

# Modulation of the kappa and mu opioid axis for the treatment of chronic pruritus: A review of basic science and clinical implications



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**Introduction:** Treating chronic pruritus is challenging for dermatologists due to the lack of therapeutic options. We review the effects of  $\kappa$ -opioid receptor (KOR) and  $\mu$ -opioid receptor (MOR) in the modulation of itch, summarize evidence supporting the efficacy and safety of opioid receptor–targeting agents in chronic pruritus, and address clinical considerations.

**Results:** Preclinical studies have found neural pathways underlying detection, transmission, and modulation of itch signaling and spotlighted the importance of neuronal KOR and MOR in itch perception. Clinical reports suggest that opioid axis modulation may be the basis for the successful treatment of chronic itch. Several agents (MOR antagonist naltrexone; KOR agonists nalfurafine and difelikefalin; dual-acting KOR agonists/MOR antagonists butorphanol and nalbuphine) have been evaluated for treating chronic pruritus in case series, small studies, and clinical trials; nalbuphine has progressed through preliminary (phase II/III) studies in uremic pruritus and prurigo nodularis. The antipruritic efficacy of these agents has been observed across multiple disorders with disparate etiologies, suggesting the potential utility of this class to provide a unified approach to chronic pruritus treatment.

**Conclusions:** The relative safety of these agents, including a reduced potential for dependence versus MOR-agonist analgesics, should help overcome resistance to the use of opioid receptor–targeting agents in chronic pruritus treatment. (JAAD Int 2022;7:156-63.)

**Key words:** antipruritic; butorphanol; difelikefalin; end-stage renal disease; itch; nalbuphine; naltrexone; neural pathways; opioid; prurigo; pruritus; receptors; renal dialysis.

## BACKGROUND

Chronic pruritus is a signature symptom of disorders spanning a range of underlying etiologies that substantially affect the quality of life, sleep, and mood, and it is associated with a significant economic burden.<sup>1-7</sup> Recent studies have shown that the perception and transmission of itch sensations are regulated in part by the opioid receptors (ORs) present on somatosensory and spinal neurons (Fig 1).<sup>8-13</sup> In preclinical models and human studies,

the activation of  $\kappa$ -opioid receptors (KORs) is associated with itch attenuation, whereas the activation of  $\mu$ -opioid receptors (MORs) is associated with itch intensification.

Because the imbalances in KOR and MOR signaling pathways are believed to contribute to the pathophysiology of chronic pruritus,<sup>14-18</sup> there is an interest in investigating KOR agonists and/or MOR antagonists as novel treatments for severe itch.<sup>15,17,19</sup> Given the evolving understanding of

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Funding sources: Medical writing support was provided by Stephen Collins, MS, of Peloton Advantage, LLC, an OPEN Health Company, and funded by Trevi Therapeutics.

IRB approval status: Not applicable.

Accepted for publication March 8, 2022.

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2666-3287

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<https://doi.org/10.1016/j.jdin.2022.03.007>

itch transmission and modulation, effective antipruritic treatments may target both peripheral and central ORs. Treatments aimed specifically at the pathophysiology common to itch, regardless of the etiology, may be important adjuncts to treatments aimed at the underlying pruritogenic condition (eg, helping to break the itch-scratch cycle of disorders such as prurigo nodularis [PN]).

We review here the effects of KOR and MOR in the modulation of itch, summarize evidence supporting the efficacy and safety of OR-targeting agents in treating chronic pruritus, and address clinical considerations as these agents proceed through development.

## PERIPHERAL AND SPINAL ITCH SIGNALING PATHWAYS

Over the past decade, preclinical studies employing gene knockout and knockin technologies and gene expression profiling have illuminated the somatosensory and spinal pathways that detect and transmit itch sensations. These findings characterize the neural pathways for chemical and mechanical itch, distribution of ORs throughout these pathways, and role of spinal interneurons in modulating itch sensations. In addition, they help provide the foundation for OR modulation as a clinical strategy for treating chronic pruritus.

