Targeting Peripheral Kappa Opioid Receptors For Pruritus and Pain

July 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.

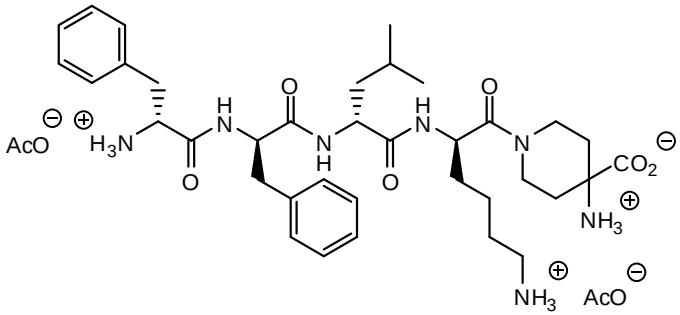
Developing First-in-Class Kappa Receptor Agonists

- Novel, first-in-class “kappa” receptor agonist: CR845
  - Designed to function without traditional opioid side effects (“mu” agonist effects)
  - Peripherally acting – unique pharmacology; designed to limit CNS liability
  - MOA: designed to be 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 US 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

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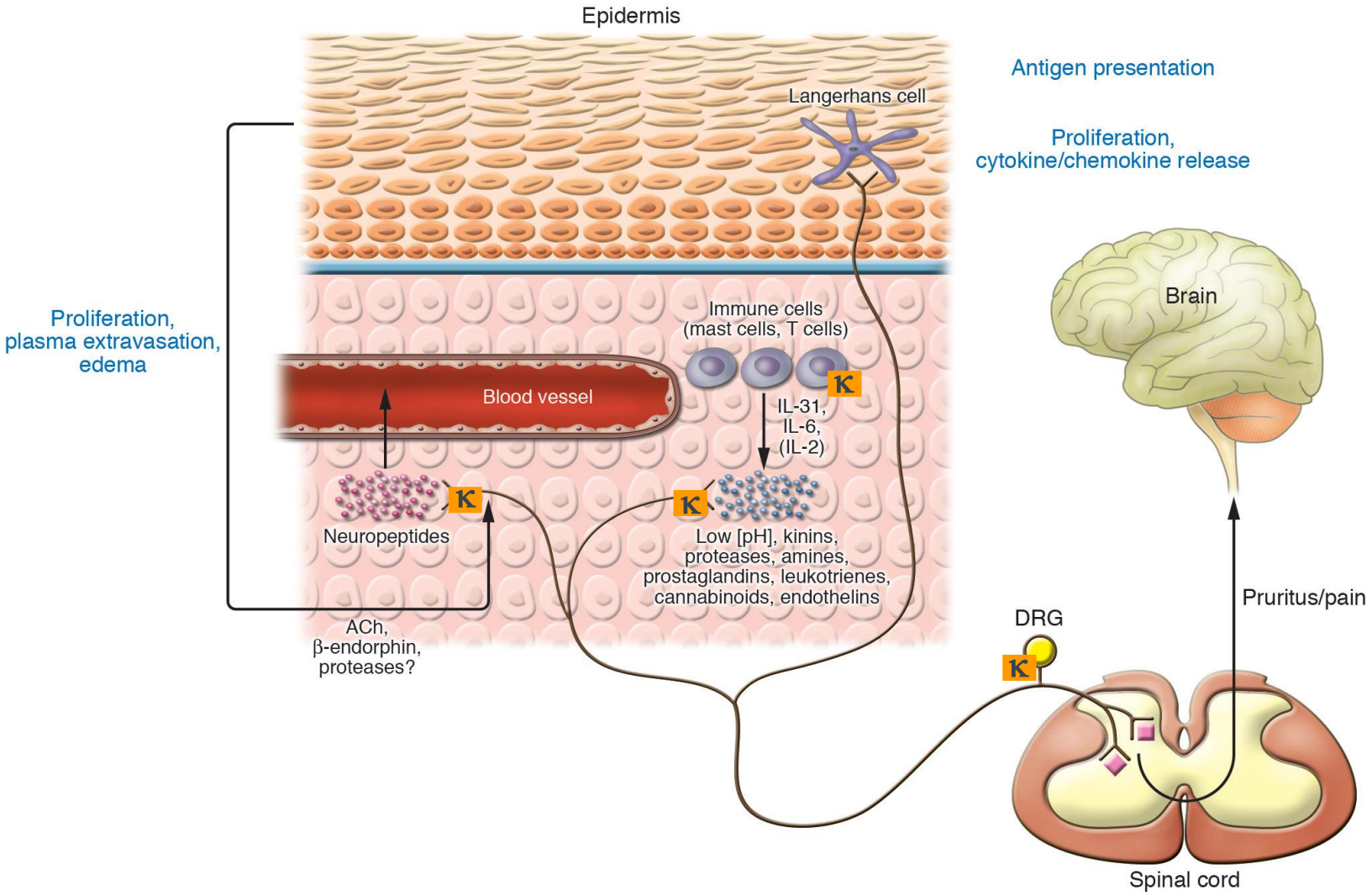
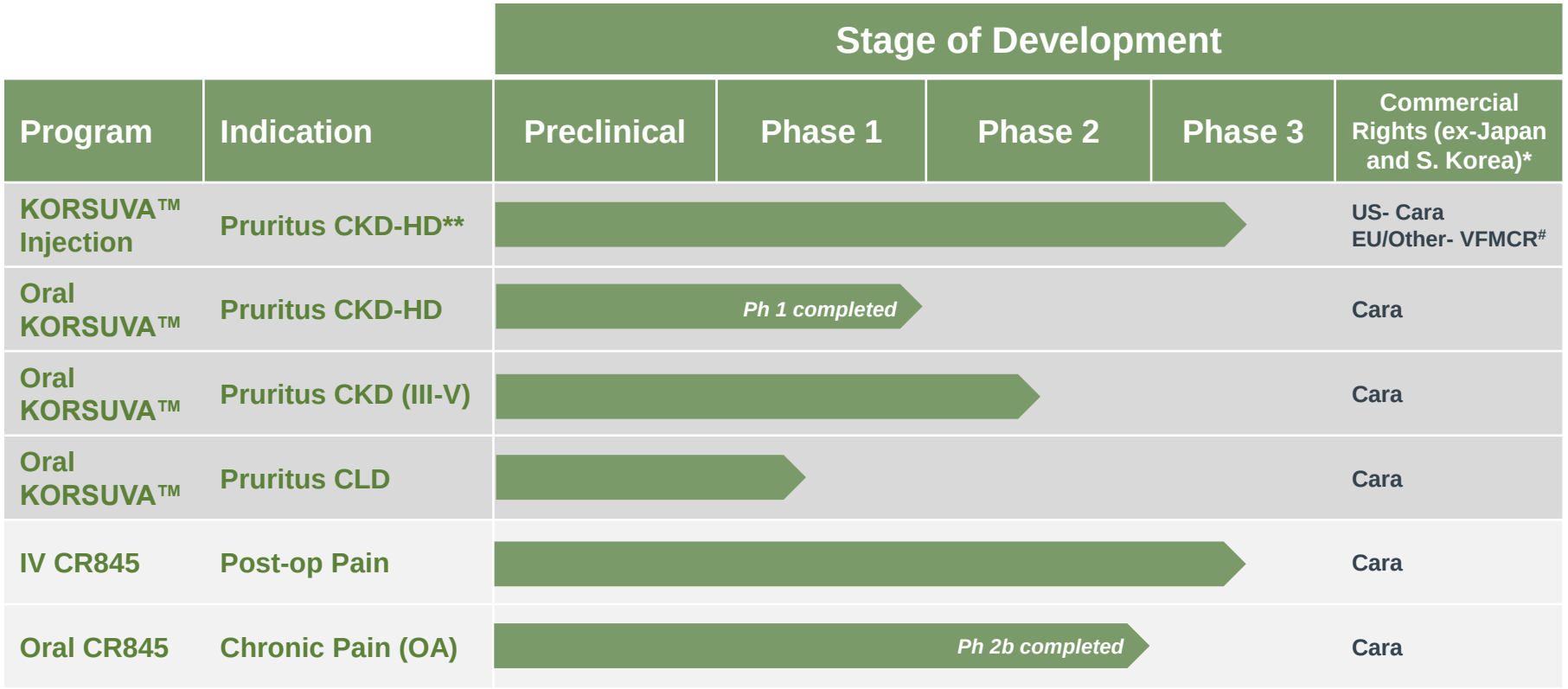
Pruritus And Pain – Common Pathway



