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ORIGINAL ARTICLE

Chronic kidney disease–associated pruritus and quality of life with difelikefalin treatment: a *post hoc* analysis of phase 3 data using the Skindex-10 questionnaire

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ABSTRACT

Background. Pruritus is a common condition in chronic kidney disease (CKD), especially for patients receiving haemodialysis. CKD-associated pruritus (CKD-aP) can be distressing and have a negative impact on quality of life (QoL). This *post hoc* analysis aimed to assess the relationship between pruritus relief and QoL.
Methods. Data from phase 3 trials [(NCT03422653, NCT03636269 grouped), and NCT03998163] of the novel antipruritic difelikefalin ($N = 914$) were used to assess the relationship between reductions in pruritus intensity at Week 12 (24-h Worst Itching Intensity Numeric Rating Scale; WI-NRS), perceived improvement in itch (Patient Global Impression of Change, PGI-C) and pruritus-related QoL (Skindex-10 questionnaire).
Results. Patients receiving difelikefalin had greater improvements in Skindex-10 total scores than those receiving placebo [LS mean treatment difference –3.4; 95% confidence interval (CI) –5.5, –1.3; $P = .002$] and greater improvements across Skindex-10 domains (disease, mood and social functioning) at Week 12. In patients receiving difelikefalin, those with clinically meaningful improvements in pruritus (≥3-point reduction in WI-NRS score) at Week 12 had a greater improvement in Skindex-10 total score (mean difference 14.2; 95% CI 11.0, 17.3; $P < .001$) and Skindex-10 domains than those with a <3-point reduction in WI-NRS score. Improvements in Skindex-10 total scores correlated with PGI-C.
Conclusions. Improvements in pruritus intensity following 12 weeks of treatment with difelikefalin were associated with improvements in QoL. Larger improvements in Skindex-10 scores were seen in patients with a greater reduction in pruritus intensity, indicating that improvements in pruritus are associated with a range of factors, such as mood and social functioning, that affect pruritus-related QoL.

Keywords: chronic kidney disease, haemodialysis, patient-reported outcomes, pruritus, quality of life

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KEY LEARNING POINTS

What was known:

- Pruritus is known to have a potentially large impact on the quality of life (QoL) of patients with chronic kidney disease (CKD).
- Difelikefalin is a novel antipruritic that has previously been shown to reduce itch in patients with CKD-associated pruritus (CKD-aP) versus placebo.

This study adds:

- This *post hoc* analysis reports that patients with CKD-aP undergoing haemodialysis who experienced a reduction in pruritus intensity—as measured by the Worst Itching Intensity Numeric Rating Scale—also reported improvements in several factors affecting QoL—as measured by the Skindex-10 questionnaire, such as mood and social functioning.
- Greater improvements in pruritus intensity and QoL were reported in those receiving difelikefalin versus those receiving placebo.

Potential impact:

- This analysis highlights that a reduction in pruritus intensity for patients with CKD results in improvements in various aspects of the patient's QoL.

INTRODUCTION

Pruritus can be an extremely distressing condition and is estimated to affect 18%–55% of patients with chronic kidney disease (CKD), depending on factors such as dialysis, age, severity of CKD and geographical location [1–7]. Recent data from the International Dialysis Outcomes and Practice Patterns Study estimated that over one-third of patients undergoing haemodialysis (HD) experienced moderate-to-extreme symptoms of CKD-associated pruritus (CKD-aP) [2, 3], while a separate study using the Kidney Disease Quality of Life survey estimated that fewer patients (14.5%) were very much/extremely bothered by pruritus [5].

Patients with CKD-aP often experience diminished quality of life (QoL) [5, 6, 8–10], with chronic pruritus as impactful on QoL as chronic pain in some cases [9]. Worse CKD-aP intensity has been associated with reduced sleep quality [3, 11–13], increased likelihood of patients suffering from depression, risk of hospitalization and increased mortality [10, 12, 14–18]. The importance of QoL in patients with CKD has been highlighted by initiatives such as the Standardized Outcomes in Nephrology partnership [19, 20]. Despite this, there has historically been a lack of approved treatments for CKD-aP, leading clinicians and patients to resort to off-label treatments that may have limited efficacy or tolerability for some patients [2, 21].

Difelikefalin is a novel antipruritic agent approved in the USA, EU and other locations for the treatment of moderate-to-severe CKD-aP in adults undergoing HD [22–27]. Efficacy and safety of difelikefalin in CKD-aP was assessed in three phase 3 trials: KALM-1, KALM-2 and Study 3105 [28–30]. Difelikefalin is a selective κ-opioid receptor agonist that acts by activating κ-opioid receptors on peripheral sensory neurons and immune cells [31–33]. The KALM trials demonstrated that difelikefalin significantly reduced pruritus intensity and improved pruritus-related QoL versus placebo [28, 30, 34], while the single-arm safety study, Study 3105, reported that difelikefalin was well tolerated and showed improved effects on sleep and pruritus-related QoL [29]. Difelikefalin demonstrated a favourable safety profile across the clinical trial programme, including during long-term use [28, 29, 35].

Patient-reported outcome (PRO) tools are key to effective disease monitoring in conditions with subjective symptoms such as pruritus [36]. A wide variety of PRO instruments are available for measuring generic and disease-specific health-related QoL, and can be used in clinical trials and in the clinical management of CKD-aP [10]. However, in routine practice, PRO tools are seldom utilized in clinical decision-making [37]. One such tool for the measurement of pruritus-related QoL, the Skindex-10 questionnaire, has been validated in patients with CKD-aP [10, 16] and was used in the phase 3 difelikefalin studies [28–30, 34]. Other PRO tools used in difelikefalin phase 3 studies include the Patient Global Impression of Change (PGI-C), which has previously been utilized in conjunction with the 24-h Worst Itching Intensity Numerical Rating Scale (WI-NRS) to confirm whether the improvement in pruritus intensity correlates with the patients' perception of the change in their condition [38, 39].

The present *post hoc* analysis of data from the pooled KALM-1 and -2 trials, and Study 3105, aimed to assess the relationship between pruritus relief—categorized as a $</\geq$3-point improvement (reduction) in 24-h WI-NRS score from baseline to Week 12—and QoL assessed by Skindex-10 question, domain and total score changes from baseline to Week 12 for patients receiving difelikefalin (KALM-1 and -2, and Study 3105) or placebo (KALM-1 and -2). The relationship between Skindex-10 score changes from baseline to Week 12 and PGI-C scores at Week 12 were also assessed (KALM-1 and -2).

