STATISTICAL ANALYSIS PLAN

STUDY TITLE:

PHASE 2A, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY AND PHARMACOKINETIC PROFILE OF CPL-01 IN THE MANAGEMENT OF ACUTE POSTOPERATIVE PAIN AFTER MINI-ABDOMINOPLASTY SURGERY

PROTOCOL NUMBER:

CPL-01_AB_001

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VERSION HISTORY

SAP Version	Version Date	Change(s)	Rationale
1.0	2020-03-07	First draft	

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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
AE	Adverse Event
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
Cm	Centimeters
CRF	Case Report Form
ECG	Electrocardiogram
g	Gram
GCP	Good Clinical Practice
ICH	International Council for Harmonization
IP	Investigational Product
ITT	Intent-to-treat
kg	Kilograms
LAST	Local Anesthetic Systemic Toxicity
LS	Least Squares
m	Meters
mg	Milligram
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MEQ	Morphine Equivalent
MI	Multiple Imputation
MNAR	Missing Not at Random
NRS	Numeric Rating Scale
PK	Pharmacokinetic
RASS	Richmond Agitation and Sedation Scale
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD	Standard Deviation

SE	Standard Error
SOC	System Organ Class
SPI	Summed Pain Intensity
TEAE	Treatment Emergent Adverse Events
WHO-DD	World Health Organization Drug Dictionary

2. PURPOSE OF THE ANALYSES

This statistical analysis plan (SAP) provides a detailed description of the strategy and statistical methodology to be used for analysis of data from the CPL-01_AB_001 protocol, version 3.0, dated 25NOV2019.

The purpose of the SAP is to describe the pre-specified statistical approaches to the analysis of study data prior to database lock. This analysis plan is meant to supplement the study protocol. If differences occur between analyses described in the SAP and the current protocol, those found in this SAP will assume primacy. Any deviations from this plan will be described in the Clinical Study Report.

3. PROTOCOL SUMMARY

This is a randomized, double-blind, single-site study to evaluate the safety, pharmacokinetic (PK) profile, and analgesic duration of action of CPL-01 in men and women ≥18 and ≤70 years of age for the management of postoperative pain after mini-abdominoplasty surgery.

The study will evaluate approximately 20 subjects who will be enrolled and randomly assigned in a 3:1 ratio to either 2% CPL-01 (200 mg ropivacaine [10 mL]) or placebo (0.9% NaCl).

The study will include 4 periods: Screening Period, Surgical/Anesthesia Period (Confinement), Post-anesthesia Period (Confinement); and Post-treatment Follow up Period.

Screening Period (Day -42 up to Day -1): Subjects will be screened within 42 days before the planned surgery; however, Screening can be performed as late as on the morning of the surgery if all inclusion/exclusion criteria can be verified. Subjects who give written informed consent will be assessed for eligibility. Screening evaluations will include collection of demographic information, medical history, full neurological examination, complete physical examination, vital signs (resting blood pressure, heart rate, respiratory rate, and oral body temperature), height, weight, body mass index (BMI), 12-lead electrocardiogram (ECG), clinical laboratory tests (hematology, chemistry, and urinalysis), serology tests, serum pregnancy test (women of childbearing potential only), urine drug screen, and recording of concomitant medications. Additionally, subjects will be trained on the use of the numeric rating scale (NRS) for pain assessment at Screening.

Surgical/Anesthesia Period (Day 1 through Hour 1, Confinement): On Day 1, at check in, inclusion/exclusion criteria will be confirmed and medical history, full neurological examination, vital signs, 12 lead ECG, urine pregnancy test, urine drug screen, and concomitant medications will be updated. Before surgery, subjects will be trained again on the NRS and assigned a randomization number.

Subjects will be administered general anesthesia according to a standard regimen (Appendix D of the protocol), during which they will undergo a mini-abdominoplasty. At the end of the surgical procedure but before the wound is closed, the investigational product (IP) will be administered by wound infiltration and instillation (Time 0). Blood samples will be collected for PK analysis at baseline (before IP administration) and 15, 30, and 45 minutes after administration of IP. Continuous pulse oximetry will be monitored immediately following surgery, throughout transport, and in the post-anesthesia care unit, until subjects switch from intravenous morphine to oral rescue analgesia medication. If O_2 saturation drops below 93% or if subjects have clinical signs or symptoms that suggest respiratory depression while on the oral medication, or subjects switch back to intravenous morphine, they will be kept on continuous pulse oximetry as required. Following surgery, subjects will be admitted and confined to the study site through Day 4 (72 hours).

