PROTOCOL

PRODUCT NAME/NUMBER:	CPL-01
PROTOCOL NUMBER:	CPL-01_AB_001
IND NUMBER:	136759
DEVELOPMENT PHASE:	Phase 2a
PROTOCOL 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 DATE:	25-Nov-2019, Final Version 3.0
COORDINATING/PRINCIPAL INVESTIGATOR:	Ira J. Gottlieb, DPM 8030B Governor Ritchie Hwy Suite 100 Pasadena, MD 21122, United States +1 410-761-0118
SPONSORED BY:	CALI Pharmaceuticals 9675 Businesspark Ave San Diego, CA 92131, United States +1 858-546-0924
CONTRACT RESEARCH ORGANIZATION:	Rho 2635 E NC Hwy 54 Durham, NC 27713, United States

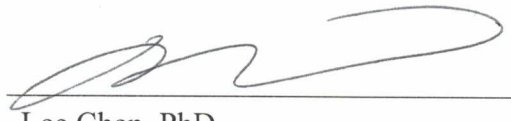
This study will be performed in compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and applicable regulatory requirements, including the archiving of essential documents. Information contained in this protocol is confidential in nature, and may not be used, divulged, published, or otherwise disclosed to others except to the extent necessary to obtain approval of the institutional review board (IRB), or as required by law. Persons to whom this information is disclosed should be informed that it is confidential and may not be further disclosed without the express permission of CALI Pharmaceuticals.

1 APPROVAL SIGNATURES

PROTOCOL NUMBER:	CPL-01_AB_001
PROTOCOL 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

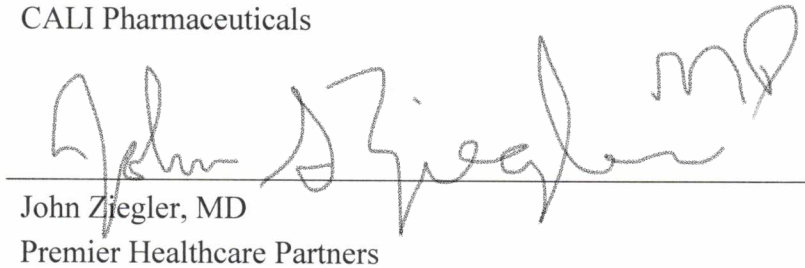
I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

SIGNATURE **DATE:**



NOV-26-2019

Lee Chen, PhD
Chief Operating Officer
CALI Pharmaceuticals



26-NOV-2019

John Ziegler, MD
Premier Healthcare Partners

2 PROTOCOL SUMMARY

2.1 Synopsis

PRODUCT NAME/NUMBER	CPL-01
PROTOCOL NUMBER	CPL-01_AB_001
DEVELOPMENT PHASE	Phase 2a
PROTOCOL 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
INDICATION	Postoperative pain management
OBJECTIVES	• To assess the safety and tolerability of CPL-01 in the management of acute postoperative pain after mini-abdominoplasty as compared with placebo. • To characterize the pharmacokinetic (PK) profile of CPL-01 during mini-abdominoplasty. • To explore the efficacy and analgesic duration of action of CPL-01 for postoperative pain during mini-abdominoplasty. • To assess the analgesic duration of action of CPL-01 as compared with placebo. • To inform the design of an ascending dose phase 2 trial of CPL-01. • To evaluate the opioid-sparing effect of CPL-01. • To evaluate the effect of CPL-01 on postoperative wound healing.
RATIONALE	NAROPIN® Injection (ropivacaine hydrochloride; Fresenius Kabi, Lake Zurich, Illinois) is approved for local or regional anesthesia for surgery and for acute pain management. The maximum approved daily dose is 300 mg when administered as a major nerve block for surgical anesthesia, and up to 200 mg as the infiltration dose for postoperative pain management. Pain relief is observed within 1 to 5 minutes but only for a duration of 2 to 6 hours when delivered by infiltration. Therefore, because of its short duration of effect, frequent injections or infusion by catheter are required if protracted local analgesia is required for postoperative pain management. A long-acting formulation could potentially prolong the duration of local analgesia for several days after a single local administration by infiltration. CALI Pharmaceuticals LLC (CALI) is developing an extended-release injectable gel formulation of ropivacaine hydrochloride (CPL-01) to prolong its duration at the local site, leading to an extended local analgesic effect as observed in several nonclinical animal models. CALI proposes opening the investigational new drug program with healthy elective surgery subjects (phase 2) rather than with healthy volunteers (phase 1) because healthy elective surgery subjects will be the clinically relevant model with an appropriate administration route (i.e., wound infiltration and instillation as opposed to subcutaneous injections) for this product. The maximum approved dose of NAROPIN (200 mg) has been selected because ropivacaine is known to be safe for postsurgical infiltration at this dose level.
STUDY DESIGN	This is a randomized, double-blind, single-site study to evaluate the safety, 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). **Study Periods:** 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), 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), 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).

	Rescue analgesia: 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 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 should be used every 6 to 8 hours as needed for analgesia (not to exceed 4000 mg 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 need 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. *Post-treatment Follow-up Period* (Days 5 and 6, 7 to 10 days, and 30 days after administration of IP): Subjects will return to the study site for collection of PK blood samples and for pain intensity assessment using an NRS at 96 and 120 hours after administration of IP (Days 5 and 6). Assessments at the Day 7-10 Follow-up Visit (7 to 10 days after administration of IP) include a full neurological examination, abbreviated physical examination, vital signs, 12-lead ECG, surgical wound site assessment (including photograph), clinical laboratory evaluations, concomitant medications, and AEs. Subjects will return their completed diary at the Day 7-10 Follow-up Visit (7 to 10 days after administration of IP or upon early termination). At the Day 30 Follow-up Visit (30 days after administration of IP), AEs and concomitant medications will be recorded and a surgical wound site assessment (including photograph) will be performed. **Study Assessments** **Pharmacokinetic measurement**: Blood samples will be collected for PK analysis at baseline (before IP administration), 15, 30, and 45 minutes (Surgical/Anesthesia Period), and at 1, 2, 4, 6, 8, 10, 12, 18, 24, 30, 36, 48, 60, and 72 hours (Post-anesthesia Period) after administration of IP. Subjects will return to the study site for collection of PK blood samples at 96 and 120 hours after administration of IP (Days 5 and 6). **Efficacy assessment**: Subjects will evaluate pain intensity 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 to collect PK blood samples (Days 5 and 6). **Safety assessments**: Safety will be assessed based on AEs, vital signs, clinical laboratory evaluations, 12-lead ECGs, physical examination, full neurological examination, LAST assessment, and wound evaluation. Safety assessments will be performed during the study at the time points shown in the Schedule of Events table.
PLANNED NUMBER OF SUBJECTS	Approximately 20 subjects 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).
STUDY ENTRY CRITERIA	Inclusion criteria: 1. Subject provides signed, written informed consent before participation in the study. 2. Subject is aged ≥18 and ≤70 years at the time of informed consent and is male or female. 3. Subject is scheduled to undergo elective mini-abdominoplasty surgery under general anesthesia without collateral procedures. 4. Subject has a BMI >19 and <30 kg/m^2. 5. Subject has an American Society of Anesthesiology subject (physical) classification status of I or II (as assessed at Screening).

	6. Female subjects are eligible only if all the following apply: a. Not pregnant (female subjects of childbearing potential must have a negative serum pregnancy test within 42 days before surgery [Screening] and a negative urine pregnancy test prior to surgery [check-in]) b. Not breastfeeding c. Not planning to become pregnant during participation in the study d. Committed to the use of an acceptable form of birth control (i.e., hormonal contraception, intrauterine device, condoms in combination with a spermicidal cream or total sexual abstinence, includes surgical sterilization and confirmed postmenopausal state) for the duration of the study until at least 30 days after administration of IP. 7. Male subjects must commit to the use of a reliable method of birth control for the duration of the study until at least 30 days after administration of IP or be surgically sterile (biologically or surgically). 8. Subject has the ability to read and understand the study procedures, use the pain scale, and to communicate meaningfully with the investigator and staff, in the opinion of the investigator. 9. Subject is free of any physical, mental, or medical conditions which, in the opinion of the investigator, make mini-abdominoplasty or study participation inadvisable. Exclusion criteria: 1. Subject has been receiving or has received chronic opioid therapy defined as any opioid for greater than 3 out of 7 days per week over a 1-month period (consecutively and/or accumulatively) within 12 months of IP initiation. 2. Subject has taken chaparral, comfrey, germander, jin bu huan, kava, pennyroyal, skullcap, St. John's wort, or valerian within 14 days before surgery. 3. Subject has a chronic pain condition or any significant medical disease, laboratory abnormality (including ECG abnormality), or condition that, in the investigator's judgment, could compromise his or her welfare, ability to communicate with the study staff, complete study activities, may confound the assessments of postoperative pain, or otherwise contraindicate study participation. 4. Subject has known hypersensitivity or known allergy, as determined by the investigator, to ropivacaine, sesame oil, soy beans, oxycodone, other opioids, acetaminophen, or the inactive ingredients (i.e., excipients) of the IP or any peri- or postoperative medications used in this study. 5. Subject has known, suspected, or reported history of alcohol or drug abuse or dependence within the previous 2 years as assessed by the investigator. 6. Subject has impaired liver function (e.g., aspartate aminotransferase/alanine aminotransferase greater than 3 times the upper limit of the reference range, bilirubin greater than 1.5 times the upper limit of the reference range unless due to Gilbert's syndrome, active hepatic disease, evidence of clinically significant liver disease, or other condition such as alcoholism, cirrhosis, or hepatitis, etc.) that suggests the potential for an increased susceptibility to hepatic toxicity with IP exposure. 7. Subject has clinically significant renal abnormalities (creatinine $\geq 1.5 \times$ upper limit of normal). 8. Subject has hemoglobin A1c $\geq 7.0\%$. 9. Subject has been treated with monoamine oxidase inhibitors within 14 days before surgery. 10. Subject has participated in another clinical study and/or received an IP (marketed or premarket) within 30 days before surgery.

	11. Subject has a history of, or positive test results for, human immunodeficiency virus, hepatitis B surface antigen, or hepatitis C virus antibody at Screening. 12. Subject has a history of a migraine headache (within past 6 months or 2 within the past 12 months) or frequent headaches (≥2 events per week requiring analgesics) as determined by the investigator, seizures, or is currently taking anticonvulsants. 13. Subject has a history of malignant hyperthermia. 14. Subject has glucose-6-phosphate dehydrogenase deficiency. 15. Subject has a positive urine drug screen test result at Screening or at check-in on the day of surgery for amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, or tetrahydrocannabinol; indicating drug use. 16. Subject has used a concurrent therapy that could interfere with the evaluation of efficacy or safety, such as any drugs that in the investigator's opinion may exert significant analgesic properties or act synergistically with the IP. 17. Subject has used corticosteroids, either systemically or by intra-articular injection, within 6 weeks prior to the study surgical procedure; inhaled, nasal, and topical steroids are allowed. 18. Subject concurrently uses potent CYP1A2 inhibitors, including cimetidine, enoxacin, fluvoxamine, ciprofloxacin (Cipro), gemifloxacin (Factive), levofloxacin (Levaquin), moxifloxacin (Avelox), norfloxacin (Noroxin), or ofloxacin (Floxin). 19. Subject has persistent or recurrent nausea and/or vomiting because of other etiologies, including, but not limited to, gastric outlet obstruction, hypercalcemia, active peptic ulcer, increased intracranial pressure, chemotherapy, or brain metastases. 20. Subject experiences a clinically significant event during surgery prior to the administration of the IP (e.g., excessive bleeding, hemodynamic instability) that would render him or her medically unstable, complicate their postsurgical course, or significantly increase the risk of IP administration as per the judgment of the investigator. 21. Subjects who have a difficult airway on preoperative screening or history of airway difficulties in the past. 22. Subject with an upper respiratory infection/cough in the 14 days before surgery. 23. Subjects with a history of significant postoperative nausea and vomiting.
TEST PRODUCT	**Name:** CPL-01 is an extended-release injectable gel formulation of ropivacaine hydrochloride **Dose, route, frequency:** 2% CPL-01 200 mg ropivacaine (10 mL) To be administered into soft tissue before closure by wound infiltration and instillation.
CONTROL PRODUCTS	**Name:** Placebo (0.9% NaCl) **Dose, route, frequency:** 0.9% NaCl (10 mL) To be administered into soft tissue before closure by wound infiltration and instillation.
TREATMENT REGIMENS	Each subject will receive 2% CPL-01 (200 mg ropivacaine [10 mL]) or placebo (0.9% NaCl) administered into soft tissue before closure after mini-abdominoplasty by wound infiltration and instillation. Subjects will be randomly assigned (3:1 ratio) to receive either 2% CPL-01 (200 mg ropivacaine) or placebo (0.9% NaCl). The following dosing method of the IP will be performed. **Materials** • Two 1 cc Luer-lock syringes • Two 5 cc Luer-lock syringes

