Targeting Pruritus with First-In-Class Therapeutics

March 2021

CARA THERAPEUTICS

Forward Looking Statements

Statements contained in this presentation regarding matters that are not historical facts are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Examples of these forward-looking statements include statements concerning the expected timing of the enrollment and data readouts from the Company's ongoing clinical trials, the potential results of ongoing clinical trials, timing of future regulatory and development milestones for the Company's product candidates and potential commercialization of KORSUVA Injection for CKD-aP, the expected timeline for conducting meetings with the FDA concerning the Company's product candidates, the potential for the Company's product candidates to be alternatives in the therapeutic areas investigated, the Company's expected cash reach, and the potential impact of COVID-19 on the Company's clinical development and regulatory timelines and plans. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Risks are described more fully in Cara Therapeutics' filings with the Securities and Exchange Commission, including the "Risk Factors" section of the Company's most recent Annual Report on Form 10-K for the year ending December 31, 2020 and its other documents subsequently filed with or furnished to the Securities and Exchange Commission. All forward-looking statements contained in this press release speak only as of the date on which they were made.

Cara Therapeutics undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made.

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Pruritus: Large Opportunity Across Different Disease Areas

Chronic Kidney Disease (CKD)

Pruritus occurs in both patients on hemodialysis and those with CKD not yet on dialysis.

~40 to 50%

Chronic Liver Disease (CLD)

Patients with CLD, especially cholestatic liver disease experience significant pruritus

.

~20% to 30%

Atopic Dermatitis (AD)

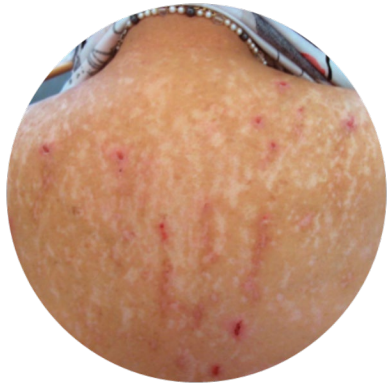
Pruritus is a defining symptom of AD

~100%

Notalgia Paresthetica (NP)

Pruritus is the defining symptom of NP

100%



U.S. Patients
Treated for Pruritus:

> 20 Million

SCRIPTS ANNUALLY#

IQVIA Analysis, 2013

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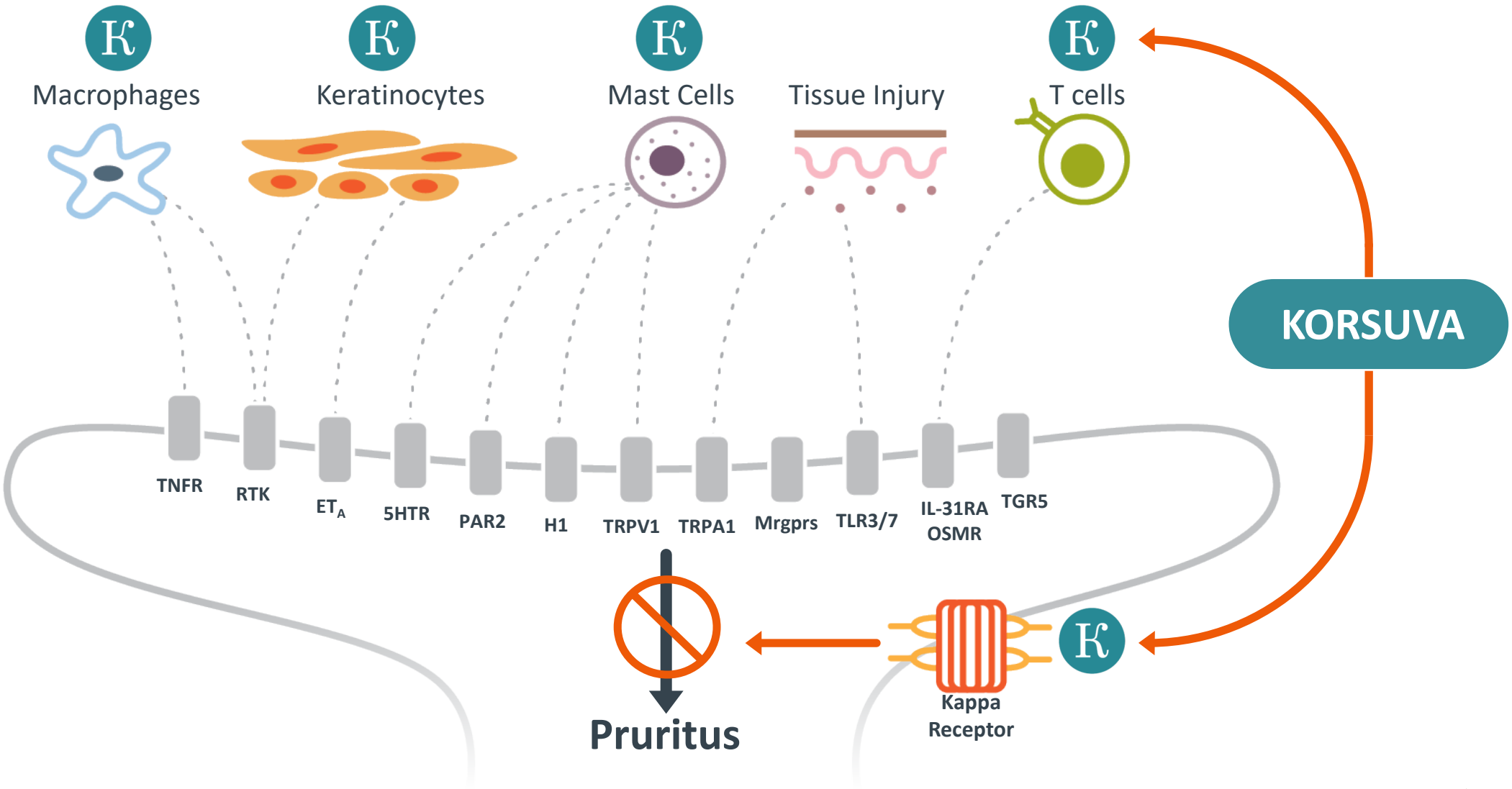
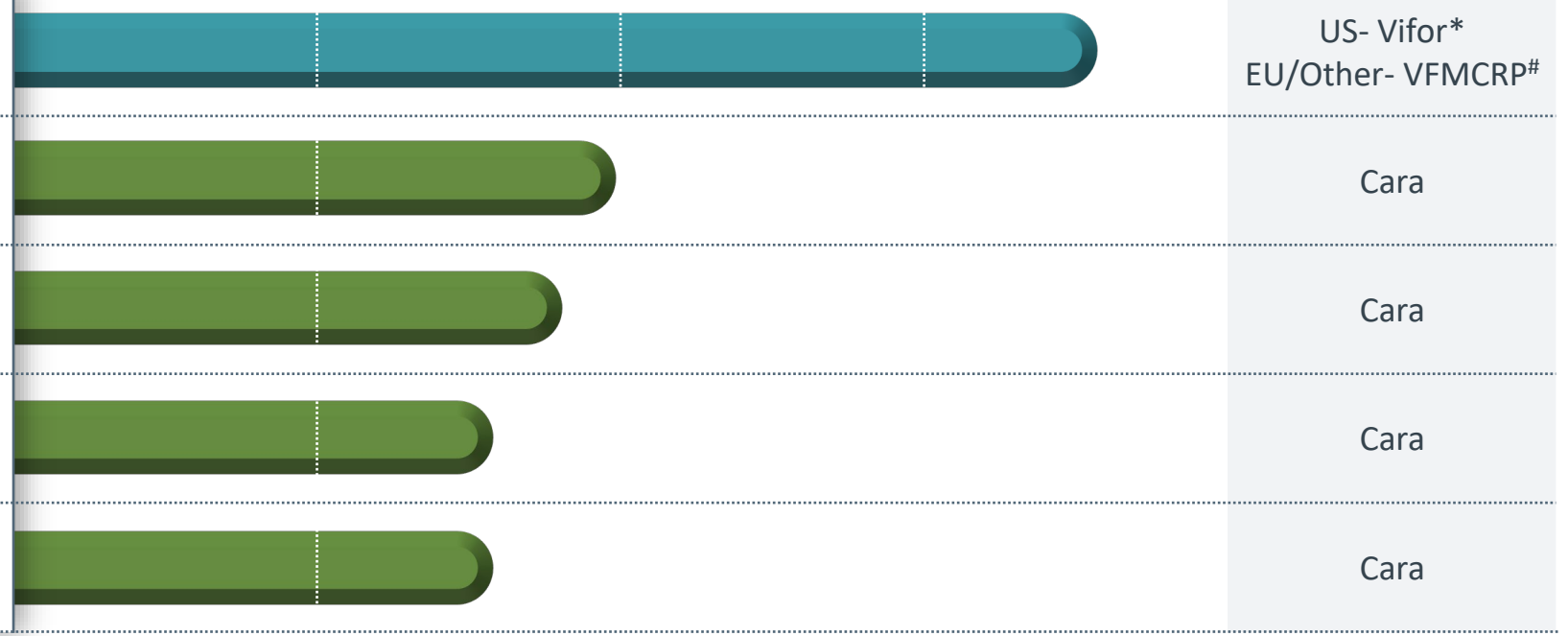
KORSUVA™ (Difelikefalin) Directly Blocks Pruritus Sensory Neurons



Source: Adapted from Pflugers Arch . 2013 December ; 465(12): . doi:10.1007/s00424-013-1284-2

Development Pipeline

Program	Indication	STAGE OF DEVELOPMENT: Phase 1	Phase 2	Phase 3	NDA Review	Commercial Rights (ex-Japan and S. Korea)^
KORSUVA™ Injection	Pruritus CKD-HD**					US- Vifor* EU/Other- VFMCRP#
Oral KORSUVA™	Pruritus CKD (III-V)					Cara
Oral KORSUVA™	Pruritus Atopic Dermatitis					Cara
Oral KORSUVA™	Pruritus CLD					Cara
Oral KORSUVA™	Pruritus in NP					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; Q1 2021 NDA accepted with priority review PDUFA date Aug 23rd, 2021
# VFMCRP and Cara have rights to promote in Fresenius Medical Care dialysis clinics in the US under a profit share agreement
* Vifor has commercial rights in Non-US Fresenius clinics under a profit-share arrangement

