Renal Replacement Therapy

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Long-term efficacy and safety of difelikefalin in moderate-to-severe pruritus in Japanese hemodialysis patients: a 52-week open-label extension period of a phase 3 trial

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Abstract

Background Difelikefalin, a potent and highly selective agonist of kappa opioid receptors, is used to treat moderate-to-severe pruritus in hemodialysis patients.

Methods This was a 52-week, open-label phase 3 trial following a 6-week randomized double-blind placebo-controlled treatment period to investigate the efficacy and safety of difelikefalin in Japanese hemodialysis patients. Having completed the 6-week double-blind period, patients received difelikefalin 0.5 μg/kg three times per week intravenously for 52 weeks. Efficacies were assessed using numerical rating scale (NRS) scores, proportion of patients whose NRS score improved by ≥ 3 points and ≥ 4 points, Shiratori severity score, proportion of patients with a nighttime Shiratori severity score of ≤ 2, the Skindex-16 score, 5-D itch scale score, and patient global impression of change (PGIC). Safety was assessed on the basis of adverse events, clinical laboratory tests, vital signs, body weight, 12-lead electrocardiography, and dependency.

Results The number of patients who entered the extension treatment period from the difelikefalin (MR–MR) and placebo (P-MR) groups was 85 and 83, respectively. The weekly mean NRS scores (mean ± SD) in the MR–MR group at baseline, week 6, and week 58 were 6.57 ± 1.32, 4.04 ± 2.24, and 2.36 ± 1.86, respectively. The weekly mean scores in the P-MR group, at baseline, week 6, and week 58 were 6.42 ± 1.29, 4.85 ± 1.90, and 2.73 ± 2.14, respectively. In patients receiving difelikefalin, there was a decline in the score from treatment initiation, and this decline continued until week 58. Similarly, improvements were seen until week 58 in the proportion of responders, Shiratori severity score, proportion of responders based on the Shiratori severity score, the Skindex-16 score, 5-D itch scale score, and PGIC. A correlation was seen between the change in NRS and itch-related quality of life (QOL), including the Shiratori severity score, Skindex-16 score, 5-D itch scale score, and PGIC. Difelikefalin was well tolerated and safe even when used long term.

Conclusions Difelikefalin improved itching and itch-related quality of life during long-term treatment in hemodialysis patients with moderate-to-severe pruritus whose response to conventional medications had been inadequate. It also demonstrated excellent safety and tolerability.

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Trial registration: ClinicalTrials.gov; NCT04711603. Registered 15 January 2021, https://www.clinicaltrials.gov/study/NCT04711603?term=NCT04711603&rank=1.

Keywords Difelikefalin, 5-D itch scale score, Itching, Itch-related quality of life, Numerical rating scale, Shiratori severity score, Skindex-16 score, Hemodialysis

Background

Difelikefalin is a synthetic peptide agonist of the κ-selective opioid receptor (KOR) and regulates visceral and inflammatory pain, itch, and inflammatory signals by activating KOR in peripheral nerves and immune cells [1]. Difelikefalin has a more favorable safety profile and better tolerability than other KOR agonists due to its physicochemical properties of membrane permeability and limited transfer to the central nervous system (CNS) [2–4]. As it is an intravenous formulation, difelikefalin can be administered directly into the dialysis circuit at the end of the dialysis session, under the supervision of a nephrologist [1]. On the basis of the efficacy and safety findings in the phase 3 trials, difelikefalin has been used for the treatment of moderate-to-severe pruritus in hemodialysis patients worldwide [2–4]. The long-term efficacy of difelikefalin has only been reported in relation to improvements in itch-related QOL as measured by the 5-D itch scale score [5]. Here, we report on the long-term efficacy including improvements in terms of itch intensity and itch-related QOL, and the safety of intravenous difelikefalin 0.5 μg/kg in patients with moderate-to-severe pruritus undergoing maintenance hemodialysis in Japan.

Method

Study design

This was a long-term (52-week), prospective, open-label, multicenter phase 3 trial following the randomized placebo-controlled double-blind treatment period to investigate the efficacy and safety of intravenous difelikefalin. The phase 3 trial including this trial consisted of a 2-week run-in period, a 6-week double-blind treatment period, and a 52-week open-label extension period. It was conducted at 73 sites in Japan between January 2021 and September 2022.

The study protocol, informed consent form, and other relevant study documents were approved by the institutional review board. All patients gave written informed consent before initiation of any study-specific procedures. The study was conducted in accordance with the ethical principles originating in or derived from the Declaration of Helsinki and International Council for Harmonisation (ICH) Good Clinical Practice Guidelines. The study was designed and conducted by the sponsor in collaboration with the principal investigators. The trial is registered with ClinicalTrials.gov; NCT04711603.

Participants and treatment

The patients enrolled in the extension treatment period were those who completed the double-blind treatment period, who had received ≥ 14 treatments and made entries in the symptom diary ≥ 70% of time during the double-blind treatment period. The eligibility criteria prior to start of double-blind treatment are described in the previous report [4]. Briefly, male or female patients aged ≥ 20 years who were undergoing maintenance hemodialysis three times a week for ≥ 12 weeks were enrolled. Moderate-to-severe pruritus was defined as a mean score of > 4 points on the 24-h Worst Itching Intensity numerical rating scale (NRS) calculated using patients' daily assessments made during a 7-day run-in period before randomization. Other inclusion criteria were patients who had a history of receiving conventional pruritus therapies, but with an inadequate response/intolerance to these therapies, and whose highest Shiratori severity score during either daytime or nighttime was ≥ 3 points (moderate itching or greater) for ≥ 2 days during the 7-day run-in period.

Patients allocated to either placebo or difelikefalin in the double-blind treatment period received difelikefalin intravenously at the end of each hemodialysis session three times a week for 52 weeks (total 156 treatments). The administration volume from week 6 to week 34 was determined at week 6 according to the dry weight (Table S1) [6]. The administration volume from week 34 to week 58 was determined similarly at week 34. Throughout the trial, use of nalfurafine, opioids, any opioid antagonist, and phototherapy was prohibited. Use of anti-pruritus agents including oral antihistamines and antiallergic agents, topical moisturizers, and steroids was allowed; however, changes in the regimen for these drugs and new use were to be avoided as much as possible from the start of the extension treatment period to the end of the follow-up period.

As well as in the double-blind treatment period, patients were asked to continue making entries in an electronic symptom diary in which they reported their worst itching intensity over the preceding 24 h using the NRS and their worst level of daytime and nighttime

itching in the preceding 24 h on the basis of a pruritus severity scale using the Shiratori severity score. Other itch-related QOL factors were assessed using the Skindex-16 score [4] and the 5-D itch scale score [4] at weeks 10, 18, 26, 34, 46, and 58 according to the procedure reported in the previous trial. Patient global impression of change (PGIC) was assessed at weeks 10, 18, 26, 34, 46, and 58 according to the patient's overall impression of changes in itch in comparison with their impression of their symptoms in the pre-observation period.

