PP24

Decrease of Itch Intensity by CR845, a Novel Kappa Opioid Receptor Agonist

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INTRODUCTION

- CR845 is a novel selective kappa opioid receptor (KOR) agonist being developed for the treatment of moderate-to-severe pruritus in hemodialysis (HD) patients (ie, uremic pruritus [UP])
  - Approximately 40% of HD patients in the US experience moderate-to-severe itching, which negatively affects their mental and physical health (eg, sleep loss, depression, higher antibiotic and erythropoietin use, and increased mortality)
  - The etiology of this condition is likely multifactorial, including immune system dysfunction and imbalance of mu/kappa endogenous opioids
  - Despite the availability of off-label treatments, UP remains highly prevalent. At present, nalfurafine (Remitch™), a mixed non-selective mu partial agonist/kappa opioid agonist, has been approved in Japan, whereas there are no therapies approved for the treatment of UP in the US
- CR845 is a small synthetic peptide designed to limit its entry into the central nervous system (CNS), thereby predominantly activating KORs expressed on peripheral neurons (PNS) and immune cells
  - CR845 differs from small organic heterocycle kappa agonists that are most commonly active within the CNS, such as nalfurafine (**Figure 1**)
  - CR845 is a potent, selective, and full agonist at human KORs (EC_{50} = 0.16 nM), with no significant detectable activity at other receptors (including mu or delta opioid receptors), ion channels, or transporters (**Table 1**)

Figure 1. CR845 Is Restricted From Entry Into the CNS

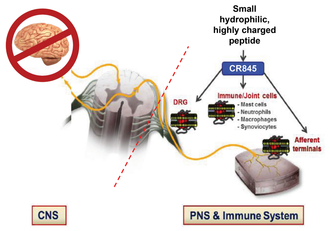


Table 1. CR845 Is Potent and Highly Selective for KORs (Receptor Binding)

Compound	hKOR (Ki, nM)	hMOR (Ki, nM)	hDOR (Ki, nM)
CR845	0.32	>10,000	>10,000
Nalfurafine	0.36	0.71	49.9
Morphine	14.7	4.4	150

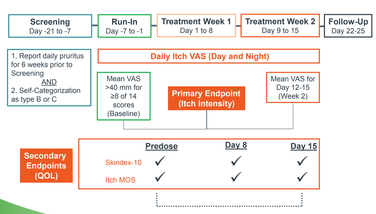
h, human; KOR, kappa opioid receptor; MOR, mu opioid receptor; DOR, delta opioid receptor.

METHODS

The goal of the present studies was to characterize the antipruritic properties of CR845 in animal models and in HD patients with moderate-to-severe UP

- Mouse Studies
  - *Dose-response*: Male Swiss Webster mice were administered either the kappa antagonist, 5′-GNTI (0.3 mg/kg), or the mast cell secretagogue, compound 48/80 (50 mcg), subcutaneously (behind the neck) 15 min after IV injection of vehicle or CR845. The number of hind leg scratching movements directed at the neck were then counted for 30 min
  - *Time-course*: The duration of action of CR845 was compared to nalfurafine upon IV injection of each drug 3, 6, 12, and 24 hours prior to the administration of compound 48/80 in male Swiss Webster mice
  - Studies were performed under blinded conditions
- Clinical Study
  - Phase 2 double-blind, randomized (1:1), placebo-controlled clinical study
    - Multicenter (21 US sites)
  - 65 prevalent HD patients with persistent (~5 years) moderate-to-severe UP
  - IV dosing following each dialysis session (3 times/week) for 2 weeks
    - Placebo (n = 32)
    - 1 mcg/kg CR845 (n = 33)
  - Antihistamines were discontinued 1 week prior to study
  - Primary endpoint: change from baseline to Day 12-15 in worst itch intensity measured by Visual Analog Scale (VAS; 0 = no itch, 100 mm = worst itch) (**Figure 2**)
  - Secondary endpoints: changes from baseline to Day 15 in pruritus-related quality of life (QOL), measured by Skindex-10, and sleep quality, measured by Itch Medical Outcome Survey (MOS)

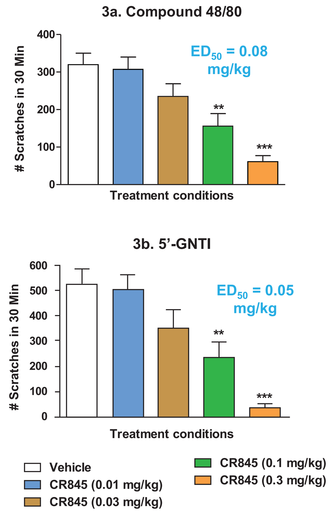
Figure 2. Clinical Study Design Schematic



RESULTS

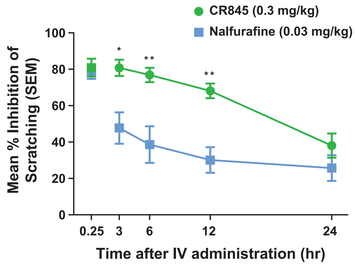
- Mouse Studies
  - CR845 pretreatment attenuated scratching in mice induced by the compound 48/80 (**Figure 3a**) or 5′-GNTI (**Figure 3b**) in a dose-dependent manner, with a duration of action of ≥12 hours after a single dose (**Figure 4**)

Figure 3. Efficacy of CR845 in Mouse Models of Itch



**P < 0.01, ***P < 0.001 vs. vehicle; one-way ANOVA followed by Newman-Keuls (mean ± SEM) (n = 10-11/group).

Figure 4. Duration of Action of CR845 Relative to Nalfurafine (Compound 48/80)



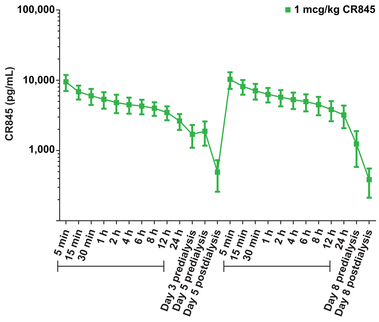
*P < 0.05, **P < 0.01 nalfurafine vs. CR845; one-way ANOVA followed by Newman-Keuls (n = 6-10/group).

