



Safety and Effectiveness of Difelikefalin in Patients With Moderate-to-Severe Pruritus Undergoing Hemodialysis: An Open-Label, Multicenter Study

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Rationale & Objective: Individuals with chronic kidney disease frequently suffer from chronic kidney disease-associated pruritus (CKD-aP), impacting sleep quality and quality of life (QoL) and increasing the likelihood of depression. Difelikefalin is a kappa-opioid receptor agonist recently approved in the United States for the treatment of moderate-to-severe CKD-aP in hemodialysis patients. Study 3105 was conducted to further assess the safety of difelikefalin and the effects on pruritus and QoL.

Study Design: Open-label, multicenter, single-arm intervention trial.

Setting & Participants: Maintenance hemodialysis patients with moderate-to-severe CKD-aP at enrollment.

Intervention: Intravenous difelikefalin 0.5 µg/kg after each hemodialysis session for 12 weeks.

Outcomes: The primary outcome was safety of difelikefalin. Secondary outcomes included: effectiveness of reducing itch intensity, assessed by the Worst Itching Intensity Numerical Rating Scale (WI-NRS); improving itch-related QoL, assessed with 5-D itch and Skindex-10 scales; and improvement of sleep, assessed with the Sleep Quality Numerical Rating Scale. Clinically meaningful thresholds for improvement in itch and QoL were previously established in this population.

Results: Among 222 participants with baseline WI-NRS ≥ 5 , mean [standard deviation] WI-NRS was 7.6 [1.3], mean age 58 years, 55% were male, and mean dialysis duration was 5.9 years; 197 participants (89%) completed treatment. Treatment-related treatment-emergent adverse events were reported in 16 participants (7.2%); those most commonly reported were somnolence (1.8%), hypoesthesia (1.4%), nausea (0.9%), and dizziness (0.9%). No deaths or serious treatment-emergent adverse events were considered treatment-related. Clinically meaningful reduction in itch intensity (≥ 3 -point improvement) was reported by 74% of participants, with 70% and 63% also reporting a clinically relevant improvement in QoL as measured by 5-D itch and Skindex-10. Sleep quality improvement (≥ 3 -point reduction on the Numerical Rating Scale) was reported in 66% of participants.

Limitations: No placebo control group.

Conclusions: Difelikefalin was well tolerated, and treatment was associated with clinically meaningful improvements in itch intensity and itch-related QoL measures as well as improvements in sleep quality among individuals receiving hemodialysis who had moderate-to-severe CKD-aP, providing important insights into expected real-world effectiveness.

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Visual Abstract included

Complete author and article information provided before references.

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Individuals with chronic kidney disease (CKD), particularly those receiving maintenance dialysis, frequently suffer from CKD-associated pruritus (CKD-aP).^{1,2} CKD-aP prevalence estimates vary, but recent data from the international Dialysis Outcomes and Practice Patterns Study indicate that approximately 40% of hemodialysis (HD) patients are ‘moderately bothered’ to ‘extremely bothered’ by itching.³ CKD-aP has been associated with poor sleep quality, anxiety, and depression, with the Dialysis Outcomes and Practice Patterns Study also showing that, among HD patients who were very much or extremely bothered by itchy skin, 60% had restless sleep, compared with patients ‘not at all’ bothered by itch, of whom 29% reported restless sleep.⁴⁻⁶ Data from the Dialysis Outcomes and Practice Patterns Study, as well as recent systematic reviews of CKD-aP, report an association between pruritus and worse clinical outcomes, including a greater risk of infection, hospitalizations, and mortality.^{2,3,7} Further,

patients extremely bothered by pruritus, comprising 7% of the Dialysis Outcomes and Practice Patterns Study cohort, are more likely to withdraw from dialysis or miss dialysis sessions.³

Until recently, no therapies were approved for CKD-aP in the United States or Europe, with commonly prescribed treatments used off-label. Oral antihistamines are most frequently used as a treatment for pruritus, with an international survey of 268 medical directors noting prescription of antihistamines for pruritus as initial treatment by 57%, with gabapentin prescribed by 45%.⁶ Treatment with gabapentin has reported efficacy in several small randomized, controlled trials, with 2 recent, similar meta-analyses suggesting efficacy in terms of itch reduction with gabapentin in the treatment of uremic pruritus in HD patients.⁸⁻¹² Reporting of adverse events was inconsistent across analyzed studies.^{11,12} Difelikefalin (CR845) was approved by the US Food and Drug Administration in

PLAIN-LANGUAGE SUMMARY

Chronic kidney disease-associated pruritus (CKD-aP) is an extremely unpleasant condition that causes unbearable itching, which frequently affects chronic kidney disease patients undergoing hemodialysis. Difelikefalin, the only treatment approved specifically for CKD-aP in the United States and Europe, has demonstrated reduction of itch severity in phase 3 clinical trials. We assessed the expected real-world efficacy and safety of difelikefalin in an open-label study (Study 3105), where all participants were aware they were taking an active treatment. We found that difelikefalin was well tolerated, significantly reduced itch severity and sleep disruption, and was associated with improved quality of life in participants with moderate-to-severe CKD-aP who were undergoing hemodialysis.

August 2021 for the treatment of moderate-to-severe pruritus in adults undergoing HD. Difelikefalin is a kappa-opioid receptor agonist, with a primary mode of action that is outside of the central nervous system, acting mainly on peripheral neurons and cells of the immune system.^{13,14} In the KALM-1 phase 3 clinical trial involving individuals with moderate-to-severe pruritus undergoing HD 3 times weekly, difelikefalin provided a significantly greater reduction in itch intensity and improvement in itch-related quality of life (QoL), compared with placebo, and was shown to have an acceptable safety profile.¹⁵

The aim of the present multinational, multicenter, open-label phase 3 trial was to further evaluate the safety and effectiveness of difelikefalin in reducing the intensity of itch and in improving sleep quality and itch-related QoL in patients with moderate-to-severe pruritus undergoing HD.

