KARE Phase 2 Topline Data:

Oral KORSUVA™ for Pruritus in Atopic Dermatitis

APRIL 2021

KARE Phase 2 study evaluated the efficacy and safety of oral difelikefalin for moderate to severe pruritus in adult subjects with atopic dermatitis (AD). 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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Disclaimers

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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, 2020, 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.

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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

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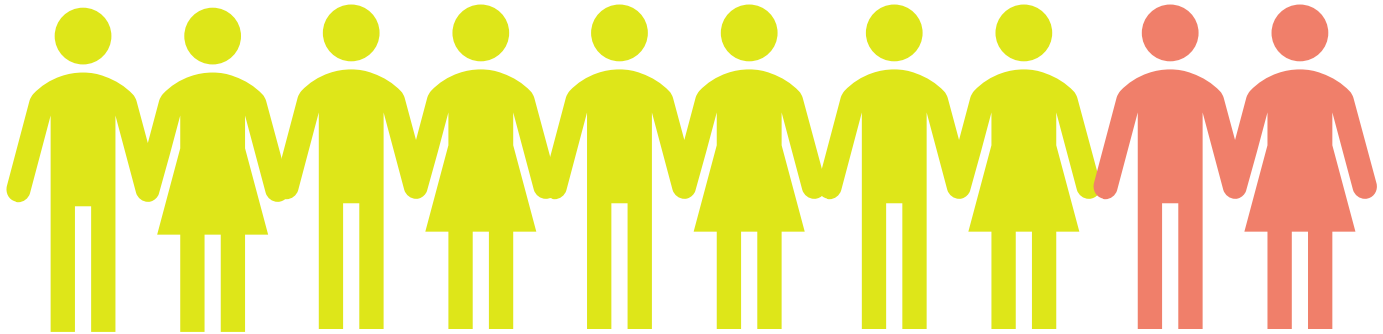
Oral KORSUVA™ (Difelikefalin) For Atopic Dermatitis-Associated Pruritus

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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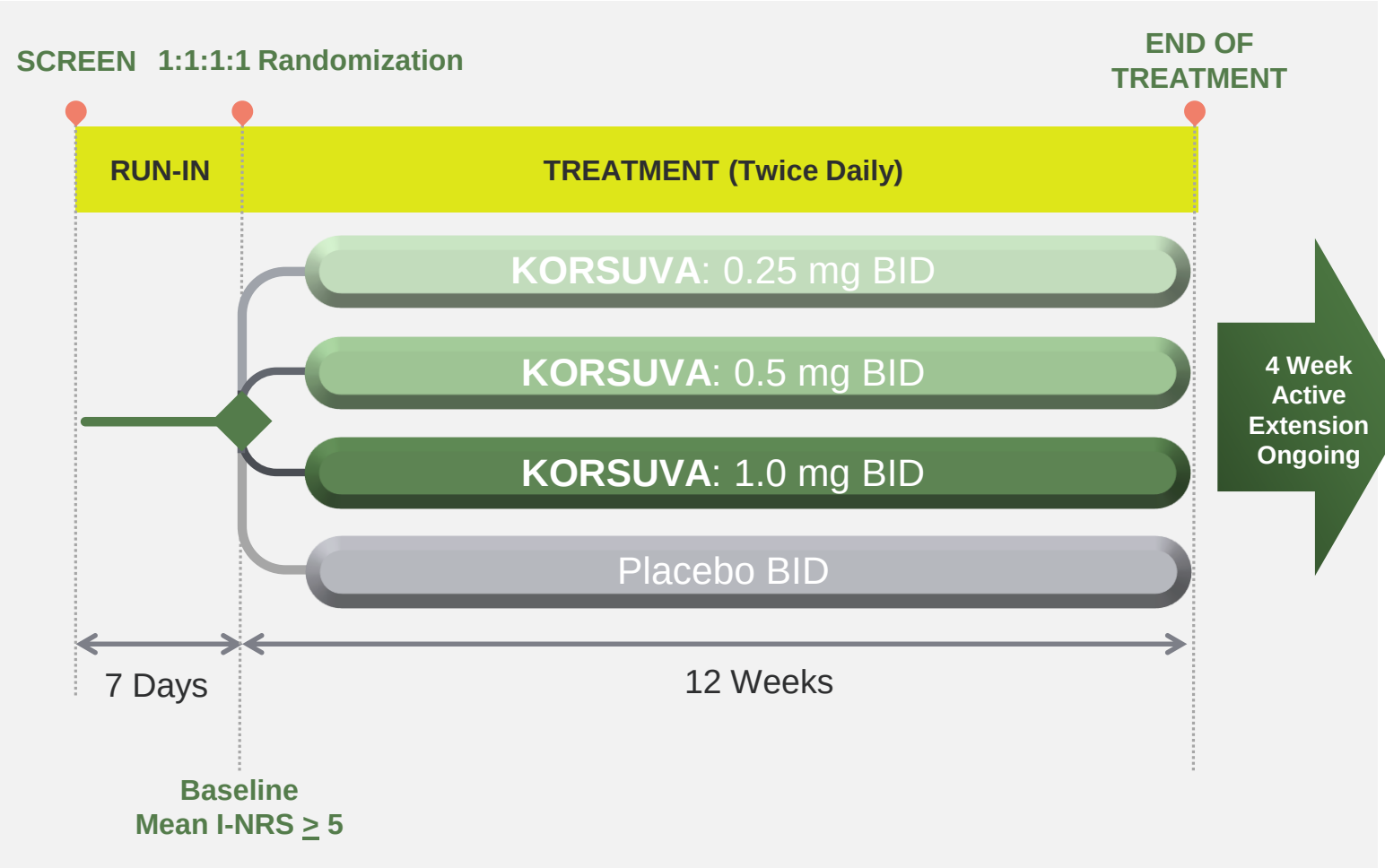
KARE: Phase 2 Study Design



