Efficacy and Safety of Difelikefalin for Moderate-to-Severe Chronic Kidney Disease–Associated Pruritus: a Global Phase 3 Study in Hemodialysis Patients (KALM-2)

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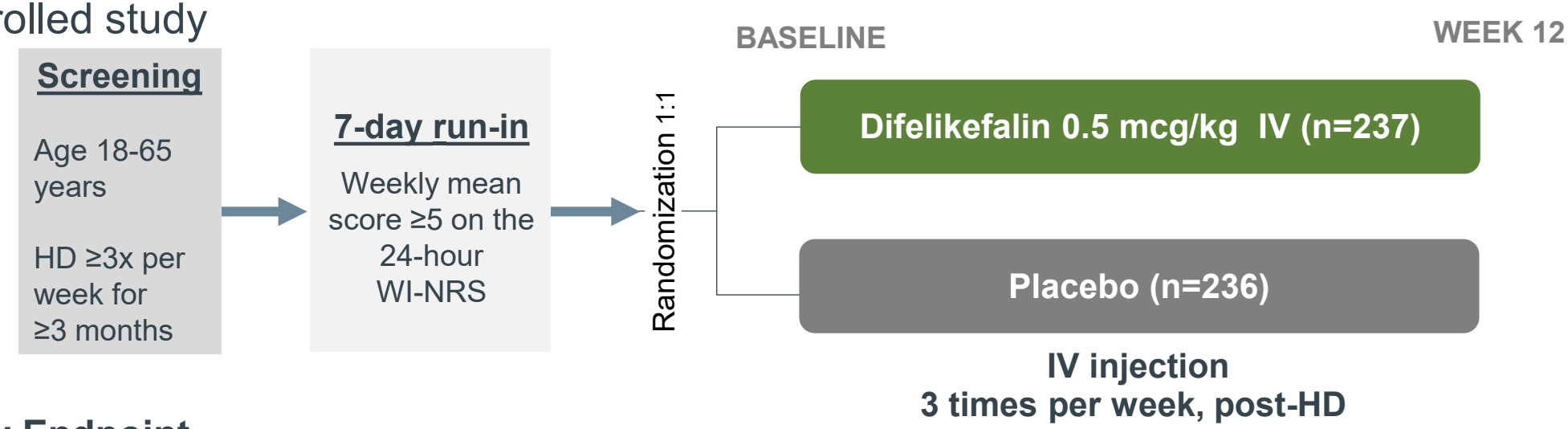
Background

- Chronic kidney disease (CKD)–associated pruritus (CKD-aP) is a common and distressing condition in patients with CKD and has a serious negative impact on quality of life (QOL)[1,2]
- There is no recognized standard of care and no approved treatment in the US or Europe[3,4]
- Difelikefalin (DFK) is a novel, peripherally restricted and selective kappa opioid receptor agonist[5]
  - Small hydrophilic peptide with limited central nervous system penetration[5]
  - Does not bind to mu or delta opioid receptors or any other known receptors[5]
  - Antipruritic effect via activation of kappa opioid receptors located on peripheral sensory neurons and immune cells[5]
- DFK demonstrated efficacy in a US phase 3 study (KALM-1) in patients with CKD-aP undergoing hemodialysis (HD)[6]
- We report primary results from the global phase 3 study of DFK in patients with CKD-aP undergoing HD (KALM-2; NCT03636269)

1. Mathur VS, et al. *Clin J Am Soc Nephrol*. 2010;5:1410-1419. 2. Rayner HC, et al. *Clin J Am Soc Nephrol*. 2017;12:2000-2007. 3. Combs SA, et al. *Semin Nephrol.* 2015;35:383-391. 4. Mettang T, et al. *Kidney Int.* 2015;87:685-691. 5. Albert-Vartanian A, et al. *J Clin Pharm Ther.* 2016; 41:371-382. 6. Fishbane S, et al. *N Engl J Med*. 2020;382:222-232.

