

Novel Peripheral Kappa Opioid Products: Pain Relief Without Opioid Side Effects

October, 2014

Corporate Presentation



CR845: Human Abuse Liability Trial Design

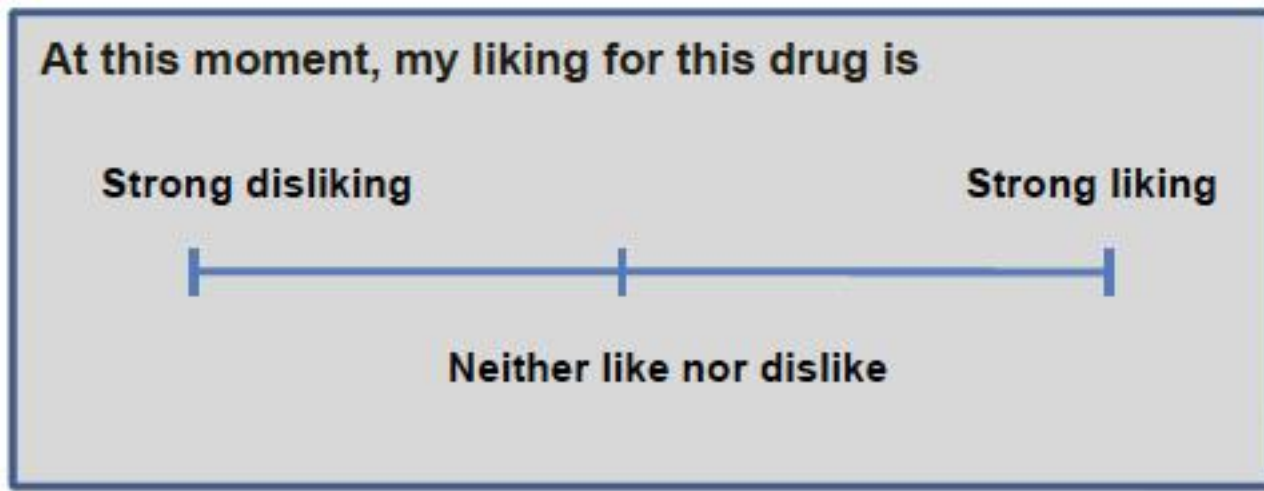
CLIN1006 Trial

- ▶ Evaluate relative abuse potential of IV CR845 vs. pentazocine
- ▶ Non-dependent recreational opioid & hallucinogen abusers
 - 40 Subjects – four-way crossover design
 - 2 doses IV CR845, IV pentazocine, placebo
- ▶ “Drug liking” VAS Emax is FDA-mandated primary endpoint
- ▶ “Feeling high” and other subjective measures are exploratory
- ▶ Results used by FDA to:
 - Indicate degree of abuse liability in labeling
 - Provide scheduling recommendation to DEA
- ▶ Scheduling is related to active Comparator
 - Pentazocine is schedule 4 (CIV)
 - HAL study assesses abusability *relative to Comparator*

