



ORIGINAL ARTICLE

Nemolizumab efficacy in prurigo nodularis: onset of action on itch and sleep disturbances

S. Ständer,^{1,*} G. Yosipovitch,² J.-P. Lacour,³ F.J. Legat,⁴ C. Paul,⁵ A. Reich,⁶  K. Chaouche,⁷ F. Ahmad,⁸ C. Pickett⁷ 

¹Department of Dermatology and Center for Chronic Pruritus, University Hospital Münster, Münster, Germany

²Itch Center, Dr Phillip Frost Department of Dermatology and Cutaneous Surgery, University of Miami Hospital, Miami, FL, USA

³Department of Dermatology, Medical University of Nice, Nice, France

⁴Department of Dermatology and Venereology, Medical University of Graz, Graz, Austria

⁵Department of Dermatology, Medical University of Toulouse, Toulouse, France

⁶Department of Dermatology, University of Rzeszow, Rzeszow, Poland

⁷Galderma R&D, Lausanne, Switzerland

⁸Galderma Laboratories LP, Fort Worth, Texas, USA

*Correspondence: S. Ständer. E-mail: sonja.staender@ukmuenster.de

Abstract

Background Patients with prurigo nodularis (PN) have multiple itchy nodules, impaired quality of life and sleep deprivation. Prurigo nodularis patients have a high burden of disease, primarily due to the intensity of the itch. It is reasonable to expect that rapid relief of itch – and associated improvement of sleep – are highly valued clinical outcomes for patients. Nemolizumab is an IL-31A-receptor inhibitor that modulates the neuroimmune response with reported positive efficacy and safety data in a phase 2 study of PN.

Objectives To evaluate the onset of action of nemolizumab on itch and sleep disturbances.

Methods *Post hoc* analysis of a phase 2 trial of nemolizumab 0.5 mg/kg SC vs. placebo in patients ($n = 70$) with moderate-to-severe PN (≥ 20 nodules) and severe pruritus (NRS ≥ 7). Time to significant reduction was assessed for peak pruritus (PP) and sleep disturbance (SD) using numerical rating scales (NRS), also assessed was scratching time during sleep.

Results Nemolizumab significantly reduced itch vs. placebo within 48 h (PP NRS -19.5% vs. -5.8% , respectively, $P = 0.014$). Significant difference between nemolizumab and placebo in reducing itch by ≥ 4 on PP NRS was achieved at Day 3 (23.5% vs. 0% , $P < 0.001$). A significant difference in SD NRS was reported by Day 4 (-24.0% vs. -4.3% placebo, $P = 0.012$). In addition, there was a separation between groups in SD responders (decrease of ≥ 4 points) in favour of nemolizumab by Day 2 (8.8% vs. 0% , $P = 0.037$). Sleep continued improving through Week 4, when there was a -56.0% reduction in SD NRS vs. -22.9% placebo ($P < 0.001$). Actigraphy data showed improvement in scratch/sleep duration for nemolizumab vs. placebo, respectively, by Week 1 (-32.15 vs. $+28.15$ min/h, $P = 0.001$).

Conclusion Nemolizumab has a rapid and robust onset of action in PN with itch reduction and improvement of sleep within 48 h.

