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A Novel Topical Spray which Efficiently Provides Relief for Patients Suffering from Pruritus

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Abstract
Background: *Pruritus is defined as an "unpleasant sensation that elicits the desire or reflex to scratch". It can occur without injury or disease, serves no apparent biological purpose and has no recognizable endpoint. It appears along with a number of skin and systemic diseases.*
Aim: *to determine the benefit of a novel topical anti-pruritic spray containing Camellia sinensis and Tambourissa spp leaf polyphenol extracts, and enoxolone in patients with atopic dermatitis (AD), psoriasis, chronic idiopathic urticaria (CIU) or senile pruritus.*
Methodology: *multicenter, prospective, observational, non-comparative study in 120 patients, 30 in each disease group. AD patients were to be aged between4monthsand 4years, psoriasis and CIU patients were to be of at least 18 years and senile pruritus patients of at least 65 years. At baseline and day 21, investigators assessed pruritus evolution using the 5-D pruritus scale, clinical efficacy and quality of life (QOL) through the Skindex-29 questionnaire in adults, the Infants' Dermatitis OOL Index and Family Dermatitis Index in children. Local tolerance was assessed.*
Results: *The spray quickly and significantly provided relief from pruritus. The QOL of patients and the impact on their families significantly improved. A large majority of the patients appreciated the spray for its efficacy and its cosmetic properties. One adverse effect was reported in the AD group after 14 days of application, leading to the patient's discontinuation. Local tolerance was good.*
Conclusion: *The spray product significantly decreased pruritus severity, allowing an improvement in the daily life of patients with pruritic diseases.*
Keywords: *Pruritus, atopic dermatitis, psoriasis, chronic idiopathic urticaria, senile pruritus, itching, relief, spray.*

Introduction

Pruritus, or itching, is defined as a "sensation that elicits the desire to scratch"[(1)].Chronic pruritus is defined as pruritus lasting 6 weeks or longer. Like pain, it can occur without injury or disease, serves no apparent biological purpose and has no recognizable endpoint[(2)]. It appears along with a number of skin diseases including atopic

dermatitis, psoriasis, chronic urticaria and senile pruritus, as well as systemic conditions including kidney failure, liver cirrhosis and some cancers, and greatly affects the patient's quality of life[3].

Pruritus is undoubtedly the most frequent symptom in dermatology in, for example, one third of patients in German dermatological consultations[4]. The point prevalence of pruritus ranges from 13 to 38%; with a lifetime prevalence ranging from 23 to 26%[5]. Among adolescents, its prevalence was estimated at 8.8%[6]. Pruritus has been reported in 91% of all AD patients[7] and 63.8% to 97.5% of psoriasis patients, depending on the study, reported chronic pruritus[8]. In patients with chronic idiopathic urticaria (CIU), the incidence of pruritus was 68%[3]. In patients older than 65 years, the prevalence of pruritus resulting from age-related physiological changes of the skin, especially dryness, was 37.5%, with important geographic variations[9].

In addition to histamines, many other mediators such as proteases, neuropeptides, opioids, growth factors and interleukins may trigger pruritus, depending on its aetiology[10].This may, for example, explain why antihistamines are not always effective in the treatment of pruritus in AD patients[11]. Studies suggest that the cytokine Thymic Stromal Lymphopoietin (TSLP) acts as a master switch that triggers both the initiation and maintenance of AD and the atopic march[12]. Over-expression of TSLP in keratinocytes triggers pruritus-induced scratching and the development of an AD-like skin phenotype(13).

In psoriasis plaques, the over-expressed nerve growth factor (NGF) is involved in the mediation of pruritus as well as in inflammatory and immunological processes[14]. When treating pruritus in psoriasis, inhibiting the synthesis of NGF in keratinocytes was therefore considered a specific and relevant target.

The stimuli for urticaria and its mechanisms of action are multiple. The mechanism involves the activation of mastocytes stimulated by an exogenous agent, resulting in an influx of calcium ions in the cells, thus inducing the degranulation of histamines, which leads to pruritus and erythema. Treatments include antihistamines (type H1), mast-cell stabilizers or anti-inflammatory drugs[15].

In the elderly, pruritus, also called senile pruritus, is a typical symptom of physiological skin changes related to ageing. Skin in the elderly is characterized by intense dryness, caused by an altered skin barrier due to the thinning of the epidermis, a reduction in the terminal differentiation of keratinocytes, a decrease in lipid synthesis, the alteration of the hydrolipidic film related to a decline in the excretory function of the sweat and sebaceous glands, and increased transepidermal water loss[9,16]. The condition may be exacerbated by irritants (soap, wool, etc.) and environmental factors such as temperature and humidity[17]. Senile pruritus may cause considerable discomfort, insomnia and scratching[18]. Currently, only the use of emollients and moisturizers reduces the intensity of pruritus, but without any medical treatment.

