Preclinical and Clinical Assessments of the Abuse Potential of the Kappa-Opioid Receptor Agonist CR845 Suggest Low Abuse Potential

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INTRODUCTION

- CR845 is a highly potent, peripherally acting kappa-opioid receptor agonist (KORA) with no affinity for either delta- or mu-opioid receptors and no other detectable off-target activity at other receptors, ion channels, or transporters
- CR845 exhibits analgesic effectiveness in clinical studies of acute and chronic pain
- Although the analgesic activity of KORAs has been recognized for more than 15 years, their development has been hampered due to central nervous system (CNS) mediated adverse events, in particular dysphoria and hallucinations
- CR845's hydrophilic, tetrapeptide structure greatly limits its entry into the brain, and thus CR845 should be devoid of the centrally mediated adverse psychoactive effects
- Preclinical and clinical studies were undertaken to determine whether the compound has the potential for recreational abuse in humans
- We investigated whether CR845 would generalize to the discriminative cue elicited in rats by (-)pentazocine, a mixed kappa/delta-opioid receptor agonist and mu-partial agonist
- The ability of CR845 to serve as a positive reinforcer was also evaluated in rats that had been trained to self-administer a low dose of heroin
- These preclinical findings were reported along with results obtained with CR845 in a drug-experienced human volunteer trial

METHODS

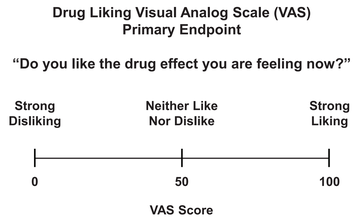
Preclinical

- 30 female Lister hooded rats were trained to discriminate (-)pentazocine (5 mg, intraperitoneally [ip]) from saline on a fixed reward 5 (FR5) schedule for sweetened milk rewards
  - Rats were then challenged with intravenous (iv) doses of pentazocine, butorphanol (a mixed kappa/mu-opioid receptor agonist), or CR845 to validate the model and assess the generalization of CR845 to (-)pentazocine
- 40 male Sprague Dawley rats were trained to self-administer heroin on an FR5 schedule
  - After saline extinction, separate groups of rats were evaluated with iv doses of CR845 or (-)pentazocine to assess their reinforcing effects

Clinical

- 44 recreational polydrug users (18 to 55 years old) who were experienced but not dependent on opioid and hallucinogenic drugs were enrolled in a double-blind, single-center, randomized, active- and placebo-controlled, 4-way crossover study assessing the abuse potential of CR845
  - All subjects could discriminate between iv doses of placebo or pentazocine (Talwin lactate injection, 0.5 mg/kg)
  - 4 iv treatments were given in a balanced Williams crossover design with 48 hours between doses
    - Placebo
    - CR845 – 5 mcg/kg (therapeutic dose)
    - CR845 – 15 mcg/kg (supratherapeutic dose)
    - Pentazocine – 0.5 mg/kg
  - Response to each drug was assessed up to 8 hours after each dose using a bipolar Drug Liking Visual Analog Scale (VAS) in which 0 indicated "strong disliking" and 100 indicated "strong liking" (**Figure 1**)
  - The primary endpoint variable was the maximum Drug Liking VAS during the 8 hours after dosing (Emax)

Figure 1. Drug Liking Visual Analog Scale (VAS)



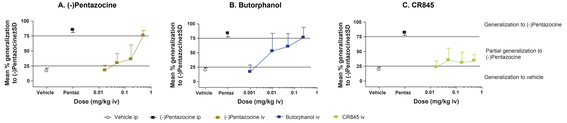
- Similar VAS instruments were used to assess other aspects of abuse potential
- Pupil diameter was measured periodically after each treatment to provide an objective measure of centrally mediated mu-receptor drug response
- The primary analysis population for the clinical studies was the Modified-Intent-to-Treat (MITT) population, defined as all randomized subjects who received at least 1 dose of study medication in the Treatment Phase and who had at least 1 post-dose assessment (primary endpoint) during any treatment completed in the Treatment Phase