Received: 17 December 2021; Accepted: 2 June 2022

Conflict of interest

Pr Ständer has served as a member of an advisory board and/or received consulting fees from Ammiral, Bayer, Beiersdorf, Bellus, Bionorica, Cara, Therapeutics, Celgene, Clexio, DS Biopharma, Galderma, Menlo Therapeutics, Novartis, Perrigo and Trevi Therapeutics and has served as an investigator for Dermalence, Galderma, Kiniksa, Menlo Therapeutics, Novartis, Sanofi, Trevi Therapeutics and Vanda Therapeutics; Dr Yosipovitch has served as an advisory board member, investigator and/or received consulting fees from Galderma, Pfizer, Sanofi Regeneron, Novartis, Eli Lilly, Kiniksa, Vellus and Cell Dex; Pr Lacour has served as an advisor or consultant for Eli Lilly and Sanofi and as an investigator and consultant for Galderma; Pr Legat is/was an investigator for DS Biopharma, Eli Lilly, Galderma, Pfizer, Menlo Therapeutics, Trevi Therapeutics, a consultant for Galderma and a member of advisory boards and/or has received speaker honoraria/travel fees from AbbVie, Ammiral, Celgene, Eli Lilly, Janssen, Leo Pharma, Menlo Therapeutics, Novartis, Pfizer, Trevi Therapeutics and Vifor Fresenius Medical Care Renal Pharma; Pr Paul has received grants and has been a consultant for Ammiral, Amgen, AbbVie, Bristol Myers Squibb, Boehringer, Celgene, Eli Lilly, Janssen, Leo Pharma, Merck, Mylan, Novartis, Pfizer, Pierre Fabre, Sanofi and UCB Pharma and has been an investigator for Eli Lilly, Leo Pharma,

Pierre Fabre, Regeneron and Sanofi; Pr Reich has served as an investigator for AbbVie, Drug Delivery Solutions Ltd, Genentech, Janssen-Cilag, Kymab Ltd, Leo Pharma, Menlo Therapeutics, MetrioPharmAG, Merck Sharp and Dohme, Novartis, Pfizer and Trevi Therapeutics and has received consulting fees and/or honoraria from AbbVie, Bioderma, Celgene, Chema-Elektronet, Eli Lilly, Galderma, Janssen-Cilag, Leo Pharma, Medac, Menlo Therapeutics, Novartis, Pierre Fabre, Sandoz and Trevi Therapeutics; Dr Chaouche, Mr Ahmad and Dr Piketty are employees of Galderma.

Funding sources

This study was sponsored by Galderma R&D, Entre-deux-villes, Switzerland.

Introduction

Patients with chronic prurigo nodularis (PN) have intensely itchy nodular lesions that result in markedly impaired quality of life and sleep deprivation.^{1–3} While the pathophysiology of the disease is not well understood, itch-scratch in this disease is likely due to neuroimmune dysregulation.^{1,4,5} The disease burden of PN is quite substantial, with significant reduction in quality of life and sleep quality.^{6,7} In a population of 1128 patients with PN, Zeidler *et al.*⁸ reported disease was present for a median duration of 2.9 years and that more than 90% of patients scratch their skin, despite most being aware that this exacerbated their disease. In addition, PN has been associated with long median length of hospital stay and higher cost of care compared with patients without PN. Treatment of PN is very challenging, as there are presently no FDA-approved therapies and the limited understanding of pathophysiology has translated to a lack of effective agents.^{5,9,10} Currently, PN represents a high unmet medical need, since although multiple topical and systemic agents have been employed, they have had only limited efficacy.^{7,11} To our knowledge, there has not yet been a patient survey to define the impact of rapid relief of PN symptoms on their perceived burden of disease. However, recent data reported by patients have shown that itch causes the highest burden of chronic nodular prurigo, and hence, it is plausible to assume that relieving itch in the fastest possible manner is an important treatment goal for patients with PN. Furthermore, in terms of daily function, relief of itch is likely to translate to less sleep disturbance and enhance overall quality of life.

