Targeting Pruritus with Novel Peripherally-Restricted Kappa Agonist Therapeutics

July 2019

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 and regulatory submissions; 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 pruritus market and the potential commercialization of Korsuva™.

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, 2018, 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.

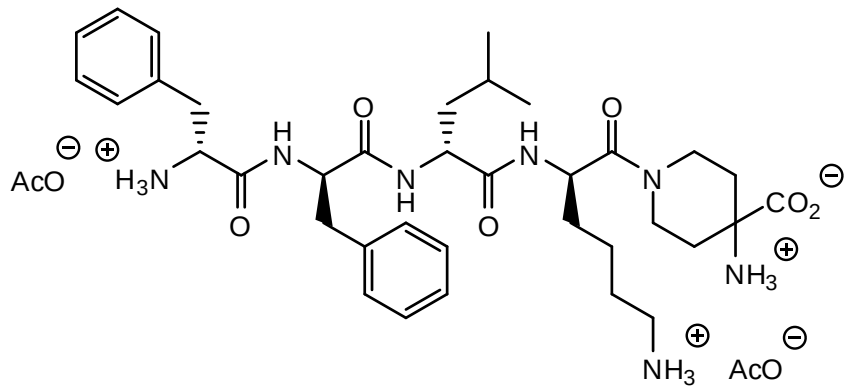
The Company undertakes no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise except as required by law.

Cara Therapeutics Overview

Developing KORSUVA™: novel, first-in-class, peripherally-acting "kappa" opioid receptor agonist for multiple pruritus indications

- KORSUVA Injection: lead program
  - Two Phase 3 efficacy studies for CKD-associated pruritus (CKD-aP) in hemodialysis patients
    - KALM-1: positive topline data reported in May 2019
    - KALM-2: topline data expected in Q4, 2019
  - Breakthrough Therapy Designation in the US for CKD-aP in hemodialysis patients (first and only designation granted in CKD-aP)
  - Regional partnerships with Vifor/Fresenius - VFMCRP (EU/ select territories), Maruishi Pharma (Japan) and Chong Kun Dang Pharma (South Korea)
- Oral KORSUVA: multiple programs
  - CKD-aP in non-dialysis patients - Ph 2 trial ongoing; data expected in Q4, 2019
  - Chronic liver disease-associated pruritus - Ph 2 trial initiated in patients with Primary Biliary Cholangitis Q2, 2019
  - Atopic dermatitis- associated pruritus - Ph 2 trial initiated in July, 2019

CR845: A Peripherally-Restricted Kappa Receptor Agonist



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

- Novel, first-in-class “kappa” receptor agonist
- Designed to function **without traditional opioid side effects** (“mu” agonist effects)
- Peripherally restricted - hydrophilic, tetra-peptidic scaffold
- High therapeutic index
- ≥30,000-fold selectivity for κ-receptors versus μ- or δ- receptors

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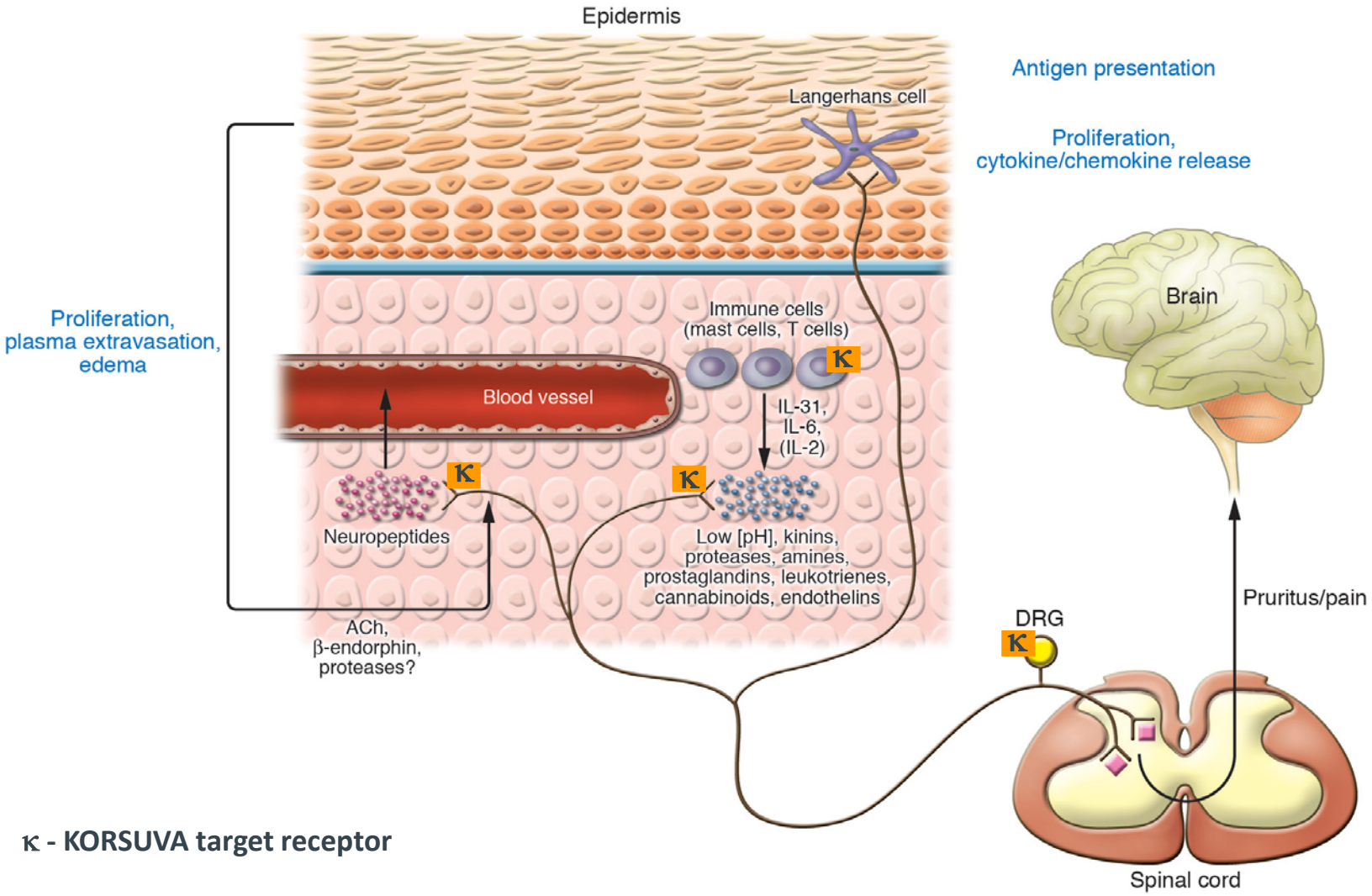
KORSUVA™ Acts on Neuronal and Inflammatory Targets in Pruritus Pathway



κ - KORSUVA target receptor

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

Development Pipeline

Program	Indication	STAGE OF DEVELOPMENT				
		Preclinical	Phase 1	Phase 2	Phase 3	Commercial Rights (ex-Japan and S. Korea)^
KORSUVA™ Injection	Pruritus CKD-HD**					US- Cara EU/Other- VFMCRP#
Oral KORSUVA™	Pruritus CKD (III-V)					Cara
Oral KORSUVA™	Pruritus CLD					Cara
Oral KORSUVA™	Pruritus Atopic Dermatitis			*		Cara

