Journal of Dermatological Treatment

http://informahealthcare.com/jdt
ISSN: 0954-6634 (print), 1471-1753 (electronic)

J Dermatolog Treat, 2016; 27(2): 120–127
 DOI: 10.3109/09546634.2015.1083935

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Superior efficacy of calcipotriene and betamethasone dipropionate aerosol foam versus ointment in patients with psoriasis vulgaris – A randomized phase II study

John Koo[1], Stephen Tyring[2], William P. Werschler[3], Suzanne Bruce[4], Martin Olesen[5], John Villumsen[5], and Jerry Bagel[6]

[1]Department of Dermatology, University of California, San Francisco, San Francisco, CA, USA, [2]Department of Dermatology, University of Texas Health Science Center, Houston, TX, USA, [3]University of Washington School of Medicine, Seattle, WA, USA, [4]Suzanne Bruce and Associates, PA, Houston, TX, USA, [5]LEO Pharma A/S, Ballerup, Denmark, and [6]Psoriasis Treatment Center of Central New Jersey, East Windsor, NJ, USA

Abstract

Background: An aerosol foam formulation of fixed combination calcipotriene 0.005% (as hydrate; Cal) plus betamethasone dipropionate 0.064% (BD) was developed to improve psoriasis treatment. *Objectives*: To compare the efficacy and safety of Cal/BD aerosol foam with Cal/BD ointment after 4 weeks. *Methods*: In this Phase II, multicenter, investigator-blind, 4-week trial, adult patients with psoriasis vulgaris were randomized to Cal/BD aerosol foam, Cal/BD ointment, aerosol foam vehicle or ointment vehicle (3:3:1:1). The primary efficacy endpoint was the proportion of patients at week 4 who achieved treatment success (clear or almost clear with at least a two-step improvement) according to the physician's global assessment of disease severity. *Results*: In total, 376 patients were randomized. At week 4, significantly more patients using Cal/BD aerosol foam achieved treatment success (54.6% versus 43.0% [ointment]; $p = 0.025$); mean modified (excluding the head, which was not treated) psoriasis area and severity index score was significantly different between Cal/BD aerosol foam and Cal/BD ointment (mean difference –0.6; $p = 0.005$). Rapid, continuous itch relief occurred with both active treatments. One adverse drug reaction was reported with Cal/BD aerosol foam (application site itch). *Conclusions*: Cal/BD aerosol foam demonstrates significantly greater efficacy and similar tolerability compared with Cal/BD ointment for psoriasis treatment.

Keywords

Aerosol foam, betamethasone dipropionate, calcipotriene, psoriasis vulgaris, topical treatments

History

Received 31 July 2015
Accepted 31 July 2015
Published online 5 October 2015

Introduction

Psoriasis vulgaris is a chronic, inflammatory, immune-mediated skin disorder (1,2) affecting 2–4% of the Western population (3), characterized by well-defined red, scaly plaques (1,2). A World Health Organization resolution (4) recognizes psoriasis as a painful, debilitating disease associated with an elevated risk of serious comorbidities, including cardiovascular disease, diabetes and psoriatic arthritis (5,6). Additionally, psoriasis patients face many psychosocial issues, including depression, anxiety and the burden of stigma (6); physical and psychosocial symptoms can significantly and negatively impact patients' quality of life (6,7).

Topical therapy remains the mainstay of psoriasis treatment (8). Nearly 80% of psoriasis vulgaris cases involve less than 10% of the patient's skin, which can be effectively managed by topical treatment alone (9,10). Current guidelines for first-line treatment of psoriasis vulgaris recommend topical use of vitamin D analogues and corticosteroids, either as separate products used in combination or as fixed combination treatment (10,11). Indeed, a recent Cochrane review has shown that combined treatment with vitamin D and corticosteroid is significantly better than vitamin D alone or corticosteroid alone (12).

There are risks associated with topical steroid use, albeit with rare incidence. In a recent review of 16 clinical trials, pathological adrenal suppression or clinical signs of Cushing's syndrome were reported within only one of these trials and involved excessive use of superpotent steroids (13). Safety concerns are also associated with high-dose use of topical vitamin D analogues, including skin irritation and hypercalcaemia (14,15). Fewer adverse events (AEs) are reported with fixed combination calcipotriene 0.005% (as hydrate; Cal) plus betamethasone dipropionate 0.064% (BD; potent steroid) ointment and gel products compared with active components used as monotherapies (12,16,17). Fixed combination Cal/BD products further confer therapeutic benefits of superior efficacy over monocomponent therapies and are potentially steroid-sparing and as such, are first-line treatments for psoriasis vulgaris (18,19).

Correspondence: John Koo, Psoriasis Treatment Center, 515 Spruce Street, San Francisco, CA, 94118, USA. Tel: +1 415 476 4701. Fax: +1 415 502 4126. E-mail: John.Koo@ucsfmedctr.org

An innovative aerosol foam formulation containing the Cal/BD fixed combination has been developed to improve psoriasis treatment. Early phase studies indicate that Cal/BD aerosol foam is an effective, well-tolerated topical therapy for psoriasis. An *in vitro* skin penetration model demonstrated greater diffusion into skin and significantly higher steady-state Cal and BD levels in skin following Cal/BD aerosol foam application compared with Cal/BD ointment (20). Furthermore, an exploratory study using a modified psoriasis plaque test, demonstrated significantly greater antipsoriatic effect with Cal/BD aerosol foam compared with Cal/BD ointment (21). In a maximal use systemic exposure (MUSE) study, Cal/BD aerosol foam exhibited a favorable safety profile with no clinically relevant impact on the hypothalamic–pituitary–adrenal axis or calcium metabolism (22,23). Furthermore, a Phase III study (PSO-FAST) has shown that Cal/BD aerosol foam is efficacious and well tolerated in patients with psoriasis of the body of all disease severities (24).

