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Efficacy and safety of fixed-dose combination calcipotriol/ betamethasone dipropionate foam for the treatment of psoriasis

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SUPPLEMENT ARTICLE

Efficacy and safety of fixed-dose combination calcipotriol/betamethasone dipropionate foam for the treatment of psoriasis

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Abstract

The fixed-dose combination calcipotriol (Cal; 50 μg/g) plus betamethasone dipropionate (BD; 0.5 mg/g) ointment and gel formulations have well-established efficacy profiles in the treatment of psoriasis vulgaris (chronic plaque psoriasis); this combination has been shown to produce favourable outcomes versus either monotherapy. To improve upon the efficacy and cosmetic acceptability of these treatments Cal/BD foam was developed, demonstrating superior efficacy in Phase II/III studies compared with either of its monocomponents, Cal/BD ointment, Cal/BD gel and various other therapies for the treatment of psoriasis. Multiple outcome measures were evaluated in the clinical studies, including physician's global assessment of disease severity and modified psoriasis area and severity index. Of note, 38–55% of patients across studies achieved a physician's global assessment of 'clear' or 'almost clear' after 4 weeks of Cal/BD treatment. This superior efficacy was not associated with an increased frequency or severity of adverse events, and there was no evidence for dysregulation of the hypothalamic–pituitary–adrenal axis or calcium homeostasis. Overall, Cal/BD foam was efficacious, with a good tolerability profile consistent with established Cal/BD formulations.

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Conflicts of interest

LSG served as a scientific consultant, speaker or clinical study investigator for AbbVie, Arcutis, Galderma, Dermavant, Lilly, LEO Pharma, Novartis, Pfizer, Sun and UCB. CP has been investigator or consultant for Abbvie, Almirall, Astellas, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Galderma, Janssen Cilag, Leo Pharma, Meda, Merck, Novartis, Pfizer, UCB, Pierre Fabre, Regeneron and Sanofi. RR has served as a scientific consultant, speaker or clinical study investigator for AbbVie, Boehringer Ingelheim, Galderma, Janssen-Cilag, Lilly, LEO Pharma, Novartis, Pfizer, TEVA and UCB.

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Introduction

Effective treatment of psoriasis vulgaris (chronic plaque psoriasis) relies on adherence to therapy, which can be attributed to many factors, including cosmetic acceptability of the vehicle, such as its oiliness or stickiness.[1] Although topical treatments have proven clinically effective in the treatment of psoriasis, acceptability and efficacy in real-world use are suboptimal.[2] The fixed-dose combination of calcipotriol (Cal; 50 μg/g) and betamethasone dipropionate (BD; 0.5 mg/g) is available for the treatment of psoriasis in ointment and gel formulations, and more recently a cutaneous foam. The foam formulation of Cal/BD treatment was developed to provide a therapeutic option giving increased skin penetration compared with the ointment formulation while being as cosmetically acceptable as the gel formulation, thus aiming to improve patients' management of their psoriasis.[3]

Fixed-dose combination Cal/BD foam (Enstilar®; LEO Pharma, Ballerup, Denmark) has been investigated alongside monotherapy of its active ingredients (Cal and BD), as well as against Cal/BD ointment, Cal/BD gel and various other treatments for psoriasis, such as medicated plasters containing corticosteroid and in indirect comparisons with systemic treatments (e.g. methotrexate).[2–6] Data from these studies showed that Cal/BD foam provided superior efficacy data compared with many

of the comparative treatments, with high acceptability and local tolerability; here, we present the data from studies examining the efficacy and safety of Cal/BD foam.

Efficacy

Following the promising early efficacy and associated favourable safety results seen in patients treated with Cal/BD foam (discussed in Tada *et al.*[7] of this supplement), further studies were carried out to compare Cal/BD foam with various other psoriasis treatments, including: Cal and BD as monotherapies, Cal/BD ointment, Cal/BD gel, betamethasone 17-valerate 2.25 mg (BV)-medicated plasters and systemic treatments (e.g. methotrexate). Here, we present the efficacy data from key Phase II/III studies evaluating Cal/BD foam (Table 1).

A Phase II study investigated the comparative efficacy of Cal/BD foam compared with its active monotherapies (Cal foam and BD foam; randomised 1 : 1 : 1) in patients with body psoriasis, as well as evaluating the treatment effect on scalp psoriasis (NCT01536938).[3] The study enrolled adult patients ($N = 302$) with psoriasis of at least mild severity [per physician's global assessment of disease severity (PGA)], total psoriatic involvement of the trunk, limbs and scalp of ≤30% body surface area (BSA) and modified Psoriasis Area and Severity Index (mPASI) score of ≥2 on the trunk and/or limbs at baseline.[3] At Week 4, treatment success (PGA 'clear' or 'almost clear' from moderate/severe disease at baseline; 'clear' from mild disease at baseline) was achieved by a significantly greater percentage of patients receiving Cal/BD foam (45.0%) compared with Cal foam (14.9%; $P < 0.001$) and BD foam (30.7%; $P = 0.047$; Fig. 1). In addition, the percentage of patients achieving treatment success of the scalp was significantly greater for those treated with Cal/BD foam compared with Cal foam (53.0% versus 35.6%; $P = 0.021$), though not versus BD foam (47.5%; $P = 0.45$). All groups saw an improvement in mean mPASI score for body psoriasis, with Cal/BD foam resulting in a significant decrease compared with Cal and BD foams (Fig. 2a).