METHODS

Study 3105 was an open-label, multicenter, phase 3 trial (NCT03998163) conducted at 31 facilities in the United States and 12 facilities in Europe, enrolling maintenance HD patients with moderate-to-severe CKD-aP, defined as a baseline Worst Itching Intensity Numerical Rating Scale (WI-NRS) score ≥ 5 points (for a list of trial investigators, see [Item S1](#)). The study was funded by Cara Therapeutics. Eligible individuals (18-85 years of age) had been receiving HD 3 times weekly for at least 3 months before screening and were also required to demonstrate dialysis adequacy (at least 2 single-pool Kt/V measurements of at least 1.2 or at least 2 urea reduction ratio measurements $\geq 65\%$ over the 3-month period before screening). Key exclusion criteria were scheduled kidney transplant and concomitant disease or a history of any medical condition that, in the opinion of the investigator, could pose undue risk to the patient, impede completion of the study procedures, or would compromise the validity of the study measurements. Additionally, individuals were

ineligible if they had pruritus attributed to a cause other than kidney failure or its complications or had been prescribed new treatments (including current treatment with ultraviolet B) or treatment changes for itch, including antihistamines and corticosteroids (oral, intravenous, or topical) within 14 days before screening; had new prescriptions or a change in prescription for opioids, gabapentin, or pregabalin within 14 days before screening; or had known history of allergic reactions to opiates (not including side effects from opiates such as nausea and constipation).

Patients could be rescreened if they failed the inclusion/exclusion criteria at their initial screening visit. Rescreening was considered on an individual patient basis and must first have been approved by the Sponsor or designee. However, rescreening was not permitted if a patient missed the entry criteria for itch intensity, ie, mean WI-NRS score ≥ 5 . Additionally, a patient could only be rescreened once, and rescreening could only occur at least 2 weeks after the original screening visit.

Target enrollment for Study 3105 was approximately 200 participants. The study was approved by the institutions' ethical approval review boards with the WCG institutional board (IRB) serving as the central IRB (contract number 20190622) and was performed in accordance with the principles of the Declaration of Helsinki.¹⁶ All participants gave written informed consent before study enrollment.

Study 3105 consisted of a screening period, a treatment period of 12 weeks, and a follow-up visit 7-10 days after the end of treatment. The screening period included a screening visit and 1-week run-in period (within 28 days before treatment initiation), which enabled measurement of baseline itch intensity via the WI-NRS, to confirm that individuals entering the study had moderate-to-severe pruritus, and recording baseline use of medications aimed at managing pruritus. Additionally, baseline characteristics of the disease were recorded, including etiology of CKD, years since diagnosis of kidney failure, duration of pruritus, and years since initiating maintenance HD. From day 1 of the treatment period, participants received difelikefalin after each HD session (generally 3 times weekly) for up to 12 weeks, administered as a 0.5 $\mu\text{g}/\text{kg}$ (based on prescribed estimated dry weight) intravenous bolus into the venous line at the end of the participant's HD treatment.

The primary objective of Study 3105 was to evaluate the safety of difelikefalin assessed through monitoring of adverse events, vital signs, 12-lead electrocardiogram, and clinical laboratory values. All adverse events were coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities version 22.0. Gait disturbance, falls, dizziness, somnolence, seizures, syncope, mental status changes, mood changes, unusual feeling/sensation, tachycardia, and palpitation were recorded as adverse events of special interest. The secondary objectives of the study were to evaluate the effectiveness of difelikefalin for reducing the intensity of itch and improvement of quality of sleep and itch-related QoL.

Participants reported the “intensity of the worst itching experienced over the past 24 hours” for the period preceding the start of the dialysis visit using the WI-NRS 11-point scale (range 0 to 10; higher scores indicate greater itch intensity), which has been validated in patients with CKD-aP.¹⁷⁻¹⁹ Reduction of ≥ 3 points on the WI-NRS has been shown to be associated with a clinically meaningful change in itch intensity for patients with moderate-to-severe pruritus undergoing HD.¹⁹ Change from the mean baseline weekly WI-NRS score to Week 12 and the proportions of individuals achieving a clinically meaningful ≥ 3 -point and ≥ 4 -point improvement from baseline to Week 12 were evaluated.

Sleep quality was assessed by a Sleep Quality Numerical Rating Scale (NRS) at the start of the dialysis visit, which asks patients to indicate how much their itch interfered with their sleep over the preceding 24 hours, with responses ranging from 0 (“did not interfere”) to 10 (“completely interfered”). Changes from baseline in Sleep Quality NRS score to Week 12 and the proportion of participants achieving a ≥ 3 -point and ≥ 4 -point improvement from baseline to Week 12 were evaluated.

Additionally, the proportion of patients reporting a “complete resolution” for itch intensity or for sleep quality (defined as $\geq 75\%$ of weekly mean WI-NRS scores equal to 0 or 1 or all Sleep Quality NRS scores equal to 0) was assessed. Changes from baseline to Week 12 in itch-related QoL were evaluated using 2 validated questionnaires: the 5-D itch Scale and the Skindex-10 Scale, which were completed on the first dialysis visit of Week 1 and after the last dose of difelikefalin.^{17,20} Preferably, the 5-D itch questionnaire was to be completed first. The Skindex-10 was developed as a multidimensional tool to evaluate the impact on itch-related QoL of CKD-aP across 3 separate itch-related domains: disease, mood/emotional distress, and social functioning [18]. Skindex-10 scale total scores range from 0 to 60, with worsening itch-related QoL indicated by higher scores. Analysis of prior phase 2 clinical trial data in adult HD patients with moderate-to-severe pruritus indicated that a ≥ 15 -point reduction (improvement) from baseline in the total Skindex-10 score represents a clinically meaningful change.²¹ Analyses of clinically relevant improvements in subdomains has not yet been performed.

