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Randomized, Placebo-Controlled Study on the Efficacy of CR845 in Reducing Chronic Kidney Disease-associated Pruritus in Hemodialysis Patients

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BACKGROUND

Chronic Kidney Disease (CKD)-Associated Pruritus

- Intractable itch condition observed across CKD patient population
  - ~60-70% of CKD patients on hemodialysis (US patients)
  - ~30% of non-dialysis CKD patients (US patients)
- No approved therapies in the US
  - No standard of care for this condition
- Profound negative effect on quality of life (QoL) and higher rate of mortality

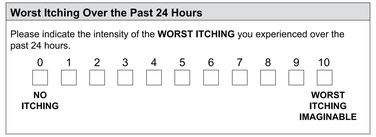
CR845

- A novel selective kappa opioid receptor (KOR) agonist[1]
  - Hydrophilic synthetic D-amino acid peptide
  - Designed to limit entry into the central nervous system
  - Potent, selective, and full agonist at human KORs (EC50 = 0.16 nM) with no detectable activity at mu or delta opioid receptors
  - Activates KORs expressed on peripheral neurons and immune cells
  - No known potential for drug-drug interactions
  - Primarily excreted renally in healthy subjects (~90%) with no known metabolites
  - In end-stage renal disease patients, CR845 is removed by dialysis and therefore is administered following dialysis
- Inhibits scratching behavior elicited by pruritogen in mouse model[1]
- Under development for treatment of moderate-to-severe pruritus in hemodialysis patients (ie, uremic pruritus)[2]
- Here we present the results of a Phase 2 clinical trial conducted to evaluate the anti-pruritic efficacy of CR845 over an 8-week period of treatment in hemodialysis patients with moderate-to-severe pruritus

METHODS

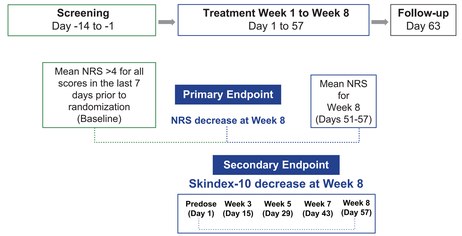
- Randomized, double-blind, placebo-controlled study (ClinicalTrials.gov Study NCT02858726)
- Multi-center
  - 33 US sites
- Eligibility
  - 18 years and older, male or female
  - Hemodialysis 3 times per week for at least 3 months prior to study
  - Communicate clearly, able to understand and answer questionnaires, understand study procedures
  - Self-categorize as moderate-to-severe itch
    - Mean Numerical Rating Scale (NRS) >4 over 1 week prior to randomization
      - 0 (no itching)–10 (worst itching imaginable)
- Doses of IV CR845 evaluated: 0.5, 1.0, and 1.5 mcg/kg
- 8-week treatment period
- Dosing after each dialysis (3 times per week)
- Patients were permitted use of any anti-itch medications they were taking but were required to continue the same regimen throughout the treatment period
- Primary endpoint: Reduction in mean weekly average of NRS scores calculated from worst daily itching score from baseline to Week 8 (**Figure 1**)

Figure 1. Worst Itching Intensity Numeric Rating Scale (NRS)



- Secondary endpoint: Reduction in Skindex-10 Score (QoL measure)
  - 10 questions covering 3 QoL domains:
    - Disease (3 questions)
    - Mood/emotional distress (3 questions)
    - Social functioning (4 questions)
- Patient Global Impression of Change, 7-point scale (ranging from 1="very much improved" to 7="very much worse)
- Study design in provided in **Figure 2**

Figure 2. Study design



RESULTS

174 patients randomized and treated with study drug (safety population).

Patient disposition and demographics and baseline features are provided in **Figure 3** and **Table 1**.

- Well balanced across treatment groups

Figure 3. Patient disposition

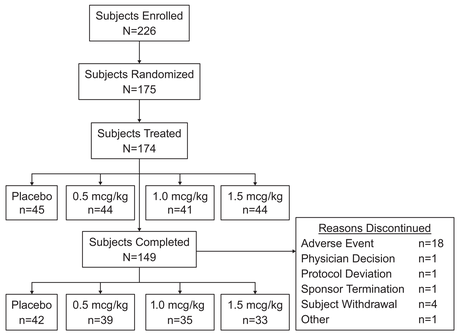
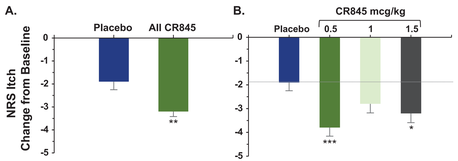


Table 1. Baseline characteristics

Characteristic	Placebo (n=45)	CR845 0.5 mcg/kg (n=44)	CR8451.0 mcg/kg (n=41)	CR8451.5 mcg/kg (n=44)	All (N=174)
Age (years)					
Mean (range)	59.0 (27, 84)	57.9 (29, 80)	58.2 (26, 84)	54.1 (29, 74)	57.3 (26, 84)
Gender, n (%)					
Female	17 (37.8)	18 (40.9)	18 (43.9)	16 (36.4)	69 (39.7)
Male	28 (62.2)	26 (59.1)	23 (56.1)	28 (63.6)	105 (60.3)
Race, n (%)					
Black or African American	25 (55.6)	24 (54.5)	22 (53.7)	31 (70.5)	102 (58.6)
White	16 (35.6)	17 (38.6)	19 (46.3)	10 (22.7)	62 (35.6)
Other	4 (8.9)	3 (6.8)	0	3 (6.8)	10 (5.7)
Pruritus duration (years)					
Mean (range)	4.4 (0.1, 18.6)	4.7 (0.0, 15.8)	4.6 (0.2, 16.6)	3.9 (0.3, 18.5)	4.4 (0.0, 18.6)
Years on hemodialysis					
Mean (range)	5.9 (0.3, 19.6)	5.4 (0.2, 24.9)	6.3 (0.8, 17.3)	5.5 (0.4, 18.5)	5.8 (0.2, 24.9)
Worst itch NRS score					
Mean±SD	6.8±1.5	7.1±1.4	6.7±1.5	6.7±1.4	6.8