The tested spray product is anemulsion containing dipropylen glycol, a moisturizing agent, squalane,a cutaneous protecting agent and isostearyl isostearate that stabilizes the lamellar lipid structure of the stratum corneum as well as polyphenols from *Camellia sinensis* (green tea) and *Tambourissa spp.* leaves, both known for their anti-inflammatory properties[19]. Polyphenols, especially Epigallocatechin-3-gallates (EGCG) extracted from *Camellia sinensis* leaves areknown for their antihistamine properties, inhibiting histidine decarboxylase, which is responsible for histamine synthesis in mastocytes, and reducing the influx of calcium in mastocytes and therefore the release of histamine in the extracellular matrix[20]. Moreover, the tested formulation contains enoxolone extract from liquorice root containing saponosides and flavonoids, reducing the impact of pruritus-triggering factors[21]. Enoxolone reduces the activity of histidine decarboxylase, responsible for converting L-histidine into histamine, inhibits the expression of protein kinase C (nPKC delta), involved in the

synthesis of histamine, and prevents cytoplasmic granules from releasing histamine[22].

Unpublished *in vitro* studies (NAOS internal data) showed that a combination of enoxolone and *Tambourissa spp.* extracts reduces the over expression of thymic stromal lymphopoietin (TSLP), a cytokine involved in the onset of pruritus in AD and that all three active compounds have antihistaminic properties, confirming previously made observations[12,20]. In other non-published *in vitro* studies (NAOS internal data), *Camellia sinensis* and *Tambourissa spp extracts* were both shown to be powerful inhibitors of induced NGF synthesis. Their combination potentiated the effects of each ingredient by inhibiting NGF over-expression by almost 100% in keratinocytes. The aim of this study was to determine the beneficial effect of a novel topical anti-pruritic spray containing polyphenols from *Camellia sinensis* and *Tambourissa spp* leaf extracts and enoxolone in patients with AD, psoriasis, CIU or senile pruritus through investigator assessments and patient perception of product efficacy and quality of life.

Methods

This multicenter, prospective, observational, non-comparative study was conducted by nine dermatologists and four pediatricians in Poland between September and December 2016 and complied with the Principles of the Declaration of Helsinki, Good Clinical Practices and local legal requirements for the conduct of such investigations. The study did not require any approval from local ethic committees prior to any inclusion of patients. However, patients and patients' care givers consented prior to participation.

Suitable patients were: (1) children aged between 4 months and 4yearswith mild to moderate AD with no episode of flare-up and receiving no medication for their AD, (2) adults with mild to moderate psoriasis with no episode of flare-up,(3) adults with CIU, and (4) patients aged 65 years or older with senile pruritus. All patients had to have, at inclusion, a disease-related pruritus score of at least 4 on a subject pruritus severity scale ranging from 0=none to 9 =severe[23]. During the observation period, patients were not allowed to apply any other cosmetic product to manage their pruritus.

Suitable patients received the test product in a neutral packaging and were instructed to use it for 21 days as often as necessary, holding the spray at a distance of about 20 cm from pruritic zones (body and face).

The evolution of pruritus at baseline and during the clinical study was assessed by using a validated questionnaire: the 5-D pruritus scale [24]. This scale ranged from 5 (=no pruritus) to 25 (=severe pruritus). The investigator assessed the clinical efficacy through the following clinical signs and symptoms: itching sensation, skin dryness, roughness, suppleness and desquamation. At baseline and after 21 days, the patients/ patient's care givers assessed on a 10-point scale from 0 = none to 9 = maximum their perception of their pruritus using a self-administered question-naire. Moreover he/she queried its impact on the patients' emotions, symptoms and functioning. The patients' quality of life (QOL) during the week preceding inclusion was assessed at baseline and after 21 days using the Polish version of the Skindex-29 questionnaire in adults. The Infants' Dermatitis QOL Index (IDQOL) and Family Dermatitis Index in children (FDI) were used for the AD group at the same time points[25, 26].

Moreover, a telephone interview, 24 hours after the first application, was carried out by the investigator to assess the perception and time of onset of efficacy of the spray. The investigators also collected information concerning the number of daily applications.

Whenever necessary, tolerance follow-up was carried out, in which case the investigators determined the nature and relationship to the tested product, as well as the need to interrupt applications or to administer corrective treatments.

