Targeting Pruritus with First-In-Class Therapeutics

MAY 10, 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.

CARA™ THERAPEUTICS

Creating life-changing pruritus therapeutics

Cara Therapeutics is a close-knit group of scientists, medical experts, and industry leaders deeply committed to the science of changing lives. Our proprietary, novel therapies are poised to make a significant impact for the millions who have been overlooked.

Our Mission:	Our Vision:
Transform the way pruritus is treated to bring quality to the lives of those who suffer.	Inspire new ways of thinking about pruritus treatment to elevate the standard of care far beyond what has been considered possible.

The Far-Reaching Impact of Pruritus

Chronic Kidney Disease (CKD)

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

~40-50%

Chronic Liver Disease (CLD)

Patients with CLD, especially cholestatic liver disease experience significant pruritus

~20-30%

Atopic Dermatitis (AD)

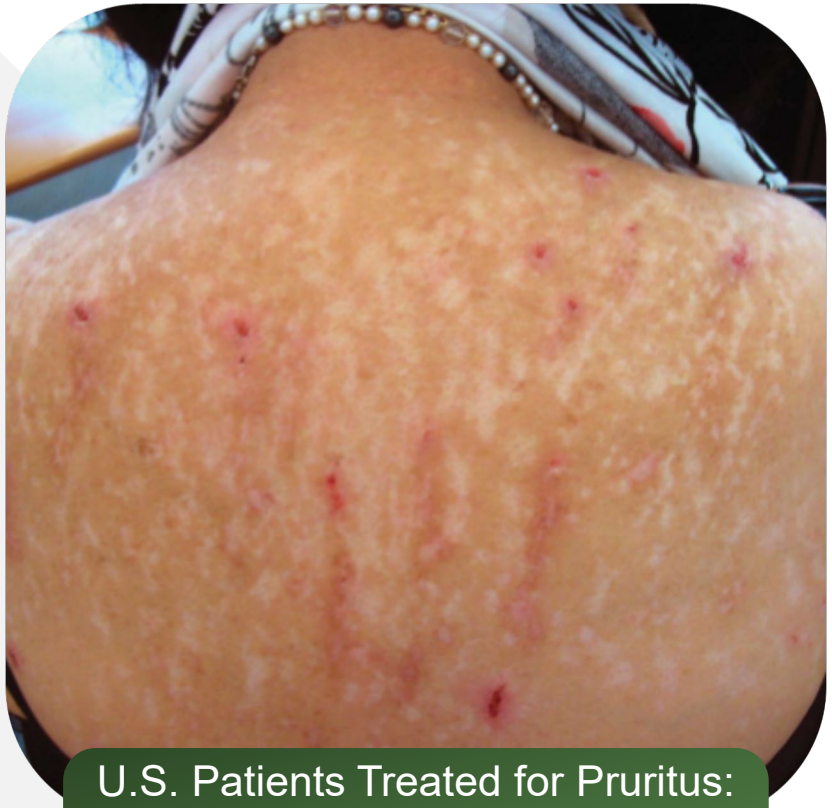
Pruritus is a defining symptom of AD

~100%

Notalgia Paresthetica (NP)

Pruritus is the defining symptom of NP

~100%



U.S. Patients Treated for Pruritus:

>20 Million

SCRIPTS ANNUALLY[1]

 Source: 1IQVIA Analysis, 2013.

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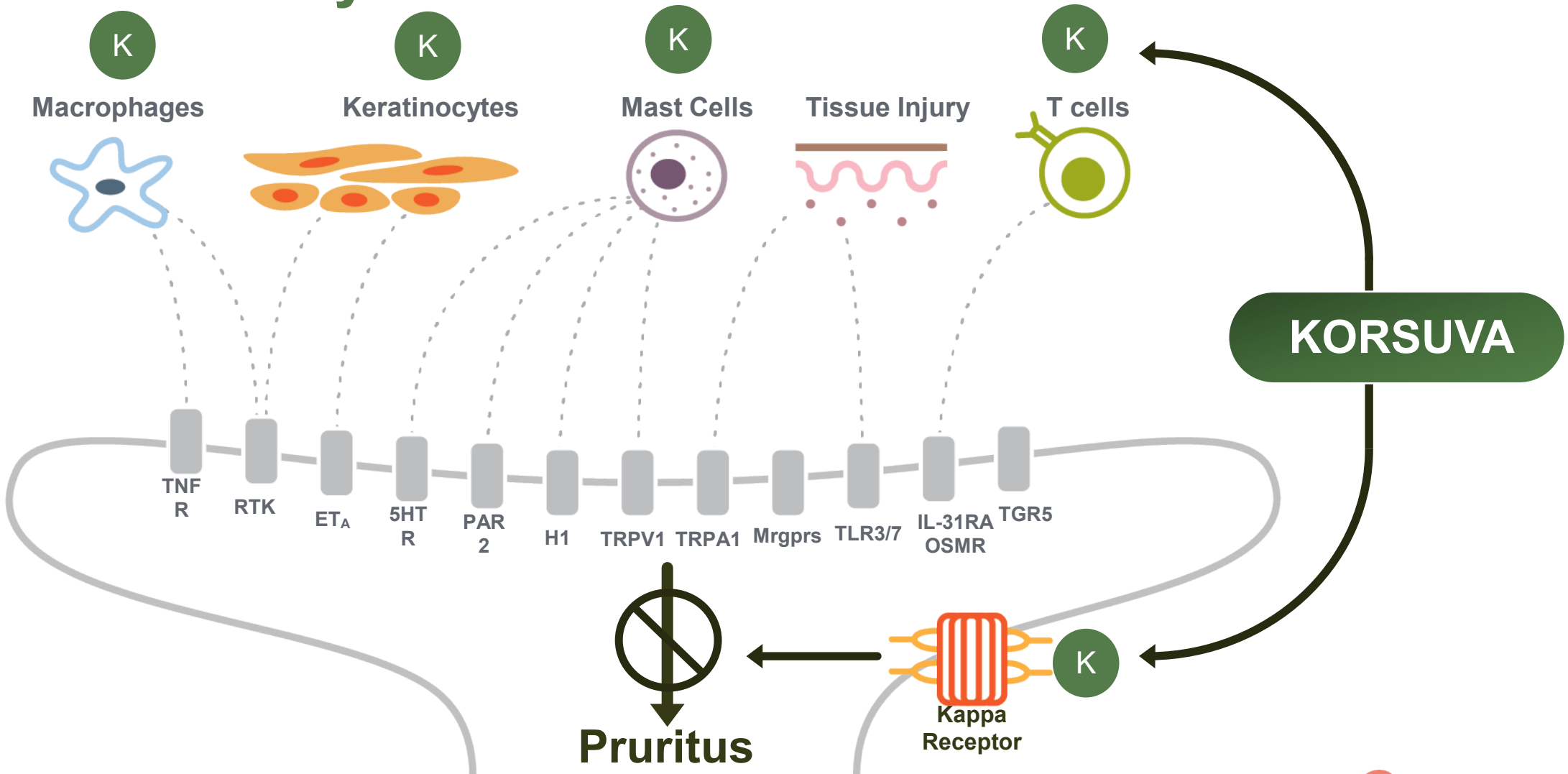
KORSUVA[1] (Difelikefalin) Directly Blocks Pruritus Sensory Neurons



 Source: Adapted from Pflugers Arch . 2013 December ; 465(12): doi:10.1007/s00424-013-1284-2. [1]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.

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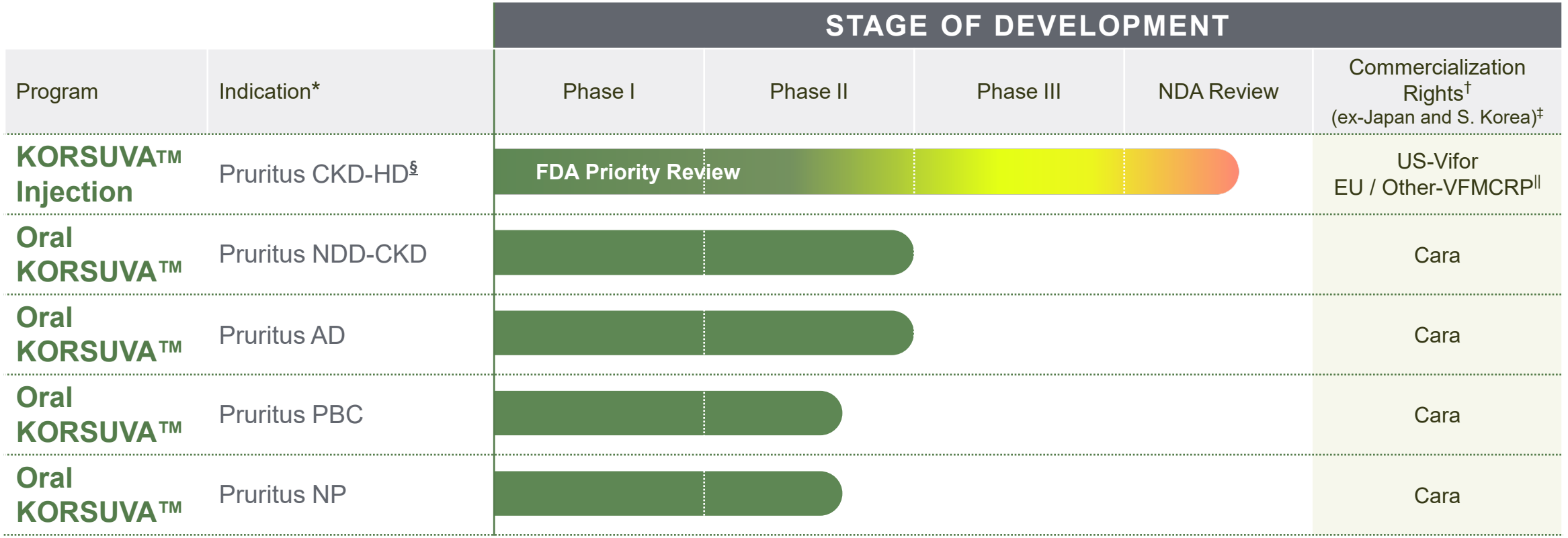
Cara Therapeutics Pipeline



**Cara Therapeutics has investigated KORSUVA™ for post-operative pain.*
†Vifor has commercial rights in Non-US Fresenius Medical Care dialysis clinics under a profit-share arrangement.
‡Commercialization rights to KORSUVA™ in defined indications—Japan: Maruishi Pharma; South Korea: CKD Pharma.
§PDUFA date is August 23, 2021.
||VFMCRP and Cara have rights to promote in Fresenius clinics in the US under a profit-share agreement.
CKD-HD: Chronic Kidney Disease-Hemodialysis; NDD—CKD: Non-Dialysis Dependent-Chronic Kidney Disease; AD: Atopic Dermatitis; PBC: Primary Biliary Cholangitis; NP: Notalgia Paresthetica.

