# Targeting Peripheral Kappa Opioid Receptors For Pruritus and Pain

June, 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,” “projected”, 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, statements concerning plans, strategies and expectations for the future, including statements regarding the expected timing of our 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; the potential commercialization of Korsuva in the licensed territories; the potential benefits of license agreements entered by the Company, including the potential milestone and royalty payments payable to Cara; 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, 2017, 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.

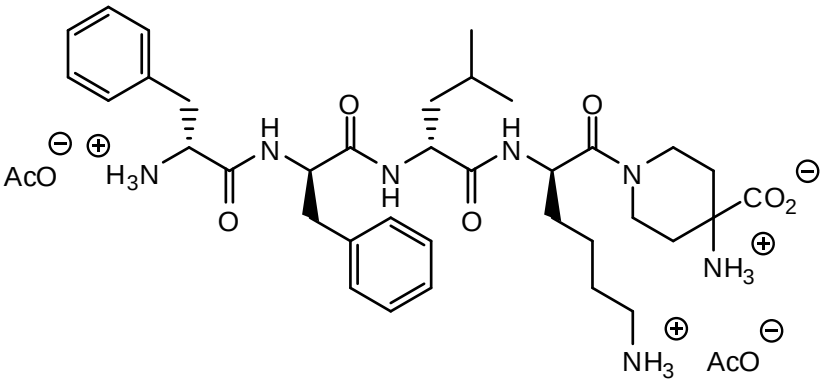
# Developing First-in-Class Kappa Receptor Agonists

- **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**
  - Vifor/Fresenius - VFMCRP – (EU and select territories)
  - Maruishi Pharmaceuticals (Japan)
  - Chong Kun Dang Pharma (South Korea)



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

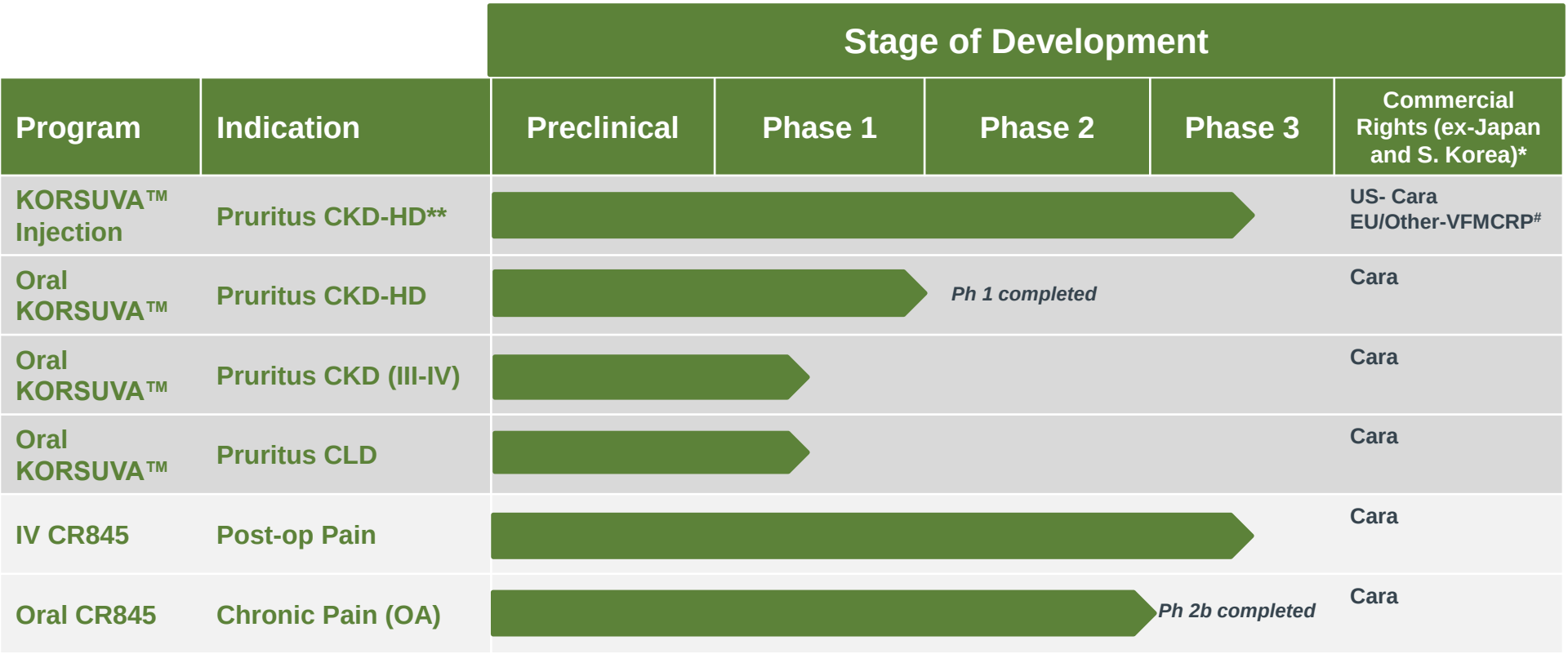
# CR845: A Peripherally-Acting Kappa Receptor Agonist