Traditionally, ointments have been considered to provide better efficacy in the topical treatment of psoriasis. However, the stickiness and inconvenience of applying ointments have been the main limiting factors for translating this clinical efficacy into real-world effectiveness. In this Phase II trial in patients with psoriasis vulgaris, we aimed to determine whether the efficacy of the innovative fixed combination Cal/BD aerosol foam was superior to the well-known Cal/BD ointment, when applied once daily for 4 weeks.

Methods

Patients

Patients were at least 18 years old, with a clinical diagnosis of psoriasis vulgaris of at least 6 months' duration and amenable to treatment with at most 90 g of study medication/week. All patients were required to have psoriasis vulgaris on the body, involving 2–30% of body surface area (BSA), of at least mild severity according to the physician's global assessment of disease severity scale (PGA), and a modified psoriasis area and severity index (mPASI; excluding the head, which was not treated) score $\geq$2.

Patients were excluded if they received any of the following systemic treatments within the following time limits prior to randomization: etanercept, 4 weeks; adalimumab, alefacept or infliximab, 8 weeks; ustekinumab, 16 weeks; other biological therapies, 4 weeks/five half-lives (whichever was longer); other systemic treatments with possible effects on psoriasis vulgaris (e.g. corticosteroids, retinoids, immunosuppressants), 4 weeks. Patients were also excluded if they received any of the following concomitant treatments prior to randomization: psoralen combined with ultraviolet light A (UVA) therapy within 4 weeks; UVB therapy within 2 weeks, topical antipsoriatic treatment on the body within 2 weeks; topical treatment on the face, skin folds or scalp with class 1–5 corticosteroids or vitamin D_3 analogues within 2 weeks. Other exclusion criteria included: planned excessive exposure to natural or artificial sunlight; planned initiation or changes to concomitant medications that may affect psoriasis vulgaris; current diagnosis of guttate, erythrodermic, exfoliative or pustular psoriasis; hypersensitivity to component(s) of investigational products; any skin infection or other inflammatory skin disease; severe renal or hepatic disorders; disorders of calcium metabolism associated with hypercalcemia. All patients provided written informed consent.

Study design

This was a Phase II, multicenter, investigator-blinded study (NCT01536886; Figure 1). Patients previously treated with antipsoriatic treatments or other relevant treatments (according to exclusion criteria) underwent a washout period of up to 4 weeks prior to start of study treatment. Patients were then randomized 3:3:1:1 (according to a central interactive web response system) to the following once-daily treatments: calcipotriene 0.005% (Cal) plus betamethasone dipropionate 0.064% (BD) aerosol foam, Cal/BD ointment, aerosol foam vehicle, or ointment vehicle. Patients were instructed in how to apply treatments and the first application was applied under investigator supervision. Treatment was applied to psoriasis plaques on the trunk, arms and legs only; scalp, face, genitals and skin folds were not treated. Vehicle controls were included to ensure that patients were blinded to active or vehicle treatment. Investigator blinding was achieved by assigning each trial site with two separate groups of investigators, one group handling study procedures, the other performing clinical assessments. Additionally, patients were instructed not to reveal their treatment to investigators. Patients classified by the investigator as clear, according to the PGA, at weeks 1 and 2 stopped treatment. If psoriasis reappeared, the patient reinitiated treatment. The institutional review boards or independent ethics committees of all investigational sites approved the protocol; the study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice.

Study objectives

The primary objective was to compare the investigator-assessed 4-week efficacy of once-daily Cal/BD aerosol foam with Cal/BD ointment in patients with psoriasis vulgaris. Secondary objectives were efficacy after 1 week of treatment and safety throughout the study.

Assessments

Assessments were performed at baseline and each treatment visit (weeks 1, 2 and 4). Investigators assessed psoriasis severity according to the five-point PGA scale (clear, almost clear, mild, moderate, severe) (25). The extent and severity of clinical signs were assessed to determine an mPASI score; each area (arms, trunk and legs) was assessed separately. Extent of psoriatic involvement was recorded as percentage BSA using a seven-point scale (no involvement, <10, 10–29, 30–49, 50–69, 70–89, 90–100%) and severity of clinical signs (redness, thickness, scaliness) was assessed using a five-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe) (26). Patients assessed the severity of itch during the 24 h prior to treatment visit using a visual analog scale (VAS; 0 = none, 100 = most severe).

Safety and tolerability were assessed at baseline and throughout the study by evaluating AEs, including serious adverse events (SAEs) and adverse drug reactions (ADRs; all lesional/perilesional AEs were considered ADRs and treatment-related). Blood and spot urine samples were collected at baseline and week 4 to evaluate albumin-corrected serum calcium levels and spot urinary calcium:creatinine ratio, respectively.

Statistical analysis

Treatment success was defined as patients who achieved ''clear'' or ''almost clear'' with at least a two-step improvement, according to the PGA. Primary efficacy response was the proportion of patients who achieved treatment success according to the PGA at week 4. Secondary efficacy responses included the proportion of patients who achieved treatment success according to the PGA at week 1; mPASI at weeks 1 and 4; the proportion of patients with a 50% (PASI50) or a 75% (PASI75) reduction from baseline in mPASI score at week 4; and patient assessment of itch by VAS. Categorical outcomes were compared between treatment

