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ORIGINAL RESEARCH ARTICLE

Efficacy of an Innovative Aerosol Foam Formulation of Fixed Combination Calcipotriol plus Betamethasone Dipropionate in Patients with Psoriasis Vulgaris

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Abstract

Background and Objective The antipsoriatic effect of an innovative aerosol foam formulation of fixed combination calcipotriol 50 μg/g (as hydrate; Cal) and betamethasone 0.5 mg/g (as dipropionate; BD) was explored in order to compare the effect with that of the first-line treatment Cal/BD ointment.

Methods This was a Phase IIa, single-centre, investigator-blinded, exploratory study, with intra-individual comparison using a modified psoriasis plaque test. Patients were treated once daily (6 days/week) for 4 weeks with Cal/BD foam, Cal/BD ointment, BD foam and Cal/BD foam vehicle, randomized to four plaque test sites (5 cm^2 each). The primary efficacy endpoint was change in total clinical score (TCS; sum of erythema, scaling and lesional thickness). Secondary endpoints included ultrasonographic changes in total skin thickness and echo-poor band thickness, and adverse events.

Results Twenty-four patients, median age 52.5 years (range 21–75), completed this study. At week 4, test sites treated with Cal/BD foam had a significantly greater decrease in mean (±SD) TCS (−6.00 ± 1.27) versus those treated with Cal/BD ointment (−5.25 ± 1.78; difference −0.75; 95 % CI −1.46 to −0.04; $p = 0.038$), BD foam (−4.96 ± 1.85; difference −1.04; 95 % CI −1.75 to −0.33; $p = 0.005$) or foam vehicle (−1.88 ± 1.12; difference −4.13; 95 % CI −4.83 to −3.42; $p < 0.001$). Total skin thickness and echo-poor band thickness of Cal/BD foam-treated sites were reduced to a greater extent than those treated with comparators. Eleven patients reported 17 adverse events, the most frequent being headache (five patients). There were no lesional/perilesional adverse events or adverse drug-related events.

Conclusions Cal/BD foam demonstrated a significant improvement in antipsoriatic effect over Cal/BD ointment, BD foam and foam vehicle alone.

Key Points

An innovative aerosol foam formulation of a fixed combination of calcipotriol 50 μg/g (as hydrate) and betamethasone 0.5 mg/g (as dipropionate) has been developed to provide a highly effective topical psoriasis treatment delivered in a more patient-acceptable vehicle.

This aerosol foam formulation demonstrated a significant improvement in clinical signs of psoriatic lesions compared with the fixed combination ointment, betamethasone aerosol foam and aerosol foam vehicle alone.

The aerosol foam formulation may represent a more efficacious alternative to current first-line topical treatment options for patients with psoriasis vulgaris.

Clinical trial registration: NCT01347255.

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1 Introduction

Psoriasis vulgaris (plaque psoriasis) is a chronic, inflammatory disorder, typically with well-demarcated, erythematous, thickened, scaly plaques on the body and scalp [1–3]. The World Health Organization (WHO) recognizes that psoriasis is a painful and debilitating disease [4] associated with serious co-morbidities, such as cardiovascular disease, diabetes mellitus and psoriatic arthritis [5, 6], as well as a number of psychosocial disorders, including depression [6]. As such, the negative impact of psoriasis on patients' quality of life can be considerable [6, 7].

Topical therapy remains the mainstay of psoriasis treatment, with more than 80 % of patients being able to manage their psoriasis with topicals alone [8, 9]. Guidelines recommend the topical use of corticosteroids and vitamin D analogues (be it as monotherapies used in combination or as fixed combinations) as first-line treatment for psoriasis [8, 9]. The fixed combination of calcipotriol 50 μg/g (as hydrate; Cal) and betamethasone 0.5 mg/g (as dipropionate; BD) has demonstrated increased efficacy and reduced side effects compared with either of the active ingredients when used as monotherapies [10–12]. Furthermore, the presence of calcipotriol may also provide an additive, steroid-sparing effect on betamethasone dipropionate [3]. This combination is currently available in gel or ointment formulations (Taclonex®/Daivobet®/Dovobet®), both of which are first-line treatment options for patients with mild-to-moderate psoriasis vulgaris [8, 9].

