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ORIGINAL ARTICLE

Safety and efficacy of fixed-dose combination calcipotriol (50 μg/g) and betamethasone dipropionate (0.5 mg/g) cutaneous foam in adolescent patients (aged 12 to <17 years) with plaque psoriasis: results of a phase II, open-label trial

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Abstract

Background Fixed-dose combination of calcipotriol (50 μg/g; Cal) and betamethasone dipropionate (0.5 mg/g; BD) foam is approved for plaque psoriasis treatment in adults, with a paucity of data supporting use in adolescents.

Objectives To evaluate safety of 4 weeks' treatment with Cal/BD foam in adolescent patients with psoriasis, and additional safety outcomes in patients with more severe disease (HPA-axis cohort). Primary objectives included treatment-emergent adverse events (TEAEs) and systemic calcium levels in the overall population, and HPA-axis function, change in calcium excretion and the calcium:creatinine ratio in the HPA-axis cohort. Secondary objectives included exploratory efficacy endpoints [treatment success: change in Psoriasis Area and Severity Index (PASI)]. Systemic exposure to Cal/BD was also assessed.

Methods A phase II, open-label, study (NCT02387853) in patients (12 to <17 years) with at least mild psoriasis, to evaluate Cal/BD foam applied once daily for ≤4 weeks.

Results In patients assigned to treatment (n = 106), 32 TEAEs occurred in 22 patients (20.8%). All but two TEAEs were mild; none led to study withdrawal or death. Changes (0–4 weeks) in albumin-corrected serum calcium (overall population) and urinary calcium excretion (HPA-axis cohort) were small, transient and not considered clinically relevant. In the HPA-axis cohort, no change in urinary calcium:creatinine ratio was observed and responses to adrenocorticotropic–hormone (ACTH) challenge did not suggest disruption of the HPA-axis. Prespecified treatment success on the body and scalp was achieved by 71.8% and 75.7% of the overall population, respectively. Mean PASI decreased by 82.0% vs. baseline at Week 4. Systemic exposure to Cal/BD was minimal.

Conclusions Cal/BD foam was well tolerated in adolescent patients with body/scalp psoriasis. There was no evidence for dysregulation of the HPA-axis nor calcium homoeostasis in patients with more severe disease. Exploratory efficacy data in the overall population were encouraging.

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Conflicts of interest

M. Seyger has received grants for consultancy and travel expenses from LEO Pharma, paid to her institution, and has received grants and other fees for research, lecturing, consultancy and travel expenses from AbbVie, Lilly and Pfizer, and grants for research, lecturing and consultancy from Janssen. W. Abramovits has received honoraria or fees for serving on advisory boards as a speaker and as a consultant, and has received grants as an investigator from AbbVie, Akros, Allergan, Amgen, Anacor Pharm, Aqua Pharma, Celgene, Centocor, Conversant Bio, Dermavant, Eli Lilly, Exeltis, Galderma, Genentech, Glenmark, GSK, Innocutis, Innovaderm, Janssen Biotech, LEO Pharma, MediMetriks, Merck, Novartis, Novan, Novum, Otsuka, Parexel, PharmaDerm, Perrigo, Pfizer, Premier, Promius, Prothena, PuraCap, Quinnova, Ranbaxy, Regeneron, Rho, Sanofi, Serono, Taro, Teva, Tioga, Theorem, Tolmar, UCB, Valeant and Xenoport. M. Liljedahl and M. Hoejen are employees of LEO Pharma. J. Teng has no relevant conflicts of interest to disclose.

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Introduction

Population-based studies estimate the prevalence of psoriasis in children and adolescents at 0%–2%,[1] increasing linearly between the ages of 1 and 18 years.[2] Age of onset is thought to be bimodal, with the first peak between 15 and 20 years and the second between 55 and 60 years.[3]

Topical, fixed-dose combination of calcipotriol (50 μg/g; as monohydrate; Cal) and betamethasone (0.5 mg/g; as dipropionate; BD) foam is currently approved in the United States and EU for the treatment of plaque psoriasis in adults.[4,5]

The safety profile of Cal/BD foam has not previously been established in adolescents with psoriasis. On the basis of clinical evidence, the overall risk of TEAEs with Cal, a vitamin D analogue, is low,[6] and the current trial was designed to investigate specific safety concerns of interest.

