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Efficacy and safety of oral difelikefalin in stage 3-5 chronic kidney disease patients with moderate-to-severe pruritus: a response analysis from a randomised, placebo-controlled, phase 2 trial

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Objectives: Pruritus is a common and burdensome condition in non-dialysis and hemodialysis patients with chronic kidney disease (CKD), for which there are no approved treatments. Difelikefalin (DFK) is a novel peripherally restricted, selective kappa opioid receptor agonist being developed for the treatment of pruritus.

Methods: In this phase 2, double-blind, randomized, placebo-controlled, dose-ranging study, 269 patients with stage 3-5 CKD were equally randomized to oral DFK (0.25, 0.5, or 1.0 mg) or placebo once daily for 12 weeks. The primary endpoint was the change from baseline at week 12 in the weekly mean of daily Worst Itching Intensity Numerical Rating Scale (WI-NRS) scores. An additional analysis was also conducted to determine the proportion of patients with a complete response at the end of treatment, defined as ≥ 80% of the daily NRS scores equal to 0 or 1 during week 12.

Results: Baseline WI-NRS scores were 7.1 (SD ±1.2) in DFK (all doses) and 7.0 (SD ±1.1) in placebo. The primary endpoint was met in the DFK 1.0 mg group vs. placebo (-4.4 vs. -3.3, p=0.018). Treatment effect was evident at week 2 and maintained through week 12. A significantly greater proportion of patients who received DFK 1.0 mg achieved a complete response at Week 12 compared to PBO (37.0% vs. 14.3%, p=0.006). Most commonly reported adverse events in the DFK groups were dizziness, fall, diarrhea, constipation, and worsening GERD.

Conclusions: Oral DFK 1.0 mg daily was identified as the optimal dose based on significant reduction in itch intensity and an acceptable safety profile. Further evaluation of DFK is warranted in CKD patients with pruritus, where there is a high unmet need.