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Efficacy and safety of PAC-14028 cream – a novel, topical, nonsteroidal, selective TRPV1 antagonist in patients with mild-to-moderate atopic dermatitis: a phase IIb randomized trial*

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Summary

Background Transient receptor potential vanilloid subfamily, member 1 (TRPV1) may play an important role in pruritus and inflammation induction in atopic dermatitis (AD). The treatment effect of TRPV1 antagonist via topical application in patients with AD remains unknown.

Objectives To assess the clinical efficacy and safety of PAC-14028, a TRPV1 antagonist, via topical application in patients with AD.

Methods In this 8-week, phase IIb, randomized, double-blind, multicentre, vehicle-controlled study, patients with mild-to-moderate AD were randomized to receive PAC-14028 cream 0·1%, 0·3%, 1·0% or vehicle cream twice daily. The primary efficacy end point was the Investigator's Global Assessment (IGA) success rate defined as the percentage of patients with an IGA score of 0 or 1 at week 8. The secondary efficacy end points included the severity Scoring of Atopic Dermatitis (SCORAD) index and Eczema Area and Severity Index (EASI) 75/90.

Results A total of 194 patients were enrolled. IGA success rates at week 8 were 14·58% for vehicle cream, 42·55% for PAC-14028 cream 0·1% ($P = 0·0025$ vs. vehicle), 38·30% for PAC-14028 cream 0·3% ($P = 0·0087$ vs. vehicle) and 57·45% for PAC-14028 cream 1·0% ($P < 0·001$ vs. vehicle). In particular, statistically significant differences were found between the vehicle and treatment groups in the IGA success rates with two-grade improvement. The SCORAD index, EASI 75/90, sleep disturbance score and pruritus visual analogue scale showed a trend towards improvement. No significant safety issues were reported.

Conclusions PAC-14028 cream may be an effective and safe treatment modality for the treatment of patients with mild-to-moderate AD.

What is already known about this topic?

- Atopic dermatitis (AD) is one of the most common inflammatory skin diseases characterized by pruritic erythematous skin lesions and barrier dysfunction.
- Transient receptor potential vanilloid subfamily, member 1 (TRPV1) antagonists suppress the release of pruritic and proinflammatory mediators.
- The preclinical results demonstrate the feasibility of TRPV1 as a potential therapeutic target for the treatment of AD.

What does this study add?

- TRPV1 regulates inflammation and pruritus in patients with AD.

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Conflicts of interest
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- PAC-14028 cream, a novel TRPV1 antagonist, was superior to vehicle in improving clinical symptoms and signs with a favourable safety profile in adults with mild-to-moderate AD.
- TRPV1 antagonism may play a role as a promising nonsteroidal topical treatment target for AD with a new mechanism of action.

Atopic dermatitis (AD) is a chronic, relapsing inflammatory disease characterized by intolerable pruritus, an impaired epidermal barrier and eczematous lesions.[1,2] The prevalence ranges are about 15–30% in children and 2–10% in adults in industrialized countries.[3,4]

In an effort to alleviate AD, topical therapies such as topical corticosteroids (TCSs) and topical calcineurin inhibitors (TCIs) have long been the mainstay of AD flare treatment. However, TCSs may provoke significant risk of adverse events (AEs), such as skin atrophy and rebound phenomenon in some patients requiring long-term application. Several issues related to steroid phobia have been raised.[1] TCIs are also associated with AEs, such as skin burning sensation and pruritus, and a boxed warning about a theoretical risk of malignancy (including lymphoma) has been added to TCI product labels.[5] In addition, emerging targets of interest in the treatment of AD include intracellular enzyme phosphodiesterase (PDE)-4 inhibitors and Janus kinase (JAK) inhibitors. Crisaborole is a small molecule that inhibits PDE-4 activity and is the first in its class to be approved by the Food and Drug Administration.[1,5] Although crisaborole showed significant clinical efficacy and an acceptable safety profile across two phase III trials, the conclusions on its efficacy should be cautiously interpreted because the minimal clinically important difference was not defined for the reported outcome measure.[1] The JAK inhibitors also have potential risk for AEs caused by immunosuppression, with nasopharyngitis and upper respiratory infections as the most commonly reported AEs.[5,6] Therefore, given the chronicity of AD and the need for long-term pharmacological therapy, new treatment options with better benefit–risk profiles are still needed.

Transient receptor potential vanilloid subfamily, member 1 (TRPV1) is expressed not only on sensory nerves but also on keratinocytes, dendritic cells and sebocytes in the skin.[7] It is directly activated by pain-producing stimuli such as capsaicin, heat, and acid, or activated when intracellular signal transduction is conducted by pruritogens.[8] The selective TRPV1 antagonist, PAC-14028 (Asivatrep, $C_{21}H_{22}F_5N_3O_3S$), has shown antipruritic effects, improved skin barrier function, and suppressed allergic inflammation in AD-like murine models by blocking the secretion of neuropeptides, such as substance P, modulating epidermal differentiation markers and suppressing T helper 2 cytokines.[9–11]

A phase IIa trial of PAC-14028 cream was conducted in patients with AD. The efficacy of PAC-14028 cream was superior to that of the vehicle, and similar to pimecrolimus. Furthermore, PAC-14028 cream showed a good safety profile with a far lower incidence of treatment-related AEs than pimecrolimus. Safety findings in the treatment arms were comparable with those in the vehicle group, and there was no other safety concern requiring further investigation (ClinicalTrials.gov: NCT02583022). Based on these results, this phase IIb clinical trial aimed to evaluate the safety and efficacy of PAC-14028 cream in patients with mild-to-moderate AD and to determine the optimal dosage by reviewing the responses to PAC-14028 cream 0·1%, 0·3% and 1·0% by dose step (NCT02757729).