The 5-D itch scale is a multidimensional tool that assesses itch-related QoL and itch intensity across 5 separate itch-related domains (duration, degree, direction, disability, and distribution) over a 2-week recall period.²⁰ 5-D itch scale total scores range from 5 to 25, with worsening itch intensity and itch-related QoL indicated by higher scores. Analysis of a prior phase 2 clinical trial of difelikefalin indicates that a clinically meaningful improvement was represented by a reduction from baseline of ≥ 5 -point in the total 5-D itch score.²¹ Analyses of clinically relevant improvements in subdomains has not yet been performed.

No sample size calculation was performed because of the single-arm design of the trial; target enrollment was

based on recruitment feasibility. Baseline WI-NRS was calculated as the average of the 24-hour WI-NRS scores collected at each dialysis session during the run-in period, including assessments collected on day 1 before the first dose. The baseline Sleep Quality NRS scores were calculated as the average of the scores collected over the run-in period, including assessments collected on day 1 before the first dose. The Week 12 WI-NRS and Sleep Quality NRS scores were defined as the sum of the scores collected on each dialysis visit of Week 12 and on the first dialysis visit of Week 13, divided by the number of days with nonmissing scores over the same time period. If a participant was missing more than 2 WI-NRS scores during a collection period, the WI-NRS was recorded as “missing.” A similar algorithm was used for the Sleep Quality NRS. Scores collected at the Early Termination Visit or unscheduled visits contributed to the Week 12 WI-NRS or Sleep Quality NRS scores if collected from day 76 to day 86, inclusive. Missing data were not imputed. For the analysis of 5-D itch and Skindex-10 scores, missing scores were not imputed. A post hoc subgroup analysis compared the change in WI-NRS and Sleep Quality NRS for patients using concomitant anti-itch medications and those not using additional anti-itch medications. In addition, a statistical assessment of the change from baseline for all outcomes was conducted using paired differences.

RESULTS

Among the 286 individuals enrolled, 72 failed initial screening (of whom 8 participants were rescreened and ultimately received treatment). The main reasons for screen failure were participants not completing ≥ 3 NRS questionnaires during the run-in period with a mean baseline NRS score ≥ 5 (24 participants), or participants having a concomitant disease or a history of any medical condition that, in the opinion of the investigator, could pose undue risk to the patient, impede completion of the study procedures, or would compromise the validity of the study measurements (16 participants) (Table S1).

Overall, 222 participants received at least 1 dose of difelikefalin, and 197 participants (88.7%) completed 12 weeks of study treatment (Fig 1). The median duration of treatment with difelikefalin was 85 (range 3-92) days (12.1 weeks). The most common reasons for early discontinuation from the study were adverse events (5.9%), followed by withdrawal of consent (3.2%) (Table S2). The majority of participants (91%) were enrolled at sites in the United States.

The mean age of treated participants was 58.1 ± 12.8 years; 54.5% were male and approximately half (49.5%) were Black or African American (Table 1). Mean dialysis vintage was 5.9 ± 4.7 years, with a mean duration of pruritus and HD of 3.9 ± 3.3 and 5.4 ± 4.4 years, respectively. Mean calcium at baseline was 8.8 ± 0.8 mg/dL and mean phosphate was 5.9 ± 1.9 mg/dL.

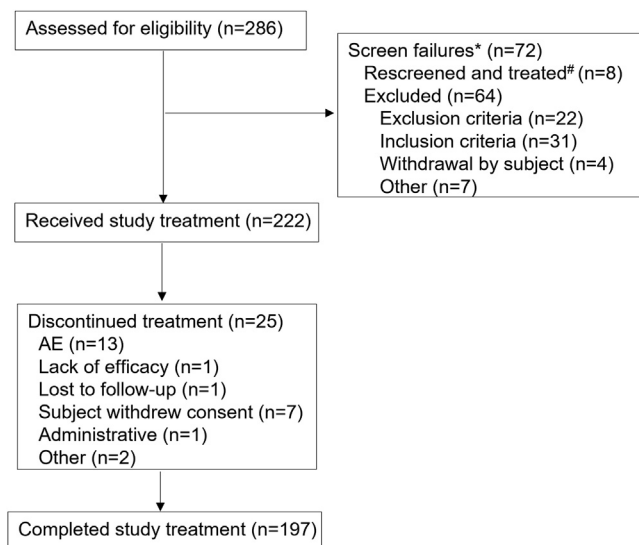


Figure 1. Study disposition flow diagram. *The screen failures patient count for the category “Exclusion criteria” excluded 1 patient, who was rescreened and enrolled. #Patients could be rescreened if they failed the inclusion/exclusion criteria at their initial screening visit. Rescreening was considered on an individual patient basis and must first have been approved by the Sponsor or designee. However, rescreening was not permitted if a patient missed the entry criteria for itch intensity, ie, mean Worst Itching Intensity NRS score >5. Additionally, a patient could only be rescreened once, and rescreening could only occur at least 2 weeks after the original screening visit. Seven of the 14 patients who failed initial screening were included upon rescreening. For patients who screen-failed more than once, the reason for failure was the final screen failure. Abbreviation: AE, adverse event.

Mean baseline scores were 7.6 ± 1.3 (WI-NRS), 6.6 ± 2.2 (Sleep Quality NRS), 17.1 ± 3.5 (5-D itch), and 32.9 ± 14.3 (Skindex-10). Antipruritic medications were used by 71 participants (32.0%) at study entry; the antihistamines diphenhydramine and hydroxyzine were the most common medications used by 22.1% and 6.3% of total participants, respectively. There were 46 (20.7%) participants taking gabapentin as a prior medication for any indication. Of these, 3 (2.3%) were taking this medication for an antipruritic indication.

