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

Brian S. Kim, MD, MTR[1]; Robert Bissonnette, MD, FRCPC[2]; Kristine Nograles, MD[3]; Catherine Munera, PhD[3]; Nilam Shah, PharmD[3]; Alia Jebara, MD[3]; Josh Cirulli, PharmD[3]; Joana Goncalves, MD[3]; Mark Lebwohl, MD[1]

[1]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]Innovaderm Research, Montreal, QC, Canada; [3]Cara Therapeutics, Stamford, CT, USA

Presented at: the 31st European Academy of Dermatology and Venereology (EADV) Congress; September 7–10, 2022, Milan, Italy

Acknowledgments, Correspondence, and Disclosures

ACKNOWLEDGMENTS

This study was sponsored by Cara Therapeutics.

The authors thank the study investigators and patients who participated in this study. We also gratefully acknowledge Illyce Nunez, PhD, and Callie Grimes, PhD (Peloton Advantage, LLC, an OPEN Health company, Parsippany, NJ), for medical writing and editorial support, which was funded by Cara Therapeutics, under the direction of the authors.

CORRESPONDENCE

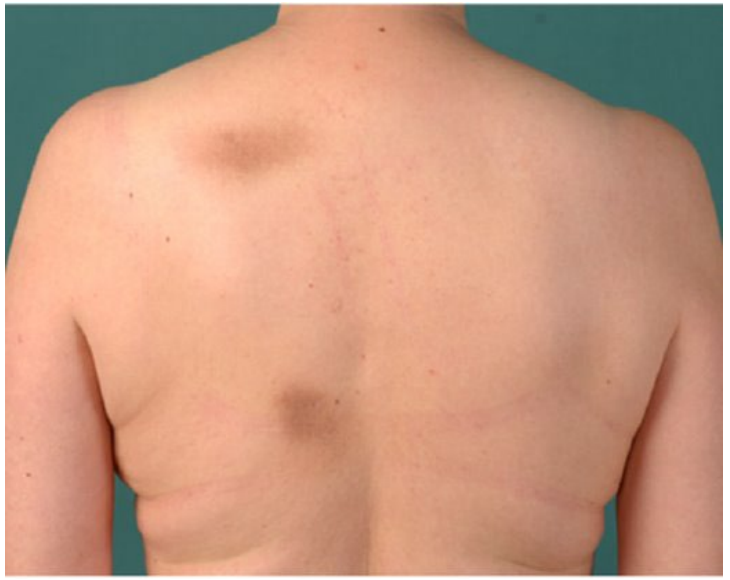
Mark Lebwohl – lebwohl@aol.com

DISCLOSURES

- **BSK**: AbbVie, Abrax Japan, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Escient Pharmaceuticals, Galderma, GlaxoSmithKline, Granular Therapeutics, Incyte, LEO Pharma, Lilly, Pfizer, Recens Medical, Regeneron, Sanofi, Trevi Therapeutics – consulting. Cara Therapeutics and LEO Pharma – research grant.
- **RB:** AbbVie, Arcutis, Arena Pharma, Asana BioSciences, Bellus Health, Bluefin Biomedicine, BioMimetix, Boehringer Ingelheim, Boston, Brickell, Cara Therapeutics, Clexio, Dermavant, Eli Lilly, EMD Serono, Evidera, Galderma, GlaxoSmithKline, Incyte, Inmagene Bio, Janssen, Kiniksa, Kyowa Kirin, LEO Pharma, Novan, Novartis, Pfizer, Ralexar, RAPT Therapeutic, Regeneron, Respivant, Sanofi, Sienna, Target RWE, and Vyne Therapeutics – advisor, consultant, speaker, investigator, and/or research grant. Innovaderm Research – employee and shareholder.
- **KN, CM, NS, AJ, JC, & JG:** Cara Therapeutics, Inc. – employment.
- **ML:** Mount Sinai – employee. AbbVie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Cara Therapeutics, Dermavant Sciences, Eli Lilly, Incyte, Janssen Research & Development, LLC, Ortho Dermatologics, Regeneron, and UCB – research funds. Aditum Bio, Almirall, AltruBio Inc., AnaptysBio, Arcutis, Inc., 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, Inc., Facilitation of International Dermatology Education, Forte Biosciences, Foundation for Research and Education in Dermatology, Helsinn Therapeutics, Hexima Ltd., LEO Pharma, Meiji Seika Pharma, Mindera, Pfizer, Seanergy, and Verrica – consultant.

