

ORIGINAL ARTICLE

Safety and efficacy of topical, fixed-dose combination calcipotriene (0.005%) and betamethasone (0.064% as dipropionate) gel in adolescent patients with scalp and body psoriasis: a phase II trial

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Abstract

Background Psoriasis is a disease that commonly manifests in adolescence. Up to half of adults with psoriasis develop it before the age of 20. Topical formulations containing corticosteroids and/or vitamin D3 analogs are recommended for treatment.

Objective This phase II study aimed to evaluate the safety, including any potential effect on the hypothalamic–pituitary–adrenal axis and calcium metabolism, and efficacy of fixed-dose combination calcipotriene (0.005%) and betamethasone (0.064% as dipropionate) (Cal/BD) gel in adolescents with psoriasis.

Methods Patients aged 12 to <17 years, with at least mild psoriasis on the body and scalp, received topical Cal/BD gel once daily for ≤8 weeks. Safety response criteria included adverse drug reactions [ADRs; any adverse event (AE) possibly or probably related to treatment as determined by the investigator; a primary response criterion] and AEs (a secondary response criterion). Only treatment-emergent AEs (events that occurred after the first application of Cal/BD gel or events which started before this and increased in intensity after the first application of Cal/BD gel) are presented here. Efficacy response criteria included controlled disease, by physician's global assessment of disease severity (PGA), following Cal/BD gel treatment.

Results A total of 107 patients (median age 14 years; range 12–16) were enrolled and treated. Eight ADRs were observed in 7 (7%) patients and 38 (36%) patients experienced ≥1 AE. The most common AEs were headache [6 (6%) patients], nasopharyngitis [6 (6%) patients] and blood parathyroid hormone increased [4 (4%) patients]. One severe AE was reported (attempted suicide) but was considered unrelated to treatment. At the end of treatment, 58% of patients had controlled disease on the body and 69% on the scalp according to PGA.

Conclusion In this uncontrolled phase II study, Cal/BD gel was well tolerated and effective for treating scalp and body psoriasis in adolescents.

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Conflicts of interest

Dr Eichenfield is a clinical investigator for Abbvie, Eli Lilly, Pfizer, LEO Pharma and Ortho-Derm and a consultant for Amgen, Celgene, Dermavent, LEO Pharma, Eli Lilly, Novartis and Ortho-Derm. Dr Marcoux is a principal investigator for Abbvie, Celgene, Eli Lilly, Janssen, LEO Pharma, Pfizer and Sanofi/Regeneron, an advisory board member of Abbvie, Celgene, Janssen, LEO Pharma, Pfizer and Sanofi/Regeneron, and a speaker for Abbvie, Pfizer and Sanofi/Regeneron. Dr Kurvits and Dr Liljedahl are employees of LEO Pharma.

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Introduction

Psoriasis is a chronic, recurrent, immune-mediated inflammatory disease with skin and joint manifestations¹ and is associated

with serious comorbidities, such as cardiovascular disease, metabolic syndrome, depression and psoriatic arthritis.^{2–4} Psoriasis will develop in many patients before the age of 20.^{5,6} Prevalence

of psoriasis in children and adolescents aged <18 years ranges from 0% to 1.37% worldwide.⁷ In the United States, incidence increases with age: 30 per 100 000 in the 0- to 3-year-old group versus 205 per 100 000 in the 12- to 17-year-old group.⁸

In children and adolescents, psoriasis has a significant impact on quality of life (QoL), as symptoms such as itch and sleep disturbance can negatively impact social interactions as well as self-esteem and personal image.^{9–12} Itch has one of the greatest negative impacts on QoL in this population; a decline in it leads to the greatest increase in QoL.^{13,14}

Topical formulations containing corticosteroids and/or vitamin D3 analogs are recommended for treating mild-to-moderate psoriasis.^{1,10} The US Food and Drug Administration (FDA) has approved fixed-dose combination calcipotriene (0.005%) and betamethasone (0.064% as dipropionate) (Cal/BD) gel for treating body and scalp psoriasis in adults, and scalp psoriasis in adolescents.¹⁵ Approval of Cal/BD gel in adolescents was based on data from two prospective, open-label, uncontrolled trials of adolescent patients with scalp psoriasis.^{15–17}