- Hydrophilic, tetra-peptidic scaffold
- Peripherally restricted
- High therapeutic index
- ≥30,000-fold selectivity for κ-receptors compared with μ- or δ- receptor

| | Human Opioid Receptor Binding (nM) | | |
|---|---|---|---|
| **Drug** | **Kappa** | **Mu** | **Delta** |
| **CR845** | **0.16** | >10,000 | >10,000 |
| Morphine | 50 | 1 | 140 |
| Fentanyl | 85 | 1 | 153 |

# Development Pipeline Q2, 2018




***Commercialization rights to CR845 in all indications - Japan: Maruishi Pharma ; South Korea: CKD Pharma**
**# VFMCRP and Cara have rights to promote in U.S. Fresenius Medical Care dialysis clinics under a profit share agreement**

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.

**Breakthrough Designation for IV CR385 for Pruritus CKD-HD

**CKD-HD**: Chronic Kidney Disease- Hemodialysis; **OA**: Osteoarthritis; CLD: Chronic Liver Disease



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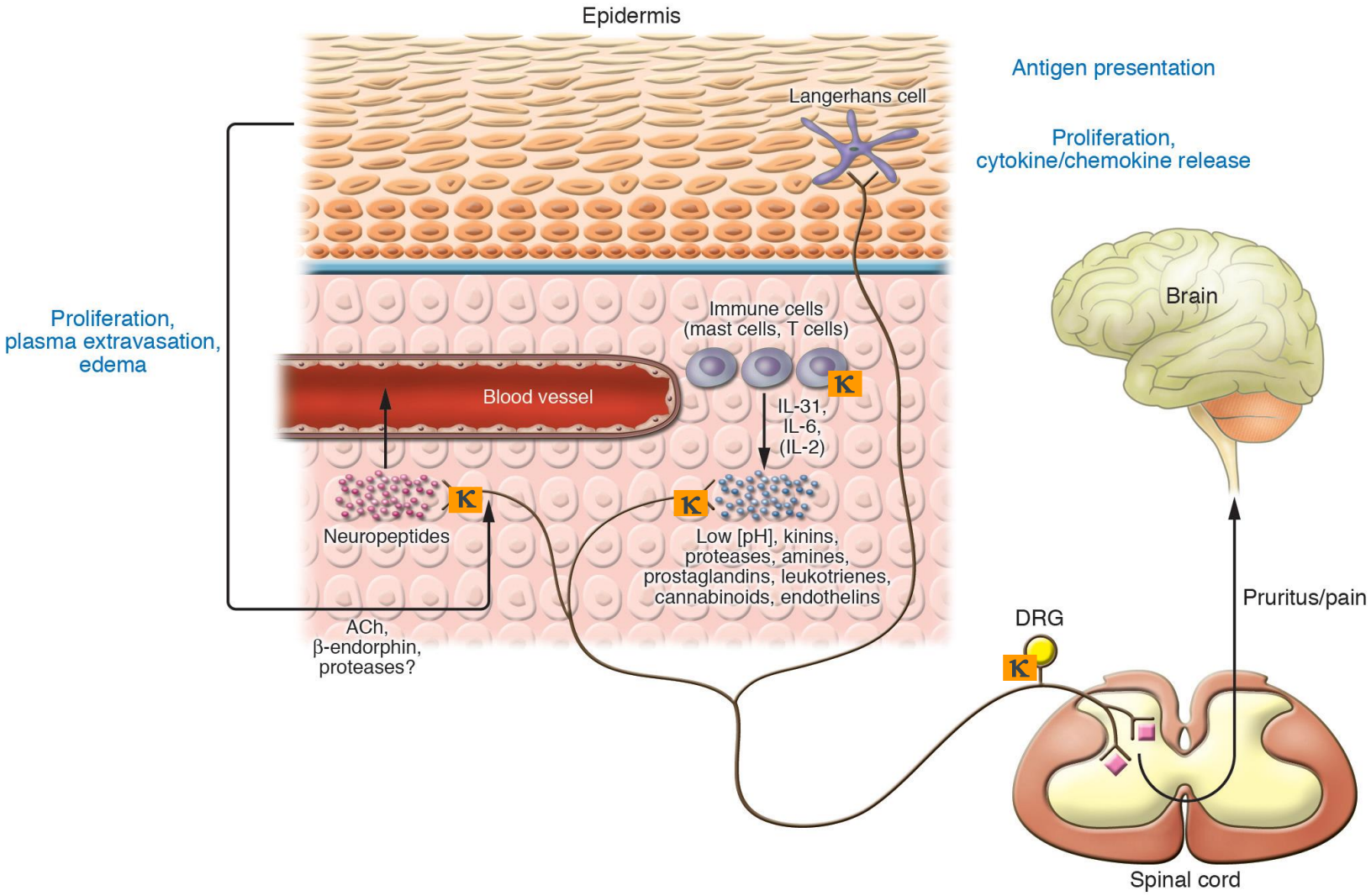
# Pruritus And Pain – Common Pathway