RESULTS

Preclinical

- Drug discrimination was validated by dose dependent generalization of iv (-)pentazocine to the ip (-)pentazocine training cue (**Figure 2A**)
- A similar response was observed with increasing iv doses of butorphanol, used as a reference comparator (**Figure 2B**)
- In contrast, CR845 produced low-level, non-dose-dependent, partial generalization to (-)pentazocine, a result that is consistent with its potent KORA activity coupled with its poor CNS penetration (**Figure 2C**)

Figure 2. Effects of Intravenously Administered (-)Pentazocine, Butorphanol, and CR845 in Rats Trained to Discriminate (-)Pentazocine (5 mg/kg ip) From Vehicle (Saline) Determined 15 min After Dosing



The drugs were evaluated in a group of 15 rats that had successfully learned to discriminate (-)pentazocine (5 mg/kg ip) and saline. Rats were tested 15 min after iv injection of (-)pentazocine, butorphanol, or CR845. Results are reported as the mean percentage generalization to (-)pentazocine±SD. Each dose of test compound was evaluated in a group of 6 to 8 rats.

ip, intraperitoneal; iv, intravenous; Pentaz, pentazocine; SD, standard deviation.

- Peak plasma concentration (C_{max}) was in excess of the human plasma concentration at therapeutic doses (**Table 1** and **2**)

Table 1. Maximal Plasma CR845 Concentrations (C_{max}) in the Drug Discrimination Experiment in Lister Hooded Rats

	CR845 dose (mg/kg/infusion iv)				
	0.125	0.250	0.300	0.375	0.500
C_{max} (ng/mL), mean±SD	1666±1470	1127±61.1	1750±390.4	1760±113.6	2487±159.5

n=3 per dose group.

For the highest dose tested in the drug-discrimination test (0.5 mg/kg iv), the maximal plasma concentration of CR845 (C_{max}) was 9.0-fold greater than that observed at the maximum dose evaluated in humans (0.04 mg/kg).

iv, intravenous; SD, standard deviation.

Table 2. Maximal Plasma CR845 Concentrations (C_{max}) in the Self-administration Experiment in Sprague Dawley Rats

	CR845 dose (mg/kg/infusion iv)			
	0.001	0.005	0.025	0.125
C_{max} (ng/mL), mean±SD	5.64±3.7	21.4±3.1	95.2±4.6	555.3±83.5
Mean accumulated dose (mg/kg)	0.004	0.019	0.089	0.350
C_{max} (ng/mL), mean±SD	14.9±0.76	101.3±35.3	325.3±29.9	1345±35.4

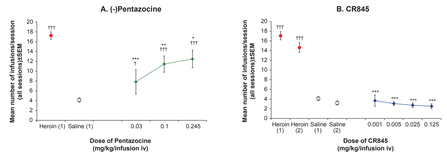
n=2 to 3 per dose group.

The plasma exposure to CR845 produced by the various doses of the drug tested in the model ranged between 2.0% and 200% of the C_{max} at the highest dose tested clinically (0.04 mg/kg), and the mean accumulated drug intake by the rats produced plasma concentrations of CR845 between 5.0% and 487.0% of that value.

iv, intravenous; SD, standard deviation.

- Pentazocine also substituted for heroin in heroin-maintained rats at all doses tested demonstrating that it serves as a positive reinforcement (**Figure 3**)

Figure 3. Evaluation of the Reinforcing Effects of (-)Pentazocine and CR845 in Rats Trained to Self-administer Heroin



Data are presented as the mean±SEM number of infusions per 2-hour test session obtained during the last 3 sessions for responding under a FR5 schedule of drug reinforcement. (-)Pentazocine (0.03, 0.1, or 0.245 mg/kg/infusion iv, n=8 rats/group for each dose) and CR845 (0.001, 0.005, 0.025, or 0.125 mg/kg/infusion iv for n=7, 7, 8, and 5 rats/group, respectively) were evaluated in separate groups of heroin-maintained rats. Some rats were tested at more than 1 dose of (-)pentazocine or CR845. Significance versus saline by multiple t test: $^{\dagger}P<0.05$, $^{\dagger\dagger\dagger}P<0.001$. Significance versus heroin by Dunnett's test: *$P<0.05$, **$P<0.01$, ***$P<0.001$.