In these trials, Cal/BD gel was well tolerated with an acceptable safety profile. Patients also had favourable efficacy outcomes, with most achieving treatment success by investigator's global assessment at the end of treatment (55% and 85% in the two trials, respectively).^{16,17} In one trial, the effect of Cal/BD gel on the hypothalamic–pituitary–adrenal (HPA) axis was assessed in 30 patients using the adrenocorticotrophic hormone (ACTH) test, to measure adrenal function.^{16,18} Adrenal suppression was observed in one patient who showed a decrease in cortisol response to ACTH challenge after 4 weeks of treatment, which was mild and reversible.¹⁶

As part of postapproval requirements of the FDA, we evaluated the overall safety and efficacy of Cal/BD gel in adolescents (aged 12 to <17 years) with scalp and body psoriasis; additional safety assessments included examining any potential effect on the HPA axis and calcium metabolism. Our findings are reported here.

Materials and methods

Trial design and study treatments

This was a phase II, international, prospective, multicentre open-label, non-controlled, single-arm study. Adolescent patients applied Cal/BD gel once daily for ≤8 weeks, with visits at baseline, weeks 2, 4, 6 and 8.

All enrolled patients were to be included in the overall population; a subset with more severe disease was to constitute a maximal-use group, termed the HPA axis group. All patients were to apply Cal/BD gel once daily.

Patients were instructed to discontinue treatment on individual lesions if or when they cleared. Patients with clear skin by physician's global assessment of disease severity (PGA) at week 4 discontinued the study.

Withdrawal from the study or discontinuation of treatment occurred in the event of unacceptable treatment efficacy; unacceptable adverse events; exclusion criteria that became apparent during the study; and voluntary withdrawal. Any other reasons were to be specified.

This trial conformed to the principles of the Declaration of Helsinki. Patients and their parent(s) or legal guardian(s) received written and verbal information concerning the study. The study protocol and any relevant amendments were approved by/received favourable opinion from the relevant institutional review boards/independent ethics committees in the seven countries where the trial was conducted, as applicable, prior to screening of patients.

Objectives

The primary objective was to evaluate the safety of Cal/BD gel in adolescent patients with psoriasis. The secondary objective was to evaluate the efficacy of the treatment in this patient group.

Response criteria

The primary response criteria were as follows: the incidence of adverse drug reactions (ADRs), i.e. adverse events (AEs) considered possibly or probably related to treatment according to the investigator; serum cortisol concentration ≤18 µg/dL 30 min after ACTH challenge at weeks 4 and 8; changes in albumin-corrected serum calcium and 24-h urinary calcium excretion from baseline to weeks 4, 8 and end of treatment (EoT). The ACTH challenge was carried out as previously described.^{18,19}

Occurrence of AEs was a secondary safety response criterion. Events were considered treatment emergent if they started after the first application of Cal/BD or if they started before this and increased in intensity after the first application. All AEs described here were treatment emergent and will therefore be referred to as AEs herein. Other secondary safety response criteria included patients with serum cortisol concentration ≤18 µg/dL at both 30 and 60 min after ACTH challenge at weeks 4 and 8; change in urinary calcium:creatinine ratio and change in serum alkaline phosphatase (ALP) from baseline to week 4 and week 8. Pharmacokinetic (PK) parameters [area under the curve: from time 0 to the last measurable concentration (AUC_{0-t}) and from time 0 extrapolated to infinite time ($AUC_{0-\infty}$), maximum serum concentration (C_{max}), time to C_{max} (T_{max}), half-life ($T_{1/2}$)] were to be calculated for the quantification of calcipotriene, betamethasone dipropionate (BDP) and the metabolites, MC1080 and betamethasone 17-propionate (B17P), in plasma samples at week 4.