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 defined 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; **CLD**: Chronic Liver Disease

KORSUVA™ Injection for Dialysis Patients

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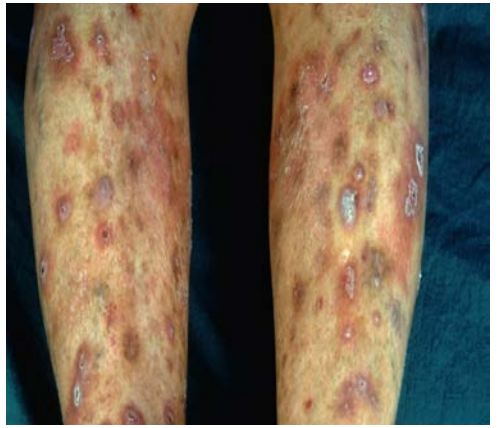
CKD-associated Pruritus (CKD-aP) in Hemodialysis (HD) Patients

Serious itching condition directly related to kidney failure

- Reported by ~60 to 70% of HD patients
  - 30% to 40% patients with moderate to severe itch intensity
- In contrast to dermatological pruritus, primary skin lesions are not observed
  - Superimposed complications of itching may include excoriations with impetigo, linear crusts, papules, ulcerations, and less commonly prurigo nodularis



Courtesy of Dr. Gil Yosipovitch

Itching severity associated with worsening Quality of Life (QoL) [social, emotional and physical]

- Sleep disturbance, depressed mood/anxiety, socialization
- Increased mortality risk

Pisoni RL et al. *Nephrol Dial Transplant* 2006; Rayner et al., Clin J Am Soc Nephrol 2017; Fishbane et al. *NDT* 2001;
Ramakrishnan et al. *International Journal of Nephrology and Renovascular Disease* 2014; Narita et al 2006;
Shirazian et al. Int J Nephrol Renovasc Dis. 2017; Mathur et al., Clin J Am Soc Nephrol 2010; Szepietowski et al., Neprol Dial Transplant 2004;

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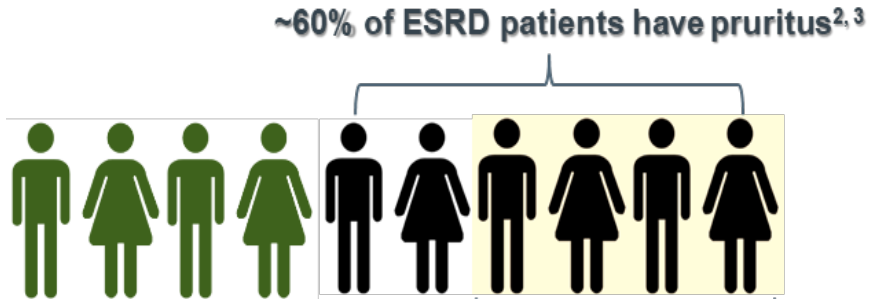
US Market Opportunity for KORSUVA™ Injection in Dialysis Patients

>500K patients on dialysis



~40%

have moderate to severe pruritus

Per NKF, >500K patients undergoing dialysis in the US[1]

- ~60% have some form of pruritus[2,3]
- Itching severity associated with worsening Quality of Life (QoL) Sleep disturbance, depressed mood/anxiety, socialization
- Increased mortality risk

KORSUVA™ granted Breakthrough Therapy Designation for CKD-aP

- Significant unmet need
- No FDA approved therapies

Per Nov. 2018 CMS rule:

within the ESRD Prospective Payment System all new dialysis drugs eligible for reimbursement at ASP for 2 yrs under TDAPA, effective Jan. 1, 2020[4]

1. National Kidney Foundation
2. Pisoni RL, Wikstrom B, Elder SJ, et al. Nephrol Dial Transplant. 2006;21:3495-3505.
3. Ramakrishnan et al. International Journal of Nephrology and Renovascular Disease. 2014:7 1–12
4. https://www.govinfo.gov/content/pkg/FR-2018-11-14/pdf/2018-24238.pdf

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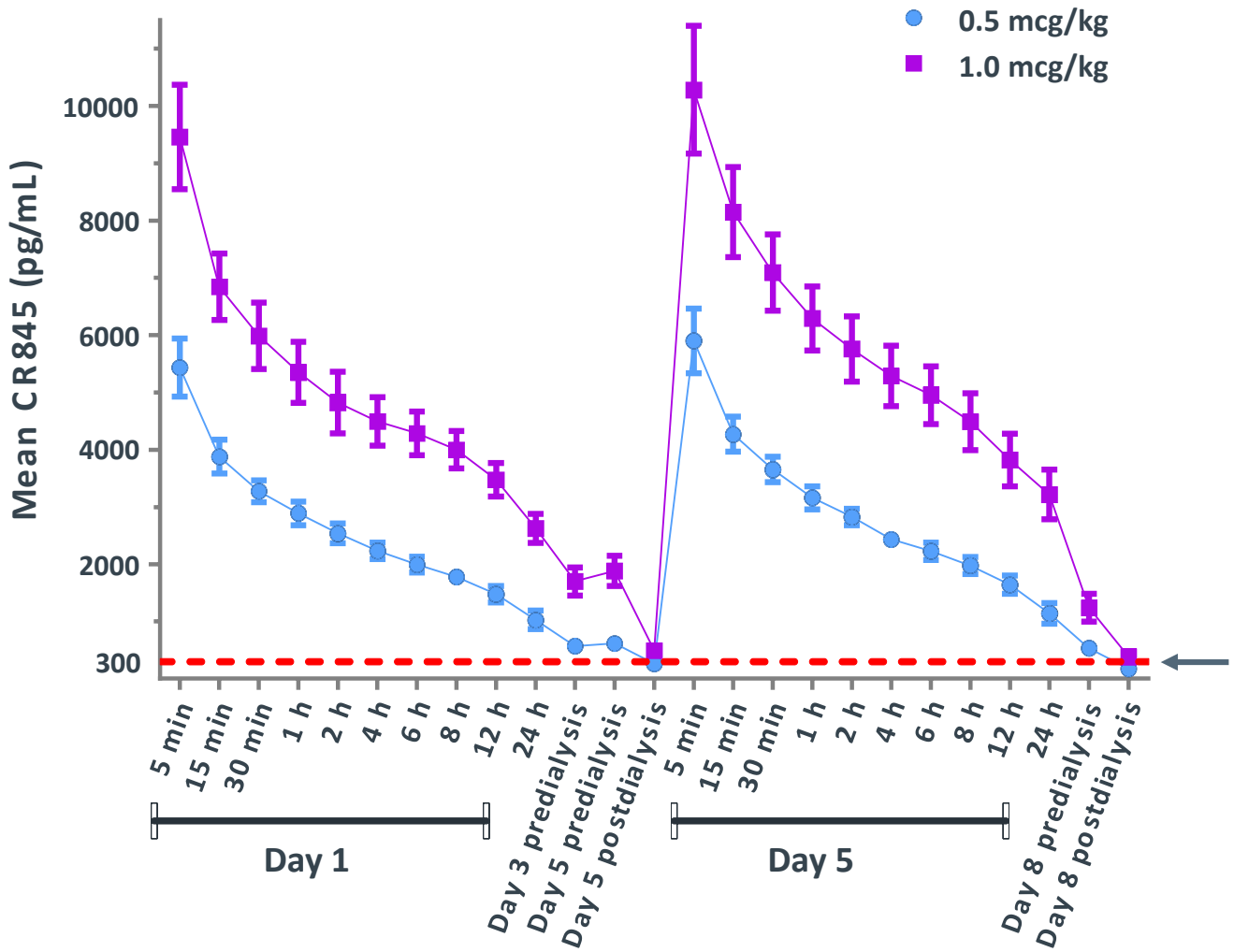
KORSUVA: Convenient Dosing After Each Dialysis Session