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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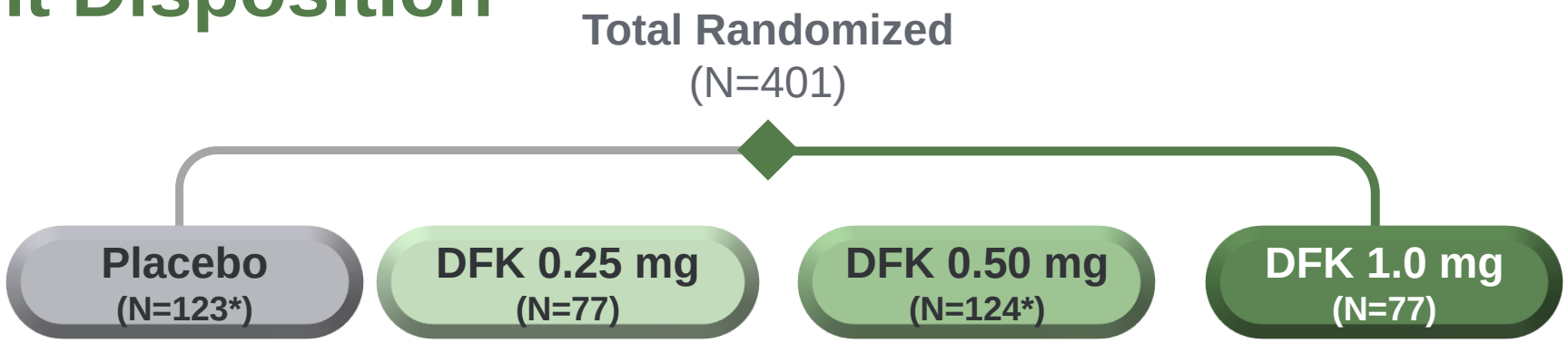
KARE: Patient Disposition



	Placebo (N=123*)	DFK 0.25 mg (N=77)	DFK 0.50 mg (N=124*)	DFK 1.0 mg (N=77)
Completed	97 (79%)	63 (82%)	102 (82%)	61 (79%)
Discontinued	26 (21%)	14 (18%)	22 (18%)	16 (21%)
Adverse event	4	3	1	9
Subject withdrew consent	5	3	8	4
Subject non-compliance	6	2	7	0
Lost to follow-up	5	2	1	2
Lack of therapeutic efficacy	3	1	2	0
Other	3	3	3	1
Use of Rescue Medication	2 (1.6%)	4 (5.2%)	1 (0.8%)	1 (1.3%)

**The sample size for DFK 0.5 mg and placebo was increased based on the results of the Interim Assessment for sample size re-estimation*

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KARE: Patient Demographics

	Placebo (N=123)	DFK 0.25 mg (N=77)	DFK 0.50 mg (N=124)	DFK 1.0 mg (N=77)
Female, n (%)	80 (65)	54 (70)	83 (67)	53 (69)
Age - Mean (SD)	40 (15.6)	43 (16.2)	42 (15.4)	41 (14.0)
Race, n (%)				
White	71 (58)	44 (57)	74 (60)	40 (52)
Black	42 (34)	31 (40)	40 (32)	33 (43)
Asian	5 (4)	1 (1)	5 (4)	2 (3)
BMI – Mean (SD)	29 (7)	30 (8)	32 (9)	31 (8)

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KARE: Baseline Disease Characteristics

