Efficacy and Safety of Oral Difelikefalin in Chronic Kidney Disease Patients With Moderate-to-Severe Pruritus: A Randomised, Placebo-Controlled, Phase 2 Trial

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Disclosures

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Background

- Pruritus is a common and burdensome condition in patients with chronic kidney disease (CKD)[1]
  - Present at all stages of CKD, not only in patients undergoing hemodialysis[1]
- No approved treatments in any country for non-dialysis patients with CKD
- Patients with stage 3-5 CKD with moderate-to-severe pruritus have not been evaluated before
- We report findings from the first randomized, phase 2 study to assess the safety and efficacy of oral difelikefalin (DFK) in patients with moderate-to-severe CKD-associated pruritus (CKD-aP)

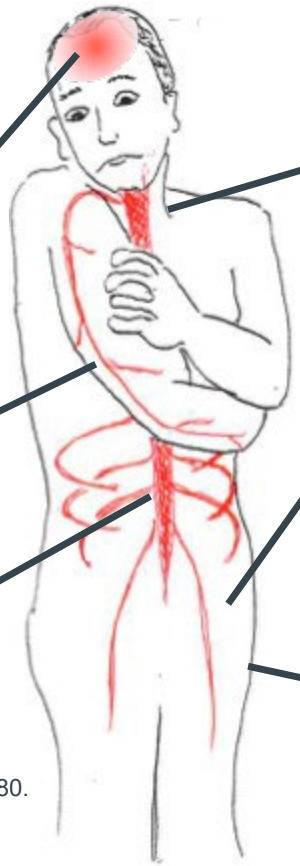
1. Sukul N, et al. *CJASN*. 2019;14:673-681.

Factors Contributing to CKD-Associated Pruritus

Functional and structural neuropathic changes of the brain

Peripheral neuropathy

Endogenous opioid imbalances



Dialysis-related substances
- Parathyroid hormone
- β2 microglobulin
- Aluminum

Altered immune status
- Th1 and IL-2, Th2 and IL-31
- IL-6 and CRP
- Albumin

Mast cell activation in the skin

CRP, C-reactive protein; IL, interleukin; Th, T helper.

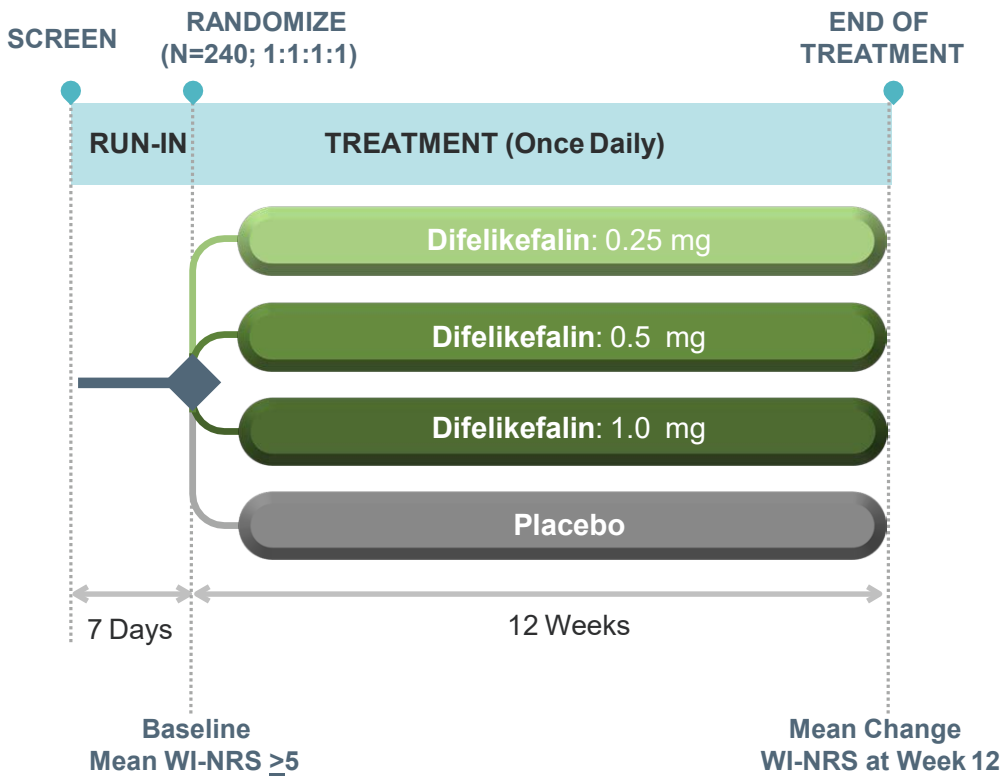
Hashimoto T, Yosipovitch G. *J Allergy Clin Immunol.*. 2019;144:375-380.
Shirazian S, et al. *Int J Nephrol Renovasc Dis*. 2017;10:11-26.