Safety

Overall, 143 participants (64.4%) had at least 1 treatment-emergent adverse event (TEAE) (ie, a symptom that appears only after beginning therapy), and 414 TEAEs were reported in total. Treatment-related TEAEs were reported in 16 participants (7.2%), none of which were serious (Table 2). The most common TEAEs of any severity, reported in $\geq 4\%$ of all participants, were diarrhea (11 participants, 5.0%), nausea (10 participants, 4.5%), and hyperkalemia (9 participants, 4.1%). In most participants, TEAEs were mild or moderate (30.6% and 25.2% of participants, respectively). Fourteen participants (6.3%) reported TEAEs that resulted in study drug discontinuation.

Table 1. Patient Demographics and Baseline Characteristics

Demographics (N = 222)	n (%) or Mean (SD)
Age (y)	58.1 (12.8)
Sex	
Male	121 (54.5)
Race	
Black or African American	110 (49.5)
White	96 (43.2)
Other ^a	16 (7.2)
Country	
United States	203 (91.4%)
Hungary	12 (5.4%)
Czech Republic	4 (1.8%)
Poland	3 (1.4%)
Clinical characteristics	
Target dry body weight at baseline (kg)	86.6 (23.5)
Years since diagnosis of kidney failure	5.9 (4.7)
Years receiving maintenance hemodialysis	5.4 (4.4)
Duration of pruritus (y)	3.9 (3.3)
Etiology of chronic kidney disease	
Hypertension	135 (60.8%)
Diabetes	110 (49.5%)
Other	25 (11.3%)
Glomerulonephritis	11 (5.0%)
Calcium (mg/dL)	8.8 (0.8)
Phosphate (mg/dL)	5.9 (1.9)
Medication use	
Baseline anti-itch medication use, n (%)	71 (32.0)
Most commonly used (>2%) anti-itch medications at baseline	
Diphenhydramine	49 (22.1)
Hydroxyzine	14 (6.3)
Gabapentin ^b	3 (1.4)
Questionnaire scores	
WI-NRS score	7.6 (1.3)
Sleep Quality NRS	6.6 (2.2)
5-D itch scale total score	17.1 (3.5)
Skindex-10 scale total score	32.9 (14.3)

Note: Baseline WI-NRS was calculated as the average of the 24-h WI-NRS scores collected over the run-in period, including assessments collected on day 1 before the first dose.

Abbreviations: NRS, numerical rating scale; SD, standard deviation; WI-NRS, Worst Itching Intensity Numerical Rating Scale.

^aRace was participant reported; “Other” category includes American Indian or Alaska native, Asian, Native Hawaiian or Pacific Islander, and other.

^b46 (20.7%) participants were taking gabapentin as a prior medication for any indication.

Serious TEAEs were reported by 45 participants (20.3%) (Table S3), none of which were judged to be related to difelikefalin. The most common system organ class of serious TEAEs was “infections and infestations,” reported in 18 participants (8.1%). The most common serious TEAEs were hyperkalemia (5 participants [2.3%]), and *Clostridium difficile* colitis, sepsis, arteriovenous fistula thrombosis, and syncope (3 participants [1.4%] each).

TEAEs that were considered related to the study drug were reported in 16 participants (7.2%). The most frequently reported TEAEs related to difelikefalin were

Table 2. Treatment-emergent Adverse Events

Patients, n (%)	(N = 222)
Patients with any adverse event	143 (64.4%)
Serious adverse events	45 (20.3%)
Adverse events leading to treatment discontinuation	14 (6.3%)
Number (%) of patients with any reported treatment-related TEAE	16 (7.2%)
Number (%) of patients with any reported treatment-related serious TEAE	0 (0%)
Most frequent adverse events ($\geq 2\%$ of patients)	
Diarrhea	11 (5.0%)
Nausea	10 (4.5%)
Hyperkalemia	9 (4.1%)
Headache	8 (3.6%)
Hypertension	8 (3.6%)
Nasopharyngitis	8 (3.6%)
Dizziness	7 (3.2%)
Abdominal pain	6 (2.7%)
Hypotension	6 (2.7%)
Pneumonia	6 (2.7%)
Somnolence	6 (2.7%)
Abdominal pain upper	5 (2.3%)
Arteriovenous fistula thrombosis	5 (2.3%)
Chest pain	5 (2.3%)
Fall	5 (2.3%)
Urinary tract infection	5 (2.3%)

Note: Serious adverse events are those which: result in death; are life-threatening; require inpatient hospitalization or prolongation of existing hospitalization; result in persistent or significant disability/incapacity; or result in a congenital anomaly/birth defect.

Abbreviation: TEAE, treatment-emergent adverse event.

somnolence (4 participants [1.8%]), hypoesthesia (3 participants [1.4%]), and nausea and dizziness (2 participants [0.9%] each). During the study period, 3 participants (1.4%) died; however, no deaths or serious TEAEs were considered treatment-related. Prespecified TEAEs of special interest were reported by 23 participants (10.4%). The most common TEAEs of special interest, occurring in $\geq 2\%$ of participants, were dizziness (3.2%), somnolence (2.7%), and falls (2.3%) (Table S4). No safety signals in laboratory test results, vital signs, or electrocardiograms were identified.

Effectiveness

A clinically meaningful (≥ 3 -point) reduction in itch intensity was reported by 73.7% of participants, and 59.3% had a ≥ 4 -point improvement with a mean change from baseline at Week 12 of -4.5 points (95% confidence interval [CI], -4.9 to -4.2 ; $P < 0.001$) (Fig 2). Mean Sleep Quality NRS scores decreased (improved) from 6.6 ± 2.2 at baseline to 2.4 ± 2.2 at Week 12, with a mean change from baseline of -4.3 (95% CI, -4.7 to -3.9 ; $P < 0.001$) (Fig 2); 66.0% had a ≥ 3 -point improvement from baseline and 56.7% had a ≥ 4 -point improvement.

