Efficacy of Difelikefalin in Subjects With Moderate-to-Severe Chronic Kidney Disease–Associated Pruritus: Pooled Subgroup Analysis of KALM-1 and KALM-2

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SYNOPSIS

- Moderate-to-severe pruritus can substantially impair quality of life (QoL) in subjects with chronic kidney disease (CKD)[1]
- Difelikefalin (DFK) is a novel, selective kappa-opioid receptor agonist with minimal central nervous system penetration[2]
  - In August 2021, intravenous (IV) DFK received approval from the US Food and Drug Administration for the treatment of moderate-to-severe pruritus associated with chronic kidney disease in adults undergoing hemodialysis (HD)[3]
- Together, the KALM-1 and KALM-2 studies comprise the largest global phase 3 program conducted in subjects with moderate-to-severe pruritus undergoing HD
- In these phase 3 studies, DFK demonstrated significant improvements in itch intensity vs placebo at week 12[2,4]

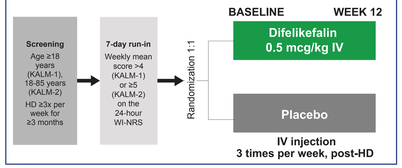
OBJECTIVE

- To further the understanding of the efficacy profile of DFK, we report efficacy and QoL outcomes in the pooled KALM-1 (NCT03422653) and KALM-2 (NCT03636269) study population, including a subgroup analysis based on baseline characteristics

METHODS

- KALM-1 and KALM-2 were randomized, phase 3, multicenter, placebo-controlled studies (**Figure 1**)
  - KALM-1 was conducted in the United States, and KALM-2 was conducted in the United States, Canada, Europe, Asia, Australia, and New Zealand
- Subjects with moderate-to-severe CKD-associated pruritus (CKD-aP) undergoing HD were randomized to IV DFK 0.5 mcg/kg or placebo 3 times/week for 12 weeks

Figure 1. KALM-1 and KALM-2 Study Designs



WI-NRS, Worst Itching Intensity Numerical Rating Scale.

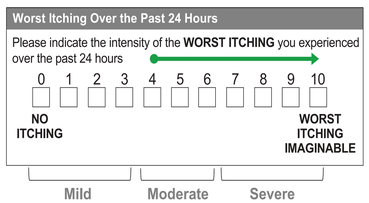
Outcomes

- The primary endpoint in KALM-1 and KALM-2 was the percentage of subjects achieving ≥3-point improvement at week 12 in weekly mean of daily WI-NRS score
- Achievement of ≥3-point improvement in weekly WI-NRS score was evaluated in subgroups based on baseline characteristics using pooled KALM-1 and KALM-2 data
- Other endpoints included achievement of complete response (ie, ≥80% of weekly WI-NRS scores equal to 0 or 1 for the preceding week); achievement of ≥15-point improvement from baseline in Skindex-10 total score; and achievement of ≥5-point improvement from baseline in 5-D Itch total score

Worst Itching Intensity Numerical Rating Scale

- The WI-NRS is a validated 11-point scale ranging from 0 to 10 (**Figure 2**)[5,6]

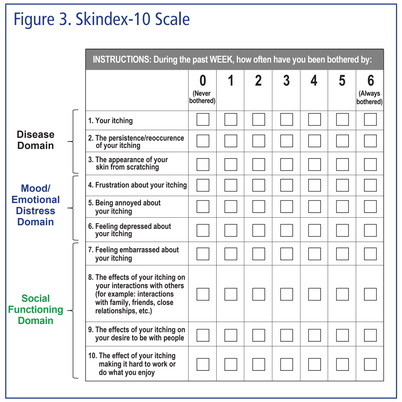
Figure 2. WI-NRS Scale



- Reduction of ≥3 points on the WI-NRS is associated with clinically meaningful change in itch severity for patients with moderate-to-severe CKD-aP[7]
- The Skindex-10 scale was developed specifically for assessing itch-related QoL across 3 domains in HD patients with pruritus (**Figure 3**)[5]
- Higher total Skindex-10 scores indicate worse itch-related QoL (range from 0 to 60)

Skindex-10 Scale

Figure 3. Skindex-10 Scale

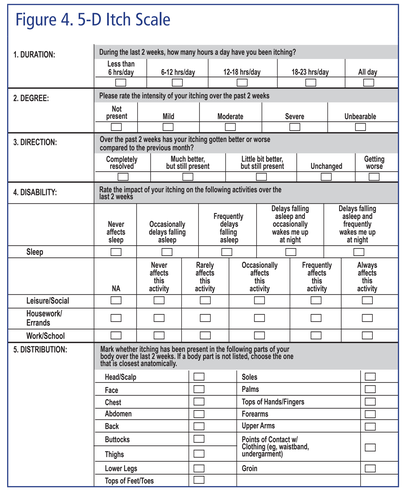


	INSTRUCTIONS: During the past WEEK, how often have you been bothered by:	0 (Never bothered)	1	2	3	4	5	6 (Always bothered)
Disease Domain	1. Your itching	☐	☐	☐	☐	☐	☐	☐
	2. The persistence/reoccurence of your itching	☐	☐	☐	☐	☐	☐	☐
	3. The appearance of your skin from scratching	☐	☐	☐	☐	☐	☐	☐
Mood/ Emotional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

