KOMFORT Phase 2 Topline Data:

Oral Difelikefalin for Pruritus in Notalgia Paresthetica

JUNE 2022

The KOMFORT Phase 2 study evaluated the efficacy and safety of oral difelikefalin for moderate to severe pruritus in adult subjects with notalgia paresthetica (NP). Oral difelikefalin is an investigational drug product and its safety and efficacy have not been fully evaluated by any regulatory authority. The FDA approved KORSUVA™ (difelikefalin) injection for the treatment of moderate-to-severe pruritus (itching) associated with chronic kidney disease (CKD-aP) in adults undergoing hemodialysis (HD).

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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 timing of the Company's planned clinical trials, potential results of ongoing and planned clinical trials, the Company's planned future regulatory submissions and potential future regulatory approvals, timing of future regulatory and development milestones for the Company's product candidates, the potential for the Company's product candidates to be an alternative for Notalgia Paresthetica, the size and growth of the potential markets for Notalgia Paresthetica, the potential for oral difelikefalin to address additional pruritic indications, 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.

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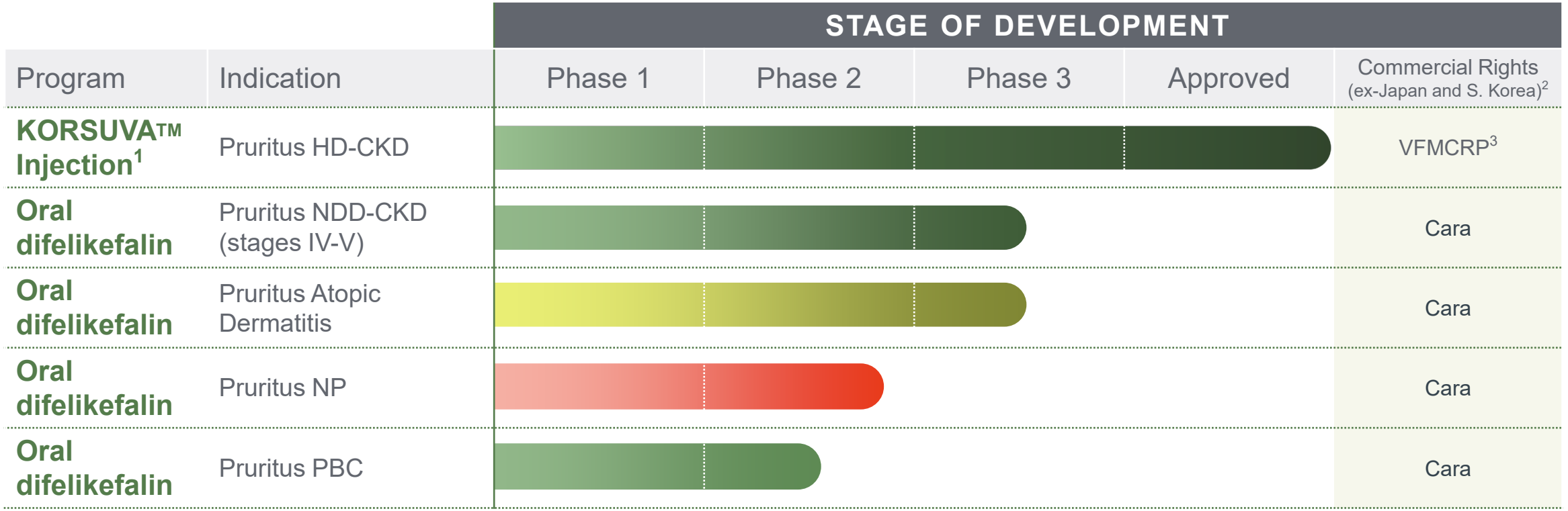
Advancing our late-stage pipeline in multiple indications



1. Approved in the EU with the tradename KapruviaTM. 2. Commercialization rights to difelikefalin in defined indications - Japan: Maruishi Pharmaceutical Co, LTD; South Korea: Chong Kun Dang Pharmaceuticals. 3. Vifor Fresenius Medical Care Renal Pharma (VFMCRP) has commercial rights under a profit-share arrangement in the US and a royalty arrangement ex-US.
HD CKD-aP: Hemodialysis Chronic Kidney Disease-associated Pruritus; NDD-CKD-aP: Non-Dialysis Dependent Chronic Kidney Disease associated Pruritus; Pruritus NP: Notalgia Paresthetica associated Pruritus; Pruritus PBC: Primary Biliary Cholangitis associated Pruritus

