Original Research

A Double-blind, Placebo-controlled, Randomized Trial of XP-828L (800 mg) on the Quality of Life and Clinical Symptoms of Patients with Mild-to-Moderate Psoriasis

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Abstract

In a placebo-controlled clinical trial, the dietary supplement XP-828L (commercialized as Dermylex™) demonstrated potential to reduce symptoms associated with mild-to-moderate psoriasis at a dose regimen of 5 g daily for 56 days. However, recent *in vivo* data in humans and animals suggest a daily dose of 800 mg could be more efficient than a 5-g dose. However, no well-structured clinical study has confirmed this hypothesis. The goal of the present study is to examine the effect of XP-828L at a daily dose of 800 mg on the quality of life and disease severity in patients with mild-to-moderate psoriasis. XP-828L at 800 mg per day (n=16) or placebo (n=10) was given orally for 56 days. Efficacy was measured by the Dermatology Life Quality Index (DLQI), Psoriasis Area and Severity Index (PASI), and itching sensation scores at day 1 and day 56. The DLQI and PASI scores and itching sensation decreased significantly by day 56 in subjects taking XP-828L compared to placebo ($p<0.05$). In summary, daily administration of 800 mg XP-828L for 56 days is adequate to improve the quality of life and decrease disease severity in patients with mild-to-moderate psoriasis. (*Altern Med Rev* 2008;13(2):145-152)

Introduction

The National Psoriasis Foundation in the United States estimates 90 percent of patients with psoriasis, representing two percent of the general population, have mild-to-moderate disease.[1] Traditionally, topical treatments including coal tar, dithranol (anthralin), and corticosteroids have been the mainstay of treatment for mild-to-moderate disease and are more effective in short-term use.[2] The diversity of topical therapies and their disparate side effects complicate treatment planning. Topical agents are also time consuming and unpleasant to use, potentially affecting compliance and compromising treatment efficacy. Furthermore, long-term use of topical agents is associated with significant side effects, including cutaneous atrophy, striae, and telangiectasia.[3] Although the effectiveness of topical agents to attenuate physical symptoms of psoriasis has been established, the inconvenience associated with their use often negatively impacts quality of life and reduces treatment compliance.[4]

XP-828L is a whey protein extract isolate from bovine whey. The activity profile of XP-828L is related to the presence of bioactive whey proteins and/or peptides in the extract, including growth factors – transforming growth factor-beta2 (TGF-ß2), in particular – and insulin-like growth factor (IGF).[5]

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Recently, in a placebo-controlled, multicenter, randomized clinical trial, XP-828L (commercialized as Dermylex™) demonstrated potential for reducing symptoms associated with mild-to-moderate psoriasis.[5,6] In this study, the oral administration of 5 g XP-828L daily significantly reduced physician's global assessment (PGA) score compared to placebo.

Initially, the XP-828L dose regimen used to treat mild-to-moderate psoriasis was strictly based on anecdotal reports and theoretical considerations of TGF-ß2 concentrations necessary to produce results.[7] However, recent unpublished *in vivo* data in humans with mild-to-moderate psoriasis and in an HLA-B27 transgenic animal model of autoimmune diseases demonstrate that a dose of 800 mg (or equivalent dose in the animal model) was more effective in reducing systemic disease parameters than a dose of 5 g, suggesting the initial proposed daily dose of 5 g might not be optimal to reduce symptoms. These data suggest that instead a daily dose of 800 mg in humans might be more appropriate to reduce symptoms. Therefore, the present study examined the effectiveness of 800 mg XP-828L daily on the quality of life and psoriasis severity in patients with mild-to-moderate psoriasis.

Methodology

Materials: XP-828L Preparation

XP-828L was produced from a whey protein isolate by acid precipitation according to the pending patent.[8] XP-828L was prepared in 400-mg tablets at a concentration of 11.5 mcg TGF-ß2 and bioactive proteins per g of powder. Bioactive proteins include ß-lactoglobulin (50-60%), α-lactalbumin (~10%), lactoferrin (2-3%), and immunoglobulins (3-5%).

