Oral Nalbuphine Extended-Release Is Effective in Severe Prurigo Nodularis–Associated Pruritus: Results From a Phase 2b/3, Double-Blind, Placebo-Controlled Study

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Background

- Prurigo nodularis is a chronic inflammatory dermatologic condition characterized by intense pruritus and raised nodular lesions, papules, and/or plaques[1]
  - The global prevalence of PN is estimated to be 730,000[2]
- Pruritus is a severe and often treatment-resistant symptom of PN[3]
- There are no approved pharmacologic therapies for patients with PN
- κ- and μ-opioid receptors are critical mediators for itch, with important roles in the itch-scratch cycle and PN-related pruritus[4]
- Nalbuphine extended-release (NAL ER) is a dual-acting κ-opioid receptor agonist/μ-opioid receptor antagonist that acts centrally and peripherally[4]
  - In contrast with activation of μ-opioid receptors, κ-opioid receptor activation is not associated with abuse or addiction[5]
- The IV formulation of nalbuphine is an unscheduled opioid (ie, not controlled under the Controlled Substances Act by the Drug Enforcement Agency) in the United States and most of Europe[6,7]
- NAL ER may improve the balance of κ- and μ-opioid receptor activity and therefore may be an oral treatment option for patients with PN-related pruritus[8]

Objective

- To assess the antipruritic and lesion-reducing efficacy and safety of oral NAL ER in patients with PN in the phase 2b/3 PRISM trial

Methods

Study Design

- PRISM (NCT03497975) was a randomized, double-blind, placebo-controlled, phase 2b/3 trial of adult patients with confirmed PN, ≥10 pruriginous nodules on ≥2 distinct anatomical areas, and WI-NRS score ≥7
- Participants received oral NAL ER 162 mg or placebo twice daily
- The study consisted of a 2-week titration phase, a 12-week fixed-dose treatment phase, and a 2-week off-treatment safety phase
- The primary end point was the percentage of responders who had ≥4-point reduction in WI-NRS score
- Key secondary end points were:
  - LSM change from baseline in ItchyQoL
  - Participants with ≥1-category improvement in PAS question 5a (to assess improvement in PN skin lesions)

Results

Table 1. Participant Demographics and Baseline Disease Characteristics

	NAL ER n = 168	Placebo n = 176
Age, mean ± SD, years	59.6 ± 13.3	55.9 ± 14.3
Female, n (%)	100 (59.5)	112 (63.6)
Weight, mean ± SD, kg	85.7 ± 20.5	84.7 ± 20.9
Race, n (%)		
White	132 (78.6)	134 (76.1)
Black or African American	24 (14.3)	23 (13.1)
Native Hawaiian or Other Pacific Islander	6 (3.6)	11 (6.3)
Asian	6 (3.6)	7 (4.0)
Multiple	0	1 (0.6)
Region, n (%)		
Europe	99 (58.9)	103 (58.5)
North America	69 (41.1)	73 (41.5)
Baseline disease		
WI-NRS,[a] mean ± SD	8.6 ± 0.9	8.7 ± 0.9
ItchyQoL, mean ± SD	84.9 ± 15.7	83.9 ± 16.2
No. of prurigo lesions,[b] n (%)		
1-19	17 (10.1)	22 (12.5)
20-100	101 (60.1)	93 (52.8)
>100	50 (29.8)	61 (34.7)

[a]For WI-NRS, the baseline value was calculated as the arithmetic mean of the daily WI-NRS values (≥5 measurements required) taken for eligibility review by site at the time of randomization.
[b]Study participation required ≥10 pruriginous nodules on ≥2 distinct anatomical areas.