## OR-TARGETING AGENTS FOR CHRONIC PRURITUS TREATMENT

To date, in the United States, agents targeting ORs (MOR antagonists and dual-acting KOR agonists/MOR antagonists) have been used off-label for the treatment of itch.<sup>2,20</sup> Several opioids that target KORs and/or MORs are in various phases of clinical development for treating chronic pruritus (Table I).

### MOR antagonists

MOR antagonists were the first class of opioid compounds to be evaluated for itch suppression. Although not currently in development for any pruritus-related indications, the MOR antagonist naloxone has been evaluated previously for treating opioid-induced pruritus.<sup>21-23</sup> However, naloxone is not available as an oral formulation and is currently indicated only for reversing opioid-induced adverse events (AEs).<sup>24</sup>

The MOR antagonist naltrexone, which is currently indicated for the treatment of alcoholism and opioid addiction,<sup>25</sup> was evaluated in 18 patients aged  $\geq 65$  years with severe chronic pruritus ( $\geq 7$  on a 0 to 10 visual analog scale [VAS]) arising from a range of conditions (PN, eczema senilis, uremic pruritus [UP], and cholestatic pruritus) that was unresponsive to other treatments, including antihistamines. Patients were maintained on current medications and received naltrexone 50 mg/day orally for a mean treatment period of 66 days.<sup>26</sup> Symptomatic improvement was observed in 16 of 18 (89%) patients, with 13 of 18 (72%) patients considered “much improved” ( $>50\%$  reduction in VAS score) and 6 of 18 (33%) patients nearly symptom free (VAS score  $\leq 1$ ). The mean itch VAS  $\pm$  standard

deviation (SD) scores declined from  $8.28 \pm 0.89$  at baseline to  $3.72 \pm 1.49$  at 2 weeks ( $P < .05$  vs baseline) and to  $2.83 \pm 1.98$  at 2 months ( $P < .05$  vs baseline and 2 weeks); there was no evidence that the underlying diagnosis affected the treatment response. Five patients experienced AEs, including insomnia, fatigue, constipation, and anorexia. All AEs but constipation were resolved within 2 weeks; constipation was manageable with laxatives.<sup>26</sup>

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### KOR agonists

Nalfurafine, a small molecule KOR agonist approved in Japan for treating UP,<sup>2</sup> was assessed in a phase 3 randomized, double-blind, placebo-controlled study that enrolled hemodialysis (HD) patients ( $N = 337$ ) with severe UP ( $\geq 50$  on a 0-100 mm VAS). Patients received 14 days of treatment with oral nalfurafine (5 or 2.5  $\mu\text{g}/\text{d}$ ) or matching placebo, adjunctive to existing antipruritic treatment(s).<sup>27</sup> At the end of the study, placebo-corrected mean reductions in VAS itch score (95% confidence interval [CI]) were  $-9$  ( $-14$  to  $-4$ ) and  $-10$  ( $-14$  to  $-4$ ) in the nalfurafine 5 and 2.5  $\mu\text{g}$  groups, respectively ( $P \leq .0002$  vs placebo; Fig 2); differences between active treatment and placebo reached statistical significance ( $P \leq .0101$ ) only after 7 days of treatment.<sup>27</sup> Significant response ( $\geq 50\%$  reduction in VAS itch score) was experienced by 32 of 112 (29%), 37 of 114 (32%), and 19 of 111 (17%) patients receiving nalfurafine 2.5  $\mu\text{g}/\text{d}$ , nalfurafine 5  $\mu\text{g}/\text{d}$ , and placebo, respectively. Nearly all patients

## CAPSULE SUMMARY

- Clinical and preclinical findings show that the modulation of the  $\kappa$ - and  $\mu$ -opioid receptor axes represents a promising therapeutic approach in the management of patients with chronic pruritus.
- Targeting the pathophysiologic commonalities of chronic pruritus may facilitate a unified approach to its treatment across a broad range of underlying disorders.

