CARA THERAPEUTICS

Meet the NP Experts

March 2024

Forward-Looking Statements

Statements contained in this presentation regarding matters that are not historical facts are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Examples of these forward-looking statements include statements concerning the Company's planned future regulatory submissions and potential future regulatory approvals, future product launches, expected timing of the initiation, enrollment and data readouts from the Company's planned and ongoing clinical trials, the potential results of ongoing clinical trials, timing of future regulatory and development milestones for the Company's product candidates, the potential for the Company's product candidates to be alternatives in the therapeutic areas investigated, including notalgia paresthetica, and the size and growth of the potential markets for pruritus management such as notalgia paresthetica, Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. These risks and uncertainties include the risks inherent in the launch of new products, including that our commercial partners, including CSL Vifor, may not perform as expected, risks inherent in the clinical and regulatory development of pharmaceutical products, and the risks described more fully in Cara Therapeutics' filings with the Securities and Exchange Commission, including the "Risk Factors" section of the Company's Annual Report on Form 10-K for the year ending December 31, 2023 and its other documents subsequently filed with or furnished to the Securities and Exchange Commission. All forward-looking statements contained in this presentation speak only as of the date on which they were made. Cara Therapeutics undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made, except as required by law.

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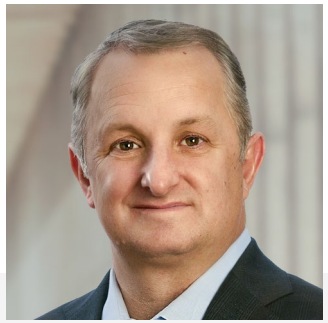
Today’s Speakers

Brian Kim, MD, MTR, FAAD
Icahn School of Medicine at Mount Sinai

Gil Yosipovitch, MD, FAAD
Miller School of Medicine at University of Miami

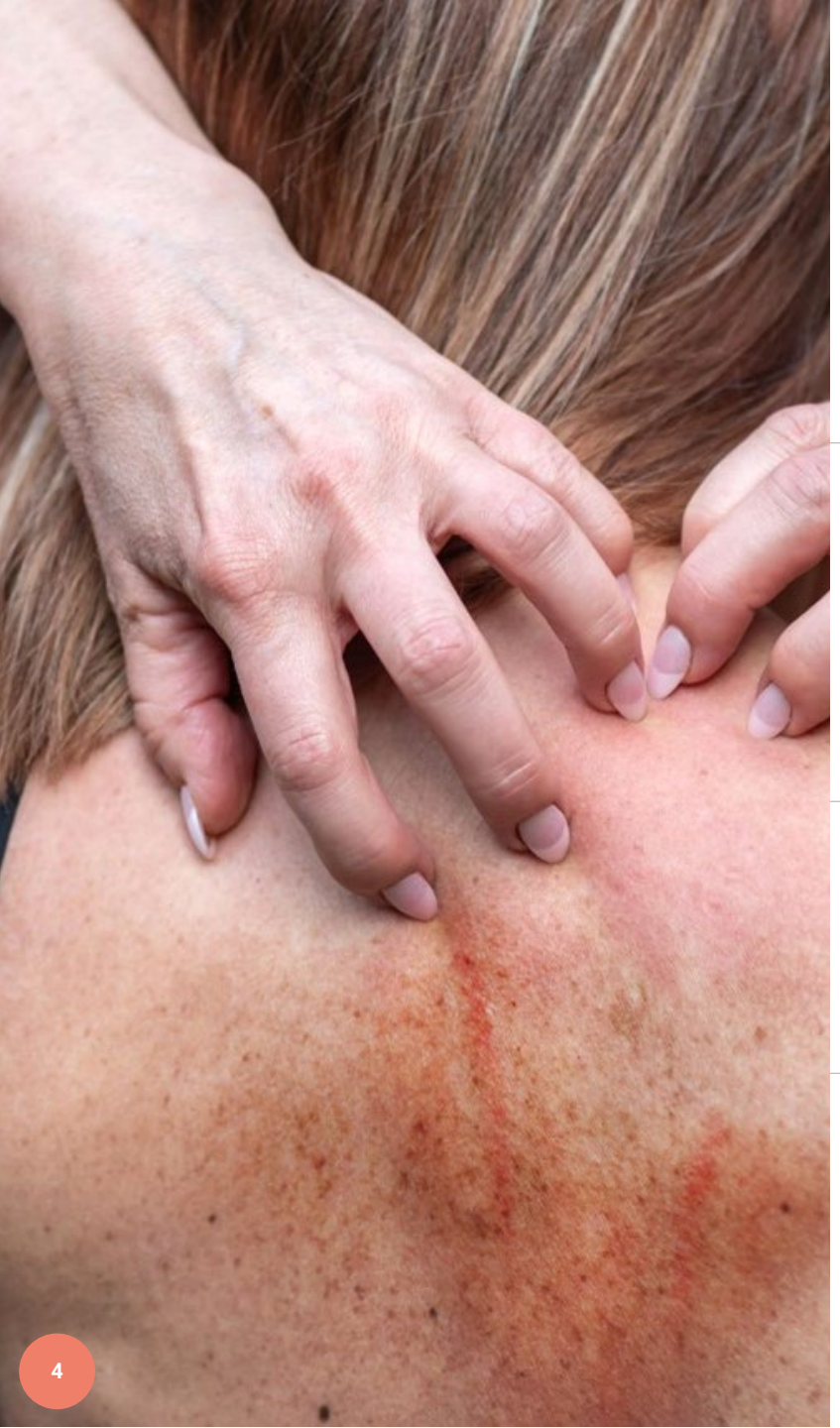
Melinda Gooderham, MSc, MD, FRCPC
SKiN Centre for Dermatology



