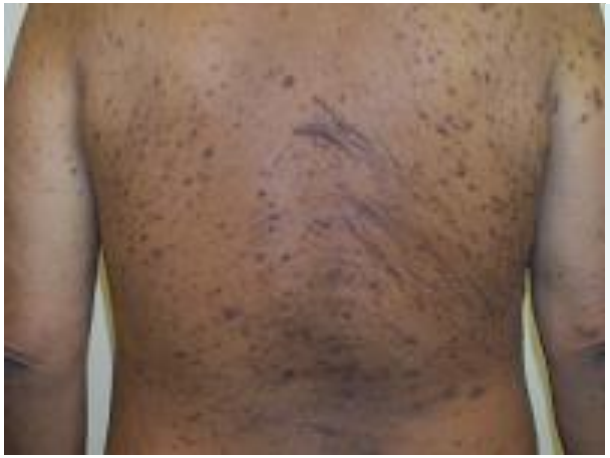
CR845: Novel Peripheral Kappa Opioid for Itch Relief Related to Chronic Kidney Disease

Corporate Presentation

Uremic Pruritus (UP) in Dialysis Patients

- Chronic Itching experienced by ESRD (End-Stage-Renal-Disease) patients requiring dialysis
- 40-60% of dialysis patients experience moderate-to-severe UP
  - Reduces quality of life, and linked to increased mortality
- Typically not responsive to antihistamines and other available treatments are limited (skin emollients, UV-B therapy, capsaicin cream)



- *Most common on back, abdomen & arms*
- *Excoriations in severe cases*

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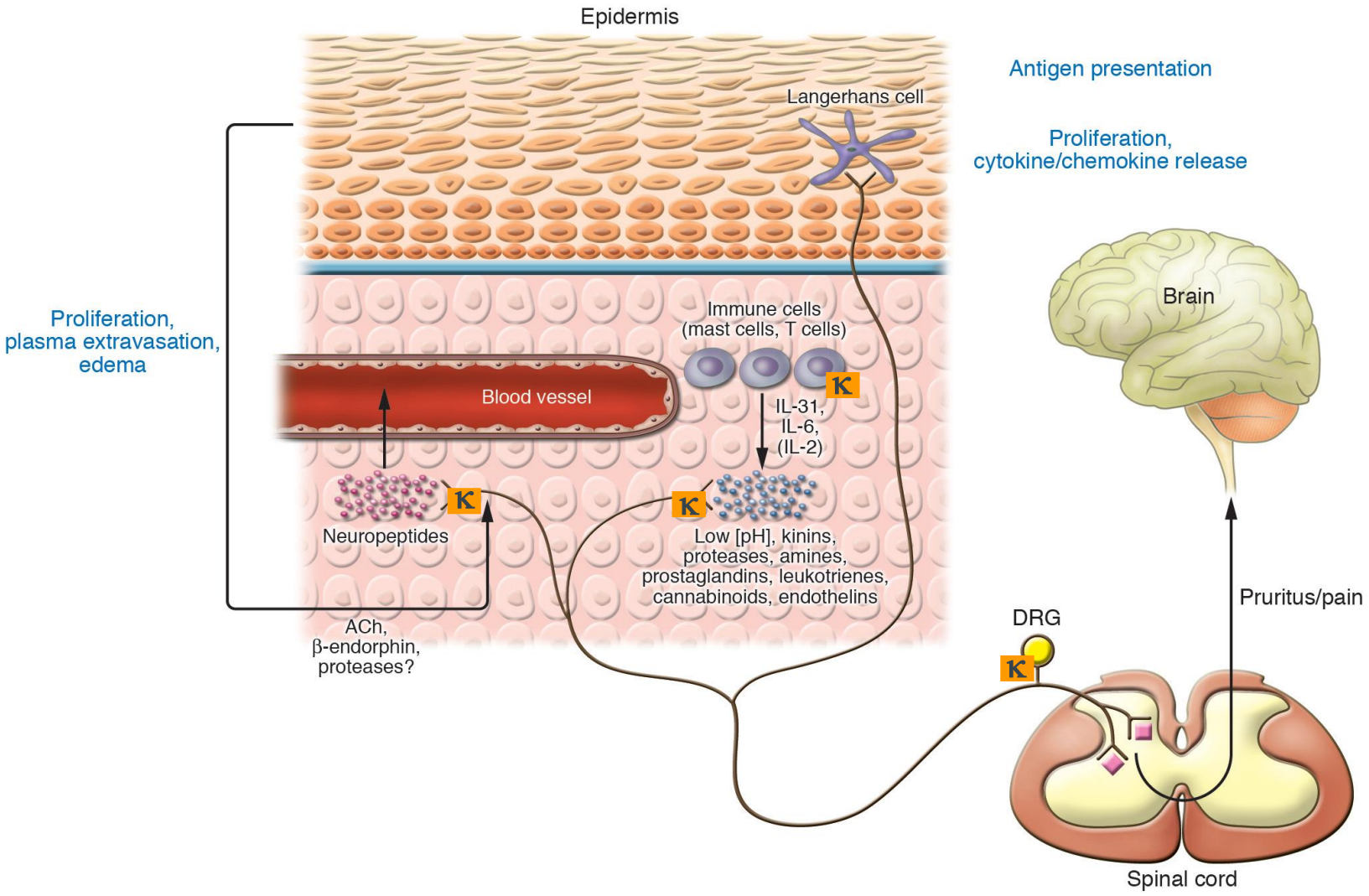
Pathophysiology of Uremic Pruritus is Unknown

- Two current hypotheses support:
  - **Inflammatory mechanisms**
    - Increases in serum CRP and IL-6 in patients with UP
    - Positive clinical data with UV-B, thalidomide and tacrolimus
  - **Opioid mechanism**
    - Imbalance resulting in increased serum β-endorphin (mu) and reduction of serum Dynorphin A (kappa)
    - Positive clinical data with nalfurafine and naltrexone

Pruritus And Pain – Common Pathway



Taken from Paus et al.,J Clin Inv, 2006.

