Randomized, Placebo-Controlled Study on the Efficacy of CR845 in Improving the Quality of Life of Hemodialysis Patients with Chronic Kidney Disease-associated Pruritus

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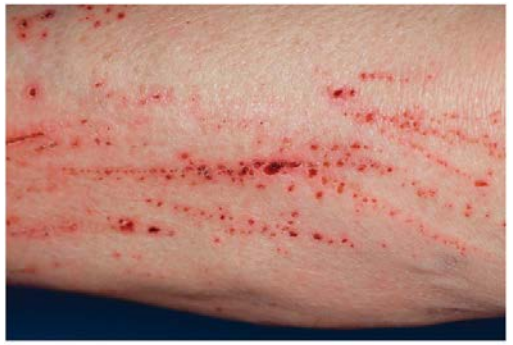
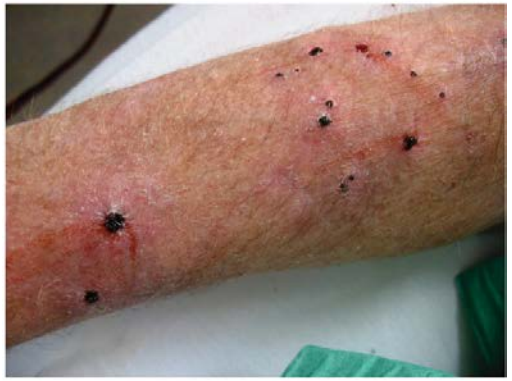
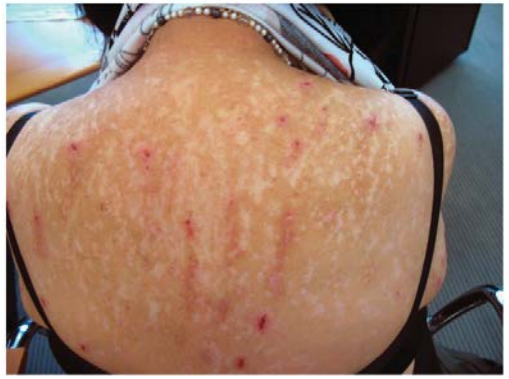
CKD-associated Pruritus







Mettang et al. *Kidney Int.* (2015)

- Serious itching condition directly related to kidney disease
  - 60-70% of hemodialysis (HD) patients
- Itching severity associated with worsening Quality of Life (QoL) (social, emotional and physical)
  - Sleep disturbance, depressed mood, increased mortality risk
- **Underrecognized by health care providers but a high priority for patients**
- Currently, no FDA approved medications and unsatisfactory off label treatments

- *Most common on back, abdomen & arms*
- *Typically bilateral*

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Intravenous CR845 (Difelikefalin)

- Novel selective and potent kappa opioid receptor agonist (Ki = 0.32 nM)
  - No activation of mu and delta opioid receptors
- Hydrophilic small D-amino acid synthetic peptide
  - Does not readily enter the CNS
  - Reduced potential for adverse effects mediated by activation central opioid receptors
- Multifactorial etiology and pathophysiology of CKD-aP supports the use of CR845
  - Dysregulated systemic inflammation (eg, high level interleukin--2, C-reactive protein)
  - Endogenous opioid dysregulation (↑ β- endorphin-mu and ↓ Dynorphin-A-kappa)

Study design

- Double-blind, randomized, placebo-controlled study in 174 HD patients with moderate or severe pruritus (ClinicalTrials.gov NCT02858726)
  - IV bolus Placebo or CR845: 0.5, 1.0, 1.5 mcg/kg
  - Dosing after each dialysis (3x/week) for 8 weeks
    - Not metabolized and excreted renally
- Multi-center – 33 US sites
- Eligibility
  - ≥ 18 years or older, HD 3x/week for at least 3 months,
  - Baseline itch intensity >4 [measured during week prior to randomization with numeric rating scale (NRS) , 0=no itching up to 10= worst itching imaginable]
  - Patients permitted to use any anti-itch medications they were taking prior randomization
  - Key Exclusion Criteria: non-compliant with HD, anticipated kidney transplant, allergy to opiates, pruritus due to other cause than CKD

