A Phase 3 Trial of Difelikefalin in Hemodialysis Patients with Pruritus

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ABSTRACT

BACKGROUND
Difelikefalin is a peripherally restricted and selective agonist of kappa opioid receptors that are considered to be important in modulating pruritus in conditions such as chronic kidney disease.

METHODS
In this double-blind, placebo-controlled, phase 3 trial, we randomly assigned patients undergoing hemodialysis who had moderate-to-severe pruritus to receive either intravenous difelikefalin (at a dose of 0.5 μg per kilogram of body weight) or placebo three times per week for 12 weeks. The primary outcome was the percentage of patients with an improvement (decrease) of at least 3 points from baseline at week 12 in the weekly mean score on the 24-hour Worst Itching Intensity Numerical Rating Scale (WI-NRS; scores range from 0 to 10, with higher scores indicating greater itch intensity). The secondary outcomes included the change from baseline in itch-related quality-of-life measures, the percentage of patients with an improvement of at least 4 points in the WI-NRS score at week 12, and safety.

RESULTS
A total of 378 patients underwent randomization. A total of 82 of 158 patients (51.9%) in the difelikefalin group had a decrease of at least 3 points in the WI-NRS score (primary outcome), as compared with 51 of 165 (30.9%) in the placebo group. The imputed percentage of patients with a decrease of at least 3 points in the WI-NRS score was 49.1% in the difelikefalin group, as compared with 27.9% in the placebo group (P<0.001). Difelikefalin also resulted in a significant improvement from baseline to week 12 in itch-related quality of life as measured by the 5-D itch scale and the Skindex-10 scale. The imputed percentage of patients with a decrease of at least 4 points in the WI-NRS score at week 12 was significantly greater in the difelikefalin group than in the placebo group (37.1% [observed data: 64 of 158 patients] vs. 17.9% [observed data: 35 of 165 patients], P<0.001). Diarrhea, dizziness, and vomiting were more common in the difelikefalin group than in the placebo group.

CONCLUSIONS
Patients treated with difelikefalin had a significant reduction in itch intensity and improved itch-related quality of life as compared with those who received placebo. (Funded by Cara Therapeutics; KALM-1 ClinicalTrials.gov number, NCT03422653.)
Chronic kidney disease–associated pruritus, also known as uremic pruritus, is a common, distressing, and underrecognized condition that affects more than 60% of patients undergoing hemodialysis, with 20 to 40% of patients reporting moderate-to-severe pruritus.\textsuperscript{1,6} Intense and generalized systemic itching in these patients is associated with poor sleep quality, depression, reduced quality of life, increased risk of infection, and an increased risk of death.\textsuperscript{1,3,7-9} There is currently no approved therapy for uremic pruritus in the United States or Europe, and off-label treatments have been reported to have limited efficacy or substantial side effects, thus indicating an unmet medical need.

The pathogenesis of chronic kidney disease–associated pruritus is incompletely understood. Several hypotheses have been proposed, including metabolic disturbances,\textsuperscript{1,10} dysregulated immune response,\textsuperscript{11-13} and imbalances in the endogenous opioid system,\textsuperscript{14,15} with peripherally distributed kappa opioid receptors potentially playing a role.\textsuperscript{16}

Difelikefalin (CR845) is a peripherally restricted, selective kappa opioid receptor agonist that exerts antipruritic effects by means of activation of kappa opioid receptors on peripheral neurons and immune cells.\textsuperscript{17-19} The hydrophilic small-peptide structure restricts passive diffusion across membranes, thereby limiting access to kappa opioid receptors in the central nervous system.\textsuperscript{20} Phase 2 trials involving patients undergoing hemodialysis who had moderate-to-severe pruritus showed clinically meaningful reductions in itch intensity and significant improvements in itch-related quality of life and sleep in patients treated with difelikefalin as compared with those who received placebo.\textsuperscript{21} Here we report the results of a phase 3 trial evaluating the efficacy and safety of difelikefalin in adult patients undergoing hemodialysis who had moderate-to-severe pruritus.

