Dear Editors,

The anti-interleukin 4 receptor alpha antibody, dupilumab, was recently approved for the treatment of atopic dermatitis (AD) and severe bronchial asthma. In clinical trials, dupilumab significantly improved adult and adolescent AD. Over 80% of patients treated with 300 mg dupilumab every other week (EOW) achieved an improvement of the Eczema Area and Severity Index by 50% or more within 12–16 weeks [1, 2].

We report on an 80-year old female patient who presented with a highly pruritic erythematous rash and dry skin on the entire integument. She reported intensive itching with 10/10 on a numerical rating scale (NRS) and no previous signs or symptoms of AD. After a full medical examination (including extensive laboratory parameters, sonography of the abdomen, skin biopsies and chest x-ray) no conclusive diagnosis was reached. Based on clinical signs and symptoms with high total IgE levels and an elevated value of the Erlangen atopy score (9) the patient was diagnosed with late onset AD. Treatment with very potent topical corticosteroids (0.5 mg/g clobetasol propionate), narrow band UVB irradiation and oral antihistamines was initiated. This led to a significant improvement of her condition, but this relapsed rapidly after switching to topical betamethasone and withdrawal of phototherapy. During follow-up, she developed extremely itchy erythematous papules/nodules disseminated over the entire integument (Figure 1a). Based on this clinical

**Figure 1** Clinical improvement of prurigo nodularis treated with dupilumab. The patient presented with multiple red nodules, most of which were excoriated. Nodules were present on the entire body. At that time the patient was treated with prednicarbate ointment for prurigo nodularis. Despite various treatments, her skin condition did not improve. After one year, dupilumab was started as off-label treatment. Thereafter, her skin condition improved (middle photograph), and under continued dupilumab treatment, the clinical response was maintained (right photograph) (a). Hematoxylin-eosin stained skin biopsy showed hyperparakeratosis, hypergranulosis and acanthosis with occasional spongiosis as well as mixed inflammatory infiltrate with a few eosinophil granulocytes, consistent with chronic prurigoform eczema (b).
presentation and a skin biopsy (Figure 1b), we diagnosed prurigo nodularis.

We initiated several treatments of the prurigo nodularis: narrow band UVB phototherapy with a cumulative dosage of 12.59 J/cm², antihistamines and topical superpotent corticosteroids (Figure 2), all of which failed to produce sustained relief. Treatment was therefore switched to topical corticosteroids of various potencies and classes (clobetasol propionate 0.5 mg/g; mometasone furoate 1 mg/g; betamethasone valerate 1.2 mg/g; prednicarbate 2.5 mg/g), topical calcineurin inhibitors (pimecrolimus 10 mg/g; tacrolimus 1 mg/g), creams/ointments containing polidocanol 30 mg/g, three different first and second generation antihistamines (hydroxyzine 2.5 mg/d, cetirizine 60 mg/d, desloratadine 20 mg/d), two antidepressants (mirtazapine 15 mg/d, paroxetine 20 mg/d), gabapentin up to 900 mg/d, cyclosporine 300 mg/d, methotrexate 10 mg/week, oral prednisolone 40 mg/d, 7 cycles of naloxone i.v. 1.2 mg/cycle, naltrexone 25 mg/d, and PUVA with a cumulative dosage of 4.25 J/cm² (Figure 2). All therapies were administered for a sufficiently long time (indicated in Figure 2) and did not result in any significant improvement of the itching or clinical findings.

The lesions persisted and the patient was additionally diagnosed with chronic lymphocytic leukemia (CLL). The CLL was treated with rituximab and bendamustine, which led to remission of CLL, but had no impact on the prurigo nodularis. In addition, two years after the initial presentation, an intraductal papillary mucinous neoplasm was detected in the pancreas while the patient was taking 100 mg cyclosporine A for prurigo nodularis. Thus, all immunosuppressive treatment was stopped. The intraductal papillary mucinous neoplasm progressed further, necessitating surgery that was scheduled one year later.

