 Overall Study Design and Plan 9
2.2.1 Study Population 12
2.2.2 Treatment Regimens 12
2.2.3 Treatment Group Assignments or Randomization 13
2.2.4 Sample Size Determination 13
3 GENERAL ANALYSIS AND REPORTING CONVENTIONS 13
4 SUBJECT POPULATIONS 14
4.1 Analysis Populations 14
4.2 Disposition of Subjects 15
4.3 Protocol Deviations 15
5 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS 15
5.1 Demographics and Baseline Characteristics 15
5.2 Medical/Surgical History 16
5.3 Prior and Concomitant Medications 16
6 MEASUREMENTS OF TREATMENT EXPOSURE and COMPLIANCE 16
7 EFFICACY EVALUATION 18
7.1 Handling of Dropouts or Missing Data 18
7.2 Assessment Time Windows 18
7.3 Exploratory Efficacy Endpoints 18
7.4 Analysis Methods 19
7.4.1 AUC Outcomes 19

7.4.2 Average Daily NPRS score of 2 daily diary assessments 19
7.4.3 Total daily opioid consumption (in oral morphine equivalents) 20
7.4.4 Proportion of patients who drop out of the study due to inadequate analgesia from Day 1 to 15. 21
7.4.5 Brief Pain Inventory-short form (BPI-SF) 21
7.4.6 PGE and IGE 21
7.4.7 Time to First Use of Rescue Medication 22
7.4.8 Percent of Subjects Taking Rescue / Use of Rescue Medication over Time 22
8 SAFETY EVALUATION 22
8.1 Overview of Safety Analysis Methods 22
8.2 Adverse Events 23
8.3 Clinical Laboratory Evaluation 25
8.4 Vital Signs 25
8.5 Physical Examination 25
8.6 Surgical Site Assessment 25
8.7 Neurosensory Assessment 25
8.8 ECG Examinations 25
8.9 Drugs of Abuse and Alcohol Screens, Pregnancy Test. 25
8.10 Patient Pain Assessment Training and Surgery Details 26
9 PHARMACOKINETIC EVALUATION 26
10 OTHER ANALYSES 27
11 INTERIM ANALYSES AND DATA MONITORING 27
12 CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL 27
13 REFERENCES 27
14 APPENDICES 28
14.1 Tables, Figures and Listings for Final Study Report 28
14.1.1 Tables 28
14.1.2 Figures 30
14.1.3 Listings 30

LIST OF IN-TEXT TABLES AND FIGURES

Table 2-1 Protocol-Specified Visits and Visit Windows 12

Table 7-1 Table of Morphine Milligram Equivalents 20

Table 8-1 Table of Imputation Rules for Missing AE Start Dates 24

LIST OF ABBREVIATIONS (COMMONLY USED)

ADaM	Analysis Data Model
AE	Adverse Event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ASA	American Society Of Anesthesiologists
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
BP	Blood Pressure
BPI-SF	Brief Pain Inventory – Short Form
CDER	Center for Drug Evaluation and Research
CMH	Cochran Mantel Haenszel Test
CRF	Case Report Form
CSR	Clinical Study Report
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EOS	End of Study
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
MEQ	morphine milligram equivalents
MMRM	Mixed Model for Repeated Measures
NPRS	Numerical Pain Rating Scale

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
TFLs	Tables, Figures and Listings
UDS	Urine Drug Screen
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-2017-101 Version 3.0 Amendment 2 (30JAN2018) 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 Objectives

- To evaluate the safety and tolerability of a single intraoperative administration of CA-008 in subjects undergoing bunionectomy.
- To evaluate the pharmacokinetics of a single intraoperative administration of CA-008.

2.1.2 Secondary Objective

- To evaluate the efficacy of CA-008 in the management of acute postoperative pain in subjects undergoing bunionectomy.

2.2 Overall Study Design and Plan

This is a single-center, randomized, double-blind, placebo-controlled, single ascending dose, sequential-group Phase 1 study in subjects undergoing bunionectomy. This trial is designed to determine the recommended dose and define the toxicity profile of CA-008.