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

# KORSUVA™ Injection for Dialysis Patients

| | | Stage of Development | | | | |
|---|---|---|---|---|---|---|
| Program | Indication | Preclinical | Phase 1 | Phase 2 | Phase 3 | Approved |
| IV CR845 | Pruritus CKD-HD | | | | | |

- Indication: CKD-aP in dialysis patients
- Breakthrough Therapy Designation
- Commercialization partnership with VFMCRP in EU/ other territories
- Next milestone: expected data in 2019 from US Ph 3 trial



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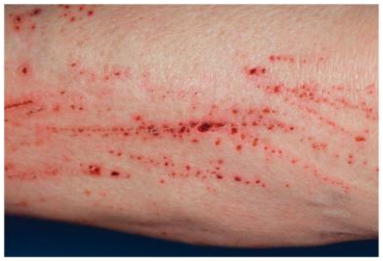
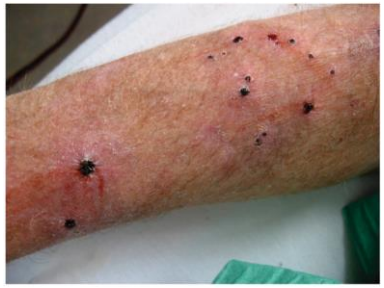
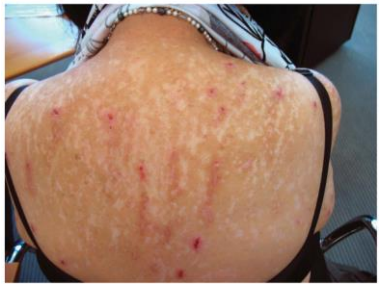
# CKD-Associated Pruritus (CKD-aP)







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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# Incidence of CKD-Associated Pruritus in Dialysis Patients: US

- Dialysis/ End Stage Renal Disease (ESRD)
  - 456K patients on dialysis in US[1]
  - 60-70% of patients with pruritus[2,3]
- Significant patient population and no FDA approved therapies, especially for moderate to severe pruritus- large unmet medical need
- KORSUVA granted Breakthrough Therapy Designation


1. ESRD Patients in 2013 - A Global Perspective. Fresenius Medical Care. 2014.
2. Pisoni RL, Wikstrom B, Elder SJ, et al. Pruritus in haemodialysis patients: international results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant.* 2006;21:3495-3505.
3. Ramakrishnan et al. Clinical characteristics and outcomes of end-stage renal disease patients with self-reported pruritus symptoms. *International Journal of Nephrology and Renovascular Disease.* 2014:7 1–12




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# I.V. CR845 in CKD-HD: Compelling Ph2 Data

- Randomized, Double-Blind, Placebo-Controlled Study in Hemodialysis Patients with Moderate-to Severe Pruritus
- Doses: 0.5, 1.0 and 1.5 mcg/kg
- 8-week treatment period:
  - Dosing after each dialysis session (3 times per week)
- Multi-center:
  - 174 patients randomized (PBO: 45 vs. CR845: 129)
- Primary endpoint:
  - Change from Baseline in Worst Itching Intensity (NRS score)
- Secondary/ exploratory endpoints:
  - Change in QoL (Skindex-10)
  - 5-D Itch Scale (multidimensional)
  - Sleep disturbance subscale (MOS)
  - Patient Global Impression of Change
  - Patient Global impression of Worst itch Severity



