

# Safety and efficacy of calcipotriol plus betamethasone dipropionate gel in the treatment of scalp psoriasis in adolescents 12–17 years of age\*

M. Gooderham,<sup>1</sup> J.-M. Debarre,<sup>2</sup> J. Keddy-Grant,<sup>3</sup> Z. Xu,<sup>4</sup> M. Kurvits<sup>4</sup> and M. Goodfield<sup>5</sup>

<sup>1</sup>SKiN Centre for Dermatology, 743 Lansdowne Street West, Peterborough, ON, Canada K9J 1Z

<sup>2</sup>Cabinet de Dermatologie, Cholet, France

<sup>3</sup>Winnipeg Clinic Dermatology Research, Winnipeg, MB, Canada

<sup>4</sup>LEO Pharma A/S, Ballerup, Denmark

<sup>5</sup>Department of Dermatology, Chapel Allerton Hospital, Leeds, U.K.

## Summary

### Correspondence

Melinda Gooderham.

E-mail: mjgooderham@gmail.com

### Accepted for publication

16 June 2014

### Funding sources

This study was sponsored by LEO Pharma A/S. Writing assistance was provided by Tamara Hirsch, PhD, from Mudskipper Business Ltd, funded by LEO Pharma.

### Conflicts of interest

M. Gooderham has received honoraria from Actelion, Astellas, Graceway and Janssen, research funding from Celgene, Dermira, Dr Reddy's Laboratories, Eli Lilly, Forward Pharma, Kyowa Hakko Kirin, Kythera, Merck and Pfizer, and research funding and honoraria from AbbVie, Amgen, Galderma, LEO Pharma and Novartis. J.-M.D. has received honoraria from LEO Pharma. M. Goodfield has received research funding and honoraria from AbbVie, Celgene, Galderma, Janssen, LEO Pharma, Novartis and Pfizer. Z.X. and M.K. are employees of LEO Pharma. J.K.-G. has no conflicts of interest to declare.

This work was previously presented as an abstract at the American Academy of Dermatology meeting, Chicago, IL, U.S.A., 6–10 August 2014; abstract number 7843.

\*Plain language summary available online.

DOI 10.1111/bjd.13235

**Background** Plaque psoriasis has a relatively high prevalence in adolescence, resulting in a significant impact on quality of life, including social interactions.

**Objectives** The primary objective was to assess the safety of once-daily application of fixed-combination calcipotriol plus betamethasone dipropionate gel in adolescent scalp psoriasis. Assessment of efficacy was a secondary objective.

**Methods** This phase II, multicentre, single-arm, open-label, 8-week trial included patients aged 12–17 years with moderate-to-very severe scalp psoriasis according to Investigator's Global Assessment (IGA) ( $\geq 10\%$  of the scalp area affected).

**Results** Seventy-eight patients received treatment. Twenty-seven patients (35%) reported a total of 64 adverse events (AEs); most were mild (33/64) or moderate (22/64) in severity and there were no serious AEs. No cases of hypercalcaemia were reported, and the mean changes from baseline to end of treatment in albumin-corrected serum calcium ( $0.00 \text{ mmol L}^{-1}$ ), 24-h urinary calcium excretion ( $-0.03 \text{ mmol per } 24 \text{ h}$ ) and urinary calcium-to-creatinine ratio ( $-0.12 \text{ mmol g}^{-1}$ ) were not considered clinically relevant. At the end of treatment 66 patients (85%) were clear or almost clear according to IGA. There was an 80% improvement in mean Total Sign Score from baseline to end of treatment. In total, at the end of treatment, 87% of patients rated their scalp psoriasis as clear or very mild, and 75 (96%) had no or mild pruritus compared with 14 (18%) at baseline.

**Conclusions** Once-daily calcipotriol plus betamethasone dipropionate gel is well tolerated and efficacious for scalp psoriasis in adolescents.

### What's already known about this topic?

- Calcipotriol plus betamethasone dipropionate gel is a well-tolerated and efficacious treatment for scalp and body psoriasis in adults.
- Psoriasis can present during childhood or adolescence and may negatively impact quality of life.

**What does this study add?**

- Calcipotriol plus betamethasone dipropionate gel is well tolerated and shows efficacy for treatment of scalp psoriasis in an adolescent population.