In a Phase II study (NCT01536886), adult patients ($N = 376$) with baseline psoriasis of at least 'mild' severity per PGA (with 2–30% BSA and mPASI ≥2) were randomised (3 : 3 : 1 : 1) to 4 weeks of treatment with Cal/BD foam, Cal/BD ointment, vehicle foam or vehicle ointment.[2] After 4 weeks, a significantly greater percentage of patients achieved treatment success (PGA 'clear' or 'almost clear' with at least a two-step improvement) with Cal/BD foam (54.6%) compared with Cal/BD ointment (43.0%; $P = 0.025$; Figs 1 and 3). A statistically significant difference was also observed in adjusted mean mPASI scores with Cal/BD foam compared with Cal/BD ointment at both Week 1 (−0.7; $P = 0.001$) and Week 4 (−0.6; $P = 0.005$; Fig. 2b). At Week 4, the mean decrease in mPASI was 74.2% with Cal/BD foam compared with 63.2% for Cal/BD ointment.

In the Phase III PSO-FAST study (NCT01866163), adult patients ($N = 426$) with psoriasis of at least 'mild' severity per PGA at baseline (with 2–30% BSA and mPASI ≥2) were randomised 3 : 1 to receive Cal/BD foam or vehicle foam once-daily for 4 weeks.[8] The primary efficacy endpoint, the proportion of patients achieving success ('clear'/'almost clear' according to PGA) at Week 4, was 53.3% for Cal/BD foam compared with 4.8% for vehicle ($P < 0.001$; Fig. 1). Furthermore, significantly lower mean mPASI scores were achieved in patients receiving Cal/BD foam compared with vehicle foam as early as Week 1 (Fig. 2c), corresponding to mean percentage changes from baseline of −38.2% and −19.6% for Cal/BD foam and vehicle foam, respectively. By Week 4, mean percentage changes in mPASI from baseline were −71.9% with Cal/BD foam and −25.8% with vehicle foam ($P < 0.001$); at this timepoint, significantly more patients achieved a ≥75% reduction in mPASI score (mPASI75) with Cal/BD foam than vehicle foam (52.9% vs. 8.2%; $P < 0.001$). A sub-analysis of the PSO-FAST study found that treatment success and mPASI75 rates were generally similar when stratified according to body mass index and body weight.[9] Furthermore, the total amount of Cal/BD foam used at Week 4 was greater in patients with higher baseline BSA, PGA and mPASI, indicating that patients used an appropriate amount of treatment for the extent and severity of their disease.

The Phase III study, PSO-ABLE, was designed to compare the efficacy and safety of Cal/BD foam with Cal/BD gel (NCT02132936).[4] Adult patients with mild-to-severe psoriasis were randomised ($N = 463$; BSA 2–30%, mPASI ≥2; 4 : 4 : 1 : 1) to once-daily Cal/BD foam, Cal/BD gel, vehicle foam or vehicle gel. Treatment success, again defined as PGA 'clear' or 'almost clear' with at least a two-step improvement (at Week 4 for Cal/BD foam, Week 8 for Cal/BD gel), was achieved by significantly more patients receiving Cal/BD foam compared with Cal/BD gel (38.3% vs. 22.5%; $P < 0.001$; Figs 1 and 4). In addition, a significantly higher percentage of patients achieved mPASI75 with Cal/BD foam at Week 4, compared with Cal/BD gel at Week 8 (52.1% versus 34.6%; $P < 0.001$). At these timepoints, mPASI90 (≥90% reduction in mPASI score) was also achieved by a significantly higher percentage of patients treated with Cal/BD foam versus gel (22.2% vs. 10.7%; $P = 0.009$).

A sub-analysis of the PSO-ABLE study, comprising only patients with moderate-to-severe psoriasis (BSA ≥10%, or mPASI >10 or Dermatology Life-Quality Index >10; $n = 77$ for Cal/BD foam and $n = 82$ for Cal/BD gel) found that a significantly greater proportion achieved mPASI75 and mPASI90 with Cal/BD foam than gel at Weeks 4, 8 and 12 (except for mPASI90 at Week 12, which was numerically greater; Fig. 5a,b).[10] Furthermore, treatment success rates were significantly higher with Cal/BD foam compared with Cal/BD gel at Weeks 1, 2, 4 and 8 (Fig. 5c). The results of this sub-analysis show that the significantly greater efficacy of Cal/BD foam compared with Cal/BD gel demonstrated in the overall population was also maintained for up to 12 weeks in patients with more severe disease.[4,10]