Christopher A. Posner
President and Chief Executive Officer

Joana Goncalves, MD
Chief Medical Officer

Iris Francesconi, PhD
Chief Strategy Officer



Agenda

1 **Cara Strategy - Pioneering Innovation in NP**
Christopher Posner, President and Chief Executive Officer, Cara Therapeutics

2 **Panel Discussion - Unmet Medical Need in NP**
Joana Goncalves, MD | Chief Medical Officer, Cara Therapeutics
Brian Kim, MD, MTR, FAAD | Icahn School of Medicine at Mount Sinai
Gil Yosipovitch, MD, FAAD | Miller School of Medicine at University of Miami
Melinda Gooderham, MSc, MD, FRCPC | SKiN Centre for Dermatology

3 **Oral Difelikefalin - Potential in NP**
Joana Goncalves, MD | Chief Medical Officer, Cara Therapeutics
Christopher Posner, President and Chief Executive Officer, Cara Therapeutics

4 **Live Q&A Session**

Oral difelikefalin is an investigational agent that has not been approved by the FDA. The efficacy and safety of oral difelikefalin have not been established.

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Cara Strategy | Pioneering Innovation in NP

Christopher Posner, President and Chief Executive Officer, Cara Therapeutics

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Notalgia Paresthetica, an Underserved Neuropathy

NP is a sensory neuropathic syndrome characterized by chronic pruritus[1]

Pruritus is burdensome and impairs quality of life[2]

Estimated >650K patients currently treated for NP[1, 3-5]

No FDA-approved treatments; off label treatments are either ineffective or have tolerability issues[2]

Oral DFK with its neuromodulatory action has the potential to be **the first and only** anti-pruritic therapy approved for NP

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PIONEERING INNOVATION IN MEDICAL DERMATOLOGY

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1. Pereira P. et al., Acta DV 2018 ; 98:82-88; 2. Howard M et al. Notalgia paresthetica: a review for dermatologists. Int J of Derm. 2017. 388-392. 3. US Census Bureau 2020 population projection; 4. Mollanazar N.K. et al., Acta Clin Croat 2018; 57:721-725; 5. Syneos Health qualitative primary research of US dermatologists, Feb 2022; 5. Syneos market research and Apollo claims database

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Panel Discussion | Unmet Medical Need in NP

Joana Goncalves, MD, Chief Medical Officer, Cara Therapeutics
Brian Kim, MD, MTR, FAAD, Vice Chair of Research, Icahn School of Medicine at Mount Sinai
Gil Yosipovitch, MD, FAAD, Professor of Dermatology, Miller School of Medicine at University of Miami
Melinda Gooderham, MSc, MD, FRCPC, Medical Director, SKiN Centre for Dermatology

Oral Difelikefalin | Potential in NP

Joana Goncalves, MD, Chief Medical Officer, Cara Therapeutics

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Difelikefalin, a New Treatment for Chronic Pruritus