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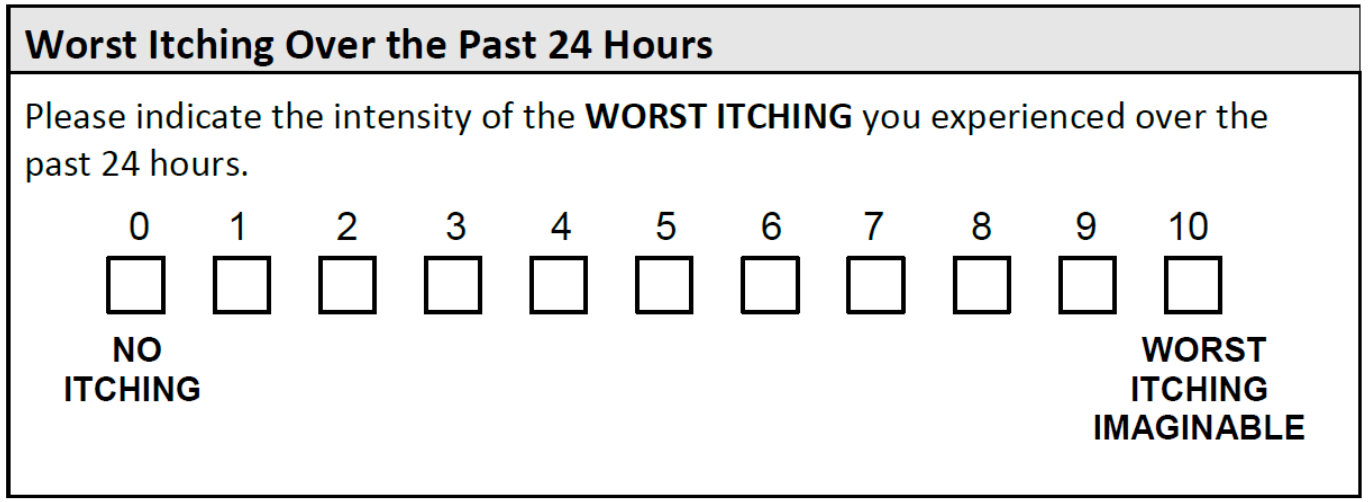
Endpoints

- **Primary:** Change from baseline to Week 8 in weekly average of daily 24-hour worst itching intensity NRS score



Baseline Worst Itch Intensity Scores ranged from 6.7 to 7.1 across group

>0<4=mild, ≥4<7=moderate; 7≥severe *

- **Secondary/Exploratory:** Change from baseline to Week 8 in itch-related QoL scores using multidimensional questionnaires
  - Skindex-10 (3 domains: disease, mood/emotional/distress, social functioning)
  - 5-D itch scale (5 domains: degree, duration of itch/day, direction [improvement/worse], disability [sleep, social, housework/errands, work/school], and body distribution of itch)
  - Sleep disturbance subscale (MOS sleep)
  - PGIC and PGIS

*Reich et al. *Acta Derm Venereol* (2012)

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Patient Demographics

Demographics well balanced across all treatment groups

		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 (%)
Gender					
	Female	17 (37.8)	18 (40.9)	18 (43.9)	16 (36.4)
	Male	28 (62.2)	26 (59.1)	23 (56.1)	28 (63.6)
Age, Mean (range)		59.0 (27 - 84)	57.9 (29 - 80)	58.2 (26 - 84)	54.1 (29 - 74)
Race					
	Black or African American	25 (55.6)	24 (54.5)	22 (53.7)	31 (70.5)
	White	16 (35.6)	17 (38.6)	19 (46.3)	10 (22.7)

- **9% of Patients ≥ 75 years old**
- **Average time on chronic dialysis = 5.8 years; Primary causes of renal failure (diabetes/hypertension)**
- **Average time with pruritus = 4.4 years**

Treatment-Emergent Adverse Events >10% In Any Treatment Group

Preferred Term	Placebo (N=45)	CR845 0.5 mcg/kg (N=44)	CR845 1.0 mcg/kg (N=41)	CR845 1.5 mcg/kg (N=44)
	n (%)	n (%)	n (%)	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)

