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Safety and Efficacy of Calcipotriene Plus Betamethasone Dipropionate Topical Suspension in the Treatment of Extensive Scalp Psoriasis in Adolescents Ages 12 to 17 Years

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Abstract: **The objective of this study was to assess the safety and efficacy of the fixed combination calcipotriene 0.005% plus betamethasone dipropionate 0.064% topical suspension in adolescents with extensive scalp psoriasis. In this phase II, open-label, 8-week study, adolescents with psoriasis (ages 12–17 years) with 20% or more of the scalp area affected (at least moderate severity according to Investigator's Global Assessment [IGA]) were assigned to once-daily treatment with calcipotriene plus betamethasone dipropionate topical suspension. The primary endpoint was safety, focusing on calcium metabolism and hypothalamic–pituitary–adrenal axis function. Secondary efficacy endpoints were the proportion of patient's achieving treatment success (clear or almost clear disease according to the IGA and clear or very mild disease according to the Patient's Global Assessment [PaGA]) and percentage change in investigator-assessed Total Sign Score (TSS). Pruritus was also assessed. Overall, 31 patients received treatment. Sixteen patients (52%) experienced a total of 20 adverse events; 19 were considered unrelated to study treatment, 14 were mild, and none were serious or lesional or perilesional on the scalp. One patient showed signs of mild adrenal suppression at week 4; the patient discontinued treatment and had normal test results at follow-up 4 weeks later. No cases of hypercalcemia were reported. By treatment end, treatment success was reported for 17 patients (55%) according to the IGA and 18 (58%) according to the PGA. Mean TSS improved from 6.9 at baseline to 2.9 at treatment end (59% improvement). By week 8, 28 patients (90%) experienced mild or no itching, versus 20 (65%) at baseline. Once-daily calcipotriene plus betamethasone dipropionate topical suspension was well tolerated and efficacious for the treatment of scalp psoriasis in adolescents.**

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Psoriasis is a common chronic inflammatory skin disease that is associated with serious comorbidities such as cardiovascular disease, depression, and psoriatic arthritis (1,2). Approximately 35% of patients with psoriasis develop the disease before the age of 20 years and 25% are diagnosed between 10 and 19 years of age (3). In this adolescent age group, psoriasis can have a particularly significant impact on quality of life, including social interactions (4). In particular, scalp lesions are a common manifestation in younger individuals with psoriasis vulgaris (5) and may represent a serious concern to patients because of the visibility of lesions and scaling, accompanied by feelings of stigmatization.

Current guidelines for the first-line treatment of mild to moderate psoriasis recommend the topical use of vitamin D analogues and corticosteroids (6). Safety concerns typically associated with these mono therapies include skin irritation and hypercalcemia for vitamin D analogues, and skin atrophy, adrenal suppression, and stunted growth with long-term use for corticosteroids. A fixed-combination topical preparation containing the vitamin D analogue calcipotriene and the corticosteroid betamethasone dipropionate has been developed and is well tolerated, with superior efficacy than the individual components for treatment of adult psoriasis vulgaris (7–9). Therapeutic benefit is achieved with the fixed combination, promoting greater anti-inflammatory and antiproliferative effects than for either active ingredient alone, coupled with a faster response and potentially fewer safety concerns (10,11) than with monotherapies.

The choice of topical treatment vehicle influences patient adherence and is a key factor that impacts upon effectiveness. Certain formulations, such as ointments, are often perceived as being messy, with time-consuming application that can deter patients from adhering to their treatment regimens (12,13). Adherence to skin disease treatments is particularly poor in adolescents, who often choose not to use medications as the result of social pressures and inconvenience (14). A fixed-combination lipophilic, alcohol-free topical suspension formulation may offer a beneficial treatment option for adolescents, providing cosmetic acceptability, convenience, and ease of use, but no specific clinical investigation of this fixed-combination formulation has previously been performed in an adolescent population.

This trial investigated the safety, with particular focus on calcium metabolism, as well as hypothalamic–pituitary–adrenal (HPA) axis function through dynamic testing, and efficacy of once-daily use of calcipotriene 0.005% plus betamethasone dipropionate (0.064%) topical suspension in adolescents with extensive psoriasis vulgaris of the scalp.