A descriptive statistical analysis was performed. An intra-group comparison of data at baseline and

Day 21 regarding the efficacy population was made using a paired Student test (paired t-test).A comparison to baseline of quality of life assessments for each group was made using the Wilcoxon test. A statistical significance threshold level of 5% was chosen.

Results

As planned, 120 patients, 30 in each group, participated in this study and received the spray to be tested. Two patients, both in the AD group, were excluded from the efficacy analysis: one withdrew due to an adverse event and one due to non-respect of the protocol.

Demographic data for the efficacy population (N=118) is provided in Table 1. The subject age ranged from 1 to 89 years; more female patients participated. All patients had a pruritus score of at least 4/9.

The overall mean score using the5-Dpruritus scale at baseline was 13.3/25; for detailed results refer to Figure 1.At baseline, the overall mean intensity of itching sensation was 5.5/9, that of skin dryness 4.9/9, of skin roughness 4.6/9, desquamation 3.7/9 and of skin suppleness 3.9/9.

According to Skindex, at baseline, 35% of all adults had their emotions impacted, 47% suffered from symptoms and 30% were impacted in their functioning. Overall, 36% of the adult patients had their QOL impacted by pruritus. In children, scores for worsening of QOL according to the IDQOL and that of the FDI reached 7/30 and 6.9/30, respectively (Figure 2).

After 24 hours of use, more than 76% of all patients perceived the tested product as efficient. Overall, 93% of all patients rated onset of efficacy as rapid (within 60 seconds).

After 21 days, duration, intensity, disability and distribution of the patients' pruritus had significantly improved, with a decrease of the global score of 40% (8/25 vs 13.3/25 at baseline, all $p<0.01$; for details see Figure 1). The total 5-D pruritus score for AD patients had decreased by 51%, by 36% for psoriasis and senile pruritus patients respectively, and by 35% for CIU patients. The difference to baseline was statistically significant ($p<0.01$) in all groups.

Globally, itching sensation, skin dryness, rough-ness and suppleness, as well as desquamation and importance of skin lesions had improved by 63%, 52%, 53%, 26% 58% and 42%, respectively. All changes were statistically significant ($p<0.01$). Detailed scores are provided in Figure 3.

At the end of the observational period, all QOL items had improved by between 47% and 89% (Figure 2a and 2b, all $p<0.01$). According to Skindex, scores for the global QOL had decreased by 49% from baseline, as did scores for emotions (47%), symptoms (50%) and functioning (50%). All improvements from baseline were statistically significant ($p<0.01$).In AD patients, the IDQOL score decreased by 80% (1.4/30) and the FDI score by 89% (0.8/30). The global Skindex score decreased by 15% in patients with psoriasis, by 15% in CIU patients and by 19% in patients with senile pruritus. Differences to baseline were all statistically significant ($p<0.01$).

In all groups, investigators rated the test product positively: 98% confirmed its anti-pruritic and 100% confirmed its soothing properties, and 98% confirmed its excellent local tolerance. Overall, 98% of the patients perceived the test product as efficient for managing their pruritus. A total of 56% reported that the anti-pruritic effect was maintained after 6 hours and 60% reported that the spray continued to soothe their skin. More than 85% ofall patients were overall satisfied by the product.