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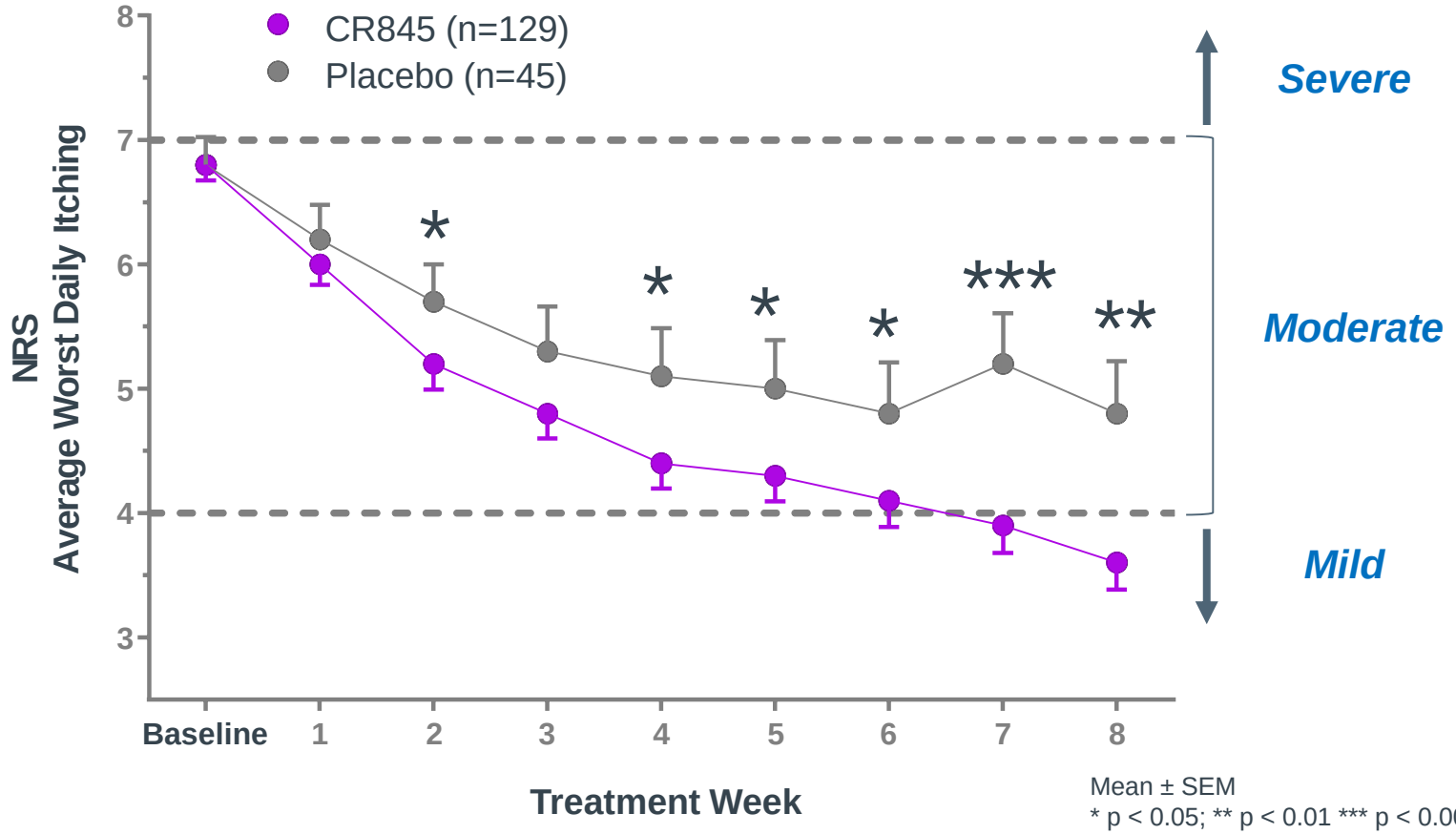
# Significant Reductions in Mean Worst Itching Score (NRS) Over Time



