Safety, Tolerability, and Effectiveness of Orally Administered CR845, a Peripherally Acting Kappa-Opioid Receptor Agonist, in Patients with Osteoarthritis of the Knee or Hip

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INTRODUCTION

- CR845 is a peripherally acting kappa-opioid receptor agonist (KORA) that is being developed for the treatment of acute and chronic pain and pruritus
  - ≥30,000-fold selectivity for kappa opioid receptors compared with mu- or delta-opioid receptors[1]
  - 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)
  - In clinical studies the adverse event profile is different than that seen with mu-opioids (eg, morphine)[2]
- CR845 administered intravenously has been investigated for its ability to reduce post-operative pain in 3 double-blind, randomized, placebo-controlled studies[2]
- Here we describe a single-blind pilot study designed to assess the safety, tolerability, pharmacokinetics, and effectiveness of orally administered CR845 in patients with osteoarthritis of the knee or hip

METHODS

Patients

- Male or female ≥25 years old with a body mass index (BMI) ≤40 kg/m^2
- Osteoarthritis of the knee or hip according to American College of Rheumatology criteria
- Patients must be willing to stop current pain medication beginning 5 days prior to Baseline and throughout the study
- Eligible patients must have an average pain intensity in the index joint ≥4 on the 0- to 10-point numerical rating scale (NRS) at Screening and during the 3 days prior to Baseline
- Key exclusion criteria include:
  - Joint replacement in the index joint
  - Had received an intra-articular injection of corticosteroids or hyaluronic acid in the index joint within 3 months of Screening
  - Serum sodium >145 mmol/L at Screening

Study Design

- Single-blind, multiple ascending-dose pilot study
- 4 cohorts of 20 patients were evaluated sequentially at escalating doses of CR845 (0.25 mg, 0.5 mg, 1.0 mg, and 5.0 mg) administered orally twice daily
- Acetaminophen (325 mg tablets) was provided to all patients for use as rescue medication
- Schedule of study activities
  - Screening visit within 14 days prior to Baseline
  - 2-week treatment period with study visits at Baseline (Day 1), Day 8, and Day 15
  - Follow-up visit 7 to 10 days after final dose of CR845
  - Average daily NRS pain intensity score recorded each evening in patient diary during treatment
  - Rescue medication use was also recorded in the patient diary
- Venous blood samples were taken before and after the morning dose on Days 1 and 2 from the first 6 patients in each dose group for the determination of CR845 pharmacokinetics
- Blood samples were taken at each study visit from all patients for assessing hematology and serum chemistry, including serum sodium concentration
- Adverse events (AEs) were monitored continuously throughout the study
- 81 patients at 5 study sites enrolled in the study (**Table 1**)

RESULTS

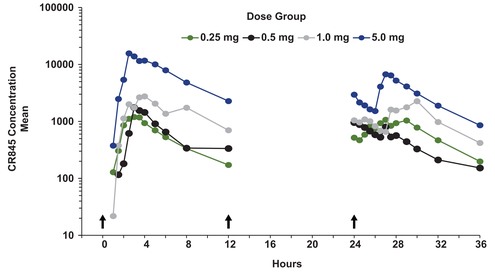
Table 1. Patient Demographics and Baseline Characteristics

	Dose Group			
	0.25 mg (n=20)	0.5 mg (n=21)	1.0 mg (n=20)	5.0 mg (n=20)
Sex (M:F)	10:10	14:7	8:12	11:9
Age, years Mean (range)	63.2 (46-77)	63.3 (32-80)	62.9 (38-81)	63.1 (40-79)
Race, n (%) Black White	5 (25) 15 (75)	4 (19) 17 (81)	1 (5) 19 (95)	5 (25) 15 (75)
Ethnicity, n (%) Hispanic or Latino	0	1 (4.8)	1 (5)	0
Baseline NRS score, mean±SD	6.5±1.2	6.8±1.4	6.6±1.6	6.1±1.1

M=male; F=female; NRS=numerical rating scale; SD=standard deviation.

- **Figure 1** shows the blood concentration-time curves after the morning dose on Study Days 1 and 2, and calculated pharmacokinetic variables are presented in **Table 2**
  - C_{max} and $AUC_{0-\infty}$ were dose-related (**Table 2**)

Figure 1. Plasma Concentration vs Time Following the Morning Dose on Study Days 1 and 2



n=6 in each dose group.
The arrow indicates when CR845 was administered.

Table 2. Pharmacokinetic Results

	Dose Group			
	0.25 mg	0.5 mg	1.0 mg	5.0 mg
C_{max} Day 1, pg/mL, mean±SD	1535±832 (n=6)	2282±2776 (n=6)	4860±3497 (n=6)	19,620±8280 (n=6)
C_{max} Day 2, pg/mL, mean±SD	1896±1015 (n=6)	1243±618 (n=6)	3827±1217 (n=6)	8896±7694 (n=6)
T_{max} Day 1, hr, median (min, max)	3.0 (2, 12) (n=6)	3.5 (2, 12) (n=6)	3.0 (2, 8) (n=6)	2.5 (2, 5) (n=6)
T_{max} Day 2, hr, median (min, max)	2.3 (0, 5) (n=5)	0.25 (0, 3) (n=6)	3.8 (0, 6) (n=6)	2.8 (0, 6) (n=6)
$AUC_{0-\infty}$ Day 1, pg•hr/mL, mean	7394 (n=5)	10,095 (n=4)	21,000 (n=4)	87,948 (n=6)
$AUC_{0-\infty}$ Day 2, pg•hr/mL, mean	8663 (n=6)	8118 (n=5)	13,912 (n=5)	39,501 (n=5)

SD=standard deviation.

