

Figure S1. Worst Itching Intensity Numerical Rating Scale (A), Skindex-10Scale (B), and 5-D Itch Scale (C)

A. Worst Itching Intensity Numerical Rating Scale

INSTRUCTIONS
Please indicate the intensity of the WORST ITCHING you experienced over the past 24 hours by marking the box with the number that best describes it. After completing the scale below, please provide your initials in the SUBJECT INITIALS box indicating that you completed the scale <u>by yourself</u> and the DATE and TIME you completed the scale.

Worst Itching Over the Past 24 Hours
Please indicate the intensity of the WORST ITCHING you experienced over the past 24 hours.
0 1 2 3 4 5 6 7 8 9 10
<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
NO ITCHING WORST ITCHING IMAGINABLE

Date Completed:
<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
D D M M M Y Y Y Y

Time:
<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>
<input type="checkbox"/> AM <input type="checkbox"/> PM

SUBJECT INITIALS
First Middle Last
<input type="text"/> <input type="text"/> <input type="text"/>

B. Skindex-10 Scale

INSTRUCTIONS: During the past WEEK , how often have you been bothered by:							
	0 (Never bothered)	1	2	3	4	5	6 (Always bothered)
1. Your itching	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. The persistence/reoccurrence of your itching	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. The appearance of your skin from scratching	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Frustration about your itching	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Being annoyed about your itching	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Feeling depressed about your itching	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Feeling embarrassed about your itching	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. The effects of your itching on your interactions with others (for example: interactions with family, friends, close relationships, etc.)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. The effects of your itching on your desire to be with people	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. The effect of your itching making it hard to work or do what you enjoy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Date Completed:										
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
D	D	M	M	M	2	0				
					Y	Y	Y	Y		

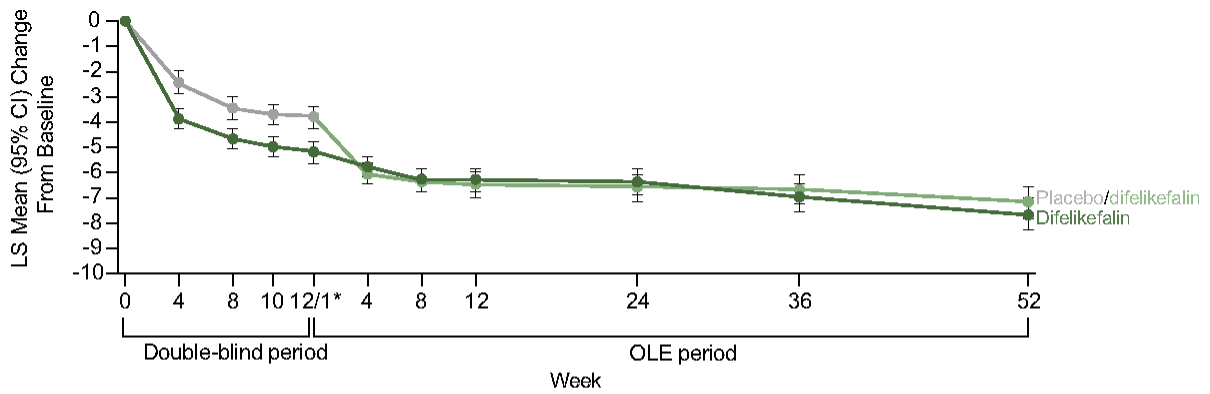
Time:			
<input type="text"/>	<input type="text"/>	:	<input type="text"/>
<input type="text"/>	<input type="text"/>		<input type="text"/>
<input type="checkbox"/>	AM	<input type="checkbox"/>	PM

SUBJECT INITIALS		
<i>First</i>	<i>Middle</i>	<i>Last</i>
<input type="text"/>	<input type="text"/>	<input type="text"/>