All Doses of KORSUVA (3x/Wk) Maintained Receptor-Saturating Plasma Concentrations

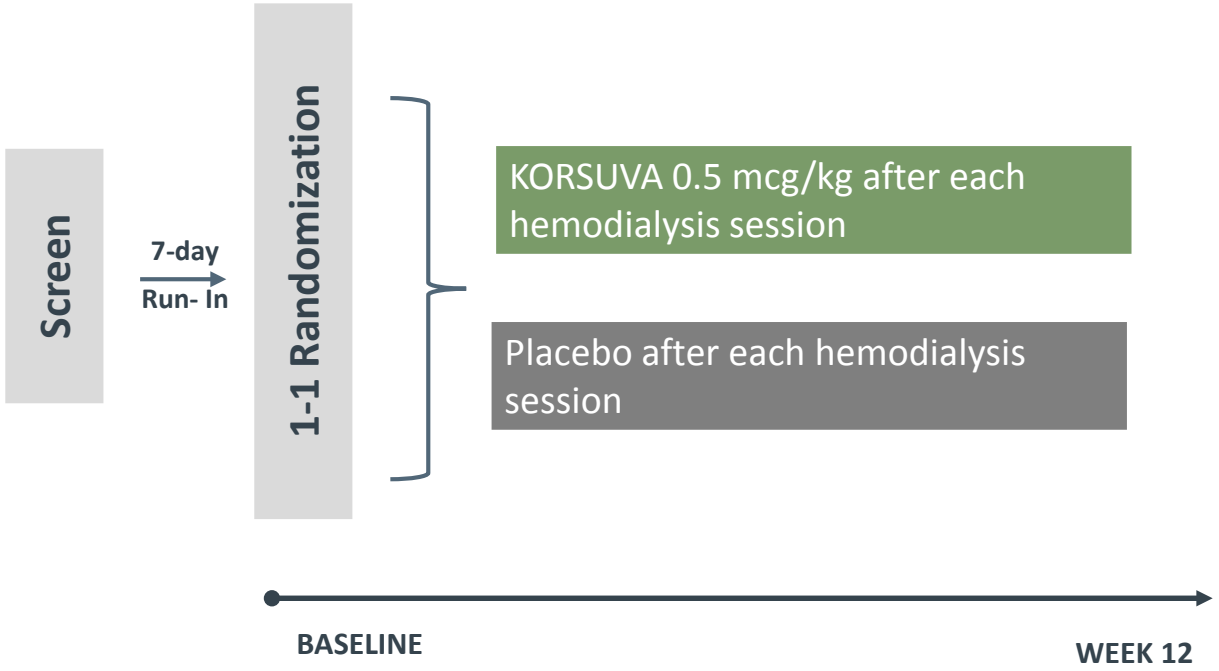


Human Kappa Receptor

K_d = 140 nM = 96 pg/mL

320 pg/mL >75% occupancy

KALM-1 Phase 3 Pivotal Study Design



52 Week Open-Label Extension Ongoing

Endpoints: Week 12

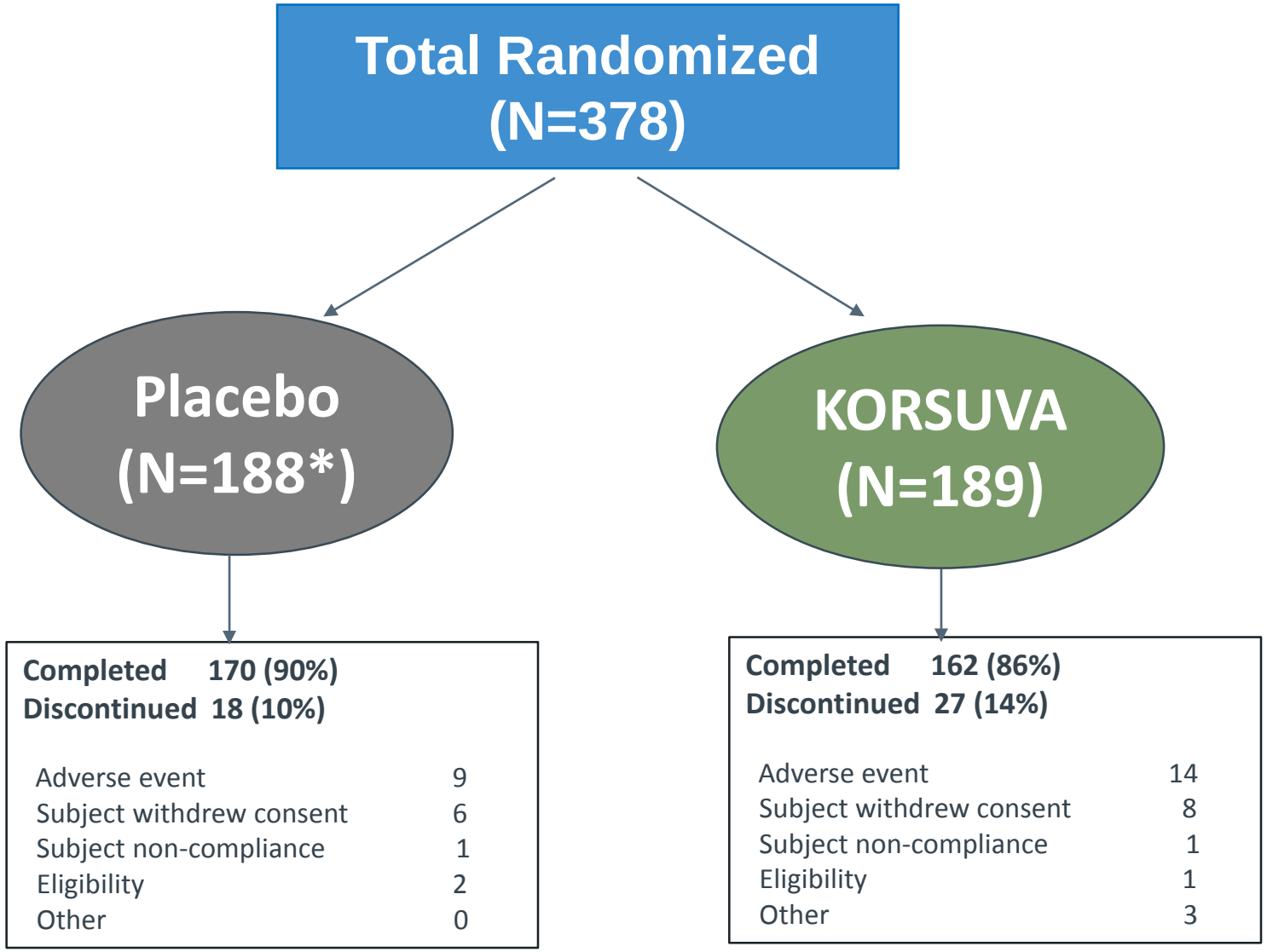
Primary

- Proportion of subjects achieving ≥3 point improvement from baseline in weekly mean of daily worst itching intensity NRS (WI-NRS)