MATERIALS AND METHODS

Patients

Eligible patients were ages 12–17 years and had a clinical diagnosis of scalp psoriasis vulgaris amenable to topical treatment (up to a maximum of 60 g of study medication per week). All patients had clinical signs or prior diagnosis of psoriasis vulgaris of the trunk or limbs as assessed during screening (see Study Design). At inclusion, psoriasis of the scalp had to involve 20% or more of the scalp area and be of at least moderate severity according to the Investigator's Global Assessment (IGA). Patients also had to have albumin-corrected serum calcium levels below the upper reference limit and normal HPA axis function before treatment (serum cortisol concentration >5 μg/dL before adrenocorticotropic hormone [ACTH] challenge and >18 μg/dL 30 minutes after ACTH challenge).

The main exclusion criteria were a history of serious allergy, allergic asthma, or serious allergic skin rash and known or suspected hypersensitivity to any medication, including synthetic ACTH (cosyntropin) or to any component of the calcipotriene plus betamethasone dipropionate topical suspension. Patients were also excluded if they had received topical or systemic treatment with corticosteroids within 2 and 12 weeks, respectively, before baseline. Patients were excluded if they had been treated with adalimumab, alefacept, or infliximab within 2 months before baseline; with etanercept within 4 weeks before baseline; or with ustekinumab within 4 months before baseline. Patients who were treated within 4 weeks before baseline with medications that might affect the HPA axis function test (e.g., estrogen, enzymatic inducers or inhibitors, antidepressants) or calcium metabolism assessments (e.g., calcium or vitamin D supplements, diuretics, antiepileptics) were also excluded. For other systemic therapies (e.g., retinoids, immunosuppressants, psoralen plus ultraviolet [UVA]), patients were excluded if they had been treated within 4 weeks before baseline. Other exclusion criteria included UVB therapy within the 2 weeks before baseline, diabetes mellitus, current diagnosis of unstable forms of psoriasis, skin infection, infestations or atrophy of the scalp, and severe renal or hepatic disorders.

Study Design

This was a phase II, multicenter, open-label, single-arm, 8-week study in the United States. The trial consisted of three phases: a washout or screening period, a treatment period, and a follow-up period (Fig. 1). Patients entered a washout period (up to 8 weeks) if they had been treated with antipsoriatic therapies or other relevant medication according to the exclusion criteria. Patients were then assigned to once-daily treatment with calcipotriene plus betamethasone dipropionate topical suspension (Taclonex topical suspension, Daivobet gel, or Dovobet gel; LEO Pharma A/S, Ballerup, Denmark) for up to 8 weeks. Patients were permitted to use other topical antipsoriatic treatments concomitantly, except for corticosteroids, on the trunk, limbs, and face, but no other scalp products were allowed during the treatment period. Patients whose scalp psoriasis cleared after 4 weeks of treatment were required to leave the trial (in accordance with the U.S. label instructions at the time, i.e., apply to the affected scalp areas for 2 weeks or until cleared; treatment may be continued for up to 8 weeks); patients who had signs of scalp psoriasis after 4 weeks continued treatment for up to a further 4 weeks. If the scalp psoriasis cleared at week 2 or 6, patients stopped treatment but remained in the trial; treatment was to be reinitiated if scalp psoriasis reappeared. The trial was conducted in accordance with the principles of the Declaration of Helsinki and good clinical practice and institutional review boards approved the protocol. The parents or legal guardians of the patients provided written informed consent for their participation in the trial.

Study Objectives

The primary objective was to evaluate the safety (with particular focus on the effect on calcium metabolism, as well as HPA axis function through dynamic testing) of once-daily use of calcipotriene plus betamethasone dipropionate topical suspension in adolescents (ages

