A Phase 2 Study of Oral Difelikefalin for Moderate-to-Severe Pruritus in Subjects With Notalgia Paresthetica (KOMFORT)

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SYNOPSIS

- Notalgia Paresthetica (NP) is a common sensory neuropathy of the back characterized by chronic pruritus[1]
- There are no approved therapies for NP
- Difelikefalin (DFK) activates kappa-opioid receptors on peripheral sensory neurons and suppresses itch predominantly by a neuromodulatory effect
  - Intravenous (IV) DFK is approved for the treatment of moderate-to-severe pruritus in adults with chronic kidney disease undergoing hemodialysis[2-5]
    - IV DFK is not addictive and is not a controlled substance
  - Oral DFK is being developed across numerous chronic pruritic conditions[6]

OBJECTIVE

- Here we report the results of the phase 2 study (KOMFORT; NCT04706975) evaluating oral DFK for the treatment of moderate-to-severe pruritus in subjects with NP

METHODS

Study Design

- KOMFORT was conducted in adults with a clinically confirmed diagnosis of NP
- The study design is shown in **Figure 1**

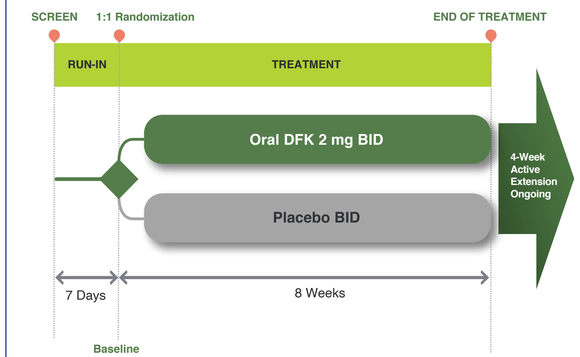
Primary Endpoint

- The primary endpoint was the change from baseline in the weekly mean of the daily 24-hour Worst Itch-Numeric Rating Scale (WI-NRS) at week 8

Other Endpoints

- ≥4-Point improvement in WI-NRS
- Complete response in WI-NRS
  - Defined as WI-NRS score of 0 or 1 for at least 70% of the daily non-missing WI-NRS scores for the week
- Safety assessments

Figure 1. KOMFORT: Phase 2 Study Design



BID, twice daily.

RESULTS

- A total of 126 subjects were randomized (placebo, n=63; DFK, n=62)
- Baseline demographics and disease characteristics were similar between groups (**Table 1**)
  - Subjects were predominantly white and female, and the mean age was approximately 60 years in both treatment groups

Table 1. Baseline Demographics and Disease Characteristics

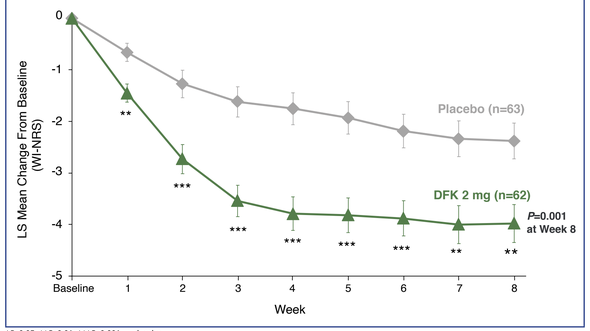
Characteristic	Placebo (n=63)	DFK 2 mg (n=62)
Age, mean (SD), y	60.2 (11.8)	59.3 (12.4)
Female, n (%)	42 (66.7)	48 (77.4)
Race, n (%)		
White	56 (88.9)	49 (79.0)
Black	4 (6.3)	10 (16.1)
Other/Not reported	3 (4.8)	3 (4.8)
BMI, mean (SD), kg/m²	28.7 (5.2)	29.7 (5.8)
Duration of notalgia paresthetica, mean (SD), y	8.2 (7.4)	8.9 (10.4)
WI-NRS score, mean (SD)	7.6 (1.4)	7.6 (1.4)
Moderate (≥5 – <7), n (%)	20 (31.7)	21 (33.9)
Severe (≥7), n (%)	43 (68.3)	41 (66.1)

BMI, body mass index.

Efficacy

- DFK resulted in a significant reduction from baseline in the weekly mean WI-NRS score at week 8 (primary efficacy outcome: DFK, 4.0; placebo, 2.4; *P*=0.001; **Figure 2**)

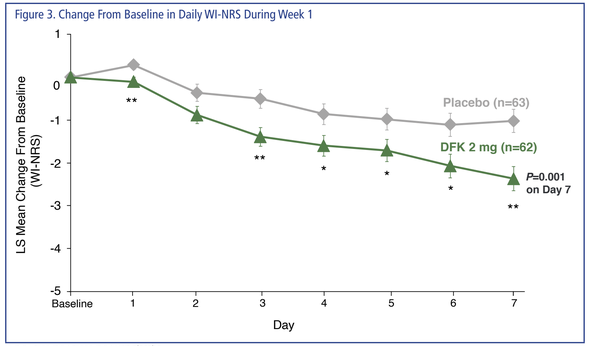
Figure 2. Primary Endpoint: Change From Baseline in WI-NRS at Week 8



*P<0.05; **P<0.01; ***P<0.001 vs placebo.
Analysis conducted in ITT population.
LS means from mixed effects model with repeated measures with terms for treatment, week, treatment by week interaction, and baseline WI-NRS score.
Bars indicate standard error. Missing data were imputed using multiple imputation under missing-at-random assumption.
ITT, intent to treat; LS, least squares.