Outcomes

The efficacies were assessed on the basis of the weekly mean NRS scores, proportion of patients whose weekly mean NRS was improved by ≥3 points and ≥4 points, itching scores on the Shiratori severity score including the worst level of daytime or nighttime itching, daytime scores, and nighttime scores among patients with a baseline nighttime mean Shiratori severity score of ≥3 points, proportion of patients whose Shiratori severity score at night was reduced to 2 points or less, the Skindex-16 overall score and subscores (symptoms score, emotions score, and functioning score), 5-D itch scale total score and component scores (duration, degree, direction, disability, and distribution scores), and PGIC at each visit.

Safety was assessed on the basis of adverse events (AEs), clinical laboratory tests, vital signs, body weight, and 12-lead electrocardiography (ECG). The investigator scored dependency using a dependency questionnaire [7] on a 4-level scale ("remarkable," "moderate," "slight," or "none") at weeks 18, 34, 58 and at the end of the follow-up period, and the Dependency Assessment Committee assessed the level of dependency.

Statistical analysis

The sample size of 100 at week 58 was determined according to the ICH E1 guideline "The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions" [8]. Safety analysis was performed for patients in the safety set (SS), which consisted of all patients who received the study drug at least once. Efficacy was analyzed according to the intention-to-treat principle in the full analysis set (FAS), which included the SS patients who met the inclusion criteria regarding NRS score and had a baseline NRS score.

Data were summarized by group and timepoint for the entire study period comprising the double-blind and extension treatment periods. Efficacy analyses were performed in the MR–MR group, which consisted of patients assigned to the difelikefalin group, and the P-MR group, which consisted of patients assigned to the placebo group in the double-blind treatment period. For the efficacy outcomes except for PGIC, summary statistics were calculated and the means and SDs were presented graphically. The number and proportion of patients with a 3-point improvement (change from baseline in the weekly mean NRS score was ≤−3 points) and with a 4-point improvement (change from baseline in the weekly mean NRS score was ≤−4 points) were presented. The number and proportion of patients whose Shiratori severity score at night was reduced to 2 points or less among the patients with a baseline score of ≥3 points were presented. For the PGIC, the number and proportion of patients by category were presented. As a post hoc analysis, the correlations of the NRS with other variables including the Shiratori severity score, Skindex-16 score, 5-D itch scale score, and PGIC were analyzed using data from all groups and timepoints. Subgroup analyses of the NRS were performed when there was a 3-point improvement to evaluate the relationship between the time of onset of an effect ascribed to difelikefaline and the change in NRS score over time. Furthermore, we performed subgroup analyses of with/without complications of insomnia, dialysis efficiency (<1.6/≥1.6 of Kt/V), and with/without history of nalfurafine use to evaluate the patient background factors on efficacy. AEs and treatment-related AEs were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1. SAS ver. 9.4 for Windows (SAS Institute, Cary, NC) was used for the statistical analyses.

Results

Patients

Among a total of 230 patients who gave informed consent, 178 patients were randomly assigned to receive difelikefalin 0.5 μg/kg ($n=89$) or placebo ($n=89$) (Fig. 1). The number of patients who completed the double-blind treatment period and entered the extension treatment period in the difelikefalin (MR–MR) and placebo (P-MR) groups was 85 and 83, respectively. A total of 122 patients completed the extension treatment period (68 for MR–MR group and 54 for the P-MR group), and 46 patients discontinued treatment with difelikefalin due to AEs ($n=24$), lack of efficacy ($n=1$), or consent withdrawal ($n=9$). Baseline characteristics were similar across treatment groups (Table 1). Treatment adherence in the MR–MR and P-MR groups was 98.9% and 99.3%, respectively.

Efficacy

In the MR–MR group, the weekly mean NRS score (mean ± SD) was 6.57 ± 1.32 at baseline, 4.04 ± 2.24 at week 6, 3.16 ± 1.90 at week 18, 2.72 ± 1.85 at week 34, and 2.36 ± 1.86 at week 58 (Fig. 2A, Table S2). The score declined from the initiation of difelikefalin treatment and this decline was maintained until the end of the extension

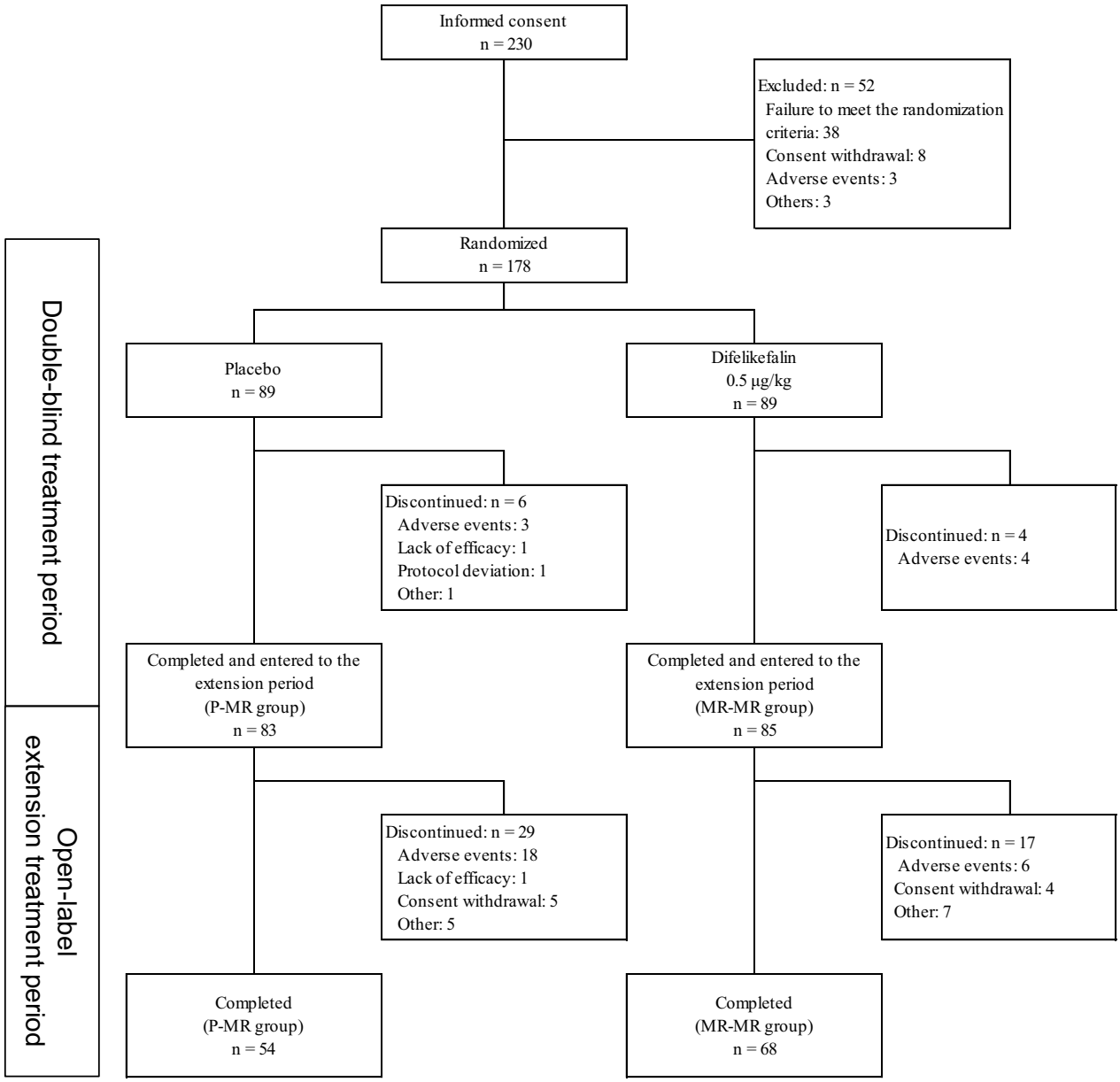


Fig. 1 Patient flow. MR–MR group, patients who were assigned to the difelikefalin group and continued difelikefalin treatment upon entering the extension treatment period; P-MR group, patients who were assigned to the placebo group and began treatment with difelikefalin upon entering the extension treatment period

