Oral Difelikefalin Reduces Pruritus in Atopic Dermatitis

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SYNOPSIS

- Pruritus is the central symptom in atopic dermatitis (AD)[1]
- Patients with mild-to-moderate AD frequently exhibit severe itch, and treatments that specifically target AD-related pruritus are lacking[1,2]
- Difelikefalin (DFK), a novel, selective kappa-opioid receptor (KOR) agonist, is being developed for chronic pruritic conditions[3,4]
  - 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[5]

OBJECTIVE

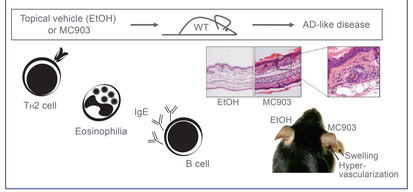
- Here, we present a mouse model of AD which was used to test the effects of DFK on itch and lesional severity
- Results are also presented from a phase 2 study of oral DFK in subjects with AD and moderate-to-severe pruritus (KARE; NCT04018027)

MOUSE STUDY

Methods

- Topical treatment of wild-type mice with MC903 or vehicle ethanol consistently induces a mouse model of AD-like disease[6] **(Figure 1)**

Figure 1. Clinical, Histological, and Immunological Features of AD Mouse Model



Adapted by permission from Springer Nature: A Mouse Model for Atopic Dermatitis Using Topical Application of Vitamin D3 or of Its Analog MC903 (Moosbrugger-Martinz V, et al, 2017).[6] MC903, calcipotriol; IgE, immunoglobulin E; TH2, T helper 2; WT, wild type.

- Using the mouse model of AD-like disease, RNA sequencing shows that key cytokines and chemokines are upregulated in lesional skin of mice **(Figure 2)**, and mice develop robust spontaneous bouts of scratching over time **(Figure 3)**[7]

Figure 2. RNA Sequencing of Genes From Skin of Mice With AD-Like Disease

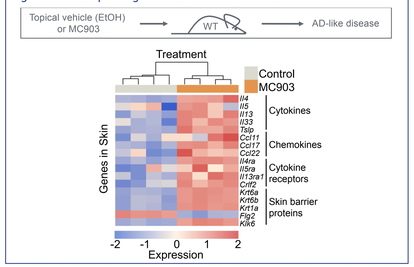


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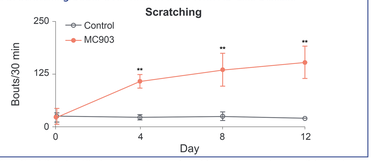
Figure 3. Scratching Bouts Over Time in Mice With AD-Like Disease



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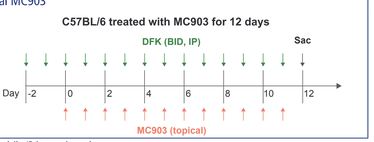
Results

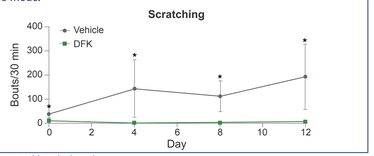
- Systemic treatment with DFK over 12 days in conjunction with topical MC903 treatment **(Figure 4)** significantly reduced bouts of scratching in mice with AD-like disease **(Figure 5)**

Figure 4. Treatment Paradigm: Systemic Oral DFK Over 12 Days in Parallel With Topical MC903



BID, twice daily; IP, intraperitoneal.

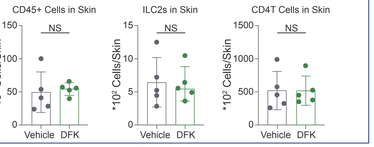
Figure 5. Oral DFK Treatment Significantly Reduced Scratching Bouts in AD Mouse Model



* $P<0.05$ vs control (unpaired t-test)

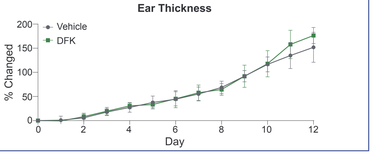
- DFK treatment did not impact the inflammatory filtrate **(Figure 6)** or reduce ear thickness in mice **(Figure 7)**, indicating that DFK works to reduce itching without exerting an anti-inflammatory effect

Figure 6. Oral DFK Does Not Impact Levels of Pathogenic Immune Cells in Mice With AD-Like Disease



ILC2, innate lymphoid type-2 cells; NS, not significant.