Nemolizumab, an interleukin (IL)-31-receptor inhibitor, rapidly and profoundly modulates neuroimmune responses.⁸ In 2020, Ständer *et al.* reported results of a randomized, controlled phase 2 trial data of nemolizumab in PN, with positive findings on all primary and secondary outcomes.⁹ In this trial, nemolizumab reduced itch on the peak pruritus numeric rating scale (PP NRS) from 8.4 to 3.9 (–53.0%) at Week 4 (primary endpoint), in comparison, itch changed from 8.4 at baseline to 6.7 (–20.2%) in the placebo group (difference between groups –32.8 percentage points, $P < 0.001$).⁹ The effect of nemolizumab on controlling prurigo nodules was apparent in that 23% of patients achieved clear/almost clear skin at Week 12 compared with just 4% of placebo patients ($P = 0.001$). Sleep disturbance

NRS was 7.4 (nemolizumab) and 6.8 (placebo) at baseline and was improved by 56.4% at Week 4 in the nemolizumab group vs. 26.6% in the placebo group ($\Delta 33.1$, $P < 0.001$).⁹ Nemolizumab therapy resolved PN lesions with a mean reduction from 17.1 to 7.6 nodules at Week 12, vs. a change of 22.4 to 13.2 in the placebo group. Finally, 75% healing of nodules was observed in 32.4% of nemolizumab patients compared with 8.4% of placebo patients. Nemolizumab is currently being assessed in phase 3 trials for PN.¹⁰ This secondary analysis of the phase 2 study data was conducted to determine time to significant onset of action in regard to itch and sleep deprivation, two primary complaints in patients suffering from PN and to report some additional endpoints which have not been published yet.

Methods

Study design

Nemolizumab was studied in a 12-week phase 2 randomized, double-blind, placebo-controlled trial of PN with results previously published (Ständer *et al.*, *N Engl J Med* 2020; NCT03181503).¹² [Correction added on 10 July 2022, after first online publication: Reference 9 citation was incorrect and was replaced with Ständer S, Yosipovitch G, Legat FJ, et al. Trial of nemolizumab in moderate-to-severe prurigo nodularis. *N Engl J Med.* 2020; 382:706–716.] Patients had moderate-to-severe PN (lesions on upper limbs and ≥ 20 nodules on the body) and severe pruritus (PP NRS ≥ 7 over the previous week, scale 0–10). Nemolizumab was administered in a dose of 0.5 mg/kg SC at baseline, Week 4 and Week 8. In addition to the primary and secondary outcomes described by Ständer *et al.*, patients were instructed to wear an actigraphy device (GeneActiv, Philips Respironics, Murrysville, PA, United States) on both wrists from 1 week before baseline visit and every day and night during the first 4 weeks to evaluate sleep quality and scratching events during the night.¹¹

In this *post hoc* analysis, time to onset of action was assessed using daily records of peak pruritus numerical rating scale (PP NRS) and the proportion of pruritus responders, defined as reduction in PP NRS by ≥ 4 points. Daily sleep disturbance (SD) was assessed using recorded values on the SD NRS, scale 0–10. SD NRS was selected because it is simple to use, readily

understood by patients, and has been validated as a sleep assessment, including in adolescents and adults with moderate-to-severe atopic dermatitis.¹³ Patients recorded pruritus and sleep disturbance daily at home. In addition, onset of changes in itch and sleep were analysed in subgroups according to several baseline characteristics: presence of atopic background (yes or no), IGA 3 vs. 4, baseline PP NRS (<8 vs. ≥8) and lesion counts (20–100 vs. >100). Changes in scratching time during sleep (ratio of scratch duration vs. sleep duration in min/h) as captured by actigraphy data were also analysed.

Statistical analysis

All efficacy analyses were performed using the intent-to-treat (ITT) population, which included all the patients who underwent randomization. Analysis of the percentage change from baseline in daily peak NRS scores for pruritus and sleep were analysed using mixed model for repeated measure (MMRM), with baseline value as covariate and treatment group, baseline

IGA severity, timepoint and interactions of treatment-by-timepoint and IGA-by-timepoint as fixed effects. Actigraphy data were analysed using a Wilcoxon sample rank-sum test. Relationship between variables were presented using Pearson correlation coefficient.

