

Welcome to Cara Therapeutics

Notalgia Paresthetica Day

SEPTEMBER 20TH, 2022



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 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 size of potential markets 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 potential impact of COVID-19 on the Company's clinical development and regulatory timelines and plans. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Risks are 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, 2021 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.

Today's Speakers



Christopher Posner
CEO, President and Director



Joana Goncalves, MD
Chief Medical Officer



Eric Vandal
SVP, Commercial



Zoe Draelos, MD
*President, Dermatology Consulting Services,
PLLC*



Brian Kim, MD, MTR
*Vice Chair of Research, Icahn School of
Medicine at Mount Sinai, NY*

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Introductory Remarks




CHRISTOPHER POSNER, CEO, PRESIDENT AND DIRECTOR, CARA THERAPEUTICS

OUR MISSION:

Transform the way pruritus is treated to bring quality to the lives of those who suffer.



Millions of US Patients Could Benefit from a Chronic Pruritus Therapy

| | | Estimated US Addressable Pruritus Population |
|---|--|--|
|  SYSTEMIC | HD-Dependent Chronic Kidney Disease (CKD)¹⁻² | 200K |
| | Non-Dialysis Dependent CKD (Stage 4-5)³⁻⁷ | 300K |
| | Chronic Liver Disease⁸⁻¹² | 3M |
|  DERMATOLOGICAL | Atopic Dermatitis¹³⁻¹⁵ | 12M |
|  NEUROLOGICAL | Notalgia Paresthetica¹⁶⁻¹⁹ | >650K |

1..National Institute of Diabetes and Digestive and Kidney Diseases. <https://www.niddk.nih.gov/health-information/health-statistics/kidney-disease>. 2. Pisoni et al. Pruritus in haemodialysis patients: international results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrology Dialysis Transplantation (2006); 21(12): 3495-3505. 3. Centers for Disease Control and Prevention <https://nccd.cdc.gov/ckd/detail.aspx?Qnum=Q372>. 4. DataMonitor 5. States Renal Data System <https://adr.usrds.org/2020/chronic-kidney-disease/1-ckd-in-the-general-population>. 6. Wong SJY et al. Decisions about Renal Replacement Therapy in Patients with Advanced Kidney Disease in the US Department of Veterans Affairs, 2000–2011. Clin Journal of Am Soc Nephrol. 2016. 11(10): 1825-1833. 7. Sukul N et al. Pruritus and patient reported outcomes in non-dialysis CKD. Clin J Am Soc Nephrol 2019. 673-681. 8.Centers for Disease Control and Prevention <https://www.cdc.gov/nchs/fastats/liver-disease.htm> 9. Odea S et al. Prevalence of pruritus in patients with chronic liver disease: A multicenter study. Hepatology Research. 2018. 28(3): E252-E262. 10. Fujino H et al. Pruritus in patients with chronic liver disease and serum autotaxin levels in patients with primary biliary cholangitis. BMC Gastroenterology. 2019. 19:169. 11. Yoshikawa et al. Pruritus is common in patients with chronic liver disease and is improved by nalfurafine hydrochloride. Scientific Reports. 2021. 11:3015. 12. Data on file. 13. National Eczema Association. <https://nationaleczema.org/eczema/types-of-eczema/atopic-dermatitis/> 14. DRG Analysis. 15. Mollanazar NK, Smith PK, Yosipovitch G. Mediators of chronic pruritus in atopic dermatitis: getting the itch out? Clin Rev Allergy Immunol. (2016) 51:263–92. 16. US Census Bureau 2020 population projection; 17. Pereira P. et al., Acta DV 2018 ; 98:82-88; 18. Mollanazar N.K. et al., Acta Clin Croat 2018; 57:721-725e.; 19. Syneos market research and Apollo claims database

Clinical Overview and Unmet Medical Need

ZOE DRAELOS, MD, PRESIDENT, DERMATOLOGY CONSULTING SERVICES, PLLC

Notalgia Paresthetica: Understanding the Itch

The “itch” you cannot scratch

The “itch” that cannot be reached

The “itch” that drives patients nuts

The “itch” that requires a collection of back scratchers

The “itch” that seeks the door jam



Notalgia Paresthetica: Patient Presentation

- Itch at the base of the shoulder blade
- Patients unable to sleep
- Varying intensity of itching with activity
- Patients are unable to concentrate due to itch
- Decreased quality of life
- Increased suicidal ideation
- Patients relate desire to “take skin off” at night and relax
- Characterized by pigmentation and thickened skin (lichenification)



Notalgia Paresthetica: Clinical Presentation

- Symptoms:
 - Chronic, intermittent, paroxysmal itching, tingling, numbness, burning, cold sensation, pins and needles sensation, and/or tenderness
 - Often accompanied by pain, hyperesthesia and other paresthesias
 - May be unilateral or bilateral
- Condition lasts multiple years, with mean duration between 21 months and 3 years
- Affects more women than men
- Diagnosed clinically, but under diagnosed due to lack of treatment, accounts for 8% of chronic itch patients
- No currently approved on-label treatment available

Notalgia Paresthetica: Treatments

- Often resistant to multiple therapies
- Conventional antipruritic therapies (i.e., antihistamines, topical corticosteroids) show poor effect
- Capsaicin commonly used as first line treatment by dermatologists
- Other anecdotal off-label therapies (no robust clinical studies):
 - Topical anesthetics
 - Tacrolimus
 - Intralesional steroids
 - Botulinum toxin A
 - Gabapentin
 - Oxcarbazepine
 - Amitriptyline
 - Surgical decompression
 - Paravertebral local anesthetic blocks
 - Transcutaneous electrical nerve stimulation (TENS)
 - Electrical Muscle Stimulation (EMS)
 - UV-B
 - Spinal manipulation
 - Physical therapy
 - Osteopathic manipulative therapy
 - Acupuncture
 - Cryotherapy

Notalgia Paresthetica: Summary



Imagine

An Itch You Cannot Scratch

It May Not Go Away Quickly, If Ever

Being Told There Is No Treatment

**The Excitement of a Potential
New Effective Treatment for NP**

Difelikefalin Potential Mechanism of Action in Notalgia Paresthetica

BRIAN KIM, MD, MTR, VICE CHAIR OF RESEARCH, ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI, NY



Understanding Itch in Notalgia Paraesthetica

Notalgia Paresthetica is a Neuropathic Itch Disorder

No FDA-approved treatments

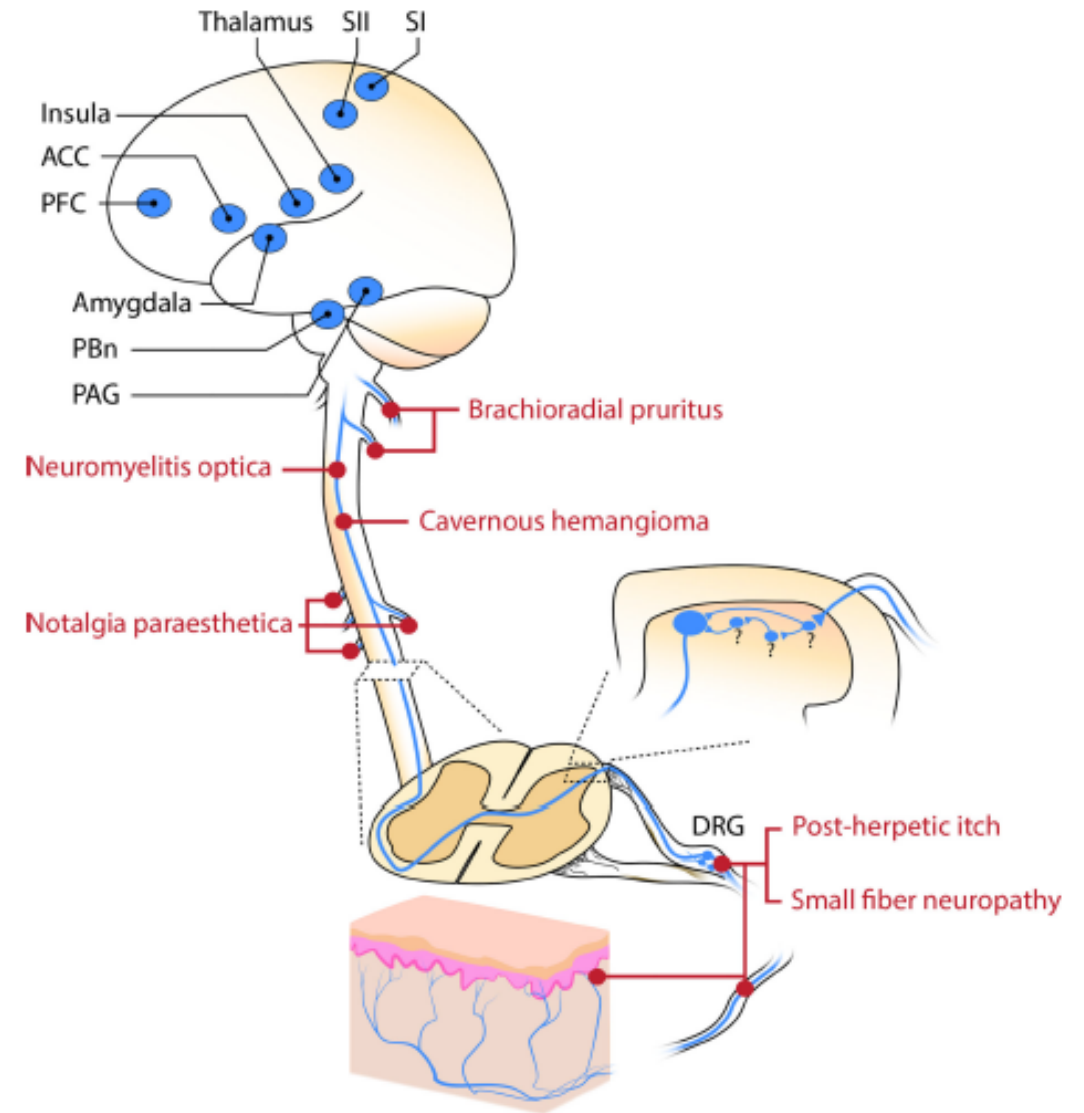
Off label treatments are either ineffective or have tolerability issues¹

- Anti-inflammatories have poor efficacy
- Neuromodulatory drugs that are currently used are limited by tolerability issues

