ANALGESIC EFFICACY OF THE PERIPHERAL KAPPA OPIOID AGONIST CR845 IN LAPAROSCOPIC HYSTERECTOMY

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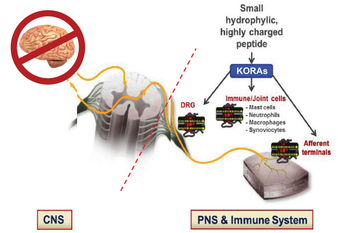
INTRODUCTION

- CR845 is a peripherally-restricted and highly selective kappa opioid receptor agonist (KORA)
  - Unique peptidic structure differentiates it from small organic heterocycle kappa agonists, which are for the most part active within the central nervous system (CNS, **Figure 1**)
- In Phase 2 of clinical development for the treatment of acute pain
  - In a previous clinical study in women undergoing laparoscopic hysterectomy, a single intravenous (IV) dose of CR845 significantly reduced pain intensity in the 8-hour postsurgical period[1]
  - In that study, CR845 was safe and well-tolerated
- The present investigation was done to further evaluate the analgesic efficacy and safety of CR845 when dosed preoperatively and postoperatively in women undergoing elective laparoscopic hysterectomy

Figure 1. CR845 Is Restricted From Entry Into the CNS



METHODS

Patients

- Women undergoing elective laparoscopic hysterectomy

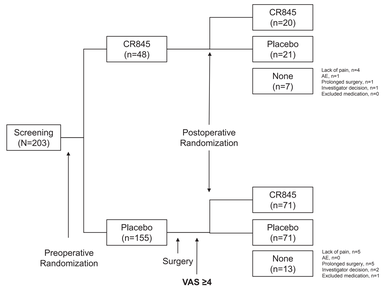
Study Design

- Phase 2
- Double-randomized, double-blind, placebo-controlled, parallel-group study
- 22 clinical sites in the US

Study Procedures (Figure 2)

- On the day of surgery, patients were randomized to receive placebo or CR845 (40 mcg/kg) in a 15-minute IV infusion starting 60 minutes prior to induction of anesthesia
- Following surgery, women reporting a pain intensity ≥4 on a 10 cm visual analog scale (VAS) were re-randomized to receive a 15-minute IV infusion of placebo or CR845 (40 mcg/kg)
- During the 24 hours after receiving the second infusion of study medication, patients were treated with morphine (2-4 mg/dose) if requested by the patient
- Pain intensity VAS and pain relief score (0=no relief from baseline, 4=complete relief from baseline) were recorded at 15, 30, 45, 60, 90, 120, 150, 180, 240, 360, 480, 720, 960, and 1440 minutes after the second infusion of study medication
- At the time of discharge or at early termination, each patient provided a global evaluation of their treatment (0=poor, 4=excellent)

Figure 2. Trial Design Schematic



RESULTS

Efficacy

- 203 women enrolled in the study and were randomized to preoperative treatment
  - Average age was 43.7 ± 9.0 years (mean ± SD)
  - Average BMI was 29.6 ± 6.2 kg/m^2
  - 84.2% Caucasian, 15.3% Black or African American, 0.5% Asian
- 20 patients were not re-randomized to postoperative treatment with study medication (**Figure 2**)
- **Figure 3** shows the change in pain intensity VAS scores in the postoperative period

Figure 3. Change in Pain Intensity VAS Scores

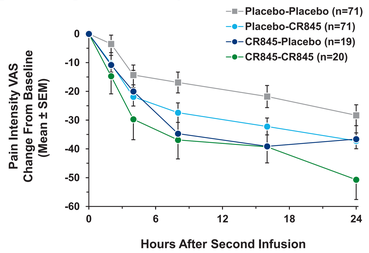


Figure 4. Summed Pain Intensity Difference (0-24 Hours)

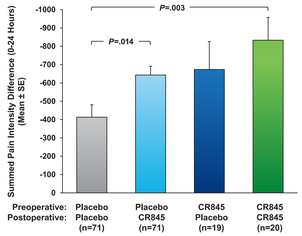
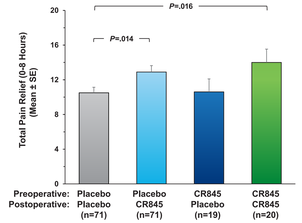


Figure 5. Total Pain Relief During the First 8 Hours After the Second Treatment Infusion



- A higher proportion of patients treated with CR845 in either the preoperative, postoperative, or both treatment periods were classified as "Responders" on the Global Evaluation of Study Drug Questionnaire (eg, answering "Excellent" or "Very good") than patients treated only with placebo (*P*=.001, Chi-square test) (**Figure 6**)

