# Targeting Peripheral Kappa Opioid Receptors For Pruritus and Pain

February, 2018

CARA THERAPEUTICS

# Forward Looking Statements

This presentation contains certain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. In some cases, you can identify forward-looking statements by the words “anticipate,” “believe,” “continue,” “estimate,” “expect,” “objective,” “ongoing,” “plan,” “propose,” “potential,” or “up-coming” and/or the negative of these terms, or other comparable terminology intended to identify statements about the future. Examples of these forward-looking statements in this presentation include, among other things, the expected timing of our other planned clinical trials; the potential results of ongoing and planned clinical trials; future regulatory and development milestones for the Company's product candidates; the size of the potential markets that are potentially addressable for the Company’s product candidates, including the postoperative and chronic pain markets, and the pruritus market; and the Company's expected cash reach.

These statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. Although we believe that we have a reasonable basis for each forward-looking statement contained in this presentation, we caution you that these statements are based on a combination of facts and factors currently known by us and our expectations of the future, about which we cannot be certain. Factors that may cause actual results to differ materially from any future results expressed or implied by any forward-looking statements include the risks described in the “Risk Factors” section of the Company’s Annual Report on Form 10-K for the year ended December 31, 2016, as well as those set forth from time to time in the Company’s other SEC filings, available at http://www.sec.gov. Any forward-looking statements speak only as of the date of this presentation.

The Company undertakes no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise except as required by law.

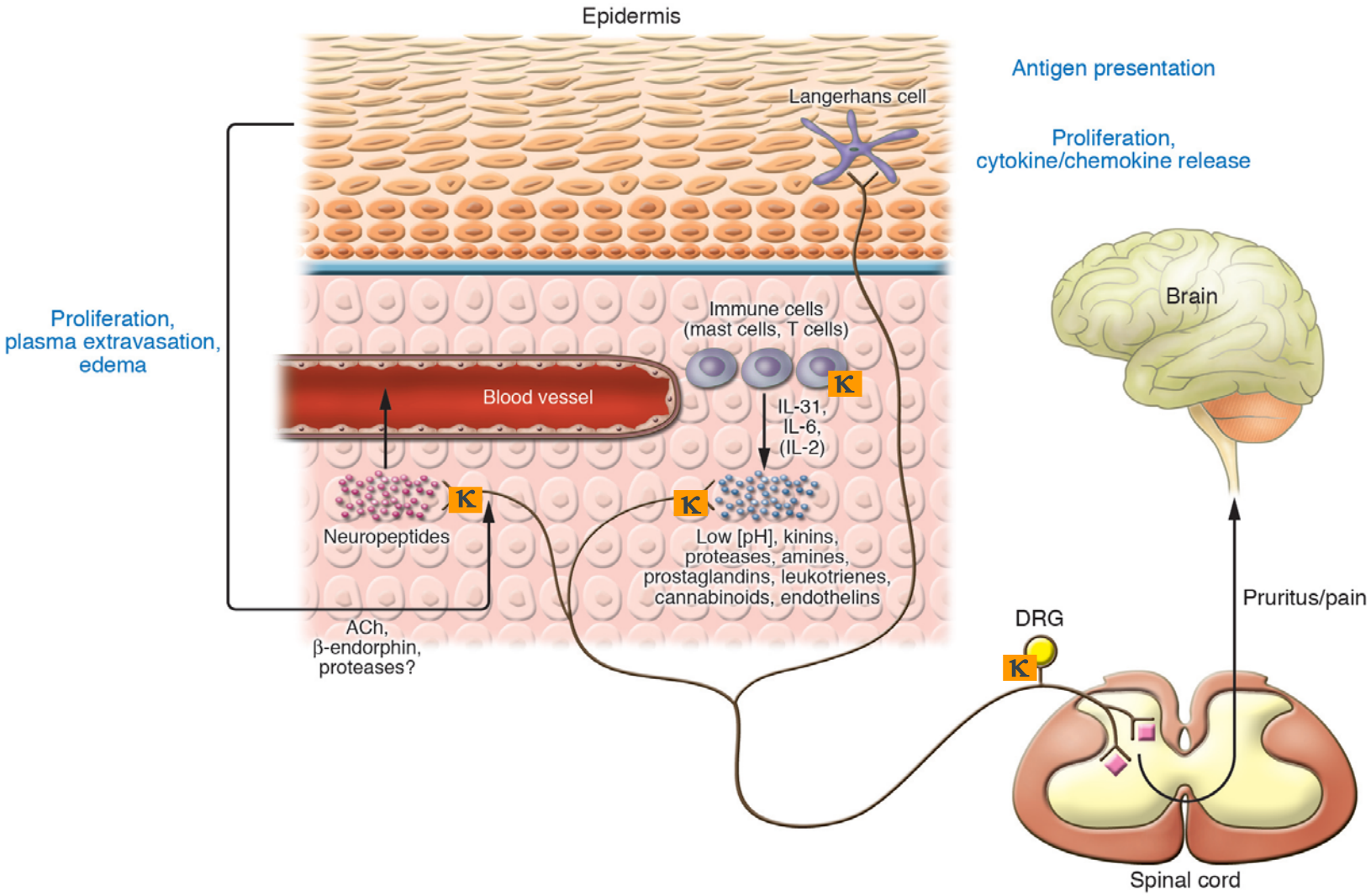
# Developing First-in-Class k-Opioid Receptor Agonists