Results

A total of 70 patients participated (nemolizumab *n* = 34, placebo *n* = 36) and the groups were comparable in baseline demographics and disease characteristics. Approximately 60% in both groups had 20–100 nodules, while the remainder had >100 nodules; baseline PP NRS was 8.4 in both groups.⁹

Onset of action for itch relief

Analysis of daily PP NRS scores demonstrated nemolizumab had a rapid onset of action (Fig. 1). Within 48 h, reduction in itch in patients treated with nemolizumab was significantly greater than in patients receiving placebo (PP NRS –19.5% vs. –5.8%,

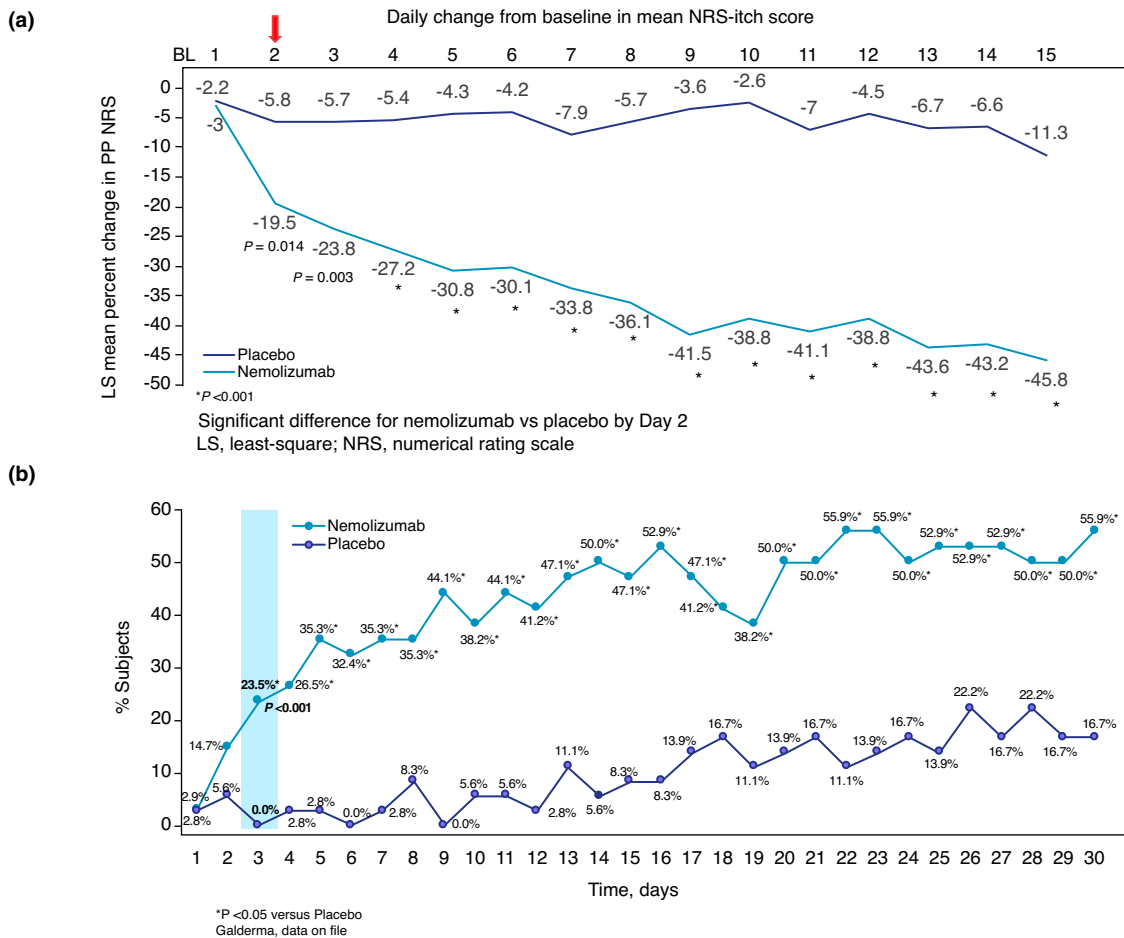


Figure 1 Mean daily reduction in PP NRS, Days 1–15 and responders (improvement in PP NRS ≥ 4), Days 1–30.

respectively, $P = 0.014$). A significant difference between nemolizumab and placebo in the proportion of patients meeting clinical response criteria for itch (a reduction of PP NRS ≥ 4) was achieved at Day 3 (23.5% vs. 0%, $P < 0.001$). 52.9% of nemolizumab patients achieved this itch response criterium at week 12 compared with 8.3% of the placebo patients ($P = 0.001$).

