Efficacy and Safety of Difelikefalin in Patients Undergoing Hemodialysis With Pruritus: Results From a Phase 3 Randomized, Controlled Study (KALM-1)

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Disclosures

- Steven Fishbane reports receipt of grants from Cara Therapeutics, Inc. and is also an investigator.
- Aamir Jamal is an investigator for Cara Therapeutics, Inc.
- Warren Wen, Catherine Munera and Frédérique Menzaghi are employees of Cara Therapeutics, Inc.

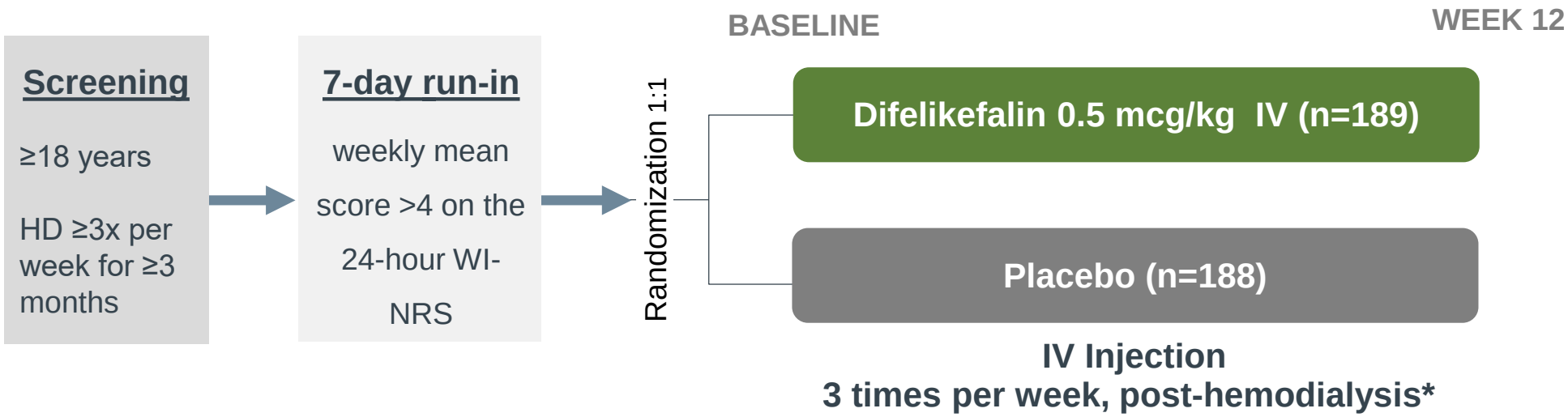
Background

- Chronic kidney disease-associated pruritus (CKD-aP) is a distressing condition
  - Moderate to severe in 20–40% of patients undergoing hemodialysis[1]
  - Associated with poor sleep quality, depression, reduced quality of life, increased risk of infection, and a potential increased risk of mortality[1]
- There is no recognized standard of care, and no approved treatment in the US or Europe[2,3]
- Difelikefalin is a novel peripherally restricted agonist at kappa opioid receptor[4,5]
  - Small synthetic peptide with limited CNS penetration
  - Does not bind to mu- or delta-opioid receptors or any other known receptors
  - Antipruritic effect via activation of kappa opioid receptors located on peripheral sensory neurons and immune cells[4,5]
- Here we report the results of the first Phase 3 study of difelikefalin in patients undergoing hemodialysis with moderate-to-severe CKD-aP

1. Pisoni RL et al. *Nephrol Dial Transplant* 2006;21:3495-3505; 2. Combs SA et al. *Semin Nephrol* 2015;35:383-391; 3. Mettang T et al. *Kidney Int* 2015;87:685-691; 4. Webster et al. *J Pain* 2015;16(suppl):S81; 5. Albert-Vartanian A et al. *J Clin Pharm Ther* 2016; 41:371-382.

KALM-1: Phase 3 Pivotal Study

- Multicenter (56 US sites) double blind, placebo-controlled study



Primary Endpoint

- Proportion of patients achieving ≥3-point improvement from baseline at Week 12 in weekly mean score of daily WI-NRS