**METHODS**

**TRIAL SITES AND PATIENT POPULATION**

KALM-1 was a randomized, double-blind, placebo-controlled, phase 3 trial that was conducted at 56 sites in the United States; an open-label extension phase to evaluate longer-term safety is ongoing. Eligible patients were adults (≥18 years of age) with end-stage kidney disease who had been undergoing hemodialysis at least three times per week for at least 3 months and who had moderate-to-severe pruritus. Moderate-to-severe pruritus was defined as a weekly mean score of more than 4 points on the 24-hour Worst Itching Intensity Numerical Rating Scale (WI-NRS). The mean score was calculated with the use of daily assessments performed during a 7-day run-in period before randomization (see the eligibility criteria in Appendix B in the Supplementary Appendix, available with the full text of this article at NEJM.org). The WI-NRS is a validated 11-point scale, with scores ranging from 0 to 10 and with higher scores indicating greater itch intensity.\textsuperscript{2-22} All the patients provided written informed consent before trial participation.

**TRIAL DESIGN AND ASSESSMENTS**

Eligible patients were randomly assigned (in a 1:1 ratio) to receive intravenous difelikefalin (at a dose of 0.5 μg per kilogram of body weight) or matched placebo three times per week for 12 weeks. Difelikefalin or placebo was administered as an intravenous bolus into the venous port of the dialysis circuit after each dialysis session. Doses were calculated on the basis of the prescription dry body weight for dialysis (i.e., the weight at which the patient’s volume status is neither overhydrated nor underhydrated, according to the physician’s determination; at each dialysis session, fluid is removed to try to lower the patient’s weight to this prescribed dry weight). If a patient underwent an additional dialysis session during a given week, an additional dose of difelikefalin or placebo was administered, up to a maximum of four doses. Concomitant treatment with stable doses of antihistamines, glucocorticoids, opioids, gabapentin, and pregabalin was permitted if used at the time of the screening visit; the initiation of new antipruritic medications after the screening visit was prohibited. Randomization was performed with the use of an interactive Web-response system and was stratified according to baseline use of concomitant antipruritic medications and history of prespecified medical conditions.

During the 12-week intervention period, patients reported their worst itching intensity over the past 24 hours daily using the WI-NRS. Itch-related quality of life was measured with the use of two validated instruments, the 5-D itch and the Skindex-10 multidimensional questionnaires.
Both questionnaires were completed by patients at prespecified intervals during the 12-week intervention period. Questionnaires were completed by each patient without any assistance. The 5-D itch scale assesses five dimensions of itch (degree, duration, direction, disability, and distribution) during a 2-week recall period. Scores on the 5-D itch scale range from 5 to 25, with higher scores indicating worse itch-related quality of life. The Skindex-10 scale was developed specifically for uremic pruritus and measures the weekly effect of itch across three domains (disease, mood and emotional distress, and social functioning). Scores on the Skindex-10 scale range from 0 to 60, with higher scores indicating worse itch-related quality of life. Safety was evaluated by monitoring adverse events, vital signs, clinical laboratory measurements, and electrocardiograms. Questions were completed by patients, research staff, and the sponsor (Cara Therapeutics) trial team remained unaware of the trial-group assignments at all times.

After the completion of the 12-week intervention period, patients entered a 2-week discontinuation period during which no difelikefalin or placebo was administered. Patients were monitored for potential signs of physical dependence with the use of the Short Opioid Withdrawal Scale (ShOWS), which measures the severity of withdrawal symptoms and which was completed daily by the patient, and the Objective Opioid Withdrawal Scale (OOWS), which includes 13 signs of withdrawal, as rated by a trained observer at each dialysis visit.

After the 12-week intervention and 2-week discontinuation periods, eligible patients were invited to enter an open-label extension phase of 52 weeks to further evaluate the safety of difelikefalin during longer-term exposure. The extension phase is ongoing.

**TRIAL OVERSIGHT**

The trial was conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonisation guidelines for Good Clinical Practice, and applicable regulatory requirements. An independent safety monitoring committee conducted unblinded monitoring of patient safety throughout the trial. The trial protocol (available at NEJM.org) was approved by the institutional review board at each participating institution.