Notalgia Paresthetica (NP)

- 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]
- Here we report the results of the phase 2 study evaluating oral DFK for the treatment of moderate-to-severe pruritus in subjects with NP

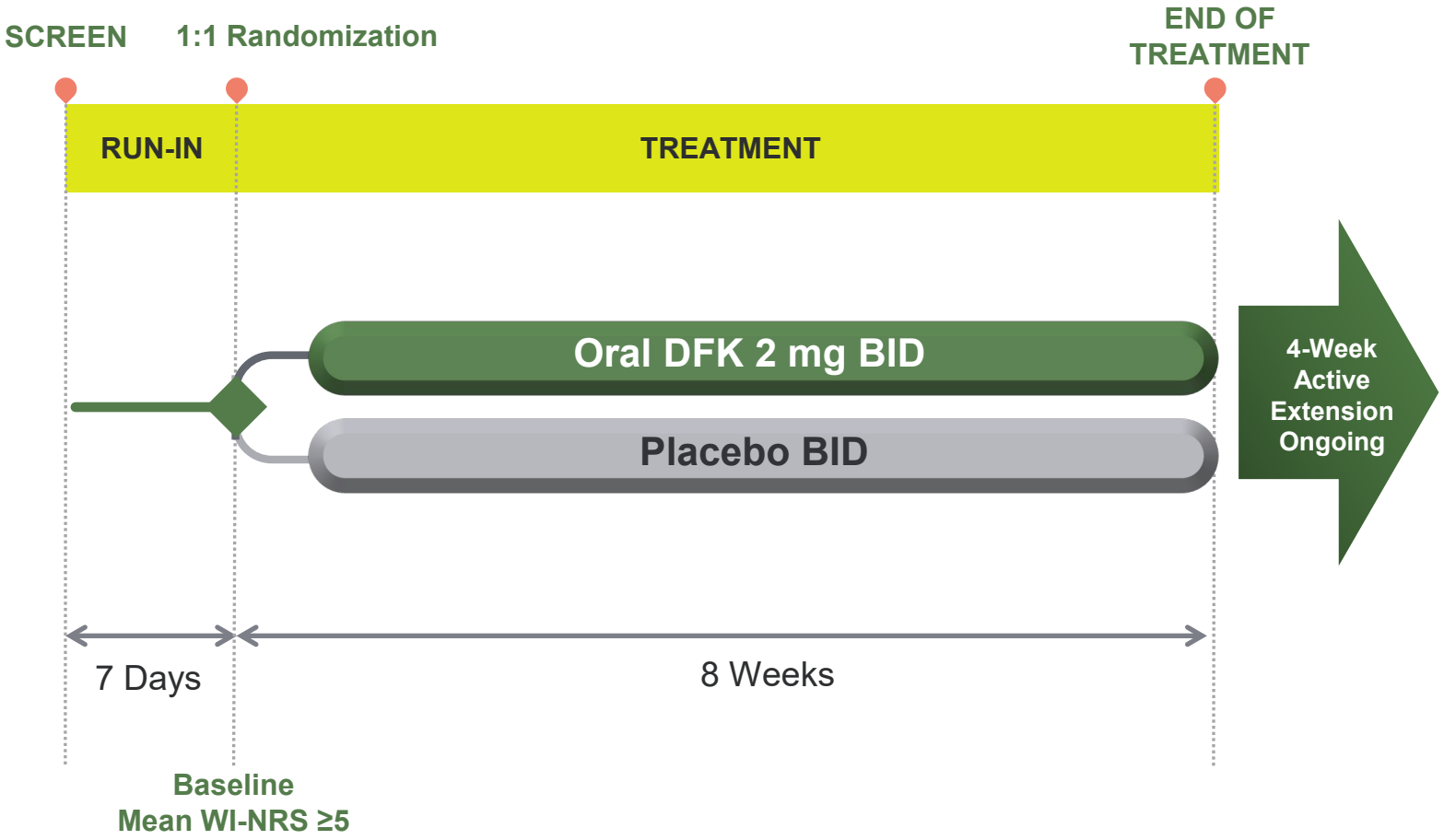


Reprinted from *Curr Opin Neurobiol*, Vol 75, Pereira MP, Schmelz M, Ständer S, Mechanisms and Therapeutic Targets for Neuropathic Itch, p102573, ©2022, with permission from Elsevier.