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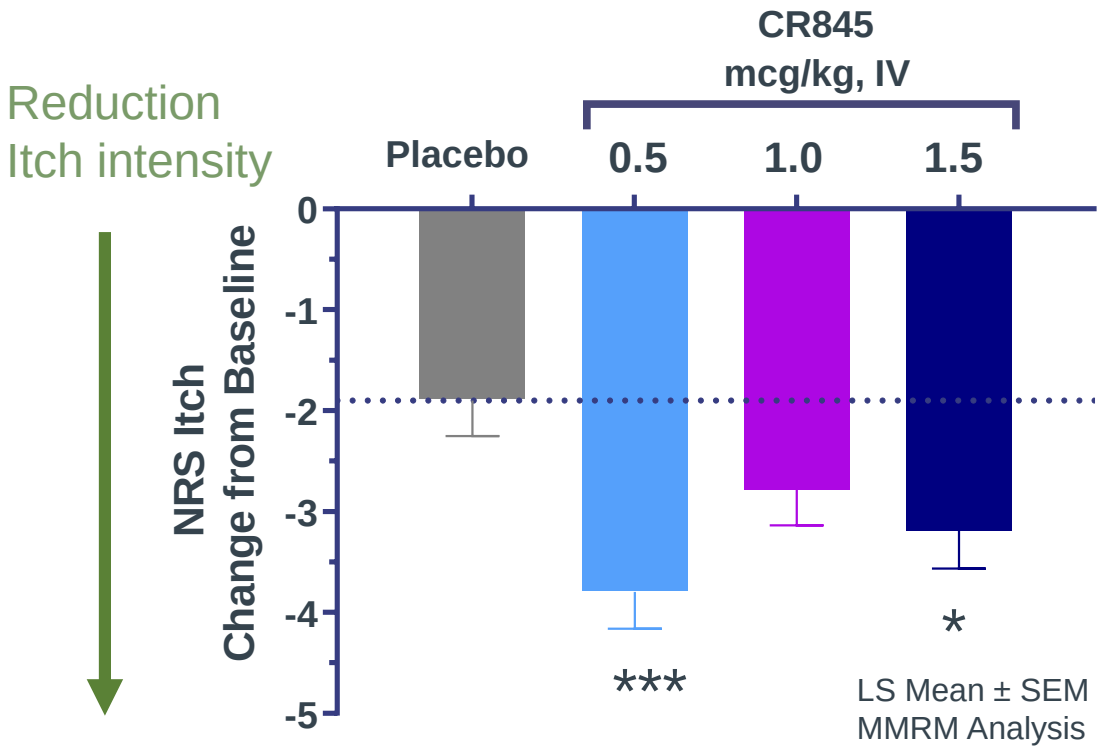
Clinically Meaningful Reduction in Itch Intensity Following an 8-Week Treatment Period with CR845