Psoriasis vulgaris is one of the most common chronic skin diseases, affecting 1–3% of the general population.<sup>1,2</sup> The total prevalence of psoriasis in children aged < 18 years is approximately 0.7%, and the rate increases linearly with age from 0 to 18 years.<sup>3</sup> Within the adolescent age group, quality of life may be significantly compromised, with social development being especially impaired.<sup>4</sup> The overt visibility of plaques can prove particularly troublesome, and lesions of the scalp frequently present within this age group, which may result in alopecia in severe cases.<sup>5</sup>

Topical vitamin D analogues and corticosteroids are established first-line treatments for scalp psoriasis,<sup>6</sup> although safety concerns may accompany their use. Vitamin D analogues can cause skin irritation and hypercalcaemia, while corticosteroids are associated with local adverse events (AEs), including skin atrophy, striae and telangiectasia, as well as systemic AEs such as adrenal suppression.<sup>6,7</sup> Combination of these topical agents capitalizes on their beneficial clinical characteristics and can allay side-effects. A fixed combination of calcipotriol plus betamethasone dipropionate in a single product is well tolerated and effective in treating psoriasis in adults and has demonstrated superior efficacy to monotherapy with its individual components.<sup>8–11</sup> Greater anti-inflammatory and antiproliferative effects are evident than for either active ingredient alone, and the onset of action is more rapid.<sup>12–14</sup>

Nonadherence to topical agents can limit their effectiveness, and, among adolescents, adherence to topical treatments is particularly poor owing to social pressures and inconvenience of using medication.<sup>15</sup> The formulation prescribed can influence patients' day-to-day use, and poor cosmetic characteristics, including greasy and sticky application, are frequently cited as discouraging the use of psoriasis treatments.<sup>16</sup> A more cosmetically acceptable and easy-to-use treatment in the form of a fixed-combination lipophilic, alcohol-free gel has demonstrated favourable patient-related benefits in adults,<sup>17,18</sup> and may have increased acceptability in adolescents with psoriasis. The objective of this trial was to investigate safety, with particular focus on calcium metabolism and the effectiveness of once-daily calcipotriol plus betamethasone dipropionate gel in an adolescent population. This trial was registered at ClinicalTrials.gov (NCT01120223).

## Patients and methods

### Patients

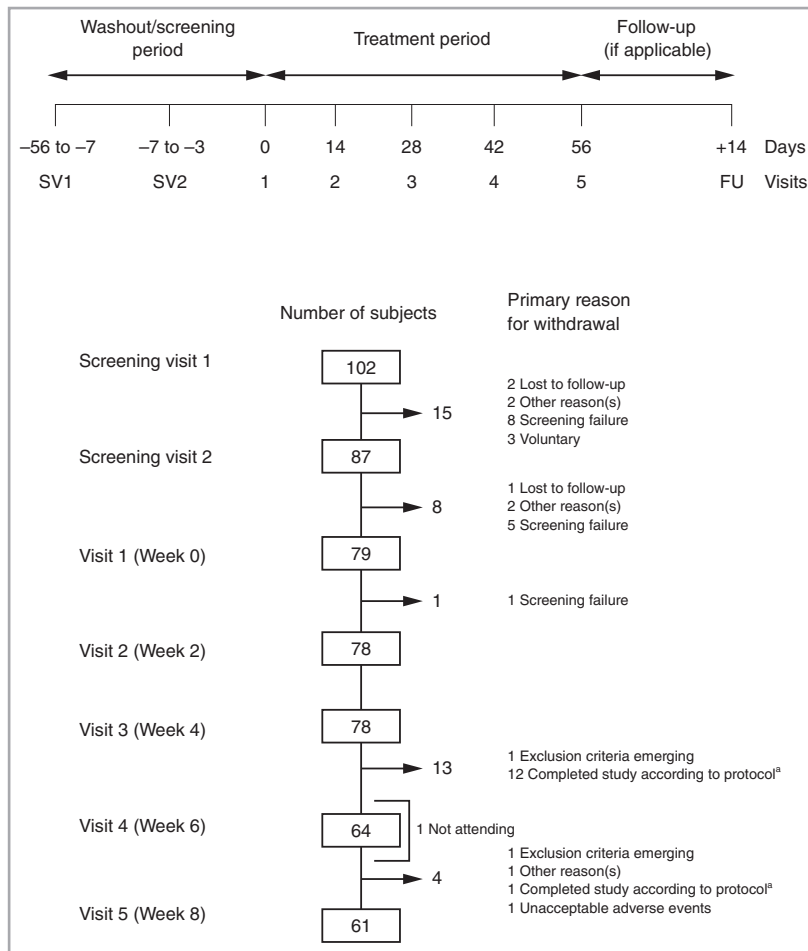
Outpatients aged 12–17 years with a diagnosis of psoriasis vulgaris affecting  $\geq 10\%$  of the scalp and of at least moderate

severity, according to the Investigator's Global Assessment (IGA), were eligible. All patients had clinical signs or a previous diagnosis of psoriasis vulgaris on the trunk or limbs. Patients were required to be amenable to topical treatment with a maximum of 60 g of study medication per week. At inclusion, patients were to have an albumin-corrected serum calcium value below the upper reference limit.