During the 1-week run-in period and at baseline, only 2.7% of participants had all Sleep Quality NRS scores equal

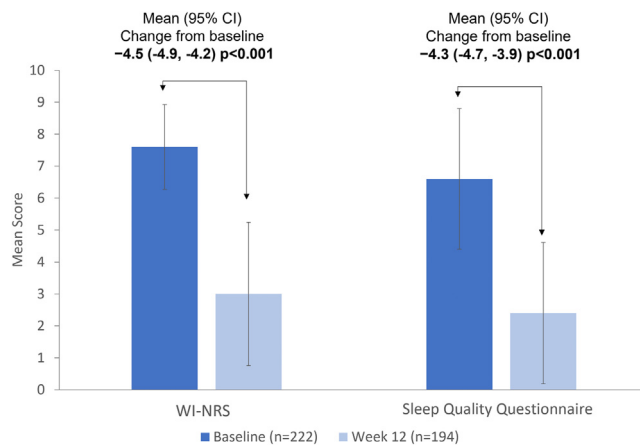


Figure 2. WI-NRS and Sleep Quality NRS scores at baseline and week 12. The Worst Itching Intensity Numerical Rating Scale, an 11-point scale (range 0 to 10; higher scores indicate greater itch intensity), which has been validated in patients with CKD-aP.¹⁷⁻¹⁹ Reduction of ≥ 3 points on the WI-NRS has been shown to be associated with a clinically meaningful change in itch intensity for patients with moderate-to-severe pruritus undergoing HD.¹⁹ Sleep Quality Numerical Rating Scale (NRS) indicates how much itch interfered with sleep over the preceding 24 hours, with responses ranging from 0 (“did not interfere”) to 10 (“completely interfered”). Abbreviations: CI, confidence interval; WI-NRS: Worst Itching Intensity Numerical Rating Scale.

to 0. At Week 12, some participants had achieved complete resolution in WI-NRS and Sleep Quality NRS scores (29.4% for WI-NRS, 19.1% for Sleep Quality NRS score) (Figure 3).

No significant difference in WI-NRS score at Week 12 was observed in participants who were using additional anti-itch medications at baseline (mean change \pm standard deviation [SD] from baseline, -4.3 ± 2.8 ; 95% CI, -5.0 to -3.6) compared with participants without anti-itch medications at baseline (mean change \pm SD from baseline, -4.6 ± 2.4 ; 95% CI, -5.1 to -4.2 ; $P = 0.34$). Similarly, no significant difference in Sleep Quality NRS score at Week 12 was observed in participants who were using additional anti-itch medications at baseline (mean change \pm SD from baseline, -4.2 ± 3.0 ; 95% CI, -5.0 to -3.5) compared with participants without anti-itch medications at baseline (mean change \pm SD from baseline, -4.3 ± 2.7 ; 95% CI, -4.7 to -3.8 ; $P = 0.96$).

The mean change from baseline to Week 12 in 5-D itch scale total score was -7.1 (95% CI, -7.7 to -6.5 ; $P < 0.001$). A clinically meaningful (≥ 5 -point) improvement in 5-D itch total score at Week 12 was achieved by 69.8% of participants. Additionally, improvements were seen in all 5 domains: disability, -1.5 ± 1.3 ; distribution, -1.0 ± 1.1 ; duration, -1.5 ± 1.0 ; degree -1.3 ± 1.1 ; and direction, -1.7 ± 1.1 (Fig 4). The mean change from baseline to Week 12 in Skindex-10 was -21.0 (95% CI, -23.2 to -18.7 ; $P < 0.001$).

A clinically meaningful (≥ 15 -point) improvement in Skindex-10 total score at Week 12 was achieved by 63.0%

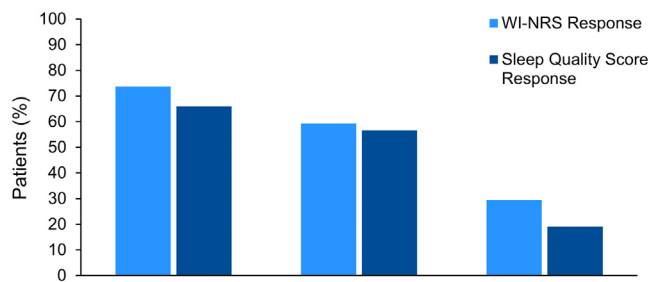


Figure 3. WI-NRS and Sleep Quality NRS response rate at Week 12. Data as observed at Week 12, N = 194. The Worst Itching Intensity Numerical Rating Scale, an 11-point scale (range 0 to 10; higher scores indicate greater itch intensity), which has been validated in patients with CKD-aP.¹⁷⁻¹⁹ Reduction of ≥ 3 points on the WI-NRS has been shown to be associated with a clinically meaningful change in itch intensity for patients with moderate-to-severe pruritus undergoing HD.¹⁹ Sleep Quality Numerical Rating Scale (NRS) indicates how much itch interfered with sleep over the preceding 24 hours, with responses ranging from 0 (“did not interfere”) to 10 (“completely interfered”). *Complete resolution defined as $\geq 75\%$ of weekly mean WI-NRS scores equal to 0 or 1 or all Sleep Quality NRS scores equal to 0. During the run-in period and at baseline, only 2.7% of patients had Sleep Quality NRS scores equal to 0 and scores for WI-NRS were ≥ 5 . Abbreviations: CI, confidence interval; WI-NRS, Worst Itching Intensity Numerical Rating Scale.

of participants. Improvements were also seen in all domains: disease total -7.4 ± 5.2 , mood and emotional distress -6.5 ± 5.6 , and social functioning -6.9 ± 6.8 (Fig 4).

No significant difference in 5-D itch scale total score or Skindex-10 score at Week 12 was observed for participants who were using additional anti-itch medications at baseline (mean \pm SD change from baseline, -6.8 ± 4.7 ; 95% CI, -8.0 to -5.6 for 5-D itch and -21.0 ± 18.0 ; 95% CI, -25.6 to -16.4 for Skindex-10) compared with participants without anti-itch medications at baseline (mean \pm SD change from baseline, -7.2 ± 4.1 ; 95% CI, -7.9 to -6.5 ; $P = 0.49$ for 5-D itch and -21.0 ± 14.4 ; 95% CI, -23.5 to -18.5 ; $P = 0.98$ for Skindex-10).