An innovative aerosol foam formulation of the Cal/BD fixed combination has now been developed to improve topical treatment of psoriasis vulgaris. In this exploratory study, the antipsoriatic effect of Cal/BD aerosol foam was compared with that of the established fixed combination Cal/BD ointment, as well as BD aerosol foam and Cal/BD aerosol foam vehicle, using a modified version of the psoriatic plaque test developed by Dumas and Scholtz [12–15].

2 Methods

2.1 Patients

Patients were at least 18 years of age, diagnosed with psoriasis vulgaris of the body with psoriatic plaques of a total size suitable for application of four different treatments. Patients were required to have stable disease and plaques with a total clinical score [TCS; sum of scores of erythema, scaling and lesional thickness (each scored from 0 to 3)] of 4–9 inclusive and a score for each individual component of ≥1. Disease stability was based on TCS component scores measured at a screening visit (within 3 weeks of start of treatment) and baseline; disease was considered stable if the change in score for any single symptom was <1 point. Exclusion criteria included: treatment with etanercept within 4 weeks, adalimumab, alefacept or infliximab within 2 months, or ustekinumab within 4 months; any other biological or systemic therapy within 4 weeks or five half-lives (whichever was longer); psoralen combined with ultraviolet A or Grenz ray therapy within 4 weeks or ultraviolet B therapy within 2 weeks; potent or very potent (WHO class III–IV) corticosteroids within 4 weeks; or emollients within 1 week. Topical antipsoriatic treatment of the scalp and/or facial psoriasis with WHO class I–II corticosteroids was allowed within 2 weeks of start of study treatment.

2.2 Study Design and Objectives

This was a single-centre, investigator-blinded, vehicle-controlled, 4-week exploratory study (ClinicalTrials.gov identifier: NCT01347255) with intra-individual comparison, in which the following investigational products were assessed: Cal/BD aerosol foam (LEO Pharma, Denmark), Cal/BD ointment (Taclonex®/Daivobet®/Dovobet®; LEO Pharma, Denmark), BD aerosol foam and Cal/BD aerosol foam vehicle. Each patient received simultaneous application (by a study nurse/assistant) of all investigational products to four predetermined target plaques on their arms, legs or trunk, applied once daily (6 days per week, excluding Sundays) for 4 weeks. Per patient, the test application site for each product was determined according to random assignment. Test sites (5 cm^2) were delimited with a disposable circular adhesive (replaced twice a week) and outlined using an indelible marker. The minimum distance allowed between two test sites was 2 cm. For application of the aerosol foam products, 50 mg of product was sprayed directly onto the appropriate test site, using a circular template. Cal/BD ointment was applied using an Eppendorf Combitip® (Eppendorf AG, Hamburg, Germany). Each product was gently massaged into the test sites with gloved fingers and then non-occlusive gauze was applied until the next treatment application.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and good clinical practice guidelines. The study protocol was approved by the independent ethics committee of the investigational site. All patients provided written informed consent before enrolment.

The primary objective was to evaluate the antipsoriatic effect of Cal/BD aerosol foam compared with Cal/BD ointment, BD aerosol foam and Cal/BD aerosol foam vehicle, using the modified psoriasis plaque test. The secondary objective was to obtain information on adverse events (AEs) for all investigational products.

2.3 Assessments

Clinical and safety assessments were performed at baseline and then twice weekly on days 4, 8, 11, 15, 18, 22, 25 and 29. Test site severity of erythema, scaling and lesional thickness (using a 0–3 half-point grading scale) was assessed by the investigator after removal of the non-occlusive gauze and prior to treatment reapplication; a single investigator performed all clinical assessments. Ultrasound measurements were performed at baseline and once weekly (days 8, 15, 22 and 29) using a B scanner equipped with a 20-MHz transducer. At each time point, three B scans were made per test site. Safety and tolerability were assessed throughout the study by evaluating AEs and adverse drug reactions (ADRs).