Study Design

This double-blind, randomized, placebo-controlled, parallel-arm, dose-comparison study was conducted by the Centre de Recherche Dermatologique du Quebec Metropolitain (CRDQ); Quebec City, Quebec, from March to June 2007. The study was approved by Health Canada and an independent ethics committee (Canadian Shield Ethics Review Board; Burlington, Ontario). Written informed consent was obtained from each patient before initiating any study procedure.

Women and men (age 18 or older) with a clinical diagnosis of stable psoriasis involving 4-15 percent of body surface were recruited. Only data from patients with body weight under 100 kg (for a minimum dosage of 8 mg XP-828L/kg), were included in the study. Inclusion and exclusion criteria are described in Table 1. Subjects were required to stop systemic psoriasis treatments (including PUVA) for at least 28 days and topical treatments including UVB phototherapy for at least 14 days, prior to randomization. Tar shampoos were allowed for scalp psoriasis as well as tar and low-potency topical corticoids for facial or genital psoriasis.

Patients were randomly allocated to receive XP-828L 400 mg or placebo twice daily for 56 days. Placebo consisted of a 400-mg tablet of food-grade microcrystalline cellulose (Wiler PCCA Inc.; London, Canada). The random allocation of patients to XP-828L or placebo was determined according to a

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Men and women • Age ≥18 years • Stable psoriasis (4-15% of body surface) • Body weight <100 kg • PASI score ≥4 • Signed inform consent	• Pustular, erythrodermic, or palmoplantar psoriasis • Active psoriatic arthritis • Pregnant or nursing women or women not using dependable contraception • Skin diseases other than psoriasis • History of drug or alcohol abuse • Intellectual deficiency • Taking lithium • History of cancer (<5 years) • HIV positive • Allergic to lactose and/or milk proteins • Sun bathing or using sunlamps • Unstable diabetes • Increased creatinine, systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or heart rate >100/min

Figure 1. Dermatology Life Quality Index Questionnaire

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date: Score:

Name: Diagnosis:

Address:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please check one box for each question:

1.	Over the last week, how itchy, sore, painful or stinging has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how embrrassed or self conscious have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant☐
4.	Over the last week, how much has your skin influenced the clothes you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant☐
5.	Over the last week, how much has your skin affected any social or leisure activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant☐
6.	Over the last week, how much has your skin made it difficult for you to do any sport?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant☐
7.	Over the last week, has your skin prevented you from working or studying?	yes no	☐ ☐	Not relevant☐
	If “No”, over the last week how much has your skin been a problem at work or studying?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant☐
9.	Over the last week, how much has your skin caused any sexual difficulties?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant☐
10.	Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant☐

computer-generated list of randomization. The list was made available only to the sponsor's clinical coordinator involved in the preparation and site distribution of the study medication. Neither the participants in the study, the investigator, nor the site personnel were aware of the code. A sealed copy of the randomization list was provided to the study manager and could be opened only in case of a serious adverse event.

Efficacy Assessments

Patients completed the Dermatology Life Quality Index (DLQI) questionnaire (Figure 1) at days 1 and 56. This document consists of 10 questions covering six domains (symptoms and feelings, daily activities, leisure, work and school, personal relationships, and bother with psoriasis treatment). The response options range from 0 (no affect) to 3 (very much affected), giving an overall range of 0-30 with lower scores representing better quality of life. The reliability, construct validity, and sensitivity to change of the DLQI have been demonstrated in psoriasis patients.[9]

Efficacy was based primarily on the Psoriasis Area and Severity Index (PASI)[10,11] and itch severity (0 = no itch and 3 = severe, bothersome itch with difficulty performing daily activities and sleep disturbances). The PASI is a physician-assessed outcome based on the extent of involved skin surface and severity of erythema, desquamation, and plaque induration, with a score ranging from 0-72.[10,11] Efficacy assessments were determined at day 1 and day 56. If a value was missing for day 1, the subject was not included in the data analysis.

All data were expressed as means ± standard error. Comparisons were made using Student's *t*-test, and significance was set at the $p<0.05$ level.