Figure 7. Oral DFK Does Not Change Ear Thickness in Mice With AD-Like Disease



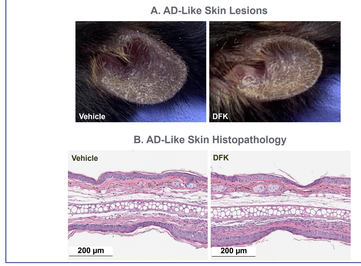
- Single cell RNA-sequencing datasets reveal expression of Oprk1 (gene encoding KOR) primarily on mechanosensory Aß neurons **(Table 1)**

Table 1. Expression Profile of Genes Participating as Operational Components of Sensory Neurons in Different Neuronal Types[8]

	A-LTMR (Touch)					C-fibers (Itch)					
Gene Symbol	NF1	NF2	NF3	NF4	NF5	NP1	NP2	NP3	PEP1	PEP2	TH
Oprk1	0	0.104	0.083	0	0	0	0	0	0	0	0
Oprm1	0	0	0	0.045	0	0.056	0.125	0.250	0.047	0.118	0.004
Nppb	0	0	0	0	0	0	0.031	0.833	0.031	0	0
Sst	0	0	0	0	0	0	0.031	0.833	0.016	0	0
Cysltr2	0	0	0	0	0	0.032	0	0.667	0	0	0
Htr1	0	0	0.083	0	0	0	0.094	0.083	0	0	0
Mrgprd	0.032	0.021	0	0	0.038	0.840	0.219	0	0.016	0	0.013
Mrgpra3	0	0	0	0	0	0.008	0.625	0.083	0	0	0.004
Il4ra	0	0	0	0.045	0	0.208	0.281	0.167	0.109	0.059	0.039
Il13ra1	0	0.021	0	0	0	0.008	0.094	0.083	0.016	0	0
Il31ra	0	0	0.083	0	0	0	0.031	0.583	0.016	0	0

- DFK reduces scratching independently of skin inflammation
- Calcium imaging demonstrated that DFK directly activated large diameter (ie, Aß) sensory neurons without impacting AD-like skin lesions **(Figure 8A)** or AD-like skin histology **(Figure 8B)**

Figure 8. AD-Like Skin Lesions (A) and Skin Histopathology (B)

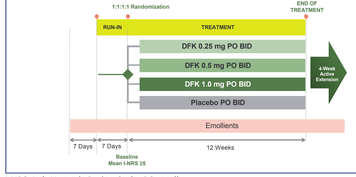


KARE PHASE 2 STUDY

Methods

- The KARE study design is shown in **Figure 9**

Figure 9. KARE Study Design



I-NRS, Itch Numeric Rating Scale; PO, orally.

- The primary endpoint was change from baseline in the weekly mean of the daily 24-hour I-NRS at week 12
- Secondary endpoints included:
  - ≥4-point improvement in weekly mean of the daily I-NRS at week 12
  - Safety
- A subgroup analysis was conducted in subjects with body surface area (BSA) <10%

Results

Subjects

- Subject disposition is shown in **Table 2**

Table 2. Subject Disposition

	Total Randomized (N=401)			
Subjects, n (%)	Placebo (n=123*)	DFK 0.25 mg (n=77)	DFK 0.5 mg (n=124*)	DFK 1.0 mg (n=77)
Completed	97 (79)	63 (82)	102 (82)	61 (79)
Discontinued	26 (21)	14 (18)	22 (18)	16 (21)
Adverse event	4	3	1	9
Subject withdrew consent	5	3	8	4
Subject non-compliance	6	2	7	0
Lost to follow-up	5	2	1	2
Lack of therapeutic efficacy	3	1	2	0
Other	3	3	3	1
Use of rescue medication	2 (1.6)	4 (5.2)	1 (0.8)	1 (1.3)

*The sample sizes for placebo and DFK 0.5 mg were increased based on the results of an interim assessment for sample size re-estimation.