2.4 Statistical Analysis

Twenty-four patients were required to achieve 80 % power of rejecting the null hypothesis with a 5 % significance level. The primary efficacy response was the change in TCS (range 0–9) from baseline to week 4. Secondary efficacy responses included change from baseline in TCS and its individual components (erythema, scaling and lesional thickness), and ultrasound-determined total skin thickness and echo-poor band thickness (a measure of superficial dermis inflammation), by visit. Efficacy endpoints were analysed by a two-way analysis of variance and are described using summary statistics. All significance tests are reported as two-sided with a 95 % confidence interval (CI). All patients who received at least one dose of study treatment were included in the full (intent-to-treat) and safety analysis sets.

3 Results

3.1 Patient Disposition and Demographics

Between May and June 2011, 24 patients were enrolled in this study, two-thirds of whom were male (Table 1). All patients were exposed to all four investigational products, completed the study, and were included in the full and safety analysis sets.

Table 1 Patient demographics and baseline characteristics

Characteristic	Value
Number of patients	24
Median (range) age, years	52.5 (21–75)
Males, *n* (%)	16 (66.7)
Fitzpatrick skin type,[a] *n* (%)	
Type II	1 (4.2)
Type III	23 (95.8)
Median (range) disease duration, years	19.5 (3–49)
Mean ± standard deviation total clinical score[b]	7.07 ± 0.78

[a] Type II: white, always burns, tans minimally; Type III: white, burns moderately, tans gradually (light brown)

[b] Sum of three scores (erythema, scaling, lesional thickness)

3.2 Efficacy

3.2.1 Clinical Assessment

At week 4, there was a significantly larger decrease in mean [±standard deviation (SD)] TCS for those test sites treated with Cal/BD aerosol foam (−6.00 ± 1.27) compared with those treated with Cal/BD ointment (−5.25 ± 1.78; difference −0.75; 95 % CI −1.46 to −0.04; $p = 0.038$), BD aerosol foam (−4.96 ± 1.85; difference −1.04; 95 % CI −1.75 to −0.33; $p = 0.005$) or Cal/BD aerosol foam vehicle (−1.88 ± 1.12; difference −4.13; 95 % CI −4.83 to −3.42; $p < 0.001$). A continuous improvement in TCS was observed for all active treatments throughout the study, with the mean decrease in TCS being consistently larger with Cal/BD aerosol foam compared with all other products, from the second on-treatment assessment time point (day 8) until the end of the study (Fig. 1a). Similarly, mean changes (±SD) in the TCS components from baseline to week 4 were also found to be higher for those test sites treated with Cal/BD aerosol foam (erythema −1.75 ± 0.71; scaling −2.13 ± 0.47; lesional thickness −2.13 ± 0.45) than for those treated with Cal/BD ointment (−1.50 ± 0.66; −2.02 ± 0.56; −1.73 ± 0.82, respectively), BD aerosol foam (−1.44 ± 0.78; −2.02 ± 0.58; −1.50 ± 0.77) and Cal/BD aerosol foam vehicle (−0.56 ± 0.47; −0.90 ± 0.47; −0.42 ± 0.43; Fig. 1b–d).

3.2.2 Ultrasound Assessment

Throughout this study, reductions in total skin thickness and echo-poor band thickness were consistently greater with Cal/BD aerosol foam treatment compared with all other treatments. At week 4, treatment with Cal/BD aerosol foam reduced the mean total skin thickness (±SD) to a greater extent (−0.81 ± 0.41 mm), although not significantly so, than with Cal/BD ointment (−0.62 ± 0.37 mm; difference, −0.19 mm; 95 % CI −0.40 to 0.03; $p = 0.088$) or BD aerosol foam (−0.66 ± 0.42 mm; difference, −0.14 mm; 95 % CI −0.36 to 0.07; $p = 0.190$), and significantly greater compared with Cal/BD aerosol foam vehicle (−0.23 ± 0.30 mm; difference, −0.58 mm; 95 % CI −0.79 to −0.36; $p < 0.001$; Fig. 2). Similarly, the mean reduction in echo-poor band thickness at week 4 was consistently greater (but