Results

Subjects

Twenty-six subjects (10 in placebo group, 16 in XP-828L group), nine females and 17 males ages 23-77 (Table 2), completed the study and constitute an assessable population used for a per-protocol analysis. The most frequent causes of discontinuation were no response (two from placebo and one from XP-828L) or lost to follow-up (three from placebo and two from XP-828L). Two subjects from the placebo group were excluded because psoriasis intensity was below the threshold required (PASI<4) or the minimal dose of 8 mg/kg/day was not attained (patients over 100 kg, one placebo and one XP-828L).

No statistically significant difference in baseline DLQI scores (4.0±2.7 and 5.1±5.0 for placebo and XP-828L, respectively) was found between groups. Also, no statistically significant difference ($p=0.3476$) was found in mean baseline PASI scores between groups (9.7±3.7 and 7.5±1.9 for placebo and XP-828L, respectively).

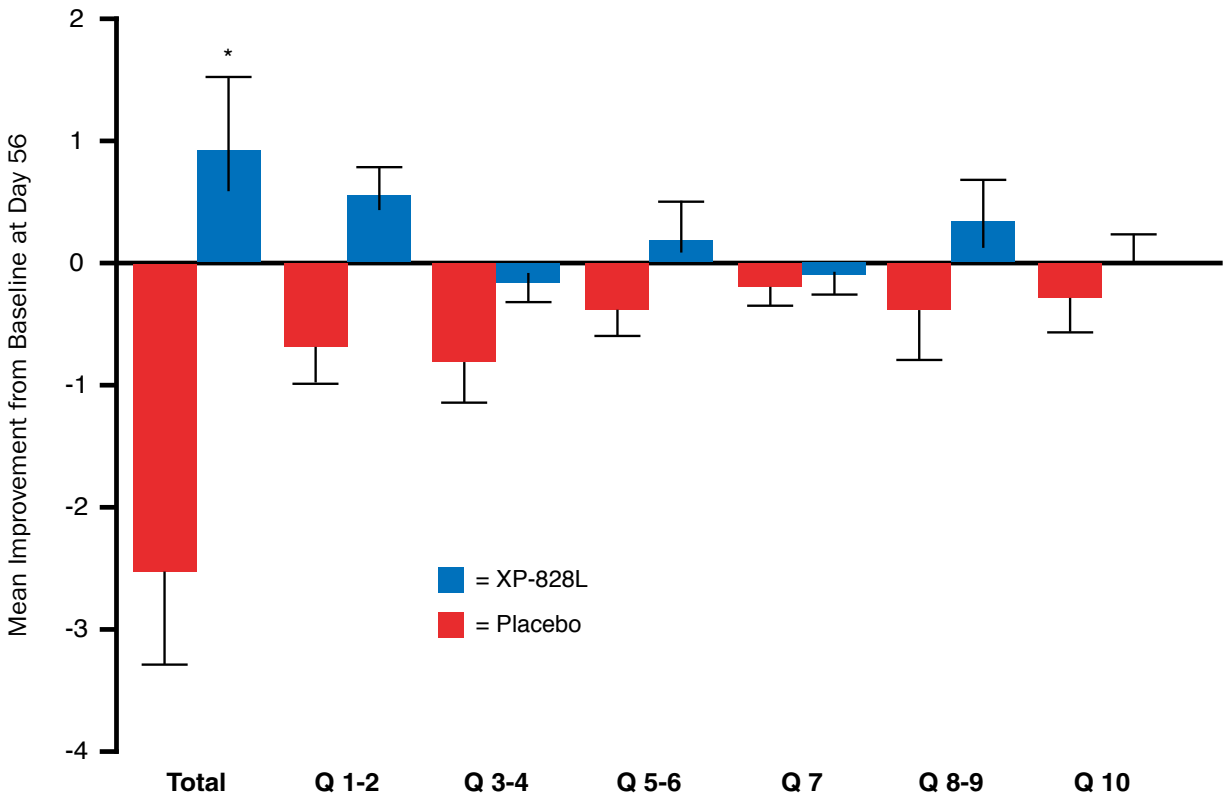
Efficacy Analysis

The DLQI is calculated by summing the score of 10 questions resulting in a maximum of 30 and a minimum of 0. Following 56 treatment days, the DLQI score for the placebo group increased to an average of 6.5±4.0 units, resulting in an average increase of 2.5±3.8 units (Figure 2), and suggesting a decreased quality of life for the placebo population. For the same period of time, the DLQI score of subjects in the XP-828L group decreased 4.2±4.7 units, an average improvement of 0.9±2.5 units from baseline and a statistically significant difference

