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Research article

CPL-01, an Investigational Long-Acting Ropivacaine, Exhibits Extended-Release Properties after Mini-abdominoplasty

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Abstract

Current local anesthesia with agents including lidocaine, prilocaine, bupivacaine, and ropivacaine have estimated half-lives of 1.5–8 hours, thereby limiting prolonged analgesia for most patients. Ropivacaine is widely believed to be a safer local anesthetic, but there are no long-acting ropivacaine products available. Therefore, the development of a long-acting ropivacaine would fill an unmet clinical need. This was a randomized, double-blind, single-site study to evaluate CPL-01 for the management of postoperative pain after mini-abdominoplasty surgery. Twenty-six subjects were screened for the study, and 20 of these subjects were enrolled and randomized, 15 to the CPL-01 group and 5 to the placebo group. The study evaluated 20 subjects enrolled and randomly assigned in a 3:1 ratio to receive either 2% CPL-01 (200 mg ropivacaine) or placebo (0.9% NaCl) administered into soft tissue by wound infiltration and instillation before surgical closure. Subjects were followed for 30 days after administration of the investigational product. PK was assessed with ropivacaine plasma concentration from pre-dose to 120 hours after IP administration. Administration of 200 mg CPL-01 by wound infiltration and instillation demonstrated an extended-release PK profile with mean Tmax of 13.0 ± 8.83 hours and t1/2 of 25.4 ± 5.44 hours. The mean Cmax of 200 mg CPL-01 was 573 ± 258 ng/mL, and AUC0-∞ was 20,400 ± 6,480 h ng/mL. CPL-01 was well tolerated and showed no evidence of local tissue reaction or impairment of wound healing. In this phase 2a study, 200 mg of CPL-01 was well tolerated . CPL-01 showed no negative impact on clinical laboratory results, vital signs, and ECGs. The systemic PK results suggested extended release of ropivacaine from the depot into the incision site that could contribute to an extended analgesic efficacy profile.

Keywords: analgesia; local infiltration; local anesthetic; ropivacaine

Introduction

Current local anesthesia with agents including lidocaine, prilocaine, bupivacaine, and ropivacaine have estimated half-lives of 1.5–8 hours, thereby limiting prolonged analgesia for most patients [1,2]. According to the US Institute of Medicine, 80% of patients who undergo surgery report postoperative pain, with 88% of these patients reporting moderate, severe, or extreme pain levels. In a national US survey of 300 adults who had undergone surgery within the previous 5 years, 86% of patients experienced postsurgical pain overall, and 75% of those who reported pain described its severity as moderate–extreme during the immediate postoperative period [3]. When the local analgesic effect wears off, the patient is forced to deal with the pain with some other medication; in the United States, this often results in patients being exposed to opioid medications. Therefore, the development of a long-acting local anesthetic formulation would be clinically useful and is medically needed. Naropin® (ropivacaine hydrochloride) Injection (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. Because of the short duration of effect and given that frequent repeat injections into the surgical space is not feasible, infusion by catheter is required if protracted local analgesia is required for postoperative pain management. This has multiple potential problems, including wet bandages, migration of the catheter tip, and the potential for dose dumping.

Several long-acting formulations of bupivacaine have been developed over the past decade, each with different delivery systems (liposomal, collagen scaffolding, sucrose) or combination products (with meloxicam). However, ropivacaine has been shown to have an improved safety profile compared to bupivacaine, with a higher dose tolerated and fewer cardiac impacts.

Cali is developing a long-acting formulation of ropivacaine, which could potentially prolong the duration of local analgesia for several days after a single local infiltration into the surgical site. While this extended-release injectable formulation of ropivacaine hydrochloride (CPL-01) has previously demonstrated a prolonged duration at the local site and consequently an extended local analgesic effect in several nonclinical animal studies, this is the first time that CPL-01 has been used in a human clinical study.

