

## Original Research Article

# Zymbilan®-PSO cream with nano-encapsulated RetileX-A®-PRO mitigates the clinical severity and relieves the symptoms of chronic plaque psoriasis: an interventional clinical study

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## ABSTRACT

**Background:** Skin psoriasis is a serious inflammatory disorder with increased risk of rheumatic, cardiometabolic and psychosocial complications. At present, >50% of patients are dissatisfied with their treatment; thus, novel approaches are in high clinical demand. Retinoids are a major group of anti-psoriatic compounds; nonetheless, dose-dependent topical side effects have limited their effective topical application. RetileX-A®-PRO (Pharma Medico, Aarhus, Denmark) is a novel nano-encapsulated retinol ester designed to minimise the risk of skin irritation. The proprietary nano-encapsulation technology used in this compound can protect retinoid molecules from degradation, and thereby prolong and stabilise its release profile. The safety and efficacy of RetileX-A®-PRO were evaluated in this study.

**Methods:** 45 patients (58% female, aged 18-80 years) with mild to moderate skin psoriasis were enrolled in a 4-week interventional study. Participants were treated once daily with Zymbilan®-PSO cream with RetileX-A®-PRO and evaluated both objectively and subjectively at baseline, after 8 hours and at endpoint.

**Results:** Our observations demonstrated that Zymbilan®-PSO cream possesses both short-term and long-term anti-psoriatic effects. Shortly after application, objective skin characteristics were improved, and itching reduced in >84% of subjects. At endpoint, 87% of skin lesions improved, 9% did not change and 4% progressed as assessed by a dermatologist. Patients' self-evaluation yielded similar results: 78% judged Zymbilan®-PSO cream as a 'good' to 'very good' skin care product with suitable cosmetic parameters. No side effects were recorded in 95% of participants.

**Conclusions:** In conclusion, Zymbilan®-PSO cream is a well-tolerated treatment that can mitigate both clinical severity and subjective symptoms of chronic skin psoriasis.

**Keywords:** Zymbilan®, RetileX-A®, Psoriasis, Retinoids, Nanoencapsulation, Topical treatment

## INTRODUCTION

As one of the most common skin conditions, psoriasis is a complex, multisystem, inflammatory skin disease with a tendency to wax and wane with intermittent flares and remission periods. Psoriasis is a disfiguring, disabling and painful disease with a dual peak of incidence: first between the ages of 30-39 years and second, after the age of 60 years. Psoriasis is more common among adults, Caucasians and residents of the Nordic countries. This

chronic disease is estimated to affect around 2% of the world population; however, its prevalence rate varies between <1% in African and Asian countries to 8.5% in Norway.<sup>1</sup> Psoriasis is far from being a benign skin condition and is closely connected with a long list of comorbidities and complications including inflammatory arthritis, cardiovascular and metabolic disorders, skin diseases and higher risk of depression, anxiety and suicidality.<sup>2</sup>

Both diagnosis and treatment of psoriasis pose significant challenges to the healthcare system. As high as 40% of individuals with psoriasis remain undiagnosed; nevertheless, even the recognised patients are at an exceptionally increased risk of not receiving a suitable and adequate treatment.<sup>3</sup> A recent scientific survey disclosed that ‘over half’ of patients with psoriasis are dissatisfied with their current treatment.<sup>4</sup> This may be due to the scarceness of effective yet safe therapeutic options suitable for long-term application.