Post-anesthesia Period (Day 1, Hour 1 [1 hour after administration of IP] through Day 4, Confinement): Assessments during the Post-anesthesia Period will include local anesthetic systemic toxicity (LAST) assessment (including vital signs, Richmond Agitation and Sedation Scale [RASS] assessment (Appendix A of the protocol), and focused neurological examination), 12 lead ECG, pain intensity assessments, surgical wound site assessment (including photograph),

concomitant medications, and adverse events (AEs). Continuous pulse oximetry will be conducted in the post-anesthesia care unit until subjects switch from intravenous morphine to oral rescue analgesia medication. If O_2 saturation drops below 93% or subjects have clinical signs or symptoms that suggest respiratory depression while on the oral medication, or subjects switch back to intravenous morphine, they will be kept on continuous pulse oximetry as required. Subjects will also receive a diary to record their pain intensity (using NRS) and rescue medication usage when they are discharged from the study site on Day 4. On non-visit days prior to the Day 7-10 Follow up Visit, a brief daily telephone call will be conducted to remind subjects to record their pain intensity (using NRS), and rescue medication usage in the diary. Subjects will be instructed to return their completed diary at the Day 7-10 Follow-up Visit (7 to 10 days after administration of IP or upon early termination).

4. 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 will be described, if applicable, in the appropriate sections of this SAP. When this situation occurs, the rules set forth in the specific section take precedence over the general policies.

For categorical variables, summary statistics will consist of the number and percentage of subjects in each category; percentages will be out of the number of subjects in the population being reported, unless otherwise noted. All percentages will be rounded to one decimal point. The number and percentage of subjects will always be presented in the form XX (XX.X%) where the percentage is in parentheses. To ensure completeness, all summaries for categorical and discrete variables will include all categories, even if none of the subjects had a response in a particular category. Denominators for each analysis will be based on the population of interest (e.g., safety population; subjects with non-missing data).

For continuous variables, summary statistics will consist of the number of subjects with data, mean, median, standard deviation (SD), minimum, and maximum values. The summary statistic n will be the number of subjects with non-missing values. All means and medians will be reported to one more significant digit than the values being analyzed. Standard errors (SE) and standard deviations will be reported to two more significant digits than the values being analyzed. The minimum and maximum will be reported to the same number of significant digits as the values being analyzed.

For tests of hypothesis of treatment group differences, the associated p-value will be reported. All p-values will be rounded to three decimal places; p-values that round to 0.000 will be presented as "<0.001". P-values are descriptive.

In general, the baseline value will be considered the last non-missing measurement observed prior to the first dose of study treatment.

For efficacy, subjects will be analyzed according to randomized treatment. For safety analyses, subjects will be analyzed according to the actual treatment received.

Data will be listed by treatment and subject. In general, listings will be sorted in the order that columns are displayed, starting with the first column on the left (treatment). Subject listings of data will be presented for all randomized subjects unless specified otherwise.

Unless otherwise specified, summaries will include the following treatment groups:

- CPL-01
- Placebo

SAS statistical software, version 9.4 or higher, will be used for all analyses.

4.1. Assessment Time Windows

Assessments should be performed within the windows stated in the protocol and will be analyzed by the visit/time point that they are entered into the case report form (CRF) under. For assessments other than the NRS pain, if an assessment is missing and an unscheduled or early termination assessment falls within the protocol-specified window, it will be assigned to that visit/time point for the purposes of summarization. If more than one unscheduled visit/ early termination visit falls into a window, the one closest to the scheduled time point will be used (with the earlier one used in case of a tie); again, scheduled visits will always take precedence, regardless of timing.

NRS assessments will use the actual times of collection; see section 8.2.1for additional details.

5. ANALYSIS SAMPLES

The following 3 analysis populations are planned for this study:

- Intent-to-treat (ITT) Population: all subjects who are successfully screened and randomized. The ITT population is the primary population for the efficacy analysis.
- Safety Population: all subjects who are treated with IP. The Safety population is the population for all safety analyses.
- PK Population: all subjects who receive IP during surgery and who have at least 1 measurable plasma concentration. All PK analyses will be based on the PK population.

In the event that a subject is administered the incorrect IP, analyses of the ITT population will be based on the randomized treatment, whereas analyses of the Safety population will be based on the actual treatment.

6. STUDY SUBJECTS

6.1. Disposition of Subjects

The number and percentage of subjects screened, enrolled, randomized, received treatment, completed the study (through day 30), and discontinued from the study, will be reported, along with the reason for discontinuation (counts only will be reported for screened and enrolled subjects). Percentages will be out of the number of subjects randomized. Additionally, the number and percentage of subjects that complete the confinement period (through day 4) will be reported. Subjects screened and enrolled will be reported overall; the remaining items will be reported by treatment group and overall. Subjects randomized will include all subjects for whom randomization is checked on the CRF; subjects receiving treatment will include all subjects that had any IP administered; subjects completing the study will be based on the recorded disposition; subjects completing the confinement period will include those that have a termination date on or after day 4.

Reasons for discontinuation include the following:

- Adverse Event
- Death
- Lack of Efficacy
- Lost to Follow-up
- Physician Decision
- Pregnancy
- Protocol Deviation
- Study Terminated by Sponsor
- Technical Problem
- Withdrawal by Subject
- Other

Additionally, the number and percent of subjects in each analysis population will be reported by treatment. Screen failures will also be included in a by-subject listing.