CKD-HD: Chronic Kidney Disease- Hemodialysis; **CLD**: Chronic Liver Disease; **NP**: Notalgia Paresthetica

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KORSUVA™ Injection for Dialysis Patients

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

KORSUVA™ Injection For CKD-associated Pruritus (CKD-aP) in Dialysis Patients

60%

of ESRD patients have pruritus[2,3]

>500K[1]

patients on dialysis

~40%

have moderate to severe pruritus

- **Serious intractable systemic pruritus**
- CKD-aP 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

Phase 3 Program complete

- NDA submission – **Q4, 2020**[4]
- Commercial launch - **2021**[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. Q1 2021 NDA accepted with priority review PDUFA date scheduled August 23, 2021

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KORSUVA Injection: U.S. Commercial Strategy
Cara/Vifor Commercial License

- **Employ Vifor Established Nephrology Commercial Organization**
  - 200 sales FTEs: *Mircera, Velphoro, Venafer*
  - Existing relationships with US LDOs, MDOs and IDOs
  - Established market access team
  - Existing supply chain organization

- **Leverage Existing Cara/Vifor Synergies From Ongoing Collaboration**
  - Global brand development

Cara/Vifor Commercialization Agreement: Summary Terms (Ex-Fresenius Medical Care Clinics)

- Up-Front: **$150M** ($100M Cash/ $50M Equity)
- U.S. Regulatory Approval Milestone: **$50M Equity**
- U.S. Market Profit Split: **Cara 60%: Vifor 40%**
  (Ex-FMC Clinics: Vifor Promotion[1])
- U.S Commercial Sales Milestones: **$240M**

1. FMC Clinics Profit Split: Cara 50%: VFMCRP 50% - 2018 Cara and Vifor/Fresenius License Agreement

Established Ex-U.S. Commercial Agreements: KORSUVA Injection

VIFOR FRESENIUS MEDICAL CARE RENAL PHARMA

Tiered Royalty By Sales: **EU**
$440 million Commercial Milestones

Maruishi Pharmaceutical Co., Ltd.

Tiered Royalty By Sales: **Japan**
~$10 million Commercial Milestone#

Chong Kun Dang

Tiered Royalty By Sales: **S. Korea**

• # 1 Billion Yen

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Oral KORSUVA™ Development Programs

Development Pipeline

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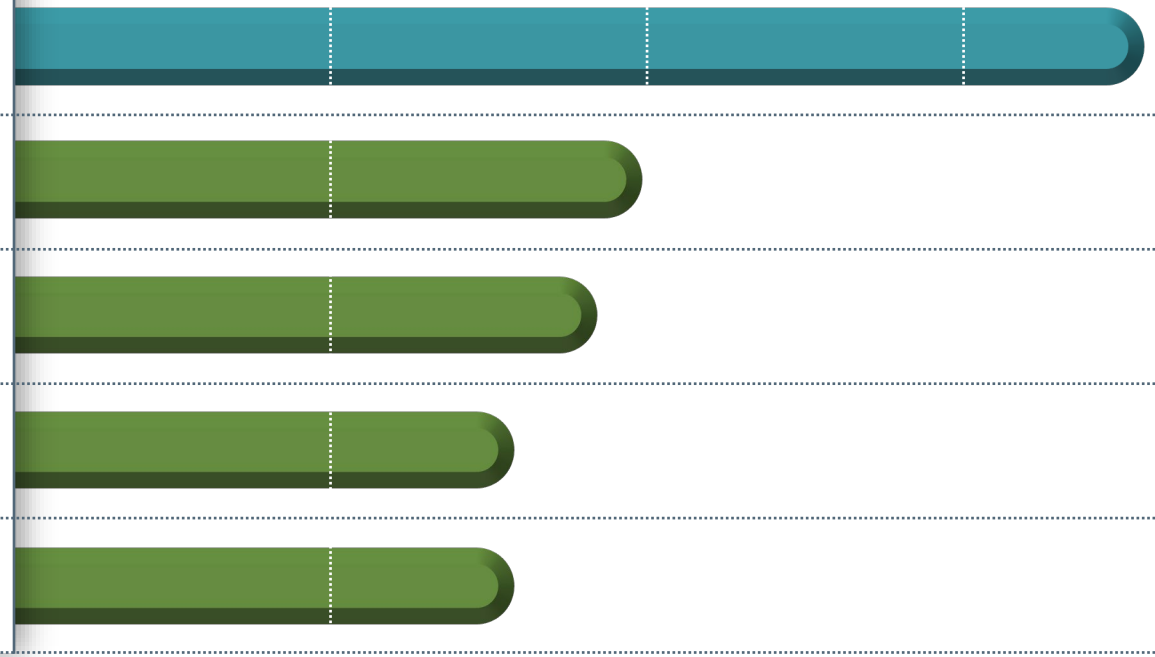

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US Market Opportunity in CKD-aP: Non-Dialysis

~7.3 million
diagnosed with CKD (IQVIA est)

33%
receive pruritus tx

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

- ~30 million people affected

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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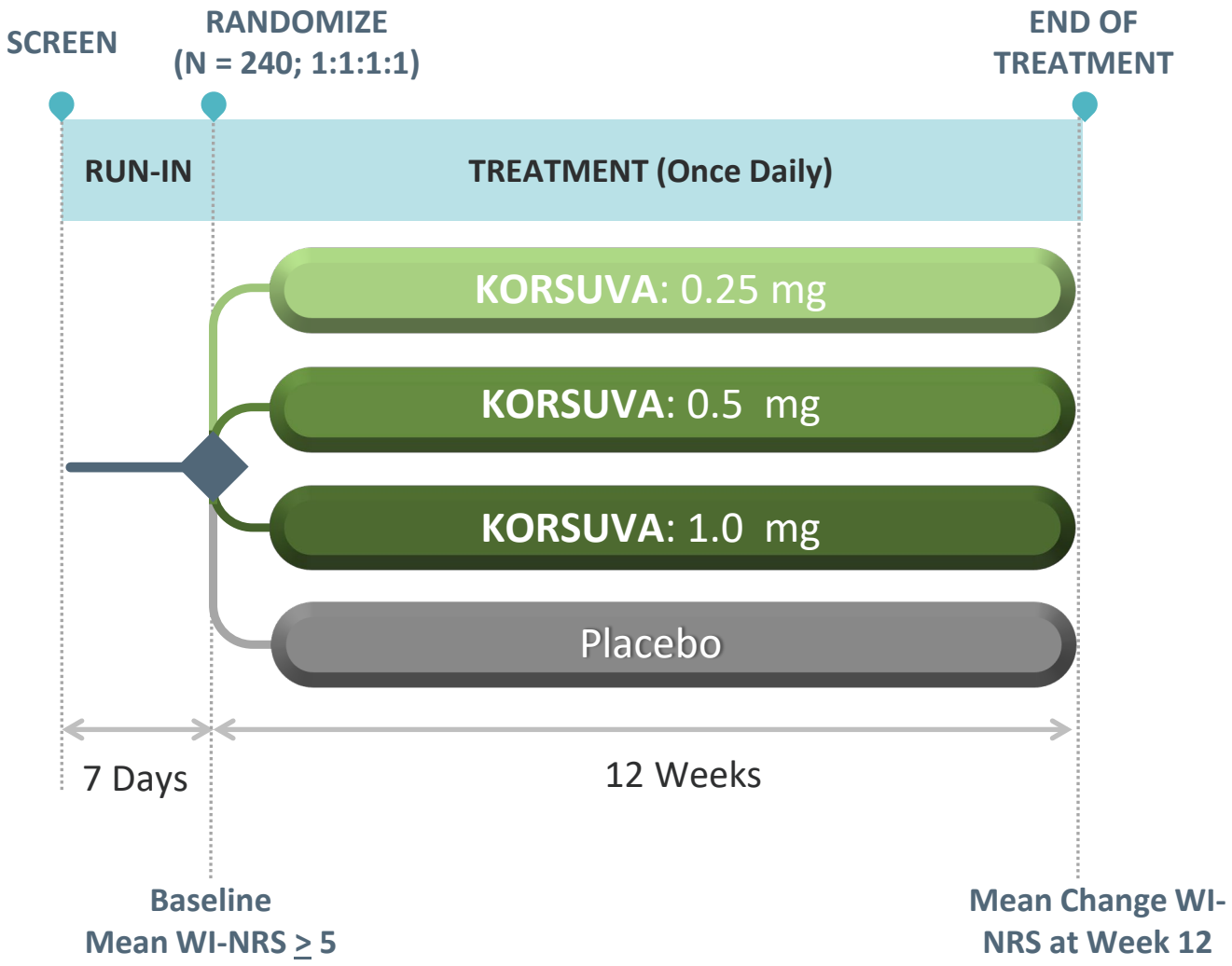
Oral KORSUVA™ for CKD-aP: Phase 2 Trial Design