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

Development Pipeline – July 2018



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.

* Commercialization rights to CR845 in all indications - Japan: Maruishi Pharma; South Korea: CKD Pharma
** Breakthrough Designation for IV CR845 for Pruritus CKD-HD
# VFMCRP and Cara have rights to promote in Fresenius Medical Care dialysis clinics in the US under a profit share agreement

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

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KORSUVA™ Injection for Dialysis Patients

		Stage of Development				
Program	**Indication**	**Preclinical**	**Phase 1**	**Phase 2**	**Phase 3**	**Approved**
KORSUVA™ Injection	**Pruritus CKD-HD**					

- Proposed 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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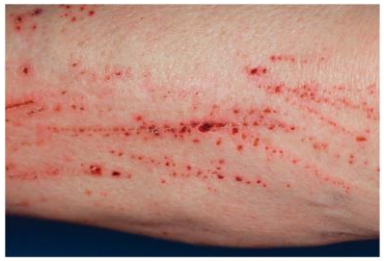
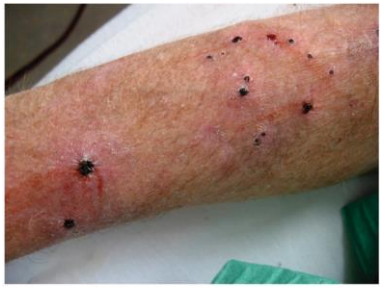
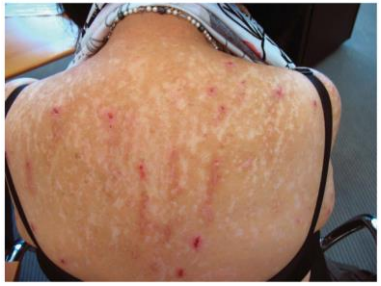
CKD-Associated Pruritus (CKD-aP)







- 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*

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

Opportunity for KORSUVA™ Injection in CKD-Associated Pruritus in Dialysis Patients: US

- Dialysis / End Stage Renal Disease (ESRD)
  - 456K patients on dialysis in US[1]
  - Approx. 60% 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
- In July 2018, CMS proposed making all new injectable or IV renal dialysis drugs eligible for reimbursement at ASP for 2 years under expanded Transitional Drug Add-on Payment Adjustment[4]

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
4. https://s3.amazonaws.com/public-inspection.federalregister.gov/2018-14986.pdf

