CR845, a Peripheral Kappa Opioid Receptor Agonist, Provides Better Pain Relief With Less Nausea and Vomiting Than Placebo in Patients After Bunionectomy

Frédérique Menzaghi, PhD,[1] Robert H. Spencer, PhD,[1] Joseph W. Stauffer, DO, MBA,[1,2] Paul J. Tiseo, PhD,[1] Nacer E.D. Abrouk, PhD[3]

[1]Cara Therapeutics, Inc., Shelton, Connecticut; [2]Johns Hopkins University School of Medicine, Baltimore, Maryland; [3]Innovexe, Mountain View, California

ABSTRACT

Objective: To assess the analgesic efficacy of CR845, a peripherally-acting, selective kappa opioid receptor agonist

Design: Double-blind, placebo-controlled clinical study

Setting: Single-center clinical research organization

Participants: Adult patients (N=51) undergoing elective primary unilateral first metatarsal bunionectomy surgery

Interventions: One day after bunionectomy, patients were randomized 2:1 to CR845 (5 mcg/kg, IV) or placebo after reporting a Visual Analog Scale (VAS) pain score ≥40 (out of 100) at rest. Within 30-60 minutes after the initial study drug dose, patients could receive an additional dose, as needed, and then every 8 hours as needed over the next 48 hours. Rescue medication (fentanyl 50 mcg IV) was available as needed.

Main Outcome Measures: Pain intensity (VAS) was assessed periodically during the 48-hour study period. The mean summed pain intensity differences from baseline over 24 hours ($SPID_{0-24}$) was the primary efficacy measurement.

Results: In the prespecified analysis of the completer population, a statistically significant reduction in $SPID_{0-24}$ with CR845 compared to placebo (P=0.033) was observed, with only CR845 having a 95% CI significantly less than 0 (P=0.0007). This observation was supported using the modified intent-to-treat population in which a greater decrease in $SPID_{0-24}$ was observed with CR845 than placebo, although this difference was not significant (P=0.116). Again, only CR845 had a 95% CI significantly less than 0 (P=0.022). The $SPID_{0-48}$ difference between treatment groups was statistically significant for the completer population (P=0.024). Compared to placebo, patients treated with CR845 experienced fewer treatment-emergent adverse events (AEs) of nausea (23.6% vs. 58.8% for placebo; P=0.028) and vomiting (5.9% vs. 23.9% for placebo; P=0.034). Mild transient facial tingling (paresthesia) and somnolence were observed with CR845 (11.8% for both), but there were no reports of psychiatric AEs characteristic of centrally-acting kappa opioids.

Conclusions: In this study, CR845 resulted in reduced pain intensity with lower incidence of nausea and vomiting versus placebo in patients after bunionectomy surgery.

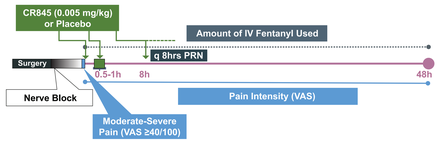
INTRODUCTION

- Treatment of pain with classical mu opioids is associated with multiple side effects, including sedation, respiratory depression, constipation, nausea, and euphoria (which may lead to abuse potential)
- CR845 is a peptidic kappa opioid receptor (KOR) agonist designed to limit its entry into the central nervous system, thereby predominantly activating peripheral KORs expressed on sensory nerves, which are responsible for transmitting pain signals, and on immune cells, which participate in inflammatory reactions and modulate nociceptor sensitivity (eg, hyperalgesia)
- Because CR845 does not activate receptors other than KORs and does not readily enter the central nervous system, it is expected to be a safer and better tolerated analgesic than opioid agonists, such as morphine, that predominantly activate mu opioid receptors
- In a previous double-blind, placebo-controlled clinical study with patients undergoing laparoscopic hysterectomy, pre- and/or postoperative intravenous (IV) CR845 produced a reduction in pain intensity as well as decreased postoperative nausea and vomiting (PONV)[1]
- Although substantial preclinical evidence exists that kappa opioids can modulate visceral pain, their potential utility in other forms of pain, such as bone-related pain, is less well understood
- The present clinical study examines the analgesic efficacy and safety of repeat doses of CR845 in patients following bunionectomy surgery

METHODS

- This investigation was a Phase 2, single-center, randomized, double-blind, placebo-controlled, parallel-group study; the overall study design is shown in **Figure 1**
- Following unilateral bunionectomy, continuous popliteal infusion of 0.2% ropivacaine was used to maintain regional anesthesia until approximately 3:00 am on the morning after surgery (Day 1)
- Following cessation of the popliteal block, eligible patients were randomized in a 2:1 ratio to CR845 or placebo, respectively, after reporting a Visual Analog Scale (VAS) pain score of ≥40 mm (on a 100-mm scale) at rest
- CR845 (0.005 mg/kg) or matching placebo was administered as an IV push, with subsequent treatments as shown in **Table 1**

Figure 1. Study Design



IV, intravenous; PRN, as needed; VAS, Visual Analog Scale.

