CONCENTRIC ANALGESICS

OFFICIAL TITLE:

An Open-Label Study of Intraoperative CA-008 Administration in Subjects Undergoing Bunionectomy

NCT NUMBER:

03885596

DOCUMENT DATE:

05 Jun 2019

STATISTICAL ANALYSIS PLAN

An Open-Label Study of Intraoperative CA-008 Administration in Subjects Undergoing Bunionectomy

Protocol Number: CA-PS-205

Protocol Version 4.0 (02MAY2019)

SPONSORED BY

Concentric Analgesics, Inc.

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

DOCUMENT VERSION CONTROL

Version Number	Date	Comments/Changes
V1.0	05JUN2019	SAP

APPROVALS

Author:

DocuSigned by:
Song Liou
Signer Name: Song Liou
Signing Reason: I am the author of this document
Signing Time: 6/5/2019 11:27:45 AM PDT
85C80776CFA1404FB9C34B43BB0AA100

05-Jun-19

Song Liou
Biostatistician
Lotus Clinical Research®, LLC

Date:

Reviewed:

DocuSigned by:
Jennifer Nezzer
Signer Name: Jennifer Nezzer
Signing Reason: I have reviewed this document
Signing Time: 6/5/2019 9:07:17 AM PDT
F51546CD923C410C87CAB1F62D450C79

05-Jun-19

Jennifer Nezzer
Director, Biometrics
Lotus Clinical Research®, LLC

Date:

Approved:

DocuSigned by:
Mike Royal
Signer Name: Mike Royal
Signing Reason: I approve this document
Signing Time: 6/5/2019 9:06:50 AM PDT
608C20EC5FAD4832ADC799E971759505

05-Jun-19

Mike A. Royal, MD, JD, MBA
Chief Medical Officer
Concentric Analgesics Inc.

Date:

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

LIST OF ABBREVIATIONS (COMMONLY USED)

ADaM	Analysis Data Model
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
BUNX	Bunionectomy
CDER	Center for Drug Evaluation and Research
CRF	Case Report Form
CSR	Clinical Study Report
ECG	Electrocardiogram
FDA	Food and Drug Administration
HCl	Hydrochloride
ICF	Informed Consent Form
ICH	International Conference on Harmonization
LOCF	Last Observation Carried Forward
MAC	Monitored Anesthesia Care
MedDRA	Medical Dictionary for Regulatory Activities
MED	morphine equivalent dose
NRS	Numerical Rating Scale for Pain Intensity
OC	Opioid Consumption in morphine equivalent dose
OTC	Over-the-counter
PACU	Post-Anesthesia Care Unit
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation

SDTM	Standard Data Table Model
SOC	System Organ Class
SPI	Sum of Pain Intensity
TEAE	Treatment Emergent Adverse Event
WHO	World Health Organization
WOCF	Worst Observation Carried Forward

1. PURPOSE OF THE ANALYSES

This statistical analysis plan (SAP) is based on protocol number CA-PS-205 Version 4.0 (02MAY2019) from Concentric Analgesics, Inc. This SAP provides details of the specific statistical methods that will be performed on data collected in this study and will be finalized and signed off before database lock.

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.

2. PROTOCOL SUMMARY

2.1 Study Objectives

2.1.1 Primary Objective

- To evaluate different standard of care anesthetic regimens on CA-008 administration in subjects undergoing an elective bunionectomy (BUNX).

2.1.2 Secondary Objective

- To confirm the safety and efficacy of CA-008 with different standard of care anesthetic regimens in subjects undergoing an elective BUNX.

2.1.3 Exploratory Objective

- To evaluate Exparel's performance in subjects undergoing an elective BUNX under a standard of care anesthetic regimen.

2.2 Overall Study Design and Plan

This is a Phase 2, single-center, open-label study of 3 cohorts of 9 subjects each evaluating a single dose of CA-008 4.2 mg administered during an elective unilateral transpositional first metatarsal osteotomy for the correction of hallux valgus deformity (bunionectomy or BUNX) under

monitored anesthesia care (MAC) and Mayo field block with or without a supplemental popliteal block with bupivacaine hydrochloride (HCl) and lidocaine HCl.

Additionally, a 4th cohort of 9 subjects will receive Exparel® (bupivacaine liposome injectable suspension; Pacira Pharmaceuticals, Inc.) under MAC and Mayo field block with bupivacaine HCl and lidocaine HCl.

The study will be conducted in two parts:

- Inpatient period which continues to $T72h_{NRS}$ (72 hours after entering Post-Anesthesia Care Unit (PACU)).
- Outpatient period which begins on discharge from the inpatient unit through various follow up visits to D29±2 after surgery (cohorts 1-3) or to D8±1 (cohort 4).