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KORSUVA[1] (Difelikefalin) Injection for Dialysis Patients

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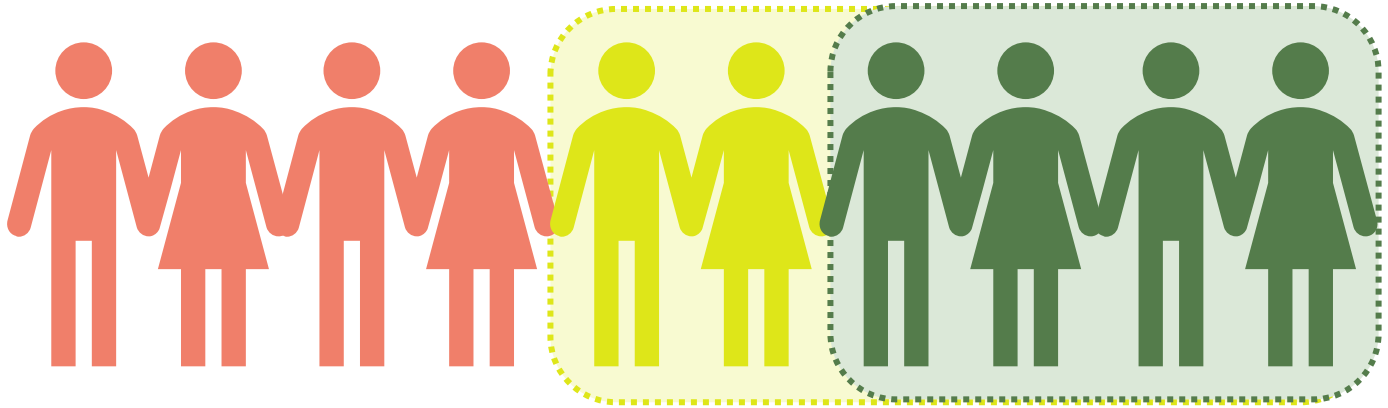
[1]*The FDA has conditionally accepted KORSUVA™ as the trade name for difelikefalin injection. Difelikefalin injection is an investigational drug product and its safety and efficacy have not been fully evaluated by any regulatory authority.*

KORSUVA[1] (Difelikefalin) Injection For CKD-associated Pruritus (CKD-aP) in Dialysis Patients



>500K[2]

patients on dialysis

60%

of ESRD patients have pruritus[3,4]

~40%

have moderate to severe pruritus

Serious intractable systemic pruritus

CKD-aP associated with worsening 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

NDA Priority Review

NDA filing – **PDUFA Aug 23 '21** [3]

U.S. launch - **2H, 2021** [3]

 1.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. 2. National Kidney Foundation.. 3. NDA accepted by FDA with priority review PDUFA date Q3 2021

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KORSUVA[1] (Difelikefalin) Injection: U.S. Commercial Strategy Cara / Vifor Commercial License

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

- Summary Terms[1] (Ex-Fresenius Medical Care Clinics)
  - $150M Up-Front ($100M Cash/$50M Equity)
  - $50M Regulatory approval ($50M Equity)
  - US Market Profit split (Ex-FMC Clinics): **Cara 60% : Vifor 40%**
  - $240M US Commercial Milestones

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

Established Ex-US 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[1] (Difelikefalin): Potential Broad Anti-Pruritic

Cara Therapeutics

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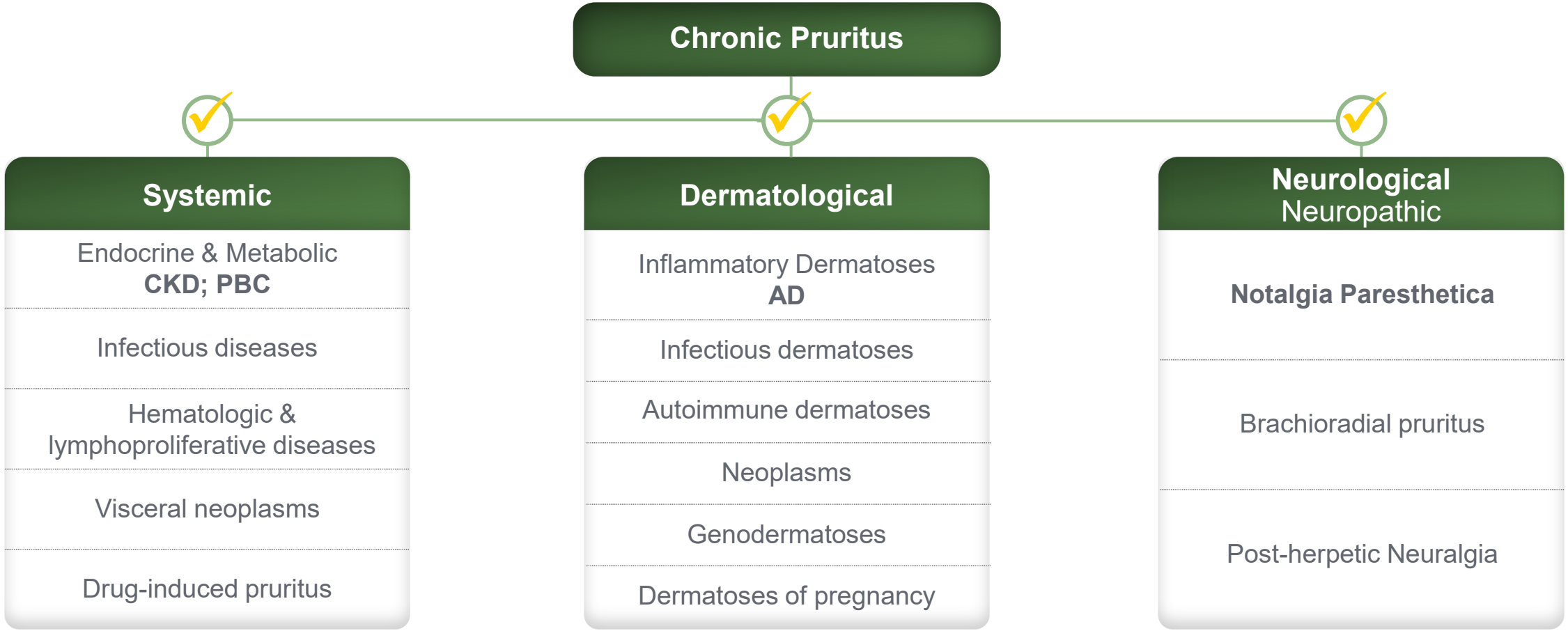
Key Chronic Pruritus Categories



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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Cara Therapeutics Pipeline

Program	Indication*	STAGE OF DEVELOPMENT: Phase I / Phase II / Phase III / NDA Review	Commercialization Rights† (ex-Japan and S. Korea)‡
KORSUVA™ Injection	Pruritus CKD-HD§	FDA Priority Review	US-Vifor EU / Other-VFMCRP‖
Oral KORSUVA™	Pruritus NDD-CKD		Cara
Oral KORSUVA™	Pruritus AD		Cara
Oral KORSUVA™	Pruritus PBC		Cara
Oral KORSUVA™	Pruritus NP		Cara

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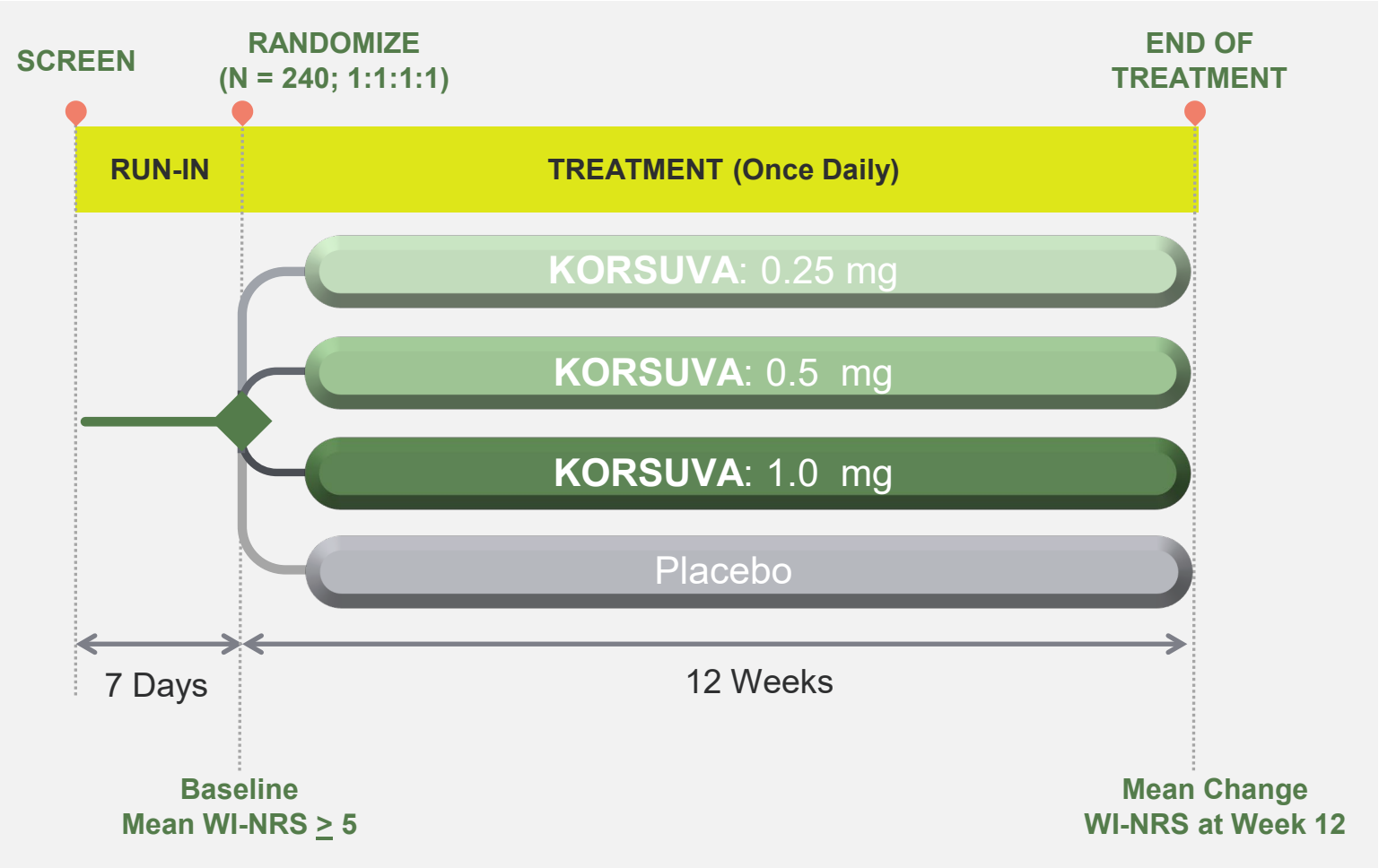
Oral KORSUVA[1] (Difelikefalin) for NDD-CKD aP: Phase 2 Trial Design