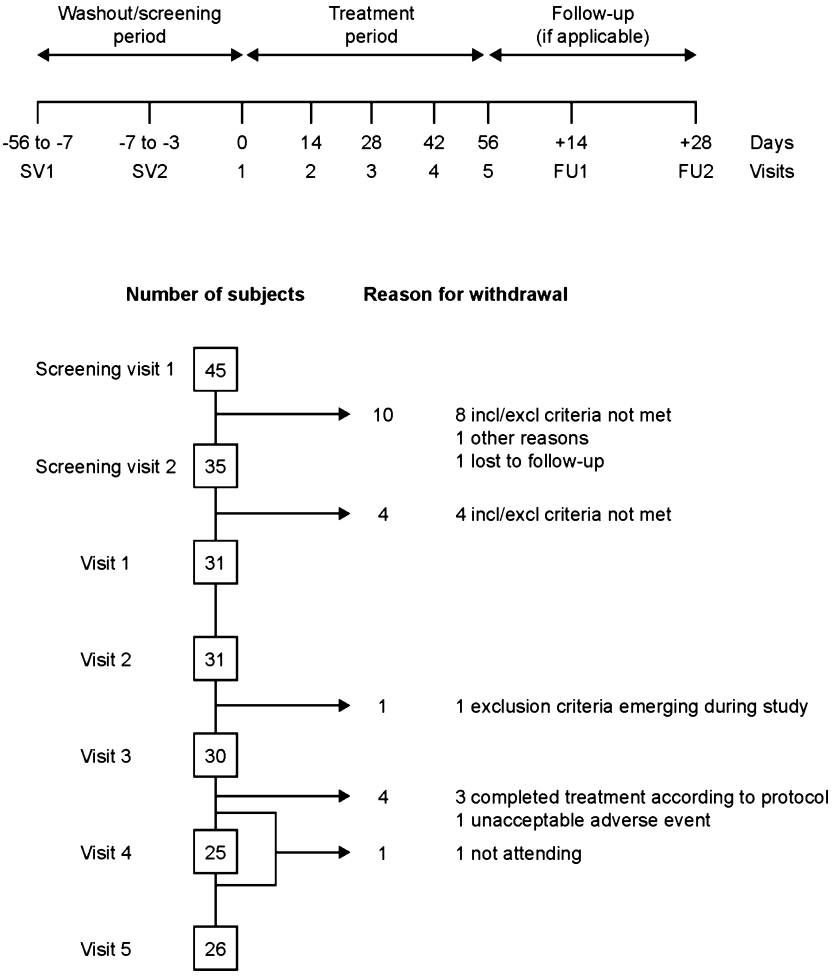

Figure 1. Study design excl, exclusion; FU, follow-up; incl, inclusion; SV, screening visit..

12–17 years) with scalp psoriasis. The secondary objective was to evaluate the investigator- and patient-assessed efficacy of the once-daily treatment regimen in this population.

Assessments

Adverse events (AEs) and efficacy were assessed at baseline (screening visit [SV2] and day 0) and at weeks 2 (day 14), 4 (day 28), 6 (day 48), and 8 (day 56). HPA axis function was assessed using a rapid standard-dose cosyntropin test (ACTH challenge test) at baseline (SV2) and weeks 4 and 8. Briefly, 2.5 mL of venous blood was drawn before an intravenous bolus injection of 250 μg of cosyntropin was administered; two additional 2.5-mL samples of venous blood were drawn 30 and 60 minutes after the injection. The primary response criterion for HPA axis evaluation was a serum cortisol level of 18 μg/dL or less at 30 minutes or at both 30 and 60 minutes after ACTH challenge, which would indicate possible adrenal suppression. Blood samples were collected at baseline (SV2) and weeks 4 and 8 before the ACTH challenge test for clinical laboratory tests including markers of calcium metabolism (calcium, phosphate, and parathyroid hormone), other biochemistry, and hematology. Before the visits at baseline (SV2) and weeks 4 and 8, a 24-hour urinary sample was collected for assessment of total excretion and creatinine-corrected ratios of calcium, phosphate, sodium, and hydroxyproline. Three days before and during urine collection, consumption of calcium-rich nutrients was to be kept constant and the daily number of "calcium servings" (corresponding to approximately 300 mg of calcium) was to be limited to five. The primary response criteria for calcium metabolism were changes from baseline in albumin-corrected serum calcium, 24-hour urinary calcium excretion, and urinary calcium:creatinine ratio. Patients with an ongoing AE possibly or probably related to study medication or those with an albumin-corrected serum calcium value above the reference range attended a follow-up visit 14 days after the end of treatment. A second follow-up at 4 weeks after treatment was required for patients with a serum cortisol value of 18 μg/dL or less 30 minutes after the ACTH challenge test.

