A Study of the Safety and Efficacy of Calcipotriol and Betamethasone Dipropionate Scalp Formulation in the Long-Term Management of Scalp Psoriasis

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Key Words

Scalp · Psoriasis · Calcipotriol · Betamethasone dipropionate

Abstract

Background: Effective and safe products are needed for long-term management of scalp psoriasis. This study investigated the long-term safety and efficacy of a two-compound formulation (calcipotriol 50 µg/g plus betamethasone dipropionate 0.5 mg/g) for scalp psoriasis. **Methods:** In this 52-week, international, double-blind study, 869 patients with moderate-to-severe scalp psoriasis were randomized to either a two-compound scalp formulation (n = 429) or calcipotriol (n = 440). **Results:** Adverse drug reactions were less frequent in the two-compound group compared with the calcipotriol group (17.2 vs. 29.5%; p < 0.001). Incidences of adverse events possibly associated with long-term corticosteroid use were low in both the two-compound (2.6%) and the calcipotriol (3.0%) groups. Disease was satisfactorily controlled in 92.3% of visits in the two-compound group versus 80.0% in the calcipotriol group (p < 0.001). **Conclusion:** The two-compound scalp formulation demonstrated a high level of safety and efficacy in long-term management of scalp psoriasis.

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Introduction

Psoriasis is a common, chronic skin disorder that is estimated to affect about 2% of the western population. The scalp is one of the most common sites of involvement, affecting more than half of the patients [1, 2]. The visibility and symptoms of scalp psoriasis make this form of the condition one of the most distressing presentations of the disease for many patients, creating a significant psychological and social burden [3]. Scalp psoriasis remains more difficult to treat compared with psoriasis of

T.A. Luger has been a speaker at and contributor to meetings and publications sponsored by Novartis, Abbott, Schering Plough, Serono, Wyeth, Hermal, Symrise, CERES, Danone, Shire, Pierre Fabre and LEO Pharma. F. Cambazard was paid by LEO Pharma for the clinical trial and has participated at meetings organized by LEO Pharma. F.G. Larsen was paid by LEO Pharma for the clinical trial. M. Bourcier has performed a number of clinical trials for LEO and has received honoraria to attend conferences and advisory boards sponsored by LEO and other companies. G. Gupta has performed a number of clinical trials for LEO and has received honoraria to attend conferences and advisory boards sponsored by LEO, Wyeth, Abbott, Serono and Schering Plough. F. Clonier and P. Kidson are salaried employees of LEO Pharma. N.H. Shear has been a paid consultant for LEO Pharma.

the body, as the skin of the scalp is less accessible to topical medications than other areas, mainly because of hair [4]. In addition, vehicles used to treat scalp psoriasis, which are not cosmetically acceptable, can impact negatively on adherence to treatment, even if they are otherwise effective. There is a need for products that are effective, safe and cosmetically acceptable for the treatment of scalp psoriasis to improve both compliance and response to treatment [5].

Topical therapies are the mainstay of treatment for scalp psoriasis, with vitamin D analogues and topical corticosteroids being the most commonly used [6]. The vitamin D analogue calcipotriol (calcipotriene in the USA) exerts its antipsoriatic action through inhibition of epidermal proliferation and inflammation, and enhancement of normal keratinization [7]. This agent has been used in the treatment of scalp psoriasis for many years and its long-term efficacy and safety are well established [8, 9]. The corticosteroid betamethasone dipropionate is also commonly used to treat scalp psoriasis. Like other corticosteroids, betamethasone dipropionate acts to suppress various components of the inflammatory response and has a rapid onset of action [10]. However, the use of corticosteroids has been associated with local adverse events (e.g. skin atrophy, striae and acne). Corticosteroids are often combined with other topical agents, including vitamin D analogues, in an effort to exploit the complementary effects of the two agents. Such combinations could result in a fast onset of action and a high level of efficacy. Compared with corticosteroid use alone, safety may also be improved when agents are combined, if this results in reduced corticosteroid exposure. Until recently, the combined use of corticosteroid and vitamin D analogue therapies for treating the scalp required patients to make at least two applications per day with different medications. With regard to the treatment of scalp psoriasis in particular, where application is difficult and the treated areas visible, a once daily treatment regimen is postulated to increase compliance compared with two or more separate applications, leading to higher treatment efficacy [11].