6.2. Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be collected during the Screening Visit.

Descriptive statistics will be provided for all demographic and baseline characteristics based on the Safety Population. For categorical variables, the number and percentage of subjects in each category will be presented. For continuous variables, summaries will include the number of subjects with data, mean, median, standard deviation, minimum, and maximum.

Variables to be summarized include:

- Age at screening (years) as recorded on the CRF
- Sex at birth
- Ethnicity
- Race
- Weight (kg)

- Height (cm)
- BMI (kg/m^2)

All demographic and other baseline characteristics will be provided in a listing.

6.3. Prior and Concomitant Medications

All medications taken during the screening period prior to the surgery through the end of the study or early termination will be recorded in the concomitant medications log in the CRF, with the exception of rescue analgesic medications, which are collected on the rescue medications page. All medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) Version GLOBALB3Sep19. Rescue medications will be limited to 2 to 4 mg of intravenous morphine per hour; 5 or 10 mg oral oxycodone (every 3-4 hours); or 1000mg acetaminophen every 6-8 hours (not to exceed 4g per day) and recorded separately.

6.3.1. Prior Medications

Prior medications are defined as all medications recorded in the CRF initiated prior to the administration of IP. Prior medications will be summarized in a table by treatment group using the Safety Population. Medications will be reported by drug class (Anatomical Therapeutic Chemical [ATC] Level 3) and preferred term; a subject will be counted only once for each medication.

6.3.2. Concomitant Medications

Concomitant medications are defined as all medications recorded in the CRF taken after the administration of IP, including those that were initiated prior to administration of IP and ongoing. Concomitant medications will be summarized in a table by treatment group using the Safety Population. Medications will be reported by drug class (Anatomical Therapeutic Chemical [ATC] Level 3) and preferred term; a subject will be counted only once for each medication.

6.4. Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1. Conditions will be listed, including the verbatim investigator description of the relevant medical condition, the coded terms (system organ class, preferred term), start date, end date, and whether or not the condition is ongoing.

7. STUDY OPERATIONS

7.1. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. Protocol deviations will be recorded on the source documents and with an explanation for the deviation. All protocol deviations will also be recorded as specified in the monitoring plan.

Protocol deviations will be identified by site staff, through medical reviews, and by clinical research associates during site monitoring. Deviations will be classified as minor or major prior to the database lock. Major protocol deviations are defined as those that result in harm to the study patients or significantly affect the scientific value of the reported results of the study. Other deviations will be considered minor.

All protocol deviations will be summarized in a table and well as presented in a listing, including their assigned severity (major/minor).

7.2. Randomization

Prior to surgery, subjects will be assigned a sequential randomization number corresponding to a sealed envelope containing a card displaying the assigned treatment, the randomization number and an area for the subject ID to be recorded. A member of the unmasked surgery team will retrieve study materials corresponding to the assigned treatment for use during surgery. Subjects will be assigned in a 3:1 ratio to either 2% CPL-01 (200 mg ropivacaine [10 mL]) or placebo (0.9% NaCl). A by-subject listing of randomized treatment group and randomization number will be presented.

7.3. Measures of Treatment Compliance

Following surgery, CPL-01 or Placebo will be administered by wound infiltration and instillation; IP will be delivered by 4 syringes in order with the following volumes: 1ml, 4ml, 4ml, and 1ml. Per the protocol, it is expected that all syringes will be used and whether each was administered will be recorded on the CRF. The number and percent of subjects receiving each syringe will be reported for the safety population, as well as the number and percent receiving all syringes. Additionally, summary statistics will be reported for the assumed total volume (for example, if the final 1ml syringe is not marked as being administered but the remainder are, the assumed volume would be 9ml).

8. ENDPOINT EVALUATION

8.1. Overview of Efficacy Analysis Methods

8.1.1. Multicenter Studies

This is a single-center study and no special considerations are required for pooling of data.

8.1.2. Timing of Analyses

All final, planned analyses will be performed after the last participant has completed all study assessments, all relevant study data have been processed and integrated into the analysis database, and the database has been locked.

Any post-hoc, exploratory analyses completed to support planned study analysis, which were not identified in this SAP, will be documented and reported in appendices to the CSR. Any results from these unplanned analyses (post-hoc) will also be clearly identified in the text of the CSR.

8.1.3. Multiple Comparisons/Multiplicity

Unless otherwise indicated, all statistical tests will be carried out at a two-sided significance level of 5%. Given that all efficacy assessments are considered as exploratory only and are intended to inform future trials, no multiplicity adjustment shall be applied to these exploratory analyses.

8.2. Primary Efficacy Endpoint

All efficacy endpoints are exploratory. However, the primary endpoint of interest is the time-weighted summed pain intensity over 1 to 24 hours (SPI_{1-24}) for CPL-01 subjects compared with placebo subjects.

