**INTRODUCTION**

CR845 is a highly potent, peripherally acting kappa-opioid receptor agonist that has been shown to have analgesic activity in preclinical models of pain, without evidence of major central effects. Preclinical and clinical studies were undertaken to determine whether the analgesic activity of CR845 is due to its ability to act as a positive reinforcer.

**METHODS**

- **Subjects:** 44 recreational polydrug users (18 to 55 years old) who were experienced in the use of opioid and hallucinogenic drugs were enrolled in a study designed to assess the reinforcing effects of CR845.
- **Materials:** 40 male Sprague Dawley rats were trained to self-administer heroin on an intravenous (iv) schedule.
- **Design:** 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.
- **Procedure:** Preclinical and clinical studies were undertaken to determine whether the analgesic activity of CR845 is due to its ability to act as a positive reinforcer.

**RESULTS**

- **Clinical Studies:**
  - Subjects who received CR845 reported scores that were not significantly different from placebo on the Visual Analog Scale (VAS).
  - The primary analysis population for the clinical studies was the Modified-Intent-to-Treat (MITT) population.
  - Pupil diameter was measured periodically after each treatment to provide an objective measure of centrally mediated adverse effects.

- **Preclinical Studies:**
  - In contrast, CR845 produced no evidence of positive reinforcement at doses as high as 5 mcg/kg.
  - The VAS measure of Drug Liking (Emax over the entire 8-hour period) was significantly higher than placebo (5.1 vs. 0.45) and did not separate from placebo after 1 hour and had no evidence of dose-related effects (Figure 8).

**DISCLOSURES**

- The results of the human abuse potential study provide complementary data that are consistent with the known properties of CR845.

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