Drug Liking VAS: Primary Endpoint

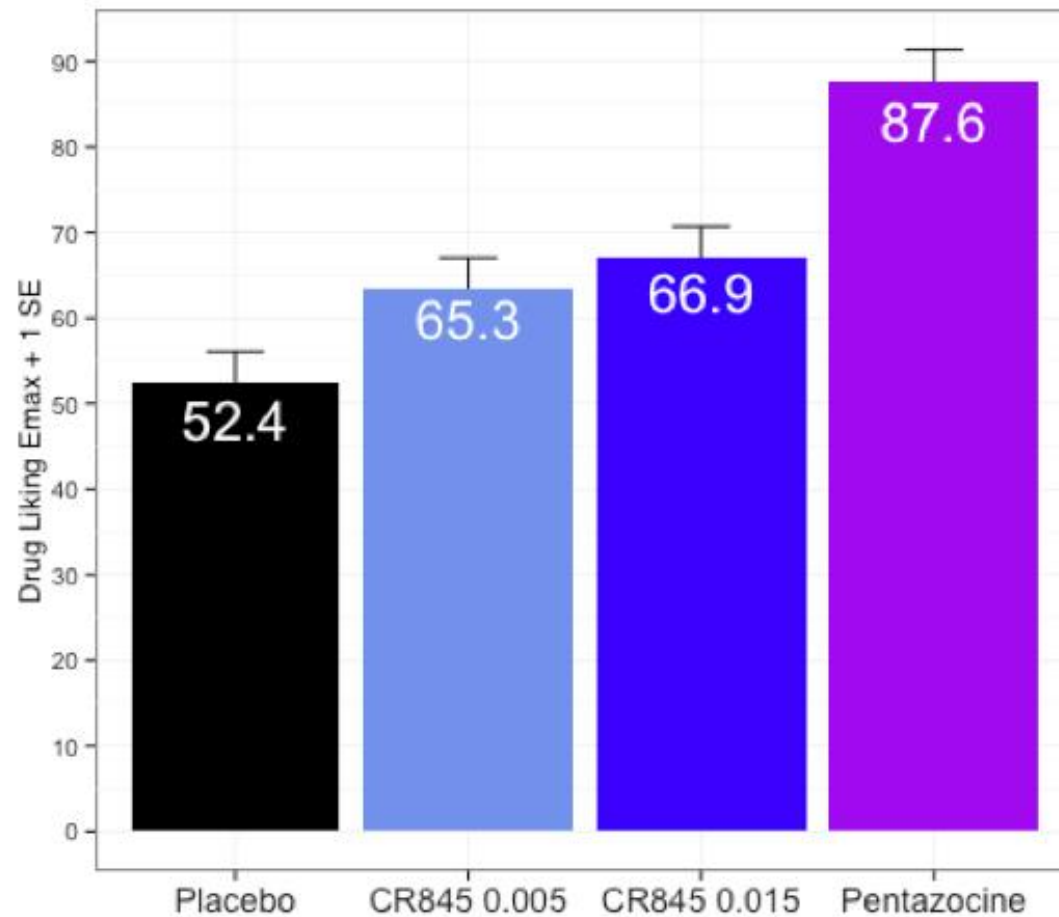
Bipolar scale:

- Sensitive to disliking (e.g., dysphoria) as well as liking (e.g., euphoria)
- Widely used and validated across multiple drug classes
- Selected by FDA as primary endpoint to determine relative abuse potential to aid in *product labelling* as well as scheduling