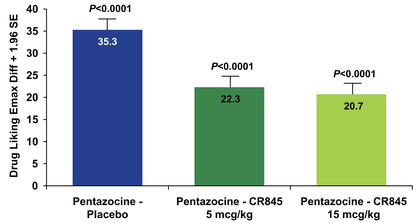
FR5, fixed reward 5; iv, intravenous; SEM, standard error of the mean.

- In contrast, CR845 produced no evidence of positive reinforcement at doses in excess of clinical doses

Clinical

- In humans, maximum possible effect (Emax) for Drug Liking was significantly higher for iv pentazocine than placebo ($P<0.0001$) confirming the validity of the study (**Figure 4**)

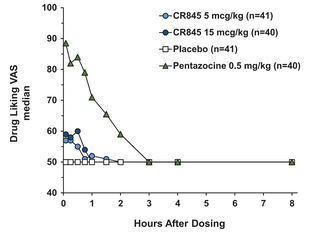
Figure 4. Pentazocine Has Significantly Higher Drug Liking Than Either Dose of CR845



The difference between the 2 doses of CR845 was not significant ($P=0.611$).

- The VAS measure of Drug Liking (Emax over the entire 8-hour observation period) for CR845 was significantly lower than pentazocine ($P<0.0001$) and did not separate from placebo after 1 hour and had no evidence of a dose-related effect (**Figure 5**)

Figure 5. Drug Liking VAS Scores



- A similar pattern was observed on measures of Any Effects, Good Drug Effects, and Drug High, with small elevations relative to placebo seen after doses of CR845 that were not dose-related and which were significantly lower than scores following pentazocine
- In the end-of-session question of Overall Drug Liking and Take Drug Again, subjects who received CR845 reported scores that were not different from placebo; the mean scores for Drug Liking and Desire were statistically significantly higher for pentazocine compared with placebo (**Table 3**)

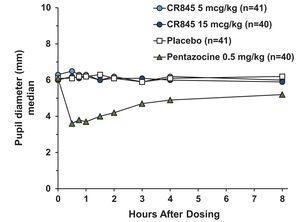
Table 3. Summary Results in MITT Population

	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, $AUE_{0\text{-}8hr}$, 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**

*$P\leq0.0005$ compared with each other treatment, **$P<0.0001$ compared with each other treatment.
†$P\leq0.0001$ compared with placebo.
AUE, area under effect curve; SEM, standard error of the mean; VAS, Visual Analog Scale.

- In agreement with these findings, pentazocine showed CNS pharmacological activity (ie, pupillary constriction), whereas CR845, like placebo, produced no evidence of pupillary constriction, consistent with its lack of mu-opioid agonist activity (**Figure 6**)

Figure 6. Effect of Treatment on Pupil Diameter in MITT Population



CONCLUSIONS

- Preclinical results and those of the human abuse potential study provide complementary data that are consistent with the known properties of CR845
- All together, these studies did not identify a significant potential of CR845 for drug-seeking behavior relative to the CNS active mixed kappa/mu comparator, pentazocine, a Drug Enforcement Administration Schedule IV drug
- These data provide evidence that the selective KORA CR845 is unlikely to be recreationally abused and may represent a new class of non- to low-abusable opioid analgesic

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DISCLOSURES

FM, CM, JS, and RS are employees of Cara Therapeutics, Inc. DH is an employee and major stockholder of RenaSci Ltd, which conducted the preclinical research. This study was funded by Cara Therapeutics, Inc.

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