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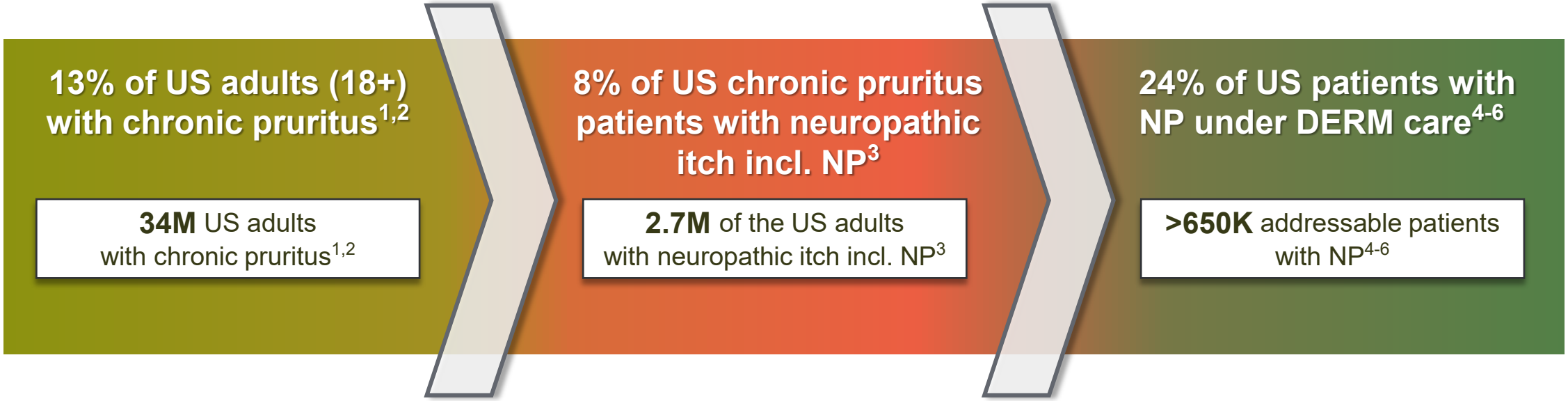
Notalgia Paresthetica: A Sizable Market Opportunity



Sizable Patient Population

Widely Underdiagnosed

No FDA-Approved Therapies

Source: 1. US Census Bureau 2020 population projection; 2. Mollanazar NK et al., Current Derm Report 2015: 4;20-29; 3. Pereira P. et al., Acta DV 2018; 98:82-88; 4. Syneos Health qualitative primary research of US dermatologists, Feb 2022; 5. Syneos Health quantitative research of derm office administrators, March 2022; 6. IQVIA, KOMODO, and RxDataScience Apollo claims database

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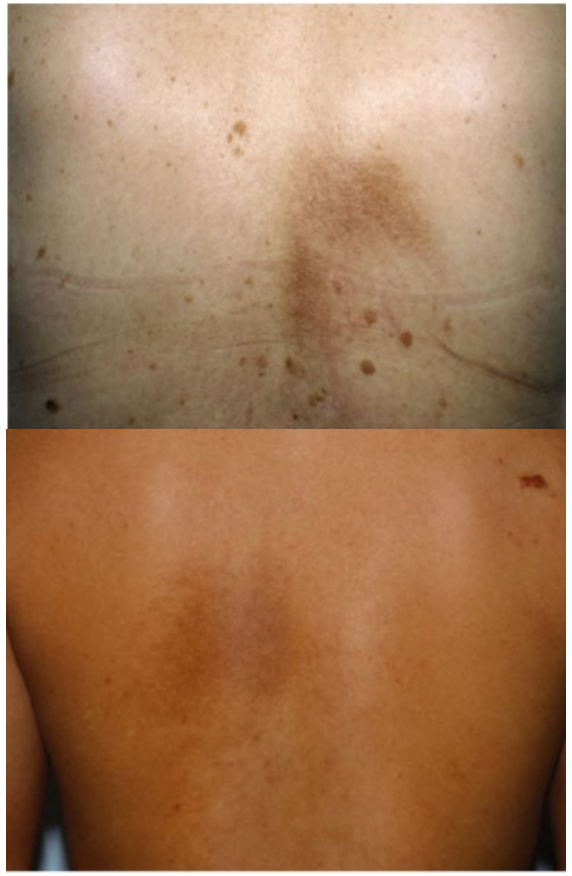
Notalgia Paresthetica: A Significant Unmet Need



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

Pruritus is burdensome and impairs quality of life[1]

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

 Source: 1. Pereira Manuel et al ActaDV 2018; 98:82-88, 2. Howard et al Int J of Derm 2018; 57; 388- 392.

