Serlopitant reduced pruritus in patients with prurigo nodularis in a phase 2, randomized, placebo-controlled trial

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Background: Anecdotal evidence suggests that neurokinin 1 receptor antagonism reduces pruritus intensity in chronic pruritic conditions such as prurigo nodularis (PN).

Objective: This study assessed safety and efficacy of the neurokinin 1 receptor antagonist serlopitant for treatment of pruritus in PN.

Methods: In this randomized, double-blind, placebo-controlled study, 128 patients with chronic, treatment-refractory PN for more than 6 weeks received serlopitant, 5 mg, or placebo orally once daily for 8 weeks. The primary end point was change in average itch visual analog scale score at weeks 4 and 8.

Results: Average itch visual analog scale scores significantly improved with serlopitant versus with placebo at weeks 4 and 8: the least squares mean difference (serlopitant minus placebo) was −1.0 at week 4 ($P = .02$) and −1.7 at week 8 ($P < .001$). The least squares mean difference between serlopitant and placebo reached statistical significance at week 2 (−0.9 [$P = .011$]). The most frequently reported treatment-emergent adverse events in the serlopitant group were nasopharyngitis, diarrhea, and fatigue.

Limitations: The 8-week duration may be insufficient to assess clinically relevant resolution of PN lesions.

Conclusions: Serlopitant reduced pruritus in patients with treatment-refractory PN and was well tolerated. (J Am Acad Dermatol 2019;80:1395-402.)

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CAPSULE SUMMARY

- In this study, the neurokinin 1 receptor antagonist serlopitant significantly reduced pruritus in patients with treatment-refractory prurigo nodularis, supporting the potential of neurokinin 1 receptor antagonism to disrupt itch signaling and reduce pruritus intensity.
- Serlopitant has potential as a therapeutic option for treatment of pruritus associated with prurigo nodularis.

Chronic prurigo is a common end point of multiple pruritic conditions, defined by the presence of severe chronic pruritus and multiple localized or generalized pruriginous lesions.[1] Prurigo nodularis (PN), a subtype of chronic prurigo, is characterized by intensely pruritic, hyperkeratotic papulonodular lesions distributed along the upper and lower limbs and back.[1-3] These lesions dramatically impair patient quality of life.[4-6] PN primarily occurs in adults and is more common in women.[3,4,7,8] PN occurs as a sequela to chronic pruritus associated with a number of conditions that result in chronic scratching.[2,3,9,10]

In the past decade, emerging research has increased understanding of the mechanisms underlying the itch process.[2,11-13] Tachykinin substance P and its receptor neurokinin 1 (NK_1R) play an important role in peripheral and central transmission of histamine-independent pruritus.[14,15] Patients with PN have an increased number of substance P–positive lesional skin nerve fibers,[2,11,16,17] and serum substance P levels are increased in patients with chronic prurigo.[17]

Comprehensive clinical trials in PN have not been undertaken; accordingly, there are currently no approved therapies for the treatment of pruritus associated with PN. Frequently used antipruritic therapies (emollients, topical corticosteroids, topical calcineurin inhibitors, systemic antihistamines, phototherapy, gabapentinoids, antidepressants, and immunosuppressants)[7] are often inadequate; some are associated with side effects that may limit their use.[7,11,18] There remains a significant unmet need for a safe antipruritic therapy that can effectively treat severe pruritus in PN and other conditions. The NK_1R antagonist, aprepitant, which is US Food and Drug Administration–approved for prevention of chemotherapy-induced and postoperative nausea and vomiting, was shown to reduce pruritus intensity in a small (N = 20) uncontrolled study of patients with PN,[19] but its use beyond 3 days is not recommended on account of significant interactions with other drugs.[20,21]

Serlopitant is a small molecule, highly potent, selective NK_1R antagonist that was developed for long-term oral administration.[22] Results from a phase 2, randomized double-blind, placebo-controlled, multicenter clinical trial of serlopitant, 5 mg daily, for pruritus in PN are reported.