	Placebo (N=123)	DFK 0.25 mg (N=77)	DFK 0.50 mg (N=124)	DFK 1.0 mg (N=77)
Duration of AD (yrs) – Mean (SD)	20 (16)	25 (14)	21 (15)	23 (16)
Baseline BSA (%) – Mean (SD)	8.4 (6.9)	8.3 (6.0)	8.4 (6.4)	9.5 (6.9)
Baseline BSA Group – n (%)				
< 10 %	79 (64)	50 (65)	82 (66)	46 (60)
≥ 10 %	44 (36)	27 (35)	42 (34)	31 (40)
Baseline EASI – Mean (SD)	5.9 (4.9)	6.9 (5.4)	5.9 (4.3)	6.5 (4.5)
Baseline IGA				
2	56 (46)	33 (43)	57 (46)	33 (43)
3	64 (52)	40 (52)	64 (52)	43 (56)
4	3 (2)	4 (5)	3 (2)	1 (1)
Baseline I-NRS – Mean (SD)	7.7 (1.3)	7.8 (1.3)	7.8 (1.2)	7.9 (1.2)

 BSA=Body Surface Area & <10% is mild/moderate AD; EASI scores ranges from 0 to 72; IGA scores range from 0 to 4; I-NRS: Worst Itching Numeric Rating Scale (0 to 10) where 0 = no itch and 10 = worst itching imaginable.

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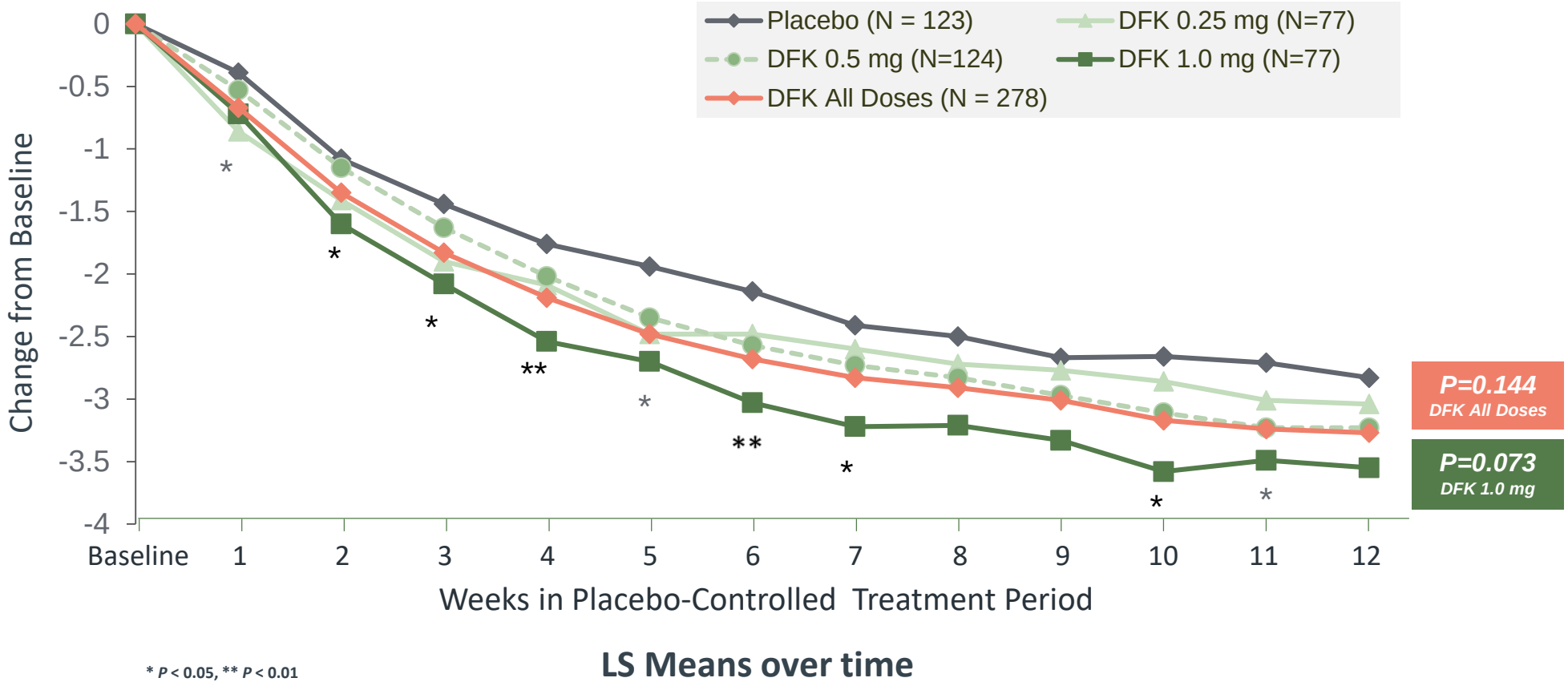
Primary Endpoint: Change from Baseline in Daily I-NRS at Week 12 (ITT)