Secondary efficacy response criteria were controlled disease according to PGA on the body ('clear' or 'almost clear' skin for patients with at least moderate disease at baseline, 'clear' for patients with mild disease at baseline) at EoT; controlled disease according to patient's global assessment of disease severity on the body (PaGA; 'clear' or 'very mild') at EoT; percentage

change in psoriasis area severity index (PASI) from baseline to EoT. PGA, PaGA and PASI were implemented as previously described.²⁰

Additionally, patients were to self-assess the intensity of itch on their scalp and body as well as their sleep loss, over the past 24 h, using a visual analogue scale (VAS) at screening visit 2 (SV2) and all subsequent visits.

Patients

Patients (aged 12 to <17 years) had psoriasis of at least mild severity (PGA), according to a clinical diagnosis, affecting $\geq 3\%$ of body surface area (BSA; trunk and/or limbs) and $\geq 10\%$ of scalp area. Inclusion in the trial was dependent upon informed consent by the parent(s)/legal guardian(s), or by the patient (according to national law) following their receipt of verbal and written information about the trial, as well as written assent to the trial, provided by the patient. Additional inclusion criteria were applied to the HPA axis group, as they were the maximal-use group and were to undergo ACTH challenge. These criteria included psoriasis that was at least moderate in severity (PGA) affecting between 10–35% BSA and $\geq 20\%$ of the scalp area; normal HPA axis function at SV2 (serum cortisol concentration $> 5 \mu\text{g/dL}$ before ACTH challenge and $> 18 \mu\text{g/dL}$ 30 min after ACTH challenge).

Exclusion criteria for this study included a history of hypersensitivity to Cal/BD gel (or its components); receipt of systemic treatments with biologics that could affect the body/scalp within 4 weeks of baseline (4 weeks prior for etanercept or experimental products, 2 months for adalimumab/infliximab and 4 months for ustekinumab) or non-biologics with a possible effect on scalp and/or body psoriasis within 4 weeks prior to visit 1; UVB therapy or any topical treatment on the scalp and body within 2 weeks of visit 1 or during the trial; systemic calcium, vitamin D supplementation $> 400 \text{ IU/day}$, antacids, diuretics, antiepileptics, diphosphonates or calcitonin within 4 weeks prior to SV2 or during the trial.

The HPA axis group had additional exclusion criteria, including a history of serious allergy or asthma; known or suspected hypersensitivity to any component of the injection used in the ACTH challenge test (a synthetic subunit of ACTH); and receipt of any medication known to affect cortisol levels or HPA axis integrity within 4 weeks prior to SV2 or during the trial.

Statistical methods

Safety and efficacy analyses were performed on the safety analysis set and full analysis set (FAS), respectively. The safety analysis set consisted of all patients who applied any treatment and for whom the presence or confirmed absence of AEs was available. The FAS was all patients who received treatment. The per protocol analysis set (PPS) was defined as those from the FAS, included in the HPA axis group, who met inclusion criteria concerning evidence of adrenal function suppression at baseline,

applied any treatment and provided results for the ACTH challenge test. Analysis of the results from the ACTH challenge test was performed on the PPS.

The trial was to be conducted in 100 evaluable adolescent patients according to FDA postapproval requirement. No formal sample size calculation evaluating the power of the trial was performed.

Data were presented by visit as observed cases, with the exception of EoT values which utilized the last observation carried forward approach. Baseline was defined as the last assessment performed before application of treatment. The EoT value for efficacy was defined as the last value recorded for that parameter up to and including week 8 and for laboratory parameters as the last value recorded after baseline up to and including week 8.

Results

Patients

Patients from 30 sites globally were screened between first patient in, 7 March 2014, and the last patient's final visit, 13 February 2018; 125 were screened, and 107 were assigned treatment (comprising the FAS and safety analysis sets). Of these, 33 were included in the HPA axis group and 31 of them in the PPS. By week 8, 90 patients remained in the study (Fig. 1). The mean duration of exposure to Cal/BD gel was 52.7 days (range: 22–70).

Between visit 1 and EoT, the mean weekly amount of gel used did not vary greatly (32.5 g/week weeks 1–4 and 26.7 g/week weeks 4–8) and remained similar to the mean weekly amount used over the duration of the treatment period (30.8 g/week). The majority of patients were treatment-adherent: 96% of patients missed no or $\leq 10\%$ of applications.