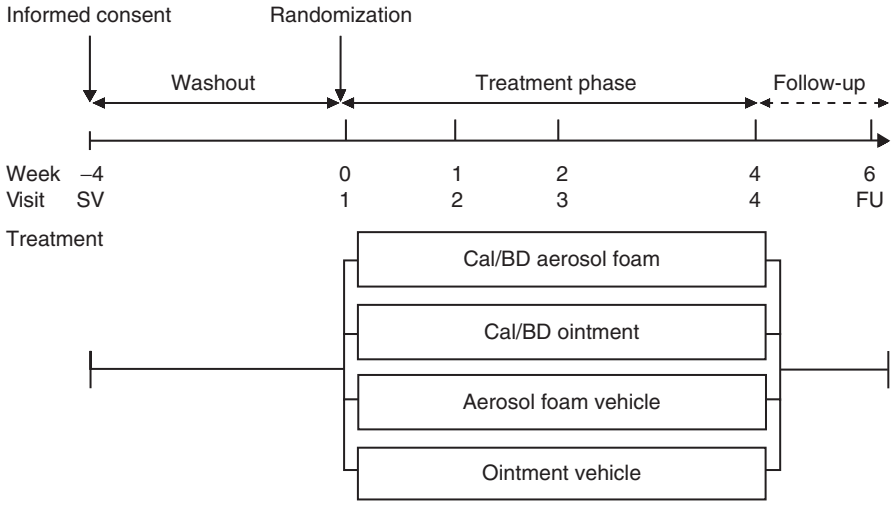

Figure 1. Study design. Calcipotriene 0.005% (Cal) plus betamethasone dipropionate 0.064% (BD); FU, follow up; SV, screening visit.

Table 1. Patient demographics and baseline characteristics.

	Cal/BD aerosol foam ($n = 141$)	Cal/BD ointment ($n = 135$)	Aerosol foam vehicle ($n = 49$)	Ointment vehicle ($n = 51$)
Median age, years (range)	51.0 (21–84)	52.0 (21–88)	46.0 (21–72)	55.0 (30–73)
Male, *n* (%)	87 (61.7)	87 (64.4)	30 (61.2)	30 (58.8)
Race, *n* (%)				
White	122 (86.5)	118 (87.4)	45 (91.8)	44 (86.3)
Black or African American	12 (8.5)	4 (3.0)	3 (6.1)	5 (9.8)
Asian	2 (1.4)	6 (4.4)	0 (0.0)	2 (3.9)
Other	5 (3.5)	7 (5.2)	1 (2.0)	0 (0.0)
Mean duration of psoriasis, years (range)	16.1 (1–51)	16.3 (1–52)	15.1 (1–51)	16.8 (1–45)
PGA, *n* (%)				
Mild	22 (15.6)	22 (16.3)	9 (18.4)	10 (19.6)
Moderate	112 (79.4)	106 (78.5)	35 (71.4)	39 (76.5)
Severe	7 (5.0)	7 (5.2)	5 (10.2)	2 (3.9)
Mean mPASI (±SD)	7.0 (4.2)	6.7 (3.3)	6.7 (4.0)	6.6 (3.1)
Mean BSA involvement, % (range)	7.7 (2–30)	7.4 (2–30)	7.5 (2–30)	6.9 (2–30)
Itch according to VAS	52.7	52.1	51.7	47.6
Previous psoriasis treatments,[a] *n* (%)				
Biologics	13 (9.2)	11 (8.1)	3 (6.1)	4 (7.8)
Systemic treatments (excluding biologics)	11 (7.8)	19 (14.1)	4 (8.2)	6 (11.8)
Photo therapy	10 (7.1)	9 (6.7)	1 (2.0)	6 (11.8)
Topical corticosteroids	85 (60.3)	78 (57.8)	24 (49.0)	27 (52.9)
Topical vitamin D analogues, plain and combination with corticosteroid	42 (29.8)	26 (19.3)	13 (26.5)	13 (25.5)
Topical calcineurin inhibitors	2 (1.4)	1 (0.7)	1 (2.0)	2 (3.9)
Coal tar	19 (13.5)	19 (14.1)	6 (12.2)	6 (11.8)
Medicated shampoos	8 (5.7)	12 (8.9)	6 (12.2)	3 (5.9)
Other	15 (10.6)	10 (7.4)	3 (6.1)	5 (9.8)

BD, betamethasone dipropionate 0.064%; BSA, body surface area; Cal, calcipotriene 0.005%; mPASI, modified psoriasis area and severity index; PGA, physician's global assessment; SD, standard deviation; VAS, visual analogue scale.
[a]All previous psoriasis treatments were recorded.

groups using the Cochran–Mantel–Haenszel method, adjusted for pooled centers. Continuous outcomes, mPASI at weeks 1 and 4 and itch according to VAS, were compared using analysis of covariance, adjusted for baseline and pooled centers. An observed cases approach was used for tabulations of data by visit. Last observation carried forward was used in cases of missing data for PGA at week 4 and mPASI at weeks 1 and 4 when assessing and testing treatment effects. Significance tests are presented two-sided with 95% confidence intervals (CIs). No statistical comparisons were performed with vehicle treatments.

Results

Patient disposition

Between May 2012 and September 2012, 427 patients from 35 US dermatology centers were enrolled; 376 patients (median age 51 years, range $21-88$) were randomized (Cal/BD aerosol foam, $n = 141$; Cal/BD ointment, $n = 135$; aerosol foam vehicle, $n = 49$; ointment vehicle, $n = 51$). Baseline characteristics were similar across all treatments (Table 1). In total, 18 patients (4.8%)