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

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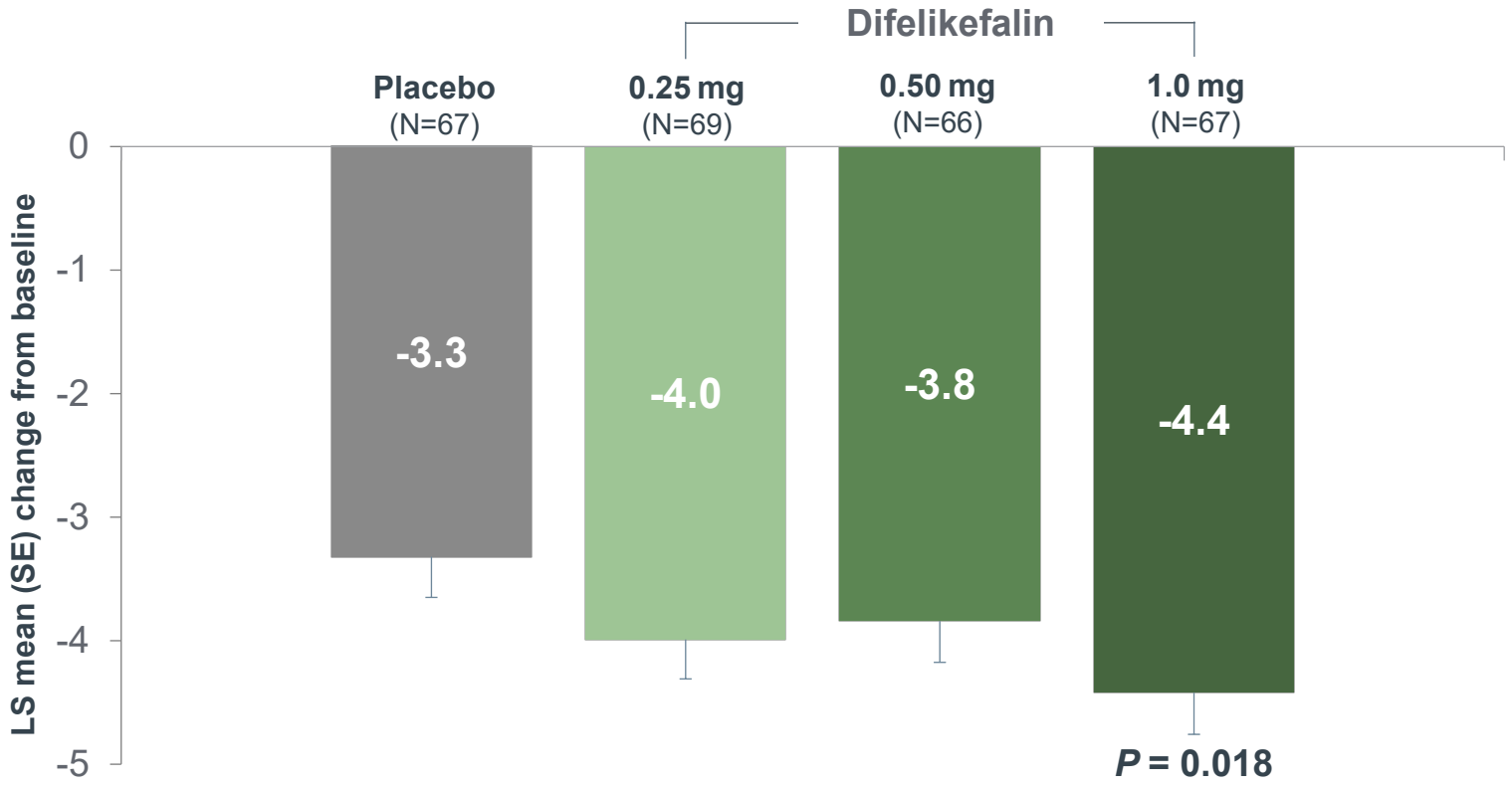
NDD-CKD aP Primary Endpoint: Change From Baseline in the WI-NRS at Week 12

Patients in the Difelikefalin 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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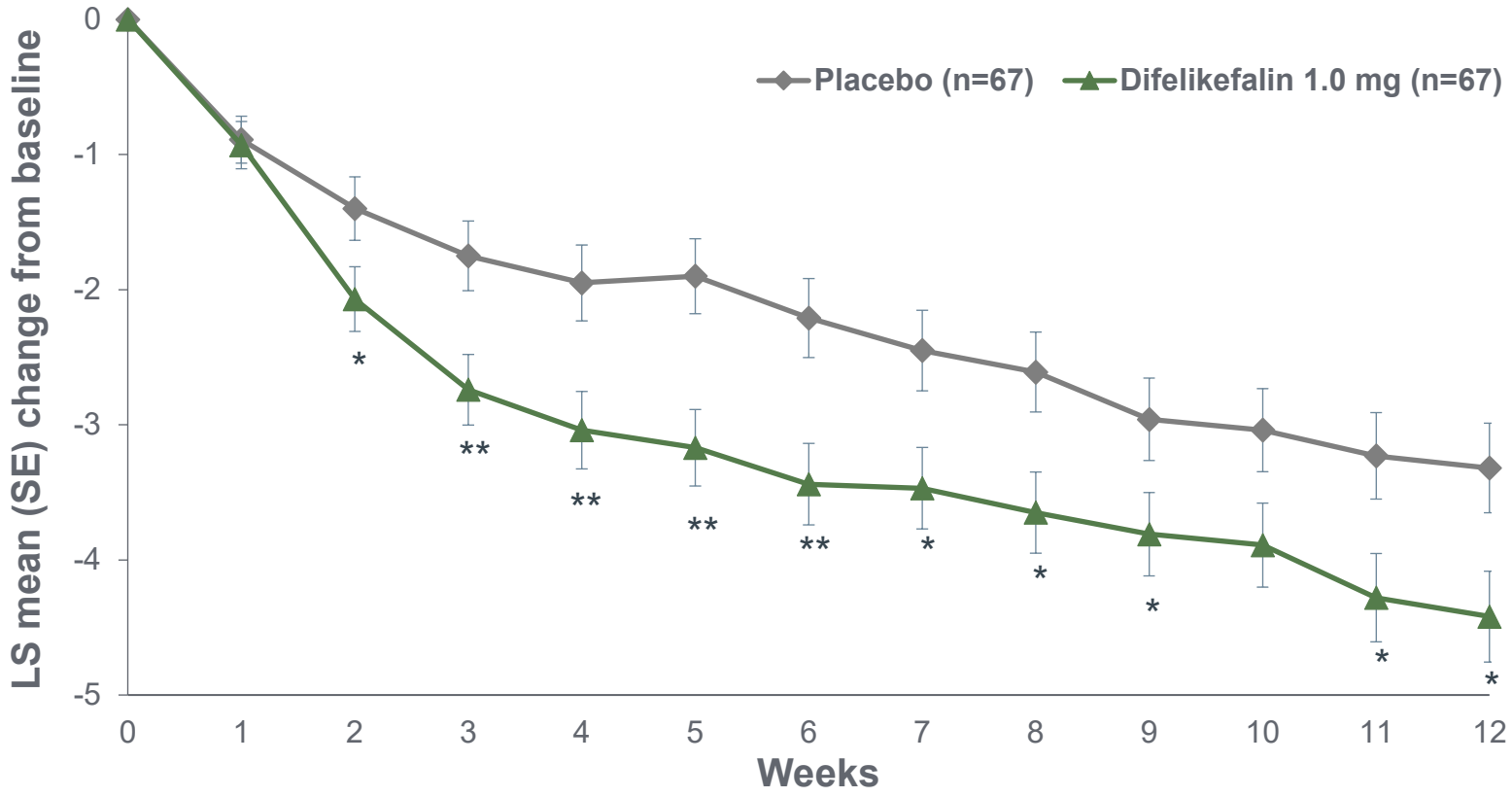
NDD-CKD aP Change From Baseline in WI-NRS Over Time

Significantly greater improvements in WI-NRS were observed with Difelikefalin 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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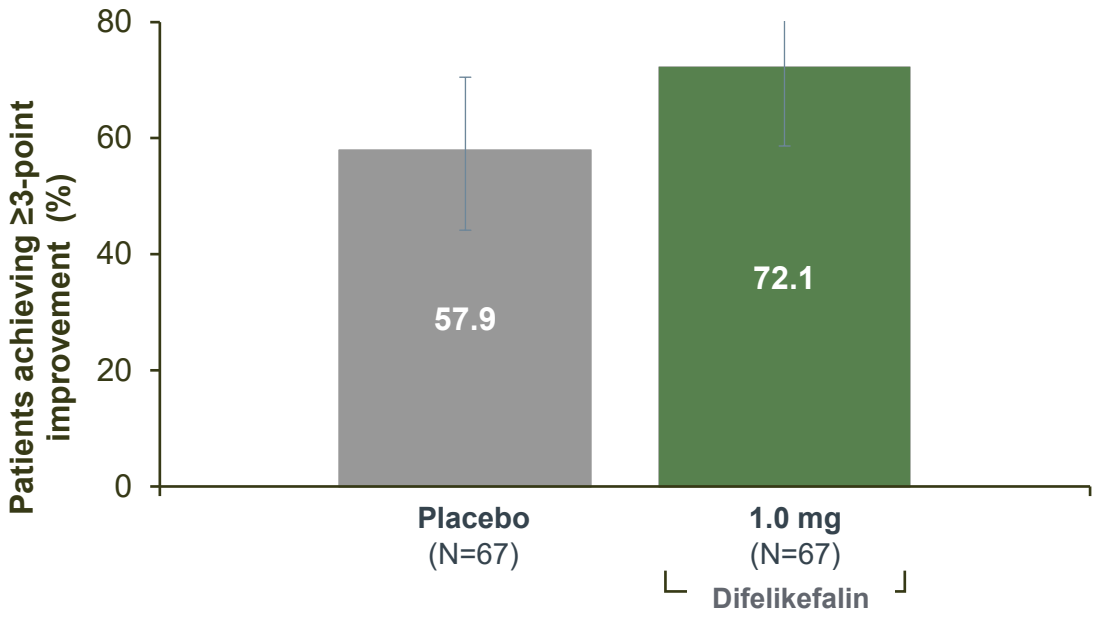
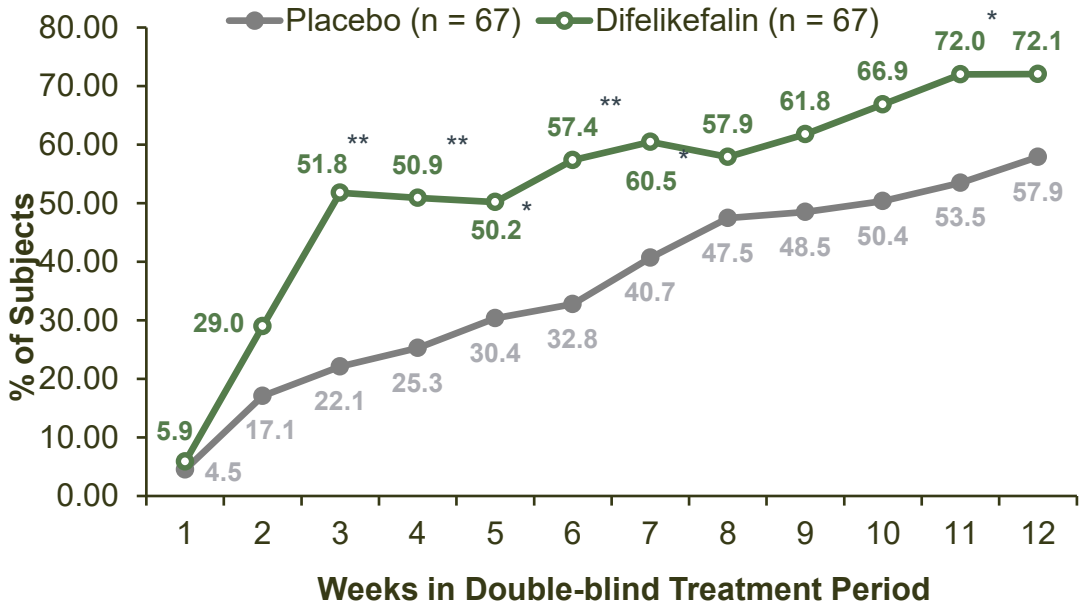
NDD-CKD aP Achievement of ≥3-Point Improvement in WI-NRS at Week 12

More than 70% of patients achieved ≥3-point improvement in WI-NRS with Difelikefalin 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.