The study will be conducted utilizing an escalating dose cohort design, with sequential groups of 8 subjects each. Within each dose cohort, 6 subjects will be randomized to active, and 2 will be randomized to placebo. The initial cohort will receive the lowest planned dose of CA-008 in a fixed

volume of administration, and will employ sentinel dosing, whereby the first 4 subjects in the first cohort will be dosed initially, before the remaining 4 subjects are dosed. If the available safety assessments for the first 4 subjects are acceptable through the first 24 hours, then the second group of 4 subjects will be dosed. Subsequent cohorts will not include sentinel dosing. There will be at least a 6-day period between cohorts, to ensure a minimum of 3 days to review safety data from the last subject in a cohort and to allow the meeting of the Data Monitoring Committee (DMC) to review the safety data from the entire cohort prior to making a decision for dose escalation. Dose escalation, or continuation of dosing, will not occur if subjects in a cohort experience intolerable treatment related AEs on active drug, as defined in the protocol.

Subjects will be screened for participation at the study site in the United States within 28 days of surgery/study drug administration. The following screening assessments will be completed: informed consent, inclusion / exclusion, demographics, medical and surgical history, prior/current medications, physical exam (PE), x-ray of surgical site, neurosensory exam of the foot / great toe (bilateral), clinical laboratory tests (chemistry/coagulation, hematology, and urinalysis), urine drug screening (UDS), alcohol breath test, serum pregnancy test, surgical site assessment, vital signs (resting blood pressure, resting pulse, oral temperature and resting respiration rate), 12-lead electrocardiograms (ECGs), subject pain assessment training, and adverse event (AE) assessment.

Subjects who meet the selection criteria at the Screening Visit and are eligible to participate in the study will be required to return to the study center within 28 days of screening. At that time, the screening assessments will again be performed (minus the x-ray and ECG) to confirm continued eligibility, and a blood draw for PK analysis will be collected. If eligible, the subject will then be randomized to treatment.

Subjects will then undergo surgery. During surgery, a total of 10 mL (for Cohorts 1-4) or 14 mL (for Cohort 5) of the investigative product will be administered into the surgical site in two applications. At time of closure of capsule, infiltration of deep soft tissue and capsule with a total of 6 mL (for Cohorts 1-4) or 9 mL (for Cohort 5) volume and instillation at cut bone with a total of 2 mL volume will be done. Then, following closure of the capsule and prior to closure of the skin and subcutaneous layer, the wound will be instilled for Cohorts 1- 4 with 2 mL volume (study drug is applied to all exposed surfaces prior to subcutaneous and skin closure) and for Cohort 5 with 2 mL of study drug will be instilled into the space under closed capsule and 1 mL of study drug applied to all exposed surfaces prior to subcutaneous and skin closure.

Time 0 will be defined as the time of completion of study drug administration. After the surgery, subjects will be monitored for 48 hours at the trial site. Safety and efficacy evaluations will be performed as follows:

- Concomitant medications and AEs will be recorded.
- Pain intensity assessed with the Numerical Pain Rating Scale (NPRS), an 11-point scale where 0 is “No Pain” and 10 is “Worst Pain Imaginable: at 0.25, 0.5, 0.75, 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 hours after the administration of study

medication. Assessments between the hours of 00:00 and 06:00 may be skipped if the subject is sleeping; however, consecutive assessments may not be skipped, and the subject must be awakened to complete the Hour 12, Hour 24, and Hour 48 assessments.

- Vital signs: 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 hours after the administration of study medication. Assessments between the hours of 00:00 and 06:00 may be skipped if the subject is sleeping; however, consecutive assessments may not be skipped, and the subject must be awakened to complete the Hour 12, Hour 24, and Hour 48 assessments must be completed even if the subject is asleep.
- Physical exam: 1, 24, and 48 hours after the administration of study medication.
- ECG: 1.5 hours after the administration of study medication.
- Surgical Site assessment: 24 and 48 hours after the administration of study medication.
- Neurosensory Exam of the Foot / Great toe (bilateral): 24 and 48 hours after the administration of study medication.
- Clinical laboratory tests (chemistry/coagulation, hematology, and urinalysis): 1.5 hours after the administration of study medication.
- Blood draw for PK analysis: are at baseline (before dosing), and at 5 minutes, 15 minutes, 30 minutes, 45 minutes, and 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, and 48 hours after dosing.