*Abbreviations used:*

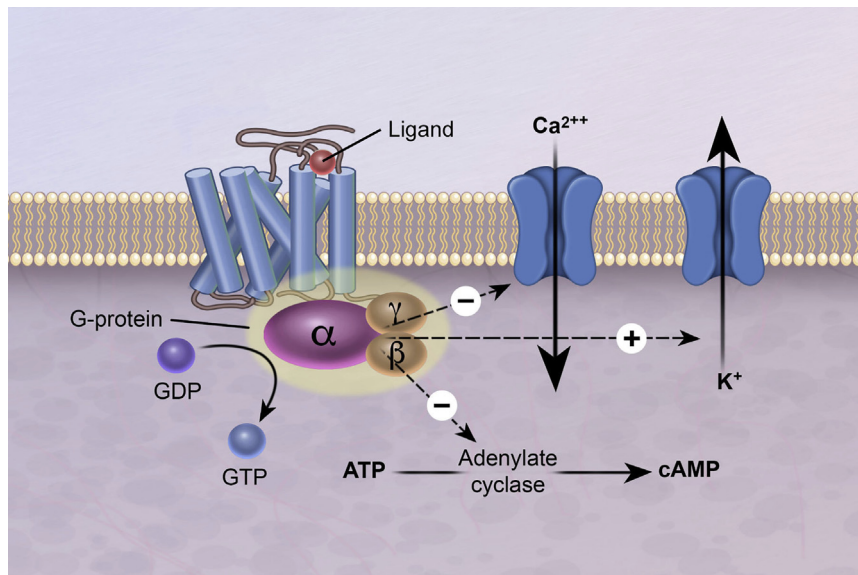
|         |                                      |
|---------|--------------------------------------|
| AE:     | adverse event                        |
| CI:     | confidence interval                  |
| HD:     | hemodialysis                         |
| KOR:    | $\kappa$ -opioid receptor            |
| MOR:    | $\mu$ -opioid receptor               |
| NAL-ER: | nalbuphine extended release          |
| NRS:    | numerical rating scale               |
| OR:     | opioid receptor                      |
| PN:     | prurigo nodularis                    |
| SD:     | standard deviation                   |
| UP:     | uremic pruritus                      |
| VAS:    | visual analog scale                  |
| WI-NRS: | Worst Itching–Numerical Rating Scale |

(97.6%) completed the study, and the most common adverse drug reactions in the nalfurafine groups were nasopharyngitis, insomnia, somnolence, and constipation.<sup>27</sup>

In a pooled analysis of 2 randomized, placebo-controlled, double-blind studies conducted in HD patients with severe pruritus ( $N = 144$ ) who received nalfurafine 5  $\mu\text{g}$  ( $n = 86$ ) via intravenous infusion 3 times weekly following their HD session,

patients treated with nalfurafine achieved significantly greater mean reductions than those receiving placebo ( $n = 58$ ) in the primary efficacy end point, change in the mean “worst itching” 0–100 mm VAS score (placebo-corrected difference [95% CI]:  $-9.53$  [ $-1.42$  to  $-17.84$ ] mm;  $P = .0202$ ). The most common adverse drug reactions were headache, nausea, vomiting, insomnia, and vertigo.<sup>28</sup>

Difelikefalin (CR845), a peripherally restricted, selective opioid peptide KOR agonist was recently approved in the United States as an intravenous formulation for the treatment of UP.<sup>29–31</sup> In a randomized, double-blind, placebo-controlled, phase 2 study (NCT02858726), HD patients ( $N = 174$ ) with moderate-to-severe pruritus were randomized to difelikefalin 0.5, 1.0, or 1.5  $\mu\text{g}/\text{kg}$  or matching placebo via intravenous bolus following thrice-weekly HD sessions for 8 weeks. The primary efficacy end point was the Worst Itching Intensity–Numerical Rating Scale (WI-NRS), which is a 0 to 10 VAS.<sup>29</sup> At the study end point, patients treated with difelikefalin (all doses) experienced