Methods

This study was designed to evaluate the safety and PK profile and to explore the efficacy of CPL-01 in men and women ≥18 and ≤70 years of age for the management of postoperative pain after mini-abdominoplasty surgery. 20 subjects were enrolled and randomly assigned in a 3:1 ratio to either 2% CPL-01 (200 mg ropivacaine [10 mL]) or placebo (0.9% NaCl). Subjects were scheduled to undergo elective mini-abdominoplasty surgery under general anesthesia without collateral procedures. Eligible subjects had a body mass index (BMI) >19 and <30 kg/m2 and an American Society of Anesthesiology subject (physical) classification status of I or II at screening. Potential subjects were excluded from enrollment if they had 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; had taken chaparral, comfrey, germander, jin bu huan, kava, pennyroyal, skullcap, St. John's wort, or valerian within 14 days before surgery; or had a chronic pain condition or any significant medical disease, laboratory abnormality (including electrocardiogram [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, confound the assessments of postoperative pain, or otherwise contraindicate study participation. Potential subjects were also excluded for clinically significant renal abnormalities, hemoglobin A1c ≥7.0%, history of, or positive test results for, human immunodeficiency virus, hepatitis B surface antigen, or hepatitis C virus antibody, history of migraine headache or frequent headaches, seizures, or current use of anticonvulsants.

After obtaining informed consent, subjects were screened within 42 days before the planned surgery, including 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 were trained on the use of the numeric rating scale (NRS) for pain assessment at Screening.

On the day of surgery, at check-in, the fact that the subject continued to meet the inclusion/exclusion criteria was confirmed. Also, the medical history, full neurological examination, vital signs, 12-lead ECG, urine pregnancy test, urine drug screen, and concomitant medications were updated. Before surgery, subjects were trained again on the NRS and assigned a randomization number.

Subjects were administered general anesthesia according to a standard regimen, during which they will undergo a mini-abdominoplasty. At the end of the surgical procedure but before the wound is closed, the investigational product (IP) was administered by wound infiltration and instillation (Time 0). Blood samples were collected for PK analysis at baseline (before IP administration) and then at 15, 30, and 45 minutes after administration of IP. Continuous pulse oximetry was monitored immediately following surgery, throughout transport, and in the post-anesthesia care unit, until subjects switched from intravenous morphine to oral rescue analgesia medication. Following surgery, subjects were admitted and confined to the study site through 72 hours.

Subjects with inadequately controlled pain symptoms could request rescue analgesia. Pain intensity using an NRS will be recorded just prior to receiving rescue analgesia. Rescue analgesia was 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.

Assessments included 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 was conducted until subjects switched to oral rescue medication. After discharge from the study site, subjects received a diary to record their pain intensity (using NRS) and rescue medication. On non-visit days prior to the Day 7-10 Follow-up Visit, a brief daily telephone call was conducted to remind subjects to record their pain intensity (using NRS), and rescue medication usage in the diary. Subjects were 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).

Subjects were to 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) included 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) was also performed.

Study assessments

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.

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).

Statistical methods

Three analysis populations were defined for this study:

1.Intent-to-treat: All subjects who were successfully screened and randomized. The ITT population was the primary population for the efficacy analyses.

2.Safety: All subjects who were treated with IP. The safety population was the population for all safety analyses.

3.Pharmacokinetic: All subjects who received IP during surgery and had at least 1 measurable plasma concentration. All PK analyses were based on the PK population.

In general, the baseline value was considered the last non-missing measurement observed prior to the first dose of study treatment. For efficacy, subjects were analyzed according to randomized treatment. For safety analyses, subjects were analyzed according to the actual treatment received. Demographic and baseline characteristics were collected during the Screening Visit. Descriptive statistics were provided for all demographic and baseline characteristics based on the safety population. For categorical variables, the number and percentage of subjects in each category were presented. For continuous variables, summaries included the number of subjects with data, mean, median, SD, min, and max.

Results

Twenty-six subjects were screened for the study, and 20 of these subjects were enrolled and randomized, 15 to the CPL-01 group and 5 to the placebo group. All 20 (100%) randomized subjects completed the confinement period (Surgical/Anesthesia and Post-anesthesia Periods through Day 4), and 19 (95.0%) subjects completed the study. One subject in the placebo group discontinued from the study due to pregnancy just prior to the Day 30 evaluation. All 20 randomized subjects were included in the ITT and safety analysis populations, and all 15 subjects in the CPL-01 group were included in the PK population. All (100%) subjects were female; 13 (86.7%) subjects in the CPL-01 group and 4 (80%) subjects in the placebo group were black or African American. The mean (SD) age was 48.5 (11.26) years in the CPL-01 group and 41.0 (12.06) years in the placebo group, and the mean (SD) BMI was 27.8 (2.39) kg/m2 and 26.4 (4.00) kg/m2, respectively. All (100%) subjects completed the NRS training (Table 1).