Subjects who elect to discontinue study participation during the inpatient phase of the study, will be asked to continue with assessments through $T72h_{NRS}$ 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 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 surgery is to be performed under MAC anesthesia (see Appendix 17.H of Protocol) supplemented with one of two different standard of care regimens to produce surgical anesthesia. In both regimens, intraoperative analgesia will include IV ketorolac 30 mg and IV acetaminophen 1 g at the onset of anesthesia. The systemic anesthesia medication doses detailed in the current protocol (including but not limited to fentanyl, ketorolac and acetaminophen) are suggested guidelines to be followed by the anesthesiologist caring for the subject. The actual doses given are at the discretion of the anesthesiologist based on the clinical status of the subject. With respect to non-analgesic medications, the anesthesiologist is free to use clinical discretion on the choice and dose.

In the 1st cohort of 9 subjects, prior to surgical incision (except as noted), perform the following local anesthetic nerve blocks:

- A popliteal block performed under ultrasound guidance using bupivacaine HCl 0.25% 30 mL (75 mg)

- A Mayo block using bupivacaine HCl 0.25% 30 mL (75 mg) also prior to surgery and lidocaine HCl 1.5% 12 mL at the end of surgery

In the 2nd cohort of 9 subjects perform the following:

- A Mayo block alone using bupivacaine HCl 0.5% 15 mL combined with lidocaine HCl and lidocaine HC1 2% 15 mL prior to surgery

In the 3rd and 4th cohorts of 9 subjects in each perform the following:

- A Mayo block alone using bupivacaine HCl 0.5% 10 mL combined with lidocaine HCl 2% 20 mL prior to surgery
- CA-008 or Exparel must be injected no sooner than 20 minutes after the Mayo block
- Total bupivacaine HCl equivalent dose 176.8 mg: 121.8 mg from Exparel and 55 mg from bupivacaine HCl

For the Mayo block, inject just distal to the base of the 1st metatarsal to provide coverage of each quadrant paying particular attention to the space between the 1st and 2nd metatarsals.

After the surgery, patients will be monitored in the PACU to ensure recovery from the anesthesia. Subjects will be monitored for 72 hours ($T72h_{NRS}$) in an inpatient unit during which time safety and efficacy evaluations will be performed. After recovery from surgery, subjects in cohorts 1 and 2 will be given: celecoxib (Celebrex®) 200 mg PO bid each day while an inpatient, and acetaminophen 1 g PO (2 doses on the day of surgery starting at 6±2h after surgery and again at 12±2h after surgery) and t.i.d. each day thereafter while an inpatient. After recovery from surgery, subjects in cohorts 3 and 4 will be given no additional non-opioid analgesics. After discharge from the inpatient unit, non-opioid analgesics may be recommended by the Principal Investigator for subject use as needed.

After completing the assessments through $T72h_{NRS}$ hours after CA-008 administration and prior to discharge from the inpatient unit, 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. Subjects are instructed to return to the study center on D8±1 for a follow-up assessment. Once discharged from the inpatient unit, all study participants will be instructed to take a combination of over-the-counter (OTC) analgesics (NSAID and acetaminophen) at an appropriate dose per medical judgment to manage any residual or breakthrough postsurgical pain through D29.

In their diary, subjects will assess their current pain intensity at rest and after ambulation each morning (08:00 ±2 hours), and each evening (20:00 ±2 hours) using the NRS. The morning NRS assessment should be obtained prior to taking any pain medication. Subjects will also record any medication they take (dose and time) whether it was taken to treat their pain or for any other reasons.

Persistent pain or pain exacerbations during outpatient period may suggest the need for an unscheduled in-person visit to assess the surgical site. If such a situation occurs, the Investigator should use clinical discretion on adequacy of analgesic treatment, but to capture this event as an adverse event (AE) and document any required treatments.

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 PACU stay) to 72
Follow-up	**Cohorts 1 - 3**: Days 8(±1 day), 15(±2 days), 29(±2 days) **Cohort 4** : Days 8(±1 day)

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

2.2.1 Study Population

Adults ages 18 to 65 years, inclusive, who are planning to undergo an elective unilateral BUNX and otherwise meet eligibility criteria (as described in the protocol Sections 8.1 and 8.2) may be considered for enrollment into the study.