72% of Difelikefalin 1.0 mg subjects experienced ≥ 3 point improvement from baseline at week 12



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

* P < .05, ** P < .01

1.0 mg dosage plan to advance into Phase 3 clinical study

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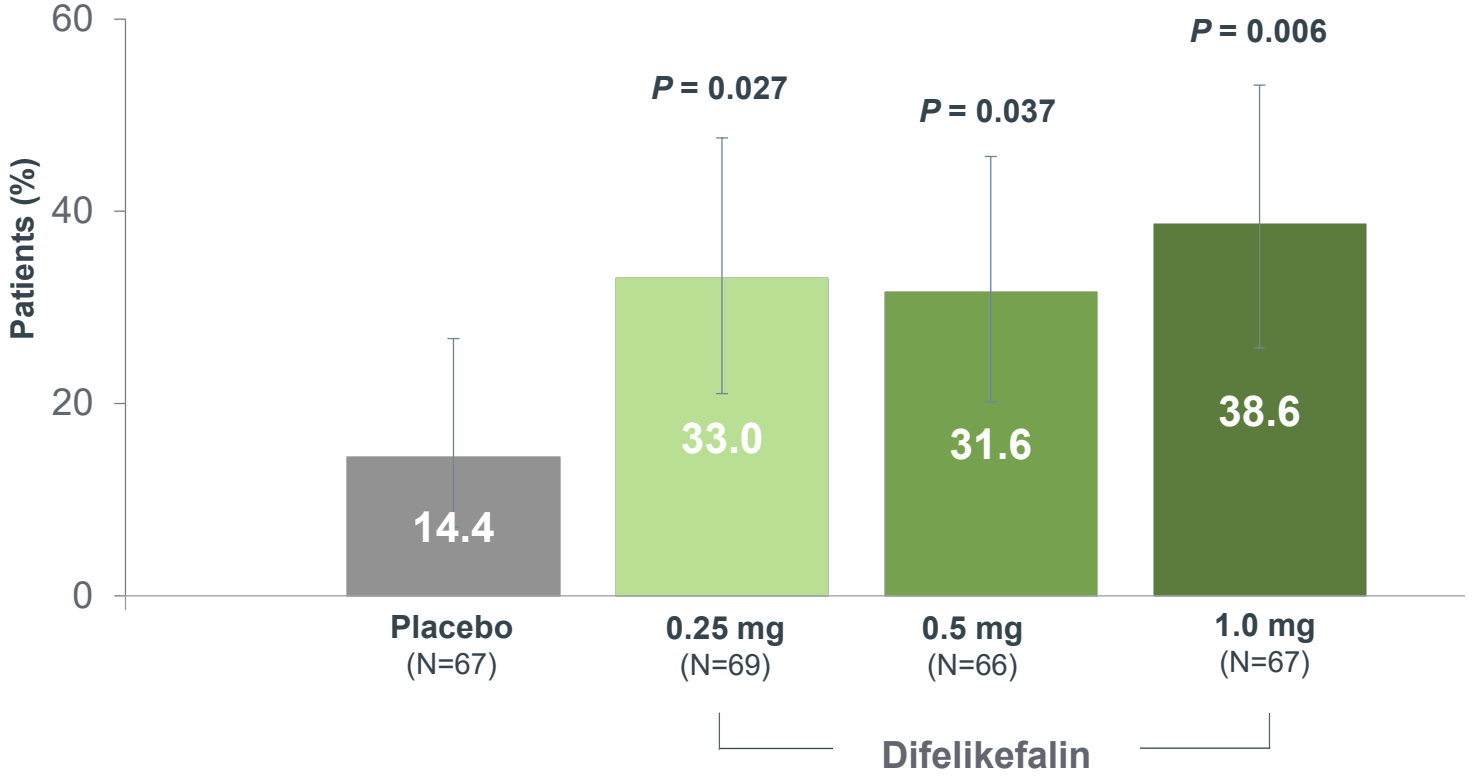
NDD-CKD aP Complete Response at Week 12

Significantly greater proportions of patients who received Difelikefalin 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.

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Oral Korsuva NDD CKD aP Next Steps

- Oral KORSUVA[1] (Difelikefalin) 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[1] (Difelikefalin) was generally well-tolerated: safety profile similar to Phase 3 Injection KORSUVA[1] (Difelikefalin) studies

Aim to initiate Phase III trial by the end of the year in 2021 in Stage 5 pre-dialysis population, planning to discuss with FDA inclusion of earlier stage CKD patients

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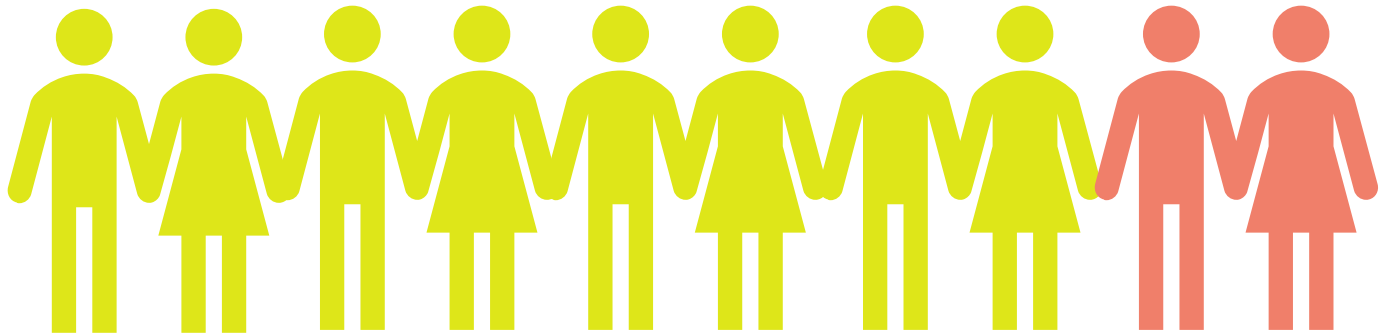
Oral KORSUVA™ (Difelikefalin) For Atopic Dermatitis-Associated Pruritus

Moderate-Severe Pruritus

30 million
US patients

~80%
Mild-Moderate Disease*



~20%
Severe Disease*

Approved Therapies

Topical Steroids & Immunomodulators

Injectable Biologic

**Silverberg JI. Public Health Burden and Epidemiology of Atopic Dermatitis. Dermatol Clin. 2017;35(3):283-289. Chiesa Fuxench ZC, Block JK, Boguniewicz M, et al. Atopic Dermatitis in America Study: A Cross-Sectional Study Examining the Prevalence and Disease Burden of Atopic Dermatitis in the US Adult Population. J Invest Dermatol. 2019;139(3):583-590. Barbarot S et al. Epidemiology of atopic dermatitis in adults: Results from an international survey. Allergy 2018; 1284-1293. Chovatiya R et al. Clinical phenotyping of atopic dermatitis using combined itch and lesional severity: A prospective observational study. Annals of Allergy, Asthma Immunology 2021.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.*

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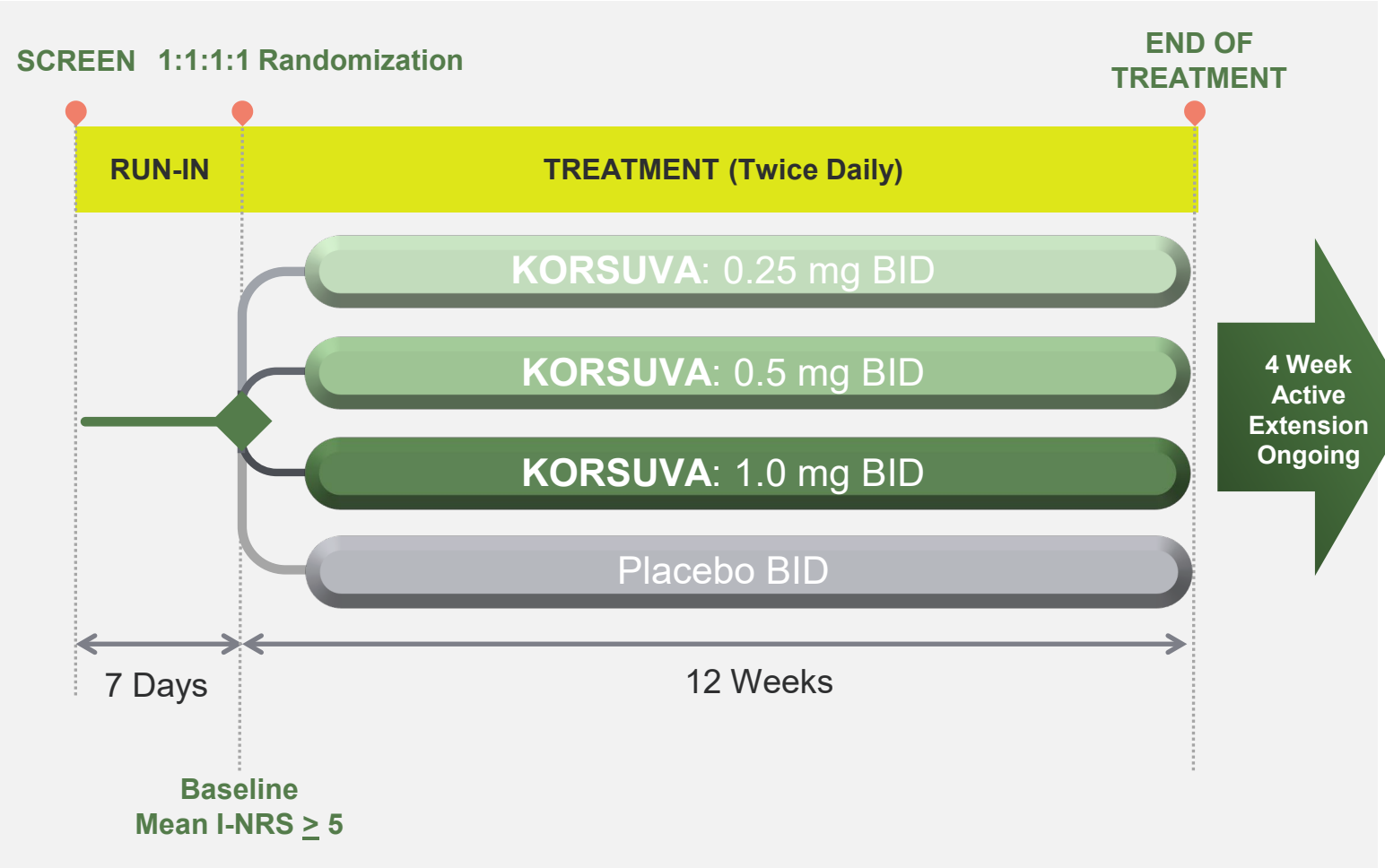
KARE: Phase 2 Study Design



Primary Endpoint

- Change from baseline in the weekly mean of the daily 24-hr Itch-Numeric Rating Scale (I-NRS) at Week 12