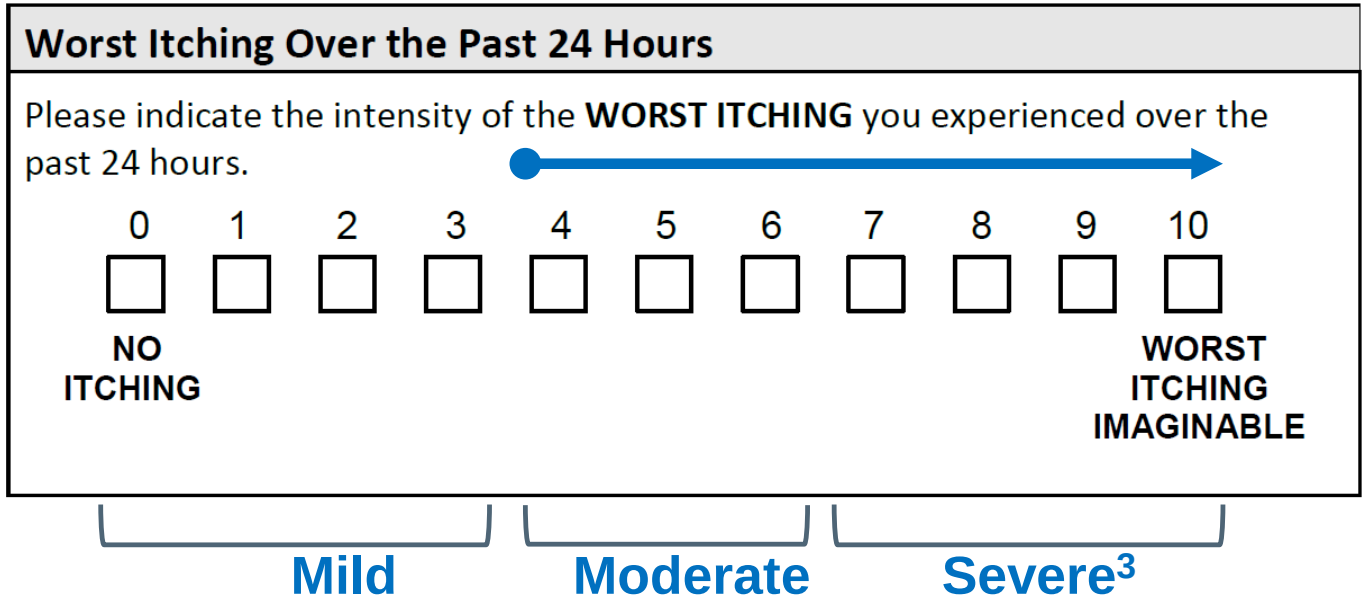
Secondary Endpoints:

- Mean change from baseline at Week 12 in itch-related quality of life as measured by 5-D Itch and Skindex-10 questionnaires
- Proportion of patients achieving ≥4-point improvement from baseline at Week 12 in weekly mean score of daily WI-NRS

WI-NRS, worst itching intensity numeric rating scale. WI-NRS is a validated 11-point scale ranging from 0 to 10, with higher scores indicating worse intensity.

WI-NRS : Worst Itching Intensity Numeric Rating Scale

WI-NRS is a validated 11-point scale ranging from 0-10[1,2]



Psychometric analyses indicated that a reduction ≥ 3 NRS points was associated with a clinically meaningful change in itch severity for patients with moderate-to-severe CKD-aP.

1.Mathur VS et al. *Clin J Am Soc Nephrol* 2010;5:1410–9; 2.Phan NQ et al. *Acta Derm Venereol* 2012;92:502–7.; 3. Reich et al. Acta Derm Venereal 2012

Skindex-10 Scale

INSTRUCTIONS: During the past **WEEK**, how often have you been bothered by:

	0 (Never bothered)	**1**	**2**	**3**	**4**	**5**	**6** (Always bothered)
1. Your itching	☐	☐	☐	☐	☐	☐	☐
2. The persistence/reoccurrence of your itching	☐	☐	☐	☐	☐	☐	☐
3. The appearance of your skin from scratching	☐	☐	☐	☐	☐	☐	☐
4. Frustration about your itching	☐	☐	☐	☐	☐	☐	☐
5. Being annoyed about your itching	☐	☐	☐	☐	☐	☐	☐
6. Feeling depressed about your itching	☐	☐	☐	☐	☐	☐	☐
7. Feeling embarrassed about your itching	☐	☐	☐	☐	☐	☐	☐
8. The effects of your itching on your interactions with others (for example: interactions with family, friends, close relationships, etc.)	☐	☐	☐	☐	☐	☐	☐
9. The effects of your itching on your desire to be with people	☐	☐	☐	☐	☐	☐	☐
10. The effect of your itching making it hard to work or do what you enjoy	☐	☐	☐	☐	☐	☐	☐

Skindex-10 scale ranges from 0 to 60, with higher scores indicating worse itch-related quality of life.

The Skindex-10 scale was developed specifically for uremic pruritus.[1]

1. Mathur VS et al. *Clin J Am Soc Nephrol* 2010;5:1410–9;

5-D Itch

1.	DURATION:	During the last 2 weeks, how many hours a day have you been itching?				
		Less than 6 hrs/day	6-12 hrs/day	12-18 hrs/day	18-23 hrs/day	All day
		☐	☐	☐	☐	☐
2.	DEGREE:	Please rate the intensity of your itching over the past 2 weeks				
		Not present	Mild	Moderate	Severe	Unbearable
		☐	☐	☐	☐	☐
3.	DIRECTION:	Over the past 2 weeks has your itching gotten better or worse compared to the previous month?				
		Completely resolved	Much better, but still present	Little bit better, but still present	Unchanged	Getting Worse
		☐	☐	☐	☐	☐
4.	DISABILITY:	Rate the impact of your itching on the following activities over the last 2 weeks				
		Never affects sleep	Occasionally delays falling asleep	Frequently delays falling asleep	Delays falling asleep and occasionally wakes me up at night	Delays falling asleep and frequently wakes me up at night
	Sleep	☐	☐	☐	☐	☐
		N/A	Never affects this activity	Rarely affects this activity	Occasionally affects this activity	Frequently affects this activity	Always affects this activity
	Leisure/Social	☐	☐	☐	☐	☐	☐
	Housework/ Errands	☐	☐	☐	☐	☐	☐
	Work/School	☐	☐	☐	☐	☐	☐