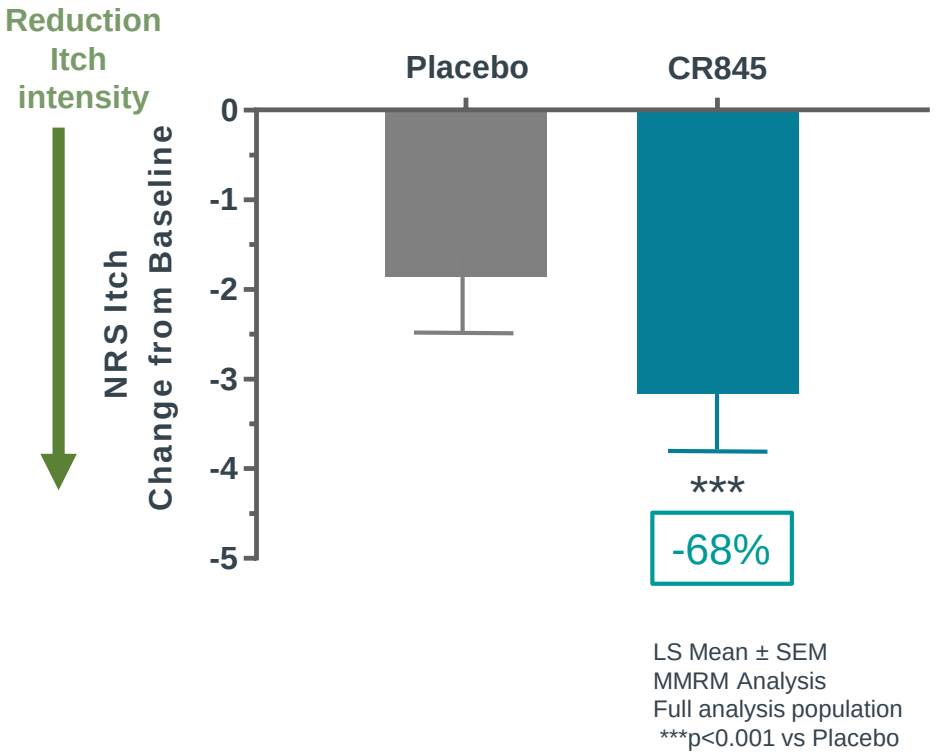

Mean ± SEM
* p < 0.05; ** p < 0.01 *** p < 0.001 vs Placebo

- Reduction of Worst itch intensity begins on Week 1 and continues to improve through Week 8.
  - Patients on placebo show initial improvement that plateaus

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

# Significant & Clinically Meaningful Reduction in Itch Intensity Following 8-Week Treatment with CR845

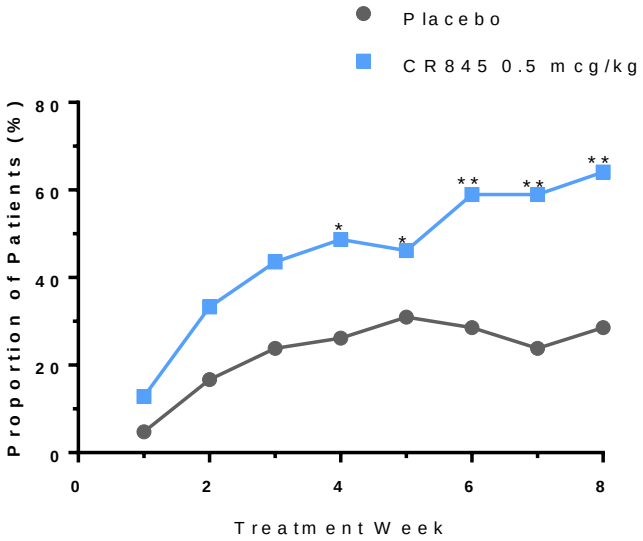
## Mean Change Worst Itch Intensity




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

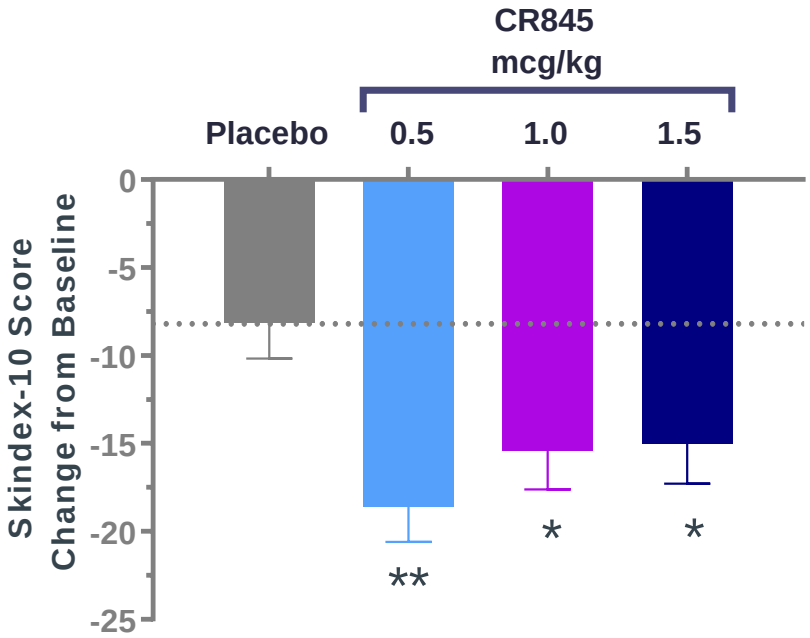



| NRS Improvement | Placebo | CR845 0.5 mcg/kg |
|---|---|---|
| ≥3-points | 29% | 64% (**) |
| ≥4-points | 24% | 51% (*) |