Table 1 Summary of study characteristics and data

Study	Reference	Number of patients	Patient population	Treatments	Efficacy	Safety
Efficacy of Cal/BD foam vs. its monocomponents (NCT01536938)	Lebwohl *et al.*[3]	302	Adults At least 'mild' disease BSA ≤30% (trunk, limbs and scalp) mPASI ≥2 (trunk and/or limbs)	Randomised 1 : 1 : 1 to once-daily: Cal/BD foam, Cal foam, BD foam	Week 4: 45.0% patients receiving Cal/BD foam achieved treatment success, vs. 14.9% for Cal foam ($P < 0.001$) and 30.7% for BD foam ($P = 0.047$) Significantly more treatment success of the scalp with Cal/BD foam vs. Cal foam ($P = 0.021$), though not BD foam ($P = 0.45$) Mean mPASI improvement significantly greater with Cal/BD foam vs. Cal foam ($P < 0.001$) and BD foam ($P < 0.001$)	Incidence of patients experiencing AEs was low and similar between groups, at 11%, 10.1% and 13.1% for Cal/BD foam, Cal foam and BD foam Week 4: Cal/BD foam had a minimal impact on calcium homeostasis parameters
Efficacy and safety of Cal/BD foam vs. Cal/BD ointment (NCT01536886)	Koo *et al.*[2]	376	Adults At least 'mild' disease BSA 2–30% mPASI ≥2	Randomised 3 : 3 : 1 : 1 to once-daily: Cal/BD foam, Cal/BD ointment, foam vehicle, ointment vehicle	Week 4: 54.6% patients achieved treatment success with Cal/BD foam vs. 43.0% ($P = 0.025$) with Cal/BD ointment Significant difference in mean mPASI scores with foam vs. ointment at Week 1 (−0.7; $P = 0.001$) and at Week 4 (−0.6; $P = 0.005$)	Incidence of AEs was low and similar between Cal/BD foam (11.3%) and Cal/BD ointment (10.4%) Most AEs were mild, no serious treatment-related AEs No clinically relevant changes in calcium homeostasis parameters
PSO-FAST: Efficacy and safety of Cal/BD foam vs. vehicle (NCT0186613)	Leonardi *et al.*[8]	426	Adults At least 'mild' disease BSA 2–30% mPASI ≥3	Randomised 3 : 1 to once-daily Cal/BD foam and foam vehicle	Week 4: Treatment success in 53.3% of Cal/BD foam group vs. 4.8% in vehicle group ($P < 0.001$) Mean decrease in mPASI significantly greater with Cal/BD vs. vehicle ($P < 0.001$)	78 AEs reported in total, incidence of AEs and ADRs in patients receiving Cal/BD was low (15.8 and 3.1%, respectively) No clinically relevant changes in calcium homeostasis parameters
PSO-FAST subgroup analysis: Efficacy and safety of Cal/BD foam vs. vehicle relative to BMI and extent/severity of disease (Sub-analysis of NCT0186613)	Stein-Gold *et al.*[9]	As described in Leonardi, *et al.* 2015	As described in Leonardi, *et al.* 2015	As described in Leonardi, *et al.* 2015	Week 4: Treatment success and mPASI75 rates were generally similar when stratified according to BMI and body weight	Amount of Cal/BD foam and vehicle used were similar (120.8 g vs. 128.9 g, respectively) Amount of Cal/BD used was greater with increased BSA and disease severity

Table 1 *Continued*

Study	Reference	Number of patients	Patient population	Treatments	Efficacy	Safety
PSO-ABLE: Efficacy and safety of Cal/BD foam vs. Cal/BD gel (NCT02132936)	Paul *et al.*[4]	463	Adults Mild-to-moderate disease BSA 2–30% mPASI ≥2	Randomised 4 : 4 : 1 : 1 to once-daily: Cal/BD foam, Cal/BD gel, foam vehicle, gel vehicle	Treatment success for foam (Week 4) vs. gel (Week 8) was achieved by 38.3% vs. 22.5% ($P < 0.001$) mPASI75 with foam (Week 4) vs. gel (Week 8) was achieved by 52.1% vs. 34.6% ($P < 0.001$) mPASI90 with foam (Week 4) vs. gel (Week 8) was achieved by 22.2% vs. 10.7% ($P = 0.009$)	Most AEs were mild or moderate AEs reported in similar proportion of patients in each group over 12 weeks (41.6% with foam vs. 45.2% with gel) No clinically relevant changes in calcium homeostasis parameters
PSO-ABLE subgroup analysis: Efficacy of Cal/BD foam vs. Cal/BD gel in patients with moderate-to-severe psoriasis (Sub-analysis of NCT02132936)	Paul *et al.*[10]	159	BSA ≥10%, or mPASI >10 or Dermatology Life-Quality Index >10	Subgroup from PSO-ABLE with moderate-to-severe disease ($n = 77$ for Cal/BD foam, $n = 82$ for Cal/BD gel)	Greater proportion achieved mPASI75 and mPASI90 with Cal/BD foam than gel at Weeks 4, 8, and 12 Treatment success rates were higher with the Cal/BD foam vs. gel at Weeks 1, 2, 4 and 8 ($P < 0.009$)	
Safety of Cal/BD foam in adolescent patients, including a cohort of patients with more severe disease (NCT02387853)	Seyger *et al.*[11]	106	Adolescents (12 to <17 years) At least 'mild' disease (HPA axis cohort comprised patients with more severe disease: at least 'moderate') BSA 2–30%	Once-daily Cal/BD foam	Week 4: 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% from baseline to Week 4	32 treatment-emergent AEs occurred in 22 patients (20.8%), all but two of which were mild in severity and none led to study withdrawal or death No evidence for dysregulation of the HPA axis or calcium homeostasis in HPA cohort
Safety and efficacy of adding Cal/BD treatment to biologic therapy regimens to achieve treat-to-target goals (NCT03080545)	Bagel *et al.*[12]	25	Patients with psoriasis who had received ≥24 weeks of biologic agents ≤5% BSA	Once-daily Cal/BD foam	Week 4: Cal/BD foam significantly improved PGA score ($P < 0.01$) and BSA involvement ($P < 0.01$) from baseline Week 4: 28% patients achieved total clearance of plaque psoriasis	Nine AEs in 6 patients, no treatment-related AEs and none were serious