Key Secondary Endpoint

- Proportion of subjects achieving ≥4-point improvement in I-NRS at Week 12

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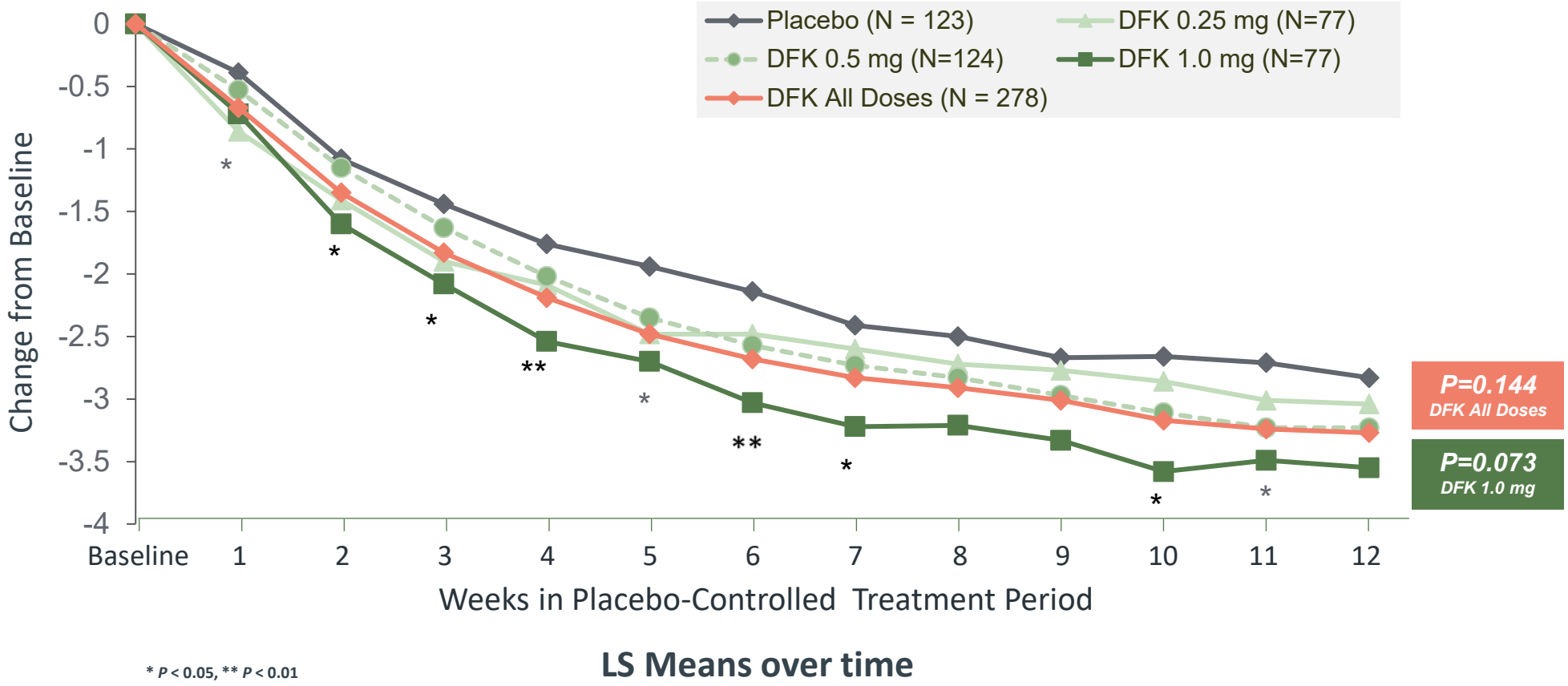
KARE Primary Endpoint: Change from Baseline in Daily I-NRS at Week 12 (ITT)

Significant improvement observed in 1.0 mg DFK vs placebo in majority of timepoints, starting at week 1



* $P < 0.05$, ** $P < 0.01$

LS Means over time

LS Means from MMRM with terms for treatment, week, week by treatment interaction, baseline score, and AD severity. Missing data imputed using multiple imputation (MI) under missing at random (MAR) assumption. I-NRS scores after use of rescue are set to missing and then imputed with MI

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KARE Key Secondary Endpoint: ≥ 4-point Improvement in I-NRS at Week 12 (ITT)

	Placebo (N=123)	DFK 0.25 mg (N=77)	DFK 0.50 mg (N=124)	DFK 1.0 mg (N=77)
Estimated Percent Responder	**29%**	**38%**	**32%**	**33%**
Odds Ratio		**1.5**	**1.2**	**1.2**
P-value		**p=0.18**	**p=0.55**	**p=0.59**

Estimated percentage & P-value based on a logistic regression model with terms for treatment group, baseline I-NRS score, and AD disease severity
Patients who d/c early or have missing data in a specific week are included as "non-responders"

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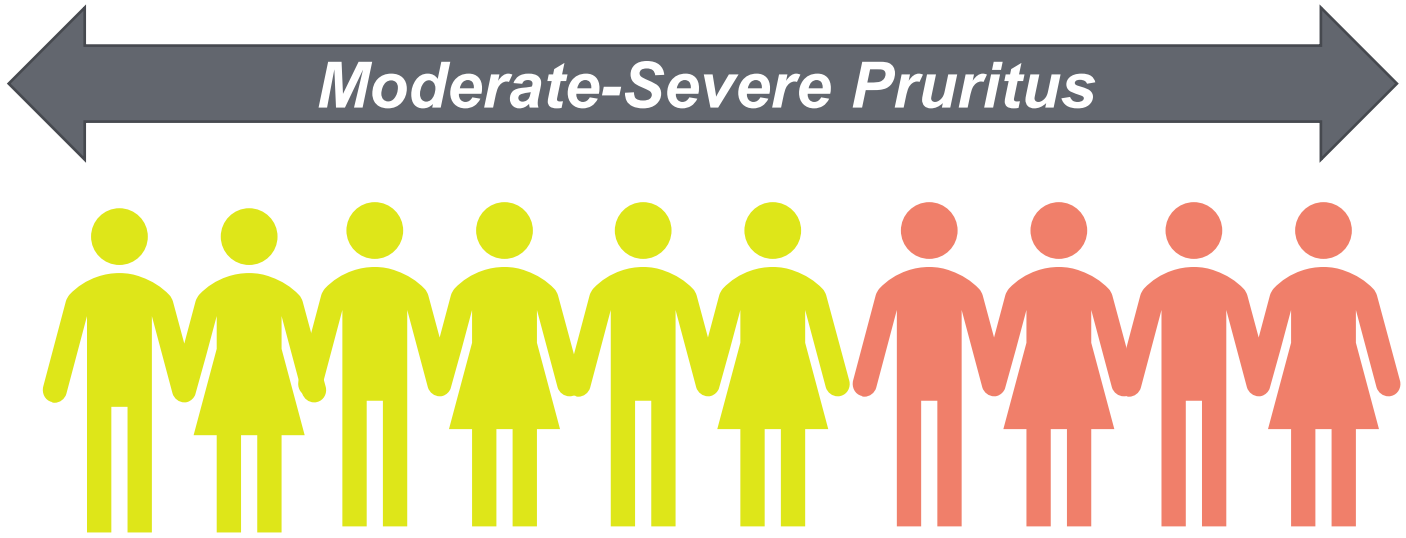
KARE Trial Patient Population



~64%

Mild-Moderate Disease
BSA < 10%
(N=257)

~36%

Moderate-Severe Disease
BSA ≥ 10%
(N=144)

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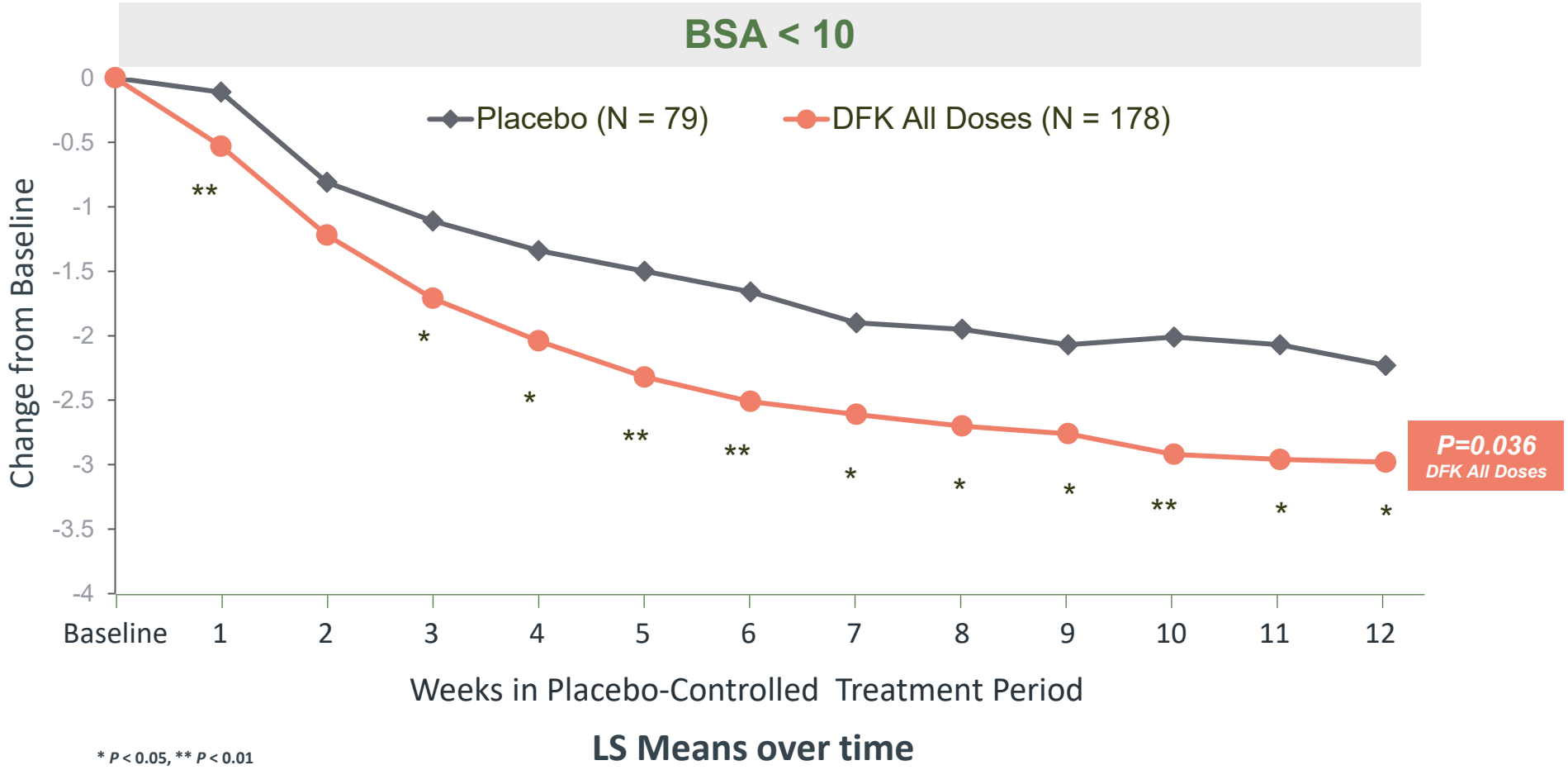
KARE: Mild to Moderate AD
Change from Baseline in Daily I-NRS Through Week 12

Significant anti-pruritic effect of DFK observed beginning Week 1 and sustained through Week 12



LS Means over time

* $P < 0.05$, ** $P < 0.01$

LS Means from MMRM with terms for treatment, week, week by treatment interaction, baseline score, and AD severity. Missing data imputed using multiple imputation (MI) under missing at random (MAR) assumption. I-NRS scores after use of rescue are set to missing and then imputed with MI