In addition to site-reaction concerns, systemic absorption of calcium has been noted with long-term topical exposure to Cal,[7] and a potential risk of hypercalcaemia has been highlighted.[8–10]

Lastly, hypothalamic–pituitary–adrenal (HPA) axis suppression has been noted with long-term use of corticosteroids[7,11]; thus, HPA-axis dysregulation with BD is a concern. The adrenocorticotropic–hormone (ACTH) challenge is used to assess HPA-axis suppression in children with psoriasis,[12] with a serum cortisol value ≤18 μg/dL at 30 min post-ACTH challenge suggestive of potential adrenal-cortisol insufficiency.[13,14]

After 4 weeks' fixed-dose combination of Cal/BD foam, we report safety outcomes in adolescents (12 to <17 years) with plaque psoriasis of the body and scalp (including endpoints to assess calcium homoeostasis), and HPA-axis testing (ACTH challenge) in those with more severe disease. Exploratory efficacy data from the overall population are also reported.

Materials and methods

Study design

A phase II, multicentre, prospective, open-label, non-controlled, single-group, 4-week trial in adolescent patients (aged 12 to <17 years) with plaque psoriasis on the body and scalp (NCT02387853) consisting of three periods: wash-out, treatment and follow-up (Fig. 1). The study was a postapproval regulatory commitment, with the design mandated by the US Food and Drug Administration (FDA).

Standard protocol approvals, registration and patient consents

The study was conducted in accordance with the principles of the Declaration of Helsinki, and the clinical trial protocol (and amendments) was approved by, or received favourable opinion from, the relevant institutional review boards or independent ethics committees. Informed written consent was obtained from all patients and their parents (or legal guardians).

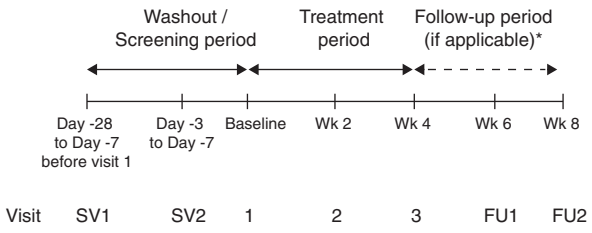

Figure 1 Study design. *Patients were only required to attend FU1 if they had an ongoing serious adverse event; any ongoing adverse event considered possibly/probably related to study treatment; or an albumin-corrected serum calcium value above the reference range. Only patients in the HPA-axis cohort who had ≤18 μg/dL at 30 min post-ACTH challenge at Week 4 were required to attend FU2. ACTH, postadrenocorticotropic–hormone; FU1, follow-up visit 1; FU2; follow-up visit 2; HPA, hypothalamic–pituitary–adrenal; SV1, screening visit 1; SV2, screening visit 2.

Patients

Patients were screened at 26 centres in the Netherlands, Poland, Romania and the USA. All those enrolled were to be included in the overall population, while a subset (approximately 30%) with more severe disease were to be part of a maximal-use group, the 'HPA-axis cohort' (details below).

In the overall population, patients were 12 to <17 years and had plaque psoriasis on the trunk and/or limbs, affecting ≥2% of body surface area (BSA), and on the scalp, affecting ≥10% of scalp surface area (SSA). Each patient's total plaque psoriasis on the trunk, limbs and scalp was ≤30% of BSA. Additional inclusion criteria included physician's global assessment (PGA) of disease (clear, almost clear, mild, moderate, severe; according to Feldman & Krueger 2005[15]) of at least mild for body and scalp at baseline, and albumin-corrected serum calcium below the upper reference limit at baseline.

Exclusion criteria included systemic treatments that could affect the body and/or scalp psoriasis within 4 weeks prior to the first screening visit (except for adalimumab/infliximab and ustekinumab, which patients must not have taken within 2 and 4 months prior, respectively); photochemotherapy within 4 weeks; UVB therapy within 2 weeks; topical treatment on the body/scalp within 2 weeks; and systemic calcium and vitamin D supplements within 4 weeks of baseline.

In the HPA-axis cohort, patients were required to have more severe disease: plaque psoriasis on the trunk and/or limbs affecting ≥10% of BSA, plaque psoriasis on the scalp affecting ≥20% of SSA and a PGA score of at least moderate for both body and scalp at baseline. These patients were also required to have normal adrenal function at baseline, measured by post-ACTH challenge test (described previously[16,17]). Patients in the overall population set but not in the HPA-axis cohort will henceforth be referred to as the 'non-HPA cohort'.

Study treatments

Cans containing 30 g of Cal/BD foam were provided. Patients were instructed to apply treatment once daily, and continue treating affected areas with Cal/BD foam throughout the 4-week treatment period [the non-HPA cohort were allowed to discontinue treatment (but required to remain in-trial) if lesions were cleared at Week 2 (W2)].