Topical therapy forms the backbone of the clinical treatment of psoriasis in outpatient practice given the fact that around 80% of patients have mild psoriasis, which can sufficiently be controlled by topical treatments alone.<sup>5</sup> Retinoids are a class of anti-psoriatic medications with a wide range of biological activities on various cutaneous and immune cell types. Retinoids regulate the expression of a large set of key genes via binding to a group of nuclear receptors known as retinoic acid receptors (RARs) and retinoid X receptors (RXRs).<sup>6</sup> These compounds are shown in controlled experiments to exhibit selective antiproliferative and pro-differentiation properties on psoriatic skin cells.<sup>7</sup> Topical natural retinoids, however, have had limited roles in standard treatment of psoriasis because of their restrictive side effects at high dosages needed for the treatment of psoriasis.<sup>8</sup> Zymbilan®-PSO cream with RetileX-A®-PRO has been developed by Pharma Medico (Aarhus, Denmark) to address this issue and to improve the care of patients with mild to moderate skin psoriasis. RetileX-A®-PRO is a proprietary form of retinyl ester that is nano-encapsulated at a molecular level. Its proprietary technology prevents the oversaturation of cutaneous tissues that happens after the administration of a large dose of free retinoids. Retinoid oversaturation followed by long-term undermedication can increase the likelihood of skin irritation and diminish the overall efficacy of the treatment.<sup>9</sup> In the case of RetileX-A®-PRO, a dynamic equilibrium forms between the encapsulated and free retinoid molecules on skin surface after application, which provides a long-term supply of the active drug molecules while protecting them from degradation. As such, the effect size and dose efficiency of RetileX-A®-PRO are higher, and its side effects are minimised. This clinical study has been carried out to verify this notion and to evaluate the safety and efficacy of psoriasis monotherapy with Zymbilan®-PSO cream from both subjective and objective perspectives.

## METHODS

This was a proof-of-concept interventional study. 45 consented volunteers (19 men and 26 women) were enrolled into a 4-week trial. Inclusion criteria were having mild to moderate stable chronic plaque psoriasis and not being under treatment with any topical or systemic medication. Patients who had skin involvement of >20% body surface area (BSA), needed systemic treatment, had psoriasis complications or any other

serious medical condition were excluded from the study. Study intervention was Zymbilan®-PSO cream containing nano-encapsulated RetileX-A®-PRO (Pharma Medico, Aarhus, Denmark) applied at least once a day on affected skin sites. Participants were allowed to use their usual skin care products but not to make any changes or to start consuming any conventional or alternative treatments during the course of the study. Before enrolment, each and all participants were informed about the study design, its objectives, probable benefits, potential risks and their rights and responsibilities. All subjects had the right to withdraw from the study without facing any questions or repercussions. All aspects of the present trial were designed and conducted in accordance with the world medical association declaration of Helsinki.<sup>10</sup>

Study subjects were interviewed by a trained researcher and examined by a collaborating dermatologist prior to the intervention and again at 4 weeks after receiving the treatment. Subject recruitment and examinations were taken place in Germany. The study's primary outcome measure was the reduction in the activity and size of skin lesions at endpoint compared to the baseline through both subjective and dermatological assessments. The secondary endpoints were to assess the efficacy of Zymbilan®-PSO cream in relieving skin itching and improving skin characteristics (suppleness, smoothness, dryness elasticity, firmness and appearance) as well as its skin compatibility and safety. The change in the activity of skin lesions and severity of itching were rated at endpoint on a 5-point rubric scale: 1= distinctly improved, 2= improved, 3= not changed, 4= slightly worsened, 5= distinctly deteriorated). Short-term changes in skin characteristics were also assessed shortly after use by a 3-point scale: 1=improved, 2=not changed, 3=worsened. In addition, participants were asked to rate the main cosmetic parameters of Zymbilan®-PSO cream at the end of the intervention.

Data from numerically coded questionnaires are reported as mean value  $\pm$  standard deviation. Otherwise, results are stated as frequencies and ratios. Statistical analyses were performed using SPSS software ver. 25.0 (IBM, Armonk, NY, USA).