All the authors participated in the interpretation of trial data. The manuscript was prepared by the authors, with medical writing assistance funded by the trial sponsor. The authors provided final approval for submission of the manuscript for publication. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

**EFFICACY OUTCOMES**

The primary efficacy outcome was the percentage of patients who had an improvement (decrease) of at least 3 points from baseline at week 12 in the weekly mean score on the daily WI-NRS. The categorical threshold of a decrease of at least 3 points was selected on the basis of a psychometric analysis of data from a previous phase 2 trial that showed that a 3-point decrease represented a clinically meaningful improvement in itch intensity in this patient population. The prespecified secondary efficacy outcomes were the mean change from baseline at week 12 in the 5-D itch scale total score, the mean change from baseline at week 12 in the Skindex-10 scale total score, and the percentage of patients who had an improvement (decrease) of at least 4 points from baseline at week 12 in the weekly mean WI-NRS score.

**STATISTICAL ANALYSIS**

We calculated that a planned sample of 350 patients would provide the trial with 79% to 90% or greater power to detect a between-group difference ranging from 15 to 20 percentage points in the primary outcome (assuming a response in 30% of the patients in the placebo group) on the basis of a two-sided chi-square continuity-corrected test at a significance level of 0.05. An interim analysis for sample-size reestimation was conducted by an independent data monitoring committee after 50% of the first 350 patients either completed the 12-week intervention period or discontinued the trial regimen.

In the primary analysis, missing weekly mean WI-NRS scores were estimated with the use of multiple imputation under a missing-at-random assumption. For each imputed data set, the difference between placebo and difelikefalin was analyzed with the use of a logistic-regression model containing terms for trial group, baseline WI-NRS score, baseline use of antipruritic med-
ication, and history of prespecified medical conditions. The multiple imputation process was implemented separately for patients contributing to the interim assessment and those who underwent randomization after the interim assessment. The final \( P \) value was calculated with the use of the Cui–Hung–Wang weighted test statistic.\textsuperscript{26,27} Testing of the primary outcome was two-sided at an alpha level of 0.05. In the prespecified primary analysis, WI-NRS scores that were reported when patients were no longer receiving difelikefalin or placebo after the completion or discontinuation of the trial regimen were censored and treated as missing data. An additional analysis was conducted that included all WI-NRS scores reported during the double-blind period, regardless of whether patients were receiving or had discontinued difelikefalin or placebo. Sensitivity analyses were performed to assess the robustness of the primary efficacy analysis under different missing-data assumptions and imputation algorithms (Appendix D in the Supplementary Appendix).

Secondary outcomes were analyzed according to a prespecified hierarchy (first 5-D itch scale, then Skindex-10 scale, and then percentage of patients with a decrease of \( \geq 4 \) points from baseline to week 12 in the weekly mean WI-NRS score). The changes in scores on the 5-D and Skindex-10 scales at week 12 were analyzed with the use of an analysis of covariance (ANCOVA) model, with trial group as a fixed effect and baseline score, stratification factors, and baseline characteristics. The mean (±SD) baseline WI-NRS score was 7.1±1.4 in the difelikefalin group and 7.3±1.6 in the placebo group. Concomitant use of an antipruritic medication was reported by 38.1\% of patients in the difelikefalin group and by 41.5\% of patients in the placebo group. Sensitivity analyses were performed for patients who had at least one visit in the discontinuation period, had undergone randomization and received at least one dose of difelikefalin or placebo; safety analyses for the discontinuation period were performed for patients who had at least one visit in the discontinuation period. Analyses for potential withdrawal during the discontinuation period were performed in the subgroup of patients who completed the 12-week intervention period, received at least six doses of difelikefalin or placebo in the last 2 weeks of the intervention period, and had at least one visit in the discontinuation period. The statistical analysis plan is available with the protocol.

RESULTS

TRIAL PATIENTS

A total of 378 patients were enrolled in the present trial between February 2018 and December 2018. The demographic and baseline clinical characteristics of the patients are summarized in Table 1 and in Table S1 in the Supplementary Appendix. The trial groups were well balanced with respect to clinically relevant baseline characteristics. The mean (±SD) baseline WI-NRS score was 7.1±1.4 in the difelikefalin group and 7.3±1.6 in the placebo group. Concomitant use of an antipruritic medication was reported by 38.1\% of the patients in the difelikefalin group and by 41.5\% of patients in the placebo group. Figure S1 shows the randomization and follow-up of the patients.