Overview of DFK

- DFK is a novel, peripherally restricted and selective kappa opioid receptor (KOR) agonist that was designed to have limited CNS penetration
- Does not bind to mu opioid receptors or any other known receptors
  - Antipruritic effect via activation of KORs located on peripheral sensory neurons and immune cells
- Results from a phase 3 trial with IV formulation of DFK demonstrated significant improvements in itch intensity and itch-related quality of life (QOL) vs placebo in hemodialysis patients with CKD-associated pruritus (CKD-aP)[1]

1. Fishbane S, et al. *N Engl J Med*. 2020;382:222-232.

Study Design With Once-Daily Oral DFK in Patients With CKD-aP



Endpoints: Week 12

Primary

- Change from baseline in weekly mean of daily WI-NRS scores

Additional

- Proportion of patients achieving ≥3-point improvement from baseline
- Complete response (defined as achievement of ≥80% of the non-missing daily NRS scores equal to 0 or 1)
- Safety (adverse events [AEs] and clinical laboratory tests)

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.

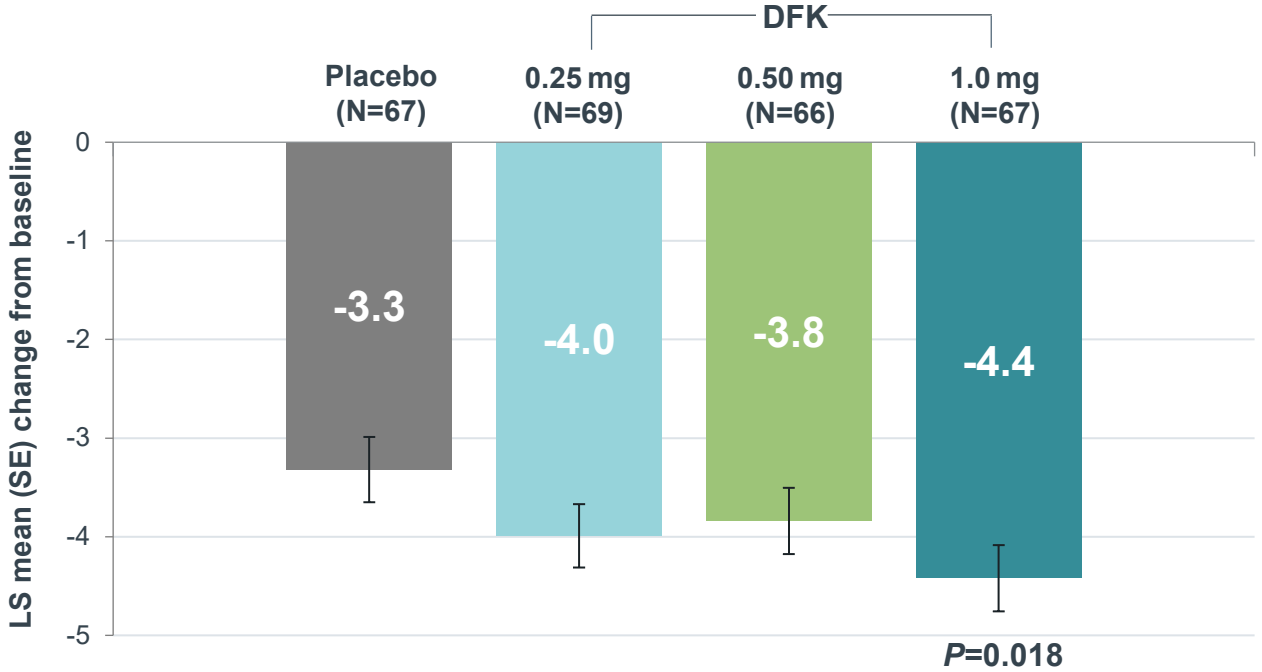
Patient Demographics and Baseline Disease and Itch Characteristics