KALM-2: Global Phase 3 Pivotal Study

- Multicenter, multinational (75 sites in the US, Europe, and Asia), double blind, placebo-controlled study



Primary Endpoint

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

Secondary Endpoints

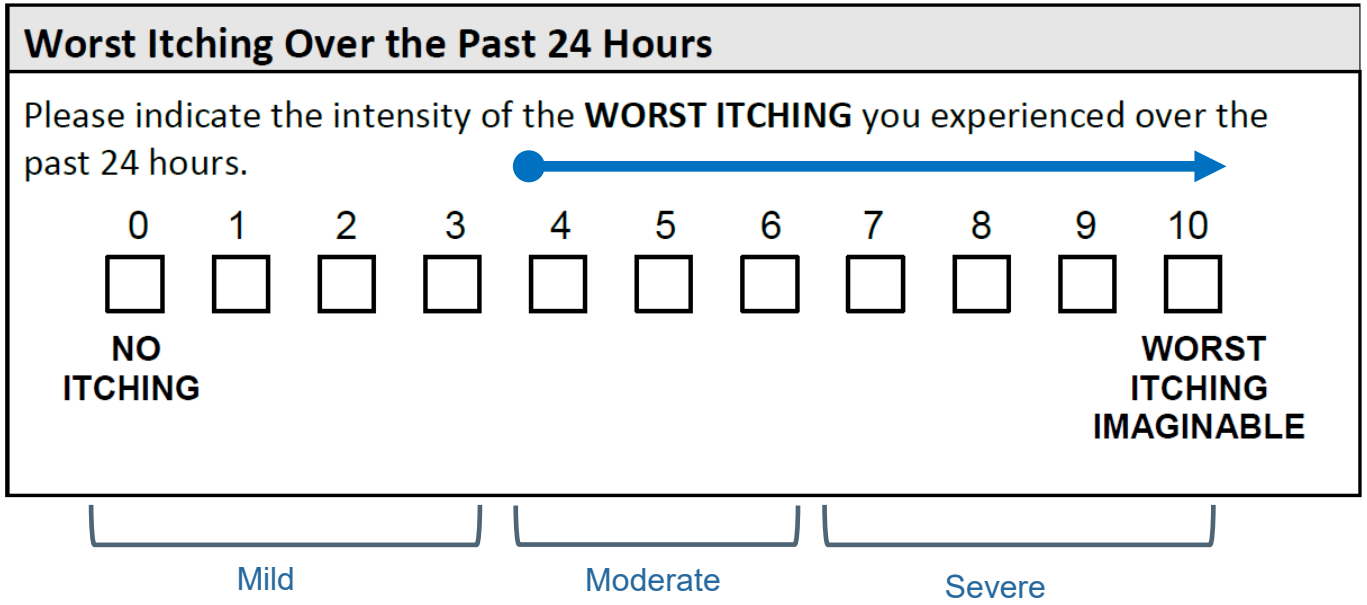
- Proportion of patients achieving ≥4-point improvement from baseline at Week 12
- Proportion of patients achieving ≥3-point improvement or ≥4-point improvement from baseline at Weeks 4 and 8
- Mean change from baseline at Week 12 in itch-related QOL as measured by Skindex-10 and 5-D Itch questionnaires

Safety Assessments

IV, intravenously; WI-NRS, Worst Itching Intensity Numerical 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 Numerical Rating Scale

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



- Reduction of ≥3 points on the NRS is associated with clinically meaningful change in itch severity for patients with moderate-to-severe CKD-aP[3]

1. Mathur VS, et al. *Clin J Am Soc Nephrol*. 2010;5:1410-1419. 2. Phan NQ, et al. *Acta Derm Venereol*. 2012;92:449-581. 3. Vernon M, et al. *J Am Acad Dermatol*. 2020 [ePub ahead of print]. doi:10.1016/j.jaad.2020.06.991.

Baseline Characteristics and Demographics

	Placebo (n=236)	DFK (n=235)
Age, mean (SD), years	59.6 (13.1)	59.7 (13.1)
Male, n (%)	139 (58.9)	135 (57.4)
Race, n (%)		
White	169 (71.6)	162 (68.9)
Black or African American	38 (16.1)	53 (22.6)
Other*	29 (12.3)	20 (8.5)
Region		
USA	133 (56.4)	145 (61.7)
Asia	12 (5.1)	8 (3.4)
Eastern Europe	60 (25.4)	54 (23.0)
Western Europe/European origin	31 (13.1)	28 (11.9)
Prescription dry body weight, mean (SD), kg	80.0 (19.5)	81.6 (19.7)
Years on chronic HD, mean (SD), years	5.1 (4.3)	4.8 (4.6)
Duration of pruritus, mean (SD), years	3.2 (3.2)	3.2 (4.6)

