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ORIGINAL RESEARCH ARTICLE

Impact of Difelikefalin on the Health-Related Quality of Life of Haemodialysis Patients with Moderate-To-Severe Chronic Kidney Disease-Associated Pruritus: A Single-Arm Intervention Trial

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Abstract

Objective Chronic kidney disease-associated pruritus (CKD-aP) can have a substantial negative impact on health-related quality of life (HRQoL), including an increased risk of depression, anxiety and sleep disturbance. This trial aimed to assess the impact of intravenous difelikefalin on HRQoL in haemodialysis patients with moderate-to-severe CKD-aP.

Methods Post hoc analysis of an open-label, multicentre, single-arm intervention trial assessed pruritus severity and HRQoL at baseline and at 12 weeks of difelikefalin treatment using Worst Itching Intensity Numerical Rating Scale (WI–NRS), Sleep Quality Numeric Rating Scale (SQ–NRS), 5-D itch scale, Skindex-10 scale, EQ-5D-5L with Pruritus Bolt-On (EQ-PSO).

Results A total of 222 patients received ≥ 1 dose of difelikefalin, and 197 patients completed 12 weeks of difelikefalin treatment. Clinically meaningful changes from baseline to 12 weeks were observed in all disease-specific measures: 73.7% of patients achieved a ≥ 3-point reduction in the weekly mean of 24 h WI–NRS scores and 66% of patients experienced ≥ 3-point improvements in SQ–NRS scores. Improvements were also observed in all Skindex-10 scale and 5-D itch scale domain scores. The percentage of patients reporting no problems in all EQ-PSO domains increased from 1.4 to 24.7% ($p < 0.001$), respectively. Patients' generic HRQoL EQ-5D-5L mean utility and EQ-5D visual analogue scale scores increased from baseline to 12 weeks: mean changes 0.04 ($p = 0.001$) and 2.8 ($p = 0.046$), respectively.

Conclusions Patients undergoing haemodialysis with moderate-to-severe CKD-aP receiving difelikefalin reported experiencing clinically meaningful improvements in both their pruritus symptoms and itch-related QoL.
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1 Introduction

Chronic kidney disease-associated pruritus (CKD-aP) is a distressing condition experienced by patients with advanced chronic kidney disease, particularly those receiving haemodialysis [1–3], and is associated with an increased risk of infection, hospitalisations and mortality [4–6]. CKD-aP has also been associated with depression, anxiety, sleep disturbance and reduced health-related quality of life (HRQoL) [7]. Until recently, there were no approved therapies for CKD-aP. Off-label treatments for pruritus, such as oral antihistamines followed by gabapentin/pregabalin, which are prescribed for pruritus [8], have limited clinical evidence to support their long-term use in treating CKD-aP, and gabapentin cannot be used at full doses in patients with kidney failure [2, 8].

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Key Points for Decision Makers

Itching can negatively impact the health-related quality of life of haemodialysis patients with chronic kidney disease.

Difelikefalin may improve both pruritus symptoms and itch-related quality of life of haemodialysis patients with moderate-to-severe pruritus associated with chronic kidney disease.

Difelikefalin is a peripheral kappa-opioid receptor agonist that acts primarily on peripheral neurons and cells of the immune system [9, 10]. It was approved by the US Food and Drug Administration (FDA) in August 2021 and by the European Medicines Agency (EMA) in April 2022 for the treatment of moderate-to-severe CKD-aP in adults undergoing haemodialysis [11]. In two double-blind, placebo-controlled, phase 3 clinical trials (KALM-1 and KALM-2) involving individuals with moderate-to-severe pruritus undergoing haemodialysis three times weekly, intravenous (IV) difelikefalin was found to generate a significantly greater reduction in pruritus intensity and improvement in pruritus-related quality of life, compared with placebo, and was also reported as having an acceptable safety profile [12–15]. Generic HRQoL information was not collected in these trials, meaning the impact of improvements in CKD-aP severity with difelikefalin treatment on generic HRQoL has not previously been assessed; however, it should be noted that the EQ-5D instrument has not been proven in patients with CKD-aP.

In an open-label, multicentre, single-arm intervention trial (ClinicalTrials.gov identifier: NCT03998163), the safety, effectiveness and HRQoL impact of IV difelikefalin were studied in a population of haemodialysis patients with moderate-to-severe CKD-aP [16]. The primary outcome of this study was a characterisation of difelikefalin's safety profile. The most common treatment-emergent adverse events related to difelikefalin, which have been published previously, were somnolence (1.8% of patients), hypoaesthesia (1.4%), nausea (0.9%) and dizziness (0.9%). No deaths or serious treatment-emergent adverse events were considered treatment related [17]. The secondary outcomes of the study included an evaluation of the effectiveness of difelikefalin in (1) reducing pruritus intensity and (2) improving pruritus-related quality of life and quality-of-sleep measures in patients with CKD who were undergoing haemodialysis and experiencing moderate-to-severe pruritus. The aim of this article is to report the post hoc analysis of pruritus-related and generic HRQoL findings from this open-label study.