5-D Itch Scale

- The 5-D Itch scale assesses 5 dimensions of itch (duration, degree, direction, disability, and distribution) during a 2-week recall period (**Figure 4**)[8]
- The 5-D Itch scale ranges from 5 to 25, with higher scores indicating worse itch-related QoL[8]

Figure 4. 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 ☐
2. DEGREE:	Please rate the intensity of your itching over the past 2 weeks				
	Not present ☐	Mild ☐	Moderate ☐	Severe ☐	Unbearable ☐
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 ☐
4. DISABILITY:	Rate the impact of your itching on the following activities over the last 2 weeks				
	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 ☐
Sleep	☐	☐	☐	☐	☐
	NA	Never affects this activity	Rarely affects this activity	Occasionally affects this activity	Frequently affects this activity	Always affects this activity
Leisure/Social	☐	☐	☐	☐	☐	☐
Housework/ Errands	☐	☐	☐	☐	☐	☐
Work/School	☐	☐	☐	☐	☐	☐
5. DISTRIBUTION:	Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically.				
	Head/Scalp ☐		Soles ☐		
	Face ☐		Palms ☐		
	Chest ☐		Tops of Hands/Fingers ☐		
	Abdomen ☐		Forearms ☐		
	Back ☐		Upper Arms ☐		
	Buttocks ☐		Points of Contact w/ Clothing (eg, waistband, undergarment) ☐		
	Thighs ☐				
	Lower Legs ☐		Groin ☐		
	Tops of Feet/Toes ☐				

Statistical Analyses

- Estimated percent, odds ratio, and *P* value were derived using logistic regression with terms for treatment group, baseline score, use of anti-itch medication during the week prior to randomization, and presence of specific medical conditions. A region/study combined variable was also included in the model for the pooled analysis
- For the primary endpoint, missing values were imputed using multiple imputation (MI) under missing at random (MAR) assumption. In the analysis of complete response, missing values were treated as nonresponders. Skindex-10 and 5-D Itch responses were analyzed without imputation for missing values

RESULTS

Subjects

- There were 851 randomized subjects in the pooled KALM-1 and KALM-2 analysis (DFK: 426; placebo: 425)
  - In KALM-1, 378 subjects were randomized (DFK: 189; placebo: 189); in KALM-2, 473 subjects were randomized (DFK: 237; placebo: 236)
- Demographics and baseline characteristics were generally comparable in the DFK and placebo groups (**Table**)

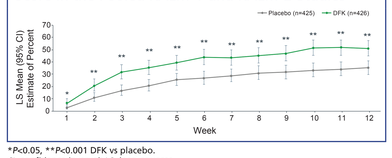
Table. Demographics and Baseline Disease and Itch Characteristics

Characteristics	Pooled KALM-1 and KALM-2	
	Placebo n=425	DFK n=426
Age, mean (SD), years	58.3 (13.5)	59.1 (12.4)
Male, n (%)	258 (60.7)	249 (58.5)
Ethnicity, n (%)		
Not Hispanic or Latino	287 (67.5)	287 (67.4)
Hispanic or Latino	136 (32.0)	133 (31.2)
Race		
White	262 (61.6)	255 (59.9)
Black or African American	114 (26.8)	135 (31.7)
Other*	49 (11.5)	36 (8.5)
Region, n (%)		
United States	322 (75.8)	335 (78.6)
Eastern Europe	60 (14.1)	54 (12.7)
Western Europe	31 (7.3)	29 (6.8)
Asia	12 (2.8)	8 (1.9)
Use of anti-itch medications, n (%)	163 (38.4)	159 (37.3)
Presence of selected medical conditions, n (%)†	65 (15.3)	67 (15.7)
Duration of pruritus, mean (SD), years	3.3 (3.3)	3.2 (4.0)
Years on chronic HD, mean (SD)	4.9 (4.3)	4.6 (4.3)
WI-NRS score, mean (SD)	7.2 (1.5)	7.2 (1.4)
Skindex-10 total score, mean (SD)	36.0 (15.1)	35.8 (14.7)
5-D Itch total score, mean (SD)	16.9 (3.5)	16.8 (3.5)

*Includes American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, unknown, and other.
†Specific medical conditions included history of fall or fracture (related to fall), confusional state, mental status change, altered mental status, disorientation, gait disturbance, or movement disorder.
Percentages were based on the number of subjects in each group. SD, standard deviation.