8.2.1. Computation of the Primary Endpoint

The time weighted SPI will be calculated using the trapezoidal rule and the available NRS pain scores. Missing values will not be imputed (with the exception of the final timepoint) for the primary analysis of the primary endpoint; the trapezoidal rule will implicitly perform a linear interpolation between the two observed values on either side of a missing value. Actual times of each NRS score will be used for calculating the SPIs.

NRS scores will be recorded just prior to administration of rescue medications. Following the administration of morphine, NRS values will be censored for two hours for the purposes of calculating the SPI; likewise, NRS values will be censored for four hours following administration of oxycodone. These values will be retained in the database, but will not be utilized for the SPI calculations, since they will be influenced by the rescue medications.

Assuming that a subject has a 24-hour nominal value, their SPI will be normalized to exactly 24hrs. Should the subject be missing the nominal 24-hour value, but have a subsequent NRS recorded, linear interpolation will be performed to impute the 24-hour value by connecting the prior and subsequent values and calculating where the 24-hour value would fall on that line. The above rules will be applied should the 24-hour value be censored due to rescue medication use;

the NRS collected from the associated rescue medication use will serve as the prior point for the imputation and the first subsequent non-censored value will be serve as the other anchor. If a subject withdraws from the study or has no values following the missing/censored 24-hour value, last observation carried forward will be employed using the last observed NRS.

8.2.2. Primary Analysis of the Primary Endpoint

An analysis of variance (ANOVA) model with a main effect for the treatment group will be used to compare the time weighted SPI_{1-24} between the treatment groups. Summary statistics will be reported as well as the least square (LS) means, difference in the LS means, 95% confidence intervals and p-value for the contrast comparing the LS means.

8.2.3. Sensitivity Analyses of the Primary Analysis

As a sensitivity analysis to the primary endpoint, the SPI will be calculated using multiple imputation (MI) instead of the procedures described above. The censoring rules for rescue medications will remain as above, but missing values will be imputed using MI within treatment group conditioned on the observed values, assuming missing at random (MAR). Nominal time points will be used for the purposes of the multiple imputation. Where values are censored for rescue medication use, the NRS score recorded just prior to the rescue administration will be substituted. The MI will use 20 repeats performed using Markov Chain Monte Carlo (MCMC) assuming non-monotone missing (Carpenter, 2013; Mallinckrodt, 2013). A list of random seeds to be used is given in Appendix 15.2.

The above estimates from the primary ANOVA model will be combined using SAS proc MI ANALYZE and the resulting least square (LS) means, difference in the LS means, 95% confidence intervals and p-value for the contrast comparing the LS means will be reported.

8.3. Secondary Endpoints

8.3.1. Time Weighted Sum Pain Intensities

An approach identical to the primary computation for the SPI_{1-24} above will be employed for the cumulative SPI for hours 1-6, 1-12, 1-48, and 1-72. Additionally, intervals 6-12, 12-24, 24-48, and 48-72 will be calculated by subtracting the associated cumulative values (so SPI_{6-12} will be calculated as SPI_{1-12} minus SPI_{1-6}). Summary statistics and results from an ANOVA modeling approach identical to the primary analysis will be reported.

8.3.2. Pain Intensities by Time Point

For each scheduled time point of collection, descriptive statistics will be reported for the pain intensities collected at that time point, both with all values included and with values censored due to rescue medication consumption; for the latter, the number of censored values will be reported.

This presentation will also include daily NRS scores recorded in the take-home diary; no special data handling will be performed to account for recue medications on the daily diaries.

8.3.3. Total Opioid Usage (Morphine Equivalents)

The total mg of opioids in morphine equivalents (MEQ) administered to each subject will be calculated through 24, 48 and 72 hours. Oxycodone mg will be converted to MEQ by multiplying by 1.5. Per the protocol, only morphine and oxycodone will be used as opioid rescue medications, but should another opioid moiety be used, the MEQ will be calculated using the CDC conversion guide (https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf).

The total MEQ through each time point will be reported with summary statistics and compared between the two groups using an ANOVA approach identical to that for the primary efficacy analysis.

8.3.4. Time to First Rescue

Time to first use of any rescue analgesia for postoperative surgical pain and the time to first opioid use will each be analyzed using the Kaplan-Meier method. The log-rank test will be used to test the hypothesis of overall treatment differences. If estimable, quantiles (25%, median, 75%) will be reported; in the case of sparse rescue medication usage, the number and percentage of subjects will be reported along with summary statistics of the time to first use among those with use.

8.3.5. Any Opioid Use

The number and percentage of subjects who used no opioid rescue through 24, 48, and 72 hours will be reported for each treatment group and compared using Fisher's exact test. Subjects that drop out prior to the given reporting period will be displayed.

This will also be reported for those that remain opioid free through the end of the confinement period starting at 24, 48, and 72 hours.

8.3.6. Pain Free Subjects

The number and percentage of subjects who report pain intensity <=1 for all recorded NRS evaluations through 24, 48, and 72 hours will be reported for each treatment group and compared using Fisher's exact test. Subjects that drop out prior to the given reporting period will be displayed.