PRIMARY OUTCOME

Difelikefalin resulted in significant improvements, as compared with placebo, in the primary outcome (Fig. 1). At week 12, the estimated percentage of patients who had an improvement (decrease) of
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (N = 188)</th>
<th>Difelikefalin (N = 189)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>56.8±13.9</td>
<td>58.2±11.2</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>118 (62.8)</td>
<td>112 (59.3)</td>
</tr>
<tr>
<td>Race — no. (%)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>93 (49.5)</td>
<td>91 (48.1)</td>
</tr>
<tr>
<td>Black</td>
<td>75 (39.9)</td>
<td>82 (43.4)</td>
</tr>
<tr>
<td>Other</td>
<td>18 (9.6)</td>
<td>15 (7.9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (1.1)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Prescription dry body weight for dialysis — kg§</td>
<td>85.0±21.1</td>
<td>85.9±20.3</td>
</tr>
<tr>
<td>Time since diagnosis of end-stage renal disease — yr</td>
<td>5.7±5.2</td>
<td>4.7±3.9</td>
</tr>
<tr>
<td>Time since initiation of hemodialysis — yr</td>
<td>4.7±4.2</td>
<td>4.4±4.0</td>
</tr>
<tr>
<td>Cause of chronic kidney disease — no. (%)¶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>95 (50.5)</td>
<td>108 (57.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>73 (38.8)</td>
<td>59 (31.2)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>7 (3.7)</td>
<td>9 (4.8)</td>
</tr>
<tr>
<td>Cystic disease</td>
<td>3 (1.6)</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Other</td>
<td>10 (5.3)</td>
<td>10 (5.3)</td>
</tr>
<tr>
<td>Duration of pruritus — yr</td>
<td>3.5±3.4</td>
<td>3.2±3.2</td>
</tr>
<tr>
<td>Blood chemical testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin — μmol/liter</td>
<td>8.56±4.77</td>
<td>10.0±15.32</td>
</tr>
<tr>
<td>Calcium — mmol/liter</td>
<td>2.12±0.19</td>
<td>2.11±0.16</td>
</tr>
<tr>
<td>Phosphorus — mmol/liter</td>
<td>1.80±0.64</td>
<td>1.77±0.58</td>
</tr>
<tr>
<td>Baseline use of antipruritic medication — no. (%)‖</td>
<td>78 (41.5)</td>
<td>72 (38.1)</td>
</tr>
<tr>
<td>Most commonly used antipruritic medications at baseline — no. (%)‖</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>71 (37.8)</td>
<td>61 (32.3)</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>21 (11.2)</td>
<td>20 (10.6)</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>8 (4.3)</td>
<td>6 (3.2)</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>3 (1.6)</td>
<td>5 (2.6)</td>
</tr>
<tr>
<td>Ammonium lactate</td>
<td>4 (2.1)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Loratadine</td>
<td>4 (2.1)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>History of specified medical condition — no. (%)**</td>
<td>28 (14.9)</td>
<td>25 (13.2)</td>
</tr>
<tr>
<td>WI-NRS score††</td>
<td>7.3±1.6</td>
<td>7.1±1.4</td>
</tr>
<tr>
<td>5-D itch scale total score‡‡</td>
<td>17.9±3.5</td>
<td>16.9±3.5</td>
</tr>
<tr>
<td>Skindex-10 scale total score§§</td>
<td>38.3±15.4</td>
<td>36.2±14.4</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. To convert values for bilirubin to milligrams per deciliter, divide by 17.1. To convert values for calcium to milligrams per deciliter, divide by 0.250. To convert values for phosphorus to milligrams per deciliter, divide by 0.3229.

† Data exclude one patient who had been randomly assigned to the placebo group and who withdrew from the trial before receiving the first dose of placebo (Fig. S1).

‡ Race was reported by the patients. Other includes American Indian or Alaska Native, Asian, and Native Hawaiian or other Pacific Islander.