- **Novel, first-in-class "kappa" receptor agonist: CR845**
  - Lacks traditional opioid side effects ( "mu" agonist effects)
  - Peripherally acting- unique pharmacology; limits CNS liability
  - MOA: anti-nociceptive(1)/anti-inflammatory & anti-pruritic
    - IV and Oral formulations for targeted indications
  - COM IP protection through at least 2027
  - Breakthrough Designation for IV CR845 for Chronic Kidney Disease (Hemodialysis)- associated Pruritus, CKD-HD-aP
- **Intend to commercialize in U.S. in multiple indications**
- **Established regional partnerships**
  - Maruishi Pharmaceuticals (Japan)
  - Chong Kun Dang Pharma (South Korea)



1. Blocking the detection of pain or injurious stimulus by sensory neurons

# Pruritus And Pain – Common Pathway




Source: Paus et al.,J Clin Inv, 2006.

# Development Pipeline Q1, 2018

| | | Stage of Development | | | | |
|---|---|---|---|---|---|---|
| **Program** | **Indication** | **Preclinical** | **Phase 1** | **Phase 2** | **Phase 3** | **Approved** |
| KORSUVA™ Injection | Pruritus CKD-HD | | | | | |
| Oral KORSUVA | Pruritus CKD-HD | | | | | |
| Oral KORSUVA | Pruritus CKD(III-IV) | | | | | |
| Oral KORSUVA | Pruritus CLD (chronic liver) | | *Ph 1 trial to initiate in early 2018* | | | |
| IV CR845 | Post-op Pain | | | | | |
| Oral CR845 | Chronic Pain (OA) | | | | *Ph 2b completed* | |

**CKD-HD**: Chronic Kidney Disease- Hemodialysis; **OA**: Osteoarthritis; *Breakthrough Designation for IV CR385 for Pruritus CKD-HD

The FDA has conditionally accepted KORSUVA™ as the trade name for CR845/ difelikefalin for pruritic indications. CR845/ difelikefalin is an investigational drug product, and its safety and efficacy have not been fully evaluated by any regulatory authority.



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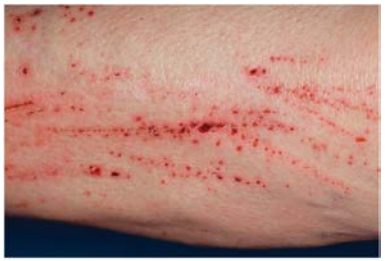
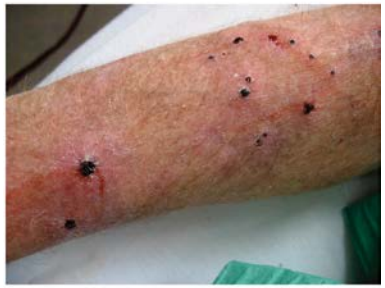
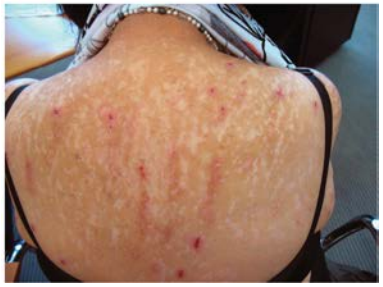
# CKD-Associated Pruritus (CKD-aP)