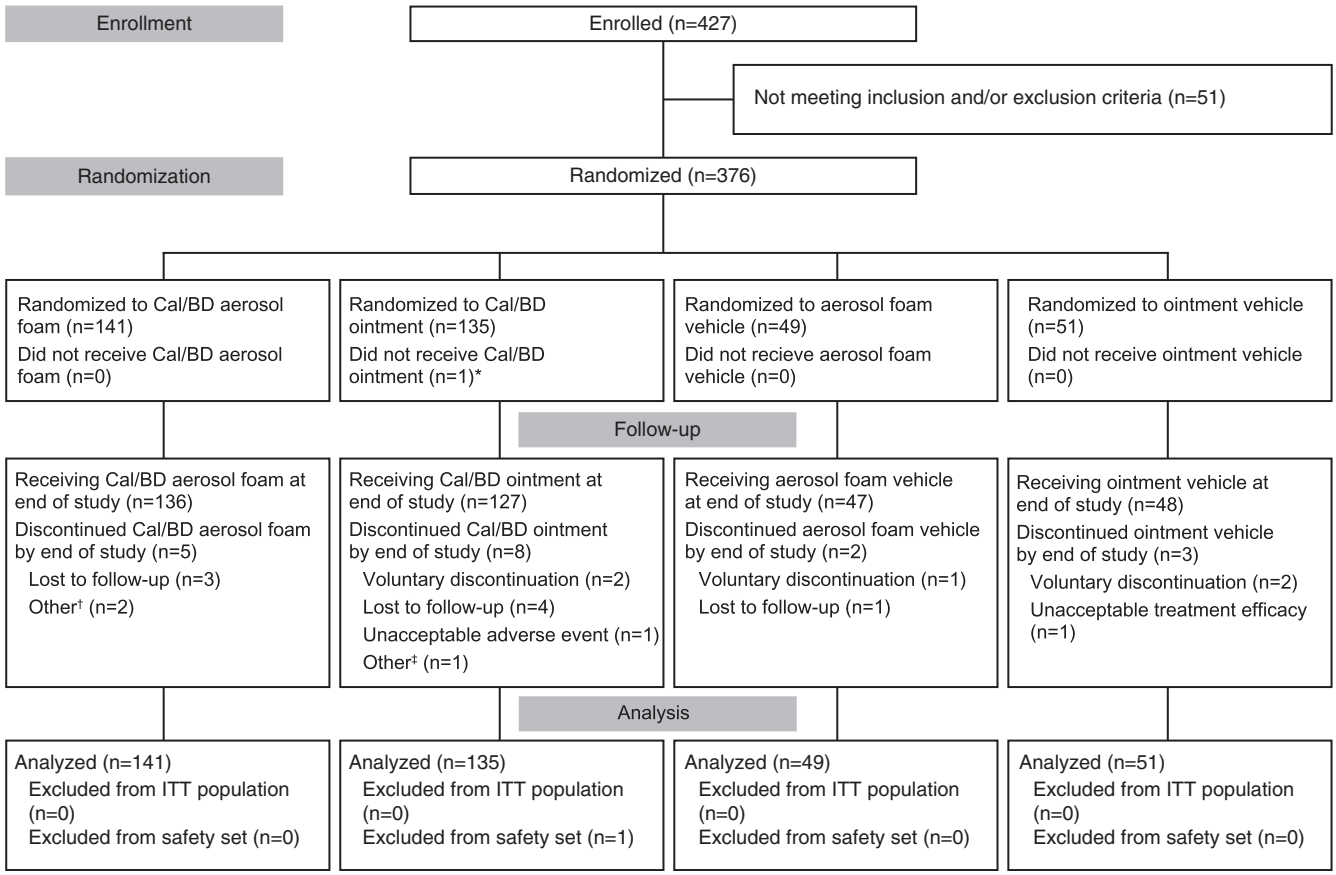

Figure 2. CONSORT diagram. *Patient did not administer any study treatment. †Other reasons included: one was unable to complete weeks 1 and 2 and one missed week 1. ‡Withdrawal of consent to start methotrexate again. BD, betamethasone dipropionate 0.064%; Cal, calcipotriene 0.005%; ITT, intention to treat.

discontinued, including 5 (3.5%) using Cal/BD aerosol foam and 8 (5.9%) using Cal/BD ointment (Figure 2). The most common reasons for withdrawal were ''lost to follow-up'' ($n = 8$) and voluntary withdrawal ($n = 5$). There was one withdrawal (0.7%) due to an unacceptable AE (heart rate increased), reported by a patient using Cal/BD ointment (not considered treatment-related). Compliance was high during the study, with 342 patients (91.0%) reporting full compliance or missing at most 10% of treatments. Mean amount of treatment used per week for the total treatment period was similar in all treatment groups (Cal/BD aerosol foam, 31.6 g; Cal/BD ointment, 30.6 g; aerosol foam vehicle, 32.9 g; ointment vehicle, 28.8 g). All randomized patients were included in the full analysis set ($n = 376$) following the intention-to-treat principle (ITT); one randomized patient was excluded from the safety analysis set ($n = 375$), because no study treatment was administered.

Efficacy

Investigator assessments

By treatment end (week 4), a significantly larger proportion of patients using Cal/BD aerosol foam achieved treatment success compared with those using Cal/BD ointment (54.6% [$n = 77/141$] vs. 43.0% [$n = 58/135$]; mean difference 11.6%; odds ratio (OR) 1.7; 95% CI 1.1, 2.8; $p = 0.025$; Figure 3). At week 1, the proportion of patients who achieved treatment success was low across all treatment groups with no significant differences between active treatments. As the study progressed the proportion of patients who achieved treatment success increased for both Cal/BD aerosol foam and ointment. As early as the week 2 assessment, a numerically larger proportion of patients using Cal/BD aerosol foam had achieved treatment success (29.7% vs. 20.9% [ointment]).