Secondary

- Proportion of subjects achieving ≥4 point improvement in WI-NRS
- Change from baseline in itch-related Quality of Life as measured by 5-D Itch and Skindex-10 questionnaires

KALM-1: Patient Disposition



*1 subject was randomized to Placebo but did not receive study drug

KALM-1: Key Baseline Disease Characteristics

Baseline Characteristic Mean (SD) or %	Placebo N = 188	KORSUVA N = 189
Years Undergoing Hemodialysis,	4.7 (4.22)	4.4 (3.98)
Years of Pruritus	3.5 (3.37)	3.2 (3.24)
Use of Anti-Itch Medication	41.5 %	38.1 %
Baseline Worst Itching Intensity NRS	7.3 (1.61)	7.1 (1.44)
Baseline 5-D Itch Total Score	17.9 (3.47)	16.9 (3.47)
Baseline Skindex-10 Total Score	38.3 (15.40)	36.2 (14.36)

NRS: Numeric Rating Scale (0 to 10) where 0 = no itch and 10 = worst itching imaginable
5-D Itch score ranges from 0 to 25 (lower scores indicate better QoL and reduced itch symptoms)
Skindex-10 scale ranges from 0 to 60 (lower scores indicate better QoL)

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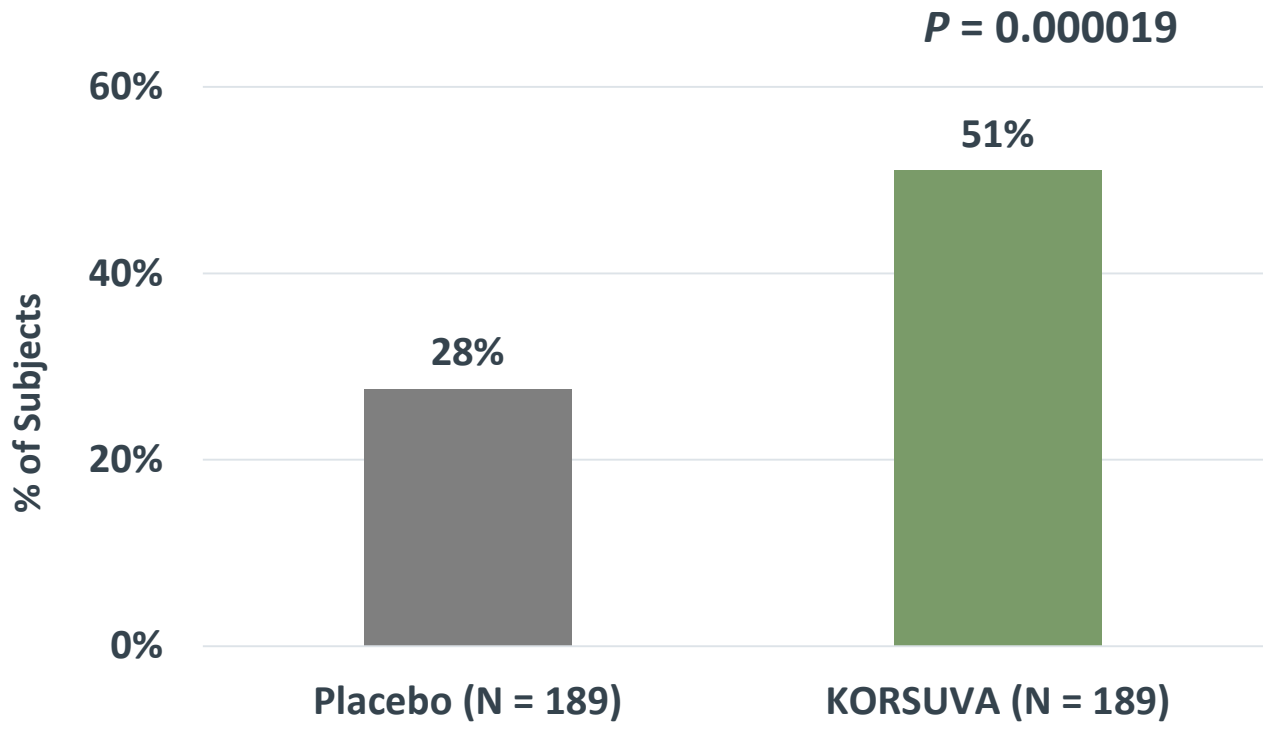
Primary Endpoint: ≥3 point improvement WI-NRS

Top-line results: KORSUVA subjects >2.5 times more likely to experience ≥3 point improvement



Estimated percentage & P-value based on a logistic regression model with terms for treatment group, baseline WI-NRS score, and strata
Missing data imputed using multiple imputation (MI) under missing at random (MAR) assumption
Odd Ratio: 2.72

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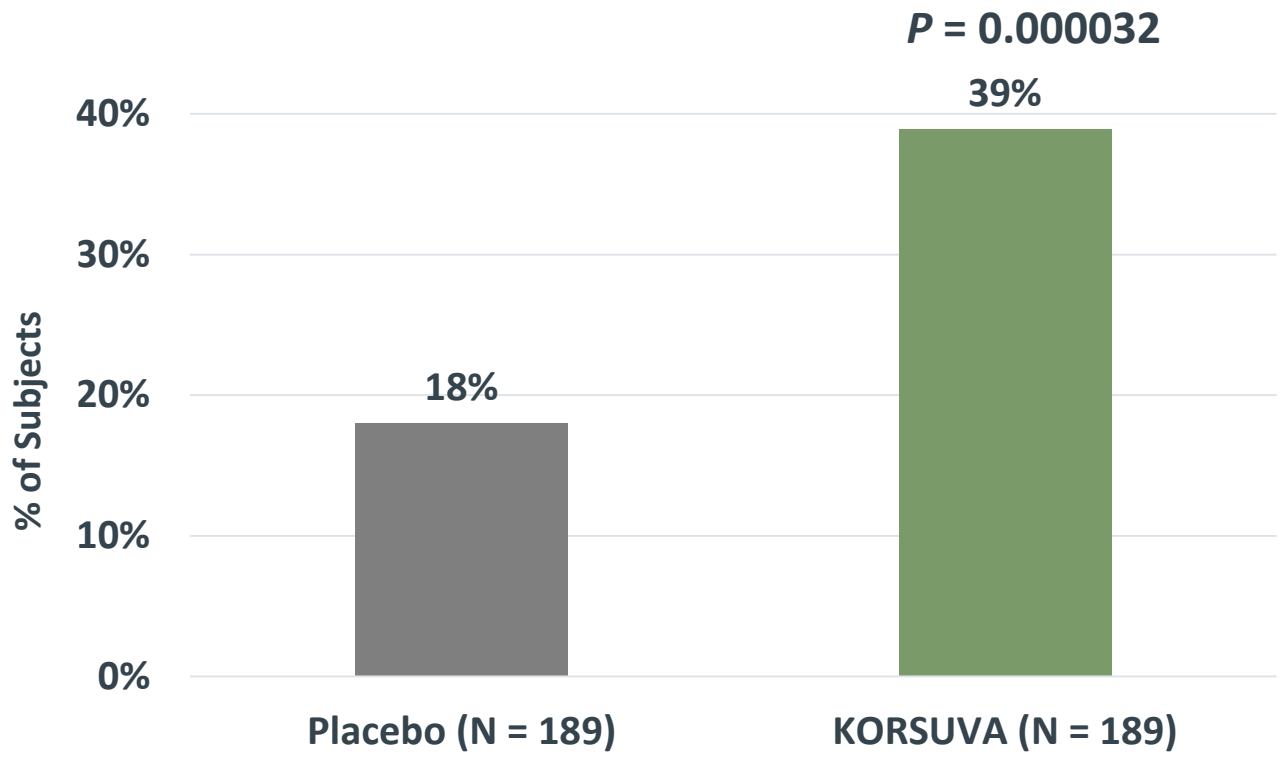
Secondary Endpoint: ≥4 point improvement WI-NRS