METHODS

Trial design, oversight, and patient population

The study TCP-102 was conducted at 15 sites in Germany. Eligible patients were 18 to 80 years of age; had PN for more than 6 weeks and were refractory to previous antipruritic therapies (topical corticosteroids and/or oral antihistamines); in addition, they had generalized PN on both arms, both legs, and/or the trunk, and they had a visual analog scale (VAS) pruritus score of 7 cm or higher at screening. Exclusion criteria included the following: chronic pruritus due to conditions other than PN; use of antihistamines, steroids, other systemic antipruritic therapies, or immunosuppressants 1 to 2 weeks before the baseline visit; recent phototherapy; use of medications known to induce pruritus; serum creatinine level higher than 2.4 mg/dL; aspartate transaminase or alanine transaminase levels more than 2 times the upper limit of normal; untreated hyperthyroidism; recent treatment with strong cytochrome P450 3A4 inhibitors; and suicidal ideation with intent to act within the previous 12 months. Use of emollients and nonsedating antihistamines (as rescue medications) was permitted during the study.

The trial was conducted in accordance with the provisions of the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, and applicable regulatory requirements. The study protocol and its amendments were approved by the appropriate institutional review boards or ethics committees. All patients provided written informed consent before participation in the trial.

Treatment and assessments

After a screening period of at least 4 weeks, patients were randomly assigned to receive serlopitant, 5 mg, or placebo orally once daily. A loading dose of 3 tablets was given on day 1, followed by 1

Abbreviations used:

AEs:	adverse events
IGA:	Investigator's Global Assessment
LS:	least squares
NK_1R:	neurokinin 1 receptor
NRS:	numeric rating scale
PN:	prurigo nodularis
SE:	standard error
TEAEs:	treatment-emergent adverse events
VAS:	visual analog scale
VRS:	visual rating scale

tablet daily at bedtime for 8 weeks. Patients were followed for a 2-week period after treatment. The primary efficacy end point was the average itch VAS pruritus intensity over the previous 24 hours, as determined by using a 10-cm scale recorded at study visits. Secondary efficacy end points included the worst itch VAS intensity over the previous 24 hours; average itch and worst itch numeric rating scale (NRS) pruritus scores over the previous 24 hours, as determined by an 11-point scale; verbal rating scale (VRS); physician-reported prurigo activity score; Investigator's Global Assessment (IGA) score; and use of rescue medication. Pruritus intensity was rated at study visits on the VAS and once daily with the NRS, VRS, and IGA in a patient diary (ItchApp eDiary[23] or paper version) from baseline to the end of the study. Baseline VAS scores were captured at the randomization visit. Patients who added their NRS scores to the electronic patient diary on day 1 were considered to have baseline NRS scores, although timing (before versus after taking the first dose of the assigned study drug) was not recorded. Subgroup analyses (ie, analyses by sex, atopic diathesis status, age, length of time with PN, and baseline average itch VAS score) were also performed. Post hoc analyses included a subgroup analysis for improvement in average itch VAS score based on history of atopic diathesis (eg, predisposition for developing hay fever, allergic rhinitis, bronchial asthma, or atopic dermatitis) and other factors, including an assessment of clinical improvement based on a 3- and 4-cm decrease in average itch VAS and a 4-point decrease in worst itch NRS as measures of response.

Safety end points were adverse events (AEs), treatment-emergent AEs (TEAEs), serious AEs, and clinical laboratory evaluations. AEs were classified by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities, version 17.1. All analyses were performed in the intention-to-treat population (ie, all randomized patients who received at least 1 dose of study drug).

Randomization and masking

Patients were assigned to treatment groups by permuted block randomization (1:1) stratified by site with an interactive web-based response system (IWRS, Almac Clinical Services and Almac Clinical Technologies; Souderton, PA). Data were kept confidential and were accessible only to authorized persons until the time of unblinding. Placebo tablets were indistinguishable from serlopitant tablets.

The total target sample size of 140 patients was selected to achieve at least 90% power for the VAS change from baseline, assuming a treatment effect of at least 1.7 cm and a standard deviation of 3 or less.

