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Vehicles Matter: Calcipotriene And Betamethasone Dipropionate Foam As A Topical Psoriasis Therapy

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VEHICLES MATTER

Leon Kircik MD

Icahn School of Medicine at Mount Sinai, New York, NY
Physicians Skin Care, PLLC, Louisville, KY
DermResearch, PLLC, Louisville, KY
Skin Sciences, PLLC, Louisville, KY

It has been known for decades that the sequential topical use of the vitamin D_3 analog calcipotriene (Cal) and the corticosteroid betamethasone dipropionate (BD) has been shown to provide greater benefit than either monotherapy.[1-3] However, early on, the use of this combination was associated with patient inconvenience. More importantly, chemical instability of these two molecules when applied one after another makes calcipotriene not compatible with topical corticosteroids; therefore, patients had to apply the medications at different times.[4]

Innovation in formulation science allowed for the development of fixed combination topical formulations of Cal/BD for improved patient convenience and, presumably, adherence. Calcipotriene and betamethasone dipropionate aerosol foam 0.005%/0.064% is one of the more recent formulations to reach the market.

Recent findings are adding to our understanding of the clinical benefits of topical Cal/BD foam for psoriasis. An analysis of various topical therapies for psoriasis found that all assessed therapies reduced epidermal thickness and improved targeted Psoriasis Area and Severity Index (PASI) scores. However, Cal/BD foam was the only treatment shown to completely suppress CD8+ T-cell influx in the epidermis and dermis and to reduce CD8 + IFN-γ+ cell counts, and significantly reduce the number of IL-17 expressing, MPO+ neutrophils.[5] Microscopic evaluations showed that, compared to corticosteroid alone, Cal/BD foam was associated with significantly greater reductions in microscopic epidermal thickness by week 4, and there were fewer telangiectasias in combination-treated lesions than clobetasol-treated lesions.[6]

Vehicles matter, and in the case of Cal/BD foam, which showed superior efficacy to the ointment and topical suspension in head-to-head studies, the unique aerosol foam formulation is associated with clinical benefits, as described above and in the pages ahead, as well as practical benefits, such as increased adherence.[7] The versatility of the topical formulation has been demonstrated across patient groups, including in skin of color, for specific presentations, such as palmoplantar psoriasis, and in combination with systemic therapies, such as apremilast.[8-10]

Whether used alone for mild-to-moderate-to-severe psoriasis or as an adjunct to systemic treatment for moderate-to-severe disease, Cal/BD foam represents a formulation advancement that may benefit a number of patients in the dermatology clinic.

Remember, "vehicles matter!"

DISCLOSURE

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ORIGINAL ARTICLE

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Real-World Evidence on the Use of Calcipotriene and Betamethasone Dipropionate Aerosol Foam 0.005%/0.064% in the Treatment of Psoriasis: A Review of Investigator-Initiated Studies Around the Globe

Kathryn Lee BA,[a] Leon Kircik MD,[b] April W. Armstrong MD MPH[c]

[a]Saint Louis University School of Medicine, Saint Louis, MO

[b]Icahn School of Medicine at Mount Sinai, New York, NY; Physicians Skin Care, PLLC Louisville, KY; DermResearch, PLLC Louisville, KY; Skin Sciences, PLLC Louisville, KY

[c]Department of Dermatology, Keck School of Medicine, University of Southern California, Los Angeles, CA

ABSTRACT

Topical medications are commonly used to manage mild-to-moderate psoriasis and serve as adjunct therapies used in combination with phototherapy and systemic treatments. Fixed-dose calcipotriene (Cal) 0.005%/betamethasone dipropionate (BD) 0.064% aerosol foam is a safe, efficacious topical therapy approved for the treatment of psoriasis vulgaris in the United States and European Union. Several investigator-initiated studies (IISs) have been conducted to provide real-world evidence related to the safety, effectiveness, and therapeutic indications of Cal/BD foam and are relevant to clinicians' every-day practice. This paper summarizes the findings of the IISs around the globe published to date and presents the real-world data related to the effectiveness and clinical considerations of Cal/BD foam as a treatment for psoriasis.

