Oral Difelikefalin Reduces Pruritus in Atopic Dermatitis

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Acknowledgments, Correspondence, and Disclosures

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DISCLOSURES

- **BK:** AbbVie, Abrax Japan, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Escient Pharmaceuticals, Galderma, GlaxoSmithKline, Granular Therapeutics, Incyte, LEO Pharma, Lilly, Pfizer, Recens Medical, Regeneron, Sanofi, and Trevi Therapeutics – consulting; Cara Therapeutics and LEO Pharma – research grants.
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Introduction and Objective

- Pruritus is the central symptom in atopic dermatitis (AD)[1]
- Patients with mild-to-moderate AD frequently exhibit severe itch, and treatments that specifically target AD-related pruritus are lacking[1,2]
- Difelikefalin (DFK), a novel, selective kappa-opioid receptor (KOR) agonist, is being developed for chronic pruritic conditions[3,4]
  - In August 2021, IV DFK received approval from the US Food and Drug Administration for the treatment of moderate-to-severe pruritus associated with chronic kidney disease in adults undergoing hemodialysis[5]
- Here, we present a mouse model of AD which was used to test the effects of DFK on itch and lesional severity
- Results are also presented from a phase 2 study of oral DFK in subjects with AD and moderate-to-severe pruritus

1. Weidinger S, et al. *Nat Rev Dis Primers*. 2018;4:1. 2. Huet F, et al. *Acta Derm Venereol*. 2019;99:279-283. 3. Fishbane S, et al. *N Engl J Med*. 2020;382:222-232. 4. Wooldridge T, et al. Efficacy and Safety of Difelikefalin for Moderate-to-Severe Chronic Kidney Disease–Associated Pruritus: a Global Phase 3 Study in Hemodialysis Patients (KALM-2). Presented at: Annual Meeting of the American Society of Nephrology; October 20-25, 2021. 5. Korsuva [package insert]. Stamford, CT: Cara Therapeutics, Inc.; August 2021.