Subjects with inadequately controlled pain may request rescue at any time. However, subjects will be encouraged to receive rescue medication only with an NPRS ≥ 4. Additionally, subjects should be encouraged to wait at least 1 hour after completion of surgery (i.e. completion of sutures) before utilizing pain rescue medication, if possible. Pain intensity (NPRS) will be completed within 15 minutes prior to use of pain rescue medication. While in-clinic, subjects will be treated with the prescribed analgesic regimen (oxycodone 5 mg every 2 hours); however, if subjects do not get adequate analgesic relief they will be discontinued from the efficacy portion of the study. At this point, subjects will receive standard of care analgesics (which may or may not include intravenous opioids). Regardless of discontinuation status, subjects will be followed for safety. Discontinuation affects the computation of the analgesic endpoint only. From Day 3 to 15, over-the-counter standard of care analgesics may be used for management of pain. If needed for management of NPRS score of 4 or higher, oxycodone 5 - 15 mg every 4 - 6 hours.

After completing the assessments through 48 hours after study medication administration, the diary for at-home use will be reviewed and subjects will be discharged from the study center with the diary to record pain assessments and pain medication at home. Subjects will be provided routine standard of care for pain management after discharge from the study center. In their diary, subjects will assess their pain intensity once in the morning (08:00 ±4 hours), and once in the evening (20:00 ±4 hours) using the NPRS. Subjects will also record any medication they take to

treat their pain, and will capture an additional NPRS within 15 minutes prior to each dose of pain medication.

Subjects will return to the study center on Day 8 [±1 day], Day 15 [±2 days] and Day 29 [±2 days], or at the time of discontinuation, for the following assessments: subject home diary review (pain intensity and pain medication at Day 8 and 15 only), in-clinic pain intensity (NPRS), vital signs, surgical site assessment, neurosensory exam of the foot / great toe (bilateral), concomitant medication use, AE assessment, brief pain inventory-short form (BPI-SF), patient global evaluation (PGE), and investigator global evaluation (IGE).

Additionally, on Day 29 [±2 days], or at the time of discontinuation, subjects will have a foot x-ray and a physical exam.

If required due to insufficient wound healing noted at the Day 29 visit, subjects will return to the study center on Day 36 [±2 days] for the following assessments: surgical site assessment, neurosensory exam of the foot / great toe (bilateral), concomitant medication use and AE assessment.

A subject is free to withdraw his/her consent and discontinue participation in the study at any time for any reason.

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 -28 to -1
In-Patient	Days 1 and 2
Follow-up	Days 8(±1 day), 15(±2 days), 29(±2 days)
Additional follow-up (if necessary)	Day 36(±2 days)

2.2.1 Study Population

The study population will consist of 40 healthy subjects between the ages of 18 and 65 years who require bunionectomy.

2.2.2 Treatment Regimens

Study Material

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

- CA-008, 0.5 mg in 10 mL of saline (50 µg/mL)
- CA-008, 1.0 mg in 10 mL of saline (100 µg/mL)
- CA-008, 2.0 mg in 10 mL of saline (200 µg/mL)

- CA-008, 3.0 mg in 10 mL of saline (300 µg/mL)
- CA-008, 4.2 mg in 14 mL of saline (300 µg/mL)

Comparator Group

- The placebo will be saline for injection.

2.2.3 Treatment Group Assignments or Randomization

The study will be conducted in a double-blinded manner. A computer-generated randomization scheme will be prepared prior to the study start. Subjects who meet the enrollment criteria will be randomly allocated in a 3:1 ratio to receive either active drug or placebo.

Upon enrollment, the site will assign each subject a 3-digit site-specific sequential screening number. The unique subject identification number will consist of a 3-digit original site number followed by a 3-digit screening number. The subject will keep the same number throughout the study. Upon randomization, a unique 4-digit study-specific randomization number will be assigned.

2.2.4 Sample Size Determination

The sample size is not based on statistical considerations but is considered appropriate for a Phase 1 dose ranging safety study.

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 cohort will be presented separately, along with a combined active dose group. Placebo subjects will be pooled across all cohorts in all summaries and analyses.

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 cohort, 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 specifications for the domain data sets and analysis data sets will be provided in a separate document.

The following conventions will be used throughout the study analysis:

- Time T0 is the time of completion of study drug administration.
- Assessment visit times are defined by time T0.
- Baseline value is defined as the last valid measurement prior to beginning study drug administration.
- 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 occur on or after taking study medication. If AE occur 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 number of days in the study is computed as: [Date of study completion or withdrawal minus the date of study drug administration (Day 1)] + 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).
- If a pre-rescue NPRS is recorded in the same minute as a rescue medication is recorded, the NPRS will be assumed to have occurred PRIOR to the administration of rescue.
- If a subject experiences inadequate analgesic relief and are discontinued from the efficacy portion of the study the date/time of the discontinuation will be assumed to be the date/time of the start of standard of care analgesic rescue.