Patients and methods

Study design and oversight

A randomized, double-blind, vehicle-controlled phase IIb clinical trial was conducted at three centres in the Republic of Korea between October 2015 and July 2016 in adults with mild-to-moderate AD (NCT02757729). This trial was performed in compliance with the provisions of the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, and applicable regulatory requirements. The institutional review board of Chung-Ang University Hospital, Asan Medical Center and Konkuk University Hospital approved all study protocols, informed consent forms, and relevant supporting data.

Patient selection

Key inclusion criteria required male or female patients to be aged between 19 years and 70 years, have a clinical diagnosis of AD according to the Hanifin and Rajka diagnostic criteria,[12] 5% or more of affected body surface area (BSA), and an Investigator's Global Assessment (IGA) score of 2 (mild) or 3 (moderate) (scores range from 0 to 5). Patients who received the following therapies were excluded: corticosteroids, antibiotics or immunosuppressants as a systemic drug treatment or history of treatment based on photochemical therapy within 28 days; TCSs, TCIs or antibiotics within 14 days. Patients with the following conditions were also excluded: serious skin diseases other than AD or widespread scarring on the AD lesion site; skin disease resulting from other medical, psychotic and neuropathic causes; hepatic dysfunction; chronic medical disease; symptoms of systemic infection or eczema herpeticum on the skin; malignant tumour and/or active pruritus caused by chronic urticaria or allergen such as scabies, insect bites, etc.

Treatment plan

Eligible patients were randomized (1 : 1 : 1 : 1) to three treatment groups (PAC-14028 cream 0·1%, 0·3% and 1·0%) or vehicle

cream based on a computer-generated randomization scheme that was balanced using a permuted block method. This study was conducted under double-blind conditions for the PAC-14028 and vehicle groups. A detailed allocation of the identification codes was managed by the principal investigator using sealed individual double-blinded envelopes for each subject. The specific patient allocation and identification code information were not disclosed until the end of the clinical trial. There was no difference in the physical appearance, colour, texture and homogeneity of each of the strengths of the PAC-14028 cream or vehicle cream. During the 8-week treatment period, patients were required to apply the provided investigational product to AD-involved areas twice daily by evenly rubbing it to form a thin film. Patients were instructed to squeeze the cream out to the length of the last section of their index finger and apply it to an area twice the size of their palm. Patients were also allowed to use acceptable bland emollients to manage dry non-AD skin lesions. Assessments were conducted at baseline and weeks 1, 3, 6 and 8.

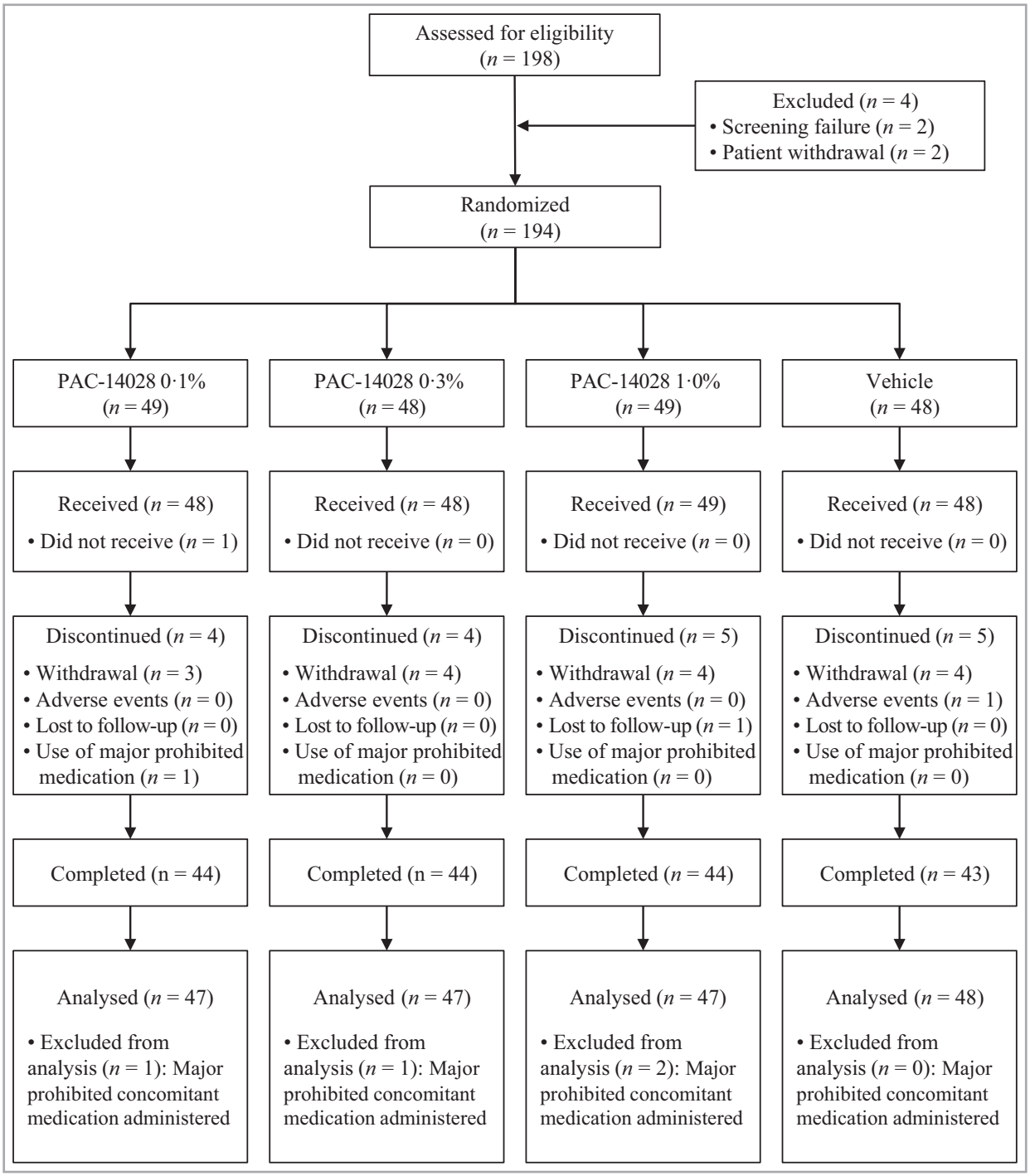

Fig 1. Patient disposition.

