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A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Titration-to-Effect Study of Orally Administered CR845 in Patients With Osteoarthritis of the Hip or Knee

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INTRODUCTION

- CR845 is a selective kappa opioid receptor agonist (KORA) with a peripheral mechanism of action
  - ≥30,000-fold selectivity over mu and delta opioid receptors[1]
  - No known activity at other non-opioid receptors, ion channels, or transporters
  - Currently being developed as a novel therapeutic agent for the treatment of acute and chronic pain
  - Unique peptidic structure significantly differs from that of small-molecule KORAs developed to date, which for the most part are active within the central nervous system (CNS)
  - Hydrophilic tetrapeptide structure limits CR845 membrane permeability by passive diffusion, therefore limiting its access to the CNS
  - The compound thus preferentially activates kappa opioid receptors located outside the CNS (eg, in peripheral sensory nerves and ganglia)
  - Nonclinical pharmacologic studies in rodents indicate CR845 can decrease pain, decrease itch, and reduce the production and release of pro-inflammatory mediators[1]
- As of July 2017, more than 1,600 healthy volunteers and patients across 20 clinical studies have received CR845; 976 have been exposed to the intravenous (IV) formulation and 626 have been exposed to an oral (PO) formulation (capsules or tablets)
- Overall, CR845 has been shown to be safe and well tolerated when administered in both single and multiple IV or PO dose forms
- Here we report preliminary results from a Phase 2b study designed to characterize the analgesic efficacy of orally administered CR845 in patients with osteoarthritis (OA) of the hip or knee (ClinicalTrials.gov NCT02944448)

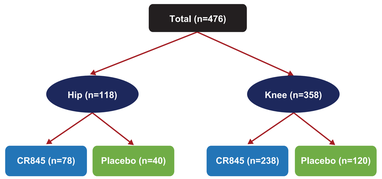
METHODS

- Double-blind, titration-to-effect study of 3 doses of CR845 (1, 2.5, and 5 mg) compared to placebo
- Key inclusion criteria
  - Male and female patients (age ≥25 years) with a body mass index (BMI) ≤40 kg/m^2
  - Patient has OA of the hip or knee according to the ACR criteria
  - Average pain intensity level ≥5 in the index joint at screening on a 0-10 numeric rating scale (NRS)
  - Either opioid-naïve (defined as taking <10 mg/day of morphine equivalent 14 days prior to screening) or opioid-experienced; if receiving opioid analgesic medication for OA, patients must be on a stable, ≤40 mg dose of morphine equivalents for 14 days prior to screening
  - Reports a daily pain intensity score in the index joint ≥5 (on a 0-10 NRS scale) during 4 or more of the last 7 days prior to randomization, with 2 consecutive days ≥5 occurring just prior to randomization
  - Willing to discontinue currently used pain medications beginning 5 days prior to the baseline visit and throughout the study
    - Acetaminophen use was allowed
- Key exclusion criteria
  - Joint replacement in the index joint
  - Has received an intra-articular injection of corticosteroids or hyaluronic acid in the index joint within 3 months prior to the screening visit
  - Has a serum sodium level >143 mmol/L at screening
- Study design
  - The study consisted of a screening period, a blinded 4-week titration-to-effect period, a blinded 4-week maintenance period, and a follow-up period
  - Following the 14-day screening period, eligible patients were randomized in a 2:1 ratio to active treatment vs placebo, respectively
  - Beginning 5 days prior to the baseline visit and throughout the study, patients discontinued all pain medications.
    - Acetaminophen 325 mg was provided as supplemental pain medication at a maximum allowable dose of up to 8 tablets per day (given as 1-2 tablets every 4-6 hours as needed)
  - CR845 (1, 2.5, or 5 mg enteric-coated tablets) or placebo (similar-appearing tablets) were provided for BID dosing for a total of 8 weeks
  - Patients were instructed to take the study drug at least 2 hours prior to or after a meal
    - Each patient was started on a 1-mg dose of CR845 or matching placebo
    - During the initial 4-week post-randomization titration-to-effect period, the dose of CR845 was increased to 2.5 or 5 mg to effect (dose was only increased if it was both tolerable and efficacious) in a double-blind fashion
    - Patients were then maintained for 4 weeks on the final individualized effective dose
  - If at any time during the titration-to-effect period, the patient's serum sodium level was >150 mmol/L, dosing was paused for patient assessment (ie, retesting of sodium approximately 1 hour after patient was given a glass of water, and clinical evaluation)
    - After evaluation of the patient by the clinical staff, the dosing of study medication was either: a) continued or b) terminated
- Outcomes
  - The primary outcome measure was the change from baseline at Week 8/Day 57 with respect to the weekly mean of the daily pain intensity score at the index joint (measured using a NRS where 0 = "no pain" and 10 = "worst possible pain")
  - Secondary outcome measures included:
    - Western Ontario and McMaster Osteoarthritis Index (WOMAC) total score and subscores for pain intensity, joint function, and stiffness
    - Patient Global Impression of Change scale (PGIC)
  - Safety and tolerability measures over the 8-week treatment period included baseline detailed medical and surgical history, monitoring of vital signs, and treatment-emergent adverse events (AEs)