Due to the lack of efficacy of the previous treatments and the need to stop immunosuppression because of the intraductal papillary mucinous neoplasm, we decided to treat the patient with dupilumab, which was administered in an initial dose of 600 mg s.c. and then 300 mg EOW. Under this therapy the skin disease gradually improved. The patient asserted that after two injections, she slept through the night for the first time in the last two years. The pruritus diminished over the subsequent weeks and the nodules regressed (Figure 1), although her condition was never rated below five points on the numeric rating scale (NRS). This relatively slow and incomplete improvement of itch is less pronounced than in other reports of dupilumab (Table 1). The reason for this is unknown, but may be due to development of an itch-scratch-cycle, an addictive and vicious cycle in chronic itch patients [3]. Dupilumab was used in combination with PUVA (for 8 weeks) and desloratadine (for 16 weeks). However, PUVA had been initiated two and a half years prior to dupilumab and did not change the skin disease. Dupilumab was therefore used as monotherapy. After five months of treatment, the patient developed shingles on her trunk (T6), which was treated with intravenous acyclovir 3 × 10 mg/kg while treatment with dupilumab was paused for one month. Dupilumab treatment was continued for ten months and prurigo nodularis remained in remission.

Dupilumab is a new biological drug approved by the European Medicines Agency since December 2017 for the treatment of moderate-to-severe AD [2]. Since it is a monoclonal antibody that primarily targets the shared alpha subunit receptor site of IL-4 and IL-13, it inhibits the Th2 response, which is probably of central pathological relevance in AD [4]. The potential importance of IL-4 and IL-13 in prurigo nodularis has been demonstrated in previous reports. Prurigo nodularis has some complaints and skin symptoms in common with AD, so that it might be considered as a special subtype of the latter with a distinct clinical and histological presentation [5]. An intralesional elevation of IL-13 has been shown [6] in actinic prurigo, a related disease with a high prevalence in American Indian populations. Another case report of IgG4-related disease with the typical presentation of prurigo nodularis demonstrated a high percentage of Th2-cells and an increase of their IL-4 and IL-13 production [7]. A more recent study showed increased IL-4 mRNA production in skin lesions of subacute and chronic forms of prurigo [8].

In addition to our case, a total of 24 prurigo nodularis patients have recently been successfully treated with dupilumab (Table 1) and another 16 were treated with dupilumab in an efficacy study by a French group (although there may be some overlap with previously reported patients) [9]. In contrast to our patient, relief from itching was much more rapid in these cases, with improvement within a few weeks [10–14]. A minority of patients have a slower response rate to dupilumab, which might be due to psychological factors and disease duration, particularly because there is evidence that there may be common neurological pathway for addiction and itching diseases in certain cases [3]. Therefore, itching could be still be perceived by the central nervous system, even if peripheral stimulation ceased for a prolonged period.

Our case report supports further exploration of dupilumab as a treatment option for refractory prurigo nodularis. However, larger clinical trials are required to confirm this observation.

Conflict of interest
RJL has received honoraria and/or research grants from the following companies: Adimix, Almirall, Amryth, ArgenX, Biotest, Biogen, Euroimmun, Incyte, Immunogenetics, Lilly, Novartis, UCB Pharma, Topadur, True North Therapeutics and TxCell. DT has received honoraria or fees for serving on advisory boards, as a speaker, as a consultant from AbbVie, Amgen, Almirall, Beiersdorf, Bioskin, Biogen,
Figure 2  Overview of treatments administered to our patient. Above: The patient's hospitalization record as an outpatient (green), inpatient (red) and daycare clinic patient (yellow). Middle: Kinetics of the numeric rating scale of itch intensity (NRS) from 0 to 10. Below: All therapies used during disease progression are listed. Medications administered for diseases other than prurigo are shown at the bottom of the Figure.
Table 1  Summary of prurigo nodularis patient treated with dupilumab.