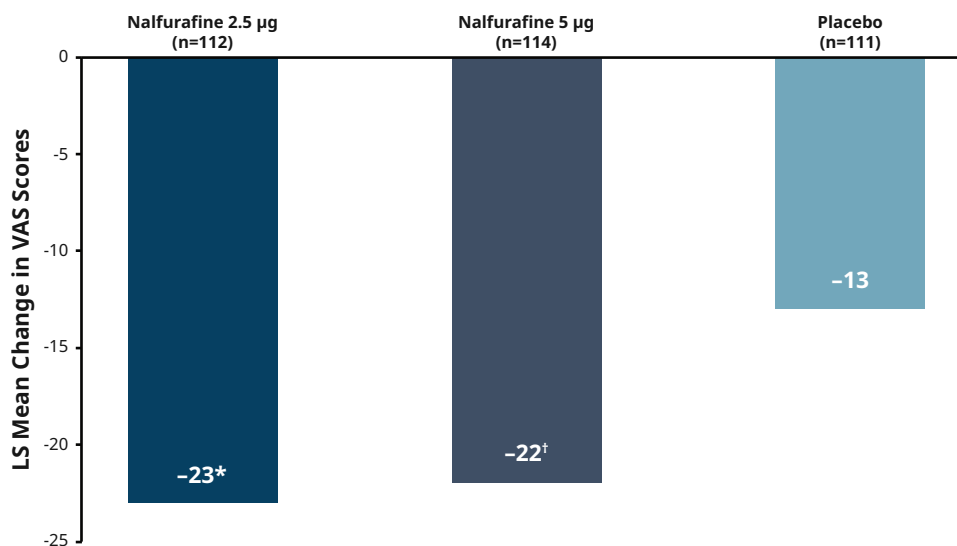


**Fig 1.** Pruritus-related opioid receptors. ORs, membrane-bound proteins with 7 transmembrane domains bearing a ligand-binding domain on the outer surface of the membrane, are GPCRs, characterized by a cytosolic coupling to a guanine nucleotide-binding protein (G protein). The binding of a ligand/agonist (activator) to neuronal ORs leads to phosphorylation/activation of the G protein receptor, leading in turn to a cascade of intracellular events (increased potassium ion efflux/hyperpolarization across the membrane, closing of voltage-sensitive calcium channels, and reduced cyclic adenosine monophosphate synthesis), culminating in reduced neuronal excitability and synaptic firing potential. The most important ORs in itch sensation are  $\kappa$ -opioid and  $\mu$ -opioid receptors, with the endogenous agonists dynorphin and endorphin, respectively.<sup>12,13</sup>  $\alpha$ , Alfa opioid receptor; *ATP*, adenosine triphosphate;  $\beta$ , beta opioid receptor; *cAMP*, cyclic adenosine monophosphate;  $\gamma$ , gamma opioid receptor; *GDP*, guanosine diphosphate; *GPCR*, G protein-coupled receptor; *GTP*, guanosine triphosphate; *OR*, opioid receptor.