Statistical analysis

The primary end point was analyzed by repeated measures analysis of covariance for average itch VAS score. The model used an unstructured covariance matrix and included change from baseline as the response variable and baseline average itch VAS score, visit, pooled site, treatment, and visit by treatment as the independent variables. Visit was included as a categoric variable. The estimated treatment difference (least square [LS] means) at weeks 2, 4, and 8 was summarized, and *P* values for these comparisons were provided. Missing data were not imputed before running the analysis. No multiplicity adjustment was prespecified for the analysis of weeks 4 and 8; therefore, the conservative Bonferroni adjustment (ie, an alpha level 2.5% for each time point) was retrospectively applied. The secondary efficacy end points, summarized with descriptive statistics, included estimates within the treatment group (eg, mean results for serlopitant). For select end points, estimates of the treatment effect, standard error (SE) (Wilson error for binary data and Wald error for continuous data), and statistical testing (*t* tests, Cochran-Mantel-Haenszel tests, or repeated measures) were performed without multiplicity control.

RESULTS

Of the 148 patients screened, 128 were randomized to serlopitant (n = 65) or placebo (n = 63); 1 patient in the serlopitant arm did not receive treatment and was not included in the analysis. In all, 23 (18.0%) patients discontinued treatment prematurely (8 [12.3%] vs 15 [23.8%] in the serlopitant and placebo arms, respectively), predominately because of withdrawal of consent (4 [6.2%] vs 8 [12.7%]) and TEAEs (3 [4.6%] vs 6 [9.5%]). Demographic and baseline characteristics were well balanced in both arms (Table I). The mean baseline average itch VAS score was approximately 7.9 in the serlopitant and placebo arms.

Table I. Patient demographics and baseline characteristics

Characteristic	Serlopitant, 5 mg (n = 64)	Placebo (n = 63)
Age, y		
Mean (±SD)	57.10 (±12.00)	58.1 (±11.14)
Median	57.0	60.0
Minimum	25.0	30.0
Maximum	78.0	77.0
Sex, n (%)		
Male	33 (51.6)	27 (42.9)
Female	31 (48.4)	36 (57.1)
Race, n (%)		
White	64 (100.0)	63 (100.0)
Atopic diathesis, n (%)		
No	35 (54.7)	37 (58.7)
Yes	29 (45.3)	26 (41.3)
Erlanger Atopy Questionnaire, sum		
Mean (±SD)	9.80 (±5.50)	9.80 (±5.40)
Median	9.5	9.0
Minimum	0	0
Maximum	27.0	24.0
Prurigo nodularis duration, n (%)		
≤6 mo	4 (6.3)	3 (4.8)
>6 to 12 mo	5 (7.8)	3 (4.8)
>1 to 5 y	25 (39.1)	23 (36.5)
>5 to 10 y	12 (18.8)	15 (23.8)
>10 y	18 (28.1)	19 (30.2)
Baseline VAS		
Average itch in past 24 h		
Mean (±SD)	7.88 (±1.31)	7.92 (±1.63)
Median	8.05	8.10
Minimum	4.0	1.4
Maximum	10.0	9.9
Average itch in past 48 h		
Mean (±SD)	7.99 (±1.34)	7.95 (±1.45)
Median	8.10	8.0
Minimum	2.0	2.4
Maximum	10.0	9.9
Average itch in past 72 h		
Mean (±SD)	8.11 (±1.35)	7.88 (±1.73)
Median	8.2	8.3
Minimum	2.0	1.3
Maximum	10.0	9.8
Worst itch NRS score, day 1		
N	48	48
Mean (±SD)	7.94 (±1.44)	8.48 (±1.29)
Median	8.0	8.5
Minimum	3.0	5.0
Maximum	10.0	10.0
Average itch NRS score, day 1		
N	48	48
Mean (±SD)	7.60 (±1.46)	7.65 (±1.67)
Median	8.0	8.0
Minimum	2.0	4.0
Maximum	10.0	10.0

NRS, Numeric rating scale; *SD*, standard deviation; *VAS*, visual analog scale.

The LS mean average itch VAS scores at weeks 2, 4, and 8 were 6.2 (SE, 0.29), 5.5 (SE, 0.33), and 4.4 (SE, 0.35), respectively, for serlopitant and 7.1 (SE, 0.29), 6.5 (SE, 0.35), and 6.1 (SE, 0.38), respectively, for placebo. At weeks 4 and 8, there was a statistically significant greater decrease from baseline in pruritus intensity (measured by average itch VAS score) with serlopitant versus with placebo, with an LS mean difference (improvement in serlopitant minus improvement in placebo) of −1.0 (95% confidence interval [CI], −1.8 to −0.1) (P = .025) at week 4 and −1.7 (95% CI, −2.6 to −0.7) (P < .001) at week 8. Reductions from baseline in pruritus intensity were observed as early as week 2 with serlopitant versus with placebo, with an LS mean difference of −0.9 (95% CI, −1.5 to −0.2) (P = .011). The mean percentage changes from baseline in mean average itch VAS score at weeks 2, 4, and 8 were −22.8%, −31.2%, and −48.3%, respectively, in the serlopitant group and −11.2%, −17.2%, and −26.3%, respectively, in the placebo group (Fig 1, *A*).