Investigators evaluated the severity of scalp psoriasis using the six-point IGA scale (clear, almost clear, mild, moderate, severe, very severe); treatment success was defined as an assessment of clear or almost clear. Clinical signs of redness, thickness, and scaliness of the scalp psoriasis plaques were assessed using a numerical scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe); the sum of the three scores constituted the Total Sign Score (TSS). TSS success was defined as a total score of 1 or less. Patient assessment of disease severity was evaluated using the five-point Patient's Global Assessment (PaGA) scale (clear, very mild, mild, moderate, severe); treatment success was defined as an assessment of clear or very mild. Patients also assessed the degree of pruritus of the scalp (none, mild, moderate, severe). Adherence to treatment was evaluated at visits from week 2 to 8 by asking each patient whether they used the medication as prescribed and recording the number of applications missed. The bottles dispensed were returned at each visit and weighed to calculate the amount of drug used.

Statistical Analysis

A sample size of 30 patients evaluable for HPA axis function was deemed adequate for this trial. No formal statistical analyses were performed and data are presented descriptively (with two-sided 95% confidence intervals for primary and secondary endpoints involving laboratory measurements and efficacy assessments). All patients who received study medication were included in the full analysis set. All patients who applied study medication and for whom the presence or confirmed absence of AEs was available were included in the safety analysis set. For analysis of HPA axis function (by means of the ACTH challenge test), a per-protocol analysis set was defined by exclusion of the following patients from the full analysis set: those who did not use the study medication, did not have normal HPA axis function at baseline, or did not have data from the ACTH challenge tests on treatment.

Baseline was defined as the last assessment performed before application of treatment. The end-of-treatment value was defined as the last value recorded for that parameter up to and including week 8. Efficacy data and laboratory data were analyzed according to visit using an observed cases approach (involving only subjects who attended each specific visit), except for the tabulation of end-of-treatment values, for which the last observation carried forward approach was used.

RESULTS

Patients

Between April 2010 and August 2012, 45 patients were enrolled and attended the initial screening assessment, and 31 patients received treatment

(Fig. 1) and were included in the full and safety analyses sets. The median age of the patients was 15.0 years (range 12–17 yrs), 12 patients (39%) were male (safety analysis set; Table 1), and for 19 patients (61%), the age of onset of scalp psoriasis was 10 to 14 years (<10 yrs for 10 patients [32%] and >14 yrs for 2 patients [7%]). At baseline, patients' TSS ranged from 4 to 11. Patients' mean body mass index (BMI) was 26.8 kg/m² and 16 patients (52%) had a BMI outside the normal range (normal range 18.5–24.9 kg/m²), and most were above the upper limit of this range. Seventeen patients (55%) treated with calcipotriene plus betamethasone dipropionate topical suspension were fully adherent to treatment, and only five (16%) missed more than 10% of applications. The mean weekly use of the topical suspension over the entire treatment period was 24.5 g (range 0.7–59.9 g).

Safety and Tolerability

Sixteen patients (52%) experienced a total of 20 AEs; 14 were mild in severity and none were serious or lesional/perilesional on the scalp. The most common AEs were cough (n = 3; 10%), oropharyngeal pain (n = 3; 10%), nasopharyngitis (n = 2; 7%), and upper respiratory tract infection (n = 2; 7%). The investigator considered only one AE to be possibly related to study treatment—a patient with laboratory signs of adrenal suppression at week 4 (serum cortisol concentration 16.8 μg/dL at 30 minutes after ACTH challenge; Fig. 2). This adverse drug reaction was judged to be mild. The patient discontinued treatment, and a normal ACTH challenge test was reported at the follow-up visit 4 weeks after the end of study treatment. No other patients showed signs of adrenal suppression.