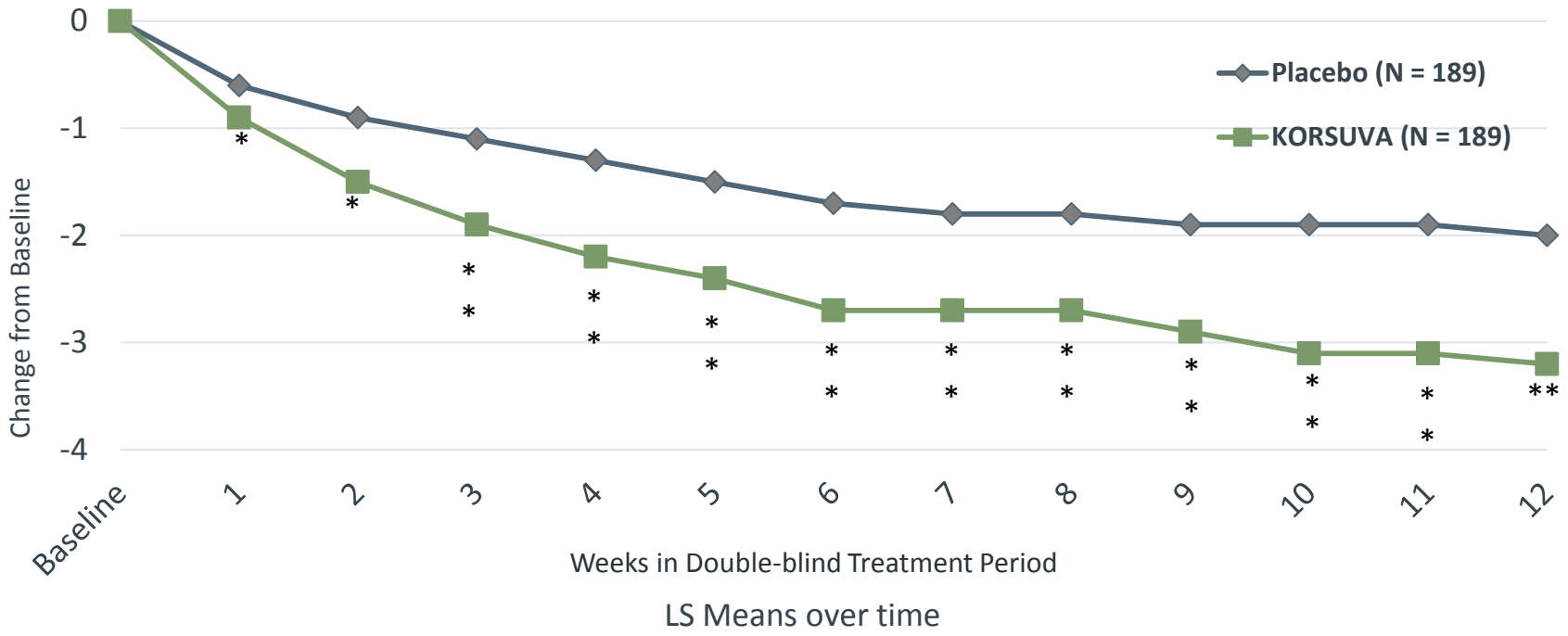
Top-line results: KORSUVA subjects ~3 times more likely to experience ≥4 point improvement



Estimated percentage & P-value based on a logistic regression model with terms for treatment group, baseline WI-NRS score, and strata
Missing data imputed using multiple imputation MI) under missing at random (MAR) assumption
Odd Ratio: 2.9

Change in Worst Itching Intensity NRS Over Time

Top-line results: significant differences observed in WI-NRS starting at week 1



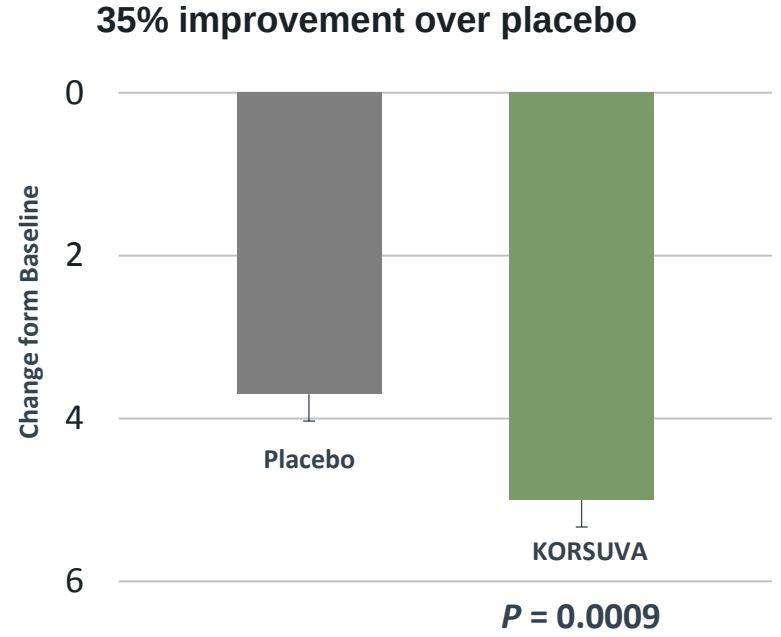
*** *P* < 0.05, ** *P* < 0.001**

LS Means from MMRM with terms for treatment group, week, week by treatment interaction, baseline score and strata
Missing data imputed using multiple imputation (MI) under missing at random (MAR) assumption