**Table I.** Selected opioid receptor–targeting agents in development for the treatment of pruritus

| Agent                       | Opioid receptor target(s)  | Itch-related indication(s) sought                                                                                                                                                   | Administration                                                                                  | Development phase/ClinicalTrials.gov No.                                                                                                                                                                       |
|-----------------------------|----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Naltrexone                  | MOR antagonist             | Atopic dermatitis                                                                                                                                                                   | Oral                                                                                            | Phase 2/NCT04325802 (not yet recruiting)                                                                                                                                                                       |
| Nalfurafine                 | KOR agonist                | UP                                                                                                                                                                                  | Oral                                                                                            | Phase 3/NCT01513161                                                                                                                                                                                            |
| Difelikefalin (CR845)       | KOR agonist                | <ul style="list-style-type: none"> <li>• UP</li> <li>• Atopic dermatitis</li> <li>• Cholestatic pruritus</li> </ul>                                                                 | <ul style="list-style-type: none"> <li>• Intravenous</li> <li>• Oral</li> <li>• Oral</li> </ul> | <ul style="list-style-type: none"> <li>• Phase 3/NCT03636269</li> <li>• Phase 2/NCT04018027</li> <li>• Phase 2/NCT03995212 (recruiting)</li> </ul>                                                             |
| Butorphanol                 | KOR agonist/MOR antagonist | No new indications/clinical studies planned                                                                                                                                         |                                                                                                 |                                                                                                                                                                                                                |
| Nalbuphine extended release | KOR agonist/MOR antagonist | <ul style="list-style-type: none"> <li>• Prurigo nodularis</li> <li>• UP</li> <li>• Opioid-induced pruritus (pediatric)</li> <li>• Intrathecal morphine-induced pruritus</li> </ul> | Oral (extended release)                                                                         | <ul style="list-style-type: none"> <li>• Phase 2/3/NCT03497975 (recruiting)</li> <li>• Phase 2/3/NCT02143648</li> <li>• Phase 3/NCT00323154 (completed)</li> <li>• Phase 2/NCT04589429 (recruiting)</li> </ul> |

KOR,  $\kappa$ -Opioid receptor; MOR,  $\mu$ -opioid receptor; UP, uremic pruritus.



**Fig 2.** Uremic pruritus. Reduction in the itch scores in hemodialysis patients treated for 14 days with intravenous 2.5- or 5- $\mu$ g nalfurafine or matching placebo immediately following thrice-weekly hemodialysis sessions.<sup>27</sup> LS, Least squares; VAS, visual analog scale. \* $P = .0001$  versus placebo. † $P = .0002$  versus placebo.

significantly greater reductions on the WI-NRS than those receiving placebo (placebo-corrected reduction:  $-1.3$  [95% CI,  $-2.1$  to  $-0.5$ ];  $P = .002$ ). In addition, significantly greater proportions of patients treated with difelikefalin than those receiving placebo achieved  $\geq 3$ -point (59% vs 29%;  $P = .001$ ) or  $\geq 4$ -point (44% vs 24%;  $P = .038$ ) WI-NRS reductions. The most common AEs among patients treated with difelikefalin were diarrhea, dizziness, nausea, somnolence, and falls.<sup>29</sup>

In a randomized, double-blind, placebo-controlled phase 3 study (NCT03422653), HD

patients ( $N = 378$ ) with moderate-to-severe pruritus were randomized to treatment with difelikefalin 0.5  $\mu$ g/kg or matching placebo via an intravenous bolus thrice-weekly following HD sessions for 12 weeks.<sup>30</sup> At study end, a significantly higher proportion of patients treated with difelikefalin than those receiving placebo achieved a  $\geq 3$ -point reduction on the WI-NRS (primary efficacy end point): 49.1% versus 27.9% (relative risk, 1.65; 95% CI, 1.26–2.14;  $P < .001$ ). The most common AEs among patients treated with difelikefalin were diarrhea, dizziness, and vomiting; these generally were

mild to moderate in severity and were resolved quickly.<sup>30</sup>

In both studies, health-related quality of life assessments were conducted using the Skindex-10 and the 5-D itch scale.<sup>29,30</sup> In both studies, difelikefalin was associated with significantly greater mean improvements than placebo on the Skindex-10 total score and 5-D itch scale total score ( $P < .001$  for all comparisons).<sup>29,30</sup>

An oral formulation of difelikefalin was studied (NCT04018027) in patients with moderate-to-severe pruritus associated with atopic dermatitis of variable severity ( $n = 401$ ). Subjects were randomized to twice-daily difelikefalin 0.25 mg, 0.5 mg, 1.0 mg or matching placebo and were stratified across treatment groups by atopic dermatitis-affected body surface area (mild-to-moderate,  $<10\%$ ; moderate-to-severe,  $>10\%$ ). Although some improvements in itch were observed in patients with mild-to-moderate atopic dermatitis, the study failed to meet its primary end point of change from baseline to week 12 in WI-NRS or the secondary end point of a 4-point responder analysis in the intention-to-treat subject population. Few study details are available, as it has yet to be published in peer-reviewed form.<sup>32</sup>