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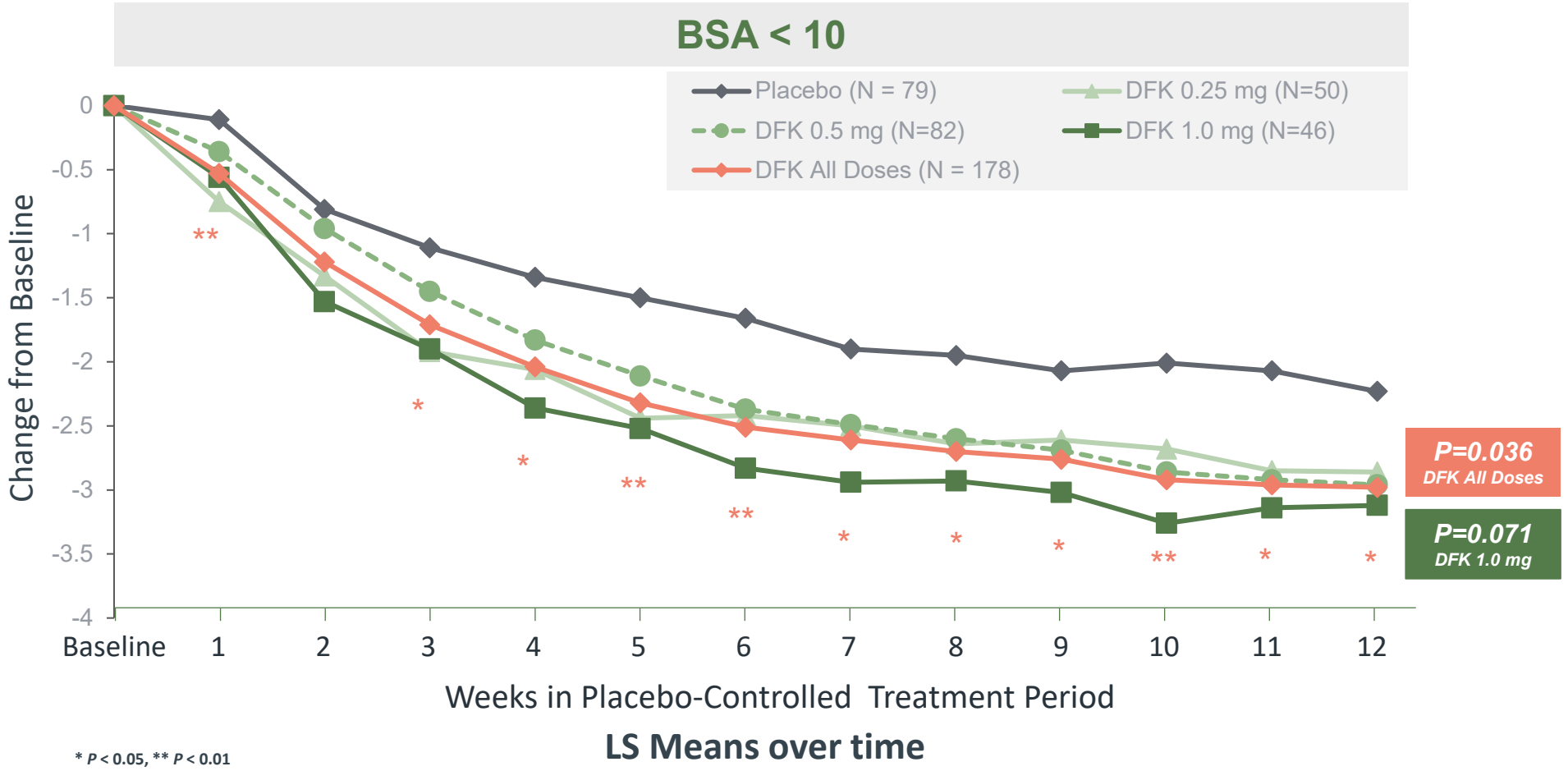
KARE: Mild to Moderate AD
Change from Baseline in Daily I-NRS through Week 12



LS Means from MMRM with terms for treatment, week, week by treatment interaction, baseline score, and AD severity. Missing data imputed using multiple imputation (MI) under missing at random (MAR) assumption. I-NRS scores after use of rescue are set to missing and then imputed with MI

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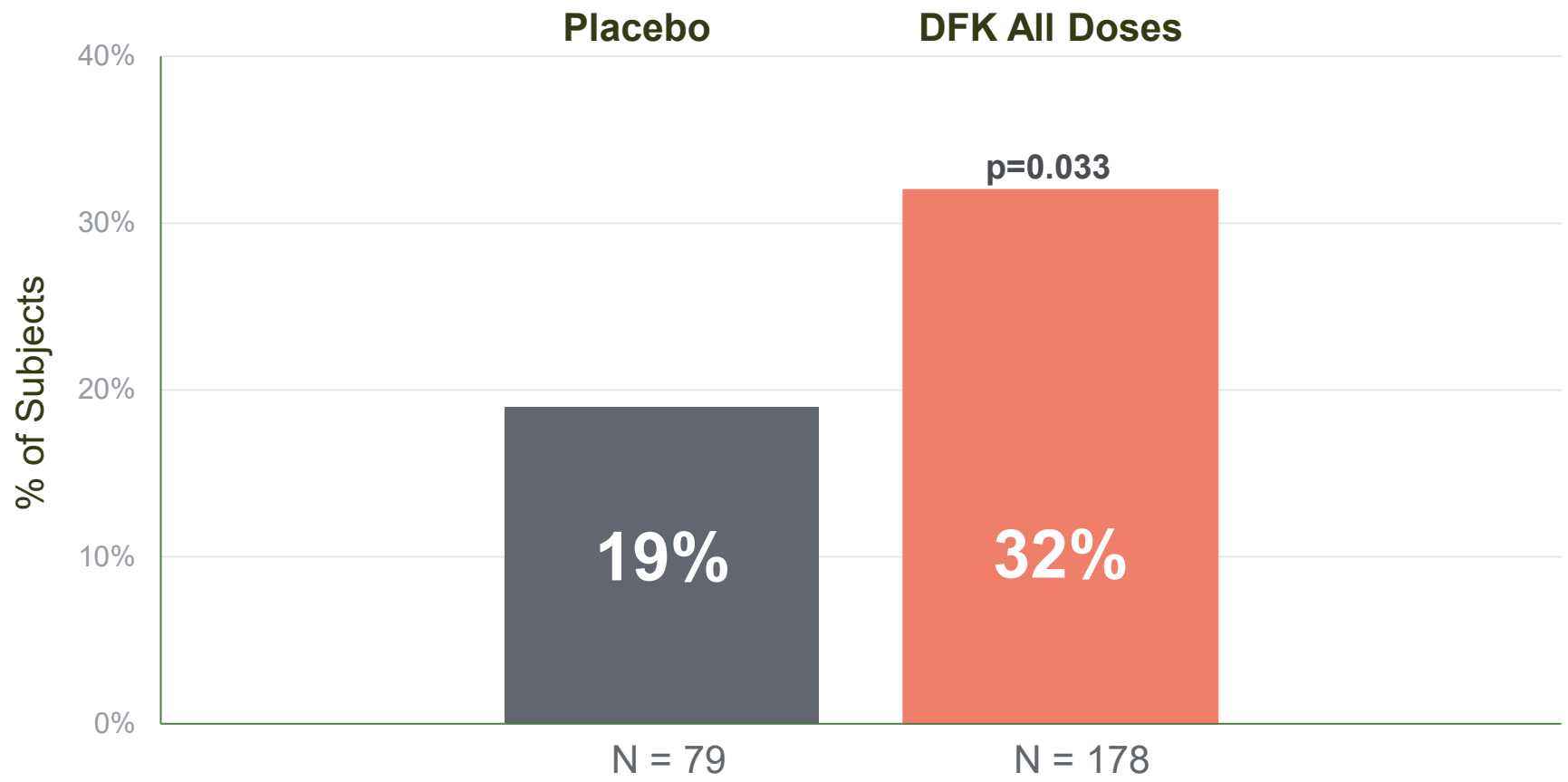
KARE: Mild to Moderate AD
Subjects with ≥ 4-point Improvement in I-NRS at Week 12

A significantly greater proportion of patients on DFK achieved 4-point improvement in I-NRS



Estimated percentage & P-value based on a logistic regression model with terms for treatment group and baseline I-NRS score. Patients who d/c early or have missing data in a specific week are included as "non-responders"

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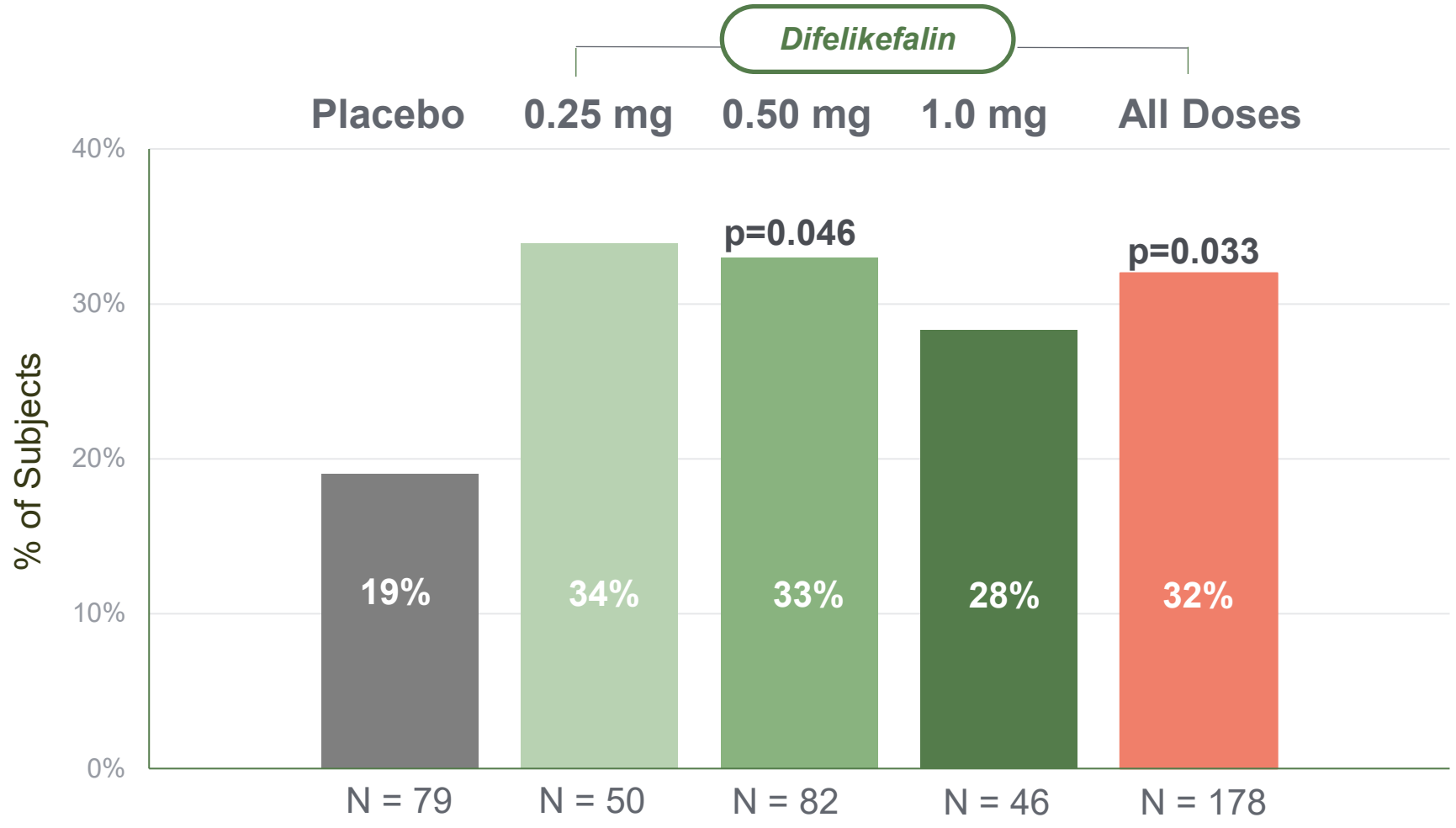
KARE: Mild to Moderate AD
Subjects with ≥ 4-point Improvement in I-NRS at Week 12