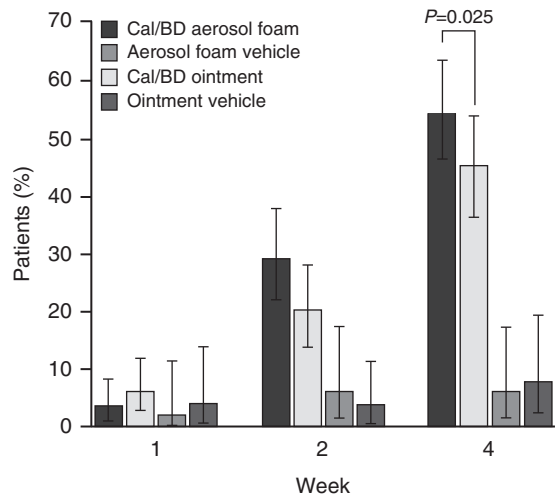

Figure 3. Proportion of patients achieving PGA-assessed treatment success* over time. *Investigator assessment by PGA as ''clear'' or ''almost clear'' with at least a two-step improvement was defined as patient having achieved treatment success. Bars show 95% confidence interval. BD, betamethasone dipropionate 0.064%; Cal, calcipotriene 0.005%.

mPASI further demonstrated statistically significant improvement in disease status for patients using Cal/BD aerosol foam versus those using ointment. There was a significant difference in

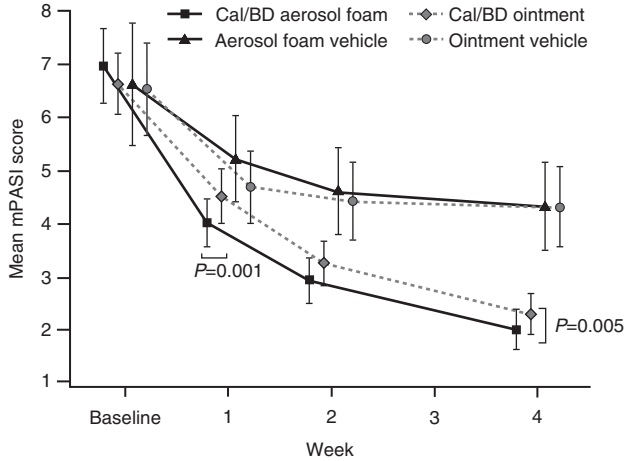

Figure 4. Change in mean mPASI over time. Bars show 95% confidence interval. BD, betamethasone dipropionate 0.064%; Cal, calcipotriene 0.005%; mPASI, modified psoriasis area severity index.

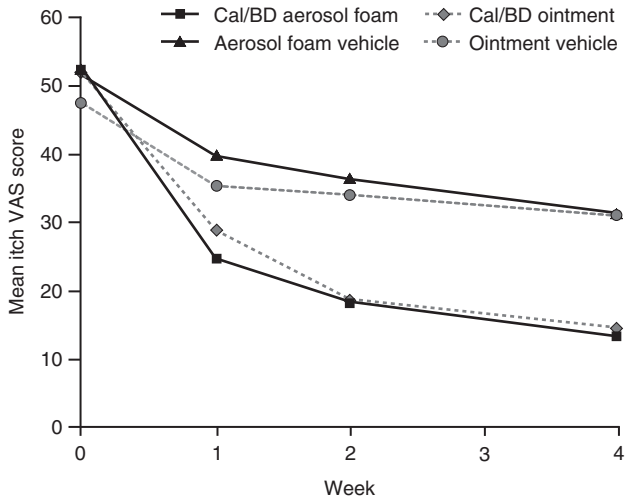

Figure 5. Mean itch (by visual analogue scale) over time. BD, betamethasone dipropionate 0.064%; Cal, calcipotriene 0.005%; VAS, visual analogue scale.

adjusted mean mPASI score between Cal/BD aerosol foam and Cal/BD ointment at week 1 (mean difference –0.7; 95% CI –1.1, –0.3; $p = 0.001$) and week 4 (mean difference –0.6; 95% CI –1.1, –0.2; $p = 0.005$; Figure 4). The mean adjusted mPASI score was 3.95 (week 1) and 1.82 (week 4) with Cal/BD aerosol foam versus 4.64 and 2.46 with Cal/BD ointment, respectively. This corresponds to a mean percentage decrease in mPASI of 43.4% at week 1 and 74.2% at week 4 for patients using Cal/BD aerosol foam compared with 30.5 and 63.2%, respectively, for patients using Cal/BD ointment. Furthermore, at week 4; a greater proportion of patients using Cal/BD aerosol foam achieved PASI75 or PASI50 compared with ointment-treated patients although the difference was not statistically significant (PASI75: 50.4 versus 40.7%; OR 1.7; 95% CI 1.0, 2.7; $p = 0.052$; PASI50: 80.9 versus 74.8%; OR 1.5; 95% CI 0.8, 2.8; $p = 0.17$).

Patient-reported outcomes

Both active treatments led to rapid and marked itch relief within the first week that was maintained throughout the study; patients using Cal/BD aerosol foam reduced from a baseline VAS score of 52.7 to 13.5 at week 4 and ointment-treated patients reduced from 52.1 to 14.5 (Figure 5; mean change –39.8, Cal/BD aerosol foam; –36.5 Cal/BD ointment).

Safety and tolerability

The incidence of AEs was low and similar across the active treatments, with most events being mild. In total, 20 AEs were reported by 16 patients (11.3%) using Cal/BD aerosol foam; 23 AEs reported by 14 patients (10.4%) using Cal/BD ointment; two AEs reported by one patient (2.0%) using aerosol foam vehicle; and two AEs reported by two patients (3.9%) using ointment vehicle (Table 2). All AEs were single events except nasopharyngitis (not treatment-related) and itch (treatment-related), which were each reported by two patients using Cal/BD ointment. ADRs were reported in one patient using Cal/BD aerosol foam (application-site itch, $n = 1$) and four patients using Cal/BD ointment (application-site dryness, application-site pain and psoriasis, each $n = 1$; itch, $n = 2$). No ADRs were reported in patients using vehicle treatment. In total, three serious AEs were reported in two patients treated with Cal/BD ointment (bile duct stone, bronchitis and hypertension); these were considered not treatment-related. One patient (using Cal/BD ointment) discontinued treatment because of an unacceptable AE of severe intensity (increased heart rate; considered not treatment-related).