Patient demographics and baseline characteristics for both the FAS and PPS (HPA axis group) are given in Table 1. More females than males were included, and the majority were white. Median age, height and weight were similar across the FAS and PPS and most patients had moderate disease severity (PGA). In the FAS, the range in patient weights was large: $> 80 \text{ kg}$.

Safety

Adverse events Eight ADRs were reported in seven patients (7%) (Table 2); decreased blood cortisol was the only ADR reported in more than one patient ($n = 2$). Three ADRs were of moderate intensity (blood parathyroid hormone increased, erythema and folliculitis), and the rest were mild (acne, blood cortisol decrease, hyperparathyroidism and headache). None of the ADRs were severe.

All AEs described here were treatment emergent. In total, 36% (38/107) of patients reported 62 AEs. Of these, the most common were headache [six (6%) patients], nasopharyngitis [six (6%) patients] and blood parathyroid hormone increased [four (4%) patients] (Table 2). All other AEs were reported by

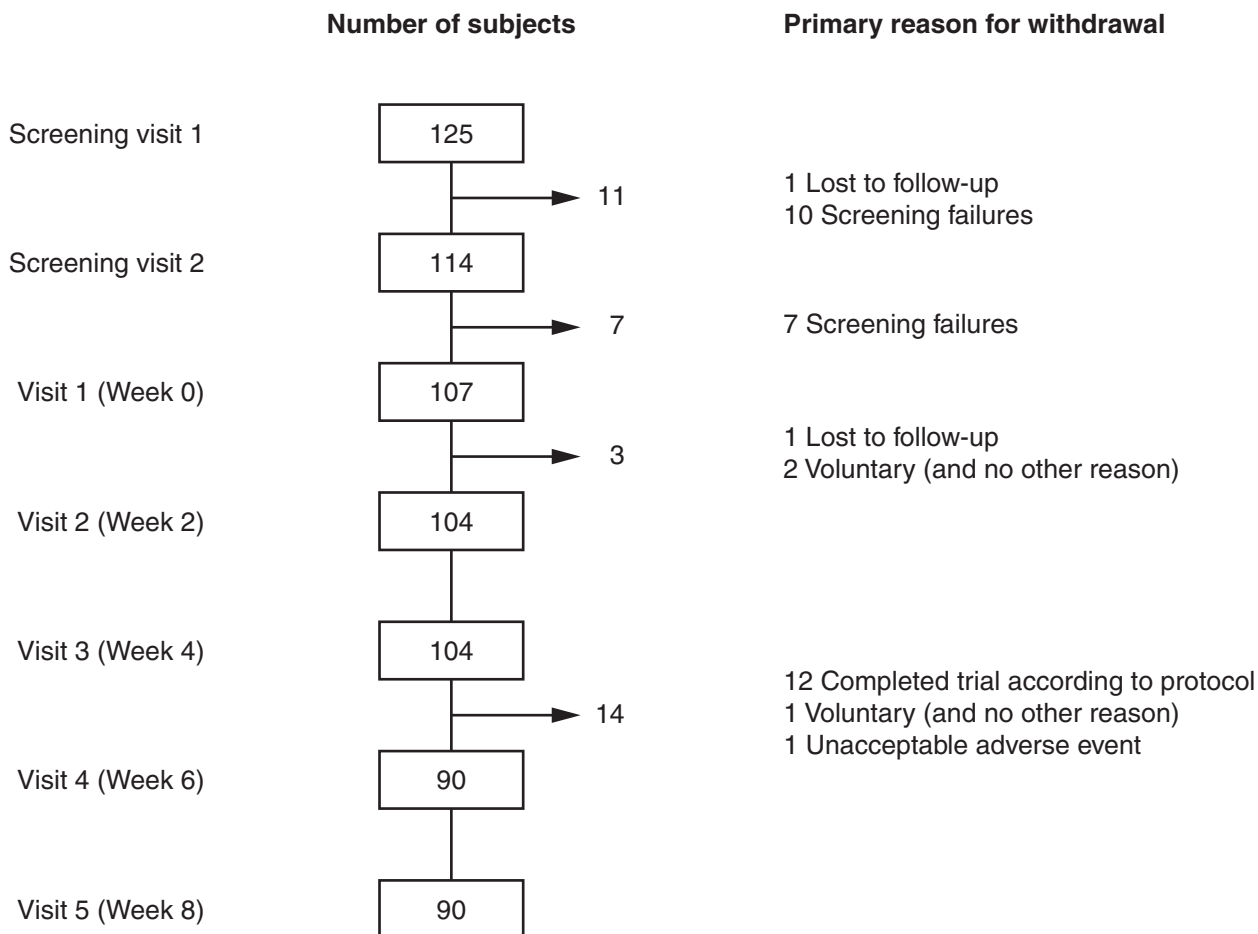


Figure 1 Disposition of patients.

less than four patients. Three lesional/perilesional events on the body (folliculitis, arthropod sting and pruritus) were reported by three patients. One AE occurring in one patient was classified as serious and severe (attempted suicide) but was considered unrelated to treatment. There were no other serious or severe events reported.

There were no deaths in this trial. One patient was withdrawn due to low plasma cortisol levels at 30 min after ACTH stimulation at week 4 (Table 2).

ACTH challenge test Data cleaning revealed that six patients in the HPA axis group did not fulfil the inclusion criteria at baseline of serum cortisol concentration >18 $\mu\text{g/dL}$ 30 min after ACTH challenge, though all displayed concentrations of >18 $\mu\text{g/dL}$ at 60 min. Five of these patients completed the trial and are included in the PPS. The ACTH challenge was repeated at weeks 4 and 8. Five patients showed a decrease in cortisol response after