MATERIALS AND METHODS

Studies

Exploratory *post hoc* analysis was conducted using pooled data from the phase 3 difelikefalin studies: KALM-1 and -2, and open-label Study 3105 (NCT03422653, NCT03636269 and NCT03998163, respectively). Detailed methods of these studies have been described in previous publications [28–30, 35].

Briefly, KALM-1 and -2 were multicentre, double-blind, placebo-controlled trials in which 851 adults with moderate-to-severe CKD-aP [baseline weekly mean WI-NRS score >4 (KALM-1) or ≥5 (KALM-2)] undergoing HD were randomized 1:1 to receive 0.5 μg/kg intravenous difelikefalin, or placebo, thrice weekly for 12 weeks [30].

Study 3105 was an open-label, multicentre, single-arm, safety study enrolling 222 adults with moderate-to-severe CKD-aP (WI-NRS ≥5 at baseline) undergoing HD, who received 0.5 μg/kg intravenous difelikefalin thrice weekly for 12 weeks [29].

Outcome measures included the proportion of patients reporting a ≥3-point improvement in WI-NRS score from

Table 1: KALM-1 and -2: changes from baseline to Week 12 in Skindex-10 scores for patients receiving difelikefalin.

	≥3-point WI-NRS improvement			<3-point WI-NRS improvement		
Skindex-10 question (mean, SD)	Baseline $n = 172$[a]	Week 12 $n = 175$[a]	Mean % change from baseline to end of Week 12 $n = 170$[a]	Baseline $n = 168$[a]	Week 12 $n = 167$[a]	Mean % change from baseline to end of Week 12 $n = 165$[a]
During the past week, how often have you been bothered by:						
1. Your itching?	4.7 (1.4)	1.7 (1.5)	−62.7 (30.7)	4.8 (1.4)	3.5 (1.6)	−24.3 (40.6)
2. The persistence/recurrence of your itching?	4.5 (1.4)	1.7 (1.5)	−60.0 (43.0)	4.4 (1.5)	3.3 (1.7)	−19.3 (50.0)
3. The appearance of your skin from scratching?	3.9 (1.9)	1.5 (1.8)	−64.2 (42.5)	3.9 (1.9)	2.9 (1.8)	−25.4 (61.3)
Disease domain (Q1–3)	13.1 (4.1)	4.9 (4.3)	−61.6 (35.1)	13.1 (4.2)	9.7 (4.6)	−20.0 (49.9)
4. Frustration about your itching?	4.6 (1.6)	1.5 (1.7)	−69.2 (35.0)	4.3 (1.8)	2.9 (1.9)	−32.6 (56.3)
5. Being annoyed about your itching?	4.4 (1.7)	1.5 (1.7)	−65.2 (45.1)	4.3 (1.9)	2.9 (1.9)	−33.1 (44.9)
6. Feeling depressed about your itching?	2.6 (2.3)	0.9 (1.4)	−66.5 (54.1)	2.6 (2.2)	2.1 (1.9)	−32.0 (51.5)
Mood/emotional distress domain (Q4–6)	11.6 (4.7)	3.8 (4.5)	−69.5 (35.0)	11.3 (5.1)	7.9 (5.3)	−30.3 (47.8)
7. Feeling embarrassed about your itching?	2.9 (2.3)	1.0 (1.6)	−68.2 (37.8)	3.2 (2.1)	2.3 (2.0)	−25.4 (79.9)
8. The effects of your itching on your interactions with others (e.g. interactions with family, friends, close relationships etc.)	2.8 (2.2)	0.9 (1.5)	−70.2 (41.4)	2.8 (2.2)	2.2 (2.0)	−27.9 (65.5)
9. The effects of your itching on your desire to be with people?	2.7 (2.2)	0.9 (1.4)	−67.8 (51.0)	2.6 (2.2)	2.1 (2.0)	−29.0 (62.7)
10. The effect of your itching making it hard to work or do what you enjoy?	2.8 (2.1)	0.9 (1.3)	−71.8 (42.4)	2.7 (2.1)	2.1 (2.0)	−28.4 (70.1)
Social functioning domain (Q7–10)	11.2 (8.1)	3.7 (5.4)	−68.2 (52.5)	11.3 (7.7)	8.6 (7.4)	4.7 (204.6)
Total score	36.0 (15.1)	12.3 (12.9)	−65.2 (42.9)	35.5 (14.9)	26.0 (16.1)	−15.4 (82.5)

[a]*n* are given for the total score.
Q, question; SD, standard deviation; WI-NRS, 24-hour Worst Itching Intensity Numeric Rating Scale.

baseline to Week 12, proportion of patients with ≥4-point improvement in WI-NRS score and change from baseline to Week 12 in pruritus-related QoL measured using the Skindex-10 questionnaire [29, 30].

This analysis assessed the change in Skindex-10 question, domain, and total scores from baseline to Week 12 in all patients with available data. The Skindex-10 questionnaire consists of 10 questions that ask patients how often in the past week they have been bothered by different aspects of their pruritus (Supplementary data, Fig. S1) [16, 30]. For each question, scores range from 0 ('never bothered') to 6 ('always bothered'). Questions can be grouped into three pruritus-related domains: disease (questions 1–3), mood/emotional distress (questions 4–7) and social functioning (questions 8–10); the total Skindex-10 score (0–60) is calculated as the sum of the numeric values of each answer [16, 30]. A ≥15-point reduction from baseline in the total Skindex-10 score has been reported to indicate a clinically relevant improvement in QoL in adult patients undergoing HD with moderate-to-severe pruritus [30, 38].

Owing to differences in study design, not all results will use data from both KALM-1 and -2 and Study 3105. Changes in Skindex-10 score from baseline to Week 12 were compared for patients receiving difelikefalin versus placebo (KALM-1 and -2), and for patients receiving difelikefalin only (Study 3105) with or without a clinically meaningful reduction in pruritus intensity (defined as a ≥3-point improvement in WI-NRS score [39, 40]) from baseline to Week 12 and reporting different PGI-C categories (KALM-1 and -2).