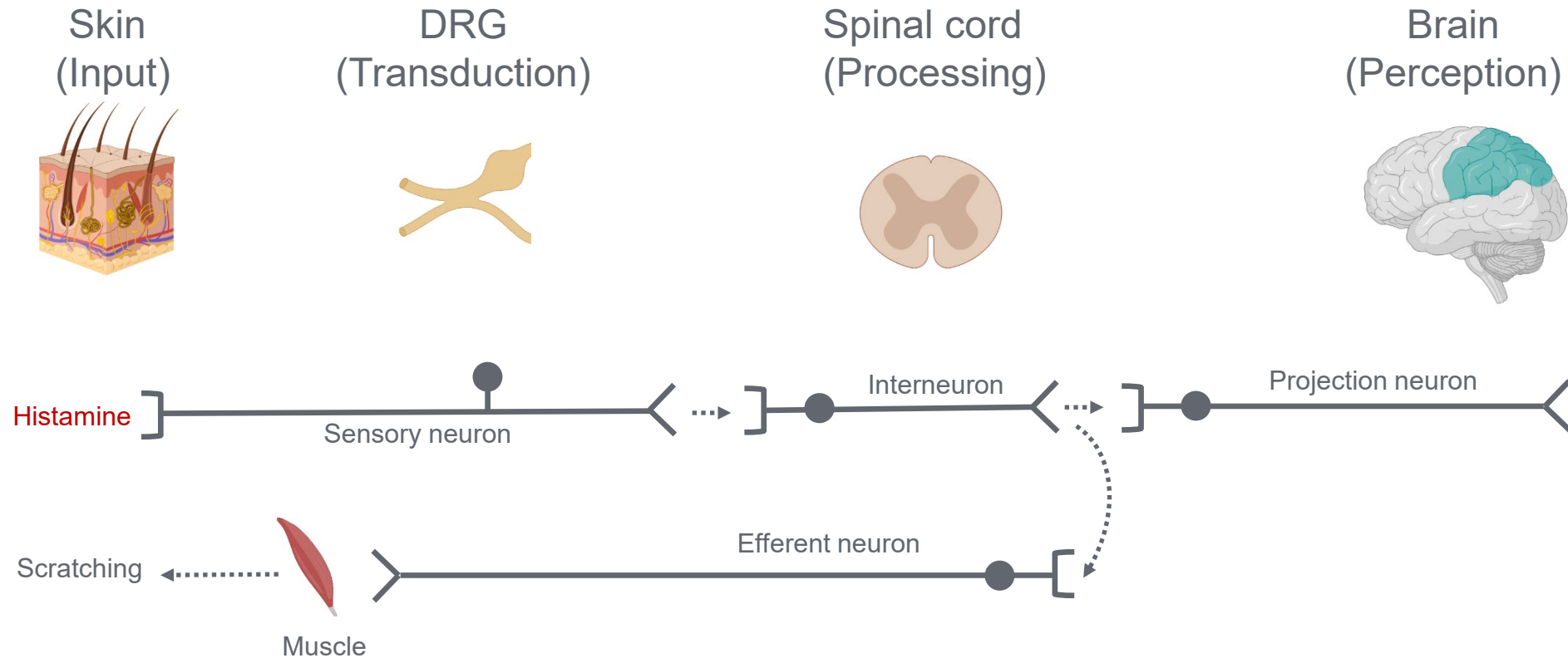


Pathogenesis

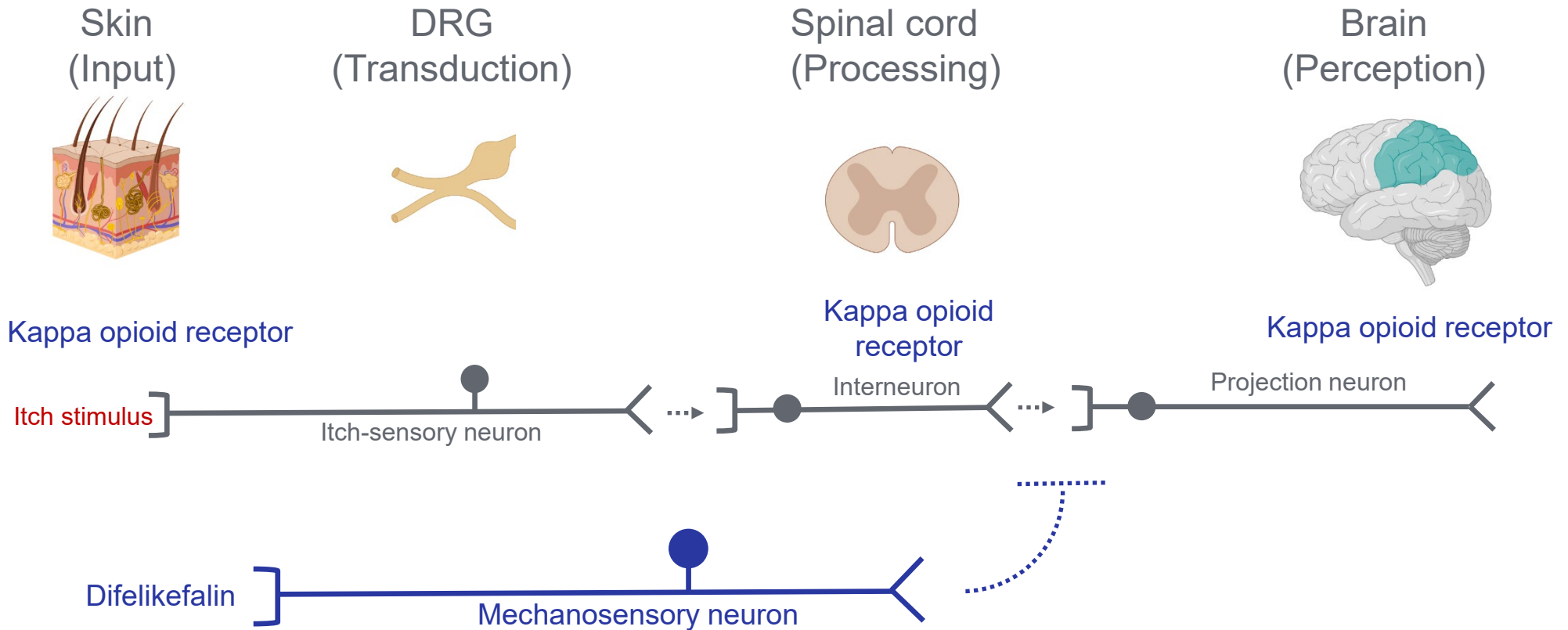
- Likely due to mechanical irritation along the spinal cord
- Believed to be caused by compression of the dorsal branches of the spinal nerves (T2-T6)
- Leads to circumscribed pruritus between the scapulae, usually unilateral but occasionally bilateral



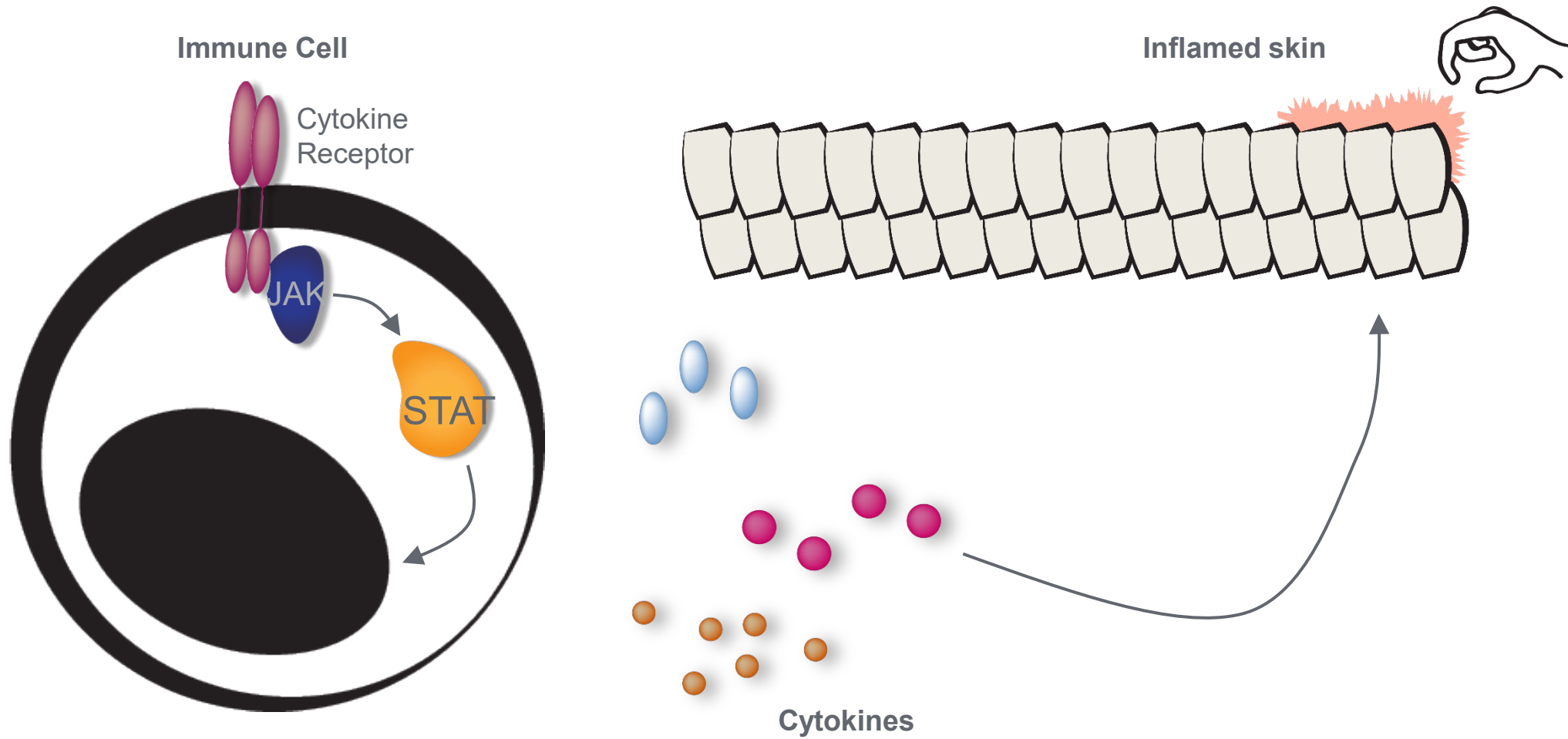
How is Itch and Scratch relayed in the Body?



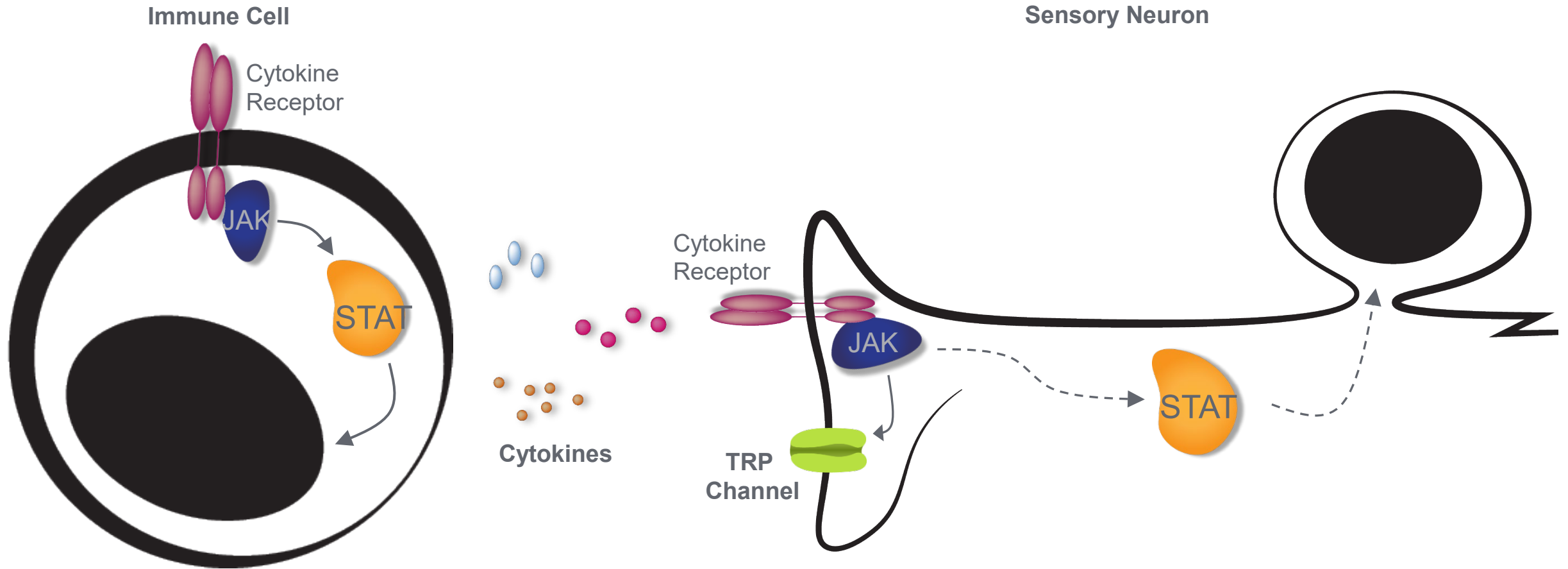
How do Kappa Opioid Receptor Agonists suppress Itch?