Table 1 *Continued*

Study	Reference	Number of patients	Patient population	Treatments	Efficacy	Safety
Efficacy of Cal/BD foam vs. apremilast, methotrexate, acitretin or FAE	Bewley *et al.*[5]	1271	Patients with psoriasis Baseline characteristics were matched between studies in the study selection process	Once-daily Cal/BD foam for 4 weeks ($N = 749$) Twice-daily apremilast for 16 weeks ($N = 148$) Mean 12 mg/wk methotrexate for 12 weeks ($N = 218$) Mean 25 mg/day acitretin for 12 weeks ($N = 41$) 30 mg FAE for 12 weeks ($N = 115$)	Compared with apremilast, Cal/BD foam significantly improved PGA 0/1 response and PASI75 response (both $P < 0.001$) Compared with methotrexate and acitretin, Cal/BD treatment significantly improved PASI75 results ($P < 0.001$ and $P = 0.009$, respectively Response to FAE was comparable, $P = 0.452$)	
Efficacy and safety of Cal/BD foam vs. BETESIL® plasters (NCT02518048)	Queille-Roussel *et al.*[6]	35	Adults with sufficient plaques for testing	All patients received: Cal/BD foam or betamethasone 17-valerate 2.25 mg medicated plasters	Week 4: Change in total clinical score significantly greater with Cal/BD foam ($P < 0.001$) Week 4: Absolute total skin and echo-poor band thickness change were also significantly greater with Cal/BD foam (both $P < 0.001$)	

ADR, adverse drug reaction; AE, adverse events; BD, betamethasone dipropionate; BMI, body mass index; BSA, body surface area; Cal, calcipotriol; FAE, fumaric acid esters; HPA, hypothalamic-pituitary-adrenal; mPASI, modified Psoriasis Area and Severity Index; PGA, physician's global assessment.

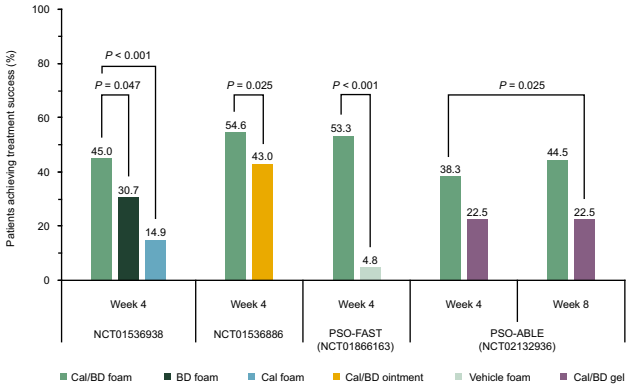

Figure 1 Percentage of patients achieving PGA treatment success in studies NCT01536938,[3] NCT01536886,[2] PSO-FAST (NCT01866163)[8] and PSO-ABLE (NCT02132936).[4] Treatment success defined as investigator assessment by PGA as 'clear' or 'almost clear' with at least a two-step improvement. In PSO-ABLE (NCT02132936), treatment success was assessed at Week 4 for Cal/BD foam and Week 8 for Cal/BD gel. BD, betamethasone dipropionate (0.5 mg/g); Cal, calcipotriol (50 μg/g); PGA, physician's global assessment.

A 4-week open-label study assessed Cal/BD foam in adolescent patients (N = 106) with psoriasis (NCT02387853; trunk/limbs ≥2% BSA, scalp ≥10% BSA and total BSA ≤30%); efficacy endpoints were exploratory and assessed after 4 weeks of treatment.[11] In the overall study population, 71.8% and 75.7% patients achieved body and scalp treatment success (defined as 'clear'/'almost clear' for patients with baseline moderate psoriasis, and 'clear' for those with mild), respectively. Patients with more severe disease experienced a greater rate of treatment success compared with the rest of the patient population (body: 93.9% vs. 78.6%; scalp: 97.0% vs. 74.3%).

Treatment with Cal/BD foam has also been shown to be a potential addition to stable biologic treatment regimens in cases where treat-to-target goals are not achieved.[12] In a prospective, open-label study (NCT03080545), 25 patients with ≤5% BSA who had received ≥24 weeks of biologic agents were administered once-daily Cal/BD foam for 4 weeks, followed by twice-weekly use on consecutive days for 12 weeks (maintenance regimen). Compared with baseline, adjunctive therapy with Cal/BD foam significantly improved PGA score (median scores of 3 at baseline and 1 at Weeks 4 and 16; P < 0.01) and BSA involvement (median of 3% at baseline and 1% at Weeks 4 and 16;