DISCUSSION

Among maintenance HD patients with moderate-to-severe CKD-aP, difelikefalin was generally well tolerated with an acceptable safety profile and was associated with reduced pruritus over 12 weeks of treatment, with associated improvements in sleep quality. The safety profile of difelikefalin was generally similar to that observed in the double-blind, randomized, placebo-controlled phase 3 KALM-1 clinical study over the same period of exposure.¹⁵ The most common TEAEs of special interest were dizziness, somnolence, and falls (occurring in 3.2%, 2.7%, and 2.3% of patients, respectively). Most TEAEs were mild or moderate; no serious TEAEs or deaths were considered by the investigators to be treatment-related and no safety signals or concerns were observed.

Nearly three-quarters of participants achieved a ≥ 3 -point reduction from baseline in the weekly mean of the daily 24-hour WI-NRS score, a change that has been established as clinically meaningful for this population,¹⁹ and more than half of participants experienced an improvement of ≥ 4 points. Marked improvements in Sleep Quality NRS score were also observed during the 12-week treatment period, suggesting that reducing itch may improve sleep quality. Clinically meaningful improvements were also reported in itch intensity and itch-related QoL by the itch-specific measures Skindex-10 and the 5-D itch scale.^{18,21}

For all 3 domains of the Skindex-10 scale (disease, mood/emotional distress, and social functioning) and all 5 domains of the 5-D itch scale (disability, distribution, duration, degree, and direction), participants treated with difelikefalin achieved an improvement in score at the end of Week 12.

CKD-aP is a potentially debilitating complication among individuals with CKD for which no approved treatment previously existed, although off-label antihistamines and gabapentin or pregabalin are being prescribed for pruritus in people receiving dialysis. Although gabapentin has demonstrated efficacy in several small, randomized controlled trials, with meta-analyses suggesting efficacy without significant evidence of harm, large-scale, randomized controlled trials in this patient population are lacking.^{11,12} Further, as CKD-aP likely occurs through a nonhistaminergic pathway, it is physiologically unlikely that there is any sustained beneficial effect of antihistamines.²² An unmet need in this patient population therefore is a licensed treatment option with proven efficacy and tolerability.

Based on the double-blind placebo-controlled clinical trials that have already demonstrated that difelikefalin is an effective and well-tolerated treatment option, difelikefalin is the first approved treatment for moderate-to-severe pruritus in adults undergoing HD. The population in Study 3105 was very similar to the population in the KALM-1 trial in terms of the itch severity at baseline. Although cross-trial comparisons should be made with caution, the lack of a placebo arm in Study 3105 means that an indirect comparison with KALM-1 may be useful. In KALM-1, approximately 30% of participants in the placebo group reported a response; it is reasonable to expect a similar or slightly higher level of non-difelikefalin-associated response in Study 3105, given the open-label nature of Study 3105. The proportion of participants who achieved a ≥ 3 -point improvement in WI-NRS after 12 weeks of difelikefalin treatment in Study 3105 was numerically higher than in KALM-1 (three-quarters of participants reported clinically significant improvements in itch severity compared with half of participants in KALM-1). Additionally, participants reported a mean improvement of 4.5 on the WI-NRS meaning that, on average, itch severity improved from a category of severe itch to mild itch. Furthermore, it should