Endpoints: Week 12

Primary

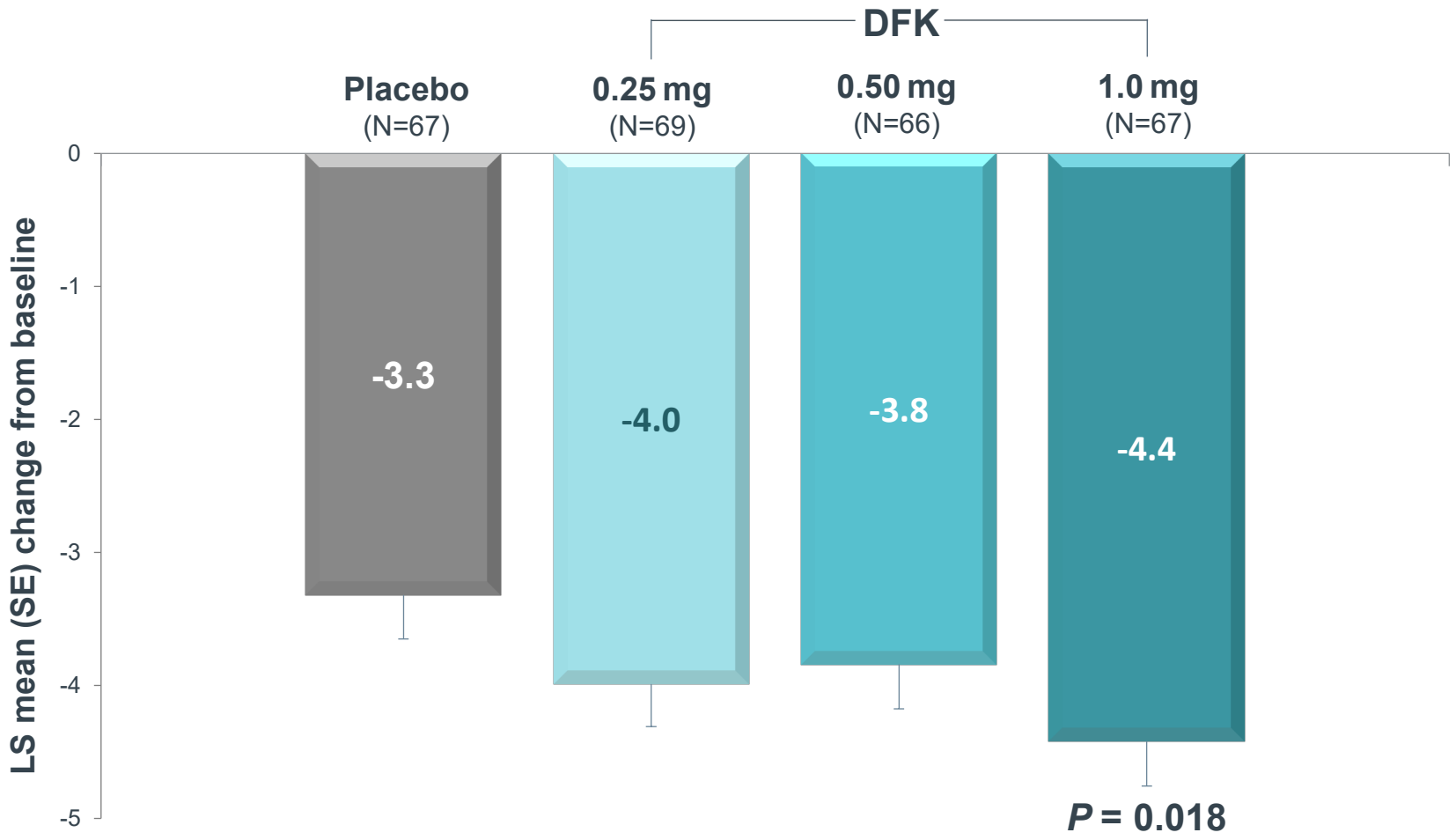
- Change from baseline in weekly mean of daily Worst Itching Intensity NRS (WI-NRS) score

Secondary & Additional

- Change from baseline in itch-related QoL
  - ✓ Skindex-10
  - ✓ 5-D Itch
- Proportion of subjects achieving >3 points improvement from baseline in weekly mean of daily WI-NRS score
- WI-NRS complete responder; patient global impression of change
- Safety Assessments

Primary Endpoint: Change From Baseline in the WI-NRS at Week 12

Patients in the DFK 1.0-mg group demonstrated significantly greater improvement in the mean WI-NRS vs placebo



P value vs placebo (*P*=NS for 0.25 mg and 0.5 mg DFK vs placebo). Statistical tests were 2-sided (alpha=0.5). LS mean from MMRM with terms for treatment group, week, week by treatment interaction as fixed effects; baseline score and strata as covariates; patient as a repeated measure. Analyzed in the full analysis population (patients receiving ≥1 dose based on randomized treatment). Error bars represent standard error (SE). Missing data imputed using MI under MAR assumption. LS, least squares; MAR, missing at random; MI, multiple imputation; MMRM, mixed model for repeated measures.

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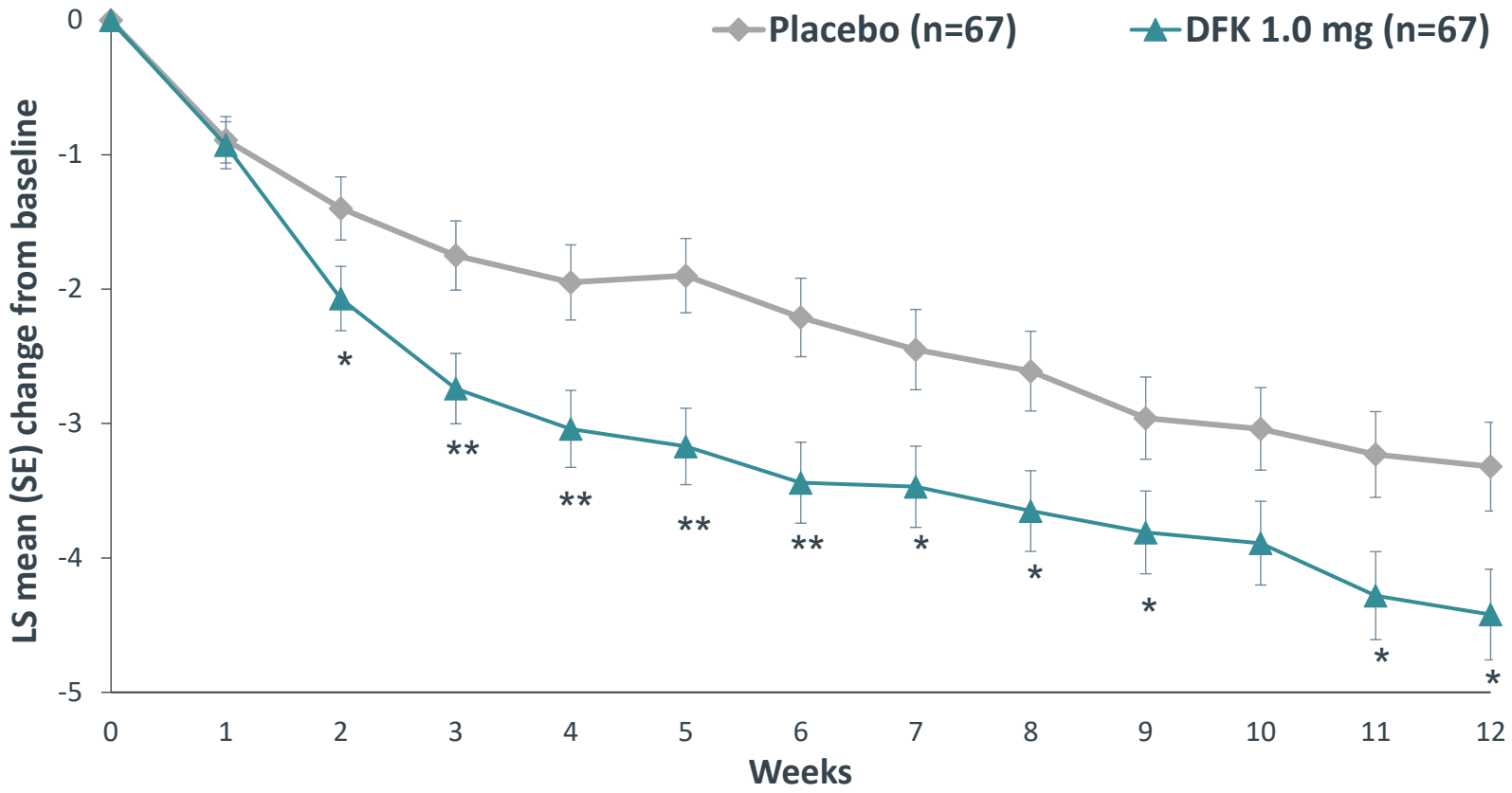
Change From Baseline in WI-NRS Over Time

Significantly greater improvements in WI-NRS were observed with DFK 1.0 mg vs placebo as early as week 2 and were maintained up to week 12



*P<0.05. **P<0.01. Statistical tests were 2-sided (alpha=0.5). LS mean from MMRM with terms for treatment group, week, week by treatment interaction as fixed effects; baseline score and strata as covariates; patient as a repeated measure. Analyzed in the full analysis population (patients receiving ≥1 dose based on randomized treatment). Error bars represent SE. Missing data imputed using MI under MAR assumption.