	• Four 21 gauge needles, length 1.5 inches • 10 mL study drug (2% CPL-01 [200 mg ropivacaine] or placebo [0.9% NaCl]) **Draw Technique** Based on the randomization schedule, draw up a total of 10 mL of the study drug into the 4 syringes as follows: • Fill TWO – 1 cc Luer-lock syringes with exactly 1 mL of study drug. • Fill TWO – 5 cc Luer-lock syringes with exactly 4 mL of study drug. **Dosing Technique** 1. Plication – After plication of the diastasis recti is complete and prior to skin closure infiltrate (inject) 1 mL of the study drug using one 1 cc syringe in 5 separate, equally spaced, injections of 0.2 mL each, along the entire length of the plication of the rectus abdominus. The injections should be precisely placed along the posterior (deep) rectus sheath. 2. External Fascial Layer – Infiltrate (inject) in 2 parallel tracks using the two 5 cc syringes (total of 8 mL), lateral to the plication line along the linea semilunaris into the deep external facial layer beneath the external oblique muscle. A total of 10 injections (5 on each side) of 0.8 mL each, at equally spaced sites along the 2 semilunaris lateral tracks (4 mL each side). Carefully orient the syringe and needle at a 45 degree angle when injecting. Visualize the entire length of the needle via the translucency of the fascia to avoid deep abdominal and intramuscular injection. 3. Prior to skin closure – Instill (surface application) 1 mL of the study drug using one 1 cc syringe onto the upper third of the subcutaneous tissue along the length of the upper and lower abdominal incisions where the subcutaneous fascia emerges from the deeper tissue. Again, apply (do not inject) the study drug through the end of the needle for controlled slow application.
ANESTHESIA REGIMEN AND RESCUE ANALGESICS:	*Anesthesia:* Subjects will undergo mini-abdominoplasty under general anesthesia administered according to a standard regimen (Appendix D). *Rescue Analgesics:* 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 as needed for analgesia will be used. After the subject's pain intensity is ≤4, oral acetaminophen 1000 mg should be used every 6 to 8 hours as needed for analgesia (not to exceed 4000 mg 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.
COORDINATING/ PRINCIPAL INVESTIGATOR	Ira J. Gottlieb, DPM 8030B Governor Ritchie Hwy Suite 100 Pasadena, MD 21122, United States +1 410-761-0118
PLANNED STUDY SITES	One study site in the United States
CRITERIA FOR EVALUATION	Safety endpoints: • Adverse events • Vital signs

	• Clinical laboratory evaluations (hematology, chemistry, and urinalysis) • 12-lead ECGs • Physical examination • Full neurological examination • LAST assessment • Surgical wound site assessment (including incidence of wound infection and wound-related AEs) Pharmacokinetic endpoints: • Maximum (peak) plasma concentration (C_{max}) • Time to reach highest observed (peak) concentration in plasma following IP administration (t_{max}) • Elimination half-life ($t_{1/2}$) • Terminal elimination rate constant (λz) with the respective $t_{1/2}$ • Area under the plasma concentration-time curve (AUC) from Time 0 to time of last quantifiable plasma concentration ($AUC_{0\text{-last}}$) (Time 0 is defined as the moment that IP is administered) • AUC from Time 0 to infinity ($AUC_{0\text{-}\infty}$) Exploratory endpoints: • Time-weighted summed pain intensity over 1 to 24 hours ($SPI_{1\text{-}24}$) for CPL-01 subjects compared with placebo subjects • SPI at other time points: $SPI_{1\text{-}6}$, $SPI_{6\text{-}12}$, $SPI_{1\text{-}12}$, $SPI_{12\text{-}24}$, $SPI_{24\text{-}48}$, $SPI_{1\text{-}48}$, $SPI_{48\text{-}72}$, and $SPI_{1\text{-}72}$ for CPL-01 subjects compared with placebo subjects • Total dose of opioid rescue analgesia (morphine equivalents) over 24, 48, and 72 hours after administration of IP • Time to administration of first dose of opioid rescue analgesia • The percentage of subjects who used no opioid rescue analgesia over 24, 48, and 72 hours after administration of IP • The percentage of subjects who remain pain free over 24, 48, and 72 hours after administration of IP (pain intensity ≤ 1).
STATISTICAL METHODS	*Analysis Populations* • Intent-to-treat (ITT) Population: all subjects who are successfully screened and randomized. The ITT population will be used 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 received 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 received.

	Subject characteristics Demographic and baseline characteristics (including age, gender, race, weight, height, BMI, and prior medication) will be summarized for each treatment group and for the overall population using descriptive statistics. Medical history will be displayed in a listing. *Pharmacokinetic analysis* The PK parameters will be estimated using non-compartmental PK analysis for each subject with sufficient data to characterize the administered dose. These parameters will be summarized and a mean concentration figure with plots will be produced both with a linear y-axis and with a log y-axis. Individual concentrations will be listed, graphed, and summarized by scheduled sampling time. *Efficacy Analyses* Descriptive summaries will be provided using number of subjects, arithmetic mean, standard deviation (SD), median, minimum, and maximum. Individual NRS pain intensity scores will be tabulated for each time point and summarized descriptively by treatment group. The analysis of continuous efficacy endpoints will be performed using an analysis of variance (ANOVA) model. The ANOVA model will include the specific endpoint as the response variable (e.g., NRS SPI-t, where t=1-6, 6-12, 1-12, 1-24, 12-24, 24-48, 1-48, 48-72, 1-72, respectively) and will have Treatment as the main effect. Contrast tests will be carried out to compare CPL-01 against placebo. Since all exploratory analyses in this study are intended for hypothesis generation, there will be no adjustment for multiplicity and each analysis will be based on a 2-sided test at the significance level of 0.05. This approach will be used to analyze all continuous exploratory efficacy variables, including total dose of opioid (morphine equivalents) used over 24, 48, and 72 hours, respectively. Time to first use of opioid rescue analgesia for postoperative surgical pain will be analyzed using the Kaplan-Meier method. The log-rank test will be used to test the hypothesis of overall treatment differences. In addition, a Cox proportional hazards model will be used to allow individual contrasts tests comparing CPL-01 against placebo. Hazard ratios as well as 95% confidence intervals will be generated for each contrast. The percentage of subjects who used no opioid rescue analgesia and the percentage of subjects who remain pain free over 24, 28, and 72 hours after IP administration will be analyzed using Fisher's exact test. Additional exploratory efficacy analyses may be conducted as required. *Imputation Methods for Missing Efficacy Data* To assess the impact of missing data, multiple imputation will be used as a sensitivity analysis for the primary endpoint. *Safety Analyses* Summaries of safety results will be presented by treatment group for the safety analysis population. The latest version of the Medical Dictionary for Regulatory Activities will be used to classify all AEs by system organ class (SOC) and preferred term (PT). The number and percentage of subjects with treatment-emergent AEs will be summarized by SOC, PT, and treatment group. Serious AEs will be summarized in a similar fashion. Treatment-emergent AEs and SAEs will also be presented by severity and by relationship. All AEs will be presented in full in a comprehensive listing. Details of SAEs and AEs leading to withdrawal will be listed separately.

	Descriptive summaries of actual values and changes from baseline for vital signs measurements, clinical laboratory values, and ECGs will be presented by study visit and by treatment group. A descriptive summary of the RASS assessment will be presented by study visit and by treatment group. A descriptive summary of surgical wound site assessment findings (including wound infection and wound related AEs) at the Day 7-10 Follow-up Visit (7 to 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. Surgical wound site assessment findings at 24, 48, 72, 96, and 120 hours after IP administration will be displayed in a listing. Physical and neurological examination results will be displayed in a listing.
RANDOMIZATION AND BLINDING	Subjects will be randomized in a 3:1 ratio to 2% CPL-01 (200 mg ropivacaine) or placebo (0.9% NaCl). Subjects and all study personnel involved in postoperative pain assessments will be blinded to the treatment assignment.
SAMPLE SIZE DETERMINATION	This is a proof-of-concept study with a primary goal of estimation rather than hypothesis testing. The sample sizes are consistent with similar studies of this type, but are not based on power considerations for specific treatment-effect sizes.
STUDY AND TREATMENT DURATION	The overall study duration is expected to be approximately 3 months. The study includes a Screening Period, Surgical/Anesthesia Period, Post-anesthesia Period; and Post-treatment Follow-up Period: The sequence and maximum duration of the study periods for each subject will be as follows: 1. Screening Period: 42 days 2. Surgical/Anesthesia Period: 1 day 3. Post-anesthesia Period: 4 days 4. Post-treatment Follow-up Period: Days 5 and 6 Assessments: 2 days Day 7-10 Follow-up Visit: 7 to 10 days after administration of IP Day 30 Follow-up Visit: 30 days after administration of IP The maximum study duration for each subject is approximately 73 days.

2.2 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 (Appendix A), 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 (Appendix D), 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 (see Section 9.2.1).

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 (see Appendix B) 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 (Appendix C). 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.

3 TABLE OF CONTENTS

3.1 List of In-Text Figures

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	EXPLANATION
AE	adverse event
ANOVA	analysis of variance
AUC	area under the plasma concentration-time curve
BMI	body mass index
CALI	CALI Pharmaceuticals LLC
CFR	Code of Federal Regulations
C_{max}	maximum peak plasma concentration
CRA	clinical research associate
CSR	clinical study report
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HED	human equivalent dose
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	Investigational New Drug
IP	investigational product
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous
IVP	intravenous push
LAST	local anesthetic systemic toxicity
MAC	minimum alveolar concentration
MOE	margins of exposure
MOS	margins of safety
MTD	maximum tolerated dose
NRS	numeric rating scale
PK	pharmacokinetic(s)
PT	preferred term
RASS	Richmond Agitation and Sedation Scale
RBC	red blood cell
SAE	serious adverse event

ABBREVIATION	EXPLANATION
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SPI_{1-24}	summed pain intensity over 1 to 24 hours
$t_{1/2}$	elimination half-life
t_{max}	time to reach highest observed (peak) concentration in plasma following drug administration
US	United States

5 INTRODUCTION

5.1 Background and Rationale

The use of local anesthetics within a surgical wound (i.e., wound infiltration) has been used extensively in a vast number of patients[1] as a relatively simple and safe means to reduce postoperative pain.[2] Local anesthetics block the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

Current local anesthetics used for infiltration are limited by their duration of effect (6-12 hours) after surgery.[3] For day-case surgery, it is estimated that 30 to 40% of patients experience moderate to severe pain during the first 24 to 48 hours. Therefore, the development of a long-acting local anesthetic formulation for this patient population is needed.[4]

NAROPIN® (ropivacaine HCl) Injection, a member of the amino amide class of local anesthetics, is approved for local or regional surgical anesthesia and for acute pain management.[5] The maximum daily dose of NAROPIN is 300 mg when administered as a major nerve block for surgical anesthesia and up to 200 mg when administered as an infiltration dose for postoperative pain management. Pain relief is observed within 1 to 5 minutes but only for a duration of 2 to 6 hours when delivered by infiltration. Therefore, frequent injections would be required if protracted local analgesia by infiltration is desired for postoperative pain management.

A long-acting formulation could potentially prolong the duration of local analgesia for several days after a single local administration by infiltration. CALI Pharmaceuticals, LLC (CALI) is developing an extended-release injectable gel formulation of ropivacaine hydrochloride (CPL-01) to prolong its duration at the local site, leading to an extended local analgesic effect. This extended-release, single-phase, slightly viscous (mineral oil like) liquid formulation has been tested in several nonclinical animal models. CPL-01 has been tested by several surgeons and demonstrated to be injectable manually through combinations of needles and syringes. The extended release is achieved by a local in-situ depot mechanism, which is generated by a novel proprietary phospholipid gel-based formulation technology (PG Depot). A long-acting formulation could potentially prolong the duration of local analgesia for several days after a single local administration.

CALI Pharmaceuticals LLC (CALI) proposes opening the Investigational New Drug application with healthy elective surgery subjects (phase 2) rather than with healthy volunteers (phase 1) because healthy elective surgery subjects will be the clinically relevant model with an appropriate administration route (i.e., wound infiltration and instillation as opposed to subcutaneous (SC) injections) for this product.

The present study is designed to evaluate the safety and pharmacokinetic (PK) profile of CPL-01 in men and women ≥18 and ≤70 years of age for the management of postoperative pain after mini-abdominoplasty surgery.

5.2 Nonclinical Experience

The efficacy of CPL-01 was evaluated in the guinea pig pin-prick pain model (Study ZJPC20170413). CPL-01 (1% or 2% ropivacaine) exhibited prolonged local anesthetic efficacy compared with 1% ropivacaine HCl aqueous solution (same as NAROPIN). The clinical strength of CPL-01 (2% ropivacaine) exhibited an analgesic effect within 15 minutes with significant efficacy (≥50%) sustained for 12 to 13 hours after administration, 4-fold longer than the 1% ropivacaine HCl aqueous solution.