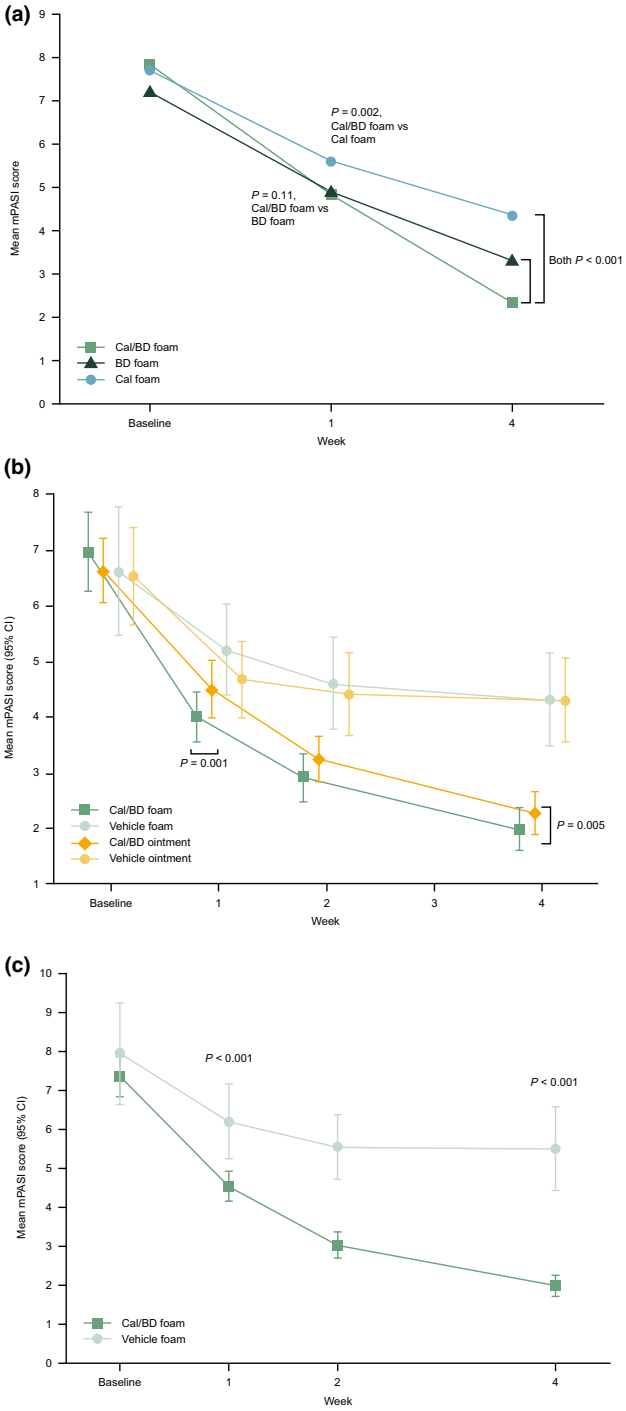

Figure 2 Mean mPASI scores over time in studies (a) NCT01536938,[3] (b) NCT01536886[2] and (c) PSO-FAST (NCT01866163).[8] Missing values were imputed using last observation carried forward (a and b) or multiple imputation (c); P values were determined by ANCOVA, adjusting for pooled centre and baseline mPASI. ANCOVA, analysis of covariance; BD, betamethasone dipropionate (0.5 mg/g); Cal, calcipotriol (50 μg/g); mPASI, modified Psoriasis Area and Severity Index. (a) Originally published in Lebwohl *et al*.[3] Reproduced with kind permission from Matrix Medical Communications. (b) Originally published in Koo *et al*.[2] Reproduced with kind permission from Taylor & Francis. (c) Originally published in Leonardi *et al*.[8] Reproduced with kind permission from Journal of Drugs in Dermatology.

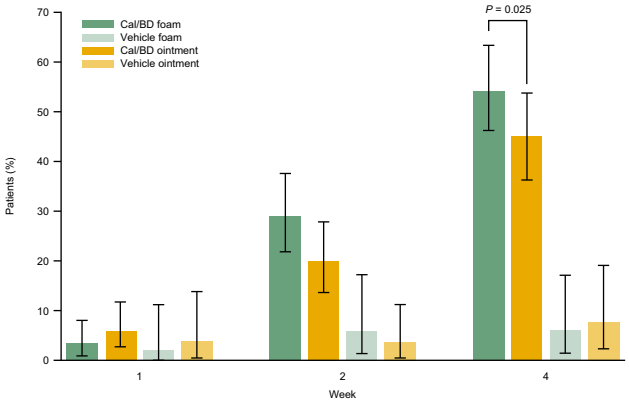

Figure 3 Proportion of patients in study NCT01536886 achieving PGA treatment success over time with Cal/BD foam compared with ointment formulations.[2] Treatment success defined as investigator assessment by PGA as 'clear' or 'almost clear' with at least a two-step improvement. Bars show 95% confidence interval. BD, betamethasone dipropionate (0.5 mg/g); Cal, calcipotriol (50 μg/g); PGA, physician's global assessment. Originally published in Koo *et al*.[2] Reproduced with kind permission from Taylor & Francis.

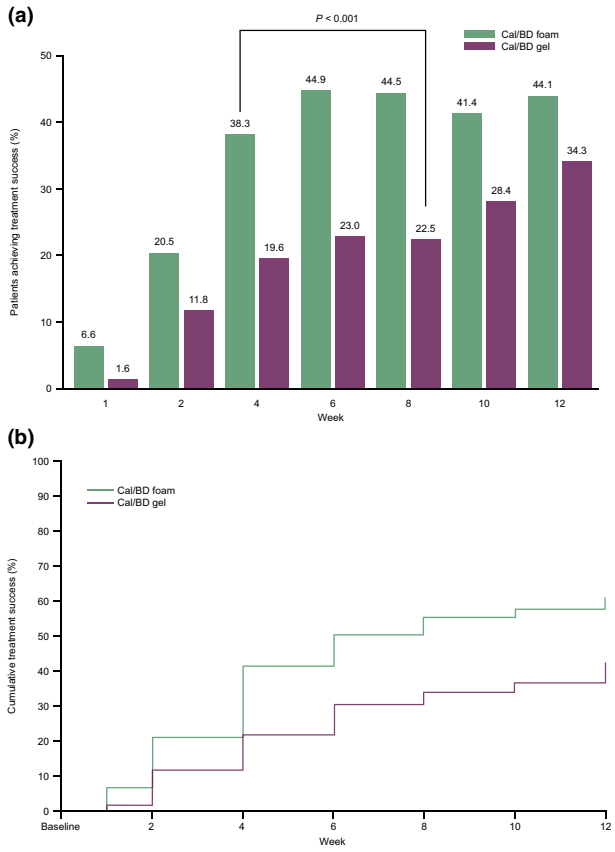

Figure 4 (a) Proportion of patients in PSO-ABLE achieving PGA treatment success rates by visit (multiple imputation); (b) Time to treatment success, according to PGA (observed cases), in Cal/BD foam and gel groups.[4] BD, betamethasone dipropionate (0.5 mg/g); Cal, calcipotriol (50 μg/g); PGA, physician's global assessment. Originally published in Paul *et al*.[4] Reproduced with kind permission from John Wiley & Sons Ltd.