The main exclusion criteria were a history of hypersensitivity to any component of the fixed-combination topical gel, topical treatment on the trunk and/or limbs with very potent (World Health Organization group IV) corticosteroids or on the face and/or genital/skin folds with potent or very potent (World Health Organization groups III–IV) corticosteroids, within 2 weeks prior to baseline or during the trial. Patients were also excluded if they had received systemic treatment with adalimumab, alefacept or infliximab within 2 months, etanercept within 4 weeks, ustekinumab within 4 months or experimental biologics within 4 weeks/five half-lives prior to baseline. Patients receiving treatment with a possible effect on scalp psoriasis (for example, corticosteroids, retinoids, immunosuppressants, psoralen combined with ultraviolet A) within 4 weeks prior to baseline or during the trial were excluded. Other exclusion criteria included severe renal or hepatic disorders, any infections of the scalp area, treatment with systemic calcium or vitamin D supplements, antacids, diuretics, antiepileptics, bisphosphonates or calcitonin within 4 weeks prior to baseline, or ultraviolet B therapy within 2 weeks prior to baseline.

### Study design

This was a phase II, open-label, single-arm, 8-week trial in adolescent patients with scalp psoriasis conducted in 17 centres in Canada, France and the U.K. The three-part trial consisted of a washout/screening period, a treatment period and a follow-up period (Fig. 1). A washout period of up to 8 weeks was applicable if patients had received antipsoriatic treatments or other relevant medication as outlined in the exclusion criteria. The treatment involved application of once-daily calcipotriol  $50 \mu\text{g g}^{-1}$  plus betamethasone  $0.5 \text{ mg g}^{-1}$  gel (as the dipropionate) (Taclonex<sup>®</sup> topical suspension/Xamiol<sup>®</sup> gel/Daivobet<sup>®</sup> gel/Dovobet<sup>®</sup> gel; all LEO Pharma, Princes Risborough, U.K.) to the scalp for up to 8 weeks. Patients were permitted the concomitant use of other topical antipsoriatic treatments (including vitamin D analogues), except for corticosteroids, on the trunk, limbs or face, but no other scalp products were allowed during



**Fig 1.** Study design. <sup>a</sup>Thirteen patients with complete clearance of scalp psoriasis exited the study, as per protocol, between days 28 ( $n = 12$ ) and 42 ( $n = 1$ ). The patient who exited at week 6 achieved complete clearance at week 4. SV, study visit; FU, follow-up.

the treatment period. Patients whose scalp psoriasis had cleared after 4 weeks of treatment were to leave the trial, whereas patients who showed signs of scalp psoriasis after 4 weeks continued treatment for another 4 weeks. After week 8, an additional 2-week follow-up period could be instituted on an individual patient basis if, at the last on-treatment visit, an ongoing serious or nonserious AE of possible, probable or not assessable relationship to the study drug was experienced, or if albumin-corrected serum calcium values above the reference range were observed. The protocol was approved by the institutional review boards and the trial was conducted in accordance with the principles of the Declaration of Helsinki and good clinical practice. Signed informed consent was provided by patients or parents/legal guardians.

### Study objectives

The primary objective was to evaluate the safety (with particular focus on calcium metabolism) of once-daily use of calcipotriol plus betamethasone dipropionate gel in adolescent patients (aged 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.

### Procedures

Assessment of AEs and efficacy took place at baseline [screening visit (SV)2 and day 0] and at weeks 2 (day 14), 4 (day 28), 6 (day 42) and 8 (day 56). Blood samples were collected at baseline (SV2) and weeks 4 and 8 for analysis of parameters, including calcium homeostasis (calcium, phosphate and parathyroid hormone). Prior to visits at baseline (SV2) and weeks 4 and 8, 24-h urine samples were collected for assessment of total excretion and creatinine-corrected ratios of calcium, phosphate, sodium and hydroxyproline. Patients' daily calcium servings (one serving approximates to a calcium content of 300 mg) were not to exceed five, and the intake of calcium-rich nutrients was to be maintained at constant levels 3 days prior to and during each 24-h urine collection. Calcium metabolism primary response criteria were evaluated according to changes from baseline in albumin-corrected serum calcium, 24-h urinary calcium excretion and urinary calcium-to-creatinine ratio. A follow-up visit was scheduled for any patient with an ongoing AE or an albumin-corrected serum calcium value above the reference range at the end of treatment.

The severity of scalp psoriasis was evaluated on a 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 erythema and induration and

the scale 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 individual scores constituted the Total Sign Score (TSS). TSS success was defined as a total score  $\leq 1$ . Patients assessed disease severity according to 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 rated the degree of pruritus of the scalp (none, mild, moderate, severe). Adherence to treatment was assessed at visits from day 14 to day 56 by asking each patient whether they used the medication as prescribed. Dispensed bottles were returned and weighed at each visit to estimate the amount of drug used.