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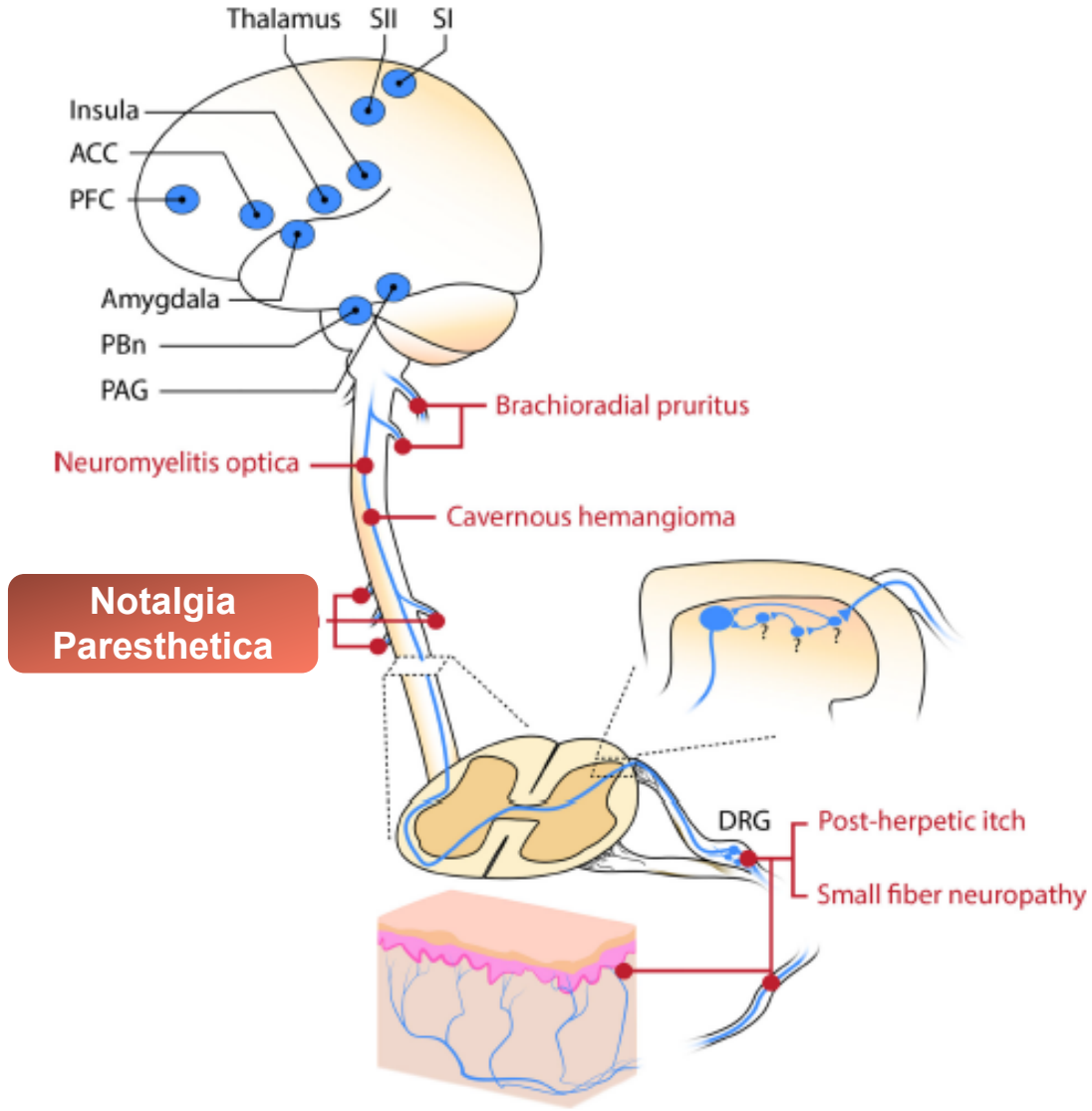