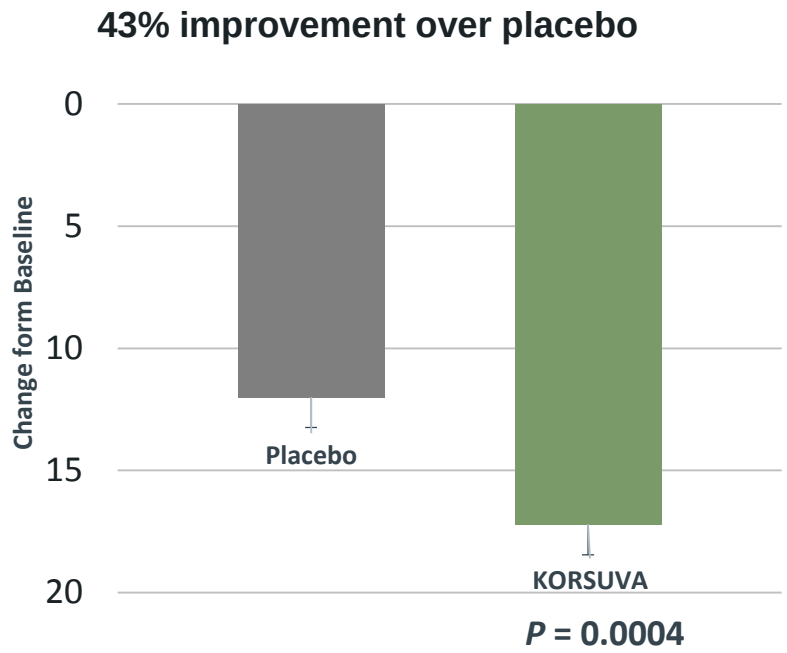
Secondary Endpoints: 5D-Itch and Skindex-10

Top-line results: Significant Improvements in Itch-Related QoL measures

5-D



Skindex-10



LS Mean, standard error & P-value based on ANCOVA with terms for treatment group, baseline score, and strata
Missing values imputed using multiple imputation (MI) under MAR assumption

KALM-1 Phase 3 Pivotal Top-line Results Summary

Study met primary and all secondary endpoints

Endpoints at Week 12 KORSUVA 0.5 mcg/kg vs placebo	*P* Value
Primary	
o Proportion subjects with ≥3 point improvement in weekly mean of daily WI-NRS	0.000019
Secondary	
1) Proportion subjects ≥4 point improvement in weekly mean of daily WI-NRS	0.000032
2) Change from baseline in 5-D Itch score	0.0009
3) Change from baseline in total Skindex-10 score	0.0004

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KALM-1 Most Commonly Reported TEAEs (Top-Line Data)

Treatment-emergent Adverse Events at ≥5% frequency	Placebo N = 188; n (%)	KORSUVA N = 189; n (%)
Diarrhea	7 (3.7)	18 (9.5)
Dizziness	2 (1.1)	13 (6.9)
Vomiting	6 (3.2)	10 (5.3)
Nasopharyngitis	10 (5.3)	6 (3.2)

KORSUVA Injection in CKD-HD: Phase 3 Program

- KALM-1 trial (US): Top-line results
  - *Met Primary and all Secondary Endpoints*
  - *Generally well-tolerated and safety findings consistent with previous trials*
- KALM-2 trial (Global): ongoing
  - Includes centers in the US, Europe and Asia Pac regions
  - Top-line data readout: Q4, 2019
- Open label safety studies: ongoing
  - US safety study: up to 52 weeks treatment and up to 300 subjects
    - >200 patients enrolled
    - ~150 patients have completed 6 months of tx; and ~40% of these pts have completed 1 year of tx
    - Safety findings consistent with the Ph 2 trial- no new safety signals observed
  - Global safety study: treatment period: up to 12 weeks and up to 400 subjects
    - Initiated in 2Q, 2019

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Vifor Fresenius Medical Care Renal Pharma (VFMCRP)

- License
  - IV CR845/ difelikefalin for the prevention, inhibition or treatment of itch associated with pruritus in hemodialysis/ peritoneal dialysis patients
- Financials
  - $70M upfront ($50M cash + $20M in Cara equity at premium)
  - Up to $470 million in regulatory and commercial milestones
  - Tiered double-digit royalty based on net sales 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 has sole promotion and profit retention in all non-Fresenius US dialysis clinics

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Oral KORSUVA™ for CKD-associated Pruritus

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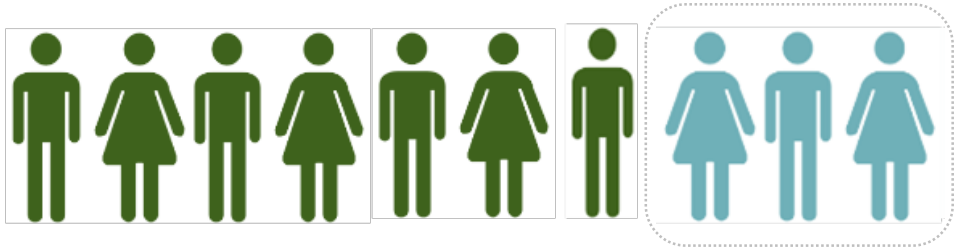
US Market Opportunity in CKD-aP: Non-Dialysis

~7.3 million
diagnosed with CKD (IQVIA est)



33%
receive pruritus tx

Per NKF, CKD is a big under-recognized US public health issue

- ~30 million people affected (causes more deaths than breast/ prostate cancer)

No FDA approved therapies – large unmet medical need

- Commonly used medications: anti-histamines, corticosteroids, gabapentin, anti-depressants etc.

Oral KORSUVA™, if approved for pre-dialysis patients, would not fall under ESRD bundle payment system

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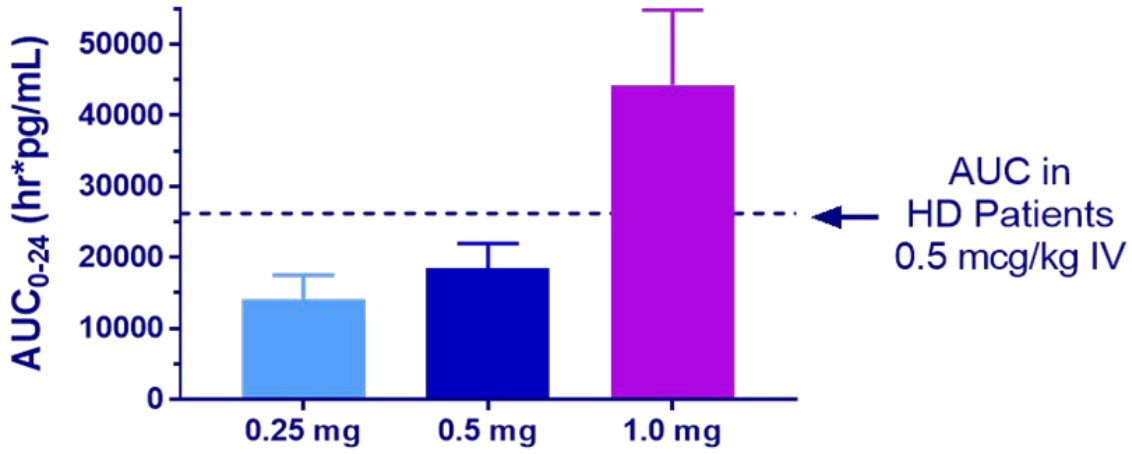
Oral KORSUVA Exposure Levels Were Similar to I.V. in CKD Patients