Table 1 Patient demographics and baseline characteristics

Characteristic	Vehicle	PAC-14028 cream			P-value
	n = 48	0·1%, n = 47	0·3%, n = 47	1·0%, n = 47	
Mean age, years (range)	26·25 (19–39)	28·32 (19–46)	28·57 (19–51)	26·85 (19–46)	0·6611[a]
Sex, male, n (%)	24 (50)	19 (40)	19 (40)	27 (57)	0·2767[b]
% TBSA, mean (range)	13·96 (5–50)	15·21 (5–52)	14·26 (5–75)	12·66 (5–50)	0·8591[a]
IGA, mean ± SD	2·63 ± 0·49	2·57 ± 0·5	2·66 ± 0·48	2·66 ± 0·48	0·8076[a]
Mild (%)	37·50	42·55	34·04	34·04	0·8063[b]
Moderate (%)	62·50	57·45	65·96	65·96	
Total SCORAD, mean (range)	41·56 (20·9–77·3)	39·40 (19–59·2)	40·60 (16·5–62·1)	40·60 (17·3–61·4)	0·8942[a]

TBSA, total body surface area; IGA, Investigator's Global Assessment; SCORAD, Scoring of Atopic Dermatitis. [a]Kruskal–Wallis test; [b]Pearson's $\chi 2$-test.

Efficacy and safety evaluations

The primary efficacy variable was the IGA success rate defined as the percentage of patients with an IGA score of 0 or 1 at week 8 as evaluated by a physician using a 6-point scale (0, clear; 1, almost clear; 2, mild; 3, moderate; 4, severe; 5, very severe).[13] The secondary efficacy variables included severity Scoring of Atopic Dermatitis (SCORAD)[14] and Eczema Area and Severity Index (EASI) score.[15] Pruritus visual analogue scale (VAS) and sleep disturbance score were also used as an assessment of subjective symptoms in the SCORAD index. Safety and tolerability were evaluated by AE reporting, clinical laboratory testing, electrocardiogram recordings, vital signs and physical examinations.

Statistical analysis

Sample size determination

Study enrolment was planned for approximately 192 patients randomized 1 : 1 : 1 : 1 into treatment groups. As no prior data existed on IGA success rate, the sample size was calculated based on data from an assessment of the SCORAD index on day 28 of the phase IIa PAC-14028 cream trial for AD. We assumed the mean changes from baseline to day 28 in the SCORAD score would be −11·12 and −5·73 for PAC-14028 1·0% cream and vehicle, respectively. Using an alpha error of 0·05 and a power of 0·95, we calculated the desired sample size to be 36 participants per group. Therefore, we chose an optimal minimum sample size of 40 participants per group. We also explored the optimum dosage based on the primary efficacy end point for PAC-14028 cream and the treatment success rate based on IGA score in this clinical trial. Accounting for an anticipated dropout rate of 15%, we ultimately selected 48 participants per group and a total of 192 participants as targets.

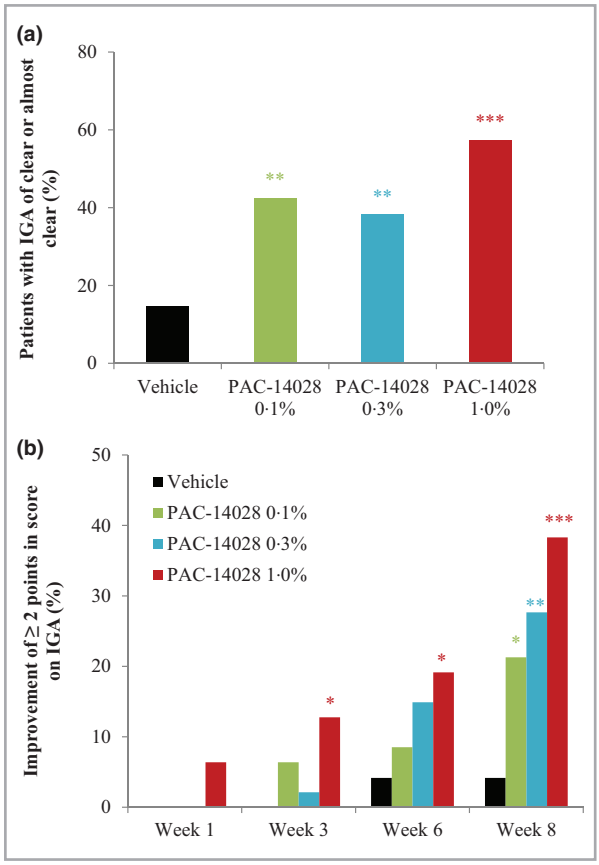

Fig 2. Treatment success rate (%) in the Investigator's Global Assessment (IGA). (a) Percentage of patients who were assessed as 0 (clear) or 1 (almost clear) according to the week-8 IGA score. (b) Percentage of patients who were assessed as 0 (clear) or 1 (almost clear) IGA score with two-grade improvement from the baseline at week 1, 3, 6 and 8 (*P < 0·05 vs. vehicle, **P < 0·01 vs. vehicle, ***P < 0·001 vs. vehicle).