$P < 0.01$). Compared with biologic monotherapy, significantly more patients receiving Cal/BD foam achieved treat-to-target criteria of PGA ≤1 at Week 4 (76% vs. 4%; $P < 0.001$) and Week 16 (68% vs. 4%; $P < 0.001$). Furthermore, 28% of patients receiving adjunctive therapy achieved total clearance of plaque psoriasis (no BSA involvement and a PGA score of 0) by Week 4.

Although few head-to-head studies have been conducted between Cal/BD foam and other products, individual data from four studies in 749 patients with psoriasis were pooled to conduct matching-adjusted indirect comparisons of Cal/BD foam efficacy with that of non-biologic systemic treatments.[13–16] Four studies of apremilast, methotrexate, acitretin or fumaric acid esters (FAE) were included based on matched/aligned patient population characteristics and similarities in methods and reported outcome measures.[5] This analysis found that significantly greater response rates were achieved following 4 weeks of Cal/BD foam treatment compared with 16 weeks of apremilast, in both PGA 0/1 (52.7% vs. 30.4%; $P < 0.001$) and PASI75 (51.1% vs. 21.6%; $P < 0.001$). Similarly, a significantly greater percentage of patients receiving Cal/BD foam achieved PASI75 at Week 4 compared with those receiving 12 weeks of treatment with methotrexate (50.8% vs. 33.5%; $P < 0.001$) or acitretin (50.9% vs. 31.7%; $P = 0.003$); a comparable response was achieved with FAE (42.4% vs. 47.0%; $P = 0.452$). Although this analysis involved an indirect comparison, it is suggestive of a higher efficacy for a 4-week flare treatment with Cal/BD foam compared with apremilast and methotrexate.

In instances where a patient presents with localised plaques in difficult-to-treat (DTT) areas, BV-medicated plasters may be used (subject to local guidelines). One 4-week, Phase IIa study investigated the comparative safety and efficacy of BV-medicated plasters versus Cal/BD foam in adult patients ($N = 35$) with psoriasis (NCT02518048), when applied once-daily to six test sites; both treatments were well tolerated.[6] At all visits after Day 4, the change in total clinical score was greater at sites treated with Cal/BD foam compared with BV-medicated plasters, from baseline to the end of treatment (Fig. 6). The thickness of the echo-poor band (EPB), a band in the upper dermis that is hypoecogenic (when measured with sonography) in patients with psoriasis, is a reflection of the thickness of the papillary dermis, as well as the degree of vascularity, oedema and inflammation; therefore, EPB thickness correlates with the clinical severity of a psoriasis plaque.[17] In areas treated with Cal/BD foam versus BV-medicated plasters, greater mean reductions from baseline to end of treatment were seen in ultrasound measurements of both EPB