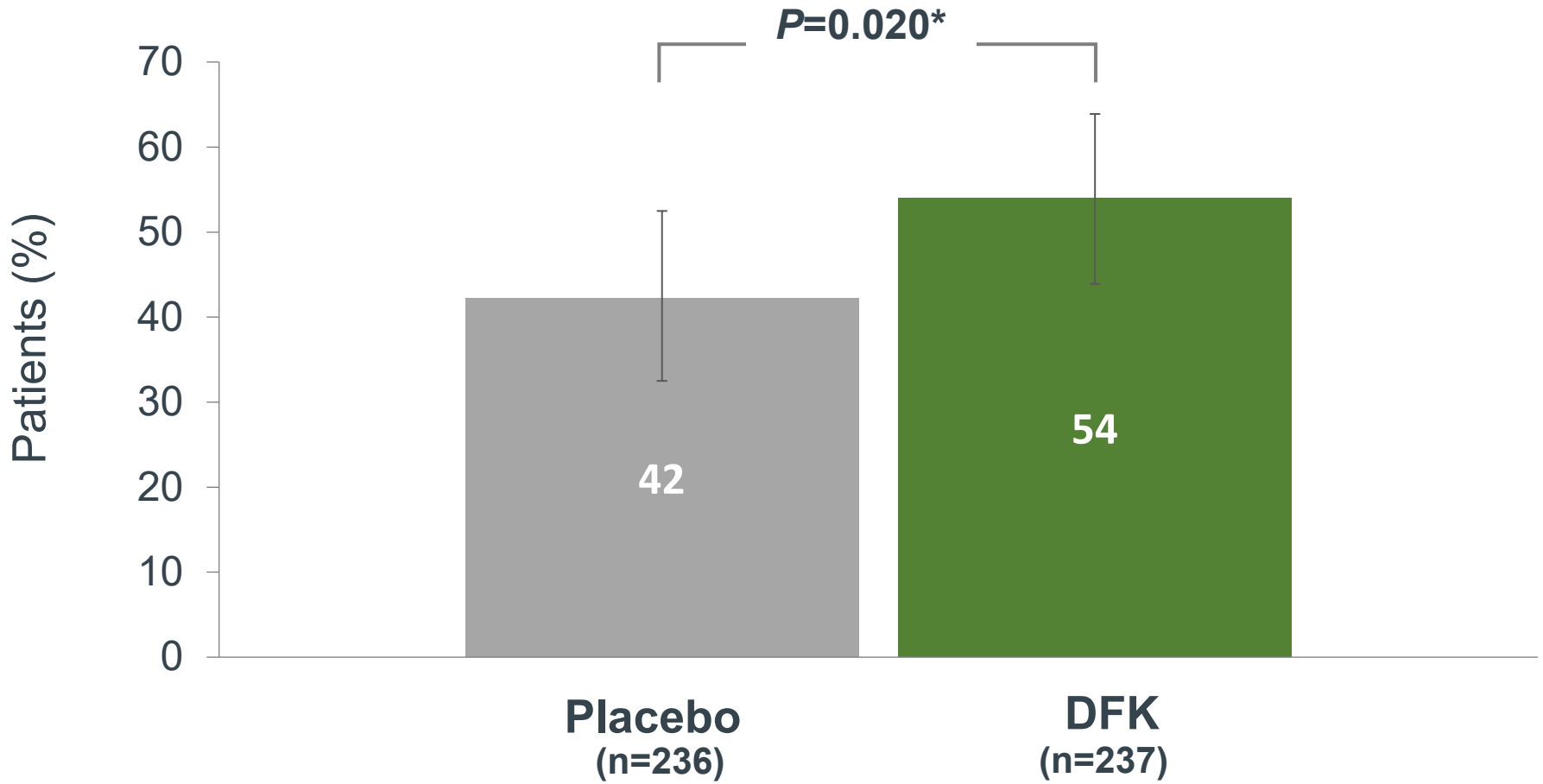
*Includes American Indian or Alaska Native, Asian, Native Hawaiian or Pacific Islander, and other.

