Long-term Safety and Efficacy of Difelikefalin in Subjects With Chronic Kidney Disease–Associated Pruritus: Analysis From KALM-1 and KALM-2

Steven Fishbane[1]; Warren Wen[2]; Catherine Munera[2]; Frédérique Menzaghi[2]; Kieran McCafferty[3]

[1]Department of Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Great Neck, NY; [2]Cara Therapeutics, Stamford, CT; [3]The Royal London Hospital - Barts Health NHS Trust, London, United Kingdom

SYNOPSIS

- Difelikefalin (DFK) is a novel, selective kappa-opioid receptor (KOR) agonist with minimal central nervous system penetration[1,2]
  - Does not bind to mu-opioid receptors or any known receptors other than KORs[1]
  - Antipruritic effect is thought to occur via activation of KORs located on peripheral sensory neurons and immune cells[1,3]
- 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)[4]
- In the phase 3 KALM-1 and KALM-2 studies of IV DFK in subjects with moderate-to-severe chronic kidney disease–associated pruritus (CKD-aP) undergoing HD, DFK showed significant improvements in itch-related quality of life (QoL) vs placebo at week 12 and an acceptable safety profile[5,6]

OBJECTIVE

- We report long-term QoL and pooled safety data from the placebo-controlled and open-label extension (OLE) periods of the KALM-1 (NCT03422653) and KALM-2 (NCT03636269) phase 3 studies

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, Europe, Asia, Australia, Canada, and New Zealand
- Subjects with moderate-to-severe CKD-aP undergoing HD were randomized to IV DFK 0.5 mcg/kg or placebo 3 times/week for 12 weeks, followed by a ≤52-week OLE in which all subjects received IV DFK 0.5 mcg/kg 3 times/week

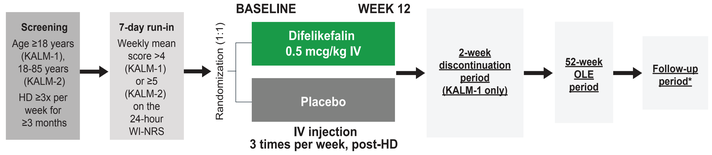
Outcomes

- Itch-related QoL was assessed with the 5-D Itch scale (**Figure 2**)
  - The 5-D Itch scale assesses 5 dimensions of itch (duration, degree, direction, disability, and distribution) during a 2-week recall period[7]
  - The 5-D Itch scale ranges from 5 to 25, with higher scores indicating worse itch-related QoL[7]
- Safety was evaluated based on adverse events (AEs), physical examinations, vital signs, electrocardiograms, and clinical laboratory tests
- Data were analyzed descriptively through week 52 of the OLE

Figure 2. 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 ☐						

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



*2 weeks in KALM-1; 7 to 10 days in KALM-2. WI-NRS, Worst Itching Intensity Numerical Rating Scale.

RESULTS

Subjects

- The pooled KALM-1 and KALM-2 population included 851 subjects (DFK: 426; placebo: 425); 340 DFK subjects and 372 placebo subjects entered the OLE
  - In KALM-1, 378 subjects were randomized (DFK: 189; placebo: 189)
  - In KALM-2, 473 subjects were randomized (DFK: 237; placebo: 236)
  - In the pooled KALM-1 and KALM-2 population, there were 796 subjects exposed to DFK in either the placebo-controlled period or the OLE
  - There were 84 subjects from the placebo-controlled period who were not included in the OLE because they were not eligible or chose not to enter the OLE
- Demographics and baseline characteristics were generally similar in the DFK and placebo groups in the pooled population (**Table 1**)

Table 1. Demographics and Baseline Disease and Itch Characteristics

	Pooled KALM-1 and KALM-2	
Characteristics	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)
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)
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)

Percentages were based on the number of subjects in each group. Three subjects were randomized but did not receive treatment. SD, standard deviation.

Safety

- In the pooled studies, subjects reported treatment-emergent AEs (TEAEs; **Table 2**) that were mostly mild to moderate in the placebo-controlled period (DFK: 57.5% [244/424]; placebo: 52.6% [223/424]) and the OLE period (DFK: 53.6% [427/796])
- The incidence rate of AEs leading to death through ≤64 weeks of treatment was within the reported rate in HD patients from the United States Renal Data System (USRDS)
  - **USRDS unadjusted incidence of death in HD patients: 164.6/1,000 pt-yrs[8]**
- Incidence rates of common AEs in the placebo-controlled period did not increase in the OLE period (**Table 3**)

