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An Open-label, Multicenter Study to Evaluate the Safety and Effectiveness of Intravenous Difelikefalin in Patients With Moderate-to-Severe Pruritus Undergoing Hemodialysis

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Acknowledgments, Correspondence, and Disclosures

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Disclosures

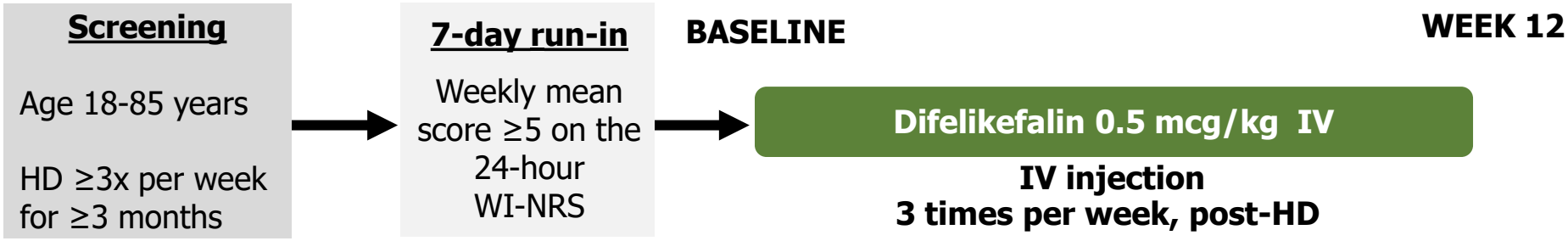
- **DW:** Clinical Research for Dialysis Clinic, Inc. – medical director, with salary support paid to institution; Akebia (honorarium paid to DCI) and Cara Therapeutics, Inc. – advisory board; VALOR Trial – chair of the adjudications committee; Ardelyx (support paid through DCI), AstraZeneca (support paid to institution), and Goldfinch Bio (support paid to institution) – site PI for clinical trials
- **FM, WW, JQ, & CM:** Cara Therapeutics, Inc. – employment
- **SB:** Cara Therapeutics, Inc. – consulting fees

Background

- Difelikefalin (DFK) is a selective, peripheral kappa-opioid receptor agonist in development for pruritus in patients with chronic kidney disease (CKD)
  - Limited central nervous system penetration[1]
- In placebo-controlled phase 3 trials of patients with moderate-to-severe pruritus undergoing hemodialysis (HD), intravenous (IV) DFK had an acceptable safety profile and demonstrated significant reductions vs placebo in itch intensity[2,3]
- We report safety and effectiveness outcomes from a phase 3, multicenter, open-label study of DFK in patients with moderate-to-severe CKD-associated pruritus (CKD-aP) conducted in the United States and Europe (NCT03998163)

1. Albert-Vartanian A, et al. *J Clin Pharm Ther.* 2016;41:371-382. 2. Fishbane S, et al. *N Engl J Med.* 2020;382:222-232. 3. Wooldridge TD, et al. *J Am Soc Nephrol.* 31(suppl):22-23.