Baseline Characteristics and Demographics (continued)

	Placebo (n=236)	DFK (n=235)
Blood chemistry		
Bilirubin, mean (SD), mg/dL	0.5 (0.3)	0.5 (0.2)
Calcium, mean (SD), mg/dL	8.7 (0.8)	8.7 (0.8)
Phosphate, mean (SD), mg/dL	5.7 (2.0)	5.7 (2.0)
Baseline use of anti-itch medications, n (%)	85 (36.0)	87 (37.0)
Most commonly used (>10%) anti-itch medications at baseline, n (%)		
Diphenhydramine	24 (10.2)	43 (18.3)
Hydroxyzine	21 (13.1)	20 (9.4)
WI-NRS score, mean (SD)	7.1 (1.4)	7.3 (1.4)
5-D itch scale total score,* mean (SD)	16.2 (3.3)	16.7 (3.5)
Skindex-10 scale total score,† mean (SD)	34.2 (14.7)	35.5 (15.0)

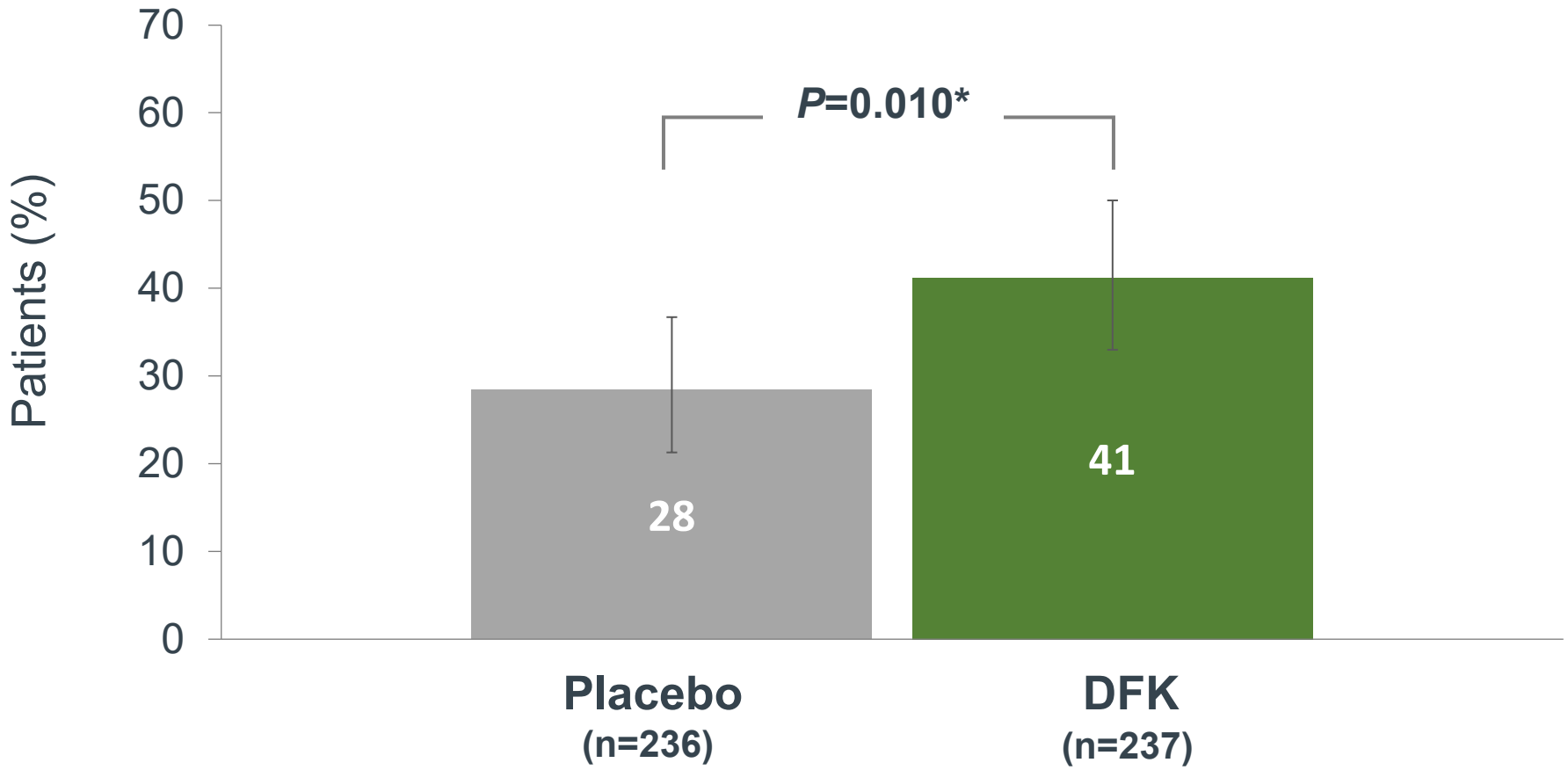
*5-D itch scale ranges from 5 to 25, with higher scores indicating worse itch-related QOL.[1]
†Skindex-10 scale ranges from 0 to 60, with higher scores indicating worse itch-related QOL.
1. Elman S, et al. *Br J Dermatol*. 2010;162:587-593.