4 SUBJECT POPULATIONS

4.1 Analysis Populations

Two analysis populations are defined as follows:

- Safety Population will include all randomized subjects who received any amount of study drug
- Pharmacokinetic (PK) population: All randomized participants who received any amount of study drug and have sufficient plasma concentrations for estimation of at least one PK parameter.

Membership in the safety analysis population will be determined before unblinding any study treatment codes. Membership in the PK analysis population will be determined after unblinding and receipt of the PK concentration and PK parameter data from the analytical lab. For all analyses, subjects will be analyzed by treatment group according to the actual product received during treatment, i.e., “as treated.”

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. Subjects who are discontinued from the efficacy portion of the study will also be presented.

A listing of CRF comments by time point and CRF section will also be presented.

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 CRFs and 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.

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, height, weight (kg), and BMI (kg/m^2). Demographics and baseline characteristics will be presented in a by-subject listing and summarized overall and by treatment group.

5.2 Medical/Surgical History

Medical and Surgical history, as collected at screening, will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 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 at screening and updated throughout the study as needed. Prior and concomitant medications will be coded using WHO/ATC classification index version September 2017. 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 48 hours after study medication administration, the diary for at-home use will be distributed to the subject to collect pain intensity (twice daily on NPRS) 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 (%) =

$$\frac{\textit{(N of non-missing NPRS recorded on Diary)}}{\textit{(N of Expected NPRS from Diary)}} \textit{ x 100}$$

Where the N of expected NPRS 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. NPRS recorded prior to a rescue use will not be included in this calculation of compliance.

For example, Subject A was discharged on Day 2, if this subject discontinues the study on Day 18, then the expected N of NPRS records on diary will be 36 (2 * (15-2)). Assuming Subject A had

10 NPRS available from his/her diary, then compliance for this subject would be 27.8% ((10/36) *100). However, if subject A had discontinued the study on Day 10 (prior to Day 15), then the expected N of NPRS for this subject would be 16 (2 * (10-2)) and compliance would be 62.5 % ((10/16) *100). A summary of compliance will be provided overall and by treatment group.

Compliance with recording an NPRS prior to rescue in the diary will be calculated as the number of NPRS 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 subjects who take protocol allowed rescue medication a windowed last pain score carried forward (LOCF) will be used. The pre-rescue pain score will be used to impute scheduled assessments for 4 hours following the rescue use. Intermittent missing pain scores (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 prior to Day 15, or who are discontinued from efficacy and given SOC analgesics for inadequate pain relief, scheduled assessments will first be imputed using the worst prior pain score carried forward (WOCF) using the worst scheduled non missing pain score prior to drop out within the AUC period being calculated (e.g., if the AUC being calculated includes hours 12-24, the worst observed pain score between hours 12 and 24 will be used). As a sensitivity, the AUC will also be calculated where assessments after drop out will be imputed using LOCF, using the last scheduled non missing pain score prior to drop out.

7.2 Assessment Time Windows

Safety assessment summaries will be based on the nominal protocol-specified assessment times. NPRS scores will be based on actual collection dates/times wherever possible. If no collection date/time is available the nearest protocol specified assessment time will be used.

7.3 Exploratory Efficacy Endpoints

- Area under the curve (AUC) of subject's NPRS will be examined over various time periods, including but not limited to: AUC(0-12), AUC(12-24), AUC(24-48), AUC(24-72), AUC(24-96), AUC(24h to Week 1), and AUC(24h to Week 2).
- Mean daily opioid consumption (in morphine equivalents) over the same time periods as the AUC calculations above.
- Proportion of patients who drop out of the study due to inadequate analgesia from Day 1 to 15.
- Brief Pain Inventory-short form (BPI-SF) scores at the Day 8 (Week 1), Day 15 (Week 2) and Day 29 (Week 4) or ET clinic visits.
- Patient Global Evaluation (PGE) at the Day 8 (Week 1), Day 15 (Week 2) and Day 29 (Week 4) clinic visits.

- Investigator Global Evaluation (IGE) at the Day 8 (Week 1), Day 15 (Week 2) and Day 29 (Week 4) clinic visits.
- Time to first use of rescue medication.
- Percent of days that rescue medication was used.