The non-HPA cohort had the maximum dose per week limited (determined by patient age and BSA at baseline):

- Patients aged 12 to <15 years
  - BSA of ≤1.3 m^2: maximum 60 g per week.
  - BSA of >1.3 m^2: maximum 90 g per week.
- Patients aged ≥15 to <17 years
  - BSA of ≤1.7 m^2: maximum 90 g per week.
  - BSA of >1.7 m^2: maximum 120 g per week.

The HPA-axis cohort was treated under maximal-use conditions (weekly dose was not limited).

Study visits took place on Day 0, W2 and Week 4 (W4), and final assessments were carried out 2 weeks after end of treatment (Fig. 1).

Objectives

Primary objectives were evaluation of the safety of once-daily Cal/BD foam in adolescent patients with plaque psoriasis on the body and scalp; and, in the HPA-axis cohort: assessment of HPA-axis function post-ACTH challenge, change in calcium excretion and the calcium:creatinine ratio. Secondary objectives included assessment of exploratory efficacy endpoints after up to 4 weeks of treatment in the overall population and the HPA-axis cohort.

Endpoints

Primary endpoints were treatment-emergent adverse events (TEAEs) and change in albumin-corrected serum calcium from baseline to W4. TEAEs were followed up until an outcome was determined, and once a patient left the trial, events classified as 'possibly' or 'probably' related to Cal/BD foam were followed up for 14 ± 2 days, or until an outcome was determined. For the HPA-axis cohort, additional primary endpoints included number of patients with serum cortisol concentration ≤18 μg/dL at 30 min post-ACTH challenge at W4; change in calcium excretion from baseline to W4 in 24-h urine; and change in calcium:creatinine ratio from baseline to W4 in 24-h urine.

Secondary endpoints included efficacy according to PGA (treatment success defined as clear/almost clear for patients with moderate psoriasis, and clear for those with mild), and treatment success according to patient's global assessment (PaGA) of disease severity (defined as clear or very mild) at W4 for the body and scalp; percentage change in PASI[15] from baseline to W4; and change in itch (assessed by visual analogue scale) from baseline to W4. For the HPA-axis cohort, the number of patients with serum cortisol concentration ≤18 μg/dL at both 30 and 60 min post-ACTH challenge at W4 was also a secondary endpoint.

Pharmacokinetics (PK) for the HPA-axis cohort and treatment adherence in the overall population were also assessed. PK was measured preapplication at W2, prior to ACTH challenge and Cal/BD application at W4, and at 1, 3 and 5 h postapplication at W4.

Statistical methods

The safety analysis set (SAS), which included all patients except those who received no treatment and/or provided no postbaseline safety evaluations, was used to analyse adverse events and change in albumin-corrected serum calcium from baseline to W4. The per-protocol analysis set included all patients in the HPA-axis cohort who received treatment, provided ACTH challenge test results at Week 4 and met the normal-adrenal-function-at-baseline inclusion criterion. The full analysis set (FAS) included all patients assigned to treatment and was used for efficacy analyses.

The trial was planned to be conducted in 100 evaluable adolescent patients, with a subset of 30 patients forming the HPA-axis cohort. This population size was deemed necessary to achieve an 86.7% probability that a true (theoretical) AE would be observed in at least one patient, with an AE frequency of ≥2%.

Observed data have been presented with 95% confidence intervals (CI). A *post hoc* analysis of efficacy endpoints (treatment success by PGA; treatment success by PaGA; change in PASI; change in itch) for the FAS and the HPA-axis and non-HPA subgroups has also been presented.

Results

Patients

Overall, 117 patients were screened and 106 (non-HPA cohort, $n = 72$; HPA-axis cohort, $n = 34$) were assigned to treatment and constituted both the FAS and SAS (Fig. 2). During the treatment period, three patients (one HPA-axis and two non-HPA) withdrew from the study after Week 0 (no reason provided). The first patient screening visit took place on 23 March 2016; the final patient follow-up visit was 28 March 2018. Patient demographics and baseline disease characteristics are