2.2.2 Treatment Regimens

Cohorts 1, 2, and 3:

CA-008 (4.2 mg in 14 mL) will be injected/instilled intraoperatively into the soft tissues and osteotomy surgical site as follows:

- Instill 2 mL at cut bone sites prior to fixation
- Prior to capsule closure, infiltrate the deep soft tissue and area proximal to the capsule with a total of 9 mL (approximately 2.25 mL into each quadrant circumferentially)
- Close the capsule, but using a small gauge catheter (or needle) infiltrate 2 mL into the closed capsule space
- Prior to closure of the subcutaneous tissues and skin, instill 1 mL to coat all exposed surfaces

Cohort 4:

Exparel 106 mg (8 mL of the 133 mg/10 mL suspension) will be infiltrated intraoperatively into the soft tissues and osteotomy surgical site prior to closure as follows:

- Infiltrate 7 mL into the tissues surrounding the osteotomy
- Infiltrate 1 mL into the subcutaneous tissues

See Exparel full prescribing information for detailed administration instructions: https://www.exparel.com/hcp/prescriptioninformation.pdf (as revised 11/2018; Pacira Pharmaceuticals, Inc.).

2.2.3 Treatment Group Assignments or Randomization

No randomization will be performed for this open label study. Subjects who have provided written informed consent will be assigned a unique number in the screening process. This number will be used to identify the subject throughout the study. Once any subject number is assigned, it cannot be reassigned to any other subject. There will be 4 treatment cohorts exploring different anesthesia regimens and subjects will be assigned to cohorts prior to dosing. Dose (CA-008 for cohorts 1-3 or Exparel for cohort 4) and treatment will be the same for all treated subjects within a cohort.

2.2.4 Sample Size Determination

This study is a follow-on exploratory study to a prior phase 2 study (CA-PS-201) which showed CA-008 4.2 mg was statistically significantly superior to placebo. This study is planned to evaluate optimal anesthesia conduct; therefore, no sample size estimation was performed. It was felt that a comparison of 9 in each cohort would be sufficient to demonstrate the effectiveness of any anesthesia combination.

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.

Cohorts will be presented separately in summaries and analyses. A CA-008 overall column (cohorts 1-3) will be provided where appropriate.

All continuous study assessments will be summarized by treatment and time point (as applicable) using the descriptive statistics n, mean, standard deviation (SD), median, and range (minimum, and maximum). All of the categorical study assessments will be summarized by cohort and time point (as applicable) using frequency counts and rates of occurrence (%). Changes from baseline for continuous outcomes will be presented as their corresponding continuous measures for post-baseline visits if applicable. All study data will be listed by 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. For final TLFs, the domain (Study data tabulation Model [SDTM]) and analysis (Analysis Data Model [ADaM]) data sets will be taken as input to the SAS programs that generate the report-ready tables, figures and

listings. The submission ready SDTM and ADaM data sets will be provided to the sponsor along with display deliveries.

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

- Day of surgery is defined as Day 0 (D0).
- Time 0 (T0) is the time the first dose of study medication (CA-008 or Exparel) was completed.
- Time 0 ($T0h_{NRS}$) for efficacy measurements is the time of entry to the PACU.
- Assessment visit times are defined by D0, T0 and/or $T0h_{NRS}$.
- Baseline value is defined as the last valid measurement prior to the dosing of study treatment (T0 of CA-008 or Exparel).
- Change from baseline is defined as post-baseline value minus baseline value.
- The date/time of early termination will be the date/time that the subject confirms they no longer want to participate in the study, regardless of whether they decide to withdraw from all or only some study procedures and regardless of if they return for to the site for assessment.
- 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.
- 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

The following analysis populations are planned for this study:

- **Safety** Population will include all subjects who received any amount of study drug.
- **Completer** Population will include all subjects who receive a full dose of study drug and complete the Day 29 visit (D29 ± 2) for cohorts 1 – 3 or the Day 8 (D8± 1) for cohort 4.

All analyses will be performed using Safety population using actual treatment received.

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 enrollment or are enrolled but not treated will be listed and summarized in the disposition summary table. Subjects who are enrolled, 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 cohort and for CA-008 groups overall in the subject disposition summary table.

4.3 Protocol Deviations

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

5. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

5.1 Demographics and Baseline Characteristics

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

5.2 Medical/Surgical History

The complete medical and surgical history will include histories of acute, chronic, or infectious disease; surgical or oncologic histories; and any reported conditions affecting major body systems. Subject's medical history will be evaluated by an Investigator for clinical significance. Medical and Surgical history, as collected at screening, will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 to determine system organ class (SOC) and preferred term (PT). Medical histories will be presented in a by-subject listing. Any events that occur prior to the study procedure will be categorized as medical history.