- The primary endpoint, proportion of subjects achieving ≥3-point improvement in WI-NRS score at week 12, was met in KALM-1 and KALM-2
- KALM-1 and KALM-2, DFK vs placebo: 50.0% vs 27.6%, *P*<0.001, and 54.0% vs 42.2%, *P*=0.02
- In the pooled population, achievement of ≥3-point WI-NRS improvement was significantly greater with DFK vs placebo at all time points from week 1 to week 12 (**Figure 5**)

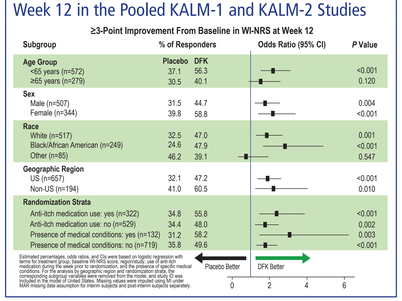
Figure 5. Achievement of ≥3-Point Improvement in WI-NRS Score in the Pooled KALM-1 and KALM-2 Studies



*P<0.05, **P<0.001 DFK vs placebo.
CI, confidence interval; LS, least squares.

- DFK reduced itch intensity in all subgroups, with the exception of "other" race (**Figure 6**)
- Findings for the "other" race subgroup may be difficult to interpret due to the small number of subjects in that subgroup

Figure 6. Subgroup Analyses for WI-NRS Response at Week 12 in the Pooled KALM-1 and KALM-2 Studies

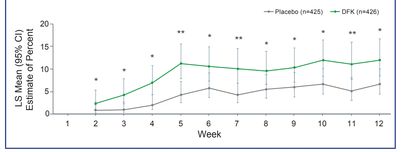


Estimated percentages, odds ratios, and CIs were based on logistic regression with terms for treatment group, baseline WI-NRS score, region/study, use of anti-itch medication during the week prior to randomization, and the presence of specific medical conditions. The region/study combined variable was not included in the corresponding subgroup if subjects were removed from the model, and study ID was included in the model of United States. Missing values were imputed using MI under MAR missing data assumption for interim subjects and post-interim subjects separately.

Achievement of WI-NRS Complete Response

- Significantly greater proportions of subjects achieved a complete response with DFK vs placebo from week 3 to week 12 (**Figure 7**)

Figure 7. Achievement of WI-NRS Complete Response in the Pooled KALM-1 and KALM-2 Studies

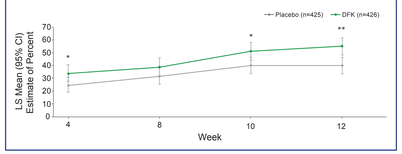


*P<0.05, **P<0.001 DFK vs placebo. Complete response was defined as achievement of ≥80% of weekly WI-NRS scores equal to 0 or 1 for the preceding week.

Achievement of Skindex-10 Improvement

- Significantly greater achievement of clinically meaningful Skindex-10 response (≥15-point improvement in Skindex-10 total score) was observed with DFK vs placebo at weeks 4, 10, and 12 (**Figure 8**)

Figure 8. Achievement of ≥15-Point Improvement in Skindex-10 Total Score in the Pooled KALM-1 and KALM-2 Studies

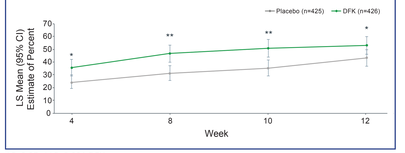


*P<0.05, **P<0.001 DFK vs placebo.

Achievement of 5-D Itch Improvement

- Achievement of clinically meaningful 5-D Itch response (≥5-point improvement in 5-D Itch total score) was significantly greater with DFK vs placebo at all time points up to week 12 (**Figure 9**)

Figure 9. Achievement of ≥5-Point Improvement in 5-D Itch Total Score in the Pooled KALM-1 and KALM-2 Studies



*P<0.05, **P<0.001 DFK vs placebo.

CONCLUSIONS

- In this pooled analysis of the US KALM-1 and global KALM-2 studies, the efficacy of IV DFK 0.5 mcg/kg was confirmed across multiple demographic and disease characteristic subgroups in subjects with moderate-to-severe CKD-aP undergoing HD
  - Notably, subjects who received IV DFK achieved clinically meaningful improvements in itch intensity regardless of prior anti-itch medication use
- Rates of complete response in WI-NRS were significantly greater with DFK versus placebo as early as week 3 in the pooled population and maintained through week 12
- Subjects who received DFK in the pooled population achieved clinically meaningful and significantly greater improvements in itch-related QoL measures compared with subjects who received placebo
- These pooled efficacy findings suggest IV DFK may play an important role in the care of CKD patients undergoing HD by reducing itch and improving QoL

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DISCLOSURES

- JT: KALM-1 – principal investigator; Cara Therapeutics, Inc. – advisory board
- WW, CM, and FM: Cara Therapeutics, Inc. – employment
- MS: none

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