Pharmacokinetic (PK) evaluation of CPL-01 (2% or 4% ropivacaine) by single subcutaneous (SC) administration has been performed in rats (Study 03051-17003, Study 03051-17005, and Study 03051-17008), and in minipigs (Study 03051-17004, Study 03051-17006, and Study 03051-17009). These studies indicated that ropivacaine t_{max} ranged from 0.5 to 4 hours postdose in rats and 5 to 11 hours postdose in minipigs, with a $t_{1/2}$ of 13 to 35 hours in rats and 17 to 46 hours in minipigs. Following wound infiltration and instillation of CPL-01 in minipigs (Study S10065), the t_{max} ranged from 1 to 5 hours postdose, with a $t_{1/2}$ ranging from 18 to 31 hours. In contrast, the t_{max} for NAROPIN (1% ropivacaine HCl) was generally between 0.25 and 1 hour in both species, with a $t_{1/2}$ of ≤1 hour in rats and 6 to 7 hours in minipigs. Overall, the t_{max} and $t_{1/2}$ of ropivacaine following CPL-01 were later and longer than NAROPIN, and the dose normalized C_{max} of CPL-01 were 70% to 95% lower than that of NAROPIN in both species.

In an SC toxicity study in rats (Study 03051-17008), single SC administration of CPL-01 at 50, 200, or 400 mg/kg in Sprague-Dawley rats was well tolerated, and test article-related toxicity was limited to reversible, non-adverse injection site reactions observed mainly in the higher dose/injection volume groups (200 and 400 mg/kg). There were no abnormalities in clinical observations or gross observation of local injection sites at 50 mg/kg. The local effects of the injection site at higher doses were the result of the formulation depot, which was designed for a slow release of ropivacaine over time prior to resorption of the formulation matrix. Compared with the NAROPIN formulation, which resulted in death after a single administration at a dose of 44 mg/kg, CPL-01 at 50 mg/kg exhibited a significantly lower systemic C_{max} (approximately 84% lower) and no systemic toxicity. Overall, the maximum tolerated dose (MTD) for single subcutaneous injection of CPL-01 in Sprague-Dawley rats was determined to be 400 mg/kg, which corresponds to a Human Equivalent Dose (HED) of 3,871 mg based on body surface area (assuming a 60 kg human).

In an SC toxicity study in minipigs (Study 03051-17009), CPL-01 15, 30 or 60 mg/kg was well tolerated. Test article-related toxicity was limited to reversible, non-adverse, minimal to mild injection site reactions, which were observed in all dosing groups, including the CPL-01 vehicle group. All injection sites had returned to normal by Day 30. No systemic clinical signs or systemic toxicity by histopathological evaluation of selected organs were noted at any CPL-01 dose. Compared with the NAROPIN formulation, CPL-01 at higher doses (2- to 8-fold) showed a similar safety profile, which likely benefits from a significantly lower C_{max} and prolonged $t_{1/2}$ of ropivacaine. Overall, the MTD for a single subcutaneous injection of CPL-01 in Ba-Ma Minipig was determined to be 60 mg/kg, which corresponds to an HED of 3,273 mg based on body surface area (assuming 60 kg human).

In a wound infiltration and instillation toxicity/wound healing study in minipigs (Study S16005), CPL-01 was administered into a 6 to 10 cm abdominal incision at midline down to the peritoneum at doses of 0 (vehicle), 10, 20, and 40 mg/kg. Each group had a 3-day and 28-day cohort (N=3 animals/group/sex/cohort). All doses of CPL-01 were well tolerated. There were no adverse

clinical observations or CPL-01-related effects on food consumption, body weight, ophthalmology, electrocardiographic assessment (heart rate, RR interval, PR interval, QRS duration, QT interval, or QTc interval), or systemic gross observations or microscopic findings in any of the non-wound site organs/tissues at any dose level. CPL-01 at 0 (vehicle control), 10, 20, or 40 mg/kg caused transient, mild to moderate local tissue reactions including local response to the vehicle (macrophage infiltrates) within the subcutis that was considered non-adverse, biocompatible, and tolerable. The majority of wounds treated with CPL-01 were completely re-epithelialized by Day 29, and tensile strength testing of the incisional site skin tissues indicated nearly completed recovery relative to normal intact skin at Day 29 for all treatment groups. In conclusion, there was no evidence of significant local or systemic toxicity due to administration, indicating that the NOAEL of CPL 01 is above 40 mg/kg for a single wound infiltration and instillation administration.

Margin of Safety (MOS) based on dose: The NOAEL dose of CPL-01 at 40 mg/kg ropivacaine (HED = 2182 mg, assumes 60 kg human) by wound infiltration and instillation in minipigs provides a 10-fold MOS for a clinical dose of 200 mg ropivacaine.

Margin of Exposure (MOE) was calculated relative to a human AUC_{0-t} of approximately 11,600 ng*h/mL ropivacaine following a dose of 300 mg ropivacaine HCl (NAROPIN) by infiltration following hernia surgery.[6] At the NOAEL dose of CPL-01 at 40 mg/kg ropivacaine by wound infiltration and instillation in minipigs, a combined male and female AUC_{0-t} of approximately 42,700 ng*h/mL was obtained, providing an approximately 4-fold safety MOE compared with the human exposure following infiltration of a surgical wound after hernia surgery.

5.3 Clinical Experience

This is a first-in-human study.

5.4 Summary of Potential Risks and Benefits

Like other amino amide local anesthetics, the adverse effects that may be associated with CPL-01 when administered by wound infiltration include the classic symptoms of local anesthetic systemic toxicity (LAST). These symptoms, though unlikely to occur, might include early neurological symptoms such as circumoral and/or tongue numbness, metallic taste, lightheadedness and/or dizziness; and cardiovascular symptoms such as hypotension and arrhythmia. Later symptoms, which are very unlikely in this study, include visual and visual and auditory disturbances (difficulty focusing and tinnitus), disorientation, drowsiness, agitation, and seizures. Given the single moderate local anesthetic dose being used in this study, respiratory and cardiovascular symptoms observed in more severe local anesthetic toxicity are a theoretical concern only and are not expected to occur.

The potential benefit of study participation is that subjects with postsurgical pain from elective abdominoplasty may experience a reduction in their pain over a longer period of time compared with NAROPIN as a result of treatment with CPL-01. With this longer duration of anesthetic effect, there is an expectation that less opioid rescue medication will be needed. No other benefits of participation are anticipated.

CPL-01 is contraindicated in subjects with known hypersensitivity to ropivacaine or to any local anesthetic agent of the amide type. A major cause of adverse reactions to this group of drugs may be associated with excessive plasma levels, which may be due to overdose, unintentional intravascular injection, or slow metabolic degradation.

A population with healthy elective surgery subjects rather than healthy volunteers was selected because they will be the clinically relevant model for wound infiltration administration of this product.

The potential risks of study participation include those associated with exposure to CPL-01 and the risks of surgery and medical evaluation, including venipuncture.

A summary of the pharmaceutical properties and known potential risks of ropivacaine HCl is provided in the prescribing information for NAROPIN.[5]

6 OBJECTIVES AND ENDPOINTS

6.1 Objectives

The objectives of the study are as follows:

- To assess the safety and tolerability of CPL-01 in the management of acute postoperative pain after mini-abdominoplasty compared with placebo.
- To characterize the pharmacokinetic (PK) profile of CPL-01 during mini-abdominoplasty.
- To explore the efficacy and analgesic duration of action of CPL-01 for postoperative pain during mini-abdominoplasty compared with placebo.
- To inform the design of an ascending dose phase 2 trial of CPL-01.
- To evaluate the opioid-sparing effect of CPL-01.
- To evaluate the effect of CPL-01 on postoperative wound healing.

6.2 Endpoints

6.2.1 Safety Endpoints

The safety endpoints are as follows:

- Adverse events (AEs)
- Vital signs
- Clinical laboratory evaluations (hematology, chemistry, and urinalysis)
- 12-lead electrocardiograms (ECGs)
- Physical examination
- Full neurological examination
- LAST assessment
- Surgical wound site assessment (including incidence of wound infection and wound-related AEs)

6.2.2 Pharmacokinetic Endpoints

The PK and bioavailability endpoints are as follows:

- Maximum (peak) plasma concentration (C_{max})
- Time to reach highest observed (peak) concentration in plasma following IP administration (t_{max})
- Elimination half-life ($t_{1/2}$)
- Terminal elimination rate constant (λz) with the respective $t_{1/2}$
- Area under the plasma concentration-time curve (AUC) from Time 0 to time of last quantifiable plasma concentration ($AUC_{0\text{-}last}$) (Time 0 is defined as the moment that IP is administered)

- AUC from Time 0 to infinity ($AUC_{0-\infty}$)

6.2.3 Exploratory Endpoints

The exploratory endpoints are as follows:

- Time-weighted summed pain intensity over 1 to 24 hours (SPI_{1-24}) for CPL-01 subjects compared with placebo subjects
- SPI at other time points: SPI_{1-6}, SPI_{6-12}, SPI_{1-12}, SPI_{12-24}, $SPI2_{4-48}$, SPI_{1-48}, SPI_{48-72}, and SPI_{1-72} for CPL-01 subjects compared with placebo subjects
- Total dose of opioid rescue analgesia (morphine equivalents) over 24, 48, and 72 hours after administration of IP
- Time to administration of first dose of opioid rescue analgesia
- The percentage of subjects who used no opioid rescue analgesia over 24, 48, and 72 hours after administration of IP
- The percentage of subjects who remain pain free over 24, 48, and 72 hours after administration of IP (pain intensity $\leq$1).

7 STUDY DESIGN

7.1 Overall Study Design and Plan

This is a randomized, double-blind, single-site study to evaluate the safety, 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. The details of the procedures for each period are included in the schedule of events (Section 2.2) and Section 10.

7.2 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 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.

7.3 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), 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.

7.4 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 LAST assessment (including vital signs, Richmond Agitation and Sedation Scale [RASS] assessment [Appendix A], and focused

neurological examination), 12-lead ECG, pain intensity assessments, surgical wound site assessment (including photograph), concomitant medications, and 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 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. 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).

Rescue analgesia: 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 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 should be used every 6 to 8 hours as needed for analgesia (not to exceed 4000 mg 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.

7.5 Post-treatment Follow-up Period (Days 5 and 6, 7 to 10 days, and 30 days after administration of IP)

Subjects will return to the study site for collection of PK blood samples and for pain intensity assessment using an NRS at 96 and 120 hours after administration of IP (Days 5 and 6). Assessments at the Day 7-10 Follow-up Visit (7 to 10 days after administration of IP) include full neurological examination, abbreviated physical examination, vital signs, 12-lead ECG, surgical wound site assessment (including photograph), clinical laboratory evaluations, concomitant medications, and AEs. Subjects will return their completed diary at the Day 7-10 Follow-up Visit (7 to 10 days after administration of IP or upon early termination).

At the Day 30 Follow-up Visit (30 days after administration of IP), AEs and concomitant medications will be recorded and a surgical wound site assessment (including photograph) will be performed.

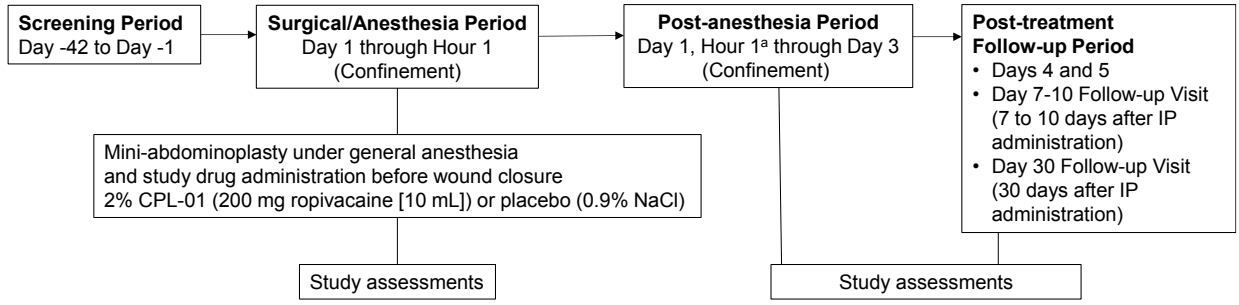
7.6 Study Assessments

Blood samples will be collected for PK analysis at baseline (before IP administration), 15, 30, and 45 minutes (Surgical/Anesthesia Period), and at 1, 2, 4, 6, 8, 10, 12, 18, 24, 30, 36, 48, 60, and 72 hours (Post-anesthesia Period) after administration of IP. Subjects will return to the study site for collection of PK blood samples at 96 and 120 hours after administration of IP (Days 5 and 6).

Subjects will evaluate pain intensity 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 to collect PK blood samples (Days 5 and 6).

Safety will be assessed based on AEs, vital signs, clinical laboratory evaluations, 12-lead ECGs, physical examination, full neurological examination, LAST assessment, and wound evaluation. Safety assessments will be performed during the study at the time points shown in the Schedule of Events table.

Figure 7-1: Study Design



IP = investigational product
a One hour after administration of IP.