treatment period. The proportion of patients with a 3-point improvement in their NRS score was 34.6% at week 6, 55.3% at week 18, 67.2% at week 34, and 72.4% at week 58 (Fig. 2B), and the proportion of those with a 4-point improvement was 27.2% at week 6, 46.1% at week 18, 49.3% at week 34, and 63.8% at week 58 (Fig. 2C). Itch in nighttime (Fig. 3A), daytime, and the most severe level of daytime or nighttime were improved by difelikefalin (Fig. S1). Among the patients with a baseline weekly mean nighttime Shiratori severity score of ≥3 points, the proportion of patients whose scores decreased to 2 points or less was 68.4% at week 6, 76.5% at week 18, 80.0% at week 34, and 92.6% at week 58 (Fig. 3B). Similar to the NRS score and Shiratori severity score, the itch-related QOL and PGIC were maintained until week 58. The Skindex-16 overall score was 39.21 ± 17.76 at baseline, 20.86 ± 18.00 at week 4, 15.01 ± 16.20 at week 18, 12.89 ± 13.42 at week 34 and 10.84 ± 14.40 at week 58 (Fig. S2). The 5-D itch scale total score was 15.7 ± 2.9 at baseline, 11.1 ± 3.0 at week 4, 10.5 ± 2.9 at week 18,

Table 1 Demographic and clinical characteristics of the patients at baseline

	All *N* = 168	MR–MR *N* = 85	P-MR *N* = 83
Age (years)			
< 65 (no. of patients, %)	74 (44.0)	39 (45.9)	35 (42.2)
65 ≤ (no. of patients, (%)	94 (56.0)	46 (54.1)	48 (57.8)
Mean ± SD	64.1 ± 11.6	64.5 ± 10.6	63.7 ± 12.5
Female (no. of patients, %)	27 (16.1)	13 (15.3)	14 (16.9)
Dry weight (kg)			
< 45 (no. of patients, %)	10 (6.0)	6 (7.1)	4 (4.8)
≥ 45 to < 65 (no. of patients, %)	92 (54.8)	47 (55.3)	45 (54.2)
≥ 65 to < 85 (no. of patients, %)	58 (34.5)	27 (31.8)	31 (37.3)
≤ 85 (no. of patients, %)	8 (4.8)	5 (5.9)	3 (3.6)
Mean ± SD	63.16 ± 12.29	62.68 ± 11.62	63.66 ± 12.99
Type of dialysis			
Hemodialysis (no. of patients, %)	64 (38.1)	27 (31.8)	37 (44.6)
Off-line HDF (no. of patients, %)	7 (4.2)	3 (3.5)	4 (4.8)
On-line HDF (no. of patients, %)	78 (46.4)	45 (52.9)	33 (39.8)
I-HDF (no. of patients, %)	19 (11.3)	10 (11.8)	9 (10.8)
Duration of dialysis (years)			
Mean ± SD	8.4 ± 7.2	8.7 ± 7.8	8.2 ± 6.7
Single-pool Kt/V			
Mean ± SD	1.512 ± 0.277	1.492 ± 0.260	1.532 ± 0.293
Urea reduction ratio (%)			
Mean ± SD	70.7 ± 6.0	70.3 ± 5.8	71.2 ± 6.2
Disease duration of itch (years)			
Mean ± SD	5.3 ± 4.8	5.8 ± 5.5	4.8 ± 3.8
Prior treatment with nalfurafine hydrochloride			
No (no. of patients, %)	76 (45.2)	39 (45.9)	37 (44.6)
Yes (no. of patients, %)	92 (54.8)	46 (54.1)	46 (55.4)

HDF, hemodiafiltration; I-HDF, intermittent infusion hemodiafiltration; SD, standard deviation

10.4 ± 2.9 at week 34, and 9.8 ± 3.1 at week 58. (Fig. S3). Improvement on the PGIC continued after the extension treatment period began, and the proportion of patients whose global improvement was "much improved" or "very much improved" was 32.8% and 20.9% at week 34, and 29.7% and 29.7% at week 58, respectively (Table S3).

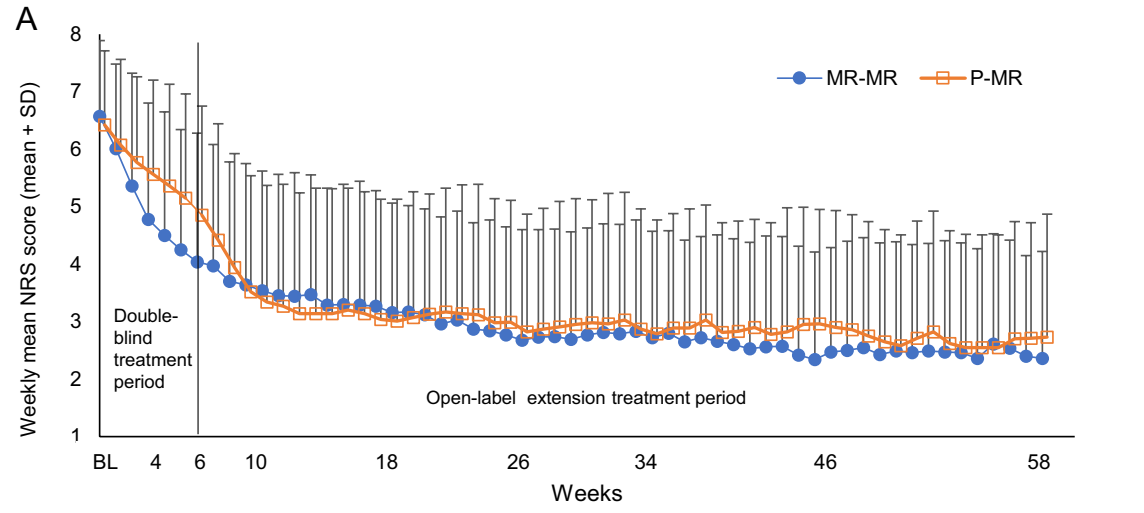
In the P-MR group, the weekly mean NRS score was 6.42 ± 1.29 at baseline, 4.85 ± 1.90 at week 6, 3.01 ± 2.12 at week 18, 2.79 ± 1.98 at week 34, and 2.73 ± 2.14 at week 58 (Fig. 2A). Similar to the NRS score, other efficacy outcomes improved after the start of difelikefalin administration and these efficacies were maintained up to week 58 as in the MR–MR group.