Characteristics	Placebo N=67	DFK 0.25 mg N=69	DFK 0.5 mg N=66	DFK 1.0 mg N=67
Male, n (%)	37 (55)	34 (49)	33 (50)	35 (52)
Age, mean (SD), years	66 (12)	66 (11)	69 (12)	68 (11)
Medical history, n (%)				
Stage 3 CKD non-dialysis	40 (60)	41 (59)	38 (58)	40 (60)
Stage 4 or 5 CKD non-dialysis	15 (22)	16 (23)	16 (24)	15 (22)
Stage 4 or 5 CKD on hemodialysis	12 (18)	12 (17)	12 (18)	12 (18)
History of diabetes	51 (76)	46 (67)	45 (68)	48 (72)
History of hypertension	66 (99)	63 (91)	61 (92)	61 (91)
WI-NRS, mean (SD)	7.0 (1.1)	7.2 (1.2)	7.0 (1.2)	7.0 (1.3)

Stage 3 CKD non-dialysis, 30≤eGFR<60 mL/min/1.73 m^2; Stage 4 or 5 CKD non-dialysis, eGFR<30 mL/min/1.73 m^2; Stage 4 or 5 CKD on hemodialysis, eGFR<30 mL/min/1.73 m^2 and receiving hemodialysis 3 times per week for ≥3 months prior to screening. eGFR, estimated glomerular filtration rate.

Primary Endpoint: Change From Baseline in the WI-NRS at Week 12

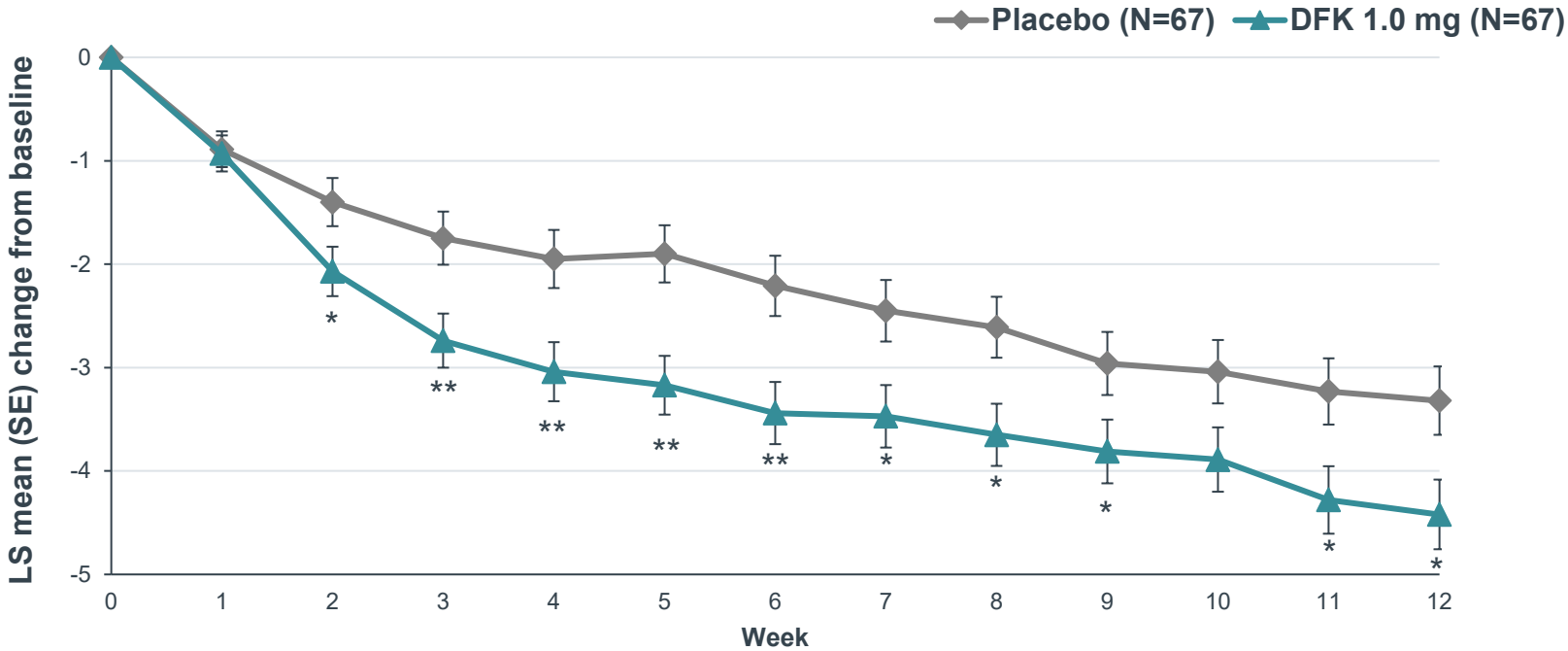
- Patients in the DFK 1.0-mg group demonstrated significantly greater improvement in the mean WI-NRS vs placebo