7.7 Rationale and Discussion of Study Design

Subjects will be randomly assigned to CPL-01 or placebo and both the subject and any individuals directly involved in pain assessment are blinded to prevent bias. It is difficult for the surgeon to remain blinded since the appearance and consistency of CPL-01 differs significantly from placebo. However randomization of the subject will prevent bias on the part of the surgeon.

This study will explore the analgesic effects of administration of CPL-01 in an accepted model of postoperative pain. Mini-abdominoplasty surgery produces generally reliable and persistent pain symptoms for a period typically lasting over 72 hours from the surgical insult, which will allow for analysis of acute analgesic effect of CPL-01 over an extended period of time.

Healthy elective surgery subjects rather than healthy volunteers were selected because they will be the clinically relevant model for wound infiltration administration of this product.

Efficacy measures will be collected to gain a better knowledge of the analgesic effect time curve of CPL-01 compared with placebo (0.9% NaCl) following a surgical procedure. In addition, the study will further characterize the safety and PK profile of CPL-01 and inform the design of future safety and efficacy trials.

The timing and frequency of the PK blood draws are designed to determine the C_{max} as well as the overall systemic exposure.

7.8 Selection of Doses in the Study

The proposed starting human clinical dose of 200 mg ropivacaine in CPL-01 is well supported by the current nonclinical results in rats and minipigs (see Section 5.2). Ropivacaine is known to be safe for postsurgical infiltration at this dose level. In rats (Study 3051-17008), the CPL-01 maximally tolerated dose (HED of 3871 mg ropivacaine) provided an approximately 19-fold MOS based on dose relative to the proposed clinical dose of 200 mg/subject. In minipigs following

wound infiltration and instillation of CPL-01 (Study S16005), the CPL-01 NOAEL dose (HED of 2182 mg ropivacaine) provided an approximately 10-fold MOS relative to the proposed clinical dose of 200 mg/subject and an approximately 4-fold safety MOE relative to the human exposure (AUC_{0-t}) at an infiltration dose of 300 mg ropivacaine HCl (NAROPIN) following hernia surgery.[6]

7.9 Study Sites

The study will take place at 1 study site in the United States (US).

7.10 End of Study Definition

The clinical trial will be considered completed when the last subject's last Day 30 Follow-up Visit (30 days after administration of IP) has occurred.

8 SUBJECT POPULATION

8.1 Selection of Study Population

Approximately 20 subjects between 18 and 70 years who are scheduled to undergo elective mini-abdominoplasty surgery will be enrolled in the study. A screening log of potential study candidates and an enrollment log of enrolled subjects must be maintained at the study site.

Subjects who do not meet all of the eligibility criteria will not be enrolled.

8.2 Study Entry Criteria

To adequately assess the PK and safety of CPL-01, only subjects who are undergoing elective mini-abdominoplasty surgery should be enrolled.

8.2.1 Inclusion Criteria

A subject will be eligible for study participation if he or she meets all of the following criteria:

1. Subject provides signed, written informed consent before participation in the study.
2. Subject is aged ≥18 and ≤70 years at the time of informed consent and is male or female.
3. Subject is scheduled to undergo elective mini-abdominoplasty surgery under general anesthesia without collateral procedures.
4. Subject has a BMI >19 and <30 kg/m^2.
5. Subject has an American Society of Anesthesiology subject (physical) classification status of I or II (as assessed at Screening).
6. Female subjects are eligible only if all the following apply:
    a. Not pregnant (female subjects of childbearing potential must have a negative serum pregnancy test within 42 days before surgery [Screening] and a negative urine pregnancy test prior to surgery [check-in])
    b. Not breastfeeding
    c. Not planning to become pregnant during participation in the study
    d. Committed to the use of an acceptable form of birth control (i.e., hormonal contraception, intrauterine device, condoms in combination with a spermicidal cream or total sexual abstinence, includes surgical sterilization and confirmed postmenopausal state) for the duration of the study until at least 30 days after administration of IP.
7. Male subjects must commit to the use of a reliable method of birth control for the duration of the study until at least 30 days after administration of IP or be surgically sterile (biologically or surgically).
8. Subject has the ability to read and understand the study procedures, use the pain scale, and to communicate meaningfully with the investigator and staff, in the opinion of the investigator.
9. Subject is free of any physical, mental, or medical conditions which, in the opinion of the investigator, make mini-abdominoplasty or study participation inadvisable.

8.2.2 Exclusion Criteria

A subject will be excluded from the study if he or she meets any of the following criteria:

1. Subject has been receiving or has received chronic opioid therapy defined as any opioid for greater than 3 out of 7 days per week over a 1-month period within 12 months of IP initiation.
2. Subject has taken chaparral, comfrey, germander, jin bu huan, kava, pennyroyal, skullcap, St. John's wort, or valerian within 14 days before surgery.
3. Subject has a chronic pain condition or any significant medical disease, laboratory abnormality (including ECG abnormality), or condition that, in the investigator's judgment, could compromise his or her welfare, ability to communicate with the study staff, complete study activities, may confound the assessments of postoperative pain, or otherwise contraindicate study participation.
4. Subject has known hypersensitivity or known allergy, as determined by the investigator, to ropivacaine, sesame oil, soy beans, oxycodone, other opioids, acetaminophen, or the inactive ingredients (i.e., excipients) of the IP or any peri- or postoperative medications used in this study.
5. Subject has known, suspected or reported history of alcohol or drug abuse or dependence within the previous 2 years as assessed by the investigator.
6. Subject has impaired liver function (e.g., aspartate aminotransferase/alanine aminotransferase greater than 3 times the upper limit of the reference range, bilirubin greater than 1.5 times the upper limit of the reference range unless due to Gilbert's syndrome, active hepatic disease, evidence of clinically significant liver disease, or other condition such as alcoholism, cirrhosis, or hepatitis, etc.) that suggests the potential for an increased susceptibility to hepatic toxicity with IP exposure.
7. Subject has clinically significant renal abnormalities (creatinine $\geq 1.5 \times$ upper limit of normal).
8. Subject has hemoglobin A1c $\geq 7.0\%$.
9. Subject has been treated with monoamine oxidase inhibitors within 14 days before surgery.
10. Subject has participated in another clinical study and/or received an IP (marketed or premarket) within 30 days before surgery.
11. Subject has a history of, or positive test results for, human immunodeficiency virus, hepatitis B surface antigen, or hepatitis C virus antibody at Screening.
12. Subject has a history of a migraine headache (within past 6 months or 2 within the past 12 months) or frequent headaches (≥ 2 events per week requiring analgesics) as determined by the investigator, seizures, or is currently taking anticonvulsants.
13. Subject has a history of malignant hyperthermia.
14. Subject has glucose-6-phosphate dehydrogenase deficiency.
15. Subject has a positive urine drug screen test result at Screening or at check-in on the day of surgery for amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, or tetrahydrocannabinol; indicating drug use.

16. Subject has used a concurrent therapy that could interfere with the evaluation of efficacy or safety, such as any drugs that in the investigator's opinion may exert significant analgesic properties or act synergistically with the IP.
17. Subject has used corticosteroids, either systemically or by intra-articular injection, within 6 weeks prior to the study surgical procedure; inhaled, nasal, and topical steroids are allowed.
18. Subject concurrently uses potent CYP1A2 inhibitors, including cimetidine, enoxacin, fluvoxamine, ciprofloxacin (Cipro), gemifloxacin (Factive), levofloxacin (Levaquin), moxifloxacin (Avelox), norfloxacin (Noroxin), or ofloxacin (Floxin).
19. Subject has persistent or recurrent nausea and/or vomiting because of other etiologies, including, but not limited to, gastric outlet obstruction, hypercalcemia, active peptic ulcer, increased intracranial pressure, chemotherapy, or brain metastases.
20. Subject experiences a clinically significant event during surgery prior to the administration of the IP (e.g., excessive bleeding, hemodynamic instability) that would render him or her medically unstable, complicate their postsurgical course, or significantly increase the risk of IP administration as per the judgment of the investigator.
21. Subjects who have a difficult airway on preoperative screening or history of airway difficulties in the past.
22. Subject with an upper respiratory infection/cough in the 14 days before surgery.
23. Subjects with a history of significant postoperative nausea and vomiting.

8.3 Premature Subject Withdrawal

All subjects will be advised that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. The investigator should make every reasonable attempt to keep subjects in the study; however, subjects must be withdrawn from the study if they withdraw consent to participate. Investigators must attempt to contact subjects who fail to attend scheduled visits by telephone or other means to exclude the possibility of an AE being the cause of withdrawal. Should this be the cause, the AE must be documented, reported, and followed as described in Section 11.2.

The sponsor reserves the right to request the withdrawal of a subject due to protocol deviations or other reasons.

The investigator also has the right to withdraw subjects from the study at any time for lack of therapeutic effect that is intolerable or otherwise unacceptable to the subject, for intolerable or unacceptable AEs, intercurrent illness, noncompliance with study procedures, administrative reasons, or in the investigator's opinion, to protect the subject's best interest.

If a subject is withdrawn before completing the study, the reason for withdrawal and the date of discontinuation will be recorded on the appropriate page of the electronic case report form (eCRF). Whenever possible and reasonable, the evaluations that were to be conducted at the completion of the study should be performed at the time of premature discontinuation.

8.4 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study noncompliance
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the participant's best interest
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the eCRF. Subjects who sign the informed consent form (ICF) and are randomized but do not receive the study intervention may be replaced. Subjects who sign the ICF, are randomized, and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study will not be replaced. For subjects not completing the 24 hours of PK sampling, additional subjects may be added at the sponsor's discretion.

A participant will be considered lost to follow-up if he or she fails to return for the Day 7-10 Follow-up Visit (7 to 10 days after administration of IP) and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9 TREATMENTS

9.1 Identification of Investigational Products

CPL-01 is an extended-release injectable gel formulation of ropivacaine hydrochloride.

CPL-01 will be provided in the form of 2% ropivacaine in 10 mL glass vials (200 mg dose/vial) at the strength of 20 mg/mL (manufactured by Bioserv; San Diego, CA).

Placebo (0.9% NaCl) will be supplied by the study site.

9.2 Treatments Administered

Each subject will be randomly assigned (3:1 ratio) to receive 2% CPL-01 (200 mg ropivacaine [10 mL]) or placebo (0.9% NaCl) administered into soft tissue before closure after mini-abdominoplasty by wound infiltration and instillation.

The mini-abdominoplasty soft-tissue model is best suited for wound infiltration into 2 anatomic areas, the plication area of the rectus sheath and along the length of the incision.

9.2.1 Investigational Product Administration

The following dosing method of the IP will be performed.

Materials

- Two 1 cc Luer-lock syringes
- Two 5 cc Luer-lock syringes
- Four 21 gauge needles, length 1.5 inches
- 10 mL study drug (2% CPL-01 [200 mg ropivacaine] or placebo [0.9% NaCl])

Draw Technique

Based on the randomization schedule, draw up a total of 10 mL of the study drug into the 4 syringes as follows:

- Fill TWO – 1 cc Luer-lock syringes with exactly 1 mL of study drug.
- Fill TWO – 5 cc Luer-lock syringes with exactly 4 mL of study drug.

Dosing Technique

1. Plication – After plication of the diastasis recti is complete and prior to skin closure infiltrate (inject) 1 mL of the study drug using one 1 cc syringe in 5 separate, equally spaced, injections of 0.2 mL each, along the entire length of the plication of the rectus abdominus. The injections should be precisely placed along the posterior (deep) rectus sheath.
2. External Fascial Layer – Infiltrate (inject) in 2 parallel tracks using the two 5 cc syringes (total of 8 mL), lateral to the plication line along the linea semilunaris into the deep external facial layer beneath the external oblique muscle. A total of 10 injections (5 on each side) of 0.8 mL each, at equally spaced sites along the 2 semilunaris lateral tracks (4 mL each side). Carefully orient the syringe and needle at a 45 degree angle when injecting. Visualize

the entire length of the needle via the translucency of the fascia to avoid deep abdominal and intramuscular injection.

3. Prior to skin closure – Instill (surface application) 1 mL of the study drug using one 1 cc syringe onto the upper third of the subcutaneous tissue along the length of the upper and lower abdominal incisions where the subcutaneous fascia emerges from the deeper tissue. Again, apply (do not inject) the study drug through the end of the needle for controlled slow application.

9.2.2 Rescue Medication

The study site will supply rescue analgesia that will be obtained locally.

Subjects with inadequately controlled pain symptoms may request 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 as needed for analgesia will be used. After the subject's pain intensity is ≤4, oral acetaminophen 1000 mg should be used every 6 to 8 hours as needed for analgesia (not to exceed 4000 mg 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.

The date and time of rescue analgesia, as well as the name and dosage regimen, must be recorded.