Efficacy and safety analysis

All analyses were conducted as a two-sided test with the significance level set at 0·05. The full analysis set (FAS) population was used for all efficacy analyses. Patients who used topical or systemic calcineurin inhibitors or corticosteroids for the purpose of treating AD were excluded from the FAS analysis. During the FAS analysis, the last observation carried forward method was used for the missing data.

The primary end point was treatment success rate (%) according to IGA score, defined as the percentage of patients with an IGA score of 0 or 1 at week 8 from baseline. For primary

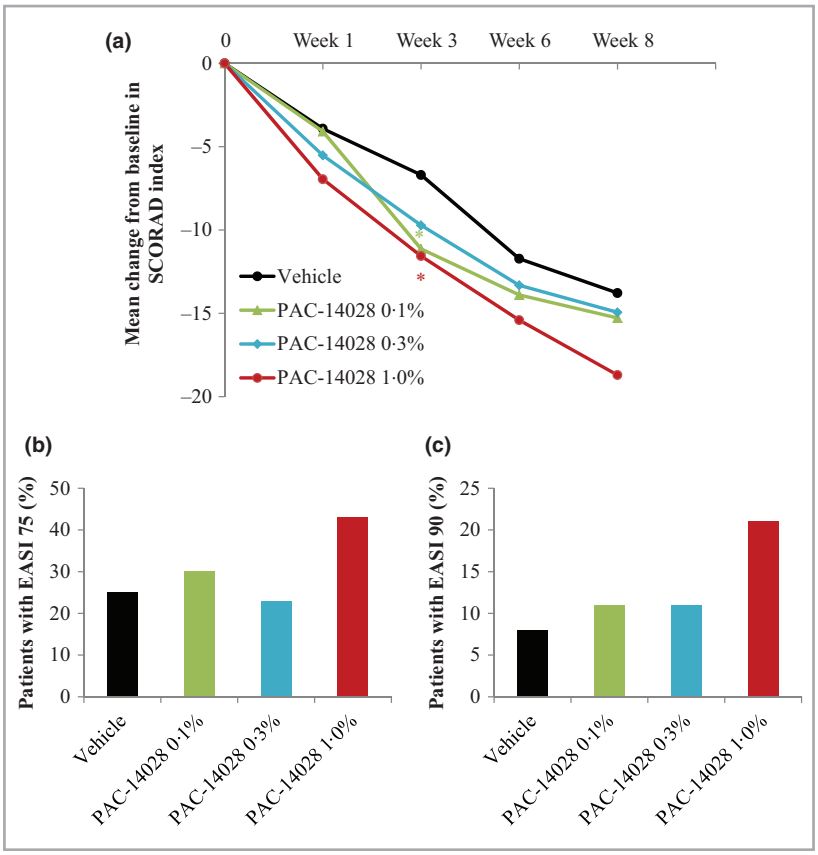

Fig 3. Efficacy analysis of severity Scoring of Atopic Dermatitis (SCORAD) index and Eczema Area and Severity Index (EASI) score. (a) Mean change in SCORAD index from the baseline at week 1, 3, 6 and 8 (*$P < 0·05$ vs. vehicle). (b) Proportion of patients achieving ≥ 75% improvement from baseline in the week-8 EASI score. (c) Proportion of patients achieving ≥ 90% improvement from baseline in the week-8 EASI score.

analysis, differences between the treatment and vehicle groups were analysed using Pearson's χ^2-test. Analyses of SCORAD, EASI, pruritus VAS and sleep disturbance score were performed using a two-sample *t*-test or Wilcoxon rank sum test.

The safety population included all patients who were administered with the investigational product at least once. The occurrence of treatment-emergent AEs and adverse drug reactions (ADRs) was analysed using Pearson's χ^2-test or Fisher's exact test.

Results

Patients

A total of 198 patients were screened and 194 were randomly assigned to one of the following four groups: PAC-14028 cream 0·1% (n = 49), 0·3% (n = 48), 1·0% (n = 49) or vehicle cream (n = 48) (Fig. 1). In total, 193 patients received at least one dose of study treatment and were analysed for safety of the materials tested. Overall, 18 patients discontinued study treatment prematurely [PAC-14028 cream 0·1% (n = 4), 0·3% (n = 4), 1·0% (n = 5) or vehicle cream (n = 5)] and 175 patients completed the study treatment. Four patients who administered major prohibited concomitant medication were excluded from the efficacy analysis and 189 patients were analysed for efficacy of the treatments.

Statistically significant differences were not found for baseline characteristics and disease severity including age, sex, percentage of total BSA, IGA and total SCORAD across study treatment groups (Table 1).

Efficacy

More patients treated with PAC-14028 cream achieved success according to IGA score compared with the vehicle-treated group (Fig. 2a). The IGA success rates were 14·6% for vehicle cream, 42·6% for PAC-14028 cream 0·1% ($P = 0·0025$ vs. vehicle), 38·3% for PAC-14028 cream 0·3% ($P = 0·0087$ vs. vehicle) and 57·5% for PAC-14028 cream 1·0% ($P < 0·001$ vs. vehicle). By week 8, the proportion of patients achieving treatment success, based on an IGA score with a two-grade improvement from baseline was significantly higher in the PAC-14028 cream 0·1% (21·3%, $P = 0·0121$), 0·3% (27·7%, $P = 0·0017$) and 1·0% (38·3%, $P < 0·001$) groups than in the vehicle cream (4·2%) group. In particular, the group who received PAC-14028 cream 1·0% showed a significantly greater proportion of patients that achieved success than the vehicle group. The measure of success was based on an IGA