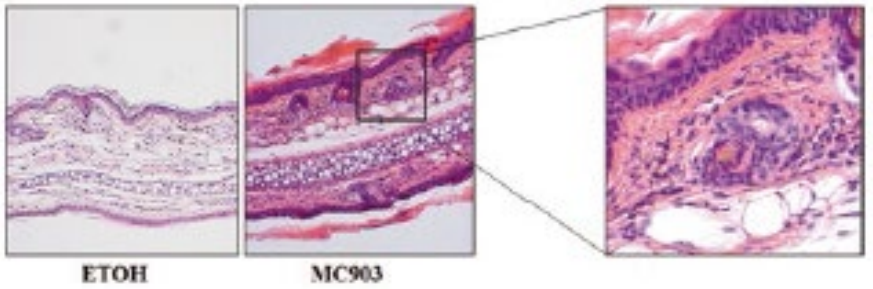
Mouse Study Methods and Results

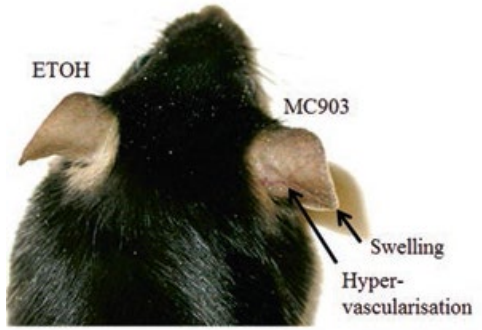
T_H2 cell

Eosinophilia

IgE

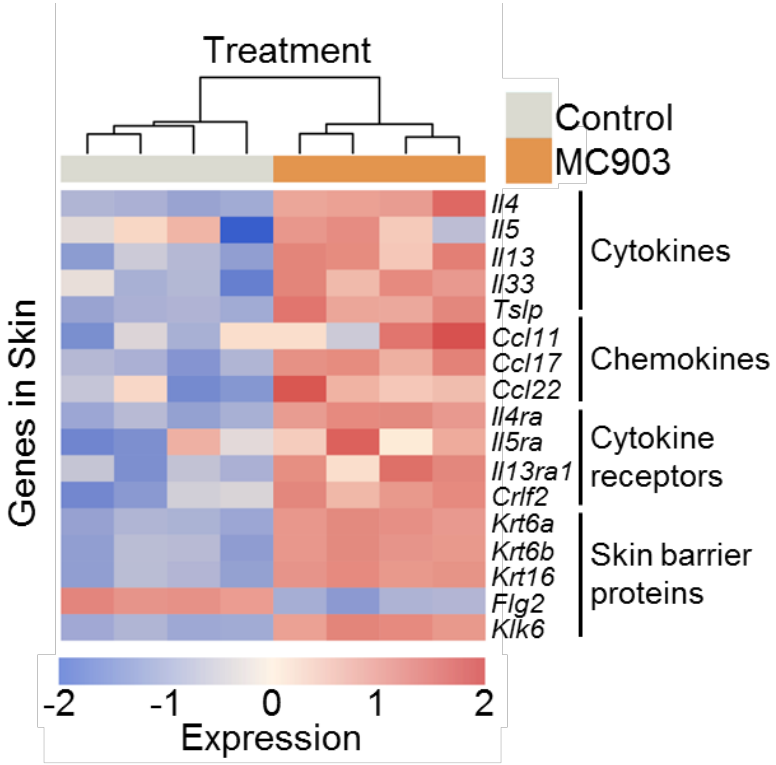
B cell

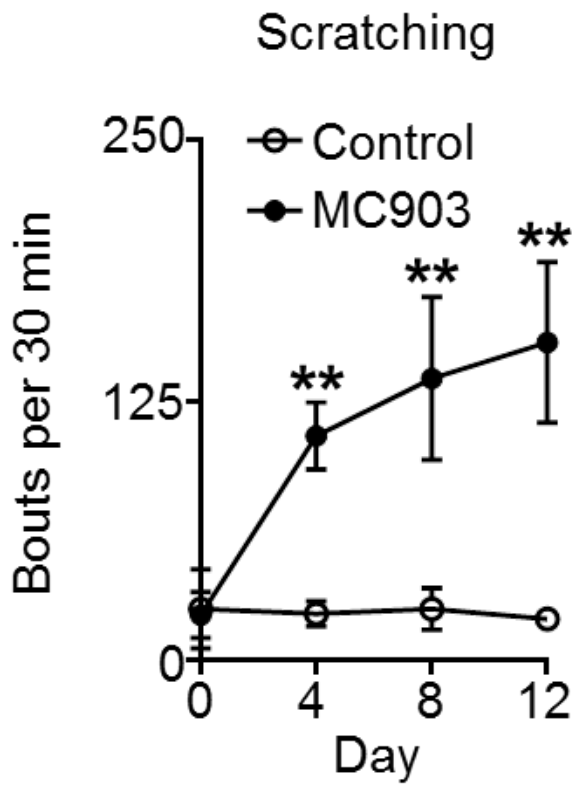




MC903, calcipotriol; IgE, immunoglobulin E; TH2, T helper 2; WT, wild type.
Moosbrugger-Martinz V, et al. *Methods Mol Biol.* 2017;1559:91-106.