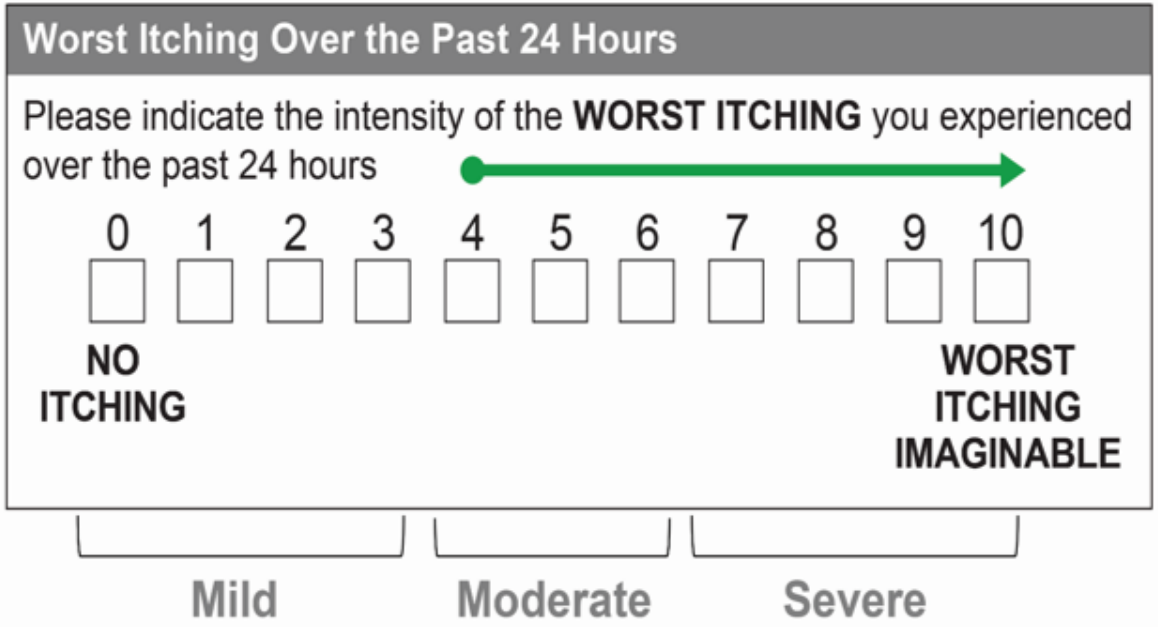
Study 3105: Open-Label Phase 3 Study



- Predefined effectiveness and itch-related quality-of-life (QoL) endpoints
  - Proportion of patients achieving ≥3-point and ≥4-point improvement from baseline at week 12 in weekly mean of daily Worst Itching Intensity Numerical Rating Scale (WI-NRS) score
  - Change from baseline in itch-related QoL at week 12, based on the 5-D Itch and Skindex-10, multidimensional itch-related questionnaires validated in CKD-aP
  - Proportion of patients with no problems on the skin irritation and self-confidence domains of the EQ-PSO questionnaire at week 12
- Post hoc endpoints
  - Complete resolution in WI-NRS at week 12
  - Sleep Quality Questionnaire total score assessments (range of possible scores, 0 [did not interfere] to 10 [completely interfered]), including ≥3-point and ≥4-point improvement in weekly mean score and complete resolution (all scores equal to 0) at week 12
- Safety assessments

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 WI-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 Dermatol Venereol*. 2012;92:502-507. 3. Vernon M, et al. *J Am Acad Dermatol*. 2021;84:1132-1134.

Demographics and Baseline Disease and Itch Characteristics

- Of the 222 patients who received DFK, 197 (88.7%) completed the study

	DFK n=222
Age, mean (SD), years	58.1 (12.8)
Male, n (%)	121 (54.5)
Race, n (%)	
Black or African American	110 (49.5)
White	96 (43.2)
Other*	16 (7.2)
Country	
USA	203 (91.4)
Hungary	12 (5.4)
Czech Republic	4 (1.8)
Poland	3 (1.4)
Prescription dry body weight, mean (SD), kg	86.6 (23.5)
Years on chronic HD, mean (SD)	5.4 (4.4)
Duration of pruritus, mean (SD), years	3.9 (3.3)

N represents the total sample. The number of patients with data available may vary.
*Includes American Indian or Alaska native, Asian, Native Hawaiian or Pacific Islander, and other.

Demographics and Baseline Disease and Itch Characteristics (cont'd)

	DFK n=222
Etiology of CKD (≥5% of patients), n (%)	
Hypertension	135 (60.8)
Diabetes	110 (49.5)
Other	25 (11.3)
Glomerulonephritis	11 (5.0)
Medical history of diabetes*	134 (60.4)
Blood chemistry	
Bilirubin, mean (SD), µmol/L	8.8 (4.2)
Calcium, mean (SD), mmol/L	2.2 (0.2)
Phosphate, mean (SD), mmol/L	1.9 (0.6)

N represents the total sample. The number of patients with data available may vary.
*Includes medical history of type 2 diabetes mellitus, type 1 diabetes mellitus, diabetes mellitus, and diabetes insipidus.