Novel, first-in-class selective and potent kappa opioid receptor (KOR) agonist

1

Differentiated MOA

- Activates KORs on peripheral sensory neurons and immune cells
- Strong neuromodulatory properties suppress itch

2

Attractive Pharmacology

- Highly selective and potent full agonist at KORs
- Does not produce mu opioid side effects (e.g., euphoria, addiction and respiratory depression)
- **Non-scheduled drug**

3

Demonstrated Efficacy

- Oral formulation has shown positive proof-of-concept data in the treatment of chronic pruritus associated with Notalgia Paresthetica (NP)
- IV formulation approved for chronic kidney disease-associated pruritus (CKD-aP) in hemodialysis patients

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 2 Trial of Difelikefalin in Notalgia Paresthetica

Brian S. Kim, M.D., M.T.R., Robert Bissonnette, M.D., Kristine Nograles, M.D., Catherine Munera, Ph.D., Nilam Shah, Pharm.D., Alia Jebara, M.D., Joshua Cirulli, Pharm.D., Joana Goncalves, M.D., and Mark Lebwohl, M.D., for the KOMFORT Trial Investigators*

N ENGL J MED 388:511-517 FEBRUARY 9, 2023

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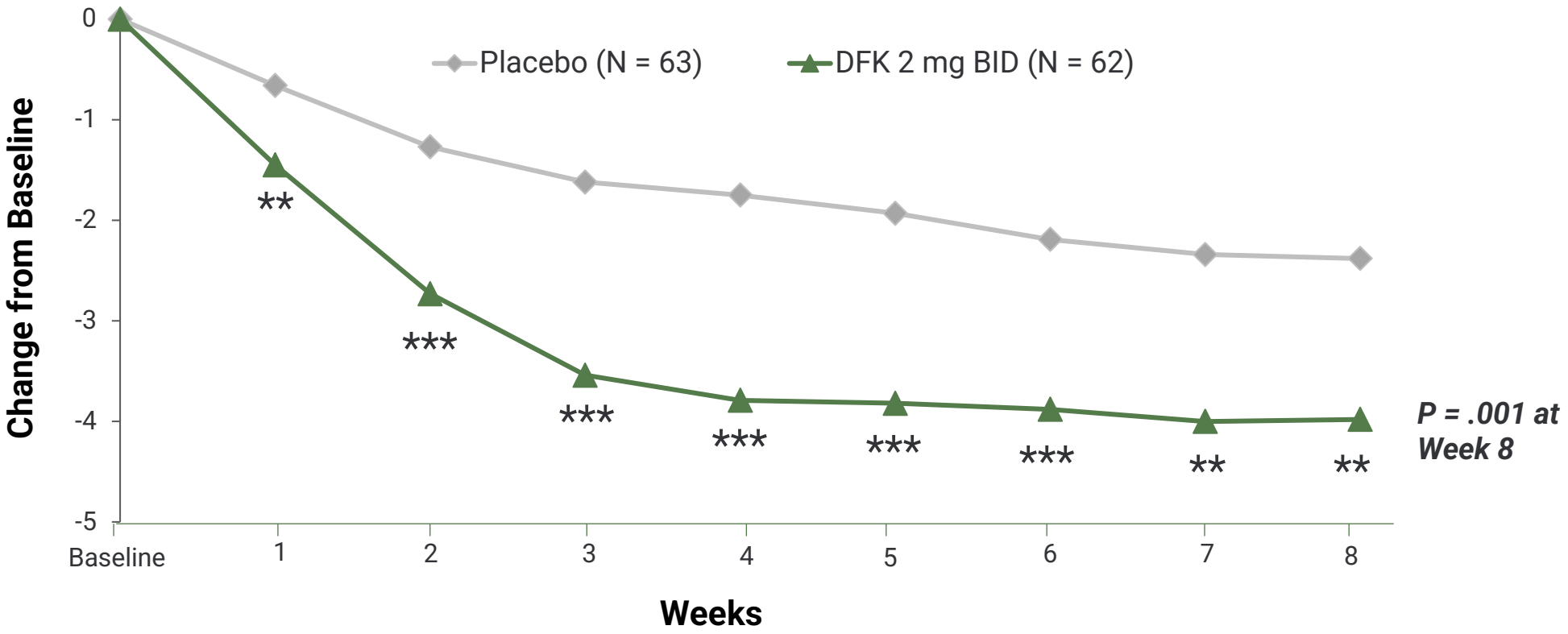
Primary Endpoint:
Change from Baseline in Daily WI-NRS at Week 8 (ITT)