RESULTS

Patients

Figure 1. Patient Disposition



- CR845 efficacy was assessed in 476 patients enrolled at 33 sites in the US (**Figure 1**)
  - 118 patients had hip OA
  - 358 had knee OA
- Similar completion rates between treatments in patients with hip OA
- Higher completion rates in placebo group in patients with knee OA
- Patient demographics are shown in **Table 1**
  - Patients were mostly White (77.1%)
  - The majority were female (62.8%)
  - Ages ranged from 25 to 84 (mean±SD, 60.5±10.3)

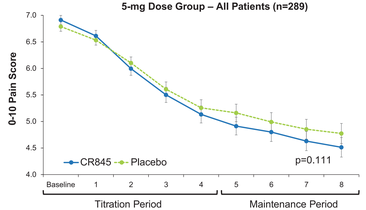
Table 1. Patient Demographics

Characteristic	Placebo (n=160) n (%)	CR845 (n=316) n (%)	All (n=476) n (%)
Age at study entry, n (%)			
25-44 years	11 (6.9)	21 (6.6)	32 (6.7)
45-64 years	92 (57.5)	187 (59.2)	279 (58.6)
65-74 years	40 (25.0)	84 (26.6)	124 (26.1)
≥75 years	17 (10.6)	24 (7.6)	41 (8.6)
Gender, n (%)			
Male	71 (44.4)	106 (33.5)	177 (37.2)
Female	89 (55.6)	210 (66.5)	299 (62.8)
Race, n (%)			
Asian	2 (1.3)	5 (1.6)	7 (1.5)
Black or African American	33 (20.6)	61 (19.3)	94 (19.7)
White	122 (76.3)	245 (77.5)	367 (77.1)
Other	3 (1.9)	5 (1.6)	8 (1.7)
Weight (kg)			
Mean (SD)	89.9 (20.75)	86.9 (17.96)	87.9 (18.98)
Median	88	86.9	87.5
Min	50	44.3	44.3
Max	144	145.1	145.1
Height (cm)			
Mean (SD)	170.1 (10.78)	168.3 (9.92)	168.9 (10.25)
Median	170	167	167
Min	149	145	145
Max	200	194	200
BMI (kg/m^2)			
Mean (SD)	30.8 (5.50)	30.6 (5.14)	30.7 (5.26)
Median	31	30	30
Min	19	18	18
Max	40	40	40
Opioid usage, n (%)			
Naive	146 (91.3)	285 (90.2)	431 (90.5)
Experienced	14 (8.8)	31 (9.8)	45 (9.5)

Efficacy

- Primary efficacy results comparing CR845 (all doses) vs placebo were not statistically significant
- Patients titrated to 5 mg (n=289) exhibited a 35% reduction in mean joint pain score, which didn't reach statistical significance compared to placebo (p=0.111) (**Figure 2**)

Figure 2. All Patients Receiving 5-mg CR845



Least squares (LS) means from mixed-effect model with repeated measures (MMRM) with treatment, week, and treatment by week interaction as terms in the model, baseline pain and strata as covariates, and subject as a random effect.

- However, patients with hip OA maintained on 5 mg (n=66) exhibited a statistically significant reduction in mean joint pain score over placebo (p=0.043) (**Figures 3 & 4**)

Figure 3. Change in Pain Score at 8 Weeks Compared to Placebo in Patients With Hip OA in 5-mg Dose Group

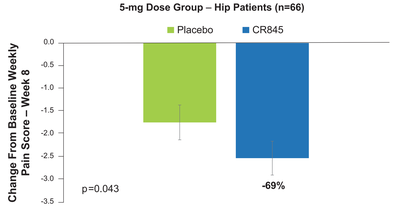
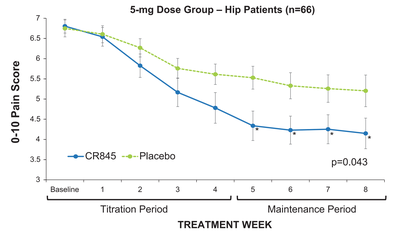


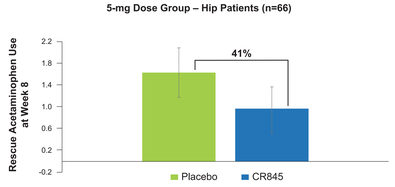
Figure 4. Change in Pain Score Over Time Compared to Placebo in Patients With Hip OA in 5-mg Dose Group



LS means from MMRM with treatment, week, and treatment by week interaction as terms in the model, baseline pain as a covariate, and subject as a random effect.