This will also be reported for those that remain pain free through the end of the confinement period starting at 24, 48, and 72 hours.

8.3.7. Diary Rescue Medication Use

Usage of rescue medications recorded in the take-home diary will be presented in a listing.

8.4. Examination of Subgroups

There are no preplanned analyses of subgroups; exploratory analyses of subgroups may be performed, but will be post-hoc.

9. SAFETY EVALUATION

9.1. Overview of Safety Analysis Methods

Safety assessments will include AEs, vital signs, clinical laboratory assessments, 12-lead ECGs, physical examination, full neurological examination, local anesthetic systemic toxicity (LAST) assessment, and wound evaluation.

9.2. Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. (Worsening of a pre-existing condition is considered an AE.)

Events that occur in subjects treated with placebo are also considered AEs.

An AE is considered to be a treatment-emergent adverse event (TEAE) if the first onset or worsening is after administration of the IP (CPL-01 or placebo) and not more than 30 days after administration of IP.

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1.

An AE summary table will be presented for the following:

- TEAEs
- TEAEs by severity
- TEAEs leading to study discontinuation
- TEAEs by relationship
- Serious AEs (defined below)

Summaries of incidence rates (frequencies and percentages) of individual AEs by MedDRA System organ class (SOC) and preferred term will be prepared. Such summaries will be displayed for all TEAEs, TEAEs by maximum severity, and TEAEs by strongest relationship to study drug.

Each participant will be counted only once within each summation level (SOC; preferred term). If a participant experiences more than one TEAE within each summation level only, the TEAE with the strongest relationship or the maximum severity, as appropriate, will be included in the summaries of relationship and severity.

In the AE data listings, all AEs will be displayed. AEs that are treatment-emergent will be flagged.

9.3. Deaths, Serious Adverse Events (SAE), and Other Significant Adverse Events

An adverse event is considered to be an SAE if it meets any of the following criteria:

• Results in death

• Is life-threatening

• Requires inpatient hospitalization or prolongation of existing hospitalization

• Results in persistent or significant disability/incapacity

• Is a congenital anomaly

• Is an important medical event

A summary of incidence rates (frequencies and percentages) of SAEs by treatment group, SOC, and preferred term will be prepared for the Safety Population. A data listing of SAEs will also be provided, displaying details of the event(s) captured on the CRF. Likewise, AEs resulting in study discontinuation and AEs resulting in death will be listed separately.

Additionally, a summary of incidence rates (frequencies and percentages) of adverse events of special interest by treatment group, SOC, and preferred term will be prepared for the Safety Population.

The following will be considered AEs of special interest because they are common symptoms of LAST.

- Neurological signs/symptoms - circumoral and/or tongue numbness, metallic taste, lightheadedness and/or dizziness, visual (e.g. difficulty focusing vision) and/or auditory disturbances (e.g. tinnitus), disorientation, drowsiness (to an unexpected or unusual degree), agitation or seizures.
- Cardiorespiratory signs/symptoms - hypotension that is clinically significant or sustained, clinically significant (new and/or sustained) arrhythmia, cardiac or respiratory arrest.

Occurrences of LAST and AEs that may be signs and symptoms of LAST will be displayed in an identical manner on a separate table.

9.4. Wound AEs and Infections

A summary of incidence rates (frequencies and percentages) of wound AEs (including surgical site infections) by treatment group, SOC, and preferred term will be prepared for the Safety Population. A data listing of wound AEs will also be provided, displaying details of the event(s) captured on the CRF. A partial list of preferred terms is given in appendix 15.3, but at a minimum AEs where the preferred term includes “wound”, “incision”, “post-procedural”, “seroma” and “abscess” will be considered and reviewed as possible wound AEs.

9.5. Clinical Laboratory Evaluation

Clinical laboratory values will be collected at the Screening Visit and the Follow-up Visit. Values collected at Screening will serve as the baseline.

Descriptive summaries (mean, SD, median, minimum, and maximum) of observed (absolute) values and changes from baseline values will be presented for clinical laboratory values for each treatment group at each time point.

The number of subjects with clinical laboratory values categorized as below, within, or above normal ranges, will be tabulated showing change from baseline to follow-up (shift tables) for each clinical laboratory analyte by treatment group. Only laboratory values that are outside the normal range will be flagged in the data listings and presented with the corresponding normal ranges. The original units for normal ranges provided the study's local lab will be utilized in determining whether parameters are in range; that is, no conversions or rounding will be performed prior to this determination. Any out-of-range values that are identified by the investigator as being clinically significant will also be shown in a data listing.

Serology tests (for HIV, Hepatitis B, Hepatitis C), pregnancy tests, and urine drug screens will be presented in a listing.