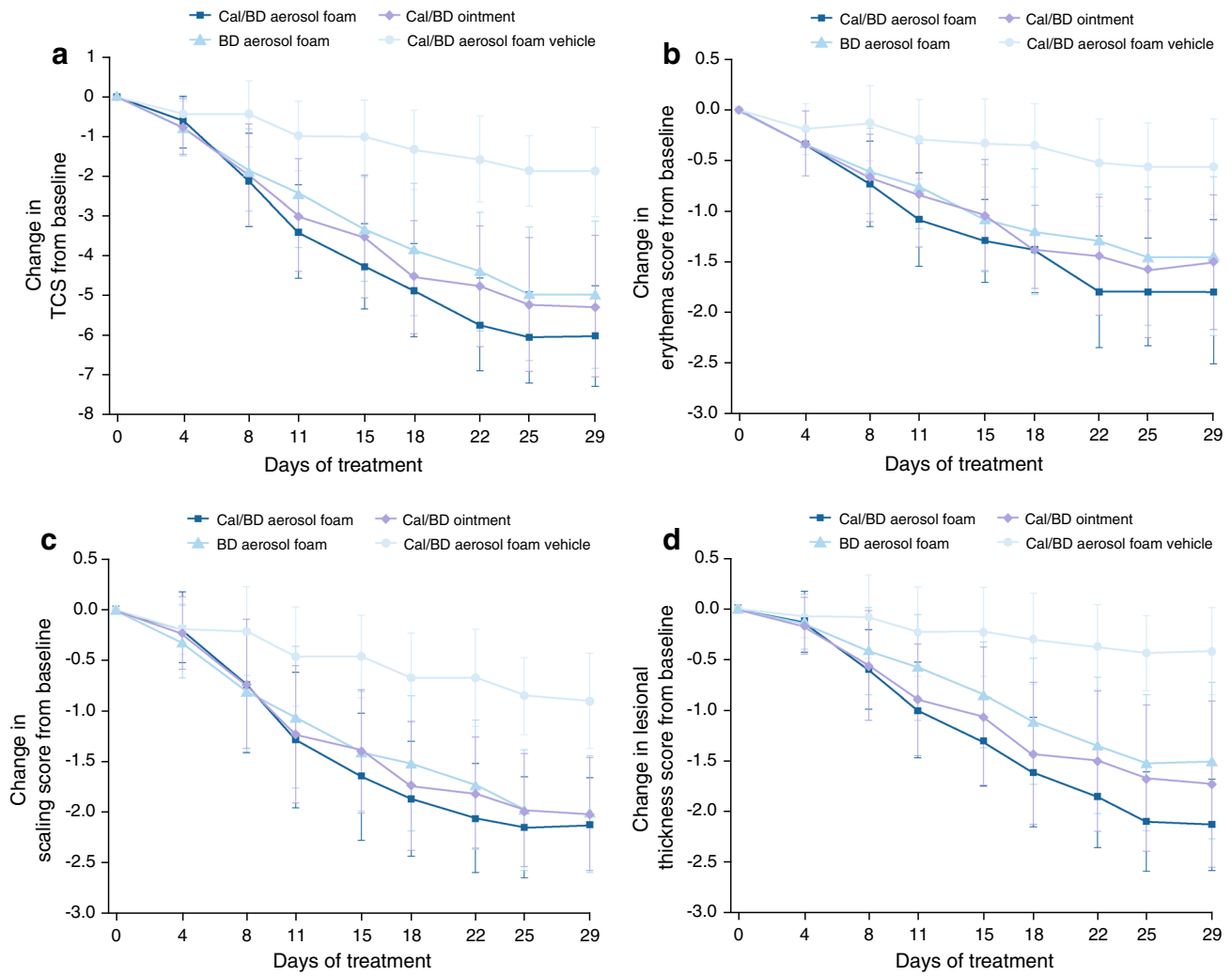

Fig. 1 Change from baseline (mean ± standard deviation) in **a** TCS, and its components **b** erythema, **c** scaling, and **d** lesional thickness, to end of treatment. *BD* betamethasone 0.5 mg/g (as dipropionate), *Cal* calcipotriol 50 μg/g (as hydrate), *TCS* total clinical score

