**TH-P01040**

See companion Poster TH-P01041

# Improvement of Quality of Life in Hemodialysis Patients with Uremic Pruritus as Measured by the Skindex-10 Questionnaire: Effect of a Novel Kappa Opioid Receptor Agonist, CR845

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## BACKGROUND

- Approximately 40% of hemodialysis (HD) patients in the United States (US) experience moderate-to-severe itching,[1] but the condition of uremic pruritus remains largely under-diagnosed[2]
- Uremic pruritus negatively affects sleep and mood and is associated with higher intravenous antibiotic and erythropoietin use, and increased mortality[1,2]
- Although the etiology of this condition is still unknown, it is likely multifactorial, including immune system dysfunction and imbalance of mu/kappa endogenous opioids
- There are no approved treatments for uremic pruritus in the US
- We conducted a multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of CR845 in HD patients with uremic pruritus. We report prespecified analyses evaluating the correlations between itch reduction and measures of quality of life (QOL) from this trial

## WHAT IS CR845?

- Novel kappa opioid receptor agonist being developed for the treatment of moderate-to-severe uremic pruritus
- Small synthetic D-amino acid peptide
- Potent and full kappa agonist at human kappa opioid receptor (hKOR), with an $EC_{50}$ of 0.16 nM
- No detectable off-target activity at other receptors, ion channels, or transporters, including human mu opioid receptor (hMOR) and human delta opioid receptor (hDOR) ($EC_{50}$ >10 μM)
- Restricted from entry into the central nervous system. Predominantly activating KORs on peripheral neurons and immune cells (eg, T-cells, mast cells, macrophages)
- Multiple mechanisms of action including anti-itch and anti-inflammatory properties
- Lack of abuse potential
- Not metabolized. 90% of excretion is renal.
- Injectable (IV) formulation of CR845 can be administered immediately after dialysis, which is convenient for patients and ensures treatment compliance

## METHODS

- Study design is shown in **Table 1**

**Table 1. Study Design**

| | |
|---|---|
| **Patient population** | • Adult male and female HD patients suffering from chronic moderate-to-severe pruritus for an average of 5 years |
| **Design** | • Multicenter (21 US sites), randomized (1:1), double-blind, placebo-controlled, parallel-group Phase 2 study with repeated IV doses of CR845 or placebo administered for 2 weeks after each dialysis<br>• Antihistamines were discontinued 1 week prior to the study |
| **Dosing (at end of each dialysis session)** | • CR845 1 mcg/kg IV<br>• Placebo |
| **Primary efficacy endpoint** | • Change from baseline to Days 12-15 in worst itch intensity measured by Visual Analog Scale (VAS, 0=no itching; 100 mm=worst itching) |
| **Secondary efficacy endpoints** | • Change from baseline to Day 15 in pruritus-related QOL as measured by Skindex-10 |

**Figure 1. Visual Analog Scale of Worst Itching Intensity**

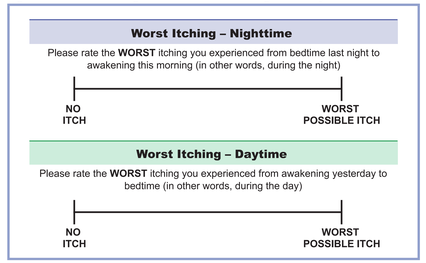



**Figure 2. Skindex-10 (Itch-Related QOL)**


Patients responded to each question on the Skindex-10 questionnaire on a scale of 0 [never bothered] to 6 [always bothered]. The total score was the sum of the numeric values of each answered question. The domain scores were sums of the following: disease domain (questions 1 to 3), mood/emotional distress domain (questions 4 to 6), and social functioning domain (questions 7 to 10).

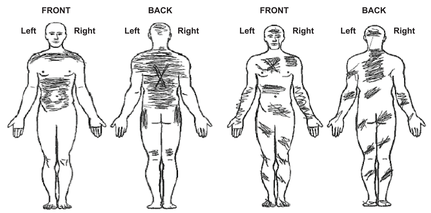
## RESULTS

- Baseline characteristics in the 2 arms were similar (**Table 2**)
- At baseline, the mean itching intensity in both groups was similarly high (~70 mm) on a scale of 0 (no itch) to 100 mm (worst possible itch)
- Anatomical distribution of itch was typically generalized and bilateral (**Figure 3**)

**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 | 60.0 | 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 |
| Years since ESRD onset, Mean±SD | 4.92±4.26 | 4.94 ± 6.18 |
| Months on chronic HD | | |
| Mean±SD | 54.9±50.6 | 50.6±59.3 |
| Median | 42.5 | 24.2 |
| Duration of daily or near daily itch (years), Mean±SD | 4.34±5.72 | 5.20±7.79 |
| Baseline weekly average of daily worst itching VAS score, Mean±SD | 69.5±15.3 | 68.4±13.4 |

**Figure 3. Examples of Patient-Reported Anatomical Distribution of Itch**




**CR845 reduced itching significantly**

- The difference between CR845 and placebo in change in the mean worst itching intensity from baseline to Week 2 was -13.0 mm; 95% CI: -23.5 to -2.5; $p$=0.016 (**Figures 5 and 6A**)