2 Methods

2.1 Study Design

This was an open-label, multicentre, Phase 3 trial (NCT03998163, May 7 2019) conducted at 31 facilities in the USA and 12 facilities in Europe, enrolling maintenance haemodialysis patients with moderate-to-severe CKD-aP, defined as mean weekly Worst Itching Intensity Numerical Rating Scale (WI–NRS) score ≥ 5 points [18].

2.2 Study Population

Individuals (aged 18–85 years) with kidney failure who had been receiving haemodialysis three times weekly for at least 3 months prior to screening were included in the study. To ensure inadequate dialysis was not responsible for the pruritus, participants had to have at least two single-pool *Kt*/*V* measurements of at least 1.2, or at least two urea reduction ratio measurements ≥ 65% over the 3-month period prior to screening in order to be eligible to participate in the study [19]. A more detailed description of the population, including exclusion and inclusion criteria has been reported elsewhere [17].

Key exclusion criteria were scheduled kidney transplant, current treatment with ultraviolet B phototherapy, and significant systolic or diastolic heart failure (e.g. New York Heart Association Class IV). Additionally, individuals were ineligible if they had pruritus attributed to a cause other than kidney failure or its complications; had been prescribed new treatments or treatment changes for pruritus, including antihistamines and corticosteroids, within 14 days prior to screening; had new prescriptions or a change in prescription for opioids, gabapentin, or pregabalin within 14 days prior to screening; or had a known history of allergic reactions to opiates (not including side effects from opiates such as nausea and constipation).

2.3 Study Protocol

The study comprised a screening period, a treatment period of 12 weeks, and a follow-up visit 7–10 days after the end of treatment or early termination visit. The screening period to assess eligibility included a screening visit and run-in period (within 28 days prior to the start of treatment), which enabled measurement of baseline pruritus intensity via the WI–NRS to confirm that individuals entering the study had moderate-to-severe pruritus, defined as mean weekly WI-NRS score ≥ 5 points [18]. Baseline use of medications

Table 1 Questionnaires used to assess HRQoL

Questionnaire	Description, clinically meaningful difference, study endpoint
WI–NRS	Single-item instrument assessing patient-reported intensity of pruritus at its worst during the previous 24 h period, scored 0 to 10 with higher scores indicating greater pruritus intensity [18] Recommended for assessment of pruritis in clinical trials and validated in patients with CKD [7, 22, 41, 42] Clinically meaningful change: ≥ 3 points moderate-to-severe pruritus undergoing haemodialysis [13, 43] Study endpoint: proportion of individuals achieving a clinically meaningful ≥ 3-point and ≥ 4-point improvement from baseline to week 12
Sleep Quality NRS	Single-item instrument assessing patient-reported impact of pruritus to interfere with sleep during the previous 24 h period, scored 0 ('did not interfere') to 10 ('completely interfered') [20] A similar 11-point NRS for sleep disruption has been used in atopic dermatitis and recently validated in prurigo nodularis, with a 2- to 4-point decrease identified as a meaningful within-patient change for this instrument [44, 45] Study endpoint: changes between baseline and week 12 in the Sleep Quality NRS score and the proportion of patients achieving a ≥ 3-point and ≥ 4-point improvement from baseline to Week 12
Skindex-10 Scale	Impact of CKD-aP across three separate pruritus-related domains: disease, mood/emotional distress and social functioning assessed with 10 questions, scored 0 ('never bothered') to 6 ('always bothered') for each of the 10 questions with a 1 week recall period [22] The Skindex-10 scale total scores range from 0 to 60, with higher scores indicating a worse pruritus-related quality of life Study clinically meaningful change: a ≥ 15-point reduction (improvement) from baseline [22]
5-D itch scale	Multidimensional tool to assess pruritus-related quality of life and pruritus intensity across five separate pruritus-related domains (duration, degree, direction, disability and distribution) over a 2 week recall period [21] Scores range from 5 to 25, with higher scores indicating worse pruritus intensity and pruritus-related quality of life Clinically meaningful improvement: reduction from baseline of ≥ 5-points in the total 5-D itch score [21]
EQ-5D-5L EQ-5D VAS EQ-PSO	Well-established and widely-used generic instrument for assessing HRQoL informed by five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each with five levels [23] Records the subject's self-rated health on a vertical visual analogue scale, with values ranging from 'The best health you can imagine' to 'The worst health you can imagine', each with five levels [23] EQ-5D-5L with psoriasis-specific 'bolt-on', comprising of two additional dimensions 'skin irritation' and 'self-confidence' to better capture pruritus-associated burdens [24]

CKD-aP chronic kidney disease-associated pruritus, *HRQoL* health-related quality of life, *NRS* Numerical Rating Scale, *VAS* visual analogue scale, *WI–NRS* Worst Itching Intensity Numerical Rating Scale

aimed at managing pruritus, and baseline characteristics of the disease were also recorded.