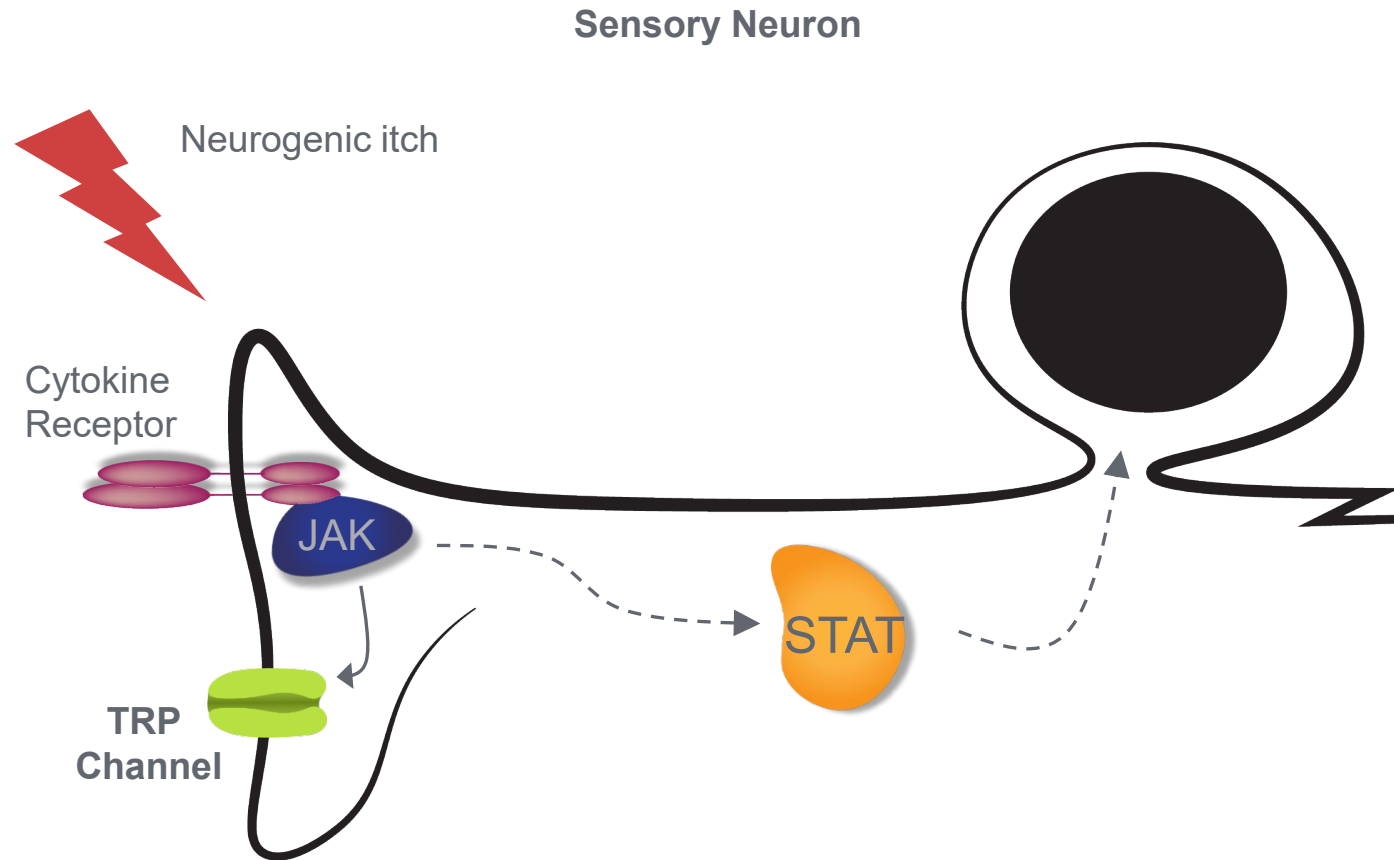
Conventional Paradigm of Skin Inflammation



Itch is Secondary in Inflammatory Itch



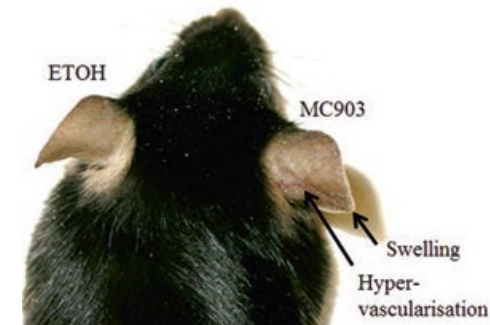
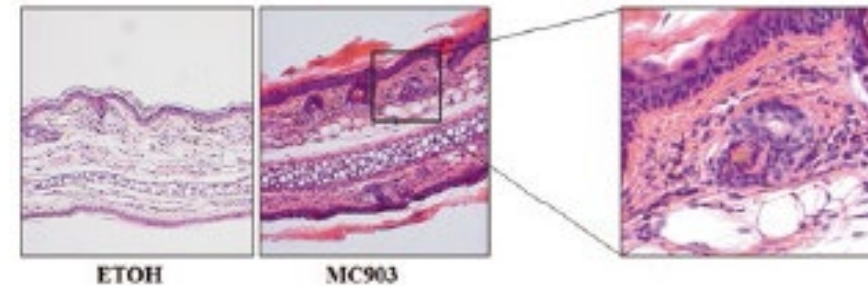
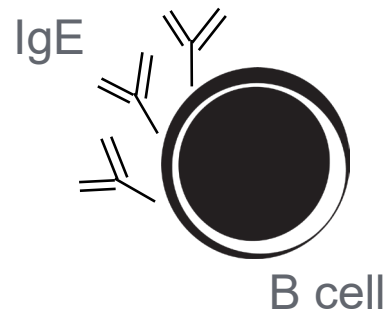
Itch is Primary in Neuropathic Itch





Difelikefalin: Mechanism of Action

Mouse Study Methods and Results

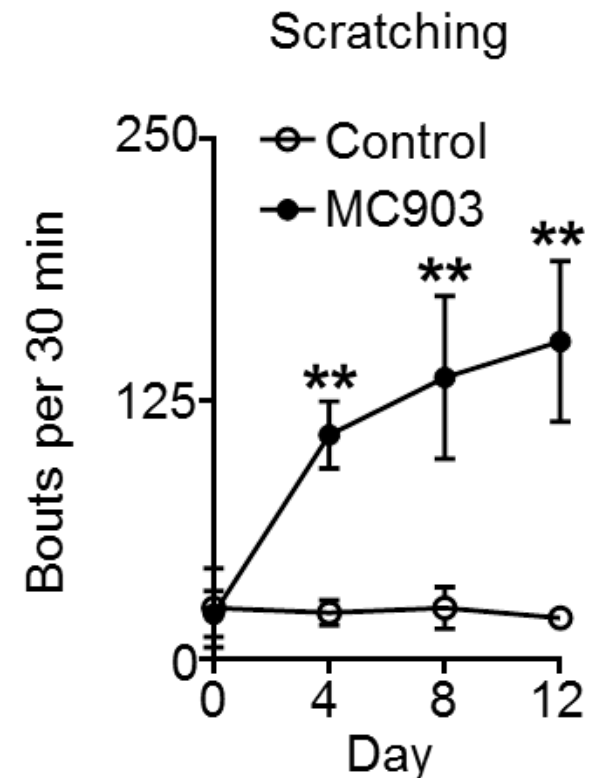
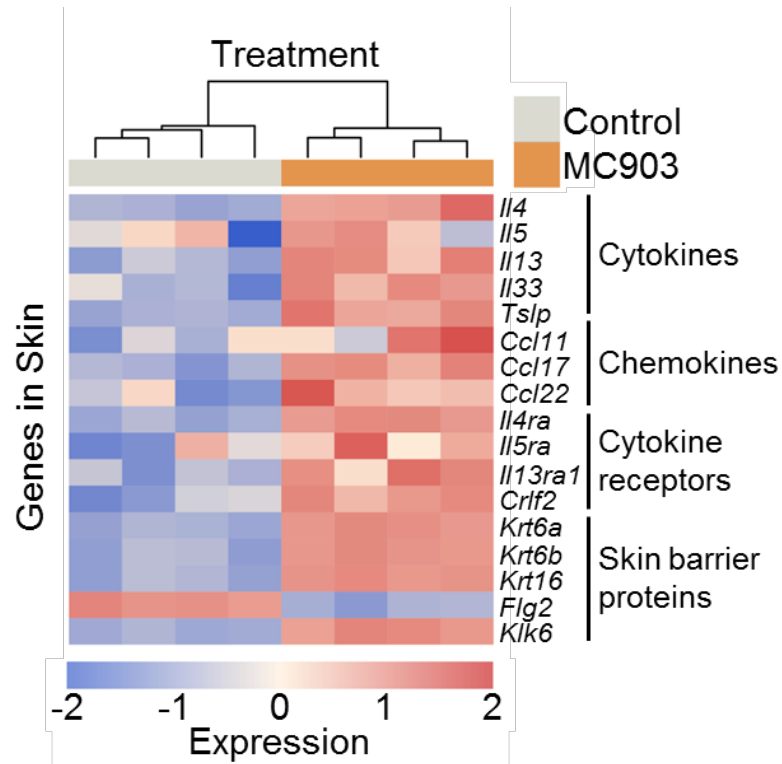