§ The prescription dry body weight for dialysis is the weight at which the patient’s volume status is neither overhydrated nor underhydrated, according to the physician’s determination; at each dialysis session, fluid is removed to try to lower the patient’s weight to this prescribed dry weight.

¶ Diabetes includes diabetes alone, diabetes and hypertension, or diabetes and other; hypertension includes hypertension (or large vessel disease) alone or hypertension (or large vessel disease) and other; and glomerulonephritis includes glomerulonephritis alone or glomerulonephritis and other.

‖ Listed are the medications that were reported by more than 2% of patients in either trial group.

** Conditions include fall, fall-related fracture, confined state, altered mental status, disorientation, gait disturbance, and movement disorder.

†† Worst itching intensity was evaluated by means of the Worst Itching Intensity Numerical Rating Scale (WI-NRS), an 11-point scale that measures the worst itching intensity during the previous 24 hours; scores range from 0 to 10, with higher scores indicating greater intensity.

‡‡ Scores on the 5-D itch scale range from 5 to 25, with higher scores indicating worse itch-related quality of life.

§§ Scores on the Skindex-10 scale range from 0 to 60, with higher scores indicating worse itch-related quality of life.
at least 3 points from baseline on the WI-NRS was significantly greater in the difelikefalin group than in the placebo group (49.1% vs. 27.9%; relative risk, 1.65; 95% confidence interval, 1.26 to 2.14; P<0.001) (Fig. 1A and Table 2). The treatment effect was evident at week 1 (Fig. 2). Similar results were reported when only data during receipt of difelikefalin or placebo were used (51.0% vs. 27.6%) (Table 2). Sensitivity analyses of the primary outcome yielded results that were consistent with those of the primary analysis (Table S2).

**SECONDARY OUTCOMES**

All secondary outcomes in the prespecified testing hierarchy showed significant improvement with difelikefalin as compared with placebo. The active agent significantly improved itch-related quality of life as measured by the total scores on the 5-D itch scale...
The least-squares mean (±SE) change from baseline in the 5-D total score was –5.0±0.3 in the difelikefalin group, as compared with –3.7±0.3 in the placebo group (Fig. 1C and Table 2). Between-group differences in favor of difelikefalin were observed for four of the five dimensions of itch, including distribution, duration, degree, and direction (Table S3).

The least-squares mean change from baseline (P<0.001) and the Skindex-10 scale (P<0.001). At week 12, the least-squares mean (±SE) change from baseline in the 5-D total score was –5.0±0.3 in the difelikefalin group, as compared with –3.7±0.3 in the placebo group (Fig. 1C and Table 2). Between-group differences in favor of difelikefalin were observed for four of the five dimensions of itch, including distribution, duration, degree, and direction (Table S3).

### Table 2. Efficacy Outcomes.†

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (N = 189)</th>
<th>Difelikefalin (N = 189)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3-Point improvement from baseline at wk 12 in the weekly mean score of the daily 24-hr WI-NRS†</td>
<td>51/165 (30.9)</td>
<td>82/158 (51.9)</td>
<td></td>
</tr>
<tr>
<td>Least-squares mean (95% CI)</td>
<td>27.9 (20.5–36.8)</td>
<td>49.1 (36.8–61.5)</td>
<td></td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>2.49 (1.57–3.94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1.65 (1.26–2.14)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Least-squares mean change from baseline at wk 12 in 5-D itch scale total score</td>
<td>–3.7±0.3</td>
<td>–5.0±0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Least-squares mean change from baseline at wk 12 in Skindex-10 scale total score</td>
<td>–12.0±1.2</td>
<td>–17.2±1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥4-Point improvement from baseline at wk 12 in the weekly mean score of the daily 24-hr WI-NRS‡</td>
<td>35/165 (21.2)</td>
<td>64/158 (40.5)</td>
<td></td>
</tr>
<tr>
<td>Least-squares mean</td>
<td>17.9 (12.1–25.8)</td>
<td>37.1 (28.3–46.9)</td>
<td></td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>2.70 (1.64–4.45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1.92 (1.37–2.68)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Other outcome</strong></td>
<td></td>
<td></td>
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<tr>
<td>≥3-Point improvement from baseline at wk 12 in the weekly mean score of the daily 24-hr WI-NRS</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Baseline use of antipruritic medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observed — no./total no. (%)</td>
<td>20/66 (30)</td>
<td>29/58 (50)</td>
<td></td>
</tr>
<tr>
<td>Least-squares mean (95% CI)</td>
<td>29 (18–42)</td>
<td>51 (37–64)</td>
<td></td>
</tr>
<tr>
<td>No baseline use of antipruritic medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observed — no./total no. (%)</td>
<td>31/99 (31)</td>
<td>53/100 (53)</td>
<td></td>
</tr>
<tr>
<td>Least-squares mean (95% CI)</td>
<td>28 (18–40)</td>
<td>47 (35–60)</td>
<td></td>
</tr>
</tbody>
</table>