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

- Serious itching condition directly related to kidney disease
  - ~60% of hemodialysis (HD) patients
- Itching severity associated with worsening Quality of Life (QoL) (social, emotional and physical)
  - Sleep disturbance, depressed mood, increased mortality risk
- Currently, no FDA approved medications and no standard of care

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



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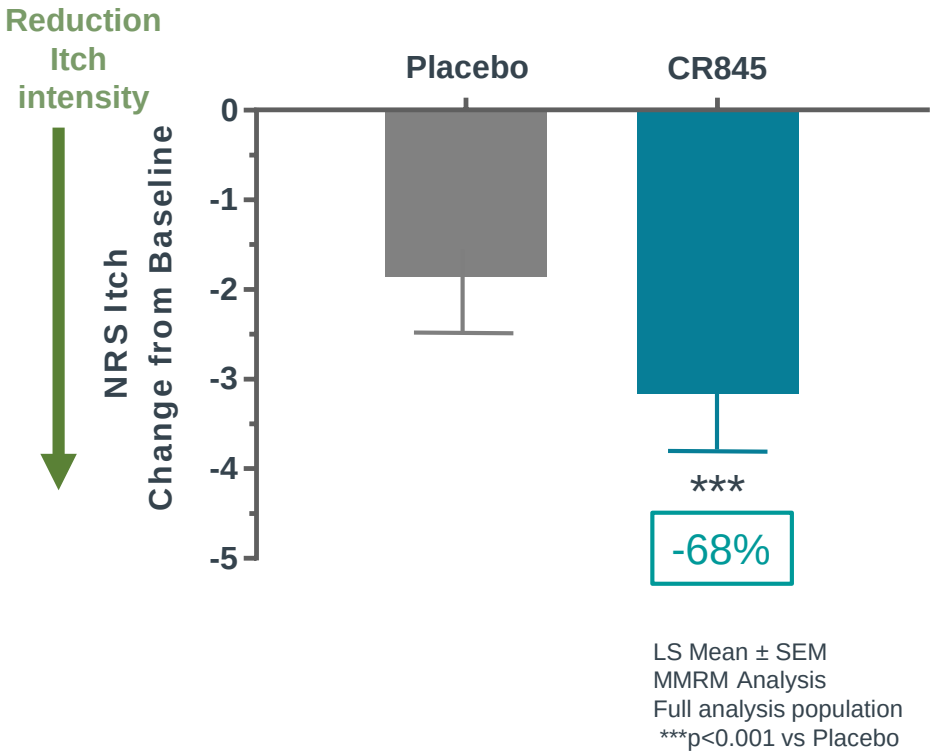
# Clinically Meaningful Reduction in Itch Intensity Following an 8-Week Treatment Period with CR845