Overall, mean changes from baseline in albumin-corrected serum calcium (reference range 8.4–10.3 mg/dL [2.1–2.6 mM]), 24-hour urinary calcium excretion (reference range 100–300 mg/24 h [2.5–7.5 mmol/24 h]), and urinary calcium:creatinine ratio (reference range 0.01–0.33 mg/g [0.2–8.2 mmol/g]) were not considered to be clinically relevant. The mean albumin-corrected serum calcium level was 9.04 mg/dL (2.26 mM) at baseline, with mean changes of –0.112 mg/dL (–0.028 mM) at week 4, 0.008 mg/dL (0.002 mM) at week 8, and –0.028 mg/dL (–0.007 mM) at the end of treatment. None of the patients had albumin-corrected serum calcium levels above the laboratory upper reference limit at these time points. At baseline the mean 24-hour urinary calcium excretion value was 121.2 mg/24 h (3.03 mmol/24 h), with mean changes of 8.00 mg/24 h (0.20 mmol/24 h) at week 4, 2.40 mg/24 h (0.06 mmol/24 h) at week 8, and 4.80 mg/24 h (0.12 mmol/24 h) at the end of treatment. The mean urinary calcium:creatinine ratio was 0.13 mg/g (3.20 mmol/g) at baseline, with mean changes of −0.007 mg/g (−0.179 mmol/g) at week 4, less than –0.001 mg/g (<−0.005 mmol/g) at week 8, and 0.004 mg/g (0.096 mmol/g) at the end of treatment. No patients had clinically relevant changes in

TABLE 1. *Demographic and Baseline Characteristics*

Characteristic	Safety analysis set (n = 31)	Per-protocol analysis set (n = 30)
Age, years, median (range)	15.0 (12–17)	15.0 (12–17)
Male, n (%)	12 (39)	11 (37)
Race, n (%)		
White	28 (90)	27 (90)
Black or African American	1 (3)	1 (3)
Asian	1 (3)	1 (3)
Other	1 (3)	1 (3)
Body mass index, kg/m², mean (range)	26.8 (15.7–47.1)	27.1 (15.7–47.1)
Duration of scalp psoriasis, years, mean (range)	4.7 (1–11)	4.8 (1–11)
Investigator-assessed extent of psoriasis, %, mean (range)		
Total body surface area	5.2 (1–13)	5.2 (1–13)
Scalp	60.4 (20–100)	61.1 (20–100)
Investigator's Global Assessment, n (%)		
Moderate	21 (68)	20 (67)
Severe	8 (26)	8 (27)
Very severe	2 (7)	2 (7)
Patient's Global Assessment, n (%)		
Very mild	3 (10)	2 (7)
Mild	5 (16)	5 (17)
Moderate	18 (58)	18 (60)
Severe	5 (16)	5 (17)

The per-protocol analysis set comprised 30 patients; one patient was excluded who did not meet the inclusion criterion of normal hypothalamic–pituitary–adrenal axis function at baseline.

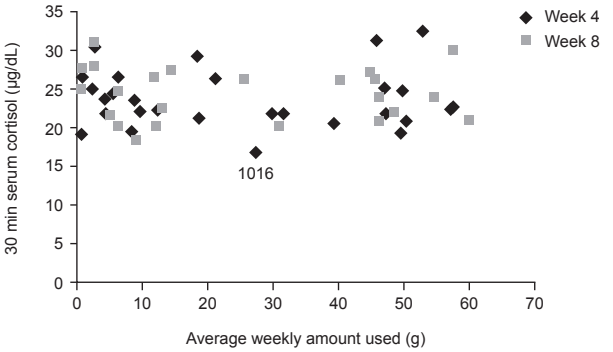

Figure 2. Serum cortisol concentration 30 minutes after adrenocorticotropic hormone challenge at weeks 4 and 8 according to the average weekly amount of study drug used during the first 4 and 8 weeks. The single patient (patient 1016) with a cortisol concentration below the defined cutoff level for a normal response is indicated in the figure.

24-hour urinary calcium excretion or urinary calcium: creatinine ratio. There were no clinically relevant changes in other markers of calcium metabolism or in any other biochemistry or hematology parameters.