9.3 Selection of Timing of Dose for Each Subject

Subjects will be administered general anesthesia according to a standard regimen (Appendix D), during which they will undergo a mini-abdominoplasty at the study site. At the end of the surgical procedure but before the wound is closed, the IP will be administered by wound infiltration and instillation (Time 0). 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 confined to the study site through Day 4 for study assessments and return to the study site at 96 and 120 hours and 7 to 10 days after administration of IP for PK and safety assessments. The study procedure details are provided in Section 2.2 and Section 10.

9.4 Treatment Compliance

All subjects will receive the IP at the study site under the surveillance of appropriate study personnel.

9.5 Method of Assigning Subjects to Treatment Groups

Subjects who meet study entry criteria will be randomly assigned in a 3:1 ratio to CPL-01 or placebo.

The randomization schedule will be computer generated using a permuted block algorithm and will randomly allocate IP to randomization numbers.

The randomization schedule will be prepared by a specified unblinded statistician before the start of the study. No subject will be randomized into this study more than once.

9.6 Blinding and Unblinding Treatment Assignment

All personnel involved with evaluating the safety and efficacy of the treatment will remain blinded to the treatment that the subjects receive. The following individuals will be unblinded: the pharmacist (or qualified designee), anesthesia provider, the surgeon at the study site, the clinical research associate (CRA) performing drug accountability, a specified statistician (who will prepare the randomization schedule), and other operating room personnel. The unblinded study personnel will not participate in postoperative evaluations or data analysis prior to unblinding of the study data to all study-related personnel.

Study site personnel will make every effort to safeguard the integrity of the study blind to minimize bias in the conduct of the study. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment.

Unblinding should be discussed in advance with the medical monitor, if possible. For emergency unblinding, study site personnel should contact the medical monitor to discuss the need to determine the IP received by the subject.

Overall unblinding will take place at the end of the study only after database lock has been achieved.

9.7 Permitted and Prohibited Therapies

All concomitant medications used (including over-the-counter medications and herbal supplements) will be recorded in the source document and on the appropriate eCRF.

9.7.1 Permitted Therapies

Subjects with inadequately controlled pain symptoms may request rescue analgesia. After administration of the IP, rescue analgesia will be restricted to 2 to 4 mg 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 should be used every 6 to 8 hours as needed for analgesia (not to exceed 4000 mg 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.

The package inserts for the rescue medications to be used during the study will be provided to each investigator.

Other non-analgesic concomitant medications are allowed, but should be limited to those medications considered necessary.

9.7.2 Prohibited Therapies

All concomitant medications used (including over-the-counter medications and herbal supplements) will be recorded in the source document and on the appropriate eCRF.

The following therapies are prohibited within the specified period and during the study:

- Chronic opioid therapy defined as greater than 15 morphine-equivalent units per day for greater than 3 out of 7 days per week over a 1-month period within 12 months of IP initiation
- Chaparral, comfrey, germander, jin bu huan, kava, pennyroyal, skullcap, St. John's wort, or valerian within 14 days before surgery
- Amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, or tetrahydrocannabinol as indicated by positive urine drug screen test result
- Concurrent therapy that could interfere with the evaluation of efficacy or safety, such as any drugs that in the investigator's opinion may exert significant analgesic properties or act synergistically with the IP
- Concurrent use of potent CYP1A2 inhibitors, including cimetidine, enoxacin, fluvoxamine, ciprofloxacin (Cipro), gemifloxacin (Factive), levofloxacin (Levaquin), moxifloxacin (Avelox), norfloxacin (Noroxin), or ofloxacin (Floxin)

Subjects receiving excluded therapies will be ineligible for study enrollment. If subjects receive excluded therapies after enrollment, continuation in the study will be at the discretion of the safety monitoring group.

9.7.3 Restrictions

There will be no dietary restrictions during the study aside from the normal surgical dietary restrictions. Subjects must be at rest for a minimum of 15 minutes in the resting position before any assessments are performed, unless otherwise indicated in the schedule of events (Section 2.2).

9.8 Treatment After End of Study

After the end of the study, each subject will be treated according to standard clinical practice.

9.9 Dispensing and Storage

The test product supplied by CALI is to be used exclusively in the clinical study according to the instructions of this protocol. The investigator is responsible for dispensing the IP according to the dosage scheme and for ensuring its proper storage.

The investigator must confirm the receipt of the IP with his or her signature. A copy of this receipt must be kept by the investigator and another copy will be stored at Rho. Until the IP is dispensed to subjects, CPL-01 must be stored at 2 to 8℃ in a securely locked area that is not generally accessible. Placebo can be stored at room temperature in a securely locked area.

The key to the storage area is to be kept by the investigator or designee responsible for the IP. The store will be accessible only to those persons authorized by the investigator to dispense the IP.

9.10 Drug Accountability

The investigator must maintain adequate records showing the receipt, dispensing, return, or other disposition of the IPs, including the date, quantity, batch or code number, and identification of subjects (subject number and initials) who received them. The investigator will not supply the IPs to any person, except those named as subinvestigators on Form FDA 1572, designated study personnel, and subjects in this study. The investigator will not dispense the IPs from any study sites other than those listed on Form FDA 1572. The IPs may not be relabeled or reassigned for use by other subjects. If any of the IPs are not dispensed, are lost, stolen, spilled, unusable, or are received in a damaged container, this information must be documented and reported to the sponsor and appropriate regulatory agencies, as required.

Drug accountability will be monitored by an unblinded CRA during the study. Their reports will go to an unblinded clinical manager who will review them for accuracy. These will not be provided to the sponsor during the study but will be placed in the eTMF until after the study is unblinded.

9.11 Labeling and Packaging

CPL-01 will be packaged in vials and labeled with study-specific information meeting all applicable regulatory requirements.

Save all empty packaging or packaging containing unused IP for final disposition by the sponsor or contract pharmacy.

10 STUDY PROCEDURES

Subjects must provide written informed consent before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

For the timing of assessments and procedures throughout the study, refer to the schedule of events (Section 2.2). Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the schedule of events for each subject. If a subject misses a study visit for any reason, the visit should be rescheduled as soon as possible.

10.1 Study Duration

The overall study duration is expected to be approximately 3 months.

The planned sequence and maximum duration of the study periods for each subject will be as follows:

1. Screening period: 42 days
2. Surgical/anesthesia period: 1 day
3. Post-anesthesia period: 4 days
4. Post-treatment follow-up:
   Days 5 and 6 Assessments: 2 days
   Day 7-10 Follow-up Visit: 7 to 10 days after administration of IP
   Day 30 Follow-up Visit: 30 days after administration of IP

The maximum study duration for each subject is approximately 73 days.

10.2 Study Periods and Visits

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 indicated.

10.2.1 Screening Period (-42 Days to -1 Day Before Surgery)

The subject must be screened within 42 days before surgery. The following procedures will be performed at Screening:

- Obtain written informed consent.
- Assess inclusion/exclusion criteria.
- Collect demographic information.
- Record medical history and concomitant medications.
- Perform a full neurological examination.
- Perform a complete physical examination.
- Measure vital signs (resting blood pressure, heart rate, respiratory rate, and oral body temperature) after the subject has been in a resting position for 5 minutes.
- Measure height, weight, and confirm BMI.
- Perform 12-lead ECG.

- Collect blood and urine samples for clinical laboratory evaluations (hematology, chemistry, and urinalysis).
- Collect blood samples for serology tests (HIV, hepatitis B surface antigen, and hepatitis C virus antibody).
- For women of childbearing potential, perform serum pregnancy test.
- Perform a urine drug screen to test for amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, and tetrahydrocannabinol.
- Train subjects how to use NRS.

Prior to enrollment in the study subjects must not be taking prohibited therapies (see Section 9.7.2).

10.2.2 Surgical/Anesthesia Period (Day 1 through Hour 1, Confinement)

Subjects will be confined to the study site from Day 1 through Day 4.

The following procedures will be performed on Day 1 through Hour 1:

- At check-in, confirm inclusion/exclusion criteria.
- At check-in, record medical history.
- Any time prior to anesthesia induction, perform a full neurological examination.
- At check-in, measure vital signs (resting blood pressure, heart rate, respiratory rate, and oral body temperature) after the subject has been in a resting position for 5 minutes.
- For women of childbearing potential, perform urine pregnancy test at check-in.
- At check-in, perform urine drug screen to test for amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, and tetrahydrocannabinol.
- Before surgery, train subjects how to use NRS.
- Before surgery, assign randomization number.
- Perform 12-lead ECG immediately prior to induction of anesthesia.
- Administer general anesthesia according to a standard regimen (Appendix D) and perform mini-abdominoplasty. At the end of the surgical procedure but before the wound is closed, administer the IP by wound infiltration and instillation. Begin continuous pulse oximetry immediately after surgery, and continue throughout transport and in the post-anesthesia care unit until the subject switches from intravenous morphine to oral rescue analgesia medication. If O_2 saturation drops below 93% or if the subject has clinical signs or symptoms that suggest respiratory depression while on the oral medication, or the subject switches back to intravenous morphine, keep the subject on continuous pulse oximetry as required.
- Collect blood samples for PK analysis at baseline (before IP administration), 15, 30, and 45 minutes after administration of IP (± 5 minutes).
- 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.

- Record concomitant medications
- Collect AEs.

10.2.3 Post-anesthesia Period (Day 1, Hour 1 through Day 4, Confinement)

The following procedures will be performed at Day 1, Hour 1 through Day 4 during confinement at the study site:

- Continue to monitor continuous pulse oximetry until the subject switches from intravenous morphine to oral rescue analgesia medication. If O_2 saturation drops below 93% or if the subject has clinical signs or symptoms that suggest respiratory depression while on the oral medication, or subject switches back to intravenous morphine, keep the subject on continuous pulse oximetry as required.
- Perform LAST assessment 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 (Appendix A), and a focused neurological examination. Vital signs should be measured after the subject has been in a resting position for 5 minutes. 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.
- Perform 12-lead ECG at 1, 2, 4, 8, 10, 12, 24, 48, and 72 hours after IP administration.
- Assess pain intensity 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.
- Subjects with inadequately controlled pain symptoms may request rescue analgesia.
    - After administration of the IP, rescue analgesia will be restricted to 2 to 4 mg 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.
- Perform surgical wound site assessment by direct visualization, including photograph at 24, 48, and 72 hours after administration of IP.
    - Record the numerical rating score on the eCRF (see Appendix B) and photograph the wound area (see Appendix C for instructions).
    - Instruct subjects 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.

- Collect PK blood samples at 1, 2, 4, 6, 8, 10, 12, 18, 24, 30, 36, 48 (Day 2), 60 (Day 3), and 72 hours (Day 4) after administration of IP (± 5 minutes for samples taken at 1 hour and ± 10 minutes for the remainder of the samples).
- Record concomitant medications.
- Collect AEs.
- Give subject a diary to record their pain intensity (using NRS), and rescue medication usage when they are discharged from the study site. Instruct subjects 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).

10.2.4 Post-treatment Follow-up Period

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

10.2.4.1 Days 5 and 6

Subjects will return to the study site on Days 5 and 6 to have the following procedures performed:

- Perform a 12-lead ECG on Day 5 only.
- Collect PK blood sample at 96 (Day 5) and 120 (Day 6) hours after administration of IP (± 1 hour).
- Assess pain intensity using an NRS at 96 (Day 5) and 120 hours (Day 6) after administration of IP.
- Perform surgical wound site assessment by direct visualization including photograph 96 (Day 5) and 120 hours (Day 6) after administration of IP. Record the numerical rating score on the eCRF (Appendix B) and photograph the wound area (see Appendix C instructions). Instruct subjects 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.
- Collect AEs.

10.2.4.2 Day 7-10 Follow-up Visit (7 to 10 days after Administration of Investigational Product or Upon Early Termination)

The following procedures will be performed at the Day 7-10 Follow-up Visit:

- Collect completed diary from the subject.
- Perform a full neurological examination.
- Perform abbreviated physical examination (changes since Screening).
- Measure vital signs (resting blood pressure, heart rate, respiratory rate, and oral body temperature) after the subject has been in a resting position for 5 minutes.
- Perform 12-lead ECG.
- Collect blood for clinical laboratory evaluations
- Perform surgical wound site assessment by direct visualization including photograph. Record the numerical rating score on the eCRF (see Appendix B) and photograph the wound area (see Appendix C for instructions).
- Record concomitant medications

- Collect AEs.

10.2.4.3 Day 30 Follow-up Visit (30 days After Administration of IP)

Thirty days after administration of IP, record AEs and concomitant medications and perform surgical wound site assessment by direct visualization including photograph. Record the numerical rating score on the eCRF (see Appendix B) and photograph the wound area (see Appendix C for instructions).

10.3 Assessments

10.3.1 Safety

Safety will be assessed based on AEs, vital signs, clinical laboratory assessments, 12-lead ECGs, physical examination, full neurological examination, LAST assessment, and wound evaluation.

10.3.1.1 Clinical Laboratory Safety Assessments

10.3.1.1.1 Clinical Laboratory Tests to be Performed

Samples for the following laboratory tests will be collected at the time points specified in the schedule of events (Section 2.2).