Calcipotriol and betamethasone dipropionate have previously been combined in an ointment formulation. This two-compound ointment has both good safety and efficacy profiles in the short- and long-term management of psoriasis vulgaris of the trunk and limbs, providing a rapid and sustained effect [12]. Recently, a combination product containing calcipotriol plus betamethasone dipropionate in a new formulation has been developed specifically for the treatment of scalp psoriasis (Xamiol®,

LEO Pharma A/S, Ballerup, Denmark). Initial studies show that the two-compound scalp formulation is effective and well tolerated, and is superior to monotherapy with betamethasone dipropionate or calcipotriol after 8 weeks of treatment of scalp psoriasis [13–15]. However, scalp psoriasis is a chronic relapsing and remitting disease and repeated treatment courses are required. There is a need to investigate the long-term safety of treatments used in the management of this condition.

The main goal of the current study was to investigate the safety of the two-compound scalp formulation over 52 weeks in the treatment of scalp psoriasis. Patients in the study used the two-compound scalp formulation once daily when required, to reflect usual clinical practice. The secondary goal of the study was to compare the efficacy of the two-compound scalp formulation with once daily calcipotriol in the same vehicle. A nonsteroid treatment was chosen as the comparator as it was anticipated that the main long-term safety concerns would be associated with the steroid component of the two-compound product. Use of a non-steroid comparator makes it possible to detect adverse events that would otherwise be, incorrectly, considered related to corticosteroid therapy.

Patients and Methods

This was an international, prospective, randomized, double-blind, active-controlled, parallel-group, 52-week safety study. It was conducted at 57 centers in Canada, Germany, Denmark, France and the United Kingdom. The study protocol was reviewed and approved by relevant Institutional Review Boards/Independent Ethics Committees, and the study was performed in accordance with the Declaration of Helsinki. All patients gave their signed informed consent before enrolment in the trial.

Patients

The study included hospital outpatients aged 18 years or above, with a diagnosis of scalp psoriasis amenable to topical treatment with a maximum of 100 g of study medication per week. The participants also had clinical signs, or earlier diagnosis, of psoriasis vulgaris on the trunk or limbs. The scalp psoriasis had to involve more than 10% of the total scalp area and disease severity was graded as at least 'moderate' according to the Investigator's Global Assessment of disease severity. The main exclusion criteria were psoralen and ultraviolet A, grenz ray or ultraviolet B therapy, use of biologicals or other systemic treatments with a potential effect on scalp psoriasis, any topical scalp treatments and disorders of calcium metabolism associated with hypercalcemia.

Study Design

After a washout period of up to 28 days (if required), patients were randomized in a 1:1 ratio to receive once daily treatment, as required, for up to 52 weeks with either the two-compound scalp formulation (calcipotriol 50 µg/g plus betamethasone dipropio-

nate 0.5 mg/g) or calcipotriol (50 µg/g) in the same vehicle. Patients whose scalp psoriasis cleared at any time during the study stopped treatment but remained in the study. These patients could restart study treatment at any time during the 52-week treatment period if they needed further treatment.

Assessments

The primary response criteria were the incidences of both adverse drug reactions (ADRs) of any type and of adverse events of concern associated with long-term corticosteroid use on the scalp. Secondary criteria included efficacy of the treatment based on the Investigator's Global Assessment of disease severity ('absence of disease', 'very mild disease', 'mild disease', 'moderate disease', 'severe disease', 'very severe disease') and patient ratings of the treatment's efficacy ('satisfactory', 'not satisfactory'). Disease was considered to be satisfactorily controlled when the investigator provided an assessment of 'absence of disease', 'very mild disease' or 'mild disease'. Safety and efficacy assessments were performed at baseline (week 0) and every 4 weeks up to week 52 (14 visits). Patients with an ongoing adverse event possibly or probably related to study medication attended a follow-up visit 14 days after their last on-treatment visit. Adverse events were recorded by the investigators and reviewed by an adjudication committee (i.e. a Data Safety Monitoring Board, DSMB) comprising three independent dermatologists blinded to the treatment assignment. This committee was responsible for identifying adverse events of concern, possibly associated with long-term corticosteroid use on the scalp (adjudicated corticosteroid reactions). Investigators recorded the extent of psoriasis on the trunk, limbs and face in order to help determine whether a possible steroid-related event was due to use of the study medication on the scalp or another steroid preparation used topically elsewhere.