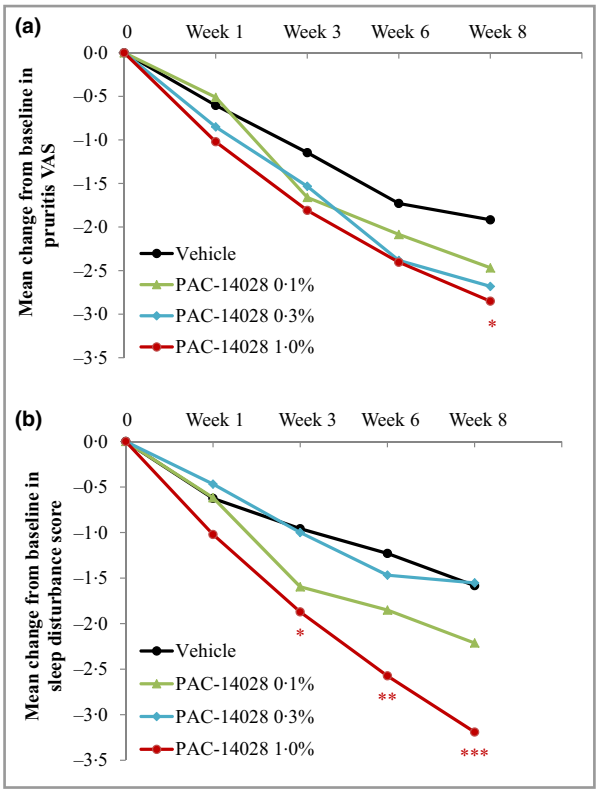

Fig 4. Patient-reported outcomes based on pruritus visual analogue scale (VAS) and sleep disturbance score. (a) Mean change from baseline in pruritus VAS at 1, 3, 6 and 8 weeks. (b) Mean change from baseline sleep disturbance score at 1, 3, 6 and 8 weeks (*P < 0·05 vs. vehicle, **P < 0·01 vs. vehicle, ***P < 0·001 vs. vehicle).

score of 0 or 1 with at least a two-grade improvement from baseline from week 3 through week 8 (Fig. 2b).

Improvement in the mean change in SCORAD index was achieved by a greater number of patients in all PAC-14028 groups compared with the vehicle group. A significant improvement was observed particularly in the groups receiving PAC-14028 cream 0·1% ($P < 0·05$) and 1·0% ($P < 0·05$) at week 3 compared with those receiving vehicle cream (Fig. 3a). Additionally, higher response rates in EASI 75/90 (the proportion of patients with an improvement in the EASI of at least 75% or 90%) were observed in the PAC-14028 groups than in the vehicle group, except for EASI 75 in the treatment group that received PAC-14028 cream 0·3% (Fig. 3b, c).

An assessment of the severity of pruritus-related VAS scores was conducted at each patient visit. All PAC-14028 groups showed decreased mean changes from baseline over the duration of the treatment period. In particular, by week 8, the PAC-14028 cream 1·0% ($P = 0·0326$ vs. vehicle) group showed a significant reduction in VAS scores from baseline (Fig. 4a). A significant reduction in the sleep disturbance score was also observed in the group receiving the PAC-14028 cream 1·0% ($P < 0·05$ vs. vehicle) from week 3 of treatment (Fig. 4b).

Representative photographs of patients treated with PAC-14028 cream 0·1%, 0·3% or 1·0% showed marked improvement (Fig. 5).

Safety

PAC-14028 cream demonstrated a favourable safety profile and the overall incidence of AEs was similar in the PAC-14028 and vehicle groups (Table 2). The incidence of AEs after administering the investigational product was 6·3% for PAC-14028 cream 0·1%, 12·5% in PAC-14028 cream 0·3%, 16·3% for PAC-14028 cream 1·0% and 18·8% for vehicle cream. The incidence of ADRs was 2·1% (one case of wound secretion) for PAC-14028 cream 0·3%, 6·3% (two cases of rash, one case of irritability) for vehicle cream and 0% for both PAC-14028 cream 0·1% and 1·0%. All AEs were considered mild or moderate in severity, and no clinically meaningful differences were found in the rate of incidence of AEs and ADRs among the treatment groups.

As for serious AEs (SAEs), one case of appendicitis (2·0%) without relationship to the study treatment was reported in the group receiving PAC-14028 cream 1·0%. Treatment-related SAEs were not reported.

No clinically significant abnormalities were found in patients' clinical laboratory values, vital signs, physical examinations or electrocardiograms.

Discussion

Cutaneous neurogenic inflammation is inflammation that is induced in the skin by the release of neuropeptides such as substance P and calcitonin gene-related peptide from sensory nerve endings, which leads to mainly sensory and vascular disorders such as pruritus, erythema and oedema.[16,17] TRPV1 is a nonselective cation channel known to participate specifically in pain and cutaneous neurogenic inflammation.[18] Indeed, TRPV1 activation regulates communication between sensory nerve endings and skin nonimmune and immune cells, increasing the release of inflammatory mediators including cytokines and neuropeptides. Several new insights have been gained regarding the control of epidermal barrier function, inflammation and chronic pruritus in the animal models of AD using a TRPV1 antagonist.[10,11,19,20]

In this phase IIb trial, the TRPV1 antagonist PAC-14028, applied topically as a 0·1%, 0·3% or 1·0% (wt/wt) cream, significantly improved the signs and symptoms of patients with AD. The positive efficacy of treatment with PAC-14028 cream for 8 weeks was based on the multiple outcome measures reflecting the objective signs of AD and the subjective symptoms (e.g. pruritus, sleep disturbance). We found improvement in the primary efficacy outcome of IGA score of 0 or 1 for all groups that applied PAC-14028 cream, compared with the vehicle cream, among patients with mild-to-moderate AD. At week 8, more patients treated with PAC-14028 cream showed a significant two-grade improvement in IGA from the baseline score compared with those