application of Cal/BD gel at 30 min postchallenge: three patients at week 4, one at week 8, and one at both weeks 4 and 8. Two of these were considered mild decreases [serum cortisol concentration of 17.4 (week 4) and 17.8 (week 8) $\mu\text{g/dL}$]; one patient showed signs of suppression at week 4 and was withdrawn.

No patients had a serum cortisol concentration ≤ 18 $\mu\text{g/dL}$ at 60 min post-ACTH challenge following Cal/BD treatment (Fig. 2).

Calcium metabolism There were no clinically relevant changes in albumin-corrected serum calcium levels or 24-h urinary calcium excretion at weeks 4, 8, or EoT.

Pharmacokinetics

For all four analytes (BDP, calcipotriene and their respective metabolites B17P and MC1080), most observations were below the lower limit of quantification (LLOQ); therefore, a full PK

Table 1 Patient demographics and baseline characteristics

Characteristic	FAS N = 107		PPS† N = 31	
Sex (%)				
Male	45 (42)		14 (45)	
Female	62 (58)		17 (55)	
Race (%)				
White	97 (91)		29 (94)	
Asian	6 (6)		1 (3)	
Black or African American	2 (2)		1 (3)	
Other	2 (2)		0	
Median age, years (range)	14 (12–16)		14 (12–16)	
Median height, cm (range)	164 (132–192)		160 (135–192)	
Median weight, kg (range)	57 (32–118)		52 (32–96)	
PGA (%)	Body	Scalp	Body	Scalp
Mild	14 (13)	15 (14)	0	0
Moderate	87 (81)	80 (75)	29 (94)	29 (94)
Severe	6 (6)	12 (11)	2 (6)	2 (6)
PaGA (%)	Body	Scalp	Body	Scalp
Very mild	5 (5)	4 (4)	2 (6)	1 (3)
Mild	21 (20)	14 (13)	3 (10)	3 (10)
Moderate	77 (72)	70 (65)	26 (84)	25 (81)
Severe	4 (4)	19 (18)	0	2 (6)
PASI, body and scalp				
Mean (SD)	11 (4)		11 (3)	
Median (range)	10 (3–28)		12 (6–20)	
Duration of psoriasis (years)				
Mean (SD)	4 (3)		4 (3)	
Median (range)	3 (1–15)		3 (1–12)	

†Includes HPA axis group.

FAS, full analysis set; HPA, hypothalamic–pituitary–adrenal; PaGa, patient's global assessment of disease severity; PASI, psoriasis area severity index; PGA, physician's global assessment of disease severity; PPS, per protocol analysis set; SD, standard deviation.

analysis could not be completed. Five observations were above LLOQ for BDP and 12 for B17P, with C_{max} of 104 and 126 pg/mL, respectively. Calcipotriene and MC1080 could not be quantified in any patient.

