
Pilot, multicenter, double-blind, randomized placebo-controlled bilateral comparative study of a combination of calcipotriene and nicotinamide for the treatment of psoriasis

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Background: Calcipotriene has limited efficacy in treating psoriasis. By inhibiting proinflammatory cytokines such as interleukin-12, interleukin-23, and tumor necrosis factor- α , nicotinamide may enhance the efficacy of calcipotriene therapy when used in combination.

Objective: We sought to determine if the combination of nicotinamide with calcipotriene is more effective than either component alone.

Methods: In this randomized, double-blinded, multicenter 7-arm bilateral comparison-controlled trial, patients were randomized to two of 7 treatments—placebo, calcipotriene 0.005% alone, nicotinamide 1.4% alone, calcipotriene plus nicotinamide 0.05%, calcipotriene plus nicotinamide 0.1%, calcipotriene plus nicotinamide 0.7%, or calcipotriene plus nicotinamide 1.4%—each administered to lesions on one side of the body or to one of two lesions at least 5 cm apart, for 12 weeks. Efficacy was measured using a clear to almost clear outcome.

Results: In all, 50.0% of patients in the calcipotriene and nicotinamide 1.4% combination group achieved a clear to almost clear outcome at week 12, compared with only 18.8% of patients treated with placebo ($P = .002$), 25% of patients treated with nicotinamide 1.4% alone ($P = .02$), and 31.5% of patients treated with calcipotriene alone ($P = .096$). A dose-response trend existed for increasing concentrations of nicotinamide, but it was not significant.

Limitations: The relatively small patient numbers, relatively high placebo effect, and maximum in-life portion of only 12 weeks of dosing are weaknesses of the study.

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of Dr Lebwohl's department own patents on short-contact tazarotene, topical genistein, and use of the excimer laser for vitiligo; he serves on speakers bureaus for Abbott Laboratories, Amgen Inc, Centocor, Galderma, Genentech, PharmaDerm, Stiefel, and Warner Chilcott; he has advisory board agreements with Abbott Laboratories, Amgen Inc, Astellas, Centocor Inc, Galderma, Genentech, Medicis, Novartis, Stiefel, and Warner Chilcott; he is a consultant for Dermipor, PharmaDerm, Sanofi-Aventis, Triax, and York Pharma. Dr Even-Chen is an employee of Dermipor. Ms Levine, Ms Lipets, Dr Pritulo, Dr Svyatenko, and Dr Andrashko have no conflicts of interest to declare.

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Conclusion: This study provides evidence that using the combination nicotinamide and calcipotriene may provide additional benefit in the topical treatment for patients with psoriasis and may be an adequate steroid-sparing substitute treatment. (J Am Acad Dermatol 2010;63:775-81.)

Key words: calcipotriene; nicotinamide; psoriasis; topical psoriasis treatment; randomized control trial.

Calcipotriene has been used for psoriatic topical therapy for many years, but its use is limited by its moderate efficacy.¹ Recent advances in the understanding of the immunologic basis of psoriatic plaques—such as the increased expression of T-helper cell 1 and T-helper cell 17 T-cell cytokines, adhesion molecules, nuclear factor- κ B activation, and prominent neutrophil accumulation and increased production of nitric oxide—have led to the development of nicotinamide as an investigational drug in patients with psoriasis.² Nicotinamide is an inhibitor of poly adenosine diphosphate-ribose polymerase-1, which enhances nuclear κ B-mediated transcription and thereby facilitates expression of inflammatory cytokines, chemokines, adhesion molecules, and inflammatory mediators such as interleukin-12, interleukin-23, and tumor necrosis factor- α .³ Nuclear factor- κ B is activated in both lesional and nonlesional skin from patients with psoriasis.⁴ Indeed, preliminary studies (Dermipor, unpublished data) showed that nicotinamide markedly impaired the proliferation and differentiation of human keratinocytes of the HaCaT cell line as early as 2 days after administration of the drug. As a result of these mechanisms, it has been proposed that nicotinamide may prove a useful addition to the antipsoriatic repertoire and may enhance the efficacy of calcipotriene therapy when used in combination.⁵