### Statistical analysis

A sample size of 70 patients was deemed appropriate for this trial. No formal statistical analyses were performed. Data are presented descriptively and with two-sided 95% confidence intervals for the primary and secondary end points involving laboratory measurements and efficacy assessments, respectively. All patients who received study medication were included in the full analysis set and were analysed for effectiveness. All patients who applied the study medication and for whom the presence or confirmed absence of AEs was available were included in the safety analysis set. 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 presented by visit using an observed-cases approach (i.e. involving only those 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 November 2010 and October 2012, 102 patients were enrolled, of whom 78 received treatment (Fig. 1) and were included in the full analysis and safety analysis sets. The mean age of patients was 14.6 years (range 12–17) and 35 patients (45%) were male (Table 1). Forty-six patients (59%) were fully compliant or missed  $\leq 10\%$  of the applications. The mean weekly use of the gel during the entire treatment period was 36 g (range 4–69), and, comparing the first 4 weeks with the second 4 weeks of treatment, there was no decrease in weekly use over time. Thirteen patients showed complete clearance of scalp psoriasis at week 4 and left the study per protocol.

### Safety and tolerability

#### Adverse events

Twenty-seven patients (35%) reported 64 AEs. Most of the AEs were mild (33 of 64) or moderate (22 of 64) in severity,

**Table 1** Demographics and baseline characteristics

	Safety analysis set (n = 78)
Age (years), mean (range)	14.6 (12–17)
Sex, n (%)	
Male	35 (45)
Female	43 (55)
Race, n (%)	
White	70 (90)
Black or African American	1 (1)
Asian	3 (4)
Other	4 (5)
Body mass index ( $\text{kg m}^{-2}$ ), mean (range)	22.4 (15–44)
Duration of scalp psoriasis (years), mean (range)	5.9 (0–17)
Investigator-assessed extent of psoriasis (%), mean (range)	
Total body surface area	5 (1–50)
Scalp	44 (10–100)
Investigator's Global Assessment, n (%)	
Moderate	58 (74)
Severe	16 (21)
Very severe	4 (5)
Total Sign Score, mean (range)	7.1 (4–12)
Patient's Global Assessment, n (%)	
Very mild	1 (1)
Mild	11 (14)
Moderate	56 (72)
Severe	10 (13)

with nine reported as severe. No serious AEs were reported. The AEs reported in most patients were headache (n = 4, 5%), pharyngitis (n = 4, 5%), upper respiratory tract infection (n = 4, 5%) and decreased urine calcium (n = 3, 4%). Two patients (3%) reported a lesional/perilesional AE on the scalp: alopecia (mild, not related to study treatment as considered by the investigator) and application-site pruritus (mild, probably related). One patient experienced unacceptable AEs (not related to study treatment as considered by the investigator), including urine calcium decrease, blood parathyroid hormone increase and urine phosphorus decrease, as the primary reason for withdrawal from the trial. Seven adverse drug reactions (AEs for which a causal relationship with the study drug was possible or probable according to the investigator) were reported in five patients as single events. Three of these events occurred in one patient: blood calcium decrease, blood parathyroid hormone increase and urine calcium decrease (notably, these events occurred in a separate patient from the aforementioned 'unacceptable AEs'). The others all occurred individually (Table 2); blood parathyroid hormone increase, urine calcium decrease and acne were moderate in severity, and all other adverse drug reactions were mild.

A mild acneiform rash (dermatitis acneiform) occurred at week 4 on the face of a female patient aged 16 years, with an 8-year history of psoriasis, who was treated concomitantly with hydrocortisone cream for flexural psoriasis behind the ears. The acneiform rash was not treated and was still ongoing 2 weeks after the last on-treatment visit. A headache was

**Table 2** Adverse drug reactions by Medical Dictionary for Regulatory Activities (version 14.1) primary system organ class and preferred term

Adverse drug reaction <sup>a</sup>	Number of patients (%) <sup>b</sup>
General disorders and administration-site conditions	
Application-site pruritus	1 (1)
Investigations	
Blood calcium decrease	1 (1)
Blood parathyroid hormone increase	1 (1)
Urine calcium decrease	1 (1)
Nervous system disorders	
Headache	1 (1)
Skin and subcutaneous tissue disorders	
Acne	1 (1)
Dermatitis acneiform	1 (1)

<sup>a</sup>According to investigator assessment; <sup>b</sup>a single patient can appear in multiple classes.

reported on day 1 of study treatment in a male patient aged 15 years (with a 5-year history of psoriasis) who was treated on the day of onset with paracetamol (acetaminophen). The headache was also still ongoing 2 weeks after the last on-treatment visit. No patients met the criteria for requiring the additional follow-up period.