Table 2. Patient Demographics and Baseline Disease Characteristics

	Placebo (n=10)	XP-828L (n=16)
Age	55.2±13.9 (26-73)	45.3±13.9 (23-77)
Gender Female, n (%) Male, n (%)	 5 (50%) 5 (50%)	 4 (25%) 11 (75%)
Body Weight (kg)	70.5±14.0 (60.7-99.4)	83.0±14.3 (57.7-98.5)
Average Dosage (mg/kg/day)	11.7±1.9 (8.0-14.0)	9.9±2.0 (8.1-13.9)
Baseline DLQI (units)	4.0±2.7 (0-8)	5.1±5.0 (0-14)
Basline PASI (units)	9.7±3.7 (5.1-17.6)	7.5±1.9 (5.2-11.9)

Figure 2. Improvements of DLQI Scores Following 56 Days of Treatment with XP-828L (■) Compared to Placebo (■)



Q1-2=symptoms and feelings; Q3-4=daily activities; Q5-6=leisure; Q7=work and school; Q8-9=personal relationships; Q10=treatment; *p<0.05 vs placebo; values are expressed as means ± SD.

from placebo (p<0.05). Subjects taking placebo experienced increased DLQI scores in all six categories of questions following 56 days of treatments. Subjects taking XP-828L demonstrated improvement in questions related to symptoms and feelings (Q1-2), leisure (Q5-6), and personal relationships (Q8-9); however, no statistical significance was attained compared to placebo for scores associated with these questions.

For patients in the XP-828L group, PASI scores significantly improved from day 1 to day 56 (Table 3) by 1.2±1.8 units (17.3±24.7%) compared to placebo (0.0±0.6 units; 0.6±6.5%; p<0.05). As illustrated in Figure 3, the majority of patients (10 of 16) demonstrated improved PASI scores from baseline following 56 days of treatment. PASI scores improved by 25 percent or higher in six of 16 patients (38%) at day 56 compared to no improvement for the placebo group. No patient in either group showed greater than 25-percent deterioration in PASI scores.

Itching sensation was significantly reduced for subjects in the XP-828L group after 56 days (-0.3±0.6 units; -20.0±52.8%; p< 0.01), while it increased in placebo patients (0.5±0.9 units; 45.8±94.4%). Itching sensation scores improved by 25 percent or higher in five of 16 patients (31%) at day 56 compared to one patient (10%) in the placebo group. Five patients taking placebo

Table 3. Delta Efficacy Scores at Day 56 from Baseline

	Placebo (n=10)	XP-828L (n=16)	P value
PASI			
Absolute Δ (units)	0.0±0.6	-1.2±1.8	
Relative Δ (%)	-0.6±6.5	-17.3±24.7	<0.05
Itching			
Absolute Δ (units)	0.5±0.9	-0.3±0.6	
Relative Δ (%)	45.8±94.4	-20.0±52.8	<0.01

p<0.05 vs placebo; values are expressed as means ± SD; Δ=change

and one taking XP-828L demonstrated deterioration in itching sensation scores. Figure 4 illustrates changes in psoriatic lesions for a patient treated with XP-828L for 56 days.