* Plus–minus values are least-squares means ±SE. Efficacy analyses were performed in the intention-to-treat population. Improvement was indicated by a decrease in score in all scale assessments. The primary and secondary outcomes were evaluated with the use of a prespecified hierarchical statistical testing procedure; the P value for each outcome was considered to be inferential if the preceding outcome in the sequential testing procedure was significant at a two-sided 0.05 significance level. CI denotes confidence interval, and NA not applicable (because P values are reported only for efficacy outcomes included in the hierarchical testing plan).

† This is a modification of the prespecified analysis that included WI-NRS scores reported during the intervention period, regardless of whether patients were receiving or had discontinued difelikefalin or placebo. In the prespecified analysis, which included only scores during receipt of difelikefalin or placebo, 51.0% of the patients receiving difelikefalin, as compared with 27.6% of the patients receiving placebo, had an improvement of at least 3 points from baseline at week 12 in the weekly mean score of the daily 24-hour WI-NRS (P<0.001) (Table S7).

‡ In this analysis, data reported during the intervention period, regardless of whether patients were receiving or had discontinued difelikefalin or placebo, were included. The prespecified analysis that included only scores during receipt of difelikefalin or placebo is shown in Table S7.

§ There were 78 patients in the placebo group and 72 in the difelikefalin group.

¶ There were 111 patients in the placebo group and 117 in the difelikefalin group.
at week 12 in the Skindex-10 total score was –17.2±1.3 in the difelikefalin group and –12.0±1.2 in the placebo group (Fig. 1D and Table 2); a greater effect was observed with difelikefalin than with placebo across all domains (Table S4). In addition, a significantly higher percentage of patients in the difelikefalin group than in the placebo group had a decrease of at least 4 points from baseline at week 12 in the weekly mean WI-NRS score (37.1% vs. 17.9%, P<0.001) (Fig. 1A and Table 2). The magnitude of the treatment effect was similar across subgroups stratified according to baseline use of antipruritic medications (Fig. 1B).

SAFETY

The overall incidence of adverse events was 68.8% (130 of 189 patients) in the difelikefalin group and 62.2% (117 of 188 patients) in the placebo group (Table 3). The most common adverse events in patients receiving difelikefalin were diarrhea, dizziness, and vomiting; these events were generally mild to moderate in severity and resolved without evident clinical consequence.

Serious adverse events occurred in 49 patients (25.9%) in the difelikefalin group and 41 patients (21.8%) in the placebo group during the 12-week intervention period. The most commonly reported serious adverse events in the difelikefalin group were hyperkalemia (in 4 patients [2.1%] in each group), pneumonia (in 3 [1.6%] in the difelikefalin group and in 5 [2.7%] in the placebo group), sepsis (in 3 [1.6%] and 4 [2.1%, respectively]), hypotension (in 3 [1.6%] and 2 [1.1%]), and chronic obstructive pulmonary disease (in 3 [1.6%] and 1 [0.5%]) (Table S5). There were two deaths in each group during the 12-week intervention period, including two deaths due to sepsis in the difelikefalin group and two deaths due to septic shock in the placebo group.

Adverse events led to discontinuation of treatment in 15 patients (7.9%) in the difelikefalin group and in 9 patients (4.8%) in the placebo group. The most common adverse events resulting in discontinuation were dizziness (in 3 patients [1.6%] in the difelikefalin group and no patients in the placebo group) and septic shock (in no patients in the difelikefalin group and 3 patients [1.6%] in the placebo group) (Table S6).