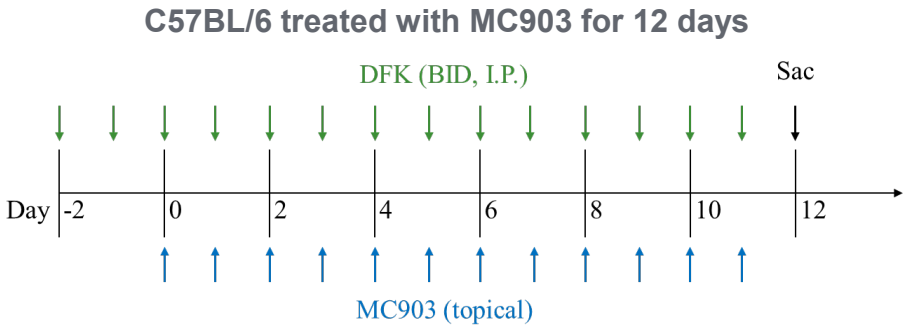
Mouse Study Methods and Results

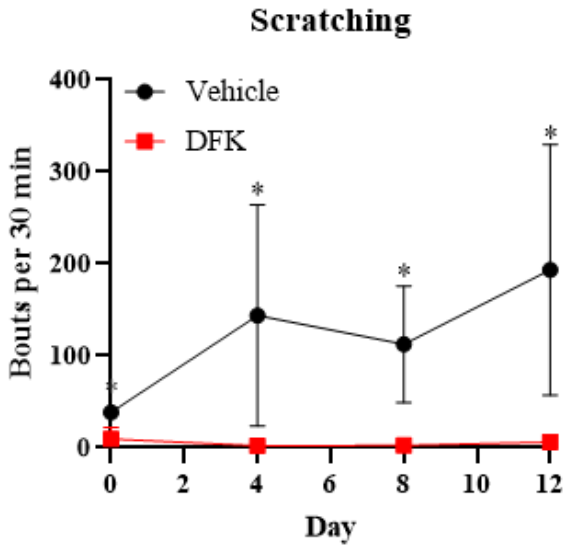


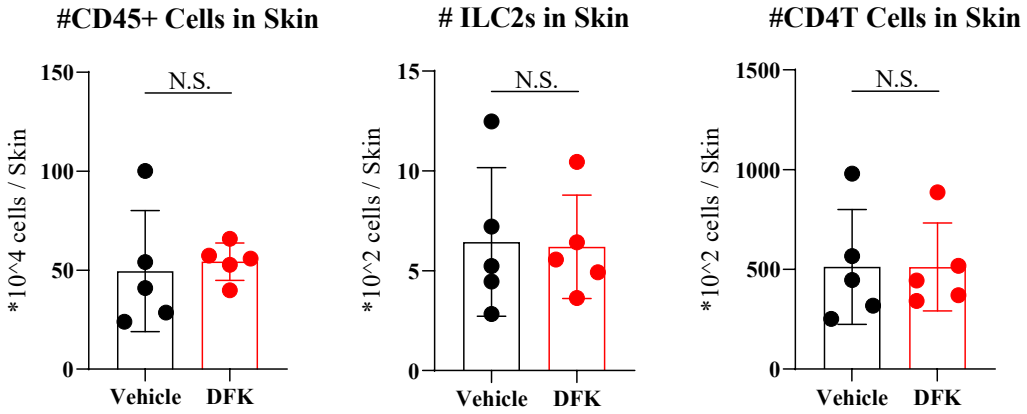


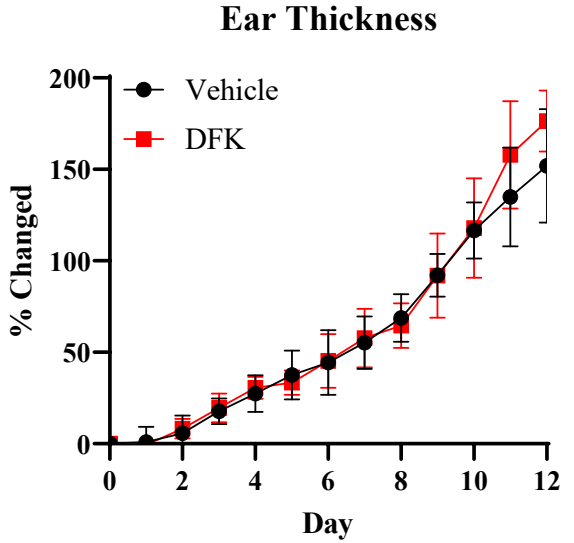
 Oetjen LK, et al. *Cell.* 2017;171:217-228.

Mouse Study Methods and Results









 * p<0.05 vs. control (unpaired t-test)
BID, twice daily; I.P., intraperitoneal; ILC2, innate lymphoid type-2 cells

Mouse Study Methods and Results

- Single cell RNA-sequencing datasets reveal expression of Oprk1 (gene encoding KOR) primarily on mechanosensory Aβ neurons

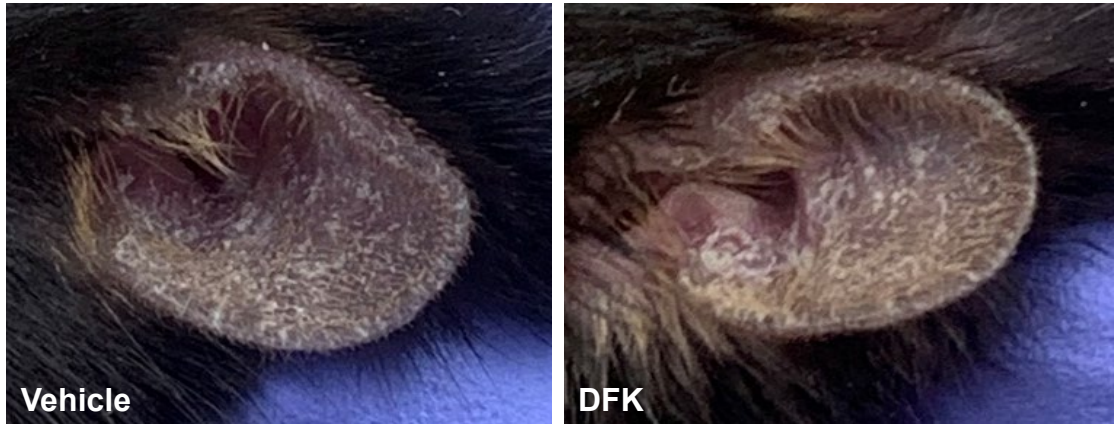
	A-LTMR (Touch)					C-fibers (Itch)					
Gene Symbol	**NF1**	**NF2**	**NF3**	**NF4**	**NF5**	**NP1**	**NP2**	**NP3**	**PEP1**	**PEP2**	**TH**
Oprk1	0	0.104	0.083	0	0	0	0	0	0	0	0
Oprm1	0	0	0	0.045	0	0.056	0.125	0.250	0.047	0.118	0.004
Nppb	0	0	0	0	0	0	0.031	0.833	0.031	0	0
Sst	0	0	0	0	0	0	0.031	0.833	0.016	0	0
Cysltr2	0	0	0	0	0	0.032	0	0.667	0	0	0
Hrh1	0	0	0.083	0	0	0	0.094	0.083	0	0	0
Mrgprd	0.032	0.021	0	0	0.038	0.840	0.219	0	0.016	0	0.013
Mrgpra3	0	0	0	0	0	0.008	0.625	0.083	0	0	0.004
Il4ra	0	0	0	0.045	0	0.208	0.281	0.167	0.109	0.059	0.039
Il13ra1	0	0.021	0	0	0	0.008	0.094	0.083	0.016	0	0
Il31ra	0	0	0.083	0	0	0	0.031	0.583	0.016	0	0

