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CR845, A Novel Peripherally-Acting Kappa-Opioid Receptor Agonist, Provides Post-operative Analgesia as Well as Reduces Post-operative Nausea and Vomiting

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INTRODUCTION

- CR845 is a peripherally-acting kappa-opioid receptor agonist in development for the treatment of acute and chronic pain
  - CR845 has ≥30,000-fold greater selectivity for kappa-opioid receptors than for mu- or delta-opioid receptors
  - Its unique D-amino acid–based peptidic structure confers limited membrane permeability by diffusion or active transport mechanisms, which results in CR845 having limited access to the central nervous system (CNS)
  - In clinical studies the adverse event (AE) profile of CR845 is different from that seen with mu-opioids (eg, morphine)
- The ability of CR845 to reduce post-operative pain has been investigated in 3 double-blind, randomized, placebo-controlled studies (**Table 1**)
- Here we present an analysis of the pooled treatment-emergent AEs of post-operative nausea and/or vomiting in these studies

METHODS

- A summary of the 3 CR845 clinical studies is presented in **Table 1**
- The mu-opioid–related AEs of nausea and vomiting reported in each study were pooled for analysis by treatment group
  - Patients who received ≥1 dose of CR845 (pre-operatively, post-operatively, or both) were included in the CR845 group
  - Patients who received only placebo were included in the placebo group
- A generalized linear model was used to analyze the distribution of the AEs between treatment groups

Table 1. CR845 for Post-operative Pain: Study Designs

Study	Surgery	Placebo (n)	CR845 (n)	CR845 Dose (µg/kg, iv)	Male:Female (%:%)	Pain Response
CLIN2001	Laparoscopic hysterectomy					
Cohort 1		25	43	8 or 24 µg/kg[a]	0:100	No difference
Cohort 2		26	20	40 µg/kg[b]	0:100	Significantly greater reduction in pain intensity at 4 and 6 hr post-infusion in CR845 group
CLIN2002	Laparoscopic hysterectomy	84	119	40 µg/kg[c]	0:100	Patients receiving CR845 both pre- and post-operatively experienced significantly less pain in both periods than patients receiving placebo
CLIN2003	Bunionectomy	17	34	5 µg/kg[d]	12:88	Significant reduction in summed pain intensity over 48 hours in the CR845 group in the completer population
TOTAL		**152**	**216**		**1.6:98.4**	

[a]Patients were randomized to receive a single dose of CR845 or placebo the day after surgery if they reported a pain intensity score of ≥40 mm on a 100-mm Visual Analogue Scale (VAS) within 1 to 4 hours after discontinuation of PCA morphine.

[b]Patients were randomized to receive a single dose of CR845 or placebo if they reported a pain intensity score between 5 and 8, inclusive, on an 11-point Numerical Rating Scale (NRS) within 3 hours after awakening from anesthesia following surgery.

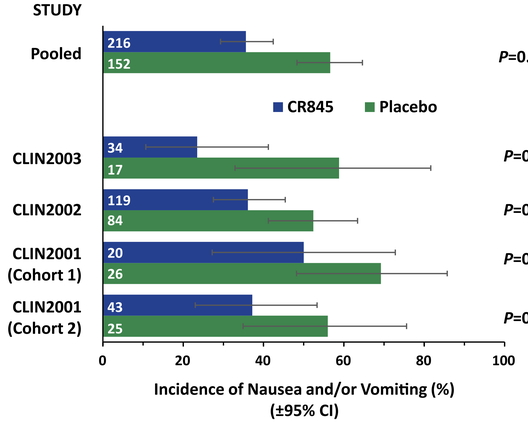
[c]Patients were randomized to receive placebo or CR845 (40 µg/kg) pre-operatively, and if they reached a post-operative pain intensity of ≥40 mm on a 100 mm VAS within 3-7 hours postoperatively, they were re-randomized to receive placebo or CR845 (40 µg/kg). Patients who did not meet the post-operative treatment pain threshold were included in the present analysis in their original pre-operative treatment group.

[d]Dose was administered post-operatively when the patient reached a post-operative pain intensity of ≥40 mm on a 100 mm VAS and could be repeated between 30 and 60 min after the first dose. Additional doses could be administered every 8 hr depending on whether the patient had required rescue medication.

RESULTS

- A total of 368 patients were enrolled in these studies and received at least 1 dose of study medication
  - 98.4% were female
  - 86.1% were enrolled in the laparoscopic hysterectomy studies
- The incidence of nausea and/or vomiting was greater in the placebo groups than in the CR845 groups in the individual studies and in the pooled analysis (**Figure 1**)
- Both nausea and vomiting were individually more common in placebo patients than in CR845 patients (**Table 2**)

Figure 1. Incidence of Nausea and/or Vomiting in Clinical Studies of CR845



The number of patients in each group is shown within each bar.

Table 2. Incidence of Nausea and Vomiting in the Pooled Analysis

	Placebo (n=152)	CR845 (n=216)
Nausea, %	55%	34%
Vomiting, %	12%	4%
Nausea and/or vomiting, %	57%	36%

- Rescue pain medication in the form of mu-opioid agonists was available at all times during the post-operative period in each study
  - Patient-controlled analgesia (ie, PCA morphine)
  - IV push of morphine or fentanyl
- Rescue medication use in the laparoscopic hysterectomy studies was less in the CR845 groups than in the placebo group (**Table 3**)
- Rescue medication use in the bunionectomy study (CLIN2003) was similar in the two treatment groups (**Table 3**)
- These observations suggest that the decreased post-operative nausea and vomiting seen in the CR845 group was not solely due to a lower use of mu-opioid pain medication

Table 3. Mean Post-operative mu-Opioid Rescue Pain Medication Use

Study/Cohort	Treatment Group	
	Placebo	CR845
CLIN2001 Cohort 1, morphine equivalents during 12-hr observation period, mg	13	18;13[a]
CLIN2001 Cohort 2, morphine during post-op hr 0-16, mg	24	16
CLIN2002, morphine in first 24 hr, mg	22	14-20[b]
CLIN2003, fentanyl in first 24 hr, µg	24	25

[a]Patients treated with 8 or 24 µg/kg, respectively.

[b]Includes patients treated with CR845 pre-operatively, post-operatively, or during both periods. The group of patients treated with CR845 both pre- and post-operatively used a mean of 14 mg of morphine in the first 24 hours after surgery, which was significantly less than the amount used by patients treated with placebo during both periods (P=0.030).

CONCLUSIONS

- This pooled analysis suggests that CR845 provides post-operative analgesia while reducing the incidence of post-operative nausea and vomiting
- This effect may not be solely related to a reduction in mu-opioid rescue pain medication use

DISCLOSURE

The 3 studies described in this pooled analysis were sponsored by Cara Therapeutics. The authors are employees of Cara Therapeutics.

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