A new medication, which consists of a macrogel, polyethylene glycol-based ointment that contains calcipotriene 0.005% and nicotinamide at different concentrations (0.05%, 0.1%, 0.7%, and 1.4%), has been found to be highly stable for 24 months. In preclinical studies, the combination drug was shown to induce a significantly larger granular layer in scaly areas of mouse tail skin with abnormal maturation (95% orthokeratosis in the 0.21% nicotinamide plus

0.005% calcipotriene group vs 68% in the control group) (Dermipor, unpublished data). Ex vivo dermal penetration studies confirmed that calcipotriene does not penetrate through the skin and does not affect the skin permeation of nicotinamide (Franz cell—porcine ear whole skin, 24 hours), which is known to have a safe absorption profile with negligible dermal irritant properties. Acute dermal irritation/corrosion in the rabbit performed by Harlan Biotech Israel Ltd (Rehovot, Israel) classified the ointment containing 0.21% nicotinamide and .005% calcipotriene as a “negligible” dermal irritant. Furthermore, repeated-insult patch test skin sensitization

of 200 healthy volunteers subjected to 9 daily exposures of 0.21% nicotinamide plus 0.005% calcipotriene with a repeated exposure after 2 weeks reported no adverse reaction at any point. Similar results were observed in photoallergy maximization testing on 50 healthy volunteers and phototoxicity potential by ultraviolet A irradiation on 30 healthy volunteers (Dermipor, unpublished data, performed at AMA Laboratories, New City, NY), thereby considering the ointment a nonprimary irritant and nonprimary sensitizer to the skin.

The goal of the current study was thus to determine if the combination of nicotinamide with calcipotriene is more effective than either component alone in patients with psoriasis. We now report the results of a multicenter, double-blind, randomized comparative study versus placebo and a dose-finding study in adult patients with chronic plaque psoriasis.

METHODS

Patients

The investigational new drug application (76,330) was cleared by the Food and Drug Administration

CAPSULE SUMMARY

- Nicotinamide might enhance the efficacy of calcipotriene when used in combination for topical psoriasis treatment.
- This randomized, double-blinded, multicenter trial found that 50.0% of patients treated with nicotinamide plus calcipotriene achieved a clear to almost clear outcome, compared with 18.8% of patients treated with placebo, 25% of patients treated with nicotinamide alone, and 31.5% of patients treated with calcipotriene alone.
- The optimal concentration of this combination treatment is 0.005% calcipotriene plus 1.4% nicotinamide.

(FDA) on November 17, 2006. In addition, the Ukraine central independent ethics committee and the institutional review board at each of the 5 investigative sites in Eastern Europe approved the study protocol. Each patient provided written informed consent before any study-related procedures were initiated. Eligible patients included men and women 18 years or older with moderate psoriasis, defined as symmetrical plaques (bilateral lesions) or two plaques at least 5 cm apart on the same side of the body, with plaque size greater than 2×2 cm but smaller than 15×15 cm. Patients with greater than 15% body surface area involvement were excluded from the study, as were patients with only scalp, nail, flexural, palmoplantar, or pustular psoriasis.

Patients who had participated in a clinical trial within the last 3 months before enrollment were excluded from the trial. Patients treated with topical treatment for psoriasis (corticosteroids, retinoids, vitamin-D derivatives) within 2 weeks of enrollment in the study; patients treated with systemic antipsoriatic therapies (biologics, methotrexate, cyclosporine, retinoids) within 1 month before enrollment; patients taking systemic niacin or multivitamins within the past 2 weeks; and patients starting or modifying a treatment with beta-blockers within 1 month of enrollment were excluded. Female patients of childbearing age were required to have a negative pregnancy test result at inclusion, 6 weeks, and at the end of the study. Before enrollment, all patients were screened for significant hematologic, renal, or liver disease/laboratory abnormalities; patients with hemoglobin below 10.0 g/dL, hematocrit below 30%, white blood cell count below $3000/\mu\text{L}$, platelets below $100,000/\mu\text{L}$, or aspartate aminotransferase or alanine aminotransferase above 3 times the upper limit of normal in the DILA Central Laboratory in Kiev, Ukraine, were excluded from the study. Patients were also screened for a history of major medical or psychiatric illness or surgery, which, in the judgment of the investigator, was deemed to potentially interfere with study medication metabolism and/or study implementation and/or assessment of study parameters. Because of the potential for nicotinamide-induced potentiation of carbamazepine and primidone activity, patients taking these medications were excluded from the study. Patients were required to be willing to self-administer the experimental ointment or have a qualified person administer it.