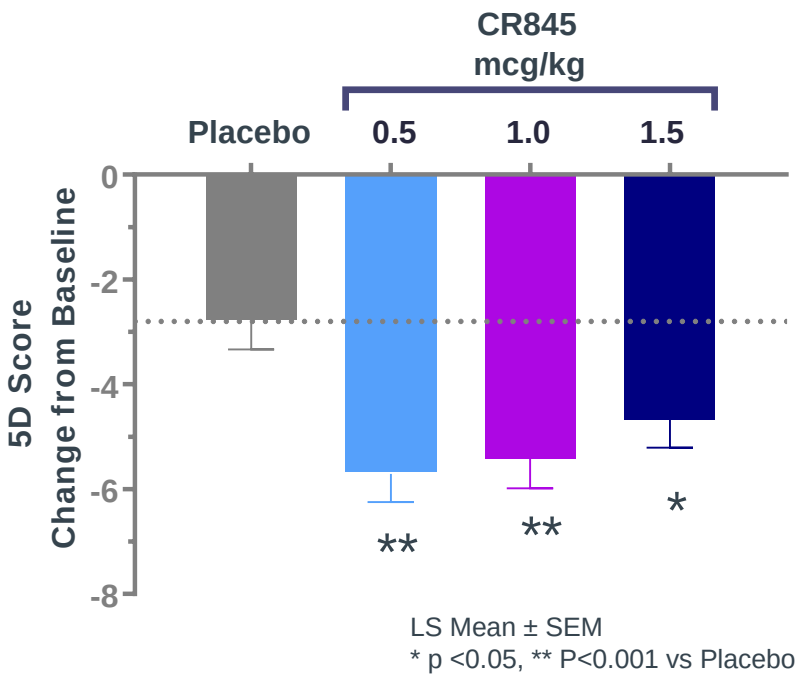
*p<0.05, **p<0.01 vs Placebo, Cochran-Mantel-Haenszel test

# 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)
- ~60 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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# Vifor Fresenius Medical Care Renal Pharma (VFMCRP)

## VFMCRP: JV - Vifor Pharma Group & Fresenius Medical Care (FMC)

- **Vifor Pharma:** Leader in iron deficiency, nephrology & cardio-renal therapies
- **FMC:** Global leading provider of services for dialysis patients

VIFOR PHARMA

STRONG IRON AND PHARMA EXPERTISE

ferinject® ferric carboxymaltose

Venofer® IRON SUCROSE

MIRCERA® methoxy polyethylene glycol-epoetin beta

Rayaldee® calcifediol ER capsules 30 mcg

Veltassa®

Biosimilar epoetin alfa[1)]

Vadadustat[1)]

Avacopan[1)]

CCX140[1)]

VELPHORO®

FRESENIUS MEDICAL CARE

GLOBAL LEADER IN DIALYSIS

55% Stake

VIFOR FRESENIUS MEDICAL CARE RENAL PHARMA

45% Stake

[1)] Pre-commercial products



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# VFMCRP Partnership Highlights

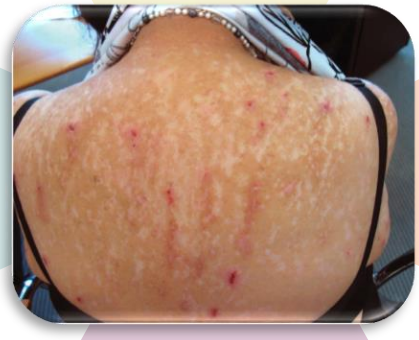
- **License:** IV CR845/ difelikefalin for the prevention, inhibition or treatment of CKD-aP in hemodialysis/ peritoneal dialysis patients
- **Upfront:** $70 million ($50 million cash + $20 million in Cara equity at premium)
- **Regulatory and commercial milestones:** up to $470 million
- **Royalty :** Tiered double digit royalty based on net sales of I.V. CR845/ difelikefalin in licensed territory
- **Licensed Territory:** Worldwide, excluding U.S., Japan & South Korea
- **VFMCRP & Cara promotion and profit share arrangement** in U.S. Fresenius Medical Care clinics
  - Cara to solely promote in all non-Fresenius U.S. dialysis clinics and retain all profits