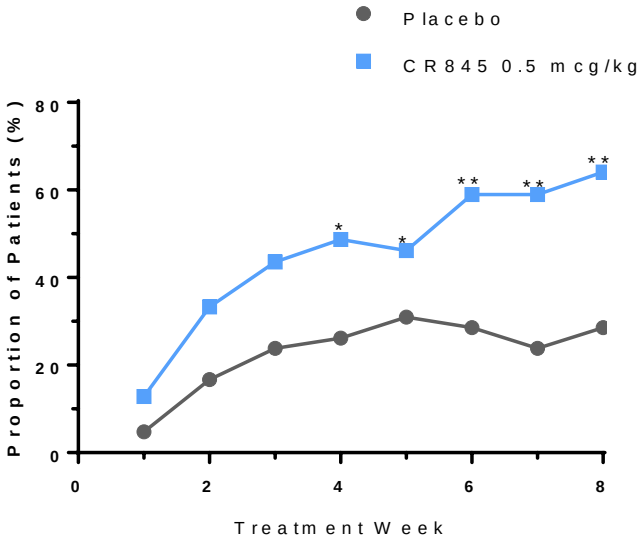
## Mean Change Worst Itch Intensity




LS Mean ± SEM
MMRM Analysis
Full analysis population
***p<0.001 vs Placebo

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

## Responder Analysis: ≥3-points

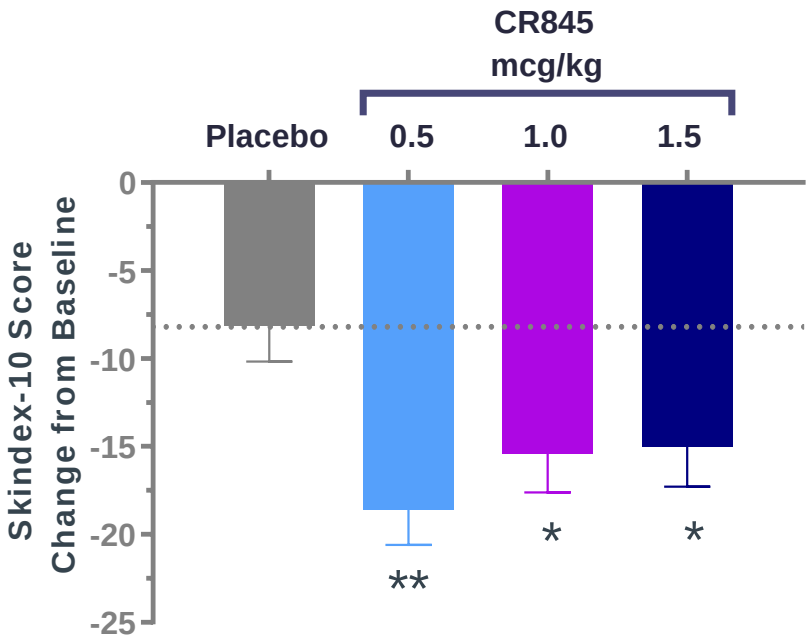



| NRS Improvement | Placebo | CR845 0.5 mcg/kg |
|---|---|---|
| ≥3-points | 29% | 64% (**) |
| ≥4-points | 24% | 51% (*) |

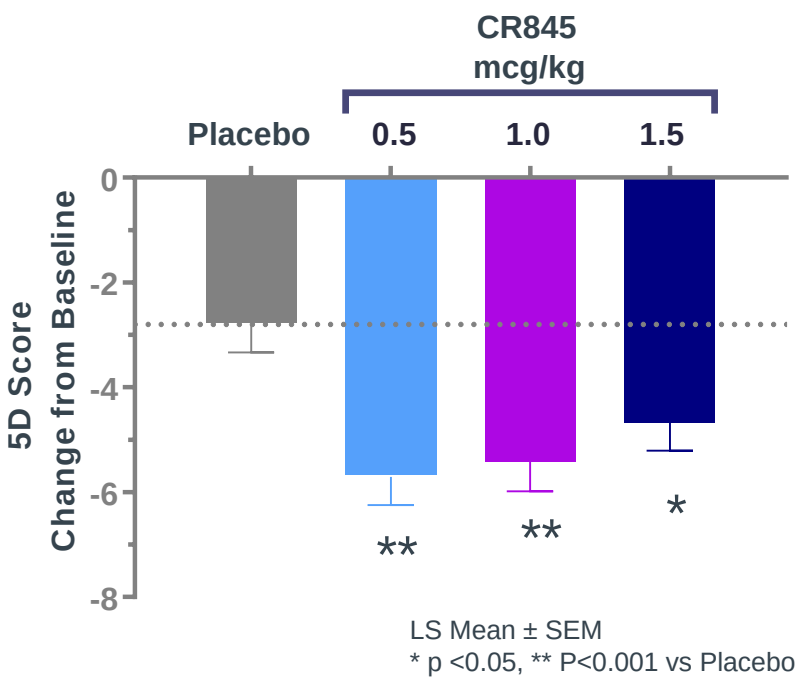
*p<0.05, **p<0.01 vs Placebo, Cochran-Mantel-Haenszel test