5.	DISTRIBUTION:	Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically.			
		Head/Scalp	☐	Soles	☐
		Face	☐	Palms	☐
		Chest	☐	Tops of Hands/Fingers	☐
		Abdomen	☐	Forearms	☐
		Back	☐	Upper Arms	☐
		Buttocks	☐	Points of Contact w/ Clothing (e.g waistband, undergarment)	☐
		Thighs	☐		
		Lower legs	☐	Groin	☐
		Tops of Feet/Toes	☐		

The 5-D itch scale assesses five dimensions of itch (degree, duration, direction, disability, and distribution) during a two-week recall period.

5-D itch scale ranges from 5 to 25, with higher scores indicating worse itch-related quality of life.

Elman S et al. *Br J Dermatol* 2010;162:587–93.

Baseline Characteristics and Demographics

	Placebo (n=188)	Difelikefalin (n=189)
Age — yr, mean (SD)	56.8 (13.9)	58.2 (11.2)
Male sex — no. (%)	118 (62.8)	112 (59.3)
Race — no. (%)		
White	93 (49.5)	91 (48.1)
Black or African American	75 (39.9)	82 (43.4)
Other*	18 (9.6)	15 (7.9)
Unknown	2 (1.1)	1 (0.5)
Prescription dry body weight — kg, mean (SD)	85.0 (21.1)	85.9 (20.3)
Time since initiation of hemodialysis — yr, mean (SD)	4.7 (4.2)	4.4 (4.0)
Duration of pruritus — yr, mean (SD)	3.5 (3.4)	3.2 (3.2)

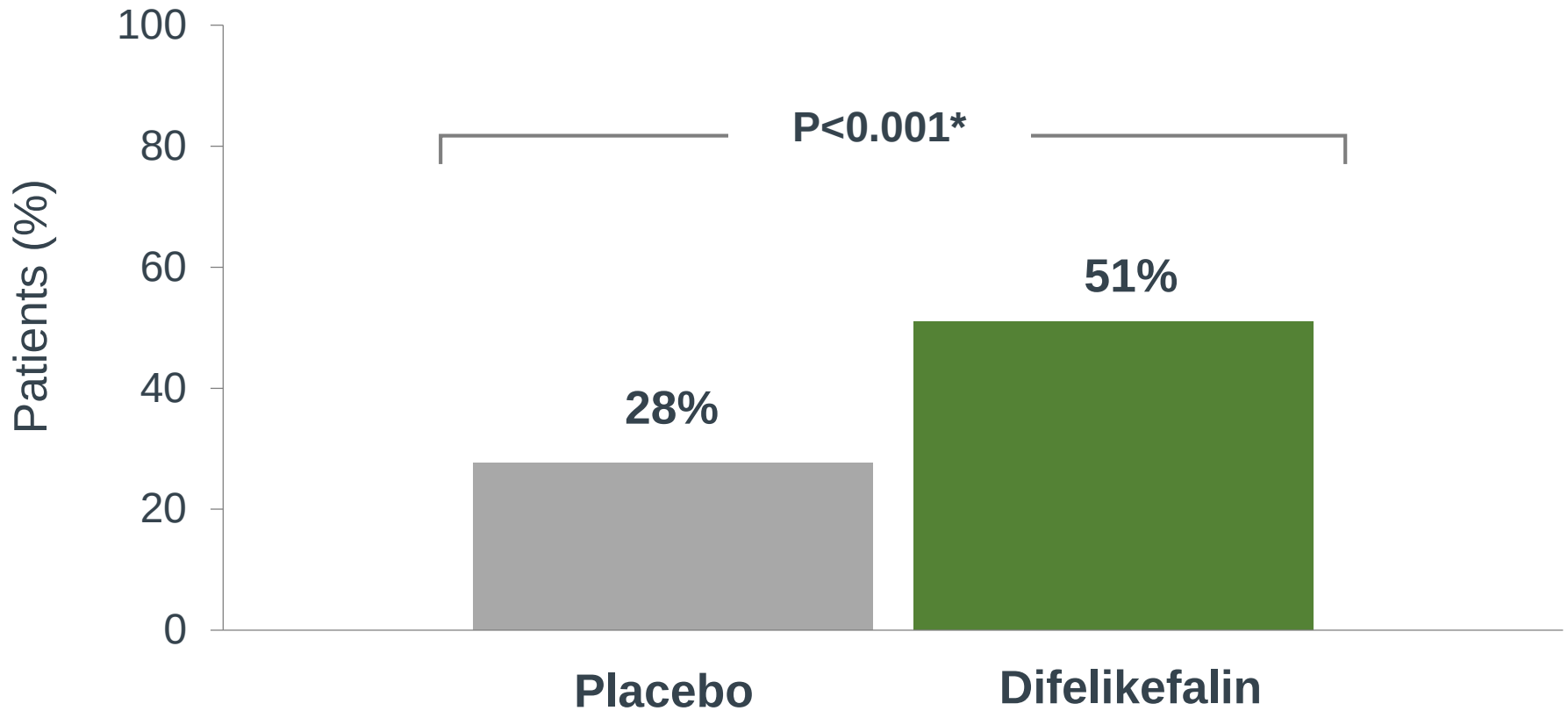
ESRD, end-stage renal disease.
*Includes American Indian or Alaska Native, Asian, and Native Hawaiian or other Pacific Islander.