Estimated percentage & P-value based on a logistic regression model with terms for treatment group, baseline I-NRS score, and AD disease severity. Patients who d/c early or have missing data in a specific week are included as "non-responders"

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Summary of Adverse Events

	Placebo (N=123)	DFK 0.25 mg (N=77)	DFK 0.50 mg (N=124)	DFK 1.0 mg (N=77)
Subjects with at least one TEAE, n (%)	54 (43.9%)	36 (46.8%)	49 (39.5%)	42 (54.5%)
Subjects with at least one serious TEAE, n (%)	0	1 (1.3%)	1 (0.8%)	2 (2.6%)
Subjects with TEAE resulting in treatment discontinuation, n (%)	4 (3.3%)	3 (3.9%)	1 (0.8%)	9 (11.7%)

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Most Commonly Reported TEAEs

Treatment-emergent Adverse Events at ≥5% frequency; n (%)	Placebo (N=123)	DFK 0.25 mg (N=77)	DFK 0.50 mg (N=124)	DFK 1.0 mg (N=77)
Abdominal pain*	13 (10.6%)	4 (5.2%)	11 (8.9%)	14 (18.2%)
Nausea	11 (8.9%)	1 (1.3%)	6 (4.8%)	5 (6.5%)
Dry Mouth	0	2 (2.6%)	2 (1.6%)	6 (7.8%)
Headache	5 (4.1%)	5 (6.5%)	3 (2.4%)	2 (2.6%)
Dizziness	2 (1.6%)	4 (5.2%)	3 (2.4%)	2 (2.6%)
Hypertension	1 (0.8%)	1 (1.3%)	1 (0.8%)	5 (6.5%)

Safety analyses performed in the safety population, defined as all randomized patients who received ≥1 dose of study drug based on actual treatment received.
**includes PTs abdominal pain, abdominal pain upper, abdominal discomfort*

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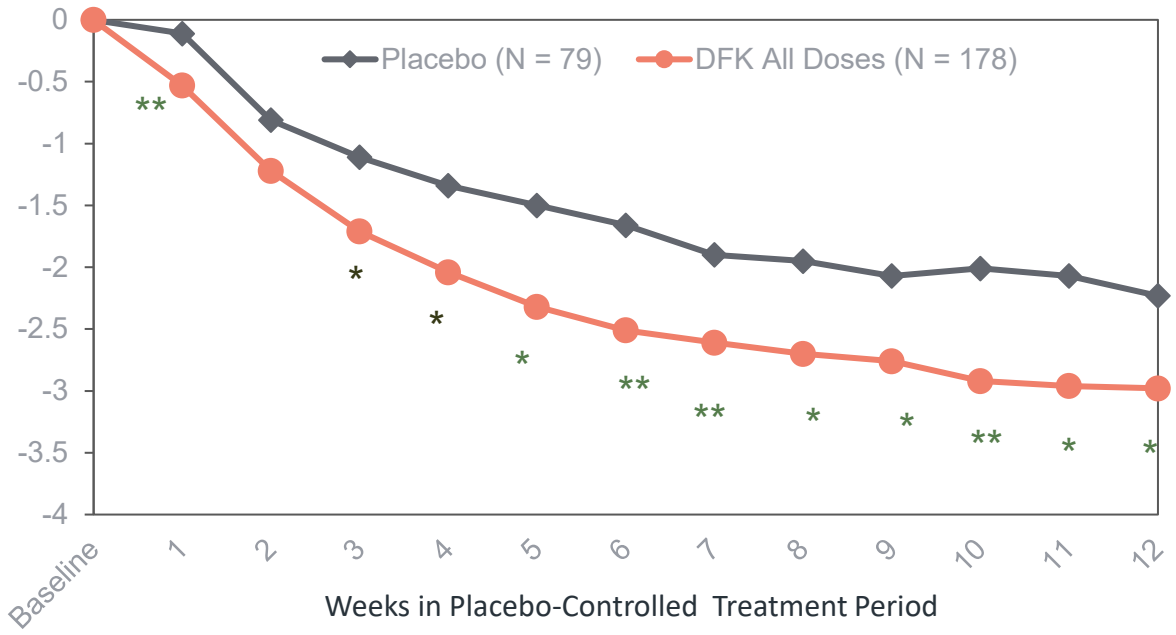
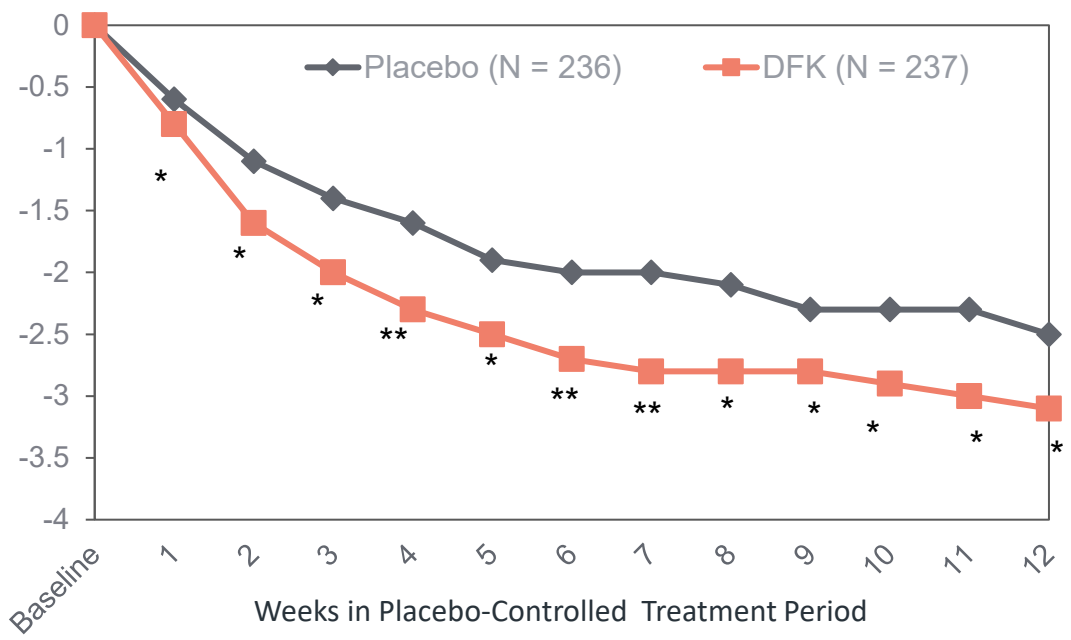
KORSUVA™ Profiles: Mild to Moderate AD-aP & CKD-aP

Similar anti-pruritic effects were observed in KARE and KALM-2 trials

Mild to Moderate Atopic Dermatitis-aP: KARE



CKD-aP: Phase 3/KALM-2 Hemodialysis Patients



LS Means over time

* $P < 0.05$, ** $P < 0.01$

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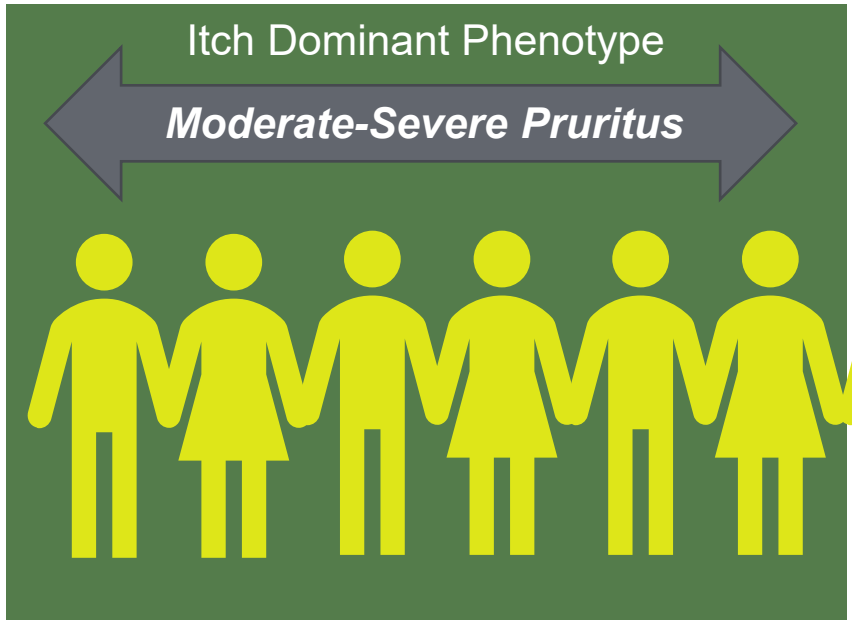
CARA THERAPEUTICS

Oral KORSUVA™ (Difelikefalin)
For Mild to Moderate AD with Moderate to Severe Pruritus

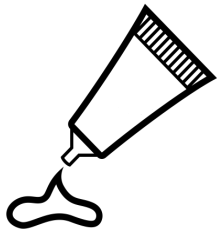
30 million
US patients

~80%
Mild-Moderate Disease*



~20%
Severe Disease*

Approved Therapies



Topical Steroids & Immunomodulators

Injectable Biologic

Silverberg JI. Public Health Burden and Epidemiology of Atopic Dermatitis. Dermatol Clin. 2017;35(3):283-289. Chiesa Fuxench ZC, Block JK, Boguniewicz M, et al. Atopic Dermatitis in America Study: A Cross-Sectional Study Examining the Prevalence and Disease Burden of Atopic Dermatitis in the US Adult Population. J Invest Dermatol. 2019;139(3):583-590. Barbarot S et al. Epidemiology of atopic dermatitis in adults: Results from an international survey. Allergy 2018; 1284-1293. Chovatiya R et al. Clinical phenotyping of atopic dermatitis using combined itch and lesional severity: A prospective observational study. Annals of Allergy, Asthma Immunology 2021.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.