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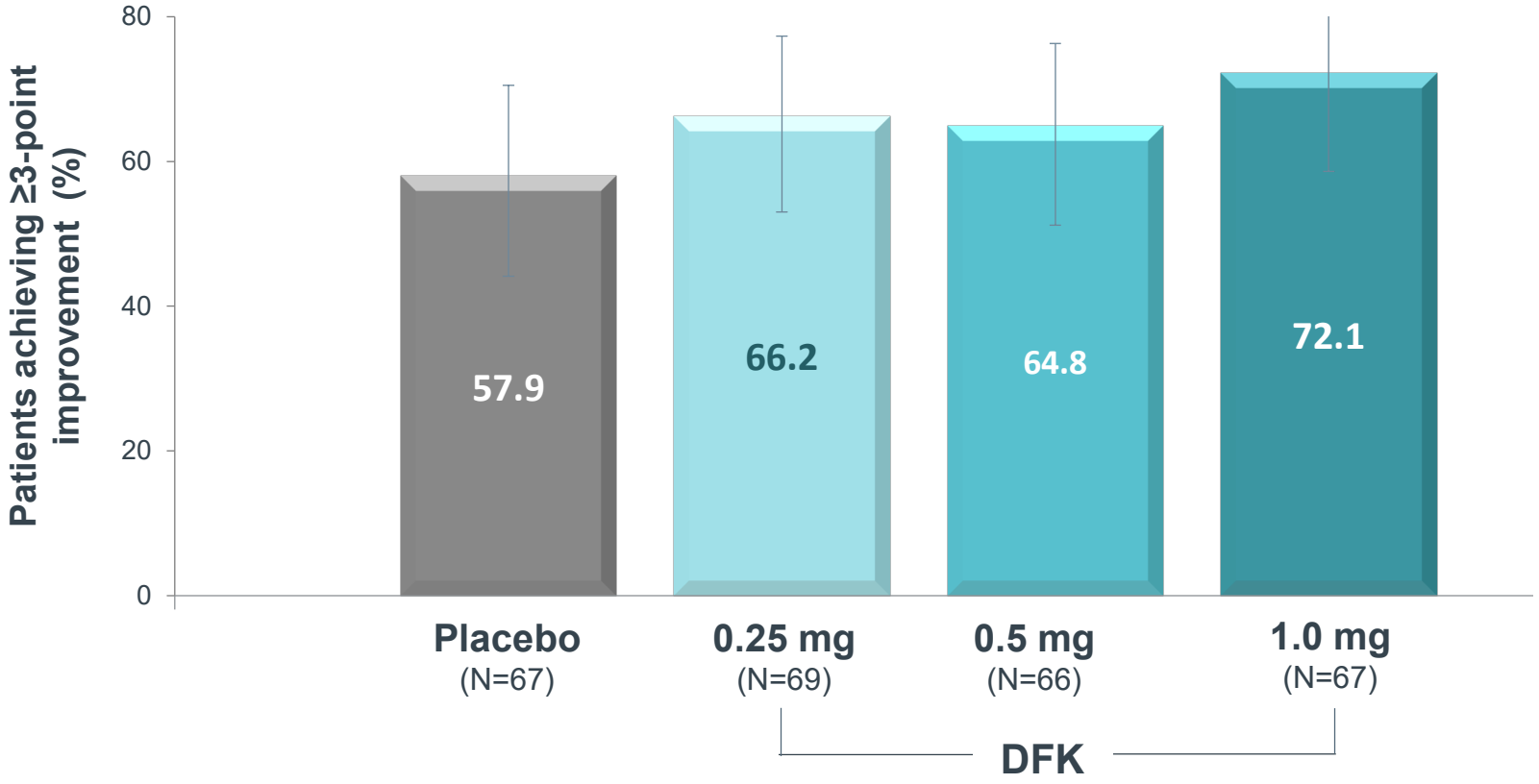
Achievement of ≥3-Point Improvement in WI-NRS at Week 12

More than 70% of patients achieved ≥3-point improvement in WI-NRS with DFK 1.0 mg



P value vs placebo (P=NS for all DFK doses vs placebo). Statistical tests were 2-sided (alpha=0.5). Estimated percentage and P values are based on a logistic regression model with terms for treatment group, baseline WI-NRS score, and renal disease status. Analyzed in the full analysis population (patients receiving ≥1 dose based on randomized treatment). Error bars represent 95% confidence interval (CI). Missing data imputed using MI under MAR assumption.

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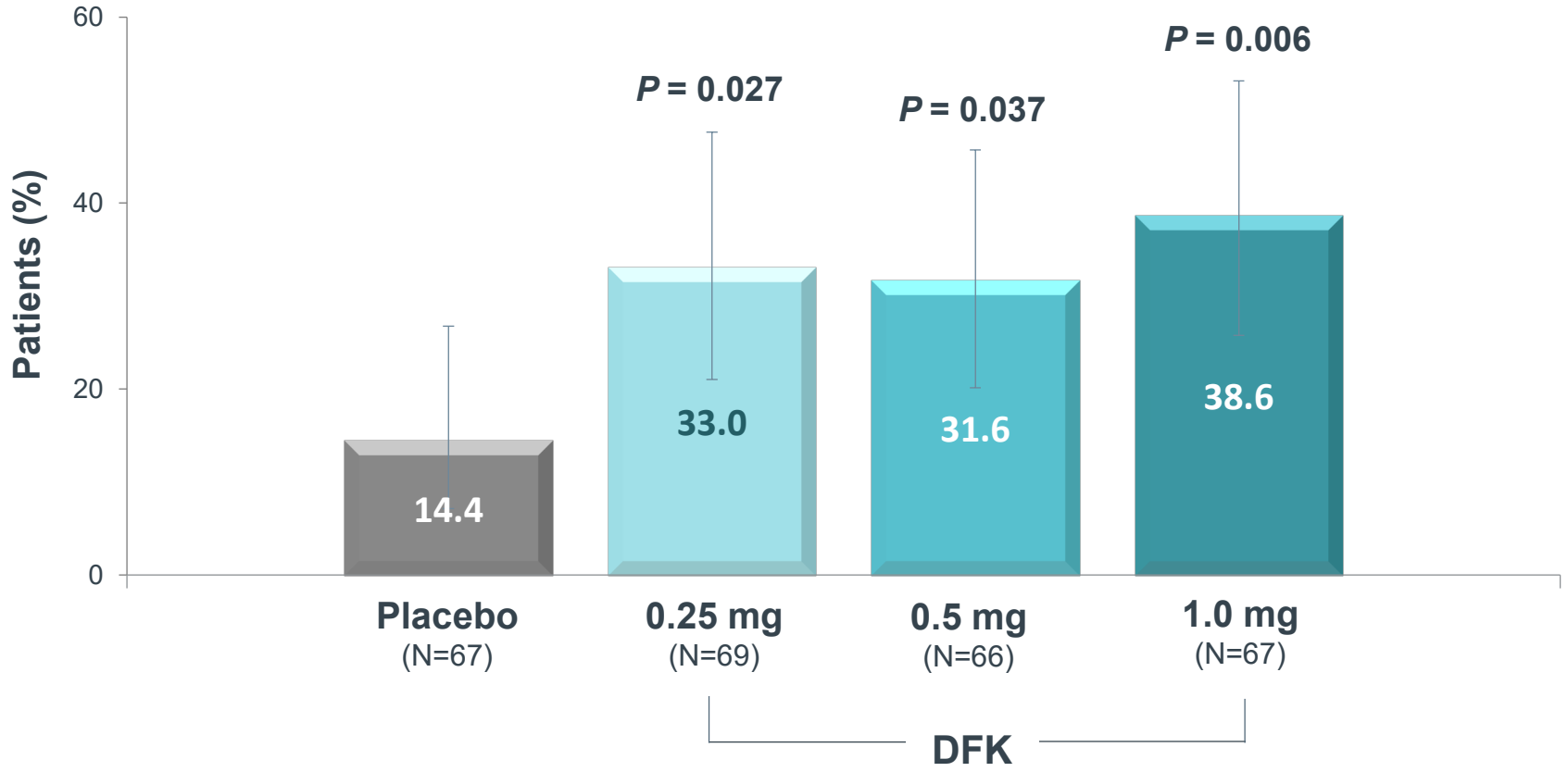
Complete Response at Week 12

Significantly greater proportions of patients who received DFK at all 3 dose levels achieved a complete response compared with placebo



P value vs placebo. Statistical tests were 2-sided (alpha=0.5). Estimated percentage and P values are based on a logistic regression model with terms for treatment group, baseline WI-NRS score, and renal disease status. Error bars represent 95% CI. Analyzed in the full analysis population (patients receiving ≥1 dose based on randomized treatment). Complete response is defined as achievement of ≥80% of the non-missing daily NRS scores equal to 0 or 1 in a week.

Executive Summary & Next Steps

- **Oral KORSUVA met the primary endpoint:1mg dose advancement to Phase 3**
  - Primary: Change from baseline in weekly mean WI-NRS score
  - Dose-dependent statistically significant improvement in Complete Responders

- **Oral KORSUVA was generally well-tolerated: safety profile similar to Phase 3 KORSUVA Injection studies**

Projected EOPII Meeting: Q2,2021

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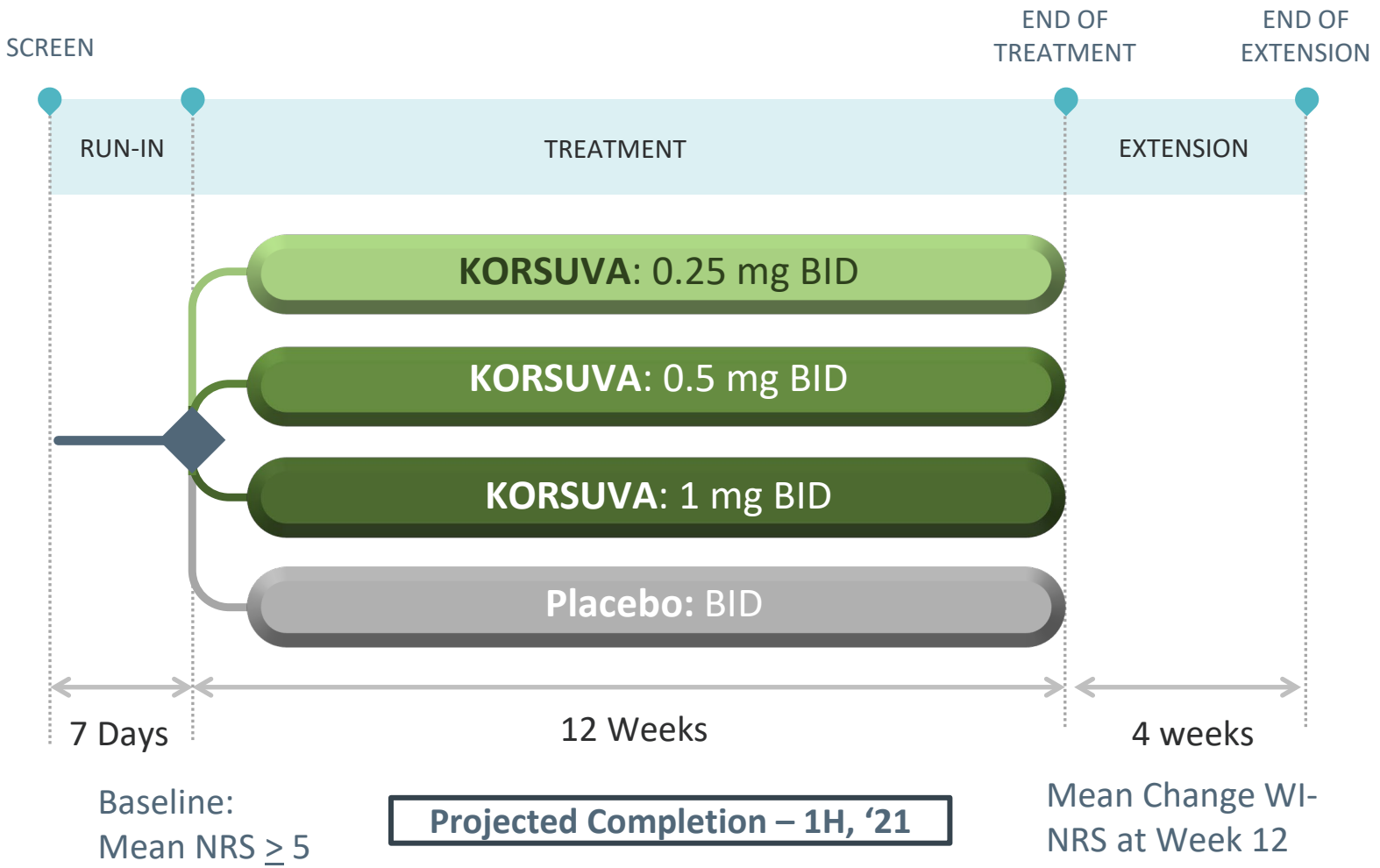
Atopic Dermatitis Associated Pruritus: Phase 2 Trial Ongoing