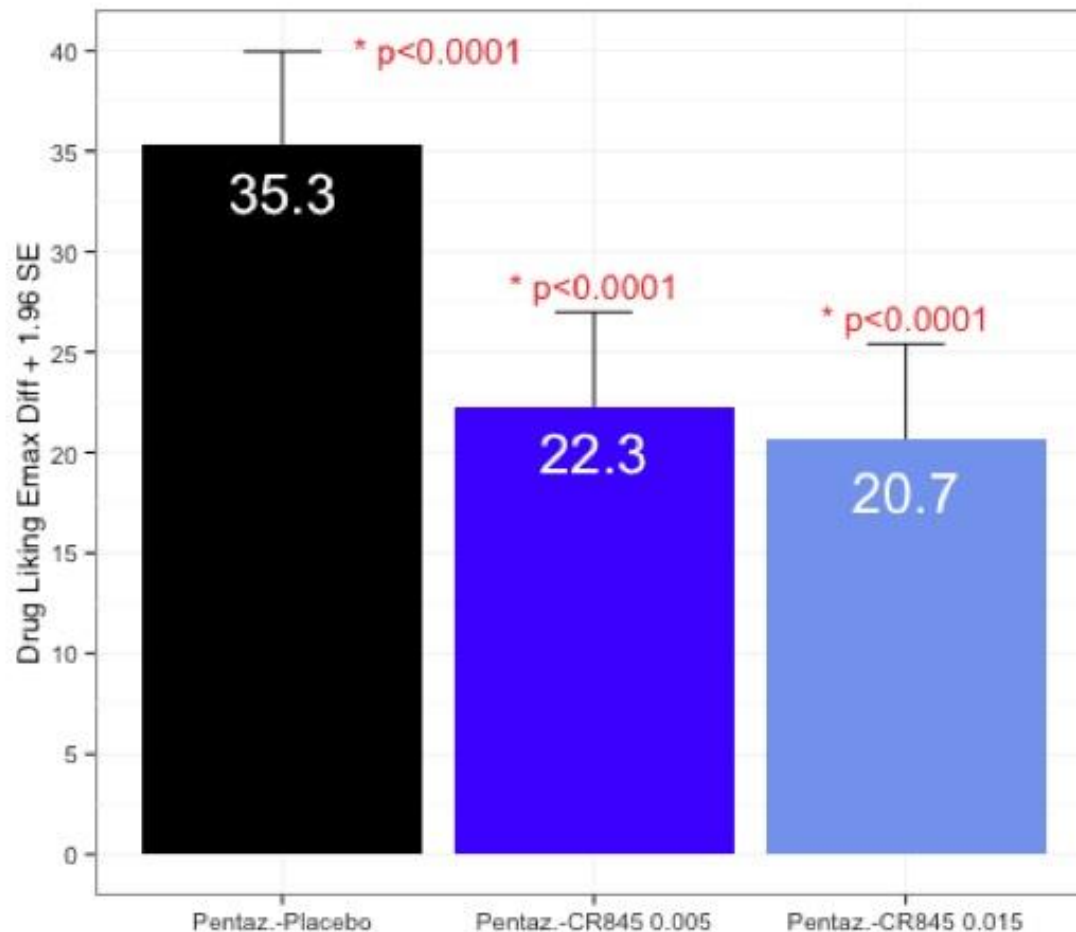
Primary Endpoint: Drug Liking VAS Emax

Group Means for Placebo and Active Control (Pentazocine) Indicate Overall Validity of Study to Assess Abuse Liability of CR845



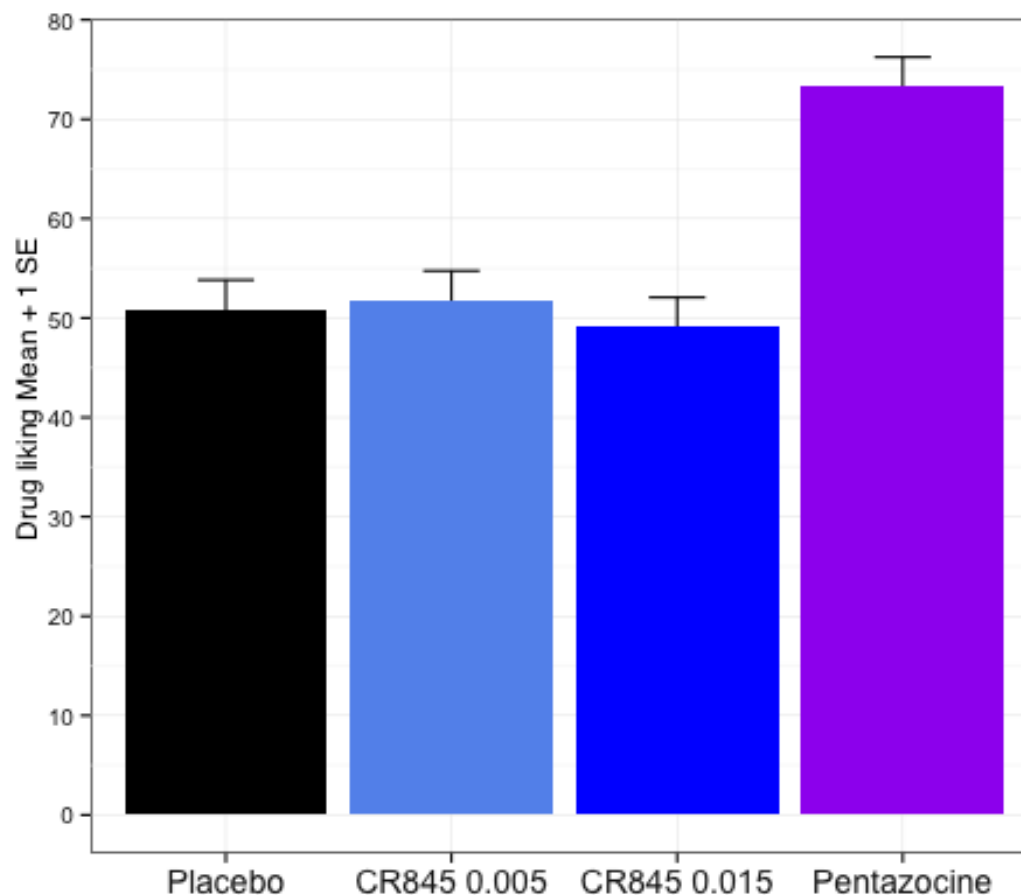
Primary Analysis: Difference Between Pentazocine and Two Doses of CR845

Pentazocine has significantly higher drug liking than either dose of CR845 or placebo