### Laboratory findings

The results of laboratory assessments related to calcium homeostasis are shown in Figure 2. No clinically relevant increases in albumin-corrected serum calcium, 24-h urinary calcium excretion or urinary calcium-to-creatinine ratio were reported. No clinically relevant changes were reported for other biochemistry or haematology parameters. No cases of hypercalcaemia were reported and the mean changes from baseline to end of treatment in albumin-corrected serum calcium ( $0.00 \text{ mmol L}^{-1}$ ), 24-h urinary calcium excretion ( $-0.03 \text{ mmol per 24 h}$ ) and urinary calcium-to-creatinine ratio ( $-0.12 \text{ mmol g}^{-1}$ ) were not considered clinically relevant.

### Efficacy

By the end of treatment, 66 patients (85%) demonstrated treatment success according to IGA (Fig. 3); 13 of these patients had clear disease (IGA) at week 4 and left the trial per protocol. By week 2, treatment success was reported in 37 patients (47%) by IGA. There was an 80% improvement in the mean TSS from 7.1 at baseline to 1.4 at the end of treatment (Fig. 4). Of note, a 63% improvement in mean TSS was already observed at week 2. The incidence of treatment success according to TSS also increased over time and was achieved by 49 patients (63%) by the end of treatment. With respect to PaGA, the number of patients reporting treatment success increased over time, reaching a total of 68 patients (87%) at the end of treatment (Fig. 3). Similarly to the inves-

tigator assessment, 44 patients (56%) had achieved treatment success by week 2. Patients also reported pruritus relief during the study, and by the end of treatment 75 patients (96%) reported no or mild pruritus, compared with 14 (18%) at baseline (Fig. 5).

### Discussion

This study showed that calcipotriol plus betamethasone dipropionate gel is well tolerated and effective in adolescents with at least moderate scalp psoriasis. In this study, the mean extent of psoriasis was 44% of the scalp area, with 26% of patients having severe/very severe scalp psoriasis.

Few AEs and no serious AEs were reported in the study, consistent with the safety and tolerability profile of calcipotriol plus betamethasone dipropionate gel reported previously in adults.<sup>9,10,19</sup> Similar proportions of patients experienced at least one AE (35% in the present study vs. 35–39% in adults) and there was a comparable incidence of lesional/perilesional events [two patients (3%) each experiencing one mild lesional/perilesional AE of the scalp in this study compared with 3–6% in adults].<sup>9,10,19</sup> In this adolescent study, five patients (6%) reported a total of seven adverse drug reactions, none of which was severe. A similarly low occurrence was reported in adults (up to 3%).<sup>9,10,19</sup> As calcipotriol can modulate vitamin D receptor activity with subsequent interaction with genes responsible for calcium and bone metabolism, there is potential for hypercalcaemia in patients using this treatment.<sup>20</sup> However, no cases of hypercalcaemia or clinically relevant increases in urinary calcium or other parameters of calcium metabolism were observed, consistent with previous studies in adults with calcipotriol plus betamethasone dipropionate gel.<sup>9,21</sup> A long-term study in adults has shown that this fixed-combination treatment is well tolerated when used as needed for up to 52 weeks in scalp psoriasis.<sup>22</sup>

The efficacy of calcipotriol plus betamethasone dipropionate gel demonstrated by the end of treatment in this study is comparable with that reported in adult studies in scalp psoriasis.<sup>9,10,19</sup> Currently, treatment success as assessed by IGA was achieved in 85% of patients at the end of treatment, and this is similar to the 68–72% demonstrated in adults.<sup>9,10,19</sup> Treatment success according to PaGA at end of treatment was reported in 87% of patients, and these findings are consistent with 69–83% of patients achieving treatment success in adult studies.<sup>9,10,19</sup> The improvement in TSS, with patients achieving a mean score of 1.4 by the end of treatment, was also similar to that seen in previous studies.<sup>9,10,19</sup> Likewise, efficacy has been widely reported with calcipotriol plus betamethasone dipropionate gel used for treatment of body psoriasis in adults.<sup>11,12,23</sup>

This study suggests a rapid response to calcipotriol plus betamethasone dipropionate gel, with treatment success reported by week 2 in 37 patients (47%) by IGA, and treatment success in 44 patients (56%) by PaGA. At week 4, 13 patients (17%) showed clear disease as evaluated by IGA and were able to leave the study per protocol. These results are