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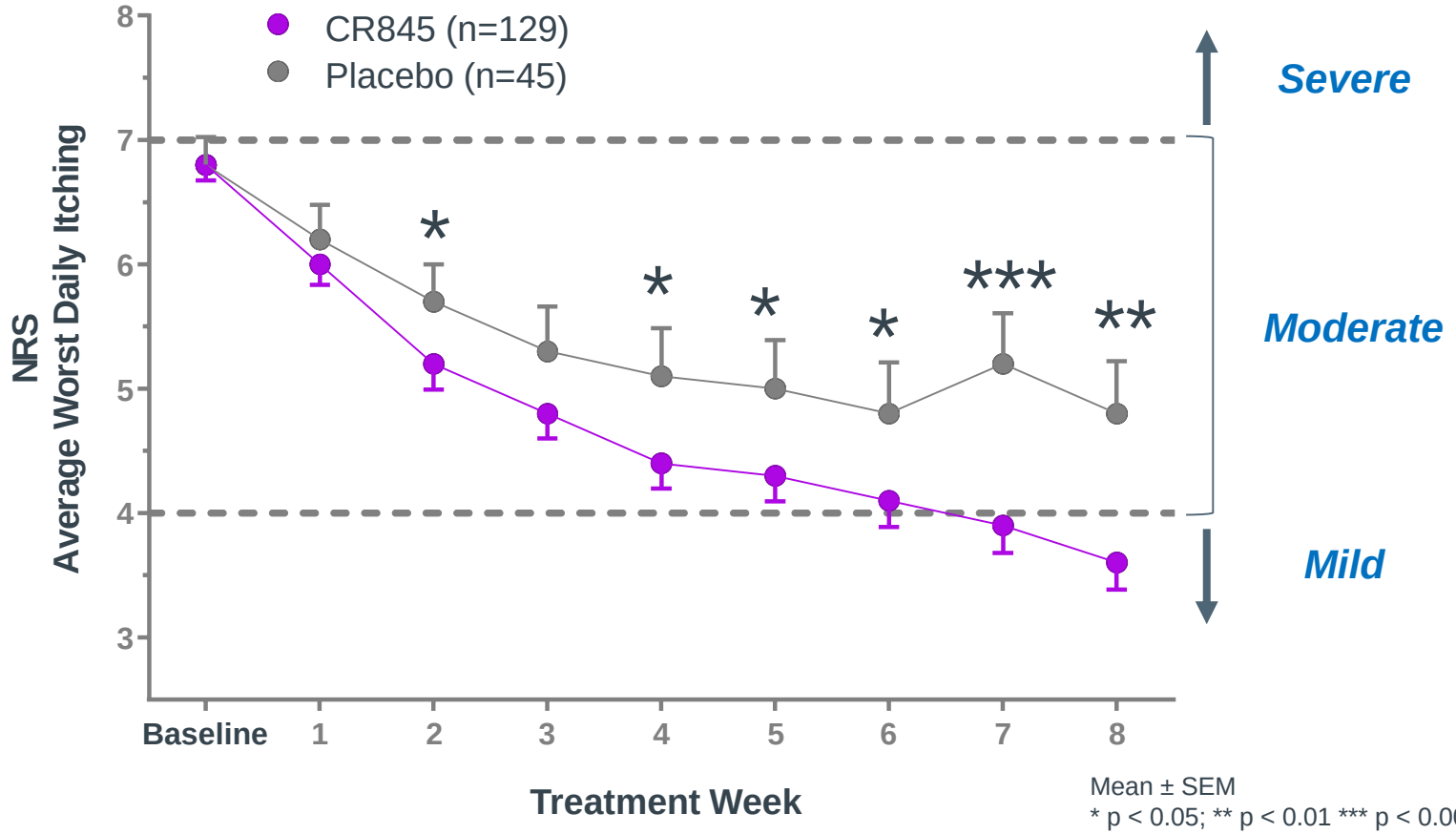
IV CR845 in CKD-HD: Compelling Ph2 Data

- 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 (Placebo: 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

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



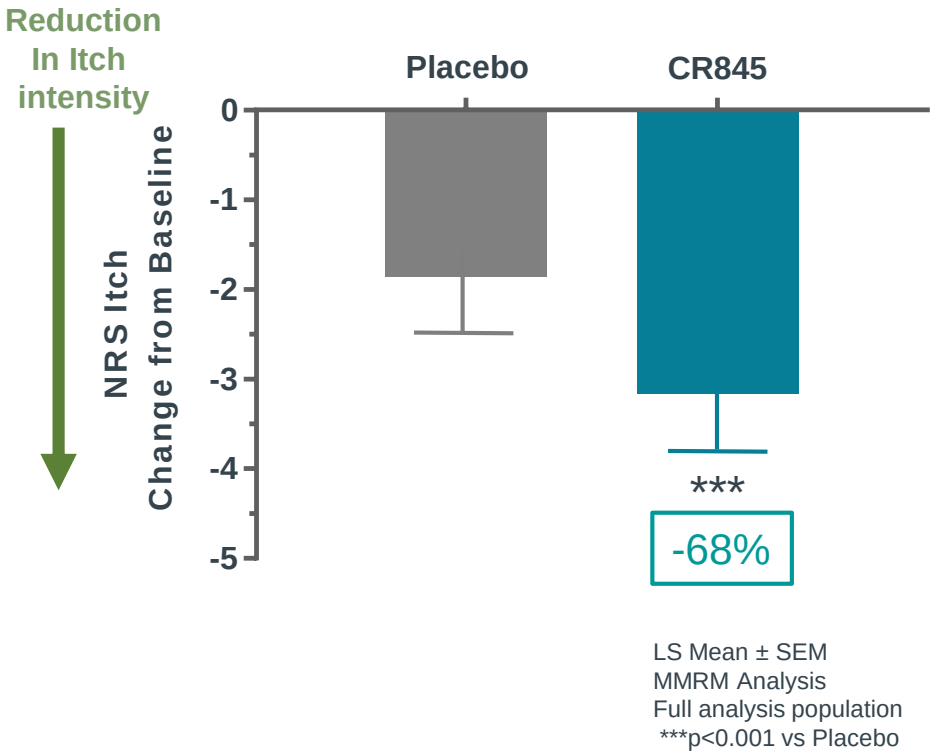
Mean ± SEM
* p < 0.05; ** p < 0.01 *** p < 0.001 vs Placebo

- Reduction of Worst Itch Intensity began on Week 1 and continued to improve through Week 8.
  - Patients on placebo showed initial improvement that plateaued

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

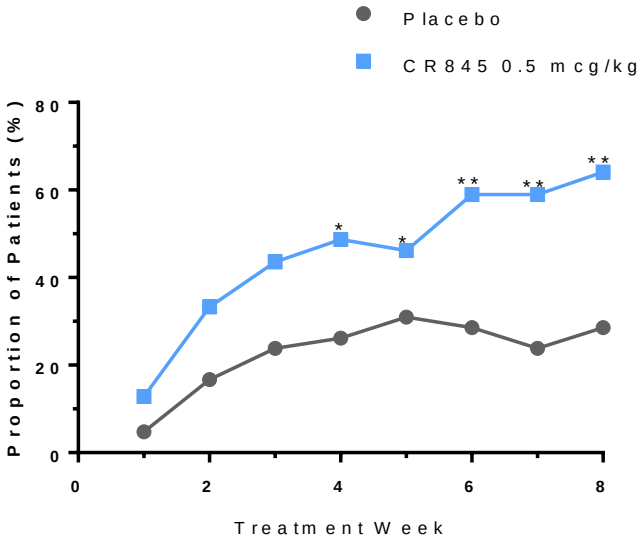
Significant & Clinically Meaningful Reduction in Itch Intensity Following 8-Week Treatment with CR845