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 region, use of anti-itch medication during the week prior to randomization, and the presence of specific medical conditions.
Prespecified primary analysis included scores collected while patients were on treatment. Missing data were imputed using multiple imputation (MI) under missing at random (MAR) assumption. Odds ratio, 1.61; 95% confidence interval (CI), 1.08-2.41. Error bars represent 95% CI.

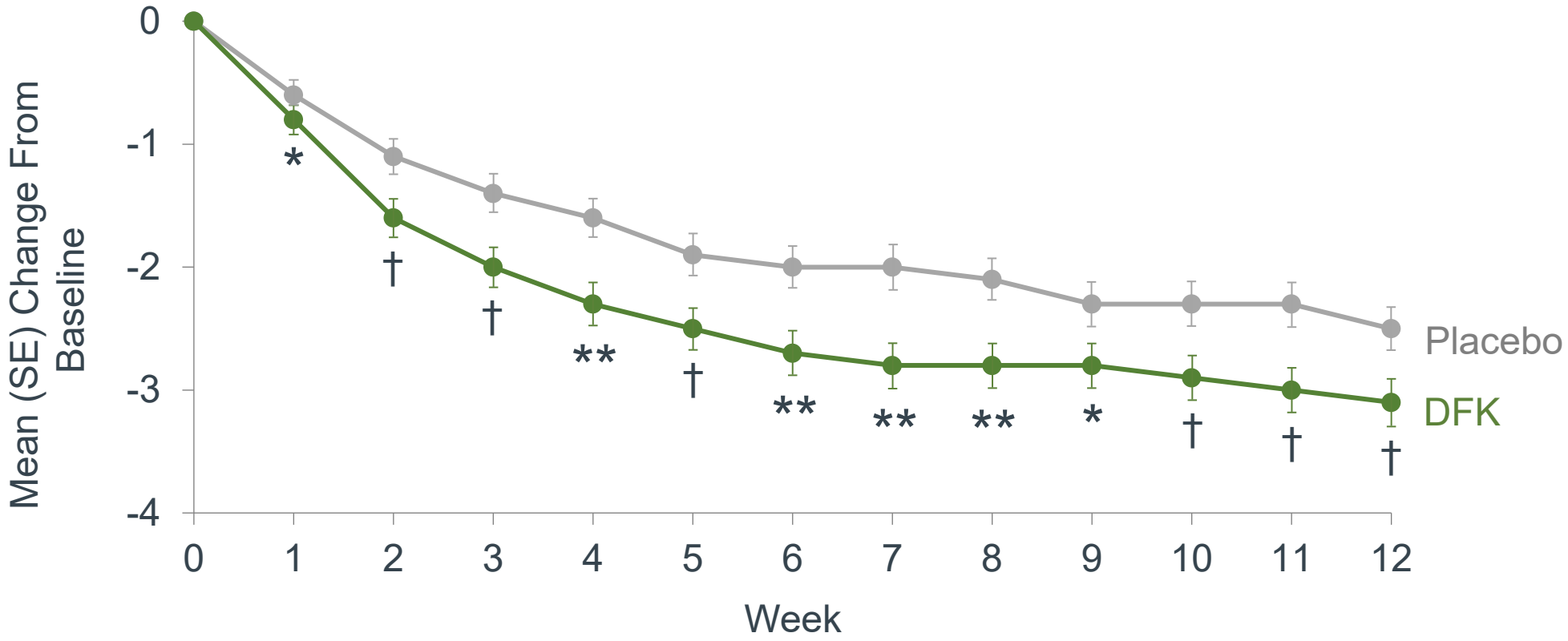
Achievement of ≥4-Point Improvement in WI-NRS



*Estimated proportions, odds ratio, and *P* value are based on a logistic regression model with terms for treatment group, baseline WI-NRS score, region, use of anti-itch medication during the week prior to randomization, and the presence of specific medical conditions.
Prespecified primary analysis included scores collected while patients were on treatment. Missing data were imputed using MI under MAR assumption. Odds ratio, 1.77; 95% CI, 1.14-2.74. Error bars represent 95% CI.