Fifteen (75.0%) subjects reported a total of 40 TEAEs during the study. Eleven (73.3%) subjects in the CPL-01 group reported 24 events, and 4 (80.0%) subjects in the placebo group reported 16 events (Table 2). Overall, the incidence and severity of TEAEs between CPL-01 and placebo were comparable. No serious TEAEs were reported, and no TEAE led to discontinuation from the study. Twelve (60.0%) subjects had a maximum TEAE severity of mild, 2 (10.0%) had a maximum TEAE severity of moderate, and 1 (5.0%) had a maximum TEAE severity of severe (in placebo group). One treatment-related TEAE was reported for 1 (6.7%) subject in the CPL-01 group (possibly related). One TEAE of special interest (dysgeusia) was reported in each of the treatment groups, and 1 wound TEAE (incision site rash) was reported in the placebo group. No deaths were reported during the study. No SAEs were reported during the study and no subject discontinued from the study due to an AE. Overall interpretation of the results of this study is limited by the small sample size.

There were no notable changes seen in most vital signs in CPL-01 and placebo groups. For both CPL-01 group and placebo group, the ECGs parameters at all time points were normal compared to baseline. No clinically significant ECG results were reported at any time point after IP administration. No subject in either treatment group had an increase in QTcF of >60 ms (Table 3).

At each visit after IP administration, all subjects in both treatment groups received a wound evaluation rating of 1 (normal healing), with the exception of 1 subject in the CPL-01 group for whom wound evaluation was inadvertently not collected on Day 3. The wound healing results showed that CPL-01 had no impact on wound healing. Following a single dose of 2% CPL-01 consisting of 200 mg ropivacaine in 10 mL of vehicle administered by wound infiltration and instillation, ropivacaine was absorbed into systemic circulation with a median (min - max) Tmax value of 10.1 (2.18 - 30.1) h. At Tmax, ropivacaine mean ±SD Cmax

Table 1. Demographic and Baseline Characteristics (Safety Population)

CharacteristiC		CPL-01 (n=15)	Placebo (n=15)	Overall (n=20)
Age (years)				
n		15	5	20
Mean		48.5	41	46.7
SD		11.26	12.06	11.63
Median		49	43	45.5
(Minimum, Maximum)		(29, 69)	(28, 59)	(28, 69)
Sex at birth				
Male		0	0	0
Female		15 (100.0)	5 (100.0)	20 (100.0)
Ethnicity				
Hispanic or Latino		0	0	0
Not Hispanic or Latino		15 (100.0)	5 (100.0)	20 (100.0)
Unknown		0	0	0
Not reported		0	0	0
Race				
American Indian or Alaskan Native		0	0	0
Asian	0		1 (20.0)	1 (5.0)
Black or African American	13 (86.7)		4 (80.0)	17 (85.0)
Native Hawaiian or Pacific Islander	0		0	0
White	2 (13.3)		0	2 (10.0)
Not reported	0		0	0
Other	0		0	0
Body mass index (kg/m2)[1]				
n	15		5	20
Mean	27.8		26.4	27.5
SD	2.39		4	2.83
Median	28.5		28	28.5
(Minimum, Maximum)	(22, 30)		(20, 29)	(20, 30)
Completed NRS training:				
Yes	15 (100.0)		5 (100.0)	20 (100.0)
No	0		0	0

NRS = numeric rating scale; SD = standard deviation

[1] Body mass index = weight (kg)/[height (m)]^2

Table 2. Summary of Adverse Events Safety Population

	CPL-01 (n=15)	Placebo (n=5)	Overall (n=20)
TEAEs			
Total Number	24	16	40
Number (%) of subjects with any	11(73.3)	4(80.0)	15(75.0)
Serious TEAEs			
Total Number	0	0	0
Number (%) of subjects with any	0	0	0
Deaths			
Number (%) of deaths	0	0	0
Treatment-related TEAEs			
Total Number	1	0	1
Number (%) of subjects with any	1(6.7)	0	1(5.0)
TEAEs resulting in study discontinuation			
Total Number	0	0	0
Number (%) of subjects with any	0	0	0
TEAEs of special interest			
Total Number	1	1	2
Number (%) of subjects with any	1(6.7)	1(20.0)	2(10.0)
TEAEs by Severity			
Mild	10(66.7)	2(40.0)	12(60.0)
Moderate	1(6.7)	1(20.0)	2(10.0)
Severe	0	1(20.0)	1(5.0)
Wound TEAEs			
Total Number	0	1	1
Number (%) of subjects with any	0	1(20.0)	1(5.0)

Treatment emergent adverse events include all events starring after the administration of investigational product.