- Baseline subject demographics and disease characteristics are shown in **Table 3**
- Approximately two-thirds (64%) of subjects had BSA <10%

Table 3. Baseline Demographics and Disease Characteristics (ITT Population)

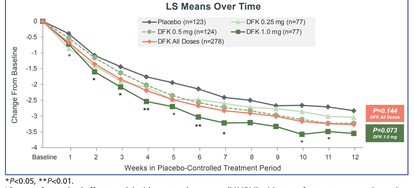
Characteristic	Placebo (n=123)	DFK 0.25 mg (n=77)	DFK 0.5 mg (n=124)	DFK 1.0 mg (n=77)
Female, n (%)	80 (65)	54 (70)	83 (67)	53 (69)
Age, mean (SD), y	40 (15.6)	43 (16.2)	42 (15.4)	41 (14.0)
Race, n (%)				
White	71 (58)	44 (57)	74 (60)	40 (52)
Black	42 (34)	31 (40)	40 (32)	33 (43)
Asian	5 (4)	1 (1)	5 (4)	2 (3)
BMI, mean (SD)	29 (7)	30 (8)	32 (9)	31 (8)
BSA (%), mean (SD)	8.4 (6.9)	8.3 (6.0)	8.4 (6.4)	9.5 (6.9)
EASI, mean (SD)	5.9 (4.9)	6.9 (5.4)	5.9 (4.3)	6.5 (4.5)
I-NRS, mean (SD)	7.7 (1.3)	7.8 (1.3)	7.8 (1.2)	7.9 (1.2)
DLQI, mean (SD)	13.0 (7.2)	12.6 (7.4)	11.5 (6.6)	13.5 (6.5)

BSA <10% is mild/moderate AD; EASI scores range from 0 to 72; I-NRS scores range from 0 to 10 (0 = no itch, 10 = worst itching imaginable).
BMI, body mass index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; ITT, intent to treat.

Primary Endpoint

- The change from baseline in I-NRS through week 12 is shown in **Figure 10**

Figure 10. Primary Endpoint: Change From Baseline in I-NRS Through Week 12 (ITT)



*$P<0.05$, **$P<0.01$.
LS means from mixed effects model with repeated measures (MMRM) with terms for treatment, week, week by treatment interaction, baseline score, and AD severity.
Missing data imputed using multiple imputation (MI) under missing at random (MAR) assumption. I-NRS scores after use of rescue are set to missing and then imputed with MI.
LS, least squares.

Subgroup Analysis

- **Table 4** shows baseline demographics and disease characteristics in the population with BSA <10% (itch-dominant AD)

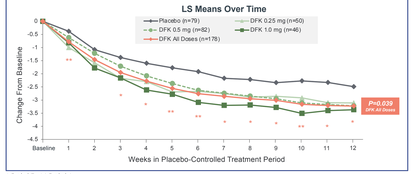
Table 4. Baseline Disease Characteristics: BSA <10% Population (Itch-Dominant AD)

Characteristic	Placebo (n=79)	DFK 0.25 mg (n=50)	DFK 0.5 mg (n=82)	DFK 1.0 mg (n=46)
BSA (%), mean (SD)	4.3 (2.5)	4.6 (2.5)	4.6 (2.8)	5.0 (2.2)
EASI, mean (SD)	3.7 (2.6)	4.3 (3.5)	4.0 (2.8)	4.5 (3.0)
I-NRS, mean (SD)	7.6 (1.3)	7.5 (1.3)	7.7 (1.2)	7.8 (1.3)
DLQI, mean (SD)	12.0 (6.8)	11.8 (7.5)	10.6 (5.9)	13.1 (6.0)

EASI scores range from 0 to 72; I-NRS scores range from 0 to 10 (0 = no itch, 10 = worst itching imaginable).