Figure 6. Global Evaluation of Study Drug

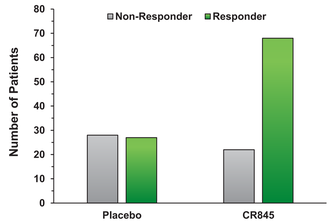


Figure 7. Time to First Rescue Medication Use

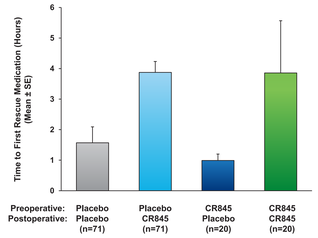


Figure 8. Kaplan-Meier Estimates of Avoiding Rescue Medication Use

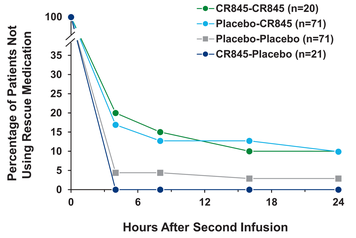
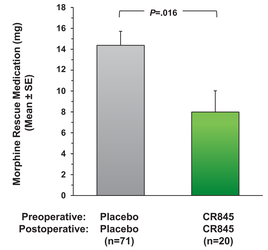


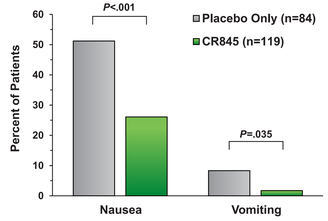
Figure 9. Rescue Medication Morphine Use 2 to 24 Hours After the Second Treatment Infusion



Safety

- The incidence of opioid-related treatment-emergent adverse events was lower in patients treated with CR845 than in patients treated only with placebo (**Figure 10**)

Figure 10. Opioid-related Adverse Events During the 24-hour Period After the Start of the First Treatment Infusion



P values are from Fisher's exact test.

Table 1. Treatment-emergent Adverse Events Occurring in ≥5% of Patients in Any Treatment Group by System Organ Class

	CR845 (n=119)		Placebo (n=84)		Total (N=203)	
System Organ Class/ Preferred Term	Patients n (%)	Events	Patients n (%)	Events	Patients n (%)	Events
Gastrointestinal disorders	54 (45.4)	70	51 (60.7)	74	105 (51.7)	144
Nausea	41 (34.5)	41	43 (51.2)	44	84 (41.1)	85
Flatulence	12 (10.1)	12	19 (22.6)	19	31 (15.3)	31
Constipation	13 (10.9)	13	3 (3.6)	3	16 (7.9)	16
Vomiting	3 (2.5)	3	7 (8.3)	7	10 (4.9)	10
Vascular disorders	34 (28.6)	37	21 (25.0)	21	55 (27.1)	58
Hypotension	29 (24.4)	29	19 (22.6)	19	48 (23.6)	48
Hypertension	8 (6.7)	8	2 (2.4)	2	10 (4.9)	10
Nervous system disorders	31 (26.1)	42	14 (16.7)	14	45 (22.2)	56
Headache	15 (12.6)	15	11 (13.1)	11	26 (12.8)	26
Dizziness	8 (6.7)	8	2 (2.4)	2	10 (4.9)	10
Paraesthesia	9 (7.6)	9	0 (0.0)	0	9 (4.4)	9
Investigations	32 (26.9)	57	4 (4.8)	4	36 (17.7)	61
Blood sodium increased	29 (24.4)	29	0 (0.0)	0	29 (14.3)	29
Blood chloride increased	23 (19.3)	23	0 (0.0)	0	23 (11.3)	23
Renal and urinary disorders	13 (10.9)	16	6 (7.1)	7	19 (9.4)	23
Urinary retention	9 (7.6)	9	1 (1.2)	1	10 (4.9)	10
Bladder spasm	2 (1.7)	2	5 (6.0)	5	7 (3.4)	7
Cardiac disorders	11 (9.2)	11	3 (3.6)	3	14 (6.9)	14
Tachycardia	11 (9.2)	11	3 (3.6)	3	14 (6.9)	14
Respiratory, thoracic, and mediastinal disorders	8 (6.7)	9	2 (2.4)	2	10 (4.9)	11
Hypoxia	7 (5.9)	7	1 (1.2)	1	8 (3.9)	8
Skin and subcutaneous tissue disorders	4 (3.4)	4	5 (6.0)	5	9 (4.4)	9
Pruritus	4 (3.4)	4	5 (6.0)	5	9 (4.4)	9

CONCLUSIONS

- CR845 represents a novel class of peripherally-acting KORAs that has demonstrated clinically significant analgesic and anti-inflammatory properties in patients undergoing laparoscopic hysterectomy
- Patients who received CR845 reported a significant decrease in pain intensity and increase in pain relief
  - CR845 was most efficacious when dosed both before and after surgery
- CR845 significantly decreased morphine consumption as well as opioid-related adverse events (eg, nausea, vomiting, pruritus)
- CR845 was safe and well-tolerated when administered perioperatively, before and/or after surgery, and patients reported higher levels of satisfaction after being treated with CR845

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REFERENCE

1. Menzaghi F, O'Connor SJ, Labissiere G, Gardell LR, Spencer RH, Chalmers DT. Analgesic and morphine-sparing effects of the kappa opioid agonist CR845 after single iv administration in women undergoing laparoscopic-assisted hysterectomy. Presented at the 2010 World Congress on Pain, August 29-September 2, 2010; Montréal, Québec, Canada.

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