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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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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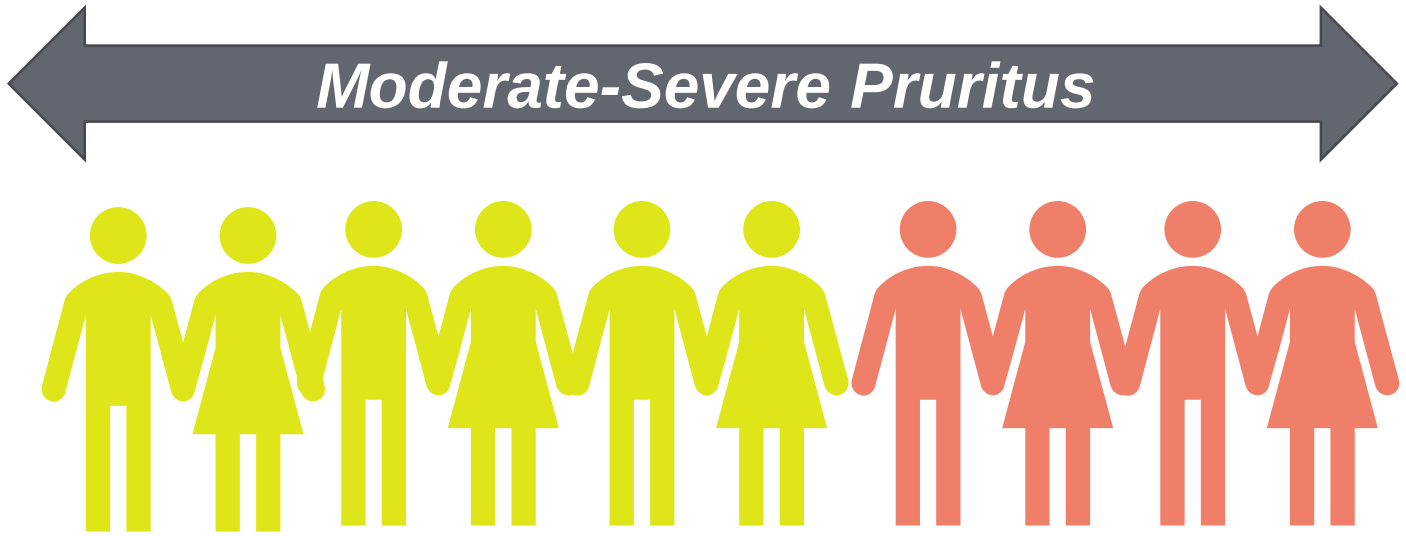
KARE Trial Patient Population