At all on-treatment visits, the patients were asked if they had used the medication as prescribed. A patient was considered fully compliant if the medication had been used once or twice daily at all visits, if applications were not made because the patient did not require treatment or if only extra applications were made. Non-compliance was defined as failure to use the treatment for any reason other than no treatment being required.

Statistical Analyses

A total of 800 patients with scalp psoriasis (400 patients/group) was planned for enrolment. Descriptive statistics are presented for demographic data and baseline characteristics. Categorical data were summarized using the number and percentage of patients in each category or group, and continuous data were summarized using descriptive statistics. Safety analyses comprised all randomized patients who received any trial medication and for whom information was available on the presence, or confirmed absence, of adverse events. χ^2 tests were applied to compare the following between-treatment effects: the proportion of patients who experienced ADRs, adverse events of concern associated with long-term corticosteroid use on the scalp, and adverse events of any type (including lesional/perilesional events on the scalp). Efficacy analyses were performed on the full analysis set, which included all randomized patients. The main efficacy criterion was analyzed using the Wilcoxon rank-sum nonparametric test. Statistical comparisons were two-sided at the 5% significance level. The average weekly amount of study medication used was assessed by weighing returned tubes, and counting all nonreturned tubes as fully used.

Fig. 1. Patient disposition throughout the study.

Results

A total of 873 patients were enrolled in the study, of whom 869 were randomized (two-compound group: $n = 429$; calcipotriol group: $n = 440$) and 850 were included in the safety analysis set (two-compound group: $n = 419$; calcipotriol group: $n = 431$). The patient disposition throughout the study is shown in figure 1. Baseline demographic and background characteristics, including duration and severity of psoriasis, were well balanced between the two treatment groups, with most patients having 'moderate' or 'severe' disease at baseline (table 1). In the two-compound group, 70.9% of patients were more than 90% compliant with study medication compared with 58.9% in the calcipotriol group.

The frequency of withdrawals (randomized patients) was significantly lower in the two-compound group ($n = 92/429$, 21.4%) than in the calcipotriol group ($n = 175/440$, 39.8%; $p < 0.001$) (table 2). The frequency of withdrawals due to unacceptable treatment efficacy was lower in the two-compound group compared with the calcipotriol group throughout the study period (fig. 2).

Safety

The percentage of patients reporting ADRs was significantly lower in the two-compound group compared with the calcipotriol group [17.2% ($n = 72/419$) vs. 29.5%

Fig. 2. Patients withdrawing due to unacceptable treatment effect (cumulative number).

($n = 127/431$); odds ratio (OR): 0.5, 95% confidence interval (CI): 0.36–0.69, $p < 0.001$] (table 3). The proportion of patients with ADRs who used the medication as needed throughout the initial 6 months of participation was lower in the two-compound group compared with the calcipotriol group [11.4% ($n = 40/350$) vs. 22.4% ($n = 66/295$)]. This was also seen in patients who used the treatment for the entire 12-month period [15.7% ($n = 44/281$) vs. 26.4% ($n = 62/235$)] (table 3). There was no increase in the most frequently observed ADRs in patients exposed to either of the study treatments during the course of the study.

The incidence of specific adverse events, such as lesional/perilesional skin irritation on the scalp, was significantly lower in the two-compound group than in the calcipotriol group [11.9% ($n = 50/419$) vs. 21.6% ($n = 93/431$); OR: 0.49, 95% CI: 0.34–0.72, $p < 0.001$]. Pruritus (4.3%; $n = 18$) was the only lesional/perilesional event on the scalp reported in at least 2% of the patients in the two-compound group. In the calcipotriol group, pruritus (10.0%; $n = 43$), skin irritation (3.9%; $n = 17$), burning sensation (2.6%; $n = 11$) and erythema (2.1%; $n = 9$) were reported in at least 2% of patients. Facial irritation occurred with a higher incidence in the calcipotriol group (3.5%; $n = 15$) compared with the two-compound group (0.2%; $n = 1$).