- Ph 1 study of Oral KORSUVA 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
- Exposure levels were observed to be approx. equivalent to those achieved with 0.5 mcg/kg dose of IV KORSUVA

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: Ph 2 Trial Ongoing

Study

- Double blind, randomized, PBO-controlled study in Stage III-V CKD patients with moderate to severe pruritus

Key Inclusion criteria

- CKD patients with moderate renal impairment with estimated GFR ≥30 and <60 mL/min/1.73 m^2 or severe renal impairment with estimated GFR <30 mL/min/1.73 m^2

Primary Endpoint:

- Change from baseline to week 12 in NRS itch score

Secondary Endpoints:

- Change in itch related QoL: Skindex-10 & 5-D Itch scales
- Responder analysis (12 week): Change from baseline in NRS score of ≥3 points

Interim Data Monitoring Committee (IDMC) recommended no increase in sample size after Interim Assessment

Oral KORSUVA for CKD-aP: Interim Conditional Power Analysis Completed 7/19/19 by IDMC

- IA based on 50% of patients completing treatment period (3 months)
  - N= 120 patients for IA
- IDMC Recommended:
  - No increase in sample size to achieve desired power for Primary Endpoint
  - No modifications in safety monitoring for trial based on unblinded analysis
- Trial Fully Enrolled at ~240 patients – topline data expected Q4, 2019

Oral KORSUVA™ : Additional Development Programs

Chronic Liver Disease & Atopic Dermatitis

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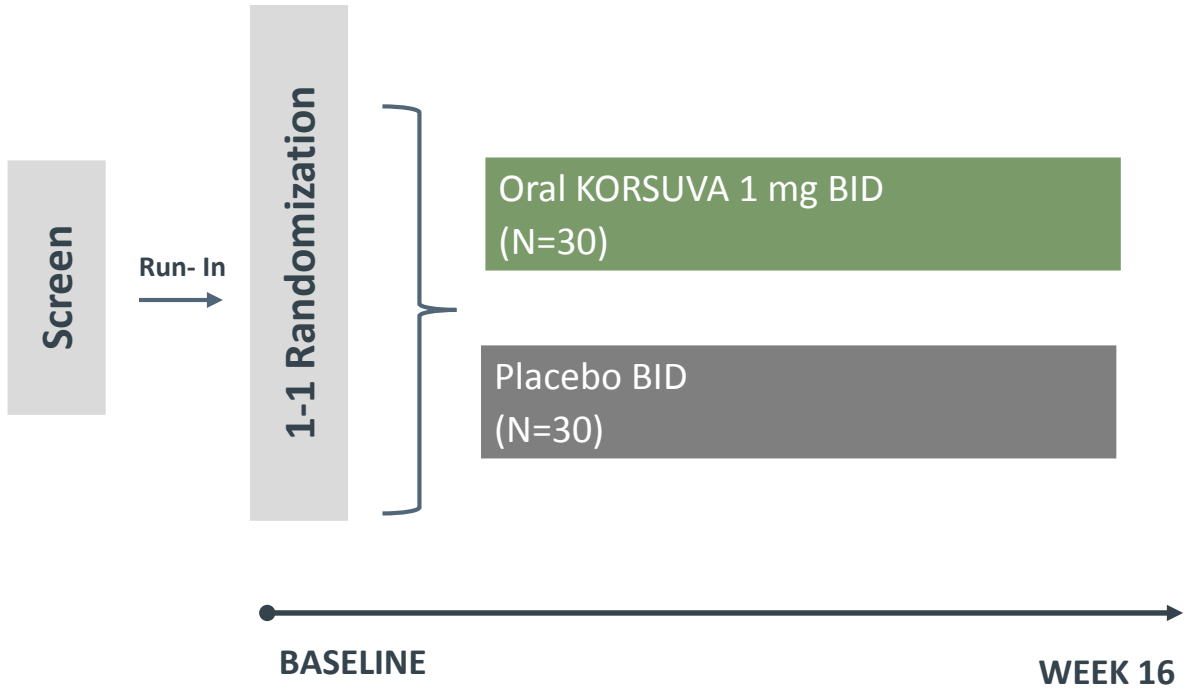
Pruritus Associated with Primary Biliary Cholangitis (PBC): Phase 2



Study

- A 16-week, double blind, randomized, PBO-controlled study in PBC patients with moderate to severe pruritus

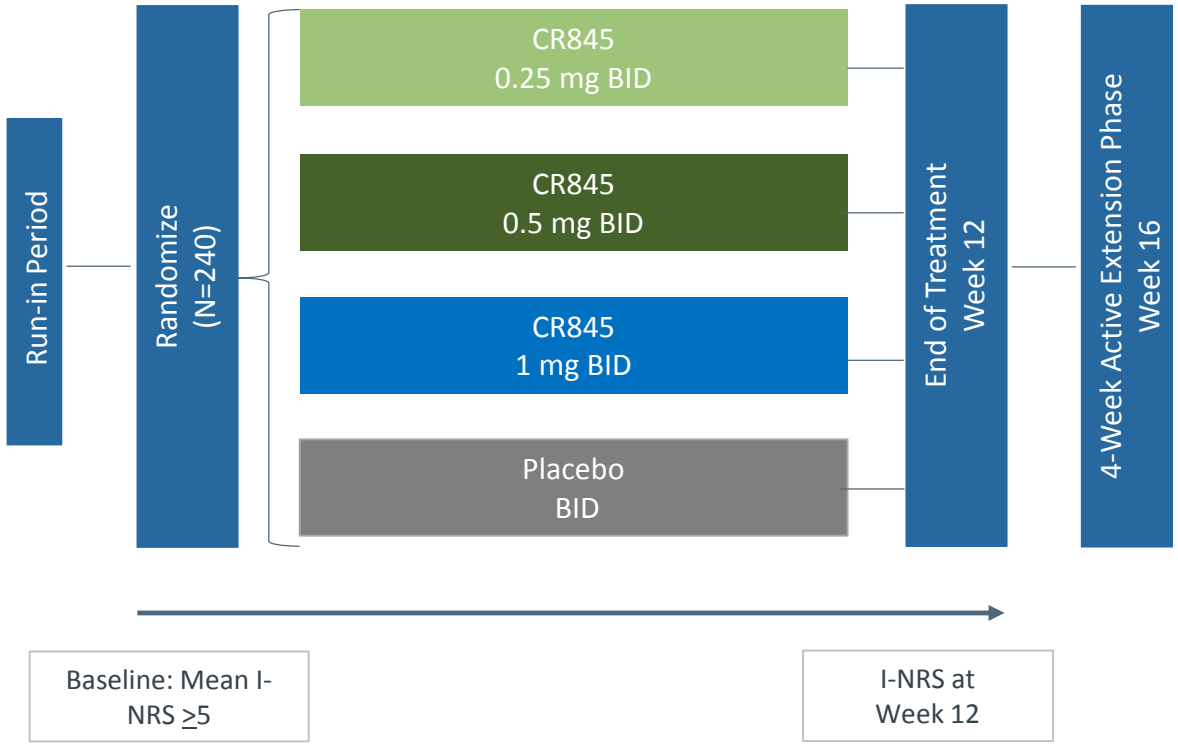
Primary Endpoint:

- Change from baseline in the weekly mean of the daily 24-hour WI-NRS score at week 16

Secondary Endpoints:

- Change in itch related QoL: Skindex-10 & 5-D Itch scales at week 16
- Responder analysis (Week 16): Change from baseline in weekly main of daily worst NRS score of ≥3 points

Atopic Dermatitis Associated Pruritus: Ph 2 Trial Ongoing



Study

- Double blind, randomized, PBO-controlled study in adult subjects with AD and moderate to severe pruritus

Primary Endpoint:

- Change from baseline in the weekly mean of the daily 24-hour I-NRS score at Week 12

Secondary Endpoints:

- Change in itch related QoL: Skindex-10, 5-D Itch scales & Sleep Quality Assessment at week 12
- Responder analysis (Week 12): Change from baseline in I-NRS score of ≥4 points

US Market Opportunity in CLD and AD

Chronic Liver Disease associated Pruritus

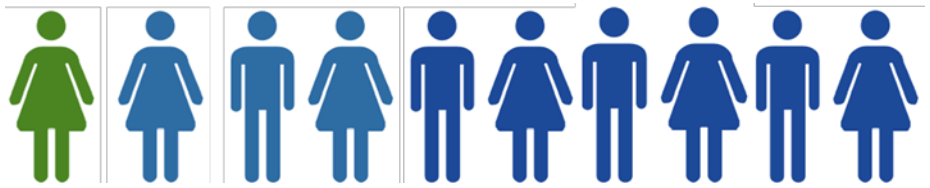
~20% to 30% experience pruritus

- Prevalence of pruritus in patients with Primary Biliary Cholangitis is as high as 70%

Ref: Rishe E, et al. Acta Derm Venereol 2008; 88: 34-37.
Satoshi O, et al. Hepatol Res. 2018; 48: E252-E262

Atopic Dermatitis associated Pruritus

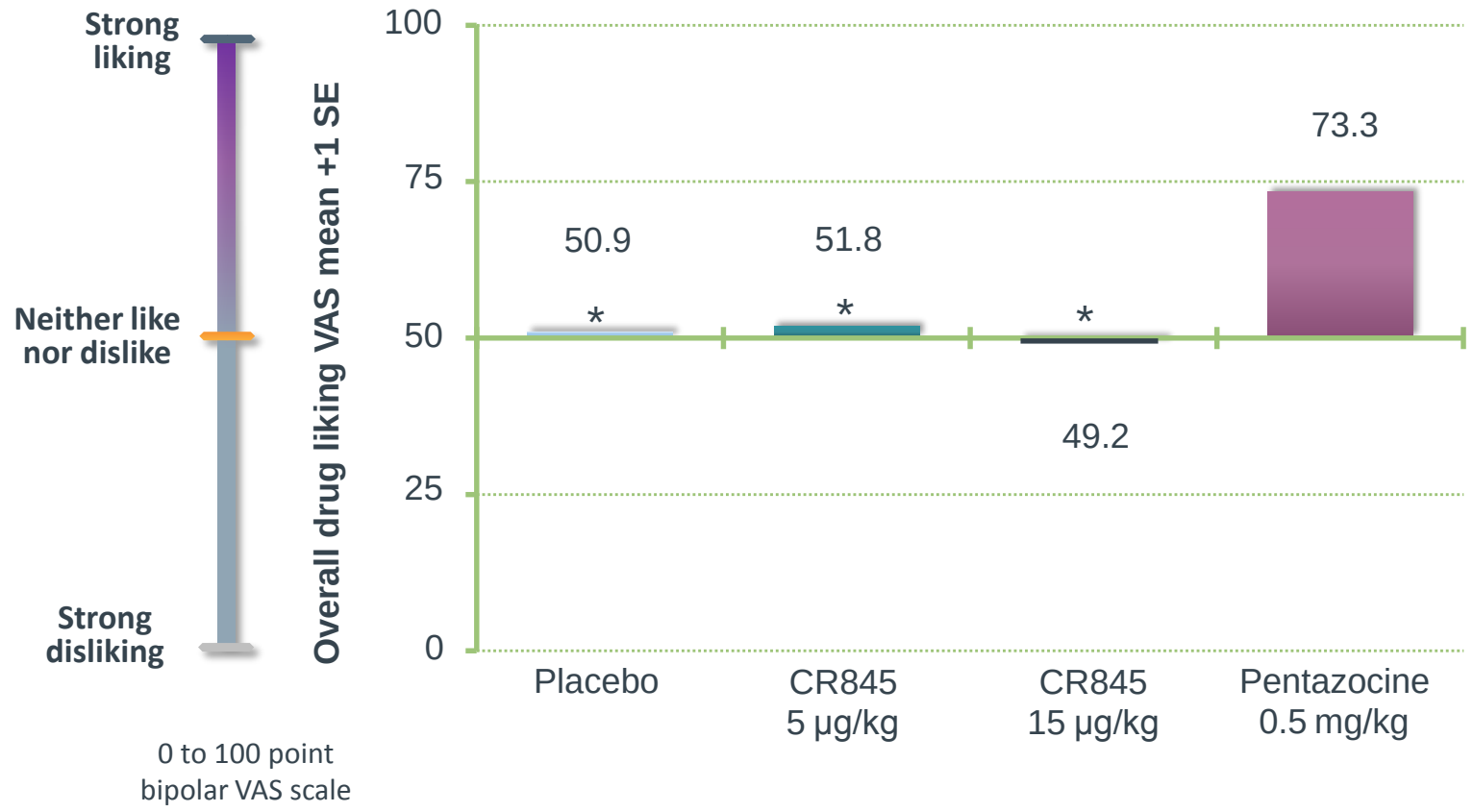
~87 to 100% experience pruritus



- AD prevalence in adults: up to 5%
- Prevalence of pruritus in AD is ~87 to 100% and ~50% of patients seek treatment for pruritus

Ref: Boguniewicz M. Immunol *Allergy Clin N Am*. 2005; 25(2):333–51; Eichenfeld L et al. *Am Acad Dermatol*. 2014; 70(2): 338–351; Barbarot S et al. *Allergy*. 2018; 73(6):1284-1293.
IMS Pruritus Market Landscape Analysis, September 2014

Human Abuse Liability Study:
CR845 Exhibited No “Drug Liking” Over 8-Hour Test Session



0 to 100 point bipolar VAS scale

*$p<0.001$ *vs* pentazocine (n=39)

Mixed-model repeated measures analysis

Projected Clinical Milestones – 2019/ 2020

	Pruritus / KORSUVA™ Injection	Pruritus / Oral KORSUVA™
4Q, 2019	Top-line data from Global Ph 3 trial, KALM-2 (CKD-aP in dialysis pts)	Top-line data from Phase 2 Trial CKD-aP (Stage III-V)
2020		Top-line data from Phase 2 Trial in AD & PBC patients with pruritus
2H, 2020	**NDA Submission**	

Financial Highlights

Pro forma Cash and marketable securities (June 30, 2019)

$135.6M

Net loss – March 31, 2019

($22M)

Shares outstanding (June 30, 2019)

~40M

Stock options (June 30, 2019)

~4.7M