There were no substantial differences between the trial groups in the incidence of clinically relevant abnormalities in vital signs, laboratory tests, or electrocardiographic findings. No signs of potential physical dependence were observed during the 2-week discontinuation period, as measured by the ShOWS and OOWS scores (Fig. S2). There were no adverse events related to withdrawal in either trial group on cessation of difelikefalin or placebo. There was one sudden death in a patient who had previously been assigned to the placebo group. There were no adverse events of dysphoria, hallucination, or euphoria reported in the difelikefalin group during the entire trial.

Figure 2. Mean Change in Worst Itching Intensity Numerical Rating Scale (WI-NRS) Score.

Shown is the least-squares mean change from baseline (point estimates) in the weekly mean WI-NRS score, as analyzed with the use of a mixed-effects model with repeated measures. Scores range from 0 to 10, with higher scores indicating greater intensity. The I bars indicate the standard error. Missing data were imputed with the use of multiple imputation under a missing-at-random assumption. There were 189 patients in each trial group.

DISCUSSION

In the present trial, difelikefalin led to significant improvement, as compared with placebo, in pruritus intensity as assessed for the primary outcome. In addition, secondary outcome scores that included itch intensity and multidimensional itch-related quality-of-life assessments favored difelikefalin over placebo. The treatment effect was rapid (evident by week 1) and persisted throughout the 12 weeks of treatment.

Exploratory sensitivity analyses of the primary outcome yielded results that were consistent with those of the primary analysis, which suggests
the robustness of the data under different missing-data assumptions and imputation algorithms. The primary-outcome result was supported by significant improvements for all secondary outcomes, which reinforces the concept that the reduction of itch intensity seen with difelikefalin treatment was associated with a positive effect on quality of life across multiple domains that are important for patients. Moreover, the magnitude of the treatment effect on itch intensity was consistent across subgroups stratified according to baseline use of antipruritic medications, which indicates that the observed abatement in pruritus severity was not attributable to concomitant treatment with antipruritic medications.

The incidence of adverse events in both trial groups was high, which is reflective of the susceptible population of patients who present with clinically significant coexisting conditions. The most commonly reported serious adverse events and deaths appeared to be balanced across the trial groups. Adverse events of diarrhea, dizziness, and vomiting were more frequent in patients receiving difelikefalin than in those receiving placebo.

In findings that were consistent with the pharmacologic and physicochemical properties of difelikefalin, there was no evidence of abuse or development of physical dependence during the 12-week trial. In receptor-binding and functional assays, difelikefalin had no detectable activity at mu or delta opioid receptors or any other receptors that have, in other work, been associated with dependency. Studies in animals and in humans that were specifically designed to evaluate the addictive properties of the molecule have suggested a low probability of abuse potential with difelikefalin. We observed no events of dysphoria or hallucination, both of which are well-documented adverse events that have been associated with centrally acting kappa opioid receptor agonists. These findings suggest a possible safety advantage of peripherally restricted selective kappa opioid agonists as compared with mu opioid and centrally acting kappa opioid receptor agonists.

The present controlled, phase 3 trial showed a clinically meaningful benefit in patients with chronic kidney disease–associated pruritus over an intervention period of 12 weeks. The results confirm and extend the findings of a previous phase 2 trial of difelikefalin that showed an effective reduction of itch intensity in patients with chronic kidney disease–associated pruritus.

This trial has certain limitations. The trial enrolled patients who were undergoing hemodialysis; the effect of treatment in patients with chronic kidney disease who are not undergoing hemodialysis requires evaluation. A phase 2 trial evaluating an oral formulation of difelikefalin in
this population is under way (ClinicalTrials.gov number, NCT03617536). The safety and efficacy of difelikefalin were assessed for 12 weeks in this trial that was based in the United States; assessments over longer durations (ongoing in an open-label phase of the present trial) as well as ongoing trials (e.g., KALM-2; NCT03636269) including patients from other regions will help support the generalizability of this treatment.

In conclusion, treatment with difelikefalin for 12 weeks resulted in a marked and rapid reduction in itch intensity among patients undergoing hemodialysis who had chronic kidney disease–associated pruritus.

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