

SUPPLEMENT ARTICLE

Early efficacy and safety data with fixed-dose combination calcipotriol/betamethasone dipropionate foam attributed to mechanism of absorption and steroid potency

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Abstract Topical therapy is the mainstay of treatment for the majority of patients with psoriasis vulgaris (chronic plaque psoriasis), with combinations of vitamin D analogues and glucocorticoids having been shown to negate many of the negative effects associated with either monocomponent individually. Following the established efficacy of fixed-dose combination calcipotriol (Cal; 50 µg/g) plus betamethasone dipropionate (BD; 0.5 mg/g) ointment and gel formulations, a novel Cal/BD foam formulation was developed. When applied, Cal/BD foam forms a supersaturated solution on the skin, increasing the penetration and bioavailability of Cal and BD. Early data indicate that this results in improved efficacy outcomes versus Cal/BD ointment, without negatively affecting safety outcomes (such as the incidence/severity of side effects or impacted calcium homeostasis or hypothalamic-pituitary-adrenal axis). This article discusses the potency and absorption of fixed-dose combination Cal/BD foam, as well as the positive early efficacy and safety data associated with its utilisation in the treatment of psoriasis vulgaris.

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Conflicts of interest

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Introduction

Psoriasis vulgaris (chronic plaque psoriasis) is a chronic, inflammatory disease that affects approximately 2% of the global population.¹ Typical presentation comprises patches or plaques of inflamed skin covered by white or silvery scales, which are sharply delineated from the surrounding unaffected skin.² In the treatment of psoriasis, guidelines list the use of topical therapy (such as corticosteroids and/or vitamin D analogues) as the mainstay of therapy for the majority of patients with psoriasis.¹ One such available option is the fixed-dose combination of the vitamin D analogue

calcipotriol (Cal; 50 µg/g) and corticosteroid betamethasone dipropionate (BD; 0.5 mg/g), which was initially made available as an ointment formulation, then as a gel equivalent. As is common with combinations of corticosteroids and vitamin D analogues, Cal/BD was shown to result in increased efficacy and decreased side effects versus either monotherapy alone.^{3,4} Following the established efficacy of Cal/BD ointment and gel, a novel aerosol foam was developed to further improve the topical treatment of psoriasis. Here, we present data from early studies investigating Cal/BD cutaneous foam (Enstilar[®]; LEO Pharma, Ballerup, Denmark), including data

on its associated efficacy, mechanism of absorption and steroid potency.

When evaluating steroids, it is important to fully evaluate any safety implications. Due to the chronic nature of psoriasis, patients typically require prolonged treatment, which may lead to an increased risk of pathologic adrenal suppression and systemic side effects.⁵ For example, suppression of the hypothalamic-pituitary-adrenal (HPA) axis, indicated by serum cortisol (s-cortisol) response to an adrenocorticotrophic hormone test, may be of concern. In severe cases, abnormally high levels of s-cortisol due to systemic uptake can lead to Cushing's syndrome, a serious systemic disorder with multiple symptoms including striae, hypertension, osteoporosis, muscle atrophy, weight gain with characteristic build-up of fatty tissue as buffalo hump or moon face and fatigue.^{6–10} The existing gel and ointment formulations of combination Cal/BD have been found to be well tolerated; here, we review the early safety and efficacy data for fixed-dose combination Cal/BD foam.

Efficacy

Although the foam and ointment formulations of Cal/BD contain the same fixed-dose combination (calcipotriol [50 µg/g] and betamethasone dipropionate [0.5 mg/g]), studies comparing the efficacy of the two formulations have found that there are notable differences between them.

An exploratory, single-centre, investigator-blinded, Phase IIa study investigated the antipsoriatic efficacy of Cal/BD foam versus Cal/BD ointment, BD foam and Cal/BD foam vehicle (NCT01347255).⁴ The study comprised intra-individual comparison in which adult patients with stable psoriasis were treated with all study products for 4 weeks ($N = 24$). At Week 4, mean (SD) total clinical score (TCS; sum of erythema, scaling and lesional thickness) was significantly decreased on test sites treated with Cal/BD foam (-6.00 [1.27]) compared with Cal/BD ointment (difference -0.75 ; 95% CI, -1.46 to -0.04 ; $P = 0.038$), BD foam (difference -1.04 ; 95% CI, -1.75 to -0.33 ; $P = 0.005$) or vehicle foam (difference -4.13 ; 95% CI, -4.83 to -3.42 ; $P < 0.001$; Fig. 1). In addition, a continuous improvement in TCS was observed throughout the study, for all active treatments, with the mean decrease in TCS being consistently larger with Cal/BD foam compared with all other treatments (from the second time point [Day 8] to the end of the study). Throughout the study, patients treated with Cal/BD foam experienced consistently greater reductions in total skin thickness and echo-poor band thickness (a measure of superficial dermis inflammation) compared with all other treatments. It was concluded that as Cal/BD foam demonstrated a significant improvement in antipsoriatic effect compared with the other products, and as such, it represented a more efficacious alternative to the current first-line topical treatment options.