Mouse Study Methods and Results

Topical vehicle (EtOH)
or MC903

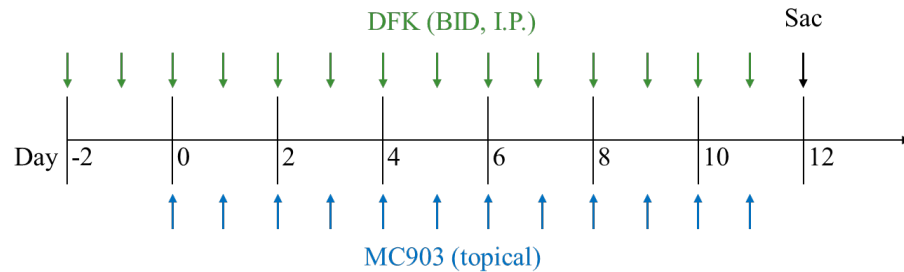


AD-like disease

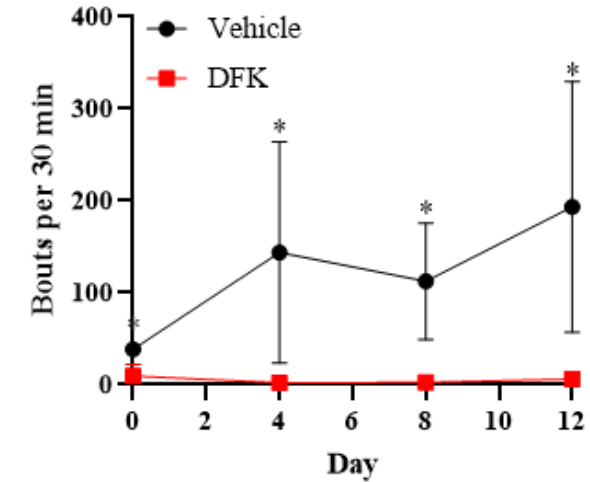


Mouse Study Methods and Results

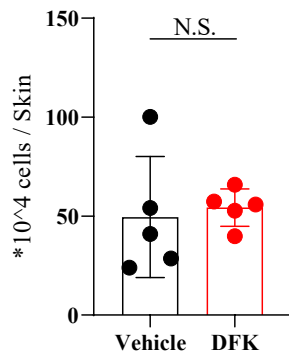
C57BL/6 treated with MC903 for 12 days



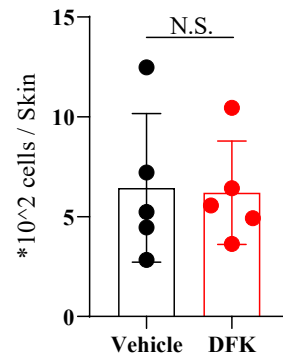
Scratching



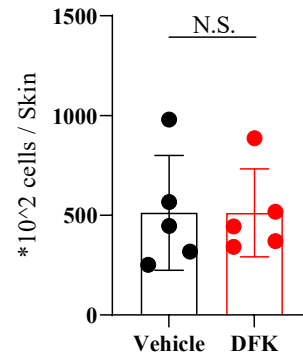
#CD45+ Cells in Skin



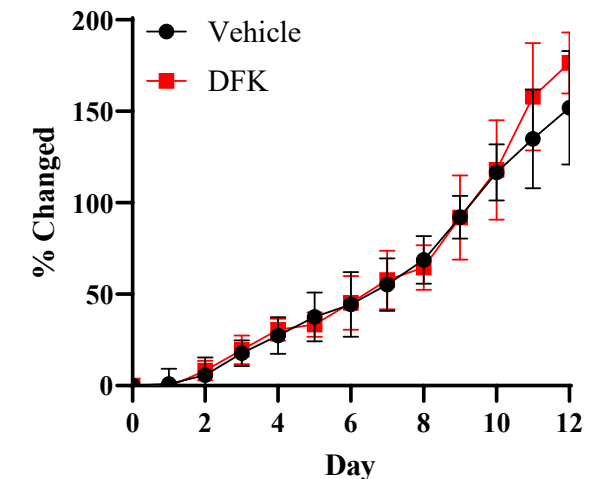
ILC2s in Skin



#CD4T Cells in Skin



Ear Thickness

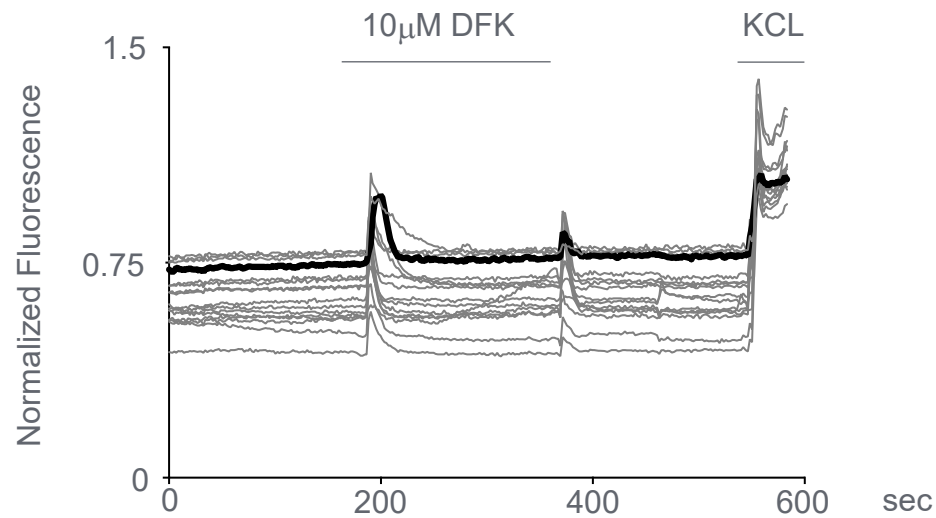


* p < 0.05 vs. control (unpaired t-test)

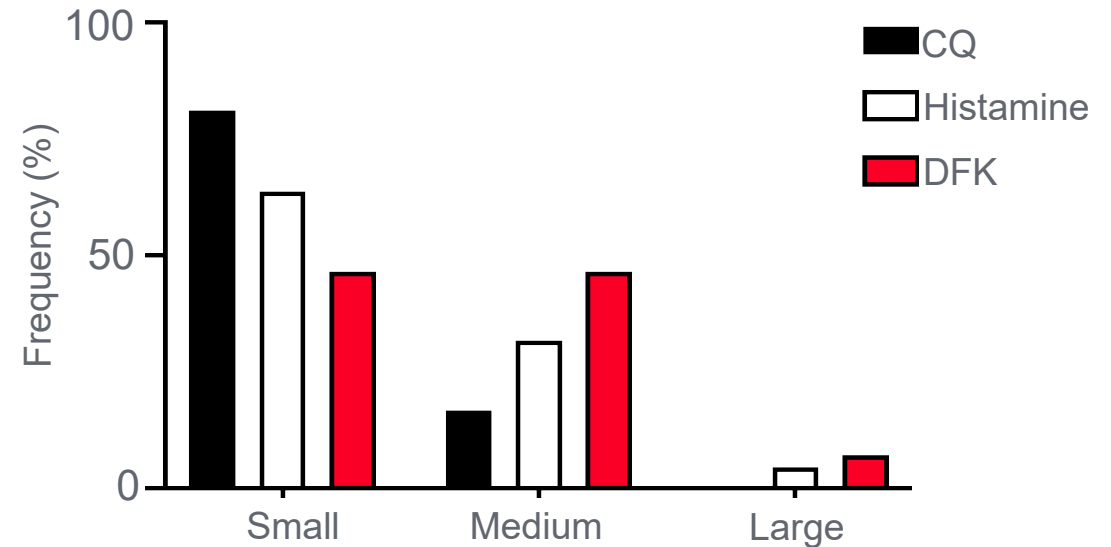
26 | BID, twice daily; I.P., intraperitoneal; ILC2, innate lymphoid type-2 cells

Mouse Study Results: DFK activates Medium Diameter (ie, A β) Sensory Neurons

Calcium Imaging



Sensory Neuron Size



Potential of Difelikefalin in Neuropathic Itch



Difelikefalin has demonstrated strong neuromodulatory action on suppressing itch in a mouse model

Difelikefalin's mechanism of action is well suited to potentially address neuropathic itch

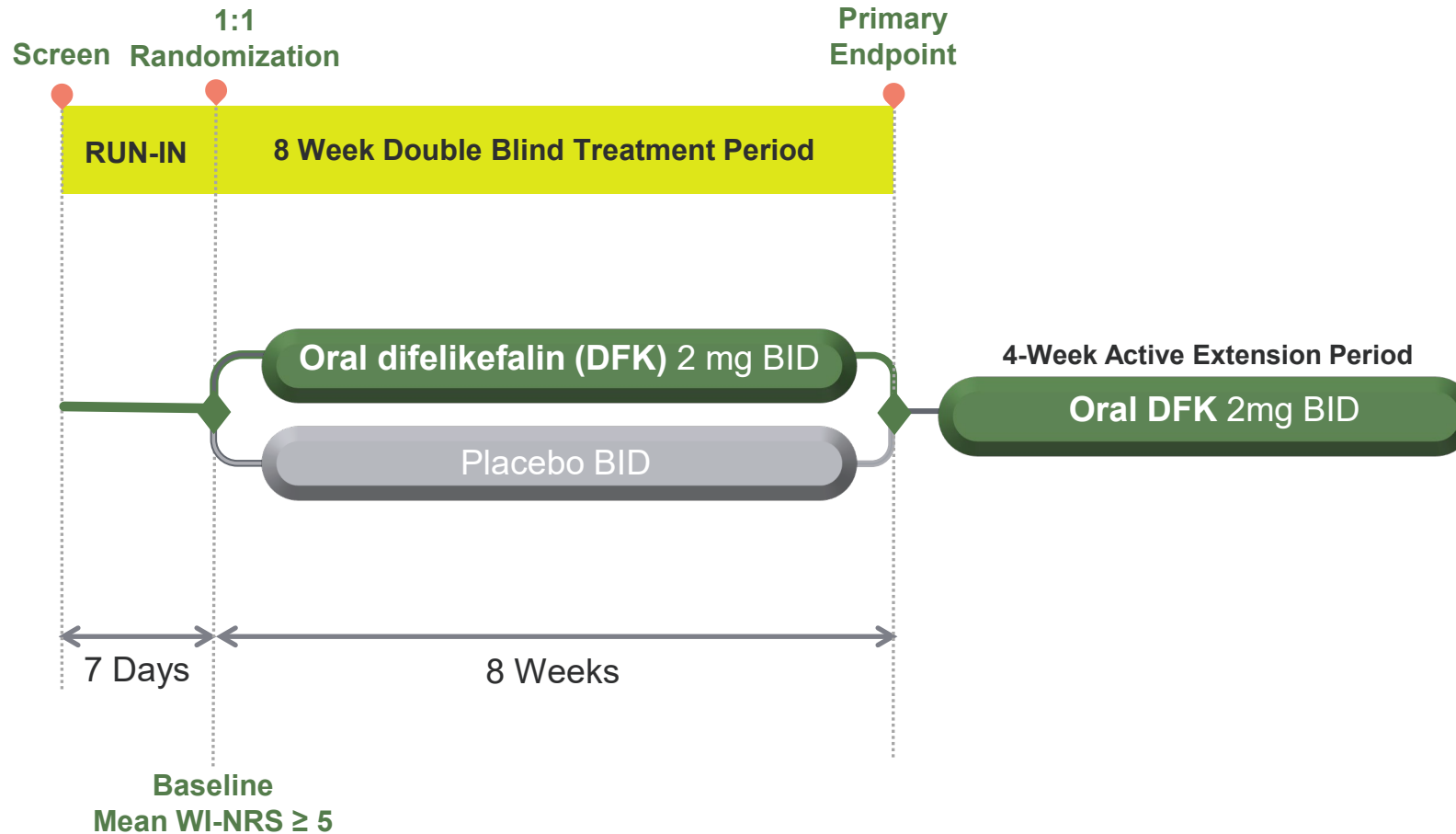
How Is Difelikefalin different?