Baseline Characteristics and Demographics (continued)

	Placebo (n=188)	Difelikefalin (n=189)
Blood Chemistry		
Bilirubin, µmol/L	8.56 (4.77)	10.0 (15.32)
Calcium, mmol/L	2.12 (0.19)	2.11 (0.16)
Phosphate, mmol/L	1.80 (0.64)	1.77 (0.58)
Baseline use of anti-itch medications — no. (%)	78 (41.5)	72 (38.1)
Most commonly used (>10%) anti-itch medications at baseline — no. (%)		
Diphenhydramine	71 (37.8)	61 (32.3)
Hydroxyzine	21 (11.2)	20 (10.6)
WI-NRS score, mean (SD)	7.2 (1.6)	7.1 (1.4)
5-D itch scale total score*	17.9 (3.5)	16.9 (3.5)
Skindex-10 scale total score†	38.3 (15.4)	36.2 (14.4)

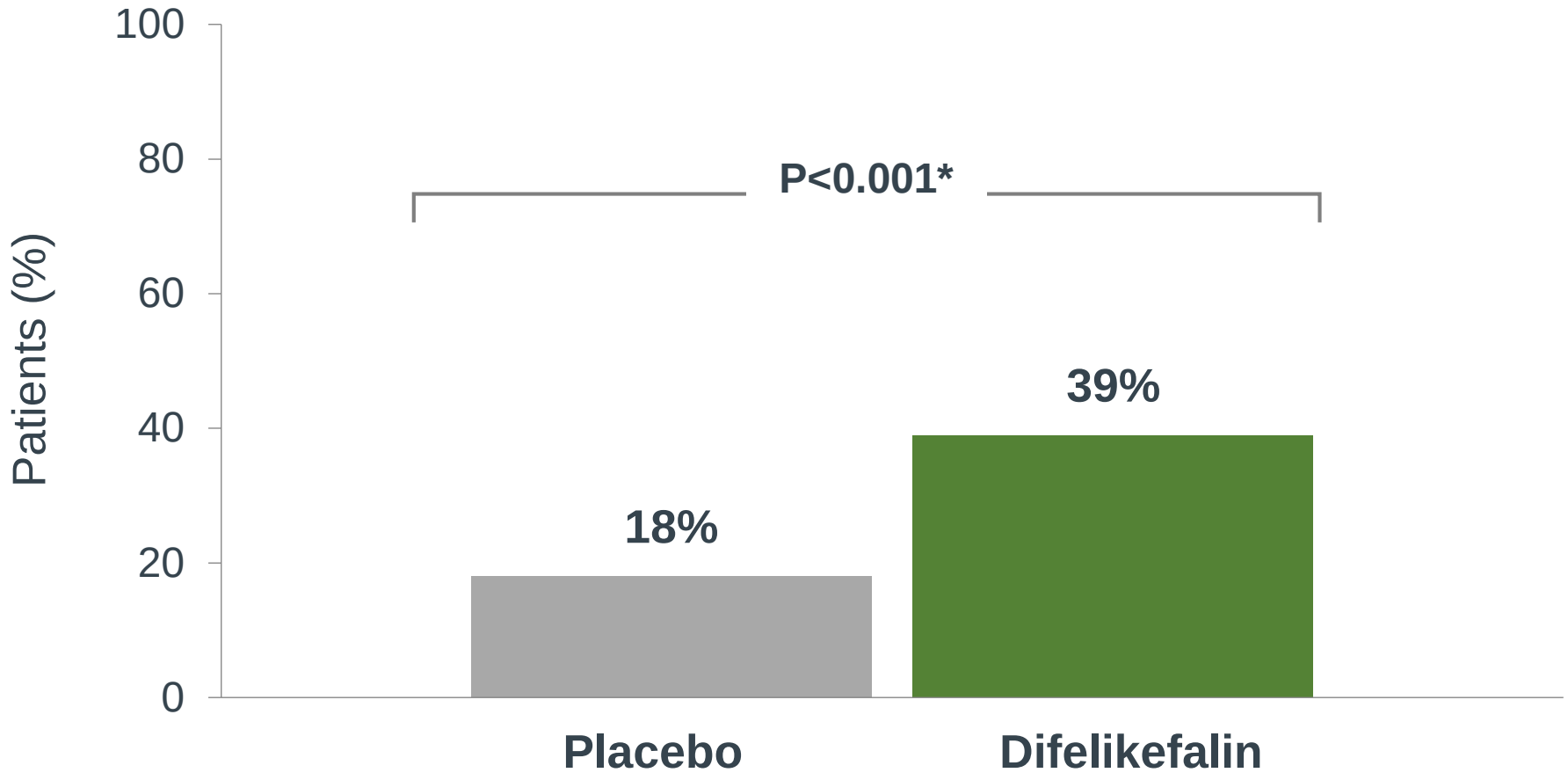
*5-D itch scale ranges from 5 to 25, with higher scores indicating worse itch-related quality of life; †Skindex-10 scale ranges from 0 to 60, with higher scores indicating worse itch-related quality of life.