Table 3. Summary of QT Prolongations

	CPL-01 (n=15)	Placebo (n=5)	Overall (n=20)
QTCF			
Subjects with increase >30 ms	3(20.0)	2(40.0)	5(25.0)
Subjects with increase >60 ms	0	0	0

QTcF = QT interval with Fridericia's correction

Note: Subjects were reported once if they had a prolongation of the shown interval at any post-baseline assessment.

was 573±258 ng/mL while the range of subject Cmax was 224 ng/mL to 1,280 ng/mL. The AUC0-24 was approximately one-half the total exposure relative to AUC0-inf at a mean ±SD value of 10,300±3,510 h·ng/mL, and AUC0-inf was 20,400±6,480 h·ng/mL. The range for AUC0-24 was 4,340 h*ng/mL to 16,000 h*ng/mL. The range for AUC0-inf was 10,200 h*ng/mL to 35,100 h*ng/mL. The %CV of the Cmax was 45.0% and for the AUC ranged from 31.6 to 53.6%. The mean ±SD value for T1/2 was 25.4±5.44 h, CL/F was 10.9±3.99 L/h, and Vz/F was 399±181 L. The summary (N, mean +/- SD and %CV) for the PK parameters of ropivacaine following a single dose of 2% CPL-01 (200 mg ropivacaine in 10 mL) administered by wound infiltration and instillation is presented in Table 4. The mean plasma concentration-time profile of ropivacaine in the linear and the semi-log scale is displayed in Figures 1 and 2, respectively.

The primary efficacy endpoint of interest was the time-weighted SPI1-24 for subjects who received CPL-01 compared with

Table 4. Summary of Ropivacaine Mean PK Parameters in Human Subjects Following a Single 2% CPL-01 (200 mg Ropivacaine in 10 mL) Local Administration by Wound Infiltration and Instillation After Mini-Abdominoplasty Surgery

PK Parameter (units)	200 mg Ropivacaiue			
	N	Mean	SD	%CV
T_{max}, h*	15	10.1	2.18-30.1	N/A
C_{max}, ng/mL	15	573	258	45
T_{lag}, h*	15	0	0.00-0.00	N/A
MRT_{last}, h	15	28.5	4.93	17.3
MRT_{inf}, h	15	31.7	6.49	20.5
AUC_{0-6}, ng h/mL	15	2,180	1170	53.6
AUC_{0-24}, ng h/mL	15	10.3	3,510	34.2
AUC_{0-t}, ng h/mL	15	19.9	6,280	31.6
AUC_{0-inf}, ng h/mL	15	20.4	6,480	31.8
%AUCextr	15	2.49	1.62	65.1
CL/F, L/h	15	10.9	3.99	36.6
Vz/F, L	15	399	181	45.3
λ, h-l	15	0.0287	6.78E-03	23.7
$T_{1/2}$, h	15	25.4	5.44	21.4

N/A - Not Applicable
* Expressed as median (minimum - maximum)

Table 5. Primary Efficacy Analysis: Summary of SPI1-24 Intent-to-treat Population

	CPL-01 (n=15)	Placebo (n=5)	Overall (n=20)
SPI_{1-24}			
n	15	5	
Mean	122.4	140.4	
SD	30.87	43.17	
Median	127.3	153.3	
Range (Min, Max)	(65,166)	(71,181)	
ANOVA Estimates [1]			
LS Mean (SE)	122.4(8.78)	140.4(15.20)	-18.0(17.55)
95% CI	(104.0,140.9)	(108.5,172.4)	(-54.9,18.9)
p-value			0.318

subjects who received placebo. Results are presented in Table 5.