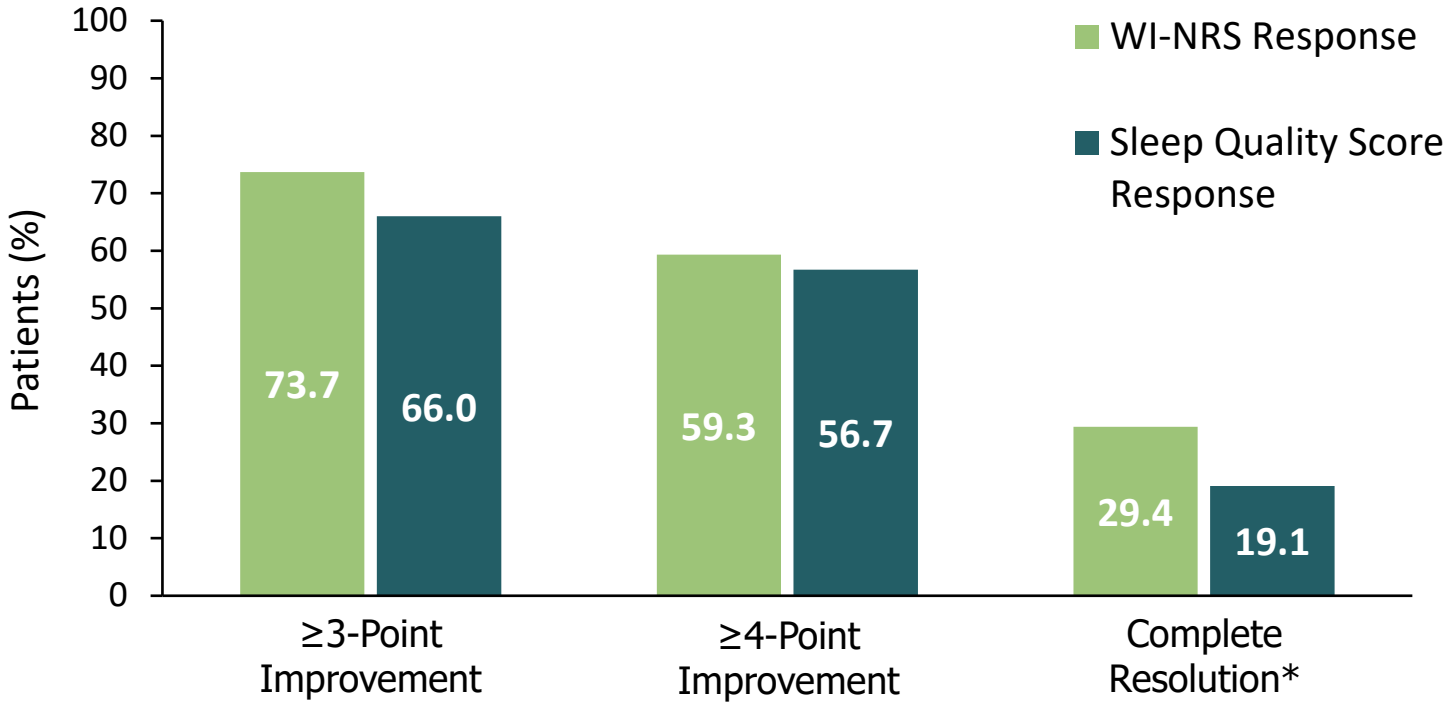
Demographics and Baseline Disease and Itch Characteristics (cont'd)

	DFK n=222
Baseline use of anti-itch medications, n (%)	71 (32.0)
Most commonly used (>5%) anti-itch medications at baseline, n (%)	
Diphenhydramine	49 (22.1)
Hydroxyzine	14 (6.3)
WI-NRS score, mean (SD)	7.6 (1.3)
Sleep Quality score,* mean (SD)	6.6 (2.2)
5-D Itch scale total score,† mean (SD)	17.1 (3.5)
Skindex-10 scale total score,‡ mean (SD)	32.9 (14.3)

N represents the total sample. The number of patients with data available may vary.
*Sleep Quality Questionnaire total score ranges from 0 (did not interfere) to 10 (completely interfered).
†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.[2]
1. Elman S, et al. *Br J Dermatol*. 2010;162:587-593. 2. Mathur VS, et al. *Clin J Am Soc Nephrol*. 2010;5:1410-1419.