C. 5-D Itch Scale

1. DURATION:	During the last 2 weeks, how many hours a day have you been itching?						
	Less than 6 hrs/day	6-12 hrs/day	12-18 hrs/day	18-23 hrs/day	All day		
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
2. DEGREE:	Please rate the intensity of your itching over the past 2 weeks						
	Not present	Mild	Moderate	Severe	Unbearable		
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
3. DIRECTION:	Over the past 2 weeks has your itching gotten better or worse compared to the previous month?						
	Completely resolved	Much better, but still present	Little bit better, but still present	Unchanged	Getting Worse		
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
4. DISABILITY:	Rate the impact of your itching on the following activities over the last 2 weeks						
	Sleep	Never affects sleep	Occasionally delays falling asleep	Frequently delays falling asleep	Delays falling asleep and occasionally wakes me up at night	Delays falling asleep and frequently wakes me up at night	
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
		N/A	Never affects this activity	Rarely affects this activity	Occasionally affects this activity	Frequently affects this activity	Always affects this activity
	Leisure/Social	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Housework/Errands	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Work/School	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

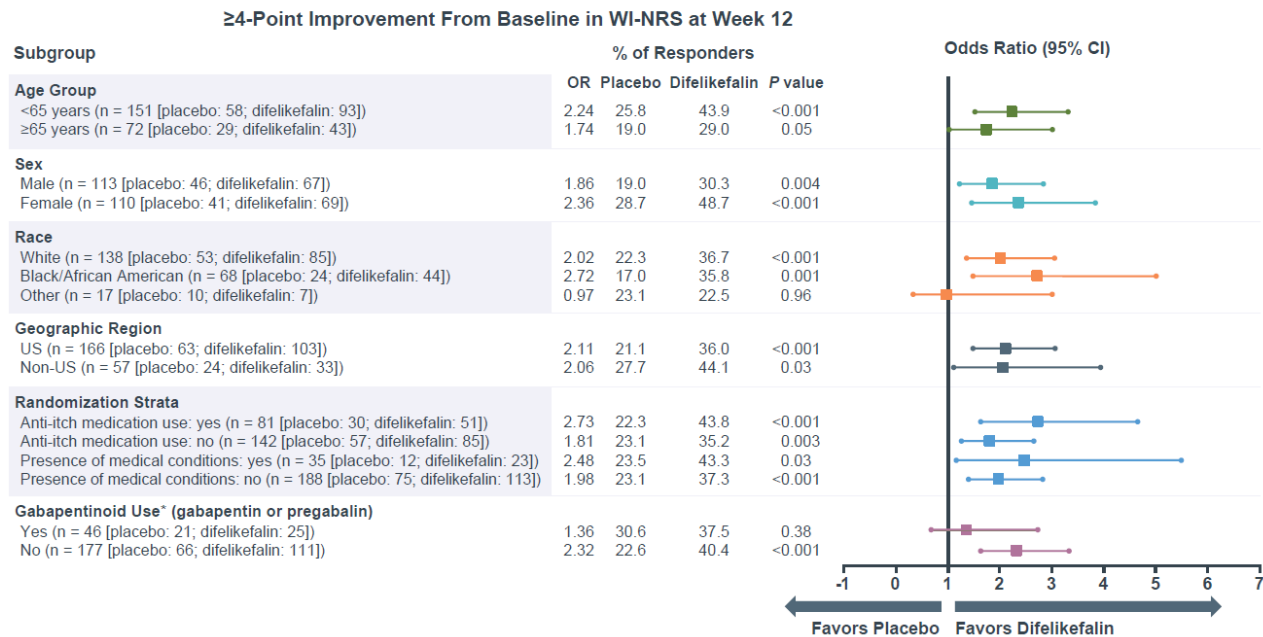
Figure S2: Improvement in 5-D Itch Total Score in the Pooled KALM-1 and KALM-2 Studies



Week	0	4	8	10	12/1*	4	8	12	24	36	52
Placebo/difelikefalin, n	372	355	363	359	364	352	312	300	206	153	97
Difelikefalin, n	335	325	324	324	331	311	276	265	193	140	92

*Week 12 of double-blind period; week 1 of OLE period. In KALM-2, in addition to the subjects who discontinued from the OLE period, 313/399 (78.4%) subjects could not complete the 52-week OLE period due to the sponsor's decision to stop the study for reasons unrelated to safety or lack of drug effect. A 2-week discontinuation following the end of the double-blind period of KALM-1 is not pictured in the figure.
 CI, confidence interval; LS, least squares; OLE, open-label extension.