Furthermore, a prospective, open-label, randomised study ($N = 36$) found that Cal/BD foam treatment resulted in a

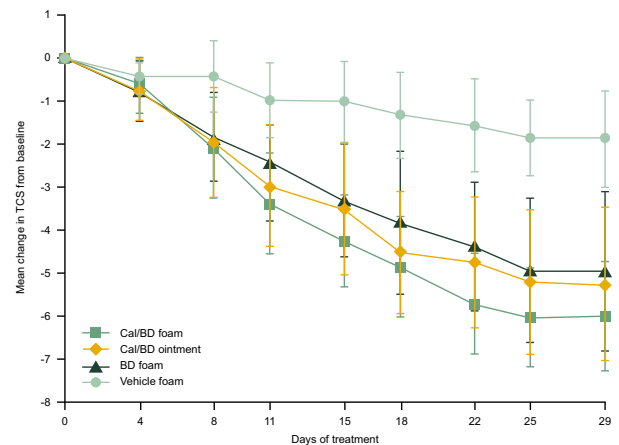


Figure 1 Change in TCS from baseline to study end.⁴ Error bars signify standard deviation. BD, betamethasone dipropionate (0.5 mg/g); Cal, calcipotriol (50 µg/g); TCS, total clinical score. Originally published in Queille-Roussel et al.⁴ Reproduced with kind permission from Springer.

significantly higher number of patients achieving total or almost total lesion clearance (TCS ≤ 1) after 4 weeks compared with clobetasol cream (63.2% vs. 18.8%, respectively; $P = 0.016$).¹¹ In addition, Cal/BD foam induced a faster and greater reduction of epidermal thickness ($P < 0.049$) and patients' treatment satisfaction was higher ($P < 0.03$).

Vasoconstrictor potency of Cal/BD foam

Topical corticosteroids used for the treatment of psoriasis are available in varying potencies, which are classified as ranging from 1–4 ('mild' to 'very potent') in Europe and 1–7 ('super-potent' to 'lowest potency') in the United States.¹² In order to ensure that a treatment is utilised appropriately, the potency of corticosteroids must be known (as excessive exposure to potent corticosteroids may lead to increased risk of adverse events [AEs]).^{12,13} The McKenzie and Stoughton vasoconstriction assay evaluates the initiation of blanching in healthy skin resulting from topical corticosteroid application, whereby increased blanching is directly related to inherent corticosteroid potency.^{12–14}

In two Phase I studies, the pharmacodynamic activity of Cal/BD foam was compared with Cal/BD ointment and other topical corticosteroids, via the assessment of vasoconstrictor potential.^{12,13} The first study (NCT01946386; $N = 35$) compared Cal/BD foam with the following: clobetasol propionate 0.5 mg/g cream (CP; very potent), Cal/BD ointment (potent), fluocinolone acetonide 0.25 mg/g ointment (FA; moderately potent), BD aerosol foam and aerosol vehicle foam.¹² In this study, skin blanching was assessed 6–32 h post-application. Skin blanching with Cal/BD foam was significantly lower than CP cream

($P < 0.001$), similar to BD foam ($P = 0.83$) and significantly greater than Cal/BD ointment ($P = 0.001$) and FA ointment ($P < 0.001$); results in patients treated with vehicle foam were comparable with those receiving no treatment. The second study (NCT02973776; $N = 36$) also compared Cal/BD foam with the very potent CP cream and vehicle foam, as well as with BD ointment (potent), mometasone furoate 1 mg/g cream (MF; potent) and hydrocortisone-17-butyrate 1 mg/g ointment (HB; moderately potent).¹³ Sixteen hours post-application, the products were removed, followed by a visual assessment of skin blanching after a further 2 h (on a scale of 1–4). Similar to the 2016 study, skin blanching with Cal/BD foam was found to be significantly lower than with CP cream ($P < 0.001$) and similar to BD ointment ($P = 0.30$). Blanching with Cal/BD foam was significantly greater than HB ointment and vehicle foam (both $P < 0.001$), while being similar to that achieved with MF cream ($P = 0.22$).