- Clinical Study
  - Patient demographics were well-balanced across treatment groups (**Table 2**)
  - Bilateral pattern of itch reported mostly across back and trunk of the body in all patients

Table 2. Patient Population Demographics

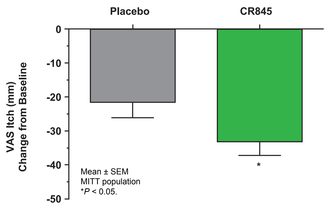
	Placebo (n = 32)	CR845 (n = 33)
Gender, n (%)		
Male	15 (47)	16 (48)
Female	17 (53)	17 (52)
Age		
Mean	60	60.1
(Range)	(35 – 88)	(26 – 84)
Race, n (%)		
White	18 (56.3)	18 (54.5)
Black or African American	10 (31.3)	12 (36.4)
Weight, kg		
Mean ± SD	87.0 ± 21.2	86.6 ± 20.7
(Range)	(52 – 145)	(37 – 124)
BMI, Mean ± SD	31.0 ± 7.9	32.1 ± 8.6

Figure 5. Pharmacokinetics of CR845 (1 mcg/kg) in HD Patients Over 1 Week



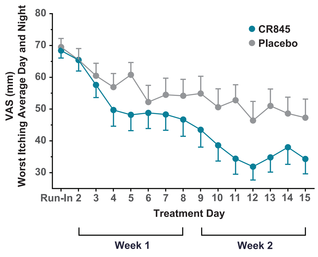
- Patients receiving IV CR845 reported a 50% decrease in itch intensity compared to their baseline (average reduction >30 mm from baseline score ranging from 42-95 mm), with a significant difference from the itch intensity reported by the placebo-treated HD patients (*P* = 0.016) (**Figure 6**)
- The placebo effect was as expected for this type of study

Figure 6. Primary Endpoint – CR845 Reduces Itch Intensity



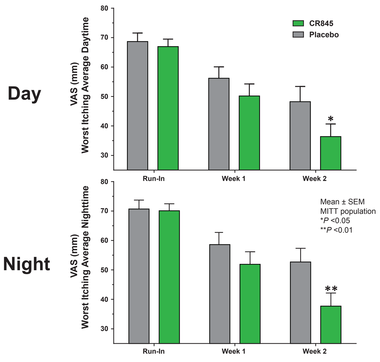
- The separation from placebo-treated patients in worst itch scores was evident by Day 3 of treatment and continued to decrease into Week 2 (**Figure 7**)

Figure 7. Itch Intensity Over 2 Weeks of Treatment



- CR845-treated patients exhibited statistically significant reductions in both daytime (*P* = 0.03) and nighttime (*P* = 0.007) worst itch scores compared with placebo treatment (**Figure 8**)

Figure 8. CR845 Reduces Worst Itch Intensity Reported for Both Day and Night Time by Week 2



- Quality of Life Secondary Endpoints
  - The secondary endpoints focused on quality of life measures associated with pruritus (sleep, mood, and socialization)
  - The total Skindex-10 score was substantially improved (*P* = 0.031), with a significant change in the mood/emotional distress subdomain (*P* = 0.046) and a trend for an improvement in social functioning and disease perception
  - A trend for improvement in the quality of sleep was also observed
- Safety Profile
  - CR845 was well tolerated, with an adverse-event profile comparable to that of placebo-treated patients (**Table 3**)
  - There was no serious treatment-related adverse event

Table 3. Safety Profile. Adverse Events in ≥2 Patients in Any Treatment Group

System Organ Class Preferred Term	Placebo (n = 32) n (%)	CR845 (n = 33) n (%)	Total (N = 65) n (%)
Gastrointestinal Disorders			
Diarrhea	2 (6.3)	1 (3.0)	3 (4.6)
Nausea	2 (6.3)	2 (6.1)	4 (6.1)
Nervous System Disorders			
Dizziness	0 (0.0)	2 (6.1)	2 (3.1)
Headache	2 (6.3)	2 (6.1)	4 (6.1)
Hypoesthesia	0 (0.0)	3 (9.1)	3 (4.6)
Skin and Subcutaneous Disorders			
Pruritus	1 (3.1)	2 (6.1)	3 (4.6)
Vascular Disorders			
Hypotension	2 (6.3)	2 (6.1)	4 (6.1)

CONCLUSION

- These results provide evidence that selective activation of peripheral KORs reduces itch intensity in HD patients with moderate-to-severe UP and may improve their quality of life

ACKNOWLEDGMENTS

The present study was fully supported by Cara Therapeutics

The mouse studies were performed by Dr. Alan Cowan's laboratory

Professional editorial, graphic art, and writing services were provided to the authors by Aric Fader, PhD, of PharmaWrite (Princeton, NJ) and were paid for by Cara Therapeutics

Presented at the 8th World Congress on Itch; September 27-29, 2015; Nara, Japan