Significant improvement observed with Difelikefalin vs Placebo at all timepoints



** P<.05; ** P<.01; *** P<.001*

LS Means from MMRM with terms for treatment, week, treatment by week interaction, and baseline WI-NRS score
Missing data imputed using multiple imputation (MI) under missing at random (MAR) assumption

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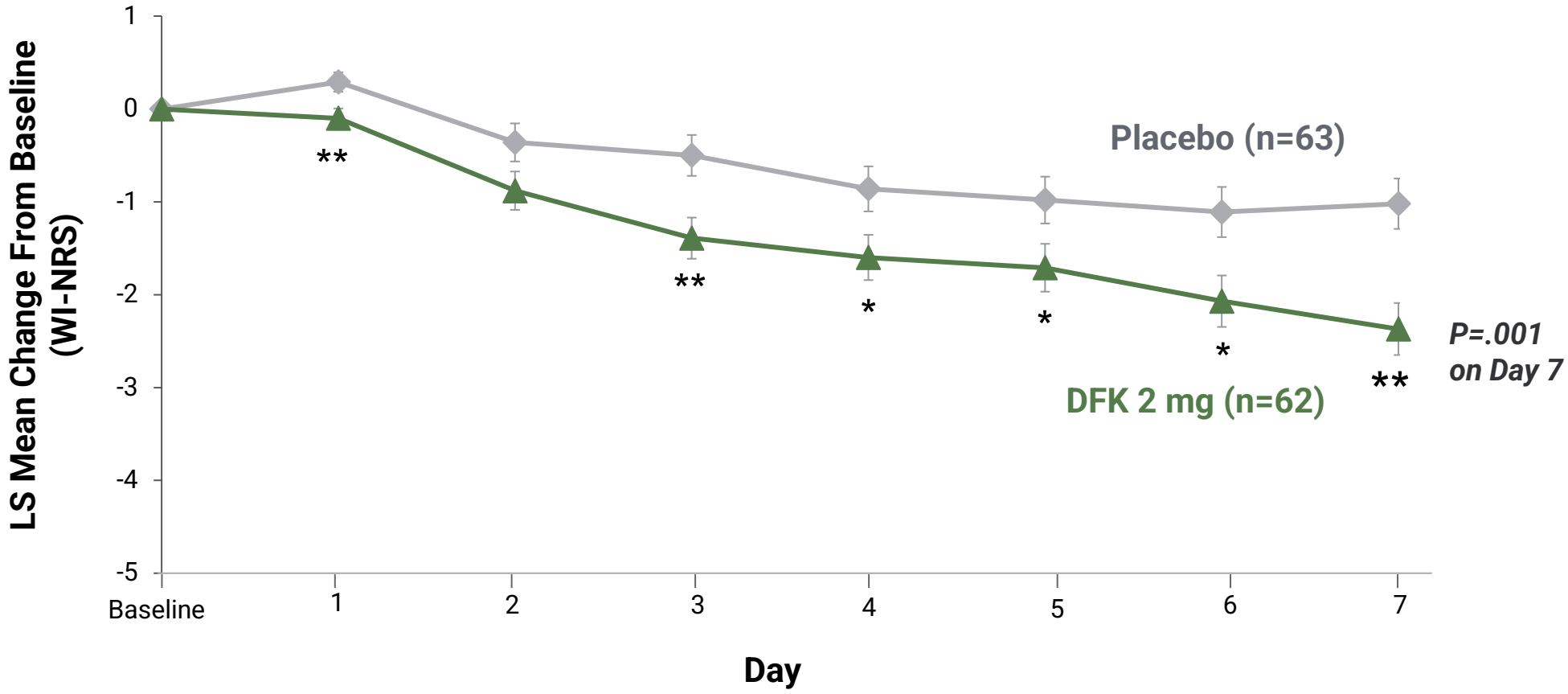
Change from Baseline in Daily WI-NRS during Week 1