Average reduction in itch NRS scores from baseline at Week 8 (LS Mean±SE) ranged from -2.8 (±0.38) in the 1.0-mcg/kg group (95% CI: -3.5 to -2.0) to -3.8 (±0.38) in the 0.5-mcg/kg group (95% CI: -4.5 to -3.1), with no significant differences between doses (**Figure 4**).

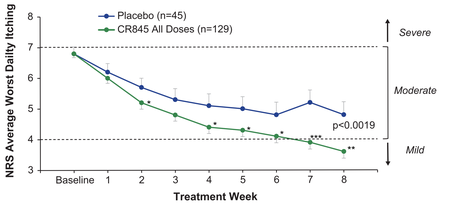
Figure 4. Change in weekly average worst itch NRS score from baseline to Week 8 (LS means±SEM)



LS means from MMRM with treatment, week, and treatment by week interaction as terms in the model, baseline itch and prior anti-itch medication use as covariates, and subject as a random effect.

Mean itch NRS scores continued to decrease from Week 1 through Week 8 (**Figure 5**).

Figure 5. Antipruritic efficacy of CR845 (all doses combined) over time during 8-week treatment period (values are mean±SEM)[†]

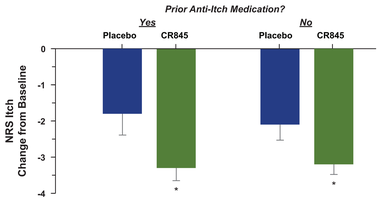


[†]Severity bands based on Reich et al.[3]

Average reduction in itch NRS scores from baseline to Week 8 in patients receiving CR845 was significantly greater than placebo regardless of whether the patient was taking concurrent anti-itch medication (**Figure 6**).

- Patients were stratified across treatments based on current use of anti-itch medication
- Approximately 40% of patients were taking anti-itch medication at baseline

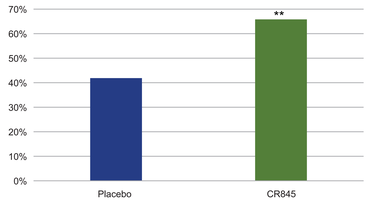
Figure 6. CR845 efficacy partitioned according to presence or absence of prior anti-itch medication



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

Significantly higher proportion of CR845 patients reported that their itch was "very much improved" or "much improved" at the end of the study compared to placebo (66% CR845 vs 42% placebo; p=0.007) as measured by the Patient Global Impression of Change (**Figure 7**)

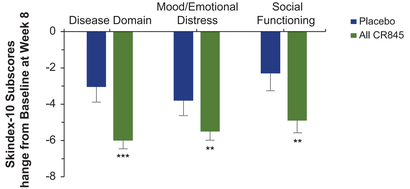
Figure 7. Improvement in proportion of CR845 patients reporting itch to be "very much improved" or "much improved"



p-value is based on Fisher's Exact test.

Significant improvement in QoL, including quality of sleep.

Figure 8. CR845 improvement in QoL (Skindex-10) individual domains and across all doses (values are mean±SEM; p-values denote significant differences from placebo)



p-values from MMRM with treatment, week, and treatment by week interaction as terms in the model, baseline itch and prior anti-itch medication use as covariates, and subject as a random effect.

- Statistically significant changes were observed for the total Skindex-10 score across all doses (data not shown)
- Change in Skindex-10 at Week 8 also correlated with significant improvement in other QoL measures (eg, 5-D itch and MOS Sleep Disturbance)

Safety

- CR845 tolerated at all doses (**Table 3**)
- No clinically important or significant safety findings were observed with respect to laboratory, vital sign, or ECG results
- No serious adverse events (SAEs) were considered related to study drug, with the exception of 1 case of moderate mental status change
- 4 deaths occurred during the study, none of which were determined to be related to the study drug

Table 3. Treatment-emergent adverse events >10% in any treatment group

Preferred Term	Placebo (n=45) n (%)	CR845 0.5 mcg/kg (n=44) n (%)	CR845 1.0 mcg/kg (n=41) n (%)	CR845 1.5 mcg/kg (n=44) n (%)
Dizziness	2 (4.4)	6 (13.6)	4 (9.8)	2 (4.5)
Somnolence	1 (2.2)	2 (4.5)	2 (4.9)	5 (11.4)
Headache	1 (2.2)	0 (0.0)	5 (12.2)	0 (0.0)
Diarrhoea	0 (0.0)	7 (15.9)	4 (9.8)	5 (11.4)
Mental status changes	0 (0.0)	0 (0.0)	1 (2.4)	5 (11.4)
Nausea	1 (2.2)	5 (11.4)	2 (4.9)	4 (9.1)

CONCLUSIONS

- CR845 effectively reduced itch intensity in hemodialysis patients with moderate-to-severe pruritus
- Based on the results of this study, a Phase 3 pivotal trial is being initiated
- For further information on this trial, please contact Adam Russell at arussell@caratherapeutics.com

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