 Usoskin D, et al. *Nat Neurosci.* 2015;18:145-153.

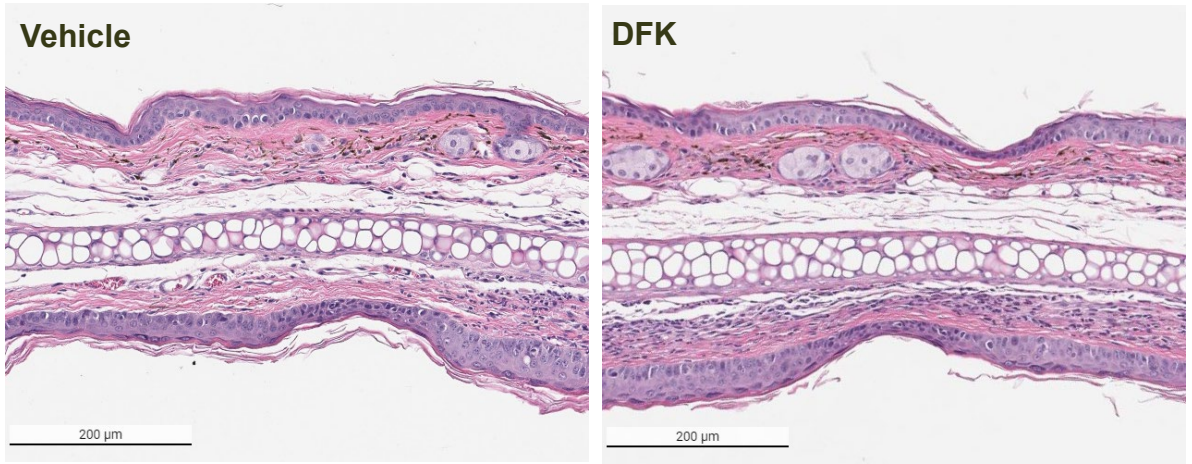
Mouse Study Results: DFK Reduces Scratching Independently of Skin Inflammation

- Calcium imaging demonstrated that DFK directly activated large diameter (ie, Aβ) sensory neurons