# 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;**

## Pruritus



## Chronic Liver Disease-aP

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

## 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

# Oral KORSUVA for CKD-associated Pruritus

| | | Stage of Development | | | | |
|---|---|---|---|---|---|---|
| Program | Indication | Preclinical | Phase 1 | Phase 2 | Phase 3 | Approved |
| Oral CR845 | Pruritus CKD (III-V) | | | | | |

- Indication: CKD-aP in Stage III-V CKD patients
- Next milestone: planned initiation of Ph2 trial in June, 2018



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# Oral KORSUVA for CLD-associated Pruritus

| | | Stage of Development | | | | |
|---|---|---|---|---|---|---|
| Program | Indication | Preclinical | Phase 1 | Phase 2 | Phase 3 | Approved |
| Oral CR845 | Pruritus CLD | | | | | |

- Indication: Chronic Liver Disease- Associated Pruritus
- Next milestone: planned initiation of Ph2 trial in 2H, 2018



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# I.V. CR845 for Post-Operative Pain

| | | Stage of Development | | | | |
|---|---|---|---|---|---|---|
| **Program** | **Indication** | **Preclinical** | **Phase 1** | **Phase 2** | **Phase 3** | **Approved** |
| **IV CR845** | **Post-op Pain** | | | | | |

- **Indication: I.V. CR845 for post-operative pain**
- **Next milestone: data in June, 2018**



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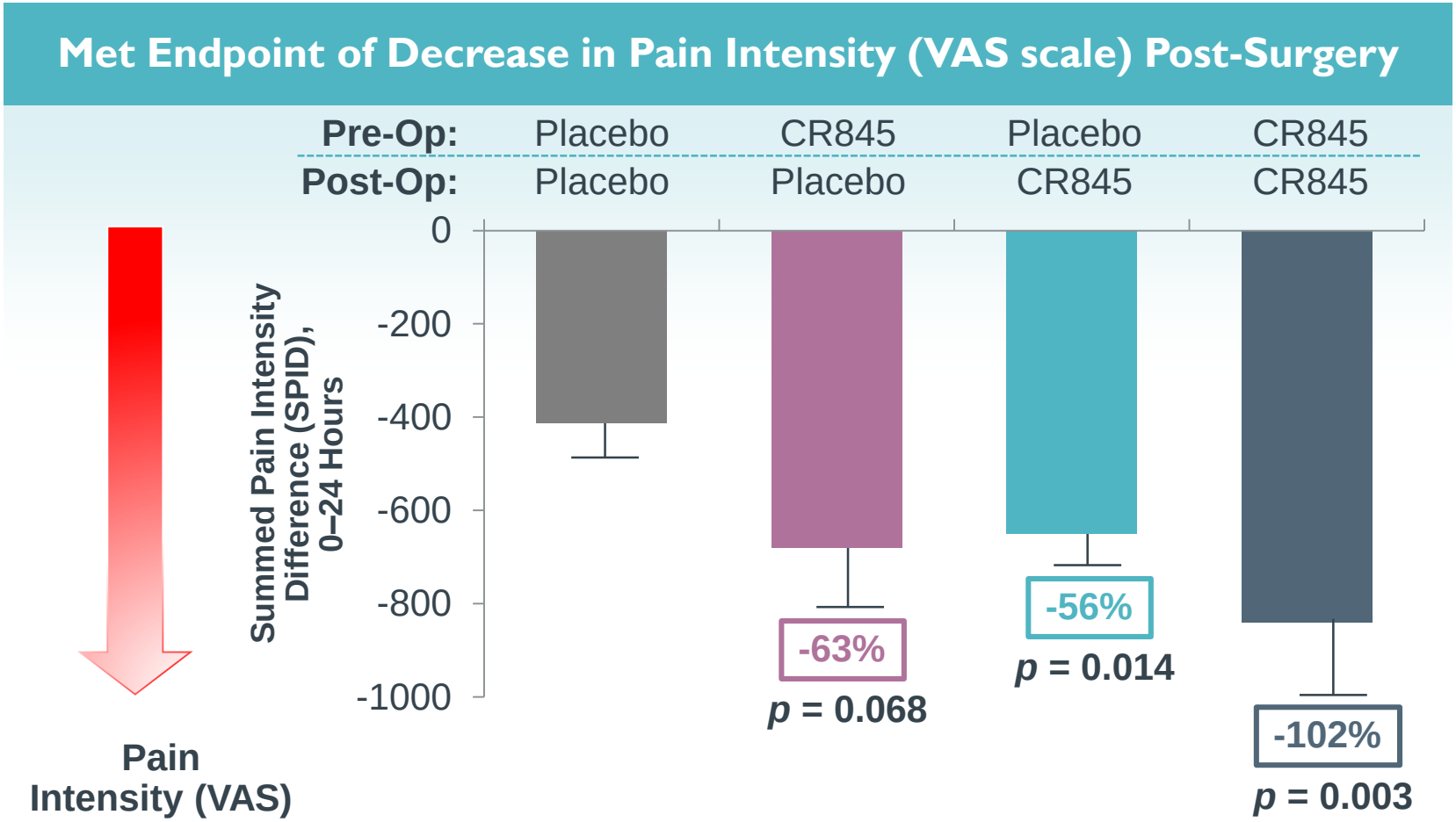
# Post-Op Pain: Significant Unmet Need