Effect of baseline characteristics on onset of itch relief The onset of itch relief was slightly slower in patients with a background of atopy; at Days 1–2 those without background atopy had a LSmean reduction in PP NRS of -11.8 , while those with atopic history had a reduction of -4.0 . However, by Days 3–4, the groups were comparable, with reductions of -27.0 for those without atopy and -23.9 for those with. Comparison of itch reduction in those with IGA 3 or 4 severity of PN at baseline also revealed differences in onset: There was a -16.7 reduction in

IGA 3 patients vs. -5.3 in IGA 4 patients at Days 1–2. Overall, there was less reduction in itch in the IGA 4 group vs. the IGA 3 group for the first 30 days. Similarly, there was numerically less reduction in itch for patients with baseline PP NRS higher than the median (≥ 8) compared with those who had lower baseline PP NRS (7 to <8). When comparing subgroups by baseline lesion count, onset of itch relief was more rapid in those who had 20–100 lesions initially vs. those with >100 lesions; however, itch reduction became comparable regardless of baseline lesion counts by Days 5–6.

Onset of action for sleep improvement

Improvements in itch translated into better sleep, and a significant difference in SD NRS was reported by Day 4 (-19.8% vs. -4.3% with placebo, $P = 0.012$; Fig. 2). In addition, there was a separation between groups in SD responders (defined as a