P=NS for 0.25 mg and 0.5 mg DFK vs placebo. Statistical tests were 2-sided (alpha=0.5). LS mean from MMRM with terms for treatment group, week, week by treatment interaction as fixed effects; baseline score and strata as covariates; patient as a repeated measure. Analyzed in the full analysis population (patients receiving ≥1 dose based on randomized treatment). Error bars represent standard error (SE). Missing data imputed using MI under MAR assumption. LS, least squares; MAR, missing at random; MI, multiple imputation; MMRM, mixed model for repeated measures.

Change From Baseline in WI-NRS Over Time

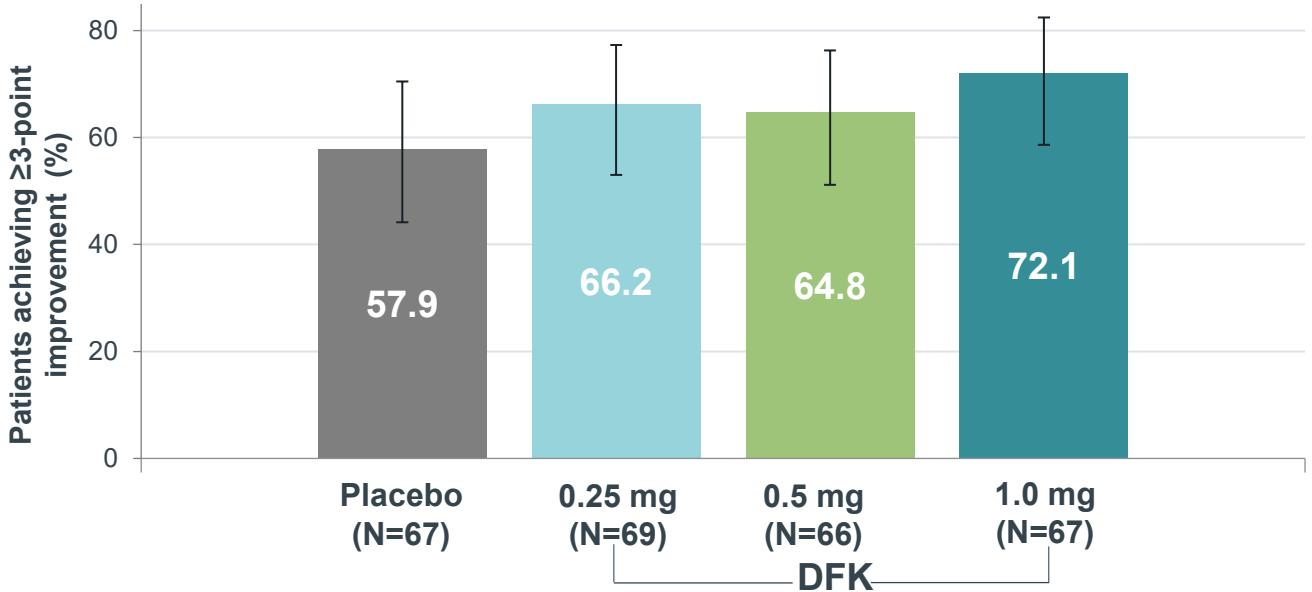
- Significantly greater improvements in WI-NRS were observed with DFK 1.0 mg vs placebo as early as week 2 and were maintained up to week 12