Supplementary Figure 3. Subgroup Analyses for ≥4-Point WI-NRS Response at Week 12



*Prior gabapentinoid use included participants who used gabapentin or pregabalin for any condition, including itch. Differences between placebo and difelikefalin with respect to proportions were analyzed using a logistic regression model containing terms for treatment group, baseline WI-NRS score, use of anti-itch medication during the week prior to randomization, presence of specific medical conditions, and region/study. Missing weekly WI-NRS scores imputed by multiple imputation under a missing at random assumption. CI, confidence interval; WI-NRS, Worst Itching Intensity Numerical Rating Scale.

Item S1: Supplementary Methods

KALM-1 and KALM-2 Study Design

KALM-1 and KALM-2 were randomized, placebo-controlled, phase 3 studies with similar study designs. Both studies assessed the efficacy and safety of intravenous (IV) difelikefalin in adult participants with moderate-to-severe pruritus undergoing hemodialysis (HD). KALM-1 was a US study, and KALM-2 was a global study conducted in North America (United States and Canada), Europe (Czech Republic, Germany, Great Britain, Hungary, and Poland), and the Asia Pacific region (Australia, New Zealand, South Korea, and Taiwan).

Participants completed a 7-day run-in period to confirm they had moderate-to-severe chronic kidney disease–associated pruritus (CKD-aP), defined as weekly mean Worst Itching Intensity Numerical Rating Scale (WI-NRS) score of >4 in KALM-1 or ≥ 5 in KALM-2. Eligible participants with moderate-to-severe pruritus undergoing HD were randomly assigned (1:1) to receive IV difelikefalin 0.5 mcg/kg or placebo 3 times/week for 12 weeks. Participants were stratified according to use of concomitant anti-itch medications (yes or no) and by the presence or absence of specific medical conditions (i.e., history of fall or fracture [related to fall]; confusional state, mental status change, altered mental status, or disorientation; gait disturbance or movement disorder) during the run-in period. The placebo-controlled, double-blind period was followed by an open-label extension in which all participants were eligible to receive IV difelikefalin 0.5 mcg/kg 3 times per week for up to 52 weeks.

KALM-2 Eligibility Criteria

Eligible patients were adults (18–85 years of age) with end-stage renal disease (ESRD) who were undergoing HD 3 times per week for at least 3 months prior to screening. Patients had moderate-to-severe pruritus, defined as weekly mean of daily WI-NRS score ≥ 5 , assessed during a 7-day run-in period conducted immediately prior to randomization. During the 3-month period prior to screening, dialysis adequacy was controlled by requiring at least 2 single-pool Kt/V measurements ≥ 1.2 , or at least 2 urea reduction ratio measurements $\geq 65\%$, or 1 single-pool Kt/V measurement ≥ 1.2 and 1 urea reduction ratio measurement $\geq 65\%$ on different dialysis days.

Patients who required an occasional additional dialysis treatment to manage fluid overload or electrolyte excesses could be enrolled if no more than 1 such treatment was expected in any given week and no more than 4 additional dialyses were to occur during the 12-week double-blind period; patients receiving routine dialysis 4 days a week were not eligible. Patients were not eligible to participate in the study if they were receiving alternate dialysis modalities (eg, nocturnal dialysis).

Patients were excluded from the study if they were scheduled to receive a kidney transplant during the study; had new or changes in treatments within 14 days prior to screening for itch (including antihistamines, corticosteroids, opioids, gabapentin, or

pregabalin); had pruritus attributed to a cause other than ESRD or its complications; had localized itch restricted to the palms of the hands; had patient-reported pruritus only during the dialysis session; or had ongoing ultraviolet B treatment.

Table S1. Demographics and Participant Characteristics at Baseline in KALM-1 and KALM-2 Phase 3 Studies