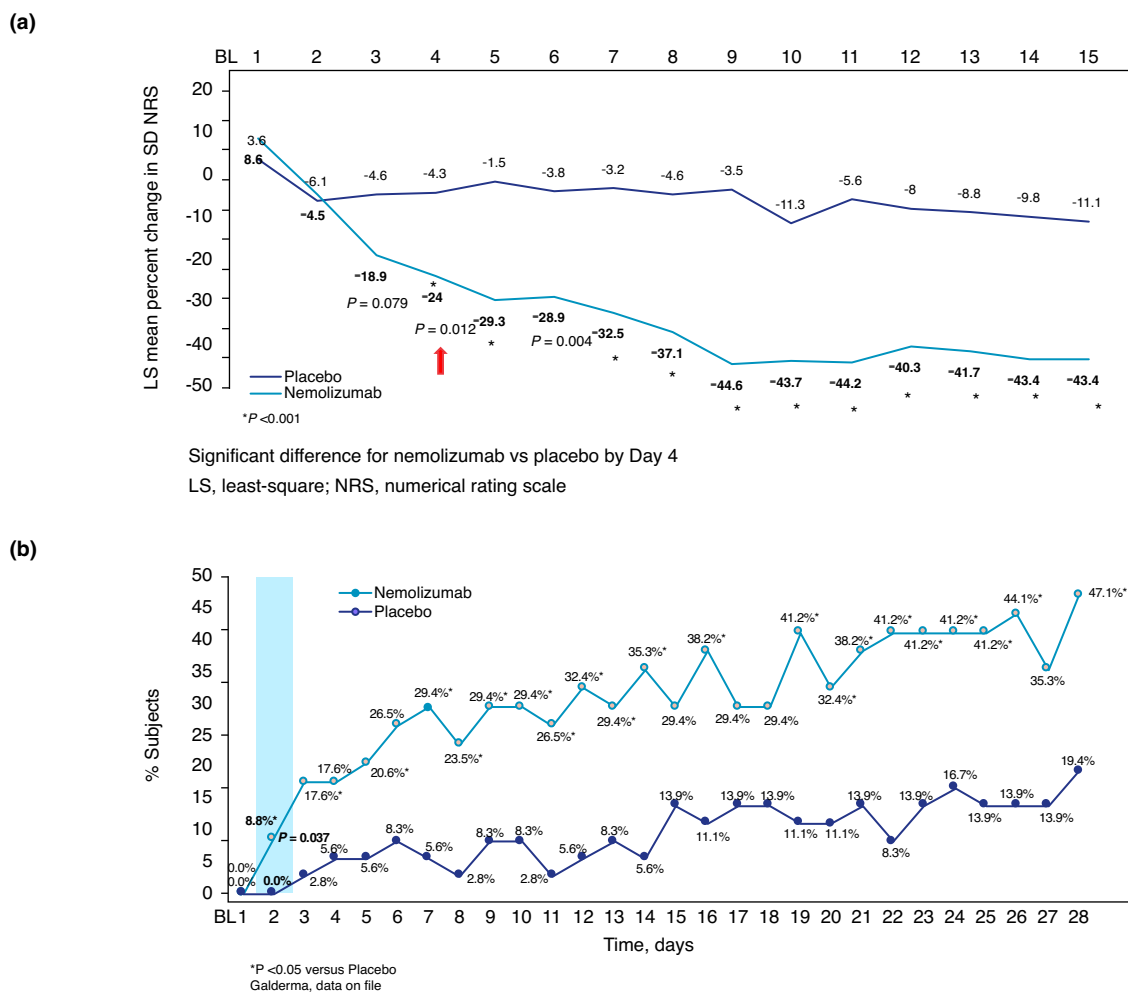


Figure 2 Mean daily reduction in sleep disturbance NRS, Days 1–15 (top) and percent of patients responding (improvement in SD NRS ≥ 4), Days 1–30. [Correction added on 10 July 2022, after first online publication: In Figure 2, the heading was removed and the legend below Figure 2a was updated.]

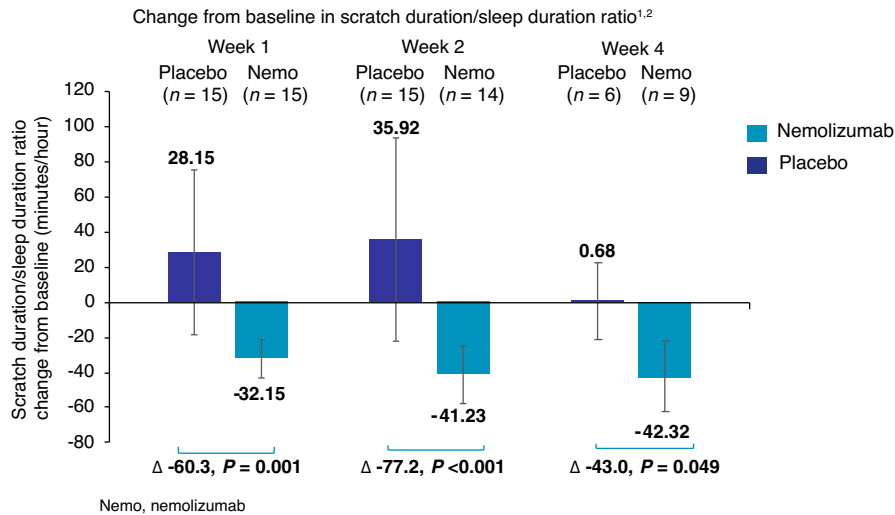


Figure 3 Prurigo nodularis. Actigraphy data showing change from baseline in scratch/sleep duration for nemozoliumab and placebo.

reduction of ≥ 4 points on SD NRS) in favour of nemozoliumab by Day 2 (8.8% vs. 0%, $P = 0.037$).