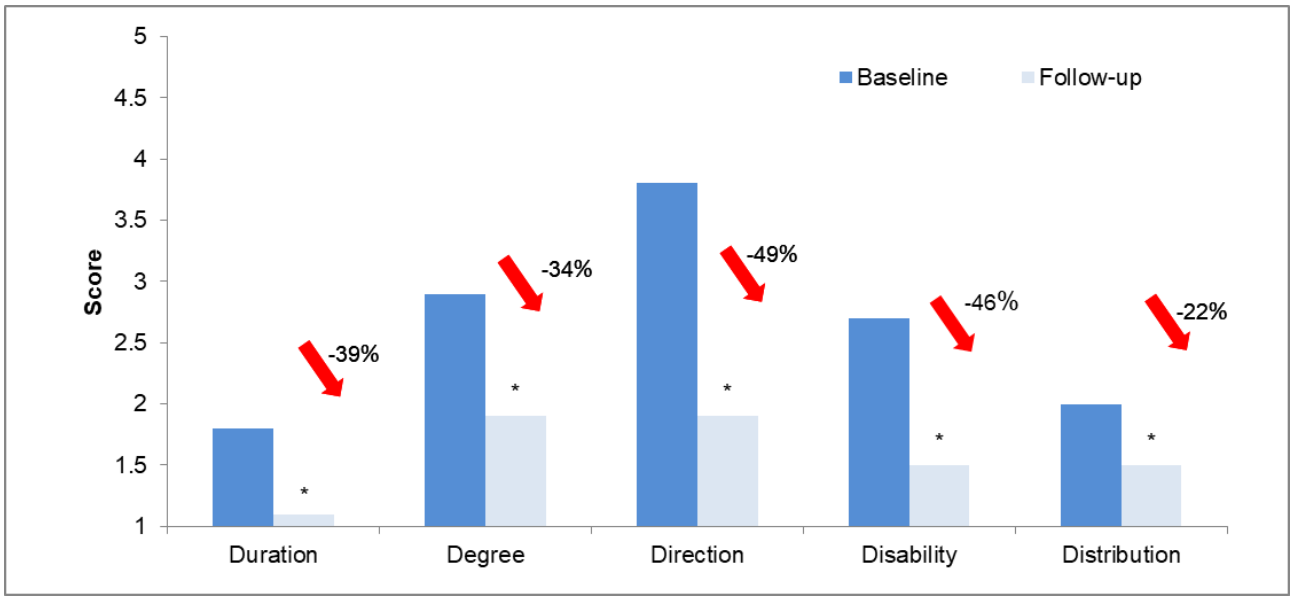
On average, patients with AD applied the spray 2.1 times/day, psoriasis patients 2.5 times / day, CIU patients 2.3 times / day and patients with senile pruritus2.9 times/ day.

When assessing local tolerance in the 118 patients suitable for the efficacy analysis, 99% tolerated the spray well. One 4-year-old infant with AD reported an intolerance reaction. The adverse event presented as erythematous patches, with a worsening of pruritus after two weeks of product use. Upon withdrawal of the product, the adverse event was immediately resolved.

Table 1: Demographic data of the efficacy population (N=118 patients)

	Atopic dermatitis	Psoriasis	Chronic idiopathic urticaria	Senile pruritus	Total
Number n	28	30	30	30	118
Female n(%)	11 (39%)	16 (53%)	18 (60%)	18 (60%)	63 (53%)
Male n(%)	17 (61%)	14 (47%)	12 (40%)	12 (40%)	55 (47%)
Mean age (years) (min, max)	3 (1, 4)	43 (21, 62)	45 (18, 82)	72 (66, 89)	41 (1, 89)

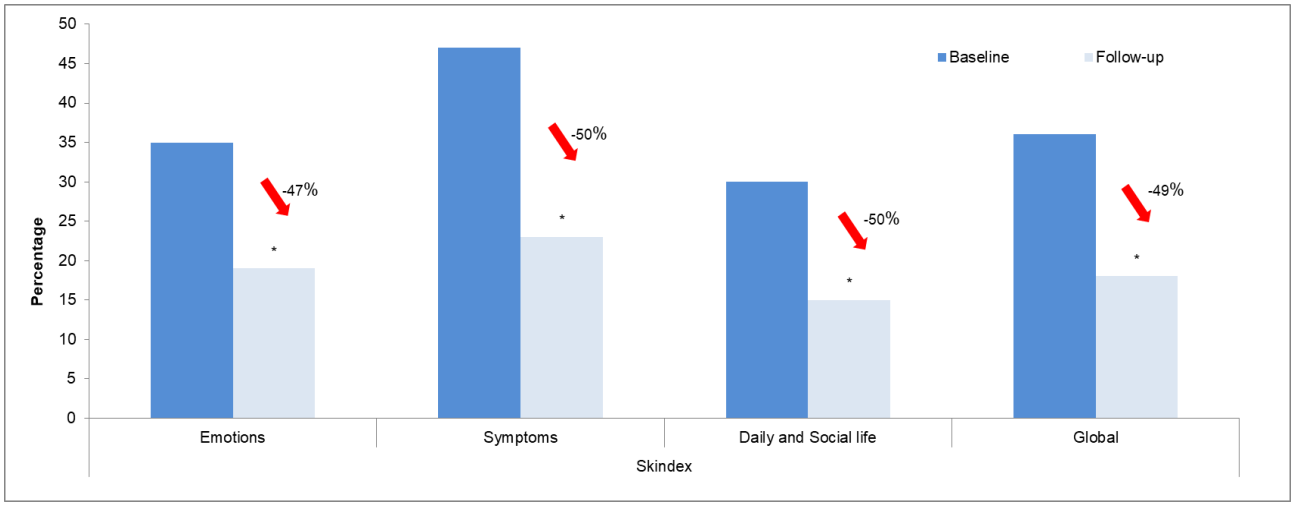
Figure 1 Mean 5-D pruritus scores at baseline and after 21 days of use (N= 118 patients)



* p<0.01 compared to Baseline
Scores ranged from 1 to 5.