Primary Endpoint: Proportion of Patients Achieving ≥3-point Improvement in WI-NRS Score at Week 12



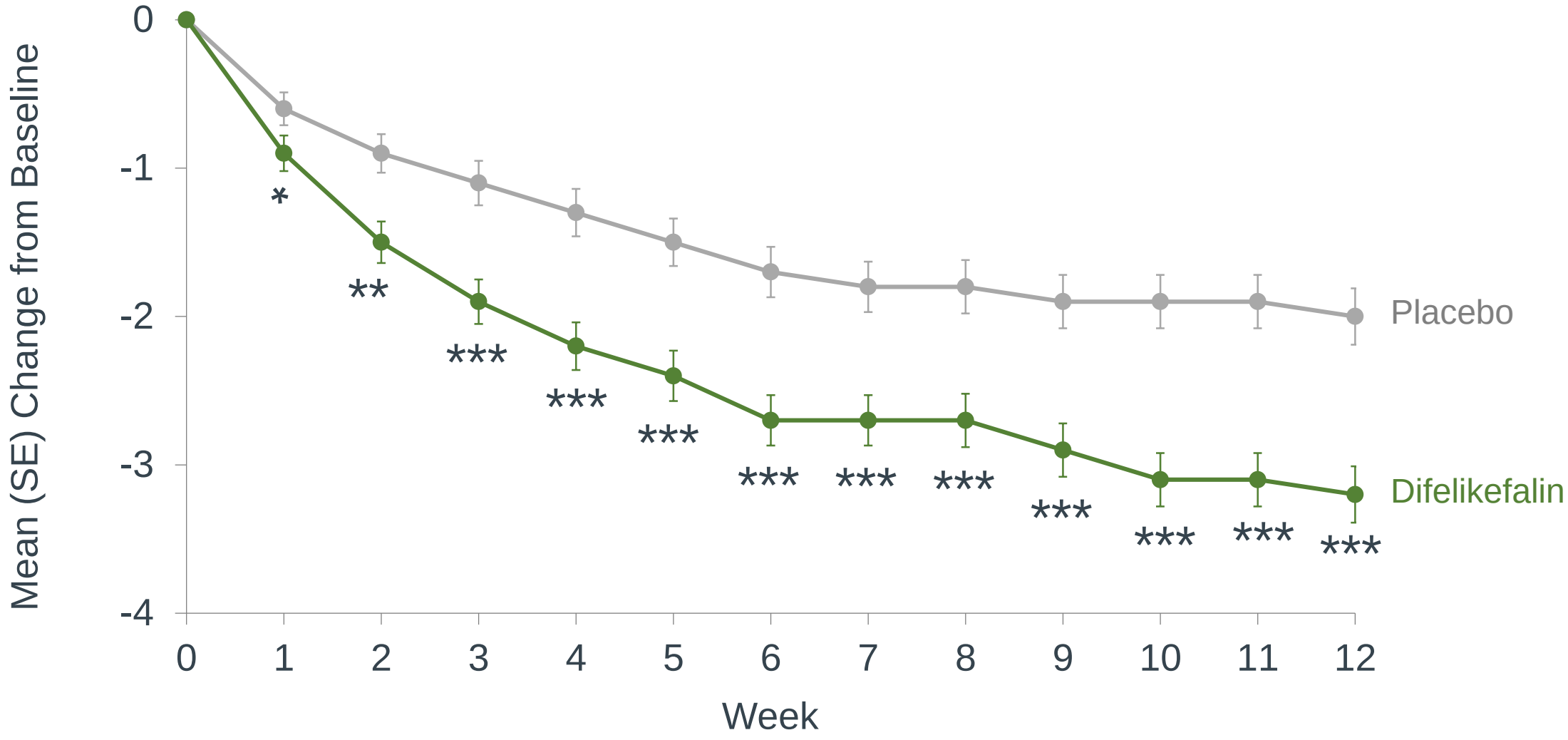
*Estimated proportions, odds ratio, and P-value are based on a logistic regression model with terms for treatment group, baseline WI-NRS score, and strata
Pre-specified primary analysis included scores collected while patients were on-treatment. Missing data was imputed using multiple imputation (MI) under missing at random (MAR) assumption. Odds ratio, 2.72; 95% CI, 1.72-4.30
An additional analysis included scores collected while patients were on- or off-treatment. Estimated proportion: 27.9% (PBO), 49.1% (DFK). Odds ratio, 2.49; 95% CI, 1.57-3.94. Relative risk, 1.65; 95% CI, 1.26-2.14, p<0.001.