Characteristics	KALM-1 ¹		KALM-2	
	Placebo (n = 189)	Difelikefalin (n = 189)	Placebo (n = 236)	Difelikefalin (n = 237)
Age, mean (SD), years	56.7 (13.9)	58.2 (11.2)	59.6 (13.1)	59.8 (13.2)
Male, n (%)	119 (63.0)	112 (59.3)	139 (58.9)	137 (57.8)
Race, n (%)				
White	93 (49.2)	91 (48.1)	169 (71.6)	164 (69.2)
Black or African American	76 (40.2)	82 (43.4)	38 (16.1)	53 (22.4)
Other*	18 (9.5)	15 (7.9)	29 (12.3)	20 (8.4)
Unknown	2 (1.1)	1 (0.5)	-	-
Region				
USA	189 (100)	189 (100)	133 (56.4)	146 (61.6)
Eastern Europe	-	-	60 (25.4)	54 (22.8)
Western Europe/ European origin	-	-	31 (13.1)	29 (12.2)
Asia	-	-	12 (5.1)	8 (3.4)
Prescription dry body weight, mean (SD), kg	85.3 (21.6)	85.9 (20.3)	80.0 (19.5)	81.4 (19.7)
Time since diagnosis of ESRD, mean (SD), years	5.7(5.2)	4.7 (3.9)	5.5 (4.5)	5.2 (4.7)
Years on chronic HD, mean (SD)	4.7 (4.2)	4.4 (4.0)	5.1 (4.3)	4.8 (4.6)
Cause of CKD, n (%)				
Hypertension**	78 (41.3)	63 (33.3)	60 (25.4)	59 (24.9)
Diabetes ^{††}	94 (49.7)	107 (56.6)	112 (47.5)	118 (49.8)

Cystic disease	2 (1.1)	0 (0)	13 (5.5)	14 (5.9)
Glomerulonephritis ^{‡‡}	4 (2.1)	7 (3.7)	12 (5.1)	11 (4.6)
Other	11 (5.8)	12 (6.3)	39 (16.5)	35 (14.8)
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Duration of pruritus, mean (SD), years	3.4 (3.4)	3.2 (3.2)	3.2 (3.2)	3.2 (4.5)
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Blood chemical testing [†]				
Bilirubin, mean (SD), mg/dL	0.5 (0.3)	0.6 (0.9)	0.5 (0.3)	0.5 (0.2)
Calcium, mean (SD), mg/dL	8.4 (0.8)	8.4 (0.8)	8.8 (0.8)	8.8 (0.8)
Phosphate, mean (SD), mg/dL	5.6 (1.9)	5.6 (1.9)	5.6 (2.2)	5.6 (2.2)
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Baseline use of anti-itch medications, n (%)	78 (41.3)	72 (38.1)	85 (36.0)	87 (36.7)
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Most commonly used (>2%) anti-itch medications at baseline, n (%)				
Diphenhydramine	71 (37.8)	61 (32.3)	24 (10.2)	43 (18.3)
Hydroxyzine	21 (11.2)	20 (10.6)	21 (13.1)	20 (9.4)
Hydrocortisone	8 (4.3)	6 (3.2)	8 (3.4)	5 (2.1)
Triamcinolone	3 (1.6)	5 (2.6)	-	-
Clemastine	-	-	10 (4.2)	7 (3.0)
Loratadine	4 (2.1)	1 (0.5)	4 (1.7)	5 (2.1)
Ammonium lactate	4 (2.1)	2 (1.1)	-	-
Cetirizine	-	-	7 (3.0)	4 (1.7)
Chlorphenamine	-	-	5 (2.1)	2 (0.9)
<hr/>				
History of specified medical condition, [‡] n (%)	28 (14.8)	25 (13.2)	37 (15.7)	42 (17.7)
<hr/>				

WI-NRS score, mean (SD)	7.2 (1.6)	7.1 (1.4)	7.1 (1.4)	7.3 (1.4)
5-D Itch scale total score, mean (SD)	17.9 (3.5)	16.9 (3.5)	16.2 (3.3)	16.7 (3.5)
Skindex-10 scale total score, mean (SD)	38.3 (15.4)	36.2 (14.4)	34.2 (14.7)	35.5 (15.0)

*Includes American Indian or Alaska Native, Asian, Native Hawaiian or Pacific Islander, and other.

†Conversion factors for units: bilirubin mg/dL to $\mu\text{mol/L}$, $\times 17.1$; calcium mg/dL to mmol/L, $\times 0.2495$; phosphate mg/dL to mmol/L, $\times 0.3229$.

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

**Hypertension included terms of "Hypertension only" and "Hypertension, Other".

††Diabetes included terms of "Diabetes only", "Diabetes, Hypertension", "Diabetes, Hypertension, Other", and "Diabetes, Other".

‡‡Glomerulonephritis included terms of "Glomerulonephritis only" and Glomerulonephritis, Other". ESRD, end-stage renal disease; HD, hemodialysis; SD, standard deviation; WI-NRS, Worst Inching Intensity Numerical Rating Scale.