7.4 Analysis Methods

Formal hypotheses testing will be not conducted. All p-values will be considered nominal in this study and no adjustments for multiplicity will be performed. All efficacy analyses will be based on the safety population.

7.4.1 AUC Outcomes

All 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: $NPRS_i$ = NPRS at time i, and ($T_{i+1} - T_i$) is the Time difference in hours between time i and time i+1.

Missing NPRS 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. In addition to the individual comparisons between each of the five CA-008 groups and the placebo group, the test for a linear trend across dose groups will be carried out using the scores 0, 0.5, 1.0, 2.0, 3.0 and 4.2 for the placebo group and the five active groups, respectively.

The AUC analyses will be presented in a summary table with standard summary statistics for each dose cohort and placebo as well as active vs. placebo mean differences, standard errors, confidence intervals and comparison p-values as appropriate. Comparisons of individual dose cohorts for dose response may be presented for certain secondary AUC endpoints.

Mean NPRS scores over time (in-clinic and diary) will be graphed over time by dose cohort. NPRS over time by each subject may also be displayed graphically as warranted. The individual NPRS and the computed AUC variables will be listed for all individual subjects.

7.4.2 Average Daily NPRS score of 2 daily diary assessments

The Average Daily NPRS scores will be computed for each subject using the NPRS scores recorded in the take-home diary from study days 3 – 15.

The Average Daily NPRS will be the average of the AM and PM scores within each day. If individual AM or PM NPRS scores are missing, the score that is present will be used as the daily average. If both scores are missing for any day, then that day will not have a daily average. The mean across all subjects of the average daily scores on each day will be graphed by day and

dose cohort. If rescue medication was taken within 4 hours of the AM or PM PI assessment, it will be replaced with the pre-rescue NPRS (if available) in the daily average.

The average daily NPRS scores will be analyzed using the same type of ANOVA model as described in Section 7.4.1 at each time point. In addition, actual date/time NPRS assessed over the outpatient period from T48h onward will be used to calculate AUC between 24 hours and Week 1 and between 24 and Week 2 and compared versus placebo.

7.4.3 Total daily opioid consumption (in 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. For summaries of opioid consumption, the rescue medications for subjects who are discontinued from the efficacy portion of the study will be counted two ways. First, all medications on days up to and including the date of the discontinuation from efficacy will be included, but medications that were continued after the date of discontinuation from efficacy will not be counted. In a second analysis, all the medication for these subjects will be counted, regardless of whether it was taken before or after the subject discontinued from the efficacy portion.

Table 7-1 will be used to calculate the morphine milligram equivalents (MEQ) for each medication. The total opioid consumption for each day for each subject will be calculated as the sum of the MEQs of all of the medications taken on that day. For example, if a subject takes 5 MEQ morphine on Day 1 and Day 2, and 10 MEQ of Oxycodone on Day 2, the total consumption for Day 1 is 5 MEQ, and the total consumption for Day 2 is 15 MEQ. 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 Morphine Milligram Equivalents

(from cdc.gov/drugoverdose/pdf)

Opioid (Doses in mg/day)	Conversion Factor
Codeine	0.15
Fentanyl transdermal (in mcg/hr)	2.4
Hydrocodone	1
Hydromorphone	4
Morphine	1
Oxycodone	1.5
Oxymorphone	3

Total opioid consumption will be calculated overall and for the same periods as the NPRS AUC values: 0-12 hours, 12-24 hours, 24-48 hours, 24-72 hours and 24-96 hours in addition, the periods 24h to Week 1 and 24h to Week 2 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.

7.4.4 Proportion of patients who drop out of the study due to inadequate analgesia from Day 1 to 15.

Proportion of subjects who drop out of the study due to inadequate analgesia from Day 1 to 15 will be analyzed using Fisher's exact tests. Inadequate analgesia will be assumed if a subject drops out of the efficacy portion of the study due to inadequate analgesia, or if a subject drops out of the study entirely due to lack of efficacy or for an AE that 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 of the study for inadequate analgesia.

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.

7.4.5 Brief Pain Inventory-short form (BPI-SF)

Individual questions will be listed.

In addition, two sub scores of the BPI will be calculated as follows:

Pain Severity Score = Mean of items 3-6

Pain Interference Score = Mean of items 9A-9G calculated only if more than 50%, or four of seven, of the total items have been completed on a given administration.