As shown in Fig. 3, actigraphy data showed significant differences in scratch/sleep duration for nemozoliumab vs. placebo, respectively, at Week 1 (-32.15 vs. 28.15 min/h, $\Delta -60.3$, $P = 0.001$), Week 2 (-41.23 vs. 35.92 , $\Delta -77.2$, $P < 0.001$) and Week 4 (-42.32 vs. 0.68 , $\Delta -43.0$, $P = 0.049$).

Discussion

As summarized here, nemozoliumab therapy was associated with rapid effects on itch and sleep disturbance significantly differing from placebo within 2 days. In addition, the efficacy on pruritus both in magnitude of effect and onset of action was similar across the atopic and non-atopic subjects; however, no definitive conclusion about the impact of an atopic background may be made due to small sample size. Furthermore, it is notable that pruritus efficacy in PN is comparable to that seen in atopic dermatitis patients, when evaluating the 30 mg (which is similar to 0.5 mg/kg) dosage in the Phase 2b study reported by Silverberg *et al.*¹⁴ The onset of effects of treatments on itch and sleep in PN is not well studied. Chiricozzi *et al.*¹⁵ described a retrospective analysis of adults with PN who were treated with dupilumab (not approved for treatment of PN) for at least 16 weeks; PP NRS was reduced by 29.2% and SD NRS by 32.9% at Week 4, the earliest reported timepoint. Husein-ELAhmed *et al.*¹⁶ searched electronic databases to determine potential response predictors and time until patient perception of improvement with dupilumab. In this retrospective data analysis, 2-month therapy was needed before patients perceived significant itch relief.¹⁶ These authors also noted that a longer treatment period

may be needed before patients with PN get relief from itch.¹⁶ Gröndel *et al.*⁷ confirmed these results and showed that patients with PN need significantly longer therapy for relief compared with patients with chronic pruritus, when using the guideline-recommended, non-approved therapies. Finally, Chiricozzi *et al.* reported that complete remission of PN was rare before 4 months in dupilumab-treated patients.¹⁶ In a serlopitant phase 2 study ($n = 128$), itch visual analogue score (VAS) was significantly reduced at Weeks 4 and 8, with a statistically significant difference from placebo at Week 2 ($P = 0.011$); changes in sleep were not reported.¹⁷

In our clinical experience, the rapid onset of action of nemozoliumab is remarkable and cannot be fully explained by a pure anti-inflammatory effect. By blocking the biologic activity of IL-31, nemozoliumab likely inhibits pro-inflammatory and fibrotic processes associated with nodule formation and itching while also exerting a direct dampening effect on the stimulation of dorsal root ganglia of sensory neurons.¹⁸ This direct inhibitory effect on the IL-31 induced sensory nerve stimulation may be accountable for the rapid onset of the effects on itch and sleep. Thus, it is thought that IL-31 has an important role in the neuroimmune dysregulation that characterizes PN pathogenesis and the detrimental itch-scratch cycle associated with PN.⁵

Study limitations include the relatively small sample size (however, it should be noted that PN is a relatively rare diagnosis), and *post hoc* analyses may lead to inflation of type I errors. Nonetheless, subgroup analyses can be very helpful in generating future hypotheses and establishing the potential clinical benefits/risks of nemozoliumab. Readers are advised to interpret the

results in the light of study limitations. Results of an ongoing phase 3 study are anticipated soon and will help define the potential role of nemolizumab in PN.

Conclusions

Nemolizumab has a rapid onset of action in modulating neuroimmune response to block itch signalling and alleviate sensory itch and sleep disturbances within 48 h.

Acknowledgements

The authors wish to thank Valerie Sanders, of Sanders Medical Writing and Galderma for providing editorial assistance.

Data availability statement

Data will be made available on reasonable request.