Statistical analysis

For KALM-1 and -2 analyses, changes from baseline to Week 12 in Skindex-10 scores were compared between treatment groups using analysis of covariance with fixed effects for treatment, baseline score, use of anti-pruritic medication during the week prior to randomization, presence of specific medical conditions and a region/study combined variable as covariates. Least squares (LS) means and 95% confidence intervals (CIs) are presented. Missing values were not imputed. For patients receiving difelikefalin, changes from baseline to Week 12 in Skindex-10 scores between clinically meaningful reduction in pruritus intensity [<3 and ≥3-point improvement (reduction) in 24-h WI-NRS score from baseline to Week 12] were compared using a *t*-test. Means and 95% CIs are presented (including for the comparison of patients reporting different PGI-C categories). Estimated % used logistic regression model with terms for baseline score, treatment group, use of anti-itch medication during the week prior to randomization, presence of specific medical conditions and the region/study combined variable. For Study 3105, all comparisons were conducted using a *t*-test; means and

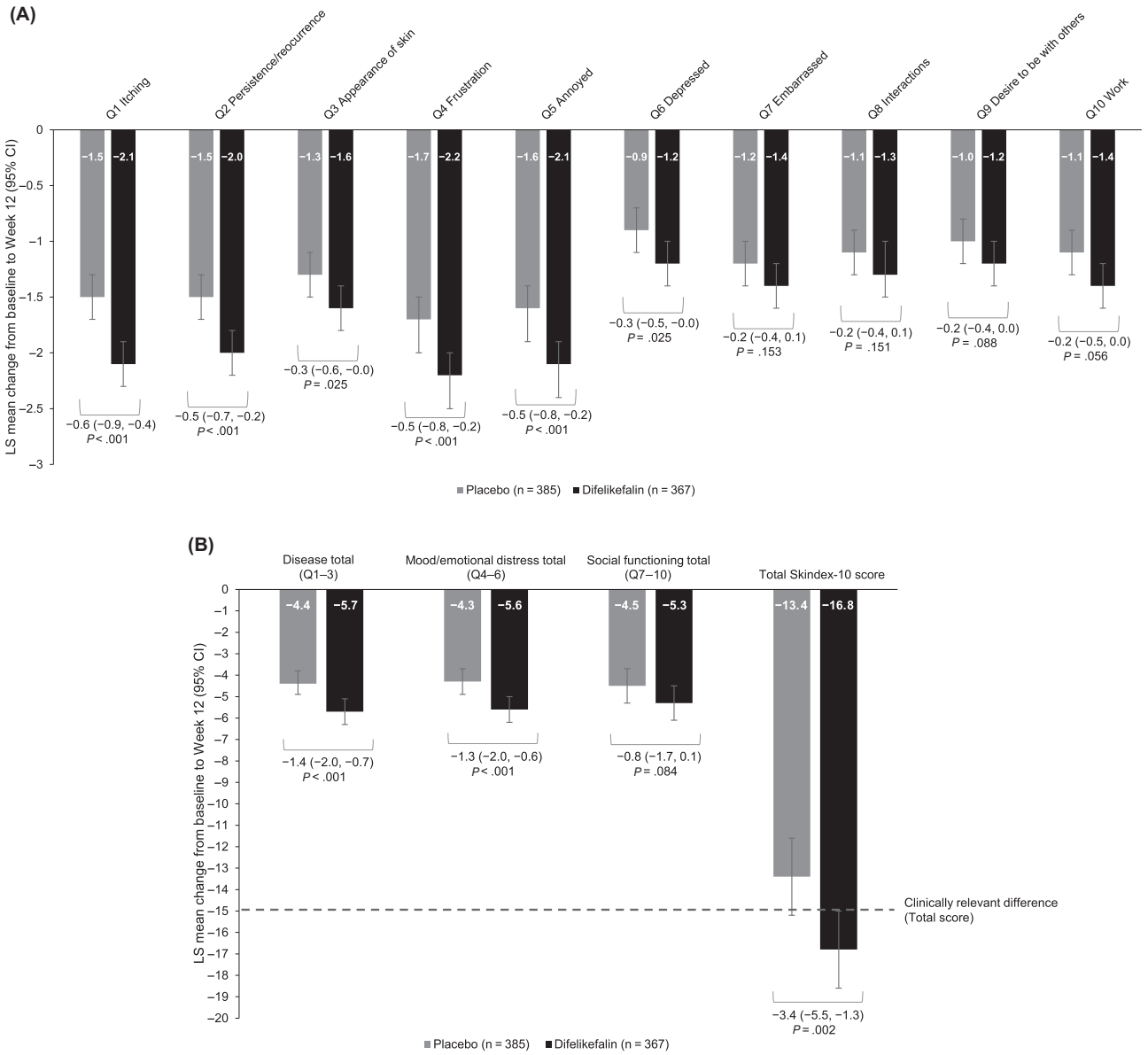

Figure 1: KALM-1 and -2: change from baseline to Week 12 in (**A**) Skindex-10 individual questions and (**B**) Skindex-10 domain and total scores for patients receiving difelikefalin versus placebo (ITT population). ANCOVA, analysis of covariance; CI, confidence interval; ITT, intention-to-treat; LS, least squares; Q, question. ANCOVA test used to determine significance; labels show treatment differences in LS mean change from baseline to Week 12 (95% CI) between difelikefalin and placebo. LS mean and 95% CIs were based on ANCOVA with fixed effects for treatment, baseline Skindex-10 score, use of anti-pruritic medication during the week prior to randomization, the presence of specific medical conditions and a region/study combined variable as covariates. Missing values were not imputed. Clinically relevant difference in Skindex-10 total score was defined as a ≥15-point improvement from baseline [28, 30].

95% CIs are presented. As this was an exploratory *post hoc* analysis, all *P*-values should be interpreted with caution.

RESULTS

Baseline characteristics

In total, 752 patients (385 patients receiving difelikefalin and 367 patients receiving placebo) from KALM-1 and -2, and 216 patients from Study 3105 had total Skindex-10 scores at baseline and were included in this analysis. Of these patients, 705 from KALM-1 and -2 (340 patients receiving difelikefalin and 365 patients receiving placebo) and 189 patients from Study 3105 reported a ≥3 or <3-point improvement in WI-NRS score at Week 12. The *n* numbers for Skindex-10 scores varied by question, domain and total scores. Baseline Skindex-10 question and domain scores were consistent across all three studies (Tables 1 and 2).