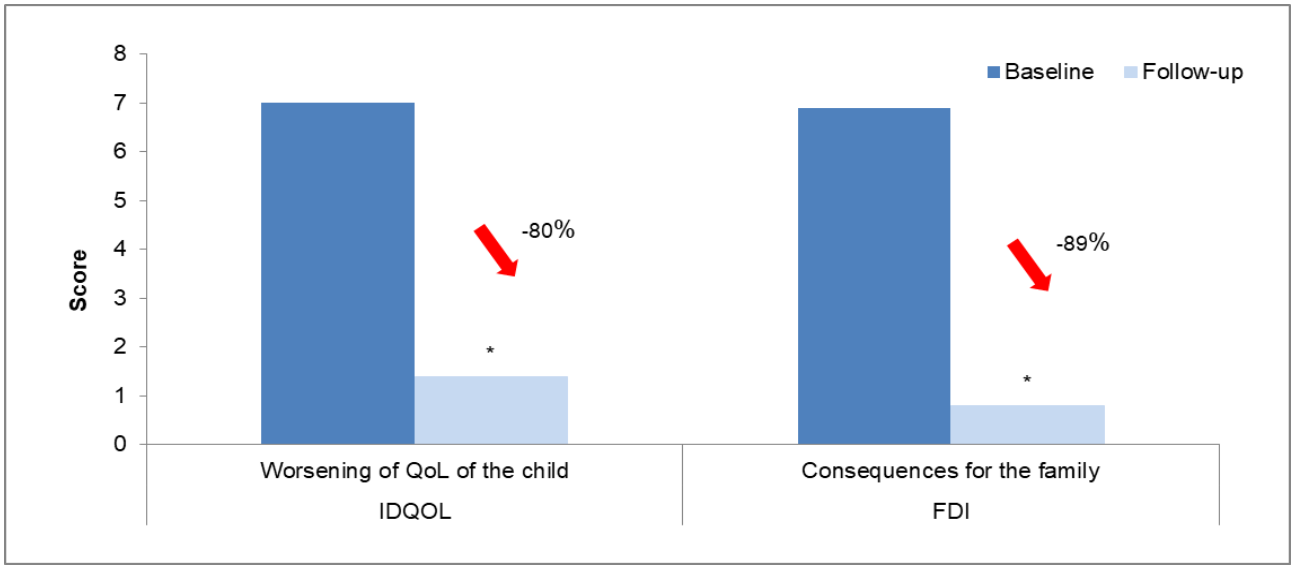
Figure 2 Skindex and Quality of Life assessments at baseline and follow-up (N= 118 patients)
Quality of life was assessed through the Skindex questionnaire for adult patients and through the IDQOL and FDI for children and their care givers, respectively.

Figure 2a Skindex



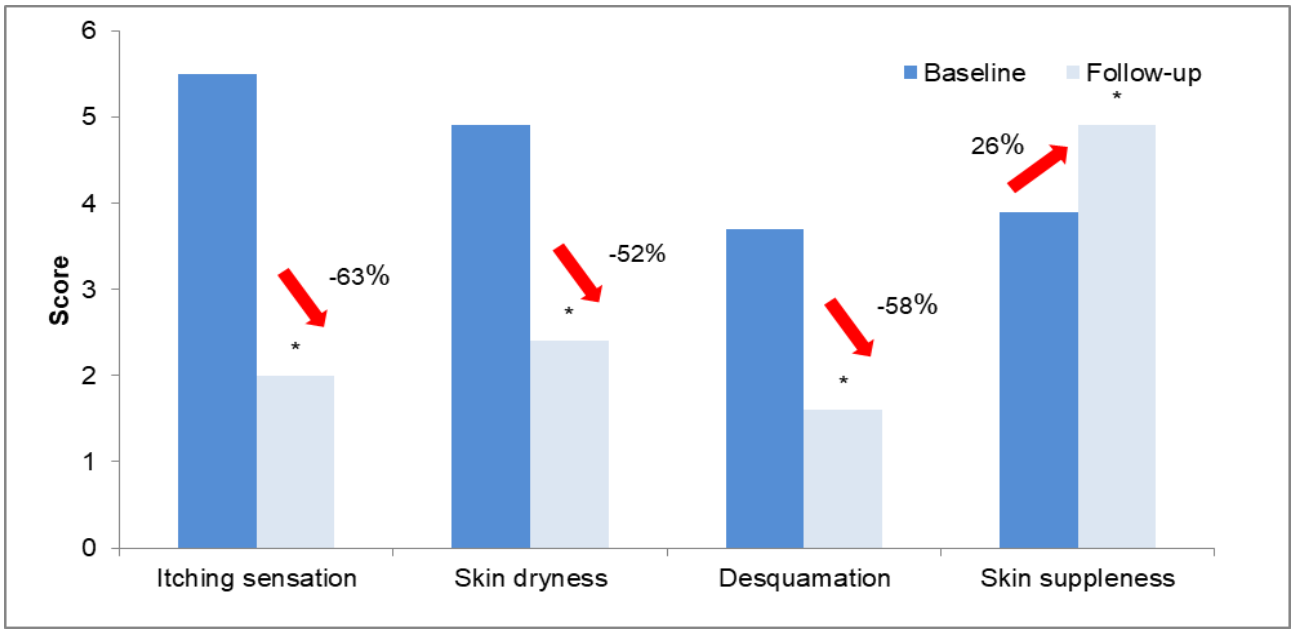
* p<0.01 compared to Baseline
Skindex scores ranged from 0 to 100%.