Mean Change Worst Itch Intensity



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

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

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

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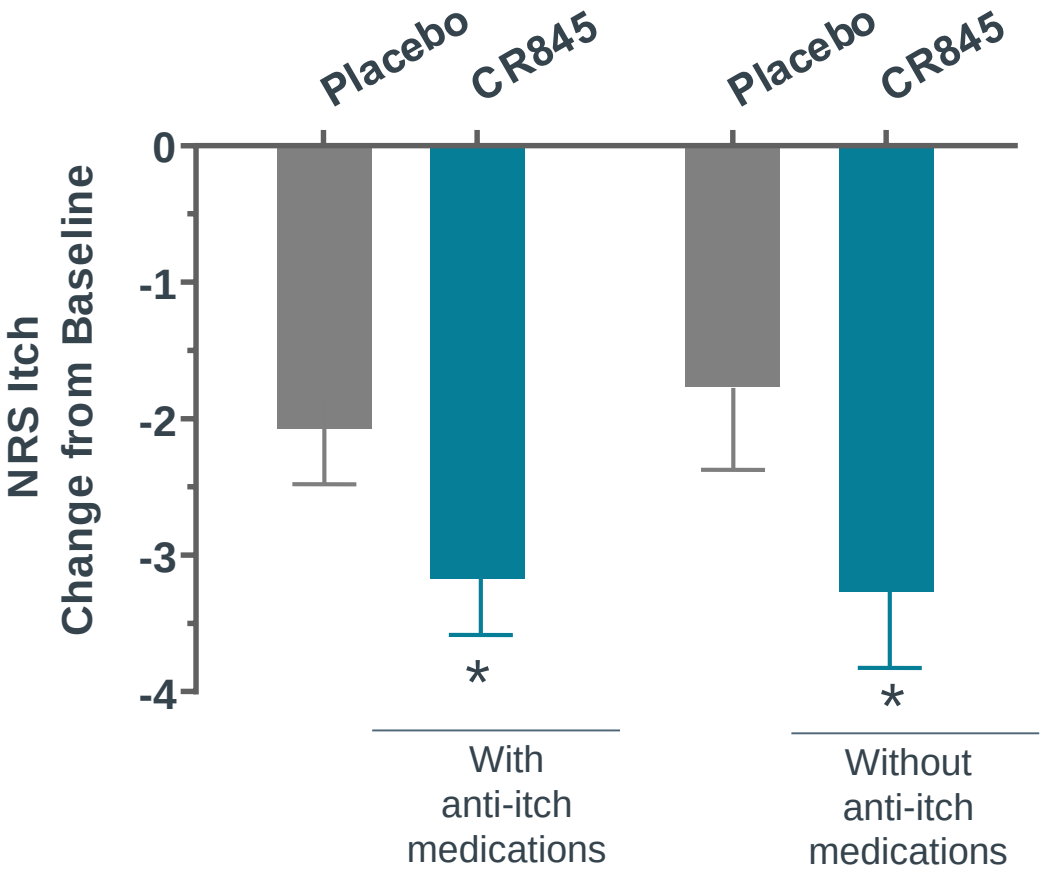
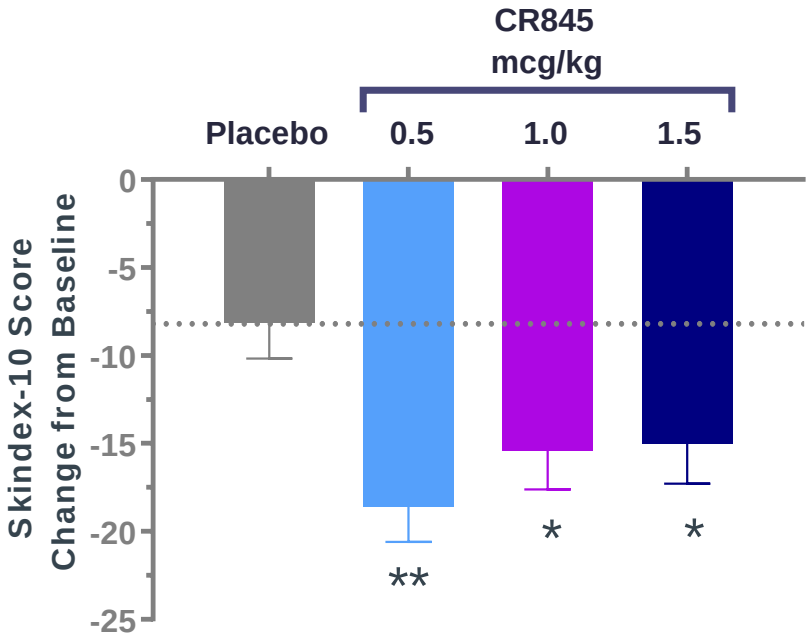
Change in NRS Worst Itch Intensity Not Different Based on Prior Use of Anti-Itch Medications



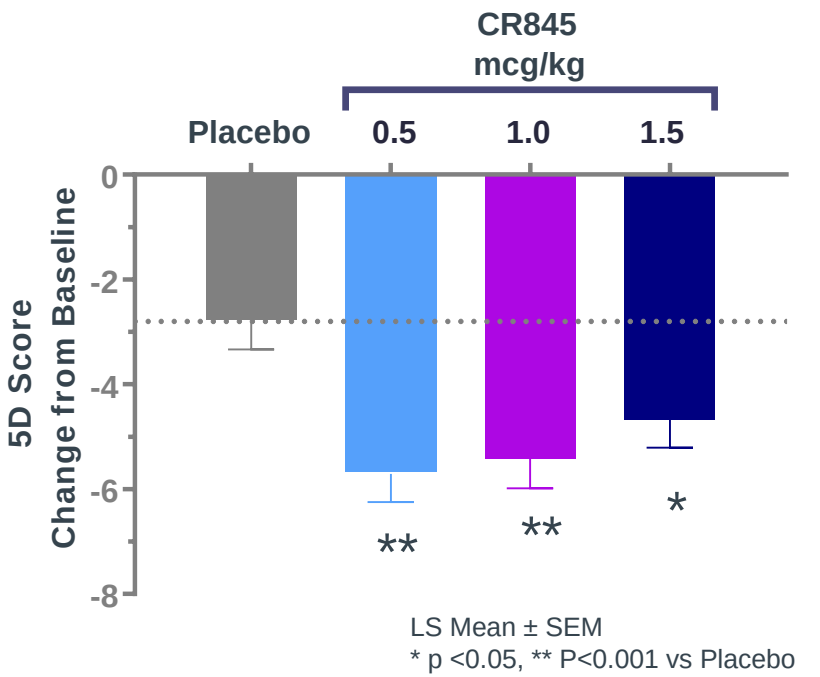
- 42% of all patients reported prior use of anti-itch medication and were stratified prior to randomization
- Anti-itch medications included primarily antihistamines and corticosteroids