≥4-point Improvement in WI-NRS Score at Week 12



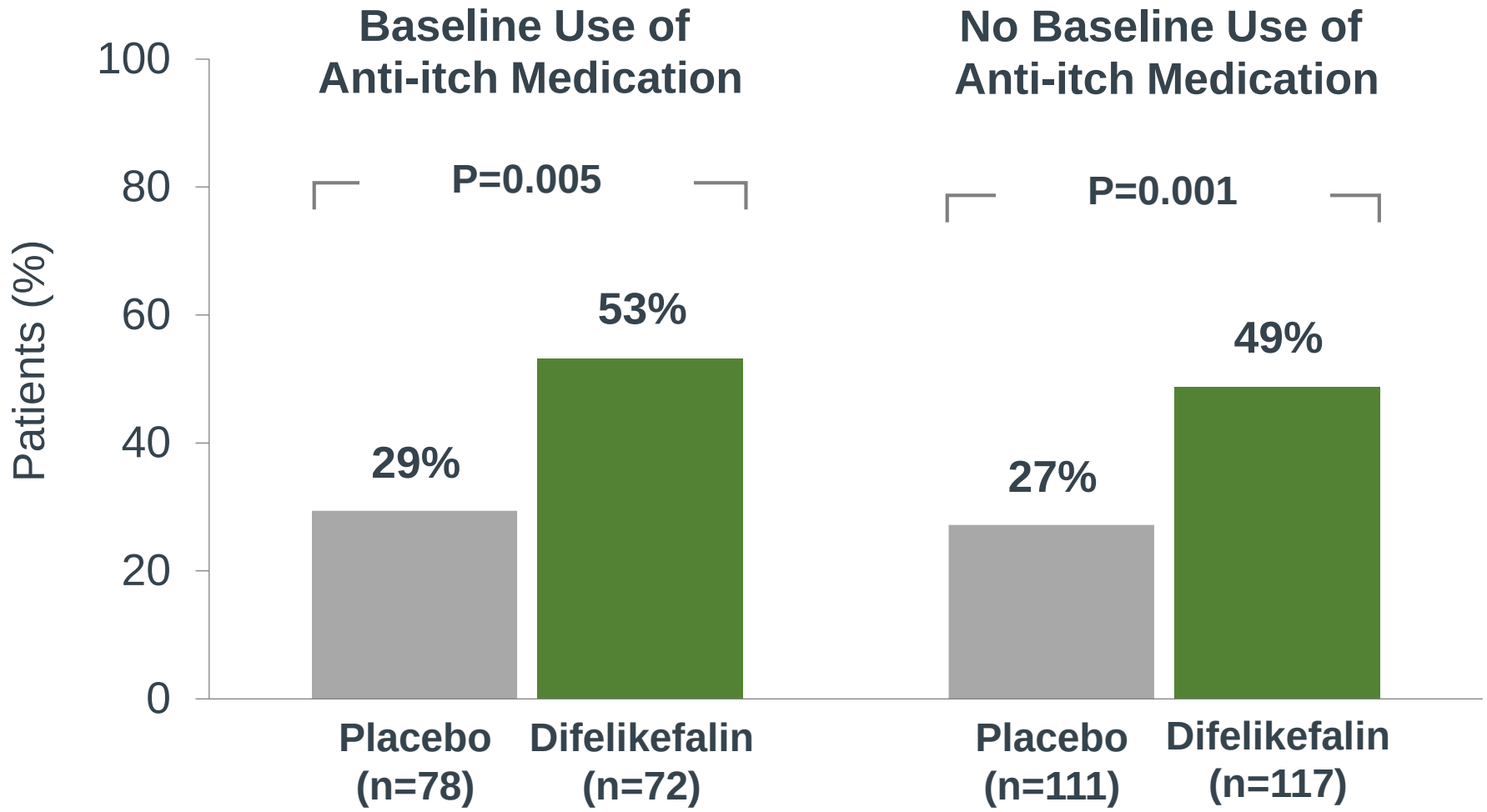
*Estimated proportions, odds ratio, and P-value are based on a logistic regression model with terms for treatment group, baseline WI-NRS score, and strata
Pre-specified primary analysis included scores collected while patients were on-treatment. Missing data was imputed using multiple imputation (MI) under missing at random (MAR) assumption. Odds ratio, 2.89; 95% CI, 1.75-4.76
An additional analysis included scores collected while patients were on- or off-treatment. Estimated proportion: 17.9% (PBO), 37.1% (DFK). Odds ratio, 2.70; 95% CI, 1.64-4.45. Relative risk, 1.92; 95% CI, 1.37-2.68, p<0.001.