Study

~400 adult patients with AD and moderate to severe pruritus

Primary Endpoint:

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

Secondary Endpoints:

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

Oral KORSUVA For Atopic Dermatitis-Associated Pruritus

Oral KORSUVA:
Potential Broad Application

Moderate-Severe Pruritus

30 Million
U.S Patients

~80% Mild-Moderate Disease*

~20% Moderate-Severe Disease*

Approved Therapies

Topical Steroids & Immunomodulators

Injectable Biologic

* Mild-Moderate AD - EASI < 12; IGA 2 and 3: Moderate-Severe AD - EASI ≥ 12; IGA ≥ 3

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Financial Highlights

(As of December 31, 2020)

Cash/marketable securities

(Q4 2020)

$251.5M

[1] Proforma Net loss

(4^{th} Qtr. 2020)

($32.7M)

Shares outstanding

~49.9M

(1) Reported Q4 Net Income of $78.9M which includes $111.6M revenue due to Vifor license agreement one-time payment

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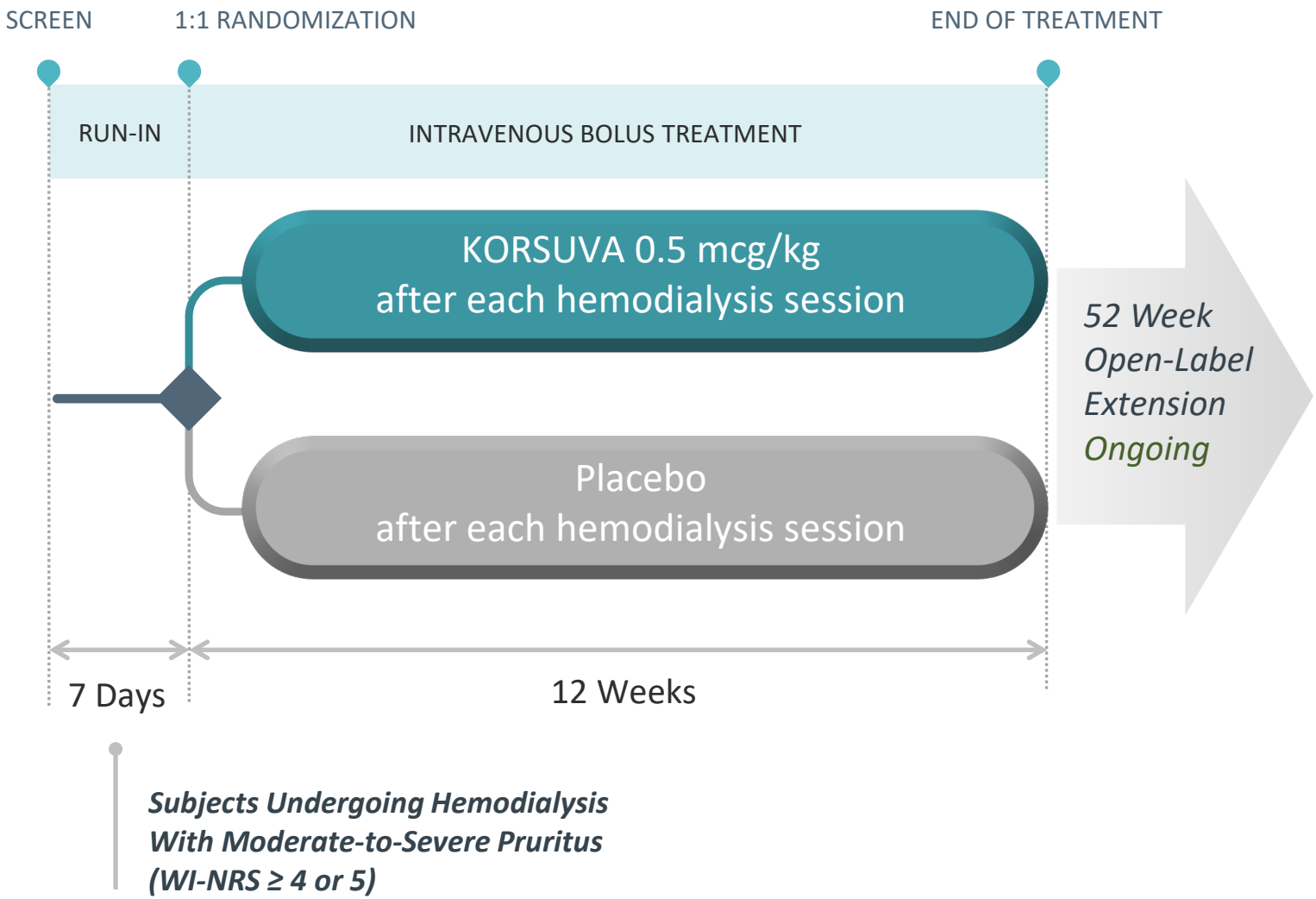
Projected Milestones –2021

	Pruritus / KORSUVA™ Injection	Pruritus / Oral KORSUVA™
1H,2021	✓ NDA Accepted Priority Review	Topline Data: Phase 2 Atopic Dermatitis
2H,2021	NDA Approval	Topline Data: Phase 2 Chronic Liver Disease
2H,2021	Commercial Launch	Initiate Phase 3 Programs: CKD-aP (Stage III-V CKD) Atopic Dermatitis

Appendix

KALM-1/2: General Pivotal Study Design



Endpoints: Week 12

Primary

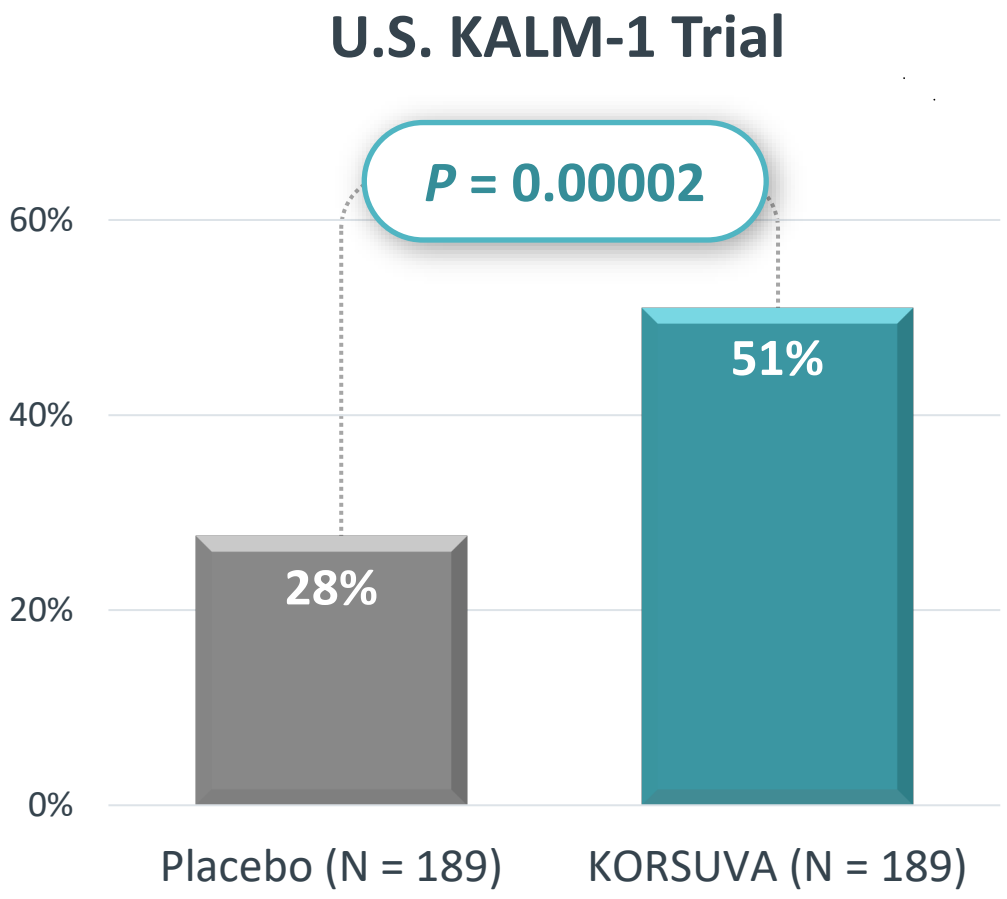
- Proportion of subjects achieving ≥3 point improvement from baseline in weekly mean of daily worst itching intensity NRS (WI-NRS)