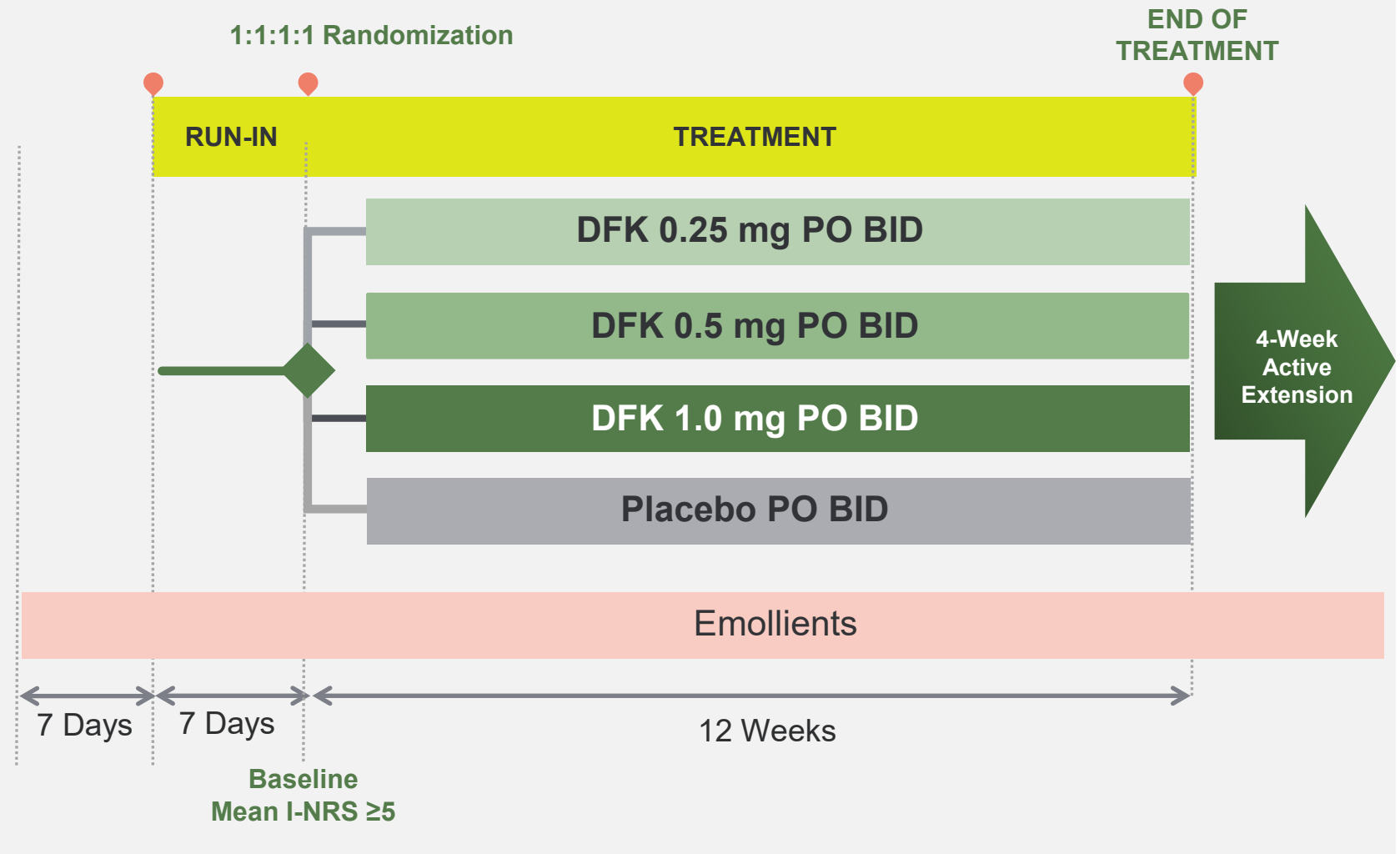
AD-Like Skin Lesions



AD-Like Skin Histopathology



KARE: Phase 2 Study Design



Primary Endpoint

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

Secondary Endpoints

- ≥4-point improvement in weekly mean of the daily I-NRS at week 12
- Safety

Subgroup Analysis

- BSA <10% population

 | BSA, body surface area; I-NRS, Itch Numeric Rating Scale.

Subject Disposition