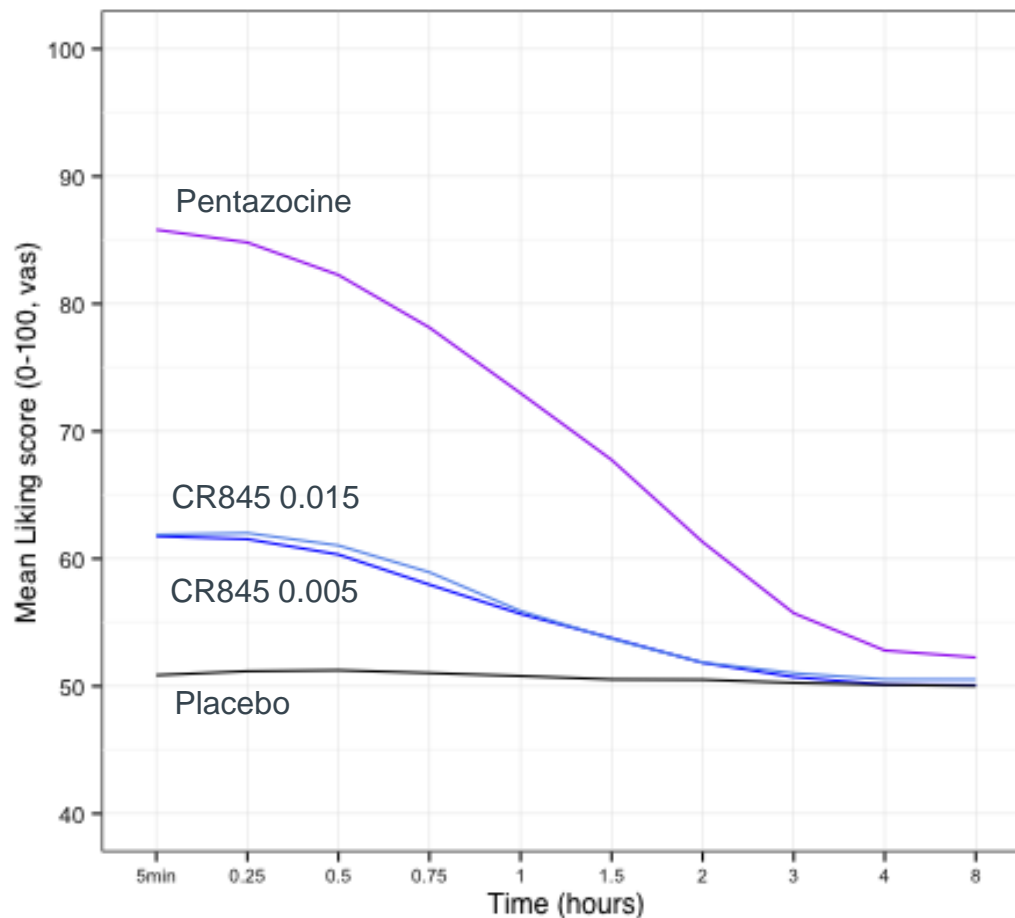
Exploratory Analysis: Drug Liking Over 8-Hour Test Session

Mixed-model repeated measures analysis of Drug Liking;
 $p < 0.0001$ for all comparisons to Pentazocine



Overall Liking Time Course

CR845 produces a much lower “drug liking” response over time compared to pentazocine, consistent with low abuse potential



Analysis of Exploratory Endpoints: Feeling High

One abuse-related exploratory endpoint of interest is “Feeling High”, which is measured using a unipolar VAS