The correlation between the change from baseline in the weekly mean NRS and the other efficacy endpoints including change from baseline in the Shiratori severity score (day or night, whichever was higher), Skindex-16 score, 5-D itch scale score, and PGIC was evaluated as a post hoc analysis. The correlation coefficients were 0.77 (Pearson) for the itch score based on the Shiratori severity criteria, 0.44 (Pearson) for the Skindex-16 overall score, 0.59 (Pearson) for the 5-D itch scale total score, and 0.57 (Spearman) for PGIC, showing a definite correlation (Fig. 4).

In the subgroup analysis, there were no differences in terms of patient background among the subgroups. Time course of mean + SD in the weekly mean NRS score classified by onset time of response (3-point decline from baseline), presence or absence of insomnia, dialysis efficiency (single-pooled Kt/V < 1.6/≥ 1.6), and with or without history of nalfurafine use in the MR–MR and P-MR groups is shown in Figs. 5 and S4, respectively. In the MR–MR group ($n = 81$), the number of the responders who had a 3-point decline in the NRS score from baseline up to week 4, during weeks 5 and 12, after week 13, and non-responders was 26, 22, 17, and 16, respectively. More than half of the patients became responders within 12 weeks, and 20% became responders after 13 weeks. Itching decreased in all subgroups regardless of the presence or absence of insomnia. However, there was a greater reduction in itching in the group with insomnia. As a result of analysis by dialysis efficiency (single-pooled Kt/V < 1.6 or ≥ 1.6), the NRS score improved in both subgroups, but the improvement was greater in patients with high dialysis efficiency (Kt/V ≥ 1.6). Regardless of the history of treatment with nalfurafine, the mean NRS score improved to < 4 points and was maintained for a prolonged period. The results of the P-MR group were similar to those of the MR–MR group.

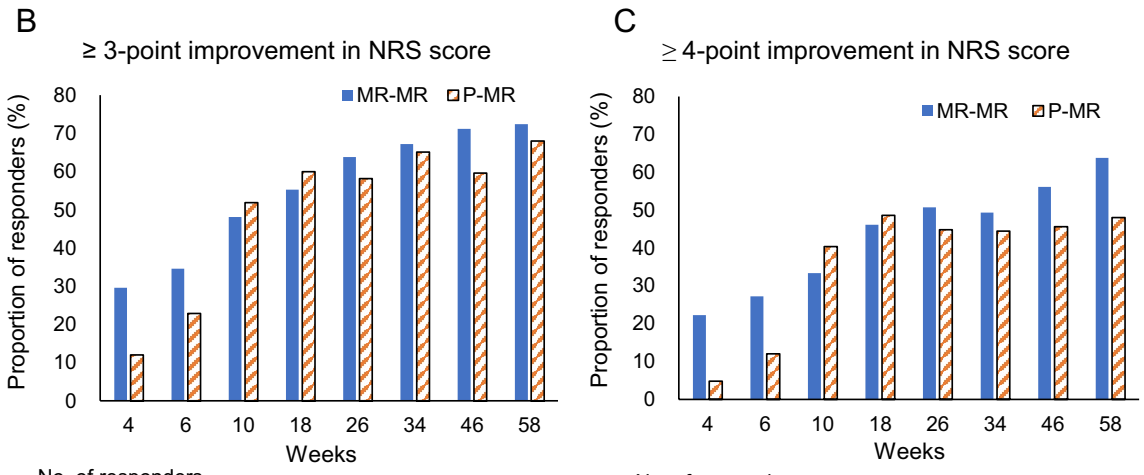
Safety

The incidence of all-cause AEs during the entire study period comprising the double-blind and extension treatment periods in the MR–MR and P-MR groups was 96.5% and 98.8%, respectively (Table 2). The incidence of treatment-related AEs in the MR–MR and P-MR groups was 18.8% and 13.3%, respectively. AEs with an incidence of ≥ 15% in any group were pyrexia (18.8% in MR–MR group and 22.9% in P-MR group), contusion (17.6% and 8.4%), vaccination complication (16.5% and 14.5%), nasopharyngitis (15.3% and 18.1%), shunt stenosis (15.3% and 16.9%), and diarrhoea (12.9% and 21.7%). Treatment-related AEs with an incidence of ≥ 2% in any group were constipation (4.7% in MR–MR group and 0.0% in P-MR group), somnolence (2.4% and 2.4%), and dizziness (1.2% and 2.4%). The severity of



No. of patients

Weeks	BL	4	6	10	18	26	34	46	58
MR-MR	81	81	81	81	76	69	67	66	58
P-MR	83	83	83	77	70	67	63	57	50



No. of responders

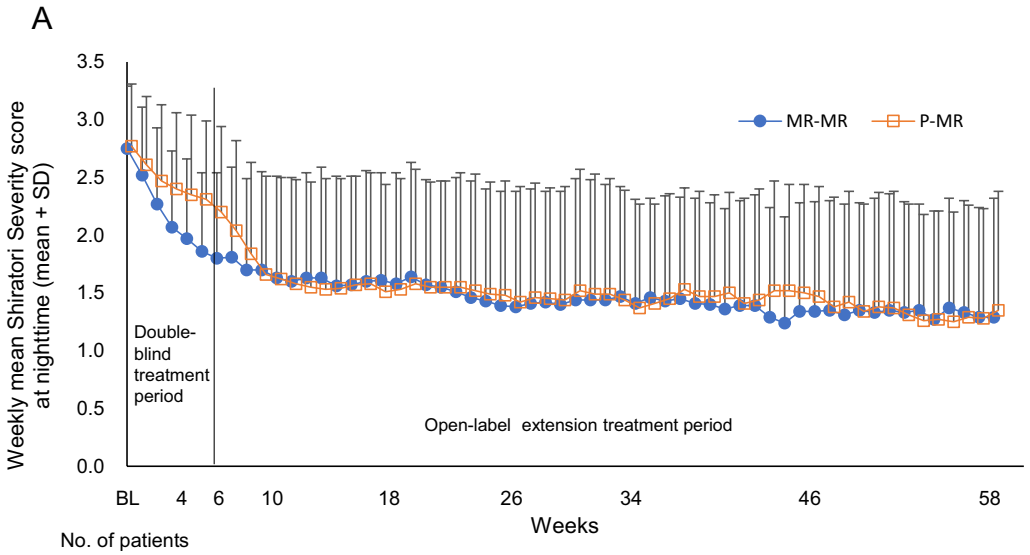
Weeks	4	6	10	18	26	34	46	58
MR-MR	24	28	39	42	44	45	47	42
P-MR	10	19	40	42	39	41	34	34

No. of responders

Weeks	4	6	10	18	26	34	46	58
MR-MR	18	22	27	35	35	33	37	37
P-MR	4	10	31	34	30	28	26	24