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.

KOMFORT: Phase 2 Study Design

- KOMFORT was conducted in adults with a clinically confirmed diagnosis of NP



Primary Endpoint

- 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[a] in WI-NRS
- Safety assessments

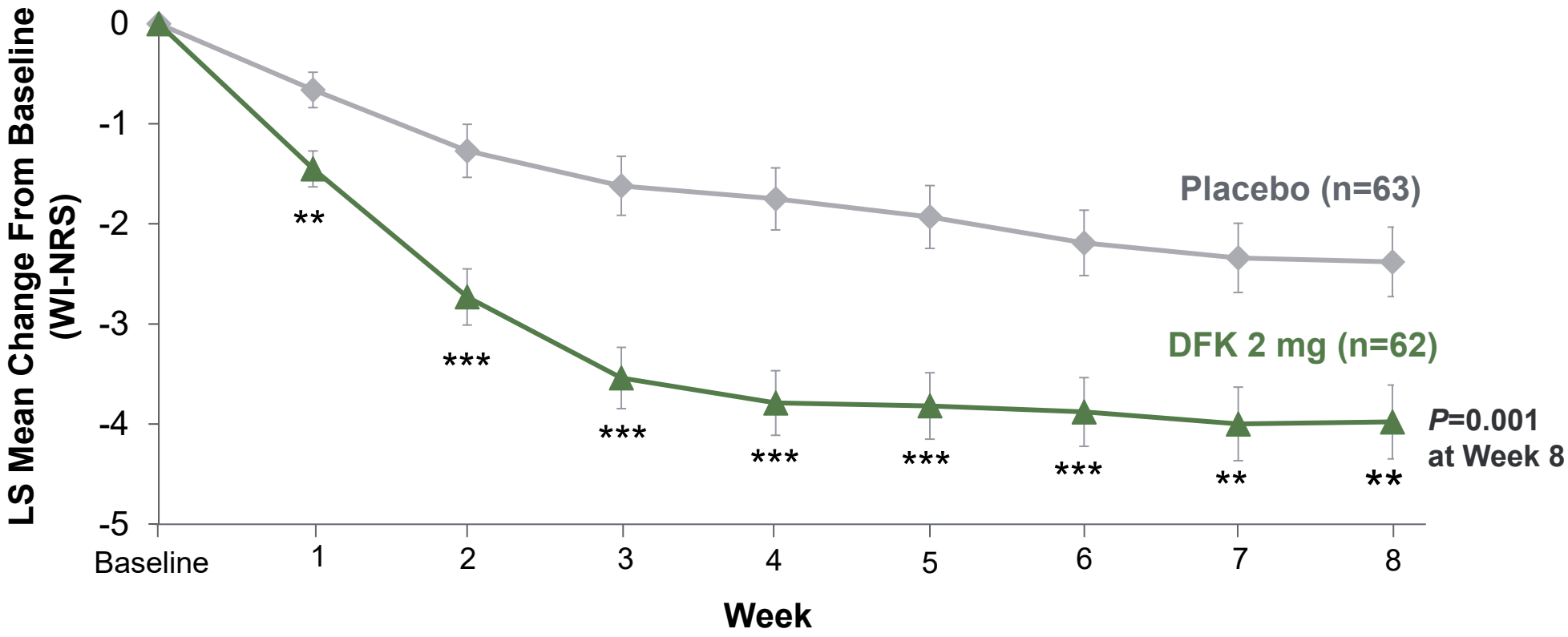
[a]Complete response was defined as WI-NRS score of 0 or 1 for 70% of the daily non-missing WI-NRS scores for the week.
BID, twice daily.