9.6. Vital Signs, Physical Findings, and Other Observations Related to Safety

9.6.1. Vital Signs

Vital signs including blood pressure, heart rate, respiratory rate and temperature will be collected at the Screening Visit, Baseline Visit (at check-in) and the Follow-up Visit. Values collected at Baseline Visit will serve as the baseline; if missing, the Screening Visit or last unscheduled visit prior to baseline will be used. Additional vital signs will be collected as part of the LAST assessments (see below), but will not be summarized.

Descriptive summaries (mean, SD, median, minimum, and maximum) of observed (absolute) values and changes from baseline values will be presented for vital sign values for each treatment group at each time point.

9.6.2. Physical and Neurological Examinations

Any abnormal findings from the neurological examination results will be displayed in a listing. Physical Exam findings will be recorded in medical history if present at screening and as adverse events if emergent at later assessments.

9.6.3. Local Anesthetic Systemic Toxicity Assessment

Subjects will be evaluated for local anesthetic systemic toxicity (LAST) throughout the confinement period. This includes AEs that may be signs and symptoms of LAST, ECG findings, vital signs, the Richmond Agitation Sedation Scale. If the clinician determines the subject to be presenting with LAST, an AE will be recorded reflecting this finding. Subjects that have a LAST AE recorded will have all their LAST assessments presented in a listing.

9.6.4. Richmond Agitation and Sedation Scale Assessment

The Richmond Agitation and Sedation Scale (RASS) is used in hospitalized patients to describe their level of alertness or agitation. The clinician observes the subject and ranks their level of sedation/agitation using the following scale and scores:

- Combative +4
- Very agitated +3
- Agitated +2
- Restless +1
- Alert and calm 0
- Drowsy -1
- Light sedation -2
- Moderate sedation -3
- Deep sedation -4
- Unarousable sedation -5

The descriptive summaries (mean, SD, median, minimum, and maximum) of observed values using the above scores will be presented for each treatment group at each time point.

9.6.5. ECGs

The number and percentage of subjects with normal and abnormal ECG findings will be summarized for each treatment group at each time point. Abnormal results will be grouped as "abnormal, clinically significant" and "abnormal, not clinically significant," and summarized in the same way. A by-subject listing of abnormal ECG findings will be provided.

Descriptive summaries of observed values and changes from baseline will be presented for ECG measures of PR interval, QRS interval, QT interval, QTc interval (Bazett's and Fridericia's correction methods), and HR for each treatment group at each time point. In addition, the number and percent of subjects in each treatment group who experienced an increase in QT and QTc interval of >30 ms or a change >60 ms at any time point will be presented.

9.6.6. Wound Healing

In addition to the wound infection and wound-related AEs presentations described in section 9.4, the subject's wound site will be evaluated using a 1 to 5 scale as follows:

1-Normal healing
2-Delayed healing
3-Excessive Drainage
4-Infection
5-Tissue breakdown

Descriptive statistics of the surgical wound site assessment findings at the Day 7-10 Follow-up Visit (7-10 days after administration of IP) and the Day 30 Follow-up Visit (30 days after administration of IP) will be presented by treatment group as well as the count and percentage of subjects with each level of the response.

Surgical wound site assessment findings at 24, 48, 72, 96, and 120 hours after IP administration will be displayed in a listing.

10. PHARMACOKINETIC EVALUATION

Blood samples (approximately 3 mL each) for PK assessments will be collected via indwelling intravenous catheter. Plasma ropivacaine concentrations will be quantified using a validated LC-MS/MS assay method. All samples for all time points should be collected within the scheduled sampling windows (± 5 minutes for samples taken during the first hour, ± 10 minutes for the samples taken at 2 through 72 hours after administration of IP, and ± 1 hour for samples taken at 96 and 120 hours after administration of IP). The exact time of blood sampling will be recorded in the source documents.

Pharmacokinetic samples will be shipped to a central laboratory for analysis.

10.1. Pharmacokinetic Endpoints

PK analyses is not in the scope of this SAP, and will be documented in a PK analysis plan separately by a third party vendor MicroConstants, Inc..

11. OTHER ANALYSES

12. INTERIM ANALYSES AND DATA MONITORING

No interim analyses are planned.

13. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

The protocol stated that a Cox proportional hazards model would be used for the analysis of time to first rescue medication use in addition to the Kaplan-Meier analysis. The Kaplan-Meier analysis was determined to be sufficient.

The protocol describes physical exams findings as being recorded separately; as described above, they will be recorded with medical history or adverse events per the current CDISC recommendations.

The analyses of any opioid use and pain free time have been expanded to look both at subjects free of opioids and pain through the described time points (included in the protocol) and subjects free of opioids/pain starting at those time points through the end of the confinement.

14. REFERENCES

Carpenter, J. R. and Kenward, M. G. (2013), Multiple Imputation and Its Application, New York: John Wiley & Sons.