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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Safety Summary: Treatment-Emergent Adverse Events (≥ 10% 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)

No Safety Findings Raised By IDMC

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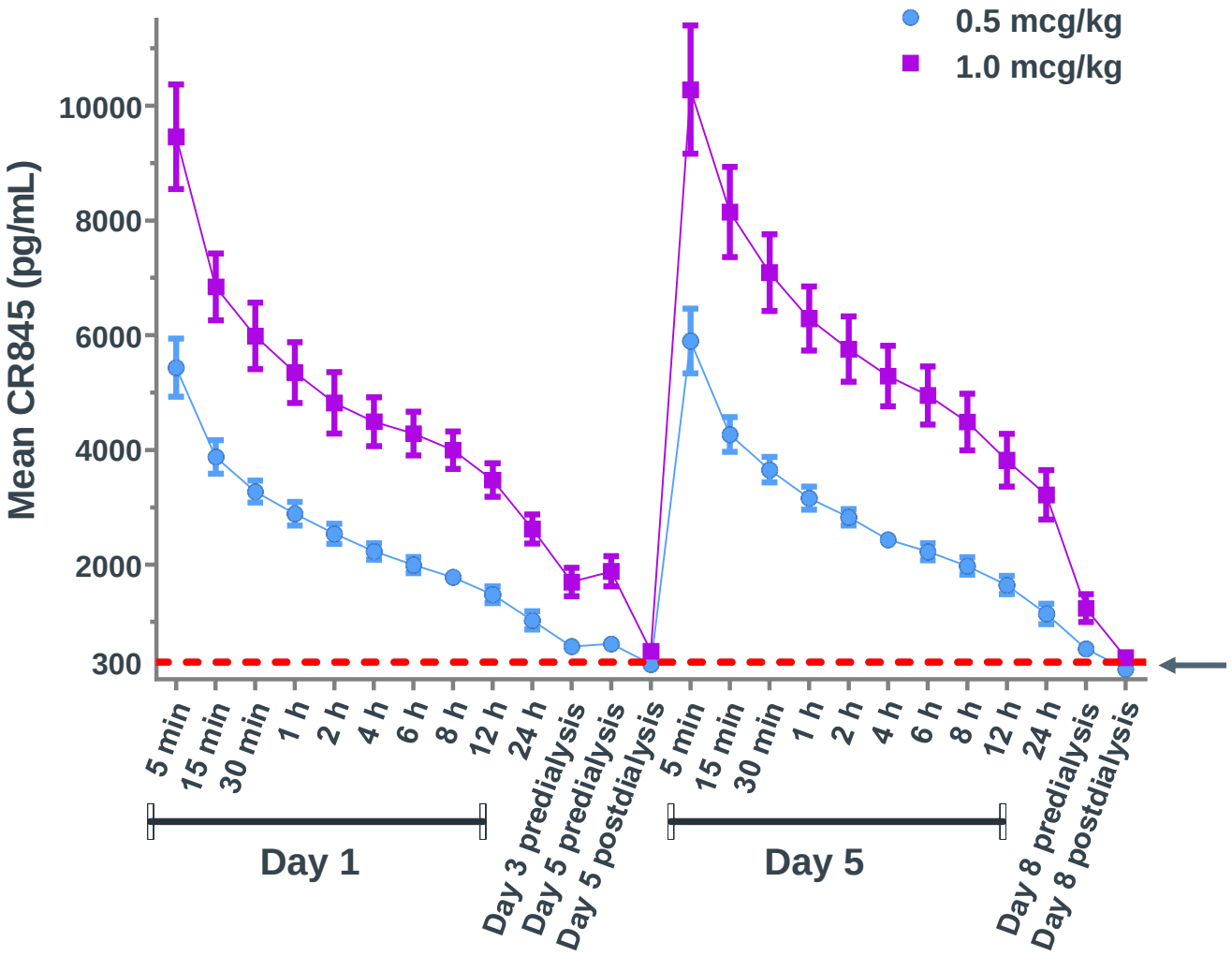
All Doses of Post-Dialysis (3x/Week) CR845: Maintenance of Receptor-Saturating Plasma Concentrations



Human Kappa Receptor

K_d = 140 nM = 96 pg/mL

320 pg/mL >75% occupancy

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KORSUVA (CR845/ difelikefalin) in CKD-HD: Onogoing 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 US 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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IV KORSUVA in CKD-HD: Ongoing Ph3 Open Label Safety Study Update

- Open label, long term extension safety study in hemodialysis patients with moderate-to severe pruritus
- Dose: 0.5 mcg/kg
  - Dosing after each dialysis session (3 times per week)
- Treatment period: up to 52 weeks and up to 240 subjects
- Study update:
  - >100 patients enrolled
  - >50 patients at 6 months of treatment
  - No unexpected adverse events reported thus far

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 itch associated with pruritus 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 IV CR845/ difelikefalin in licensed territory
- **Licensed Territory:** Worldwide, excluding US, Japan & South Korea
- **VFMCRP & Cara promotion and profit share arrangement** in US Fresenius Medical Care clinics
  - Cara to solely promote in all non-Fresenius US dialysis clinics and retain all profits

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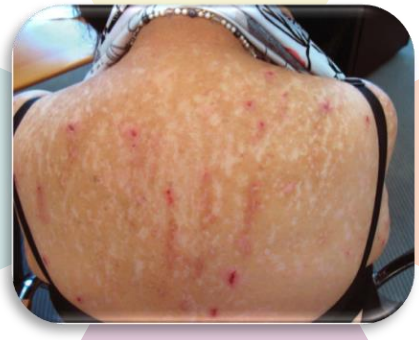
Pruritus: Large Opportunity Limited Existing Therapies