| #  | Age (years) | Gender | Previous therapies                                                                 | Concurrent therapy                           | Clinical response                                                                 | Complications                        | Reference |
|----|-------------|--------|-------------------------------------------------------------------------------------|----------------------------------------------|----------------------------------------------------------------------------------|-------------------------------------|-----------|
| 1  | 70s         | M      | Systemic and topical steroids, cryotherapy, gabapentin, PUVA, NB UVB, Goeckerman therapy, antihistamines | Goeckerman therapy                          | Reduction of NRSi from 7 to 4 within 8 weeks and to 0 at week 12                  | None                                | [11]      |
| 2  | 50s         | F      | Systemic and topical steroids, cryotherapy, bleach bath, NB UVB, antihistamines     | Fexofenadine hydrochloride, gabapentin, Goec- kerman therapy, pregabalin, thalidomide | Reduction of NRSI from 8 to 3 within 4 weeks and to 1 at week 12                  | None                                |           |
| 3  | 50s         | M      | Systemic and topical steroids, cyclosporine, NB UVB, doxycycline, antihistamines   | Cyclosporine, dronabinol, gabapentin, Goeckerman therapy, thalidomide               | Reduction of NRSi from 10 to 6 within 4 weeks and to 2 at week 12                | Herpes labials at week 9           |           |
| 4  | 50s         | F      | Mirtazapine 15 mg/day, superpotent topical steroids and topical calcineurin inhibi- tor ointments | Not indicated                               | Reduction of NRSi from 10 to 3–4 within 1 month, and to 0 at 3-month follow-up | Not indicated                      | [10]      |
| 5  | 40s         | F      |                                                                                   |                                              | Reduction of NRSi from 10 to 0 within 1 month, with maintenance of response at 3-month follow-up | Not indicated                      |           |
| 6  | 30s         | F      |                                                                                   |                                              | Reduction of NRSi from 6 to 0 within 1 month                                       | Not indicated                      |           |
| 7  | 40s         | M      |                                                                                   |                                              | Reduction of NRSi from 9 to 0 within 1 month                                       | Not indicated                      |           |
| 8  | 72          | F      | Potent corticosteroid (only mentioned in discussion)                              | Not indicated                               | Reduction of NRSi from 9 to 0 within 8 weeks                                        | Not indicated                      | [12]      |
| 9  | 28          | F      |                                                                                   |                                              | Reduction of NRSi from 9 to 6 within 1 month                                        |                                     |           |
| 10 | 43          | F      |                                                                                   |                                              | Reduction of NRSi from 10 to 0 within 1 month                                       |                                     |           |
| 11 | 55          | F      |                                                                                   |                                              | Reduction of NRSi from 8 to 5 within 1 month                                        |                                     |           |
| 12 | 58          | F      |                                                                                   |                                              | Reduction of NRSi from 10 to 0 within 20 weeks                                      |                                     |           |
| 13 | 55          | F      |                                                                                   |                                              | Reduction of NRSi from 10 to 0 within 12 weeks                                       |                                     |           |
| 14 | 63          | M      |                                                                                   |                                              | Reduction of NRSi from 7 to 0 within 1 month                                        |                                     |           |
| 15 | 49          | M      |                                                                                   |                                              | Reduction of NRSi from 9 to 0 within 2 weeks                                        |                                     |           |
| 16 | 67          | M      |                                                                                   |                                              | Reduction of NRSi from 10 to 0 within 8 weeks                                        |                                     |           |

Continued
### Table 1 Continued.

| #  | Age (years) | Gender | Previous therapies | Concurrent therapy | Clinical response | Complications | Reference |
|----|-------------|--------|--------------------|--------------------|-------------------|---------------|-----------|
| 17 | 53          | F      | Potent topical steroids, intralesional triamcinolone, antihistamines, prednisone, etanercept, methotrexate, ustekinumab, mycophenolate mofetil, lenalidomide, thalidomide, UVB therapy, cyclosporine | Improvement (NRSi not indicated) | New onset alopecia | [15]         |
| 18 | 40          | F      | Antihistamines, high-potency steroids, intralesional triamcinolone, doxepin, UVB therapy, naltrexone, gabapentin, thalidomide, Apremilast, tofacitinib, cyclosporine, prednisone, methotrexate | Improvement (NRSi not indicated) |                       |             |
| 19 | 60s         | M      | Superpotent topical steroids, topical calcineurin inhibitors | Reduction of NRSi from 7 to 0 within 1 month |                       | [16]         |
| 20 | 60s         | M      | Superpotent topical steroids, topical calcineurin inhibitors | Reduction of NRSi from 0 to 0 within 8 weeks |                       |             |
| 21 | 30          | F      | Superpotent topical steroids, cryotherapy, hydroxyzine hydrochloride, phototherapy, dapsone 50 mg/d, methotrexate 15 mg/w, thalidomide, cyclosporine | Reduction of NRSi from 9 to 0.5 within 8 months |                       | [14]         |
| 22 | 41          | M      | UVB, topical steroids, topical calcineurin inhibitors, antihistamines, gabapentin | Reduction of NRSi from 10 to 3 within 8 weeks |                       | [13]         |
| 23 | 45          | F      | Phototherapy, topical steroids, intralesional triamcinolone, pregabalin | Reduction of NRSi from 10 to 0 within 8 weeks |                       |             |
| 24 | 52          | M      | Topical steroids, cyclosporine, gabapentin | Reduction of NRSi from 10 to 4 within 12 weeks |                       |             |
| 25 | 79          | F      | Topical and systemic corticosteroids, antihistamines, topical calcineurin inhibitors, gabapentin, cyclosporine, methotrexate, naltrexone, NB UVB, PUVA | Reduction of NRSi from 10 to 5 within 10 weeks Stop of PUVA | Shingles (trunk) at 6 months of treatment | This case   |