Subgroup analyses for change from baseline in average itch VAS score at week 8 demonstrated consistent reduction in itch score across the subgroups except for patients who had a baseline average itch VAS score greater than the median of 8.1 at week 8 (Fig 1, *B*). In patients with atopic diathesis, the LS mean difference between serlopitant and placebo for change from baseline in average itch VAS score at week 8 was −2.20 (95% CI, −3.45 to −0.95). The percentages of patients who were 4-cm responders for average itch VAS score at week 8 were 54.4% for serlopitant and 25.0% for placebo (P = .002); a similar trend was observed for 3-cm responder analysis (63.2% for serlopitant and 33.3% for placebo [P = .0013]).

Serlopitant provided greater reduction in pruritus across secondary measures than placebo (Fig 2). As with the average itch VAS scores, there was a significantly greater improvement in worst itch VAS score with serlopitant versus with placebo at week 8, with a mean difference in change from baseline of −1.6 (95% CI, −2.6 to −0.6) (P = .002). LS mean (SE) average itch NRS scores at weeks 2, 4, and 8 were 5.5 (SE, 0.26), 4.9 (SE, 0.29), and 4.1 (SE, 0.31), respectively, for serlopitant and 6.3 (SE, 0.27), 5.9 (SE, 0.30), and 5.4 (SE, 0.32), respectively, for placebo. There was a significantly greater decrease from baseline in average itch NRS scores in the serlopitant group at weeks 2, 4, and 8 compared with in the placebo group, with a mean difference of −0.9 (95% CI, −1.6 to −0.2) (P = .009) at week 2; −1.2 (95% CI, −1.9 to −0.4) (P = .004) at week 4; and −1.4 (95% CI, −2.3 to −0.4) (P = .007) at week 8 (Fig 2). The mean