- Significant improvement in itch was observed at week 12 with the combined DFK group compared with placebo **(Figure 11)**
- Significant improvement was evident as early as day 2 **(Figure 11)**

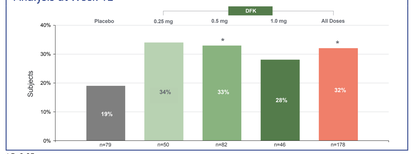
Figure 11. BSA <10% Population (Itch-Dominant AD): Change From Baseline in I-NRS Through Week 12



*$P<0.05$, **$P<0.01$.
LS means from MMRM with terms for treatment, week, week by treatment interaction, and baseline score. Missing data imputed using MI under MAR assumption. I-NRS scores after use of rescue are set to missing and then imputed with MI.

- A significantly greater proportion of subjects achieved ≥4-point improvement in daily I-NRS with DFK vs placebo at week 12 **(Figure 12)**

Figure 12. BSA <10% Population (Itch-Dominant AD): 4-Point Responder Analysis at Week 12



*$P<0.05$.
P values vs placebo. Estimated percentage and *P* value based on a logistic regression model with terms for treatment group and baseline I-NRS score. Subjects who discontinued early, took rescue medication, or have missing data at week 12 are considered nonresponders.

Safety

- A summary of treatment-emergent adverse events (TEAEs) is shown in **Table 5**
- TEAEs were mostly mild or moderate in severity (~95%)
- Most discontinuations were due to gastrointestinal-related TEAEs
- Serious TEAEs occurred in 1 subject with hypovolemia and acute kidney injury (DFK 1.0 mg), 1 subject with hyponatremia (DFK 1.0 mg), 1 subject with nephrolithiasis (DFK 0.5 mg), and 1 subject with costochondritis (DFK 0.25 mg)
  - All serious TEAEs were deemed unrelated to study drug by the investigator

Table 5. Summary of Adverse Events

Subjects, n (%)	Placebo (n=123)	DFK 0.25 mg (n=77)	DFK 0.5 mg (n=124)	DFK 1.0 mg (n=77)
At least 1 TEAE	54 (43.9)	36 (46.8)	49 (39.5)	42 (54.5)
At least 1 serious TEAE	0	1 (1.3)	1 (0.8)	2 (2.6)
TEAE resulting in treatment discontinuation	4 (3.3)	3 (3.9)	1 (0.8)	9 (11.7)

Safety analyses performed in the safety population, defined as all randomized subjects who received ≥1 dose of study drug based on actual treatment received.

- The most commonly reported TEAEs were abdominal pain, nausea, dry mouth, headache, dizziness, and hypertension **(Table 6)**

Table 6. Most Commonly Reported TEAEs

TEAEs at ≥5% Frequency, n (%)	Placebo (n=123)	DFK 0.25 mg (n=77)	DFK 0.5 mg (n=124)	DFK 1.0 mg (n=77)
Abdominal pain*	13 (10.6)	4 (5.2)	11 (8.9)	14 (18.2)
Nausea	11 (8.9)	1 (1.3)	6 (4.8)	5 (6.5)
Dry mouth	0	2 (2.6)	2 (1.6)	6 (7.8)
Headache	5 (4.1)	5 (6.5)	3 (2.4)	2 (2.6)
Dizziness	2 (1.6)	4 (5.2)	3 (2.4)	2 (2.6)
Hypertension†	1 (0.8)	2 (2.6)	3 (2.4)	5 (6.5)

Safety analyses performed in the safety population, defined as all randomized subjects who received ≥1 dose of study drug based on actual treatment received.
*Includes preferred terms abdominal pain, abdominal pain upper, abdominal discomfort. †Includes preferred terms hypertension and blood pressure increased.

CONCLUSIONS

- In a mouse model of AD:
  - A rapid and significant anti-pruritic effect of DFK was observed independently of observable effects on skin inflammation
  - Analyses in this model indicate that expression and activation of the DFK target receptor are on sensory neurons
- In the phase 2 clinical study that includes approximately two-thirds of subjects with itch-dominant AD (BSA <10% and moderate-to-severe pruritus):
  - DFK demonstrated a significant and clinically meaningful reduction in pruritus
  - DFK was well tolerated
- Taken together, these findings support the role of DFK as an antipruritic agent that may be best suited for patients with itch-dominant AD

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DISCLOSURES

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