Improvement observed with DFK vs Placebo at all timepoints, starting on Day 1



** P<.05; ** P<.01; *** P<.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.

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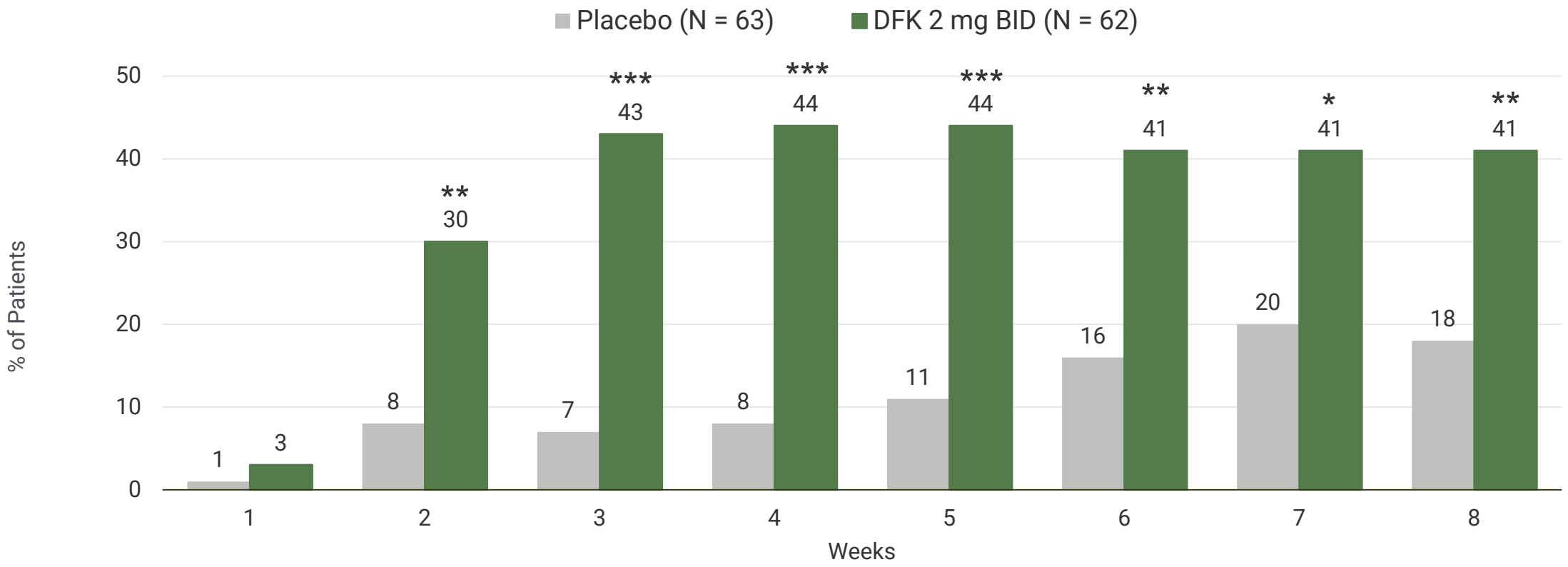
≥ 4-point Improvement in WI-NRS

Significantly greater proportion of patients achieved a ≥4-point improvement in WI-NRS score at Week 8 with DFK vs Placebo



** P<.05; ** P<.01; *** P< .001 vs placebo*

Estimated percentages & P-values from a logistic regression with terms for treatment and baseline WI-NRS score; Patients with missing weekly WI-NRS scores for a particular week are categorized as non-responders