Onset and Sustained Effect of DFK

- Significant differences in mean WI-NRS were observed starting at Week 1 and sustained through 12 weeks of treatment



- Achievement of ≥3-point and ≥4-point improvement in WI-NRS was significantly greater with DFK vs placebo at Week 4 and Week 8

*P<0.05; †P<0.01; **P≤0.001 vs placebo. Data represent least-squares (LS) mean ± SE, analyzed using a mixed-effects model with repeated measures. Missing data were imputed using MI under a MAR assumption.

Improvement in Itch-Related QOL

- The Skindex-10 scale was developed specifically for assessing itch-related QOL across 3 domains in patients undergoing HD with pruritus.[1] Higher total Skindex-10 scores indicate worse itch-related QOL (range, 0-60)
  - At Week 12, LS mean (SE) change from baseline in Skindex-10 score was –14.8 (1.3) with placebo and –16.6 (1.4) with DFK (*P*=0.171)
- The 5-D itch scale assesses 5 dimensions of itch (duration, degree, direction, disability, and distribution) during a 2-week recall period.[2] The 5-D itch scale ranges from 5 to 25, with higher scores indicating worse itch-related QOL[2]
  - At Week 12, LS mean (SE) change from baseline in 5-D itch total score was –3.8 (0.4) with placebo and –4.9 (0.4) with DFK (nominal *P*=0.002)*
- Itch severity–related domains in both scales were significant (*P*=0.003 to 0.047) and consistent with WI-NRS improvement

LS mean, SE, and *P* value based on analysis of covariance with terms for treatment group, baseline score, region, and strata Missing values imputed using MI under MAR assumption.
*Nominal *P* value based on sequential statistical analysis.
1. Mathur VS, et al. *Clin J Am Soc Nephrol*. 2010;5:1410-1419. 2. Elman S, et al. *Br J Dermatol*. 2010;162:587-593.

Safety Profile and Adverse Events Through Week 12

Patients, n (%)	Placebo (n=236)	DFK (n=235)
Any adverse event	145 (61.4)	160 (68.1)
Adverse event leading to treatment discontinuation	8 (3.4)	13 (5.5)
Serious adverse event	51 (21.6)	58 (24.7)
Death	2 (0.8)	2 (0.9)
Most frequent adverse events in >5% of patients in any group		
Diarrhea	13 (5.5)	19 (8.1)
Vomiting	14 (5.9)	15 (6.4)
Nausea	10 (4.2)	15 (6.4)
Fall	12 (5.1)	16 (6.8)
Dizziness	12 (5.1)	13 (5.5)

- Adverse events were generally mild to moderate in severity and resolved without clinical consequence
- In the placebo group, AEs resulting in death were sepsis (n=1) and cardiac arrest (n=1). In the DFK group, AEs resulting in death were cardiopulmonary failure (n=1) and cardiac arrest (n=1)

Conclusions

- In this second phase 3 study, IV DFK demonstrated rapid and sustained itch reduction in patients undergoing HD with CKD-aP in multiple regions of the world
  - Both 3- and 4-point improvement in WI-NRS endpoints were achieved
  - Treatment effect was evident by week 1 and persisted throughout 12 weeks
- Numerical improvements in itch-related QOL were observed
- DFK was generally well tolerated, and safety was consistent with findings in prior studies in patients undergoing hemodialysis
- Key efficacy results from this global study (KALM-2) are consistent with findings from the US phase 3 pivotal trial (KALM-1)
- Difelikefalin is positioned to address a significant unmet need in patients with moderate-to-severe pruritus undergoing hemodialysis
  - Data from 52-week extensions of KALM-1 and KALM-2 will help further characterize its role in the treatment of CKD-aP