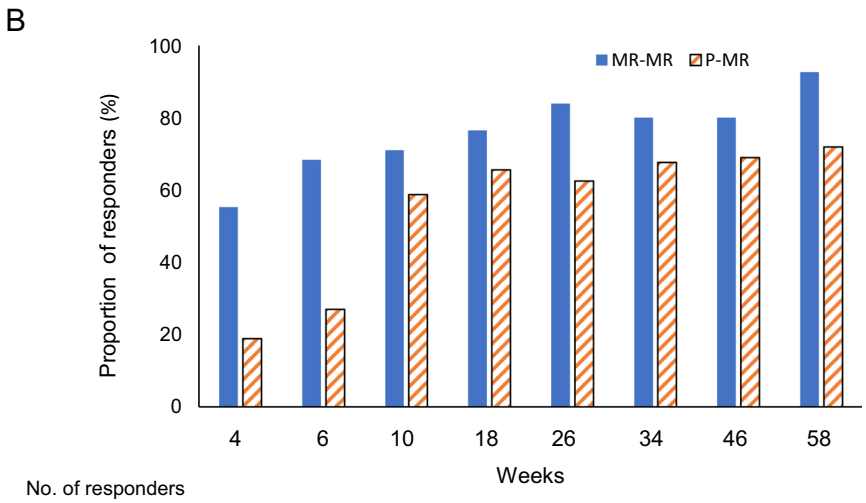
Fig. 2 Weekly mean NRS score, and the ≥ 3-point and ≥ 4-point responders in the NRS score. **A** shows the time course of the weekly mean NRS score. The bars indicate the standard deviation (SD). **B** shows the proportion of patients who had an improvement (decline) of ≥ 3 points from baseline in the weekly mean score (NRS intensity) for daily worst itching. **C** shows the proportion of patients who had an improvement (decline) of ≥ 4 points from baseline in the weekly mean score (NRS intensity) for daily worst itching. BL, baseline; NRS, numerical rating scale

AEs was mild in 42.4% in the MR–MR group and 49.4% in the P-MR group and moderate in 45.9% in the MR–MR group and 38.6% in the P-MR group. Severe AEs were reported in 8.2% in the MR–MR group and 10.8% in the P-MR group. A severe AE affecting two patients was acute myocardial infarction in MR–MR group. It was determined that none of the severe AEs had a causal relationship with the study drug (Table 2). The onset of AEs was observed to occur at similar times in all periods, and treatment-related AEs were more common in the early stages of difelikefalin administration (Table S4). There were no AEs or treatment-related AEs that manifested late and posed clinical problems. Two patients (2.4%) died in the MR–MR group due to acute myocardial infarction and two patients (2.4%) died in the P-MR group due to peripheral arterial occlusive



No. of patients

Weeks	BL	4	6	10	18	26	34	46	58
MR-MR	81	81	81	81	76	69	67	66	58
P-MR	83	83	83	77	70	67	63	57	50



No. of responders

Weeks	4	6	10	18	26	34	46	58
MR-MR	21/38	26/38	27/38	26/34	26/31	24/30	24/30	25/27
P-MR	7/37	10/37	20/34	21/32	20/32	21/31	20/29	18/25

Fig. 3 Weekly mean nighttime Shiratori severity score and the 2 points responder. **A** shows the time course of the weekly mean nighttime Shiratori severity score. The bars indicate the standard deviation (SD). **B** shows the proportion of patients whose score was reduced to 2 points or less in patients whose baseline nighttime Shiratori severity score was ≥ 3 points. BL, baseline

disease (1 case) and decreased appetite (1 case). All of these events occurred during the extension period, and none of these events were assessed as treatment-related AEs. Other serious AEs (SAEs) were observed in 33 of 85 patients (38.8%) in the MR–MR group and 37 of 83 patients (44.6%) in the P-MR group. The SAEs that occurred in ≥ 2 patients were shunt occlusion (6 patients), peripheral arterial occlusive disease (3 patients), and coronavirus disease 2019 (COVID-19), gastroenteritis, and shunt stenosis (2 patients each) in the MR–MR group and shunt stenosis (7 patients), pneumonia and shunt occlusion (4 patients each), peripheral arterial occlusive disease (3 patients), and COVID-19, cataract, coronary artery stenosis, pyrexia, and shunt aneurysm (2 patients each) in the P-MR group. No serious treatment-related AEs were