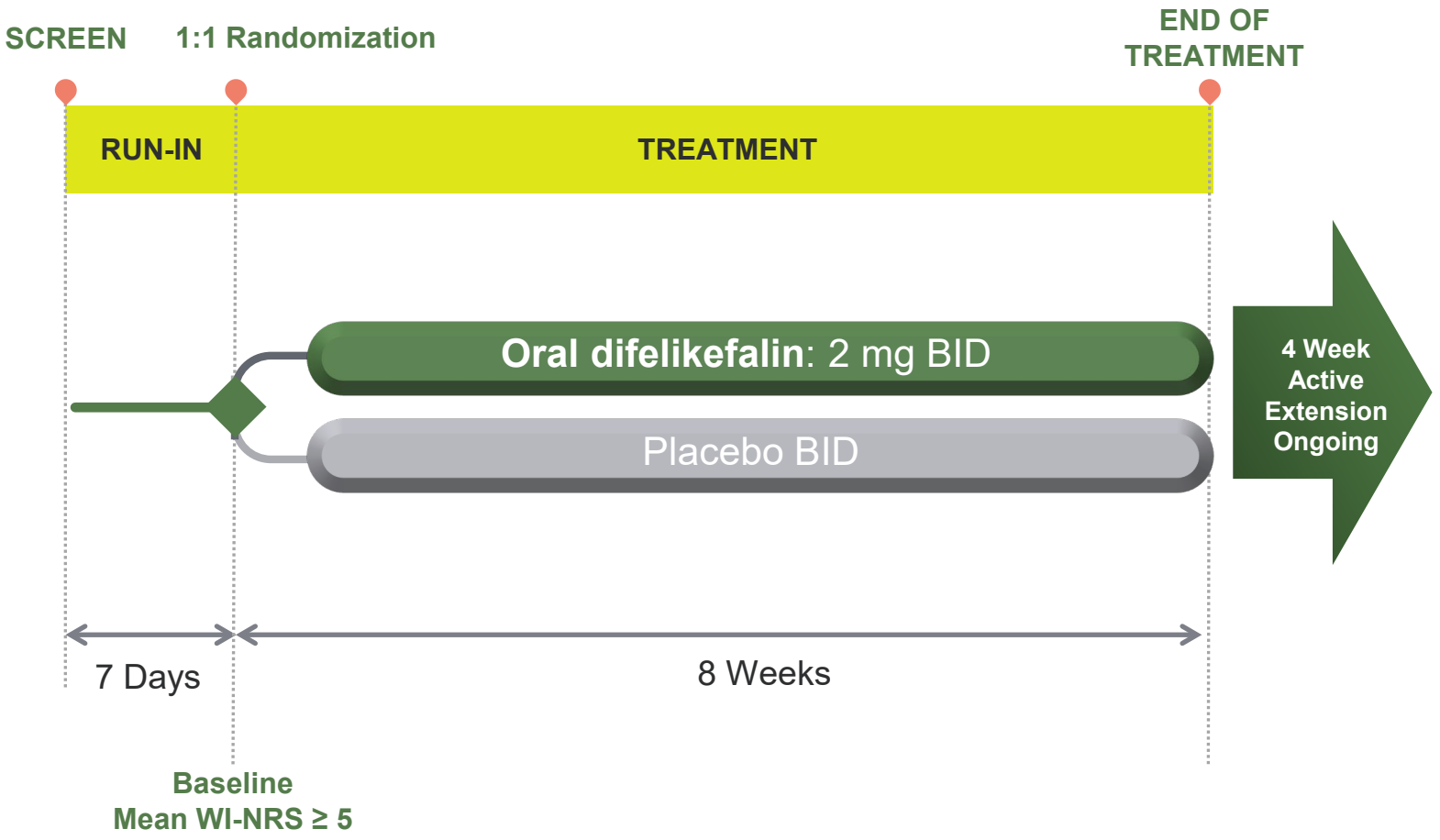
Notalgia Paresthetica