Reference

1. Fishbane S, Jamal A, Munera C, Wen W, Menzaghi F. A phase 3 trial of difelikefalin in hemodialysis patients with pruritus. *N Engl J Med*. 2020;382(3):222-232

Table S2. Summary of Efficacy Outcomes in KALM-1 and KALM-2

Endpoint	KALM-1 ¹			KALM-2		
	Placebo (n = 189)	Difelikefalin (n = 189)	P value	Placebo (n = 236)	Difelikefalin (n = 235)	P value
Primary						
≥3-Point improvement from baseline in weekly mean of daily WI-NRS scores at week 12*						
Observed, n/N (%)	51/189 (30.9)	82/157 (52.2)		77/207 (37.2)	95/191 (49.7)	
Least-squares mean (95% CI), %	28.3 (21.0, 37.1)	50.9 (41.6, 60.2)		42.6 (33.4, 52.3)	53.4 (43.7, 62.8)	
Odds ratio (95% CI)		2.62 (1.68, 4.09)	<0.001		1.54 (1.05, 2.27)	0.03
Secondary						
≥4-Point improvement from baseline in weekly mean of daily WI-NRS scores at week 12*						
Observed, n/N (%)	53/189 (28.0)	64/157 (40.8)		52/207 (25.1)	72/191 (37.7)	
Least-squares mean (95% CI), %	18.0 (12.2, 25.7)	38.4 (29.6, 48.2)		26.4 (18.5, 36.2)	37.3 (27.7, 48.1)	
Odds ratio (95% CI)		2.85 (1.73, 4.70)	<0.001		1.66 (1.09, 2.52)	0.02
Least-squares mean change from baseline at week 12 in Skindex-10 total score (95% CI)	-12.0 (-14.5, -9.6)	-17.2 (-19.6, -14.7)	<0.001	-14.8 (-17.4, -12.2)	-16.6 (-19.3, -14.0)	0.17
Least-squares mean change from baseline at week 12 in 5-D Itch total score (95% CI)	-3.7 (-4.4, -3.1)	-5.0 (-5.7, -4.4)	<0.001	-3.8 (-4.5, -3.1)	-4.9 (-5.6, -4.2)	0.002 [†]

Other

Complete WI-NRS response (score of 0 or 1) at week 12

Observed, n/N (%)	13/189 (6.9)	26/189 (13.8)		18/236 (7.6)	29/237 (12.2)	
Least-squares mean (95% CI), %	5.7 (2.8, 11.0)	11.0 (6.2, 18.8)		7.8 (4.2, 14.2)	13.3 (7.7, 21.8)	
Odds ratio (95% CI)		2.06 (1.02, 4.19)	0.05		1.80 (0.96, 3.36)	0.07
Mean change from baseline in WI-NRS at week 12						
Least-squares mean (95% CI)	-2.0 (-2.4, -1.7)	-3.2 (-3.5, -2.8)	<0.001	-2.5 (-2.8, -2.1)	-3.1 (-3.4, -2.7)	0.008

*These data were analyzed without Cui, Hung, and Wang adjustment for interim and post-interim analyses. In the primary analyses of KALM-1 and KALM-2, *P* values were adjusted to account for a planned interim analysis for sample size re-estimation; this adjustment is not applicable to the pooled analyses and is not presented in this manuscript.

†Nominal *P* value; not considered influential based on sequential statistical analysis.

For the primary and secondary categorical endpoints, estimated proportions, odds ratio, and *P* value are based on a logistic regression model with terms for treatment group, baseline WI-NRS score, region (KALM-2 only), use of anti-itch medication during the week prior to randomization, and the presence of specific medical conditions.

Continuous endpoints were analyzed by analysis of covariance (ANCOVA) with treatment group as a fixed effect, and baseline score, region (KALM-2 only), and randomization stratification as covariates. Missing data were imputed using multiple imputation under missing at random assumption.

CI, confidence interval; SE, standard error; WI-NRS, Worst Itching Intensity Numerical Rating Scale.

Reference

2. Fishbane S, Jamal A, Munera C, Wen W, Menzaghi F. A phase 3 trial of difelikefalin in hemodialysis patients with pruritus. *N Engl J Med*. 2020;382(3):222-232