Change in WI-NRS Score from Baseline Over 12 Weeks

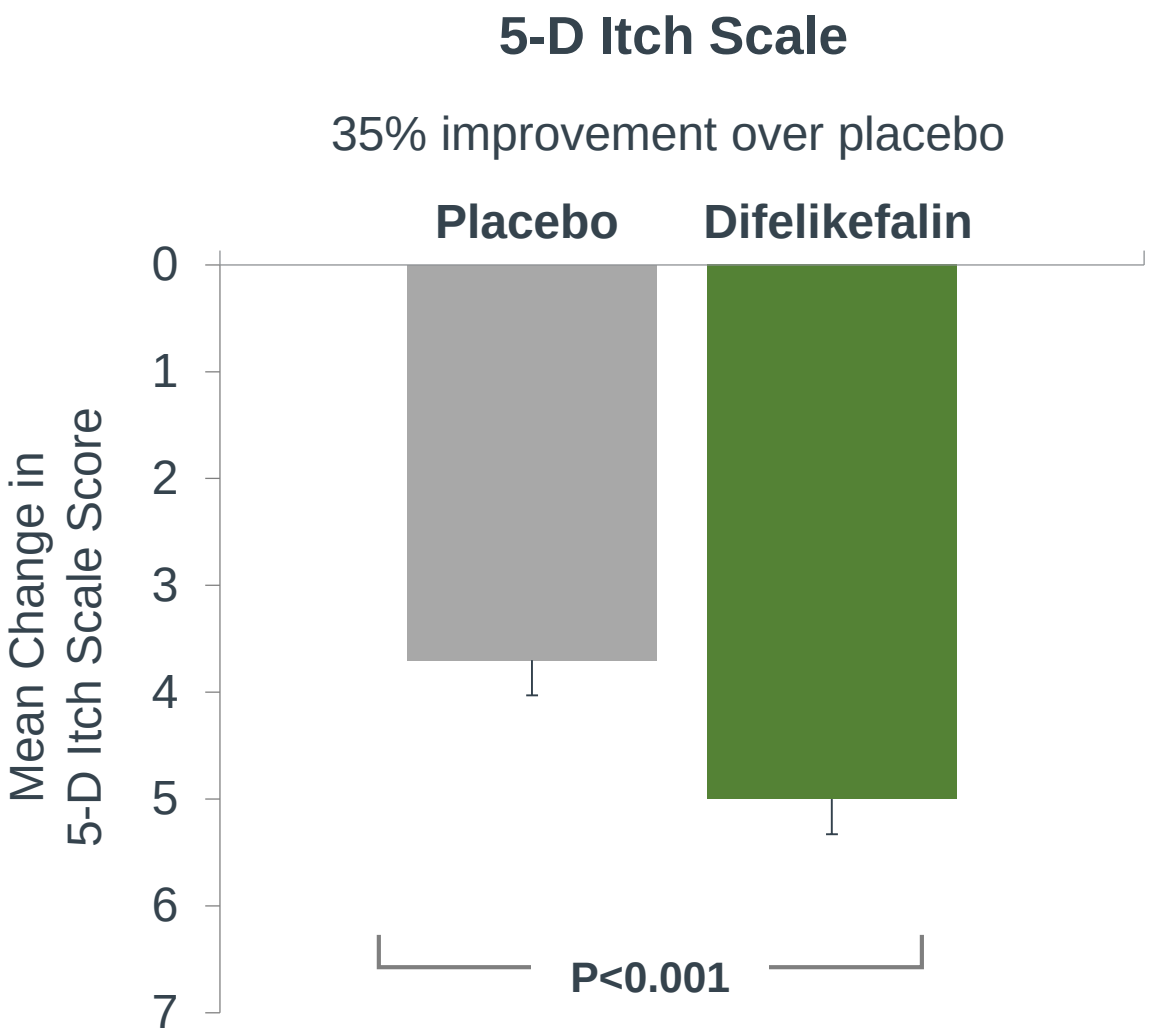


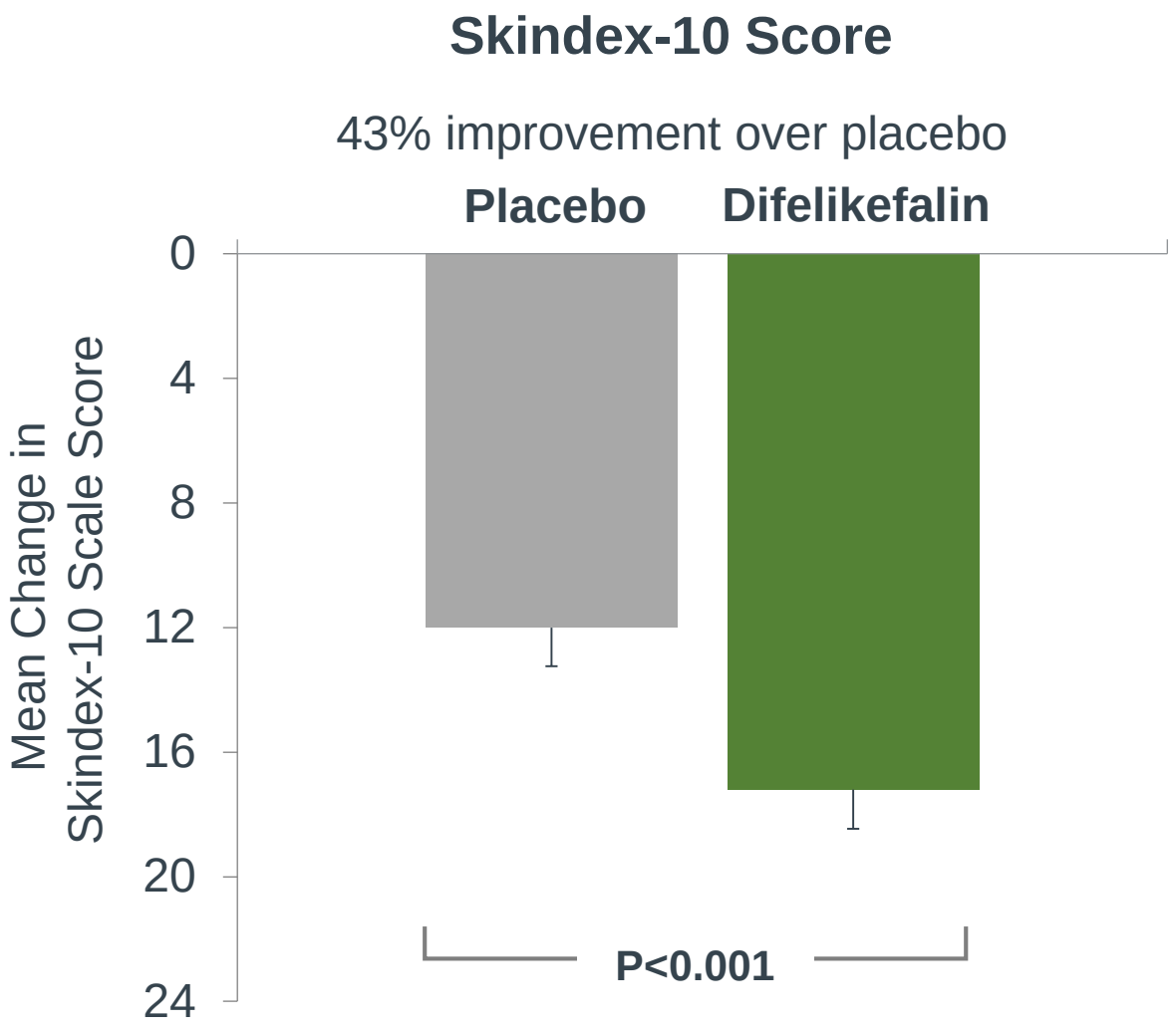
*P<0.05, **P=0.001, ***P<0.001 vs placebo.
Data represents least squares mean ± SE, analyzed using a mixed-effects model with repeated measures. Missing data is imputed using multiple imputation under a missing at random assumption.

≥3-point Improvement in WI-NRS by Baseline Use of Anti-itch Medication



Improvement in Itch-related Quality of Life from Baseline at Week 12





Data represents least square mean estimates ± SE. P-values calculated using an analysis of covariance model with terms for treatment group, baseline score, and strata. Missing values imputed using multiple imputation (MI) under MAR assumption.

Safety Profile and Adverse Events through Week 12

	Placebo n=188	Difelikefalin n=189
Any adverse event	117 (62.2)	130 (68.8)
Adverse event leading to treatment discontinuation	9 (4.8)	15 (7.9)
Serious adverse event	41 (21.8)	49 (25.9)
Death	2 (1.1)	2 (1.1)
Most frequent adverse events in >5% of patients in any group		
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)

- Adverse events were generally mild-moderate in severity and resolved without clinical consequence
- Most common events leading to treatment discontinuation were dizziness (1.6%) in the difelikefalin group and septic shock (1.6%) in the placebo group
- Deaths were due to septic shock (placebo) and sepsis (difelikefalin)

Conclusions

- Difelikefalin provided significant improvements in CKD-aP compared to placebo across several outcome measures, with:
  - Clinically meaningful reduction in itch intensity
  - Reductions in itch intensity associated with improvements in itch-related quality of life
  - Comparable effect in patients with or without prior use of itch medication
- Treatment effect evident by Week 1 and persisted throughout 12 weeks
- Difelikefalin was well tolerated with diarrhea, dizziness, and vomiting reported as the most common adverse events
- Difelikefalin may help address a significant unmet need in patients with moderate-to-severe pruritus undergoing hemodialysis
  - Data from a 52-week extension and a global Phase III study, both ongoing, will help further characterize its role in the treatment of CKD-aP

Acknowledgement

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ORIGINAL ARTICLE

A Phase 3 Trial of Difelikefalin in Hemodialysis Patients with Pruritus

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