- 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



 Source: Pereira Manuel et al ActaDV 2018; 98:82-88. Hachisuka et al Pain 2018; 159(3): 603-609.

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**
- **Safety Assessments**
- **QoL assessments**

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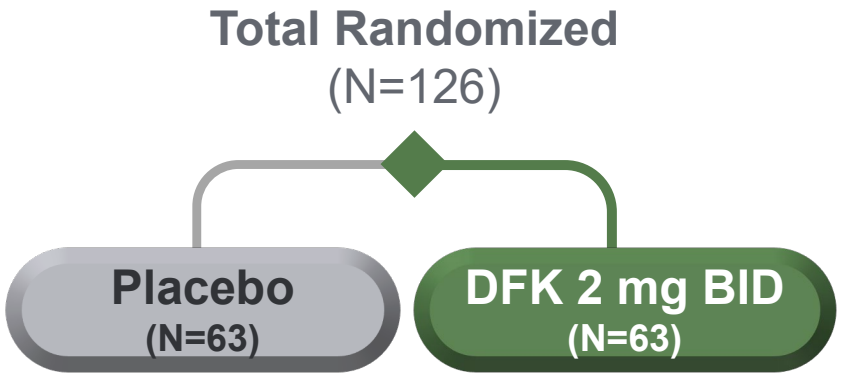
Patient Disposition



	Placebo (N=63)	DFK 2 mg BID (N=63)
Received Study Treatment	**63 (100%)**	**62 (98.4%)**
Completed	**57 (90.5%)**	**49 (77.8%)**
Discontinued	**6 (9.5%)**	**14 (22.2%)**
Adverse event	4 (6.3%)	12 (19.0%)
Lost to follow-up	2 (3.2%)	1 (1.6%)
Patient withdrew consent	0	1 (1.6%)

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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)

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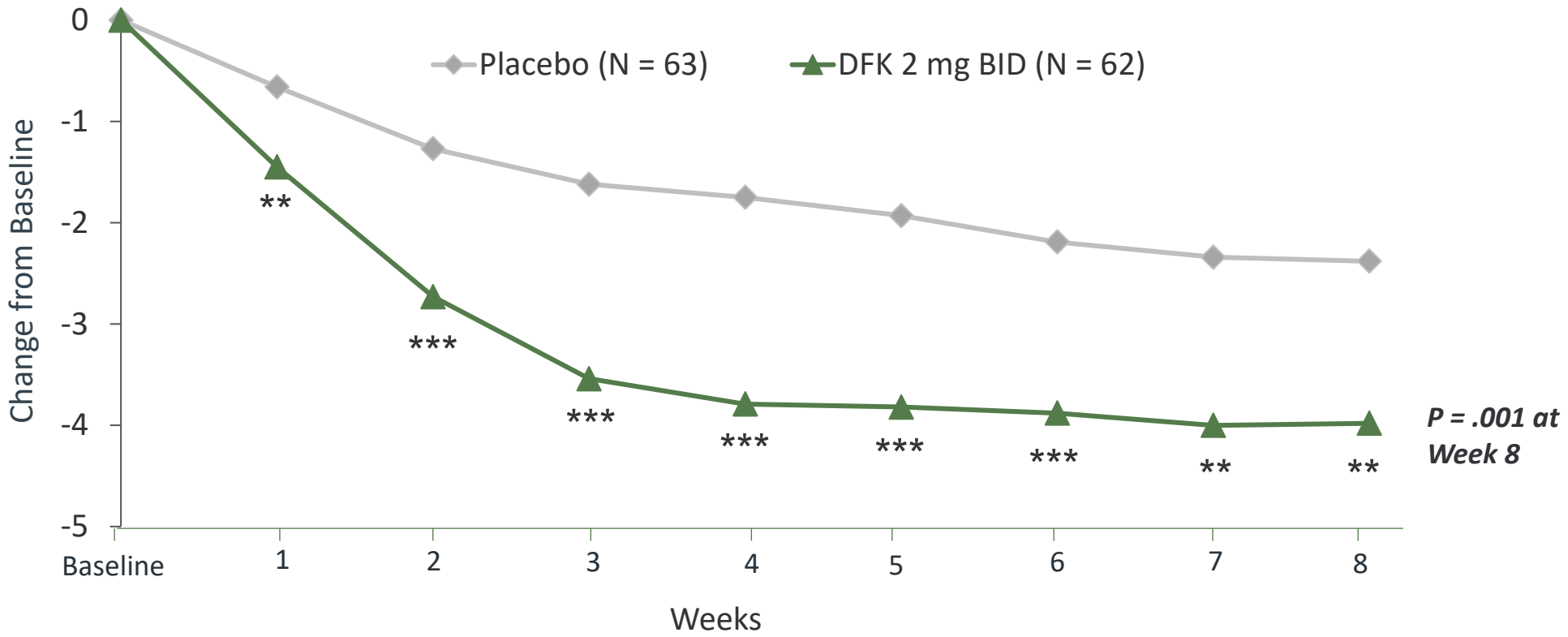
Primary Endpoint: Change from Baseline in Daily WI-NRS at Week 8 (ITT)