## RESULTS

### *Baseline characteristic*

A total of 45 patients with the age range of 18-80 years had finished the trial. 3 volunteers discontinued the study after 3 weeks but underwent the endpoint follow-up assessments, thus this had no effect on the final sample size. Table 1 demonstrates the baseline skin characteristics of the participants. Dermatological examination revealed that 53% of patients had mild (<5% of BSA) while the rest had moderate (5-10% of BSA) or moderate-to-severe (10-20% of BSA) plaque-type psoriasis. 41 of the 45 volunteers used to use products against psoriasis before enrolment into the study.

**Table 1: The relative frequency of skin types in study participants at baseline.**

Skin types	Actual skin condition	Number of volunteers
Face	Dry	6
	Combination skin	28
	Oily	11
	Sensitive	0
Extremities	Dry	43
	Combination skin	2
	Oily	0
	Sensitive	0
Body	Dry	29
	Combination skin	15
	Oily	1
	Sensitive	0

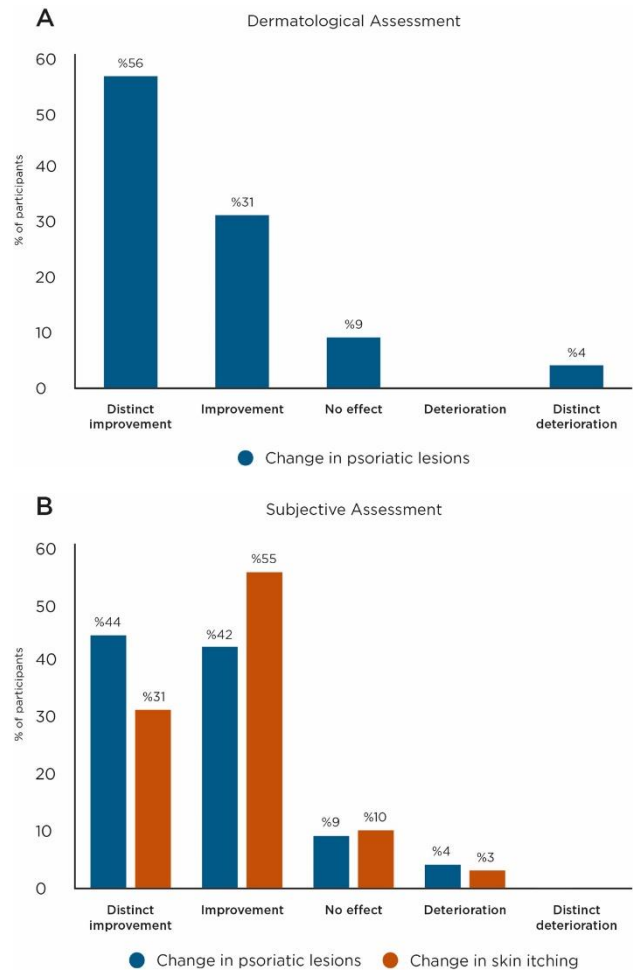
### Clinical efficacy measures

The efficacy of 4 weeks of topical treatment with Zymbilan®-PSO cream on reducing the activity and size of psoriatic skin lesions was evaluated from both subjective and objective perspectives. Figure 1A depicts the result of dermatological assessment at endpoint showing that Zymbilan®-PSO cream induced clinically meaningful improvements in 87% of the treated individuals, while only 4% exhibited deterioration of their skin condition. The mean clinical evaluation score was 1.65 ( $\pm 0.95$ ), meaning that on average Zymbilan®-PSO topical therapy either improved or distinctly improved the severity of psoriatic lesions in our subjects.