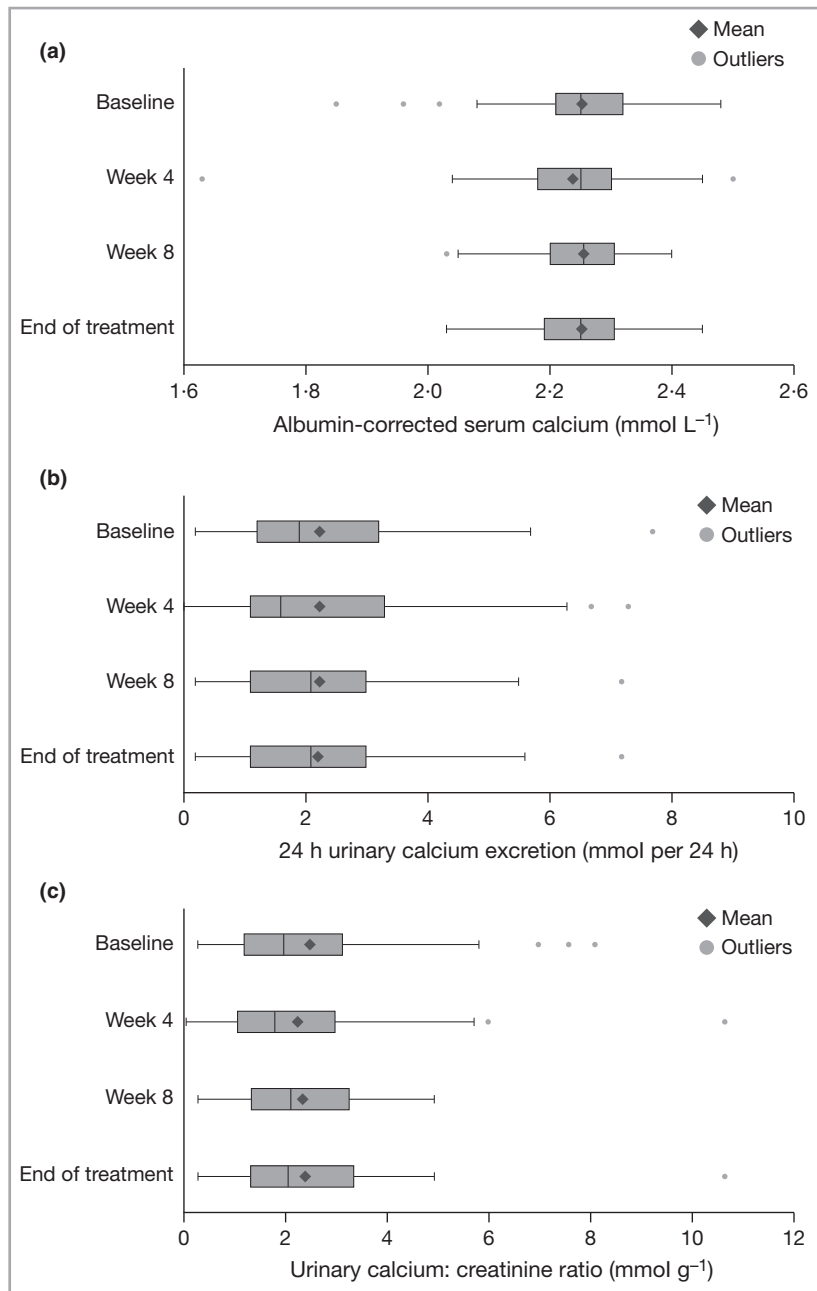


Fig 2. Calcium metabolism changes over time.

similar to those seen in adult studies with early demonstration of efficacy at 2 weeks. Adult studies also showed a rapid response to treatment as early as 1 week into treatment,<sup>9,10,19,24</sup> although 1-week data were not collected in the current study. In addition to formal assessments of IGA and PaGA, the evaluation of characteristic symptoms of psoriasis can provide further insight into treatment efficacy. Pruritus is a common symptom of scalp psoriasis that can be particularly burdensome to patients, significantly affecting their quality of life.<sup>23,25</sup> Most patients reported relief of pruritus in this study, with 96% experiencing no or mild pruritus at the end of treatment compared with 18% at baseline.

There are limited data describing the effect of topical psoriasis treatments in adolescents. Only four paediatric studies

have investigated topical psoriasis products for a minimum duration of 8 weeks.<sup>26–29</sup> Calcipotriol ointment demonstrated safety and efficacy in two 8-week studies in children aged 2–14 years and one 12- to 106-week study in 8- to 15-year-old patients.<sup>26–28</sup> The latter included only 12 patients. Calcipotriol ointment was also reported to be beneficial over 8 weeks in four adolescent patients (aged 13–17 years).<sup>29</sup> The aforementioned studies tended to group adolescents within the wider setting of childhood psoriasis without specific focus on adolescents. Our study reports on the safety of the study compound (with respect to calcium metabolism) used on the scalp over an 8-week period in the adolescent age group.