Discussion

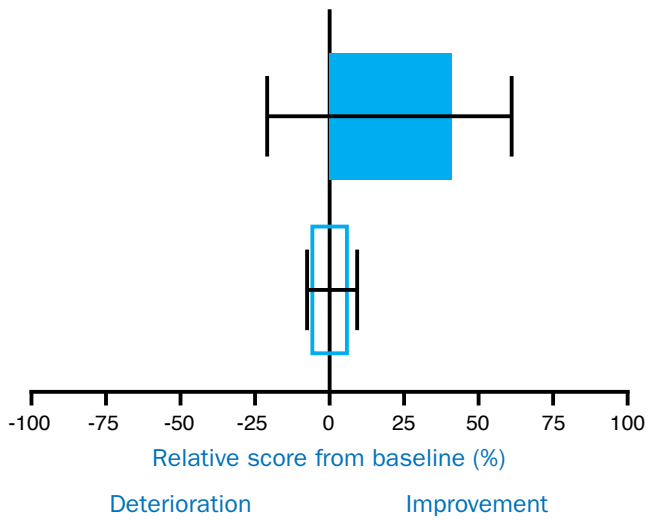
The present double-blind, randomized, clinical study confirms that 800 mg XP-828L daily for 56 days improves quality of life and psoriasis-associated symptoms in patients with mild-to-moderate psoriasis.

These results confirm unpublished data obtained in the HLA-B27 animal model demonstrating oral administration of a human equivalent dose of 800 mg XP-828L daily to HLA-B27 rats for 33 weeks reduced systemic inflammatory activity compared to untreated animals. HLA-B27 transgenic rats express HLA-B27 and human ß2-microglobulin (hß2m), resulting in a powerful model for studying human inflammatory disorders. In this study, hematocrit, hemoglobin, and bowel inflammation index were ameliorated following 33 weeks of treatment with XP-828L at a human equivalent dose of 800 mg/day compared to untreated animals. A higher dose (x10) of XP-828L was also tested in this study, but, surprisingly, results were less impressive than the present dose of 800 mg/day.

The results support data collected from patients taking XP-828L who reported good efficacy with 800 mg per day. Whether or not 800 mg daily is more effective than 5 g daily for reduction of mild-to-moderate psoriasis-associated symptoms remains to be demonstrated.

The present data confirms 800 mg daily is at least as effective as 5 g daily. Two previous studies have demonstrated the safety and efficacy of XP-828L to reduce symptoms associated with mild-to-moderate psoriasis.[5-7] In the first[7] open-label study, seven of 11 patients demonstrated a decrease in PASI score ranging from 9.5-81.3 percent (average of 24.1±28.3%) following 56 days of treatment at a dose regimen of 2.5 g twice daily. No clinical adverse events or laboratory abnormalities were reported.

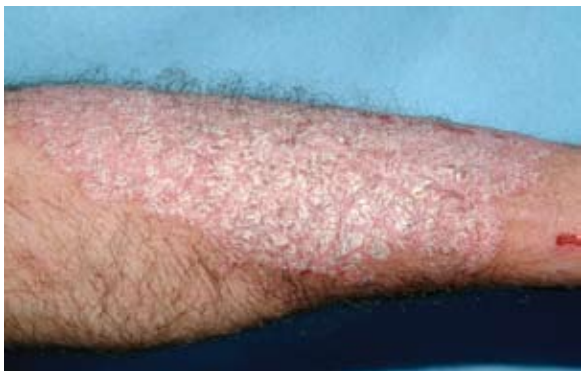
Figure 3. Relative Improvements of Study Endpoints from Baseline (Day 1) for Psoriasis Area and Severity Index



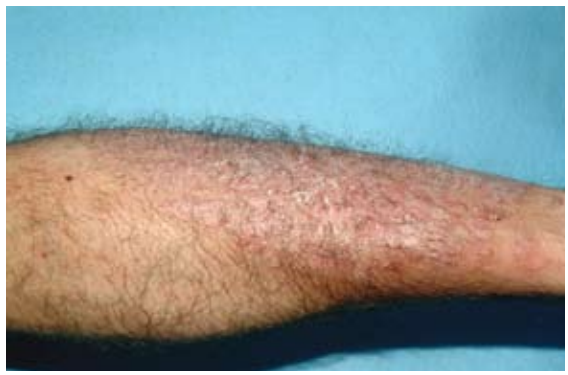
Solid bars (■) represent the distribution of patient scores taking XP-828L or placebo (□), and error bars represent extreme observations.