Patients who continued to meet all the inclusion and no exclusion criteria at the end of the run-in period started the treatment period, which began with IV difelikefalin 0.5 mcg/kg. Day 1 of the treatment period was defined as the day of administration of the first dose of study drug and occurred on the first haemodialysis day of the first treatment week. All scheduled study visits during the treatment period were conducted on dialysis days. Difelikefalin was administered to patients as an IV bolus after the end of their haemodialysis, either during or after wash back, over a treatment period of up to 12 weeks, so that each patient received difelikefalin three times weekly for a total of up to 36 doses.

End of treatment or early termination was defined as the first dialysis day following the last dose of study drug. Patients had a final safety follow-up visit 7–10 days after the early termination or end of treatment visit.

Patients completed the questionnaires at various time points throughout the study. The WI–NRS [18] and Sleep Quality Numerical Rating Scale (NRS) [20] questionnaires were completed at the start of each dialysis session during run-in and at the first dialysis visit at week 1 before the first dose of difelikefalin,, in week 12, and at the end of treatment visit after the last dose of difelikefalin (within 1 h of starting haemodialysis). The 5-D itch scale [21] and Skindex-10 Scale [22] were completed at the first dialysis session before the first dose of difelikefalin (week 1) and on the first dialysis visit after the last dose of difelikefalin. The EQ-5D-5L [23] with the Pruritus Bolt-On (EQ-PSO) questionnaire [24] was completed at the third dialysis session of the run-in period and at the start of the third dialysis visit of week 12. All questionnaires were completed at early termination. Further details of the questionnaires can be found in Table 1.

2.4 Data and Statistical Analyses

The proportion of patients reporting a 'complete resolution' for pruritus intensity or for sleep quality, defined as ≥ 75% of weekly mean WI–NRS scores equal to 0 or 1, or all Sleep Quality NRS scores equal to 0, was calculated. Changes between baseline and week 12 in pruritus-related quality of life were also evaluated using the 5-D itch scale, the Skindex-10 Scale and EQ-PSO, and in generic quality of life were evaluated using EQ-5D-5L, utilities derived from the EuroQOL EQ-5D-5L to 3L US cross-walk value set, and EQ-5D visual analogue scale (VAS).

Baseline WI-NRS and Sleep Quality NRS scores were calculated as the weekly mean of the 24 h scores collected at each dialysis session during the run-in period, including assessments collected on day 1 prior to the first dose. The week 12 WI–NRS and Sleep Quality NRS scores were defined as the weekly mean of the sum of the 24 h 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 non-missing scores over the same time period. If a patient was missing more than two WI–NRS scores during the collection period at weeks 12 and 13, 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 mean of the 24 h scores if collected from day 76 to day 86, inclusive. Missing data were not imputed.

A post hoc analysis was performed. The *p* values for the change from baseline to week 12 were computed based on the paired sample *t* test for continuous endpoints and based on the McNemar's test for dichotomous endpoints (with and without problems). All *p* values are exploratory and should be interpreted descriptively.

3 Results

3.1 Patient Characteristics

A total of 286 individuals were enrolled into the study, of whom 72 failed initial screening [17]. Of the 72 who failed, 54 did not fulfil the inclusion/exclusion criteria, 4 participants withdrew and 14 failed screening due to other reasons (8 of the 72 were rescreened and ultimately received treatment). Overall, 222 patients received at least one dose of IV difelikefalin, with 197 patients (88.7%) completing 12 weeks of study treatment and 25 patients (11.3%) discontinuing. The most common (≥ 2% of all patients) reasons for early discontinuation from study treatment were adverse events (5.9%) and subject withdrawal of consent (3.2%)[17].

The median duration of difelikefalin treatment was 85 days. The mean (± standard deviation [SD]) age of treated patients was 58.1 ± 12.8 years and 54.5% were male. The mean (± SD) time since diagnosis of end-stage renal disease was 5.9 ± 4.7 years, with a mean duration of chronic haemodialysis and pruritus of 5.4 ± 4.4 and 3.9 ± 3.3 years, respectively [17]. A summary of the patients' characteristics, which have been previously described in the manuscript reporting the primary endpoint of the study [17], can be found in the supplementary appendix.