There were 11 patients (2.6%) with adverse events judged by the independent safety panel to be possibly as-

Table 1. Demographics and baseline characteristics (safety analysis set)

	Two-compound group ($n = 419$)	Calcipotriol group ($n = 431$)
Age		
Mean ¹ , years	48.5 ± 15.3	49.0 ± 14.7
Range, years	18 – 86	19 – 84
Males	185 (44.2%)	189 (43.9%)
Caucasians	404 (96.4%)	418 (97.0%)
Duration of psoriasis		
Mean ¹ , years	17.7 ± 13.6	17.4 ± 13.6
Range, years	1 – 66	1 – 72
Investigator's assessment of disease severity		
Moderate	233 (55.6%)	239 (55.5%)
Severe	158 (37.7%)	163 (37.8%)
Very severe	28 (6.7%)	29 (6.7%)

¹ Values represent mean ± SD.

Table 2. Reasons for withdrawals (all randomized patients)

	Two-compound group ($n = 429$)	Calcipotriol group ($n = 440$)
Unacceptable adverse events	9 (2.1)	44 (10.0)
Death ¹	1 (0.2)	1 (0.2)
Unacceptable treatment efficacy	14 (3.3)	51 (11.6)
Exclusion criteria emerging	5 (1.2)	15 (3.4)
Lost to follow-up	26 (6.1)	29 (6.6)
Other reason(s) ²	24 (5.6)	47 (10.7)
Voluntary	17 (4.0)	18 (4.1)
Total number of reasons for withdrawal ³	96	205
Total number of withdrawn patients	92 (21.4)	175 (39.8)

Figures in parentheses represent percentage.

¹ The deaths (i.e. cardiac arrest and complication after surgery) were not considered treatment related.

² Other reasons include personal reasons, dissatisfaction with cosmetic appeal, unable to attend visits.

³ A patient may have had more than one reason for withdrawal.

sociated with the long-term use of corticosteroids in the two-compound group and 13 (3.0%) in the calcipotriol group ($p = 0.73$; table 4). The individual events were generally similar in nature (e.g. rosacea, folliculitis and acne) and frequency in the two groups. No case of skin atrophy was reported.

Table 3. Incidence of ADRs (safety analysis set)

	Two-com-pound group	Calcipotriol group
≥1 adverse drug reaction	72 (17.2)	127 (29.5)
OR ¹ (95% CI)	0.50 (0.36–0.69)	
<i>Specific ADRs occurring in ≥2% of patients</i>		
Total number of patients	419	431
Any ADR	72 (17.2)	127 (29.5)
Burning sensation	4 (1.0)	12 (2.8)
Erythema	9 (2.1)	14 (3.2)
Pruritus	15 (3.6)	43 (10.0)
Psoriasis	10 (2.4)	9 (2.1)
Skin irritation	6 (1.4)	24 (5.6)
<i>ADRs during 0–6 months in patients with ≥6 months exposure</i>		
Total number of patients	350	295
Any ADR	40 (11.4)	66 (22.4)
Erythema	4 (1.1)	6 (2.0)
Pruritus	6 (1.7)	20 (6.8)
Skin burning sensation	0	6 (2.0)
Skin irritation	4 (1.1)	12 (4.1)
<i>ADRs during 0–12 months in patients with ≥12 months exposure</i>		
Total number of patients	281	235
Any ADR	44 (15.7)	62 (26.4)
Burning sensation	3 (1.1)	5 (2.1)
Erythema	4 (1.4)	5 (2.1)
Pain of skin	3 (1.1)	5 (2.1)
Pruritus	6 (2.1)	21 (8.9)
Psoriasis	6 (2.1)	3 (1.3)
Skin irritation	3 (1.1)	8 (3.4)

Figures in parentheses represent percentage unless otherwise indicated.

¹ $p < 0.001$.

Efficacy

According to the Investigator's Global Assessment of disease severity, the number of patients who reached 'satisfactorily controlled disease' ('absence of disease', 'mild disease' or 'very mild disease') was higher in the two-compound group than in the calcipotriol group (fig. 3). The median number of visits per patient with satisfactorily controlled disease was superior in the two-compound group. Patients in this group were rated as having satisfactorily controlled disease in 92.3% of the assessments, which was significantly more than in the calcipotriol group (80.0%; $p < 0.001$).