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/m^2	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.

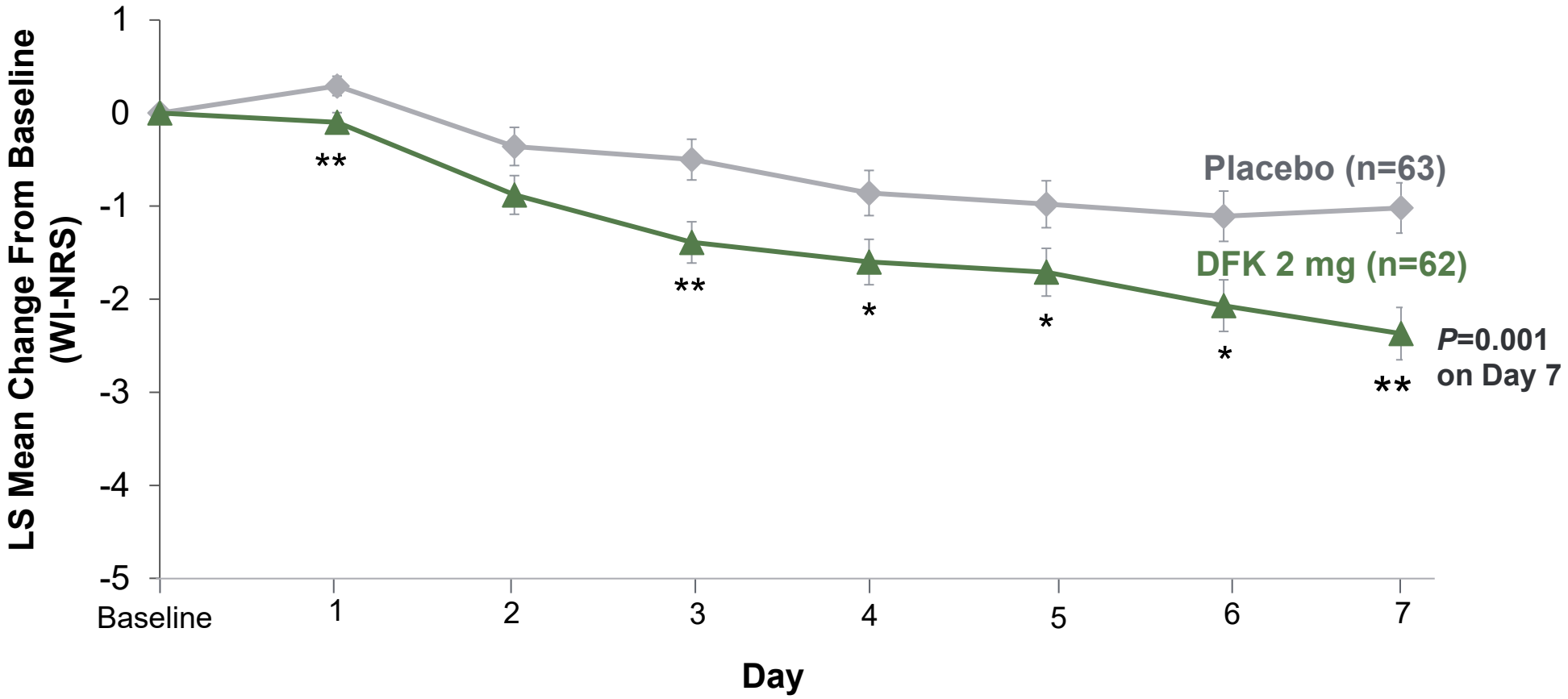
Primary Endpoint: Change From Baseline in WI-NRS at Week 8



*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.