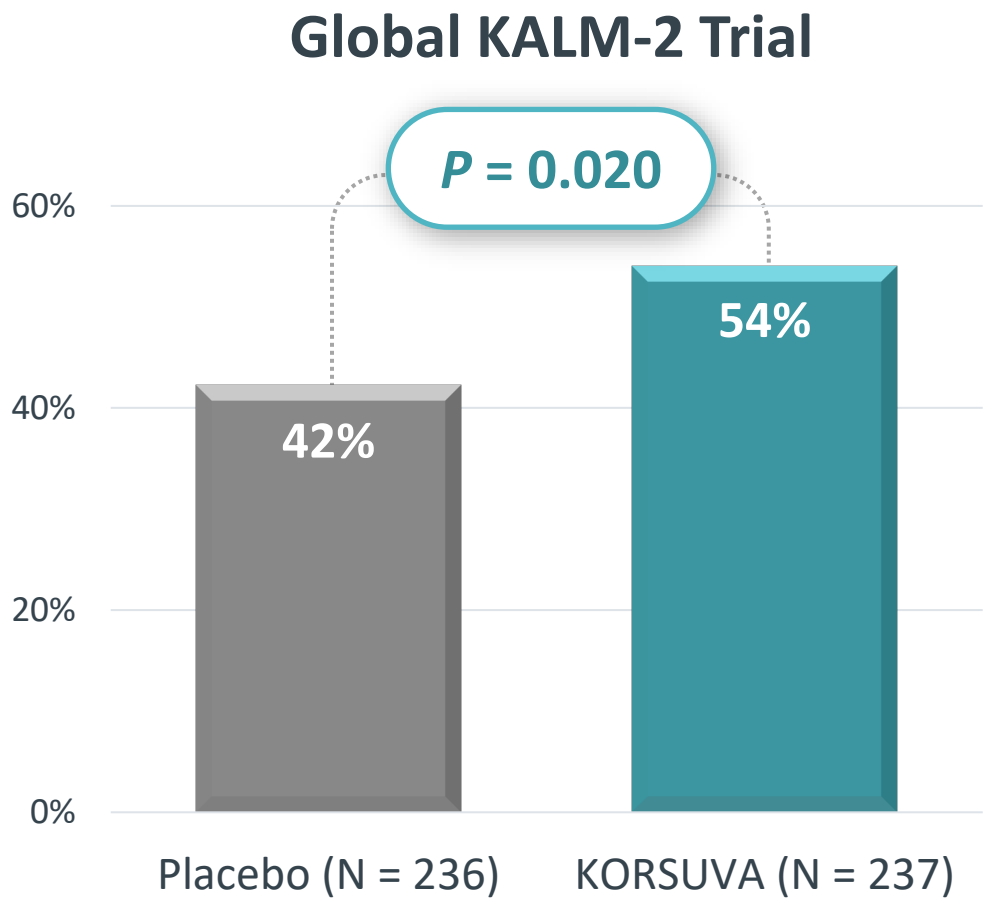
Secondary

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

Safety assessments

Primary Endpoint: ≥3 point improvement WI-NRS (Week 12)





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

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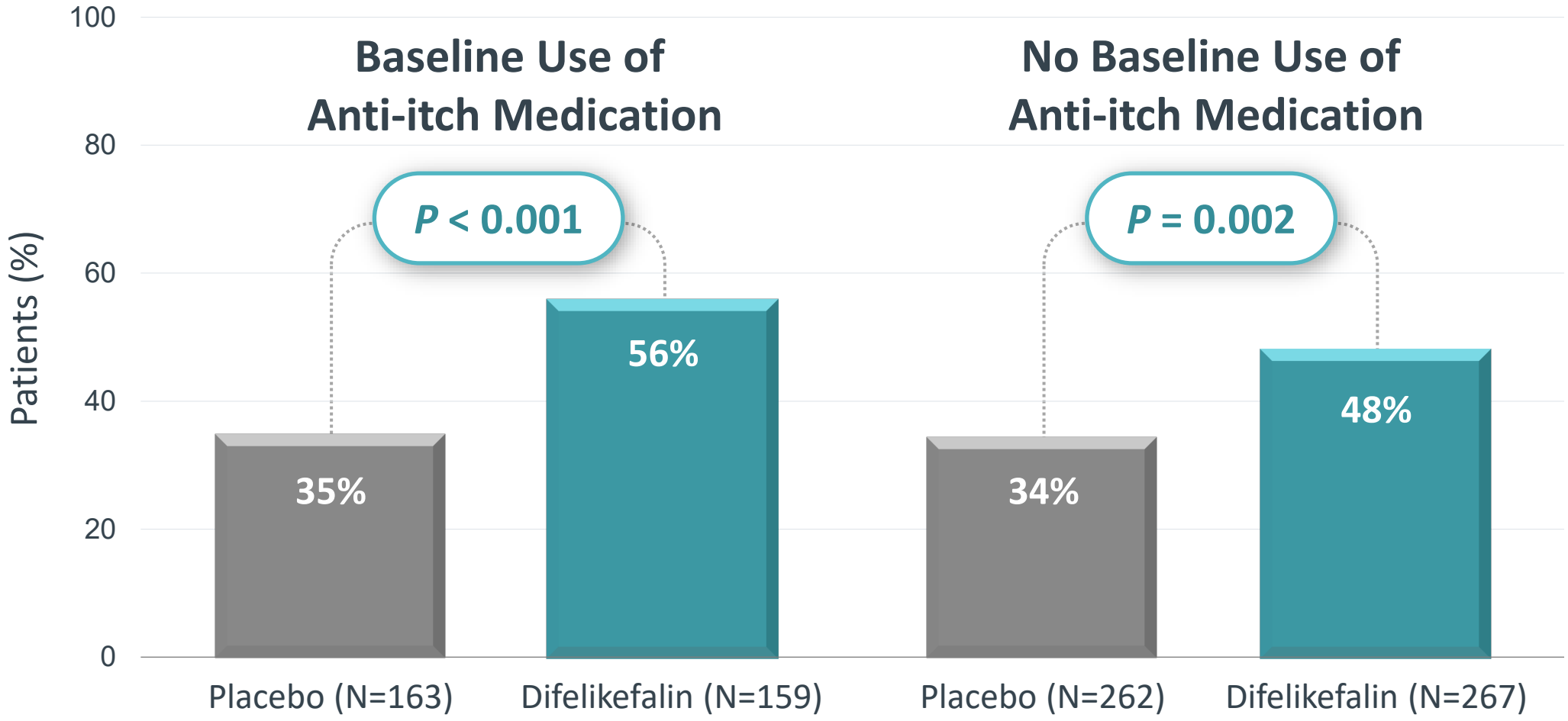
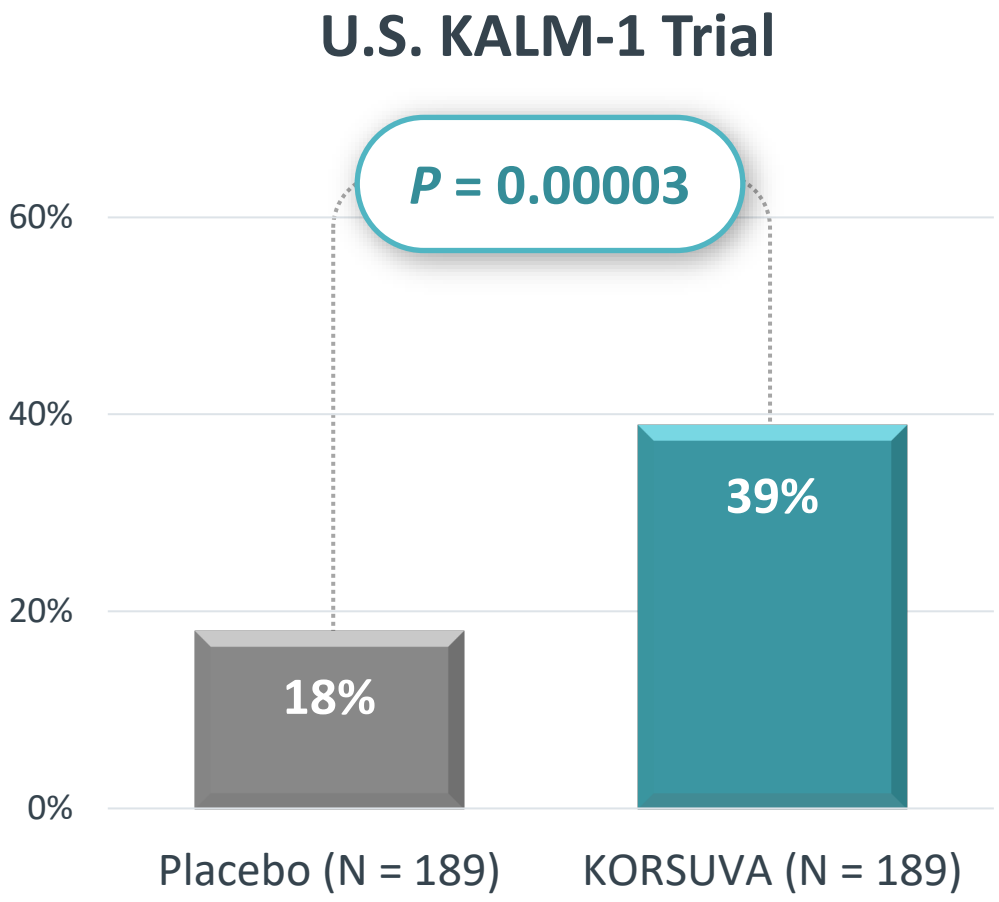
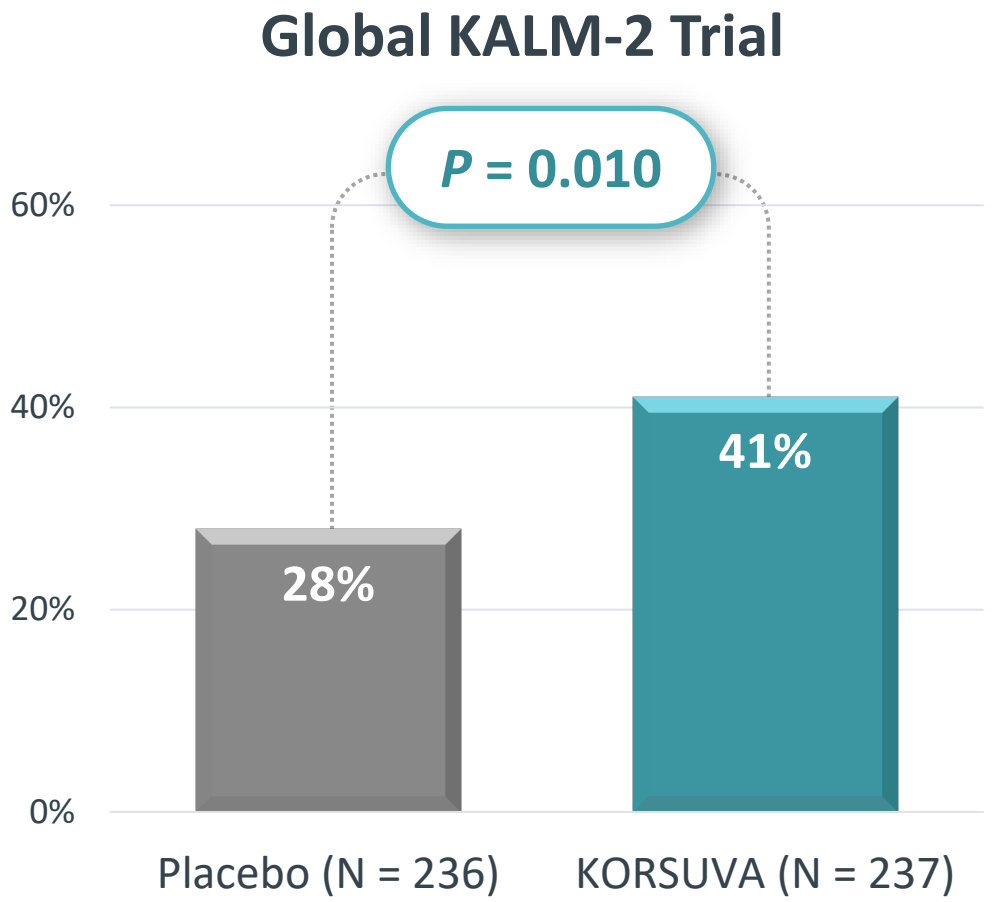
≥3-point Improvement in WI-NRS by Baseline Use of Anti-itch Medication (KALM-1 and KALM-2 Pooled)