The mean (SD) SPI1-24 was numerically lower for the CPL-01 group (122.4 [30.87]) than the placebo group (140.4 [43.17]). The LS mean (95% CI) difference between the groups was -18.0 (-54.9, 18.9).

When analyzed using all observed values and censoring for rescue medication (using the worst score within 2 hours of IV morphine administration or within 4 hours of po oxycodone administration), mean NRS scores of the CPL-01 group were numerically lower than the placebo group at most nominal time points up to 48 hours (Figure 3).

Discussion

The recent opioid crisis has sparked the development of long-acting, opioid-free postoperative analgesic alternatives, often using the amide type local anesthetic bupivacaine as active pharmaceutical ingredient. Bupivacaine was in clinical use for close to ten years before serious cardiac toxicity was reported. Several deaths were reported in obstetric patients in the United States in the 1970s [4]. In addition, recent literature showed that bupivacaine induced dose-dependent myo-, chondro-, and neurotoxicity, as well as delayed osteogenesis and disturbed wound healing in vitro [5].

The initial technology for extending the availability was to infuse them via an externally worn catheter connected to an elastomeric pump for postoperative pain management. While this approach is technically possible and has been used, it has multiple potential problems, including wet bandages, migration of the catheter tip, and the potential for dose dumping.

At present, there are several long-acting bupivacaine on the market. In 2011, FDA approved Exparel® (bupivacaine liposome injectable suspension) which is a multivesicular liposomal form (DepoFoam drug delivery systems) of encapsulated bupivacaine that allows for the slow diffusion of the drug over an extended period of time. Compared to bupivacaine, which only lasts approximately 8 hours, Exparel® lasts around 72 hours, almost a 9-fold difference. Thus far, Exparel® has been shown to provide successful prolonged analgesia after wound infiltration during several surgical procedures [6-8]. However, real-world studies evaluating the use of Exparel® have not shown consistently positive results. In 2020, FDA approved Xaracoll® (bupivacaine hydrochloride implant) which is indicated in adults for placement into the surgical site to produce postsurgical analgesia for up to 24 hours following open inguinal hernia repair[9].Such

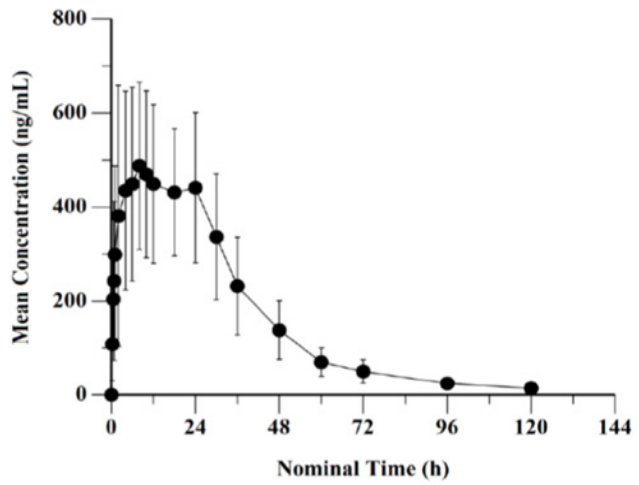

Figure 1. Mean (SD) Ropivacaine Plasma Concentration-Time Profiles in Human Subjects Following a Single Local Administration by Wound Infiltration and Instillation at a 2% CPL-01 (200 mg Ropivacaine in 10 mL) After Mini-Abdominoplasty Surgery (Linear Scale)

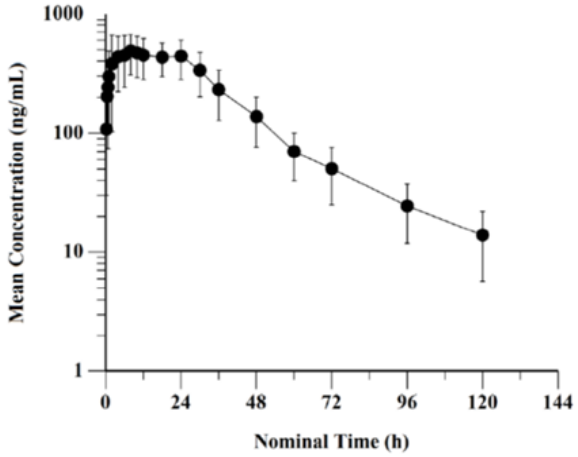

Figure 2. Mean (SD) Ropivacaine Plasma Concentration-Time Profiles in Human Subjects Following a Single Local Administration by Wound Infiltration and Instillation at a 296 CPL-01 (200 mg Ropivacaine in 10mL) After Mini-Abdominoplasty Surgery (Semi-log Scale)