Change From Baseline in Daily WI-NRS During Week 1

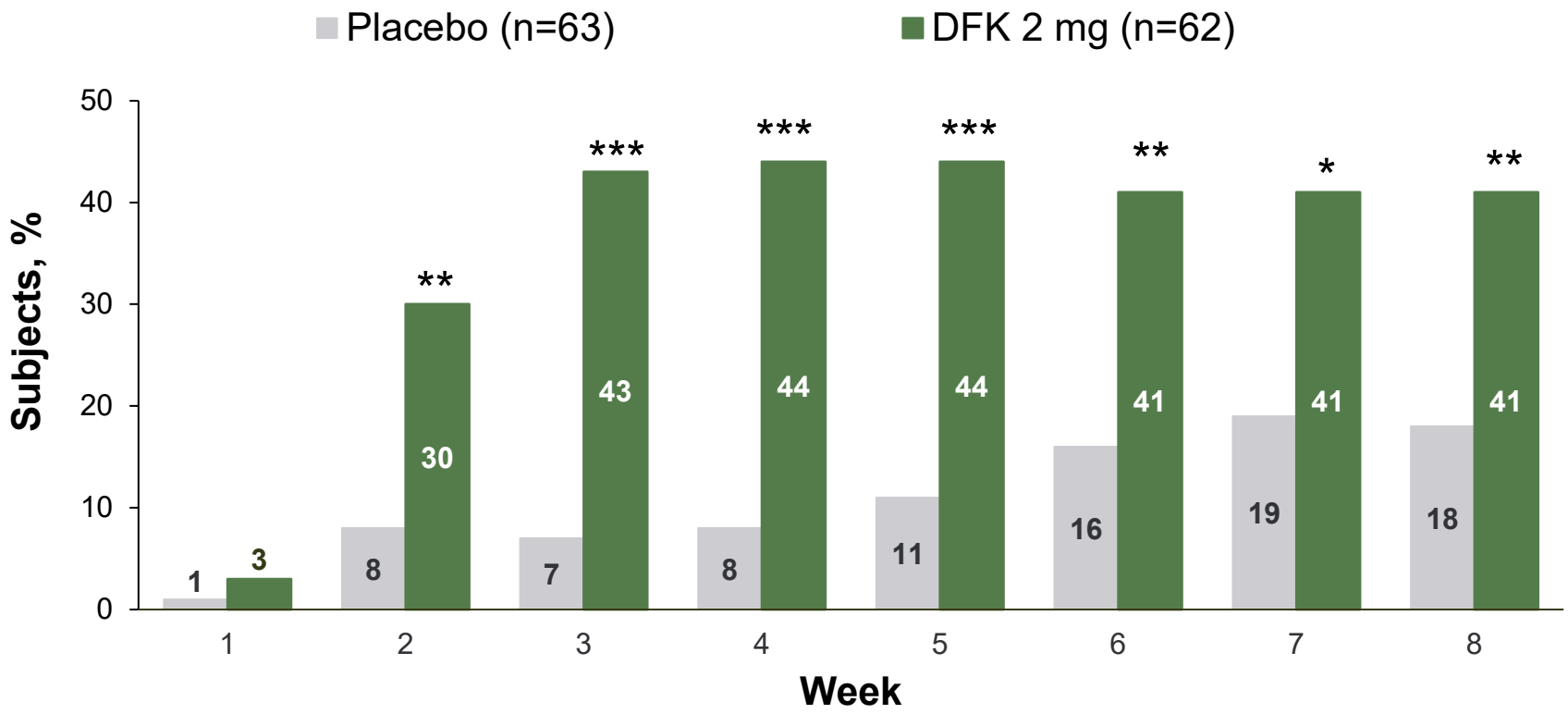
- Reduction in itch intensity was observed with DFK at day 1 compared with placebo



*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.