3.2 3.2 Worst Itching Intensity Numerical Rating Scale

There was a statistically significant improvement in pruritus intensity from baseline to the end of week 12 of the treatment period, in terms of the weekly mean of the 24 h WI–NRS score, of − 4.5 [95% confidence interval (CI) − 4.9, − 4.2]; $p < 0.001$ (Table 2). A total of 73.7% of patients reported a ≥ 3-point improvement, and 59.3% reported a ≥ 4-point improvement from baseline in the weekly mean of the 24 h WI–NRS scores at week 12 (Fig. 1). At week 12, 36.1% of patients reported a weekly mean of the 24 h WI–NRS scores equal to 0 or 1. A total of 29.4% of patients achieved complete resolution in WI–NRS scores at week 12.

3.3 3.3 Sleep Quality Numerical Rating Scale

There was a statistically significant improvement in sleep quality from baseline to the end of week 12 of the treatment period, as assessed by the Sleep Quality NRS, of − 4.3 (95% CI − 4.6, − 3.9); $p < 0.001$ (Table 2). A total of 66.0% of patients reported a ≥ 3-point improvement, and 56.7% reported a ≥ 4-point improvement from baseline to week 12 with respect to Sleep Quality NRS scores (Fig. 2). A total of 19.1% of patients achieved complete resolution in Sleep Quality NRS scores at week 12.

3.4 5-D Itch Scale

There was a statistically significant reduction in the mean overall score on the 5-D itch scale (− 7.1, 95% CI − 7.7, − 6.5; $p < 0.001$) from baseline to the end of week 12 of the treatment period (Table 2). Patients showed a statistically significant reduction in the mean 5-D itch scale scores from baseline to week 12 in all five domains: these included disability − 1.5 (95% CI − 1.7, − 1.3; $p < 0.001$), indicating patients experienced an improvement in sleep and more social activities; distribution − 1.0 (95% CI − 1.2, − 0.9; $p < 0.001$), implying that the areas of skin affected by pruritus had been significantly reduced after treatment; duration − 1.5 (95% CI − 1.7, − 1.3; $p < 0.001$), indicating that patients transitioned from being bothered by pruritus for up to 18 h per day to a maximum of 6–12 h per day; degree − 1.3 (95% CI − 1.4, − 1.1; $p < 0.001$), implying a significant trend from moderate/severe to mild pruritus; and direction − 1.7 (95% CI − 1.9, − 1.6; $p < 0.001$), indicating a significant improvement in pruritus when compared with baseline (Table 2).

3.5 Skindex-10 Scale

There was a statistically significant improvement in pruritus-related quality of life from baseline to the end of week 12 of

Table 2 HRQoL outcomes at baseline and week 12 (safety population, $N = 222$)

HRQoL instrument	Sample size at baseline	Mean (95% CI) at baseline	Sample size at week 12	Mean (95% CI) at week 12	Sample size for the mean change	Mean change from baseline (95% CI)	*p* value
WI-NRS	222	7.6 (7.4, 7.7)	194	3.0 (2.7, 3.3)	194	− 4.5 (− 4.9, − 4.2)	< 0.001
Sleep Quality NRS	222	6.6 (6.3, 6.9)	194	2.4 (2.1, 2.7)	194	− 4.3 (− 4.6, − 3.9)	< 0.001
5-D itch scale	218	17.1 (16.6, 17.5)	195	10.1 (9.6, 10.5)	192	− 7.1 (− 7.7, − 6.5)	< 0.001
Domain: disability	219	3.7 (3.5, 3.8)	197	2.2 (2.0, 2.3)	194	− 1.5 (− 1.7, − 1.3)	< 0.001
Domain: distribution	219	3.2 (3.1, 3.4)	197	2.1 (2.0, 2.3)	194	− 1.0 (− 1.2, − 0.9)	< 0.001
Domain: duration	219	2.8 (2.7, 3.0)	195	1.3 (1.2, 1.5)	192	− 1.5 (− 1.7, − 1.3)	< 0.001
Domain: degree	219	3.5 (3.4, 3.6)	197	2.2 (2.1, 2.3)	194	− 1.3 (− 1.4, − 1.1)	< 0.001
Domain: direction	218	3.9 (3.8, 4.0)	197	2.2 (2.0, 2.3)	194	− 1.7 (− 1.9, − 1.6)	< 0.001
Skindex-10 Scale	216	32.9 (31.0, 34.8)	195	12.3 (10.5, 14.1)	189	− 21.0 (− 23.2, − 18.7)	< 0.001
Domain: disease total	220	12.7 (12.2, 13.3)	197	5.5 (4.8, 6.1)	195	− 7.4 (− 8.1, − 6.7)	< 0.001
Domain: mood/emotional distress total	218	10.5 (9.9, 11.2)	195	4.0 (3.4, 4.7)	191	− 6.5 (− 7.3, − 5.8)	< 0.001
Domain: social functioning total	221	9.8 (8.8, 10.8)	197	2.9 (2.2, 3.6)	196	− 6.9 (− 7.9, − 6.0)	< 0.001
Utility derived from EQ-5D-5L	218	0.71 (0.68, 0.74)	189	0.76 (0.73, 0.79)	185	0.04 (0.02, 0.07)	0.001
EQ-5D VAS values	219	68.4 (65.9, 70.9)	190	70.7 (67.7, 73.6)	187	2.8 (0.0, 5.5)	0.046