Efficacy

Based on PGA, 58% (62/107) and 69% (74/107) of patients had controlled disease on the body and scalp, respectively, at EoT (Fig. 3). Controlled disease (as per PGA) was observed from visit 2 for both scalp (22%, 23/104) and body (14%, 15/104); controlled disease according to PaGA for body and scalp was 63% (67/107) and 69% (74/107), respectively, at EoT.

There was a mean decrease [\pm standard deviation (SD)] in PASI from baseline to EoT of $79\% \pm 32$, from mean (\pm SD) PASI of 11 ± 4 at baseline to 2 ± 3 at EoT. Mean (\pm SD) BSA of body and scalp affected by psoriasis decreased from $15 \pm 8\%$ at baseline to $8 \pm 9\%$ and $4 \pm 8\%$ at weeks 4 and 8, respectively.

Patients' assessment of itch and sleep loss improved from baseline to EoT. Mean (\pm SD) itch score on the body reduced

Table 2 Summary of AEs (safety analysis set)

AE category	Safety analysis set N = 107	
	Number of AEs	Number of patients (%)
Summary of events		
All AEs	62	38 (36)
ADRs	8	7 (7)
Serious AE	1	1 (1)
Severe AE	1	1 (1)
AE leading to withdrawal	1	1 (1)
AEs experienced by >1 patient by system organ class and preferred term		
Nervous system disorders		
Headache	8	6 (6)
Infections and infestations		
Nasopharyngitis	6	6 (6)
Rhinitis	2	2 (2)
Investigations		
Blood parathyroid hormone increased	5	4 (4)
Blood cortisol decreased	2	2 (2)
Reproductive system and breast disorders		
Dysmenorrhoea	3	3 (3)
Respiratory, thoracic and mediastinal disorders		
Cough	2	2 (2)
Oropharyngeal pain	2	2 (2)
ADRs by system organ class and preferred term		
Investigations		
Blood cortisol decreased	2	2 (2)
Blood parathyroid hormone increased	1	1 (1)
Skin and subcutaneous tissue disorders		
Acne	1	1 (1)
Erythema	1	1 (1)
Endocrine disorders		
Hyperparathyroidism	1	1 (1)
Infections and infestations		
Folliculitis	1	1 (1)
Nervous system disorders		
Headache	1	1 (1)
Total†	8	7 (7)

†Erythema and hyperparathyroidism were experienced by the same patient. ADR, adverse drug reaction; AE, adverse event.

from 28 ± 25 (baseline) to 7 ± 15 (EoT) and on the scalp from 38 ± 28 (baseline) to 10 ± 18 (EoT). Mean (\pm SD) patient-reported sleep loss reduced from 11 ± 19 (baseline) to 6 ± 14 (EoT).

Discussion

This phase II study showed that Cal/BD gel was well tolerated with no unexpected safety concerns in adolescent patients with body and scalp psoriasis, including those treated under maximal use conditions.

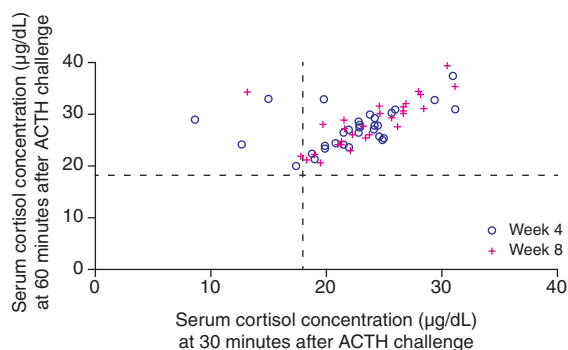


Figure 2 Serum cortisol concentration at 30 and 60 min after ACTH challenge at weeks 4 and 8. ACTH, adrenocorticotrophic hormone.