Achievement of ≥4-Point Improvement in WI-NRS

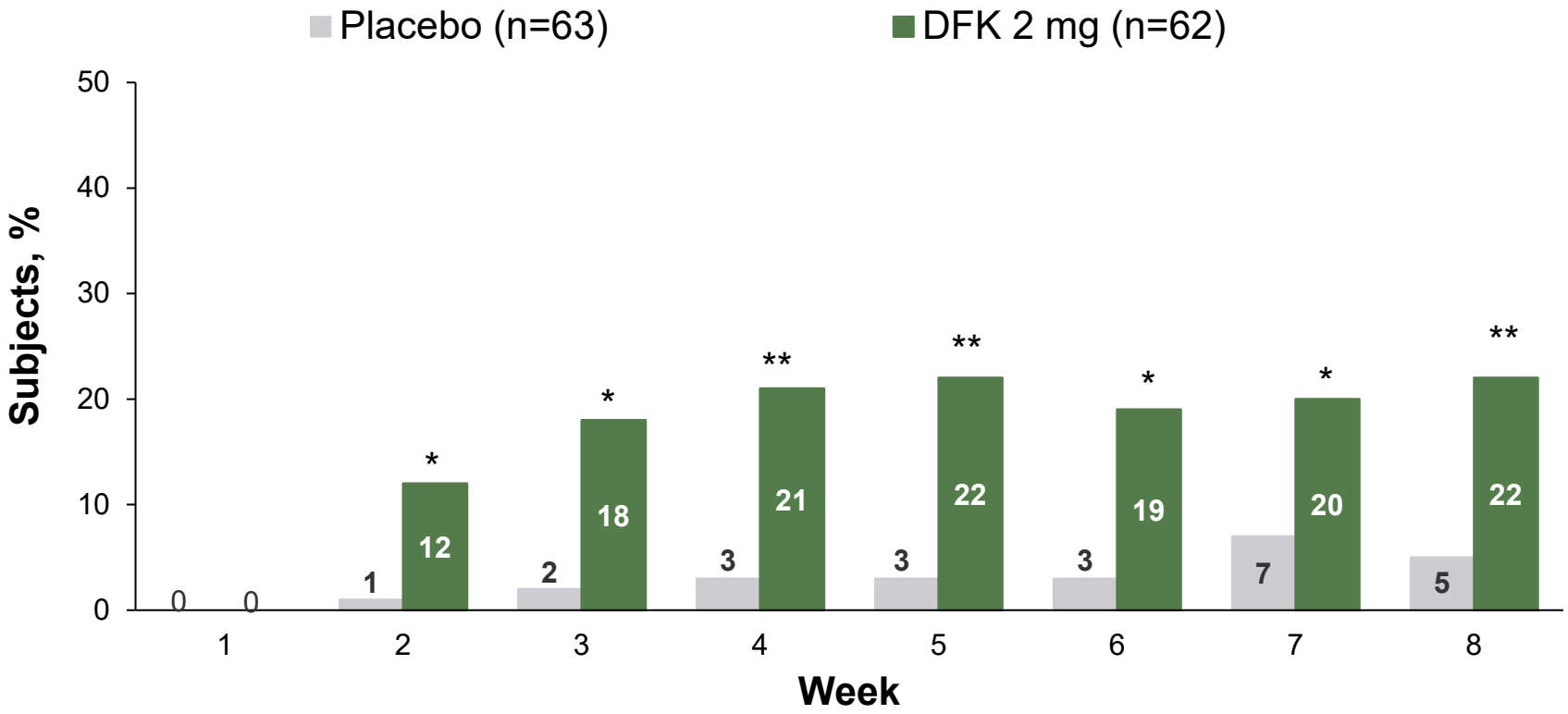
- A significantly greater proportion of subjects achieved a ≥4-point improvement in WI-NRS score at week 8 with DFK vs placebo



*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. Patients 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.

Achievement of Complete Response in WI-NRS

- At week 8, a significantly greater proportion of subjects receiving DFK achieved a complete response (WI-NRS of 0 or 1 on at least 5 of 7 days during the week) compared with placebo[a]



*P<0.05; **P<0.01; ***P<0.0001.
Analysis conducted in ITT population.
[a]Complete response was defined as WI-NRS score of 0 or 1 for 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. Patients 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. No adjustments for multiplicity were made for the secondary or exploratory outcomes.

Summary of TEAEs

- All adverse events in difelikefalin-treated patients were mild to moderate in severity
- The most common 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

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 patients who received ≥1 dose of study drug based on actual treatment received .

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 patients 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