Supersaturation and resulting increased penetration

In order for a topical therapy to be effective, the active ingredient(s) must penetrate the skin effectively, a key factor of which is the concentration of active ingredient dissolved into the vehicle.¹⁵ When a solution contains the maximum concentration of a solute that can be dissolved in a solvent at room temperature, it is referred to as being 'saturated'.¹⁶ Under certain conditions, a supersaturated solution (containing more solute than can be dissolved in the solvent at room temperature) may be prepared. Techniques to create a supersaturated solution include: the addition of excess solute at a high temperature, before rapidly cooling the solution at a faster rate than the solute's precipitation; or combining the solute with a vehicle that rapidly evaporates and allows the drug to exceed its solubility limit in the remaining aqueous phase on the surface of the skin, described in more detail for Cal/BD foam below.¹⁶ After application of foam, the vehicle solvent rapidly evaporates, immediately increasing the concentration of active ingredient on the skin. Furthermore, by virtue of being supersaturated, the increased thermodynamic activity, or transdermal driving force, of the topical agent increases skin penetration of the active ingredients (though this must be stable for clinically relevant time ranges without crystallisation).¹⁷

One study sought to investigate whether the greater efficacy of Cal/BD foam versus Cal/BD ointment was attributable to enhanced bioavailability of the active ingredients due to supersaturation and/or occlusive properties.¹⁷ In the aerosol foam formulation, Cal and BD are dissolved in a mixture of volatile propellants, butane and dimethyl ether (DME). The solubility and evaporation studies showed that the amount of DME in the Cal/BD foam ensures that the active ingredients are fully dissolved in the container, yet a limited amount of DME and butane remain in the foam 2 min post-application (Fig. 2a,b). At this point, the active ingredients may either remain in

solution to become a supersaturated solution or crystallise. Although crystals of Cal and BD were seen immediately after the application of Cal/BD ointment using microscopic imaging, none were seen following the application of the foam formulation up to 18 h after (they were observed after 15 days). Raman imaging found no crystals following foam application within the 26-h timeframe. Measurement of transepidermal water loss (via pig ear skin) found both formulations to have extensive occlusive properties; although Cal/BD ointment was found to be more occlusive than Cal/BD foam, this was not statistically significant.

In addition, the *in vitro* model of skin penetration using full-thickness pig ear skin found that Cal/BD foam administration produced steady-state levels of Cal and BD that were significantly higher versus ointment application ($P < 0.001$ and $P = 0.002$, respectively).^{17,18} The results of the study of bioavailability of Cal and BD in human skin were supportive of increased penetration with the foam versus ointment formulations. Overall, the data from this study showed that a stable, supersaturated solution of the active ingredients is formed with Cal/BD foam application, with minimal crystallisation and increased skin penetration (and therefore increased bioavailability of Cal and BD, compared with the ointment formulation).

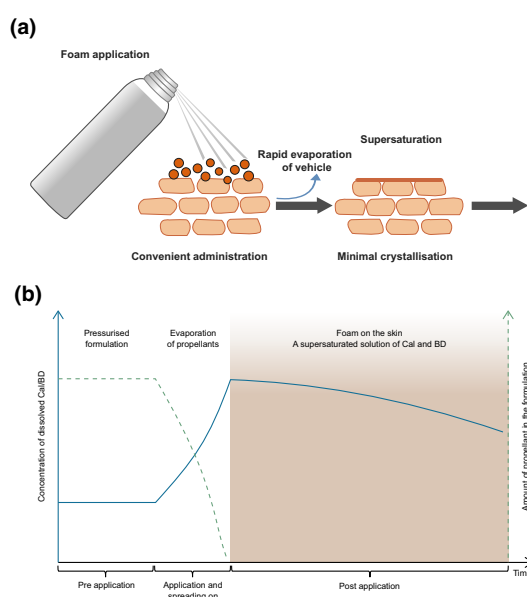


Figure 2 (a) Formation of a supersaturated formulation on the skin following application of Cal/BD foam.²³ (b) Change in concentration of active ingredients dissolved in Cal/BD foam formulation over application time.¹⁷ BD, betamethasone dipropionate (0.5 mg/g); Cal, calcipotriol (50 µg/g). (a) Originally published in Gennari *et al.*²³ Reproduced with kind permission from Eureka Science (FZC) and Bentham Science Publishers, Ltd. (b) Originally published in Lind *et al.*¹⁷. Reproduced with kind permission from Springer.