Subjects, n (%)	Placebo (n=123*)	DFK 0.25 mg (n=77)	DFK 0.5 mg (n=124*)	DFK 1.0 mg (n=77)
	Total Randomized (N=401)			
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 sizes for DFK 0.5 mg and placebo were increased based on the results of an interim assessment for sample size re-estimation.

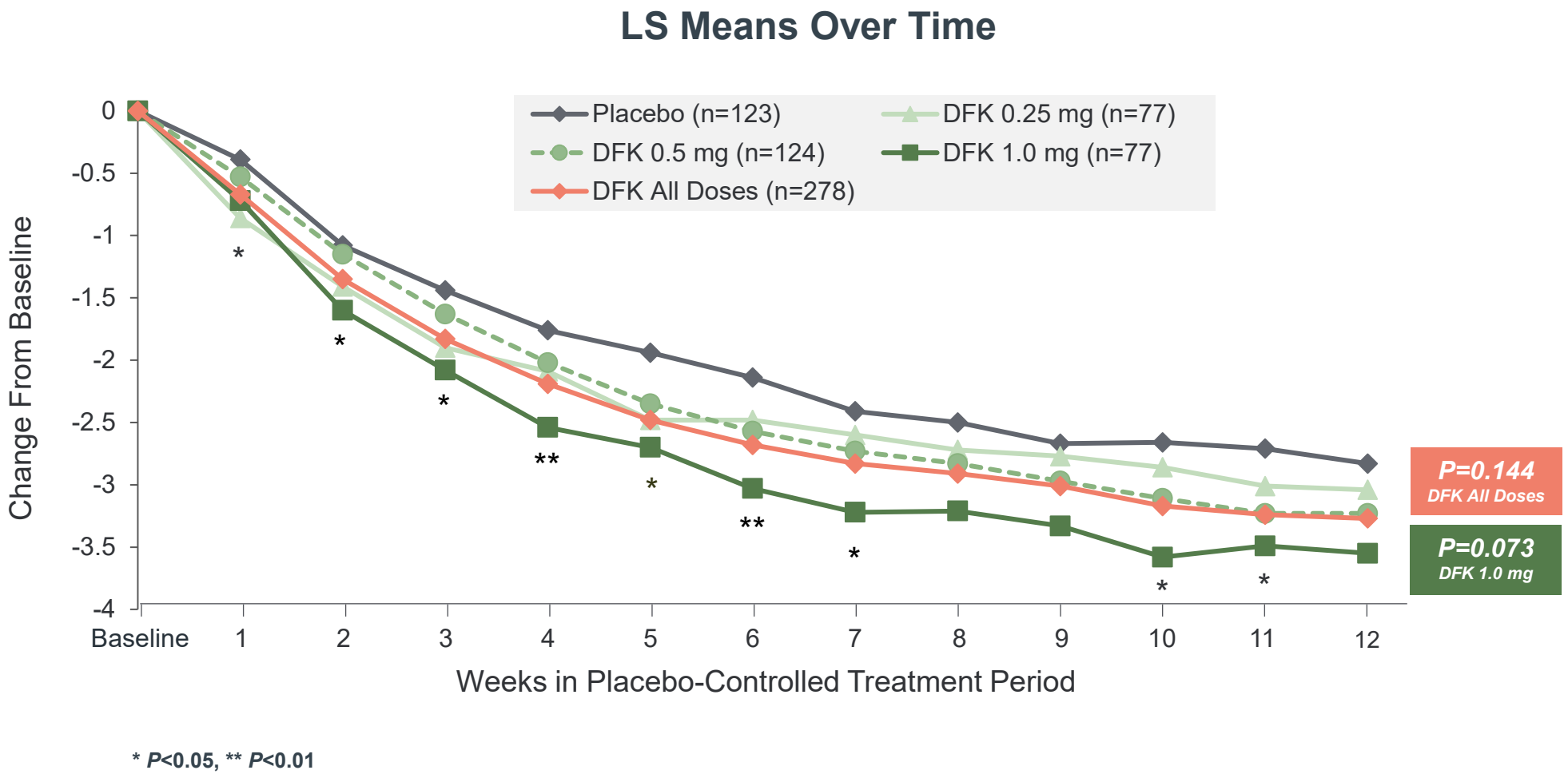
Baseline Demographics and Disease Characteristics (ITT Population)