Overdose with topical calcipotriene, a vitamin D analog, can cause hypercalcaemia due to systemic absorption.^{21,22} There were no cases of hypercalcaemia or clinically relevant changes in serum or urinary calcium levels, suggesting that calcium metabolism was unaffected. High exposure of Cal/BD gel²³ and other potent corticosteroid topical products¹⁹ may transiently impact on the HPA axis, leading to decreased cortisol levels. In this study, no patients had a serum cortisol concentration of ≤ 18 µg/dL at 60 min post-ACTH challenge, indicating transient and reversible suppression. These data are in line with previous findings for Cal/BD gel in this patient population.¹⁶

The negative impact of psoriasis on QoL in adolescents is greater compared with other age groups.^{9,14} Tackling aspects of psoriasis such as itch and sleep loss has been shown to improve QoL in adolescents.¹³ Here, we show that both these symptoms are greatly reduced between baseline and EoT with the use of Cal/BD gel, suggesting an overall improvement in QoL.

Adolescents are often non-adherent to psoriasis treatments, due to the perceived inconveniences and social pressures.^{16,24}

However, in this study, patients were highly adherent to treatment – 96% of patients missed either no applications or $\leq 10\%$. Furthermore, most patients had controlled disease on the body and scalp according to PGA by EoT, as well as a mean percentage reduction in PASI from baseline to EoT, demonstrating a notable improvement.

Despite the limitations of an uncontrolled and open-label study, our data indicate favourable clinical outcomes and reduced symptoms that impact QoL in adolescent patients, with no new safety signals. In addition, neither hypercalcaemia nor adrenocortical insufficiency were cause for concern. Therefore, fixed-dose combination Cal/BD gel is a clinically beneficial treatment, with favourable tolerability, for adolescent patients with body/scalp psoriasis.

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Data sharing statement

Will individual participant data be available (including data directories)?

Individual, de-identified participant data will be made available, per request. See further information below.

What data in particular will be shared?

The data shared are de-identified study data tabulation model (SDTM) data set.

What other documents will be available?

Redacted clinical trial protocol, redacted clinical trial report, redacted statistical analysis plan update, annotated case report form for the raw data and data set specifications, if available.

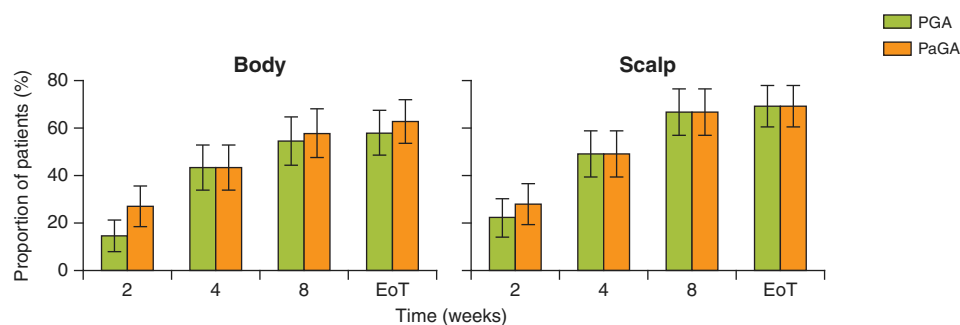


Figure 3 Controlled disease (PGA and PaGA) on the body and scalp over time. Error bars represent 95% confidence interval. EoT, end of treatment; PaGA, patient's global assessment of disease severity; PGA, physician's global assessment of disease severity.

When will data be available (start and end dates)?

After publication of the clinical trial report on leo-pharma.com. A clinical trial report synopsis will be made available around 1 year after the trial end.

With whom will the data be shared?

External researchers, with no commercial interest who provide scientifically sound research proposal.

What types of analyses will be data be available for?

As stated in the research proposal and approved by the Patient and Scientific Review Board.

By what mechanisms will data be made available?

Data feasibility requests and research proposals are sent to disclosure@leo-pharma.com. If feasibility to share the data from a trial is granted, the ultimate decision is made by an external to the company board (Patient and Scientific Review Board). Data sharing is further subject to signed data sharing agreement. Data will be available in a closed environment for a specified period on time.

Additional information can be obtained at: <http://www.leo-pharma.com/Home/Research-and-Development/Clinical-trial-disclosure/Access-to-patient-level-data.aspx>.

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