Increased bioavailability of Cal/BD foam does not result in increased AEs

Although the Cal/BD foam formulation has an increased bioavailability, as a result of the aforementioned supersaturation and increased skin penetration, this has not been found to result in increased AEs or systemic effects. Per the above vasoconstriction studies, Cal/BD foam has a lower topical steroid potency than CP cream, so these findings would suggest that the recommended dose of Cal/BD would not lead to side effects indicative of pathologic adrenal suppression. Furthermore, the combination of Cal and BD in fixed-dose Cal/BD foam has been shown to mitigate some negative effects or risks associated with the relative monocomponents, resulting in the favourable safety profile observed with fixed-dose combination treatment.¹⁹ For example, topical use of glucocorticoids is frequently associated with skin atrophy, resulting from factors such as reduced proliferation of keratinocytes and fibroblasts, as well as decreased production of extracellular matrix (ECM) proteins.²⁰ However, vitamin D receptor agonists (such as Cal) have opposing effects on many of the mechanisms underlying skin atrophy with glucocorticoid treatment. This is supported by the findings of a study in cultured skin cells, which found that Cal reduces early signs of betamethasone-induced skin atrophy via the positive modulation of key ECM components.²⁰

In a Phase I safety study with healthy volunteers ($N = 213$), Cal/BD foam, vehicle foam and white petrolatum (negative control) were randomised to three test sites on the back of each participant.²¹ Each volunteer received five applications of each product per week for 3 weeks (induction phase), followed by one application after a 2-week rest period (challenge phase). Volunteers had low maximal dermal response (MDR); in the induction phase, 79% volunteers had an MDR score of 0 ('no response') or 0.5 ('questionable or faint, indistinct erythema') with Cal/BD foam, compared with 98% for vehicle foam and control. Mean cumulative irritation index scores during the induction phase were low for all treatments (Cal/BD foam, 0.10; vehicle foam, 0.02; control, 0.02), though a comparative analysis of Cal/BD foam versus control showed a significant difference ($P < 0.001$). There was no indication of skin sensitisation, with relatively few AEs and no serious AEs.

One maximal-use systemic-exposure (MUSE) study enrolled adult patients ($N = 37$) with moderate-to-severe, extensive psoriasis who were treated with Cal/BD foam once-daily.²² At Week 4, when the adrenocorticotropic hormone (ACTH) challenge test was carried out, all patients ($n = 35$) who completed the study per protocol exhibited a normal response at both 30 and 60 min following ACTH stimulation. Furthermore, median albumin-corrected serum calcium levels and 24-h urinary calcium levels were within the normal range at baseline and Week 4; and no patients had elevations above the normal range in any calcium homeostasis parameter at Week 4. Treatment with Cal/BD foam also exhibited a favourable

tolerability profile. The results of this study showed no clinically relevant impact on the HPA axis or calcium homeostasis with 4 weeks of treatment.

Conclusion

Fixed-dose Cal/BD has been shown to reduce the potential negative side effects associated with using the respective monotherapies alone, such as betamethasone-induced skin atrophy.²⁰ To further improve upon the positive safety and efficacy data seen with existing formulations of Cal/BD therapy, a novel cutaneous foam formulation of fixed-dose Cal/BD was developed. By achieving a supersaturated state, the aerosol foam formulation of Cal/BD increases the thermodynamic activity of the drug, thus increasing its skin penetration.¹⁷ In spite of the increased penetration of the drug and resulting bioavailability, Cal/BD foam does not result in increased AEs or negative safety outcomes, and thus should be strongly considered when prescribing topicals for the treatment of psoriasis vulgaris.^{21,22}

What does this mean for clinical practice in psoriasis?

- The foam formulation of combination Cal/BD results in a greater treatment efficacy, compared with Cal/BD ointment, with no increased safety concerns. Thus, Cal/BD foam should be strongly considered when prescribing topicals for patients with psoriasis.^{4,21,22}

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