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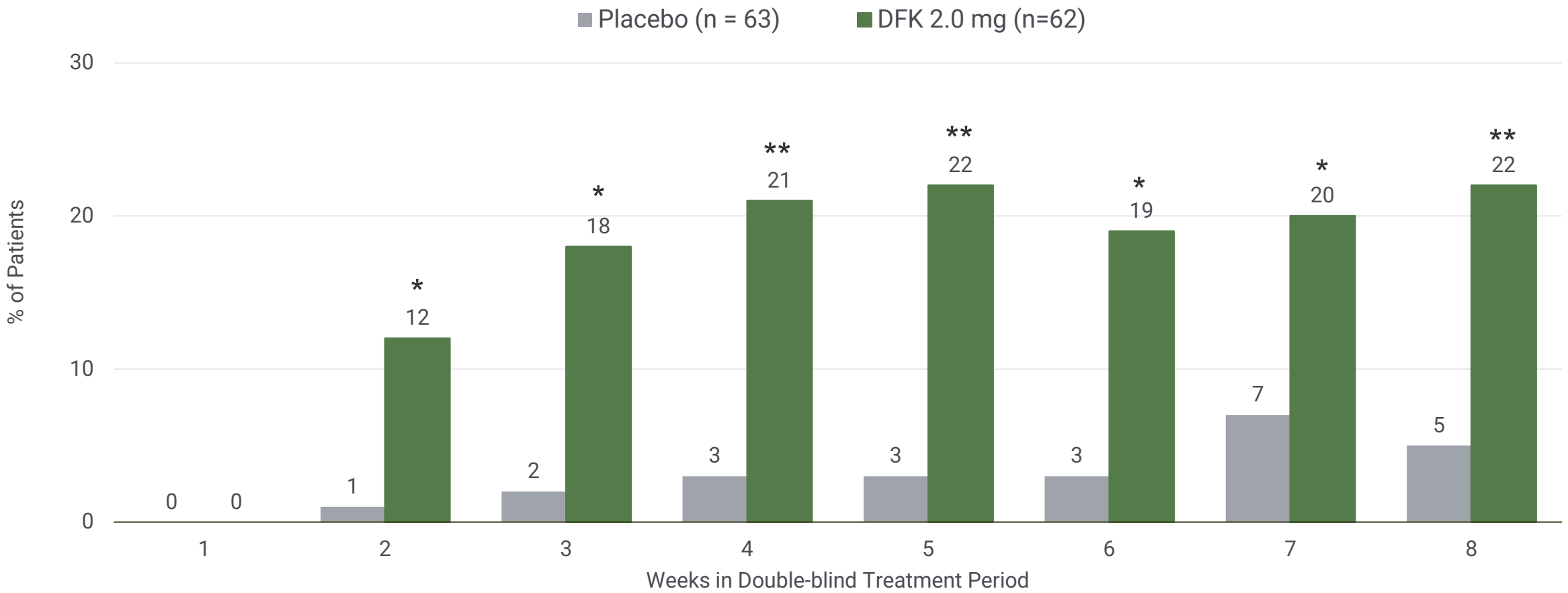
Complete Responders in WI-NRS

Significantly greater proportion of patients achieved a complete response in WI-NRS score at Week 8 with DFK vs Placebo



** P<.05; ** P<.01; *** P< .001 vs placebo*

Estimated percentages & P-values from a logistic regression with terms for treatment and baseline WI-NRS score.

Complete response defined as >= 70% of the reported daily 24-hour WI-NRS scores for a given week are either 0 or 1; Patients with missing weekly WI-NRS scores for a particular week are categorized as non-responders.

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Most Commonly Reported TEAEs

Treatment-emergent Adverse Events at ≥5% frequency; n (%)	Placebo (N=63)	DFK 2 mg BID (N=62)
Nausea	7 (11.1%)	8 (12.9%)
Abdominal pain*	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%)
Urine output increased#	1 (1.6%)	5 (8.1%)

Safety analyses performed in the safety population, defined as all randomized patients who received ≥1 dose of study drug based on actual treatment received.
*includes PTs abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower; #includes urine output increased and pollakiuria