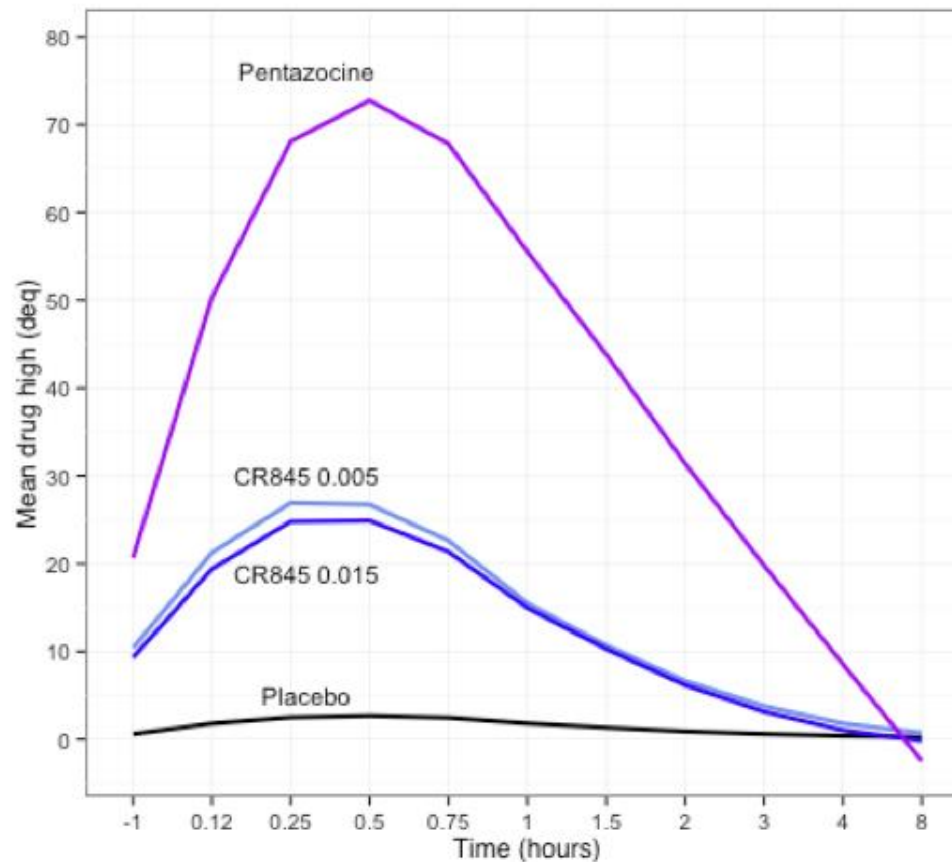
A unipolar Visual Analog Scale (VAS) for the statement "I am feeling high". The scale is represented by a horizontal line with vertical end caps. The left end is labeled "Not at all" and the right end is labeled "Extremely".

I am feeling high

Not at all **Extremely**

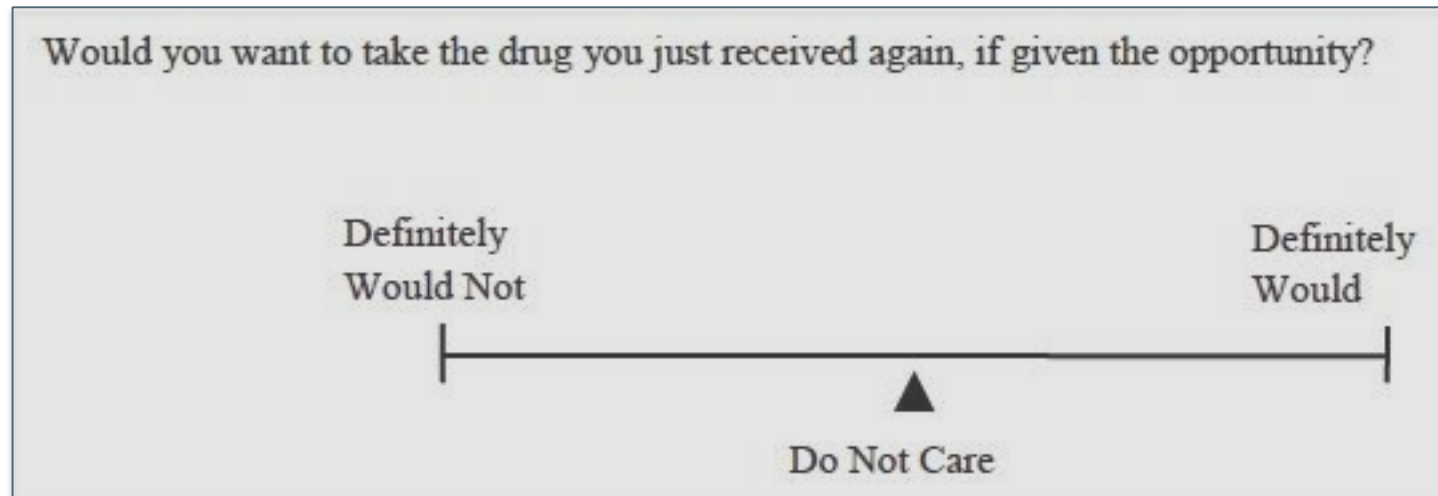
“Feeling High” Exploratory Endpoint

CR845 produces a much lower “feeling high” response compared to pentazocine ($p < 0.001$), consistent with low abuse potential



Analysis of Exploratory Endpoints: Take Drug Again

Take Drug Again is a bipolar measure that is recorded at the end of the 8-hour session and has been reported to be highly correlated with drug liking measures and predictive of future drug abuse.



Take Drug Again Exploratory Endpoint

Results are consistent with reduced risk of abuse of CR845.

($p < 0.0003$ for comparisons of placebo or 0.005 mg/kg CR845 to pentazocine; $p < 0.0001$ for the comparison with CR845.)