~64%

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

~36%

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

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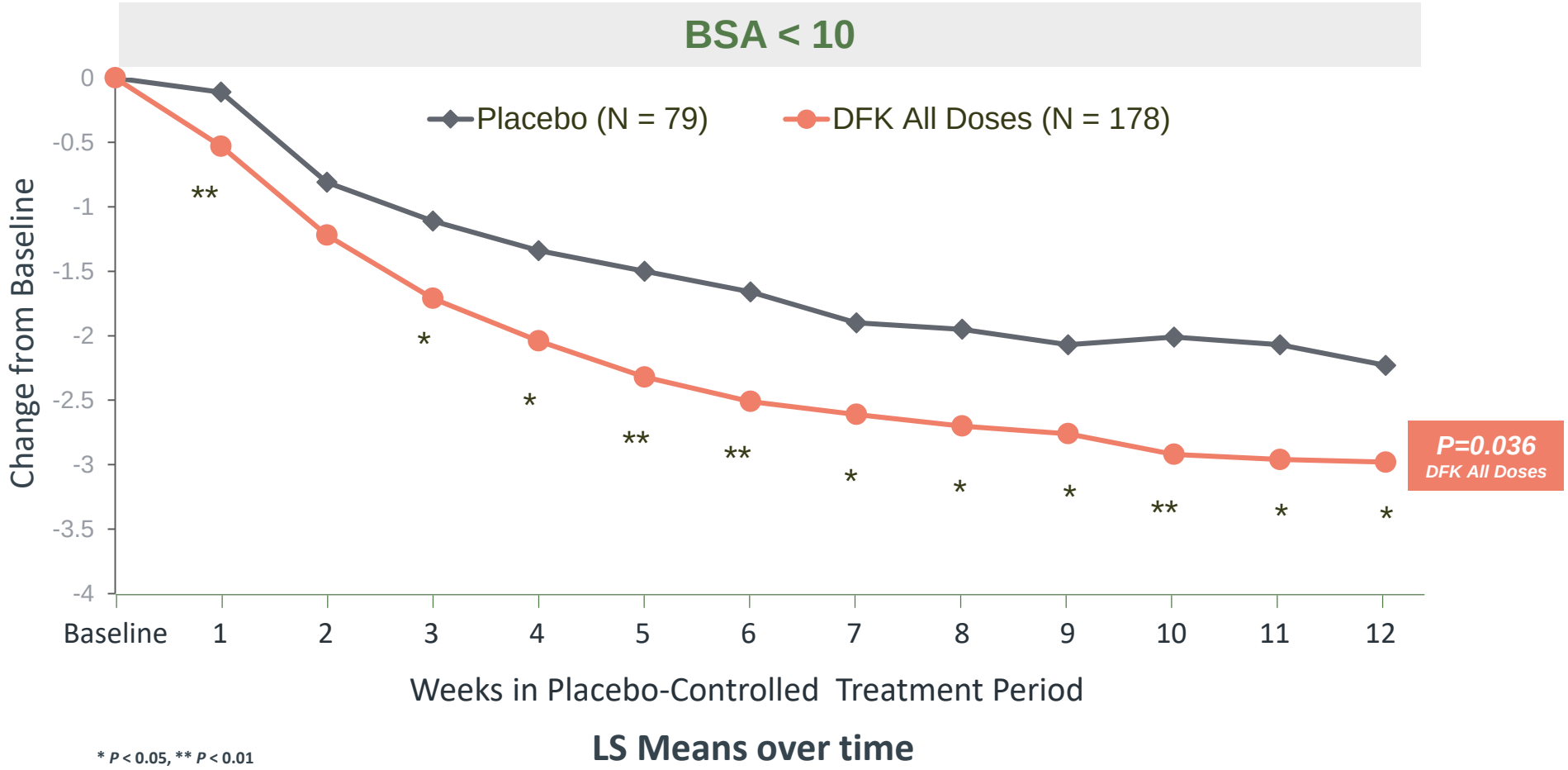
Mild to Moderate AD
Change from Baseline in Daily I-NRS Through Week 12

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



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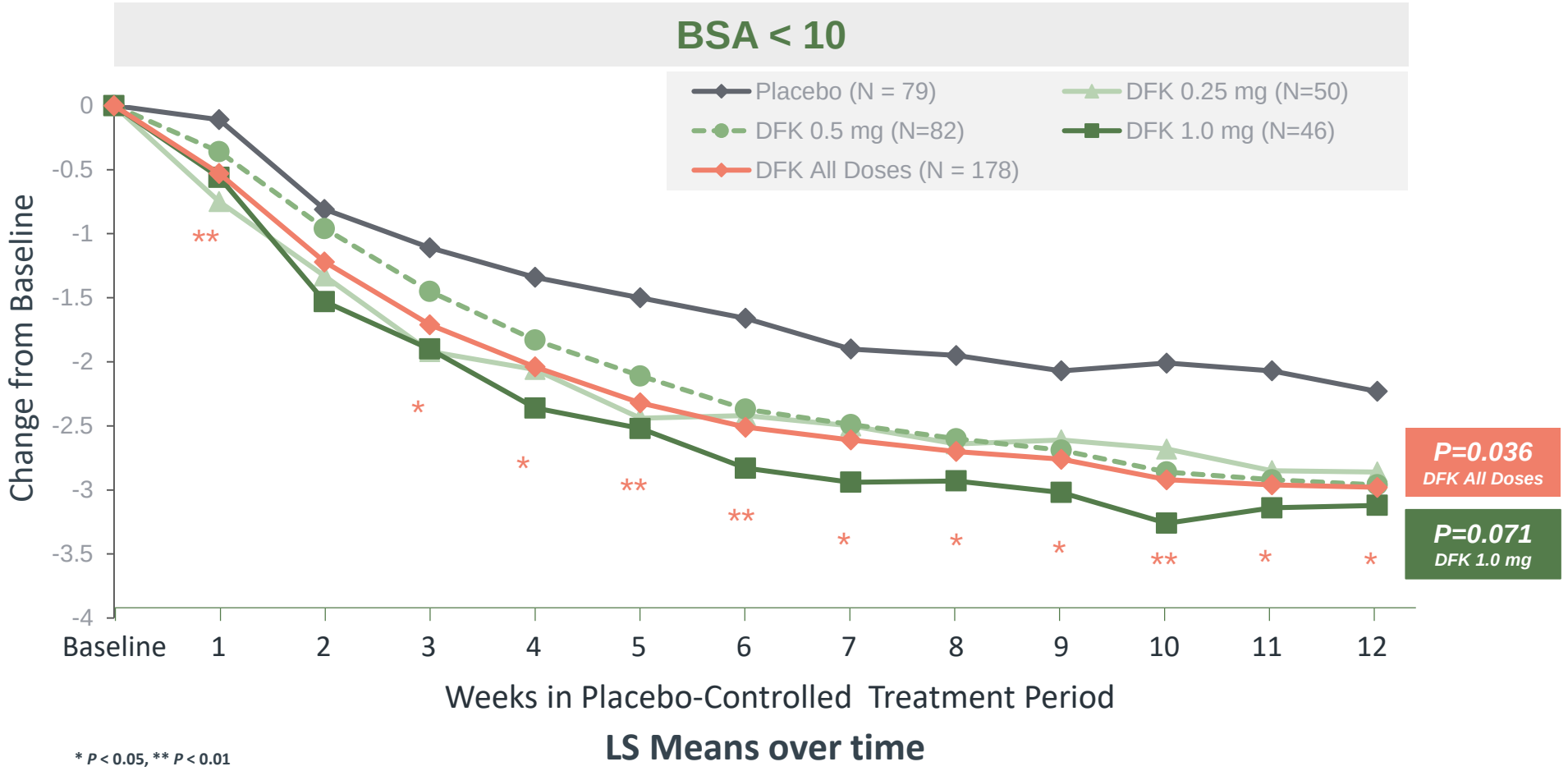
Mild to Moderate AD
Change from Baseline in Daily I-NRS through Week 12