Itch and Sleep Quality Were Improved at Week 12

- At week 12, most patients achieved ≥3-point and ≥4-point improvement and some achieved complete resolution in WI-NRS and Sleep Quality scores

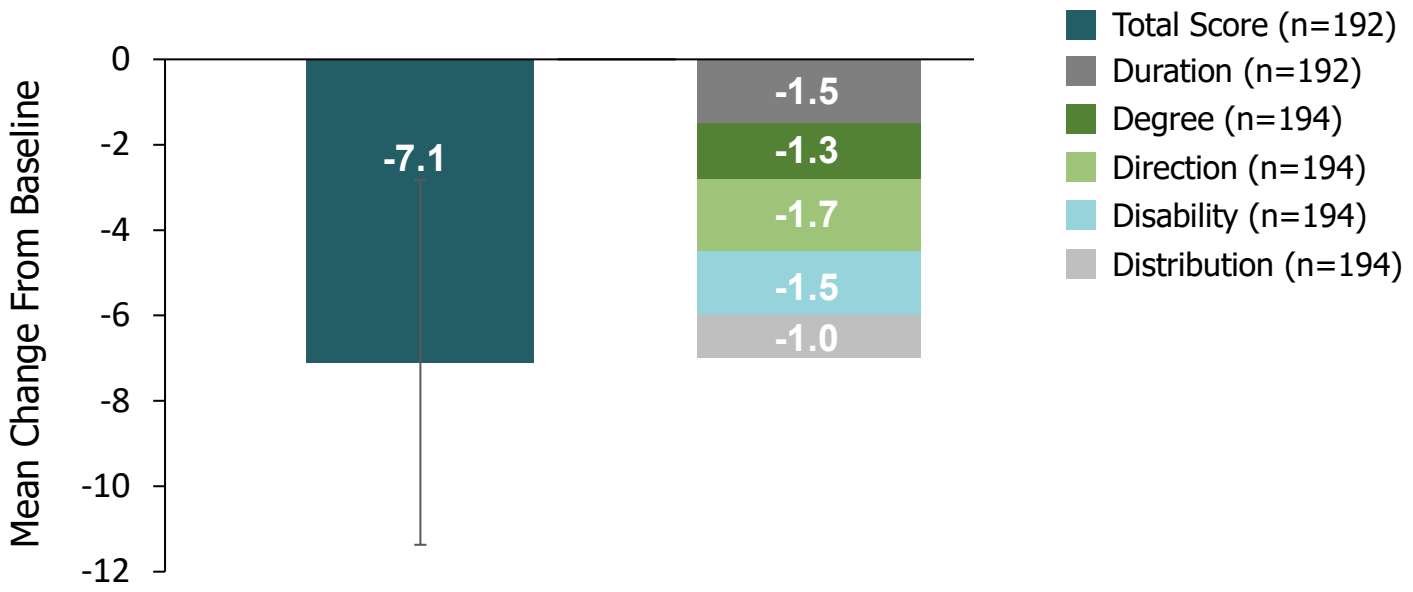


Data as observed at week 12, N=194.
*Complete resolution defined as ≥75% of weekly mean WI-NRS scores equal to 0 or 1 or all Sleep Quality scores equal to 0.
During the 1-week run-in period and at baseline, 2.7% of patients had all Sleep Quality scores equal to 0.

DFK Improved 5-D Itch Total and Subscale Scores at Week 12

- The 5-D Itch scale assesses 5 dimensions of itch (duration, degree, direction, disability, and distribution) during a 2-week recall period[1]
- Scores range from 5 to 25, with higher scores indicating worse itch-related QoL[1]
  - ≥5-point change from baseline in 5-D Itch total score represents a clinically meaningful improvement