Hematology:	hemoglobin, hemoglobin A1c, hematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count (or estimate), white blood cell count including differential
Serum Chemistry:	albumin, total bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, glucose, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase, uric acid
Coagulation Panel:	prothrombin time, partial thromboplastin time, fibrinogen
Urinalysis:	pH, specific gravity, blood, glucose, protein, ketones
Pregnancy test urine/serum:	for women of childbearing potential only
Urine Drug Screen:	amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, and tetrahydrocannabinol

Blood and urine samples for hematology, serum chemistry, coagulation panel, serum pregnancy test, and urinalysis will be sent to a local laboratory for analyses. Urine drug screens and pregnancy tests will be conducted at the study site.

10.3.1.1.2 Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be employed by all study personnel involved in the collection of blood and handling of specimens in

both the clinic and laboratory settings. Refer to current recommendations of the appropriate authorities.

In addition to appropriate handling of subject samples, specific regulations exist regarding the shipment of biologic/etiologic samples. The investigator is responsible for ensuring that all study samples that are to be transported to another location are packed and shipped appropriately according to the applicable regulations.

10.3.1.1.3 Evaluation of Clinical Laboratory Values

The normal ranges of values for the clinical laboratory assessments in this study will be provided by the responsible laboratory and submitted to CALI prior to the beginning of the study. They will be regarded as the reference ranges on which decisions will be made.

If a laboratory value is out of the reference range, it is not necessarily clinically relevant. The investigator must evaluate the out-of-range values and record his or her assessment of the clinical relevance in the appropriate eCRF.

All clinical laboratory values that in the investigator's opinion show clinically relevant or pathological changes during or after termination of treatment must be reported as AEs and followed, as described in Section 11.2.5.

All measurements described in this section are recognized standard methods.

10.3.1.2 Clinical Examinations

10.3.1.2.1 Pulse Oximetry

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. Single-point pulse oximetry values will be recorded as part of each vital sign assessment.

10.3.1.2.2 Vital Signs

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, every 4 hours after IP administration on Day 1 and at least once daily on Days 2 and 3 (as part of the LAST assessment), and at the Day 7-10 Follow-up Visit.

10.3.1.2.3 Twelve-lead Electrocardiogram

A standard 12-lead ECG will be performed after the subject has been resting for at least 5 minutes at Screening, immediately prior to induction of anesthesia, and at 1, 2, 4, 8, 10, 12, 24, 48, 72, and 96 hours after IP administration; and at the Day 7-10 Follow-up Visit. All ECG recordings will be

identified with the subject number, initials, date, and time of the recording and will be attached to the subject's eCRF.

10.3.1.2.4 Physical Examination

A complete physical examination will be performed at Screening (including height and weight). 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).

10.3.1.2.5 Full Neurological Examination

A full neurological examination will be performed at Screening, on Day 1 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, cerebellar function.

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.

10.3.1.2.6 Local Anesthetic Systemic Toxicity Assessment

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, RASS assessment (provided in Appendix A), and a focused neurological examination. 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.

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. The RASS is a validated and reliable method to assess patients' level of agitation and sedation in the intensive care unit. 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).

10.3.1.2.7 Wound Evaluation

Study site staff will evaluate the wound at 24, 48, 72, 96 (Day 5), and 120 hours (Day 6) after IP administration, at the Day 7-10 Follow-up Visit (7 to 10 days after administration of IP), and at the Day 30 Follow-up Visit. Surgical wound site assessment will be performed by direct visualization and recording the numerical rating score on the eCRF (see Appendix B). Additionally, study site staff will photograph the wound area following the standardized instructions (Appendix C). 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.

10.3.1.3 Adverse Events

The definitions and management of AEs, and any special considerations for AEs, are provided in Section 11.

10.3.2 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.

10.3.2.1 Pharmacokinetic Sampling Assessments

Plasma ropivacaine concentrations will be measured from blood samples collected at the following time points: baseline (before IP administration), 15, 30, and 45 minutes, and at 1, 2, 4, 6, 8, 10, 12, 18, 24, 30, 36, 48, 60, 72, 96, and 120 hours after administration of IP.

10.3.2.1.1 Pharmacokinetic Parameters

Pharmacokinetic parameter estimates will be completed using Phoenix WinNonlin, Version 6.4 or higher (Pharsight Corporation). Actual sampling times will be used for all parameter estimation.

The following PK parameters will be calculated from ropivacaine:

- C_{max}: maximum (peak) plasma concentration
- t_{max}: time to reach highest observed (peak) concentration in plasma following IP administration
- $t_{1/2}$: elimination half-life
- λz: terminal elimination rate constant with the respective $t_{1/2}$
- $AUC_{0\text{-last}}$: area under the plasma concentration-time curve (AUC) from Time 0 to time of last quantifiable plasma concentration (Time 0 is defined as the moment that IP is administered)
- $AUC_{0\text{-}\infty}$: AUC from Time 0 to infinity

Other parameters may be calculated as appropriate and if data permit.

10.3.3 Efficacy

10.3.3.1 Numeric Rating Scale

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, 72, 96, and 120 hours after administration of IP. Additionally, pain intensity using an NRS will be recorded just prior to receiving rescue analgesia.

The NRS is an 11-point scale from 0 to 10. The subject will rate his or her current pain intensity using the following question: “On a scale from 0 to 10, where “zero” represents “no pain” and “10” represents “the worst possible pain,” how would you rate your current pain?”

10.3.3.2 Opioid Rescue Analgesia Use

The use of opioid rescue analgesia will be assessed as follows:

- Total use of opioid rescue analgesia (morphine equivalents) over 1 to 24 hours
- Total use of opioid rescue analgesia (morphine equivalents) over 1 to 48 hours
- Total use of opioid rescue analgesia (morphine equivalents) over 1 to 72 hours
- Time to first use of opioid rescue analgesia

11 ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Events (AEs)

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.

11.1.2 Serious Adverse Events (SAEs)

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
  NOTE: An elective hospital admission to treat a condition present before exposure to the IP, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly
  NOTE: A congenital anomaly in an infant born to a mother who was exposed to the IP during pregnancy is an SAE. However, a newly diagnosed pregnancy in a subject that has received IP is not considered an SAE unless it is suspected that the IP(s) interacted with a contraceptive method and led to the pregnancy.
- Is an important medical event
  NOTE: Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, development of drug dependency, or drug abuse.

11.1.3 Treatment-Emergent Adverse Events

An AE is defined as treatment emergent 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.

11.2 Event Assessment and Follow-up of Adverse Events

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

Adverse events will be collected from the time of signing the ICF through the Day 30 Follow-up Visit (30 days after administration of IP) or upon early termination, whichever occurs first. Throughout the study, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

11.2.1 Assessment

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described previously. Throughout the study, the subject will be allowed time to spontaneously report any issues since the last visit or evaluation. The investigator will then monitor and/or ask about or evaluate AEs using nonleading questions, such as the following:

- "How are you feeling?"
- "Have you experienced any issues since your last visit?"
- "Have you taken any new medications since your last visit?"

Any clinically relevant observations made during the visit will also be considered AEs.

11.2.2 Evaluation

11.2.2.1 Severity of Adverse Events

The clinical severity of an AE will be classified as:

Mild	Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria, as described in Section 11.1.2.

11.2.2.2 Seriousness

The investigator is to evaluate whether the AE meets serious criteria, as described in Section 11.1.2.

11.2.2.3 Action(s) Taken with Investigational Product

Action(s) taken may consist of:

None	
Not applicable	Determination of a value is not relevant in the current context.
Discontinued	IP discontinued due to the adverse event

11.2.2.4 Outcome at the Time of Last Observation

The outcome at the time of last observation will be classified as:

- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Not recovered/not resolved
- Fatal*
- Unknown

*Only select fatal as an outcome when the AE results in death. If more than 1 AE is judged to be possibly related to the subject's death, the outcome of death should be indicated for each such AE. Although "fatal" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

11.2.2.5 Adverse Event Relationship to the Investigational Product

The investigator must make an assessment of each AE's relationship to the IP. The categories for classifying the investigator's opinion of the relationship are as follows:

Not related	An AE with sufficient evidence to accept that there is no causal relationship to IP administration (e.g., no temporal relationship to drug administration, because the drug was administered after onset of event; investigation shows that the drug was not administered; another cause was proven.)
Unlikely related	An AE, including laboratory test abnormality, with a temporal relationship to IP administration that makes a causal relationship possible but other drugs, events, or underlying disease provide a far more likely explanation.
Potentially related	An AE with a reasonable time sequence to administration of the IP, but that could also be explained by concurrent disease or other drugs or events. Information on drug withdrawal may be lacking or unclear.
Probably related	An AE with evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals.
Definitely related	An AE occurring in a plausible time relationship to IP administration and that cannot be explained by a concurrent disease or other drugs or events.

11.2.3 Documentation

All AEs that occur within the period of AE collection for the study must be documented in the eCRF with the following information, where appropriate. (The period of AE collection for the study is described in Section 11.2.)

- AE name or term
- When the AE first occurred (start date and time)
- When the AE stopped (stop date and time or an indication of "ongoing")
- Severity of the AE
- Seriousness (hospitalization, death, etc.)
- Actions taken
- Outcome
- Investigator opinion regarding the AE relationship to the IPs

11.2.4 Treatment of Adverse Events

Adverse events that occur during the study will be treated, if necessary, by established standards of care. The decision about whether the subject may continue in the study will be made by the sponsor after consultation with the investigator and/or medical monitor.

If AEs occur in a subject that are not tolerable, the investigator must decide whether to stop the subject's involvement in the study and/or treat the subject. Special procedures may be recommended for the specific IP, such as the collection of a serum sample for determining blood concentrations of IP, or treatment regimens, as appropriate.

For double-blinded studies, it is not necessary to unblind a subject's treatment assignment in most circumstances, even if an SAE has occurred. If unblinding is necessary, see Section 9.6 for a description of the unblinding procedures.

11.2.5 Follow-up

All nonserious AEs that are not related or unlikely to be related to IP will be followed until the end of study participation. All SAEs or AEs possibly, probably, or definitely related to treatment will be followed until resolution or stabilization. All findings relevant to the final outcome of an AE must be reported in the subject's medical record and recorded on the eCRF page.

11.2.6 Reporting

11.2.6.1 Serious Adverse Events

The investigator or designee must report all SAEs promptly to Rho Product Safety (PS) within 24 hours of first becoming aware of the event by completing the SAE eCRF in RAVE EDC. Rho PS contact information:

Email: rho_productsafety@rhoworld.com

SAE Fax number: 1-888-746-3293

SAE Help Line: 1-888-746-7231

Rho Medical Monitor email: MedicalMonitorSupport@rhoworld.com

A paper report should only be submitted if RAVE is not available. A paper SAE form is provided for this purpose in the Study Operation's Manual. At the time of first notification, the investigator or designee should provide the following information:

- Reporter (study site and investigator)
- Subject's study number
- Date of IP administration
- AE term
- Date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria(on) that were met
- Investigator's opinion of the relationship to the IP ("Is there a reasonable possibility that the IP caused the SAE? Yes or No?")
- Whether and when the investigator was unblinded as to the subject's treatment assignment

Any missing or additional relevant follow-up information concerning the SAE must be reported by the investigator via RAVE in the same timeframes.

Specific information may be requested by Rho PS using a follow-up request form or via email communication.

The investigator is required to comply with applicable regulations (including local laws and guidances) regarding the notification of his or her health authorities, institutional review board (IRB), principal and coordinating investigators, study investigators, and institutions. Each investigator is obligated to learn about the reporting requirements for investigators in his or her country.

11.2.6.2 Nonserious Adverse Events

Nonserious AEs will be recorded in the eCRF and each will be classified according to the aforementioned criteria. If a non-serious AE becomes serious, the SAE must be reported to Rho PS within 24 hours as described above.

11.3 Special Considerations

11.3.1 Adverse Events of Special Interest

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.

11.3.2 Pregnancy

All women of childbearing potential who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation. Women should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

For women of childbearing potential, pregnancy testing will be conducted at screening and at check-in. A woman who is found to be pregnant at the Screening Visit or at check-in will be excluded from the study and considered to be a screening failure.

A woman who becomes pregnant within 30 days of administration of the IP, will continue in the study for follow-up safety assessments. The investigator must report the pregnancy within 24 hours of learning of the pregnancy, to Rho PS. The pregnancy will be reported on the Pregnancy eCRF in RAVE EDC. The outcome of all pregnancies will be followed and documented by Rho PS.

Early termination visit assessments are required as soon as possible after learning of the pregnancy. The investigator is also responsible for following the pregnancy until delivery or termination.

These findings must be reported on the Pregnancy eCRF in RAVE EDC. . The pregnancy event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly.

12 DATA SAFETY MONITORING BOARD

A data safety monitoring board will not be used in this study.

13 STATISTICS

13.1 Statistical Analysis

This section presents a summary of the planned statistical analyses. A statistical analysis plan (SAP) that describes the details of the analyses to be conducted will be written prior to database lock.

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 in to inform future trials, no multiplicity adjustment shall be applied to these exploratory analyses.