Figure 4. Representative Picture of Body Lesions During Study for a Patient Treated with XP-828L (800 mg/day) for 56 Days

Day 1



Day 56



The open-label study set the stage for a double-blind, placebo-controlled study with patients diagnosed with mild-to-moderate psoriasis.[5,6] Eighty-four patients were recruited and treated with XP-828L at a dose regimen of 2.5 g or placebo twice daily for a maximum of 112 days. The most significant improvement in patients treated with XP-828L was observed in PGA scores, which decreased significantly from day 1 to day 56. Body surface area and PASI scores were also improved in patients treated with XP-828L. PASI scores improved from day 1 to day 56 ($p<0.05$) with 26 percent of patients demonstrating PASI score improvements of 25 percent or higher (average improved score, 49 percent) from initial score.

In the present study, 38 percent of subjects demonstrated improved PASI scores of 25 percent or higher, suggesting 800 mg per day is adequate to induce an equivalent or better response than the 5-g daily dose when comparing data from the present study with the previous placebo-controlled, double-blind study using 5g XP-828L daily. Like in the previous study, itching sensations were also significantly reduced in subjects taking XP-828L.

Psoriasis can have a significant negative impact on the physical, emotional, and psychosocial well-being of affected patients.[12] In fact, their quality of life, by some evaluations, is comparable to patients with other chronic diseases such as ischemic heart disease or diabetes.[12] The stigma of psoriasis can lead to depression and, in five percent of individuals, to suicidal ideation.[13] Kirby et al suggest patients should be assessed using a holistic approach, considering both physical and psychological measurements.[14] DLQI scores change significantly as clinical presentation changes, detecting small but meaningful changes in clinical status over time.[15] In the present study, participants taking XP-828L demonstrated a significantly improved quality of life compared to placebo ($p<0.05$). Subjects in the XP-828L group felt better about their skin (less itchy and painful) and were less embarrassed or self-conscious about their skin compared to subjects taking placebo. These results suggest 800 mg XP-828L daily has a positive impact on the psychological aspects of the disease.

It was previously suggested that the high content of TGFß in XP-828L might be partially responsible for its specific biological activity.[6] TGFß is a multifunctional cytokine known to regulate T-cell proliferation and function.[16-18] Specifically, TGFß2 inhibits interleukin-2 (IL-2) production, up-regulates cell-cycle inhibitors, and has a potent antiproliferative effect on CD4+ T cells.[19] In addition, TGFß2 induces Foxp3 expression in CD4+CD25- T cells and promotes the acquisition of regulatory properties in CD4+CD25+ cells.[20] CD4+CD25+ regulatory T cells are potent suppressors, playing important roles in controlling

immunity. XP-828L can also reduce *in vitro* production of proinflammatory messengers (cytokines) like IL-2 and interferon-gamma (IFN-γ),[6] which are known to play a major role in psoriasis. The potential use of TGFß proteins for medical application has been explored in many therapeutic fields, such as impaired wound healing, mucositis, fractures, ischemia-reperfusion injuries, and autoimmune diseases.[21] Studies on animal models and human patients reveal a critical function for TGFß in regulating leukocyte functions in autoimmune diseases.[22]

Although it is hypothesized TGFß might be the active ingredient of XP-828L, other growth factors, such as insulin-like growth factor, might play an important role. Proteins like ß-lactoglobulin, α-lactalbumin, and lactoferrin, individually or incorporated into a whey protein base, might also play an important role in the bioactive profile of XP-828L.[23] In fact, protein complexes derived from whey have been shown to have clinically proven health benefits in cancer, hepatitis, HIV, cardiovascular disease, and osteoporosis.[24] The exact mechanism of action of XP-828L remains to be determined.

In summary, this study demonstrated 800 mg XP-828L daily for 56 days increased the quality of life of patients and decreased psoriasis severity and itching sensation in individuals with mild-to-moderate psoriasis.