Oral Difelikefalin Phase 2 KOMFORT Study in Notalgia Paresthetica

JOANA GONCALVES, MD, CMO, CARA THERAPEUTICS

KOMFORT: POC Phase 2 Study Design



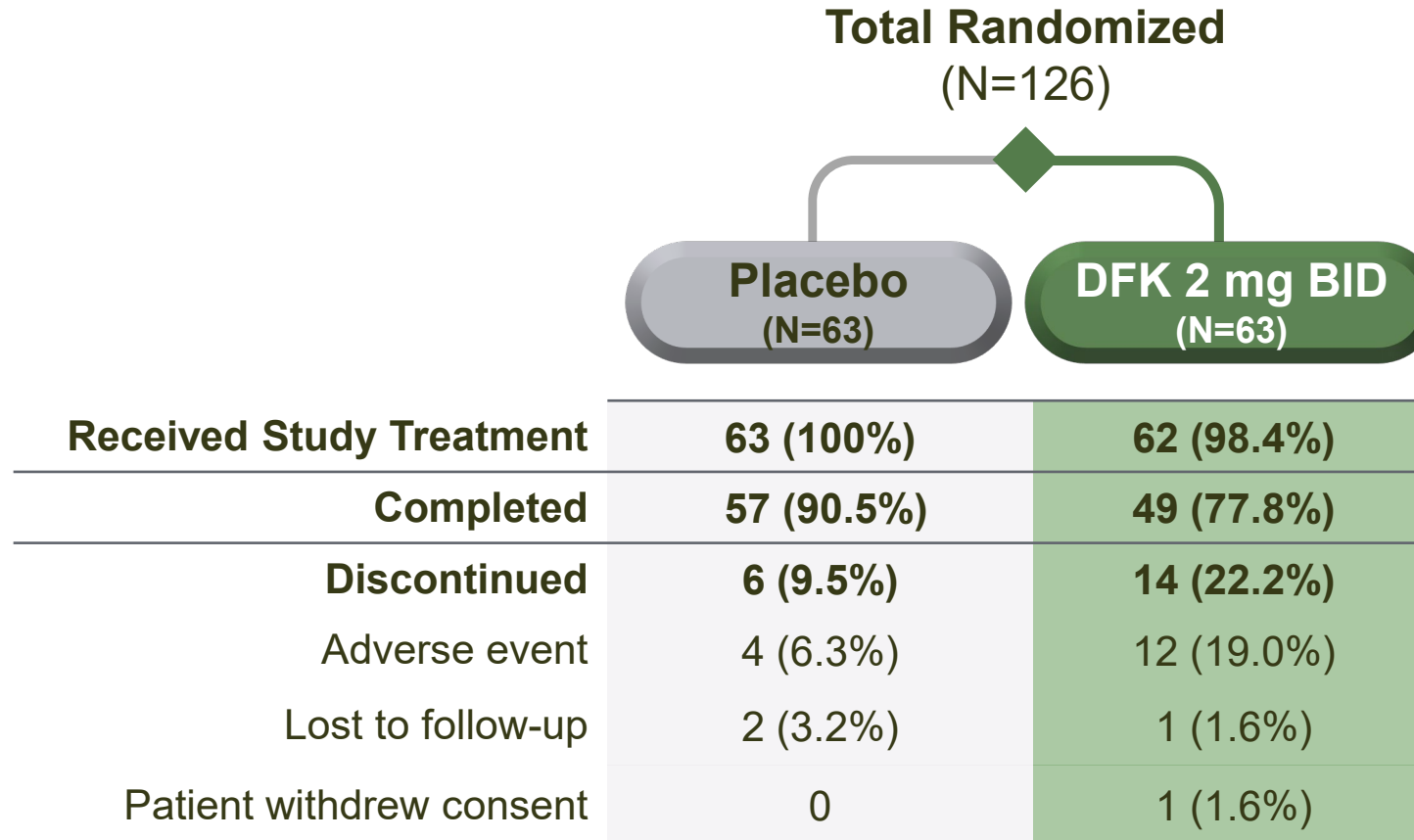
Primary Endpoint

- Change from baseline in the weekly mean of the daily 24-hr Worst Itch-Numeric Rating Scale (WI-NRS) at Week 8

Other Endpoints

- Proportion of patients achieving ≥ 4 -point improvement in WI-NRS at Week 8
- Complete response^a in WI-NRS
- QoL assessments
 - Skindex 10
 - MOS Sleep
- Safety Assessments

Placebo-Controlled Period Patient Disposition



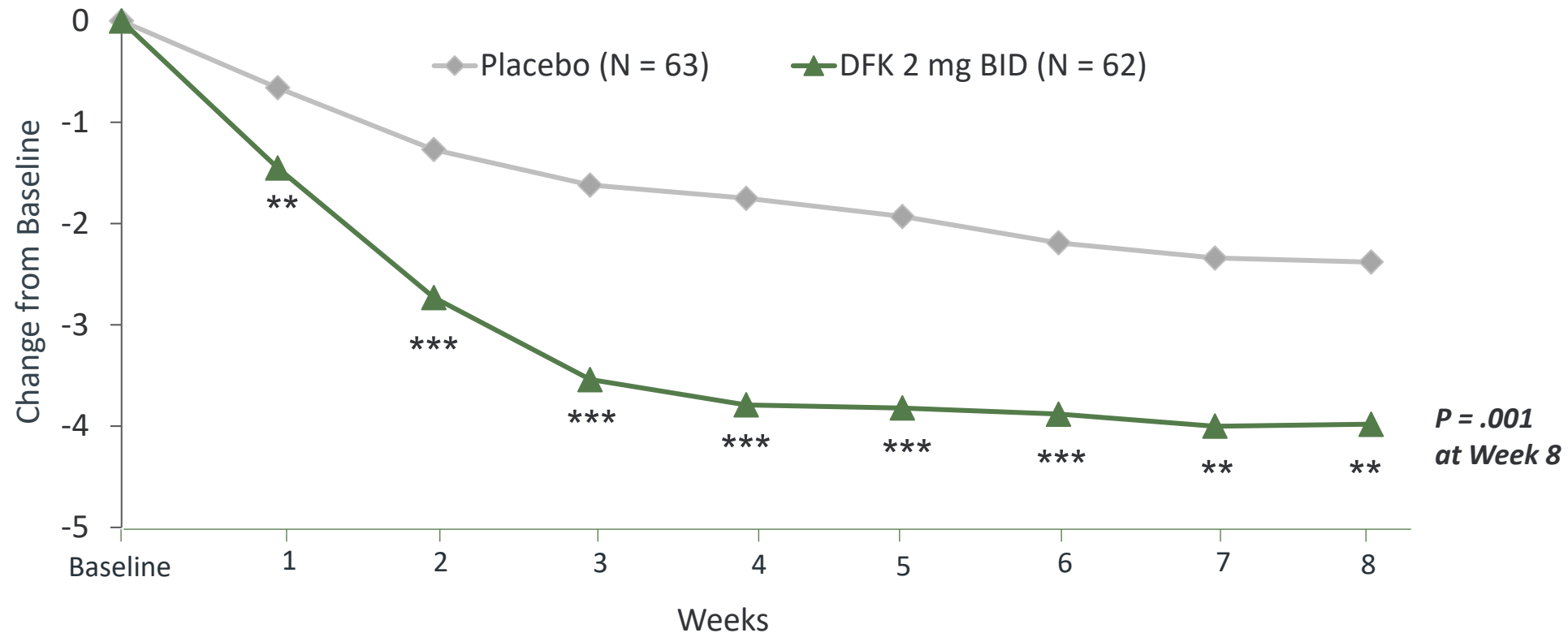
Placebo-Controlled Period

Patient Demographics & Disease Characteristics

| | Placebo (N=63) | DFK 2 mg BID (N=62) |
|----------------------------------|-------------------|------------------------|
| Female, n (%) | 42 (66.7%) | 48 (77.4%) |
| Age - Mean (SD) | 60.2 (11.8) | 59.3 (12.4) |
| Race, n (%) | | |
| White | 56 (88.9%) | 49 (79.0%) |
| Black | 4 (6.3%) | 10 (16.1%) |
| Other | 3 (4.8%) | 3 (4.8%) |
| BMI – Mean (SD) | 28.7 (5.2) | 29.7 (5.8) |
| Duration of NP (yrs) – Mean (SD) | 8.15 (7.4) | 8.9 (10.4) |
| Baseline WI-NRS – Mean (SD) | 7.6 (1.4) | 7.6 (1.4) |

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

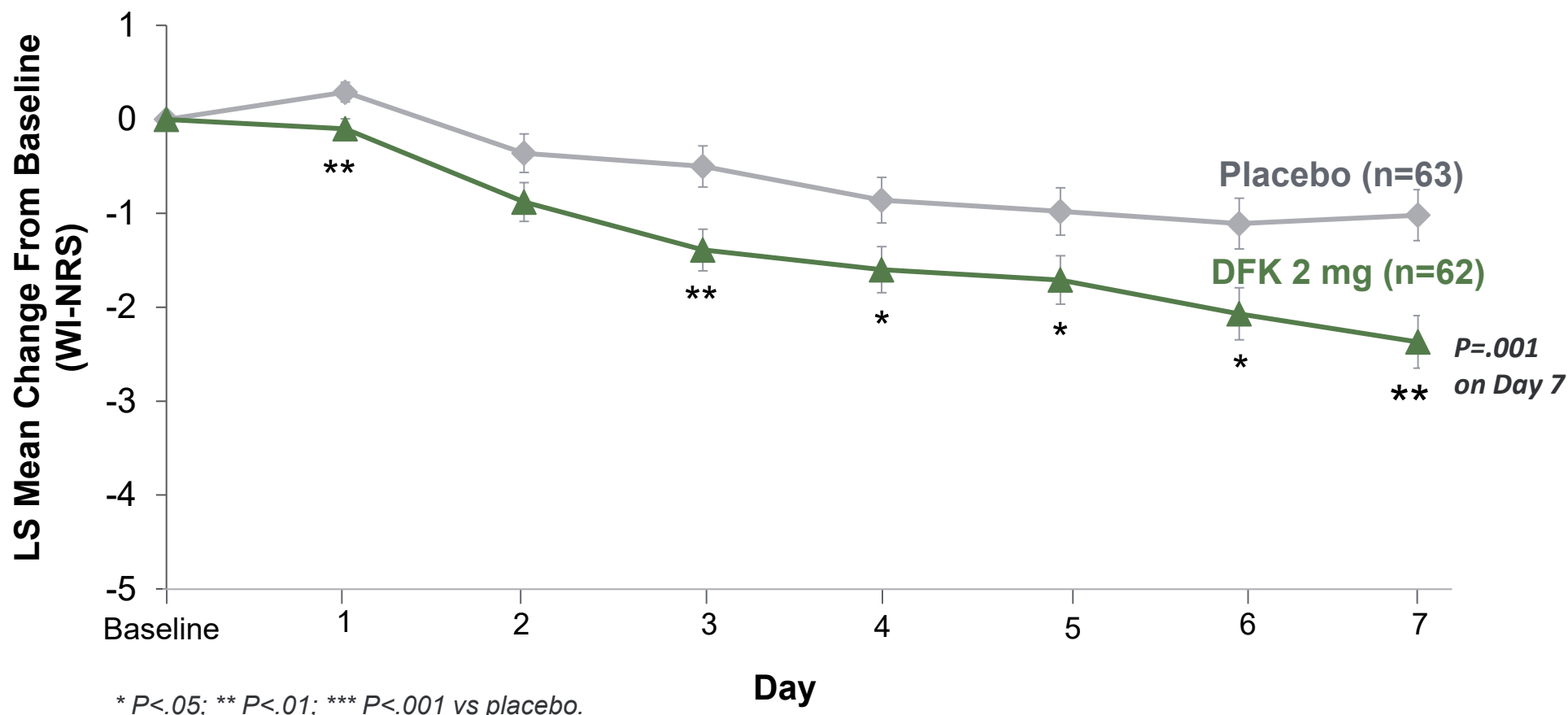
Significant Improvement observed with DFK vs Placebo at All Timepoints



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

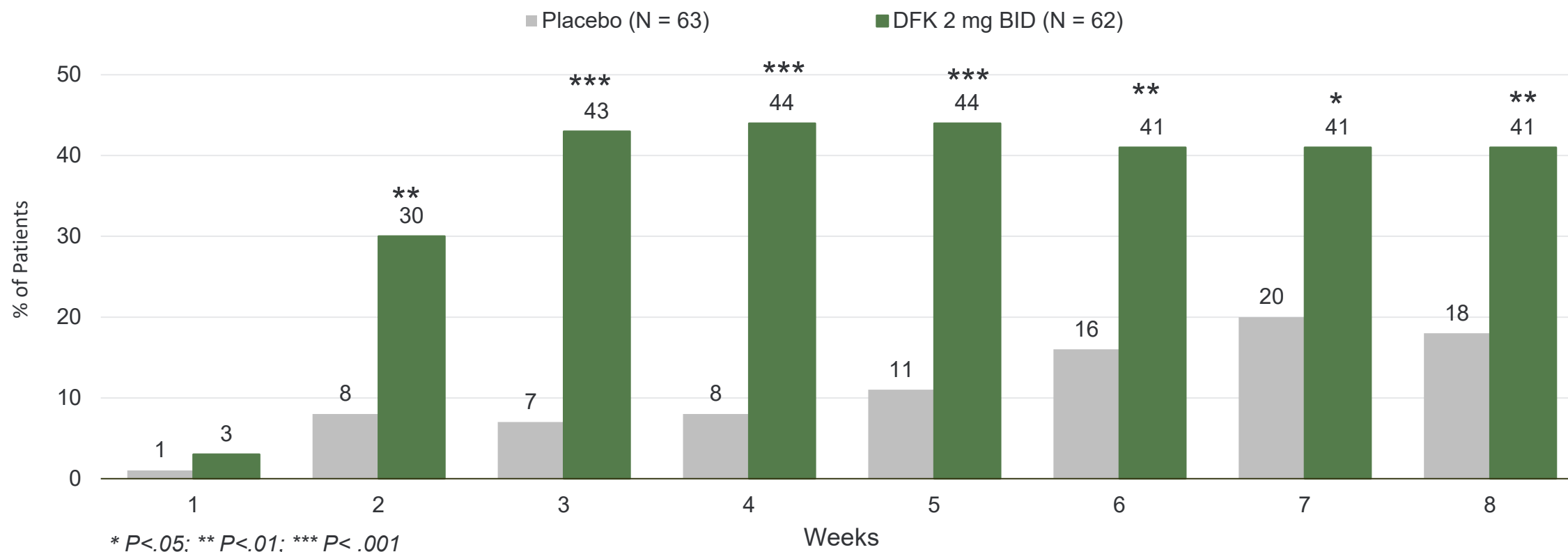
Change from Baseline in Daily WI-NRS during Week 1