Figure 2b IDQOL and FDI



* p<0.01 compared to Baseline
IDQOL and FDI Scores ranged from 0 to 30.

Figure 3 Clinical symptoms of pruritus at baseline and follow-up visit (N=118 patients)



* p<0.01 compared to Baseline
The symptom score ranged from 0 to 9.

Discussion

This was the first time a spray formulation was tested in patients with pruritus. The present multicenter, prospective, observational, non-comparative study demonstrated significant (p<0.01) and rapid (60 seconds) relief of pruritus in patients with AD, psoriasis, CIU or senile pruritus. Albeit at baseline, the impact on QOL of AD patients and that of their care-givers was low, which may be due to the disease stage requiring no treatment, the tested spray still allowed a significant improvement of the patient's QOL (p<0.01) and the patient's/ care giver's perception of AD. In the adult population, similar benefits were observed, confirming that the tested spray efficiently relieved patients from their pruritus while also significantly improving their QOL (p<0.01).

A very large majority of patients appreciated the tested spray formulation for its efficacy, its

cosmetic characteristics and its pleasant use. The tested spray was well tolerated.

We acknowledge that the chosen non-comparative design to assess the benefit of our product, the population size in each group and the use of mainly subject-reported outcome measurements may give rise to limitations and bias. However, with the nature of the assessed symptom remaining difficult to assess through objective clinical evaluations, to date, patient self-reported assessments remain the most adequate means of measuring this symptom, even though, we concede that this could have been compared to a placebo. Despite this bias and limitation, we believe that our results confirm that specifically developed skin care products are able to improve symptoms of underlying skin conditions such as pruritus, thus potentially enhancing treatment and treatment compliance of conventional therapies when used adjunctively. Moreover, results obtained through this real-life study highlighted the impact of pruritus on the quality of life of patients.

To date, emollients remain the mainstay care of pruritus, especially in AD, psoriasis and senile pruritus. Despite reducing the severity of the symptom, they do not provide a cure. Different research projects on potential anti-pruritus agents, including κ receptor agonists, μ-opioid receptor antagonists, endocannabinoids such as palmitoylethanolamide (PEA) and menthol, have been conductedin the past to determine potential treatment targets and compounds, and anti-interleukin 31, crisaborole and serlopitant seem to be the novel diagnostic marker for allergic diseases and pruritus[27-32]. However, despite research, no anti-pruritic treatment has as yet been made available.

Further investigations may be necessary to assess the benefit of the tested spray in association with the emollients when used adjunctively for patients requiring treatments to manage their disease.

In conclusion, the novel proposed spray product significantly improves pruritus, is well-tolerated, and thus improves the patient's daily life and the management of those underlying diseases.