- 36 of 81 patients (44%) reported ≥1 AE during the study, with the incidence being highest in the 1.0 and 5.0 mg dose groups (50% and 85%, respectively; **Table 3**)
- The majority of AEs were characterized as mild (67%) or moderate (31%)

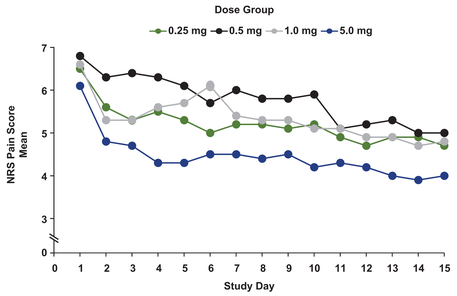
Table 3. Summary of Most Common AEs Occurring in 2 or More Patients in Any Dose Group

	Dose Group			
	0.25 mg (n=20)	0.5 mg (n=21)	1.0 mg (n=20)	5.0 mg (n=20)
Preferred term, n (%)				
Nausea	0	0	2 (10)	3 (15)
Thirst	0	0	0	2 (10)
Dizziness	2 (10)	0	1 (5)	7 (35)
Headache	0	1 (5)	1 (5)	4 (20)
Paresthesia	1 (5)	0	0	2 (10)
Anxiety	0	0	2 (10)	0
Tachycardia	2 (10)	0	1 (5)	0

n=number of patients reporting an adverse event (AE).

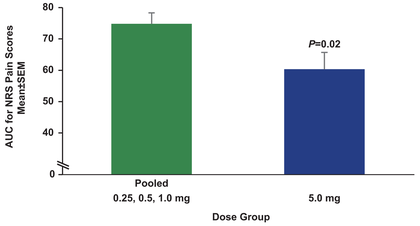
- The effect of CR845 on NRS pain scores is presented in **Figure 2**
- The area under the NRS pain score curves was significantly less in the 5.0 mg group than in the pooled results of the 0.25, 0.5, and 1.0 mg groups (**Figure 3**)
- Rescue medication use was significantly less in the 5 mg dose group compared with the pooled results of the 0.25, 0.5, and 1.0 mg groups (**Figure 4**)
- The percentage of patients who rated the change in their osteoarthritis as "Very Much Improved" or "Much Improved" increased with increasing dose (**Figure 5**)

Figure 2. Mean NRS Pain Score During Treatment With CR845



NRS=numerical rating scale.
Missing values were imputed as last observation carried forward.

Figure 3. Area Under the Curve (AUC) Analysis of NRS Pain Scores Over Time (Days 1-15)



NRS=numerical rating scale; SEM=standard error of the mean.
P value determined by Wilcoxon test.
Last observation carried forward was used to impute missing values.

Figure 4. The Effect of CR845 on Rescue Medication Use

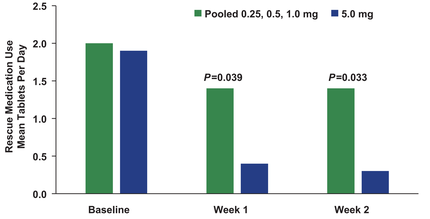
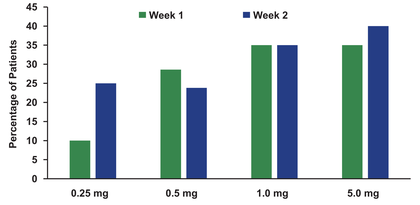


Figure 5. Patient Global Assessment of Treatment



The bars represent the percentage of patients who responded "Very Much Improved" or "Much Improved" when asked to rate the change in their osteoarthritis during the study using a 7-point rating scale.

DISCUSSION

- The magnitude of the pain response to CR845 was similar to that reported in clinical studies of other classes of analgesics used to treat chronic pain of osteoarthritis (**Table 3**)

Table 3. Analgesic Effectiveness of CR845 Compared With Other Classes of Analgesics in the Treatment of Chronic Pain of Osteoarthritis

Drug	Trial Duration (wk)	NRS Score Change From Baseline	NRS Score % Change From Baseline
Naproxen[3]	2	-2.5	-35%
Celecoxib[3]	2	-2.5	-35%
Duloxetine[4]	2	-1.6	-26%
Oxycodone CR[5]	12	-1.7	-26%
CR845 (1.0 mg)	2	-1.7	-26%
CR845 (5.0 mg)	2	-2.1	-34%

NRS=numerical rating scale.

CONCLUSIONS

- The results of this study suggest that oral CR845 may represent an effective analgesic for patients with chronic pain of osteoarthritis
- A larger double-blind, placebo-controlled Phase 2b clinical trial is planned

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DISCLOSURES

Frédérique Menzaghi, Joseph Stauffer, and Catherine Munera are employees of Cara Therapeutics, Inc.