Improvement observed with DFK vs Placebo at All Timepoints, Starting on Day 1



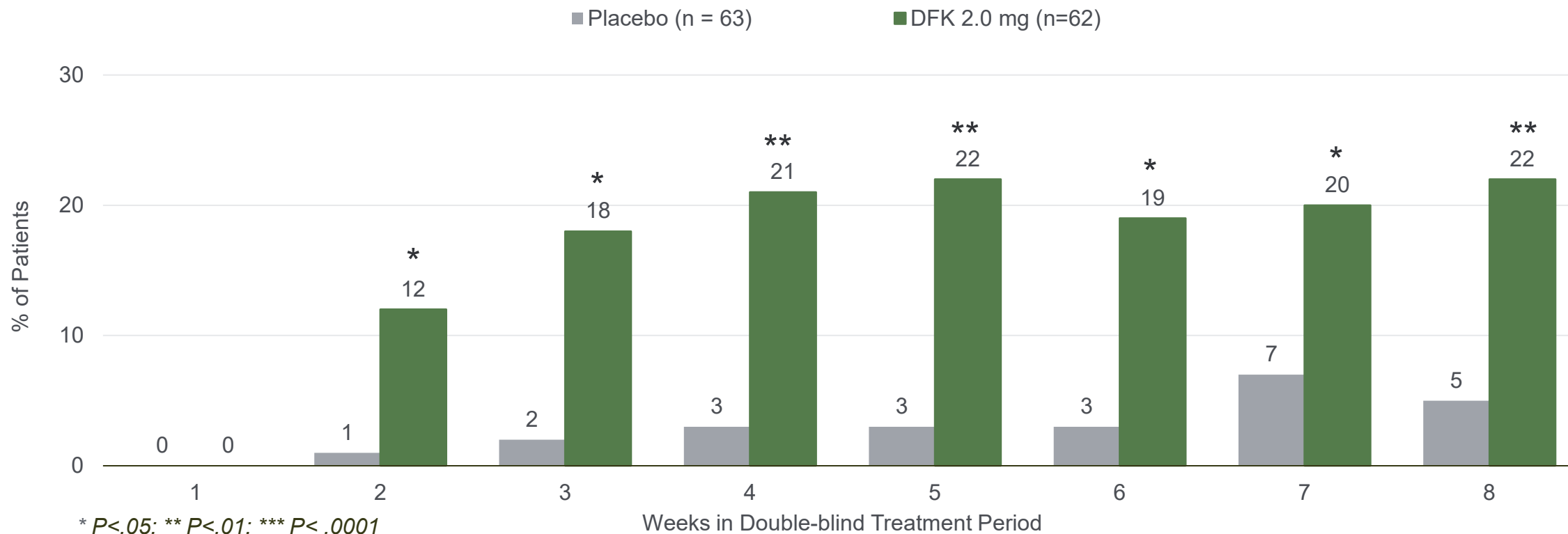
≥ 4-point Improvement in WI-NRS

Significantly Greater Proportion of Patients achieved a ≥4-point Improvement in WI-NRS score at Week 8 with DFK vs Placebo



Complete Responders in WI-NRS

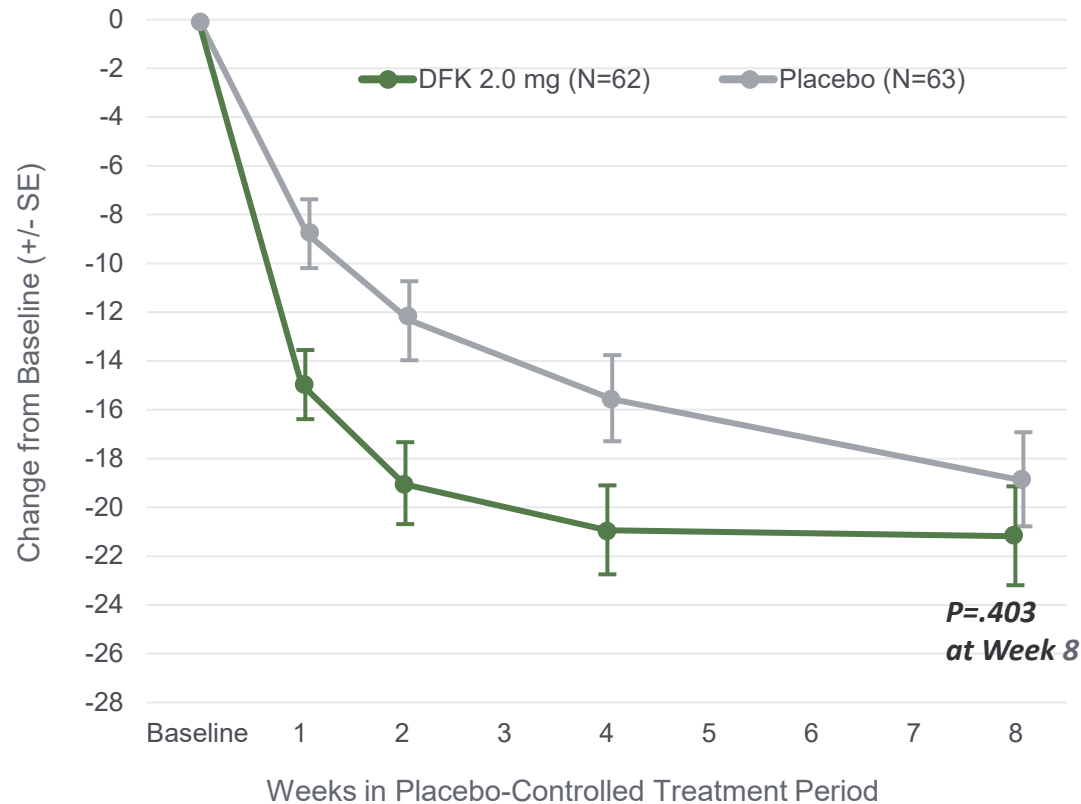
Significantly Greater Proportion of Patients achieved a Complete Response in WI-NRS score at Week 8 with DFK vs Placebo



Quality of Life

Skindex-10 Total Score

Statistically Significant Separation at Week 1, 2, 4 and Numerical Separation at Week 8

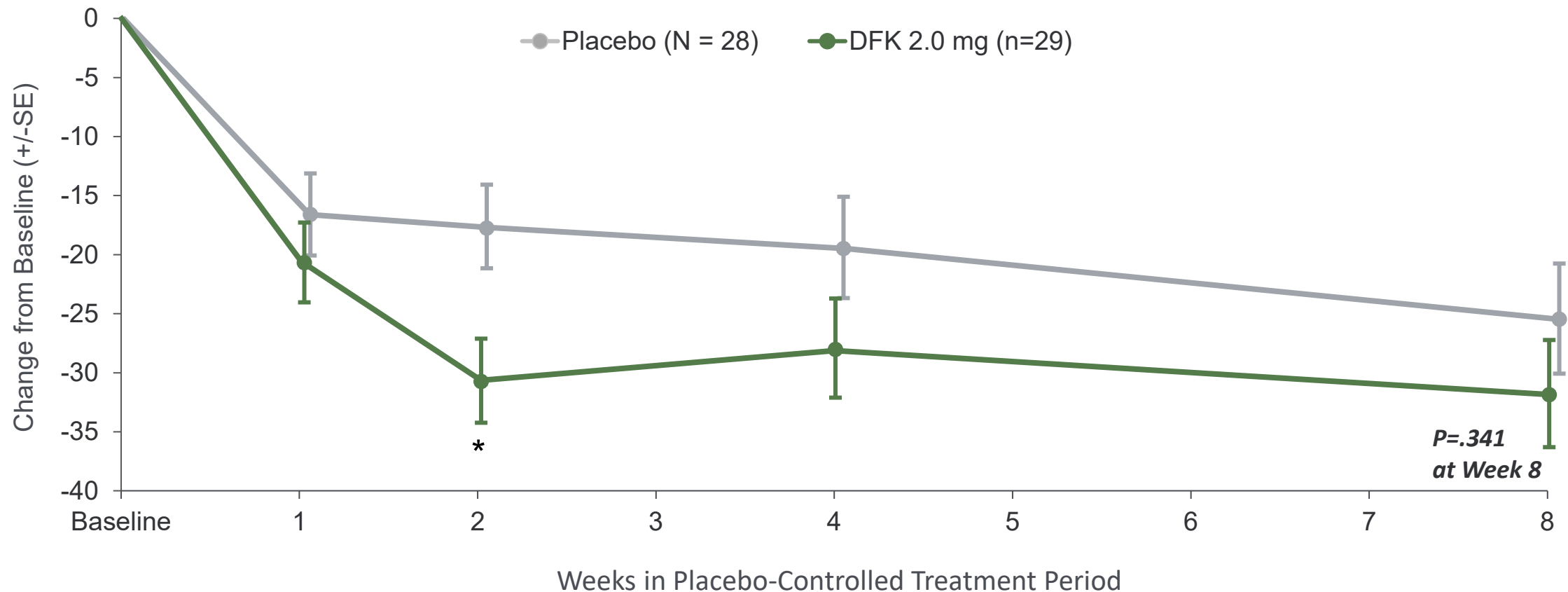


| INSTRUCTIONS: During the past WEEK, how often have you been bothered by: | | | | | | | | |
|---|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|---------------------------|
| | 0 (Never bothered) | 1 | 2 | 3 | 4 | 5 | 6 (Always bothered) | |
| 1. Your itching | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Disease Domain |
| 2. The persistence/reoccurrence of your itching | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| 3. The appearance of your skin from scratching | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| 4. Frustration about your itching | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Mood Domain |
| 5. Being annoyed about your itching | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| 6. Feeling depressed about your itching | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| 7. Feeling embarrassed about your itching | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Social Functioning Domain |
| 8. The effects of your itching on your interactions with others (for example: interactions with family, friends, close relationships, etc.) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| 9. The effects of your itching on your desire to be with people | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| 10. The effect of your itching making it hard to work or do what you enjoy | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |

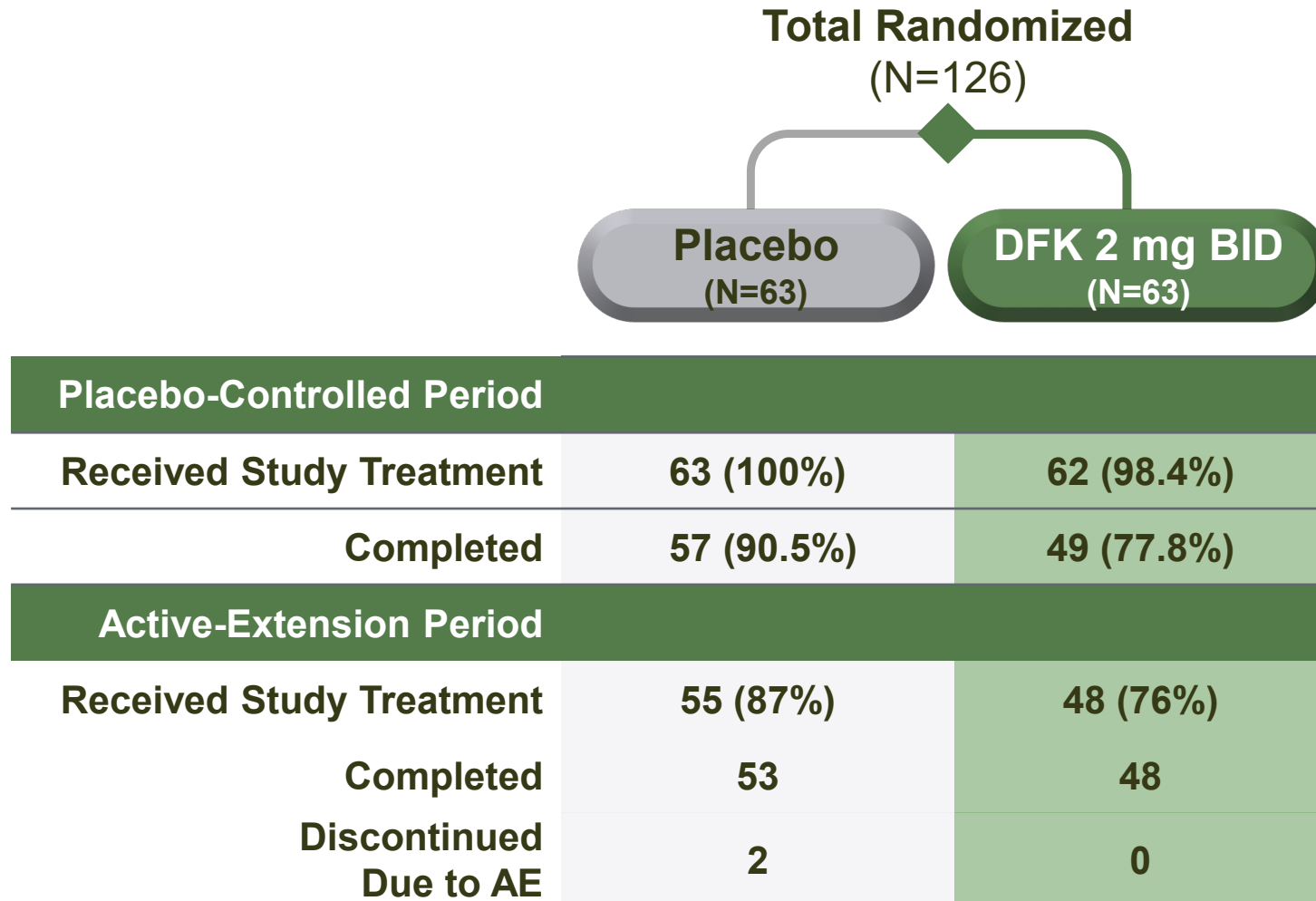
Quality of Life

Itch MOS – Itch Related Sleep Disturbance Subscale

Numerical Separation of DKF vs Placebo at All Time Points

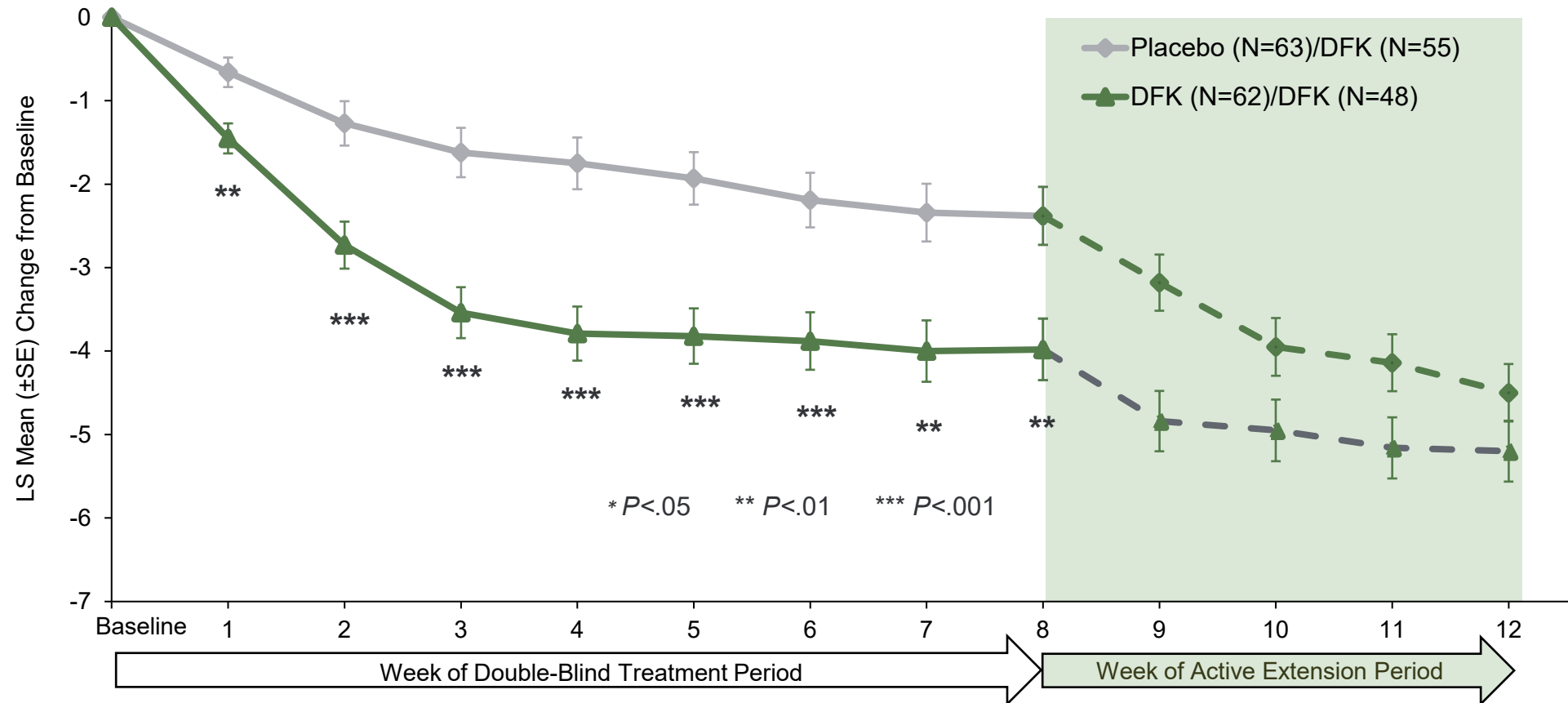


Active Extension Period Patient Disposition



Change from Baseline in Daily WI-NRS

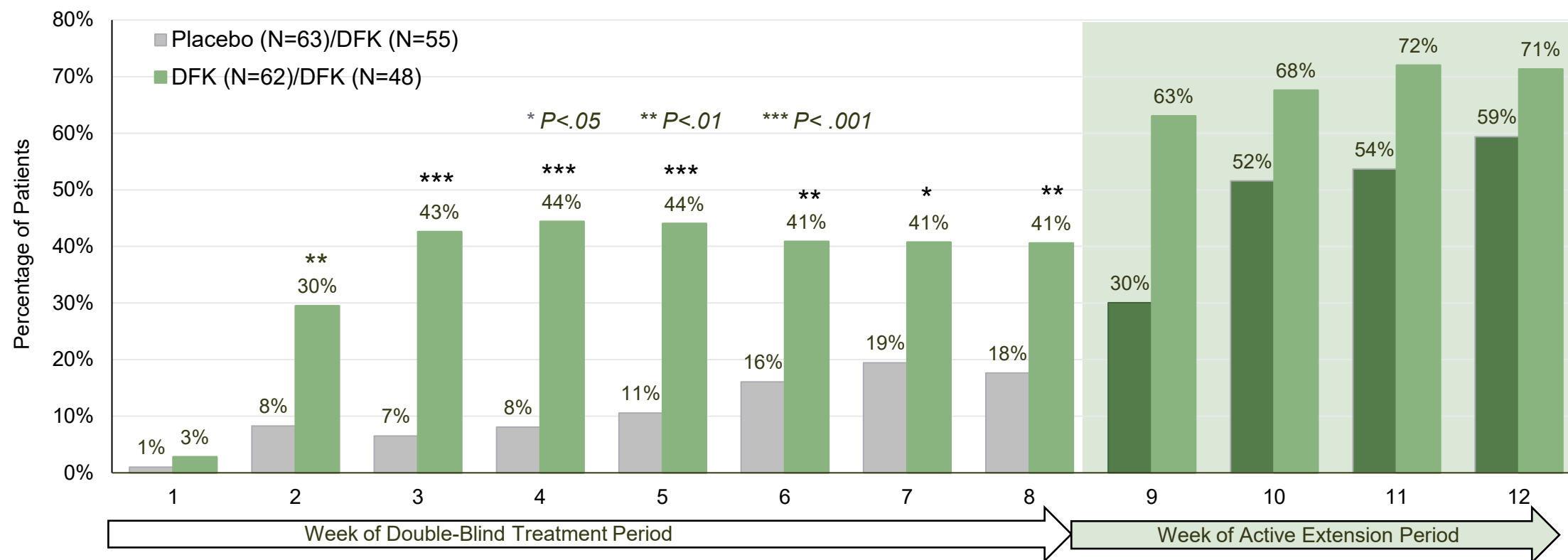
Reduction in Itch observed in Placebo-DFK Group and Maintenance of Effect seen in DFK-DFK Group through Week 12



41 | Least squares means and SEs were estimated using a mixed model with repeated measures containing terms for treatment, week, treatment by week interaction, and baseline WI-NRS score. Missing mean weekly WI-NRS values were imputed separately in each study period assuming a missing at random mechanism. P-values are presented for the double-blind treatment period. Placebo patients started DFK 2 mg bid during the active extension period.

≥ 4-point Improvement in WI-NRS

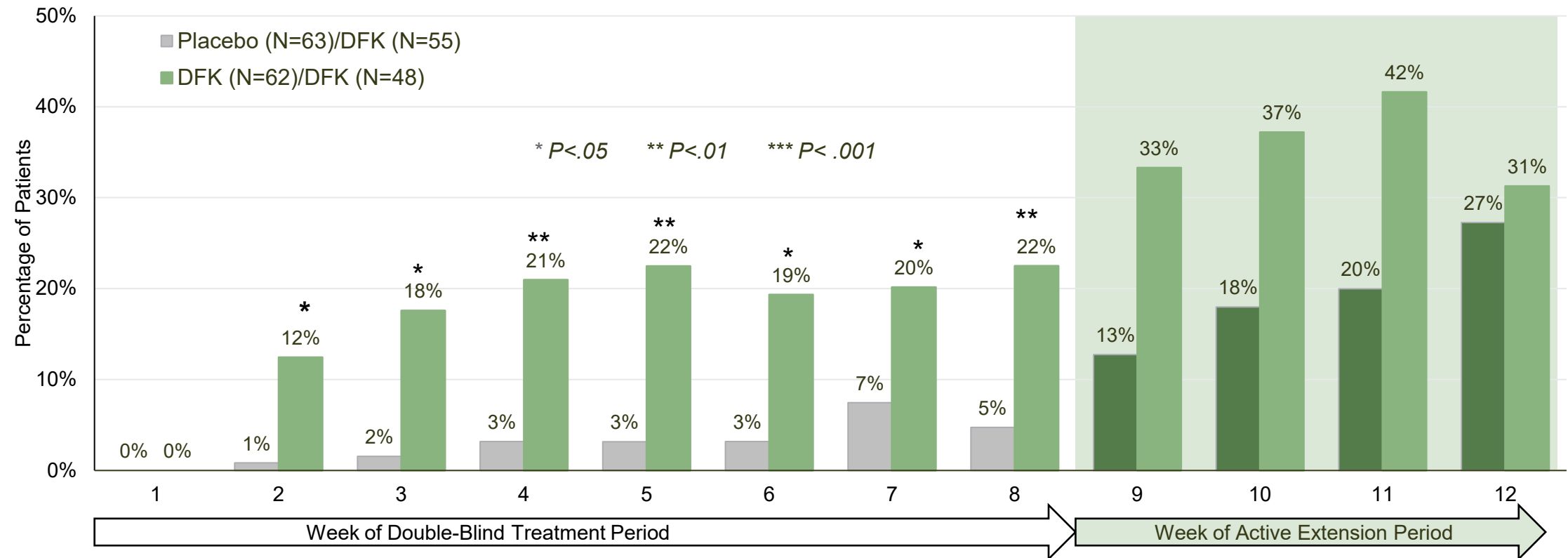
Placebo/DFK Patients achieved 4-point Improvement and DFK/DFK maintained Response through Week 12



Percentages and P-values were estimated from a logistic regression with terms for treatment and baseline WI-NRS score. Missing mean weekly WI-NRS values were imputed separately in each study period assuming a missing at random mechanism. Patients who discontinued early were categorized as non-responders in subsequent weeks. P-values are presented for the double-blind treatment period. Placebo patients started DFK 2 mg bid during the active extension period.