Table 1. Treatment with CR845 or Placebo During Postoperative Days 1 and 2*

Time After Initial Dose of CR845 or Placebo	Treatment
30-60 minutes	• Study medication (CR845 or placebo) at patient request
After 1 hour	• Rescue medication, fentanyl 50 mcg IV, permitted every 2 hours, if requested; not within 2 hours of a repeat dose of study drug, if possible • If the patient received rescue medication, the next dose of CR845 or placebo was given at 8 hours with additional doses given every 8 hours as needed • If the patient did not require rescue medication, the next dose of CR845 or placebo was given as needed

*Doses: CR845 5 mcg/kg IV.
IV, intravenous.

Patients

- Key inclusion criteria:
  - Men and women ≥18 years of age
  - Scheduled for elective primary unilateral first metatarsal bunionectomy surgery (osteotomy and internal fixation) with no collateral procedures
- Key exclusion criteria:
  - Allergies to opioids
  - Alcohol, opiate, or drug abuse within the last 12 months
  - Non-opioid analgesics taken 12 hours before bunionectomy
  - Opioids, steroids, or other medication that could confound analgesic response taken within 4 days of surgery

Selected Assessments

- Resting pain intensity (VAS) was evaluated at Days 1-3 at defined intervals (prior to initial dose, and then at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 hours after the initial dose) until discharge or early termination
  - VAS: 0=no pain, 100=worst pain you can imagine
- Vital signs, electrocardiogram, and chemistry panel were taken at screening, Days 1-3, follow-up, or early termination
- Adverse events (AEs) were recorded starting at Day 1 and continuing through postoperative Day 10, or early termination

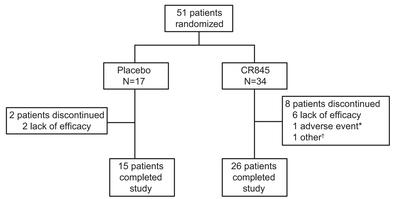
Statistical Analyses

- The primary outcome variable was the Summed Pain Intensity Differences over 24 hours ($SPID_{0-24}$) following the initial dose of study drug
  - $SPID_{0-36}$ and $SPID_{0-48}$ were also evaluated as secondary analyses
- The primary analysis for the $SPID_{0-24}$ utilized an Analysis of Variance (ANOVA) model with treatment group (placebo or CR845) as a main effect
- The differences in the least squares mean, the standard error of the differences, and one-sided P-values (ANOVA) are presented
- Missing pain intensity assessments were imputed using last observation carried forward (LOCF) or worst observation carried forward (WOCF), depending on whether they were scheduled or not, respectively
- Pain intensity scores assessed immediately prior to administration of rescue medication were carried forward for 1 hour, overriding any regularly scheduled assessment done within 1 hour of administration of the rescue medication

RESULTS

- 51 patients were randomized to treatment; 41 (80%) completed the study
- **Figure 2** illustrates the patient disposition per treatment
- 10 patients (20%) discontinued
  - 8 patients (16%) discontinued due to lack of efficacy
  - 1 patient (2%) discontinued due to an AE (fluid imbalance)
  - 1 patient (2%) discontinued due to failure to establish an IV line and subsequent refusal to consent to additional blood draws

Figure 2. Patient Disposition



*Discontinued due to fluid imbalance.
†Discontinued due to failure to establish an IV line and subsequent refusal to consent to additional blood draws.

- Demographics are shown in **Table 2**
- Age and body weight were balanced between the placebo and CR845 treatment groups
- Higher percentages of males and Hispanic or Latino patients were in the CR845 group than in the placebo group

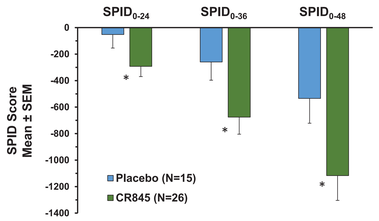
Table 2. Demographics

Characteristic	Placebo N=17	CR845 N=34
Sex, n (%)		
Female	16 (94)	29 (85)
Male	1 (6)	5 (15)
Race		
White	15 (88)	32 (94)
Black or African American	1 (6)	1 (3)
Asian	1 (6)	0
Native Hawaiian or other Pacific Islander	0	1 (3)
Ethnicity		
Hispanic or Latino	0	5 (15)
Not Hispanic or Latino	17 (100)	29 (85)
Age, years		
Mean (SD)	43.4±14.2	41.3±17.0
Weight, kg		
Mean (SD)	75.1±16.8	73.4±17.6