Relationship between improvement in Skindex-10 scores and treatment with difelikefalin or placebo

In KALM-1 and -2, a mean change from baseline to Week 12 was reported in Skindex-10 individual question scores for both difelikefalin- (Table 1 and Fig. 1A) and placebo-treated

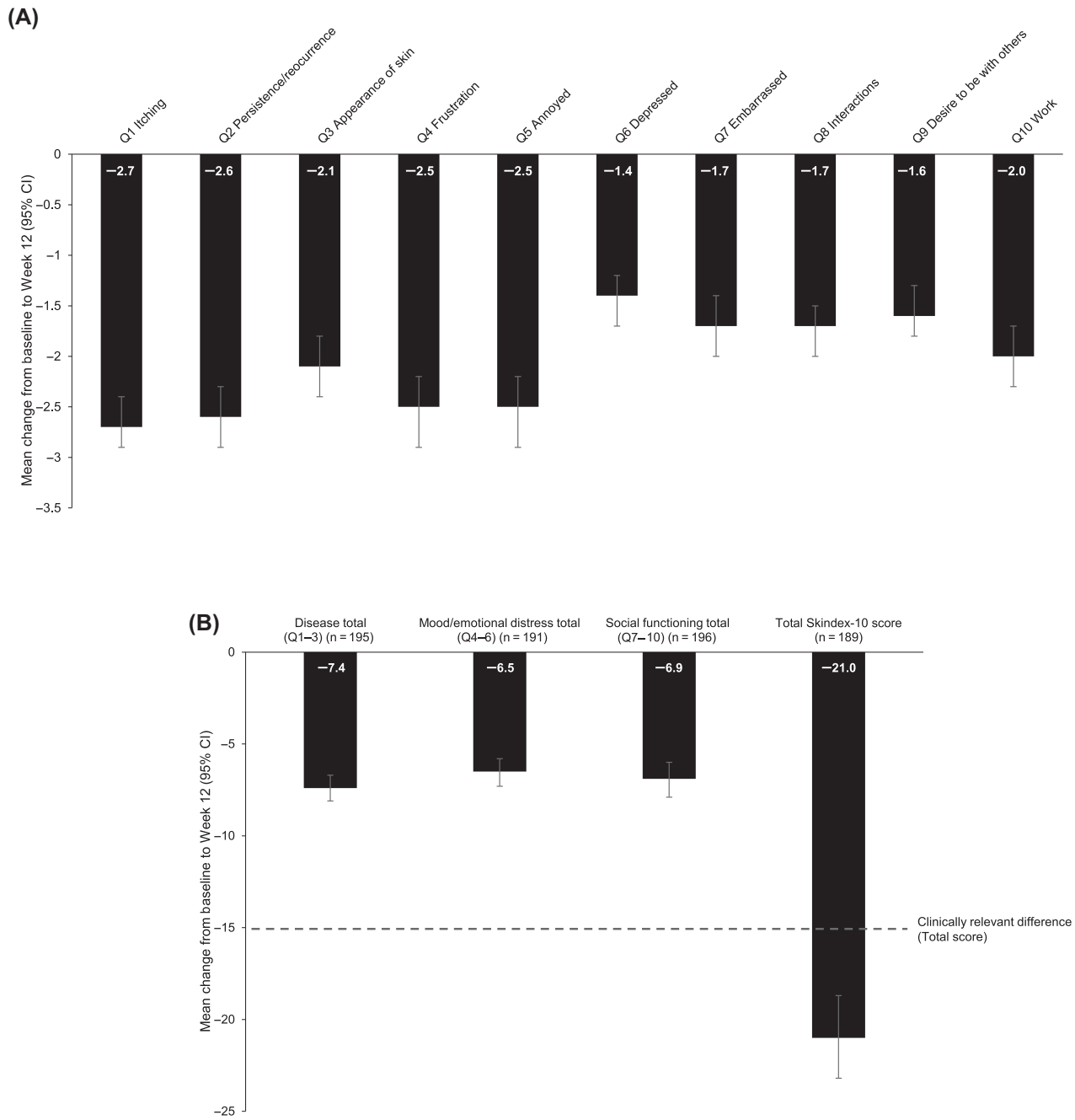

Figure 2: Study 3105: change from baseline to Week 12 in (**A**) Skindex-10 individual questions and (**B**) Skindex-10 domain and total scores for patients receiving difelikefalin (safety population). Q, question. Numbers of patients analysed for each question were: 197 (Q1 'Itching', Q2 'Persistence/reoccurrence, Q8 'Interactions', Q9 'Desire to be with others' and Q10 'Work'), 196 (Q6 'Depressed' and Q7 'Embarrassed'), 195 (Q3 'Appearance of skin' and Q5 'Annoyed'), and 194 (Q4 'Frustration'). Clinically relevant difference in Skindex-10 total score was defined as a ≥15-point improvement from baseline [30, 38].

groups (Fig. 1A), with significantly greater treatment differences (improvements) reported by patients receiving difelikefalin versus placebo for all questions in the disease and mood/emotional distress domains (questions 1–6; all $P < .05$) and numerically greater treatment differences in questions in the social functioning domain (questions 7–10) (Fig. 1A). This resulted in greater improvements with difelikefalin versus placebo in the disease (LS mean treatment difference −1.4; 95% CI −2.0, −0.7; $P < .001$) and mood/emotional distress domains (LS mean treatment difference −1.3; 95% CI −2.0, −0.6; $P < .001$), and numerically greater improvements in the social functioning domain (LS mean treatment difference −0.8; 95% CI −1.7, 0.1; $P = .084$). Greater improvements with difelikefalin versus placebo were also seen in the Skindex-10 total score (difelikefalin: −16.8; placebo: −13.4; LS mean treatment difference −3.4; 95% CI −5.5, −1.3; $P = .002$) (Fig. 1B).

Similar trends of improvement to those reported for KALM-1 and -2 were observed in Study 3105. Mean reductions (improvements) in Skindex-10 scores with difelikefalin from baseline to Week 12 were reported for all questions (Fig. 2A

Table 2: Study 3105: changes from baseline to Week 12 in Skindex-10 scores in patients receiving difelikefalin.