Characteristic	Placebo (n=123)	DFK 0.25 mg (n=77)	DFK 0.5 mg (n=124)	DFK 1.0 mg (n=77)
Female, n (%)	80 (65)	54 (70)	83 (67)	53 (69)
Age, mean (SD), y	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)
BSA (%), mean (SD)	8.4 (6.9)	8.3 (6.0)	8.4 (6.4)	9.5 (6.9)
EASI, mean (SD)	5.9 (4.9)	6.9 (5.4)	5.9 (4.3)	6.5 (4.5)
I-NRS, mean (SD)	7.7 (1.3)	7.8 (1.3)	7.8 (1.2)	7.9 (1.2)
DLQI, mean (SD)	13.0 (7.2)	12.6 (7.4)	11.5 (6.6)	13.5 (6.5)

- Approximately two-thirds (64%) of subjects had BSA <10%

 | BSA <10% is mild/moderate AD; EASI scores range from 0 to 72; I-NRS scores range from 0 to 10 (0 = no itch, 10 = worst itching imaginable).
BMI, body mass index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index.

Primary Endpoint: Change From Baseline in I-NRS Through Week 12 (ITT)



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

LS means from mixed effects model with repeated measures (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.
BL, baseline; ITT, intent to treat; LS, least squares.

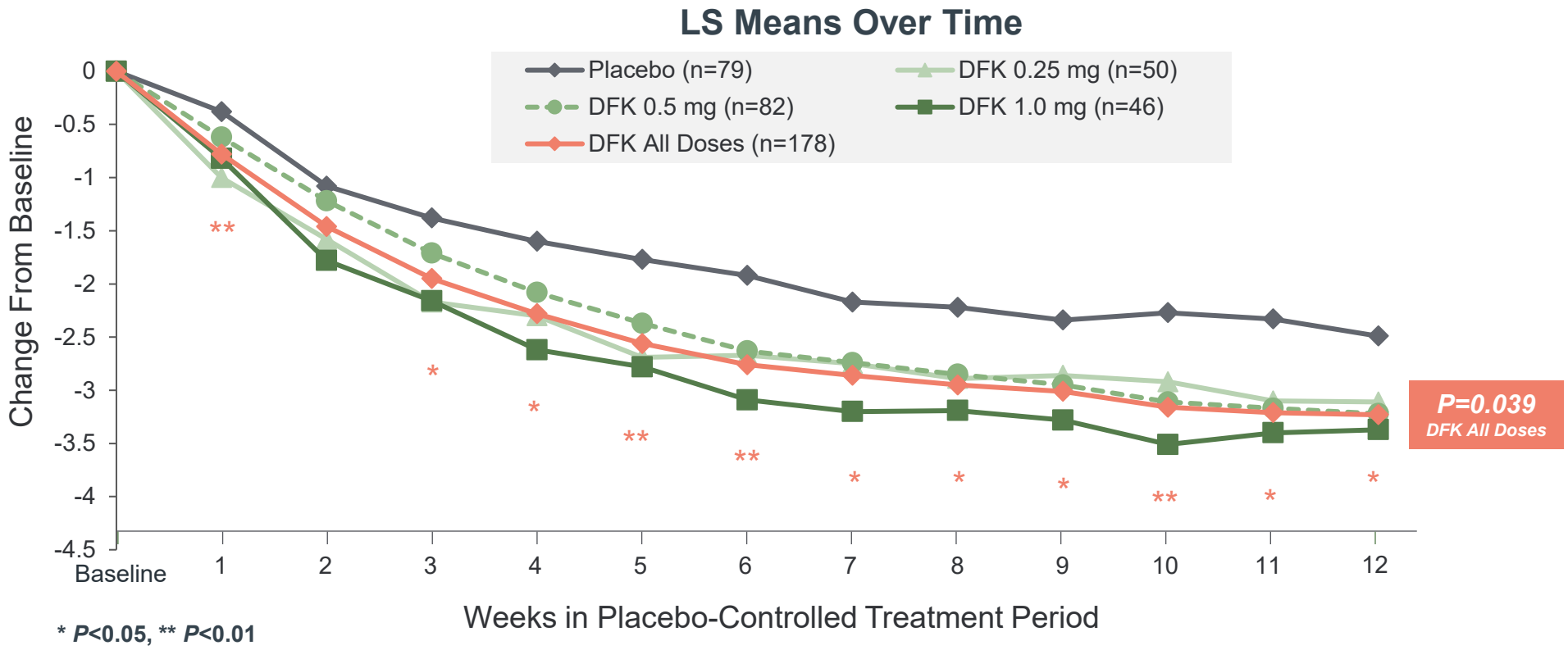
Baseline Disease Characteristics: BSA <10% Population (Itch-Dominant AD)

Characteristic	Placebo (n=79)	DFK 0.25 mg (n=50)	DFK 0.5 mg (n=82)	DFK 1.0 mg (n=46)
BSA (%), mean (SD)	4.3 (2.5)	4.6 (2.5)	4.6 (2.8)	5.0 (2.2)
EASI, mean (SD)	3.7 (2.6)	4.3 (3.5)	4.0 (2.8)	4.5 (3.0)
I-NRS, mean (SD)	7.6 (1.3)	7.5 (1.3)	7.7 (1.2)	7.8 (1.3)
DLQI, mean (SD)	12.0 (6.8)	11.8 (7.5)	10.6 (5.9)	13.1 (6.0)

EASI score ranges from 0 to 72; I-NRS score ranges from 0 to 10 (0 = no itch, 10 = worst itching imaginable).

BSA <10% Population (Itch-Dominant AD) Change From Baseline in I-NRS Through Week 12