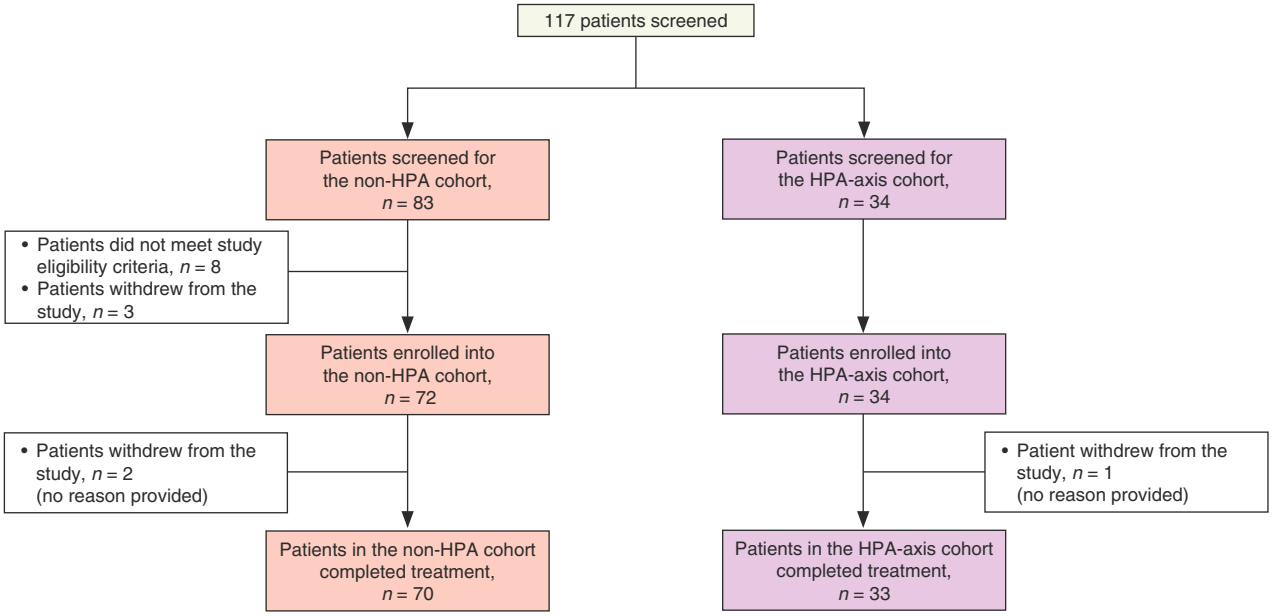

Figure 2 Patient disposition. Note that the per-protocol and non-per-protocol sets, used for reporting in Table 1, correspond to the HPA-axis and non-HPA cohorts, respectively, with the exception of one patient in the HPA-axis cohort who withdrew after the baseline visit, and are therefore included in the non-per-protocol set. HPA, hypothalamic–pituitary–adrenal.

summarized in Table 1. No noteworthy differences between the HPA-axis and non-HPA cohorts were observed, excluding those parameters in which differences were expected due to the HPA-axis cohort inclusion criteria.

Compliance and posology

Over the 4 weeks of treatment, 101 patients (95.3%) reported that they missed no applications of Cal/BD, 33 of whom were in the HPA-axis cohort (i.e. 100% compliance for completers in this cohort). One patient in the non-HPA cohort reported they had missed more than half of their treatments, while one and three patients (also in the non-HPA cohort) reported missing >10% to ≤20% and ≤10% of treatment applications, respectively. The mean weekly amount of Cal/BD foam used over the full treatment period was 47.0 g [standard deviation (SD) 22.2] and 35.8 g (SD 28.0) for the HPA-axis and non-HPA cohorts, respectively.

Safety

Adverse events Thirty-two TEAEs were reported by 22 patients (20.8%), and all but two TEAEs were of mild severity (two moderate: erythema and myopia). The most frequent TEAEs were upper respiratory tract infection [8 (7.5%) patients], nasopharyngitis [4 (3.8%) patients] and acne [2 (1.9%) patients]; all other TEAEs were not reported by more than one patient (Table 2). Six AEs reported by five patients were assessed by the investigator as related to Cal/BD treatment, with five considered possibly or probably related (acne, erythema, skin reaction, application site pain and product physical consistency issue) and one (myopia) deemed 'unknown'; therefore, for this AE, a relationship with Cal/BD foam could not be ruled out. No deaths, serious TEAEs or severe TEAEs were reported, and no TEAE led to study withdrawal.

Local reactions (≤2 cm from the border of lesions treated with Cal/BD) were few. The most frequently reported were dryness and erythema, with 6.8% (n = 7) and 3.9% (n = 4) of patients presenting with these local reactions at W2 and W4, respectively (Fig. 3). Local reactions also appeared to improve over time. At W4, no moderate reactions were reported and fewer patients had mild reactions than at baseline.