	≥3-point WI-NRS improvement			<3-point WI-NRS improvement		
Skindex-10 question (mean, SD)	Baseline $n = 140$[a]	Week 12 $n = 142$[a]	Mean % change from baseline to end of Week 12 $n = 139$[a]	Baseline $n = 49$[a]	Week 12 $n = 50$[a]	Mean % change from baseline to end of Week 12 $n = 48$[a]
During the past week, how often have you been bothered by:						
1. Your itching?	4.7 (1.3)	1.6 (1.5)	−65.0 (31.9)	4.8 (1.2)	3.3 (1.6)	−30.4 (31.8)
2. The persistence/recurrence of your itching?	4.5 (1.4)	1.4 (1.5)	−66.2 (33.8)	4.5 (1.2)	3.1 (1.6)	−31.2 (33.9)
3. The appearance of your skin from scratching?	3.7 (2.0)	1.2 (1.6)	−67.0 (43.2)	3.2 (1.9)	2.4 (1.9)	−28.6 (59.2)
Disease domain (Q1–3)	12.9 (4.0)	4.2 (4.1)	−65.9 (31.6)	12.5 (3.6)	8.7 (4.6)	−30.7 (31.4)
4. Frustration about your itching?	4.4 (1.7)	1.4 (1.6)	−65.0 (44.7)	3.8 (1.9)	2.6 (2.2)	−35.3 (58.5)
5. Being annoyed about your itching?	4.3 (1.8)	1.2 (1.6)	−66.1 (61.7)	3.8 (2.2)	2.8 (2.1)	−29.1 (69.8)
6. Feeling depressed about your itching?	2.1 (2.0)	0.5 (1.1)	−73.3 (48.4)	2.1 (2.1)	1.3 (1.9)	−42.6 (78.0)
Mood/emotional distress domain (Q4–6)	10.9 (4.7)	3.1 (3.7)	−67.3 (49.5)	9.5 (5.4)	6.7 (5.5)	−37.4 (47.5)
7. Feeling embarrassed about your itching?	2.5 (2.1)	0.6 (1.1)	−77.3 (35.6)	2.4 (2.2)	1.5 (2.0)	−34.0 (93.1)
8. The effects of your itching on your interactions with others (e.g. interactions with family, friends, close relationships etc.)	2.5 (2.0)	0.5 (1.0)	−78.5 (40.2)	2.5 (2.3)	1.4 (1.8)	−43.0 (101.6)
9. The effects of your itching on your desire to be with people?	2.2 (1.9)	0.4 (1.1)	−84.1 (44.1)	2.2 (2.2)	1.1 (1.8)	−52.3 (55.9)
10. The effect of your itching making it hard to work or do what you enjoy?	2.7 (2.0)	0.4 (1.0)	−79.9 (43.7)	2.6 (2.2)	1.3 (1.8)	−40.4 (81.3)
Social functioning domain (Q7–10)	9.9 (7.0)	2.0 (3.8)	−75.5 (45.3)	9.6 (8.1)	5.3 (6.9)	−49.4 (55.4)
Total score	33.6 (13.9)	9.2 (10.3)	−70.2 (30.5)	31.1 (14.9)	20.9 (15.3)	−35.4 (38.3)

[a]*n* are given for the total score.
Q, question; SD, standard deviation; WI-NRS, 24-hour Worst Itching Intensity Numeric Rating Scale.

and Table 2) and domains (disease: −7.4; mood/emotional distress: −6.5; social functioning: −6.9). The mean improvement in total score from baseline to Week 12 was −21.0, which was greater to that reported in KALM-1 and KALM-2 (Fig. 2B).

Relationship between WI-NRS score improvement and Skindex-10 score in patients treated with difelikefalin

Across all studies, greater improvements in Skindex-10 question scores from baseline to Week 12 were reported for patients treated with difelikefalin with a ≥3-point improvement in WI-NRS score versus patients with a <3-point improvement in WI-NRS score (all $P < .05$) (Figs 3 and 4). Reductions (improvements) in individual question scores for patients receiving difelikefalin with a ≥3-point improvement in WI-NRS score from baseline to Week 12 ranged from a mean of –1.8 to –3.1 for patients in KALM-1 and -2 (Fig. 3A) and –1.6 to –3.1 for patients in Study 3105 (Fig. 4A), compared with a mean of –0.5 to –1.5 for patients in KALM-1 and -2 (Fig. 3A) and –0.8 to –1.5 for patients in Study 3105 (Fig. 4A) for patients receiving difelikefalin with a <3-point improvement in WI-NRS score from baseline to Week 12.

In KALM-1 and -2, mean improvements in Skindex-10 domains and total score from baseline to Week 12 reported by patients receiving difelikefalin with ≥3-point improvements in WI-NRS score were greater than those reported for patients with <3-point improvements in WI-NRS score (disease domain, −8.3 versus −3.4 for ≥3-point and <3-point WI-NRS score improvement, respectively; mood/emotional distress domain, −7.9 versus −3.5; social functioning domain, −7.5 versus −2.7; and −23.8 versus −9.7 in the total score; all $P < .001$) (Fig. 3B). The corresponding mean percentage [standard deviation (SD)] change in total Skindex-10 scores from baseline to Week 12 was −65.2% (42.9) for ≥3-point improvements in WI-NRS score and −15.4% (82.5) for 3-point improvements (Table 1).

Results for Skindex-10 domain and total scores in Study 3105 followed a similar pattern. Mean improvements reported by patients receiving difelikefalin from baseline to Week 12 with a ≥3-point improvement in WI-NRS score were approximately double those reported for patients with <3-point improvements (disease domain: −8.7 versus −3.8 for ≥3-point and <3-point WI-NRS score improvement, respectively; mood/emotional distress domain: −7.8 versus −3.1; social functioning domain −8.0 versus −4.3; total score: −24.4 versus −11.4; all $P < .001$) (Fig. 4B). Absolute and relative percentage improvements were consistent in KALM-1 and -2, and Study 3105. The corresponding mean percentage (SD) change in total Skindex-10 scores from baseline to Week 12 in Study 3105 was −70.2% (30.5) for ≥3-point improvements in WI-NRS score and −35.4% (38.3) for <3-point improvements (Table 2).

Similar results were observed for patients reporting ≥4-point improvements in WI-NRS score, compared with <4-point improvements (Supplementary data, Figs S2 and S3). Patients