5.3 Prior and Concomitant Medications

Prior medications/therapies are those that stop prior to the start of the study drug administration. Any medication/therapy that stops at or after this time or on going is considered concomitant medication/therapy. Prior and concomitant medications are collected for the 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 study cohort, 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 72 hours after discharge to PACU, the diary for at-home use will be distributed to the subject to collect pain intensity (twice daily on NRS) through Day 8 visit and pain medication through Day 15 visit for cohorts 1-3 or Day 8 for cohort 4. 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 (%) =

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

Where the N of expected NRS records in the diary for each subject is calculated as 2 times the number of days between the date subject discharged to PACU and date of Day 8 visit (or the date of the last study visit (whichever is earlier)). The number of days of participation will be calculated as the date of the Day 8 visit or the date of the last study visit (whichever is earlier) minus the date of discharge. If subject is discharged after 10:00 (morning NRS that supposed to be collected at 0800h (±2h)) then subtract 1 from the obtained value, assuming that morning NRS assessed on the date of discharge was collected while subject was still inpatient. Also subtract 1 for Day 8 visit evening NRS record (since it was not supposed to be collected). NRS recorded prior to a rescue use will not be included in this calculation of compliance. For example, Subject A in cohort 1 was discharged on Day 3, 7AM, if this subject discontinues the study on Day 8, then the expected N of NRS records on diary will be 11 (2 * (8-3+1) -1). Assuming Subject A had 5 NRS available from his/her diary, then compliance for this subject would be 45% ((5/11) *100). However, if subject A had discontinued the study on Day 6 (prior to Day 8), then the expected N of NRS for this subject would be 7 (2 * (6-3+1)-1) and compliance would be 71.4% ((5/7) *100). Compliance will be calculated for both NRS at rest and after ambulation. A summary of compliance will be provided overall and by cohort.

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.
- Data collection will continue after subjects take rescue medication.

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

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

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

- 30 minutes for IV fentanyl
- 4 hours for PO oxycodone or other PO opioids.

The last NRS prior to the use of any rescue medication will be used to impute subsequent NRS at rest scores for the subsequent protocol-specified time points for measurement of pain intensity through an appropriated time window (as specified above) after the time of the dosing of the rescue medication. Note: if a pre-rescue NRS assessment occurs at the same time as a scheduled assessment, the schedule NRS will be assumed to happen first, and then the pre-rescue NRS will be assumed to occur. If an NRS assessment occurs at the same time as the time of taking a rescue medication, the NRS will be assumed to be a Pre-rescue medication result. If the NRS time is the same as the end of time window after taking the rescue medication (end of imputation period), then NRS will be considered as occurring before the 4 hours assessment and will be imputed. For example, if a rescue dose (IV morphine) is taken at 1pm, all protocol-scheduled NRS will be imputed with the appropriate NRS value up to and including through 5pm

(a 4-hour window). If multiple doses of rescue medication are taken within a 4-hour period, the pre-rescue NRS for the first rescue use will be carried forward continuously until 4 hours past the last use of rescue falling within the continuous window. For example, if rescue is used at Hour 2.3 and Hour 5.1, the pre-rescue NRS at Hour 2.3 will be carried forward till Hour 9.1 (5.1 +4). NRS scores taken after ambulation will be based on reported values and the pre-rescue 4-hour imputation rule will not be used. The scores after ambulation are collected every 12 hours and no ambulation NRS score is collected prior to taking rescue medication.

Intermittent missing pain scores at rest or after ambulation (due to subject sleeping, etc.) will not be imputed, and AUC will be calculated based on non-missing values. For subjects who drop out of the study early, scheduled assessments will first be imputed using the worst prior pain score carried forward (WOCF). Data resulting from imputation method described above will be used in the analysis of all efficacy endpoints derived from NRS (e.g., NRS at rest or with ambulation at Hours 24_{NRS}, 48_{NRS} or 72_{NRS}).

7.2 Sensitivity Analysis

The following imputation methods will be performed and analyzed as sensitivity analyses for NRS at Hours 24_{NRS}, 48_{NRS}, and 72_{NRS} efficacy endpoints:

1. Last observation carried forward (LOCF) will be imputed for missing assessment(s) after drop out.
2. Median score (from the remainder of subjects in the group continuing in the study) will be imputed for missing assessment(s) after dropping out.

7.3 Assessment Time Windows

For calculations of AUC endpoints and use of opioid endpoints, the actual dates/times of the assessments will be used in calculations. Thus, while the NRS are intended to be collected at the pre-defined protocol scheduled time points (e.g., Hour 0, 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.