again not significantly so) following treatment with Cal/BD aerosol foam (−0.57 ± 0.21 mm) than with Cal/BD ointment (−0.46 ± 0.21 mm; difference −0.11 mm; 95 % CI −0.22 to 0.00; $p = 0.052$), and was significantly greater compared with BD aerosol foam (−0.45 ± 0.25 mm; difference −0.12 mm; 95 % CI −0.23 to −0.01; $p = 0.037$) and Cal/BD aerosol foam vehicle (−0.12 ± 0.20 mm; difference −0.44 mm; 95 % CI −0.55 to −0.33; $p < 0.001$; Fig. 3).

3.3 Safety and Tolerability

Seventeen AEs were reported by 11 patients during this study, with the most common being headache ($n = 5$) and arthralgia ($n = 3$) (Table 2). There were no reports of serious AEs or ADRs and no withdrawals due to AEs.

4 Discussion

This 4-week exploratory study demonstrated significant improvement in antipsoriatic effect with the novel Cal/BD aerosol foam formulation compared with the Cal/BD ointment formulation, BD aerosol foam and Cal/BD aerosol foam vehicle. The modified version of the psoriasis plaque test employed in this study is a quick, safe, information-rich and relatively low-cost method to evaluate the antipsoriatic effect of psoriasis treatments. It enables intra-individual comparisons and increases the probability of detection of clinically relevant differences despite the relatively short study period and limited sample size [16].

The improved efficacy of other foam preparations over conventional formulations of topical treatments in psoriasis has been demonstrated in several studies. For example,

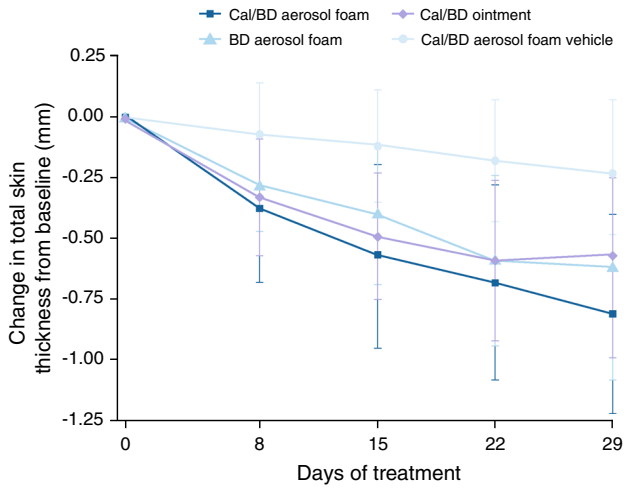

Fig. 2 Change from baseline (mean ± standard deviation) in total skin thickness (assessed by ultrasonographic imagery) to end of treatment. *BD* betamethasone 0.5 mg/g (as dipropionate), *Cal* calcipotriol 50 µg/g (as hydrate)