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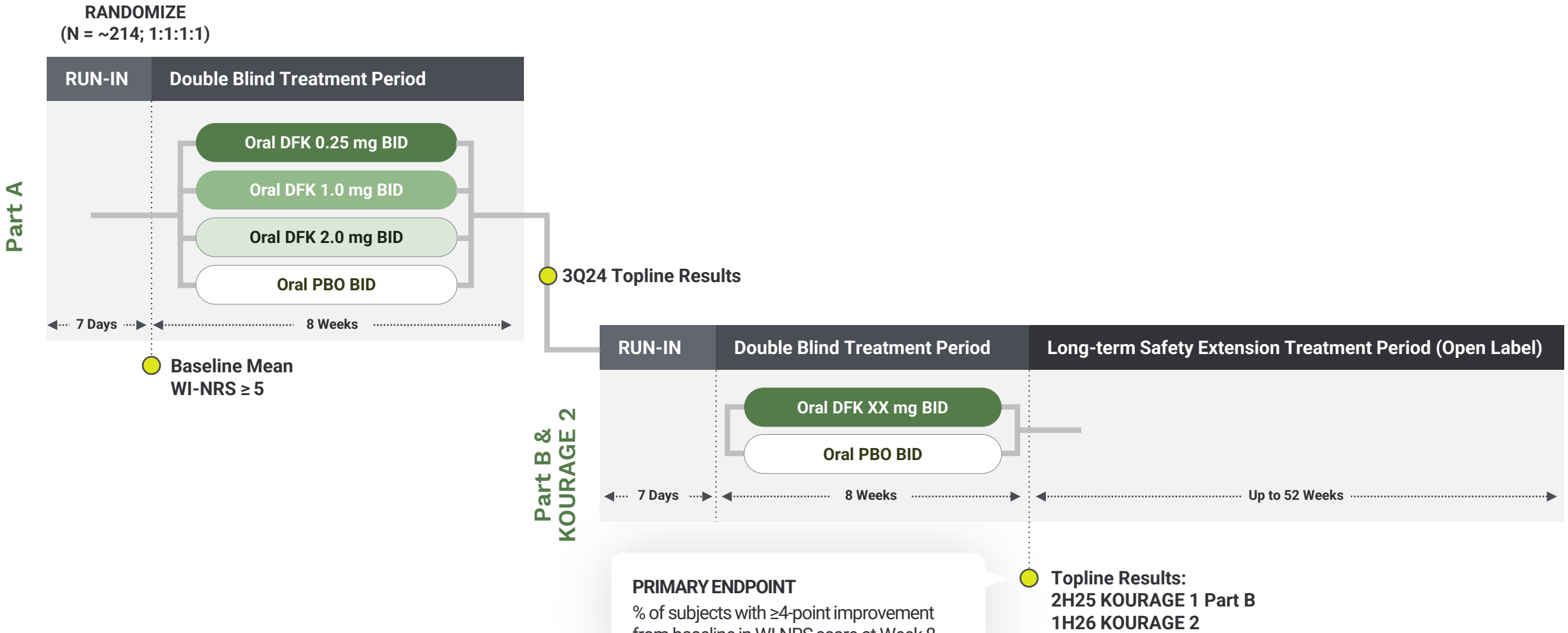
KOURAGE 1 and KOURAGE 2: Phase 2/3 Study Design in NP

Readout for Part A expected in 3Q24



Oral Difelikefalin

Potential first and only anti-pruritic therapy approved for Notalgia Paresthetica

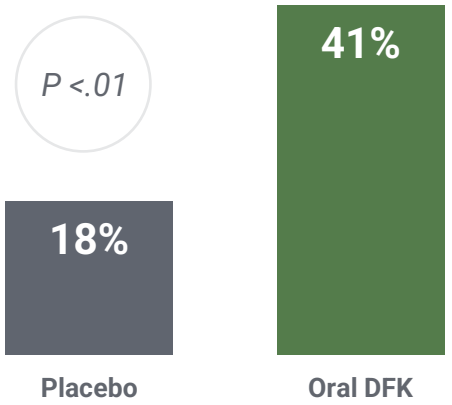
Unique Properties & MOA

- Picomolar in-vitro activity
- High selectivity for KOR
- Strong neuromodulatory action
- Peripherally acting
- No classical mu opioid side effects
- No DEA scheduling

Strong Clinical Evidence

- Strong proof-of-concept data with 2 mg BID of oral DFK

≥ 4-point Improvement
in WI-NRS at Week 8



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A Potential New Option for NP Patients

Oral DFK for the treatment of chronic pruritus associated with NP

Chronic pruritus, the defining feature of Notalgia Paresthetica (NP), is known to have an impact on the **Quality of Life (QOL)** of many patients similar to pain.[1-3]

There is a **large NP patient population** (~650K patients in the US) and it is widely underdiagnosed.[1,4-6]

The off-label therapies tried by HCPs and patients (e.g. topical steroids, gabapentin), are often ineffective in treating chronic pruritus or have limiting side effects.[2,6]

Oral difelikefalin (DFK) has the potential to be **the first and only** anti-pruritic therapy approved for Notalgia Paresthetica.

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1. Pereira P. et al., Acta DV 2018 ; 98:82-88; 2. Howard M et al. Notalgia paresthetica: a review for dermatologists. Int J of Derm. 2017. 388-392; 3. Arch Dermaltol/Vol 147 (No. 10), Oct 2011; 4. US Census Bureau 2020 population projection; 5. Mollanazar N.K. et al., Acta Clin Croat 2018; 57:721-725; 6. Syneos Health qualitative primary research of US dermatologists, Feb 2022; 6. Syneos market research and Apollo claims database

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Audience Q&A