Uremic Pruritus POC Phase 2 Trial Design

Primary Objectives

Part A

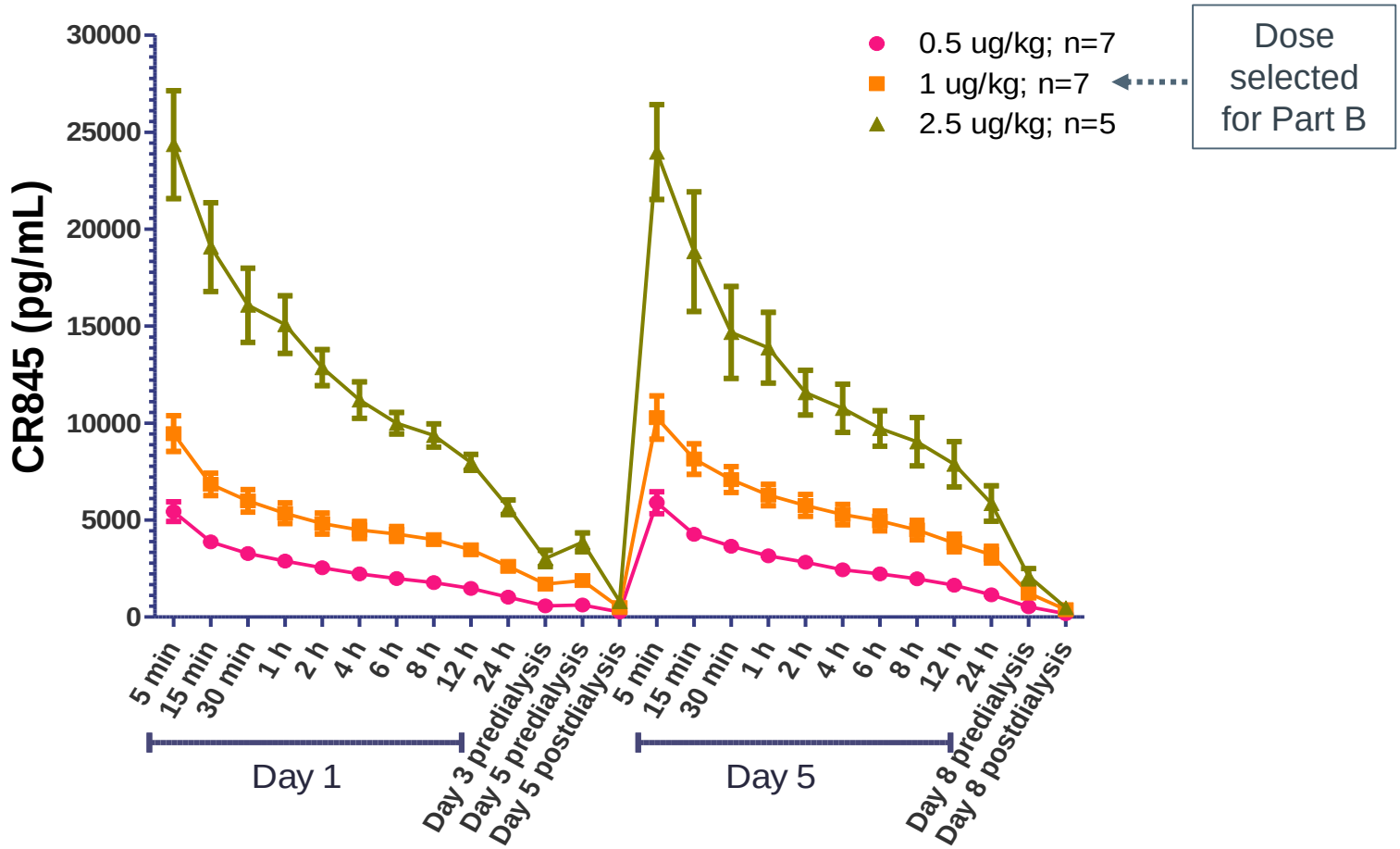
- To evaluate the PK profile of repeated doses of CR845 in hemodialysis patients over a one-week treatment period

Part B

- To evaluate the efficacy of CR845 compared to placebo in reducing the intensity of itch over a 2-week treatment period (1 dose selected based on Part A, 3 times/week post-dialysis) in hemodialysis patients with uremic pruritus