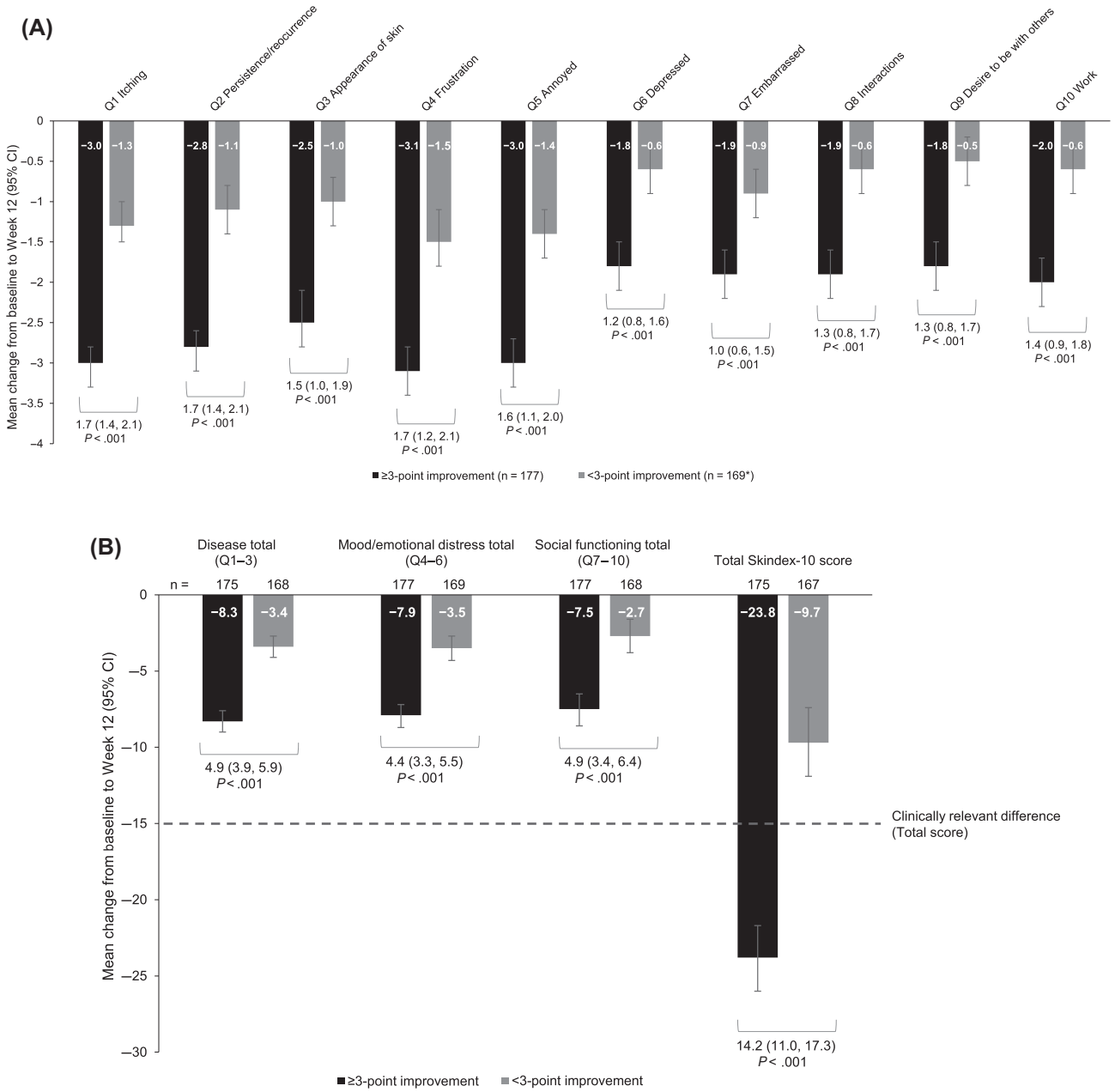

Figure 3: KALM-1 and -2: change from baseline to Week 12 in (**A**) Skindex-10 individual questions and (**B**) Skindex-10 domain and total scores for patients receiving difelikefalin with <3-point improvement versus ≥3-point improvement in WI-NRS score (ITT population). ITT, intention-to-treat; Q, question. *$n = 169$ for all questions except for Q7 'Embarrassed', for which $n = 168$. t-test used to determine significance; labels show treatment differences in mean change from baseline to Week 12 (95% CI) between patients with <3-point WI-NRS improvement and ≥3-point WI-NRS improvements at Week 12; clinically relevant difference in Skindex-10 total score was defined as a ≥15-point improvement from baseline [30, 38].

with ≥4-point improvements in WI-NRS score experienced significantly greater improvements in Skindex-10 question, domain, and total scores versus patients with <4-point improvements (all $P < .05$).

In addition, of patients with moderate itch (WI-NRS <7) at baseline, 59.7% of patients receiving difelikefalin and 30.7% of patients receiving placebo achieved a ≥15-point improvement of Skindex-10 total score. The corresponding patients with severe itch (WI-NRS ≥7) at baseline who achieved a ≥15-point improvement of Skindex-10 total score were 54.1% of patients receiving difelikefalin and 47.8% of patients receiving placebo (Supplementary data, Fig. S4A). In Study 3105, 72.1% of patients with severe CKD-aP at baseline (WI-NRS ≥7) achieved a ≥15-point improvement of Skindex-10 total score, compared with 43.3% of patients with moderate CKD-aP (WI-NRS <7) (Supplementary data, Fig. S4B).

In KALM-1 and KALM-2, patients with ≥3-point improvements in WI-NRS score at Week 12 experienced greater improvements in Skindex-10 domain and total scores (Supplementary data, Fig. S5A) versus patients with <3-point improvements