Mean values for albumin-corrected serum calcium and spot urinary calcium:creatinine ratio were similar across treatment groups and within the normal reference ranges at baseline and week 4 (Table 3). Over the course of the treatment, none of the patients using Cal/BD aerosol foam developed albumin-corrected serum calcium levels above the normal reference range (2.15–2.55 mmol/l), compared with one patient using Cal/BD ointment (Table 4). Four patients using Cal/BD aerosol foam, three using Cal/BD ointment and one using each vehicle recorded a shift from normal urinary calcium:creatinine values at baseline to high values at week 4 (normal range: men, $0.300 - 6.100$ mmol/g; women $0.225 - 8.200$ mmol/g; Table 4). Of note, in those patients with elevations in albumin-corrected serum calcium or spot urinary calcium:creatinine ratio, there was no consistency between parameters. None of the elevations in the calcium laboratory parameters were considered clinically significant or reported as AEs.

Discussion

This Phase II, randomized, vehicle-controlled study directly compared the efficacy and safety of Cal/BD aerosol foam with Cal/BD ointment in patients with psoriasis vulgaris. Over the 4-week treatment period, patients using Cal/BD aerosol foam demonstrated statistically significant improvement in disease status compared with patients using Cal/BD ointment, while maintaining the favorable tolerability profile determined with the Cal/BD fixed combination ointment, an established first-line psoriasis treatment.

The primary objective of this study was to assess the proportion of patients achieving treatment success, defined as patients who achieved ''clear'' or ''almost clear'' with at least a two-step improvement, according to the PGA; 54.6% of patients using Cal/BD aerosol foam achieved treatment success compared with 43.0% using Cal/BD ointment ($p = 0.025$). This success rate was supported by mPASI evaluation, culminating in a 74.2% mean percentage mPASI score decrease at week 4 for patients using Cal/BD aerosol foam versus 63.2% using Cal/BD ointment. Furthermore, the antipsoriatic effect was evident sooner in Cal/BD aerosol foam-treated patients than in patients using Cal/BD ointment, indicating a faster onset of action for the aerosol foam formulation.

Table 2. Adverse events, when ≥4 events/treatment group reported, by MedDRA primary system organ class; preferred term also listed.

	Cal/BD aerosol foam ($n = 141$)	Cal/BD ointment ($n = 134$)	Aerosol foam vehicle ($n = 49$)	Ointment vehicle ($n = 51$)
Total number of AEs	20	23	2	2
Total number of patients, *n* (%)	16 (11.3)	14 (10.4)	1 (2.0)	2 (3.9)
Number of patients, *n*				
Infections and infestations	5	5	1	0
Abscess	–	1	–	–
Bronchitis	–	1	–	–
Hordeolum	1	–	–	–
Impetigo	1	–	–	–
Influenza	1	–	–	–
Laryngitis	–	–	1	–
Nasopharyngitis	–	2	–	–
Staphylococcal infection	–	1	–	–
Urinary tract infection	1	–	–	–
Viral pharyngitis	1	–	–	–
Gastrointestinal disorders	4	1	0	1
Abdominal distension	1	–	–	–
Abdominal pain	1	–	–	–
Diarrhoea	–	1	–	–
Dyspepsia	1	–	–	–
Nausea	1	–	–	1
Skin and subcutaneous tissue disorders	0	4	0	0
Pruritus	0	2	0	0
Psoriasis	0	1	0	0
Swelling face	0	1	0	0

AE, adverse event; BD, betamethasone dipropionate 0.064%; Cal, calcipotriene 0.005%; MedRA, medical dictionary for regulatory activities.

Table 3. Changes in albumin-corrected serum calcium and urinary calcium:creatinine ratio over time.

	Cal/BD aerosol foam ($n = 141$)	Cal/BD ointment ($n = 134$)	Aerosol foam vehicle ($n = 49$)	Ointment vehicle ($n = 51$)
Mean albumin-corrected serum calcium, mmol/l (SD)				
Normal reference range 2.15–2.55 mmol/l				
Baseline	2.28 (0.08)	2.31 (0.08)	2.31 (0.10)	2.31 (0.09)
Week 4	2.30 (0.09)	2.30 (0.09)	2.30 (0.08)	2.30 (0.09)
Change from baseline	0.01 (0.10)	–0.01 (0.08)	–0.01 (0.08)	–0.01 (0.09)
Mean urinary calcium:creatinine ratio, mmol/g (SD)				
Normal range: men 0.300 – 6.100 mmol/g; women 0.225 – 8.200 mmol/g				
Baseline	2.52 (1.86)	2.97 (2.49)	2.56 (1.63)	2.76 (2.10)
Week 4	2.96 (3.46)	2.73 (1.85)	2.14 (1.66)	2.64 (1.96)
Change from baseline	0.41 (3.43)	–0.19 (1.98)	–0.31 (1.64)	–0.13 (2.47)

BD, betamethasone dipropionate 0.064%; Cal, calcipotriene 0.005%; SD, standard deviation.

It is hypothesized that vehicle components may affect skin permeability, influencing delivery of the active agent(s) (27). Development of vehicles that assist drug delivery is therefore an important aspect of topical drug formulation. Aerosolized formulations are considered to improve drug delivery, possibly because of greater vehicle evaporation resulting in increased drug saturation on the skin and transfer into skin compared with traditional formulations (27). The greater efficacy observed with Cal/BD aerosol foam compared with Cal/BD ointment may be attributed, in part, to enhanced properties of the aerosol foam vehicle that support superior delivery of the drug to psoriatic skin. This is indicated by the preclinical finding that steady-state Cal and BD levels in skin are significantly higher following Cal/BD aerosol foam application compared with Cal/BD ointment (28).