CR845 Pharmacokinetics In ESRD Patients

CR845 Renally Excreted – Extended Half-Life: ~24 hrs

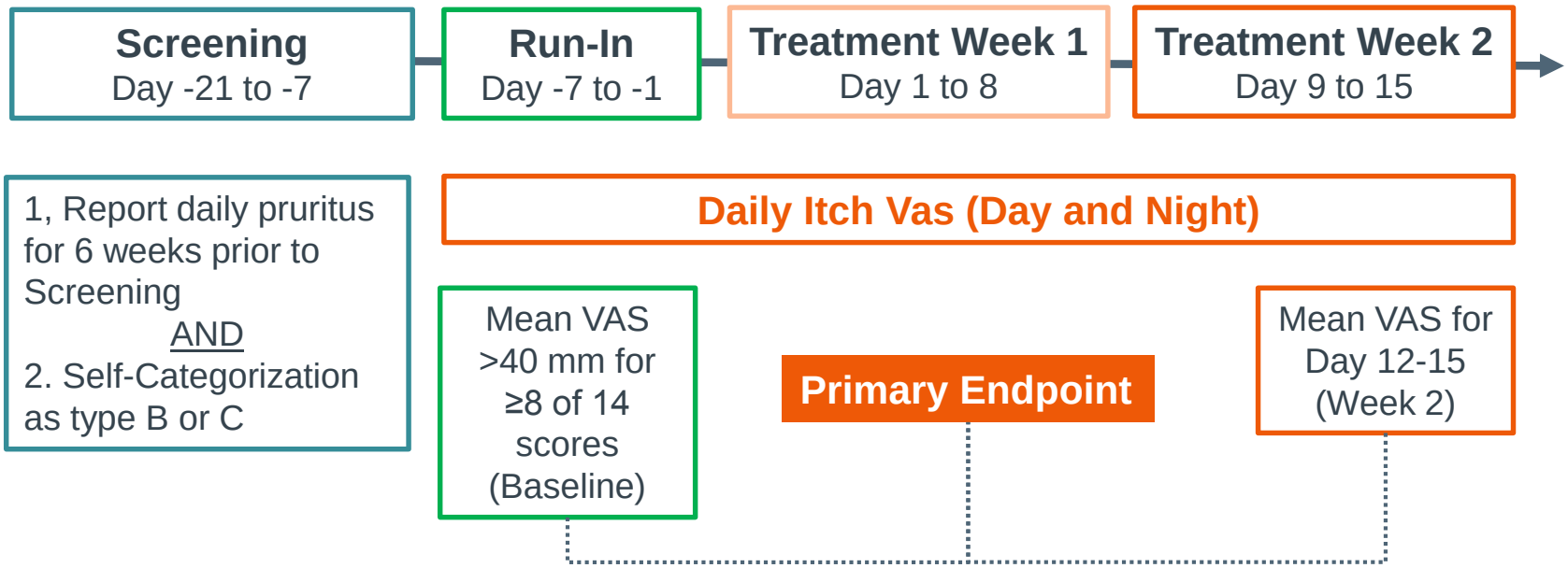


Note: AUC 10 fold greater as compared to healthy volunteers

Part B - Study Design

- Randomized, double-blind, placebo-controlled study
- Dosing after each Dialysis session, 3 x per week
- Multi-center:
  - 21 U.S. sites
  - 65 patients
    - Placebo: 32
    - CR845: 33

Part B - Study Design Schematic



Secondary Endpoints

	Predose	Day 8	Day 15
Skindex-10	✓	✓	✓
Itch MOS	✓	✓	✓

Patient Population: Demographics

- Subject demographics well balanced across treatment group

	Placebo (n= 32) N (%)	CR845 (n=33) N (%)
Gender		
Male	15 (47)	16 (48)
Female	17 (53)	17 (52)
Age, mean (range)	60 (35 – 88)	60.1 (26 – 84)
Race		
White	18 (56.3)	18 (54.5)
Black or African American	10 (31.3)	12 (36.4)
Weight (kg) Mean ± SD (range)	87.0 ± 21.2 (52 – 145)	86.6 ± 20.7 (37 – 124)
BMI (mean ± SD)	31.0 ± 7.9	32.1 ± 8.6

- **Average Duration of Daily or Near Daily Itching was ~5 years for both treatment groups**

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CLIN2005: Visual Analog Scale (VAS)

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SUBJECT ITCH ASSESSMENT WORKSHEETS
Itch Intensity Scale

SUBJECT NO.	STUDY DAY
___ - ___	

INSTRUCTIONS
Please rate your level of itching by placing a vertical (straight up and down) mark through the line on the scales below. After completing both scales, please provide your initials in the **SUBJECT INITIALS** box indicating that you completed the scales **BY YOURSELF** and the date and time you completed the scales.

Worst Itching—Nighttime

Please rate the **WORST** itching you experienced from bedtime last night to awakening this morning (in other words, during the night)

NO ITCH — WORST POSSIBLE ITCH

Date: _____

Time: ____ : ____

☐AM ☐PM

☐ **CHECK IF NOT DONE**

← itching during the previous night

Worst Itching—Daytime

Please rate the **WORST** itching you experienced from awakening yesterday to bedtime last night (in other words, during the day)

NO ITCH — WORST POSSIBLE ITCH

Date: _____

Time: ____ : ____

☐AM ☐PM

☐ **CHECK IF NOT DONE**

← itching during the previous day

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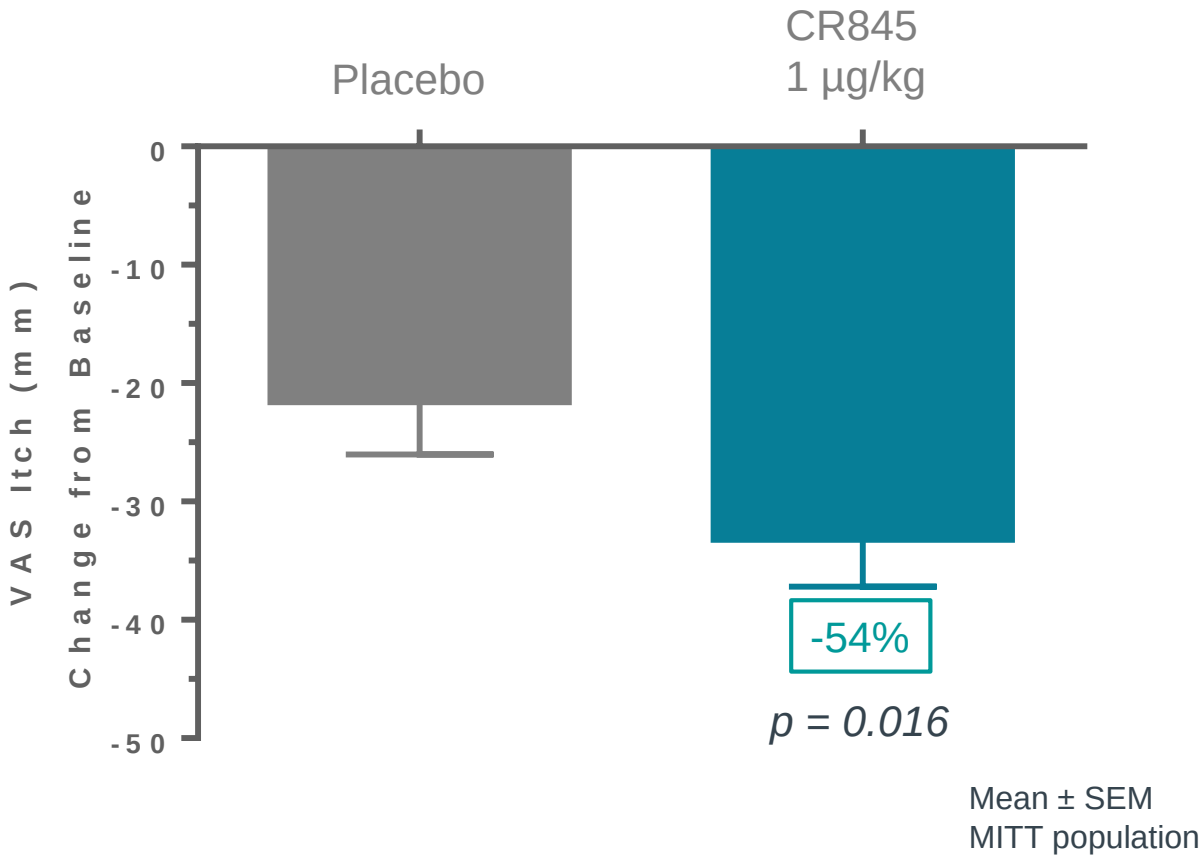
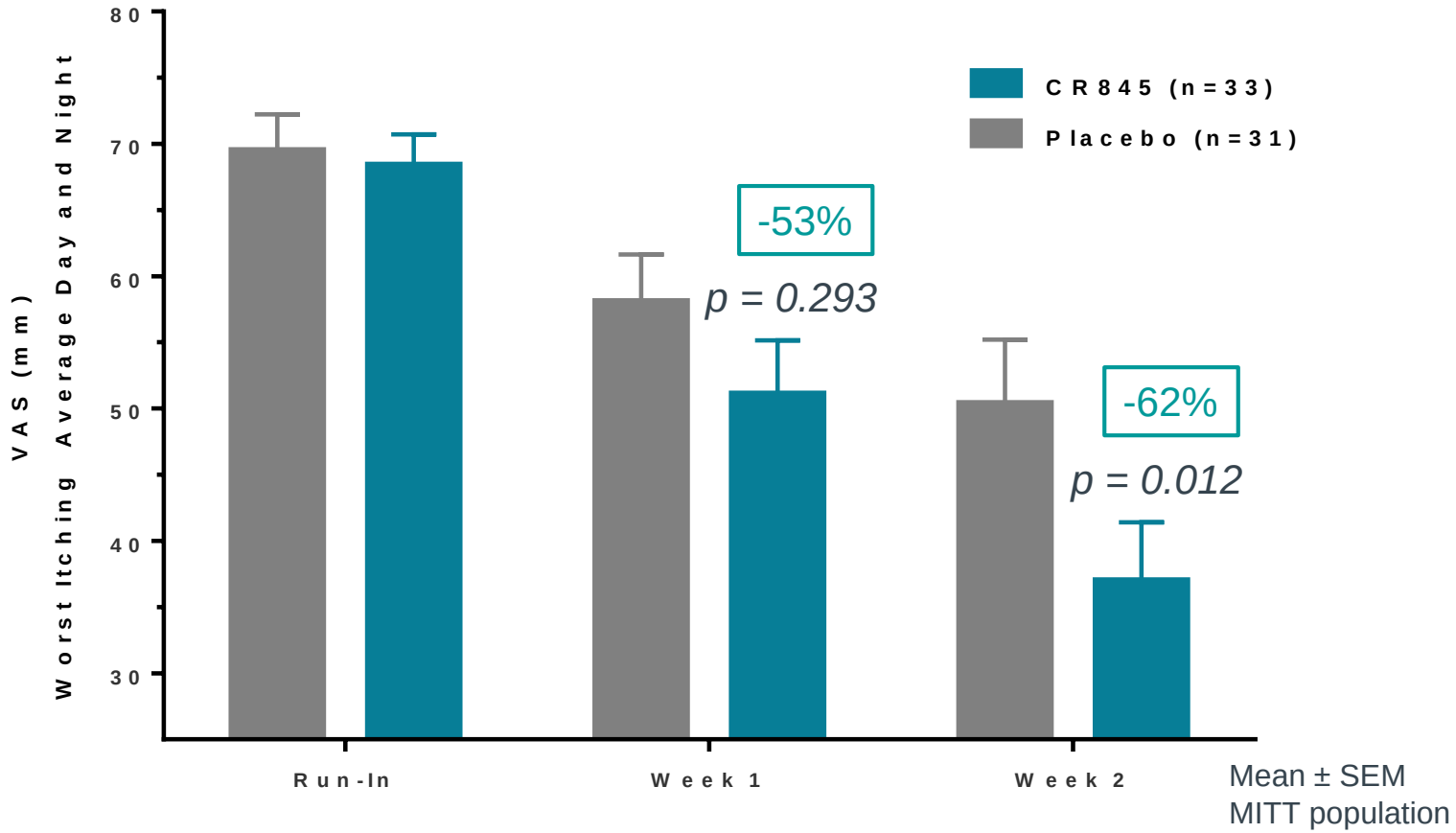
CR845 Reduces Itch Intensity – Primary Endpoint



Mean ± SEM
MITT population

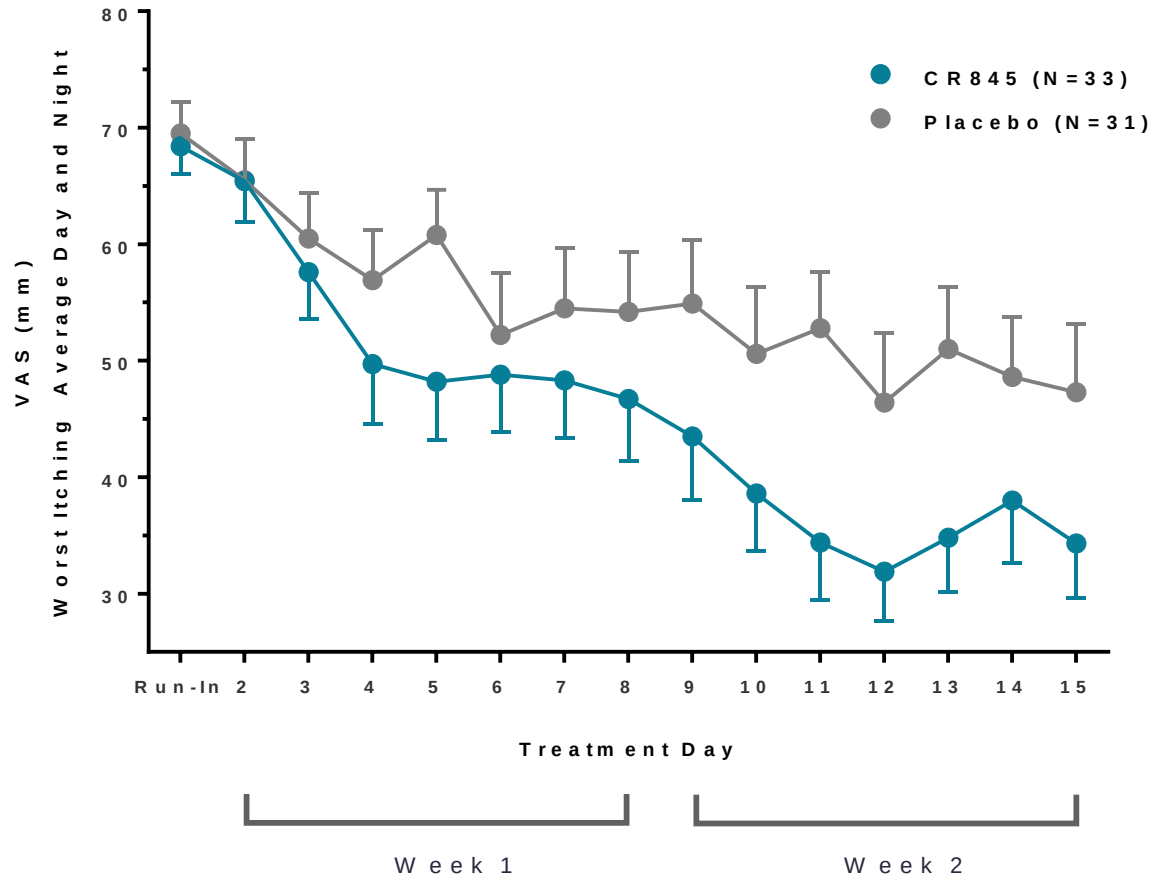
- **Mean change from baseline (Run-in) to the average of Week 2 scores (Day 12 through 15).**

Reduction in Itch Intensity by Treatment Week:
Average of All VAS Scores (Day and Night)



- Reduction in itch intensity beginning on Week 1 and is significantly different from placebo by Week 2

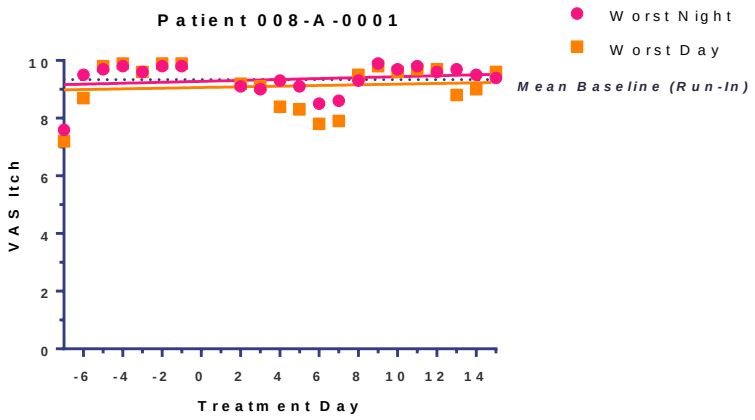
Itch Intensity Over 2 Weeks of Treatment



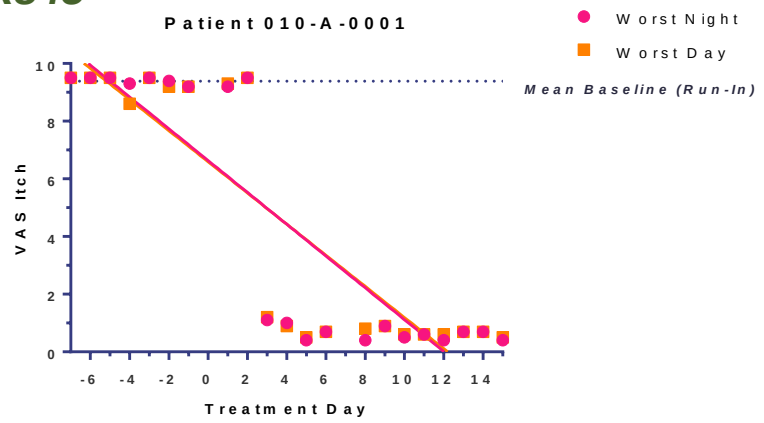
- Reduction of itch intensity for patients treated with CR845 beginning on Week 1 that continues to improve through Week 2.
  - *Patients on placebo show initial improvement that plateaus*

Example Individual VAS profile

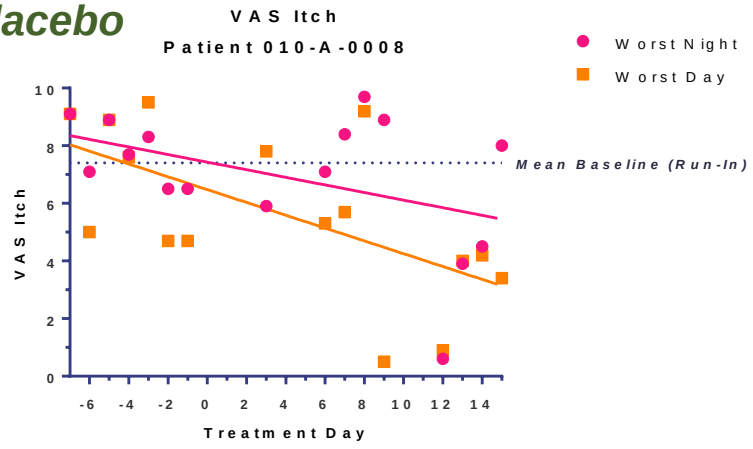
Placebo



CR845

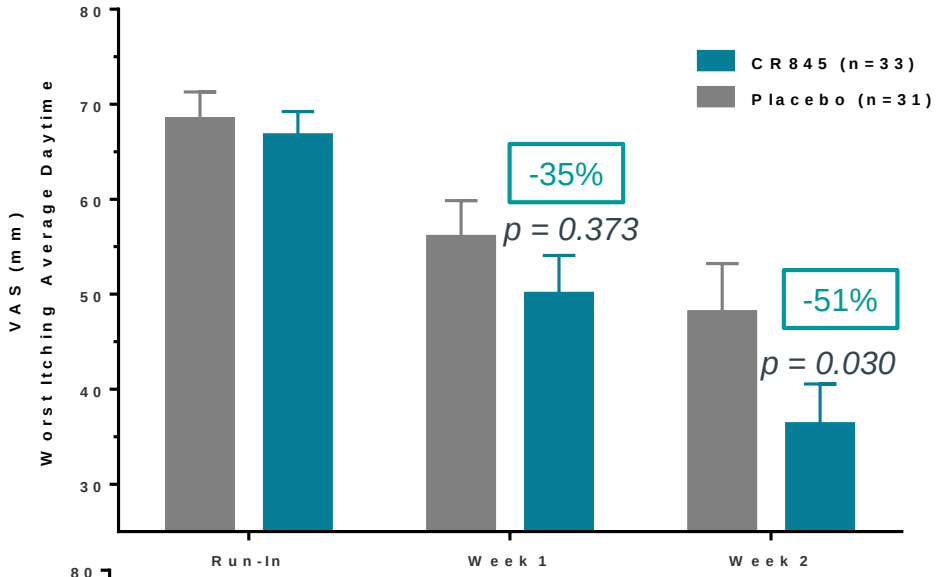


Placebo

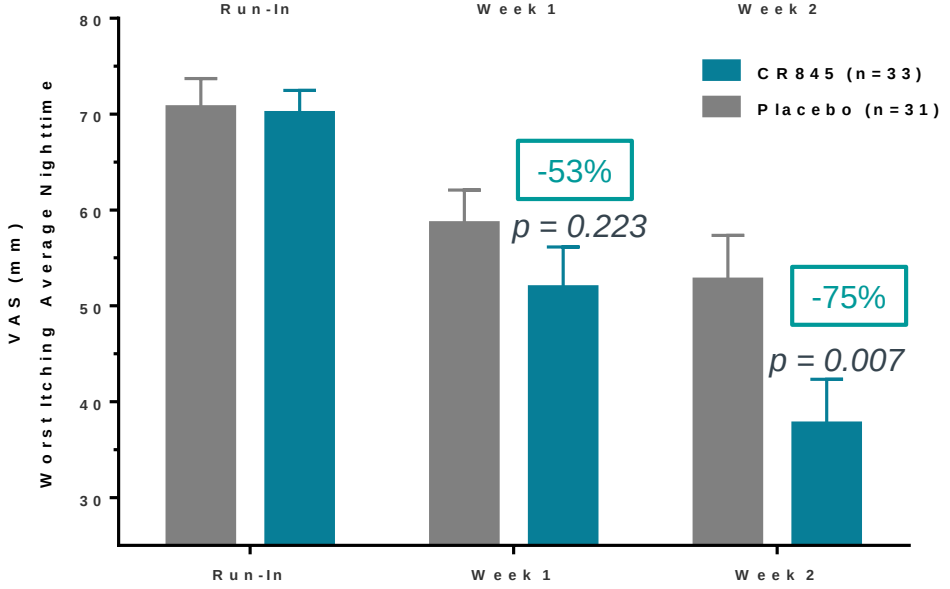


CR845: Significant reduction in Worst Itch Intensity reported for both Day and Night Time by Week 2

Day



Night



Skindex-10 (Patient-reported Outcome Scale)

- Skindex-10 consists of 10 questions used to evaluate how the patient's itch affects their Quality of Life. The total score and subdomain scores are then compared after week 1 (Day 8) and week 2 (Day 15) relative to baseline (Day 1, pre-dose).

- "During the past WEEK, how often have you been bothered by":

Disease

1. Your itching.
2. The persistence/reoccurrence of your itching.
3. The appearance of your skin from scratching.

Mood/ Emotional Distress

4. Frustration about your itching.
5. Being annoyed about your itching.
6. Feeling depressed about your itching.

Social Functioning

7. Feeling embarrassed about your itching.
8. The effects of your itching on your interactions with others.
9. The effects of your itching on your desire to be with people.
10. The effect of your itching making it hard to work or do what you enjoy.

0 = Never bothered ⟷ 6 = Always bothered

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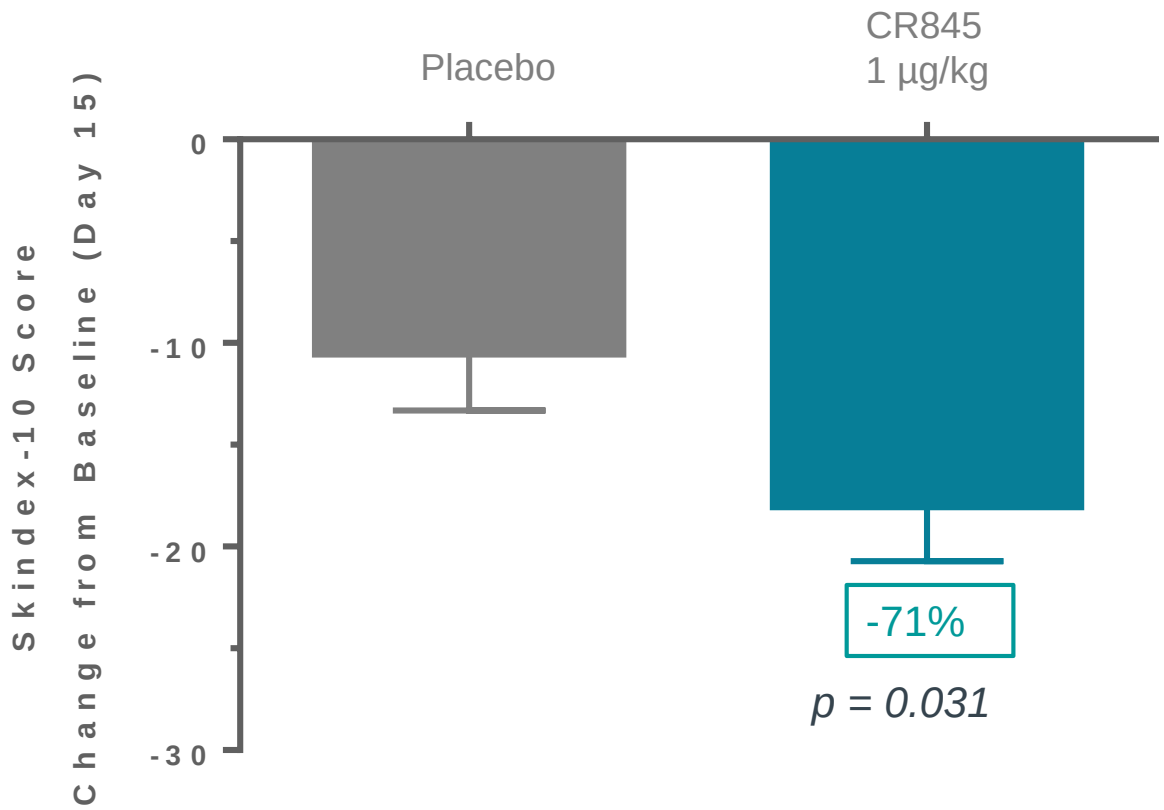
CR845 Improves Itch-related Quality of Life *(total Skindex 10 score, Secondary Endpoint)*

Demonstrated efficacy in improving itch-related Quality of Life (Skindex-10) at end of a 2 week treatment period

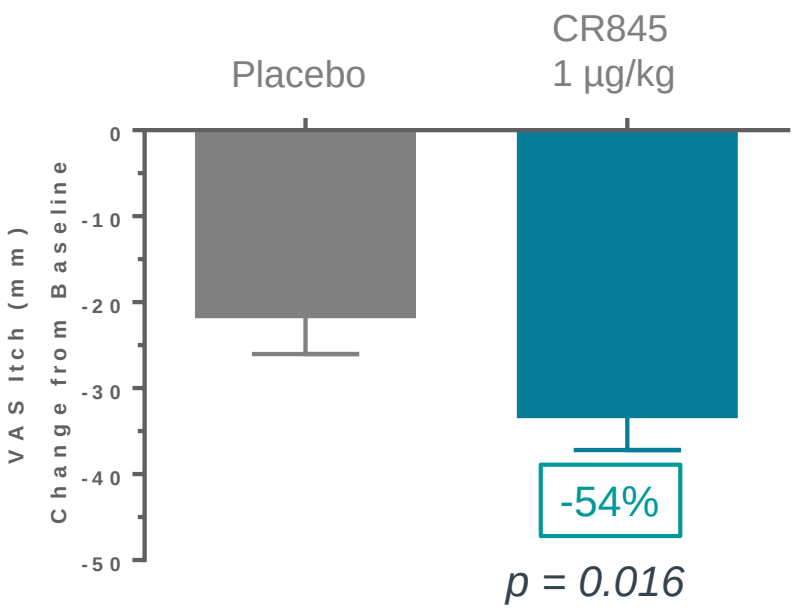


Mean ± SEM
MITT population

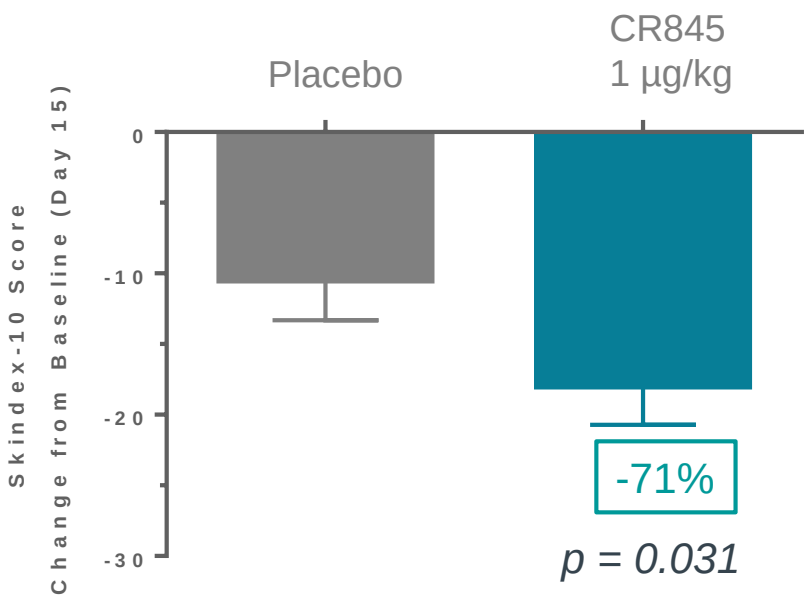
CR845 Phase 2 – Uremic Pruritus
Primary and Secondary Endpoints (MITT)

Demonstrated efficacy in reduction of itch and improvement in Quality of Life (Skindex-10) at end of 2 week treatment period