Mean Change From Baseline in 5-D Itch Total and Domain Scores at Week 12



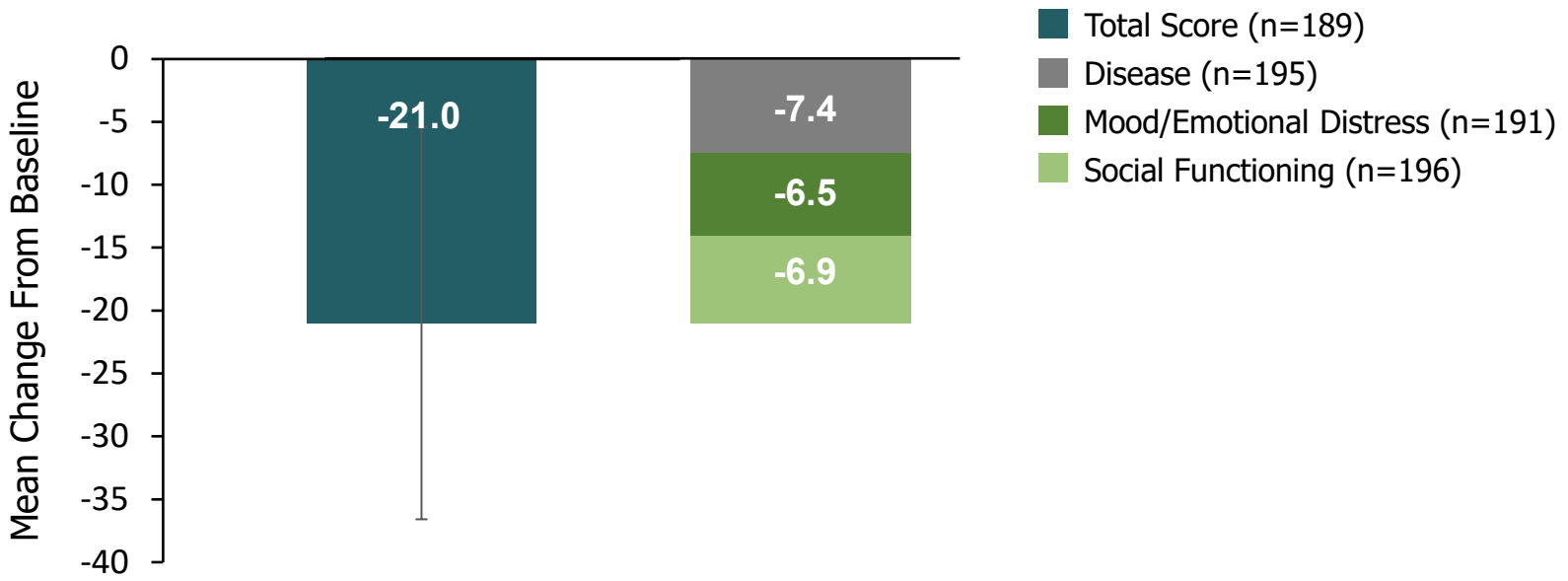
Error bar represents SD.

1. Elman S, et al. *Br J Dermatol*. 2010;162:587-593.

DFK Was Associated With Improvements in Mean Skindex-10 Total and Subscale Scores at Week 12

- The Skindex-10 scale was developed specifically for assessing itch-related QoL across 3 domains in HD patients with pruritus[1]
- Higher total Skindex-10 scores indicate worse itch-related QoL (scores range from 0 to 60)[1]
  - ≥15-point change from baseline in Skindex-10 total score represents a clinically meaningful improvement