Calcium metabolism In the overall population, mean change in albumin-corrected serum calcium from baseline to W4 was −0.016 mmol/L (SD 0.119). Based on absolute values vs. the reference range, six patients shifted from low to normal levels of albumin-corrected serum calcium from baseline to W4, while nine patients shifted from normal to low (Table 3). In the HPA-axis cohort, the mean change in calcium excretion in 24-h urine from baseline to W4 was –0.335 mmol/24 h (SD 2.076) and three patients shifted from low to normal levels, while nine shifted from normal to low (Table 3). None of these changes were considered clinically relevant. In the

Table 1 Patient demographics and baseline disease characteristics

Baseline characteristics	Overall population (*N* = 106)	HPA-axis cohort (*N* = 33)	Non-HPA cohort (*N* = 73)
Age, mean (SD), years	14.2 (1.4)	14.2 (1.3)	14.1 (1.4)
Sex, *n* (%)			
Male	45 (42.5)	17 (51.5)	28 (38.4)
Female	61 (57.5)	16 (48.5)	45 (61.6)
Race, *n* (%)			
White	102 (96.2)	33 (100.0)	69 (94.5)
Native Hawaiian or other Pacific Islander	1 (0.9)	0 (0.0)	1 (1.4)
Other	3 (2.8)	0 (0.0)	3 (4.1)
Fitzpatrick skin type, *n* (%)			
I	5 (4.7)	1 (3.0)	4 (5.5)
II	44 (41.5)	12 (36.4)	32 (43.8)
III	46 (43.4)	16 (48.5)	30 (41.1)
IV	10 (9.4)	4 (12.1)	6 (8.2)
V	1 (0.9)	0 (0.0)	1 (1.4)
Duration of psoriasis, mean (SD), years	4.3 (2.9)	3.5 (2.4)	4.7 (3.1)
PGA of psoriasis on the body, *n* (%)			
Mild	23 (21.7)	0 (0.0)	23 (31.5)
Moderate	81 (76.4)	33 (100.0)	48 (65.8)
Severe	2 (1.9)	0 (0.0)	2 (2.7)
PGA of psoriasis on the scalp, *n* (%)			
Mild	15 (14.2)	0 (0.0)	15 (20.5)
Moderate	77 (72.6)	33 (100.0)	44 (60.3)
Severe	14 (13.2)	0 (0.0)	14 (19.2)
Patient's global assessment of psoriasis on the body, *n* (%)			
Very mild	2 (1.9)	0 (0.0)	2 (2.7)
Mild	23 (21.7)	1 (3.0)	22 (30.1)
Moderate	70 (66.0)	32 (97.0)	38 (52.1)
Severe	11 (10.4)	0 (0.0)	11 (15.1)
Patient's global assessment of psoriasis on the scalp, *n* (%)			
Very mild	3 (2.8)	0 (0.0)	3 (4.1)
Mild	10 (9.4)	1 (3.0)	9 (12.3)
Moderate	67 (63.2)	28 (84.8)	39 (53.4)
Severe	26 (24.5)	4 (12.1)	22 (30.1)
Extent of BSA involvement, mean (SD), %			
Body	10.4 (7.1)	16.3 (3.4)	7.8 (6.7)
Scalp	50.6 (25.0)	55.5 (18.8)	48.4 (27.1)
Total	13.2 (7.5)	18.5 (3.4)	10.8 (7.6)
PASI, mean (SD)	8.6 (4.0)	10.5 (2.5)	7.7 (4.2)
Itch score, mean (SD)	39.3 (26.8)	43.5 (21.9)	37.3 (28.6)

Note that the per-protocol and non-per-protocol sets are used for reporting in this table. These two sets correspond to the HPA-axis and non-HPA cohorts, respectively, with the exception of one patient in the HPA-axis cohort who withdrew after the baseline visit, and is therefore included in the non-per-protocol set. BSA, body surface area; FAS, full analysis set; HPA, hypothalamic–pituitary–adrenal; PASI, Psoriasis Area and Severity Index; PGA, physician's global assessment of disease severity; SD, standard deviation.

HPA-axis cohort, all patients had normal calcium:creatinine ratios at baseline and W4; no shifts were observed (Table 3).