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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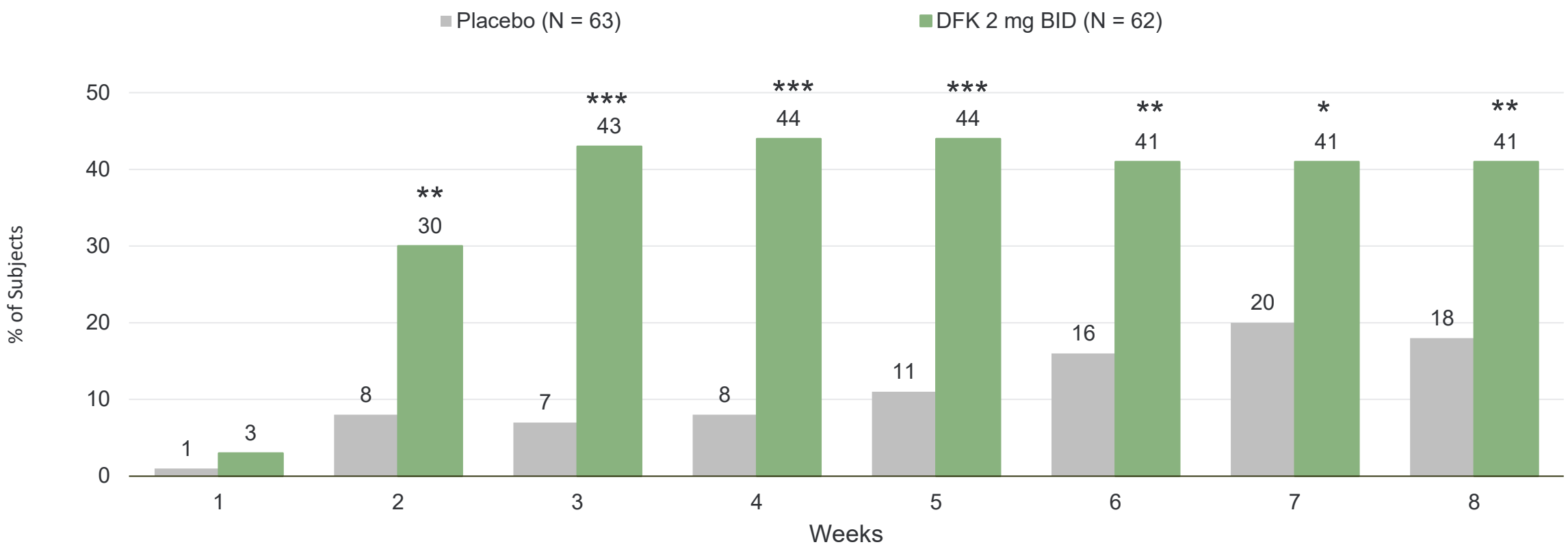
≥ 4-point Improvement in WI-NRS (ITT)

Significant improvement observed with DFK vs placebo starting at Week 2



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

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

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Summary of Adverse Events

	Placebo (N=63)	DFK 2 mg BID (N=62)
Patients with at least one TEAE, n (%)	32 (50.6%)	35 (56.5%)
Patients with at least one severe TEAE, n (%)	1 (1.6%)	0
Patients with at least one serious TEAE, n (%)	0	0
Patients with TEAE resulting in treatment discontinuation, n (%)	4 (6.3%)	12 (19.4%)

Safety analyses performed in the safety population, defined as all randomized patients who received ≥1 dose of study drug based on actual treatment received.

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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KOMFORT Phase 2 Summary

- **Oral difelikefalin demonstrated strong anti-pruritic effect in patients with Notalgia Paresthetica**
  - Primary endpoint met demonstrating statistically significant superiority of difelikefalin versus placebo in Daily WI-NRS at Week 8
  - Rapid onset of action with significant improvements achieved at Week 1 and sustained through Week 8
  - Significantly greater proportion of patients on difelikefalin had ≥ 4-point improvement starting at Week 2

- **Oral difelikefalin was generally well tolerated with a consistent safety profile**

- **Next steps planned to include finalizing additional data analyses and engaging with FDA on path forward**

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Q&A

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