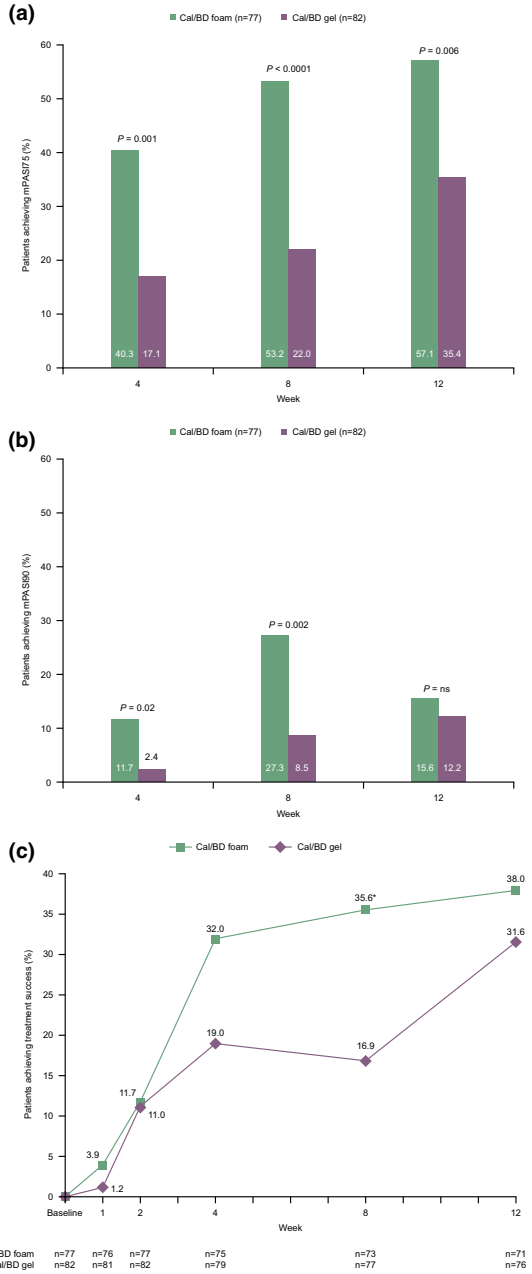

Figure 5 Proportion of patients in PSO-ABLE with moderate-to-severe psoriasis achieving (a) mPASI75 (b) mPASI90 and (c) treatment success over time.[10] Missing values were imputed using last observation carried forward (a and b) or observed case (c) methods. *P* values based on the chi-square test. BD, betamethasone dipropionate (0.5 mg/g); Cal, calcipotriol (50 μg/g); mPASI modified Psoriasis Area and Severity Index; ns not significant. Originally published in Paul *et al.*[10] http://creativecommons.org/licenses/by-nc/4.0/. Minor changes made to colour and layout. Reproduced with kind permission from John Wiley & Sons Ltd.

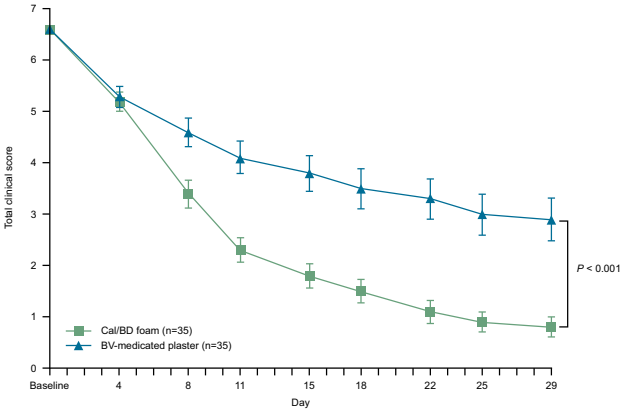

Figure 6 Mean total clinical score over time in study NCT02518048.[6] Missing values were imputed using last observation carried forward. *P* value calculated for mean change in total clinical score from baseline to end of treatment for Cal/BD aerosol foam vs. BV-medicated plaster. BV, betamethasone 17-valerate 2.25 mg; BD, betamethasone dipropionate (0.5 mg/g); Cal, calcipotriol (50 μg/g). Originally published in Quielle-Roussel *et al.*[6] http://creativecommons.org/licenses/by-nc/4.0/. Minor changes made to colour and layout. Reproduced with kind permission from John Wiley & Sons Ltd.

thickness (−1.3 mm vs. −0.7 mm; $P < 0.001$) and total skin thickness (−1.0 mm vs. −0.6 mm; $P < 0.001$). Furthermore, *post hoc* analyses demonstrated that Cal/BD foam was associated with significantly greater improvements in total clinical score in DTT areas compared with BV-medicated plasters (mean change from baseline to Week 4; −5.5 vs. −3.4; $P < 0.001$). In areas where BV-medicated plasters are indicated for psoriasis in DTT areas, Cal/BD foam would seem to be a suitable alternative.

Safety

Here, we summarise the safety data for Cal/BD foam, as well as that of other formulations of this combination and comparative treatments.

In a Phase II study by Lebwohl *et al.*,[3] in which the safety of Cal/BD foam was compared with its active ingredients as monotherapies, the overall incidence of patients experiencing adverse events (AEs) was found to be similar between treatment groups [Cal/BD foam: 11 (11.0%); Cal foam: 10 (10.1%); BD foam: 13 (13.1%)]. The most frequently reported AEs were medication residue (two patients receiving Cal foam and three patients receiving BD foam) and application-site pain (one patient in each treatment group). The majority of AEs were mild or moderate in intensity; two patients receiving Cal/BD foam and two receiving Cal foam experienced AEs leading to discontinuation [severe hypersensitivity (possibly related to drug) and irregular menstruation in the Cal/BD group; medication residue and contact dermatitis events (both probably

related to drug) in the Cal foam group]. No study treatment had a clinically significant impact on calcium homeostasis parameters; at Week 4, all three groups showed non-clinically significant changes from baseline in albumin-corrected serum calcium, urinary calcium : creatinine ratios and vital signs. Therefore, all three treatments exhibited favourable safety profiles and that the AE profile of Cal/BD foam was consistent with existing data from each individual active ingredient.

In another Phase II study (Koo *et al.*), a cohort of adult patients ($N = 376$) was randomised to receive Cal/BD foam, Cal/BD ointment, vehicle foam or vehicle ointment; the incidence of AEs was similar between groups receiving active treatments.[2] In total, 20 AEs were reported by 16 patients (11.3%) receiving Cal/BD aerosol foam; 23 AEs were reported by 14 patients (10.4%) using Cal/BD ointment; two AEs were reported by one patient (2.0%) using vehicle foam and two AEs were reported by two patients (3.9%) using vehicle ointment. All AEs were single events except nasopharyngitis (not considered treatment-related) and itch (treatment-related), which were each reported by two patients using Cal/BD ointment. Most events were mild; adverse drug reactions (ADRs) were reported in one patient receiving Cal/BD foam (application-site itch, one event) and four patients receiving Cal/BD ointment (application-site dryness, one event; application-site pain, one event and two incidences of itch). Three serious AEs were reported in two patients treated with Cal/BD ointment (bile duct stone, bronchitis and hypertension); however, these were not considered to be related to treatment. There were no clinically relevant changes in mean albumin-corrected serum calcium or spot urinary calcium : creatinine ratio, suggesting that effects on calcium homeostasis with Cal/BD foam are minimal despite improved efficacy with its formulation.