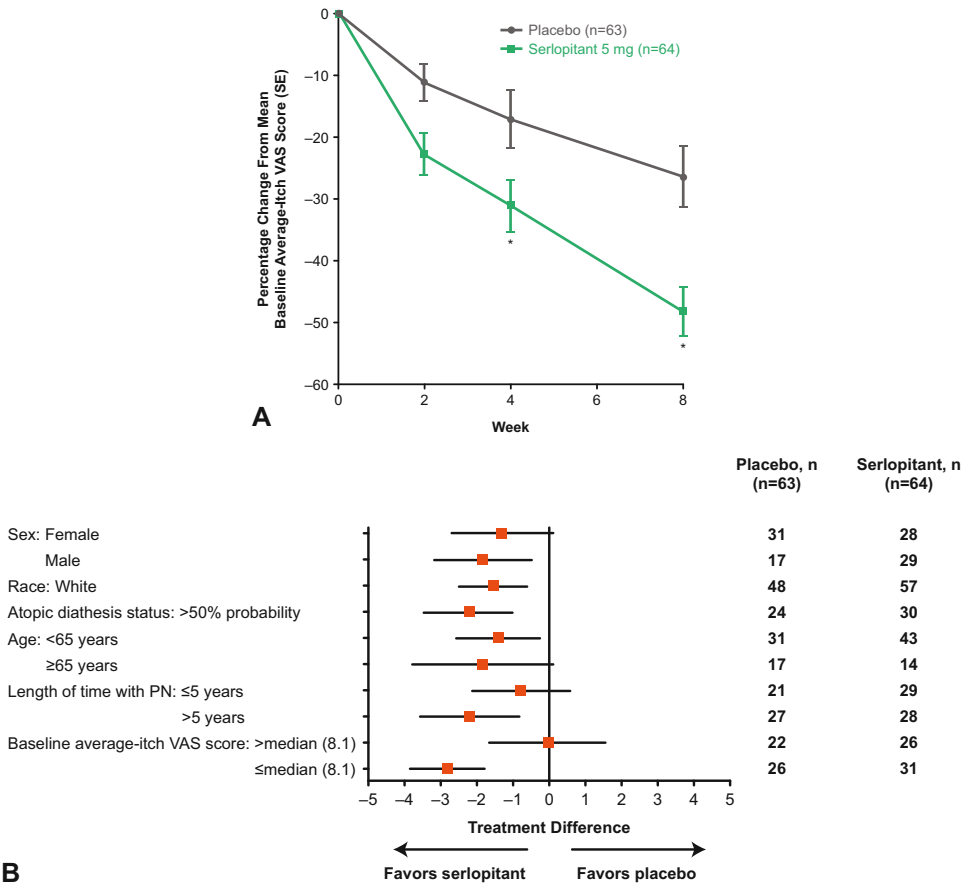

Fig 1. Changes from baseline over time. **A,** Percentage change from baseline in mean average itch visual analog scale (VAS) score at weeks 2, 4, and 8. Asterisks indicate $P < .05$ for the mean difference of serlopitant versus placebo. **B,** Forest plot of average intensity with standard error (SE) for average itch VAS score change from baseline at weeks 4 and 8, by subgroup (intention-to-treat population).

percentage changes from baseline in worst itch NRS score at weeks 2, 4, and 8 were −19.4%, −25.7%, and −37.2%, respectively, in the serlopitant group and −14.8%, −18.6%, and −26.4%, respectively, in the placebo group. At week 8, the percentages of patients who were 4-point responders for worst itch NRS score were 46.5% for serlopitant and 25.6% for placebo ($P = .045$).

Greater improvements in pruritus for serlopitant- versus placebo-treated patients were reported on the VRS (percentage of patients reporting no or mild pruritus at week 8: serlopitant 54.4% vs placebo 28.9% [$P = .006$]) and improvements in lesions on the IGA at week 8 (66.7% with serlopitant vs 40.4% with placebo [$P = .025$]). Both groups showed improvement on the prurigo activity score, but the serlopitant group appeared to show a proportionately greater level of improvement in percentage of healed excoriations of PN lesions from baseline to week 8 (for patients with ≤25% of lesions with excoriations at week 8, the percentages were 33.3% with serlopitant and 23.4% with placebo [$P = .093$]), though the differences were not significant. During the study, rescue medication was used by a lower percentage of serlopitant-treated (12.5%) than placebo-treated (19.0%) patients.

TEAEs were reported in 46 serlopitant-treated patients (71.9%) and 39 placebo-treated patients (61.9%). The most frequently reported TEAEs in the serlopitant group were nasopharyngitis (17.2%), diarrhea (10.9%), and fatigue (9.4%) (Table II). Most TEAEs were mild or moderate, and no deaths were reported. Severe TEAEs included atopic dermatitis, cough, depression, diarrhea, dizziness, fatigue, pruritus, and vertigo in the serlopitant group and pruritus, insomnia, and respiratory failure in the placebo group. TEAEs led to discontinuation in 9 patients (3 treated with serlopitant and 6 treated with placebo). Serious AEs were reported in 3 patients in the serlopitant group (vertigo and dizziness,

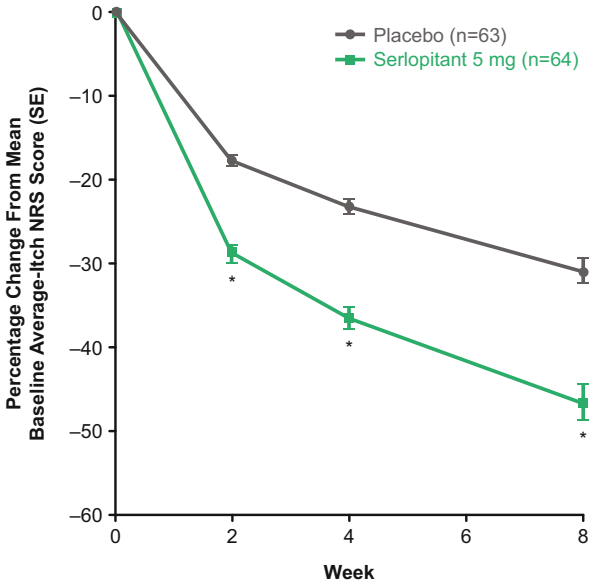

Fig 2. Changes from baseline over time. Percentage change from baseline in least squares mean average itch numeric rating scale (NRS) score at weeks 2, 4, and 8. Asterisk indicates $P \leq .05$ for the mean difference of serlopitant versus placebo. *SE*, Standard error.

depression, and actinic elastosis in 1 patient each) and 2 patients in the placebo group (bradycardia, syncope, and respiratory failure in 1 patient and neurodermatitis in 1 patient). There were no clinically relevant differences in laboratory parameters, electrocardiogram, or vital signs observed between treatment groups.