All patients were treated with subcutaneous injections of dupilumab at an initial dose of 600 mg, followed by 300 mg every other week.

Abbr.: m, male; f, female; PUVA, psoralen–UVA; NB, narrow band; NRSi, numeric rating scale itch intensity.
Correspondence

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References

1. Beck LA, Thaçi D, Hamilton JD et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med 2014; 371(2): 130–9.
2. Thaçi D, Simpson EL, Beck LA et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. Lancet 2016; 387(10013): 40–52.
3. Ishiuji Y. Addiction and the itch-scratch cycle. What do they have in common? Exp Dermatol 2019; 28(12): 1448–54.
4. Grobe W, Bieber T, Novak N. Pathophysiology of atopic dermatitis. J Dtsch Dermatol Ges 2019; 17(4): 433–40.
5. Pugliarello S, Cozzi A, Gisondi P, Girolomoni G. Phenotypes of atopic dermatitis. J Dtsch Dermatol Ges 2011; 9(1): 12–20.
6. Santos-Martinez L, Llorente L, Baranda L et al. Profile of cytokine mRNA expression in spontaneous and UV-induced skin lesions from actinic prurigo patients. Exp Dermatol 1997; 6(2): 91–7.
7. Takamura S, Suyama T, Teraki Y. Immunoglobulin G4-related disease presenting with prurigo: Circulating T-helper 2 cells may be involved in the pathogenesis. J Dermatol 2016; 43(9): 1067–70.
8. Park K, Mori T, Nakamura M, Tokura Y. Increased expression of mRNAs for IL-4, IL-17, IL-22 and IL-31 in skin lesions of subacute and chronic forms of prurigo. Eur J Dermatol 2011; 21(1): 135–6.
9. Calugareanu A, Jachiet M, Tauber M et al. Effectiveness and safety of dupilumab for the treatment of prurigo nodularis in a French multicenter adult cohort of 16 patients. J Eur Acad Dermatol Venereol 2019; jdv.15957.
10. Mollanazar NK, Smith PK, Yosipovitch G. Mediators of chronic pruritus in atopic dermatitis: getting the itch out? Clin Rev Allergy Immunol 2016; 51(3): 263–92.
11. Beck KM, Yang EJ, Sekhon S et al. Dupilumab treatment for generalized prurigo nodularis. JAMA Dermatol 2019; 155(11): 118.
12. Zhai LL, Savage KT, Qiu CC et al. Chronic pruritus responding to dupilumab – a case series. Medicines 2019; 6(3): 72.
13. Almustafa Z, Weller K, Autenrieth J et al. Dupilumab in treatment of chronic prurigo: a case series and literature review. Acta Derm Venereol 2019; 99(10): 905–6.
14. Ferrucci S, Tavecchio S, Berti E, Angileri L. Dupilumab and prurigo nodularis-like phenotype in atopic dermatitis: our experience of efficacy. J Dermatolog Treat 2019; 30(1): 1–2.
15. Rambhia PH, Levitt JO. Recalcitrant prurigo nodularis treated successfully with dupilumab. JAAD Case Rep 2019; 5(5): 471–3.
16. Mollanazar NK, Qiu CC, Aldrich JL et al. Use of dupilumab in patients who are HIV positive: report of four cases. Br J Dermatol 2019; 181(6): 1311–2.