In the Phase III PSO-FAST study ($N = 426$), the incidence of AEs was found to be similar between adult patient groups receiving Cal/BD foam and vehicle foam, with 78 AEs reported overall [Cal/BD foam: 51 (15.8%); vehicle foam: 12 (11.7%)].[8] The most frequently reported AEs were nasopharyngitis [Cal/BD foam: six (1.9%)] and application-site pain [Cal/BD foam: three (0.9%); vehicle foam: two (1.9%)]. Most AEs were mild or moderate in severity, and the incidence of ADRs was low (Cal/BD foam: 3.1%; vehicle foam: 1.9%). Two serious AEs were reported in patients receiving Cal/BD foam (bipolar disorder and substance-induced psychotic disorder). Again, no clinically significant changes in mean albumin-corrected serum calcium or urinary calcium : creatinine ratio were seen in either treatment group in this study. The sub-analysis of the PSO-FAST study found that the total amount of Cal/BD foam and vehicle foam used were similar (120.8 g vs. 128.9 g, respectively), suggesting good adherence to active treatment.[9] The total amount of active treatment and vehicle foam used at Week 4 was greater with increasing BSA and increasing severity of baseline PGA and mPASI, which indicates that patients used an appropriate amount for the extent/severity of their disease.

When comparing Cal/BD foam and gel formulations, the PSO-ABLE study found that most AEs were mild or moderate and were reported in a similar percentage of patients in each group over the 12-week treatment period [77 (41.6%) vs. 85 (45.2%), respectively].[4] The most frequently reported AEs overall were upper respiratory tract infection [Cal/BD foam: five (2.7%) Cal/BD gel: nine (4.8%); vehicle foam: one (2.1%); vehicle gel: two (4.7%)], nasopharyngitis [Cal/BD foam: seven (3.8%); Cal/BD gel: four (2.1%); vehicle gel: two (4.7%)] and vitamin D deficiency [Cal/BD foam: six (3.2%); Cal/BD gel: five (2.7%); vehicle gel: two (4.7%)]. Serious AEs were reported in four patients (2.2%) receiving Cal/BD foam [congestive heart failure, gastro-oesophageal reflux, prostate cancer, exacerbation of psoriasis (considered to be treatment-related)] and three (1.6%) receiving Cal/BD gel (postprocedural haemorrhage, type 2 diabetes mellitus and ischaemic stroke). ADRs were reported in 14 (7.6%) patients receiving Cal/BD foam and seven (3.7%) receiving Cal/BD gel. Four patients (2.2%) in the Cal/BD foam group and three (1.6%) in the Cal/BD gel group experienced serious AEs; one serious AE was considered related to the treatment (Cal/BD foam group, exacerbation of psoriasis after 69 days of treatment). As with the previous studies, no clinically significant changes in mean albumin-corrected serum calcium or spot urinary calcium : creatinine ratio were observed.

Consistent with results in adult populations, Seyger *et al.*[11] also found Cal/BD foam to be generally well tolerated in adolescent patients. As well as the overall cohort of adolescent patients who had psoriasis of at least mild severity ($N = 106$), outcomes in a subset of patients with more severe disease ($n = 33$) were also investigated. Over 4 weeks of treatment with Cal/BD foam, 32 treatment-emergent AEs occurred in 22 patients (20.8%), all but two of which were mild in severity (no treatment-emergent AEs were serious or severe) and none led to study withdrawal or death. The most frequently reported AEs were upper respiratory tract infection [eight (7.5%)], nasopharyngitis [four (3.8%)] and acne [two (1.9%)]. There was no evidence for dysregulation of the HPA axis or calcium homeostasis in patients with more severe disease.

When Cal/BD foam was employed as adjunctive treatment to stable biologic regimens in a study by Bagel *et al.*,[12] it was found to be generally well tolerated. A total of six patients reported nine AEs, none of which were treatment-related or serious; all AEs were of grade I severity except one bone fracture and one renal haematoma (grade II). These results are supportive of using Cal/BD foam in patients who have significant disease activity and have not reached treat-to-target goals, despite being on stable biologic therapy for more than 24 weeks.

Conclusion

In adult patients with psoriasis vulgaris, fixed-dose combination Cal/BD is effective and has a favourable safety profile, with Cal/

BD foam leading to significant improvements in treatment success compared with its monocomponents, Cal/BD ointment or Cal/BD gel.[2–4] This is mirrored in results seen in adolescent patients, in whom the proportion achieving treatment success was also high.[11] Furthermore, Cal/BD foam is a suitable adjunctive therapy in instances where patients have not reached the treat-to-target goals while on stable biologic therapy, providing an attractive alternative to the escalation or switching of biologic therapy used.[12] The increased efficacy of Cal/BD foam compared with the various treatment options outlined here was not associated with increases in AEs or their severity; in addition, there was no evidence for dysregulation of the HPA axis or calcium homeostasis. Overall, Cal/BD foam was highly efficacious while maintaining the favourable tolerability profile of established Cal/BD formulations.

What does this mean for clinical practice in psoriasis?

- Cal/BD foam is an effective treatment option for patients with psoriasis vulgaris.[2–4,8]
- Cal/BD foam is also effective in patients with more severe disease.[9]
- Treatment with Cal/BD foam also has a good safety profile, comparable with other Cal/BD formulations.[2–4,8]
- Cal/BD foam has shown effect as adjunctive therapy to stable biologic treatment regimens providing a suitable option to avoid switching biologic treatment.[12]

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