Other efficacy and safety assessment summaries will be based on the nominal protocol-specified assessment times.

7.4 Efficacy Endpoints

Pain intensity over the 72 hours inpatient stay (at 24_{NRS}, 48_{NRS} and 72_{NRS} hours) will be assessed using NRS score at rest and with ambulation.

In addition,

- NRS scores at scheduled timepoints other than Hours 24_{NRS}, 48_{NRS} or 72_{NRS}.
- Area Under the Curve (AUC) of the NRS at rest from $T0h_{NRS}$ to $T72h_{NRS}$ ($AUC_{0\ to\ 72h}$).
- Daily and total opioid consumption (OC) in oral morphine dose equivalents (MEDs) as recorded during the inpatient and outpatient period.

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). NRS will be assessed as follows:

- At $T0h_{NRS}$ (entry to PACU), 1_{NRS}, 2_{NRS}, 3_{NRS}, 4_{NRS}, 6_{NRS}, 8_{NRS} and 12_{NRS} hours and every 6 hours thereafter while an inpatient.
- Pain scores may be skipped between the hours of midnight and 6 a.m., but the subject may not miss two consecutive assessments due to sleeping.
- The 24_{NRS} - and 48_{NRS} -hour assessments must be completed even if the subject is asleep at these times.
- An additional NRS assessment must be obtained within 15 min of the time of rescue medication request but prior to administration of rescue.
- Starting in the evening of the 1st postoperative day through the D8 visit, NRS assessments twice daily at approximately 0800h (±2h) and each evening prior to bedtime at approximately 2000h (±2h) at rest and with ambulation of approximately 10 yards. Note that the actual time of these assessments must be documented in the diary.

7.5.2 Pain Intensity Scores at $T24h_{NRS}$, $T48h_{NRS}$ and $T72h_{NRS}$ at Rest and with Ambulation

Missing NRS at Hours 24, 48 or 72 scheduled hours after $T0h_{NRS}$ will be handled as discussed in Sections 7.1 and 7.2.

Descriptive summaries will be presented overall and for each cohort of the mean NRS at the 24, 48 and 72 hour timepoints. Similar summaries will also be displayed at each time point without imputation for early drop out. In addition, Mean NRS value by Cohort and Individual NRS values over time will be displayed graphically.

7.5.3 AUC 0-72h at Rest

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: NRSi = NRS at rest at time I, and (Ti+1 – Ti) is the Time difference in hours between time i and time i+1.

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

The AUC analyses will be presented in a summary table with standard summary statistics for each cohort.

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

7.5.4 Daily and Total Opioid Consumption (OC) in Oral Morphine equivalents

Opioid use is recorded on the rescue medication eCRF from the end of surgery through 14 days for cohorts 1-3 (or 7 days for cohort 4) after the end of surgery (D15/D8 visit) or to Early termination (ET) visit if applicable. The amount of opioids taken as rescue will be calculated using the rescue medication page of the eCRF. If additional opioids, other than the study rescue medications, appear on the concomitant medications page and can be identified, those opioids will also be included (in terms of morphine equivalents) in the total consumed. Table 3 will be used to calculate the morphine equivalent dose (MED) for each medication. The total opioid consumption for each day for each subject will be calculated as the sum of the MEDs of all of the medications taken on that day. For example, if a subject takes 5 MED morphine on Day 1 and Day 2, and 10 MED of Oxycodone on Day 2, the total consumption for Day 1 is 5 MED, and the total consumption for Day 2 is 15 MED. Subjects that take no opioids on a day will have a total opioid consumption value of zero for that day.

Table 3 Equianalgesic Conversion Table

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

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

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

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

*Note that for non-tolerant patients, we are using the 6:1 conversion for IV to PO morphine, or in other word, 10 mg IV morphine = 60 mg PO morphine.

Total opioid consumption will be calculated for 0-72 hours ($OC_{0\ to\ 72h}$) and 24-72 hours ($_{OC24\ to\ 72h}$). A 1-way will be performed. A separate summary containing only subjects that have taken at least one dose of rescue will be performed if warranted.

8. SAFETY EVALUATION

8.1 Overview of Safety Analysis Methods

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

- Incidence of treatment-emergent adverse events (TEAEs) or treatment-emergent serious adverse events (SAEs)
- Clinically significant changes in surgical site assessments and neurosensory testing
- X-ray healing (cohorts 1-3 only)

- Absence of rebound pain at the surgical site (cohorts 1-3 only)
- Physical examination
- Vital signs
- Drug screen

8.2 Adverse Events and SAEs

All AEs and SAEs are documented and followed from the time the subject have signed the informed consent form (ICF) until D29 (for cohorts 1-3) or D8 (for cohort 4), and, if necessary, later. All events will be documented and followed from the time of administration of CA-008 until D29 or Exparel until D8. AEs will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA Version 21.0) reporting system. All coding will be reviewed prior to database lock. All recorded AEs will be listed, but only TEAEs will be summarized.