p values based on paired sample *t* test

CI confidence interval, *HRQoL* health-related quality of life, *NRS* Numerical Rating Scale, *VAS* visual analogue scale, *WI–NRS* Worst Itching Intensity Numerical Rating Scale

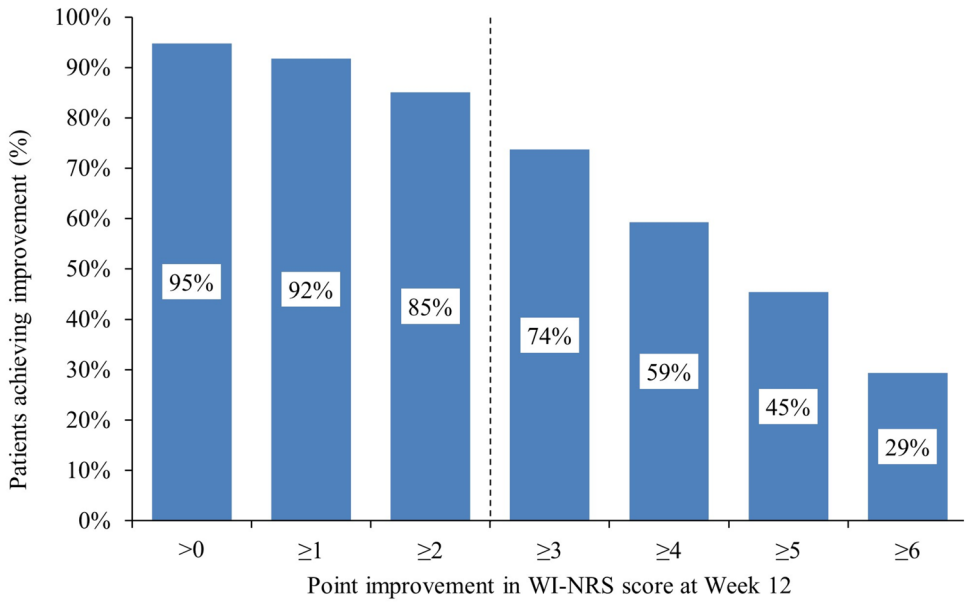

Fig. 1 Percentage of patients achieving a > 0-, ≥ 1-, ≥ 2-, ≥ 3-, ≥ 4-, ≥ 5- and ≥ 6-point improvement in WI-NRS score at Week 12 (safety population; $N = 222$). The baseline score was the average of the individual scores collected over the run-in period, including Day 1 prior to the first dose. The Week 12 score was average of the scores collected during Week 12 and on the first visit of Week 13. Out of 222 patients in the safety population, only 194 had available change from baseline to Week 12 data. Number of subjects with non-missing data at baseline and Week 12 are presented. A reduction of ≥ 3 points on the WI-NRS scale is considered clinically meaningful. *WI-NRS* Worst Itching Intensity Numerical Rating Scale