Mallinckrodt C, Roger J, Chuang-Stein C, Molenberghs G, Lane PW, O'Kelly M, Ratitch B, Xu L, Gilbert S, Mehrotra DV, Wolfinger R, Thijs H. (2013), Missing Data: Turning Guidance Into Action, Statistics in Biopharmaceutical Research, 5:4, 369-382

15. APPENDIX

15.1. Schedule of Events

	Screening Period (-42 days to -1 day before surgery)[a]	**Surgical/ Anesthesia Period** (Confinement)[b]	**Post-anesthesia Period** (Confinement)				**Post-treatment Follow-up Period**		
		Day 1 through Hour 1	**Day 1, Hour 1** (1 hour after administration of IP) **to Hour 24**	**Day 2**	**Day 3**	**Day 4**	**Days 5 and 6**	**Day 7-10 Follow-up Visit** (7 to 10 days after administration of IP or upon early termination)[c]	**Day 30 Follow-up Visit** (30 days after administration of IP)
Written informed consent	X								
Inclusion/exclusion criteria	X	X (at check-in)							
Demographics	X								
Medical history	X	X (at check-in)							
Full neurological examination[d]	X	X						X	
LAST assessment[e]			X	X	X				
Physical examination[f]	X							X	
Vital signs[g]	X	X (at check-in)						X	
Height, weight, and BMI	X								
12-lead electrocardiogram	X	X[h]	X[h]	X[h]	X[h]	X[h]	X[h] (Day 5 only)	X	
Clinical laboratory evaluations[i]	X							X	
Serology tests[j]	X								
Pregnancy test[k]	X	X (at check-in)							
Urine drug screen[l]	X	X (at check-in)							
Train subjects how to use NRS	X	X (before surgery)							
Dispense diary and discharge[m]						X			
Assign randomization number		X (before surgery)							

	Screening Period (-42 days to -1 day before surgery)[a]	**Surgical/ Anesthesia Period** (Confinement)[b]	**Post-anesthesia Period** (Confinement)				**Post-treatment Follow-up Period**		
		Day 1 through Hour 1	**Day 1, Hour 1** (1 hour after administration of IP) **to Hour 24**	**Day 2**	**Day 3**	**Day 4**	**Days 5 and 6**	**Day 7-10 Follow-up Visit** (7 to 10 days after administration of IP or upon early termination)[c]	**Day 30 Follow-up Visit** (30 days after administration of IP)
Mini-abdominoplasty and IP administration[n]		X							
Rescue analgesia[o]		X	X	X	X	X			
Continuous pulse oximetry[p]		X	X	X	X	X			
Pain intensity assessments[q]			X	X	X	X	X		
Wound evaluation, including photograph[r]				X	X	X	X	X	X
PK blood sample collection[s]		X	X	X	X	X	X		
Concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events[t]		X	X	X	X	X	X	X	X
Subject returns completed diary								X	

Abbreviations: AE = adverse event; BMI = body mass index; ECG = electrocardiogram; HIV = human immunodeficiency virus; IP = investigational product; LAST = local anesthetic systemic toxicity; NRS = numeric rating scale; PK = pharmacokinetic; RASS: Richmond Agitation and Sedation Scale

a Screening can be performed as late as on the morning of the surgery if all inclusion/exclusion criteria can be verified. Subjects must be at rest for a minimum of 15 minutes in the resting position before any assessments are performed during each study visit, unless otherwise specified.

b Subjects will be admitted to the study site on the morning of the scheduled surgery and confined at the study site through Day 4.

c On non-visit days prior to the Day 7-10 Follow-up Visit, a brief daily telephone call will be conducted to remind subjects to record their pain intensity (using NRS), and rescue medication usage in the diary.

d A full neurological examination will be performed at Screening, on Day 1 any time prior to anesthesia induction, and at the Day 7-10 Follow-up Visit or upon early termination. The full neurological examination will include a mental status examination and evaluation of cranial nerve, motor, sensory, and cerebellar function. In addition, the findings will be summarized in a neurologic assessment. The examiner will be asked to record whether the subject's overall neurologic status is normal or abnormal.

e Signs and symptoms of LAST will be monitored every 4 hours on Day 1 and at least once daily on Days 2 and 3 using the following: vital signs (resting blood pressure, heart rate, respiratory rate, and oral body temperature), RASS assessment, and a focused neurological examination. The focused neurological examination will include a basic mental

status examination and an evaluation to see if the subject is tremulous or complaining of any unusual symptoms (e.g., perioral paresthesias, metallic taste, or dizziness). If abnormal neurological findings are observed during the LAST assessment, a full neurological examination will be performed. If any signs or symptoms of LAST are observed, including a change in the ECG, the following will be performed: unscheduled PK sample collection, 12- lead ECG, and vital sign measurements.

f A complete physical examination will be performed at Screening (including height and weight), and an abbreviated physical examination (changes since Screening), will be performed at the Day 7-10 Follow-up Visit (7 to 10 days after administration of IP or upon early termination).