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

- Non-serious AEs with onset on the date of treatment with the study drug through D29 (cohorts 1-3) or D8 (cohort 4) or Early Termination, whichever occurs first.
- Serious AEs with onset on the date of treatment with the study drug through D29 (cohorts 1-3) or Day8 (cohort 4) or Early Termination, whichever occurs first.
- AEs that start before the start of treatment but increase in severity or relationship at the time of or following the start of treatment through D29 (cohorts 1-3) or D8 (cohort 4) or Early Termination, whichever occurs first.

For evaluation of causal relatedness to treatment, the categories are probably related, possibly related or unlikely related. For categorization in the summary tables, AEs designated as probably or possibly related will be considered to be related.

For the evaluation of event severity terms, the criteria are mild, moderate or severe. In addition to a listing of all TEAEs, treatment related TEAEs, serious TEAEs, Deaths, and TEAEs leading to premature discontinuation from the study will be provided.

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

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

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

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

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

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

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

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

Table 4 Table of Imputation Rules for Missing AE Start Dates

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

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

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

8.3 Physical Examination

A complete medical history and physical examination including all major body systems will be performed at Screening. In addition, a targeted reassessment will be performed prior to surgery, at discharge from the inpatient unit, and at the last visit (D29 for cohorts 1-3 or D8 for cohort 4) or if the subject terminates early, at that time if allowed.

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

8.4 Vital Signs

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

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

8.5 Surgical Site Assessments and Rebound Pain Assessments

Surgical sites will be assessed at 72 hours (prior to discharge from the unit) and then as an outpatient on Days 8, 15 and 29 (for cohorts 1-3 only). The investigator will evaluate their satisfaction with the healing of the wound during this surgical site assessment using an 11-point scale (0- 10) where a score of 0 is “completely unsatisfied” and a score of 10 is “completely satisfied). In addition, subjects will report whether they have noted any rebound pain (rebound pain; Y/N) at the surgical site since the prior visit at Days 8, 15 and/or 29 (for cohorts 1-3 only).

All data will be presented in data listings.

8.6 Neurosensory Test

Neurosensory testing near the incision (compared to a similar site on the opposite leg) will be performed at screening, T72h (prior to discharge from the unit) and then as an outpatient on Days 8, 15 and 29 (for cohorts 1-3 only).

The neurosensory assessment results will be listed in data listing.

8.7 X-ray of the Surgical Site

X-ray of the surgical site will be performed for subjects in cohorts 1-3 during screening (or verified as previously done) and at D29/ET.

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

8.8 Electrocardiogram (ECG) at Screening

ECG examination will be assessed at screening only. Findings at screening (normal, abnormal – not clinically significant or abnormal – clinically significant) will be provided in a data listing.

8.9 Clinical Laboratory Test Results at Screening

Appropriate screening labs will be performed at the site's local laboratory. It is the responsibility of the Investigator to review and sign all lab reports expeditiously, and to document appropriate safety monitoring of study subjects.

Laboratory test results and sample collection information will be listed.

8.10 Drugs of Abuse and Alcohol Screens, Pregnancy Test

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

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

8.11 Subject pain Assessment Training and Surgery Details

Subjects will undergo study participation education on pain assessments and written testing procedures during screening and prior to surgery.

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

9. 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.

10. INTERIM ANALYSES

There are no planned interim analyses for this study.

11. 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.