Efficacy

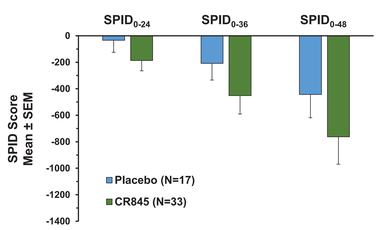
- In patients who received treatment for the 48-hour postoperative recovery period (Completers), CR845 produced a significantly greater decrease in pain intensity over time (mean negative SPID scores from time 0 to 24, 36, or 48 hours) than placebo (**Figure 3**)
- In the modified intent-to-treat (mITT) population, which included all patients who received double-blind study drug and completed at least 1 pain assessment, CR845 produced a numerically greater (but not statistically significant) decrease in pain intensity over time (mean negative SPID scores from time 0 to 24, 36, or 48 hours) than placebo (**Figure 4**)
- Numerical superiority in favor of CR845 was observed in both analysis populations. The amount of fentanyl rescue medication used was not different between the CR845 and placebo groups over the 48-hour period

Figure 3. Summed Pain Intensity Difference From 0-24 Hours ($SPID_{0-24}$), 0-36 Hours ($SPID_{0-36}$) and 0-48 Hours ($SPID_{0-48}$) in Completer Population



*One-sided P≤0.05 (ANOVA with treatment group as a main effect).

Figure 4. Summed Pain Intensity Difference From 0-24 Hours ($SPID_{0-24}$), 0-36 Hours ($SPID_{0-36}$) and 0-48 Hours ($SPID_{0-48}$) in mITT Population (Completers Plus Non-Completers)



Safety

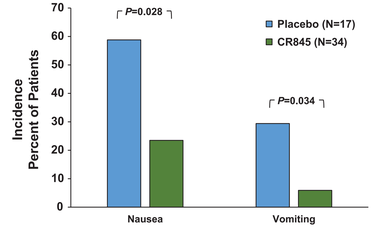
- AEs are listed in **Table 3**
- Similar proportions of treatment-emergent AEs were reported for placebo and CR845
- Patients treated with CR845 experienced significantly fewer opioid–related AEs of nausea and vomiting than placebo (P=0.028 and P=0.034, respectively), as shown in **Figure 5**
- Mild transient facial tingling (paraesthesia) and somnolence were reported in several patients treated with CR845
  - But there were no reports of psychiatric AEs characteristic of centrally acting kappa opioids

Table 3. Adverse Events*

	Placebo N=17 (100%)	CR845 N=34 (100%)
At least 1 treatment-emergent AE	14 (82)	29 (85)
At least 1 serious AE	0	0
AE leading to study drug discontinuation	0	1 (3)
Death	0	0
At least 1 treatment-related AE	10 (59)	16 (47)
Nausea	8 (47)	6 (18)
Dizziness	2 (12)	5 (15)
Paraesthesia	0	4 (12)
Somnolence	0	4 (12)
Constipation	1 (6)	2 (6)
Vomiting	5 (29)	2 (6)
Feeling hot	1 (6)	1 (3)
Decreased appetite	1 (6)	0

*Data are n (%).
AE, adverse event.

Figure 5. CR845 Reduction of Postoperative Nausea and Vomiting (PONV)



P-values calculated using Fisher's exact test.

CONCLUSIONS

- This study demonstrated that postoperative administration of IV CR845 significantly reduced pain intensity in bunionectomy patients treated over a 48-hour period
- The substantial reduction in PONV with IV CR845 compared with placebo, despite similar use of fentanyl, raises the possibility of a direct anti-nausea/anti-emetic effect of CR845
- In addition to analgesic activity against visceral postoperative pain (laparoscopic hysterectomy), IV CR845 exhibits analgesic activity against severe bone-related pain (bunionectomy), suggesting broad analgesic utility of CR845

REFERENCE

1. Gan et al, "Analgesic and Morphine-Sparing Effects of the Peripherally-Restricted Kappa Opioid Agonist CR845 after Intravenous Administration in Women Undergoing a Laparoscopic Hysterectomy" presented at the 2013 annual meeting of the International Anesthesia Research Society; San Diego California, USA; May 4-7, 2013.

ACKNOWLEDGEMENTS

This study was sponsored by Cara Therapeutics, Inc.

Professional medical writing, editing, and artistic support was provided by Edward Weselcouch, PhD, Diana Talag, ELS, and Shana Cambareri of PharmaWrite (Princeton, NJ, USA) and was paid for by Cara Therapeutics, Inc.

FM, RHS, JWS, and PJT are employees of Cara Therapeutics, Inc.