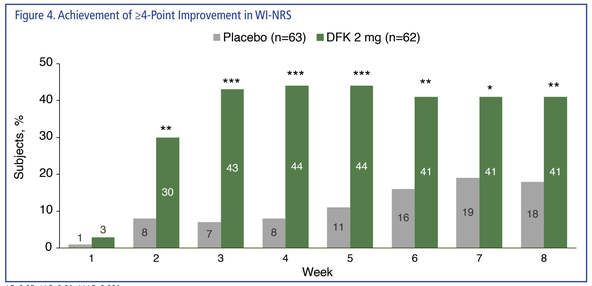
- Reduction in itch intensity was observed with DFK at day 1 compared with placebo (**Figure 3**)
- A significantly greater proportion of subjects achieved a ≥4-point improvement in WI-NRS score at week 8 with DFK vs placebo (**Figure 4**)
- At week 8, a significantly greater proportion of subjects receiving DFK achieved a complete response (WI-NRS of 0 or 1 on at least 70% of the daily non-missing WI-NRS scores for the week) compared with placebo (**Figure 5**)

Figure 3. Change From Baseline in Daily WI-NRS During Week 1



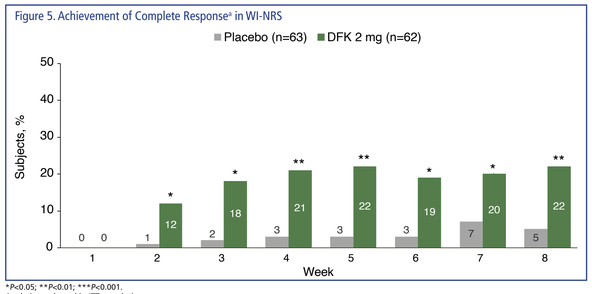
*P<0.05; **P<0.01; ***P<0.001 vs placebo.
Analysis conducted in ITT population.
LS means from mixed effects model with repeated measures with terms for treatment, day, treatment by day interaction, and baseline WI-NRS score.
Bars indicate standard error. Missing data were imputed using multiple imputation under missing-at-random assumption.

Figure 4. Achievement of ≥4-Point Improvement in WI-NRS



*P<0.05; **P<0.01; ***P<0.001.
Analysis conducted in ITT population.
Estimated percentages from a logistic regression with terms for treatment and baseline WI-NRS score.
Subjects with missing weekly WI-NRS scores for a particular week due to early termination were categorized as non-responders.
No adjustments for multiplicity were made for the secondary or exploratory outcomes.

Figure 5. Achievement of Complete Response[a] in WI-NRS



*P<0.05; **P<0.01; ***P<0.001.
Analysis conducted in ITT population.
[a]Complete response was defined as WI-NRS score of 0 or 1 for at least 70% of the daily non-missing WI-NRS scores for the week.
Estimated percentages from a logistic regression with terms for treatment and baseline WI-NRS score.
Subjects with missing weekly WI-NRS scores for a particular week due to early termination were categorized as non-responders.
No adjustments for multiplicity were made for the secondary or exploratory outcomes.

Safety

- All adverse events (AEs) in DFK-treated subjects were mild to moderate in severity (**Table 2**)
- The most common treatment-emergent AEs (TEAEs) leading to discontinuation were dizziness (n=5; 8.1%) and nausea (n=4; 6.5%) in the DFK group and abdominal pain (n=2, 3.2%) in the placebo group
- Headache, dizziness, constipation, and increased urine output were more commonly reported in subjects treated with DFK (**Table 3**)

Table 2. Summary of TEAEs

Subjects, n (%)	Placebo (n=63)	DFK 2 mg (n=62)
≥1 TEAE	32 (50.8)	35 (56.5)
≥1 Serious TEAE	0	0
TEAEs leading to discontinuation of trial regimen	4 (6.3)	12 (19.4)

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

Table 3. Most Commonly Reported TEAEs

TEAEs (≥5% frequency), n (%)	Placebo (n=63)	DFK 2 mg (n=62)
Nausea	7 (11.1)	8 (12.9)
Abdominal pain[a]	8 (12.7)	7 (11.3)
Headache	3 (4.8)	7 (11.3)
Dizziness	2 (3.2)	7 (11.3)
Constipation	4 (6.3)	6 (9.7)
Increased urine output[b]	1 (1.6)	5 (8.1)

Safety analyses were conducted in the safety population, which was defined as all randomized subjects who received ≥1 dose of study drug based on actual treatment received.
[a]Includes the preferred terms abdominal pain, upper abdominal pain, abdominal discomfort, and lower abdominal pain.
[b]Includes increased urine output and pollakiuria.

CONCLUSIONS

- The phase 2 KOMFORT study demonstrated that oral DFK significantly reduced itch intensity compared with placebo in subjects with NP
- The onset of action was evident at day 1 and maintained through week 8
- A significantly greater proportion of subjects receiving DFK vs placebo achieved a complete response
- DFK was generally well tolerated
- The most commonly reported AEs were headache, transient dizziness, constipation, and increased urine output
- The results of this phase 2 trial support the role of kappa-opioid receptor activation for the control of neuropathic itch
- These findings underscore that DFK has the potential to fill a significant unmet need and warrants further clinical development in NP

REFERENCES

1. Ellis C. *Dermatol Pract Concept.* 2013;3:3-6. **2.** Fishbane S, et al. *N Engl J Med.* 2020;382:222-232. **3.** Topf J, et al. *Kidney Med.* 2022;4(8):100512. **4.** Korsuva. Package insert. Cara Therapeutics, Inc.; 2021. **5.** Kapruvia. Summary of product characteristics. Vifor Fresenius Medical Care Renal Pharma France; 2022. **6.** Kim BS, et al. Oral difelikefalin reduces pruritus in atopic dermatitis. Presented at: the 30th European Academy of Dermatology and Venereology Congress; September 29–October 2, 2021.

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DISCLOSURES

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