### Dual-acting KOR agonists/MOR antagonists

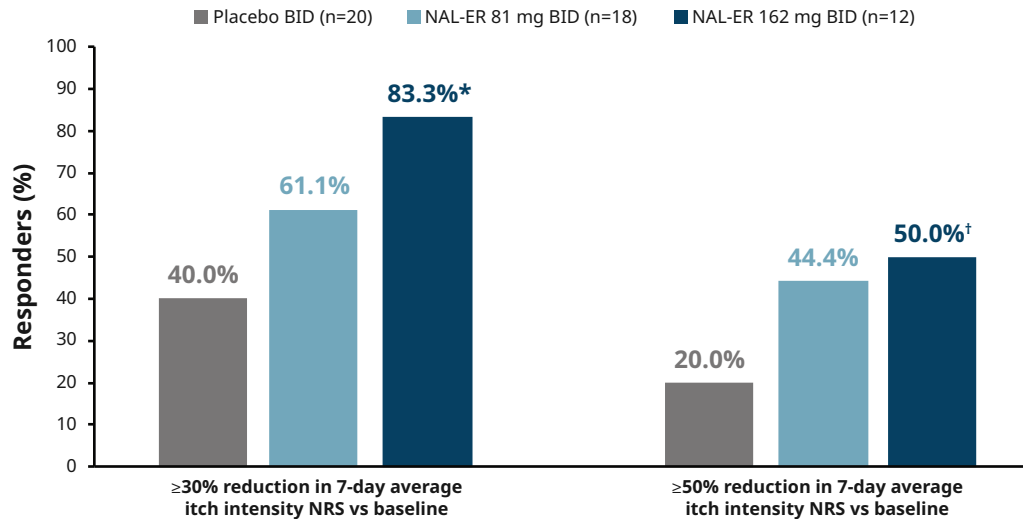
Butorphanol is a dual-acting KOR agonist/MOR antagonist currently indicated for pain management as a nasal spray<sup>33</sup> that has been evaluated in opioid-induced pruritus<sup>34-36</sup> and to a more limited extent for chronic pruritus.<sup>2,37,38</sup> In a case series of 16 patients with pruritus of various etiologies (including atopic pruritus, PN, neuropathic pruritus, and idiopathic pruritus) from a university hospital itch clinic, patients were treated off-label with butorphanol nasal spray (10 mg/mL) as needed, up to once every 4 hours.<sup>37</sup> Based on patient reporting and change in WI-NRS scores, 13 of 16 (81.3%) patients experienced improvement in itch severity; 2 patients were lost to follow-up, and 1 patient did not improve. Improvements of  $\geq 4$  points on the WI-NRS were reported by 6 of 13 (46.2%) patients, and significant improvements from the baseline were noted for mean total Dermatology Life Quality Index ( $n = 9$ ;  $P = .004$ ) and Beck Depression Inventory score ( $n = 9$ ;  $P = 0.005$ ). Three patients reported AEs, including insomnia, lightheadedness, and lethargy.<sup>37</sup>

Nalbuphine is a selective, dual-acting KOR agonist/MOR antagonist<sup>39</sup> that is currently approved for pain management in an injectable formulation.<sup>40</sup> An oral extended-release nalbuphine (NAL-ER) formulation has been evaluated for the treatment of chronic pruritus in both UP and PN.<sup>41,42</sup>