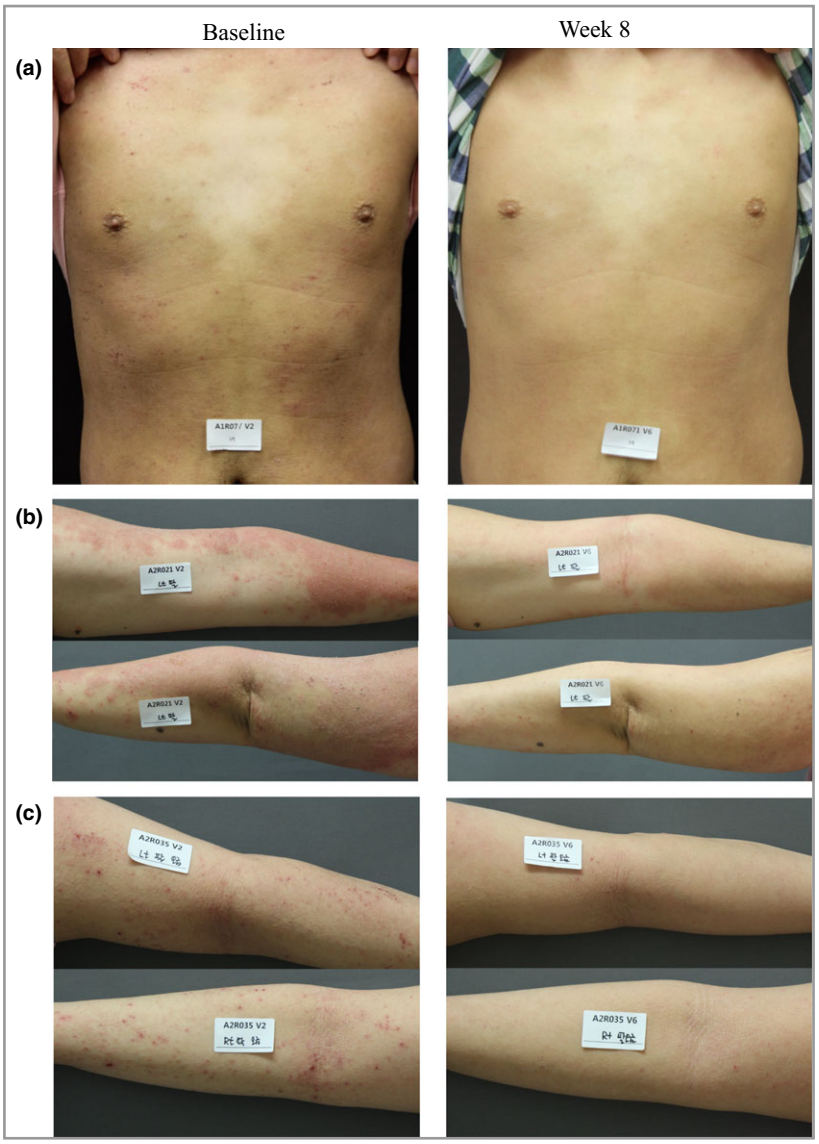

Fig 5. Clinical photographs of three patients treated with PAC-14028 cream 1·0% (a), PAC-14028 cream 0·3% (b), PAC-14028 cream 0·1% (c) from baseline to week 8.

who received vehicle treatment. Although a direct comparison study with PDE-4 inhibitor has not been performed, PAC-14028 cream 1·0% demonstrated a higher success rate in two-grade reduction from the baseline IGA score at week 8 than the vehicle cream (38·3% vs. 4·2%), compared with the success rate based on the IGA score at day 29 as reported for the crisaborole ointment (32·1% vs. 21·7%).[21] In addition, meaningful improvement was observed with regard to scores for both SCORAD and EASI following treatment with PAC-14028 cream. However, the treatment effects were not statistically significant owing to the relatively small sample size and the lack of children included in the study. The typical forms of clinical presentations of AD in adults differ from those in children and generally include inflammatory eczema with a larger area of lichenification, nummular eczema, and/or prurigo and are more resistant to topical therapy.[22] Successful treatment of AD with tacrolimus 0·03% or crisaborole was achieved in a greater proportion of patients in paediatric groups than those in adult groups.[23,24]

Treatment with PAC-14028 cream was also associated with improvements in patient-reported symptoms of AD including the effect on pruritus and sleep in the 1·0% formulation relative to the vehicle. Pruritus, a hallmark of AD, can lead to skin damage by excoriation and the development of secondary infection, which further aggravates AD and negatively affects patients' quality of life.[25–27] The mechanism through which TRPV1 plays a key role in mediating pruritus signalling in AD is well understood. Histaminergic itch signalling pathways excite sensory neurons, predominantly C-fibres by phospholipase A2 and 12-lipoxygenase-stimulated activation of TRPV1.[28] This directly leads to increased release of substance P and calcitonin gene-related peptide, which increase pruritogens. Although TRPV1 is an ion channel expressed on C-fibre neurons that is associated with the itch sensation, pruritus VAS