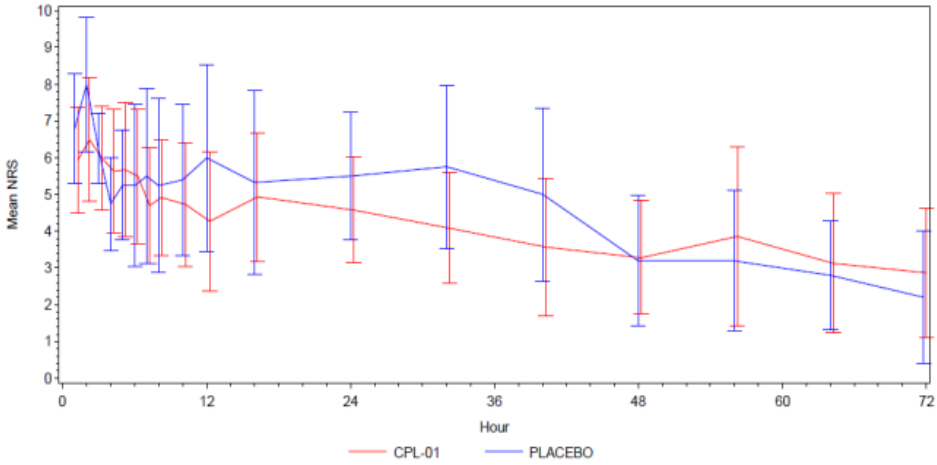

Figure 3. Numeric Rating Scale Pain Scores at Each Nominal Time Point(Intent-to-treat Population). NRS=numeric rating scale

Note: Means excluded NRS pain values when they fell within 2 hours of morphine being administered or within 4 hours of oxycodone being administered.

an implant would require more complex clinical procedures than injection, and the narrow indications and sustained analgesia only for 24 hours do not seem to offer much advantage. In 2021, FDA approved Posimir ® (bupivacaine solution) which is a sustained-release amide typelocal anesthetic formulation indicated for post-surgical pain reduction following arthroscopic subacromial decompression shoulder surgery [10] Posimir ® is administered as a single dose into the subacromial space under direct arthroscopic visualization (used to confirm proper placement of the needle tip). The post-surgical analgesia can last for up to 72 hours. Similar to Xaracol®, however, the narrow indication limits its widespread used in clinic. There is also an extended-release local anesthetic named ZYNRELEF® (bupivacaine and meloxicam), approved in adults for soft tissue or periarticular instillation to produce postsurgical analgesia for up to 72 hours after foot and ankle, small-to-medium open abdominal, and lower extremity total joint arthroplasty surgical procedures. ZYNRELEF® has been shown in the company's studies to deliver better pain management than standard of care bupivacaine HCl solution over 72 hours and to significantly reduce opioid utilization following surgery, but its utilization in the real world has also been slow after initial narrow approval by the FDA in May 2021 and, in December 2021, an expansion of ZYNRELEF's indication [11].

The exploration for a replacement for bupivacaine began in the 1980s. Two local anesthetics were developed after the evidence of bupivacaine-related severe toxicity: levobupivacaine and ropivacaine. Both these are pure left-isomers and, based on their three-dimensional structure, they have less toxic potential both on the central nervous system and on the heart [12]. Although levobupivacaine has been developed to reduce the adverse effects of bupivacaine, its cardiac and neurological toxicity has not been well studied [13,14]. Ropivacaine was first tested in 1988 and appeared to have many of the anesthesia characteristics of bupivacaine but was much less toxic [15]. Ropivacaine seems to be less chondrotoxic than bupivacaine [16]. And there are numerous other experimental studies confirm this hypothesis, showing that ropivacaine has fewer cardiotoxic effects than bupivacaine in equal concentrations [17,18]. However, as postoperative analgesic drugs, its action duration is a key shortcoming,

the duration of action (0.75% concentration) is about 3-5 hours [19]. Therefore, a drug with wide indications, good efficacy and good safety is needed in clinical practice. It was necessary to develop long-acting ropivacaine.

