CR845, a Novel Peripherally-Acting Kappa Opioid Receptor Agonist, Has Low Abuse Potential Compared With Pentazocine

Lynn R. Webster, MD,[1] Frédérique Menzaghi, PhD,[2] Joseph W. Stauffer, DO, MBA,[2,3] Paul J. Tiseo, PhD,[2] Robert H. Spencer, PhD[2]

[1]PRA Health Sciences, Salt Lake City, Utah; [2]Cara Therapeutics, Inc., Shelton, Connecticut; [3]Johns Hopkins University School of Medicine, Baltimore, Maryland

ABSTRACT

Objective: To examine the relative abuse potential of CR845, a potent, peripherally-acting, selective kappa opioid receptor agonist (KORA), compared with placebo and pentazocine, a schedule IV opioid analgesic.

Design: Randomized, double-blind, active- and placebo-controlled study

Setting: Single-center clinical research organization

Participants: Recreational polydrug users with experience using opioids and hallucinogenic agents

Interventions: Subjects received a single bolus IV dose of the following 4 treatments in random order: CR845 5 mcg/kg (therapeutic dose), CR845 15 mcg/kg (supra-therapeutic dose), placebo, and pentazocine 0.5 mg/kg. Treatments were separated by a 48-hour washout period.

Main Outcome Measures: Drug liking bipolar Visual Analog Scale (VAS) was the primary measurement and was assessed periodically between 5 minutes and 8 hours after dosing.

Results: Drug liking scores for pentazocine were significantly greater than that of placebo and either dose of CR845 (P<0.0001 for each comparison to pentazocine). The least squares mean for the maximum drug liking VAS (Emax) scores (±standard error of LS mean) were 87.6±1.9 for pentazocine, 65.3±1.9 for CR845 5 mcg/kg, 66.9±1.9 for CR845 15 mcg/kg, and 52.4±1.9 for placebo, demonstrating that both doses of CR845 had significantly lower drug liking response compared with pentazocine. Additional bipolar VAS measurements were lower for CR845 compared with pentazocine for "overall drug liking" (P<0.0001 for both doses of CR845) and "take drug again" (P<0.0003 for CR845 5 mcg/kg and P<0.0001 for CR845 15 mcg/kg). These VAS scores for CR845 were equivalent for both doses and were similar to those of placebo.

Conclusions: These results suggest that the novel and selective peripherally acting KORA, CR845, may present a low risk for abuse liability in humans.

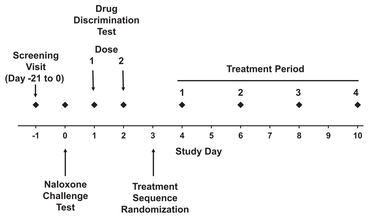
INTRODUCTION

- CR845 is a peripherally acting kappa opioid receptor agonist that is being developed for the treatment of acute and chronic pain
  - ≥30,000-fold selectivity for kappa opioid receptors compared with mu or delta opioid receptors
  - Its unique D-amino acid–based peptidic structure confers limited membrane permeability by diffusion or active transport mechanisms and results in CR845 having limited access to the central nervous system (CNS)
  - Therefore CR845 preferentially interacts with kappa opioid receptors outside of the CNS
- Kappa opioid receptors and abuse potential
  - Kappa opioid receptor agonists that act within the CNS are reported to produce dysphoria and hallucinations
  - These symptoms have not been reported with single or multiple intravenous doses of CR845
  - The present study was conducted to further assess the abuse potential of CR845 and was based on guidance from the Food and Drug Administration (FDA) regarding the evaluation of the abuse potential of drugs
  - Pentazocine, a schedule IV opioid analgesic with kappa agonist activity, was selected as the positive control in this study