12. APPENDICES

12.1 Planned Tables, Figures and Listings

12.1.1 Tables

Table 14.1.1	All Subjects	Summary of Subject Disposition
Table 14.1.2	Safety Population	Summary of Demographics and Baseline Characteristics
Table 14.1.3	Safety Population	Summary of Concomitant Medications by ATC Class and Preferred Term
Table 14.1.4	Safety Population	Summary of Subject NRS and NRS at Rescue Diary Compliance
Table 14.2.1.1	Safety Population	Summary of Hours 24, 48 or 72 NRS at Rest – WOCF (Primary Analysis)
Table 14.2.1.2	Safety Population	Summary of Hours 24, 48 or 72 NRS at Rest – LOCF
Table 14.2.1.3	Safety Population	Summary of Hours 24, 48 or 72 NRS at Rest – Median
Table 14.2.2	Safety Population	Summary of NRS at Rest by Hour – Observed Data
Table 14.2.3	Safety Population	Summary of NRS at Rest by Morning/Night – Observed Data
Table 14.2.4.1	Safety Population	Summary of NRS with Walking by Morning/Night through Hour 72– WOCF
Table 14.2.4.2	Safety Population	Summary of NRS with Walking by Morning/Evening through Hour 72– LOCF
Table 14.2.4.3	Safety Population	Summary of Inpatient NRS with Walking by Morning/Evening through Hours 72 – Median
Table 14.2.5	Safety Population	Summary of NRS with Walking by Morning/Night – Observed Data
Table 14.2.6	Safety Population	Summary of AUC (0-72) NRS at Rest - WOCF
Table 14.2.7	Safety Population	Summary of Opioid Consumption (in Morphine Equivalents)
Table 14.2.8	Safety Population	Summary of Opioid Consumption (in Morphine Equivalents) by Day
Table 14.3.1.1	Safety Population	Overall Summary of Treatment-Emergent Adverse Events (TEAEs)
Table 14.3.1.2	Safety Population	Summary of Treatment-Emergent Adverse Events (TEAEs) by System organ Class and Preferred Term
Table 14.3.1.3	Safety Population	Summary of Treatment Related Treatment-Emergent Adverse Events (TEAEs) by System organ Class and Preferred Term
Table 14.3.1.4	Safety Population	Summary of Serious Adverse Events by System organ Class and Preferred Term
Table 14.3.1.5	Safety Population	Summary of Treatment-Emergent Adverse Events (TEAEs) Leading to Study Discontinuation by System organ Class and Preferred Term

Table 14.3.1.6	Safety Population	Summary of Treatment-Emergent Adverse Events (TEAEs) by System organ Class, Preferred Term and Severity
Table 14.3.1.7	Safety Population	Summary of Treatment-Emergent Adverse Events (TEAEs) by System organ Class, Preferred Term and Relationship to Study Drug
Table 14.3.2	Safety Population	Summary of Vital Signs: Results and Change from Baseline

12.1.2 Figures

Figure 14.2.1.1	Safety Population	Mean NRS over Time by Cohort – WOCF at Hours 24, 48 and 72
Figure 14.2.1.2	Safety Population	Mean NRS over Time by Cohort - LOCF at Hours 24, 48 and 72
Figure 14.2.1.3	Safety Population	Mean NRS over Time by Cohort - Median at Hours 24, 48 and 72
Figure 14.2.2	Safety Population	Spaghetti Plot of NRS for each Subject by Cohort

12.1.3 Listings

Listing 16.2.1	All Subjects	Screening and Study Population
Listing 16.2.2	All Subjects	Informed Consent and Re-Consent
Listing 16.2.3	All Subjects	Eligibility
Listing 16.2.4	All Subjects	Protocol Deviations
Listing 16.2.5	All Subjects	Subject disposition/ Early Termination
Listing 16.2.6	All Subjects	Demographics and Baseline Characteristics
Listing 16.2.7	All Subjects	Medical/ Surgical History
Listing 16.2.8.1	All Subjects	Prior and Concomitant Medications
Listing 16.2.8.2	All Subjects	Rescue Medication Administration
Listing 16.2.8.3	All Subjects	Non-Medication Therapies
Listing 16.2.9	All Subjects	Surgery
Listing 16.2.10	All Subjects	Study Drug Administration and Pain Assessment Training
Listing 16.2.11	All Subjects	Discharge
Listing 16.2.12	All Subjects	Subject NRS and NRS at Rescue Diary Compliance
Listing 16.2.13	All Subjects	Pain Intensity Assessment (NRS at Rest)
Listing 16.2.14	All Subjects	Pain Intensity Assessment (NRS with Walking)
Listing 16.2.15	All Subjects	List of NRS Efficacy Endpoints
Listing 16.2.16.1	All Subjects	Adverse Events
Listing 16.2.16.2	All Subjects	Serious Adverse Events
Listing 16.2.16.3	All Subjects	Treatment Related Adverse Events
Listing 16.2.16.4	All Subjects	Adverse Events Leading to Study Discontinuation
Listing 16.2.17.1	All Subjects	Chemistry Laboratory Test Results
Listing 16.2.17.2	All Subjects	Hematology Laboratory Test Results
Listing 16.2.17.3	All Subjects	Urinalysis Laboratory Test Results
Listing 16.2.18	All Subjects	Vital Signs
Listing 16.2.19	All Subjects	Alcohol and Urine Drug Screen Tests
Listing 16.2.20	All Subjects	Pregnancy Tests
Listing 16.2.21	All Subjects	Physical Examination and Targeted Physical Exam Assessment
Listing 16.2.22	All Subjects	X-Ray of Surgical Site
Listing 16.2.23	All Subjects	Surgical Site Assessment and Rebound Pain Assessment
Listing 16.2.24	All Subjects	Neurosensory Exam
Listing 16.2.25	All Subjects	12-Lead Electrocardiogram