Even with the greater efficacy reported with Cal/BD aerosol foam, our findings indicate that this is not accompanied with any compromise in safety. Indeed, we demonstrate that Cal/BD aerosol foam maintains the favorable safety and tolerability profile established with Cal/BD ointment and gel (18,29–31). Local safety and tolerability reactions were infrequent and mild and application-site irritation rarely occurred ($n = 1$, 0.7%) with Cal/BD aerosol foam. Of note, there were no clinically relevant changes in mean albumin-corrected serum calcium or spot urinary calcium:creatinine ratio. This observation suggests that effects on calcium homeostasis with Cal/BD aerosol foam are minimal, despite improved efficacy with the aerosol foam formulation, and is in alignment with a MUSE study that demonstrated once-daily treatment for 4 weeks in patients with extensive psoriasis was not associated with any clinically relevant impact on calcium homeostasis (23).

One additional aspect evaluated within this study was the degree of itch relief provided by these formulations. Rapid, effective and continued itch relief was reported by patients across all treatment groups, although this was greatest with Cal/BD aerosol foam. From week 1, both vehicle treatments also provided a degree of itch relief, with the effect being more pronounced in patients using the aerosol foam vehicle, which may be a benefit of the vehicle's emollient action. Itch is a common distressing aspect of psoriasis (32) that can cause pronounced discomfort, often associated with loss of sleep and can negatively impact on daily

Table 4. Individual laboratory values for patients who developed high levels of albumin-corrected serum calcium and urinary calcium:creatinine by week 4.

	Age (years)	Sex	Baseline	Week 4
Albumin-corrected serum calcium (mmol/l)				
Normal reference range 2.15–2.55 mmol/l				
Cal/BD ointment ($n = 1/134$)	71	M	2.45	2.58
Spot urinary calcium:creatinine ratio (mmol/g)				
Normal range: men 0.300 – 6.100 mmol/g; women 0.225 – 8.200 mmol/g				
Cal/BD aerosol foam ($n = 4/141$)	48	F	4.30	15.95
	58	M	5.62	11.95
	50	M	3.97	9.37
	58	F	0.47	33.32
Cal/BD ointment ($n = 3/134$)	52	M	1.87	6.20
	48	M	5.77	6.75
	39	M	6.10	6.62
Aerosol foam vehicle ($n = 1/49$)	64	M	4.30	6.52
Ointment vehicle ($n = 1/51$)	60	M	4.45	9.22

BD, betamethasone dipropionate 0.064%; Cal, calcipotriene 0.005%.

life (33). Therefore, alleviation of itch can improve a patient's quality of life, forming a key feature of symptom relief with the Cal/BD aerosol foam together with the immediate goal of improving disease status.

Although topical treatment of psoriasis vulgaris is usually effective and safe, adherence can be poor. Reduced adherence can be due to a number of factors, including acceptability of treatment vehicle (34,35). Some topical formulations, such as ointments, may be considered messy, time consuming and difficult to apply (36,37), so the choice of topical treatment vehicle contributes to patient adherence and ''real-life'' effectiveness. The Cal/BD aerosol foam formulation was developed to offer patients a convenient and easy to use topical treatment option. Since Cal/BD aerosol foam provides enhanced efficacy delivered in a non-skin-drying emollient vehicle that is potentially more convenient to apply and more cosmetically acceptable, it may provide an enhanced treatment option and promote greater adherence over conventional topical formulations.

Conclusion

In conclusion, this 4-week study in patients with psoriasis vulgaris demonstrated that Cal/BD aerosol foam provides a statistically significantly greater improvement in psoriasis disease status than Cal/BD ointment, while maintaining a similar, favorable safety and tolerability profile. The high efficacy and good itch alleviation may improve patient experience with topical treatment.

Acknowledgements

We would like to thank the study investigators, and Anders Ninn Hansen, International Clinical Trial Manager and Eric Sorenson and Catherine Nguyen for providing editorial support to Professor Koo. Additionally, we thank Catherine Risebro, PhD, from Mudskipper Business Ltd, who provided medical writing support.

Declaration of interest

This study was sponsored by LEO Pharma. Medical writing support was provided by Catherine Risebro, PhD, from Mudskipper Business Ltd, funded by LEO Pharma.

J. Koo reports participation as a speaker for LEO, AbbVie and Celgene and receiving research funding from Amgen, Janssen, PhotoMedex, Merck and Pfizer. S Tyring reports participation as a speaker for LEO and receiving research funding from LEO. W. P. Werschler reports participation as a speaker for AbbVie, Celgene, Galderma and LEO and receiving research funding from AbbVie, Galderma, Janssen, LEO, Merck and Pfizer. S. Bruce reports receiving research funding from LEO, Pfizer, Maruho and Stiefel. J. Bagel reports LEO, Amgen, AbbVie, Janssen, Eli-Lilly, Novartis, Coherus, Boehringer Ingelheim and Celgene. M. Olesen reports previous employment with LEO. J. Villumsen reports employment with LEO.

Poster presented at the 33rd Anniversary Fall Clinical Dermatology Conference, Las Vegas, Nevada, USA (16–19 October 2014)