METHODS

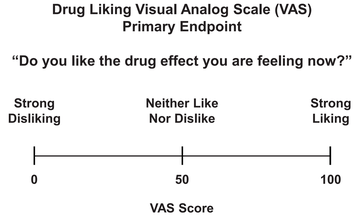
- Patients
  - 18 to 55 years old
  - Opioid user (not currently physically dependent based on naloxone challenge test) who has experience using opioids for nontherapeutic purposes
  - Prior experience with hallucinogenic substances, most recently within 60 days of the screening visit
  - Successfully discriminate between IV doses of placebo and pentazocine (0.5 mg/kg) administered in random order 24 hours apart
- Study Design (**Figure 1**)
  - Single-center, randomized, double-blind, active- and placebo-controlled, 4-way crossover study
  - 4 intravenous (IV) treatments in balanced Williams crossover design
    - Placebo
    - CR845 – 5 mcg/kg (therapeutic dose)
    - CR845 – 15 mcg/kg (supratherapeutic dose)
    - Pentazocine – 0.5 mg/kg
  - Sequential treatments were separated by a 48-hour washout period

Figure 1. Study Schedule of Events



- Study Assessments
  - Periodically between 5 minutes to 8 hours after dose
  - Drug Liking Visual Analog Scale (VAS) – primary endpoint
    - Bipolar VAS (**Figure 2**)
    - Sensitive to both disliking (eg, dysphoria) as well as liking (eg, euphoria)
    - Widely used and validated

Figure 2. Drug Liking VAS



- Take Drug Again Bipolar VAS
  - "Would you want to take the drug you just received again, if given the opportunity?"
- Overall Drug Liking Bipolar VAS
  - "Overall, my liking for this drug is:"
- Safety
  - Treatment-emergent adverse events (AEs) were recorded throughout the study
- Statistical Analysis
  - The primary analysis population was the Modified-Intent-to-Treat (MITT) population
  - The primary endpoint variable was the maximum Drug Liking score during the 8 hours after dosing (Emax)
  - Each outcome variable was analyzed by analysis of variance using a mixed model with the outcome variable as the dependent variable and treatment sequence, treatment period, and treatment as fixed effects and patient nested within sequence as a random effect
  - If residuals were not normally distributed, nonparametric analysis was performed

RESULTS

- Demographics (MITT)
  - 44 patients entered the Treatment Phase and comprised both the Safety and MITT populations; 39 patients completed all 4 treatment periods
    - Mean Age (±SD): 28.0 (7.72) years
    - Gender: 35 Males (79.5%) and 9 Females (20.5%)
    - Race: 38 White (86.4%), 2 Black or African American (4.5%), 2 Asian (4.5%), and 1 American Indian or Alaska Native (2.3%)
    - Mean Weight (± SD): 72.1 (11.04) kg
    - Mean BMI (± SD): 24.2 (3.2) kg/m^2
- Drug Liking VAS scores (MITT)
  - 5 minutes after dosing with pentazocine 0.5 mg/kg, the median Drug Liking VAS scores were much greater relative to placebo and gradually returned to similar values by 3 hours after dosing (**Figure 3**)
  - 5 minutes after dosing with either dose of CR845, the median Drug Liking VAS scores were slightly increased relative to placebo and returned to similar values by 1 to 2 hours after dosing (**Figure 3**)
  - The maximum Drug Liking VAS score (Emax) following administration of pentazocine 0.5 mg/kg was significantly higher compared with each of the other 3 treatments (**Figure 4**)
  - Drug Liking Emax values were similar following either dose of CR845 and were significantly lower than Emax values with pentazocine 0.5 mg/kg (**Figure 4**)

Figure 3. Drug Liking VAS Scores (MITT)

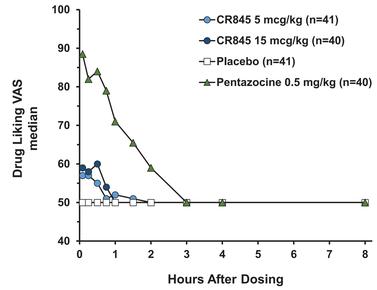
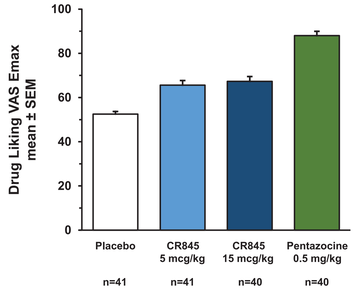


