Efficacy and Safety of Oral Nalbuphine Extended Release in Prurigo Nodularis: Results of a Phase 2, Randomized, Controlled Trial with an Open-Label Extension Phase

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INTRODUCTION

- Prurigo nodularis (PN) is a relatively rare, intensely pruritic dermatologic disease that develops from prolonged itching and scratching, with a high associated quality-of-life impact.[1]
- The current guidelines for treating PN are based on empirical observations and single, randomized, controlled trials.[2,3,4]
- Therapies such as calcineurin inhibitors, topical steroids, and systemic antihistamines have limited data to support their use.
- The synthetic opioid nalbuphine, a dual-acting μ antagonist and κ agonist, has shown efficacy in morphine-induced pruritus and uremic pruritus,[5,6] but an evaluation of the efficacy and safety of nalbuphine in PN is currently lacking.

OBJECTIVE

- To evaluate the efficacy and safety of oral nalbuphine extended release (NAL-ER) tablets in a phase 2, multicenter, randomized, double-blind, placebo-controlled trial with an open-label extension phase.

METHODS

- Patients with moderate-to-severe PN (pruritus duration ≥ 6 weeks) were randomized 1:1:1 to receive either NAL-ER 81 mg or 162 mg tablets twice-daily (b.i.d.), or placebo for 8 weeks of stable dosing following a 2-week titration period (for dose-escalation from 30 mg once-daily to the assigned target dose).
- Itch scores based on Worst Itch (WI) and average itch Numerical Rating Scale (NRS) with 24-hour recall were collected daily by an electronic diary (DIARYpro®).
- The primary efficacy endpoint was the proportion of patients with a ≥ 30% reduction in 7-day mean WI-NRS from baseline to Week 10/last observation.
- The primary safety endpoint was the incidence of opioid-type adverse events of nausea, vomiting, constipation, somnolence, sedation, dizziness, and vertigo in each treatment group.

RESULTS

- Of 62 treated patients, 50 completed 10 weeks of treatment. The primary efficacy endpoint of percentage of responders with ≥ 30% reduction from baseline in 7-day WI intensity was not significant for the primary modified intent-to-treat analysis but, was significant for NAL-ER 162 mg (66.7%) compared with placebo (40.0%; p = 0.026) among completers (**Table 1**).

RESULTS, continued

Table 1. Primary and secondary efficacy outcomes (mITT) of responders

Endpoints, n/N (%)	NAL-ER 81 mg	NAL-ER 162 mg	Placebo
Primary endpoints			
≥ 30% reduction in 7-day WI intensity NRS vs baseline			
Last observation	6/22 (27.3)	8/18 (44.4)	8/22 (36.4)
Completers	6/18 (33.3)	8/12 (66.7)	8/20 (40.0)
≥ 50% reduction in 7-day WI intensity NRS vs baseline			
Last observation	3/22 (13.6)	6/18 (33.3)	4/22 (18.2)
Completers	3/18 (16.7)	6/12 (50.0)*	4/20 (20.0)
Secondary endpoints			
≥ 30% reduction in 7-day average itch intensity NRS vs baseline			
Last observation	11/22 (50.0)	11/18 (61.1)	9/22 (40.9)
Completers	11/18 (61.1)	10/12 (83.3)*	8/20 (40.0)
≥ 50% reduction in 7-day average itch intensity NRS vs baseline			
Last observation	8/22 (36.4)	6/18 (33.3)	4/22 (18.2)
Completers	8/18 (44.4)	6/12 (50.0)*	4/20 (20.0)

Study completers were analyzed as a subset of all mITT. Completers are patients who completed Week 10 of the study and attended Visit 5. *p ≤ 0.05 vs placebo. mITT, modified intent-to-treat.

Table 2. Treatment-emergent adverse events (safety population)

Adverse event, n (%)	NAL-ER 81 mg (n = 22)	NAL-ER 162 mg (n = 18)	Placebo (n = 22)
TEAE	17 (77.3)	16 (88.9)	14 (63.6)
Serious TEAE	1 (4.5)	0 (0)	1 (4.5)
Related TEAE	12 (54.5)	13 (72.2)	8 (36.4)
TEAE onset during			
Titration period	16 (72.7)	13 (72.2)	10 (45.5)
Fixed dose period	8 (36.4)	8 (44.4)	8 (36.4)
Washout/safety	6 (27.3)	6 (33.3)	4 (18.2)
TEAE with > 15% incidence overall by System Organ Class / Preferred Term			
Gastrointestinal disorders			
Nausea	4 (18.2)	7 (38.9)	1 (4.5)
General disorders and administration-site conditions			
Fatigue	5 (22.7)	2 (11.1)	0
Nervous system disorders			
Dizziness	5 (22.7)	7 (38.9)	1 (4.5)
Headache	6 (27.3)	5 (27.8)	2 (9.1)

RESULTS, continued

- Treatment-emergent adverse events (TEAEs) occurred predominantly during the titration period in both studies. During double-blind, stable-dose treatment that followed titration, TEAE incidence was similar for both active treatment arms and placebo (**Table 2**).
- Common TEAEs were nausea, dizziness, headache, and fatigue; the majority of these events were also considered treatment-related in all 3 arms (**Table 2**).
- In the extension study, 34 patients reported 154 TEAEs, including 26 patients with ≥ 1 drug-related TEAE. TEAEs included nausea (n = 9; 25.0%), and dizziness and fatigue (n = 8 for each; 22.2%).

CONCLUSION

- The findings of this study indicate that in patients with PN, NAL-ER tablets, at a dose of 162 mg b.i.d., appear to have a measurable antipruritic effect for patients who successfully maintain the initial therapy for at least 10 weeks.
- The significantly greater response rate for NAL-ER 162 mg patients who completed the full 10 weeks of double-blind treatment compared with placebo is consistent with a clinical benefit that requires compliance with the designated dosing schedule and duration.
- Further evaluation of NAL-ER, including further elucidation of its underlying mechanism of action, is thus warranted in this difficult-to-treat disease, with a larger phase 2b/3 clinical trial currently evaluating the 162 mg b.i.d. dose.

CONFLICTS OF INTEREST

EW is an investigator in clinical trials for Kiniksa, Menlo Therapeutics, and Trevi Therapeutics. **TRS** is an employee of Trevi Therapeutics. **SST** is an investigator for Dermasence, Galderma, Kiniksa, Menlo Therapeutics, Trevi Therapeutics, Novartis, Sanofi, and Vanda Therapeutics; a consultant and/or advisory board member for Almirall, Bayer, Beiersdorf, Bellus Health, Bionorica, Cara Therapeutics, Celgene, Clexio, DS Biopharma, Galderma, Kiniksa, Lilly, Menlo Therapeutics, Novartis, Pfizer, Sanofi, and Trevi Therapeutics.

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