Clinically Meaningful Itch Reduction By CR845: An 8-Week Randomized, Placebo-Controlled Study 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

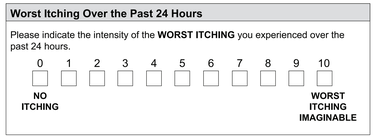
- A novel selective kappa-opioid receptor (KOR) agonist[1]
  - Hydrophilic synthetic D-amino acid peptide
  - Designed to limit entry into the central nervous system
  - Potent, selective, and full agonist at human KORs (EC_{50} = 0.16 nM) with no detectable activity at mu or delta opioid receptors
  - 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

Patients and Study Design

- 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
  - Report a mean Worst Itching Intensity Numerical Rating Scale (NRS) score >4 during the last 7 days prior to randomization
    - 0 (no itching)–10 (worst itching imaginable; **Figure 1**)
- Doses of IV CR845 evaluated: 0.5, 1.0, and 1.5 mcg/kg
- Study assessments included a 14-day screening period, an 8-week treatment period, and a 1-week follow-up visit
- Dosing after each dialysis (3 times per week)
- Patients were permitted to continue the use of prior anti-itch medications during the study but were required to follow the same regimen throughout the treatment period

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



Analysis

- Primary endpoint: Change in the weekly mean of the daily 24-hour Worst Itching Intensity NRS scores from baseline to Week 8
- Clinically meaningful change in the Worst Itching Intensity NRS score was evaluated using the Patient Global Impression of Change (PGIC) scale
  - 7-point scale (ranging from 1="very much improved" to 7="very much worse")

RESULTS

- 174 randomized patients were treated with study drug (safety population) (**Figure 2**)
- Patient demographics and baseline characteristics were balanced across treatment groups (**Table 1**)
- The proportion of patients who completed the treatment period ranged from 93% (placebo) to 75% (CR845 1.5 mcg/kg)

Figure 2. Patient disposition

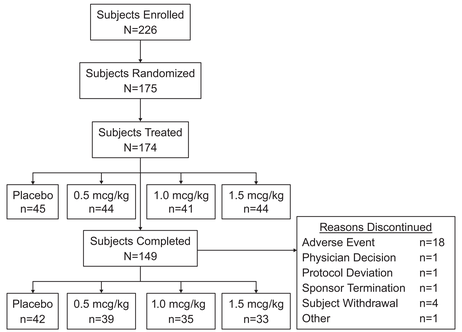
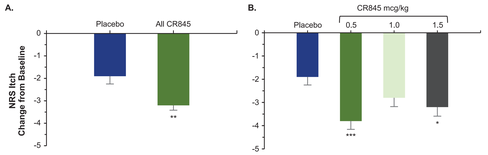


Table 1. Patient demographics and baseline characteristics

Characteristic	Placebo (n=45)	CR845 0.5 mcg/kg (n=44)	CR845 1.0 mcg/kg (n=41)	CR845 1.5 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

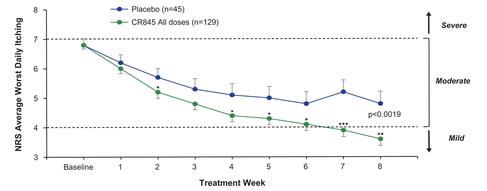
- The change in Worst Itching Intensity NRS scores from baseline to Week 8 (LS [least squares] mean±SEM) ranged from -2.8 (±0.38) in the 1.0-mcg/kg group (95% CI: -3.5 to -2.0) to -3.8 (±0.36) in the 0.5-mcg/kg group (95% CI: -4.5 to -3.1), with no significant differences between doses (**Figure 3**)
- Differences in the weekly mean of the Worst Itching Intensity NRS scores between placebo and CR845 increased with time and were statistically significant from Week 4 to Week 8 (**Figure 4**)

Figure 3. Change in weekly mean Worst Itching Intensity NRS score from baseline to Week 8 (LS means±SEM)



*p<0.05, **p<0.01, ***p<0.001 vs placebo. LS means from mixed model repeated measures analysis 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.

Figure 4. 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]
*p<0.05, **p<0.01, ***p<0.001 vs placebo, mixed model repeated measures analysis 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.