CPL-01 is that drug: a sustained-release injection of Ropivacaine hydrochloride injection, for the treatment of surgical pain and to reduce the need for opioids. The PG-Depot technology platform is a multifunctional parenteral drug delivery platform, suitable for applications that require sustained release of small molecules, peptides, and proteins for 1 to 7 days by injecting drugs into soft tissues or body cavities to achieve a customizable and long-acting drug release profile. The development of CPL-01 was based on the PG-Depot technology platform, that short-acting local anesthetic was developed into sustained-release dosage form, so as to prolong the duration of its local action, thus prolonging the local analgesic effect.

In this phase 2a study, 200 mg of CPL-01 was administered into the surgical site before wound closure by infiltration and instillation. Systemic exposure to ropivacaine was below the LAST limit. The systemic PK results validated extended release of ropivacaine from the depot into the incision site that could contribute to an extended analgesic efficacy profile. The primary exploratory efficacy endpoint of interest, SPI1-24, supported a numerical efficacy benefit [mean (SD) was 122.4 (30.87) for the CPL-01 group and 140.4 (43.17) for the placebo group]. The mean SPI1-24 was numerically lower (indicating less pain) in the CPL-01 group than in the placebo group. The difference was not statistically significant (P = 0.318). However, the dose was intentionally low and quite possibly sub-therapeutic as this is the first time that CPL-01 has been used in a human clinical study. CPL-01 was well tolerated and showed no evidence of local tissue reaction or impairment of wound healing. No subject was assessed as having LAST by the investigator. CPL-01 showed no negative impact on clinical laboratory results, vital signs, and ECGs.

Although this study is limited by the small sample size, there were no safety or tolerability issues with CPL-01 based on the PK and safety results. A larger phase 2b dose escalation study will be needed to identify the optimal dose range for efficacy and safety.

Conclusion

In this "first in human" phase 2a study, administration of 200 mg CPL-01 by wound infiltration and instillation demonstrated an extended release PK profile, validating that CPL-01 acted as an extended-release formulation of ropivacaine. CPL-01 was well tolerated and showed no evidence of local tissue reaction or impairment of wound healing. No subject was assessed as having LAST by the investigator. No serious AEs were observed in the study. No subject in either group experienced a clinically significant ECG change. An initial exploration of efficacy confirmed a numeric advantage for 200 mg CPL-01 for the efficacy endpoints; however, statistical significance was not reached (likely due to the small size of the study, which was not powered to detect statistical significance). However, the findings demonstrate that a long-acting ropivacaine has been found and possesses an adequate margin of safety to proceed with further clinical trials.

Conflicts of Interest

PJ Chen, Erol Onel, Christine Pan, Lee Chen and Hanghang Tommy Xu are the employees of Cali Biosciences. Other than that, the authors declare no confilict of interest.

Publication Ethics Statement

The study was conducted in compliance with the April 1996 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidance for Industry Good Clinical Practice (GCP) E6 (including archiving of essential study documents), the Integrated Addendum to ICH E6 (R2) of November 2016, and the applicable regulations of the United States, where the study was conducted.

The investigator was thoroughly familiar with the appropriate use of the study drug as described in the protocol, Investigator's Brochure, and all other study-related manual(s).

Essential clinical documents were maintained to demonstrate the validity of the study and the integrity of the data collected. A study master file was established and retained according to the appropriate regulations.

Abbreviations

AEs: Adverse Events; ANOVA : Analysis of Variance; AUC: Area under the Plasma Concentration-Time curve; BMI: Body Mass Index; ECG: Electrocardiogram; IP: Investigational Product; ITT: Intent-to-Treat; LAST: Local Anesthetic Systemic Toxicity; Min: Minimum; NRS: Numeric Rating Scale; PK: Pharmacokinetics; QTcF: QT interval with Fridericia's correction; RASS: Richmond Agitation and Sedation Scale; SD: Standard Deviation; TEAEs: Treatment-emergent Adverse Events; Tmax: Time to Reach Highest Observed (Peak) Concentration in Plasma Following Drug Administration

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