ACTH challenge test Of the 33 patients who underwent the ACTH challenge test at W4, three individuals [9.1%; two evaluable and one who did not meet HPA-axis cohort enrolment criteria (see details below)] had serum cortisol concentrations ≤18 μg/dL at 30 min post-ACTH challenge (17.6, 16.5, 15.0 μg/dL, respectively). Of the two evaluable patients, serum cortisol normalized (>18 μg/dL) at 60 min post-ACTH challenge. In one of these patients, a second ACTH challenge was carried out during a follow-up visit 2 weeks after completing treatment and serum cortisol levels were normal at both 30 and 60 min postchallenge. In the third patient, in whom the serum cortisol

Table 2 Treatment-emergent adverse events at Week 4 in the safety analysis set (N = 106) by preferred term

Preferred term	Number of patients, *n* (%)
Upper respiratory tract infection	8 (7.5)
Nasopharyngitis	4 (3.8)
Acne	2 (1.9)
Application site pain	1 (0.9)
Arthralgia	1 (0.9)
Arthropod bite	1 (0.9)
Erythema	1 (0.9)
Folliculitis	1 (0.9)
Haemangioma of liver	1 (0.9)
Impetigo	1 (0.9)
Myalgia	1 (0.9)
Myopia	1 (0.9)
Oral herpes	1 (0.9)
Pharyngitis	1 (0.9)
Product physical consistency issue	1 (0.9)
Pruritus generalized	1 (0.9)
Psoriasis	1 (0.9)
Pulpitis dental	1 (0.9)
Rhinitis	1 (0.9)
Skin neoplasm excision	1 (0.9)
Skin reaction	1 (0.9)

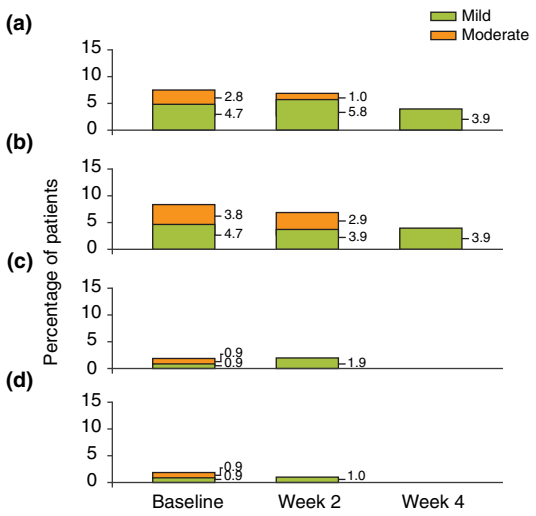

Figure 3 Local safety and tolerability profile of Cal/BD. Presented as percentage of patients with (a) erythema, (b) dryness, (c) erosion and (d) oedema at baseline, Week 2 and Week 4. All data shown are percentages, based on observed cases.

concentration was ≤18 µg/dL at 30 min post-ACTH challenge at W4 (15.0 µg/dL), values were not normalized at 60 min (16.0 µg/dL). Further evaluation demonstrated that this patient had only shown a minimal cortisol response to the ACTH challenge test at baseline (18.0 and 21.0 µg/dL at 30 and 60 min post-ACTH challenge, respectively) and, as such, should not have been enrolled into the HPA-axis cohort. None of the three patients with HPA-axis suppression had detectable PK analytes.

Pharmacokinetics

Pharmacokinetics data were available for 33 patients in the HPA-axis cohort. BD was detectable, systemically, for at least one time-point in 12 patients (36%), with the highest detected concentration, 480 pg/mL, 1 h after final application of Cal/BD in W4. A full PK profile (C_{max}, AUC_{all}, AUC_{∞} and $T_{½}$) was calculable for only one of the 12 patients as just this patient had detectable BD levels at enough time points. The BD metabolite, betamethasone 17-propionate, was detectable systemically in six patients (18%); again, the full PK profile was only calculable in one patient. None of these patients (with detectable BD or betamethasone 17-propionate) experienced any AE considered related to treatment with Cal/BD foam (mild AEs in three patients). Neither Cal, nor its metabolite MC1080, was detectable in any patient samples.

Efficacy

At W4, 71.8% and 75.7% of patients in the overall population achieved treatment success by PGA on the body and scalp, respectively (Fig. 4); rates were comparable between patients aged 12–14 years and 15 to <17 years (data not shown). By PaGA, treatment success rates were 83.5% and 81.6% on the body and scalp, respectively (Fig. 5). Rates of treatment success were lower in the non-HPA cohort than in the HPA-axis cohort by both PGA (body: 61.4% vs. 93.9%; scalp: 65.7% vs. 97.0%, respectively) and PaGA (body: 78.6% vs. 93.9%; scalp: 74.3% vs. 97.0%) (Figs 4,5).