DISCUSSION

There is no approved therapy for pruritus in PN, and patients often experience pruritus that is refractory to commonly used treatments.[7,11,18,24] This trial investigated the safety, tolerability, and efficacy of the NK_1R antagonist serlopitant in the treatment of pruritus in PN.

In a prior proof-of-concept study, serlopitant was well tolerated and demonstrated superior reduction in chronic pruritus compared with placebo.[25] In the current study, serlopitant, 5 mg, was superior to placebo at weeks 4 and 8 for the reduction of pruritus, as measured by average itch VAS score. The minimal clinically important difference for measuring benefit in pruritus as rated on the VAS is a decrease of 3 cm.[26] Here, at week 8, a significantly greater proportion of patients in the serlopitant group than in the placebo group were 3-cm and 4-cm responders on the average itch VAS. Further, reductions in pruritus were observed as early as 2 weeks following serlopitant administration.

Table II. Common TEAEs in more than 1 patient in either treatment group

TEAE, n (%)	Serlopitant, 5 mg (n = 64)	Placebo (n = 63)
Any	46 (71.9)	39 (61.9)
Nasopharyngitis	11 (17.2)	2 (3.2)
Diarrhea	7 (10.9)	3 (4.8)
Fatigue	6 (9.4)	4 (6.3)
Dizziness	5 (7.8)	1 (1.6)
Headache	4 (6.3)	4 (6.3)
Edema peripheral	4 (6.3)	0
Pruritus	3 (4.7)	7 (11.1)
Hypertension	3 (4.7)	0
Vomiting	2 (3.1)	1 (1.6)
Bronchitis	2 (3.1)	0
Cough	2 (3.1)	1 (1.6)
Nausea	1 (1.6)	2 (3.2)
Urinary tract infection	0	4 (6.3)
Abdominal pain upper	0	2 (3.2)
Asymptomatic bacteriuria	0	2 (3.2)
Bradycardia	0	2 (3.2)
Eczema	0	2 (3.2)
Insomnia	0	2 (3.2)
Oral herpes	0	2 (3.2)

Counts reflect numbers of patients reporting 1 or more TEAEs that map to preferred terms from the Medical Dictionary for Regulatory Activities. A patient could be counted once only in each row of the table. Because only the most common TEAEs are shown in detail, counts do not sum to equal the number of reported as any TEAE.
TEAE, Treatment-emergent adverse event.

Subgroup analyses for change from baseline in average itch VAS score at week 8 confirmed the findings of the overall study population, except for patients with a baseline average itch VAS score greater than the median of 8.1. The lack of treatment effect observed in this subgroup may have been driven by an increased early withdrawal rate in the placebo group (7 patients) compared with in the serlopitant group (1 patient). Specifically, the increased rate of withdrawal of patients in the placebo group, which had the highest baseline average itch VAS scores, may have reduced the difference in average itch VAS scores between treatment groups. Notably, in patients with atopic diathesis, there was a numerically greater treatment effect at week 8 with serlopitant versus with placebo than was observed in the full study population. This is consistent with findings from a previously published case series of patients with atopic diathesis, in which treatment with aprepitant resulted in significant reductions in pruritus ($P < .01$).[19] Results from a of trial of tradipitant used to treat chronic atopic dermatitis showed significant improvement in worst itch VAS (secondary end point) but not in average itch VAS (primary end point) compared with placebo

(NCT02651714).[27] However, in a trial of serlopitant in patients with pruritus and a history of atopic dermatitis, the primary and secondary end points did not reach statistical significance (NCT02975206),[28] indicating that further exploration of the anti-inflammatory effects of NK_1R antagonists is needed.