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Oral AD Conclusions from KARE Phase II Trial

- Oral KORSUVA™ did not meet Primary Endpoint of I-NRS change from baseline at week 12 in ITT population
  - However, statistically significant improvement was observed in mild-to-moderate subjects throughout Week 12

- Oral KORSUVA™ resulted in statistically significant improvement in the registration endpoint 4-point responder analysis in subjects with mild to moderate AD at Week 12

- Oral KORSUVA™ was generally well tolerated across all doses

Efficacy and safety data support further development of KORSUVA in mild-to-moderate AD patients –
EOP2 FDA meeting target for 2H, 2021

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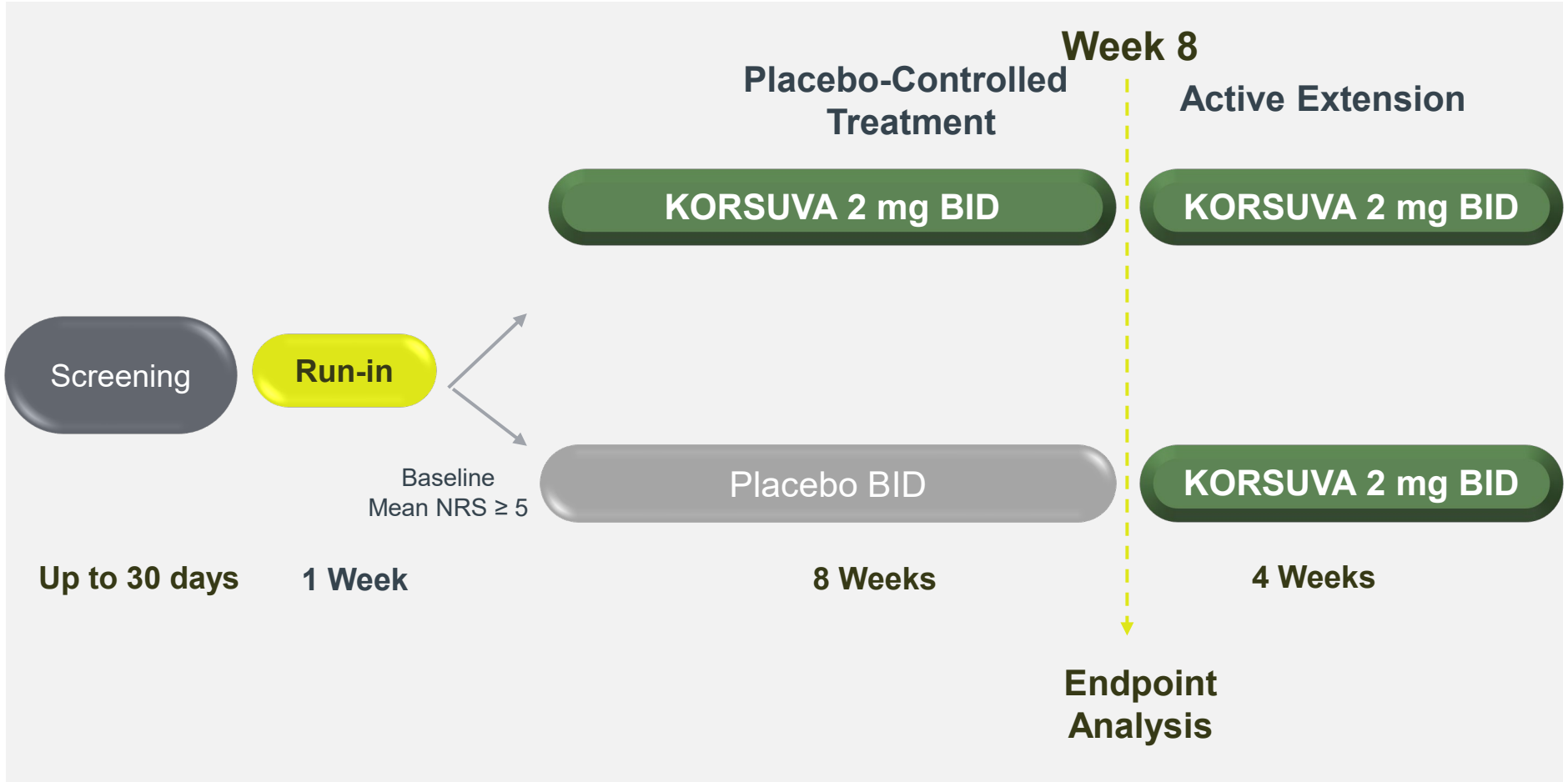
Notalgia Paresthetica Associated Pruritus: POC / Phase 2 Study (KOMFORT)



Endpoints Week 8

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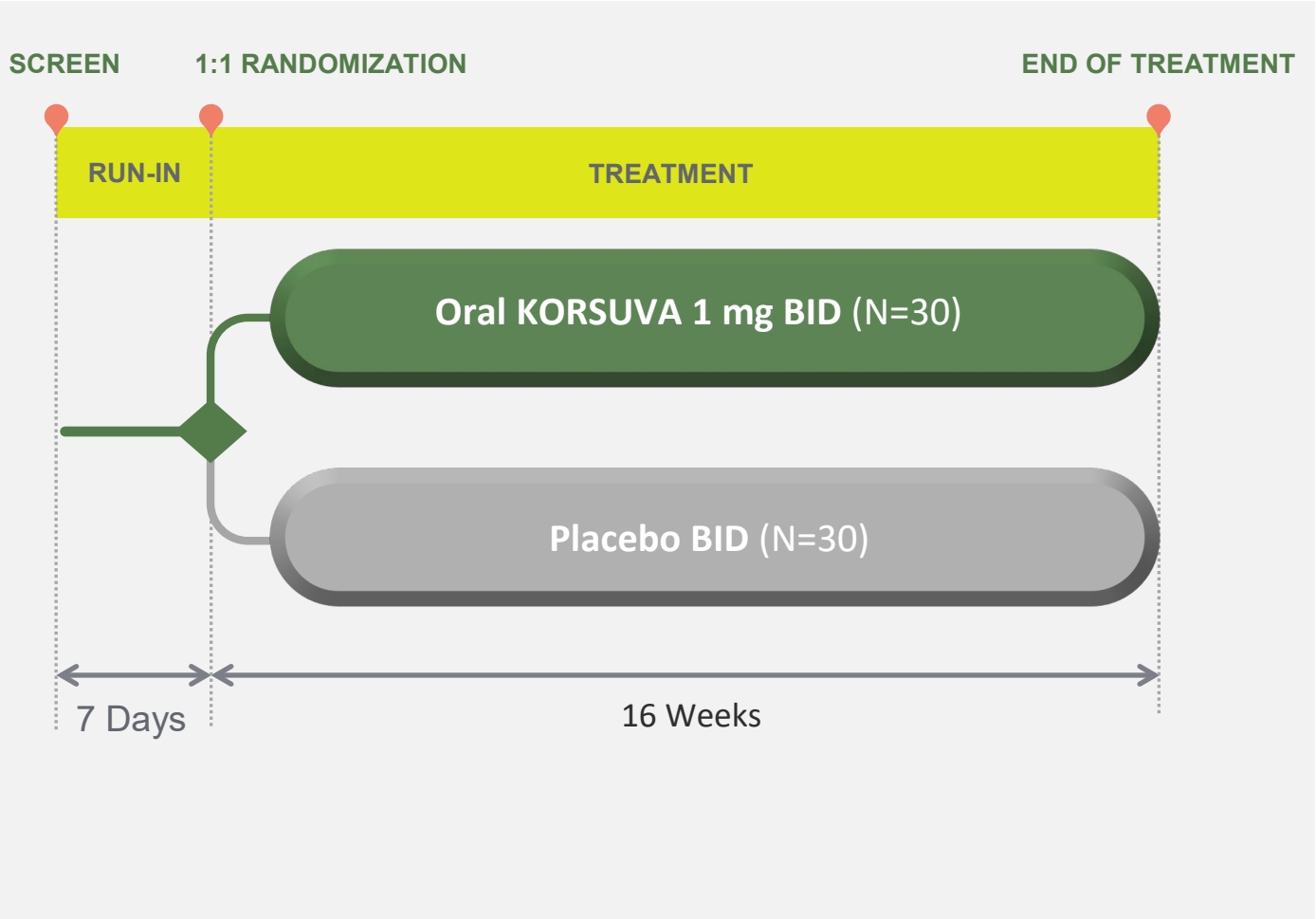
Pruritus Associated with Primary Biliary Cholangitis (PBC): Phase 2



Endpoints Week 16

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
- Safety assessments

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Financial Highlights

(AS OF MARCH 31, 2021)

Cash/marketable securities
(March 31, 2021)
$228M

Net loss
(1st Qtr. 2021)
($23.3M)

Shares outstanding
~50M

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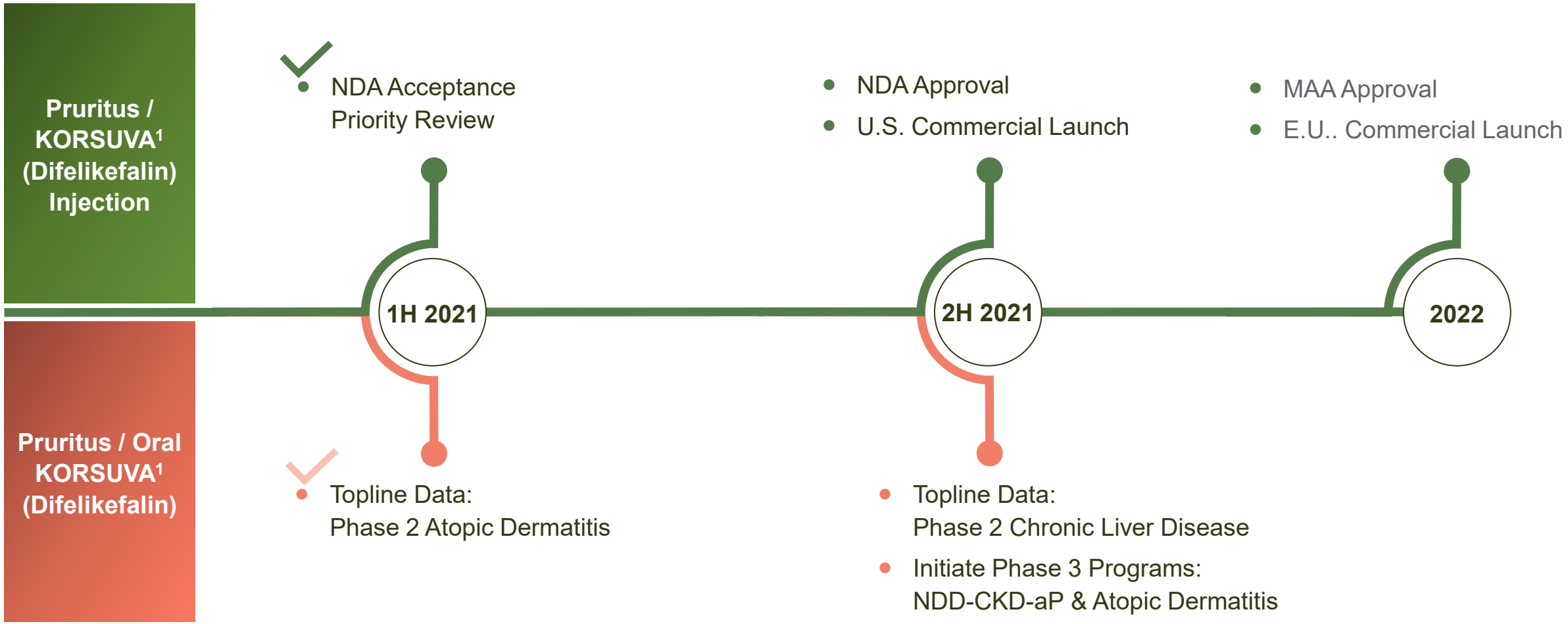
Projected Milestones–2021 & 2022



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