13. DOCUMENT HISTORY

Version #	Summary of Changes	Section Changed	Date
1.0	Initial document released	NA	05JUN2019

Certificate Of Completion

Envelope Id: 912AFA3F2BE74BBFBE1E3F20A1E209C6
Status: Completed
Subject: Please DocuSign: CA-PS-205 SAP_Final_ v1.0_05JUN2019.pdf
Source Envelope:
Document Pages: 34
Signatures: 3
Certificate Pages: 4
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Enabled
Time Zone: (UTC-08:00) Pacific Time (US & Canada)

Envelope Originator:
Caitlyn Avila
100 W California Blvd., Unit 25
Pasadena, CA 91105
cavila@lotuscr.com
IP Address: 205.197.253.177

Record Tracking

Status: Original
6/5/2019 8:58:42 AM
Holder: Caitlyn Avila
cavila@lotuscr.com
Location: DocuSign

Signer Events	Signature	Timestamp
Jennifer Nezzer jnezzer@lotuscr.com Director, Biometrics Lotus Clinical Research, LLC-Sub Account Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: F51546CD-923C-410C-87CA-B1F62D450C79 Using IP Address: 45.18.125.80 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I have reviewed this document	Sent: 6/5/2019 9:06:03 AM Viewed: 6/5/2019 9:07:05 AM Signed: 6/5/2019 9:07:20 AM
Electronic Record and Signature Disclosure: Accepted: 8/16/2017 8:46:58 AM ID: a2e3d9e3-0ef1-4b5e-8f0a-26d3d9799cc6		
Mike Royal Mike@concentricanalgesics.com Chief Medical Officer Concentric Analgesics, Inc Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 608C20EC-5FAD-4832-ADC7-99E971759505 Using IP Address: 174.194.15.186 Signed using mobile With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 6/5/2019 9:06:03 AM Viewed: 6/5/2019 9:06:35 AM Signed: 6/5/2019 9:06:53 AM
Electronic Record and Signature Disclosure: Accepted: 5/30/2018 1:05:32 PM ID: 41453062-babe-431e-8e37-146f718ab8aa		

Signer Events	Signature	Timestamp
Song Liou sliou@lotuscr.com Biostatistician Lotus Clinical Research Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 85C80776-CFA1-404F-B9C3-4B43BB0AA100 Using IP Address: 108.51.237.84 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 6/5/2019 9:06:03 AM Viewed: 6/5/2019 9:11:57 AM Signed: 6/5/2019 11:27:50 AM
Electronic Record and Signature Disclosure: Accepted: 2/16/2018 10:40:34 AM ID: 33003533-520a-46d0-b1ac-311cccf15c53		
In Person Signer Events	**Signature**	**Timestamp**
Editor Delivery Events	**Status**	**Timestamp**
Agent Delivery Events	**Status**	**Timestamp**
Intermediary Delivery Events	**Status**	**Timestamp**
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**
Kelly Miller kmiller@lotuscr.com Lotus Clinical Research, LLC-Sub Account Security Level: Email, Account Authentication (Required) **Electronic Record and Signature Disclosure:** Accepted: 12/27/2017 1:37:18 PM ID: 72e9a421-51ec-4869-a587-8cd23d58749a	COPIED	Sent: 6/5/2019 9:06:03 AM Viewed: 6/5/2019 10:03:38 AM
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**
Envelope Summary Events	**Status**	**Timestamps**
Envelope Sent	Hashed/Encrypted	6/5/2019 9:06:04 AM
Certified Delivered	Security Checked	6/5/2019 9:11:57 AM
Signing Complete	Security Checked	6/5/2019 11:27:50 AM
Completed	Security Checked	6/5/2019 11:27:50 AM
Payment Events	**Status**	**Timestamps**
Electronic Record and Signature Disclosure		

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

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

Getting paper copies

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

Withdrawing your consent

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

Consequences of changing your mind

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

All documents will be sent to you electronically

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

How to contact Lotus Clinical Research, LLC:

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

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

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

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

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

To request paper copies from Lotus Clinical Research, LLC

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

To withdraw your consent

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

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

Required hardware and software

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

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

Acknowledging your access and consent to receive materials electronically

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

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

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

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