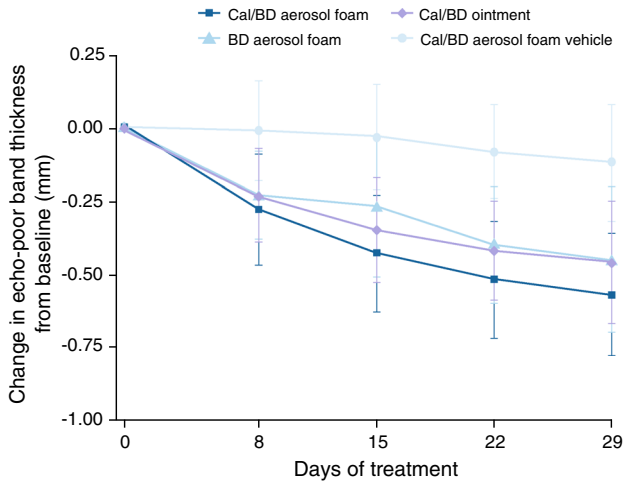

Fig. 3 Change from baseline (mean ± standard deviation) in echo-poor band thickness (assessed by ultrasonography) to end of treatment. *BD* betamethasone 0.5 mg/g (as dipropionate), *Cal* calcipotriol 50 µg/g (as hydrate)

clobetasol propionate in a foam formulation is more effective than the cream and solution formulations in decreasing Psoriasis Area and Severity Index score [17]. Similarly, betamethasone valerate is more effective in improving psoriasis symptoms when delivered as foam versus lotion [18, 19]. In addition to their application advantage, foam vehicles have unique characteristics and properties that can be engineered to enhance topical drug delivery. Foam formulations of clobetasol propionate and betamethasone valerate absorb more rapidly into the skin, with greater total skin absorption than their respective comparison formulations, namely, clobetasol propionate solution and betamethasone valerate lotion

Table 2 Adverse events according to the Medical Dictionary for Regulatory Activities (MedDRA) primary system organ class and preferred term

Adverse event	Patients, *n* (%)[a]
Nervous system disorders	6 (25.0)
Headache	5 (20.8)
Sciatica	1 (4.2)
Musculoskeletal and connective tissue disorders	4 (16.7)
Arthralgia	3 (12.5)
Back pain	1 (4.2)
Gastrointestinal disorders	3 (12.5)
Diarrhoea	1 (4.2)
Toothache	2 (8.3)
Infections and infestations	2 (8.3)
Gastroenteritis	1 (4.2)
Nasopharyngitis	1 (4.2)
Eye disorders	1 (4.2)
Conjunctivitis	1 (4.2)
General disorders and administration site conditions	1 (4.2)
Pyrexia	1 (4.2)

Classification according to MedDRA version 6.1

[a] Patients may have had more than one adverse event

[20]. Furthermore, using an in vitro skin permeation model, Huang et al. showed that foam vehicle delivers more clobetasol propionate than other formulations (solution, cream and lotion) and does so more efficiently [21]. Consistent with these findings, an in vitro study assessing skin penetration of the Cal/BD aerosol foam demonstrated that the levels of diffusion of each active ingredient into a skin model were consistently higher for Cal/BD aerosol foam, with significantly higher steady-state levels of Cal and BD, than Cal/BD ointment [22].

As well as providing a highly effective treatment, optimizing drug delivery to the skin, the vehicle has also been designed to provide a better user experience—to be a more cosmetically acceptable preparation than current formulations. Treatment non-adherence has been recognized as an important and complex issue in disease management [23–25]. For psoriasis treatment, the patient's preference for certain formulations and their perception of the efficacy of their treatment are key factors affecting adherence [26–29]. Psoriasis patients are less willing to adhere to their topical treatment if they find application to be cumbersome and time consuming [26, 27, 30], and comparisons of treatment vehicles have shown that patients prefer more cosmetically elegant formulations, such as foam vehicles, which are convenient and easy to use, thereby minimizing impact on daily life [31, 32].

5 Conclusion

In conclusion, this exploratory study has demonstrated a superior antipsoriatic effect with Cal/BD aerosol foam compared with Cal/BD ointment, BD aerosol foam and Cal/BD aerosol foam vehicle. The aerosol foam formulation may represent a more efficacious and acceptable alternative to well-established, conventional formulations of Cal/BD.

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Conflict of interest CQR and JPL have no conflicts of interest to declare. MO was an employee of LEO Pharma A/S at the time of this study. JV is an employee of LEO Pharma A/S.

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