Efficacy

Treatment success according to IGA was reported in 17 patients (55%) by the end of treatment (Fig. 3), including three patients who achieved clear disease status at week 4 and completed the study at this time point according to the protocol. The mean TSS improved from 6.9 at baseline to 2.9 at the end of treatment (59% improvement). The proportion of patients with TSS success was 39% (n = 12) at the end of treatment, compared with 0% at baseline. Changes in disease severity as evaluated by patients (PaGA) demonstrated similar results to the investigator assessments, with the number of patients reporting treatment success increasing from 3 (10%) at baseline to 18 (58%) at the end of treatment. Already by week 2, 45% of the patients achieved treatment success according to the PaGA, and 32% were assessed as showing treatment success according to the IGA. Patients also reported itch relief, with 28 (90%) experiencing mild or no itching at the end of treatment compared with 20 (65%) at baseline (Fig. 4).

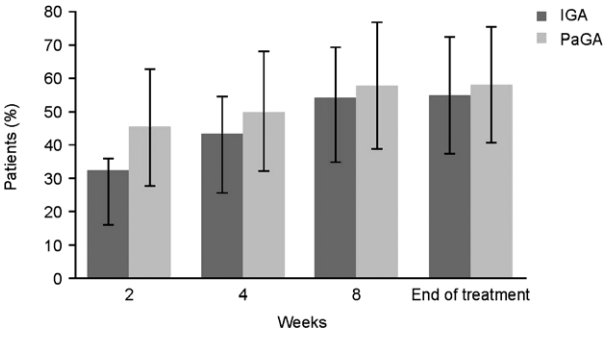

Figure 3. Proportion of patients experiencing treatment success as determined according to Investigator's Global Assessment (IGA) and Patient's Global Assessment (PaGA) and 95% confidence intervals. Treatment success was defined as an assessment of clear or almost clear for the IGA or clear or very mild for the PaGA. Week 8 data include only observed cases at that time point and end-of-treatment data include the last value recorded for that parameter.

DISCUSSION

This study assessed the safety and efficacy of calcipotriene plus betamethasone dipropionate topical suspension in adolescents with moderate to very severe scalp psoriasis. The topical treatment was well tolerated and efficacious in these patients with extensive scalp psoriasis (mean coverage 60.4% of the scalp area).

Our safety findings are comparable with those of adult studies of once-daily administration of calcipotriene plus betamethasone dipropionate topical suspension (8,15). No adolescents experienced lesional or perilesional events on the scalp in this study, whereas in adult studies, 3% to 6% of patients typically report such events (16–18). In the current study, reversible adrenal suppression was observed in one patient at 4 weeks, although this was without clinical manifestation. This patient used 94 g of product during the first 2 weeks of the study period, compared with an average 51 g in the study population. In adults, two patients (5%) showed laboratory signs of adrenal suppression after 4 weeks of treatment of extensive body and scalp psoriasis with calcipotriene plus betamethasone dipropionate topical suspension, but normal serum cortisol response was documented in these patients at a follow-up visit 4 weeks later (15). A recent systematic review showed that reversible

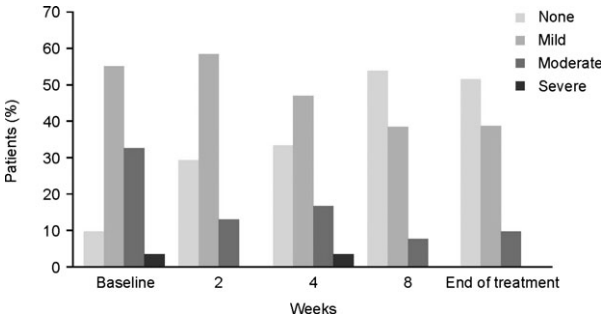

Figure 4. Patient assessment of itching. Week 8 data include only observed cases at that time point and end-of-treatment data include the last value recorded for that parameter.

adrenal suppression with clinical manifestations was rarely reported in adults, compared with the large numbers of patients using topical steroid treatments for psoriasis worldwide, but laboratory signs of transient reduction of HPA axis function were frequent (19). Instances of adrenal suppression in short-term psoriasis studies were usually seen early on in treatment, with cortisol levels returning to normal within weeks, which is probably analogous to restoration of the epidermal barrier helping to lower steroid absorption with healing (19). High doses of topical vitamin D analogues, such as calcipotriene, have been associated with hypercalcemia (20) resulting from interaction between the vitamin D receptor and genes regulating calcium metabolism. In line with previous studies of calcipotriene plus betamethasone dipropionate topical suspension, no cases of hypercalcemia or clinically relevant increases in urinary calcium or other parameters of calcium metabolism were observed (9,15,16).