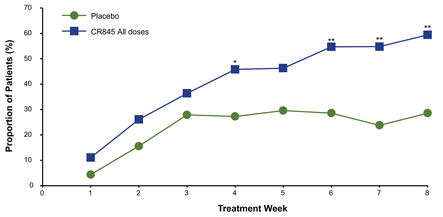
- The proportion of patients with an improvement in weekly mean Worst Itching Intensity NRS scores ≥3 points was higher in all CR845 treatment groups compared to placebo, ranging from 47% to 64%, with statistically significant differences at the 0.5 and 1.5 mcg/kg doses (**Table 2**)
- The proportion of patients randomized to CR845 who reported an improvement from baseline ≥3 points in weekly mean Worst Itching Intensity NRS scores increased steadily from 11% at Week 1 to 59% at Week 8 (**Figure 5**)

Table 2. Proportion of patients experiencing reduction in Worst Itching Intensity NRS scores following an 8-week treatment period with CR845

NRS Improvement	Placebo	CR845 All doses	CR845 0.5 mcg/kg	CR845 1.0 mcg/kg	CR845 1.5 mcg/kg
≥2 Points	41%	70%**	82%***	53%	73%**
≥3 Points	29%	59%**	64%**	47%	67%**
≥4 Points	24%	44%*	51%*	34%	43%

*p<0.05, **p<0.01, ***p<0.001 vs placebo, logistic regression.

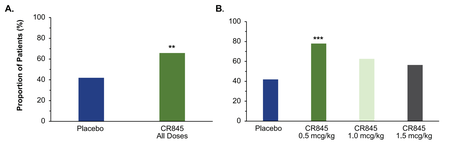
Figure 5. Time course for reduction from baseline in weekly mean Worst Itching Intensity NRS scores ≥3 points



*p<0.05, **p<0.01 vs placebo, logistic regression with terms for treatment group, baseline itch and prior anti-itch medication use.

- 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 PGIC (**Figure 6**)

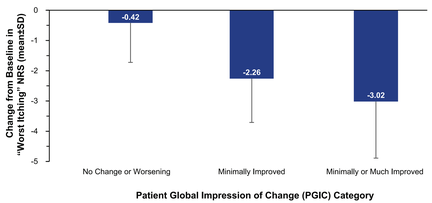
Figure 6. Improvement in proportion of CR845 patients reporting itch to be "very much improved" or "much improved"



**p<0.01, ***p<0.001 vs placebo, Fisher's exact test.

- The mean reduction from baseline in Worst Itching Intensity NRS score for patients who reported a minimal or a minimal/moderate improvement of their condition on the PGIC at Week 8 ranged from 2.26 to 3.02 (**Figure 7**)

Figure 7. Clinically meaningful change thresholds for Worst Itching Intensity NRS score at Week 8



Safety

- CR845 was 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
- The proportion of patients with clinically meaningful changes in Worst Itching Intensity NRS scores at Week 8 was significantly higher in CR845-treated patients across all doses
- An improvement from baseline ≥3 points in daily Worst Itching Intensity NRS score can be used to identify responders to treatment
- 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

ACKNOWLEDGEMENTS

We thank all of the investigators and patients who participated in this study. We are also grateful to Dr. Sarbani Bhaduri and Dr. Vandana Mathur for their medical monitoring and input on trial design. Medical writing and editorial support were provided by PharmaWrite.

REFERENCES

1. Gardell LR, Spencer RH, Chalmers DT, Menzaghi F. Preclinical profile of CR845: a novel, long-acting peripheral kappa opioid receptor agonist. 12th World Congress on Pain; 2008 August 17-22; Glasgow, Scotland.
2. Spencer RH, Lewis ME, Stauffer JW, Mathur VS, Menzaghi F. Antipruritic effect of the long-acting peripheral kappa opioid receptor agonist CR845: A novel approach for the treatment of uremic pruritus in hemodialysis patients. Kidney Week 2016; 2016 November 15-20; Chicago, IL.
3. Reich A, Heisig M, Phan NQ, et al. Visual analogue scale: evaluation of the instrument for the assessment of pruritus. *Acta dermato-venereologica* 2012;92:497-501.

Presented at the 2018 Spring Clinical Meetings of the National Kidney Foundation, April 10-14, Austin, TX