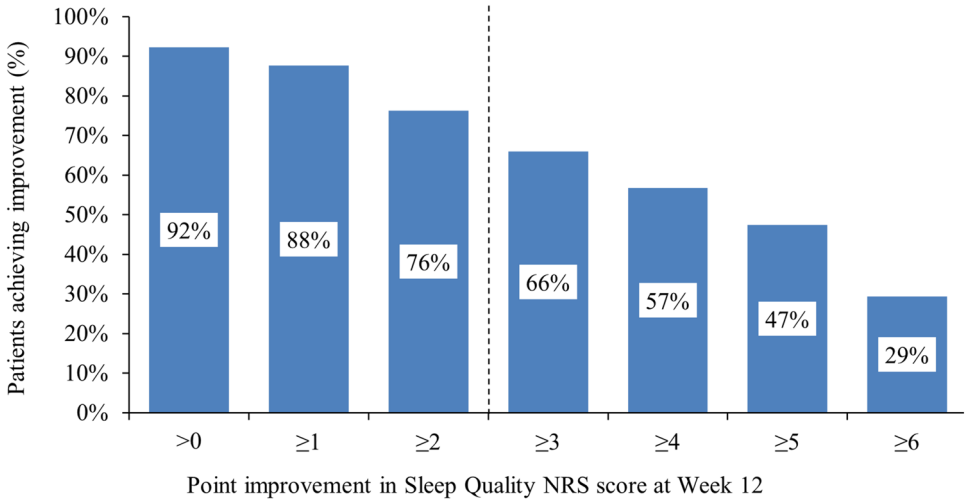

Fig. 2 Percentage of patients achieving a > 0-, ≥ 1-, ≥ 2-, ≥ 3-, ≥ 4-, ≥ 5- and ≥ 6-point improvement in Sleep Quality NRS score at Week 12 (safety population; $N = 222$). The baseline score was the average of the individual scores collected over the run-in period, including Day 1 prior to the first dose. The Week 12 score was average of the scores collected during Week 12 and on the first visit of Week 13. Out of 222 patients in the safety population, only 194 had available change from baseline to Week 12 data. Number of subjects with non-missing data at baseline and Week 12 are presented

the treatment period, as assessed by the Skindex-10 Scale (mean change: − 21.0, 95% CI − 23.2, − 18.7; $p < 0.001$) (Table 2). Patients showed a statistically significant reduction in the mean scores from baseline to week 12 across all three domains, which included: disease total − 7.4 (95% CI − 8.1, − 6.7; $p < 0.001$); mood and emotional distress − 6.5 (95% CI − 7.3, − 5.8; $p < 0.001$); and social functioning − 6.9 (95% CI − 7.9, − 6.0; $p < 0.001$).

3.6 3.6 EQ-5D-5L

Overall, there was a statistically significant increase in the percentage of all patients who reported no problems in all five domains of the EQ-5D-5L over the treatment period (from 16.9% at baseline to 22.6% at week 12—a relative increase of 34%; $p = 0.041$ for the percentage of patients with and without problems at baseline and week 12). The percentage of patients who reported no problems in the pain and discomfort domain of the EQ-5D-5L descriptive dimensions significantly increased from 25.1% at baseline to 32.1% at week 12 ($p = 0.028$ for the percentage of patients with and without problems at baseline and week 12). However, self-care, usual activities, anxiety and depression and mobility did not significantly alter (Table 3). The percentage of patients with a ≥ 1-level improvement between baseline and week 12 in the EQ-5D-5L domains were 19.9% ($n = 37$) for mobility, 12.8% ($n = 24$) for self-care, 18.3% ($n = 34$) for usual activities, 33.2% ($n = 62$) for pain and discomfort, and 19.8% ($n = 37$) for anxiety and depression.

There was a significant increase in patients' preference-weighted HRQoL from an EQ-5D-5L mean utility score of 0.71 at baseline to 0.76 at week 12 (a change of 0.04 based on patients with data at both timepoints; $p = 0.001$) (Table 2). Additionally, there was a significant increase in their self-rated health from a mean score of 68.4 at baseline to 70.7 at week 12, based on their completion of the EQ-5D VAS (a mean change of 2.8 based on patients with data at both timepoints; $p = 0.046$) (Table 2).

The percentage of patients who reported no problems in both skin irritation and self-confidence domains of the EQ-PSO improved from 1.4% at baseline to 24.7% ($p < 0.001$ for the percentage of patients with and without problems at baseline and week 12) at 12 weeks. This was informed by improvements in individual domains of skin irritation, which increased from 1.4% at baseline to 28.9% at week 12 ($p < 0.001$), and self-confidence, which increased from 63.5% at baseline to 73.2% at week 12 ($p = 0.004$ for the percentage of patients with and without problems at baseline and week 12) (Table 3). The percentage of patients with a ≥ 1-level improvement between baseline and week 12 in the EQ-PSO skin irritation and self-confidence domains were 78.1% ($n = 146$) and 21.9% ($n = 41$), respectively.

4 Discussion

CKD-aP is a potentially debilitating complication affecting individuals with CKD, for which no approved treatment existed prior to the approval of difelikefalin. When pruritus is severe and unrelenting, despite treatment, sleep and social functioning can be affected [25, 26], and if left untreated these patients can develop stress reactions, anxiety

Table 3 EQ-PSO outcomes, stratified by domain (safety population, $N = 222$)

EQ-PSO domain	Percentage of subjects at baseline	Percentage of subjects at week 12
Mobility problems	$n = 219$	$n = 189$
None	43.4%	44.4%
Slight	19.2%	25.4%
Moderate	20.1%	16.9%
Severe	8.2%	7.9%
Extreme	9.1%	5.3%
Patients without problems with mobility[a]	43.4%	44.4%
Patients with problems with mobility[a]	56.6%	55.6%

Self-care problems	$n = 219$	$n = 190$
None	66.70%	69.5%
Slight	16.90%	15.3%
Moderate	10.50%	10.5%
Severe	4.60%	3.7%
Extreme	1.40%	1.1%
Patients without problems with self-care[a]	66.70%	69.5%
Patients with problems with self-care[a]	33.30%	30.5%