According to the patient assessments, the percentage of satisfactory visits per patient was significantly in favor of the two-compound scalp formulation ($p < 0.001$). A

Fig. 3. Number of patients with satisfactorily controlled disease ('absence of disease', 'very mild disease' or 'mild disease') at each visit (Investigator's Global Assessment of disease severity; full analysis set).**Table 4.** Incidence of adverse events judged to be at least possibly associated with long-term corticosteroid use on the scalp (safety analysis set)

	Two-com- pound group (n = 419)	Calcipotriol group (n = 431)
Any corticosteroid-related event	11 (2.6)	13 (3.0)
OR ¹ (95% CI)	0.87 (0.38–1.96)	
<i>Specific corticosteroid-related events</i>		
Ocular hypertension	0	1 (0.2)
Infected dermatitis	0	1 (0.2)
Folliculitis	3 (0.7)	3 (0.7)
Impetigo	0	1 (0.2)
Pustular rash	1 (0.2)	0
Acne	1 (0.2)	2 (0.5)
Dermatitis	3 (0.7)	1 (0.2)
Rosacea	3 (0.7)	5 (1.2)

Values in parentheses represent percentage unless otherwise indicated. Assessed by a blinded safety panel of experts.

¹ $p = 0.73$.

total of 76.2% of patients assessed the treatment response as satisfactory at every visit in the two-compound group versus 50.2% in the calcipotriol group.

The average weekly weight of study medication used was 10.6 g in the two-compound group and 12.8 g in the

calcipotriol group. The mean weight of drug used over the whole study period was 470.8 and 440.0 g, respectively, for the two-compound and calcipotriol formulations. The mean duration of treatment was 44 weeks for the two-compound scalp formulation and 37 weeks for the calcipotriol formulation.

Discussion

This is the first study to investigate the long-term safety and efficacy of a new two-compound scalp formulation for the management of scalp psoriasis. Importantly, it is the first reported study that formally examined, over a 12-month period, the safety of a steroid-containing topical product for use on the scalp as needed.

The International Conference on Harmonisation [16] requires long-term safety data on treatments for chronic non-life-threatening conditions to be submitted as part of the regulatory process. These formal standards drove the design of the present trial in terms of its duration and patient number. It was planned to enrol a minimum of 400 patients in each of the two treatment arms.

The overall withdrawal rate for the study (21.4%) was noticeably higher than that reported in two previous, 8-week efficacy trials (11.3 and 8.5%, respectively) [14, 15]. Similar rates were observed in another year-long trial with a topical two-compound agent [17] and during long-term (5 months) topical treatment of atopic dermatitis [18]. The frequency of withdrawals due to unacceptable treatment efficacy was very low in the two-compound group throughout the entire study period (fig. 2). This withdrawal rate increased steadily during the first 6 months of treatment but did not change much in the last 6 months. These data show that if a patient is treated for 6 months, with a satisfactory response, then there is a high possibility that the patient will keep applying the treatment as needed, and achieve a satisfactory response to treatment.

Before the study was initiated, the highest anticipated risk for patients was deemed to be the potential of significant adverse events associated with the long-term use of corticosteroids. To reveal the true frequency of such events, the noncorticosteroid treatment calcipotriol was considered to be an appropriate comparator as data exist on its long-term safety profile in patients with scalp and/or body psoriasis [8]. In the long-term safety study on calcipotriol, 32% of the patients withdrew over 1 year [8].

The absence of formal, long-term safety data for the use of topical corticosteroids on scalp psoriasis made the

design and outcome of the present trial particularly interesting. One of the most interesting findings was the lack of any reported skin atrophy in the two-compound group. Furthermore, telangiectasia was not reported, and rosacea and acne, which are well-known adverse effects of corticosteroid use, were more frequent in the calcipotriol group – a surprising finding as they are not usually associated with calcipotriol therapy. There was no evidence that year-long use of the two-compound scalp formulation produced a higher risk of classical corticosteroid-associated adverse events than did a noncorticosteroid treatment.