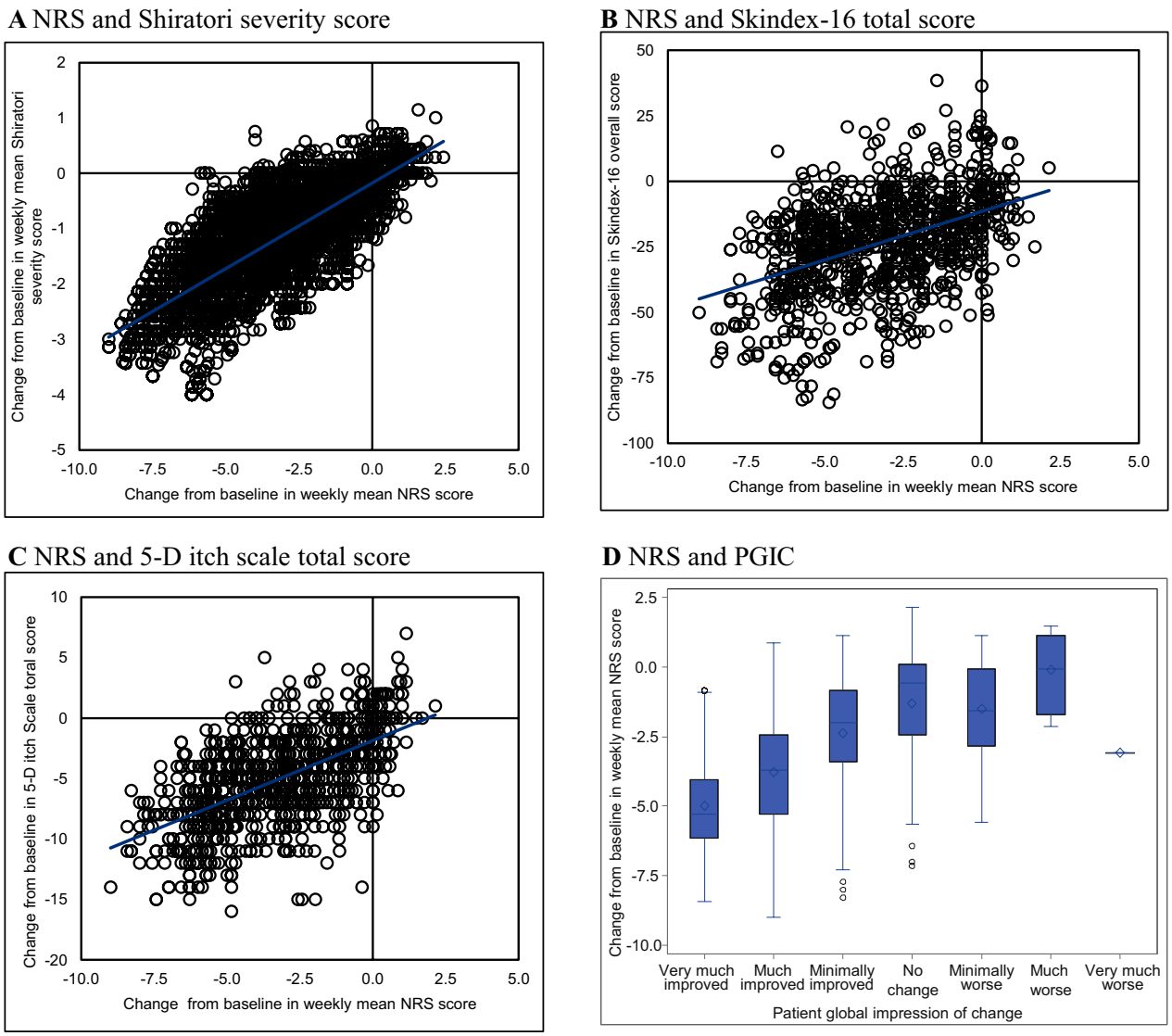
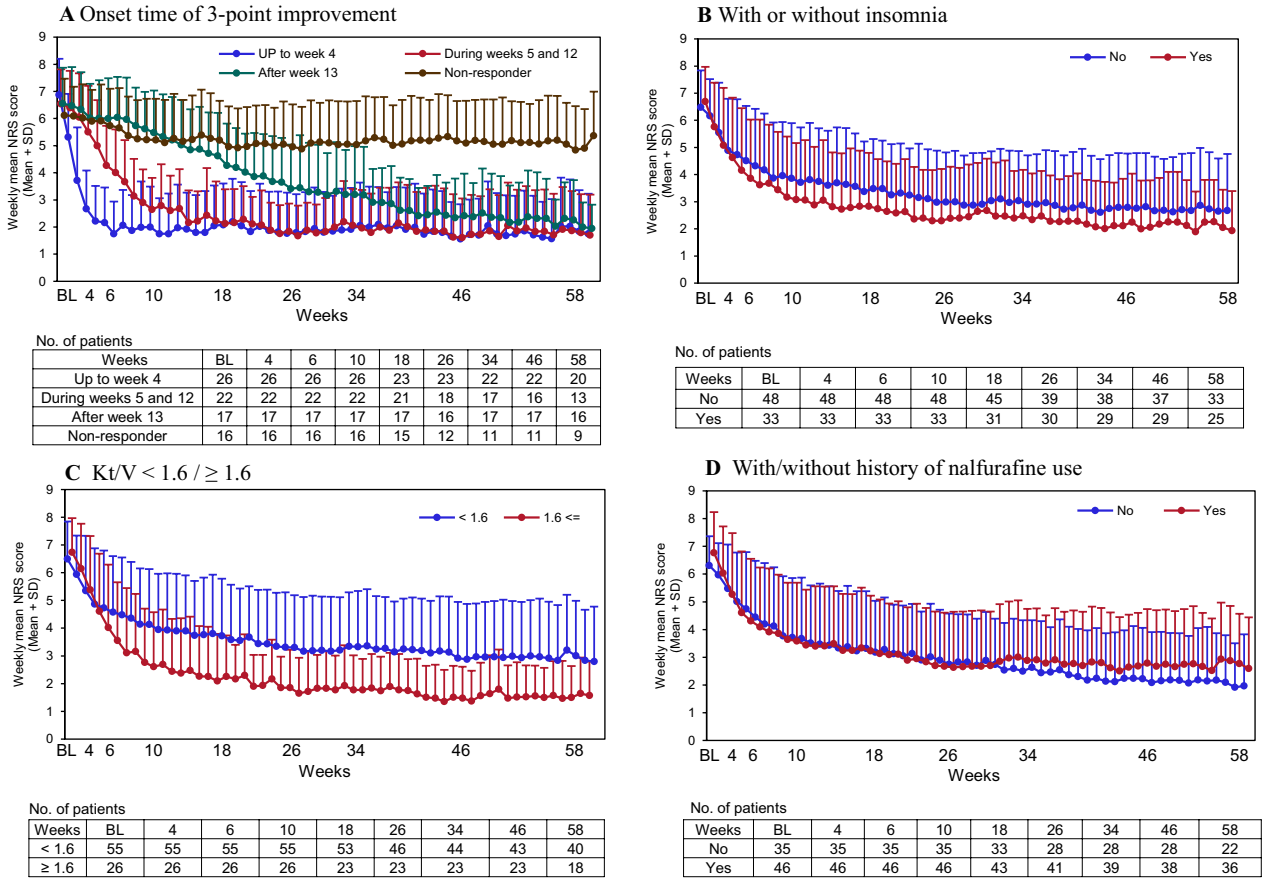


Fig. 4 Correlation between the change from baseline in the weekly mean NRS and itch-related QOL. **A** shows the correlation between the change from baseline in the weekly mean NRS and Shiratori severity score using data from all groups and timepoints. The Pearson's correlation coefficient was 0.77. **B** shows the correlation between the change from baseline in the weekly mean NRS and Skindex-16 overall score using data from all groups and timepoints. The Pearson's correlation coefficient was 0.44. **C** shows the correlation between the change from baseline in the weekly mean NRS and 5-D itch scale total score using data from all groups and timepoints. The Pearson's correlation coefficient was 0.59. **D** shows the correlation between the change from baseline in the weekly mean NRS and the PGIC category using data from all groups and timepoints. The center line inside the box represents the median, the hinges are the 25th and 75th percentiles, the whiskers extend to1.5 times the interquartile range from the top and bottom of the box, and the circles beyond the whiskers are outliers. The Spearman's correlation coefficient was 0.57. NRS, numerical rating scale; PGIC, patient global impression of change; QOL, quality of life

observed. The treatment-related AEs leading to discontinuation of difelikefalin administration in either group were dizziness, palpitations, headache, paraesthesia, pruritus allergic, hallucination, and shunt stenosis. Most treatment-related AEs leading to discontinuation of difelikefalin administration were mild and resolved following discontinuation of difelikefalin. The severity of treatment-related AEs is presented in Table S5. No notable changes in clinical laboratory tests, vital signs, body weight, and 12-lead ECG were observed. All evaluable patients were determined not to have become dependent during the study period, and it was concluded that difelikefalin does not cause dependency.



No. of patients

Weeks	BL	4	6	10	18	26	34	46	58
Up to week 4	26	26	26	26	23	23	22	22	20
During weeks 5 and 12	22	22	22	22	21	18	17	16	13
After week 13	17	17	17	17	17	16	17	17	16
Non-responder	16	16	16	16	15	12	11	11	9

No. of patients

Weeks	BL	4	6	10	18	26	34	46	58
No	48	48	48	48	45	39	38	37	33
Yes	33	33	33	33	31	30	29	29	25

No. of patients

Weeks	BL	4	6	10	18	26	34	46	58
< 1.6	55	55	55	55	53	46	44	43	40
≥ 1.6	26	26	26	26	23	23	23	23	18

No. of patients

Weeks	BL	4	6	10	18	26	34	46	58
No	35	35	35	35	33	28	28	28	22
Yes	46	46	46	46	43	41	39	38	36

Fig. 5 Time course of the weekly mean NRS score by subgroup. Classified by **A** onset time of response (3-point decline from baseline); up to week 4, during week 5 and week 12, after week 13, and non-responder, **B** presence of absence of insomnia, **C** dialysis efficiency (single-pooled Kt/V < 1.6 or ≥ 1.6), and **D** with or without history of use of nalfurafine in the MR–MR group. BL, baseline; NRS, numerical rating scale; SD, standard deviation

Discussion

This long-term phase 3 trial following the randomized placebo-controlled double-blind treatment period demonstrated that difelikefalin was safe and clinically useful when administrated intravenously to hemodialysis patients with moderate-to-severe pruritus at the end of each hemodialysis session. The reduction in itching confirmed in the 6-week double-blind treatment period was maintained over a 58-week period when assessed by the NRS score and Shiratori severity score. This effectiveness was supported by improvements in itch-related QOL as indicated by the Skindex-16 score, 5-D itch scale score, and PGIC. Furthermore, a close correlation was found to exist between the change in NRS score and itch-related QOL including the Skindex-16 score, 5-D itch scale score, and PGIC, suggesting difelikefalin improved QOL by relieving itching.