*P<0.05. **P<0.01. Statistical tests were 2-sided (alpha=0.5). LS mean from MMRM with terms for treatment group, week, week by treatment interaction as fixed effects; baseline score and strata as covariates; patient as a repeated measure. Analyzed in the full analysis population (patients receiving ≥1 dose based on randomized treatment). Error bars represent SE. Missing data imputed using MI under MAR assumption.

Achievement of ≥3-Point Improvement in WI-NRS at Week 12

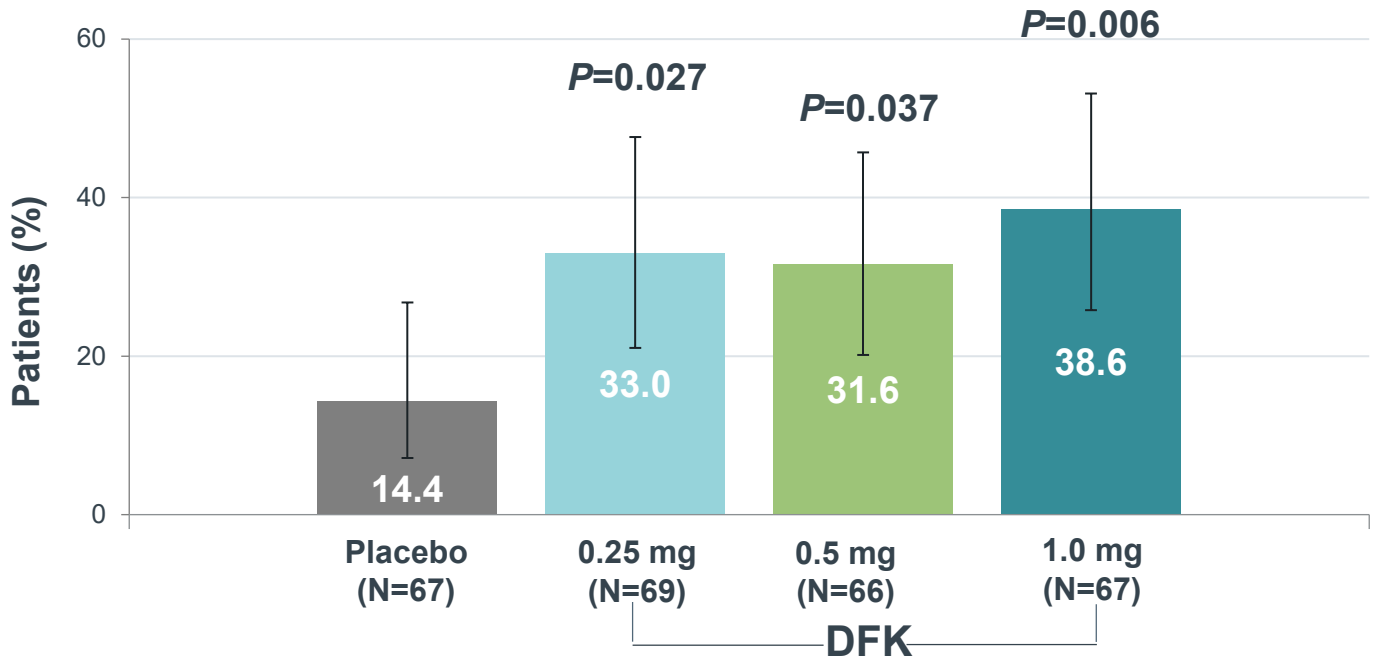
- More than 70% of patients achieved ≥3-point improvement in WI-NRS with DFK 1.0 mg (**Figure**)
- 64.8% of patients treated with DFK 1.0 mg achieved ≥4-point improvement vs 49.8% with placebo



P=NS for all DFK doses vs placebo. Statistical tests were 2-sided (alpha=0.5). Estimated percentage and *P* values are based on a logistic regression model with terms for treatment group, baseline WI-NRS score, and renal disease status. Error bars represent 95% confidence interval (CI). Analyzed in the full analysis population (patients receiving ≥1 dose based on randomized treatment). Missing data imputed using MI under MAR assumption.