Topical psoriasis treatments are typically associated with low adherence rates and there is patient preference for more

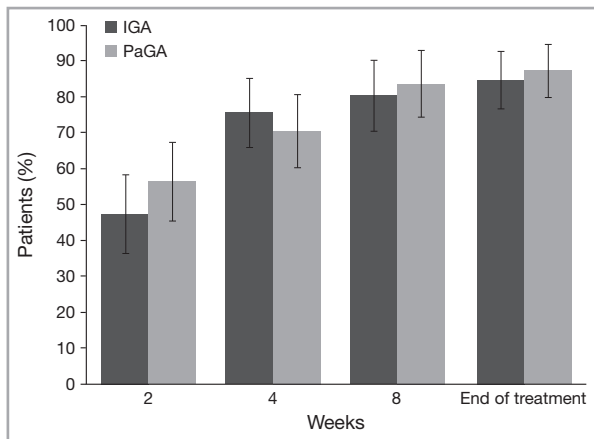


Fig 3. Proportions of patients experiencing treatment success as determined by Investigator's Global Assessment (IGA) and Patient's Global Assessment (PaGA) and 95% confidence intervals. Treatment success was defined by an assessment of clear or almost clear for IGA, or clear or very mild for PaGA. Week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

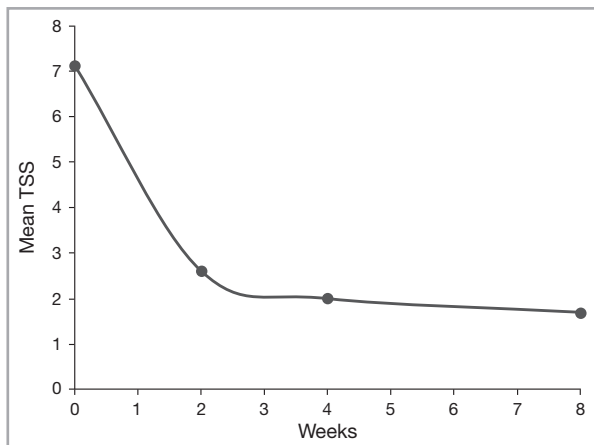


Fig 4. Mean Total Sign Score (TSS) over time.

cosmetically elegant products.<sup>16,30</sup> In this study, the amount of drug used was higher than that seen in adult studies (the mean weekly amount used over the entire treatment period being 36 g compared with 17–20 g in adult studies)<sup>9,10,19</sup> and remained high throughout the treatment period, with the majority of patients adherent to drug application. This suggests that patients were not inconvenienced by using the fixed-combination gel, although interpretation is limited by the short duration of the study and the clinical trial setting. Such regular use of medication is encouraging given that adolescents generally have poor adherence rates. Poor adherence rates seen in real-world settings have recently been reviewed, and recommendations include employing a patient-centric approach to improve adherence to topical psoriasis therapies.<sup>31,32</sup>

In conclusion, the results of this study indicate that calcipotriol plus betamethasone dipropionate gel is a well-tolerated

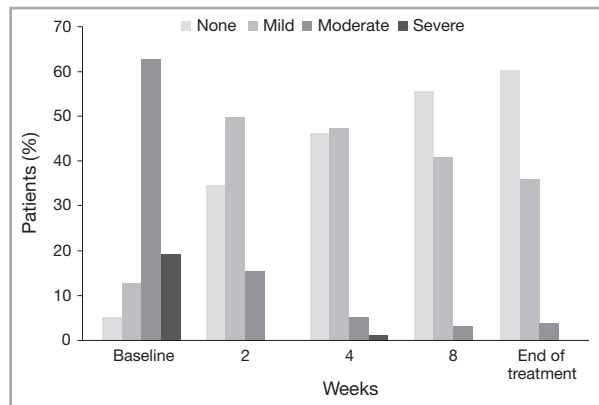


Fig 5. Patients' assessment of pruritus. Week 8 data include only observed cases at that time point and end-of-treatment data include the last value recorded for that parameter.

and effective once-daily treatment regimen for scalp psoriasis vulgaris in adolescents. This study is one of two (the other being U.S.A. based) to assess the safety and efficacy of the topical gel in adolescents with at least moderate scalp psoriasis.

## Acknowledgments

We would like to thank the study investigators: A. Abdullah, A.V. Anstey, K. Barber, A. Bewley, J.-J. Grob, L. Guenther, G. Gupta, P. Hull, R. Kunyetz, J.-P. Lacour, A. Layton, C. Lynde, M. Raman, G. Rostain and M. Ruer-Mulard; as well as B. Hui, LEO Pharma, for clinical trial management. Additionally, writing assistance was provided by Tamara Hirsch, PhD, from Mudskipper Business Ltd, funded by LEO Pharma.