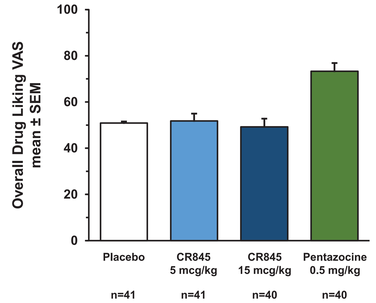
Figure 4. Maximum Drug Liking VAS Scores (primary endpoint; MITT)



All comparisons are P<0.0001 except for the comparison of the 2 doses of CR845 (P=0.611).

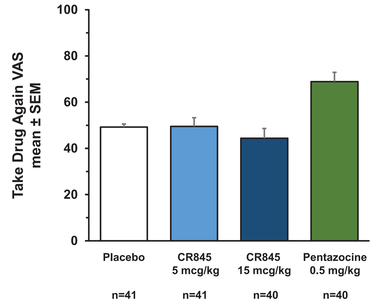
- Overall Drug Liking and Take Drug Again VAS scores (MITT)
  - Overall Drug Liking and Take Drug Again VAS scores were significantly higher after pentazocine 0.5 mg/kg than after either dose of CR845 (P<0.0001, **Figures 5** and **6**)
  - Overall Drug Liking and Take Drug Again VAS scores following either dose of CR845 were similar to those observed after placebo (**Figures 5** and **6**)

Figure 5. Overall Drug Liking VAS Scores (MITT)



Drug Liking for pentazocine was significantly greater than for the other treatments (P<0.0001). No significant difference was found for comparisons between placebo, CR845 5 mcg/kg, and CR845 15 mcg/kg.

Figure 6. Take Drug Again VAS Scores (MITT)



Take Drug Again VAS scores for pentazocine were significantly greater than for the other treatments (P≤0.0005). No significant difference was found for comparisons between placebo, CR845 5 mcg/kg, and CR845 15 mcg/kg.

- Safety Results
  - Summary of treatment-emergent AEs is presented in **Table 1**

Table 1. Number of Patients With Treatment-Emergent AEs Occurring in 2 or More Patients During Any Treatment in the Safety Population

AE	Placebo n=41	CR845 5 mcg/kg n=41	CR845 15 mcg/kg n=40	Pentazocine 0.5 mg/kg n=40
Any AE[a]	6 (14.6)	10 (24.4)	16 (40.0)	13 (32.5)
Abdominal Pain	0	1 (2.4)	2 (5.0)	0
Abdominal Pain Upper	0	0	2 (5.0)	0
Constipation	0	0	2 (5.0)	1 (2.5)
Dyspepsia	0	2 (4.9)	1 (2.5)	0
Nausea	0	1 (2.4)	1 (2.5)	5 (12.5)
Vomiting	1 (2.4)	0	2 (5.0)	5 (12.5)
Chills	0	1 (2.4)	0	2 (5.0)
Groin Pain	0	2 (4.9)	1 (2.5)	0
Dizziness	0	1 (2.4)	5 (12.5)	2 (5.0)
Headache	1 (2.4)	3 (7.3)	4 (10.0)	4 (10.0)
Hypoaesthesia	0	2 (4.9)	1 (2.5)	1 (2.5)
Hot Flush	0	0	0	3 (7.5)

The safety population included all patients who received at least one treatment during the double-blind treatment period (N=44).
[a]Number of patients (% of patients during that treatment period).

CONCLUSION

- The results of this clinical study suggest that CR845, a novel and selective peripherally restricted kappa opioid receptor agonist, may present a low risk for abuse in humans

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