References

1. Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol. 2008;58:826–50.
2. Schön MP, Boehncke W-H. Psoriasis. N Engl J Med. 2005;352:1899–912.
3. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol. 2013;133:377–85.
4. World Health Organization. Psoriasis: Sixty seventh World Health Assembly Agenda item 13.5. 2014. Available from http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R9-en.pdf. Accessed September 2, 2015.
5. Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. Lancet. 2007;370:263–71.
6. Kimball AB, Gieler U, Linder D, et al. Psoriasis: is the impairment to a patient's life cumulative? J Eur Acad Dermatol Venereol. 2010;24:989–1004.
7. Gelfand JM, Feldman SR, Stern RS, et al. Determinants of quality of life in patients with psoriasis: a study from the US population. J Am Acad Dermatol. 2004;51:704–8.
8. Lebwohl M, Ting PT, Koo JY. Psoriasis treatment: traditional therapy. Ann Rheum Dis. 2005;64 Suppl 2:ii83–ii86.
9. Stern RS, Nijsten T, Feldman SR, et al. Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. J Investig Dermatol Symp Proc. 2004;9:136–9.
10. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. J Am Acad Dermatol. 2009;60:643–59.
11. Samarasekera E, Sawyer L, Parnham J, Smith CH. Assessment and management of psoriasis: summary of NICE guidance. BMJ. 2012;345:e6712.
12. Mason AR, Mason J, Cork M, et al. Topical treatments for chronic plaque psoriasis. Cochrane Database Syst Rev. 2013;3:CD005028.
13. Levin E, Gupta R, Butler D, et al. Topical steroid risk analysis: differentiating between physiologic and pathologic adrenal suppression. J Dermatolog Treat. 2014;25:501–6.
14. Kragballe K, Iversen L. Calcipotriol. A new topical antipsoriatic. Dermatol Clin. 1993;11:137–41.
15. Bourke JF, Berth-Jones J, Iqbal SJ, Hutchinson PE. High-dose topical calcipotriol in the treatment of extensive psoriasis vulgaris. Br J Dermatol. 1993;129:74–6.
16. Kragballe K, Austad J, Barnes L, et al. Efficacy results of a 52-week, randomised, double-blind, safety study of a calcipotriol/betamethasone dipropionate two-compound product (Daivobet®/Dovobet®/Taclonex®) in the treatment of psoriasis vulgaris. Dermatology. 2006;213:319–26.
17. 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.
18. Douglas WS, Poulin Y, Decroix J, et al. A new calcipotriol/betamethasone formulation with rapid onset of action was superior

to monotherapy with betamethasone dipropionate or calcipotriol in psoriasis vulgaris. Acta Derm Venereol. 2002;82:131–5.
19. Menter A, Stein Gold L, 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.
20. Basse LH, Olesen M, Lacour JP, Queille-Roussel C. Enhanced *in vitro* skin penetration and antipsoriatic effect of fixed combination calcipotriol plus betamethasone dipropionate in an innovative foam vehicle. J Invest Dermatol. 2014;134:S33 (abst 192).
21. Queille-Roussel C, Olesen M, Villumsen J, Lacour JP. Efficacy of an innovative aerosol foam formulation of fixed combination calcipotriol plus betamethasone dipropionate in patients with psoriasis vulgaris. Clin Drug Investig. 2015;35:239–45.
22. Taraska V, Tuppal R, Olesen M, et al A novel aerosol foam formulation of calcipotriol and betamethasone has no impact on HPA axis and calcium homeostasis in patients with extensive psoriasis vulgaris. J Cutan Med Surg. 2015 (In press). [Epub ahead of print].
23. Taraska V, Tuppal R, Olesen M, et al. Fixed combination aerosol foam calcipotriene 50 mcg/g and betamethasone 0.5 mg/g exhibits minimal impact on the HPA axis and calcium metabolism in patients with extensive psoriasis vulgaris: a multicenter, single arm, Phase II, 4-week MUSE study. Semin Cutan Med Surg. 2014;33(4 (Suppl 5)):abst PA-13.
24. Leonardi C, Bagel J, Yamauchi P, et al. Efficacy and safety of an innovative aerosol foam formulation of the fixed combination calcipotriene plus betamethasone dipropionate in patients with psoriasis – the PSO-FAST study. J Am Acad Dermatol. 2015;72 (Suppl 1):AB232.
25. Cappelleri JC, Bushmakin AG, Harness J, Mamolo C. Psychometric validation of the physician global assessment scale for assessing severity of psoriasis disease activity. Qual Life Res. 2013;22: 2489–99.
26. Faria JR, Aarao AR, Jimenez LM, et al. Inter-rater concordance study of the PASI (Psoriasis Area and Severity Index). An Bras Dermatol. 2010;85:625–9.
27. Bhutani T, Koo J, Maibach HI. Efficacy of clobetasol spray: factors beyond patient compliance. J Dermatolog Treat. 2012;23: 11–15.
28. Basse LH, Olesen M, Lacour JP, Queille-Roussel C. Enhanced *in vitro* skin penetration and antipsoriatic effect of fixed combination calcipotriol plus betamethasone dipropionate in an innovative foam vehicle. 44th Annual Meeting of the European Society for Dermatological Research (ESDR). Copenhagen, Denmark, 10–13 September 2014.
29. McCormack PL. Calcipotriol/betamethasone dipropionate: a review of its use in the treatment of psoriasis vulgaris of the trunk, limbs and scalp. Drugs. 2011;71:709–30.
30. Kragballe K, Austad J, Barnes L, et al. A 52-week randomized safety study of a calcipotriol/betamethasone dipropionate two-compound product (Dovobet®/Daivobet®/Taclonex®) in the treatment of psoriasis vulgaris. Br J Dermatol. 2006;154:1155–60.
31. Langley RG, Gupta A, Papp K, Wexler D, Østerdal ML, Curcic D. 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.
32. Kimball AB, Jacobson C, Weiss S, Vreeland MG, Wu Y. The psychosocial burden of psoriasis. Am J Clin Dermatol. 2005;6:383–92.
33. Globe D, Bayliss MS, Harrison DJ. The impact of itch symptoms in psoriasis: results from physician interviews and patient focus groups. Health Qual Life Outcomes. 2009;7:62. doi: 10.1186/1477-7525-7-62.
34. Brown KK, Rehmus WE, Kimball AB. Determining the relative importance of patient motivations for nonadherence to topical corticosteroid therapy in psoriasis. J Am Acad Dermatol. 2006;55: 607–13.
35. Reich K, Bewley A. What is new in topical therapy for psoriasis? J Eur Acad Dermatol Venereol. 2011;25 (Suppl 4):15–20.
36. Bewley A, Page B. Maximizing patient adherence for optimal outcomes in psoriasis. J Eur Acad Dermatol Venereol. 2011;25 (Suppl 4):9–14.
37. Augustin M, Holland B, Dartsch D, et al. Adherence in the treatment of psoriasis: a systematic review. Dermatology. 2011;222:363–74.