According to an analysis of the time of efficacy onset, the NRS score of more than half the patients declined from the early stage of administration, and a decline from baseline of more than 3 points was achieved within 12 weeks. These were the clinically meaningful primary endpoints in a US phase 3 study [3]. Furthermore, it was also notable that even in the slow responders, the efficacy of treatment appeared after week 12 and the level of efficacy matched that of the quick responders during the subsequent period up to week 58. A treatment algorithm for hemodialysis-associated pruritus in Japan recommends [9] that the period during which the effect of KOR agonist on itching should be assessed is 2–4 weeks. Although difelikefalin produced significantly greater improvement compared with placebo at week 4 [4],when assessing efficacy, more than 12 weeks of treatment with difelikefalin may be required to obtain an adequate antipruritic effect.

It has been reported [10–12] that itching in hemodialysis patients is generally most intense at night, and patients with more severe pruritus tend to lose an average of 2 h of sleep, resulting in poorer quality of sleep than in those without pruritus. In this study, nighttime itching and QOL were assessed using the Shiratori severity score [13]. In patients with a score of 0–2, itching did not

Table 2 Summary of safety

	MR–MR *N* = 85 No. (%)	P-MR *N* = 83 No. (%)
Any adverse events	82 (96.5)	82 (98.8)
Mild	36 (42.4)	41 (49.4)
Moderate	39 (45.9)	32 (38.6)
Severe	7 (8.2)	9 (10.8)
Any treatment-related adverse events	16 (18.8)	11 (13.3)
Mild	16 (18.8)	9 (10.8)
Moderate	0 (0)	2 (2.4)
Severe	0 (0)	0 (0)
Death	2 (2.4)	2 (2.4)
Other serious adverse events	33 (38.8)	37 (44.6)
Adverse events leading to discontinuation	6 (7.1)	18 (21.7)
Treatment-related adverse events leading to discontinuation	1 (1.2)	4 (4.8)
Adverse events leading to interruption	7 (8.2)	9 (10.8)
Onset time of adverse events (week)		
< 12	64/85 (75.3)	64/83 (77.1)
12 to < 24	57/83 (68.7)	52/76 (68.4)
24 to < 36	49/75 (65.3)	52/70 (74.3)
36 to < 48	50/70 (71.4)	43/63 (68.3)
≥ 48	51/70 (72.9)	36/58 (62.1)
Onset time of treatment-related adverse events (week)		
< 12	12/85 (14.1)	8/83 (9.6)
12 to < 24	4/83 (4.8)	2/76 (2.6)
24 to < 36	1/75 (1.3)	1/70 (1.4)
36 to < 48	1/70 (1.4)	0/63 (0)
≥ 48	0/70 (0)	0/58 (0)
Most frequent adverse events (≥ 10% in any group)		
Pyrexia	16 (18.8)	19 (22.9)
Contusion	15 (17.6)	7 (8.4)
Vaccination complication	14 (16.5)	12 (14.5)
Nasopharyngitis	13 (15.3)	15 (18.1)
Shunt stenosis	13 (15.3)	14 (16.9)
Constipation	12 (14.1)	8 (9.6)
Diarrhoea	11 (12.9)	18 (21.7)
Back pain	11 (12.9)	10 (12.0)
Pain in extremity	9 (10.6)	8 (9.6)
Shunt occlusion	9 (10.6)	6 (7.2)
Skin abrasion	8 (9.4)	12 (14.5)
Headache	6 (7.1)	10 (12.0)
Dizziness	5 (5.9)	9 (10.8)
Myalgia	4 (4.7)	9 (10.8)
Dialysis hypotension	3 (3.5)	9 (10.8)

MedDRA version 23.1

interfere with sleep; however, those with a score of 3–4 experienced sleep disturbance. A decline in the nighttime Shiratori severity score was observed from the start of treatment with difelikefalin and efficacy was maintained up to week 58. A certain percentage of patients (92.6% in MR–MR group and 72.0% in P-MR group) who had a

baseline nighttime symptom score of more than 3 points attained a score of 2 points or less by week 58. While there were differences between the groups, no differences were observed in patient background characteristics, and a reason for these apparent discrepancies could not be identified. In the subgroup analysis based on the presence or absence of insomnia, the improvement in the NRS score was greater in patients with insomnia than in those without insomnia. In a recent US study by Weiner et al., it was reported [14] that itch reduction with intravenous difelikefalin was associated with improved sleep quality in hemodialysis patients with moderate-to-severe pruritus.

These findings suggest that difelikefalin could potentially improve the quality of sleep over the long term by alleviating nighttime itching.

Higher dialysis efficiency is reported to reduce the prevalence of pruritus; however, many hemodialysis patients still have pruritus despite adequate Kt/V targets being met [15, 16], suggesting that an opioid imbalance may affect the occurrence of pruritus in these dialysis patients [17]. In this trial, difelikefalin reduced the NRS score regardless of the dialysis efficiency ($Kt/V < 1.6/\geq 1.6$), but the score reduction was more significant in patients with $Kt/V \geq 1.6$. For hemodialysis patients with pruritus who still have itching despite increased dialysis efficiency, difelikefalin could be useful for the treatment of dialysis pruritus by adjusting the opioid balance.

Difelikefalin was tolerated and safe for up to 58 weeks of treatment. AEs related to gastrointestinal symptoms were frequently reported, similar to those observed in the double-blind treatment period. Major AEs were pyrexia, contusion, vaccination complication, nasopharyngitis, shunt stenosis, and diarrhoea, most of which are commonly observed in hemodialysis patients. Treatment-related AEs with an incidence of ≥ 2% in any group were constipation, somnolence, and dizziness. On the basis of the onset time of AEs, there was no increase in the incidence of AEs associated with long-term administration, nor were there delayed AEs. Most of the AEs related to the gastrointestinal tract appeared early in treatment.

The safety profile of difelikefalin reflects the low lipophilicity of difelikefalin, which limits CNS access [1, 18]. The incidence of treatment-related AEs associated with CNS was low. Treatment-related insomnia, which is frequently reported in patients treated with centrally acting KOR agonists, was not observed. Furthermore, dependency was not observed in this study. This result is supported by other clinical trials of difelikefalin conducted to evaluate the potential for abuse and physical dependence [19, 20].