A treatment success rate (according to the IGA) of 55% was achieved in this study. In adult studies in scalp psoriasis, 68% to 72% of patients achieved treatment success according to the IGA at week 8, although eligibility criteria tended to include all disease severities and ≥ 10% total scalp involvement (16–18). The 58% treatment success according to the PaGA achieved here compares with 69% to 83% in 8-week studies in adults (16–18). Treatment success was already demonstrated by week 2, at which point 45% of patients reported treatment success (PaGA) and 32% were assessed as showing treatment success by the investigator (IGA). The evidence of early efficacy of the fixed-combination topical suspension in adolescents is consistent with findings in adult studies (16–18).

Clinically relevant relief of pruritus, as assessed by patients, was also observed in this study, with 90% reporting mild or no itching by the end of treatment, compared with 65% at baseline. Pruritus is a common distressing aspect of psoriasis (21), and it may be particularly disturbing on the scalp (22). It can cause pronounced discomfort, often associated with a loss of sleep, and can negatively affect daily activities, such as the ability to attend school or work and a reduction in productivity (23). Alleviation of pruritus can therefore afford significant improvement to a patient's quality of life and is an important feature of symptom relief with the calcipotriene plus betamethasone dipropionate topical suspension that goes beyond the direct objective of improving skin lesions.

Data concerning topical psoriasis treatments in adolescent patients are limited. Only four reported pediatric studies have investigated topical psoriasis products for a minimum duration of 8 weeks (24–27). Calcipotriene ointment was well tolerated and effective in two 8-week studies in children ages 2 to 14 years and one 12- to 106-week study in 8- to 15-year-olds, although the latter included only 12 patients (24–26). Calcipotriene ointment was reported to be of benefit over 8 weeks in four adolescent patients (ages 13–17 years) (27). In the current study we assessed efficacy and safety after treatment with calcipotriene plus betamethasone dipropionate topical suspension specifically in adolescents spanning the full age range of 12 to 17 years. Previous studies have included adolescents within the wider setting of childhood, not addressing this specific age group.

In conclusion, the results of this study indicate that calcipotriene plus betamethasone dipropionate topical suspension is a well tolerated and efficacious once-daily treatment regimen for scalp psoriasis in adolescents. This is one of two studies (the other being conducted in Europe and Canada) evaluating the safety and efficacy of this topical suspension in adolescents with moderate to very severe scalp psoriasis.

CONFLICT OF INTEREST DISCLOSURES

Dr. Ganslandt was an employee of LEO Pharma at the time the study was conducted and is currently an employee of AbbVie. Dr. Eichenfield served as an investigator and consultant to LEO Pharma. Dr. Kurvits is an employee of LEO Pharma.

REFERENCES

1. Greaves MW, Weinstein GD. Treatment of psoriasis. N Engl J Med 1995;332:581–588.
2. Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. Lancet 2007;370:263–271.
3. Farber EM, Nall ML. The natural history of psoriasis in 5,600 patients. Dermatologica 1974;148:1–18.
4. de Jager ME, de Jong EM, Evers AW et al. The burden of childhood psoriasis. Pediatr Dermatol 2011;28:736–737.
5. Mercy K, Kwasny M, Cordoro KM et al. Clinical manifestations of pediatric psoriasis: results of a multicenter study in the United States. Pediatr Dermatol 2013;30:424–428.
6. Menter A, Korman NJ, Elmets CA et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. J Am Acad Dermatol 2009;60:643–659.
7. Douglas WS, Poulin Y, Decroix J et al. A new calcipotriol/betamethasone formulation with rapid onset of action was superior to monotherapy with betamethasone dipropionate or calcipotriol in psoriasis vulgaris. Acta Derm Venereol 2002;82:131–135.