Summary statistics will be provided for the variables described below. For continuous variables, these statistics will typically include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, these statistics will typically include the number and percentage of subjects in each category.

Additional exploratory analyses may be carried out as deemed necessary and specified in the SAP.

13.1.1 Analysis Populations

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 received.

13.1.2 Study Subjects and Demographics

13.1.2.1 Disposition and Withdrawals

The numbers of subjects randomized, receiving IP, and withdrawing, along with reasons for withdrawal, will be tabulated overall and by treatment group. The number of subjects in each analysis population will be reported.

13.1.2.2 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or International Council for Harmonisation 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.

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.

Major protocol deviations that meet the criteria for a serious breach of ICH GCP should be reported to the sponsor immediately. No deviation from the inclusion/exclusion criteria shall be permitted.

Protocol deviations will be listed.

13.1.2.3 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics (including age, gender, race, weight, height, and BMI) will be summarized for each treatment group and for the overall population using descriptive statistics. Medical history will be displayed in a listing.

Prior and concomitant medications will be summarized by treatment group, by the number and percentage of subjects taking each medication, classified using World Health Organization Drug Dictionary Anatomical Therapeutic Chemical classes and preferred terms (PTs).

13.1.3 Exposure and Compliance

The number of subjects who successfully receive IP will be summarized as part of subject disposition.

13.1.4 Pharmacokinetics

The PK parameters will be estimated using non-compartmental PK analysis for each subject with sufficient data to characterize the administered dose. These parameters will be summarized and a mean concentration figure with plots will be produced both with a linear y-axis and with a log-y axis. Individual concentrations will be listed, graphed, and summarized by scheduled sampling time.

13.1.5 Safety and Tolerability Analyses

Summaries of safety results will be presented by treatment group for the safety analysis population (as defined in Section 13.1.1). Safety variables include treatment-emergent AEs, clinical laboratory values, vital signs, ECG readings, full neurological examination results, LAST assessment results, wound evaluation, and physical examination results. No formal inferential analyses will be conducted for safety variables, unless otherwise noted.

13.1.5.1 Adverse Events

All AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities.

Treatment-emergent AEs are defined as:

- AEs with onset at the time of or following administration of the IP through the Day 30 Follow-up Visit or Early Termination Visit, whichever occurs first, or
- AEs starting prior to the administration of the IP but increasing in severity or relationship at the time of, or following, administration of the IP through the Day 30 Follow-up Visit or Early Termination Visit, whichever occurs first.

The number and percentage of subjects with treatment-emergent AEs will be summarized for each treatment group by system organ class (SOC), PT, and treatment group. Serious AEs will be summarized in a similar fashion. Treatment-emergent AEs and SAEs will also be presented by severity and by relationship. All AEs will be presented in full in a comprehensive listing. Details of SAEs and AEs leading to withdrawal will be listed separately.

13.1.5.2 Clinical Laboratory Evaluations

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 (shift tables) for each clinical laboratory analyte by treatment group and by study visit.

Laboratory values that are outside the normal range will also be flagged in the data listings and presented with the corresponding normal ranges. Any out-of-range values that are identified by the investigator as being clinically significant will also be shown in a data listing.

13.1.5.3 Vital Signs

Descriptive summaries of observed values and changes from baseline for vital signs measurements will be presented by study visit and by study group.

13.1.5.4 Twelve-lead Electrocardiograms

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 a change in QT and QTc interval of >30 ms or a change >60 ms will be presented.

Descriptive summaries (mean, SD, median, minimum, and maximum) will be presented for ECG measures of PR interval, QRS interval, QT interval, QTc interval (both correction methods), and HR for each treatment group at each time point.

13.1.5.5 Wound Evaluation

A descriptive summary of the surgical wound site assessment findings (including wound infection and wound-related AEs) 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. Surgical wound site assessment findings at 24, 48, 72, 96, and 120 hours after IP administration will be displayed in a listing.

13.1.5.6 Physical and Neurological Examination Findings

Physical and neurological examination results will be displayed in a listing.

13.1.5.7 Richmond Agitation and Sedation Scale Assessment

A descriptive summary of the RASS assessment will be presented by study visit and by treatment group.

13.1.6 Efficacy Analysis

13.1.6.1 Efficacy Exploratory Endpoints

The efficacy exploratory endpoints are the following:

- Time-weighted summed pain intensity over 1 to 24 hours (SPI_{1-24}) for CPL-01 subjects compared with placebo subjects
- SPI at other time points: SPI_{1-6}, SPI_{6-12}, SPI_{1-12}, SPI_{12-24}, SPI_{24-48}, SPI_{1-48}, SPI_{48-72}, and SPI_{1-72} for CPL-01 subjects compared with placebo subjects
- Total dose of opioid rescue analgesia (morphine equivalents) over 24, 48, and 72 hours after administration of IP
- Time to administration of first dose of opioid rescue analgesia
- The percentage of subjects who used no opioid rescue analgesia over 24, 48, and 72 hours after administration of IP
- The percentage of subjects who remain pain free over 24, 48, and 72 hours after administration of IP (pain intensity ≤ 1).

13.1.6.2 Analysis

Individual NRS pain intensity scores will be tabulated for each time point and summarized descriptively by treatment group.

The analysis of continuous efficacy endpoints will be performed using an analysis of variance (ANOVA) model. The ANOVA model will include the specific endpoint as the response variable (e.g., NRS SPI t, where t=1-6, 6-12, 1-12, 1-24, 12-24, 24-48, 1-48, 48-72, 1-72 hours, respectively) and will have Treatment as the main effect. Contrast tests will be carried out to compare CPL-01 against placebo. Since all exploratory analyses in this study are intended for hypothesis generation, there will be no adjustment for multiplicity and each analysis will be based on a 2-sided test at the significance level of 0.05. This approach will be used to analyze all continuous exploratory efficacy variables, including total dose of opioid (morphine equivalents) used over 24, 48, and 72 hours, respectively.

Time to first use of rescue analgesia for postoperative surgical pain will be analyzed using the Kaplan-Meier method. The log-rank test will be used to test the hypothesis of overall treatment differences. In addition, a Cox proportional hazards model will be used to allow individual contrasts tests comparing CPL-01 against placebo. Hazard ratios and 95% confidence intervals will be generated for each contrast.

The percentage of subjects who used no opioid rescue analgesia and the percentage of subjects who remain pain free over 24, 28, and 72 hours will be analyzed using Fisher's exact test.

To assess the impact of missing data, multiple imputation will be used as a sensitivity analysis for the primary endpoint.

Additional exploratory efficacy analyses may be conducted as required.

13.1.7 Interim Analysis

No interim analyses are planned.

13.2 Sample Size Determination

This is a proof-of-concept study with a primary goal of estimation rather than hypothesis testing. The sample sizes are consistent with similar studies of this type, but are not based on power considerations for specific treatment-effect sizes.

14 STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel before the study, periodic monitoring visits, and meticulous data management.

14.1 Sponsor and Investigator Responsibilities

14.1.1 Sponsor Responsibilities

The sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 16). The sponsor reserves the right to withdraw a subject from the study (Section 8.3), to terminate participation of a study site at any time (Section 14.7), and/or to discontinue the study (Section 14.6).

CALI agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study according to the study protocol.

14.1.2 Investigator Responsibilities

By signing the Investigator's Agreement (Section 18.1), the investigator indicates that he or she has read the protocol carefully, fully understands the requirements, and agrees to conduct the study in accordance with the procedures and requirements described in this protocol.

The trial will be conducted in accordance with ICH GCP and applicable US Code of Federal Regulations (CFR) (Appendix E). The principal investigator will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor, funding agency and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP training.

Investigators should ensure that all persons who are delegated study-related responsibilities are adequately qualified and informed about the protocol, the IP(s), and their specific duties within the context of the study. Investigators are responsible for providing CALI with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study may be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

14.1.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies, or pharmaceutical company supplying study product may inspect all

documents and records required to be maintained by the investigator, including, but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Rho. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Rho staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at Rho.

14.2 Site Initiation

Study personnel may not screen or enroll subjects into the study until after receiving notification from the sponsor or its designee that the study can be initiated at the study site. The study site will not be authorized for study initiation until:

1. The study site has received the appropriate IRB approval for the protocol and the appropriate ICF.
2. All regulatory documents have been submitted to and approved by the sponsor or its designee.
3. The study site has a Clinical Trial Agreement in place.
4. Study site personnel, including the investigator, have participated in a study initiation meeting.

14.3 Screen Failures

Subjects who fail inclusion and/or exclusion criteria may not be rescreened for the study.

14.4 Study Documents

All documentation and material provided by CALI for this study are to be retained in a secure location and treated as confidential material.

14.4.1 Informed Consent

A consent form describing in detail the study intervention, study procedures, and risks is given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants

will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date) and the form signed before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

14.4.2 Investigator's Regulatory Documents

The regulatory documents are listed in the study plan.

The regulatory documents must be received from the investigator and reviewed and approved by CALI or its designee before the study site can initiate the study and before CALI will authorize shipment of IP to the study site. Copies of the investigator's regulatory documents must be retained at the study site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), eCRF completion guidelines, copies of regulatory references, copies of IRB correspondence, and IP accountability records should also be retained as part of the investigator's regulatory documents. It is the investigator's responsibility to ensure that copies of all required regulatory documents are organized, current, and available for inspection.

14.4.3 Case Report Forms

By signing the Investigator's Agreement (Section 18.1), the investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all subjects who sign an ICF.

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific eCRFs system used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual subject visits should be completed as soon as possible after the visit. All requested information must be entered in the electronic data capture (EDC) system according to the completion guidelines provided by the sponsor or its designee.

The eCRFs must be signed by the investigator or a subinvestigator. These signatures serve to attest that the information contained in the eCRFs is accurate and true.

14.4.4 Source Documents

Information recorded in the EDC should be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

14.5 Data Quality Control

CALI and its designees will perform quality control checks on this clinical study.

14.5.1 Monitoring Procedures

CALI and/or its designee will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned CRA will visit the investigator and study site at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRA(s) and other authorized CALI personnel access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. While on site, the CRA(s) will review the following:

- Regulatory documents, directly comparing entries in the EDC system with the source documents
- Consenting procedures
- Adverse event procedures
- Storage and accountability of IP and study materials (unblinded CRA only)

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRF are described in the study plan. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (Section 18.1), the investigator agrees to meet with the CRA(s) during study site visits; to ensure that study staff is available to the CRA(s) as needed; to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the investigator agrees to allow CALI or designee auditors or inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

For additional information, please refer to the clinical monitoring plan.

14.5.2 Data Management

CALI or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and Rho's standard operating procedures. A comprehensive data management plan will be developed, including a data management overview, description of database contents, annotated eCRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data.

14.5.3 Quality Assurance/Audit

This study will be subject to audit by CALI or its designee. Audits may be performed to check compliance with GCP guidelines and can include:

- Site audits
- Trial Master File audits
- Database audits
- Document audits (e.g., protocol and/or clinical study report [CSR])

CALI or its designee may conduct additional audits on a selection of study sites, requiring access to subject notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with CRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify CALI immediately.

14.6 Study Termination

The study may be terminated at CALI's discretion at any time and for any reason.

14.6.1 Premature Study Termination

The study may be temporarily suspended or terminated prematurely if there is sufficient reasonable cause at any time by CALI, IRBs, regulatory authorities, respective steering committees, or the coordinating investigator.

Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, the IND sponsor, and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator will promptly inform study participants, the IRB, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

AE-related criteria that may warrant termination of the study include, but are not limited to:

- One subject has a generalized seizure or a hemodynamically significant cardiac arrhythmia
- One subject has multiple signs and/or symptoms that, in aggregate, suggest that LAST is occurring.
- Two or more subjects have an SAE that is assessed as related to investigational product
- Two or more subjects show evidence of severe local drug product reaction or clearly impaired wound healing
- One subject death occurs possibly related to study drug

Study sites may be asked to have all subjects currently participating in the study complete all of the assessments for the Early Termination Visit.

The study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the sponsor, IRB, and/or Food and Drug Administration (FDA).

14.7 Study Site Closure

At the end of the study, all study sites will be closed. CALI may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines
- Inadequate subject enrollment

14.7.1 Record Retention

The investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including, but not limited to, those defined by GCP as essential until:

- At least 2 years after the last marketing authorization for the IP has been approved or the sponsor has discontinued its research with the IP, or
- At least 2 years have elapsed since the formal discontinuation of clinical development of CPL-01.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor has 30 days to respond to the investigator's notice, and the sponsor has further opportunity to retain such materials at the sponsor's expense.

14.7.2 Sample Retention

Samples may be used for purposes related to this research. The samples will be stored until the sponsor has determined that specimens are no longer needed, and the decision has been made that none of the samples needs to be reanalyzed. In addition, identifiable samples can be destroyed at any time at the request of the subject.

14.8 Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of CALI. The protocol amendment must be signed by the investigator and approved by the IRB before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the study.