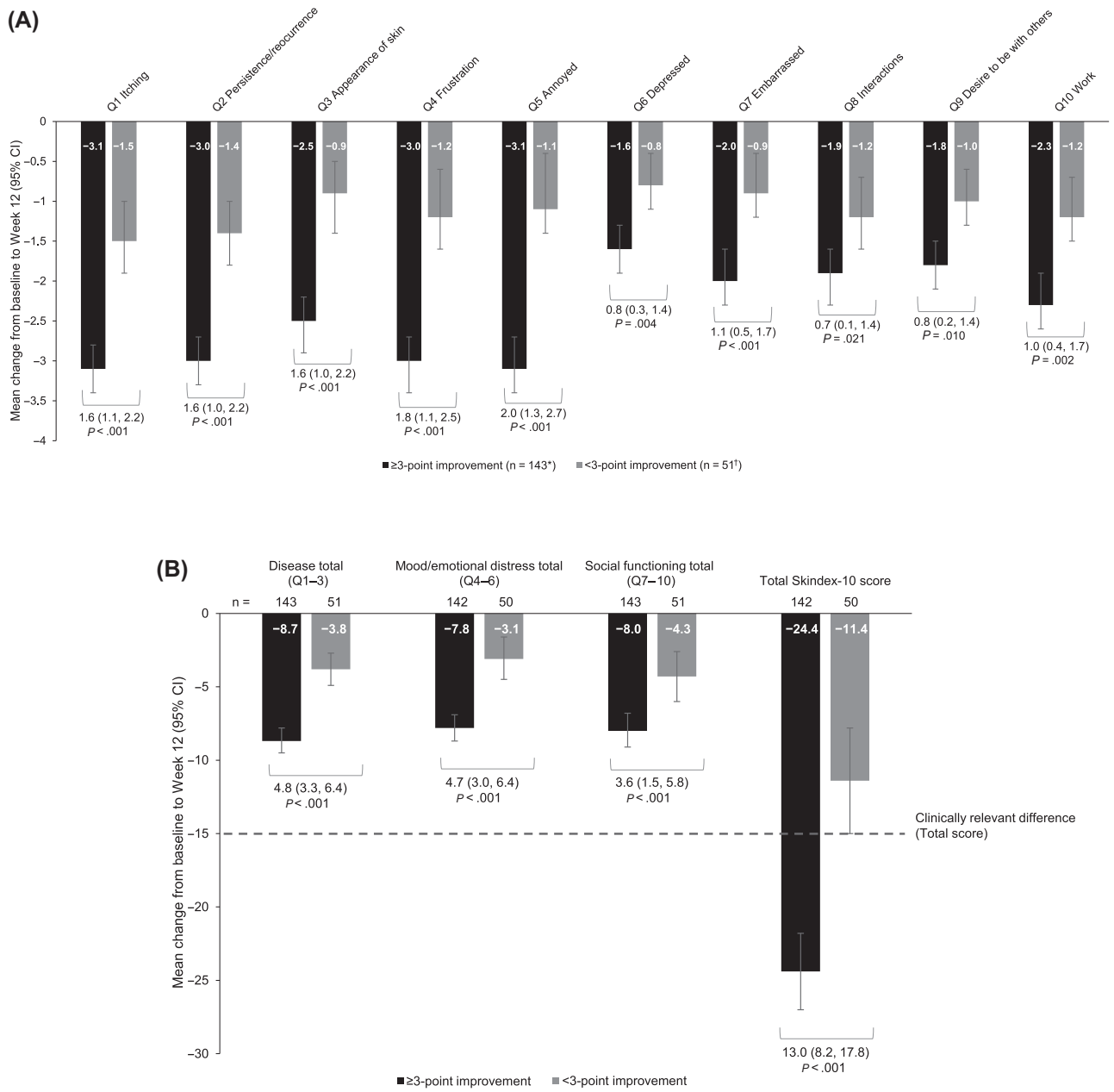

Figure 4: Study 3105: change from baseline to Week 12 in (**A**) Skindex-10 individual questions and (**B**) Skindex-10 domain and total scores for patients receiving difelikefalin with <3-point improvement versus ≥3-point improvement in WI-NRS score (safety population). Q, question. *$n = 143$ for all questions except for Q4 'Frustration', for which $n = 142$; †$n = 51$ for all questions except for Q5 'Annoyed', for which $n = 50$. *t*-test used to assess significance labels show treatment differences in mean change from baseline to Week 12 (95% CI) between patients with <3-point WI-NRS improvement and ≥3-point WI-NRS improvements at Week 12; clinically relevant difference in Skindex-10 total score was defined as a ≥15-point improvement from baseline [30, 38].

in WI-NRS scores (Supplementary data, Fig. S5B), regardless of whether they were receiving difelikefalin or placebo.

Assessment of relationships between Skindex-10 scores and PGI-C categories at Week 12 in KALM-1 and -2

Greater improvements in mean Skindex-10 total and domain scores were associated with greater improvements in PGI-C from baseline to Week 12 (Fig. 5A and B). Patients reporting that their pruritus had 'much improved' or 'very much improved' had greater improvements in Skindex-10 total score (Fig. 5A), whereas patients with 'no change' or worsened pruritus achieved minimal, if any, improvements in Skindex-10 domains/total scores. For those who reported that their pruritus had 'minimally' to 'very much improved' at Week 12, consistent improvements were seen across all Skindex-10 domains (Fig. 5B).

DISCUSSION

This analysis is the first to suggest an association between reduced pruritus intensity and improved QoL in patients with

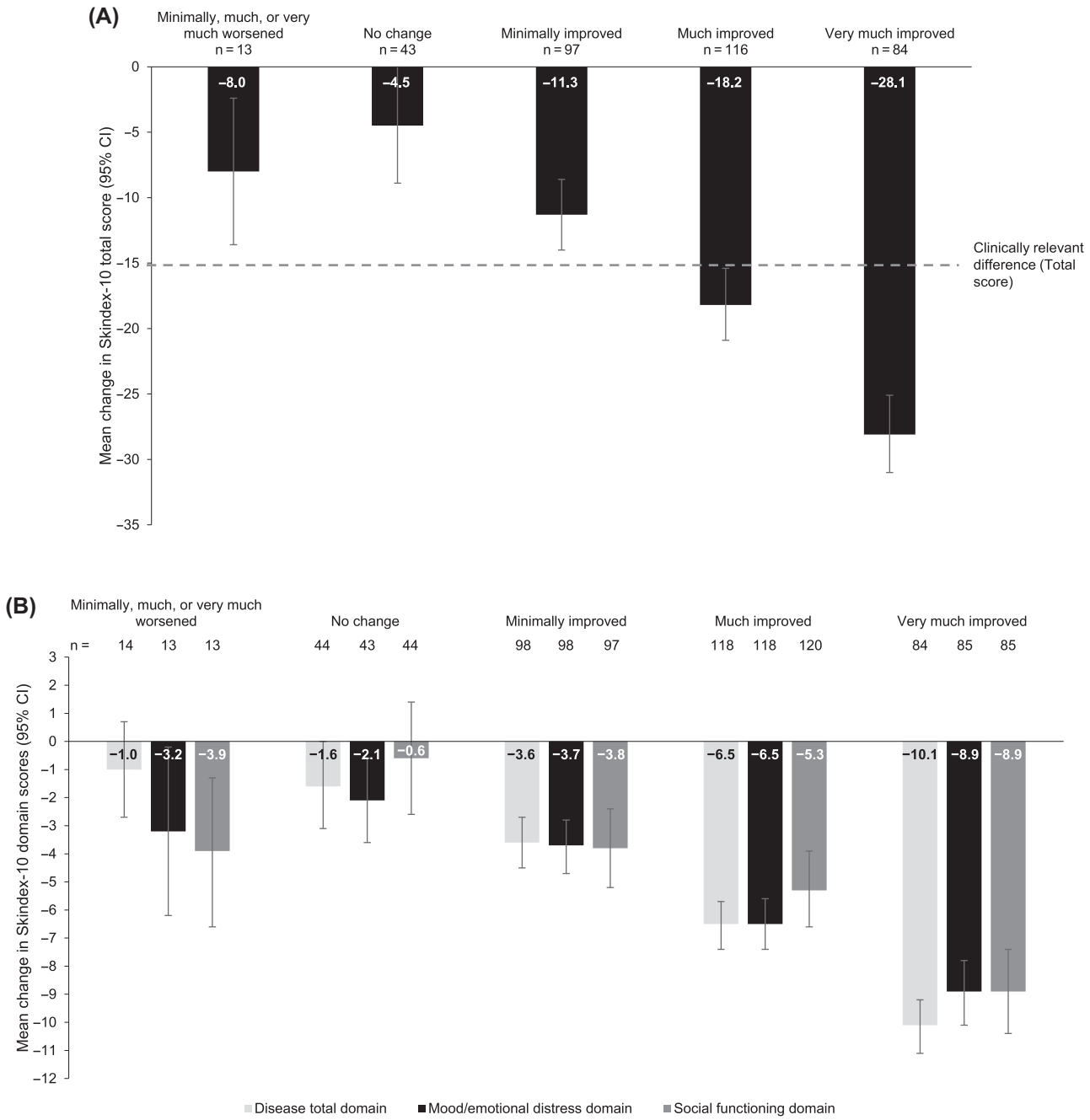

Figure 5: KALM-1 and -2: change from baseline to Week 12 in Skindex-10 (**A**) total and (**B**) domain scores in patients receiving difelikefalin by PGI-C categories at Week 12 (ITT population). ITT, intention-to-treat. Error bars denote 95% CIs; clinically relevant difference in Skindex-10 total score was defined as a ≥15-point improvement from baseline [30, 38].