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References

1. Weisshaar E, Szepietowski JC, Darsow U, Misery L, Wallengren J, Mettang T, Gieler U, Lotti T, Lambert J, Maisel P, Streit M, Greaves MW, Carmichael AJ,Tschachler E, Ring J, Ständer S.European guideline on chronic pruritus. Acta Derm Venereol. 2012;92(5):563-81. doi: 10.2340/00015555-1400
2. Bautista DM, Wilson SR, Hoon MA. Why we scratch an itch: the molecules, cells and circuits of itch. Nat Neurosci. 2014;17(2):175-82. doi: 10.1038/nn.3619
3. Pereira MP, Stander S. Assessment of severity and burden of pruritus. Allergol Int. 2017;66(1):3-7. doi: 10.1016/j.alit.2016.08.009.
4. Kopyciok ME, Stander HF, Osada N, Steinke S, Stander S. Prevalence and Characteristics of Pruritus: A One-Week Cross-sectional Study in a German Dermatology Practice. Acta Derm Venereol. 2016;96(1):50-5. doi: 10.2340/00015555-2166.
5. Ikoma A, Steinhoff M, Stander S, Yosipovitch G, Schmelz M. The neurob-iology of itch. Nat Rev Neurosci. 2006;7(7):535-47.
6. Halvorsen JA, Dalgard F, Thoresen M, Thoresen M, Bjertness E, Lien L. Itch and mental distress: a cross-sectional study among late adolescents. Acta Derm Vener-

eol. 2009;89(1):39-44. doi: 10.2340/0001-5555-0554.
7. Dawn A, Papoiu AD, Chan YH, Rapp SR, Rassette N, Yosipovitch G. Itch characteristics in atopic dermatitis: results of a web-based questionnaire. Br J Dermatol. 2009;160(3):642-4. doi: 10.1111/j.1365-2133.2008.08941.x.
8. Roblin D, Wickramasinghe R, Yosipovitch G. Pruritus severity in patients with psoriasis is not correlated with psoriasis disease severity. J Am Acad Dermatol. 2014;70(2):390-1.
9. Al-Nuaimi Y, Sherratt MJ, Griffiths CE. Skin health in older age. Maturitas. 2014;79(3):256-64.doi: 10.1016/j.maturitas.2014.08.005.
10. Nakamura M, Toyoda M, Morohashi M. Pruritogenic mediators in psoriasis vulgaris: comparative evaluation of itch-associated cutaneous factors. Br J Dermatol. 2003;149(4):718-30.
11. Akiyama T, Carstens E. Neural processing of itch. Neuroscience. 2013;250:697-714.
12. Wilson SR, Thé L, Batia LM, Beattie K, Katibah GE, McClain SP, Pellegrino M, Estandian DM, Bautista DM.The epithelial cell-derived atopic dermatitis cytokine TSLP activates neurons to induce itch. Cell. 2013;155(2):285-95.doi: 10.1016/j.cell.2013.08.057.
13. Ziegler SF, Roan F, Bell BD, Stoklasek TA, Kitajima M, Han H. The biology of thymic stromal lymphopoietin (TSLP). Adv Pharmacol. 2013;66:129-55.doi: 10.1016/B978-0-12-404717-4.00004-4.
14. Schafer PH, Truzzi F, Parton A, Wu L, Kosek J, Zhang LH, Horan G, Saltari A, Quadri M, Lotti R, Marconi A, Pincelli C. Phosphodiesterase 4 in inflammatory diseases: Effects of apremilast in psoriatic blood and in dermal myofibroblasts through the PDE4/CD271 complex. Cell Signal. 2016;28(7):753-63.doi: 10.1016/j.cellsig.2016.01.007.
15. Soter NA. Treatment of chronic spontaneous urticaria. J Drugs Dermatol. 2015;14(4):332-4.
16. Blume-Peytavi U, Tan J, Tennstedt D, Boralevi F, Fabbrocini G, Torrelo A, Soares-Oliveira R, Haftek M, Rossi AB, Thouvenin MD, Mangold J, Galliano MF, Hernandez-Pigeon H, Aries MF, Rouvrais C, Bessou-Touya S, Duplan H, Castex-Rizzi N, Mengeaud V, Ferret PJ, Clouet E, Saint Aroman M, Carrasco C, Coutanceau C, Guiraud B, Boyal S, Herman A, Delga H, Biniek K, Dauskardt R.. Fragility of epidermis in newborns, children and adolescents. J Eur Acad Dermatol Venereol. 2016;30 Suppl 4:3-56.doi: 10.1111/jdv.13636.
17. Wolf R, Parish LC. Effect of soaps and detergents on epidermal barrier function. Clin Dermatol. 2012;30(3):297-300.doi: 10.1016/j.clindermatol.2011.08.021.
18. Humbert P, Dréno B, Krutmann J, Luger TA, Triller R, Meaume S, Seité S. Recommendations for managing cutaneous disorders associated with advancing age. Clin Interv Aging. 2016;11:141-8.doi: 10.2147/CIA.S96232. eCollection 2016.
19. Segond C, Chanteloube F, Loiseau A, Petit V, Theron E. Patent WO2010037545A1: Use of polyphenols to treat skin conditions. 2015, United States, Bayer Consumer Care AG (Basel, CH), 9114115. Available on http://www.freepatentso-nline.com/y2003/0175234.html.Last accessed: 30 January 2018.
20. Ruiz-Perez MV, Pino-Angeles A, Medina MA, Sanchez-Jimenez F, Moya-Garcia AA. Structural perspective on the direct inhibition mechanism of EGCG on mammalian histidine decarboxylase and DOPA decarboxylase. J Chem Inf Model. 2012;52(1):113-9.doi: 10.1021/ci200221z.
21. Akasaka Y, Yoshida T, Tsukahara M, Hatta A, Inoue H. Glycyrrhetinic acid prevents cutaneous scratching behavior in