Key Secondary Endpoint: ≥4 point improvement WI-NRS (Week 12)





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

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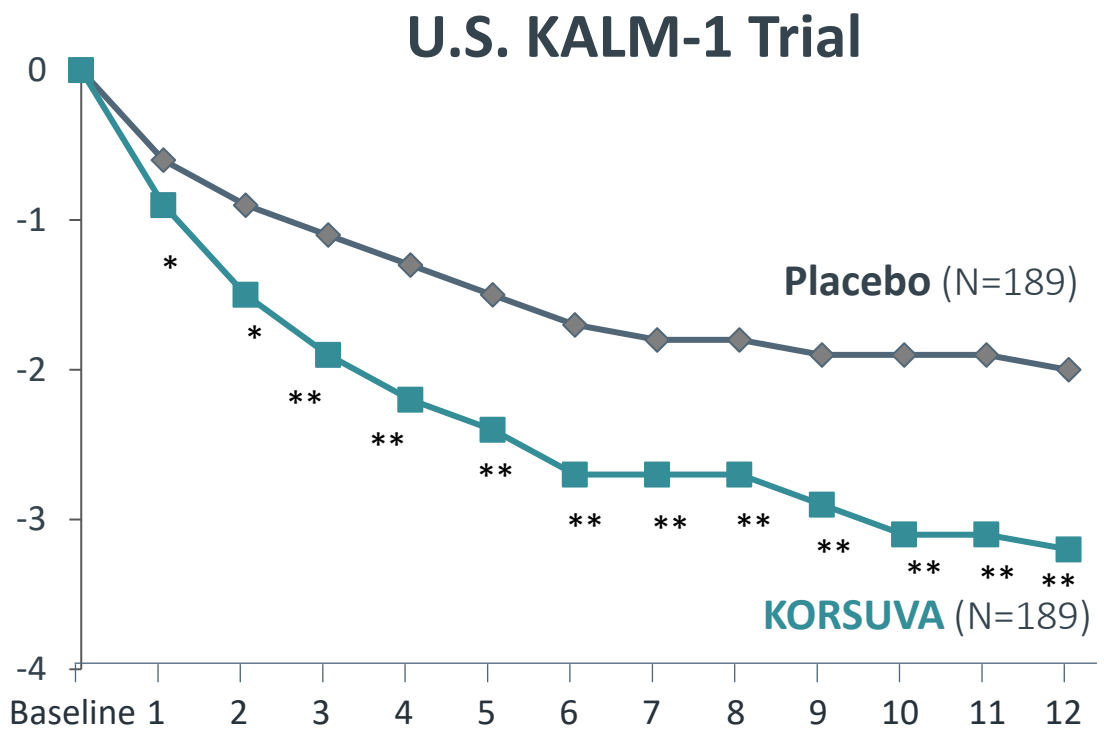
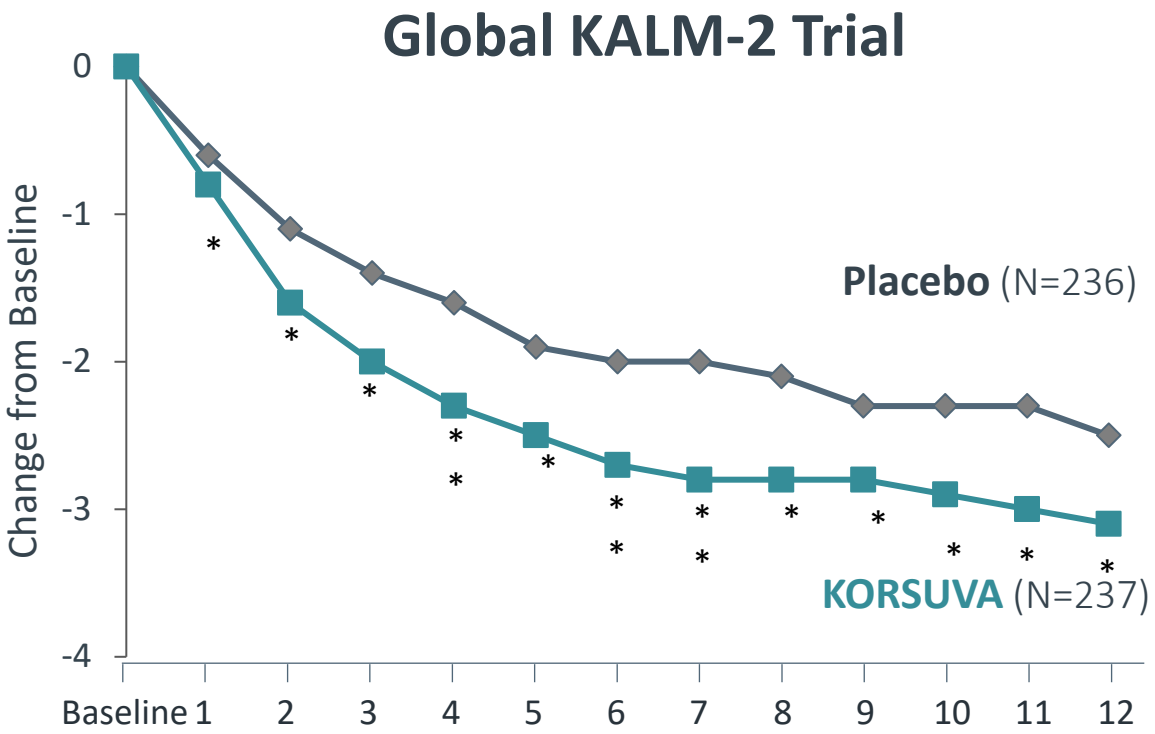
Change from Baseline in WI-NRS Over Time

Significant differences observed in WI-NRS starting at Week 1 and sustained through treatment period