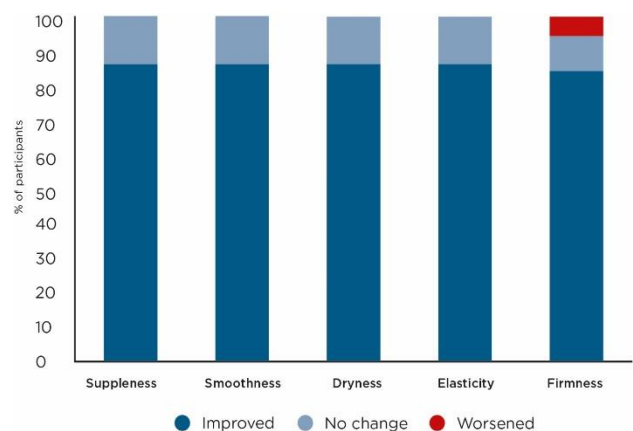
Patients' self-evaluation of long-term outcomes are displayed in part B of Figure 1. As seen, 39 out of 45 (87%) subjects experienced substantial improvement in the affected parts of their skin, which shows a close correlation with the objective outcomes presented earlier. Our patients expressed that the main change during the treatment was disappearance of skin flaking in affected areas. The mean subjective scaling score for psoriasis improvement was 1.73 ( $\pm 0.81$ ). When asked to provide an overall evaluation of the test product, 78% of patients judged Zymbilan®-PSO cream to be a 'good' to 'very good' skin care product, 20% evaluated it as 'satisfactory' and 2% found it 'less than satisfactory'. Of note is that around two thirds of the volunteers complained of skin itching prior to the treatment; whereas regular use of Zymbilan®-PSO cream caused the majority of those subjects (87%) to feel considerably relieved with the mean score of 1.86 ( $\pm 0.74$ ) (Figure 1B). In most cases, the itching was soothed between 1.5 and 6.5 hours after first application with an average period of 3.5 hours.

Zymbilan®-PSO cream was also proven effective in producing skin improvements immediately after application. Several parameters of skin structure and appearance were considerably ameliorated within a short

time after applying Zymbilan®-PSO cream in the majority of the patients as illustrated in Figure 2.



**Figure 1: Changes in the activity and size of psoriatic lesions and skin itching induced by Zymbilan®-PSO cream after 4 weeks of monotherapy based on dermatological examination (A) and patients' self-assessment (B).**



**Figure 2: Effects of Zymbilan®-PSO cream on various parameters of skin structure and appearance immediately after application.**

### Cosmetic parameters

At the end of the study, participants evaluated a number of cosmetic parameters of the test product and gave a score from 1=very good to 5= poor. All cosmetic parameters received “good” ratings on average and no participant believed that the product’s parameters were unsatisfactory. The mean scores recorded were as follows: appearance=2.13, absorption=2.00, consistency=2.02, spreadability=2.00 and stickiness=2.00.

### Safety and tolerability

Throughout the intervention period, more than 95% of participants had not reported any relevant signs of intolerance or skin reaction. Two individuals who reported moderate skin redness and itching had discontinued their potent anti-psoriatic medications just before starting Zymbilan®-PSO therapy. No drop out was recorded due to treatment intolerance or side effects.

## DISCUSSION

In this clinical study, we evaluated the efficacy and safety of topical treatment with Zymbilan®-PSO cream containing a novel proprietary nano-encapsulated retinoid, RetileX-A®-PRO. We observed that 8 out of 10 treated patients with psoriasis experienced immediate improvement in several parameters of their lesional skin, which lasted for several hours but faded after 6-8 hours. A similar relieving effect on skin itching was also noted. This observation signifies that, at least during the first weeks of treatment, a two-to-three-time daily application of Zymbilan®-PSO cream is necessary. Continuing the treatment, for 4 weeks resulted in visible improvements in severity and size of skin lesions in 87% of the patients based on both dermatological and subjective evaluations. Furthermore, more than half of the subjects experienced a distinct improvement after Zymbilan®-PSO topical therapy. When taking into account that around 47% of subjects were suffering from moderate or moderate-to-severe degrees of skin involvement, this outcome can be judged clinically significant. A notable point in this trial is the strong agreement between patient self-assessment reports and objective dermatological evaluations, which demonstrated that Zymbilan®-PSO cream produces high patient satisfaction by inducing tangible clinical improvements.