This trial has some limitations. First, the placebo effect of the double-blind period needs to be considered to better understand the influence this effect may have had on the long-term efficacy results obtained in this study. At the end of the double-blind period (week 6), the mean NRS score in the P-MR group was 1.56 points lower than baseline. Second, this extension treatment period was open-label and the efficacy of difelikefalin was assessed by comparison with the baseline and changes over the passage of time. Therefore, a long-term, randomized, double-blind, two-arm trial using a comparator is desirable to confirm long-term effectiveness. Finally, hemodialysis is required for the entire remaining life span of patients with Chronic Kidney Disease (CKD) in Japan. The expected remaining life expectancy of hemodialysis patients aged 60 is 11.9 years for male patients and 14.1 years for female patients [21]. An evaluation longer than 58 weeks may be desirable to confirm the efficacy and safety of difelikefalin in real-world clinical practice.

Conclusions

Difelikefalin is a novel drug that reduces itching and improves itch-related quality of life over the long term in hemodialysis patients with pruritus whose response to treatment with conventional medications has been inadequate; it has also demonstrated excellent safety and tolerability.

Abbreviations

AE	Adverse events
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
ECG	Electrocardiography
FAS	Full analysis set
ICH	International Council for Harmonisation
KOR	κ-Selective opioid receptor
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numerical rating scale
PGIC	Patient global impression of change
QOL	Quality of life
SAE	Serious adverse events
SD	Standard deviation
SS	Safety set
USA	United States

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41100-024-00557-9.

Supplementary Material 1.

Acknowledgements

The authors thank all the patients and their families who participated in this trial. The study was funded by Kissei Pharmaceutical Co., Ltd. (Tokyo, Japan) and supported by Maruishi Pharmaceutical Co., Ltd. (Osaka, Japan). Medical writing support for the development of this manuscript under the direction of the authors was provided by Tetsuji Asao, PhD (SunFlare Co., Ltd., Tokyo, Japan), which was funded by Kissei Pharmaceutical Co., Ltd. Yasuo Fukaya, Southern TOHOKU General Hospital; Takahiro Yajima, Matsunami General Hospital; Yukihiro Hamamoto, Matsunami General Hospital; Noriyasu Hagiwara, Matsunami General Hospital; Noritomo Itami, ITAMI KIDNEY CLINIC; Masami Komeda, Tondabayashi Hospital; Jong Il Kim, Chibune Clinic;

Hideaki Hattori, Chibune Clinic; Sakae Ishii, Higashimatsuyama Kohjin Clinic; Masahito Imanishi, Ishikiriseiki Hospital; Satoshi Funakoshi, Nagasaki Renal Center; Isao Ohsawa, Saiyu Soka Hospital; Noriyuki Degawa, Yamagata City Hospital Saiseikan; Toko Endo, H. N. Medic; Mariko Toyoda, Japanese Red Cross Kumamoto Hospital; Yorihiro Akamatsu, Katta General Hospital; Sadayoshi Ito, Katta General Hospital; Takashi Sato, Kaikoukai Central Clinic; Takashi Udagawa, Nippon Koukan Hospital; Masakazu Otsuka, Tokiwa Clinic; Masatsugu Sato, SATO Nephrology and Urology Clinic; Tomomasa Oguchi, Aizawa Hospital; Shintaro Yano, Maebashi Hirosegawa Clinic; Yosuke Saka, Kasugai Municipal Hospital; Hiroyuki Shimizu, Hasegawa Hospital; Haruyuki Ogura, Kurosawa Hospital; Toru Kagawa, Kochi Memorial Hospital; Yutaka Senga, Chigasaki Central Clinic; Yuji Kawaguchi, Minamiosaka Hospital; Kiichiro Fujisaki, Iizuka Hospital; Hideaki Shimizu, Daido Hospital; Nobuyuki Aizawa, Shizuoka Tokushukai Hospital; Tetsuya Shigehara, Jyoumou Ohashi Clinic; Toshiki Nishio, Omi Medical Center; Hideki Matsukawa, Naka Clinic; Ikuto Masakane, Yabuki Hospital; Hiroshi Kikuchi, Kikuchi Medical Clinic; Noriyuki Okada, Kajimoto Clinic; Hiroaki Obayashi, Kinashi Obayashi Hospital; Ryota Yoshitomi, Yoshitomi Medical Clinic; Harumichi Oka, Oka Hospital; Kyoko Ito, Heisei Hidaka Clinic; Naoaki Kimura, Okehazama Clinic; Shigeki Ando, Tohoku Medical and Pharmaceutical University Wakabayashi Hospital; Toshiro Shibata, Takayama Red Cross Hospital; Hisaki Shimada, Shinrakuen Hospital; Masahiro Yanase, Sunagawa City Medical Center; Motohide Isono, Shiga Hospital; Kouji Shibuya, Sumiyoshigawa Hospital; Isoji Sasagawa, Yamagata Tokushukai Hospital; Satoshi Sugiyama, Kanayama clinic; Hiroshi Ogawa, Kanayama clinic; Shuta Motonishi, Higashiyamato Nangai Clinic; and Nozomu Hiraiwa, Otowakinen Hospital; Masatomo Taniguchi, Fukuoka renal clinic; Yuichi Yoshida, Higashinaebo Hospital; Akira Kurosawa, Sakura Memorial Hospital; Kenichi Oguchi, Bousei Hospital; Momoyo Omata, Hachioji Azumacho Clinic; Masaharu Oura, Yaizu City Hospital; Hiroyuki Kinuno, Toyama Rosai Hospital; Akira Ohishi, Ohishi Naika Clinic; Makoto Watanabe, Makita Clinic Omori; Takayuki Toyoyama, H. N. Medic Kitahiroshima; Yoshiro Fujita, JOHAS Chubu Rosai Hospital; Kouichi Hirayama, Tokyo Medical University Ibaraki Medical Center; Yasuyuki Maruyama, Iwatsukiminami Hospital; Suguru Obunai, Yu Dialysis Clinic; Takashi Yamagishi, Tomei Fuji Clinic; Chikako Takaeda, Public Central Hospital of Matto Ishikawa; Daiki Hayashi, Public Central Hospital of Matto Ishikawa.

Author contributions

I.N., T.U., M.M., and S.O. contributed to the conception and design of the study and contributed to drafting the manuscript. T.U. and S.O. contributed to the collection and assembly of data. S.O. contributed to the analysis. All authors contributed to the critical review and final approval of the manuscript.

Funding

This study was funded by Kissei Pharmaceutical Co., Ltd. (Tokyo, Japan), which was involved in study design, data collection, data analysis, data interpretation, and writing of the clinical study report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Availability of data and materials

The study protocol and statistical analysis plan are published with previous report (reference 4). Research data are not shared due to a lack of patients' consent to release the data for researchers who are interested.

Declarations

Ethics approval and consent to participate

The study protocol, informed consent form, and other relevant study documentations were approved by the institutional review board. All patients gave written informed consent before initiation of any study-specific procedures.

Consent for publication

Not applicable.

Competing interests

N.T. and T.E. received consultant fees from Kissei Pharmaceutical. T.U., M.M., and S.O. are employees of Kissei Pharmaceutical. The other authors declare that they have no competing interests.

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Received: 18 March 2024 Accepted: 27 June 2024
Published online: 19 July 2024

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