Mean PASI scores in the overall population decreased, from baseline, by 59.1% by W2 (95% CI 54.7%–63.5%) and 82.0% by W4 (95% CI 78.6%–85.5%). By subgroup analysis, decreases were generally consistent between cohorts, with mean reductions of 58.7% and 80.2% in the non-HPA cohort and 59.9% and 85.9% in the HPA-axis cohort by W2 and W4, respectively (Fig. 6). Mean change in itch intensity from baseline to W4 was −32.5 (95% CI −37.8 to −27.1), according to VAS. Mean changes of −27.7 and −42.5 were reported in the non-HPA and HPA-axis cohorts, respectively (Fig. 7).

Discussion

In this phase II, open-label, non-controlled, 4-week study in adolescents with plaque psoriasis on the body and scalp, Cal/BD foam was well tolerated. The TEAE profile was comparable with those previously reported in an adult population.[18] In addition, very few TEAEs were considered related to Cal/BD treatment. It should be noted that acne (which was considered possibly or

Table 3 Shifts in albumin-corrected serum calcium (in the safety analysis set), calcium excretion (in the HPA-axis cohort) and calcium: creatinine ratio (in the HPA-axis cohort) from baseline to Week 4

Level shifts (baseline–Week 4)	Albumin-corrected serum calcium (*n* = 106)†	24-h urinary calcium excretion (*n* = 34)†	24-h urinary calcium:creatinine ratio (*n* = 34)†
Low–Low	3	14	0
Low–Normal	6	3	0
Normal–Low	9	9	0
Normal–Normal	83	6	31

†Only patients with laboratory parameters below, within or above the reference range are reported.

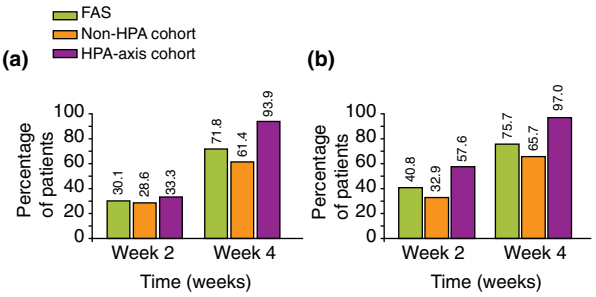

Figure 4 Percentage of patients with treatment success by PGA at Week 2 and Week 4 for (a) the body and (b) the scalp. All data are presented as percentages, based on observed cases. FAS, full analysis set; HPA, hypothalamic–pituitary–adrenal; PGA, physician global assessment of disease.

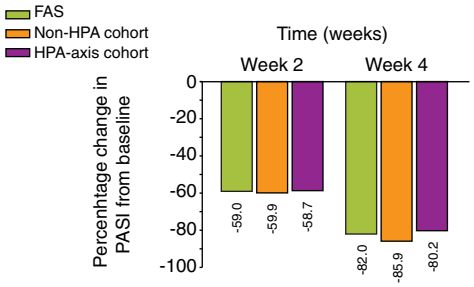

Figure 6 Mean percentage change in PASI scores from baseline at Week 2 and Week 4 for the FAS, HPA-axis cohort and non-HPA cohort. FAS, full analysis set; HPA, hypothalamic–pituitary–adrenal; PASI, Psoriasis Area and Severity Index.

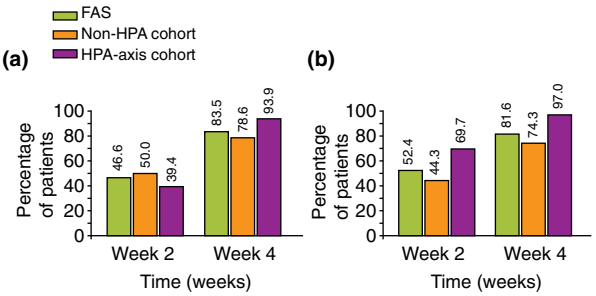

Figure 5 Percentage of patients reporting treatment success by patient's global assessment of disease severity at Week 2 and Week 4 for (a) the body and (b) the scalp. All data are presented as percentages, based on observed cases. FAS, full analysis set; HPA, hypothalamic–pituitary–adrenal.