**Effects of CR845 were robust**

- Both daytime itching ($p$=0.030) and nighttime itching ($p$=0.007) were significantly improved with CR845 vs placebo (**Figures 4 and 5**)
- Both dialysis day ($p$=0.030) and non-dialysis day ($p$=0.007) itching were significantly improved (**Figure 4**), although the drug was dosed post-dialysis 3 times per week
- Patients with both moderate (ie, VAS ≥40 and <70 mm) and severe itch (ie, VAS ≥70 mm) at baseline responded equally to CR845, suggesting that CR845 was similarly effective regardless of the itch severity

**Figure 4. Time Course of Itching Reduction**

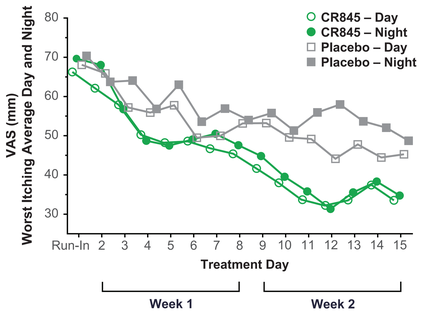
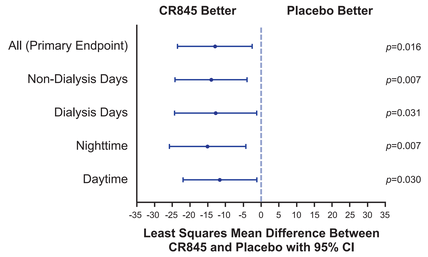



**Figure 5. Itching Intensity Improved with CR845**



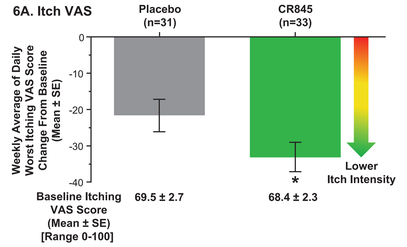

**CR845 significantly improved QOL**

- Itch-related QOL, the first secondary endpoint as measured by the total Skindex-10 score, was significantly improved in patients receiving CR845 compared with placebo, with a between-group difference of -7.5; 95% CI: -14.3 to -0.7; $p$=0.031 (**Figure 6B**)
- Improvements in the total score resulted from improvement within each of the 3 domains of the Skindex-10 (**Figure 7**)
  - Bothersomeness of itching ("disease domain")
  - Mood/emotional distress related to itching
  - Effects of itching on social functioning
- 63% of the CR845-treated patients vs 39% in the placebo group had a change in Skindex-10 score greater than 30% from baseline (**Figure 8**)

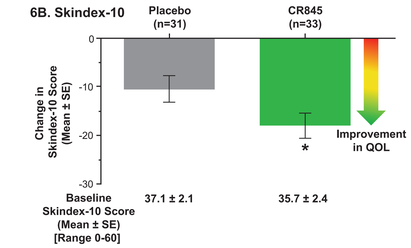
**Itch reduction correlated with improved QOL**

- Changes in Skindex-10 at Day 15 correlated strongly with the mean change in itching intensity during Week 2 among patients receiving CR845 (Pearson's chi-square correlation coefficient: 0.83; $p$<0.001). The correlation coefficient in the placebo group was 0.59

**Figure 6. (A) Change in Weekly Average of Daily Worst Itching VAS Score from Baseline to Week 2 of Treatment and (B) Change in Total Skindex-10 Score from Baseline to Week 2 of Treatment**

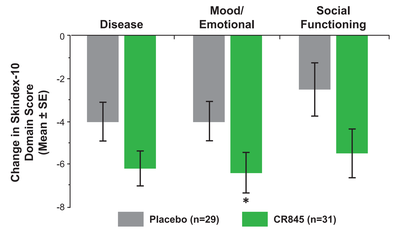



*$P$<0.05.



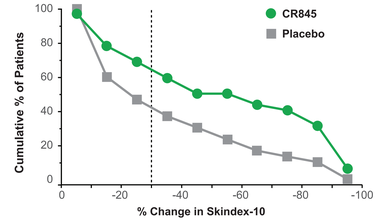

*$P$<0.05.

**Figure 7. Change from Baseline for Skindex-10 Domain Scores**




*$P$<0.05.

**Figure 8. Cumulative Distribution for % Change from Baseline in Total Skindex-10 Score at Day 15**




Note: 1 patient in the CR845 group did not have a baseline value and could not be included in this analysis.

## CONCLUSIONS

- Peripheral kappa opioid receptors appear to play an important role in the modulation of itch signals and represent a target for the development of a novel antipruritic agent
- CR845 significantly reduced itch intensity and improved measures of QOL compared with placebo in patients with chronic kidney disease receiving HD 3 times weekly
- These results support the continued development of CR845 for the treatment of pruritus in patients with chronic kidney disease

## REFERENCES

1. Pisoni RL, et al. *Nephrol Dial Transplant.* 2006;21:3495-505.
2. Ramakrishnan K, et al. *Int J Nephrol Renovasc Dis.* 2013;7:1-12.

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