TH-PO1041

See companion Poster TH-P01040

Antipruritic Effect of the Long-Acting Peripheral Kappa Opioid Receptor Agonist CR845: A Novel Approach for the Treatment of Uremic Pruritus in Hemodialysis Patients

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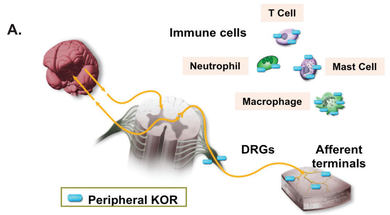
INTRODUCTION

- 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 uremic pruritus, 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 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. (A) Distribution of Peripheral Kappa Opioid Receptors; (B) CR845 Is Not Detectable in the CNS



- When administered intravenously (IV) to rats, CR845 is detectable in the plasma but not in the brain

Table 1. CR845 Is Potent and Highly Selective at 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

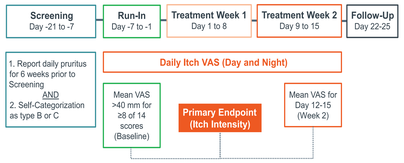
h, human; KOR, kappa-opioid receptor; MOR, mu-opioid receptor; DOR, delta-opioid receptor.
*Data are from Vanderah TW et al. *Eur J Pharmacol.* 2008; 583: 62-72.

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 Design (**Figure 2**)
  - Phase 2 double-blind, randomized (1:1), placebo-controlled clinical study
    - Multicenter (21 US sites)
  - 65 prevalent HD patients with chronic moderate-to-severe UP (~5 years)
  - 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**)

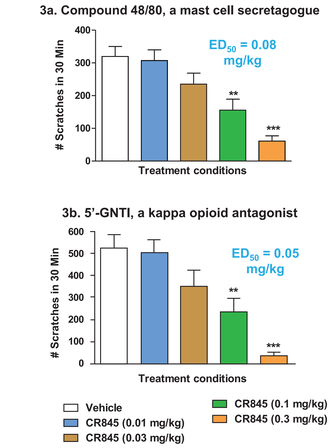
Figure 2. Clinical Study Design Schematic



RESULTS

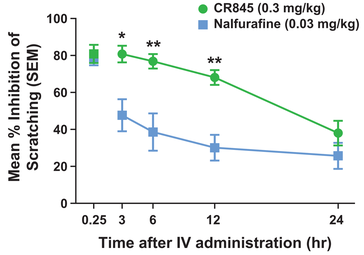
- Non-Clinical Studies
  - CR845 pretreatment attenuated scratching in mice induced by the compound 48/80 (**Figure 3a**) or 5′-GNTI (**Figure 3b**) in a dose-dependent manner, with a duration of action of ≥12 hours after a single dose (**Figure 4**)

Figure 3. Efficacy of IV 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 IV CR845 Relative to Nalfurafine in a Mouse Model of Itch (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

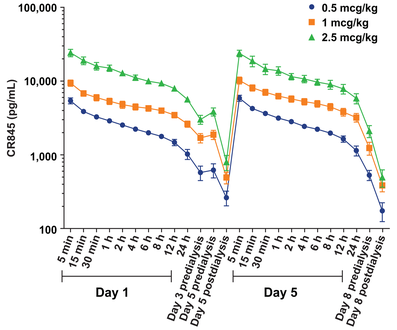
Table 2. Patient Population Demographics

	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

Pharmacokinetics in HD Patients

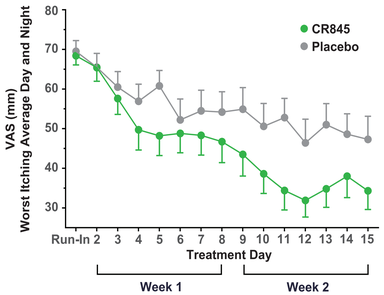
- The pharmacokinetics of repeated IV doses of CR845 in HD patients was evaluated in a separate substudy, which showed:
  - Dose-proportional increase in C_{max} and AUC (**Figure 5**)
  - Minimal to no accumulation with repeated dosing (cleared by dialysis)

Figure 5. Pharmacokinetics of CR845 in HD Patients Over 1 Week (n=5-7 per group)



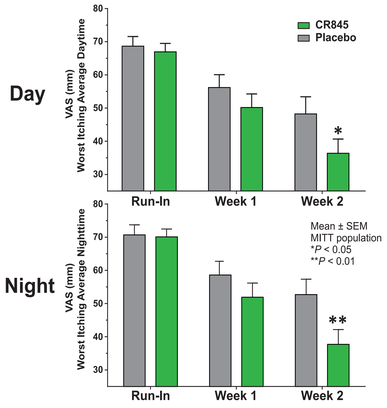
- Patients receiving IV CR845 reported a 50% decrease in itch intensity compared to their baseline (average reduction >30 mm from baseline score ranging from 42-95 mm), with a significant difference from the itch intensity reported by the placebo-treated HD patients (P = 0.016) (**Figure 6**)
- The separation from placebo-treated patients in worst itch scores was evident by Day 3 of treatment and continued to decrease into Week 2 (**Figure 6**)

Figure 6. 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 7**)

Figure 7. CR845 Reduces Worst Itch Intensity Reported for Both Daytime and Nighttime by Week 2



- Safety Profile
  - CR845 was well tolerated, with an adverse event profile comparable to that of placebo-treated patients (**Table 3**)
  - There were no serious treatment-related adverse events

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

- CR845 potently inhibits scratching behavior in several rodent models of itch and does not readily penetrate into the CNS, suggesting that peripheral KOR activation may help reduce itch severity
- Results from a Phase 2 clinical study with IV CR845 provide further evidence that selective activation of peripheral KORs may relieve itch in HD patients with moderate-to-severe UP

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