Complete Response at Week 12

- Significantly greater proportions of patients who received DFK at all 3 dose levels achieved a complete response compared with placebo



P value vs placebo. Statistical tests were 2-sided (alpha=0.5). Estimated percentage and *P* values are based on a logistic regression model with terms for treatment group, baseline WI-NRS score, and renal disease status. Error bars represent 95% CI. Analyzed in the full analysis population (patients receiving ≥1 dose based on randomized treatment). Complete response is defined as achievement of ≥80% of the non-missing daily NRS scores equal to 0 or 1 during week 12.

Summary of Adverse Events

Patients, n (%)	Placebo N=67	DFK 0.25 mg N=69	DFK 0.5 mg N=66	DFK 1.0 mg N=67
≥1 TEAE	34 (50.7)	35 (50.7)	34 (51.5)	39 (58.2)
≥1 Serious TEAE	5 (7.5)	9 (13.0)	9 (13.6)	9 (13.4)
Death	3 (4.5)	0 (0)	0 (0)	1 (1.5)
TEAE resulting in treatment discontinuation	1 (1.5)	4 (5.8)	5 (7.6)	8 (11.9)

- Treatment-emergent AEs (TEAEs) were generally mild to moderate in severity
- Deaths in the placebo group were due to acute respiratory failure (3.0%) and cardiac arrest (1.5%); the death in the DFK 1.0-mg group was due to coronary arterial disease (1.5%)
- The most commonly reported serious TEAEs (>2 patients) in the combined DFK groups included falls (1.5%)
- The most common TEAEs leading to treatment discontinuation were diarrhea (1.0%), nausea (1.0%), fatigue (1.0%), and dizziness (1.0%) in the DFK groups and muscle spasms (1.5%) in the placebo group

Safety analyses were performed in the safety population, defined as all randomized patients who received ≥1 dose of study drug based on actual treatment received.

Most Commonly Reported TEAEs

Patients, n (%)	Placebo N=67	DFK 0.25 mg N=69	DFK 0.5 mg N=66	DFK 1.0 mg N=67
Dizziness	0	0	2 (3.0)	5 (7.5)
Fall	0	0	3 (4.5)	4 (6.0)
Constipation	2 (3.0)	2 (2.9)	2 (3.0)	4 (6.0)
Diarrhea	1 (1.5)	2 (2.9)	3 (4.5)	4 (6.0)
Fatigue	1 (1.5)	4 (5.8)	1 (1.5)	3 (4.5)
Urinary tract infection	0	4 (5.8)	2 (3.0)	3 (4.5)
Hypertension	1 (1.5)	4 (5.8)	0	1 (1.5)
Gastroesophageal reflux disease	0	0	4 (6.1)	0

Most common TEAEs include those with incidence ≥5% in ≥1 treatment group and strictly greater than placebo. Safety analyses were performed in the safety population, defined as all randomized patients who received ≥1 dose of study drug based on actual treatment received.

Conclusions

- CKD-aP is an under-recognized but distressing condition which presents across all stages of CKD[1]
- This is the first randomized, placebo-controlled trial in patients with stage 3-5 CKD (non-dialysis and dialysis) with moderate-to-severe pruritus
- Oral DFK 1.0 mg met the primary endpoint, demonstrating significantly greater improvement in WI-NRS vs placebo in patients with CKD-aP
  - Treatment effect starting at week 2 and persisting through 12 weeks
- DFK 1.0 mg was associated with clinically meaningful improvements in pruritus; nearly 40% of patients achieved a complete response, which was more than 2.5 times greater than placebo
- Oral DFK was generally well tolerated, with a safety profile consistent with prior studies of intravenous DFK[2]
- Further evaluation of oral DFK 1.0 mg is warranted in phase 3 trials in CKD patients with pruritus

1. Sukul N, et al. *CJASN*. 2019;14:673-681. 2. Fishbane S, et al. *N Engl J Med*. 2020;382:222-232.