Questions 3-6, the Pain Severity Score and the Pain Interference Score will be analyzed using ANOVA with treatment as the main effect similar to previous analyses. The analysis results will be presented in a summary table with active vs. placebo difference means, standard errors, confidence intervals and p-values.

7.4.6 PGE and IGE

The proportions of subjects in each individual PGE and IGE category will be summarized by treatment group and time point and analyzed using the Cochran-Mantel-Haenszel mean score test (using equally spaced scores) at each time point 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). The continuous PGE and IGE scores will also be analyzed using ANOVA with treatment as a main effect similar to presented previously. Individual PGE and IGE scores will be listed.

7.4.7 Time to First Use of Rescue Medication

The time to first rescue will be measured from Time 0 (time of completion of study drug administration). If a subject does not take rescue medication but prematurely discontinues from the study or discontinues from the efficacy portion of the study, then for analysis purposes the subject's observation time will be the time of the discontinuation. For subjects who discontinue from the efficacy portion of the study, the discontinuation time will be considered to be a rescue event. The time will be considered to be a rescue event if the discontinuation from the study was due to lack of efficacy, 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 dose cohort. Individual times to event will be listed.

7.4.8 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 be summarized for each study day through Day 15. For summaries, subjects who discontinued from the efficacy portion of the study will be counted two ways. First, all medications on days up to and including the date of the discontinuation from efficacy will be included, but medications that were continued after the date of discontinuation from efficacy will not be counted. In a second analysis, all the medication for these subjects will be counted, regardless of whether it was taken before or after the subject discontinued from the efficacy portion.

In addition, the proportion of subjects taking any rescue medication during the following periods: 0 to 48 hours, 0 to 72 hours, 0 to 96 hours, Days 1 to 8, Days 3-8, and Days 9-15 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 TEAEs
- Clinical laboratory test results

- Vital sign measurements
- Electrocardiogram (ECG) results
- Physical Exam findings
- Surgical Site assessment findings
- Neurosensory Exam results

8.2 Adverse Events

Any untoward medical event that occurs after signing the ICF is considered to be an adverse event (AE). Treatment-emergent AEs are defined as AEs that start or worsen in severity after the first exposure to study drug and up to Day 29 for non-SAEs (up to Day 59 for SAEs). 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 19.1). 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 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 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 system organ class (SOC), and then by preferred term (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 11:59*		

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 Clinical Laboratory Evaluation

Clinical laboratory test results (blood chemistry/coagulation, hematology and urinalysis) will be listed for individual subjects. Baseline for clinical laboratory parameters will be defined as the last evaluation before dosing with study treatment. For each individual lab test value, the raw value and change from baseline will be summarized by treatment and time point.

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 baseline (and vice versa) to each follow-up visit will be summarized by treatment and time point.

8.4 Vital Signs

Vital signs results including BP (systolic and diastolic), pulse rate, respiration rate, 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.

8.5 Physical Examination

Physical examination abnormality results will be listed for individual subjects.

8.6 Surgical Site Assessment

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

8.7 Neurosensory Assessment

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

8.8 ECG Examinations

ECG examination abnormality results will be listed for individual subjects and number of subjects with abnormal results will be summarized descriptively by treatment and time point.

8.9 Drugs of Abuse and Alcohol Screens, Pregnancy Test.

Pregnancy (for female subjects of childbearing potential), urine drug screen and alcohol breath tests will be performed at screening and pre-procedure. Results will be listed for individual subjects. Each test result will be defined to be “negative” or “positive”.

8.10 Patient 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

Blood draws for PK analysis will be done at baseline (before dosing), and at 5 minutes, 15 minutes, 30 minutes, 45 minutes, and 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, and 48 hours after dosing. Blood levels of CA-008, CA-101, capsaicin and capsaicin glucuronide metabolite will be determined. PK sample collections and drug levels will be listed.

There will be a separate PK Analysis Plan that will describe the analyses of all PK concentrations.

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 AND DATA MONITORING

There are no planned interim analyses for this study.

A DMC will regularly monitor safety data in a blinded fashion throughout the study. To determine appropriate dose escalation in the next planned cohort, safety data will be reviewed by a DMC after the final dosing within each cohort. Details regarding the DMC are included in the DMC Charter.

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.

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.