8. McCormack PL. Calcipotriol/betamethasone dipropionate: a review of its use in the treatment of psoriasis vulgaris of the trunk, limbs and scalp. Drugs 2011;71:709–730.
9. Menter A, Gold LS, Bukhalo M et al. Calcipotriene plus betamethasone dipropionate topical suspension for the treatment of mild to moderate psoriasis vulgaris on the body: a randomized, double-blind, vehicle-controlled trial. J Drugs Dermatol 2013;12:92–98.
10. Guenther LC. Treatments for scalp psoriasis with emphasis on calcipotriol plus betamethasone dipropionate gel (Xamiol®). Skin Therapy Lett 2009;14:1–4.
11. Langley RG, Gupta A, Papp K et al. Calcipotriol plus betamethasone dipropionate gel compared with tacalcitol ointment and the gel vehicle alone in patients with psoriasis vulgaris: a randomized, controlled clinical trial. Dermatology 2011;222:148–156.
12. Fouéré S, Adjadj L, Pawin H. How patients experience psoriasis: results from a European survey. J Eur Acad Dermatol Venereol 2005;19(Suppl 3):2–6.
13. Hol K. Patient preference for topical psoriasis formulations. Poster presented at the EADV Congress, Gothenburg, Sweden, October 6–10, 2010.
14. Ou HT, Feldman SR, Balkrishnan R. Understanding and improving treatment adherence in pediatric patients. Semin Cutan Med Surg 2010;29:137–140.
15. Silver S, Tuppal R, Gupta AK et al. Effect of calcipotriene plus betamethasone dipropionate topical suspension on the hypothalamic-pituitary-adrenal axis and calcium homeostasis in subjects with extensive psoriasis vulgaris: an open, non-controlled, 8-week trial. J Drugs Dermatol 2013;12:882–887.
16. Jemec GB, Ganslandt C, Ortonne J-P et al. A new scalp formulation of calcipotriene plus betamethasone compared with its active ingredients and the vehicle in the treatment of scalp psoriasis: a randomized, double-blind, controlled trial. J Am Acad Dermatol 2008; 59:455–463.
17. Kragballe K, Hoffmann V, Ortonne JP et al. Efficacy and safety of calcipotriol plus betamethasone dipropionate scalp formulation compared with calcipotriol scalp solution in the treatment of scalp psoriasis: a randomized controlled trial. Br J Dermatol 2009; 161:159–166.
18. van de Kerkhof PC, Hoffmann V, Anstey A et al. A new scalp formulation of calcipotriol plus betamethasone dipropionate compared with each of its active ingredients in the same vehicle for the treatment of scalp psoriasis: a randomized, double-blind, controlled trial. Br J Dermatol 2009;160:170–176.
19. Castela E, Archier E, Devaux S et al. Topical corticosteroids in plaque psoriasis: a systematic review of risk of adrenal axis suppression and skin atrophy. J Eur Acad Dermatol Venereol 2012;26 (Suppl 3):47–51.
20. Kragballe K, Iversen L. Calcipotriol. A new topical antipsoriatic. Dermatol Clin 1993;11:137–141.
21. Kimball AB, Jacobson C, Weiss S et al. The psychosocial burden of psoriasis. Am J Clin Dermatol 2005;6:383–392.
22. Wozel G, Klein E, Mrowietz U et al. Scalp psoriasis. J Dtsch Dermatol Ges 2011;9:70–74.
23. Globe D, Bayliss MS, Harrison DJ. The impact of itch symptoms in psoriasis: results from physician interviews and patient focus groups. Health Qual Life Outcomes 2009;7:62.
24. Darley CR, Cunliffe WJ, Green CM et al. Safety and efficacy of calcipotriol ointment (Dovonex) in treating children with psoriasis vulgaris. Br J Dermatol 1996; 135:390–393.
25. Oranje AP, Marcoux D, Svensson A et al. Topical calcipotriol in childhood psoriasis. J Am Acad Dermatol 1997;36:203–208.
26. Park SB, Suh DH, Youn JI. A pilot study to assess the safety and efficacy of topical calcipotriol treatment in childhood psoriasis. Pediatr Dermatol 1999;16:321–325.
27. Perez A, Chen TC, Turner A et al. Pilot study of topical calcitriol (1,25-dihydroxyvitamin D3) for treating psoriasis in children. Arch Dermatol 1995;131:961–962.