References

- 1 Whang KA, Mahadevan V, Bakhshi PR *et al.* Prevalence of prurigo nodularis in the United States. *J Allergy Clin Immunol Pract* 2020; **8**: 3240–3241.
- 2 Brenaut E, Halvorsen JA, Dalgard FJ *et al.* The self-assessed psychological comorbidities of prurigo in European patients: a multicentre study in 13 countries. *J Eur Acad Dermatol Venereol* 2019; **33**: 157–162.
- 3 Ständer HF, Elmariah S, Zeidler C *et al.* Diagnostic and treatment algorithm for chronic nodular prurigo. *J Am Acad Dermatol* 2020; **82**: 460–468.
- 4 Kowalski EH, Kneiber D, Valdebran M, Patel U, Amber KT. Treatment-resistant prurigo nodularis: challenges and solutions. *Clin Cosmet Investig Dermatol* 2019; **12**: 163–172.
- 5 Williams KA, Roh YS, Brown I *et al.* Pathophysiology, diagnosis, and pharmacological treatment of prurigo nodularis. *Exp Rev Clin Pharmacol* 2021; **14**: 67–77.
- 6 Zeidler C, Pereira MP, Dugas M *et al.* The burden in chronic prurigo: patients with chronic prurigo suffer more than patients with chronic pruritus on non-lesional skin: a comparative, retrospective, explorative statistical analysis of 4,484 patients in a real-world cohort. *J Eur Acad Dermatol Venereol* 2021; **35**: 738–743.
- 7 Gründel S, Pereira MP, Storck M *et al.* Analysis of 325 patients with chronic nodular prurigo: clinics, burden of disease and course of treatment. *Acta Derm Venereol* 2020; **100**: adv00269.
- 8 Zeidler C, Pereira MP, Stander S. Chronic prurigo: similar clinical profile and burden across clinical phenotypes. *Front Med* 2021; **8**: 649332.
- 9 Whang KA, Kang S, Kwatra SG. Inpatient burden of prurigo nodularis in the United States. *Medicines* 2019; **6**: 88.
- 10 Maredia H, Kwatra SG. Emerging novel therapeutic agents for the treatment of patients with prurigo nodularis. *J Dermatol Treat* 2020; **32**: 741–744.
- 11 Ständer S, Pereira MP, Berger T *et al.* IFSI-guideline on chronic prurigo including prurigo nodularis. *Itch* 2020; **5**: 42.
- 12 Ständer S, Yosipovitch G, Legat FJ *et al.* Trial of nemolizumab in moderate-to-severe prurigo nodularis. *N Engl J Med.* 2020; **382**: 706–716.
- 13 Puelles J, Fofana F, Rodriguez D *et al.* Psychometric validation and responder definition of the sleep disturbance numerical rating scale in moderate-to-severe atopic dermatitis. *Br J Dermatol* 2022; **186**: 285–294.
- 14 Silverberg JI, Pinter A, Pulka G *et al.* Phase 2B randomized study of nemolizumab in adults with moderate-to-severe atopic dermatitis and severe pruritus. *J Allergy Clin Immunol* 2020; **145**: 173–182.
- 15 Chiricozzi A, Maurelli M, Gori N *et al.* Dupilumab improves clinical manifestations, symptoms, and quality of life in adult patients with chronic nodular prurigo. *J Am Acad Dermatol* 2020; **83**: 39–45.
- 16 Husein-ElAhmed H, Steinhoff M. Dupilumab in prurigo nodularis: a systematic review of current evidence and analysis of predictive factors to response. *J Dermatol Treat* 2020; **33**: 1547–1553.
- 17 Stander S, Kwon P, Hirman J *et al.* Serlopitant reduced pruritus in patients with prurigo nodularis in a phase 2, randomized, placebo-controlled trial. *J Am Acad Dermatol* 2019; **80**: 1395–1402.
- 18 Nemmer JM, Kuchner M, Datsi A *et al.* Interleukin-31 signaling bridges the gap between immune cells, the nervous system and epithelial tissues. *Front Med* 2021; **8**: 639097.