Safety

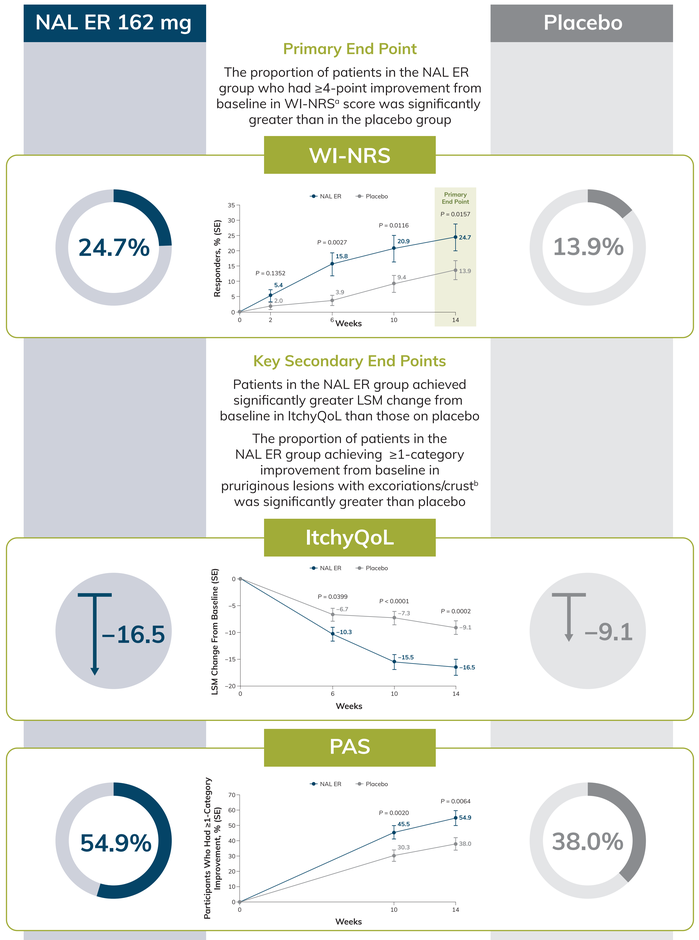
Table 2. Safety

	NAL ER n = 168		Placebo n = 176	
	Titration	Fixed-Dose	Titration	Fixed-Dose
Participants who had ≥1 TEAE	111 (66.1)	81 (48.2)	55 (31.3)	79 (44.9)
Treatment-related AEs	86 (51.2)	52 (31.0)	24 (13.6)	22 (12.5)
Participants who had TEAEs leading to study discontinuation	33 (19.6)	23 (13.7)	5 (2.8)	7 (4.0)
Participants who had any SAEs[a]	8 (4.8)		6 (3.4)	
TEAEs that had >15% incidence in any treatment arm[b]				
Gastrointestinal disorders	84 (50.0)		37 (21.0)	
Nausea	51 (30.4)		16 (9.1)	
Constipation	26 (15.5)		7 (4.0)	
Nervous system disorders	81 (48.2)		28 (15.9)	
Dizziness	51 (30.4)		5 (2.8)	
Headache	26 (15.5)		14 (8.0)	

[a]No SAEs were considered treatment related.
[b]By MedDRA SOC and PT.

Efficacy

Figure 1. Efficacy of NAL ER Versus Placebo in Patients With PN



[a]Based on 7-day WI-NRS scores.
[b]As measured by responses to PAS question 5a.

Summary

- The PRISM study met its primary end point and all key secondary end points
  - A significantly higher percentage of participants experienced an antipruritic response on week 14 with NAL ER (24.7%) versus placebo (13.9%)
  - Compared with placebo, NAL ER treatment also resulted in
    - Greater improvement in ItchyQoL at weeks 6, 10, and 14
    - Greater improvement in pruriginous lesions with excoriations/crusts at weeks 10 and 14
- The safety profile of NAL ER was consistent with its known safety profile
  - A 36-week open-label study is ongoing to assess the long-term safety and efficacy
- Use of NAL ER may provide a novel oral treatment approach

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Abbreviations

ItchyQoL, Itchy Quality of Life; IV, intravenous; LSM, least squares mean; MedDRA, Medical Dictionary for Regulatory Activity; NAL ER, nalbuphine extended release; PAS, prurigo activity score; PN, prurigo nodularis; PT, preferred term; SAE, serious adverse event; SOC, system organ class; SD, standard deviation; SE, standard error; TEAE, treatment-emergent adverse event; WI-NRS, Worst Itch Numerical Rating Scale

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