14.9 Use of Information and Publication

All information concerning CPL-01, CALI's operations, patent applications, formula, manufacturing processes, basic scientific data, and formulation information supplied by CALI or its designee to the investigator, and not previously published, is considered confidential and remains the sole property of CALI. Case report forms also remain the property of CALI. The investigator agrees to use this information for purposes of study execution through finalization.

The information developed in this study will be used by CALI in connection with the continued development of CPL-01 and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this study is the property of CALI. Publication or other public presentation of CPL-01 data resulting from this study requires prior review and written approval of CALI. Abstracts, manuscripts, and presentation materials should be provided to CALI for review at least 30 days prior to the relevant submission deadline.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition, or publication by the investigator until CALI has reviewed and commented on such a presentation or manuscript for publication. If applicable, this study will be registered at ClinicalTrials.gov, and results information from this study will be submitted to ClinicalTrials.gov.

15 FINAL CLINICAL STUDY REPORT

CALI will retain ownership of the data.

The final CSR will be written within 6 months of completion of the clinical part of the study. This report will include a summary of the study results based on a statistical evaluation and clinical assessment of the protocol-defined endpoints.

The final CSR may be submitted to the regulatory authorities.

16 ETHICAL AND LEGAL CONSIDERATIONS

16.1 Good Clinical Practice

This study will be conducted in compliance with the April 1996 ICH Guidance for Industry GCP E6 (including archiving of essential study documents), the Integrated Addendum to ICH E6 (R2) of November 2016, and the applicable regulations of the country in which the study is conducted.

16.2 Subject Information and Informed Consent

A properly constituted, valid IRB must review and approve the protocol, the investigator's ICF, and related subject information and recruitment materials before the start of the study.

It is the responsibility of the investigator to ensure that written informed consent is obtained from the subject before any activity or procedure is undertaken that is not part of routine care.

16.3 Approval by Institutional Review Board

For IND studies, the minimum standards of conduct and requirements for informed consent are defined in the FDA regulations.

A valid IRB must review and approve this protocol before study initiation. Written notification of approval is to be provided by the investigator to the sponsor's representative before shipment of investigational drug supplies, and will include the date of the committee's approval and the chairperson's signature. This written approval must consist of a completed IRB Approval Form or written documentation from the IRB containing the same information.

Until written approval by the IRB has been received by the investigator, no subject may undergo any procedure not part of routine care for the subject's condition.

Protocol amendments must also be reviewed and approved by the IRB. Written approval from the IRB, or a designee, must be received by CALI before implementation. This written approval will consist of a completed IRB Approval Form or written documentation from the IRB containing the same information.

16.4 Finance and Insurance

Details on finance and insurance will be provided in a separate agreement between the investigator and the sponsor.

17 REFERENCES

1. Dahl J, Moiniche S, Kehlet H. Wound infiltration with local anaesthetics for postoperative pain relief. Acta Anaesthesiol Scand. 1994; 38(1):7-14.
2. Moiniche S, Mikkelsen Wetterslev J, et al. A qualitative systematic review of incisional local anaesthesia for postoperative pain relief after abdominal operations. Br J Anaesth. 1998;81(3):377-383.
3. Kehlet H., Andersen LO. Local infiltration analgesia in joint replacement: the evidence and recommendations for clinical practice. Acta Anaesthesiol Scand. 2011;55(7):778-784.
4. Rawal N. Analgesia for day-case surgery. Br J Anaesth. 2001;87(1):73-87.
5. NAROPIN® (ropivacaine HCl Injection, USP) Package Insert. Lake Zurich, IL, Fresenius Kabi USA, LLC, 2015.
6. Pettersson N, Emanuelsson B-M, Reventlid H, Hahn RG. High-dose ropivacaine wound infiltration for pain relief after inguinal hernia repair: A clinical and pharmacokinetic evaluation. Reg Anesth Pain Med. 1998 March-April;23(2):189-196.

18 ATTACHMENTS

18.1 Investigator's Agreement

PROTOCOL NUMBER:	CPL-01_AB_001
PROTOCOL 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
FINAL PROTOCOL:	V3.0 25-Nov-2019

I have read this protocol and agree to conduct this clinical study as outlined herein. I will ensure that all subinvestigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with CALI Pharmaceuticals and Rho during the study. I will adhere to all FDA, ICH, and other applicable regulations and guidelines regarding clinical studies on an IP during and after study completion.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

19 APPENDICES

A. Richmond Agitation and Sedation Scale

B. Surgical Wound Site Assessment

C. Wound Photography Instructions

D. Standardized General Anesthesia Regimen

E. Regulations and Good Clinical Practice

A. Richmond Agitation and Sedation Scale

Richmond Agitation Sedation Scale (RASS) *

Score	Term	Description	
+4	Combative	Overtly combative, violent, immediate danger to staff	
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive	
+2	Agitated	Frequent non-purposeful movement, fights ventilator	
+1	Restless	Anxious but movements not aggressive vigorous	
0	Alert and calm		
-1	Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to *voice* (≥**10 seconds**)	Verbal Stimulation
-2	Light sedation	Briefly awakens with eye contact to *voice* (<**10 seconds**)	Verbal Stimulation
-3	Moderate sedation	Movement or eye opening to *voice* **(but no eye contact)**	Verbal Stimulation
-4	Deep sedation	No response to voice, but movement or eye opening to *physical* stimulation	Physical Stimulation
-5	Unarousable	No response to *voice or physical* stimulation	Physical Stimulation

Procedure for RASS Assessment

1. Observe patient
   a. Patient is alert, restless, or agitated. **(score 0 to +4)**
2. If not alert, state patient's name and *say* to open eyes and look at speaker.
   b. Patient awakens with sustained eye opening and eye contact. **(score –1)**
   c. Patient awakens with eye opening and eye contact, but not sustained. **(score –2)**
   d. Patient has any movement in response to voice but no eye contact. **(score –3)**
3. When no response to verbal stimulation, physically stimulate patient by shaking shoulder and/or rubbing sternum.
   e. Patient has any movement to physical stimulation. **(score –4)**
   f. Patient has no response to any stimulation. **(score –5)**

* Sessler CN, Gosnell M, Grap MJ, Brophy GT, O'Neal PV, Keane KA et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care patients. Am J Respir Crit Care Med 2002; 166:1338-1344.

* Ely EW, Truman B, Shintani A, Thomason JWW, Wheeler AP, Gordon S et al. Monitoring sedation status over time in ICU patients: the reliability and validity of the Richmond Agitation Sedation Scale (RASS). JAMA 2003; 289:2983-2991.

B. Surgical Wound Site Assessment

The surgical wound will be examined and scored by the investigator or designee using a 5-point numerical rating scale as follows:

Numerical Rating	Description
1-Normal healing	Findings that may include bruising, erythema, edema and drainage at expected normal levels based upon the time point of the wound assessment.[a]
2-Delayed healing	Findings that may include bruising, erythema or edema beyond expected normal levels based upon the timepoint of the wound assessment.
3-Excessive Drainage	Any purulent drainage. Serous or hemoserous drainage beyond expected normal levels based upon the time point of the wound assessment.[b]
4-Infection	Evidence of cellulitis such as excessive heat, spreading erythema, purulent discharge.
5-Tissue breakdown	Complete wound dehiscence, hematoma any of which would require surgical intervention

[a] Inflammation - (bruising, erythema and edema) are normal post-operative findings and may be present at the timepoint evaluated.

[b] Drainage - Postoperative wound drainage may refer to the following: Serous exudate – drainage of a clear, thin, watery fluid from a surgical wound. This type of wound ooze is a normal and expected part of the healing process. - Haemoserous (serosanguinous) exudate – drainage of a thin, watery, pink colored fluid composed of blood and serum and may be a normal and expected part of the healing process based upon the time point evaluated.

This numerical rating will be included in the electronic Case Report Form. Any rating of 2 or above will be reported as an AE. Refer to Section 11.1.1 for additional information regarding AEs. For further guidance regarding normal versus impaired healing refer to Table 1 from the 2018 World Union of Healing Societies Consensus Document.

Table 1: Signs of Progression and Impaired Incision Healing

Parameter	Relationship to TIME framework*	Signs that incisional healing is progressing well	Signs that healing is impaired
Incision colour	**T**issue	■ Days 1–4: red ■ Days 5–14: bright pink ■ Day 15–1 year: pale pink, progressing to white or silver in light-skinned patients or to darker than usual skin colour in patients with darkly-pigmented skin	■ Days 1–4: may be red, tension in the incision line ■ Days 5–9: edges may be well-approximated and the tension remains ■ Days 10–14: if SWD does not occur, colour may remain red or progress to pink and may be followed ultimately by hypertrophic scarring
Healing ridge		■ Days 5–9: a healing ridge of thickened tissue indicating newly formed collagen can be felt about 1cm either side of the incision along its length, and persists into the remodelling phase	■ Lack of healing ridge
Peri-incisional area	**I**nfection/ inflammation	■ Signs of inflammation: - Mild oedema, erythema, warmth or skin discolouration that resolves by day 5 - Pain	■ Signs of inflammation may be absent in the first few days after surgery ■ Signs of inflammation and ongoing pain may be present for extended periods
Exudate	**M**oisture	■ Days 1–4: decreasing in volume from moderate to minimal and changing from sanguineous (blood) to serosanguineous (mixture of blood and serum) to serous (clear, amber serum) ■ Resolves by day 5	■ Exudate persists beyond days 1–4 ■ Exudate may be serosanguineous, serous or purulent (e.g. cloudy, green, yellow or brown)
Wound margins	**E**dge	■ Epithelial closure should be seen by day 4 along the entire incision ■ Approximated	■ Epithelial resurfacing may be only partially present or entirely absent ■ Area(s) of separation (SWD) may be present by day 14

Source: Excerpt from World Union of Wound Healing Societies Consensus Document: Surgical wound dehiscence, Improving prevention and outcomes, 2018, page 12. Free download available from www.woundsinternational.com.

C. Wound Photography Instructions

Materials

- Camera (*specify type and model*, *identify camera settings)*
- Memory card for each subject
- Background cloth
- Identification tag: Complete for Protocol #, Subject #, Study visit, date, time, and location "abdomen"
- Adhesive backed decal ruler (on a roll)

Instructions

1. Ensure the batteries in the camera are charged. If low, replace the batteries prior to using the camera.
2. Place the subject's memory card in the camera.
3. Expose the entire abdomen to be photographed and place the background cloth under the area to be photographed.
4. Remove any dressing and place the completed identification tag adjacent to the area to be photographed, taking care not to obscure any area of the wound itself.
5. Apply the adhesive backed ruler decal in an area of the abdomen not obscuring the wound area itself.
6. Take 3 photographs with the camera, looking down at the abdomen so that the abdominal area fills the camera window, showing the entire surgical abdominal incision, the identification tag information and the ruler.
7. Remove the subject's memory card.

D. Standardized General Anesthesia Regimen

Protocol Number: CPL-01_AB_001	
General Anesthesia Regimen	
Monitors	• All routine required ASA monitors
IV Fluids	• Lactated Ringer at 1-3 cc/kg/h at discretion of anesthesia provider
Premedication	• Midazolam 1-3 mg IVP as needed
Induction	• Propofol 1-3 mg/kg IV • Rocuronium 0.6-1.2 mg/kg IV • Fentanyl 1-2 ug/kg IV
Maintenance	• No N_2O • Air/O_2 as required to maintain intraoperative O_2 saturation >95% • Sevoflurane or desflurane are preferred agents at 0.8 to 1.2 MAC as tolerated • Isoflurane at 0.8 to 1.2 MAC as tolerated can be used only if both sevoflurane and desflurane are not available • Rocuronium 0.1 to 0.2 mg/kg as needed per train-of four monitoring and at discretion of anesthesia provider • Fentanyl 2-4 ug/kg IV as needed
AW device	• Oral endotracheal tube or supraglottic device (laryngeal mask airway, etc.) at discretion of anesthesia provider
Reversal of NMB if needed	• Neostigmine 0.025 to 0.05 mg/kg IVP per TOF monitoring • Glycopyrrolate 0.01 mg/kg IVP or atropine 0.02 mg/kg IVP

ASA = American Society of Anesthesiologists; IV = intravenous; IVP = intravenous push; MAC = minimum alveolar concentration; NMB = neuromuscular blockade.

E. Regulations and Good Clinical Practice

1. Regulations

Refer to the following US Code of Federal Regulations (CFR):

- FDA Regulations 21 CFR, Parts 50.20 – 50.27
  Subpart B – Informed Consent of Human Subjects
- FDA Regulations 21 CFR, Parts 56.107 – 56.115
  Part 56 – Institutional Review Boards
  Subpart B – Organization and Personnel
  Subpart C – IRB Functions and Operations
  Subpart D – Records and Reports
- FDA Regulations 21 CFR, Parts 312.50 – 312.70
  Subpart D – Responsibilities of Sponsors and Investigators

2. Good Clinical Practice Guidelines

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use GCP guidelines can be found at the following URLs:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf