# CR845-CLIN2101: (Part A)

*A Two-part, Phase 2/3, Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Safety and Efficacy of Intravenous CR845 in Chronic Kidney Disease Hemodialysis Patients with Moderate-to-Severe Pruritus*

## Study Results

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# CR845-CLIN2101: (Part A) Overview

**Chronic Kidney Disease (CKD)-Associated Pruritus:**

- Intractable itch condition observed across CKD patient population:
  ~60-70% of CKD patients on hemodialysis (200-300k U.S. patients)
  ~30% of non-dialysis CKD patients ( ~4M U.S. patients)
- No approved therapies in the U.S. – unresponsive to conventional medications
- Increases mortality, morbidity; profound negative effect on quality of life (QoL)

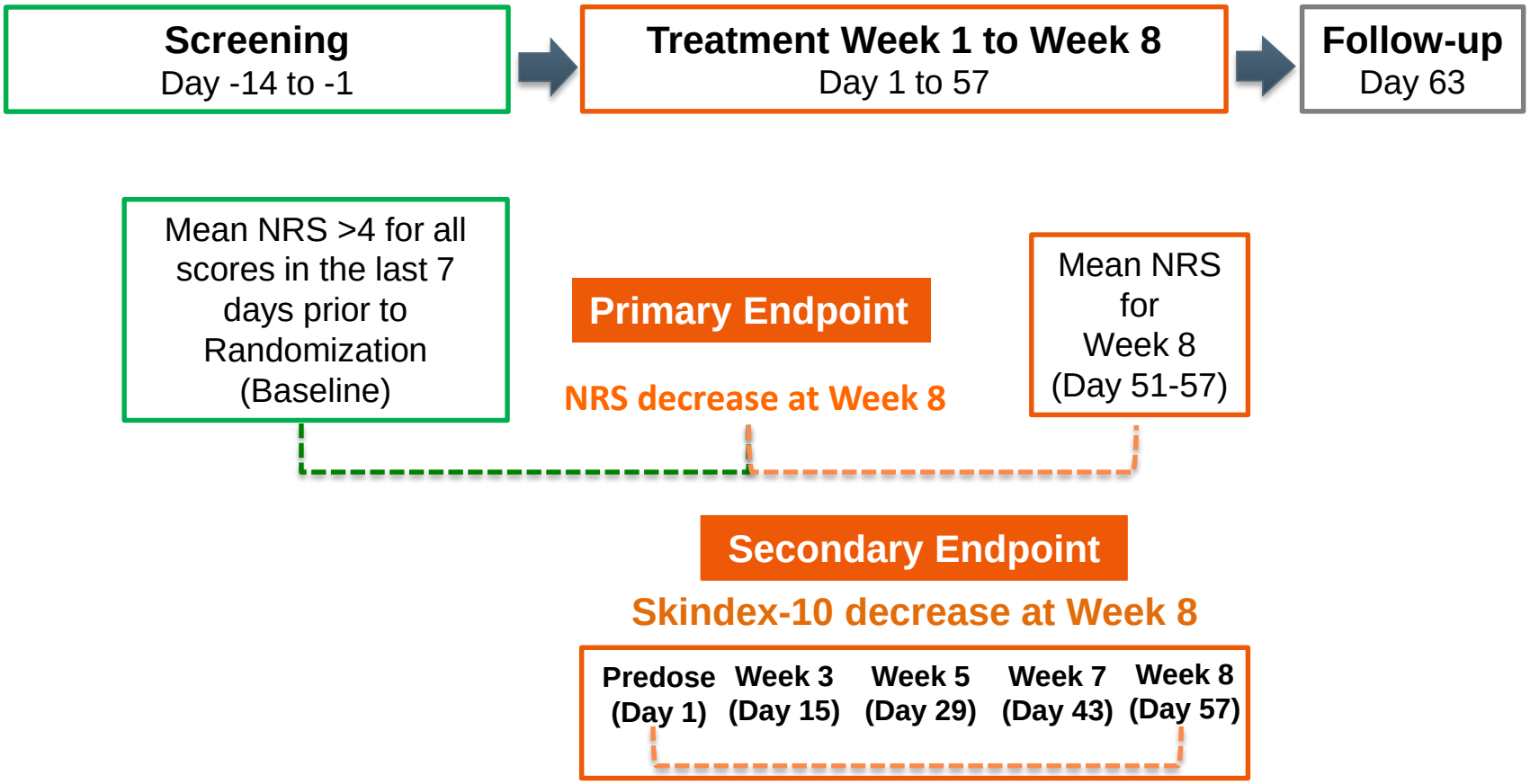
**Overview of CLIN2101 Results:**

- I.V. CR845 met both primary (itch) and secondary (QoL) endpoints
- Correlation of reduced itch intensity and improvement in quality of life measures
- Demonstrated sustained, increasing treatment benefit over 2 months
- CR845 appears safe, well-tolerated for chronic use in CKD dialysis patients

# CR845-CLIN2101: Study Design (Part A)

- Randomized, Double-Blind, Placebo-Controlled Study in Hemodialysis Patients with Moderate-to Severe Pruritus
- 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)
- Multi-center:
  - 35 U.S. sites
  - 174 patients randomized and treated with study drug (Safety Population)
    - Placebo: 45
    - CR845: 129

# CR845-CLIN2101: Part A
# Study Design Schematic




**Mean Weekly Avg NRS Scores Calculated From Worst Daily Itching Score**

***NRS measures worst itching and Skindex measures QoL***



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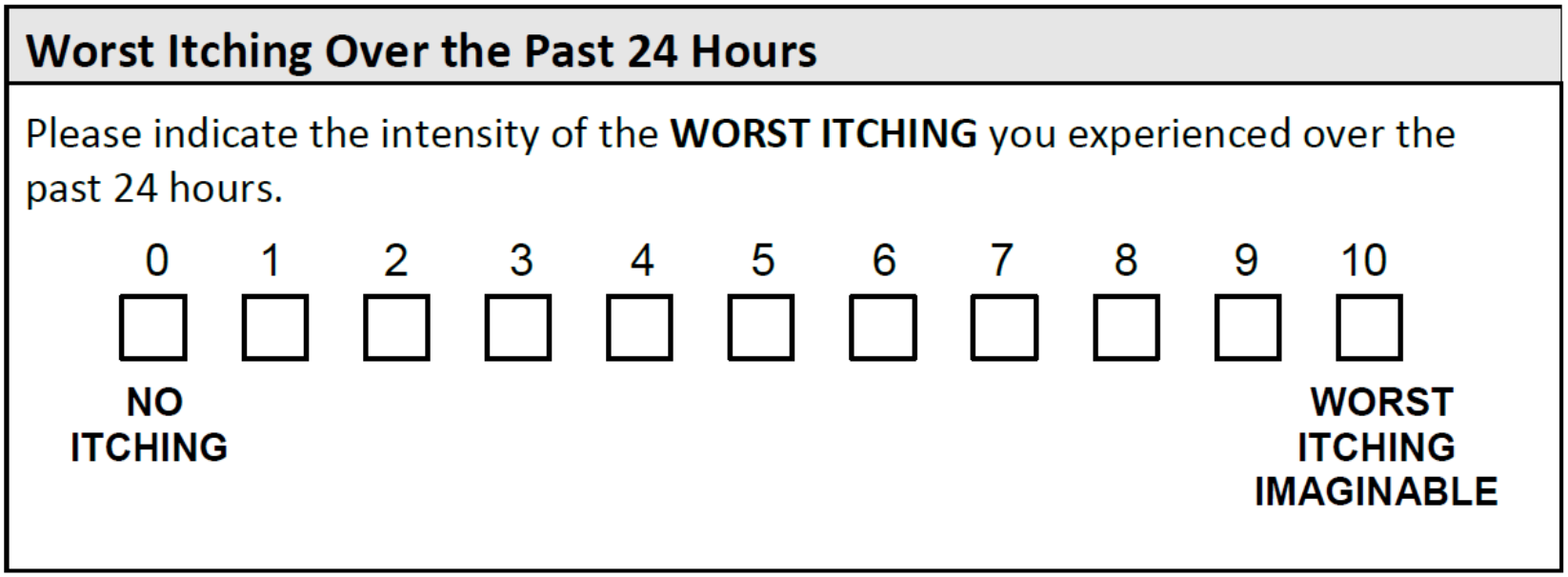
# Numeric Rating Scale (Primary Endpoint)




Patients indicate WORST ITCHING scores daily through treatment period

# Skindex-10 (Secondary Endpoint)

- Skindex-10 consists of 10 questions used to evaluate how the patient's itch affects **three important domains of** quality of life.

"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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# Patient Population: Demographics

## Subject 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) |

**Average time on chronic dialysis = 5.8 years**
**Average time with pruritus = 4.4 years**

# Baseline Scores for Worst Itch Intensity (NRS) & Quality of Life (Skindex-10)

## Baseline scores well balanced across all treatment groups

| Mean ± SD | | Placebo (N=45) | CR845 0.5 mcg/kg (N=44) | CR845 1.0 mcg/kg (N=41) | CR845 1.5 mcg/kg (N=44) |
|---|---|---|---|---|---|
| | NRS | 6.8 (1.50) | 7.1 (1.35) | 6.7 (1.47) | 6.7 (1.42) |
| | Skindex-10 | 35.5 (12.37) | 35.1 (13.43) | 33.1 (11.69) | 32.4 (12.35) |

# Use of Prior and Concurrent Anti-Itch Medication ≥ 2% of Subjects

## "Anti-Itch" drugs well balanced across all treatment groups

| Mean±SD | 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 (%) |
|---|---|---|---|---|
| Any Prior Anti-Itch Medication | 18 (40.0) | 20 (45.5) | 17 (41.5) | 18 (40.9) |
| Diphenhydramine | 11 (24.4) | 11 (25.0) | 11 (26.8) | 11 (25.0) |
| Hydroxyzine | 2 (4.4) | 6 (13.6) | 2 (4.9) | 3 (6.8) |
| Hydrocortisone | 5 (11.1) | 1 (2.3) | 2 (4.9) | 1 (2.3) |
| Triamcinolone | 2 (4.4) | 0 (0.0) | 1 (2.4) | 1 (2.3) |

**CR845 efficacy assessed in patients refractory to traditional "anti-itch" drugs used prior to and during study period**



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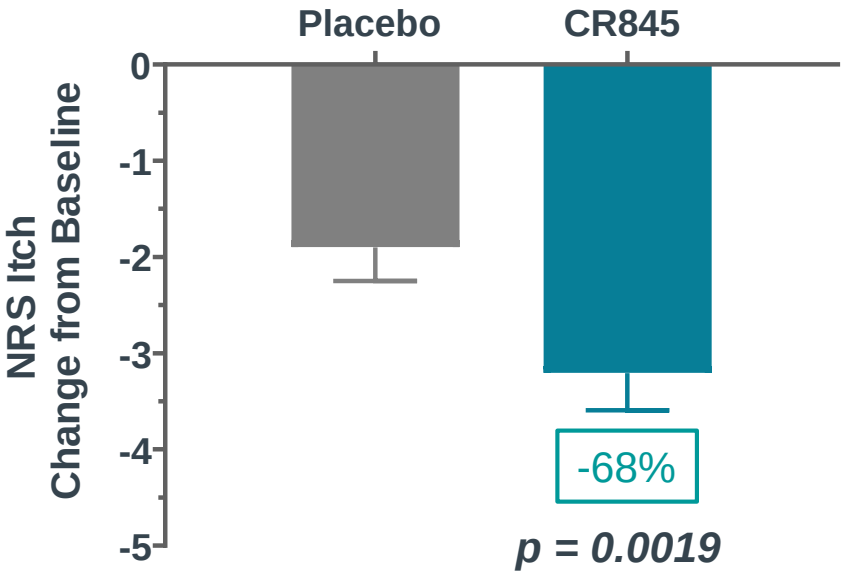
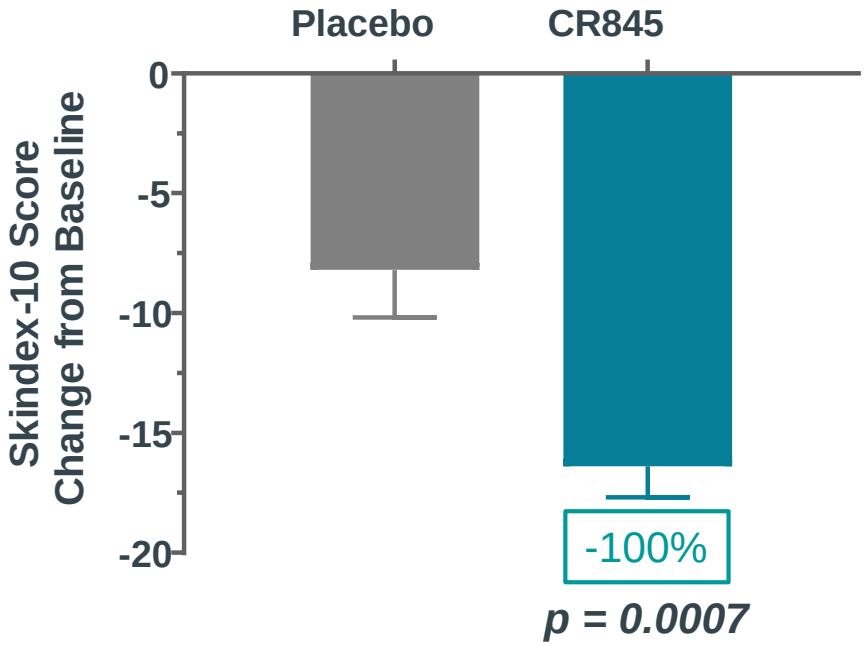
# CR845-CLIN2101 (Part A)
# Primary and Secondary Endpoints

## Demonstrated efficacy in reduction of itch (NRS) and improvement in Quality of Life (Skindex-10) at end of the 8 week treatment period

### CR845: Reduces Itch Intensity




### CR845: Improves Quality of Life




Mean ± SEM
Full Analysis Population

***Full Analysis Population is defined as the group of all randomized patients who received at least 1 dose of double-blind study drug.***



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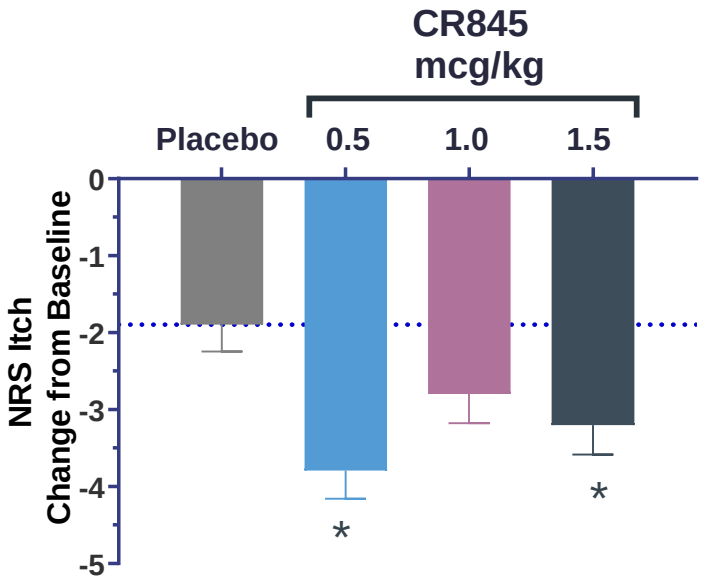
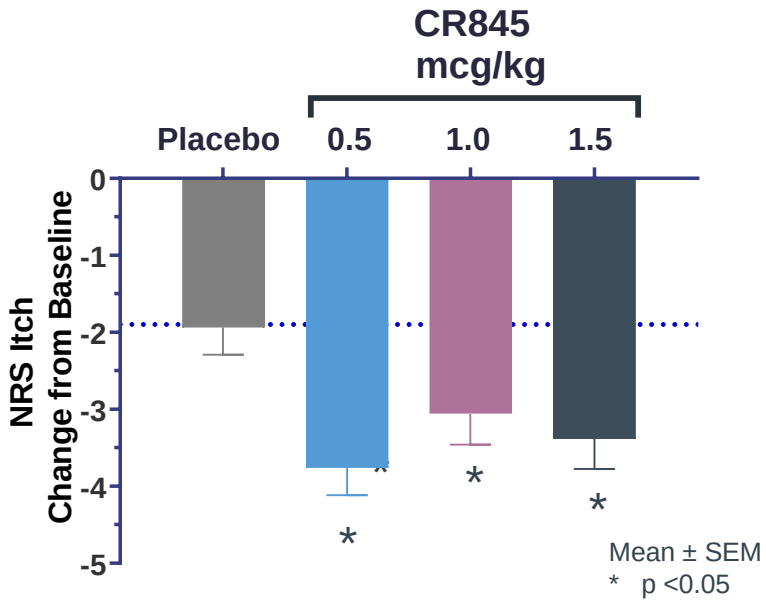
# CR845 Reduces Itch Intensity Across Doses:

## Change in Weekly Average of Daily Worst Itching NRS Score From Baseline to Week 8 of Treatment

### Full Analysis Population




### Per-Protocol Population




***Per-Protocol Population includes only patients who received at least 80% of the planned study drug doses.***



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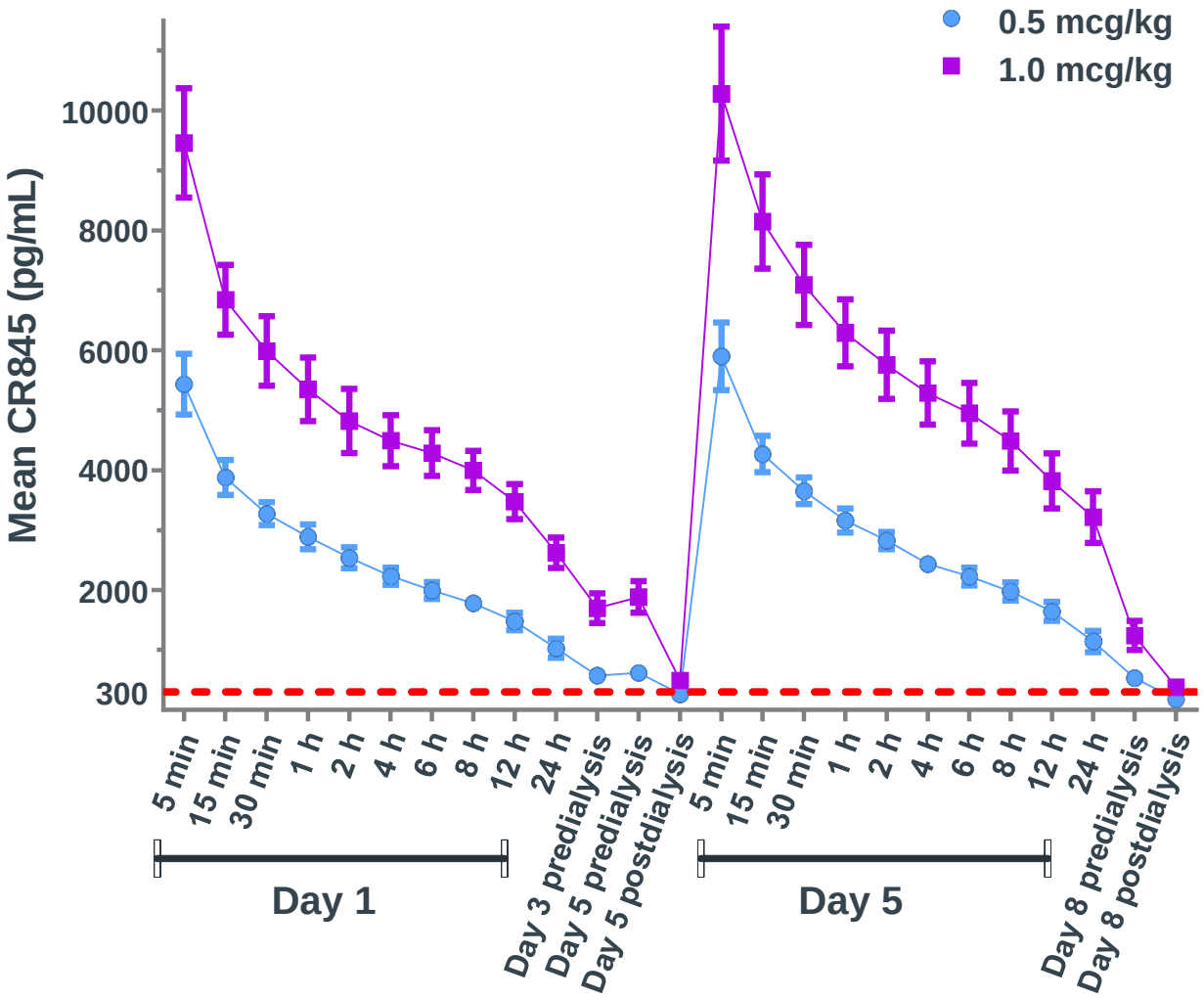
# All Doses of Post-Dialysis (3x/Week) CR845: Maintenance of Receptor-Saturating Plasma Concentrations

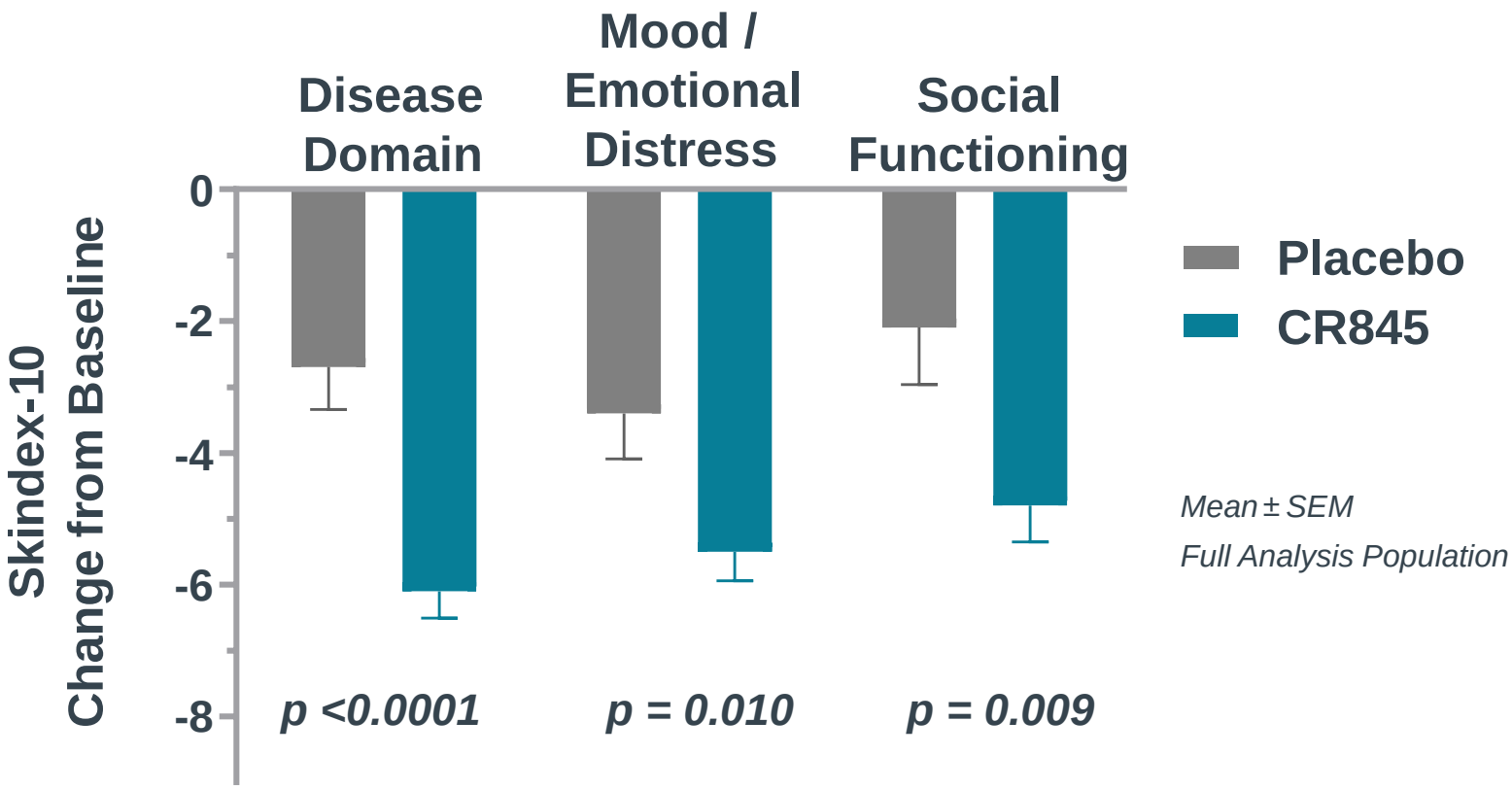



***Human Kappa Receptor***

*$K_d$ = 140 nM = 96 pg/mL*

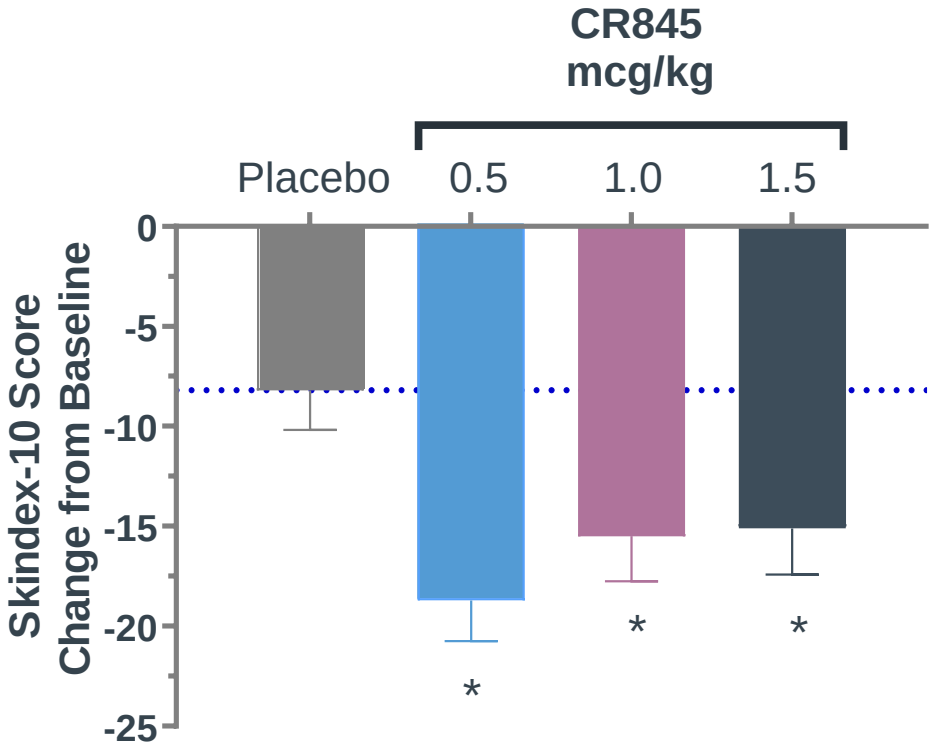
***320 pg/mL >75% occupancy***

# CR845 Improves Quality of Life (Skindex-10) Measures




**CR845-treated Patients Exhibit Statistically Significant Improvement Across All QoI Domains**

# CR845 Improves Quality of Life Measures Across Doses

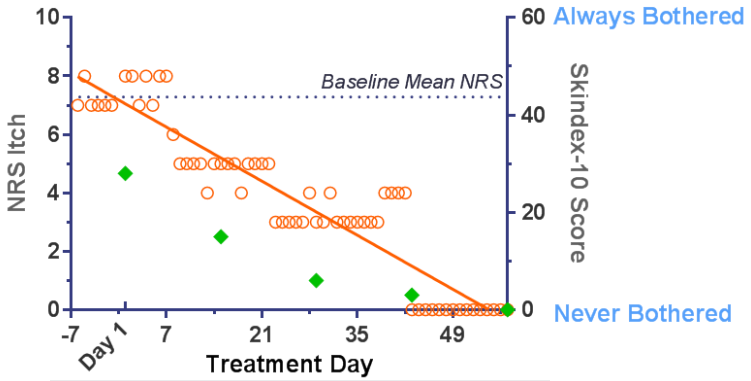



Mean ± SEM
* p <0.05

**CR845-treated Patients Exhibit Statistically Significant Improvement Across All Doses Tested**

# Examples of Individual NRS Profiles

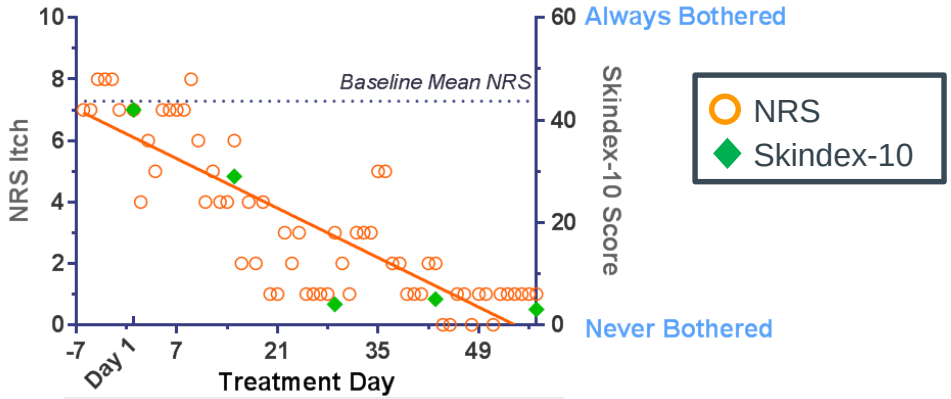
## CR845: 0.5 mcg/kg




| | Day 1 | Day 57 |
|---|---|---|
| PGIS | Severe | None |
| PGIC | --- | Very Much Improved |

Patient Global Impression Severity; Patient Global Impression Change

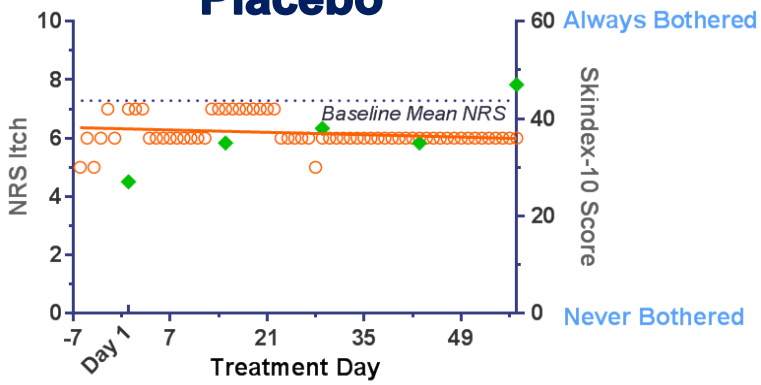
## CR845: 1.0 mcg/kg




| | Day 1 | Day 57 |
|---|---|---|
| PGIS | Severe | Mild |
| PGIC | --- | Much Improved |

Patient Global Impression Severity; Patient Global Impression Change

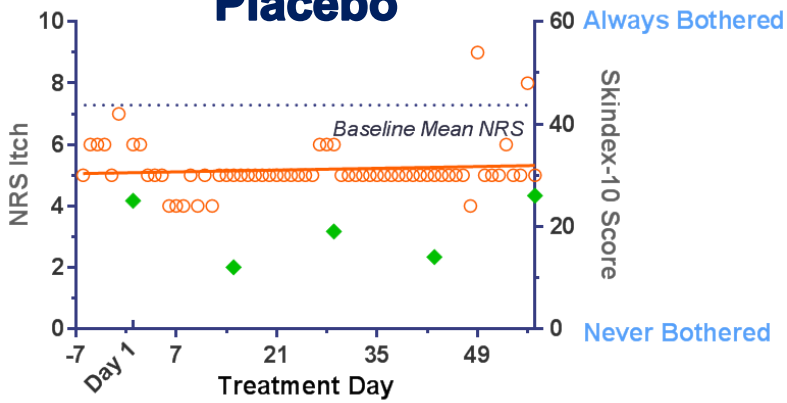
## Placebo




| | Day 1 | Day 57 |
|---|---|---|
| PGIS | Moderate | Moderate |
| PGIC | --- | No Change |

Patient Global Impression Severity; Patient Global Impression Change

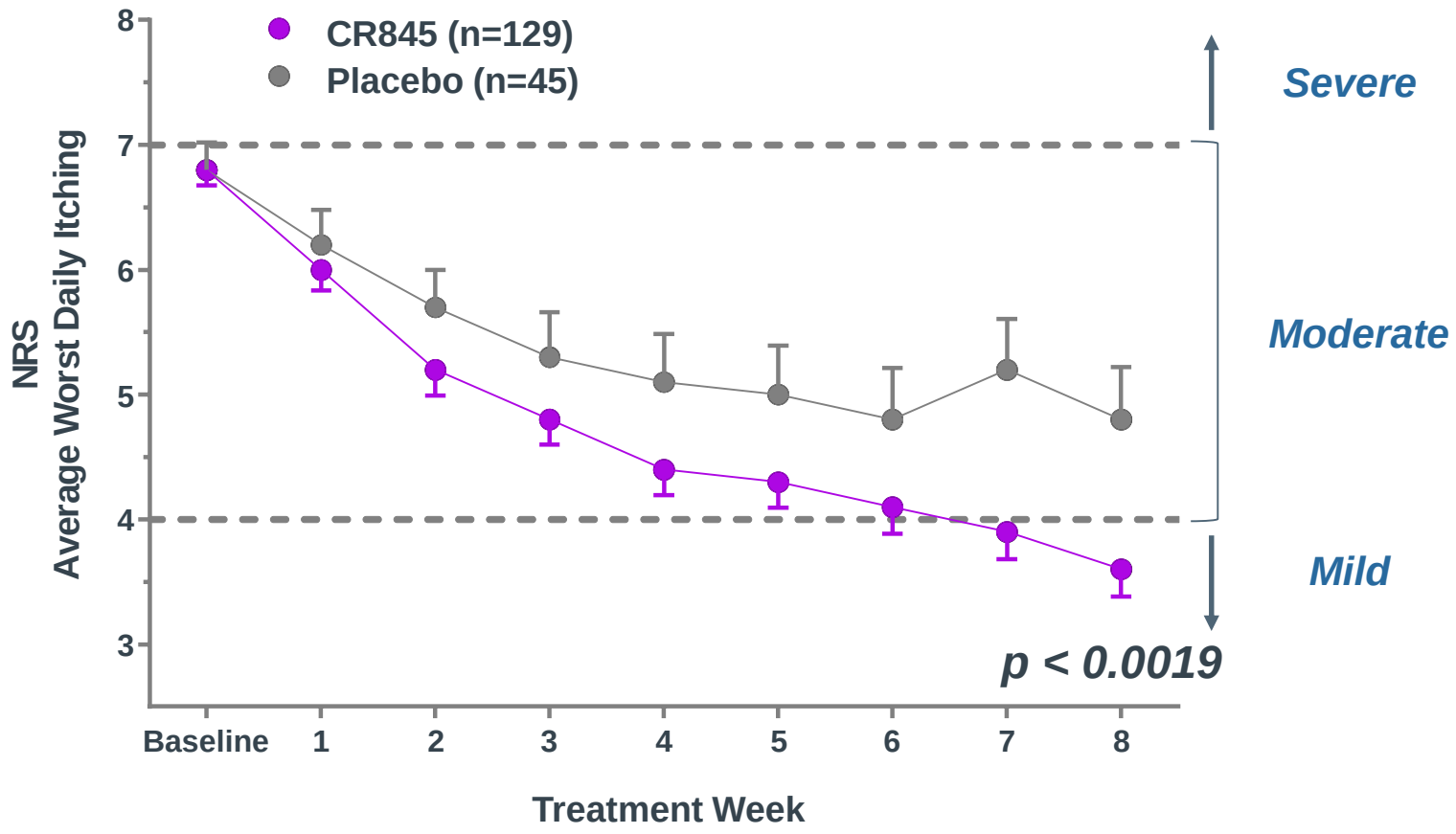
## Placebo




| | Day 1 | Day 57 |
|---|---|---|
| PGIS | Moderate | Severe |
| PGIC | --- | No Change |

Patient Global Impression Severity; Patient Global Impression Change

# Antipruritic Efficacy of CR845 Increases Over Time During 8-Week Treatment Period




*Severity Bands based on Reich et al, Acta Derm Venereol 2012*

# Safety Summary:
# Treatment-Related Adverse Events (≥ 5% Any Treatment Group)

## No safety findings by IDMC

| System Organ Class<br>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 (%) |
|---|---|---|---|---|
| Nervous system disorders | | | | |
| Dizziness | 1 (2.2) | 4 (9.1) | 2 (4.9) | 2 (4.5) |
| Headache | 0 (0.0) | 0 (0.0) | 3 (7.3) | 0 (0.0) |
| Paraesthesia | 0 (0.0) | 1 (2.3) | 1 (2.4) | 3 (6.8) |
| Somnolence | 1 (2.2) | 1 (2.3) | 2 (4.9) | 4 (9.1) |



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# Conclusions

## Part A of Phase 2/3 CR845-CLIN2101 Study is Successful

- Statistically significant efficacy in primary and secondary endpoints
- Efficacy increases with duration of exposure over 8-week period
- Exhibits very favorable safety profile suitable for chronic dosing

## Next Steps for CKD Pruritus Program

- Plan end-of-Phase 2 meeting
- Initiate pivotal Phase 3 program in 2017
- Initiate Open Label Safety Study in hemodialysis patients (2Q,2017)
- Report results from oral PK/PD study (2Q,2017)

# Other Upcoming Data Milestones for CR845

## CLIN2101:
## I.V. CR845 – Uremic Pruritus

- Target 90 patients – Pharmacokinetic/Safety
- ***Data Readout: Q2, 2017***

## CLIN3001:
## I.V. CR845 – Acute Post-Op Pain

- Target 450 patients
- 23 Sites Active
- ***Interim Readout: Q2, 2017***

## CLIN2002:
## Oral CR845 – OA Chronic Pain

- Target 330 patients – expanded to 480
- 31 Sites Active
- ***Topline Readout: Q2, 2017***



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