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

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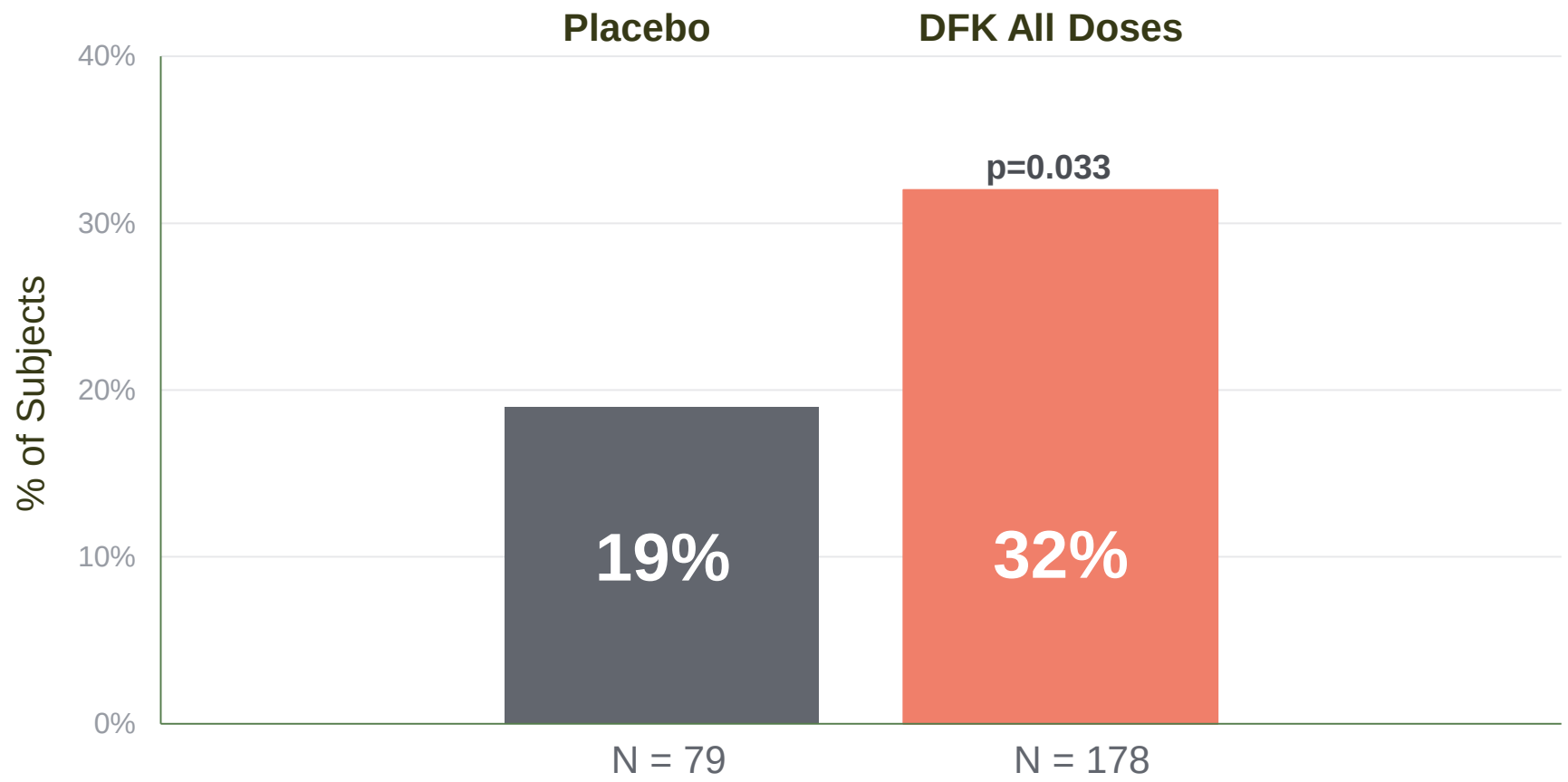
Mild to Moderate AD
Subjects with ≥ 4-point Improvement in I-NRS at Week 12