CKD receiving a pharmacological intervention, with pruritus intensity measured using a validated, standardized instrument (the WI-NRS) and patient QoL measured by the Skindex-10 tool. Several previous studies have reported an association between pruritus intensity and poor QoL, indicating that patients with more severe pruritus intensity experience worse QoL than those with mild pruritus symptoms [3, 5, 6, 9, 10, 14, 16], and that improvements in pruritus intensity may lead to improvements in pruritus-related QoL, as shown in the phase 3 difelikefalin studies [16, 28–30, 34]. The results of this *post hoc* analysis add to this evidence by showing greater improvements in Skindex-10 total scores for patients receiving difelikefalin versus placebo, and in those receiving difelikefalin with a clinically meaningful ≥3-point improvement in WI-NRS score than those with a <3-point improvement in WI-NRS score.

In KALM-1 and -2, patients receiving difelikefalin for 12 weeks had greater improvements in total Skindex-10 scores than those receiving placebo [30], irrespective of baseline pruritus severity. In patients who had severe itch at baseline, the percentage of those who achieved an improvement in QoL

(≥15-point improvement of Skindex-10 total score) at Week 12 was comparable with those with moderate itch at baseline. Notably, even patients treated with placebo experienced improvements in QoL, albeit not to the same extent as those treated with difelikefalin. It has previously been reported that participation in clinical trials may result in better outcomes for patients, irrespective of treatment provided [41, 42], possibly owing to enhanced care and monitoring over the study period. In addition, CKD-aP is known to be underestimated, underreported and likely underdiagnosed [11, 43]. Acknowledgement of the severity of symptoms and their impact on patients, as well as the potential for pruritus-relief while taking part in clinical trials, may improve patients' responses to QoL questionnaires. However, the greater improvements in QoL and pruritus intensity reported by patients receiving difelikefalin versus placebo imply that the greater improvements seen are related to difelikefalin treatment. In Study 3105 a higher share of patients who had severe CKD-aP at baseline achieved an improvement in QoL (≥15-point improvement in Skindex-10 total score) at Week 12 compared with those with moderate CKD-aP at baseline, which could be attributable to a larger absolute improvement in itch intensity in patients with severe CKD-aP at baseline [44].

Improvements in QoL from baseline to Week 12 following difelikefalin treatment were reported for all questions in the Skindex-10 questionnaire in KALM-1 and -2, and Study 3105. This may be indicative of the impact that pruritus-related discomfort has on many aspects of patients' lives. Notably, patients receiving difelikefalin and reporting clinically meaningful ≥3-point improvements in pruritus intensity via the WI-NRS also reported consistent improvements across Skindex-10 domains, suggesting that multiple aspects contributing to patients' QoL can be improved by achieving reductions in pruritus intensity.

In the current analysis the subset of patients receiving difelikefalin reporting that they felt that their itch was 'much' or 'very much' improved (via the PGI-C) at Week 12 also reported greater improvements in Skindex-10 total, further indicating the positive effect of perceived improvement in pruritus on QoL. It was also observed that only the subset of patients with 'much' improved or 'very much' improved itch had a ≥5-point improvement in Skindex-10 domain scores. This ≥5-point improvement may therefore represent a clinically relevant threshold for Skindex-10 domains. If that were the case, in this *post hoc* analysis, the ≥5-point improvements in Skindex-10 domain scores for patients with a ≥3-point improvement in WI-NRS score in the KALM-1 and -2 trials, and from Study 3105, could be clinically relevant. However, further analyses are needed before conclusions can be made regarding the clinical relevance of this ≥5-point threshold.

The *post hoc* nature of the analysis means that the data presented should be considered exploratory and interpreted with caution. Validation of clinically relevant Skindex-10 domain improvements may provide clarity on the importance of the reported score improvements, which is beyond the scope of this analysis.

Conclusion

In this *post hoc* analysis of the phase 3 difelikefalin clinical trial programme in patients with CKD-aP, an improvement in pruritus intensity (≥3-point reduction in WI-NRS) from baseline to Week 12 with difelikefalin treatment was associated with greater improvements in QoL, as assessed by the Skindex-10 questionnaire, versus those who did not achieve as great an improvement in pruritus intensity (<3-point reduction in WI-NRS score). The patients' perception of the change in their pruritus correlated with a measured improvement in pruritus (WI-NRS) and with QoL. This analysis suggests that a reduction in pruritus intensity may improve QoL in patients with CKD-aP.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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AUTHORS' CONTRIBUTIONS

All authors participated in the data analysis and preparation of the manuscript and approved the final manuscript for publication.

DATA AVAILABILITY STATEMENT

The data underlying this article were provided by Cara Therapeutics, Inc., with permission. Data will be shared on request to the corresponding author with permission from Cara Therapeutics, Inc.

CONFLICT OF INTEREST STATEMENT

S.S. reports consulting fees from Almirall, Beiersdorf, Bellus Health, Cara Therapeutics, Inc., Celgene Corporation, Galderma Laboratorium, Galderma R&D, LEO Pharma, Menlo Therapeutics, Novartis, Sienna Biopharmaceuticals, Trevi Therapeutics and Vanda Pharmaceuticals; lecture fees from Sanofi; and is an investigator for Dermasence, Kiniksa, Menlo Therapeutics, Novartis and Trevi Therapeutics. S.F. reports receipt of grants from Cara Therapeutics, Inc. T.S., D.R. and I.M. are employees and shareholders of CSL Vifor. F.M. and W.W. are employees and shareholders of Cara Therapeutics, Inc. K.K.-Z. reports commercial honoraria and support from Abbott, AbbVie, Alexion, Amgen, AstraZeneca, Aveo, Chugai, DaVita, Fresenius, Genentech, Haymarket Media, Hospira, Kabi, Keryx, Novartis, Pfizer, Relypsa, Resverlogix, Sandoz, Sanofi, Shire, Vifor, UpToDate and ZS Pharma.

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