A number of reasons are postulated for the lack of corticosteroid-related ADRs in patients who received the two-compound formulation. Most importantly, the two-compound formulation was applied 'as required', which means that the patient applied the treatment only when it was necessary. Compared with steroid monotherapy, the amount of the two-compound formulation applied to the scalp, and consequently the degree of steroid exposure, may be lower. This is supported by data from studies of the two-compound scalp formulation, which demonstrate that the onset of action is more rapid and efficacy is superior to that of betamethasone dipropionate alone [14, 15]. In addition, existing topical steroid treatments for scalp psoriasis are either applied twice daily [19, 20] or have a stronger potency than betamethasone dipropionate [21]. In combination, these factors may contribute to the two-compound scalp formulation reducing deleterious steroid-related side effects, as compared with existing steroid monotherapy. Assessment of the skin of the scalp is more difficult than assessing skin in nonglabrous body regions, and this may partially explain the differences in results. However, a previous study on the long-term use of a combination of calcipotriol and betamethasone dipropionate in an ointment is in agreement with the present results in demonstrating very low levels of corticosteroid-related ADRs from the combination product [17].

The overall incidence of ADRs in our study was significantly lower in the two-compound group (17.2%) than in the calcipotriol group (29.5%). In particular, facial irritation was reported in only 1 patient in the two-compound group compared with 15 patients in the calcipotriol group. Furthermore, the incidence of pruritus, one of the most distressing symptoms of scalp psoriasis [3], was also lower in the two-compound group (3.6%) compared with the calcipotriol group (10%). A likely explanation for the low irritation profile observed for the two-compound scalp formulation is the anti-inflammatory action of be-

tamethasone dipropionate, which reduces the irritation caused by calcipotriol [22, 23]. The incidence and nature of ADRs in patients receiving the two-compound scalp formulation was similar after 6 and 12 months of therapy. This suggests a lack of any significant accumulation of effect of study drug on the relevant tissues, which could lead to a changing safety profile with repeated exposures.

The two-compound scalp formulation, used once daily, had superior efficacy compared with calcipotriol monotherapy, based on both the investigators' and patients' assessments. These findings are similar to those reported in other studies of scalp psoriasis [14, 15].

In conclusion, treatment of scalp psoriasis with the two-compound scalp formulation, used once daily as needed, was well tolerated for up to 52 weeks. It was associated with a lower incidence of ADRs and superior efficacy compared with once daily calcipotriol. No group difference in adverse events related to long-term corticosteroid use on the scalp was observed and there was no incidence of skin atrophy.

Acknowledgements

The study was sponsored by LEO Pharma, Ballerup, Denmark. The authors would like to thank Caudex Medical, UK (supported by LEO Pharma) for assisting in preparing the manuscript. The authors would also like to thank the Data Safety and Monitoring Board (DSMB), including Dr. N.K. Veien, Denmark and Prof. M. Bagot, France (the third member was one of the authors, Dr. N. Shear, Canada), and the following participating investigators. *Canada:* K. Barber, M. Bourcier, J.-P. DesGroseilliers, M. Gilbert, A. Gupta, A. Katz, I. Landells, R. Langley, C. Maari, M. Raman, G. Searles, R. Sibbald, J. Tan, J. Taradash, R. Tremaine, N. Wasel, L. Weatherhead, D. Wexler, J. Willoughby and S. Wine. *Germany:* V. Jasnoch, D. Keil, T.A. Luger, M. Mockenhaupt, M. Sebastian and G. Wozel. *France:* F. Cambazard, M. Baspeyras, R. Besnier, S. Body, D. Brive, S. Dahan, I. De Capele, B. Guillot, B.J. Halioua, M.-P. Hill-Sylvestre, I. Le Hir-Garreau, M. Mauboussin-Gautron, J.-L. Michel, M. Perrussel, G. Reuter, H. Roger, G. Rostain, M. Ruer-Mulard, V. Salmon-Ehr, M. Souied, S. Truchet and P. Zukervar. *United Kingdom:* J. Berth-Jones, A. Chu, C. Fleming, C. Griffiths, G. Gupta, C. Holden and R. Ratnavel.

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