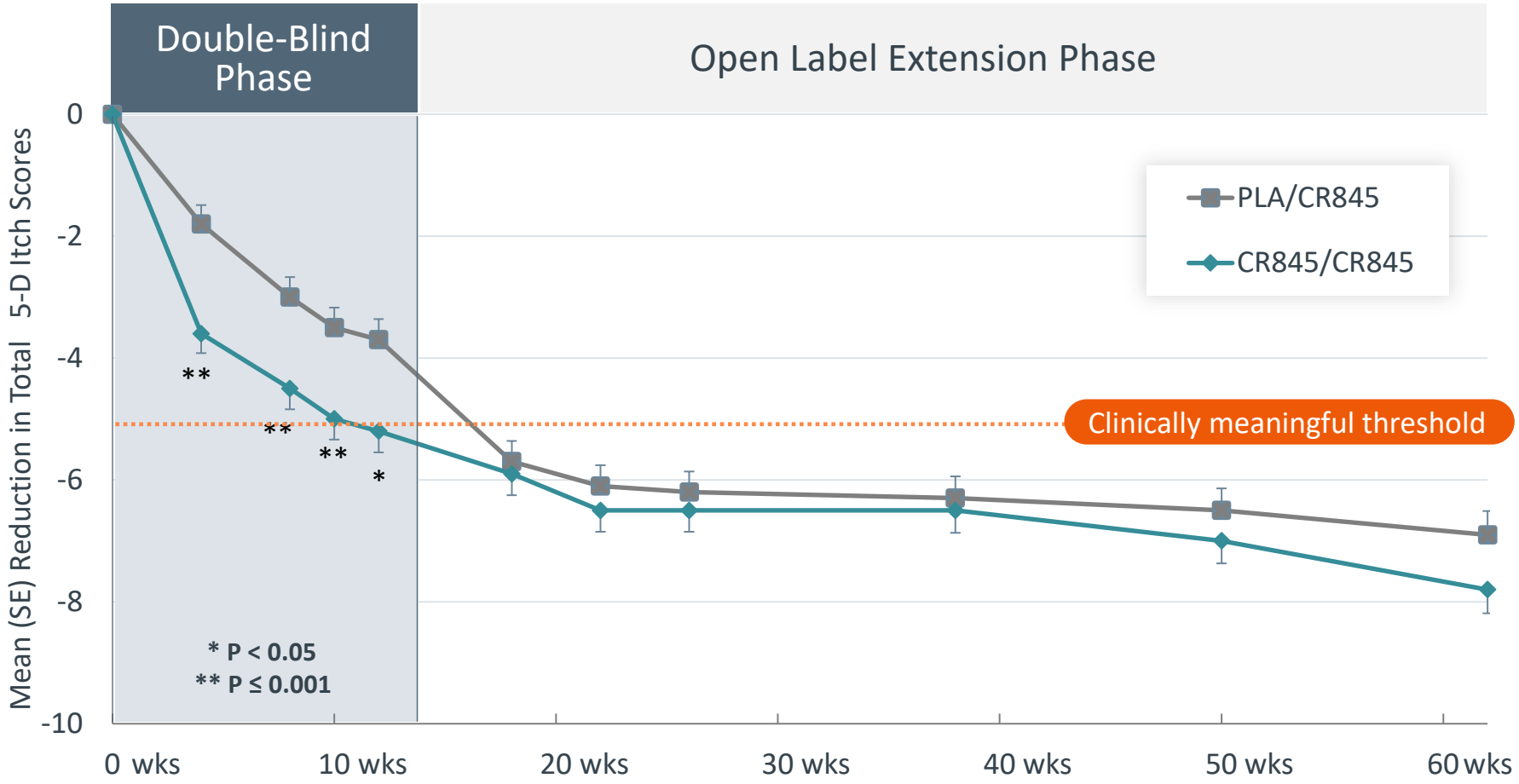




* $P < 0.05$, ** $P < 0.001$

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

Korsuva: Sustained Benefit over 15 Month Treatment Period



5D-Itch Scale

- Multidimensional questionnaire evaluating Itch-related Quality of Life
- Questions on characteristic of itch (intensity, duration, change) and disability due to itch (impact on sleep, social interaction, and work)

Clinically meaningful threshold in HD patients with CKD-aP:
≥ 5 points reduction

Incidence of Common TEAEs: KALM-1 & KALM-2
(≥2% in DFK arm and ≥1 % Difference versus PBO)

PREFERRED TERM	PBO (n=424)	DFK (n=424)
Subjects with any event	**277 (65.3%)**	**302 (71.2%)**
Diarrhea	**24 (5.7%)**	**38 (9.0%)**
Dizziness	**16 (3.8%)**	**29 (6.8%)**
Nausea	**19 (4.5%)**	**28 (6.6%)**
Headache	11 (2.6%)	19 (4.5%)
Hyperkalaemia	15 (3.5%)	20 (4.7%)
Somnolence	10 (2.4%)	18 (4.2%)
Back pain	4 (0.9%)	11 (2.6%)

Most common adverse events >5% in DFK arm

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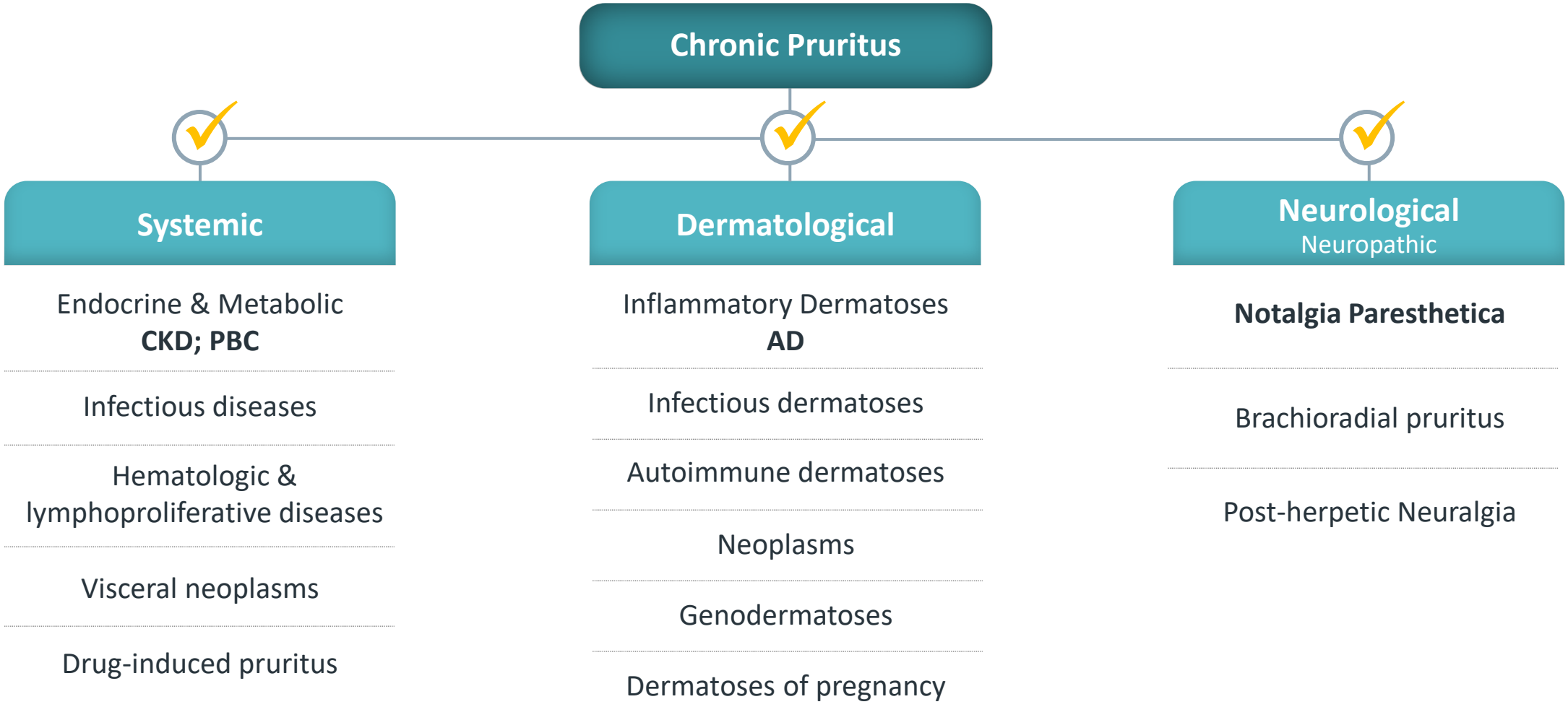
Key Chronic Pruritus Categories



Adapted from: Weisshaar et al. European S2k Guideline on Chronic Pruritus. Acta Derm Ven April 2019; 99(5): 469-506; Stander et al Clinical Classification of Itch Acta Derm Ven 2007; 87:291-294

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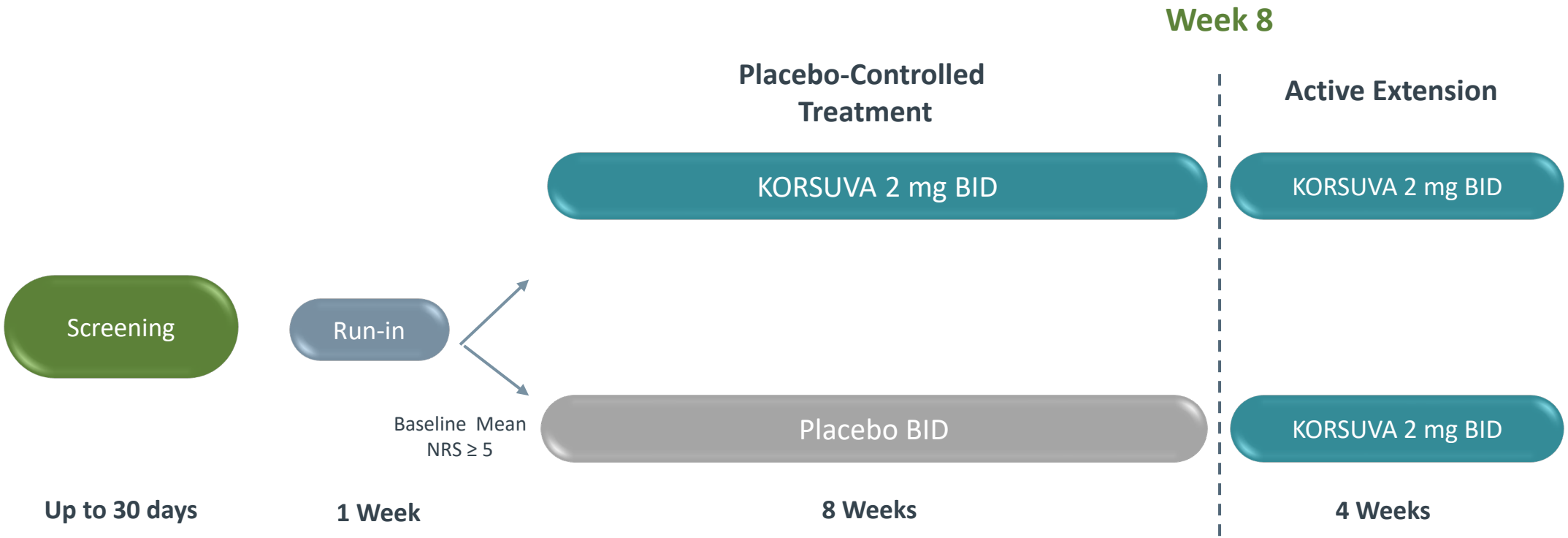
Notalgia Paresthetica Associated Pruritus: POC / Phase 2 Study (KOMFORT)



Study
- ~120 adult patients with NP and moderate-to-severe pruritus

Primary Endpoint:
- Change from BL in weekly mean of daily 24-hr WI-NRS at week 8

Other Endpoints:
- QoL, Sleep, Responder Analyses, Safety

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