Study design

The study was a randomized, double-blinded, multicenter 7-arm bilateral comparison-controlled trial whose purpose was to find an optimal, safe

dose of the nicotinamide component of the medication while comparing the various doses of the medication with placebo or calcipotriene alone or nicotinamide alone. In accordance with a randomization table generated by Data Management and Statistics (Technostat Ltd, Raanana, Israel), eligible patients were randomized in equal ratios to two of 7 treatments—placebo, calcipotriene 0.005% alone, nicotinamide 1.4% alone, calcipotriene 0.005% plus nicotinamide 0.05% (a combination hitherto referred to as Dermipsor 101 [DPS-101] [Demipsor, Rehovot, Israel] 0.05%), calcipotriene 0.005% plus nicotinamide 0.1% (DPS-101 0.1%), calcipotriene 0.005% plus nicotinamide 0.7% (DPS-101 0.7%), or calcipotriene 0.005% plus nicotinamide 1.4% (DPS-101 1.4%)—each administered to lesions on one side of the body or to one of two lesions at least 5 cm apart, for 12 weeks. The patients, investigators, study site personnel, sponsor, and laboratories were unaware of the treatment assignments; throughout the study, the study investigator retained a set of code envelopes that were to be opened by the investigator only if deemed necessary after a serious adverse event. The 7 treatment types were provided in identical 60-g aluminum tubes, and the patients were to apply the ointments twice daily, in the morning and at bedtime, on the lesion areas only. Compliance was assessed during all posttreatment visits using the weight of the used medication (tube with cap) compared with the weight of the original medication. The ointments were provided by Dermipsor Ltd, Rehovot, Israel.

A qualified investigator from each of the 5 sites performed clinical assessments at each of 7 visits. The investigators remained blinded to all treatments and laboratory results. In compliance with regulations set forth by Good Clinical Practice and the International Conference on Harmonisation guidelines, the clinical research associate at each site checked the data in the case report forms through direct access to the source documents or medical files.

Efficacy assessment

The primary efficacy end point of the study was the percentage of patients who achieved clear to almost clear psoriatic symptoms at the end of the study period. In this case, “clear” was defined as no elevation above normal-appearing skin, no scaling, and no erythema; “almost clear” was defined as no elevation above normal-appearing skin, surface dryness with some white coloration, and slight-to-moderate red coloration. This definition of “clear to almost clear” is similar to the Physician Global Assessment definition of “absent to very mild

disease,” in which “absent” disease is defined as no evidence of redness, thickness, or scaling, and “very mild disease” is defined as lesions with some discoloration and minimal thickness. During the introductory meeting for the study, a scoring training session was conducted using photographs of various types of psoriatic lesions. The percentage of patients achieving a state of clear to almost clear was recorded in each of the 7 groups during each week of the trial.

Safety

Collection and follow-up of adverse events and hematology and blood chemistry laboratory results were assessed throughout the study and for a period of 30 days after the study ended.

Statistical analysis

The sample size was estimated based on the following assumptions: a parabolic dose-response curve if the optimal nicotinamide dose is either 0.1% or 0.7% and a linear dose-response curve if the optimal nicotinamide dose is either 0.05% or 1.4%; expected mean improvement in psoriasis severity of 16% for placebo, 58% for calcipotriene alone, and 20% for nicotinamide 1.4% alone; an overall SD for each treatment of 30%; a ratio of between-subject variance to total variance of 0.9; and the conditions that the optimal dose was chosen correctly, the optimal dose average improvement being higher than the average improvement of placebo and of calcipotriene alone and of nicotinamide alone. Based on the above assumptions, 126 patients were deemed to be needed to obtain at least 80% power—85.7%, 80.7%, 96.3%, and 94.8% for optimal doses of nicotinamide 0.05%, 0.1%, 0.7%, and 1.4%, respectively. Allowing for a 20% dropout rate, 168 patients were thus required for the study.