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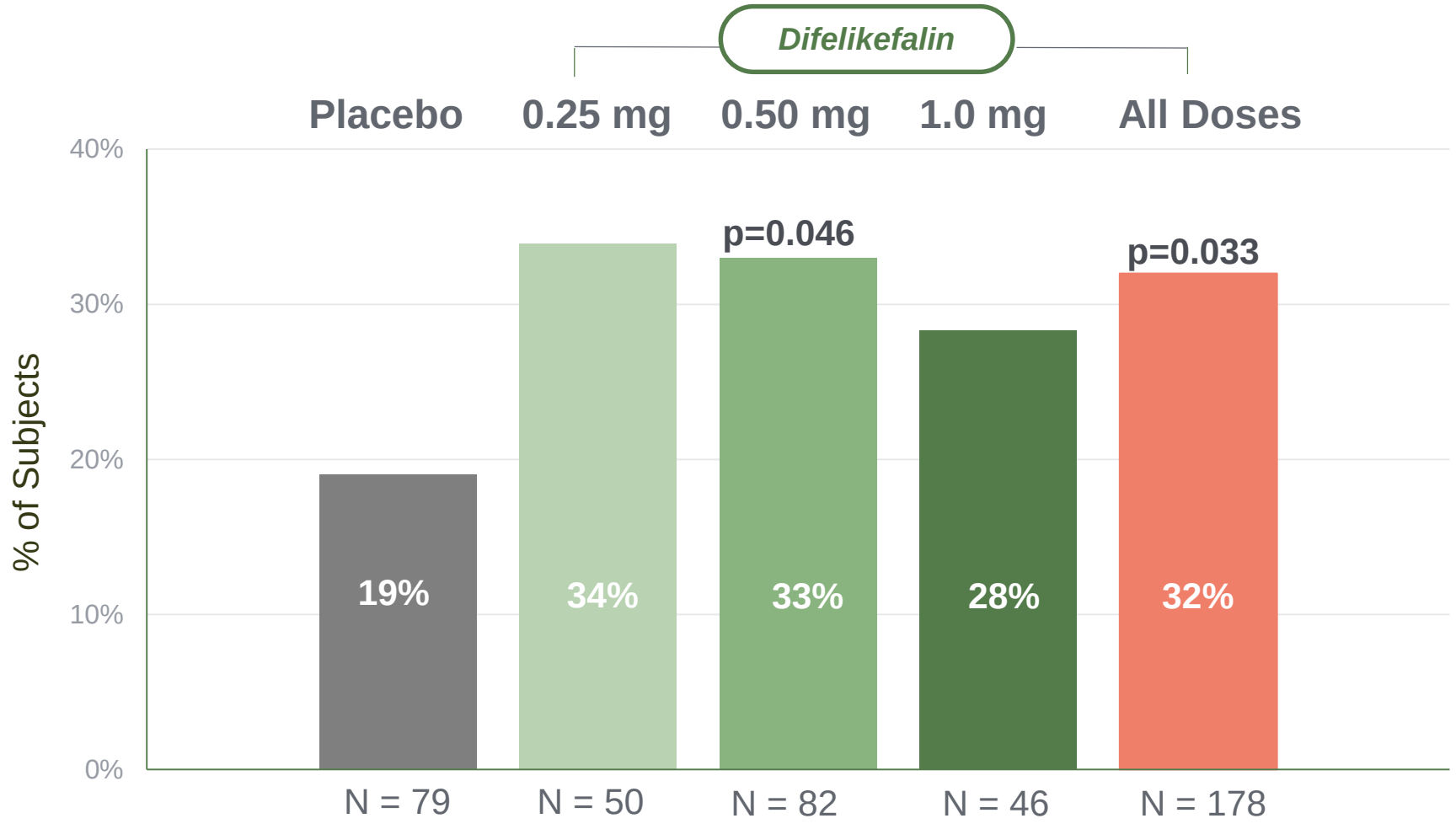
Mild to Moderate AD
Subjects with ≥ 4-point Improvement in I-NRS at Week 12