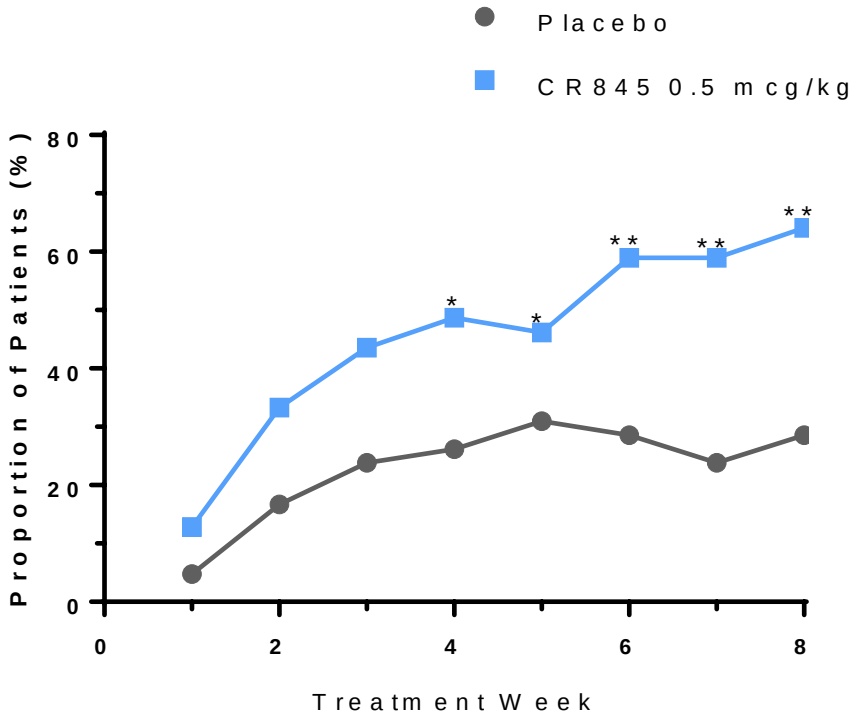
Mean Change in NRS Itch at Week 8



LS Mean ± SEM
MMRM Analysis
Full analysis population
N = 41-45
*p<0.05, ***p<0.001 vs Placebo

Full Analysis Population: all randomized patients who received at least 1 dose of double-blind study drug.

Responder Analysis: Worst Itch Intensity Change ≥3 Points

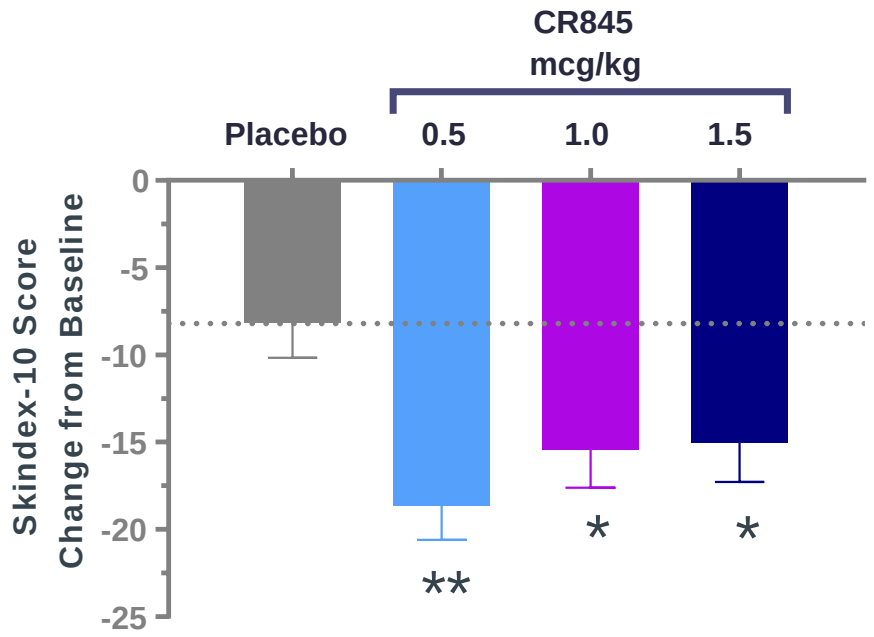


NRS Improvement	Placebo	CR845 0.5 mcg/kg
≥3-points	29%	64% (**)
≥4-points	24%	51% (*)

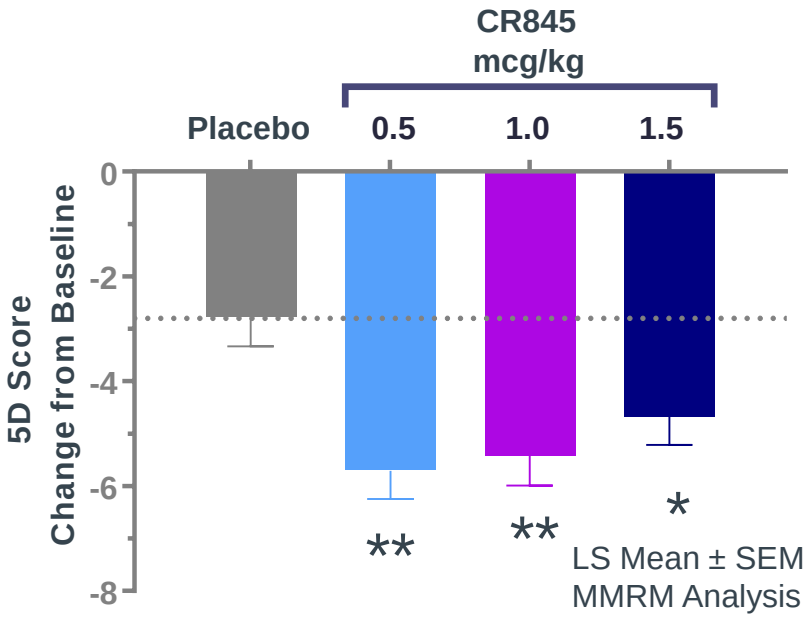
*p<0.05, **p<0.01 vs Placebo, Cochran-Mantel-Haenszel test