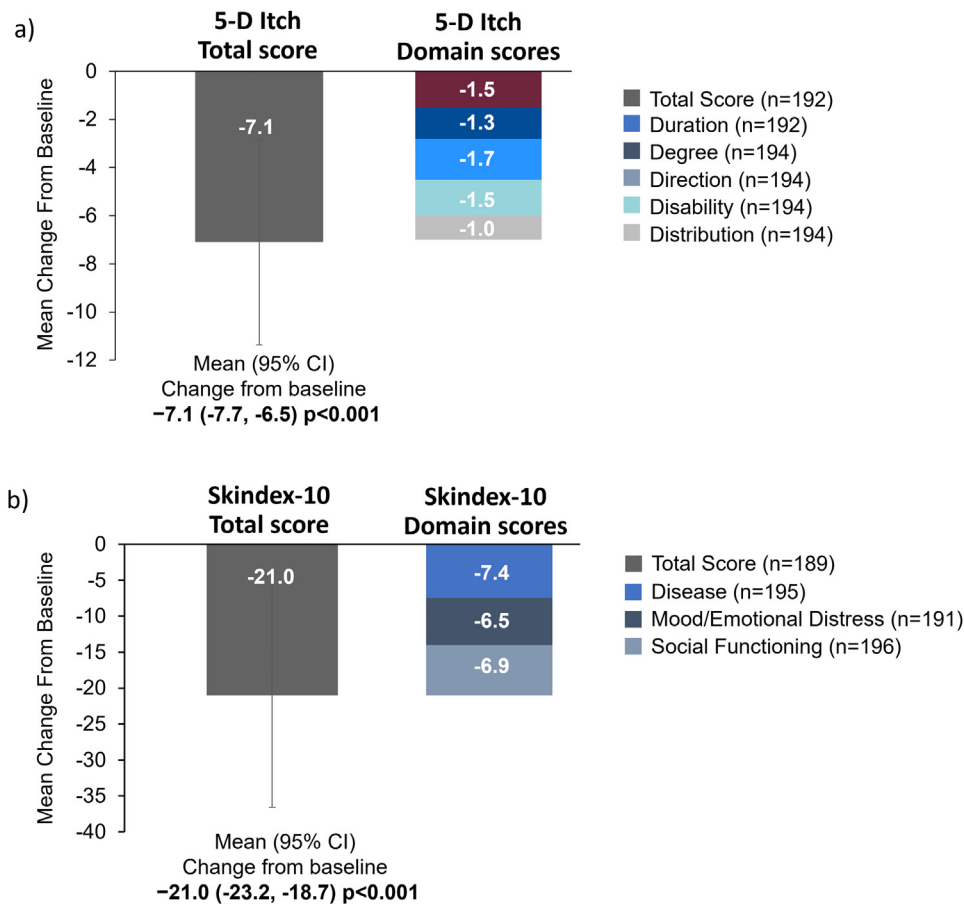


Figure 4. Mean change from baseline in total and domain scores at Week 12 for (A) 5-D itch scale and (B) Skindex-10 scale. Error bar represents standard deviation. (A) The 5D-itch scale, a multidimensional tool that assesses itch-related quality of life and itch intensity across 5 separate itch-related domains (duration, degree, direction, disability, and distribution). The scores for each domain are added separately and then summed together to obtain a total 5-D score. 5-D scores can potentially range between 5 (no pruritus) and 25 (most severe pruritus).²⁰ A clinically meaningful improvement has been reported for a reduction from baseline of ≥ 5 -point in the total 5-D itch score.²¹ (B) Skindex-10 scale: Score: 0 (never bothered) to 6 (always bothered). The total score is the sum of the numeric value of each answered question. The domain scores are the sum of the following: disease domain (questions 1-3); mood/emotional distress domain (questions 4-6); social functioning domain (questions 7-10). A clinically meaningful improvement has been reported for a reduction from baseline of ≥ 15 -points.²¹

be noted that difelikefalin was effective, even though almost a third of participants reported that, at baseline, they were using other agents prescribed to treat pruritus, with participants authorized to continue other prescribed pruritus treatments throughout the course of the study. This open-label clinical trial therefore further shows the level of effectiveness and improvement in QoL that can be reasonably expected in this patient population in a real-world scenario, in which both patients and healthcare professionals are aware of the treatment regimen. In the clinical setting, all treatment effects, including the placebo effect, work in an additive fashion to the active compound effect.

This study has several limitations. The majority of participants enrolled were in the United States (91%), 49% were Black or African American, and all participants were required to have adequate dialysis based on Kt/V or urea reduction ratio measurements; the results may therefore not be generalizable to other populations with different

protocols for dialysis optimization or with differing treatment algorithms for CKD-aP. A minimum clinically meaningful change for the Sleep Quality NRS has not yet been established for this patient population; however, the substantial improvements reported suggest that these changes are likely to be of clinical relevance. Additionally, this was a single-arm, open-label trial design; however, the efficacy observed was consistent with, though greater than, that observed in the KALM-1 trial. Because this was an open-label study, this greater overall improvement, compared with KALM-1, could be because of the additive placebo effect and/or simply the variability between trials. However, the open-label trial design of Study 3105 corresponds more closely to real-world clinical practice, in which the patient is aware they are receiving an active therapy (although the population remains constrained by inclusion/exclusion criteria, which do not apply in a full real-world scenario).

In conclusion, similarly to a previous placebo-controlled trial, difelikefalin was well tolerated and treatment was associated with clinically meaningful improvements in itch intensity and substantial improvements in sleep quality in most patients, with corresponding improvements in itch-related QoL among patients undergoing HD who had CKD-aP. As the first approved treatment for moderate-to-severe pruritus associated with CKD in adults undergoing HD, difelikefalin appears to be a valuable treatment in this patient population, with Study 3105 providing important insights into expected real-world safety and effectiveness.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Item S1: Principal investigators and locations in CR845.

Table S1: Reasons for Screening Failure.

Table S2: Reasons for Discontinuation.

Table S3: Serious Adverse Events Reported in 2 or More Patients.

Table S4: Incidence of TEAEs of Special Interest During the Treatment Period.

ARTICLE INFORMATION

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Financial Disclosure: Dr Weiner is a Medical Director of Clinical Research for Dialysis Clinic, Inc, served on advisory boards for Akebia representing Dialysis Clinic, Inc and Cara Therapeutics (2020) and on the adjudications committee for VALOR Trial (Tricida), and is a Site PI for Ardelyx, AstraZeneca, Cara Therapeutics, CSL Behring, and Goldfinch Bio. Dr Germain is a consultant and investigator for Cara Therapeutics. Drs Menzaghi, Munera, and Wen are employees and shareholders of Cara Therapeutics. Dr Vervloet received research support and

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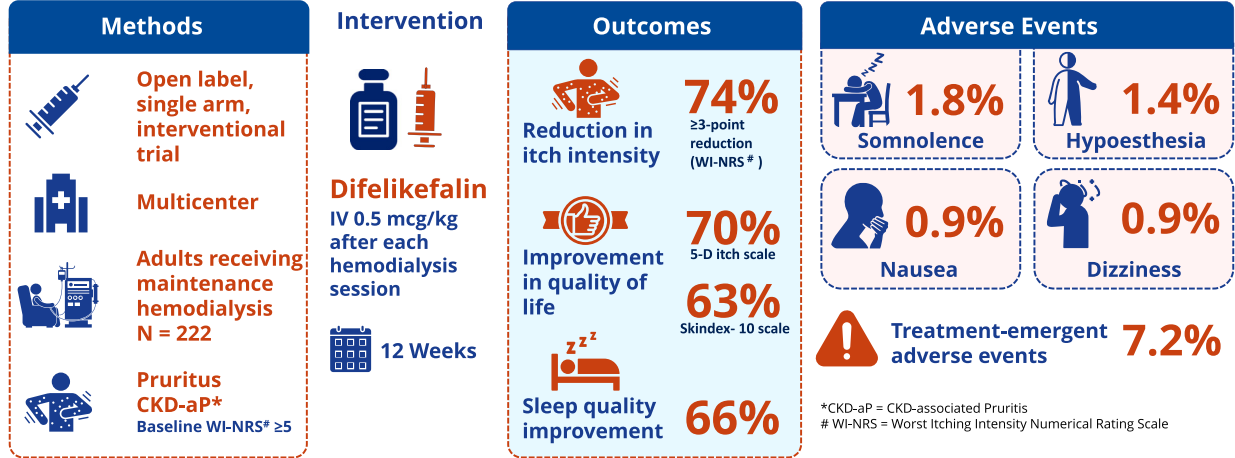
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REFERENCES