(CKD-aP)

- Chronic kidney disease-associated pruritus (CDK-aP), is chronic itching that occurs in patients with renal disease
- **Affects ~40 to 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

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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)**					

- Proposed Indication: CKD-aP in Stage III-V CKD patients
- Next milestone: Ph2 Data - 2019

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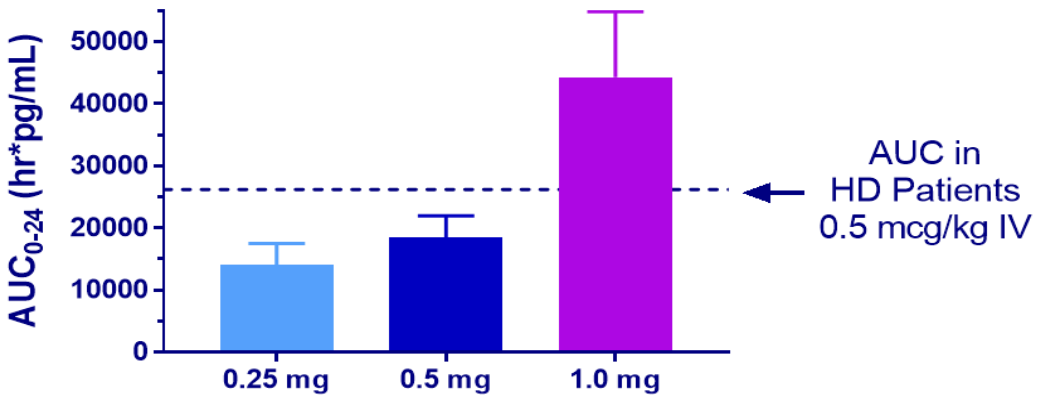
Oral KORSUVA Exposure Levels Were Similar to I.V. in CKD Patients

- Ph 1 study conducted with KORSUVA tablets in CKD patients with moderate and severe renal impairment (Stage III-V)
  - Doses: 0.25 mg, 0.5 mg & 1 mg tablets; once daily dosing
- The exposure levels were approximately equivalent to those achieved with 0.5 mcg/kg dose of IV KORSUVA (clinically active dose in HD patients with moderate to severe CKD-aP)

Systemic Exposure in Patients with Moderate CKD With Once Daily Dosing of Oral CR845



Data for oral dosing represent the arithmetic mean ± SEM.
Mean exposure (AUC) in hemodialysis patients is normalized to an equivalent 24 hour interval.

Oral KORSUVA for CKD-aP: Planned Ph 2 Trial

- Randomized, double-blind, placebo-controlled study in moderate to severe CKD patients (stage III–V) with moderate-to-severe pruritus
- Doses: 0.25 mg, 0.5 mg & 1 mg tablets
- 12-week treatment period
  - Daily dosing
- 240 patients (60/ tx group); may be increased to 120/ tx group
  - Unblinded interim analysis at ~50% enrollment and completed 12-week treatment.
- Primary endpoint:
  - Change from baseline to week 12 in weekly average of daily 24-hour Worst Itching Intensity NRS score
- Secondary endpoints:
  - Change in itch related QoL by Skindex-10
  - Change in itch related QoL by 5-D Itch Scale
  - Proportion of patients with ≥3 point improvement from baseline in Worst Itching Intensity NRS score - responder analysis
  - Safety

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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	→				

- Proposed Indication: Chronic Liver Disease-associated Pruritus
- Next milestone: planned initiation of Ph 2 trial in 2H18

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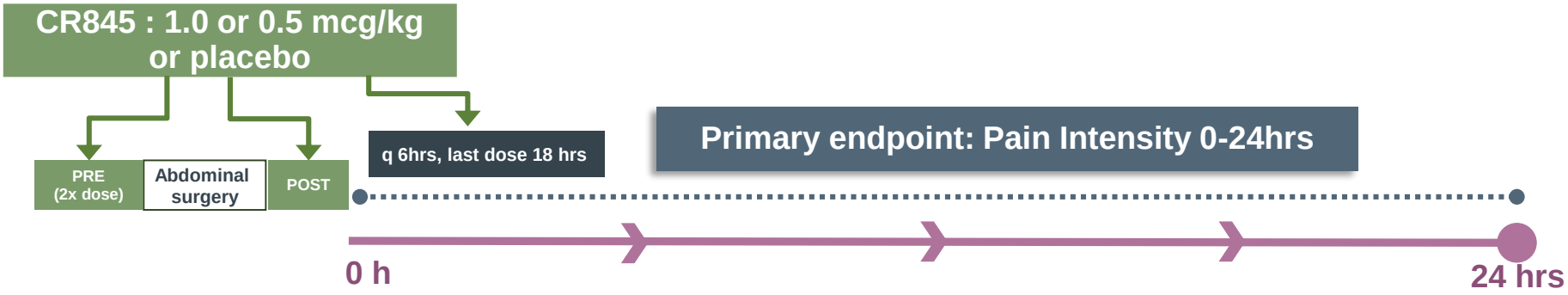
Post-Op Pain: Significant Unmet Need

- 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

CR845 CLIN3001: Study Design



- Multi-center: 22 US hospital sites, 444 patients
- Randomized, double-blind, placebo controlled, adaptive design
- Dose: 0.5 mcg/kg, 1.0 mcg/kg or placebo
- Primary endpoint:
  - Area Under the Curve (AUC) assessment of the pain intensity measured by NRS scale from 0 to 24 hours post surgery - significant reduction in pain with 1.0 mcg/kg dose
- Secondary endpoints:
  - Incidence of vomiting over 24 hours - significant reduction with 1.0 mcg/kg dose
  - Post operative nausea & vomiting (PONV) Impact scores - significant reductions with both doses
  - Rescue medication used (IV morphine) within 24 hours - not significant
  - Patient global assessment of medication at 24 hours - not significant
  - Safety