# Significant Improvement in Quality-of-Life Measures Across All Dose Groups

## Skindex-10




## 5-D Itch




LS Mean ± SEM
* p <0.05, ** P<0.001 vs Placebo

Pearson's Correlations of the Worst Itching Intensity NRS and Skindex-10 with 5-D Itch: r=0.71 and r=0.74, respectively; p<0.0001

**The 5-D Itch scale covers 5 domains: duration of itch/day, degree, direction (improvement/worse), disability (sleep, social, housework/errands, work/school), distribution (parts of the body)**



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# KORSUVA (CR845/ difelikefalin) in CKD-HD: Ph3 KALM-1 Trial

- Randomized, Double-Blind, Placebo-Controlled Study in Hemodialysis Patients with Moderate-to Severe Pruritus
- Dose: 0.5 mcg/kg
- 12-week treatment period (with a 52-week open label extension phase):
  - Dosing after each dialysis session (3 times per week)
- Up to 80 U.S. Sites:
  - 350 patients (175/group); may be increased up to 500 patients (250/ group)
- Primary endpoint:
  - Change (≥3 point improvement) from Baseline in Worst Itching Intensity (NRS score) - responder analysis
- Secondary:
  - Change in itch related QoL by 5-D Itch Scale (multidimensional)
  - Change in QoL (Skindex-10)
  - Safety and tolerability
  - Change (≥4 point improvement) from Baseline in Worst Itching Intensity (NRS score)- responder analysis



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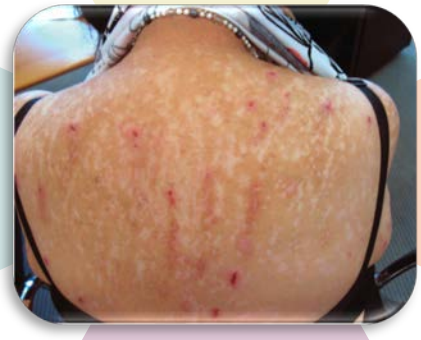
# Pruritus: Large Opportunity Limited Existing Therapies

## (CKD-aP)

- Chronic kidney disease-associated pruritus (CDK-aP), is chronic itching that occurs in patients with renal disease
- **Affects ~40-50% of patients with renal failure, associated with comorbidity; ~4.5M treated for pruritus***

## Pruritus



## Chronic Liver Disease-aP

- Sensation of itch due to any liver disease, **20% to 30% of patients with cholestatic liver disease experience pruritus - ~2M US patients***

## Atopic dermatitis (AD)

- **Pruritus is a defining symptom of AD**
- 20mm AD patients in the US - **~50% of the patients seek treatment for pruritus***
- Current treatments consist of high-dose antihistamines and antidepressants

## Psoriasis

- Common skin condition marked by red, itchy, scaly patches
- 8mm patients in the US - **~50% of the patients seek treatment for pruritus***

*: IMS Pruritus Market Landscape Analysis September 2014



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# Projected Milestones

## Upcoming Cara Events

| | |
|---|---|
| **Pruritus / KORSUVA™ Injection** | |
| Mid-2018 | Phase 3 (Int'l) CKD-aP Dialysis Trial Initiation |
| **Pruritus / Oral KORSUVA** | |
| 1Q18 | Phase 1 Chronic Liver Disease (CLD) Trial Initiation |
| 1Q18 | Phase 2 CKD-aP Non-Dialysis Trial Initiation |
| 2H18 | Phase 2 CLD-aP Trial Initiation |
| **Pain / IV CR845** | |
| 1Q18 | Phase 3 Post-surgical Pain Enrollment Completion |
| 1H18 | Phase 3 Post-surgical Pain Data Readout |

# Financial Highlights

## As of September 30th, 2017

| | |
|---|---|
| Cash and Marketable Securities | $103M |
| Net loss – Q3, 2017 | ($12.4M) |
| Shares outstanding | 32.6M |
| • Stock options | ~3.5M |

➢ Follow-On Offering 3/31/17 - $86M



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