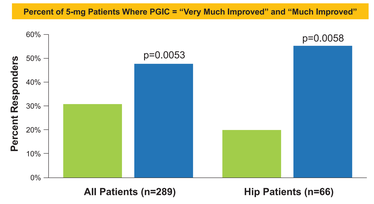
- The reduction in pain score in this subgroup was accompanied by a reduction in mean rescue medication of 41% at Week 8 vs placebo (**Figure 5**)

Figure 5. Reduction in Rescue Medication in Patients With Hip OA in 5-mg Dose Group



- There was a statistically significant increase in the proportion of patients maintained on the 5-mg dose whose OA pain was "Very much improved" or "Much improved" as indicated by PGIC score in all patients (p<0.01 vs placebo) and in patients with hip OA (p<0.01 vs placebo) (**Figure 6**)

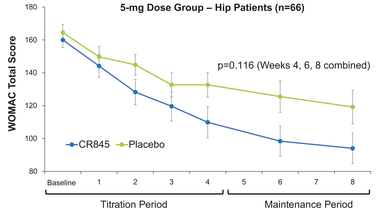
Figure 6. OA Pain "Very Much Improved" or "Much Improved" in Patients With Hip and Knee OA in 5-mg Dose Group



Cochran-Mantel-Haenszel test, 2-sided.

- WOMAC scores for the 5-mg dose hip patients improved to 62% of baseline (38% improvement) over the 8-week treatment period (p=0.116 vs placebo) (**Figure 7**)

Figure 7. WOMAC Scores by Week in Hip OA Patients in 5-mg Dose Group



LS Means from MMRM with treatment, week, and treatment by week interaction as terms in the model, baseline pain as a covariate, and subject as a random effect.

- Patients maintained on 1-mg and 2.5-mg doses did not exhibit significant reductions in mean joint pain scores compared to placebo nor did patients with knee OA at any dose, possibly due to a larger placebo effect observed in this subgroup

Safety

- All doses were generally well tolerated with no drug-related serious AEs
- For all doses of CR845, the most common AEs at a ≥5% incidence level were constipation (13%), dizziness (8%), and dry mouth (6%) (**Table 2**)
  - 86% of AEs occurred within the first 4 weeks during dose titration
  - The majority of AEs were transient and resolved spontaneously without treatment or intervention

Table 2. Adverse Events at ≥5% Incidence

Adverse Event	Placebo (n=160) n (%)	CR845 5 mg (n=181) n (%)	CR845 All (n=316) n (%)
Dizziness	3 (1.9%)	5 (2.8%)	26 (8.2%)
Dry mouth	3 (1.9%)	11 (6.1%)	18 (5.7%)
Constipation	3 (1.9%)	21 (11.6%)	42 (13.3%)

- Importantly, there were no clinically significant changes in serum sodium levels observed during the 8-week treatment period for any dose group

CONCLUSIONS

- Despite lack of overall significance between CR845 and placebo for OA patients, post-hoc analyses demonstrated that hip OA patients titrated to CR845 5 mg had a significant pain reduction compared to placebo patients
- The PGIC measure of pain in both hip and knee patients combined also showed significant benefit vs placebo of 5-mg CR845, while other pain measures showed improvement but not statistical significance

NEXT STEPS

- The observed beneficial effects combined with a positive safety profile warrant a further trial, exploring a different design to assess the potential efficacy advantages offered by a longer treatment duration and/or higher doses of CR845

References

1. Gardell L, Spencer R, Chalmers D, Menzaghi F. Preclinical profile of CR845: a novel, long-acting peripheral kappa opioid receptor agonist. Presented at: 12th World Congress on Pain; August 17-22, 2008, Glasgow, Scotland. Poster PW-231.

Acknowledgements & Disclosure

This study was funded by Cara Therapeutics. SB, CM, PB, and JS are employees of Cara Therapeutics. Medical writing and editorial support were provided by Gregory A. Kopja, PhD, CMPP, and Donald Fallon, ELS, of PharmaWrite, LLC (Princeton, NJ) and was funded by Cara Therapeutics.

Presented at the American College of Rheumatology Annual Meeting, November 4-8, 2017