Populations analyzed were the safety analysis set, which included all randomized patients who used one of the study medications at least once, and the intention-to-treat population, which included all patients included in the safety analysis set and with at least one postbaseline measurement. Primary efficacy analysis, conducted on the intention-to-treat cohort, incorporated descriptive statistics by visit and improvement from baseline by group. A general linear model was estimated using software (SAS, Version 9.1, SAS Institute Inc, Cary, NC); all pairwise comparisons between treatments accounting for multiple comparisons with a Tukey adjustment were performed. Primary efficacy was deemed to have been met if the optimal DPS-101 dose—0.05%, 0.1%, 0.7%, or 1.4%—would lead to a higher percentage of patients having achieved clear to almost clear

compared with placebo, calcipotriene alone, and nicotinamide 1.4% alone. Dose-response curves fitted using a quadratic model where the dependent variable was the improvement in psoriatic lesions and the independent variables were the nicotinamide dose (as a continuous variable from 0%–1.4%) and the subject effect were constructed for 5 groups: the 4 groups treated with calcipotriene and nicotinamide, and the calcipotriene group.

RESULTS

Patients

In all, 168 patients were randomized as part of the intention-to-treat population for the study; of this group, 164 (97.6%) completed the study (Fig 1). Four patients (2.4%) discontinued the study: one patient treated with nicotinamide monotherapy and calcipotriene monotherapy, because of patient noncompliance; one patient treated with DPS-101 0.1% and calcipotriene monotherapy, because of withdrawal of consent; one patient treated with DPS-101 0.7% and DPS-101 0.05%, because of protocol violation; and one patient treated with DPS-101 1.4% and DPS-101 0.7%, because of patient noncompliance. Treatment groups were balanced by age and sex, with similar prevalence of medical history (data not shown).

Adherence

The percent of missed treatments (patients who missed at least one treatment during the entire period between the visits) did not exceed 16.7% (at visit 5 from the DPS-101 1.4% group). The average number of missed treatments did not exceed 5 per visit group. Further, the average amount of used ointment had a tendency to decrease over time in all groups. However, no major differences were apparent in average consumption between the groups in any of the visits.

Treatment efficacy

There were no significant differences in the psoriatic lesions among the patients in the different treatments at the onset of the study. After 12 weeks of treatment, 50% (24 of 47) of patients treated with DPS-101 1.4% achieved the stage of clear to almost clear of disease symptoms, compared with only 18.8% (9 of 48) of patients treated with placebo ($P = .002$), 25% (12 of 47) of patients treated with nicotinamide 1.4% alone ($P = .02$), and 31.5% (15 of 46) of patients treated with calcipotriene alone ($P = .096$) (Fig 2 and Table 1). Because of the small cohort size, statistical significance was not achieved when comparing the DPS-101 groups to the calcipotriene alone group, but a trend toward significance was