1. Pisoni RL, Wikström B, Elder SJ, et al. Pruritus in haemodialysis patients: international results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant*. 2006;21(12):3495-3505.
2. Shirazian S, Aina O, Park Y, et al. Chronic kidney disease-associated pruritus: impact on quality of life and current management challenges. *Int J Nephrol Renovasc Dis*. 2017;10:11-26.
3. Sukul N, Karaboyas A, Csomor PA, et al. Self-reported pruritus and clinical, dialysis-related, and patient-reported outcomes in hemodialysis patients. *Kidney Med*. 2021;3(1):42-53.e1.
4. Weiss M, Mettang T, Tschulena U, Weisshaar E. Health-related quality of life in haemodialysis patients suffering from chronic itch: results from GEHIS (German Epidemiology Haemodialysis Itch Study). *Qual Life Res*. 2016;25(12):3097-3106.
5. Plewig N, Ofenloch R, Mettang T, Weisshaar E. The course of chronic itch in hemodialysis patients: results of a 4-year follow-up study of GEHIS (German Epidemiological Hemodialysis Itch Study). *J Eur Acad Dermatol Venereol*. 2019;33(7):1429-1435.
6. Rayner HC, Larkina M, Wang M, et al. International comparisons of prevalence, awareness, and treatment of pruritus in people on hemodialysis. *Clin J Am Soc Nephrol*. 2017;12(12):2000-2007.
7. Simonsen E, Komenda P, Lerner B, et al. Treatment of uremic pruritus: A systematic review. *Am J Kidney Dis*. 2017;70(5):638-655.
8. Lau T, Leung S, Lau W. Gabapentin for uremic pruritus in hemodialysis patients: a qualitative systematic review. *Can J Kidney Health Dis*. 2016;3:14.
9. Nofal E, Farag F, Nofal A, Eldesouky F, Alkot R, Abdelkhalik Z. Gabapentin: A promising therapy for uremic pruritus in hemodialysis patients: A randomized-controlled trial and review of literature. *J Dermatolog Treat*. 2016;27(6):515-519.
10. Yue J, Jiao S, Xiao Y, Ren W, Zhao T, Meng J. Comparison of pregabalin with ondansetron in treatment of uraemic pruritus in dialysis patients: a prospective, randomized, double-blind study. *Int Urol Nephrol*. 2015;47(1):161-167.
11. Hercz D, Jiang SH, Webster AC. Interventions for itch in people with advanced chronic kidney disease. *Cochrane Database Syst Rev*. 2020;12:CD011393.
12. Eusebio-Alpapara KMV, Castillo RL, Dofitas BL. Gabapentin for uremic pruritus: a systematic review of randomized controlled trials. *Int J Dermatol*. 2020;59(4):412-422.
13. Gardell LR, Spencer RH, Chalmers DT, Menzaghi F. Preclinical profile of CR845: a novel, long-acting peripheral kappa opioid

- receptor agonist. Poster presented at: 12th World Congress on Pain; Glasgow, Scotland; August 17-22, 2008.
14. Menzaghi F, Spencer R, Abrouk N, Lewis M, Chalmers D. (422) CR845, a peripheral kappa opioid, provides better pain relief with less nausea and vomiting than placebo in patients after bunionectomy. *J Pain*. 2015;16(4):S81.
 15. Fishbane S, Jamal A, Munera C, Wen W, Menzaghi F, KALM-1 Trial Investigators. A phase 3 trial of difelikefalin in hemodialysis patients with pruritus. *N Engl J Med*. 2020;382(3):222-232.
 16. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194.
 17. Mathur VS, Lindberg J, Germain M, et al. A longitudinal study of uremic pruritus in hemodialysis patients. *Clin J Am Soc Nephrol*. 2010;5(8):1410-1419.
 18. Phan NQ, Blome C, Fritz F, et al. Assessment of pruritus intensity: prospective study on validity and reliability of the visual analogue scale, numerical rating scale and verbal rating scale in 471 patients with chronic pruritus. *Acta Derm Venereol*. 2012;92(5):502-507.
 19. Vernon M, Ständer S, Munera C, Spencer RH, Menzaghi F. Clinically meaningful change in itch intensity scores: an evaluation in patients with chronic kidney disease-associated pruritus. *J Am Acad Dermatol*. 2021;84(4):1132-1134.
 20. Elman S, Hynan LS, Gabriel V, Mayo MJ. The 5-D itch scale: a new measure of pruritus. *Br J Dermatol*. 2010;162(3):587-593.
 21. Fishbane S, Mathur V, Germain MJ, et al. Randomized controlled trial of difelikefalin for chronic pruritus in hemodialysis patients. *Kidney Int Rep*. 2020;5(5):600-610.
 22. Papoiu AD, Emerson NM, Patel TS, et al. Voxel-based morphometry and arterial spin labeling fMRI reveal neuropathic and neuroplastic features of brain processing of itch in end-stage renal disease. *J Neurophysiol*. 2014;112(7):1729-1738.

How Safe and Effective is Difelikefalin in Patients With Moderate-to-Severe Pruritus Undergoing Hemodialysis?



Conclusion: Difelikefalin was well tolerated and resulted in clinically meaningful improvements in itch intensity and itch-related QoL measures as well as improvements in sleep quality among individuals receiving hemodialysis who had moderate-to-severe CKD-aP, providing important insights into expected real-world effectiveness.

Reference: Weiner DE, Vervloet MG, Walpen S et al. Safety and effectiveness of difelikefalin in patients with moderate-to-severe pruritus undergoing hemodialysis: an open-label, multicenter study. *Kidney Medicine*, 2022.

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*CKD-aP = CKD-associated Pruritus
 # WI-NRS = Worst Itching Intensity Numerical Rating Scale