Usual activities problems	$n = 218$	$n = 190$
None	45.40%	50.0%
Slight	24.30%	24.2%
Moderate	21.10%	17.4%
Severe	5.00%	4.7%
Extreme	4.10%	3.7%
Patients without problems with usual activities[a]	45.40%	50.0%
Patients with problems with usual activities[a]	54.60%	50.0%

Pain/discomfort	$n = 219$	$n = 190$
None	25.1%	32.1%
Slight	32.0%	30.5%
Moderate	25.6%	27.4%
Severe	11.0%	5.3%
Extreme	6.4%	4.7%
Patients without problems with pain/discomfort[a]	25.1%	32.1%
Patients with problems with pain/discomfort[a]	74.9%	67.9%

Anxiety/depression	$n = 219$	$n = 190$
None	61.2%	63.7%
Slight	18.3%	21.1%
Moderate	13.2%	10.0%
Severe	4.6%	3.2%
Extreme	2.7%	2.1%
Patients without problems with anxiety/depression[a]	61.2%	63.7%
Patients with problems with anxiety/depression[a]	38.8%	36.3%

Skin irritation	$n = 219$	$n = 190$
None	1.4%	28.9%
Slight	7.8%	40.5%
Moderate	38.4%	22.6%

Table 3 (continued)

EQ-PSO domain	Percentage of subjects at baseline	Percentage of subjects at week 12
Severe	38.8%	6.3%
Extreme	13.7%	1.6%
Patients without problems with skin irritation[a]	1.4%	28.9%
Patients with problems with skin irritation[a]	98.6%	71.1%

Self-confidence	$n = 219$	$n = 190$
None	63.5%	73.2%
Slight	24.2%	17.9%
Moderate	8.2%	5.8%
Severe	3.7%	2.6%
Extreme	0.5%	0.5%
Patients without problems with self-confidence[a]	63.5%	73.2%
Patients with problems with self-confidence[a]	36.5%	26.8%

Counts and percentages were based on non-missing data for that visit and dimension

[a]'With problems' includes patients with a slight to extreme problem; 'without problems' includes patients with no problems

and depression [7]. Difelikefalin is the first approved treatment for moderate-to-severe pruritus in adults undergoing haemodialysis [11]. The KALM-1 and KALM-2 trials have already shown that difelikefalin is an effective and well-tolerated treatment option [12–15], with demonstrated efficacy regardless of baseline itch severity and in patients with severe pruritus [27, 28]. Here, we report the potential real-world impact of difelikefalin on HRQoL. Over 12 weeks, statistically significant improvements in the 5-D itch, Skindex-10 and Sleep Quality NRS were observed. While the EQ-5D-5L utility value, recognised as insensitive in skin conditions [24], improved significantly, it is unclear whether these changes are clinically meaningful.

This study recruited patients with similar HRQoL, based on EQ-5D scores reported in other dialysis studies [29] and similar to the conditions of atopic dermatitis, psoriasis and connective tissue diseases reported in studies performed across 13 European countries [30], but worse than those with similar age and sex in the general population [31]. Patients and healthcare professionals have prioritised other measures of HRQoL in people on dialysis [32], and other randomised controlled trials (RCTs) have shown the relative insensitivity of the EQ-5D instrument in this patient group [33]. A recent systematic review of the impact of CKD-aP on HRQoL reported that RCTs that showed improvements in CKD-aP severity were associated with clinically meaningful improvements in HRQoL [34]. It was also noted that disease-specific HRQoL instruments reported greater changes with reduced CKD-aP severity than generic instruments [34], and this has been shown in other skin conditions [35]. This recognised lack of sensitivity led to the development of the disease-specific 'bolt-on' module – EQ-PSO [24]; this added 'skin irritation' and 'self-confidence', which were observed to improve in this study. The relative prominence of the EQ-5D has been driven by cost-effectiveness analysis [36]; however, the National Institute for Health and Care Excellence concluded that evidence suggests the EQ-5D works well for most diseases except sensory disorders and some mental health conditions [36].

Considering the holistic experience of severe pruritus, the previously mentioned systematic review suggested that the relationship between CKD-aP and HRQoL is partially mediated by the sleep disturbances, and significant improvements in the Sleep Quality NRS scores over the treatment period in this analysis support this hypothesis. Three-quarters of patients achieved a ≥ 3-point improvement in WI-NRS after 12 weeks of difelikefalin treatment in this open-label study compared with around half those in the KALM placebo-controlled RCTs [15]. Treatment responses seen in RCTs tend to be smaller than those observed in open-label studies owing to the 'patients' beliefs effect', where a proportion of patients do not expect any improvement because of the possibility that they may be receiving a placebo [37, 38]. The open-label trial design of the present study gives insights to efficacy in real-world clinical practice, where patients are aware of the therapy they are receiving. For instance, a recent real-world study [39] showed 13/15 patients on haemodialysis with moderate-to-severe CKD-aP achieved a ≥ 3-point improvement in WI-NRS with difelikefalin treatment, and 12/15 patients experienced a health-related quality of life improvement, evaluated using the Self-Assessed Disease Severity score.