Complete Response ≥70% Weekly WI-NRS Values 0 or 1

Placebo/DFK Patients achieved Complete Response and DFK/DFK maintained Efficacy through Week 12



43 | Percentages and P-values were estimated from a logistic regression with terms for treatment and baseline WI-NRS score. Patients who discontinued early were categorized as non-responders in subsequent weeks. Patients with fewer than 4 daily WI-NRS scores in a week were categorized as non-responders for that week. P-values are presented for the double-blind treatment period. Placebo patients started DFK 2 mg bid during the active extension period.

Summary of Adverse Events

| | Placebo-Controlled Period | | Active-Extension Period | |
|--|---------------------------|------------------------|-------------------------|-------------------|
| | Placebo (N=63) | DFK 2 mg BID (N=62) | Placebo/DFK (N=55) | DFK/DFK (N=48) |
| Patients with at least one TEAE, n (%) | 32 (50.6%) | 35 (56.5%) | 17(30.9%) | 12 (25%) |
| Patients with at least one serious TEAE, n (%) | 0 | 0 | 0 | 0 |
| Patients with TEAE resulting in treatment discontinuation, n (%) | 4 (6.3%) | 12 (19.4%) | 2 (3.6%) | 0 |

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%) |
| Constipation was the only AE reported >5% during the Active Extension Period; Placebo/DFK 3 (5.5%) versus DFK/DFK 0 (0%). | | |

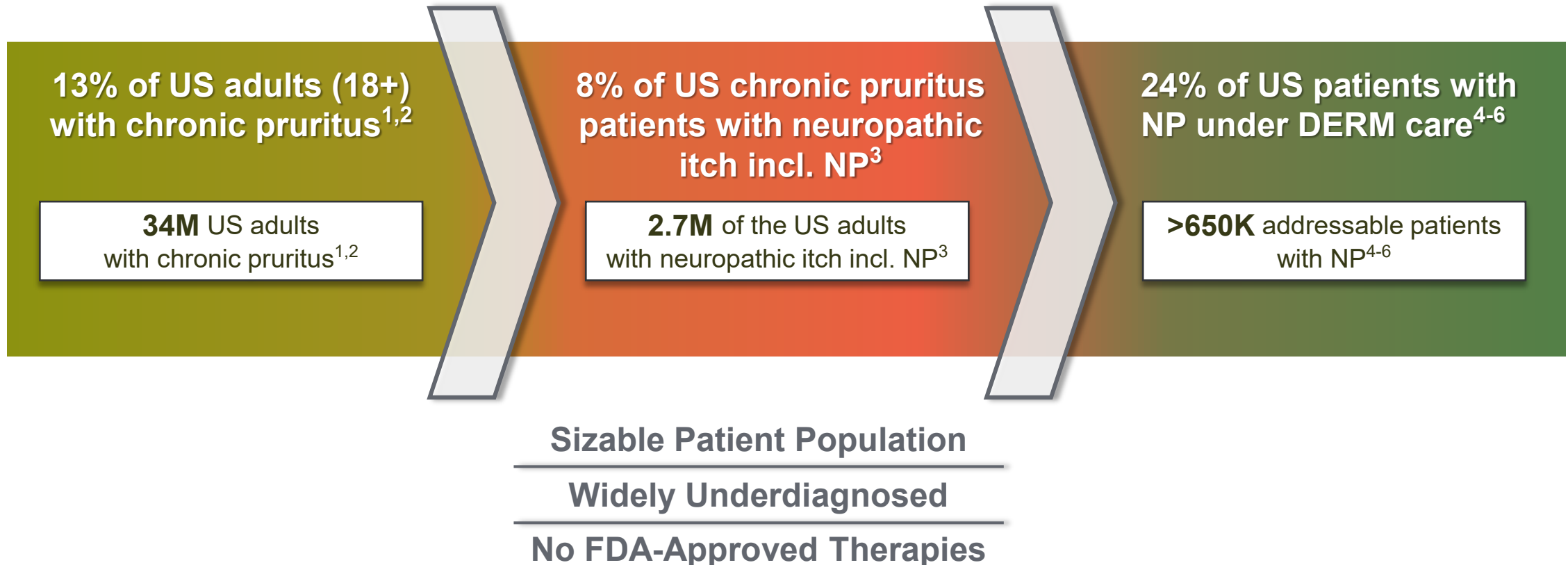
KOMFORT Phase 2 Summary

- Oral difelikefalin demonstrated strong anti-pruritic effect in patients with Notalgia Paresthetica
 - **Primary endpoint met**
 - Rapid onset of action with significant improvements achieved **at Day 1** and **maintained through Week 12**
 - Significantly greater proportion of patients on difelikefalin had **≥ 4-point improvement** and **complete response starting at Week 2** and **sustained through Week 12**
 - **Improvements in QoL and sleep** reported through Week 8
 - Similar efficacy noted for placebo/DFK cross-over
- Oral difelikefalin was generally **well tolerated** with a **favorable safety profile**
- Next steps include engaging with FDA on path forward **by Q4 2022**

Market Assessment and Commercial Opportunity in Notalgia Paresthetica

ERIC VANDAL, SVP, COMMERCIAL, CARA THERAPEUTICS

Notalgia Paresthetica: A Sizable Market Opportunity



Notalgia Paresthetica: Patient Qualitative Survey

Diagnosis

93% diagnosis by dermatologist

90% back itching reason to see a doctor

Symptoms

83% itching daily on upper/middle portion of the back

Treatment

67% treatments were not helpful

73% currently not on therapy

Impact on Patient's Life

70% impacted emotions or mood

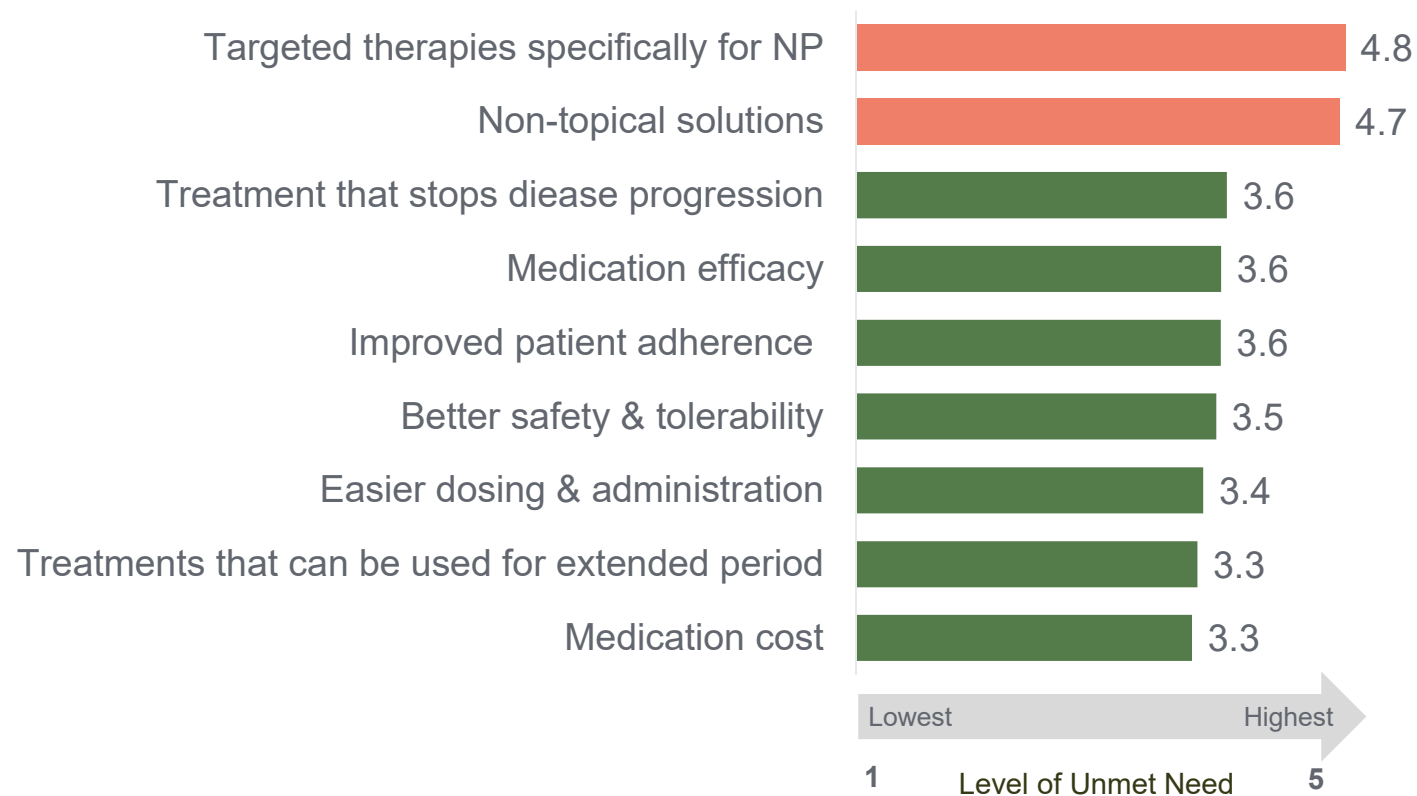
40% impacted sleep

Dermatologists try a Number of Off-label Treatments with Limited Success

| Treatment Options for NP | Comments |
|---|---|
| Topical Corticosteroids, Capsaicin | <ul style="list-style-type: none"> • Corticosteroids are a commonly used treatment. Also used in combination with other drugs • Some patients have difficulty applying topicals due to the location of the itch |
| Oral Gabapentin, Pregabalin, Antidepressants | <p>Key issues include:</p> <ul style="list-style-type: none"> • Side effects • Lack of predictable efficacy |
| Other Nerve Block, Botox A, Phototherapy | <ul style="list-style-type: none"> • These treatments can require referrals to other specialties (e.g., radiologists, orthopedists, neurologists) • Insurance coverage can be an issue |

Dermatologists are Frustrated by the Lack of Efficacy with Current Off-Label Options

Avg. Ratings of Unmet Needs in NP (N=17)



Oral DFK may help address a Significant Unmet Need

Oral DFK can potentially address a significant patient population that is widely underdiagnosed

There are no approved therapies to treat pruritus related to NP

Dermatologists are looking for a product that is approved for NP with demonstrated safety and efficacy in this patient population

Dermatologists looking for an oral product that is easier for patients to use given the location of their itch



Thank you