The reduction in pruritus by serlopitant was demonstrated by multiple secondary pruritus measures, including the NRS and VRS. Healing of PN lesions is expected to require several months or longer,[1] necessitating a longer duration of treatment than in this 8-week trial. Accordingly, the course of PN as observed here did not improve significantly. Serlopitant-treated patients were less likely to use rescue medication than placebo-treated patients were. Overall, serlopitant was well tolerated among patients with treatment-refractory PN.

The primary limitation of this study is the 8-week treatment duration, which was not sufficient to determine whether the reductions in pruritus will lead to substantial, clinically relevant resolution of PN lesions. In addition, we could not compare the effects of serlopitant observed in this study with those of other treatments for PN, as randomized, controlled trials have not been performed. In an open-label, prospective study of 12 patients who received the antihistamines fexofenadine (240 mg twice daily) and montelukast (10 mg once daily) for 4 weeks, 75% of patients reported some improvement in pruritus and number of lesions; however, most of these improvements were deemed only slight.[29] An open-label trial of the opioid antagonist naltrexone (50 mg daily) in 17 patients with PN demonstrated a high antipruritic effect in 53% of patients.[30] A small (N = 4) case series of use of gabapentin (900 mg once daily) in patients with PN reported reductions in pruritus after about 3 to 4 months of treatment.[31] In an open-label, prospective study of 30 patients with PN, 76% had a response to pregabalin (75 mg once daily) after 3 months, defined as disappearance of pruritus and reduction of nodules.[32] Nevertheless, without randomized, controlled trials, the efficacy of these interventions can be considered only anecdotal.

In conclusion, serlopitant has potential as a therapeutic option for the treatment of pruritus in patients with treatment-refractory PN. The results from this randomized, controlled study support its continued evaluation in this patient population.

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REFERENCES

1. Pereira MP, Steinke S, Zeidler C, et al. European Academy of Dermatology and Venereology European Prurigo Project: expert consensus on the definition, classification and terminology of chronic prurigo. *J Eur Acad Dermatol Venereol*. 2018; 32:1059-1065.
2. Zeidler C, Ständer S. The pathogenesis of prurigo nodularis—'super-itch' in exploration. *Eur J Pain*. 2016;20:37-40.
3. Fostini AC, Girolomoni G, Tessari G. Prurigo nodularis: an update on etiopathogenesis and therapy. *J Dermatolog Treat*. 2013;24:458-462.
4. Iking A, Grundmann S, Chatzigeorgakidis E, Phan NQ, Klein D, Ständer S. Prurigo as a symptom of atopic and non-atopic diseases: aetiological survey in a consecutive cohort of 108 patients. *J Eur Acad Dermatol Venereol*. 2013; 27:550-557.
5. Wallengren J. Prurigo: diagnosis and management. *Am J Clin Dermatol*. 2004;5:85-95.
6. Tan WS, Tey HL. Extensive prurigo nodularis: characterization and etiology. *Dermatology*. 2014;228:276-280.
7. Saco M, Cohen G. Prurigo nodularis: picking the right treatment. *J Fam Pract*. 2015;64:221-226.
8. Lee MR, Shumack S. Prurigo nodularis: a review. *Australas J Dermatol*. 2005;46:211-218.
9. Ständer S, Weisshaar E, Mettang T, et al. Clinical classification of itch: a position paper of the International Forum for the Study of Itch. *Acta Derm Venereol*. 2007;87:291-294.
10. Ständer S, Pogatzki-Zahn E, Stumpf A, et al. Facing the challenges of chronic pruritus: a report from a multidisciplinary medical itch centre in Germany. *Acta Derm Venereol*. 2015;95:266-271.
11. Yosipovitch G, Bernhard JD. Clinical practice. Chronic pruritus. *N Engl J Med*. 2013;368:1625-1634.
12. Sanders KM, Nattkemper LA, Yosipovitch G. Advances in understanding itching and scratching: a new era of targeted treatments. *F1000Res*. 2016;5.
13. Steinhoff M, Bienenstock J, Schmelz M, Maurer M, Wei E, Biro T. Neurophysiological, neuroimmunological, and neuroendocrine basis of pruritus. *J Invest Dermatol*. 2006;126:1705-1718.
14. Andoh T, Nagasawa T, Satoh M, Kuraishi Y. Substance P induction of itch-associated response mediated by cutaneous NK1 tachykinin receptors in mice. *J Pharmacol Exp Ther*. 1998; 286:1140-1145.
15. Steinhoff MS, von Mentzer B, Geppetti P, Pothoulakis C, Bunnett NW. Tachykinins and their receptors: contributions to physiological control and the mechanisms of disease. *Physiol Rev*. 2014;94:265-301.
16. Haas S, Capellino S, Phan NQ, et al. Low density of sympathetic nerve fibers relative to substance P-positive nerve fibers in lesional skin of chronic pruritus and prurigo nodularis. *J Dermatol Sci*. 2010;58:193-197.
17. Ohanyan T, Schoepke N, Eirefelt S, et al. Role of substance P and its receptor neurokinin 1 in chronic prurigo: a randomized, proof-of-concept, controlled trial with topical aprepitant. *Acta Derm Venereol*. 2018;98(1):26-31.
18. Stull C, Lavery MJ, Yosipovitch G. Advances in therapeutic strategies for the treatment of pruritus. *Expert Opin Pharmacother*. 2016;17(5):671-687.