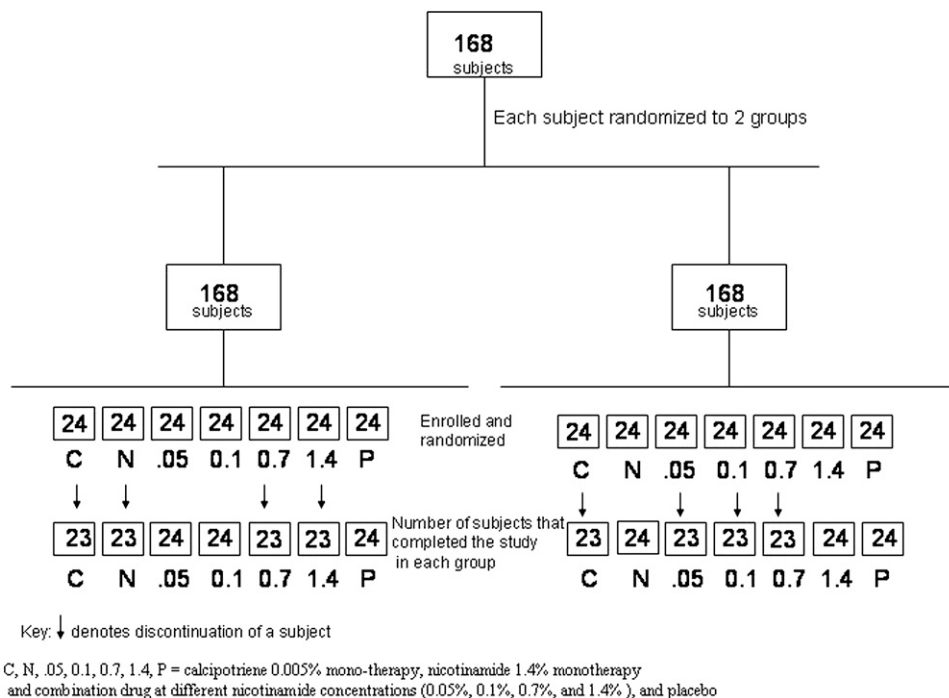


Fig 1. Participation flow diagram.

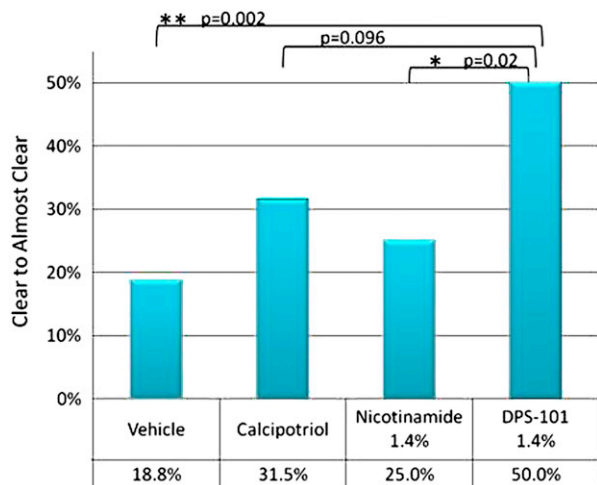


Fig 2. Fisher exact *P* values for percent of patients achieving clear to almost clear at week 12. Patients were randomized to receive two of 7 topical treatments as described in "Study design"; *n* = 48 for each treatment. Scores were then recorded at onset of study and at week 12 of study. Percent of patients achieving clear to almost clear for each treatment is shown under treatment name. *P* values shown were calculated for each treatment compared with its bracketed treatment. Asterisk(s) signifies statistical significance.

demonstrated. Furthermore, a limited dose-response curve was evident among the DPS-101 groups, with the largest improvement observed at week 12 in the DPS-101 1.4% group. In the DPS-101 1.4% group,

Table I. Fisher exact *P* values achieving clear to almost clear

	Placebo	Calcipotriol 0.005%	Nicotinamide 1.4%
Placebo			
Calcipotriol 0.005%	.238		
Nicotinamide 1.4%	.622	.650	
DPS 101 0.05%	.042	.522	.190
DPS 101 0.1%	.002	.096	.020
DPS 101 0.7%	.339	1.000	.819
DPS 101 1.4%	.002	.096	.020

DPS 101, Dermipsor 101.

weeks 4 to 6 showed initial onset of action. Clear to almost clear results increased from 2% at week 4 to 14.6% at week 6, to 16.7% at week 8, to 33.3% at week 10, and to 50% at week 12.

Adverse events and safety

The total number of patients who reported any adverse event was 11 (23%) in the placebo group, 9 (19%) in the calcipotriene monotherapy group, 12 (25%) in the DPS-101 0.05% group, 9 (19%) in the DPS-101 0.1% group, 15 (31%) in the DPS-101 0.7% group, 15 (31%) in the DPS-101 1.4% group, and 16 (33%) in the nicotinamide monotherapy group. No patients discontinued the study as a result of adverse events. A total of 65% of the reported adverse events were mild; one (hypertensive crisis) was severe, in a