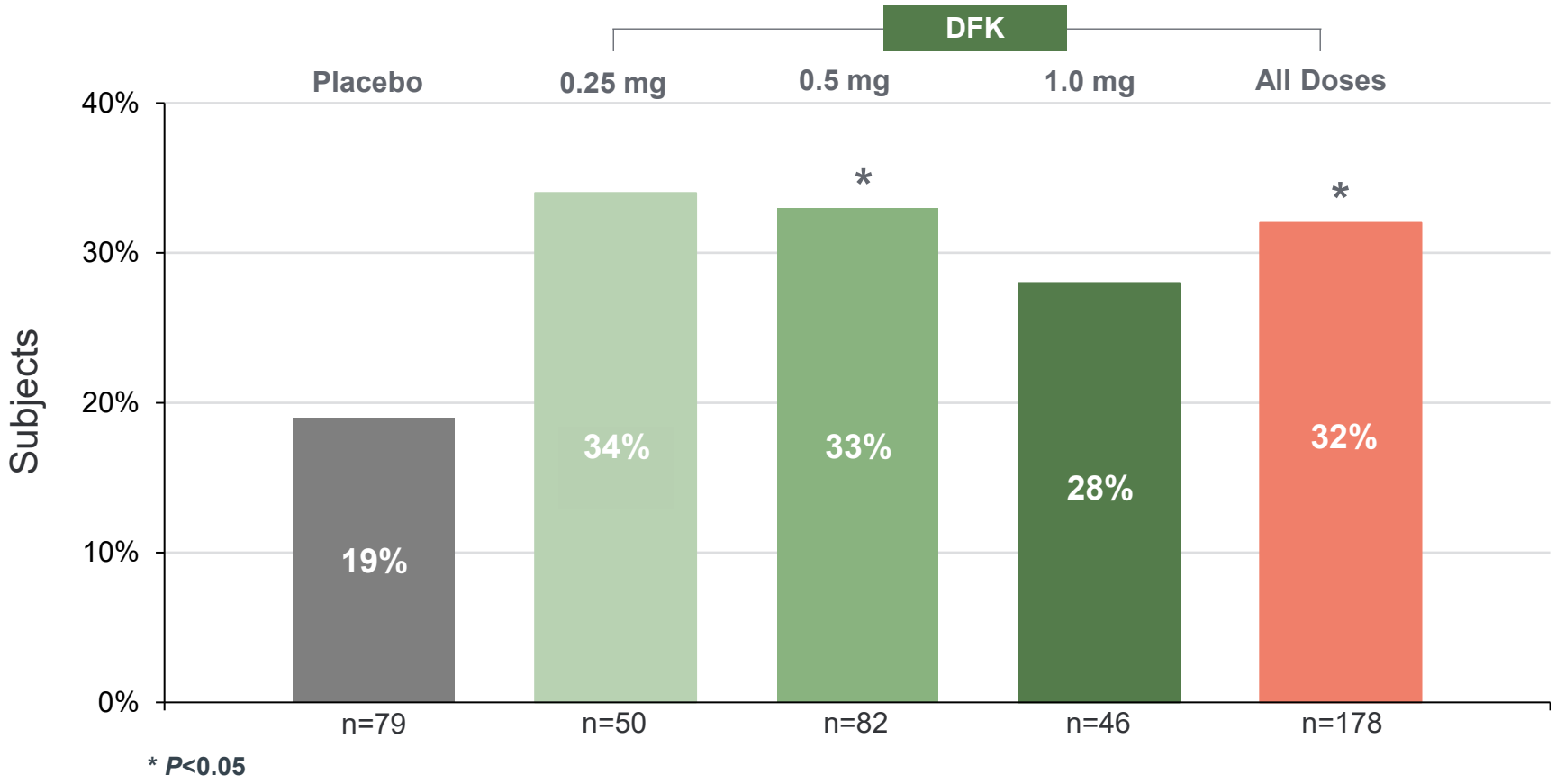
- Significant improvement in itch was observed at week 12 with the combined DFK group compared with placebo
- Significant improvement was evident as early as day 2



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

BSA <10% Population (Itch-Dominant AD) 4-Point Responder Analysis at Week 12

- A significantly greater proportion of subjects achieved ≥4-point improvement in daily I-NRS with DFK vs placebo at week 12



P values vs placebo. Estimated por percentage and *P* value based on a logistic regression model with terms for treatment group and baseline I-NRS score. Subjects who discontinued early or who took rescue medication or have missing data at week 12 are considered nonresponders.

Summary of Adverse Events (ITT Population)

Subjects, n (%)	Placebo (n=123)	DFK 0.25 mg (n=77)	DFK 0.5 mg (n=124)	DFK 1.0 mg (n=77)
At least 1 TEAE	54 (43.9)	36 (46.8)	49 (39.5)	42 (54.5)
At least 1 serious TEAE	0	1 (1.3)	1 (0.8)	2 (2.6)
TEAE resulting in treatment discontinuation	4 (3.3)	3 (3.9)	1 (0.8)	9 (11.7)

- TEAEs were mostly mild or moderate in severity (~95%)
- Most discontinuations were due to gastrointestinal-related TEAEs
- Serious TEAEs occurred in 1 subject with hypovolemia and acute kidney injury (DFK 1.0 mg), 1 subject with hyponatremia (DFK 1.0 mg), 1 subject with nephrolithiasis (DFK 0.5 mg), and 1 subject with costochondritis (DFK 0.25 mg)
  - All SAEs were deemed unrelated to study drug by the investigator

Safety analyses performed in the safety population, defined as all randomized subjects who received ≥1 dose of study drug based on actual treatment received.
TEAE, treatment-emergent adverse event.

Most Commonly Reported TEAEs (ITT Population)

TEAEs at ≥5% Frequency, n (%)	Placebo (n=123)	DFK 0.25 mg (n=77)	DFK 0.5 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)	2 (2.6)	3 (2.4)	5 (6.5)

Safety analyses performed in the safety population, defined as all randomized subjects who received ≥1 dose of study drug based on actual treatment received.
*Includes preferred terms abdominal pain, abdominal pain upper, abdominal discomfort. †Includes preferred terms hypertension and blood pressure increased.

Conclusions

- In a mouse model of AD:
  - A rapid and significant anti-pruritic effect of DFK was observed independently of observable effects on skin inflammation
  - Analyses in this model indicate that expression and activation of the DFK target receptor is on sensory neurons
- In the phase 2 clinical study that includes approximately two-thirds of subjects with itch-dominant AD (BSA <10% and moderate-to-severe pruritus):
  - DFK demonstrated a significant and clinically meaningful reduction in pruritus
  - DFK was well tolerated
- Taken together, these findings support the role of DFK as an antipruritic agent that may be best suited for patients with itch-dominant AD