19. Ständer S, Siepmann D, Herrgott I, Sunderkotter C, Luger TA. Targeting the neurokinin receptor 1 with aprepitant: a novel antipruritic strategy. *PLoS One*. 2010;5:e10968.
20. Mir O, Coriat R. Aprepitant for pruritus: drug-drug interactions matter. *Lancet Oncol*. 2012;13:964-965.
21. Merck & Co. Inc. *EMEND® (aprepitant) capsules*. Whitehouse Station, NJ: US FDA Label; 2003.
22. Frenkl TL, Zhu H, Reiss T, Seltzer O, Rosenberg E, Green S. A multicenter, double-blind, randomized, placebo controlled trial of a neurokinin-1 receptor antagonist for overactive bladder. *J Urol*. 2010;184:616-622.
23. Gernart M, Tsianakas A, Zeidler C, et al. ItchApp: an app-based eDiary for assessment of chronic pruritus in clinical trials. *Acta Derm Venereol*. 2017;97:601-606.
24. Tsianakas A, Zeidler C, Ständer S. Prurigo nodularis management. *Curr Probl Dermatol*. 2016;50:94-101.
25. Yosipovitch G, Ständer S, Kerby MB, et al. Serlopitant for the treatment of chronic pruritus: results of a randomized, multicenter, placebo-controlled phase 2 clinical trial. *J Am Acad Dermatol*. 2018;78:882-891.e810.
26. Reich A, Riepe C, Anastasiadou Z, et al. Itch assessment with visual analogue scale and numerical rating scale: determination of minimal clinically important difference in chronic itch. *Acta Derm Venereol*. 2016;96:978-980.
27. Heitman AM, Xiao C, McKee SE, et al. *Tradipitant improves worst itch and disease severity in patients with atopic dermatitis*. Utrech, The Netherlands: International Symposium on Atopic Dermatitis; 2018:P067.
28. Menlo Therapeutics Inc. Menlo Therapeutics announces results from a phase 2 trial of serlopitant for pruritus associated with atopic dermatitis Available at: https://globenewswire.com/news-release/2018/04/08/1466633/0/en/Menlo-Therapeutics-Announces-Results-from-a-Phase-2-Trial-of-Serlopitant-for-Pruritus-Associated-with-Atopic-Dermatitis.html. Accessed October 12, 2018.
29. Shintani T, Ohata C, Koga H, et al. Combination therapy of fexofenadine and montelukast is effective in prurigo nodularis and pemphigoid nodularis. *Dermatol Ther*. 2014;27:135-139.
30. Metze D, Reimann S, Beissert S, Luger T. Efficacy and safety of naltrexone, an oral opiate receptor antagonist, in the treatment of pruritus in internal and dermatological diseases. *J Am Acad Dermatol*. 1999;41:533-539.
31. Gencoglan G, Inanir I, Gunduz K. Therapeutic hotline: Treatment of prurigo nodularis and lichen simplex chronicus with gabapentin. *Dermatol Ther*. 2010;23:194-198.
32. Mazza M, Guerriero G, Marano G, Janiri L, Bria P, Mazza S. Treatment of prurigo nodularis with pregabalin. *J Clin Pharm Ther*. 2013;38:16-18.