Mean Change From Baseline in Skindex-10 Total and Domain Scores at Week 12

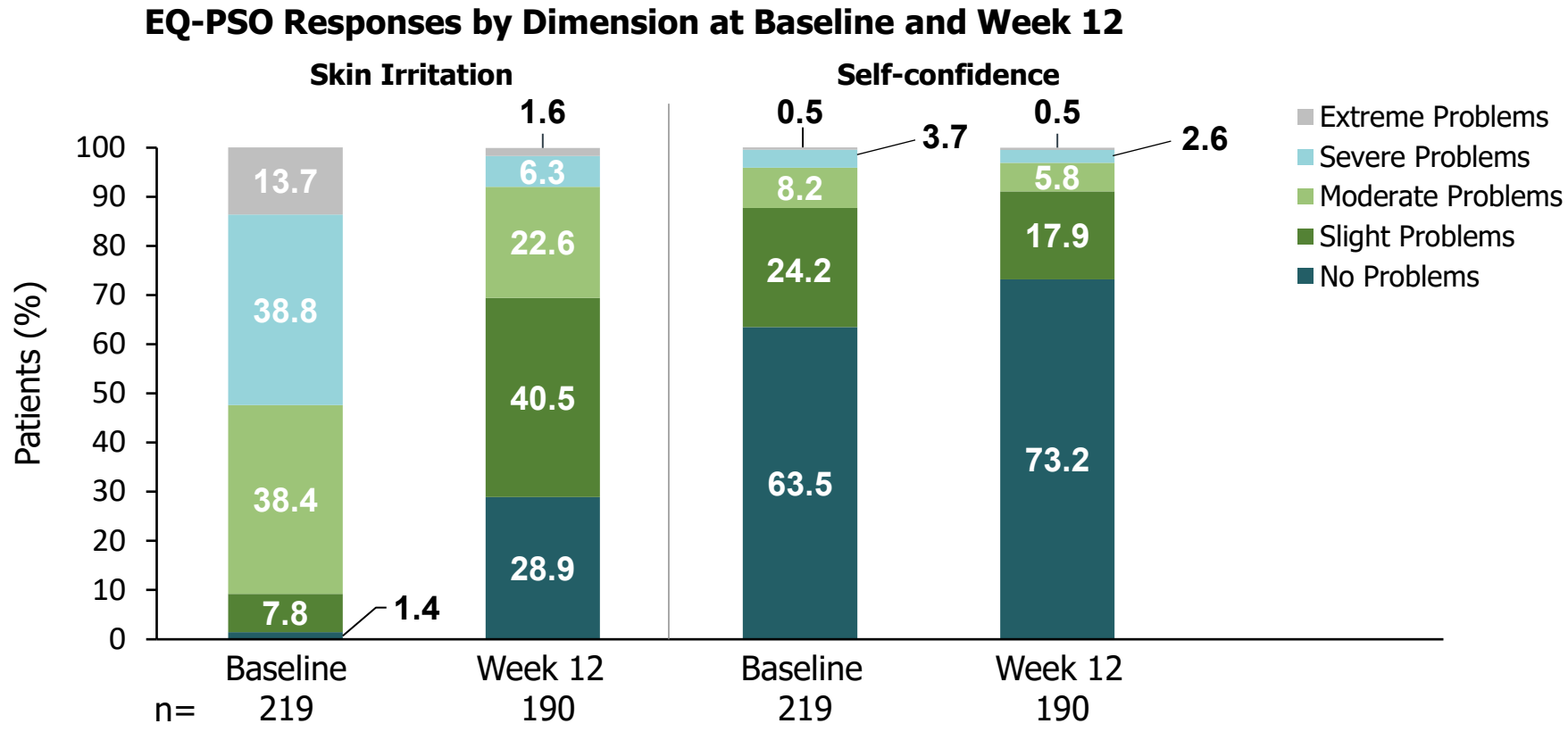


Error bar represents SD.

1. Mathur VS, et al. *Clin J Am Soc Nephrol*. 2010;5:1410-1419.

DFK Improved Skin Irritation and Self-confidence (EQ-PSO)

- The proportion of patients reporting no problems in the skin irritation and self-confidence EQ-PSO domains increased from baseline to week 12



Safety Profile and Adverse Events Through Week 12

Patients, n (%)	DFK n=222
Any TEAE	143 (64.4)
Serious TEAEs	45 (20.3)
TEAEs leading to treatment discontinuation	14 (6.3)
Most frequent TEAEs (≥4% of patients)	
Diarrhea	11 (5.0)
Nausea	10 (4.5)
Hyperkalemia	9 (4.1)

- No serious TEAEs were related to study drug

TEAE, treatment-emergent adverse event.

Conclusions

- In this phase 3 open-label study in patients with moderate-to-severe pruritus, DFK was effective at reducing itch intensity and improving sleep quality and itch-related QoL
- DFK was generally well tolerated with an acceptable safety profile
- Findings from this study confirm the efficacy and safety results of the phase 3 placebo-controlled studies of DFK in hemodialysis patients with moderate-to-severe pruritus[1,2] and provide insight into potential real-world effectiveness

1. Fishbane S, et al. *N Engl J Med.* 2020;382:222-232. 2. Wooldridge TD, et al. *J Am Soc Nephrol.* 31(suppl):22-23.