- Need for multimodal analgesia (ASA and ERAS)
  - Different MOAs to maximize analgesia
  - Anti-inflammatory benefits vs. mu opioids
- Need to reduce mu opioid usage and side effects
  - Respiratory Depression
  - Nausea / Vomiting
  - Abuse Liability
- Goal to improve patient outcomes, decrease length of hospital stay and reduce overall health care costs

# I.V. CR845 Ph 2 Data: Significantly Reduced Post-Op Pain (Hysterectomy)

## CLIN2002 Trial

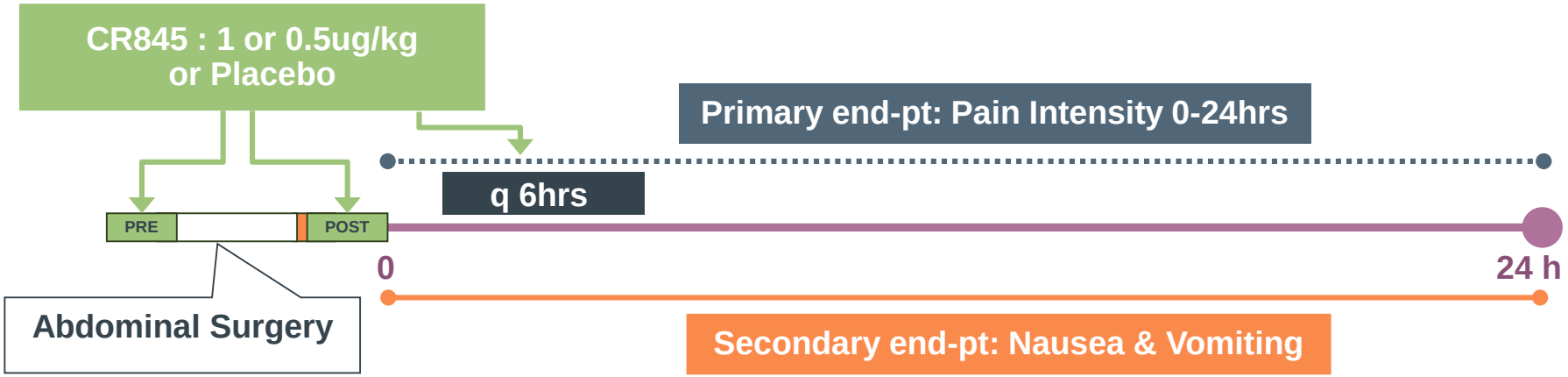



**CR845: Single I.V. dose of 0.04 mg/kg pre or post-op**.

$SPID_{0-24}$ (mITT), Mean ± SEM. N = 71, 19, 71 and 20, respectively.

# I.V. CR845: Ph 3 in Post-Op Pain Readout June 2018

## Design:




- Multi-center: 25 U.S. hospital sites, max. 450 patients
- Randomized, double-blind, placebo controlled, adaptive design
- Endpoints:
  - Pain intensity 0-24hrs – Numeric Rating Scale (primary)
  - Nausea & Vomiting
  - Rescue medication used (IV morphine)
  - Patient global assessment of medication
  - Safety



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# Projected Clinical Milestones

## Upcoming Cara Events

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



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# Financial Highlights

## As of March 31st, 2018

| | |
|---|---|
| Cash and Marketable Securities | $74.5M |
| Net loss – Q1 2018 | ($16.8M) |
| Shares outstanding | 32.7M |
| • Stock options | ~3.9M |

- *May, 2018*
  - *Additional Cash of $70M (VFMCRP agreement)*
  - *Additional shares (Vifor): 1,174,827*



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