# Rapid Reduction and Free or Almost Free of Itch Response With Oral Difelikefalin in Subjects With Notalgia Paresthetica and Moderate-to-Severe Pruritus

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## INTRODUCTION

- Notalgia paresthetica (NP) is a common, but underdiagnosed, neuropathic itch characterized by pruritus of the upper back[1]
  - There are currently no approved treatments for NP[2]; however, kappa-opioid receptor agonists have emerged as a new therapeutic target for pruritus[3]
  - Antihistamines and topical corticosteroids are not efficacious in reducing itch in NP,[4] making treatment challenging
  - Neuromodulators, including capsaicin and gabapentinoids, may have some efficacy in reducing itch for patients with NP, but treatment is hindered by compliance and tolerability limitations[5,6]
- Studies of oral difelikefalin (DFK), a selective kappa-opioid receptor agonist in development, have shown improvement in systemic and inflammatory forms of chronic pruritus, such as those associated with chronic kidney disease[7] and atopic dermatitis[8]
  - Intravenous DFK was first approved in 2021 for the treatment of moderate-to-severe pruritus in adults undergoing hemodialysis[7,9]

## OBJECTIVES

- To evaluate free or almost free of itch response rates with oral DFK for the treatment of moderate-to-severe pruritus in subjects with NP in the KOMFORT study
- To examine itch response over time with oral DFK in individual subjects with moderate-to-severe pruritus associated with NP in the KOMFORT study

## METHODS

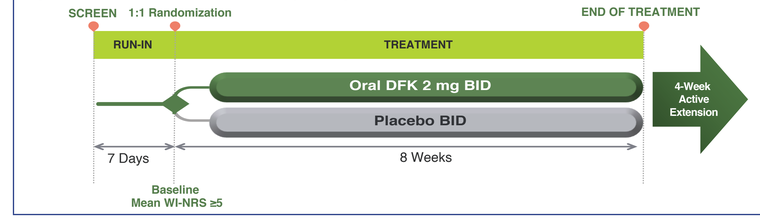
### Study Design

- Phase 2, multicenter, randomized, double-blind study conducted in subjects with NP and moderate-to-severe pruritus who were randomized to oral DFK 2 mg or placebo twice daily for 8 weeks (**Figure 1**)
  - Study design[10] and primary results[11] were previously reported

### Assessments

- Proportion of subjects who were free or almost free of itch
- Itch severity over time, as measured by weekly mean Worst Itch Numeric Rating Scale (WI-NRS) scores
  - Free or almost free of itch: NRS 0 or 1
  - Mild: NRS >1 to <4
  - Moderate: NRS 4 to <7
  - Severe: NRS 7 to 10

Figure 1. KOMFORT: Phase 2 Study Design

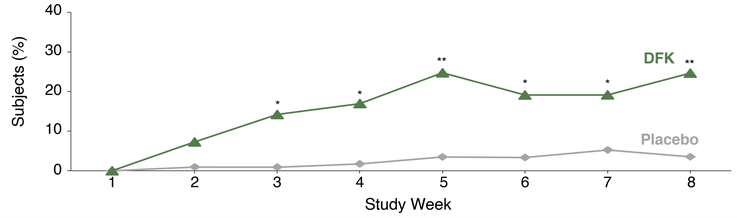



ClinicalTrials.gov: NCT04706975.
BID, twice daily.

## RESULTS

- In total, 126 subjects were randomized to treatment with oral DFK (n=63) or placebo (n=63)
- Free or almost free of itch response rates were significantly greater in subjects treated with DFK (14%) versus placebo (1%) as early as week 3 (*P*=0.045; **Figure 2**)
- Statistically significant differences in the proportion of subjects who were free or almost free of itch were maintained through week 8 (DFK [25%] vs placebo [4%]; *P*=0.006; **Figure 2**)

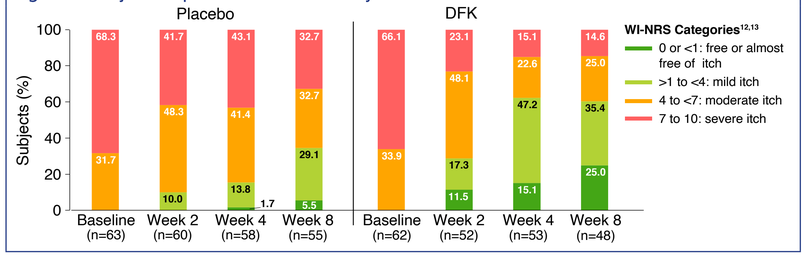
Figure 2. Free or Almost Free of Itch Response Rates Through Week 8




*$P$<0.05; **$P$<0.01.

- At baseline, two-thirds of subjects in each treatment group had severe pruritus, and the rest had moderate pruritus (**Figure 3**)
- At week 8, 60% of subjects randomized to DFK had experienced an improvement in itch
  - 25% of subjects treated with DFK were free or almost free of itch compared with 6% in the placebo group
  - 35% of subjects treated with DFK had mild itch compared with 29% in the placebo group

Figure 3. Subject Response Based on Weekly WI-NRS Scores From Baseline to Week 8




## CONCLUSIONS

- One in four subjects were free or almost free of itch after 8 weeks of treatment with DFK
  - A statistically significant difference in the proportion of subjects who were free or almost free of itch was observed as early as week 3 with DFK versus placebo
  - More than four times as many subjects were free or almost free of itch at week 8 with DFK versus placebo
- Individual subject responses support the rapid onset and robust, durable efficacy of DFK vs placebo in improving itch
- These findings support the role of kappa-opioid receptor activation in controlling neuropathic itch

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## DISCLOSURES

**ML:** Mount Sinai – employee. AbbVie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Dermavant Sciences, Eli Lilly, Incyte, Janssen Research & Development, Ortho Dermatologics, Regeneron, and UCB – research funds. Aditum Bio, Almirall, AltruBio, AnaptysBio, Arcutis, Aristea Therapeutics, Arrive Technologies, Avotres Therapeutics, BiomX, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Castle Biosciences, Corrona, Dermavant Sciences, Dr. Reddy's Laboratories, Evelo Biosciences, Evommune, Facilitation of International Dermatology Education, Forte Biosciences, Foundation for Research and Education in Dermatology, Helsinn Therapeutics, Hexima, LEO Pharma, Meiji Seika Pharma, Mindera, Pfizer, Seanergy, and Verrica – consultant.
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