14 APPENDICES

14.1 Tables, Figures and Listings for Final Study Report

14.1.1 Tables

Table 14.1.1	All Subjects	Summary of Subject Disposition
Table 14.1.2	All Randomized Population	Summary of Protocol Deviations
Table 14.1.3	All Randomized Population	Summary of Demographic and Baseline Characteristics
Table 14.1.4	Safety Population	Summary of Concomitant Medications by ATC Class and Preferred Term
Table 14.1.5	Safety Population	Summary of Subject NPRS and NPRS at Rescue Diary Compliance
Table 14.2.1.1	Safety Population	ANOVA Analysis of AUC of NPRS - WOCF
Table 14.2.1.2	Safety Population	ANOVA Analysis of AUC of NPRS - LOCF
Table 14.2.2.1	Safety Population	ANOVA Analysis Mean Average Daily NPRS of 2 Daily Diary Assessments
Table 14.2.3.1.1	Safety Population	Summary of Daily Opioid Consumption (in Morphine equivalents) by Study Day
Table 14.2.3.1.2	Safety Population	Summary of Daily Opioid Consumption (in Morphine equivalents) by Study Day up to Discontinuation of Efficacy Portion
Table 14.2.3.2.1	Safety Population	ANOVA Analysis Mean Daily Opioid Consumption (in Morphine Equivalents)
Table 14.2.3.2.2	Safety Population	ANOVA Analysis Mean Daily Opioid Consumption (in Morphine Equivalents) up to Discontinuation of Efficacy Portion
Table 14.2.3.3	Safety Population – Subjects Who Took Any Opioid Medication	ANOVA Analysis Mean Daily Opioid Consumption (in Morphine Equivalents)
Table 14.2.4	Safety Population	Fishers Analysis of Proportion of Drop Out Due to Inadequate Analgesia
Table 14.2.5	Safety Population	ANOVA Analysis Brief Pain Inventory (BPI-SF) Pain and Interference Subscales

Table 14.2.6	Safety Population	CMH and Fishers Analysis of Patient Global Evaluation (PGE)
Table 14.2.7	Safety Population	CMH and Fishers Analysis of Investigator Global Evaluation (IGE)
Table 14.2.8.1.1	Safety Population	Fishers Analysis of Percent of Subjects using Rescue Medication Over Time
Table 14.2.8.1.2	Safety Population	Fishers Analysis of Percent of Subjects using Rescue Medication Over Time up to Discontinuation of Efficacy Portion
Table 14.2.8.2.1	Safety Population	Summary of Percent of Subjects Using Rescue Medication by Day
Table 14.2.8.2.2	Safety Population	Summary of Percent of Subjects Using Rescue Medication by Day up to Discontinuation of Efficacy Portion
Table 14.2.9	Safety Population	Kaplan-Meier Analysis of Time to First Use of Rescue Medication by Dose (if needed)
Table 14.3.1.1	Safety Population	Overall Summary of Treatment-Emergent Adverse Events (TEAEs)
Table 14.3.1.2	Safety Population	Summary of TEAEs by System Organ Class and Preferred Term
Table 14.3.1.3	Safety Population	Summary of Treatment Related TEAEs by System Organ Class and Preferred Term
Table 14.3.1.4	Safety Population	Summary of SAEs by System Organ Class and Preferred Term
Table 14.3.1.5	Safety Population	Summary of TEAEs Leading to Discontinuation from Study
Table 14.3.1.6	Safety Population	Summary of TEAEs by System Organ Class, Preferred Term and Severity
Table 14.3.1.7	Safety Population	Summary of TEAEs by System Organ Class, Preferred Term and Relationship to Study Drug
Table 14.3.2.1.1	Safety Population	Summary of Blood Chemistry/Coagulation Laboratory Tests: Results and Change from Baseline
Table 14.3.2.1.2	Safety Population	Summary of Blood Chemistry/Coagulation Laboratory Tests: Shifts from Baseline
Table 14.3.2.2.1	Safety Population	Summary of Hematology Laboratory Tests: Results and Change from Baseline
Table 14.3.2.2.2	Safety Population	Summary of Hematology Laboratory Tests: Shifts from Baseline
Table 14.3.2.3.1	Safety Population	Summary of Urinalysis Laboratory Tests: Results and Change from Baseline

Table 14.3.2.3.2	Safety Population	Summary of Urinalysis Laboratory Tests: Shifts from Baseline
Table 14.3.4	Safety Population	Summary of Vital Signs: Results and Change from Baseline
Table 14.3.5	Safety Population	Summary of Surgical Site Assessment
Table 14.3.6.1	Safety Population	Summary of Neurosensory Exam –Target Foot
Table 14.3.6.2	Safety Population	Summary of Neurosensory Exam –Non-Target Foot
Table 14.3.7	Safety Population	Summary of ECG Exam Abnormal Findings