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References

1. National Psoriasis Foundation Benchmark Survey. http://www.psoriasis.org/files/pdfs/press/npfsurvey.pdf [Accessed April 3, 2006]
2. Menter A, Griffiths CE. Current and future management of psoriasis. *Lancet* 2007;370:272-284.
3. Bruner CR, Feldman SR, Ventrapragada M, Fleischer AB Jr. A systematic review of adverse effects associated with topical treatments for psoriasis. *Dermatol Online J* 2003;9:2.
4. Zaghloul SS, Goodfield MJ. Objective assessment of compliance with psoriasis treatment. *Arch Dermatol* 2004;140:408-414.
5. Drouin R, Lamiot E, Cantin K, et al. XP-828L (Dermylex), a new whey protein extract with potential benefit for mild to moderate psoriasis. *Can J Physiol Pharmacol* 2007;85:943-951.
6. Poulin Y, Bissonnette R, Juneau C, et al. XP-828L in the treatment of mild to moderate psoriasis: randomized, double-blind, placebo-controlled study. *J Cutan Med Surg* 2006;10:241-248.
7. Poulin Y, Pouliot Y, Lamiot E, et al. Safety and efficacy of a milk-derived extract in the treatment of plaque psoriasis: an open-label study. *J Cutan Med Surg* 2005;9:271-275.
8. Juneau C, Drouin R, Moroni O. Process for the manufacture of an anti-inflammatory composition. Patent No. 13431-15USPR, 2007.
9. Hongbo Y, Thomas CL, Harrison MA, et al. Translating the science of quality of life into practice: what do Dermatology Life Quality Index scores mean? *J Invest Dermatol* 2005;125:659-664.
10. Langley RG, Ellis CN. Evaluating psoriasis with Psoriasis Area and Severity Index, Psoriasis Global Assessment, and Lattice System Physician's Global Assessment. *J Am Acad Dermatol* 2004;51:563-569.
11. Feldman SR, Krueger GG. Psoriasis assessment tools in clinical trials. *Ann Rheum Dis* 2005;64:ii65-68.
12. Langley RG, Krueger GG, Griffiths CE. Psoriasis: epidemiology, clinical features, and quality of life. *Ann Rheum Dis* 2005;64:ii18-23.
13. Gupta MA, Schork NJ, Gupta AK, et al. Suicidal ideation in psoriasis. *Int J Dermatol* 1993;32:188-190.
14. Kirby B, Richards HL, Woo P, et al. Physical and psychologic measures are necessary to assess overall psoriasis severity. *J Am Acad Dermatol* 2001;45:72-76.
15. Mazzotti E, Picardi A, Sampogna F, et al. Sensitivity of the Dermatology Life Quality Index to clinical change in patients with psoriasis. *Br J Dermatol* 2003;149:318-322.
16. Massague J, Wotton D. Transcriptional control by the TGF-beta/Smad signaling system. *EMBO J* 2000;19:1745-1754.
17. Wahl SM, Chen W. Transforming growth factor-beta-induced regulatory T cells referee inflammatory and autoimmune diseases. *Arthritis Res Ther* 2005;7:62-68.
18. Li MO, Wan YY, Sanjabi S, et al. Transforming growth factor-beta regulation of immune responses. *Annu Rev Immunol* 2006;24:99-146.
19. Gorelik L, Flavell RA. Immune-mediated eradication of tumors through the blockade of transforming growth factor-beta signaling in T cells. *Nat Med* 2001;7:1118-1122.
20. Fantini MC, Becker C, Monteleone G, et al. Cutting edge: TGF-beta induces a regulatory phenotype in CD4+CD25- T cells through Foxp3 induction and down-regulation of Smad7. *J Immunol* 2004;172:5149-5153.
21. Flanders KC, Burmester JK. Medical applications of transforming growth factor-beta. *Clin Med Res* 2003;1:13-20.
22. Prud'homme GJ, Piccirillo CA. The inhibitory effects of transforming growth factor-beta-1 (TGF-beta1) in autoimmune diseases. *J Autoimmun* 2000;14:23-42.
23. Zimecki M, Kruzel ML. Milk-derived proteins and peptides of potential therapeutic and nutritive value. *J Exp Ther Oncol* 2007;6:89-106.
24. Marshall K. Therapeutic applications of whey protein. *Altern Med Rev* 2004;9:136-156.