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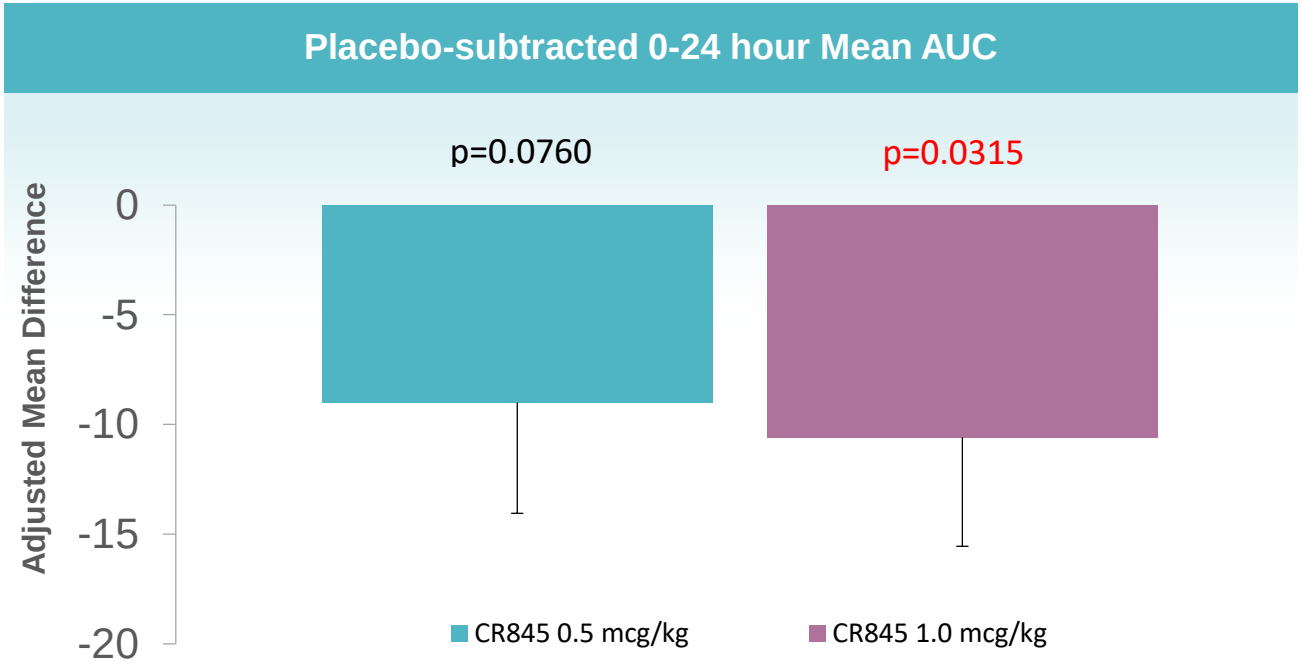
0-24 Hour Pain AUC: Primary Endpoint

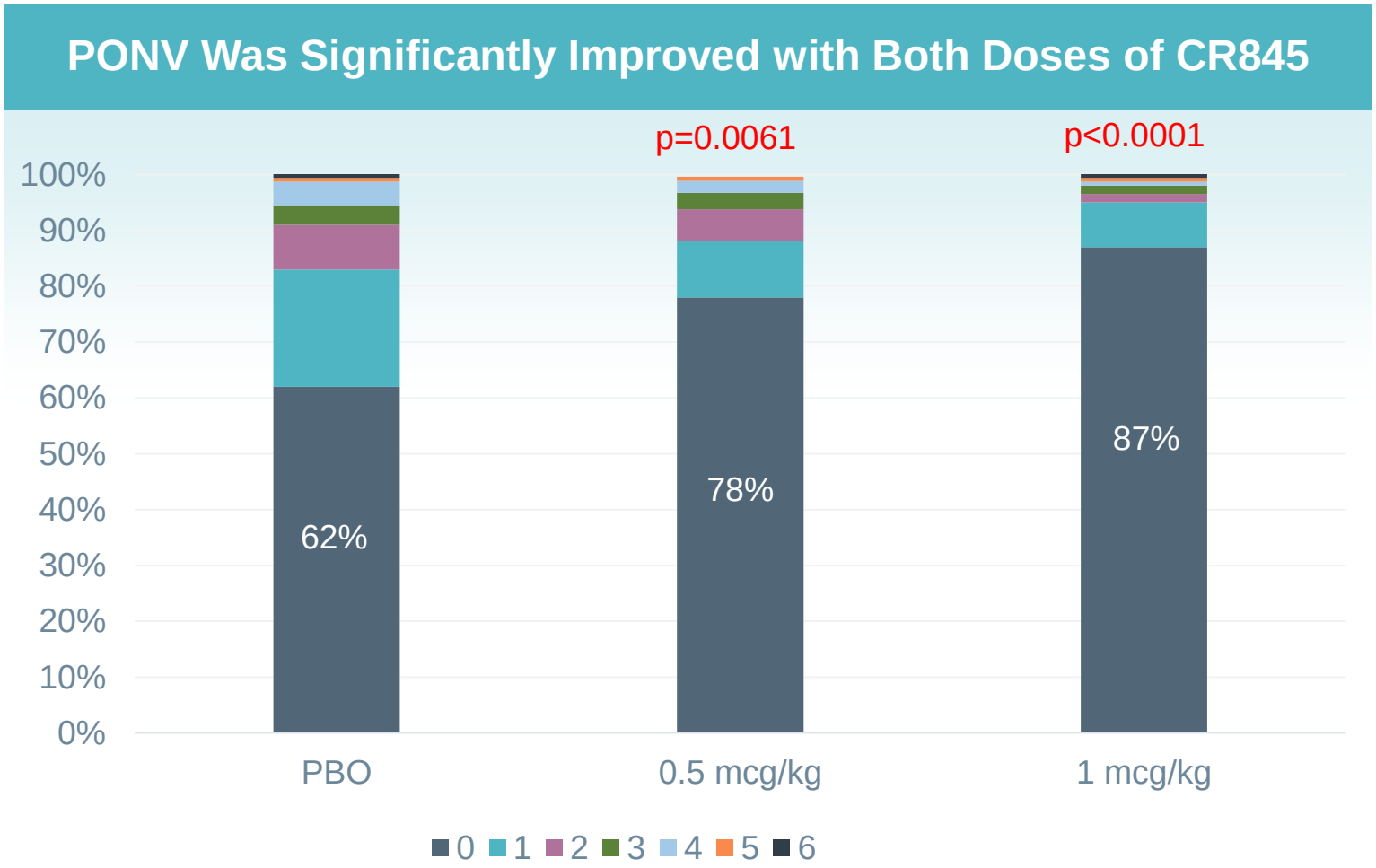
CR845 (1.0 mcg/kg Dose) Demonstrated Significant Improvement in Pain Relief