mice elicited by substance P or PAR-2 agonist. Eur J Pharmacol. 2011;670(1): 175-9.doi: 10.1016/j.ejphar.2011.08.043.

22. Imanishi N, Kawai H, Hayashi Y, Yatsunami K, Ichikawa A. Effects of glycyrrhizin and glycyrrhetinic acid on dexamethasone-induced changes in histamine synthesis of mouse mastocytoma P-815 cells and in histamine release from rat peritoneal mast cells. Biochem Pharmacol. 1989;38(15):2521-6.
23. Reich A, Heisig M, Phan NQ, Taneda K, Takamori K, Takeuchi S, Furue M, Blome C, Augustin M, Ständer S, Szepietowski JC.Visual analogue scale: evaluation of the instrument for the assessment of pruritus. Acta Derm Venereol.. 2012;92(5):497-501.doi: 10.2340/00015555-1265.
24. Elman S, Hynan LS, Gabriel V, Mayo MJ. The 5-D itch scale: a new measure of pruritus. Br J Dermatol. 2010;162(3):587-93.doi: 10.1111/j.1365-2133.2009.09586.x.
25. Lewis-Jones MS, Finlay AY, Dykes PJ. The Infants' Dermatitis Quality of Life Index. Br J Dermatol. 2001;144(1):104-10.
26. Janowski K, Steuden S, Bereza B. The Polish version of Skindex-29: psychometric properties of an instrument to measure quality of life in dermatology. Postepy Dermatol Alergol. 2014;31(1):12-20.doi: 10.5114/pdia.2014.40654.
27. Pandey M, Zhang JH, Mishra SK, Adikaram PR, Harris B, Kahler JF, Loshakov A, Sholevar R, Genis A, Kittock C, Kabat J, Ganesan S, Neubig RR, Hoon MA, Simonds WF. A central role for R7bp in the regulation of itch sensation. Pain. 2017;158(5):931-44.doi: 10.1097/j.pain.0000000000000860.
28. Soeberdt M, Molenveld P, Storcken RP, Bouzanne des Mazery R, Sterk GJ, Autar R, Bolster MG, Wagner C, Aerts SN, van Holst FR, Wegert A, Tangherlini G, Frehland B, Schepmann D, Metze D, Lotts T, Knie U, Lin KY, Huang TY, Lai CC,Ständer S, Wünsch B, Abels C.Design and Synthesis of Enantiomerically Pure Decahydroquinoxalines as Potent and Selective kappa-Opioid Receptor Agonists with Anti-Inflammatory Activity in Vivo. J Med Chem. 2017;60(6):2526-51.doi: 10.1021/acs.jmedchem.6b01868.
29. Mettang T, Stander S, Kremer AE. [Treatment of chronic itch in systemic disease. Current standards]. Internist (Berl). 2015;56(12):1369-78.
30. Onuki Y, Machida Y, Yokawa T, Seike C, Sakurai S, Takayama K. Magnetic resonance imaging study on the physical stability of menthol and diphenhydramine cream for the treatment of chronic kidney disease-associated pruritus. Chem Pharm Bull (Tokyo). 2015;63(6):457-62.doi: 10.1248/cpb.c15-00192.
31. Kulczycka-Siennicka L, Cynkier A, Waszczykowska E, Wozniacka A, Zebrowska A. The Role of Intereukin-31 in Pathogenesis of Itch and Its Intensity in a Course of Bullous Pemphigoid and Dermatitis Herpetiformis. Biomed Res Int. 2017;2017:5965492.doi: 10.1155/2017/5965492.
32. Paller AS, Tom WL, Lebwohl MG, Blumenthal RL, Boguniewicz M, Call RS, Eichenfield LF, Forsha DW, Rees WC, Simpson EL, Spellman MC, Stein Gold LF,Zaenglein AL, Hughes MH, Zane LT, Hebert AA. 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(3):494-503.e6.doi: 10.1016/j.jaad.2016.05.046.