In a randomized, double-blind, placebo-controlled phase 2/3 study (NCT02143648), HD patients ( $N = 373$ ) with moderate-to-severe UP were randomized to oral NAL-ER 60 mg, NAL-ER 120 mg, or matching placebo twice daily for 8 weeks.<sup>41</sup> At the end of the study, the mean (SD) score reductions on a 0 to 10 itch severity numerical rating scale (NRS) (primary end point) were significantly greater among patients receiving NAL-ER 120 mg than among those receiving the placebo (3.5 [2.4] vs 2.8 [2.2];  $P = .017$ ). In a post hoc subgroup analysis of patients with severe UP (baseline NRS itch severity  $\geq 7$ ), the mean (SD) NRS itch scores declined significantly more in the NAL-ER 120 mg group compared with placebo (4.5 [2.5] vs 3.2 [2.7];  $P < .01$ ); net reductions from baseline were 55% and 40%, respectively. The severe UP subgroup also demonstrated significantly greater improvement in itch-related sleep disruption scores among those receiving NAL-ER 120 mg versus placebo ( $P = .006$ ). The most common AEs leading to discontinuation among patients randomized to NAL-ER were characteristic of opioid treatment (eg, nausea, vomiting, and somnolence), mostly occurring during the titration period.<sup>41</sup>

In a randomized, double-blind, placebo-controlled phase 2 study (NCT02174419), patients with moderate-to-severe PN ( $N = 62$ ) were randomized to receive treatment with NAL-ER 81 mg or 162 mg or matching placebo twice daily for 8 weeks.<sup>42</sup> Patients who completed the study were eligible for enrollment in an open-label extension study for up to 50 weeks of treatment with NAL-ER (NCT02174432); a total of 36 of 50 subjects who completed the phase 2 trial were enrolled.

In an analysis of the modified intention-to-treat population, a  $\geq 30\%$  reduction from baseline in WI-NRS score (primary end point) was achieved by 36.4%, 27.3%, and 44.4% of patients in the placebo, NAL-ER 81 mg, and NAL-ER 162 mg groups, respectively; the differences between groups were not statistically significant.<sup>42</sup> However, among patients who completed the double-blind phase, a significantly greater proportion of patients receiving NAL-ER 162 mg, compared with placebo, achieved reductions in the 7-day average itch intensity of  $\geq 30\%$  and  $\geq 50\%$  (Fig 3). These patients also demonstrated significantly greater mean improvement (reduction) from baseline versus placebo in an itch-related health-related quality of life assessment (ItchyQoL  $-13.8$  vs  $-5.5$ ;  $P = .022$ ). During the double-blind phase, the most common AEs in the NAL-ER 162 mg group were nausea and dizziness (each reported by 7 of 18 [39%] patients) and headache (5 of 18 [28%] patients). Most patients



**Fig 3.** Prurigo nodularis. Proportions of patients experiencing  $\geq 30\%$  or  $\geq 50\%$  reduction in the 7-day average itch intensity (Worst Itch-Numerical Rating Scale) following twice-daily administration of 81- or 162-mg NAL-ER or matching placebo for 8 weeks.<sup>42</sup> NAL-ER, nalbuphine extended release; NRS, Numerical Rating Scale. \* $P = .008$  versus placebo. † $P = .028$  versus placebo.

who entered the extension study and completed 26 or 50 weeks of open-label treatment with NAL-ER 162 mg demonstrated improvement in excoriation/crusting and/or healing of skin lesions.

### CLINICAL CONSIDERATIONS

The evidence supporting the use of dual-acting KOR agonists/MOR antagonists across a range of disorders, using multiple routes of administration, suggests that the modulation of the OR axis is an effective treatment strategy and an essential component of treating chronic pruritus. Chronic pruritus presents a novel problem for developing consensus treatment recommendations because it arises neither from a single disorder nor a single well-defined pathophysiologic process,<sup>43</sup> emerging instead from multiple distinct clinical entities. Although chronic pruritus may be addressed in disorder-specific, specialist-focused guidelines, itch management is typically relegated to secondary status. Even in itch-dominant disorders, systemically administered treatments for itch are mentioned as a second- or third-line option, to be explored only after non-pharmacologic and approved topical therapies prove inadequate. For example, a recent UP treatment algorithm mentions off-label use of naltrexone as a possible second-line therapy<sup>44</sup>; draft consensus PN guidelines recommend OR-targeting agents only after topical agents, antidepressants, and gabapentinoids have failed.<sup>45</sup> Conversely, current guidelines regarding the use of OR-targeting agents focus

primarily on the safe use of MOR agonists in the context of analgesia.