Table 2 Treatment-related adverse events and treatment-emergent adverse events

	PAC-14028 0·1%, n = 48	PAC-14028 0·3%, n = 48	PAC-14028 1·0%, n = 49	Vehicle, n = 48
Treatment-related adverse event, n (%)				
Skin and subcutaneous tissue disorders	0 (0)	0 (0)	0 (0)	2 (4)
Rash	0 (0)	0 (0)	0 (0)	2 (4)
General disorders and administration site conditions	0 (0)	0 (0)	0 (0)	1 (2)
Irritability	0 (0)	0 (0)	0 (0)	1 (2)
Injury, poisoning and procedural complications	0 (0)	1 (2)	0 (0)	0 (0)
Wound secretion	0 (0)	1 (2)	0 (0)	0 (0)
Treatment-emergent adverse event, n (%)				
Infections and infestations	1 (2)	3 (6)	2 (4)	0 (0)
Appendicitis	0 (0)	0 (0)	1 (2)	0 (0)
Folliculitis	0 (0)	1 (2)	0 (0)	0 (0)
Herpes zoster	0 (0)	1 (2)	0 (0)	0 (0)
Influenza	0 (0)	1 (2)	0 (0)	0 (0)
Nasopharyngitis	1 (2)	0 (0)	0 (0)	0 (0)
Otitis externa	0 (0)	0 (0)	1 (2)	0 (0)
Respiratory, thoracic and mediastinal disorders	1 (2)	1 (2)	1 (2)	3 (6)
Rhinorrhoea	1 (2)	1 (2)	1 (2)	2 (4)
Cough	0 (0)	0 (0)	1 (2)	3 (6)
Skin and subcutaneous tissue disorders	0 (0)	1 (2)	1 (2)	2 (4)
Rash	0 (0)	0 (0)	1 (2)	2 (4)
Pigmentation disorder	0 (0)	0 (0)	0 (0)	1 (2)
Urticaria papular	0 (0)	1 (2)	0 (0)	0 (0)
Musculoskeletal and connective tissue disorders	1 (2)	0 (0)	1 (2)	1 (2)
Arthralgia	0 (0)	0 (0)	1 (2)	0 (0)
Back pain	1 (2)	0 (0)	0 (0)	0 (0)
Pain in extremity	0 (0)	0 (0)	0 (0)	1 (2)
Eye disorders	0 (0)	1 (2)	1 (2)	0 (0)
Conjunctivitis allergic	0 (0)	0 (0)	1 (2)	0 (0)
Eye haemorrhage	0 (0)	1 (2)	0 (0)	0 (0)
General disorders and administration site conditions	0 (0)	0 (0)	1 (2)	1 (2)
Irritability	0 (0)	0 (0)	0 (0)	1 (2)
Pyrexia	0 (0)	0 (0)	1 (2)	0 (0)
Injury, poisoning and procedural complications	0 (0)	1 (2)	0 (0)	1 (2)
Ankle fracture	0 (0)	0 (0)	0 (0)	1 (2)
Wound secretion	0 (0)	1 (2)	0 (0)	0 (0)
Nervous system disorders	0 (0)	0 (0)	1 (2)	1 (2)
Dizziness	0 (0)	0 (0)	1 (2)	0 (0)
Headache	0 (0)	0 (0)	0 (0)	1 (2)
Reproductive system and breast disorders	0 (0)	0 (0)	2 (4)	0 (0)
Dysmenorrhoea	0 (0)	0 (0)	1 (2)	0 (0)
Uterine haemorrhage	0 (0)	0 (0)	1 (2)	0 (0)
Vaginal haemorrhage	0 (0)	0 (0)	1 (2)	0 (0)
Gastrointestinal disorders	0 (0)	0 (0)	1 (2)	0 (0)
Nausea	0 (0)	0 (0)	1 (2)	0 (0)
Vomiting	0 (0)	0 (0)	1 (2)	0 (0)

Data are presented as n (%).

scores in patients treated with PAC-14028 cream remained continuously and substantially decreased after treatment, however, the differences were statistically significant only at week 8 compared with baseline. The observed trend may be due to greater experimental deviations resulting from the small sample size, vehicle effects related to emollient bases, the transdermal administration route and/or a relative effect size caused by disruptions of skin barrier function. However, we previously reported that orally administered PAC-14028 exhibited immediate antipruritic effects in murine scratching models evoked by diverse pruritogens.[9] Therefore, this evidence indicates that PAC-14028 cream has a positive and direct impact on controlling pruritus, while simultaneously decreasing inflammation in the affected skin.

Twice-daily application of PAC-14028 cream for 8 weeks demonstrated a favourable tolerability profile in this study. The nature and number of AEs, combined with the negligible systemic exposure after PAC-14028 cream application, indicated that the novel topical formulation of PAC-14028 allows a targeted therapy at the inflammation site. Hyperthermia, which

has been observed with oral TRPV1 antagonists, was not reported in patients treated with PAC-14028. The incidence and types of AEs that were associated with PAC-14028 cream were similar to those in the vehicle group. Patients treated with PAC-14028 cream did not show cutaneous TCS- or TCI-induced AEs, such as application site burning or stinging. Additionally, PAC-14028 cream 1·0% exhibited much lower rates of treatment-related AEs than the vehicle cream (0·0% vs. 6·3%) compared with the rates of treatment-related AEs reported in crisaborole ointment (4·4% vs. 1·2%).[9] However, our study has limitations owing to the relatively small sample size, and the lack of direct comparison with TCSs, TCIs or crisaborole. Moreover, further investigations in paediatric patient populations will be needed.

In conclusion, PAC-14028 cream is a promising new treatment option for patients with mild-to-moderate AD based on the favourable tolerability profile and the improved efficacy in treating AD observed in the present study. Based on these results, a phase III programme is underway to assess the efficacy and safety of PAC-14028 topical cream 1·0% in adolescent and adult patients with mild-to-moderate AD (NCT02965118).