Improvement in Itch-related Quality-of-Life Measures Following an 8-Week Treatment Period with CR845

Skindex-10



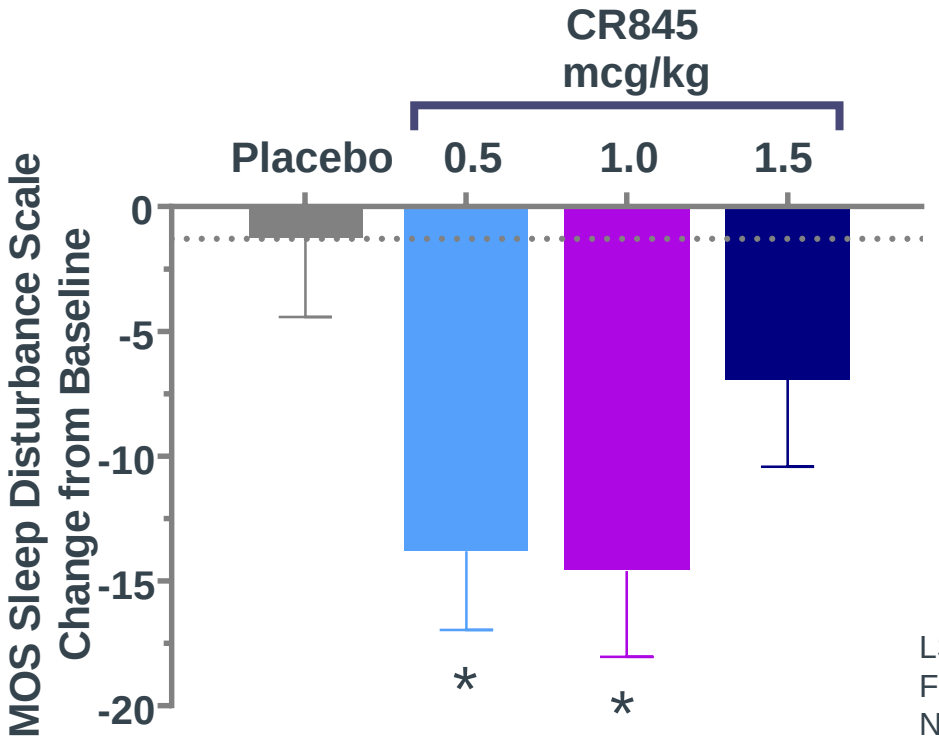
5-D Scale



LS Mean ± SEM
MMRM Analysis
Full analysis population
N = 41-45
* p <0.05, ** P<0.001 vs Placebo

- CR845-treated patients exhibited statistically significant improvement across all QoL domains
- Mean change in QoL measures correlated with the change in itch intensity (Pearson's correlation ranging from r=0.67 to 0.74, p<0.0001).

Reduced Sleep Disturbance Following an 8-Week Treatment Period with CR845



LS Mean ± SEM
Full analysis population
N = 41-45
* p <0.05 vs Placebo

Items contain in the Sleep Disturbance subscale of the MOS Sleep scale:	
• Trouble falling asleep	• Awaken during sleep
• Sleep restlessness	• Time to fall asleep

Conclusion

- CR845 was well tolerated and produced a clinically meaningful reduction in itch intensity in hemodialysis patients with moderate or severe CKD-aP
- This reduction was associated with substantial improvement in multiple measures of itch-related quality of life and sleep sustained over 2 months of treatment
- Currently recruiting dialysis sites for initiation of Pivotal Phase 3 trials

CR845 was recently granted Breakthrough Designation for this indication by the FDA

Major need to improve the wellbeing of patients with CKD-aP

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Interested in participating in our program?
Contact fmenzaghi@caratherapeutics.com

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