The therapeutic effects of topical natural retinoids on skin psoriasis were also documented in former clinical studies. Fry et al reported clinical improvement in more than 90% of psoriatic patients treated with topical retinoic acid compared with no improvements in control lesions. The proliferation rate of skin cells was reduced, and the granular layer of the skin was reformed in half of the patients after treatment.<sup>11</sup> Additionally, there is evidence that add-on treatment with natural retinoids can meaningfully enhance the efficacy of corticosteroids in clearing psoriatic lesions.<sup>12</sup> An extra benefit of add-on

treatment with natural retinoids is their ability to prevent corticosteroid-induced skin atrophy, which can happen in up to one third of long-term users. Interventional evidence indicates that co-treatment with a natural retinoid ameliorates steroid-induced epidermal atrophy in psoriatic patients.<sup>13</sup>

In real-world practice, despite the existence of a strong mechanistic background and clinical evidence, conventional forms of natural retinoids have not found their place in the routine treatment of uncomplicated skin psoriasis. The failure of conventional formulations in clinic may be rooted in their high degradation rate on skin surface. This causes a transient retinoid oversaturation followed by a long period of undertreatment between applications. Such a fluctuant release profile of the conventional products is inefficient in maintaining a constant and lasting drug concentration in skin tissues. RetileX-A®-PRO addresses this major shortcoming by its unique molecular-level nano-encapsulation that is a proven technology in protecting drug molecules from degradation and ensuring a long-term constant release rate.<sup>14,15</sup> This remarkable pharmacokinetic advantage is, therefore, the key mechanism that makes Zymbilan®-PSO cream an effective treatment for mild to moderate psoriasis.

Retinoid oversaturation of cutaneous tissues after application of conventional products also causes a high, dose-dependent rate of skin irritation. This common adverse effect further limits the utilisation of an effective dosage of conventional natural retinoids in psoriatic patients.<sup>8</sup> Retinoid reaction is an inflammatory response mainly mediated by monocyte chemoattractant protein-1 (MCP-1) and interleukin-8 (IL-8). In-vivo evidence suggests that retinol induces a milder degree of skin reaction compared with retinoic acid.<sup>16</sup> Since most psoriatic patients merely suffer from a limited skin affliction and need a long-term treatment, safety is an essential quality for an applicable first-line treatment for mild to moderate chronic psoriasis. Our study revealed a desirable degree of skin compatibility for Zymbilan®-PSO cream. The low rate of treatment-related side effects in our subjects is evidence for the effectiveness of RetileX-A®-PRO nano-encapsulation technology in protecting the skin from the irritating effects of retinoid molecules.

Since RetileX-A®-PRO is a novel compound, more mechanistic and histological studies are needed to expand our knowledge on how this treatment modifies different aspects of skin psoriatic transformation, including cellular hyperproliferation, inflammatory dysregulation and neo-angiogenesis. The present study strived to open up new vistas for basic and clinical scientists to use RetileX-A®-PRO in in-vitro and in-vivo experiments on different models of skin psoriasis. Future controlled trials will further define the clinical potential and position of Zymbilan®-PSO cream in a comprehensive management program for skin psoriasis.

## CONCLUSION

Based on our clinical observations in this study, Zymbilan®-PSO cream with nano-encapsulated RetileX-A®-PRO provides short-term symptomatic relief as well as long-term clinical improvement in patients with mild to moderate skin psoriasis. Treated patients reported substantial relief in skin itching and skin quality within a few hours after applying the product. Visible clinical improvement in the severity and size of skin lesions was noted after 4 weeks by patients and during dermatological examination. Common irritating side effects of topical retinoids were not observed with RetileX-A®-PRO in this study. Accordingly, we conclude that Zymbilan®-PSO cream is a safe and effective therapy that can be used in clinic as a first line measure against mild to moderate skin psoriasis as a monotherapy or in combination with other topical or systemic treatments.

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