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References

1 Nygaard U, Deleuran M, Vestergaard C. Emerging treatment options in atopic dermatitis: topical therapies. *Dermatology* 2017; **233**:333–43.
2 Ring J. *Atopic Dermatitis*. Heidelberg: Springer International Publishing, 2016.
3 Bieber T. Atopic dermatitis. *N Engl J Med* 2008; **358**:1483–94.
4 Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *Br J Dermatol* 2006; **155**:145–51.
5 Paller AS, Kabashima K, Bieber T. Therapeutic pipeline for atopic dermatitis: end of the drought? *J Allergy Clin Immunol* 2017; **140**:633–43.
6 Cotter DG, Schairer D, Eichenfield L. Emerging therapies for atopic dermatitis: Jak inhibitors. *J Am Acad Dermatol* 2018; **78**(3 Suppl. 1): S53–62.
7 Bonchak JG, Swerlick RA. Emerging therapies for atopic dermatitis: TRPV1 antagonists. *J Am Acad Dermatol* 2018; **78**(3 Suppl. 1):S63–66.
8 Imamachi N, Park GH, Lee H *et al.* TRPV1-expressing primary afferents generate behavioral responses to pruritogens via multiple mechanisms. *Proc Natl Acad Sci USA* 2009; **106**:11330–5.
9 Yun JW, Seo JA, Jang WH *et al.* Antipruritic effects of TRPV1 antagonist in murine atopic dermatitis and itching models. *J Invest Dermatol* 2011; **131**:1576–9.
10 Yun JW, Seo JA, Jeong YS *et al.* TRPV1 antagonist can suppress the atopic dermatitis-like symptoms by accelerating skin barrier recovery. *J Dermatol Sci* 2011; **62**:8–15.
11 Lee JH, Choi CS, Bae IH *et al.* A novel, topical, nonsteroidal, TRPV1 antagonist, PAC-14028 cream improves skin barrier function and exerts anti-inflammatory action through modulating epidermal differentiation markers and suppressing Th2 cytokines in atopic dermatitis. *J Dermatol Sci* 2018; https://doi.org/10.1016/j.jdermsci.2018.04.017
12 Hanifin JM, Rajka J. Diagnostic features of atopic dermatitis. *Acta Dermatol Venereol (Stockh)* 1980; **92**:44–7.
13 Eichenfield LF, Lucky AW, Boguniewicz M *et al.* Safety and efficacy of pimecrolimus(ASM981) cream 1% in the treatment of mild and moderate atopic dermatitis in children and adolescents. *J Am Acad Dermatol* 2002; **46**:495–504.
14 European Task Force on Atopic Dermatitis. Severity scoring of atopic dermatitis: the SCORAD index. Consensus report of the European Task Force on Atopic Dermatitis. *Dermatology* 1993; **186**:23–31
15 Hanifin JM, Thurston M, Omoto M *et al.* The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. *Exp Dermatol* 2001; **10**:11–18.
16 Gouin O, Lebonvallet N, L'Herondelle K *et al.* Self-maintenance of neurogenic inflammation contributes to a vicious cycle in skin. *Exp Dermatol* 2015; **24**:723–6.
17 Roosterman D, Goerge T, Schneider SW *et al.* Neuronal control of skin function: the skin as a neuroimmunoendocrine organ. *Physiol Rev* 2006; **86**:1309–79.
18 Vincent L, Vang D, Nguyen J *et al.* Mast cell activation contributes to sickle cell pathobiology and pain in mice. *Blood* 2013; **122**:1853–62.
19 Cevikbas F, Wang X, Akiyama T *et al.* A sensory neuron-expressed IL-31 receptor mediates T helper cell-dependent itch: involvement of TRPV1 and TRPA1. *J Allergy Clin Immunol* 2014; **133**:448–60.
20 Lim KM, Park YH. Development of PAC-14028, a novel transient receptor potential vanilloid type 1 (TRPV1) channel antagonist as a new drug for refractory skin diseases. *Arch Pharm Res* 2012; **35**:393–6.
21 Paller AS, Tom WL, Lebwohl MG *et al.* Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. *J Am Acad Dermatol* 2016; **75**:494–503.
22 Silvestre Salvador JF, Remero-Perez D, Encabo-Duran B. Atopic dermatitis in adults: a diagnostic challenge. *J Investig Allergol Clin Immunol* 2017; **27**:78–88.
23 Chapman MS, Schachner LA, Breneman D *et al.* Tacrolimus ointment 0.03% shows efficacy and safety in pediatric and adult patients with mild to moderate atopic dermatitis. *J Am Acad Dermatol* 2005; **53** (2 Suppl. 2):S177–85.
24 Paller AS, Luger TA, Hebert AA *et al.* Crisaborole ointment improves global atopic dermatitis severity across patients with varying baseline characteristics: pooled results from two phase 3 trials. Presented at the 10th Georg Rajka International Symposium on Atopic Dermatitis, ISAD 2018, Utrecht, the Netherlands, 11–13 April 2018; abstr. P060.
25 Hong J, Buddenkotte J, Berger TG, Steinhoff M. Management of itch in atopic dermatitis. *Semin Cutan Med Surg* 2011; **30**:71–86.
26 Halvorsen JA, Dalgard F, Thorsen M *et al.* Itch and pain in adolescents are associated with suicidal ideation: a population-based cross-sectional study. *Acta Derm Venereol* 2012; **92**:543–6.
27 O'Hare E, Flanagan D, Penzel T *et al.* A comparison of radio-frequency biomotion sensors and actigraphy versus polysomnography for the assessment of sleep in normal subjects. *Sleep Breath* 2015; **19**:91–8.
28 Shim WS, Tak MH, Lee MH *et al.* TRPV1 mediates histamine-induced itching via the activation of phospholipase A2 and 12-lipoxygenase. *J Neurosci* 2007; **27**:2331–7.

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