14.1.2 Figures

Figure 14.2.1.1	Safety Population	Mean NPRS Over Time by Treatment (WOCF)
Figure 14.2.1.2	Safety Population	Mean NPRS Over Time by Treatment (LOCF)
Figure 14.2.2	Safety Population	Mean NPRS Over Time by Subject (Observed Data, no imputation for Drop Out)
Figure 14.2.3	Safety Population	Average Daily NPRS of 2 Daily Diary Assessments by Treatment
Figure 14.2.4	Safety Population	Time to First Use of Rescue Medication

14.1.3 Listings

Listing 16.2.1	All Subjects	Informed Consent, Randomization and Study Population
Listing 16.2.2	All Randomized Subjects	Eligibility
Listing 16.2.3	All Randomized Subjects	Protocol Deviations
Listing 16.2.4	All Randomized Subjects	Subject Completion/Early Termination
Listing 16.2.5	All Randomized Subjects	Demographics and Baseline Characteristics
Listing 16.2.6	All Randomized Subjects	Medical/Surgical History
Listing 16.2.7.1	All Randomized Subjects	Prior and Concomitant Medications
Listing 16.2.7.2	All Randomized Subjects	Rescue Medication Administration
Listing 16.2.7.3	All Randomized Subjects	Non-Medication Therapies

Listing 16.2.7.4	All Randomized Subjects	Time to First Use of Rescue Medication and AUC of Total MEQ
Listing 16.2.8	All Randomized Subjects	X-Ray of Surgical Site
Listing 16.2.9	All Randomized Subjects	Bunionectomy Surgery
Listing 16.2.10	All Randomized Subjects	Study Drug Administration
Listing 16.2.11	All Randomized Subjects	Subject NPRS and NPRS at Rescue Diary Compliance
Listing 16.2.12	All Randomized Subjects	Discharge from Clinic
Listing 16.2.13	All Randomized Subjects	Paper Diary Collection
Listing 16.2.14.1	All Randomized Subjects	Pain Intensity Assessment (NPRS)
Listing 16.2.14.2	All Randomized Subjects	AUC of Pain Intensity Assessment (NPRS) - WOCF
Listing 16.2.14.3	All Randomized Subjects	AUC of Pain Intensity Assessment (NPRS) - LOCF
Listing 16.2.15.1	All Randomized Subjects	Brief Pain Inventory (BPI-SF) – Pain Scale
Listing 16.2.15.2	All Randomized Subjects	Brief Pain Inventory (BPI-SF) – Pain Interference
Listing 16.2.16	All Randomized Subjects	Patient Global Evaluation (PGE)
Listing 16.2.17	All Randomized Subjects	Investigator Global Evaluation (IGE)
Listing 16.2.18.1	All Randomized Subjects	Adverse Events
Listing 16.2.18.2	All Randomized Subjects	Serious Adverse Events
Listing 16.2.18.3	All Randomized Subjects	Treatment Related Adverse Events
Listing 16.2.18.4	All Randomized Subjects	Adverse Events Leading to Premature Study Discontinuation
Listing 16.2.19.1	All Randomized Subjects	Blood Chemistry/Coagulation Laboratory Results
Listing 16.2.19.2	All Randomized Subjects	Hematology Laboratory Results

Listing 16.2.19.3	All Randomized Subjects	Urinalysis Laboratory Test Results
Listing 16.2.20	All Randomized Subjects	Alcohol Breath and Urine Drug Screen Tests
Listing 16.2.21	All Randomized Subjects	Pregnancy Test
Listing 16.2.22	All Randomized Subjects	Vital Signs
Listing 16.2.23	All Randomized Subjects	Physical Exam and Brief Physical Exam Assessment
Listing 16.2.24	All Randomized Subjects	Surgical Site Assessment
Listing 16.2.25	All Randomized Subjects	Neurosensory Exam
Listing 16.2.26	All Randomized Subjects	12-Lead Electrocardiogram
Listing 16.2.27	PK Population	Pharmacokinetic (PK) Concentration Data

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Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	4/5/2018 9:33:40 AM
Certified Delivered	Security Checked	4/5/2018 4:15:37 PM
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