Table 2. Overview of TEAEs

	Placebo-Controlled Weeks 0 to 12				Placebo-Controlled + OLE Weeks 0 up to 64	
Subjects, pooled KALM-1 and KALM-2 safety population*	Placebo n=424 101.1 subject-yrs		DFK n=424 98.0 subject-yrs		DFK N=796 537.4 subject-yrs	
	n (%)	IR/1,000 subject-yrs	n (%)	IR/1,000 subject-yrs	n (%)	IR/1,000 subject-yrs
≥1 TEAE	277 (65.3)	9,597.8	302 (71.2)	10,862.9	640 (80.4)	8,249.6
≥1 Nonfatal serious TEAE	96 (22.6)	1,860.2	107 (25.2)	2,040.0	354 (44.5)	1,829.3
AEs leading to death	5 (1.2)	49.5	3 (0.7)	30.6	37 (4.6)	68.9
TEAE leading to discontinuation	17 (4.0)	395.8	29 (6.8)	428.4	72 (9.0)	174.9

*n's and IRs are based on the safety population, defined during the double-blind period as randomized subjects who received at least 1 dose of double-blind study drug during the placebo-controlled period, and defined during the OLE period as subjects who received at least 1 dose of study drug during the placebo-controlled or OLE period. IR is calculated as 1,000 times the number of events divided by the total subject-years of exposure. IR, incidence rate.

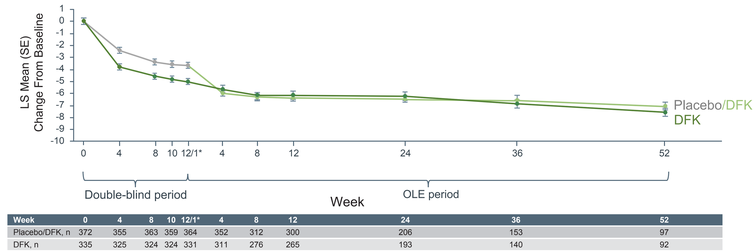
Table 3. Most Commonly Reported TEAEs (≥2% during the placebo-controlled period and ≥1% higher incidence with DFK vs placebo)

	Placebo-Controlled Weeks 0 to 12				Placebo-Controlled + OLE Weeks 0 up to 64	
Subjects, pooled KALM-1 and KALM-2 safety population*	Placebo n=424 101.1 subject-yrs		DFK n=424 98.0 subject-yrs		DFK N=796 537.4 subject-yrs	
Most common TEAEs	n (%)	IR/1,000 subject-yrs	n (%)	IR/1,000 subject-yrs	n (%)	IR/1,000 subject-yrs
Diarrhea	24 (5.7)	267.2	38 (9.0)	469.2	102 (12.8)	273.6
Dizziness	16 (3.8)	188.0	29 (6.8)	316.2	72 (9.0)	163.8
Nausea	19 (4.5)	207.8	28 (6.6)	326.4	89 (11.2)	210.3
Hyperkalemia	15 (3.5)	158.3	20 (4.7)	234.6	74 (9.3)	161.9
Headache	11 (2.6)	118.7	19 (4.5)	214.2	57 (7.2)	119.1
Somnolence	10 (2.4)	98.9	18 (4.2)	204.0	20 (2.5)	40.9
Back pain	4 (0.9)	39.6	11 (2.6)	112.2	39 (4.9)	87.5

Itch-Related QoL

- Mean 5-D Itch improvement with DFK was maintained through the 52-week OLE with continued DFK treatment and emerged in subjects who switched from placebo to DFK during the OLE (**Figure 3**)

Figure 3. Mean Improvement in 5-D Itch Total Score



Week	0	4	8	10	12/1*	4	8	12	24	36	52
Placebo/DFK, n	372	355	363	359	364	352	312	300	206	153	97
DFK, 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, 313/399 (78.4%) subjects could not complete the 52-week OLE due to the sponsor's decision to stop the study for reasons unrelated to safety or lack of drug effect. The 2-week discontinuation period in KALM-1 is not pictured in the figure. LS, least squares; SE, standard error.

CONCLUSIONS

- In this pooled analysis of the phase 3 KALM-1 and KALM-2 studies, DFK demonstrated maintenance of efficacy over 1 year in itch-related symptoms and QoL
- IV DFK 0.5 mcg/kg was well tolerated with an acceptable long-term safety profile in subjects with CKD-aP undergoing HD
  - TEAEs were mostly mild to moderate in severity
  - The incidence rate of common TEAEs and serious TEAEs did not increase with longer-term exposure
  - The incidence of death in the pooled studies was lower than the unadjusted incidence of death reported for patients undergoing HD in the USRDS 2020 annual report
- These findings suggest that DFK may help to address the unmet need for treatments that are well tolerated and efficacious over the long term for moderate-to-severe CKD-aP in patients undergoing HD

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CORRESPONDENCE

- Sfishbane@northwell.edu

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