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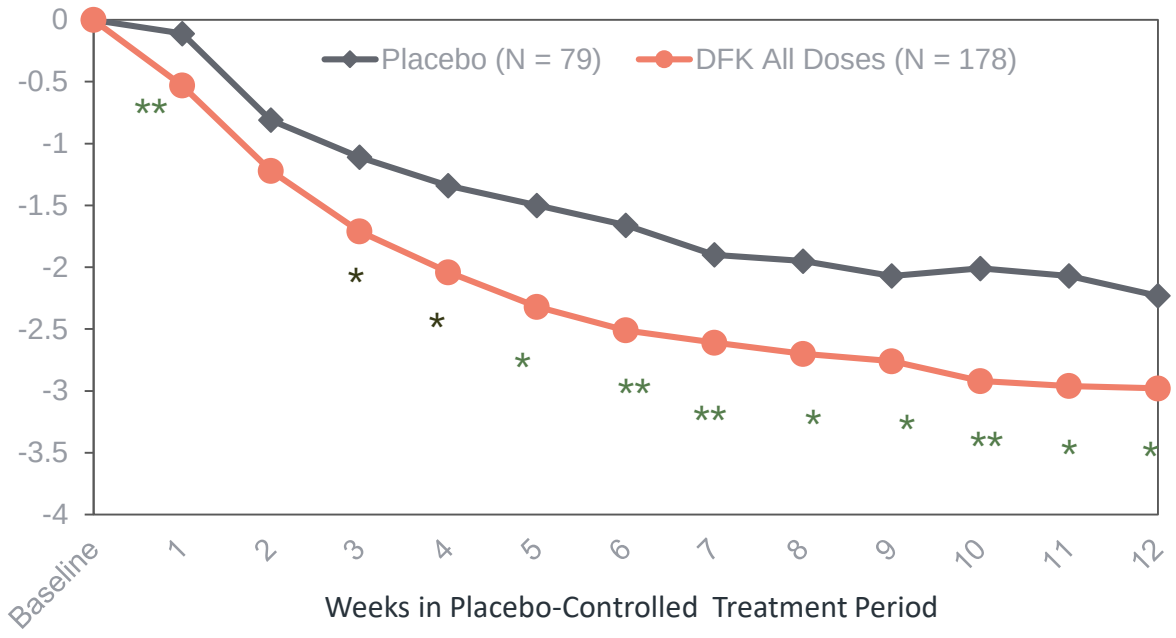
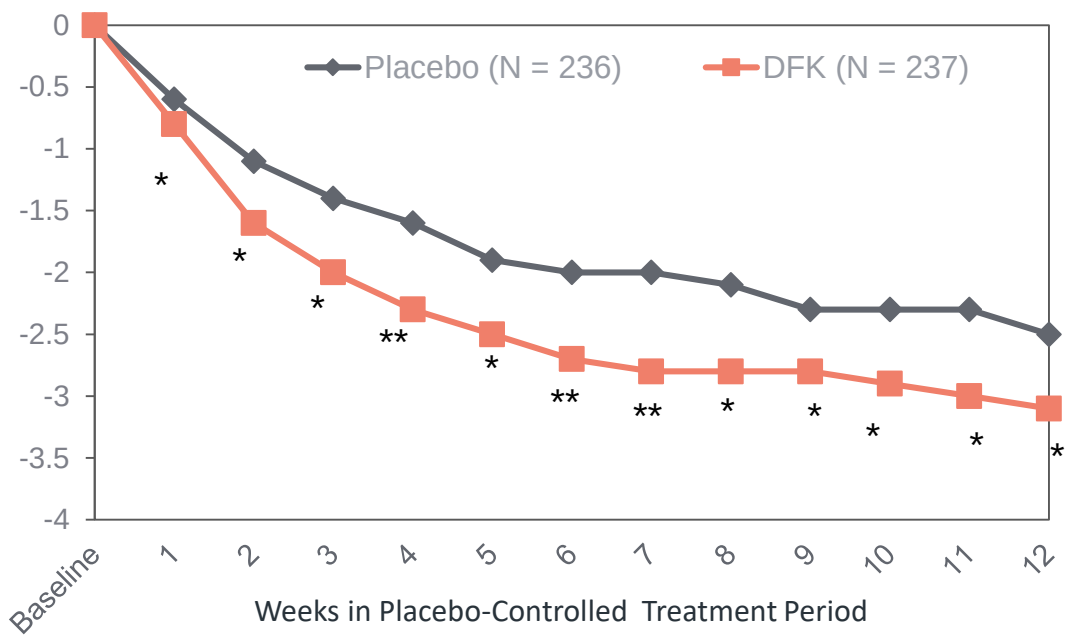
KORSUVA™ Profiles: Mild to Moderate AD-aP & CKD-aP

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

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Conclusions

- 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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