- CR845 Reduces Itch Intensity

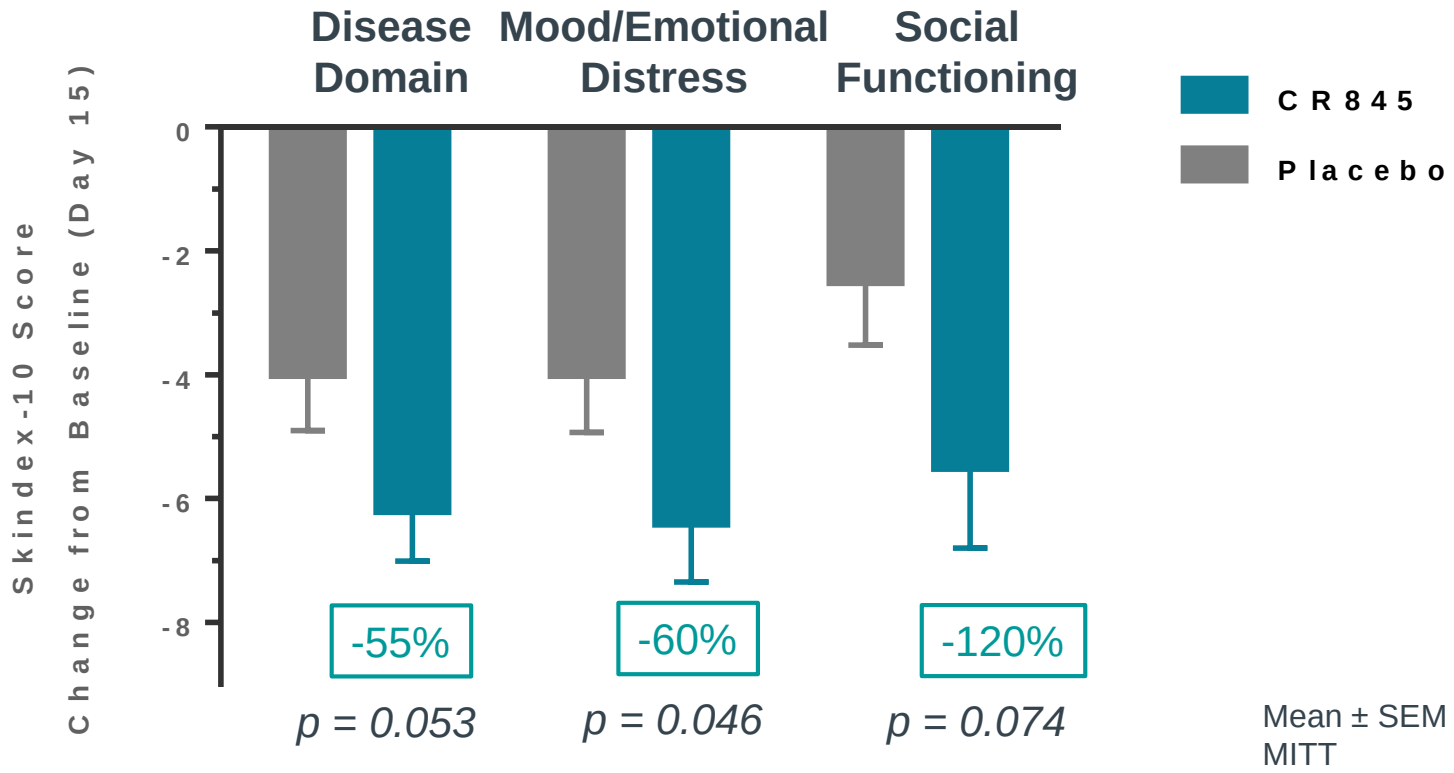


- CR845 Improves Quality of Life



Mean ± SEM
MITT population

CR845 Improves Itch-related Quality of Life: *Skindex 10 scores by Domain*



- After 2 weeks of treatment, patients reported trend for improvements across all aspects of their Quality of Life
- Baseline defined as assessments collected on Day 1 prior to first dose

Itch MOS Sleep Index (SLP-9)

- Itch MOS Sleep Index II is used to evaluate how the patient's itch affects their Sleep. Scoring is based on total of 9 questions (SLP-9) to compare week 1 (Day 8) and week 2 (Day 15) relative to baseline (Day 1, pre-dose).

- SLP-9 questions:
  - How long did it usually take you to fall asleep during the past week?
    (1 = 0-15 minutes 5 = More than 60 minutes)

"How often during the past week did you…"

- feel that your sleep was not quiet due to itchiness or scratching?
- get enough sleep to feel rested upon waking in the morning?
- awaken because of itchiness?
- feel drowsy or sleepy during the day?
- have trouble falling asleep because of itchiness?
- awaken during your sleep time and have trouble falling asleep again because of itching?
- have trouble staying awake during the day?
- get the amount of sleep you needed?

1 = All of the Time  6 = None of the Time

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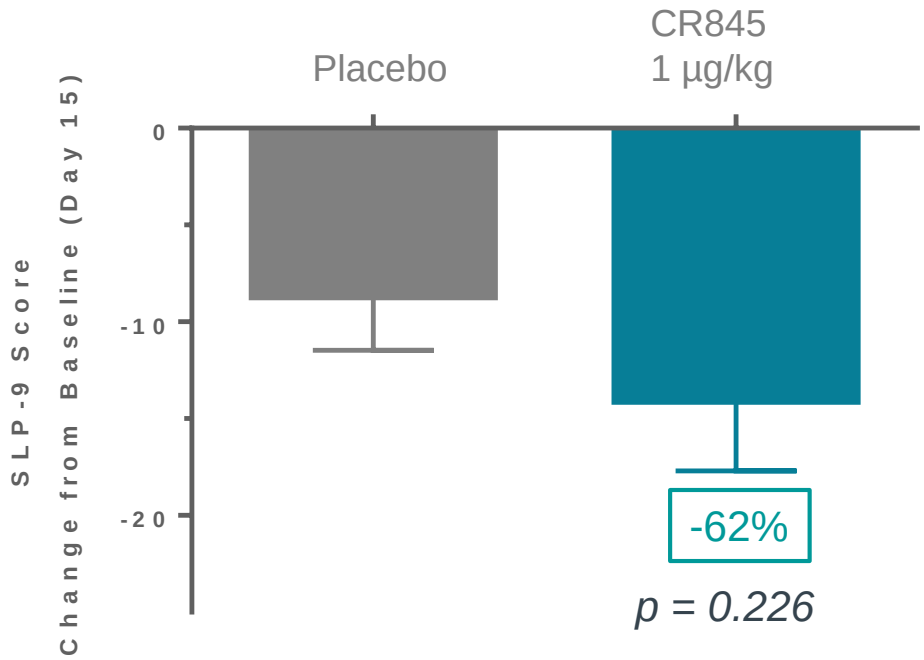
Effect of CR845 on Itch-related Sleep Disturbances based on the Itch MOS Sleep Problems Index II (SLP-9)



Mean ± SEM
MITT

- Trend observed for patients treated with CR845 on overall improvement in their sleep compared to placebo

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			
Diarrhoea	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)	2 (6.1)	2 (3.1)
Headache	2 (6.3)	2 (6.1)	4 (6.1)
Hypoaesthesia	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)

- No severe adverse events; most TEAEs were mild – moderate in severity with only dizziness, hypoaesthesia and 1 episode of hypotension considered related to CR845
- No treatment-related serious adverse events; No discontinuations due to AEs

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I.V. CR845 Uremic Pruritus: Next Steps

- Considering application For Orphan & Breakthrough Designation
- FDA Meeting – Define Phase 3 Registration Package
- Initiate Phase 3 Trial – Q1 2016
- Planned NDA Submission – 2017