The 2019 European consensus treatment guidelines for chronic pruritus observe that with respect to pathogenesis and potential therapies, itch demonstrates sufficient commonality across multiple diagnoses that a unified guideline for most forms of chronic pruritus may produce more positive outcomes than the current fragmented disorder-by-disorder approach. Notably, this guideline explicitly recognizes the modulation of ORs as an important element of treating pruritus.<sup>43</sup> Other systemic therapies being developed for managing chronic pruritus that may further facilitate this approach include neurokinin receptor 1 inhibitors and tropomyosin receptor kinase A antagonists.<sup>2,20</sup>

Real and perceived safety concerns may present a barrier to adopting OR-targeting agents for the routine management of chronic pruritus. In contrast to MOR agonists, KOR agonists and/or MOR antagonists have generally been shown to have a lower potential for abuse.<sup>46,47</sup> Notably, the injectable formulation of nalbuphine is not scheduled as a controlled substance in the United States,<sup>48</sup> whereas butorphanol nasal spray is designated as a schedule IV controlled substance.<sup>33</sup> In clinical studies, the most frequent AEs have been insomnia, headache, and gastrointestinal effects, which are characteristic of opioid-modulating agents. In addition, the use of MOR antagonists raises the possibility of attenuating or reversing the analgesic effects of MOR agonists; however, this has not emerged as an issue in clinical

evaluations (of note, the dual-acting KOR agonists/MOR antagonists [butorphanol and nalbuphine] discussed here are currently indicated for analgesia). Finally, in early studies of the analgesic properties of KOR agonists, some patients developed central nervous system—related AEs, potentially because of the ability to cross the blood-brain barrier, including dysphoria and psychotomimesis.<sup>49</sup> However, the safety of new antipruritic agents as a function of their in vivo distribution will be determined empirically, not based on theoretical concerns.

Several of the conditions associated with chronic pruritus disproportionately affect the older patients. Moreover, recent health surveys have suggested that pruritus is the most common dermatologic complaint in this population, and its prevalence increases with age.<sup>43</sup> In addition to pathophysiologic changes in aging skin, older patients frequently present with multiple chronic comorbidities and consequent polypharmacy. In these patients, non-pharmacologic approaches tailored to restoring the skin barrier integrity continue to be emphasized before resorting to systemic care. Systemic treatments (including OR-targeting agents) must be tailored specifically for each patient based on careful consideration of comorbidities, drug interactions, and potential AEs.<sup>43</sup> In particular, somnolence, dizziness, and respiratory suppression may be important considerations for the older population.

## CONCLUSION

Recent advances in the understanding of itch signaling pathways and the relationship to KORs and MORs have led to the development of OR-targeting agents for treating pruritus. Moreover, the emerging realization that common pathophysiologic mechanisms propel the development and progression of chronic pruritus across multiple disorders may help facilitate a new “itch-forward” approach to managing pruritus, regardless of the underlying disorder.

## Conflicts of interest

Dr Elmariah has served as an advisory board member, consultant, or speaker for Sanofi, Trevi Therapeutics, Celldex Therapeutics, Eli Lilly, and Galderma and has served as an investigator for Trevi Therapeutics. Dr Chisolm is an investigator for Incyte; has received research support from Pfizer; and has served as a scientific advisor or advisory board member for companies including Menlo Therapeutics, AbbVie, Janssen Pharmaceutical, Kiniksa Pharmaceuticals, Pfizer, Regeneron Pharmaceuticals, and Kimberly-Clark. Dr Kwatra is an advisory board member/consultant for AbbVie, Celldex Therapeutics, Galderma, Incyte Corporation, Pfizer, Regeneron Pharmaceuticals, and Kiniksa Pharmaceuticals and has served as an

investigator for Galderma, Kiniksa Pharmaceuticals, Pfizer, and Sanofi. Dr Sciascia does not have any conflicts of interest to declare.

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