g Vital signs (resting blood pressure, heart rate, respiratory rate, and oral body temperature) will be measured after the subject has been in a resting position for 5 minutes. Vital signs will be measured and recorded at Screening, at check-in on Day 1, and at the Day 7-10 Follow-up Visit.

h A 12-lead ECG will be performed immediately prior to induction of anesthesia and at 1, 2, 4, 8, 10, 12, 24, 48, 72, and 96 hours after IP administration.

i The clinical laboratory evaluations will be hematology, chemistry, and urinalysis.

j The serology tests will be HIV, hepatitis B surface antigen, and hepatitis C virus antibody.

k For women of childbearing potential only, a serum pregnancy test will be done at Screening and a urine pregnancy test will be done at check-in on Day 1.

l The urine drug screen will test for amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, and tetrahydrocannabinol.

m Subjects will receive a diary to record their pain intensity (using NRS) and rescue medication usage when they are discharged from the study site on Day 4. They will be instructed to complete the diary daily until they return to the study site for the Day 7-10 Follow-up Visit (7 to 10 days after administration of IP or upon early termination).

n Subjects will be administered general anesthesia according to a standard regimen, during which they will undergo a mini-abdominoplasty. At the end of the surgical procedure but before the wound is closed, the IP will be administered by wound infiltration and instillation.

o Subjects with inadequately controlled pain symptoms may request rescue analgesia. Pain intensity using an NRS will be recorded just prior to receiving rescue analgesia. After administration of the IP, rescue analgesia will be restricted to 2 to 4 mg of intravenous morphine every hour as needed until the subject is able to tolerate oral medication. Once oral medication can be tolerated, oxycodone 5 to 10 mg every 3 to 4 hours will be used as needed for analgesia. After the subject's pain intensity is ≤4, oral acetaminophen 1000 mg will be used every 6 to 8 hours as needed for analgesia (not to exceed 4 g within 24 hours). For breakthrough pain intensity >4 that is not relieved by the oral acetaminophen, oral oxycodone 5 to 10 mg every 3 to 4 hours as needed for pain may continue to be used. For breakthrough severe pain intensity >8, intravenous morphine 2 to 4 mg every hour as needed may be allowed. Subjects should receive a prescription for rescue analgesia for use after they are discharged from the study site.

p Continuous pulse oximetry will be monitored immediately following surgery, throughout transport, and in the post-anesthesia care unit until subjects switch from intravenous morphine to oral rescue analgesia medication. If O_2 saturation drops below 93% or if subjects have clinical signs or symptoms that suggest respiratory depression while on the oral medication, or subjects switch back to intravenous morphine, they will be kept on continuous pulse oximetry as required.

q Pain intensity will be assessed using an NRS at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 32, 40, 48, 56, 64, and 72 hours after administration of IP. Additionally, pain intensity using an NRS will be recorded just prior to receiving rescue analgesia. The pain intensity will also be recorded when subjects return to the study site at 96 and 120 hours after administration of IP.

r Study site staff will evaluate the wound by direct visualization and record the numerical rating score on the eCRF at 24, 48, 72, 96 (Day 5), and 120 hours (Day 6) after administration of IP, and also at the Day 7-10 and Day 30 Follow-up Visits. Additionally, study site staff will photograph the wound area following the standardized instructions. Subjects will be instructed to call with any concerns about the appearance of the wound after being discharged from the study site. If subjects call with concerns, they will be asked to return to the study site for an unscheduled visit.

s Blood samples will be collected for PK analysis at baseline (before IP administration), 15, 30, and 45 minutes, and at 1, 2, 4, 6, 8, 10, 12, 18, 24, 30, 36, 48, 60, and 72 hours after administration of IP (± 5 minutes for samples taken during the first hour and ± 10 minutes for the remainder of the samples). Subjects will return to the study site for collection of PK blood samples at 96 and 120 hours after administration of IP (± 1 hour) (Days 5 and 6).

t Adverse events will be monitored throughout the study. If a subject has an AE after being discharged from the study site, he or she will return to the study site for safety assessments, including a photograph of the wound.

15.2. Random Seeds

The following list of number will be used in order for programming tasks that require random seeds. If additional numbers are required, programming will return to the start of the list and add one to each value for additional seeds.

95757437
73846758
65831589
86284444
90876999
43543977
78974612
22334268
66674922
78467583

15.3. Wound AEs

The following is a partial list of potential preferred terms to identify wound AEs:

Abdominal abscess
Burning sensation
Cellulitis
Incision site cellulitis
Incision site complication
Incision site erythema
Incision site haematoma
Incision site haemorrhage
Incision site hypoaesthesia
Incision site infection
Incision site inflammation
Incision site pain
Incision site pruritus
Incision site rash
Incision site swelling
Local swelling
Post procedural contusion
Post procedural discharge
Post procedural haematoma
Post procedural haemorrhage
Postoperative wound infection
Scar
Secretion discharge

Seroma
Skin induration
Suture related complication
Wound complication
Wound dehiscence
Wound infection
Wound secretion

16. ATTACHMENTS