Post-Op Interval	0.5 mcg/kg (N=147)	1.0 mcg/kg (N=147)
0-6 hours	p=0.041	p=0.001
0-12 hours	p=0.035	p=0.004
0-18 hours	p=0.072	p=0.013

ANCOVA with terms for treatment, surgery type and site nested within surgery type

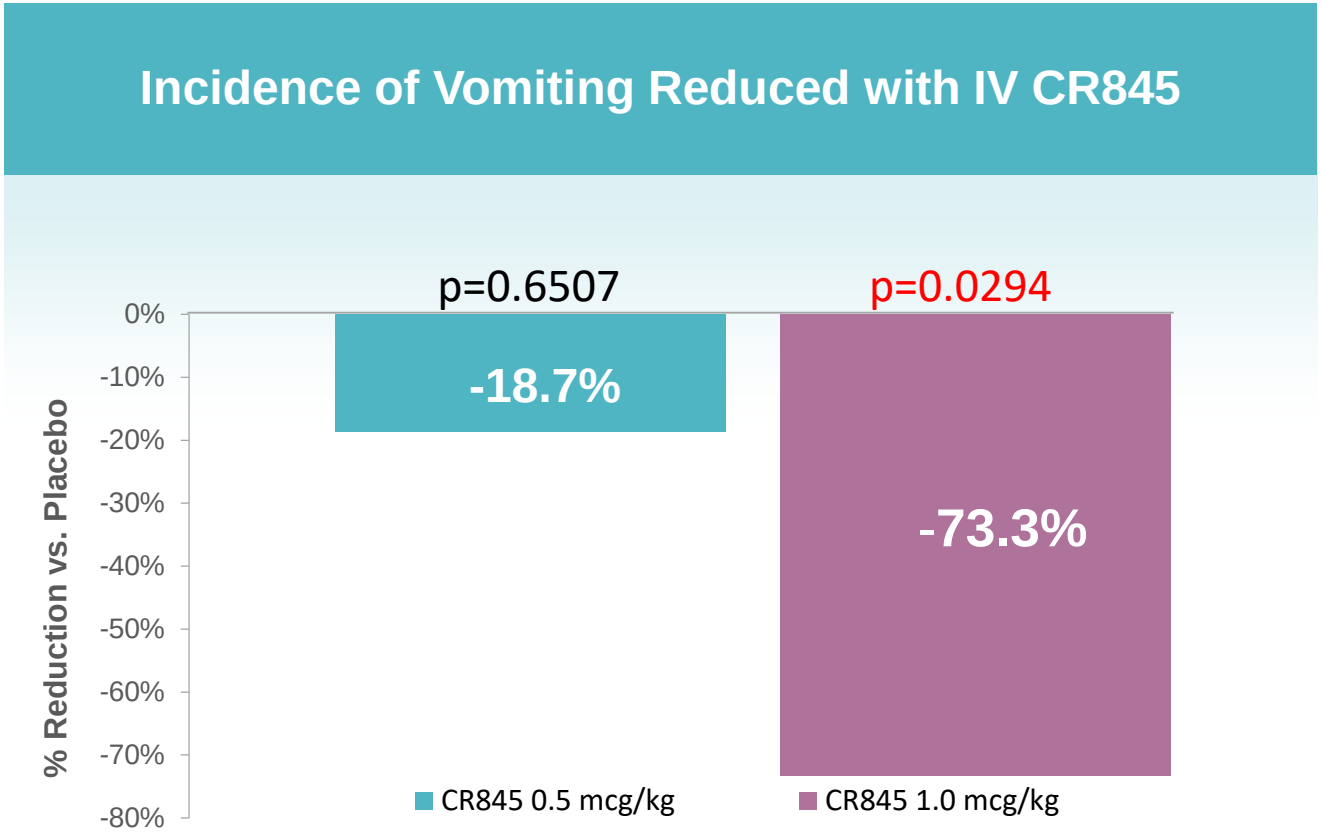
PONV Impact Score at 24 Hours: Secondary Endpoint



% of subjects who did not use any ondansetron was 70% in the CR845 0.5 mcg/kg (N= 147) and 81% in the CR8451 (N=147) mcg/kg group versus 56% in the placebo (N=146) group

PONV Scores: 0- not at all, and 6-Worst score; Wilcoxon rank sum test stratified by surgery type

Incidence of Vomiting Over 24 Hours: Secondary Endpoint



Mantel-Haenszel test stratified by surgery type based on Vollset et al (1991)

CR845 CLIN3001: Summary

- Met primary endpoint of AUC 0-24 hours for pain relief at 1.0mcg/kg
  - Significant reductions in AUC (0-6) & AUC (0-12) for both 0.5 mcg/kg & 1.0 mcg/kg
- Met Secondary Endpoints:
  - Significant reduction in PONV impact scores (0.5 mcg/kg & 1.0 mcg/kg)
  - Significant reduction in incidence of vomiting (1mcg/kg)
- Incidence of adverse events was generally low and similar between placebo and IV CR845 groups
- Next Steps – FDA meeting & consultation on development path and trial design

Projected Clinical Milestones – 2018/19

Upcoming Cara Events

Pruritus / KORSUVA™ Injection	
Mid-18 / 3Q18	Phase 3 (Global) CKD-aP Dialysis Trial Initiation
2019	Data from US & Global Ph 3 trials in CKD-aP (Dialysis)
Pruritus / Oral KORSUVA™	
2Q18	Phase 2 CKD-aP Non-Dialysis Trial – Recently Initiated
3Q18	Phase 1 Chronic Liver Disease (CLD) Trial Completion
2H18	Phase 2 CLD-aP Trial Initiation
2019	Data from Phase 2 CKD-aP Non-Dialysis Trial

Financial Highlights

As of March 31, 2018

- Cash and marketable securities — $74.5M
- Net loss – Q1 2018 — ($16.8M)
- Shares outstanding — 32.7M
  - Stock options — ~3.9M

In May 2018

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

In July 2018

- Follow on Offering: $92.4M
- Additional shares: 5,175,000

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