The value and associated strengths of this analysis is that it gives real-world insight into the effectiveness of

difelikefalin on generic and disease-specific HRQoL, without the doubt associated with potential placebo administration, as previously mentioned. Naturally, its weaknesses are the absence of a control arm (although this evidence exists elsewhere) [12–15], uncertainty around clinically meaningful changes of some instruments in this specific patient group and the conduct of post hoc statistical analyses potentially leading to false positive (type I) errors.

The results of this analysis suggest that patients with CKD-aP receiving difelikefalin can have significant improvements in their pruritus symptoms, disease-specific HRQoL (as assessed by Skindex-10, 5D-itch, and EQ-PSO scores) and Sleep Quality NRS in routine clinical practice. Further research should assess whether the changes in EQ-5D generic HRQoL and Sleep Quality NRS observed following difelikefalin treatment are clinically meaningful since thresholds to determine this have not been established in CKD-aP. These assessments would build on the results of this analysis and further contribute to the argument for disease-specific HRQoL measures in decision-making to improve patients' access to CKD-aP therapies.

5 Conclusions

Difelikefalin is the first and only licensed treatment for CKD-aP with demonstrated benefits on itching severity as demonstrated by previous clinical trials. The results of this analysis further suggest that difelikefalin can improve both pruritus symptoms and disease-specific HRQoL for patients undergoing haemodialysis with CKD-aP. Pruritus severity assessed by 5-D itch improved from moderate/severe to mild following difelikefalin treatment, with significant improvements also reported in disease-specific HRQoL in terms of Skindex-10 and EQ-PSO scores as well as in Sleep Quality NRS scores.

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Declarations

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Conflicts of interest James Fotheringham reports speaker honoraria from Fresenius Medical Care and Novartis, and conducts research funded by CSL Vifor and Novartis. Julian Guest reports consultancy fees from Vifor Fresenius Medical Care. Joerg Latus reports consultancy fees from CSL Vifor. Edgar Lerma reports speaker/advisory board/steering committee involvements with Akebia, AstraZeneca, Bayer, Glaxo Smith Kline, Otsuka, Travere and CSL Vifor. Isabelle Morin, Thilo Schaufler and Marco Soro report that they are employees and shareholders of CSL Vifor. Sonja Ständer has received consulting and advisory board fees from AbbVie, Almirall, Beiersdorf, Bellus Health, Benevolent, Bionorica, Cara, Clexio, DS Biopharma, Eli Lilly, Galderma, Integrity CE, Kiniksa, Klinge Pharma, Leo Pharma, Pfizer, Sanofi Regeneron, TouchIME, Trevi, Vifor and WebMD; speaker fees from Almirall, BMS, Eli Lilly, Sanofi, Galderma, L'Oréal, Omnicuris, Beiersdorf, Leo Pharma, Novartis, P.G. Unna Academy, Pfizer, UCB and Vifor; and research grants from Almirall, German Research Foundation (DFG), European Academy of Dermatology and Venereology (EADV), Leo Pharma, Novartis, Sanofi and Trevi Therapeutics. Steven Zeig reports consultancy fees from CSL Vifor.

Availability of data and materials The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author (James Fotheringham).

Ethics approval This study was approved by a combination of institutional review boards or independent ethics committees depending on the geographical location of the study centre. The institutional review boards/independent ethics committees reviewed and approved all study documentation to safeguard the rights, safety, and well-being of the patients. The study protocol was reviewed and approved by institutional review boards before the study commenced (Study 3105: WCG IRB, approval number 20190622). The study was carried out in accordance with the principles of the Declaration of Helsinki [40].

Consent to participate All patients gave written informed consent prior to study enrolment.

Consent to publish Not applicable as individual patient data are not presented.

Author contributions All authors participated in the data analysis and preparation of the manuscript and approved the final manuscript for publication. Research idea: James Fotheringham, Thilo Schaufler, Marco Soro, Steven Zeig; data acquisition: Isabelle Morin, Thilo Schaufler, Marco Soro, James Fotheringham; data analysis and interpretation: James Fotheringham, Julian Guest, Joerg Latus, Edgar Lerma, Isabelle Morin, Thilo Schaufler, Marco Soro, Sonja Ständer, Steven Zeig. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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