Table II. Adverse events in relation to treatment

Relation to treatment	Placebo	Calcipotriol 0.005%	DPS 101 0.05%	DPS 101 0.1%	DPS 101 0.7%	DPS 101 1.4%	Nicotinamide 1.4%
Probable	8%	2%	2%	2%	13%	8%	10%
Possible	4%	2%	6%	0%	6%	10%	10%
Probably not	6%	8%	8%	2%	4%	6%	2%
Not related	8%	8%	8%	15%	8%	8%	10%
Any adverse event	23%	19%	25%	19%	31%	31%	33%

DPS 101, Dermiporsor 101.

patient randomized to both the DPS-101 0.7% and calcipotriene monotherapy groups, but was deemed to be a result of the patient's underlying hypertension, and this patient completed the study after resolution of her hypertensive crisis in the hospital. There were no statistically significant differences between groups in the rate of adverse events that were considered to have a probable or possible relationship to treatment (Table II). The adverse events in the probable or possibly related categories were related to the drug administration site including burning, erythema, and pruritus. Other adverse events nonrelated to the study included gastrointestinal upset, respiratory inflammation or infection, headache, fatigue, angina, and hypertension.

DISCUSSION

The data presented in this report suggest that DPS-101 1.4% may prove effective as an alternative therapeutic option to calcipotriene monotherapy and may provide an attractive option for patients seeking an effective corticosteroid-sparing topical psoriatic agent.

Corticosteroids have traditionally served as the mainstay of topical psoriatic therapy because of their short-term efficacy and ease of use. Nevertheless, there remains great interest in identifying corticosteroid-sparing topical psoriatic therapies to avoid many of the detrimental effects of long-term corticosteroid use, which include skin breakdown, infections, and drug dependence. Corticosteroid-sparing psoriatic agents include topical immunosuppressants, the vitamin-D analogs calcipotriene and tacalcitol, the vitamin-A analog tazarotene, tars, and anthralin. As calcineurin inhibitors, the immunosuppressants tacrolimus and pimecrolimus have been studied as corticosteroid-sparing agents in patients with plaque psoriasis, but a recent FDA warning linking these medications with certain types of lymphoma has curtailed their use of late.⁶

The vitamin-A and -D analogs are effective in reversing keratinocyte hyperproliferation and thereby reducing the severity of psoriatic plaques. Calcipotriene specifically, a topical vitamin-D

analog, has been used for more than a decade worldwide to treat psoriasis and is safe for long-term use. In the United States, calcipotriene is often used in combination with other topical treatments, not as monotherapy. A number of recent trials found that combined use of daily calcipotriene and super-potent corticosteroids—either halobetasol in a pulse therapy pattern or daily betamethasone—may actually be more efficacious and better tolerated than either agent alone.⁷ Similarly, Kragballe et al⁸ recently identified a trend toward efficacy with a calcipotriol-betamethasone compound product over a 52-week period, compared with 4 weeks of the two-compound product followed by 48 weeks of calcipotriol alone.

In this pilot study, we used a compound product that does not include corticosteroid—calcipotriene and nicotinamide—and demonstrated a similar trend toward efficacy. Our results demonstrate statistical significance for DPS-101 0.1% and 1.4% versus placebo and versus nicotinamide monotherapy, with a promising trend versus calcipotriene monotherapy. As noted above, 50% of patients treated with DPS-101 1.4% achieved the stage of clear to almost clear of disease symptoms, similar to the results reported for calcipotriol-betamethasone in which 48% of patients reached the disease stage of absent to very mild disease.⁸ In our study, all study groups shared identical safety profiles, and the trend toward improved lesions with the DPS-101 1.4% group suggests that the DPS-101 1.4% combination is most effective. Weaknesses of this study include relatively small patient numbers, relatively high placebo effect, and maximum in-life portion of only 12 weeks of dosing.

CONCLUSION

In summary, this is a promising dose-ranging study that, in our opinion, justifies further investigation using the 1.4% combination product (DPS-101 1.4%) compared with nicotinamide alone, calcipotriene alone, placebo arm, and ultimately comparing it with calcipotriene-corticosteroid combination therapy to determine whether nicotinamide-based therapy has potential as a steroid-sparing agent.

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