SUBJECTIVE AND OBJECTIVE EVIDENCE OF LOW ABUSE POTENTIAL OF THE PERIPHERALLY-ACTING KAPPA OPIOID, CR845, COMPARED WITH PENTAZOCINE

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ABSTRACT

Aims: CR845, a potent, peripherally-acting, selective kappa opioid, is being developed for the treatment of acute and chronic pain. The primary objective of the trial was to measure the relative abuse potential of 2 doses of CR845 compared to an intravenous (iv) dose of pentazocine, a Schedule IV opioid analgesic with mixed mu and kappa opioid activity.

Methods: Recreational polydrug users with opioid and hallucinogenic drug experience were enrolled in this single-center, randomized, double-blind, active- and placebo-controlled study. Subjects (N=39) received a single bolus iv dose of the following 4 treatments in a balanced Williams crossover design, with 48-hour washout periods: CR845 5 mcg/kg (therapeutic dose), CR845 15 mcg/kg (supra-therapeutic dose), placebo, and pentazocine 0.5 mg/kg. In addition to subjective measures of drug abuse liability, changes in pupillary diameter were measured.

Results: The primary measure of "drug liking" Emax on a visual analog scale (VAS) for CR845 was significantly lower than pentazocine ($p < .0001$). Similarly, the VAS scores for "drug liking" and drug effect "high" for CR845 were lower than those for pentazocine over the entire 8-hour observation period. In addition, "overall drug liking" and "take drug again" VAS scores were lower for CR845 compared to pentazocine ($p < .0001$) and were equivalent to placebo. Pentazocine produced a decrease in the mean pupillary diameter compared with no change with either dose of CR845 or placebo ($p < .0001$).

Conclusions: This study provides evidence that CR845 exhibits substantially less abuse potential than pentazocine. The lack of effect of CR845 on pupillary diameter is consistent with preclinical studies demonstrating an absence of CNS mu opioid activity, which further supports a low abuse potential compared with mu opioids.

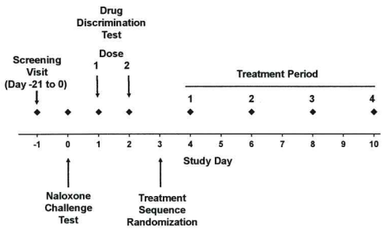
INTRODUCTION

- 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 (iv) 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

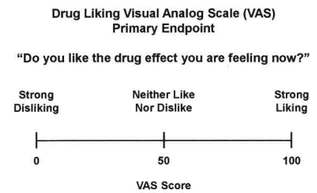
- Subjects
  - 18 to 55 years old
  - Opioid user (not currently physically dependent based on naloxone challenge test) who has experience using opioids for nontherapeutic purposes
  - Prior experience with hallucinogenic substances, most recently within 60 days of the screening visit
  - Successfully 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 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:"
- Pupillometry
  - Pupil diameter measurements were made before and periodically after each dose using NeurOptics® VIP™-200 Pupillometer
  - Measurements were performed in a dimly lit room after a minimum of 1 minute acclimation to the dark
- 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 subject nested within sequence as a random effect
  - If residuals were not normally distributed, nonparametric analysis was performed

RESULTS

- Demographics (MITT)
  - 44 subjects entered the Treatment Phase and comprised both the Safety and MITT populations; 39 subjects 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/m²
- 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)

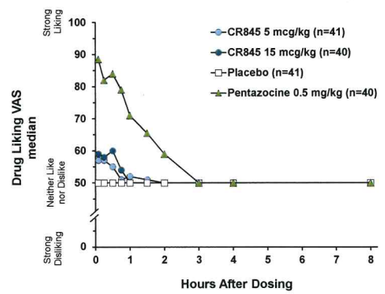
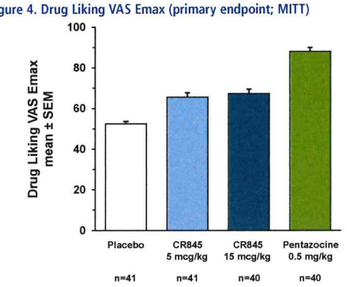


Figure 4. Drug Liking VAS Emax (primary endpoint; MITT)



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

- Abuse Potential Assessments
  - Overall Drug Liking, Take Drug Again, and Drug Effect "High" VAS scores were significantly higher after pentazocine 0.5 mg/kg than after either dose of CR845 ($Ps \leq 0.0005$, **Table 1**)
  - Overall Drug Liking and Take Drug Again VAS scores following either dose of CR845 were similar to those observed after placebo (**Table 1**)
- Pupillometry results
  - The subjects treated with pentazocine demonstrated a median 2.3 mm decrease in pupil diameter within 30 min after dosing (**Figure 5**)
  - No substantial change was observed following placebo or either dose of CR845
  - The maximum change in pupil diameter was significantly greater in the pentazocine group than in the placebo, CR845 5 mcg/kg, and CR845 15 mcg/kg groups (**Table 1**)

Figure 5. Effect of Treatment on Pupil Diameter (MITT)

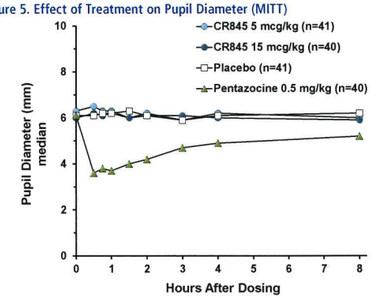


Table 1. Summary Results in the MITT Population

	Treatment			
	Placebo (n=41)	CR845 5 mcg/kg (n=41)	CR845 15 mcg/kg (n=40)	Pentazocine (n=40)
Drug Liking VAS, Emax, mean±SEM	52.5±1.19	65.6±2.11†	67.3±2.18†	88.0±1.98**
Drug Effect "High" VAS, AUE_{0-8h}, mean±SEM	6.0±2.71	40.6±7.10†	48.7±7.67†	155.0±13.89**
Overall Drug Liking, mean±SEM	50.9±0.63	51.8±3.19	49.2±3.57	73.3±3.57**
Take Drug Again VAS, mean±SEM	49.2±1.34	49.5±3.78	44.4±4.20	68.9±4.02*
Maximum Change in Pupil Diameter, mm, mean±SEM	-0.4±0.1	-0.6±0.11	-0.4±0.08	-2.5±0.14**

AUE, area under effect curve
*$P \leq 0.0005$ compared with each other treatment, **$P<0.0001$ compared with each other treatment
†$P \leq 0.0001$ compared with placebo

- Safety Results
  - Summary of treatment-emergent AEs is presented in **Table 2**

Table 2. Number of Subjects With Treatment-Emergent AEs Occurring in 2 or More Subjects 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*	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 subjects who received at least 1 treatment during the double-blind treatment period (N=44).
*Number of subjects (% of subjects during that treatment period)

CONCLUSIONS

- The subjective and objective 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

CONFLICT OF INTEREST

J.W. Stauffer, F. Menzaghi, R. Spencer, and D. Chalmers are employees of Cara Therapeutics. M.E. Lewis is a non-employee consultant, serving as Chief Scientific Advisor and Corporate Secretary of Cara Therapeutics.

L.R. Webster received research funding from Cara Therapeutics to conduct this clinical study.

N.E.S. Abrouk performed the statistical analysis that was funded by Cara Therapeutics.

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