## References

- Gelfand JM, Weinstein R, Porter SB *et al.* Prevalence and treatment of psoriasis in the United Kingdom: a population-based study. *Arch Dermatol* 2005; **141**:1537–41.
- Schäfer T. Epidemiology of psoriasis. Review and the German perspective. *Dermatology* 2006; **212**:327–37.
- Augustin M, Glaeske G, Radtke MA *et al.* Epidemiology and comorbidity of psoriasis in children. *Br J Dermatol* 2010; **162**:633–6.
- de Jager ME, de Jong EM, van de Kerkhof PC *et al.* An inpatient comparison of quality of life in psoriasis in childhood and adulthood. *J Eur Acad Dermatol Venereol* 2011; **25**:828–31.
- Benoit S, Hamm H. Childhood psoriasis. *Clin Dermatol* 2007; **25**:555–62.
- Lebwohl M, Ting PT, Koo JY. Psoriasis treatment: traditional therapy. *Ann Rheum Dis* 2005; **64** (Suppl. 2):ii83–6.
- Levin C, Maibach HI. Topical corticosteroid-induced adrenocortical insufficiency: clinical implications. *Am J Clin Dermatol* 2002; **3**:141–7.
- Douglas WS, Poulin Y, Decroix J *et al.* A new calcipotriol/beta-methasone formulation with rapid onset of action was superior to monotherapy with betamethasone dipropionate or calcipotriol in psoriasis vulgaris. *Acta Derm Venereol* 2002; **82**:131–5.
- Jemec GB, Ganslandt C, Ortonne JP *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**:455–63.
- 10 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**:170–6.
  - 11 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**:92–8.
  - 12 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**:148–56.
  - 13 Rosina P, Giovannini A, Gisoni P, Girolomoni G. Microcirculatory modifications of psoriatic lesions during topical therapy. *Skin Res Technol* 2009; **15**:135–8.
  - 14 Segært S, Røpke M. The biological rationale for use of vitamin D analogs in combination with corticosteroids for the topical treatment of plaque psoriasis. *J Drugs Dermatol* 2013; **12**:e129–37.
  - 15 Ou HT, Feldman SR, Balkrishnan R. Understanding and improving treatment adherence in pediatric patients. *Semin Cutan Med Surg* 2010; **29**:137–40.
  - 16 Devaux S, Castela A, Archier E *et al.* Adherence to topical treatment in psoriasis: a systematic literature review. *J Eur Acad Dermatol Venereol* 2012; **26**(Suppl. 3):61–7.
  - 17 Bewley A, Page B. Maximizing patient adherence for optimal outcomes in psoriasis. *J Eur Acad Dermatol Venereol* 2011; **25**(Suppl. 4):9–14.
  - 18 Sticherling M, Eicke C, Anger T. Practicability of combined treatment with calcipotriol/betamethasone gel (Daivobet® Gel) and improvement of quality of life in patients with psoriasis. *J Dtsch Dermatol Ges* 2013; **11**:420–7.
  - 19 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**:159–66.
  - 20 Scott LJ, Dunn CJ, Goa KL. Calcipotriol ointment. A review of its use in the management of psoriasis. *Am J Clin Dermatol* 2001; **2**:95–120.
  - 21 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**:882–7.
  - 22 Luger TA, Cambazard F, Larsen FG *et al.* A study of the safety and efficacy of calcipotriol and betamethasone dipropionate scalp formulation in the long-term management of scalp psoriasis. *Dermatology* 2008; **217**:321–8.
  - 23 Wozel G, Klein E, Mrowietz U *et al.* Scalp psoriasis. *J Dtsch Dermatol Ges* 2011; **9**:70–4.
  - 24 Buckley C, Hoffmann V, Shapiro J *et al.* Calcipotriol plus betamethasone dipropionate scalp formulation is effective and well tolerated in the treatment of scalp psoriasis: a phase II study. *Dermatology* 2008; **217**:107–13.
  - 25 Kimball AB, Jacobson C, Weiss S *et al.* The psychosocial burden of psoriasis. *Am J Clin Dermatol* 2005; **6**:383–92.
  - 26 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**:390–3.
  - 27 Oranje AP, Marcoux D, Svensson A *et al.* Topical calcipotriol in childhood psoriasis. *J Am Acad Dermatol* 1997; **36**:203–8.
  - 28 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**:321–5.
  - 29 Perez A, Chen TC, Turner A, Holick MF. Pilot study of topical calcitriol (1,25-dihydroxyvitamin D<sub>3</sub>) for treating psoriasis in children. *Arch Dermatol* 1995; **131**:961–2.
  - 30 Augustin M, Holland B, Dartsch D *et al.* Adherence in the treatment of psoriasis: a systematic review. *Dermatology* 2011; **222**:363–74.
  - 31 Zschocke I, Mrowietz U, Karakasili E, Reich K. Non-adherence and measures to improve adherence in the topical treatment of psoriasis. *J Eur Acad Dermatol Venereol* 2014; **28**(Suppl. 2):4–9.
  - 32 Dauden E, Bewley A, Lambert J *et al.* Expert recommendations: the use of the fixed combination calcipotriol and betamethasone dipropionate gel for the topical treatment of psoriasis. *J Eur Acad Dermatol Venereol* 2014; **28**(Suppl. 2):22–32.