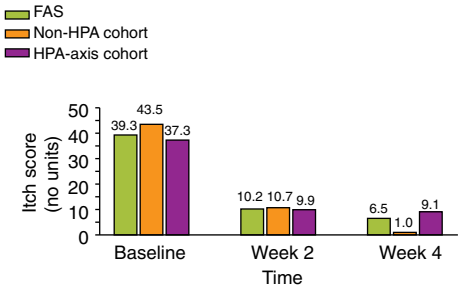

Figure 7 Mean itch scores at baseline, Week 2 and Week 4 for the FAS, HPA-axis cohort and non-HPA cohort. FAS, full analysis set; HPA, hypothalamic–pituitary–adrenal.

probably related to treatment) is a particularly common condition among adolescents more generally.[19]

The data did not indicate any abnormalities in calcium metabolism; changes were small, transient and not considered clinically relevant. These observations were in line with previous studies of calcium homoeostasis in patients treated with Cal/BD.[18,20]

Slight decreases in serum cortisol were observed in two evaluable patients in the HPA-axis cohort at 30 min post-ACTH challenge, but cortisol values normalized by 60 min post-ACTH challenge. There was no apparent association between these decreases and the extent of BSA involvement, PK parameters or the amount of Cal/BD foam used. As such, it is unlikely these minor and short-lived decreases are of clinical significance. Moreover, all evaluable patients had normal cortisol levels by

60 min post-ACTH challenge, which is the standard time used in clinical practice to search for adrenal insufficiency.[17,21]

Exploratory efficacy data were encouraging, with PGA- and PaGA-assessed success rates over 70% and 80%, respectively. Positive outcomes were also reflected by the PASI and itch scores [decreases of 82% and 32.5% (measured by VAS), respectively, from baseline to W4]. Greater improvements in efficacy outcomes were generally observed in the HPA-axis cohort compared with the non-HPA cohort. Efficacy data in this study are higher than previous reports of Cal/BD foam in adults [treatment success on the body (by PGA) 71.8% vs. 53.3%],[22] despite similarities in severity of psoriasis (mean PASI/mPASI scores) at baseline (8.6 vs. 7.5).[22] Higher efficacy might partially be explained by the high compliance rates observed in our study despite non-adherence to treatment being a particularly common problem among adolescents[23] and patients who receive topical treatments.[24] However, these compliance rates may be a reflection of the higher patient adherence typically observed in clinical trials vs. clinical practice.[25]

Cal/BD metabolites were generally present at very low levels, and consequently pharmacokinetic parameters were only calculable in one patient for the BD metabolite betamethasone 17-propionate. Neither Cal, nor its metabolite MC1080, was detectable in any patients. These data indicated minimal systemic exposure to Cal and BD.

It is important that conclusions drawn in relation to Cal/BD tolerability are based on the amount of Cal/BD foam received by the patients in this trial [HPA-axis and non-HPA cohorts received a mean 47.0 g/week (SD 22.2) and 35.8 g/week (SD 28.0), respectively]. In line with a previous study that did not report disturbance of calcium homoeostasis with Cal 45 g/m^2 for 8 weeks in children (age 3–14 years; mean PASI 6.1),[26] the present did not suggest disruption of calcium homoeostasis with 4 weeks' Cal/BD in adolescents, the majority of whom had moderate disease at baseline.

The mean weekly amount of Cal/BD used in this study was below the theoretical permitted amount. The exact reasons are unknown; however, this may be due to the age of the cohort. Median age in this study was 14.0 years (maximum 16 years), meaning most subjects were eligible to receive 60 g/week Cal/BD. In a maximum-use systemic exposure trial with this product in 37 adults, the mean weekly amount of Cal/BD used was 62 g.[20] Disease severity may also have contributed: in the current study, mean PASI score in the overall population was not indicative of extensive psoriasis [8.6 (SD 4.0)], which may mean less product was used than supplied.

There were several limitations to this study. The current study was not designed to determine a maximum tolerated dose. The open-label design could not exclude the possibility of investigator bias, while lack of a placebo control group precluded determination of the true efficacy and safety of Cal/BD foam in adolescents. Moreover, no patient enrolled into the HPA-axis cohort had severe psoriasis by PGA. The duration of the treatment period (as stipulated by the FDA) was relatively short; 4 weeks' treatment would be expected to detect site reactions (e.g. local skin irritation), but may not suffice to categorically exclude perturbations of calcium homoeostasis or HPA-axis reported following long-term exposure to Cal and BD, respectively. Similarly, over the short treatment period, no plateau was observed with the efficacy results in either cohort. Therefore, further improvements may occur in both groups (particularly in patients with more severe disease) with a longer course of treatment.

Further trials, to establish a maximum tolerated dose in adolescent psoriasis patients and to assess safety in adolescent patients with severe disease by PGA, are warranted.

In conclusion, in this phase 2 trial, fixed-dose combination of Cal/BD foam was well tolerated in adolescent patients with mild–moderate body/scalp psoriasis, and exploratory efficacy data were encouraging.

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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 is 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, annotated case report form for the raw data and data set specifications, if available.

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 the 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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