J Drugs Dermatol. 2023;22:9(Suppl 2):s5-14.

INTRODUCTION

Psoriasis is a chronic inflammatory disease that affects approximately 8 million adults in the United States.[1] It is characterized by sharply demarcated, erythematous plaques with overlying scales that can involve a large percentage of one's body surface area.[1-2] Itching, pain, and scaling of the skin are among the most frequently reported symptoms.[2] Without adequate treatment, patients may face considerable quality-of-life impairment.

Topical agents may be used to manage mild-to-moderate psoriasis or serve as adjunct therapies used in combination with phototherapy and systemic treatments. Fixed-dose combination calcipotriene (Cal) 0.005%/betamethasone dipropionate (BD) 0.064% aerosol foam (Enstilar; LEO Pharma, Ballerup, Denmark) is a topical therapy approved for the treatment of plaque psoriasis (hereinafter ''psoriasis'') in the United States and European Union.[3,4] Several investigator-initiated studies (IISs) have been conducted globally to better understand the role of Cal/BD foam in treating psoriasis. These studies provide real-world evidence related to the safety, effectiveness, and therapeutic indications relevant to clinicians' every-day practice. Clinicians around the world have examined various aspects of treatment with fixed-dose combination Cal/BD aerosol foam, such as the drug's mechanism of action, impact on patient outcomes, and effectiveness in managing moderate-to-severe psoriasis. This paper summarizes the findings of the IISs around the globe published to date and presents the real-world data related to Cal/BD foam as a treatment for psoriasis.

Summary of Phase III Pivotal Studies

PSO-ABLE (NCT02132936) was an international, prospective, parallel-group, investigator-blinded Phase III clinical trial that evaluated the efficacy and safety of fixed-combination Cal/BD foam with Cal/BD gel.[5] Enrolled patients were randomized in a 4:4:1:1 manner to either once-daily Cal/BD aerosol foam, Cal/BD gel, foam vehicle, or gel vehicle treatment for 12 weeks. Enrolled patients had 2% to 30% of body surface involvement and underwent washout if receiving treatment prior to randomization. The study compared the proportion of participants who achieved a ≥ 2-point improvement in Physician's Global Assessment (PGA) score (*clear* or *almost clear* status) at week 4 for Cal/BD aerosol foam vs those at week

8 for Cal/BD gel. Significantly more patients treated with Cal/BD aerosol foam attained *clear* or *almost clear* status at week 4 compared to patients treated with Cal/BD gel at week 8.[5]

Difference in treatment efficacy was observed as early as week 1 and maintained throughout the 12 weeks of treatment. Study findings showed that treatment with Cal/BD aerosol foam was safe and well-tolerated.[5]

PSO-FAST (NCT01866163) was a national, multicenter, prospective, randomized, double-blinded Phase III clinical trial.[6] The study aimed to compare treatment efficacy and safety of Cal/BD aerosol foam with aerosol foam vehicle in patients with mild-to-severe psoriasis vulgaris on the body. Study participants were randomized in a 3:1 fashion to apply Cal/BD foam or vehicle once daily for 4 weeks.[6] The study's primary efficacy endpoint was to assess the proportion of patients with psoriasis who achieved treatment success (defined as *clear skin* PGA rating in mild disease patients and *clear*/*almost clear skin* status in moderate-to-severe disease patients) at week 4.[6] A significant proportion of patients with psoriasis using Cal/BD foam achieved treatment success when compared to the vehicle group. Overall, once-daily Cal/BD dosing was found to be a well-tolerated and safe treatment with few medication-related adverse reactions.[6]

Mechanism of Action of Cal/BD Foam and Clinical Features of Treatment-Response

Combination Cal/BD foam has demonstrated superior efficacy and safety compared to treatment with individual betamethasone and calcipotriene components.[7] In consideration of these findings, Heim et al conducted a prospective, randomized double-blind trial to examine the impact of Cal/BD treatment on cellular inflammation and cytokine production in active psoriasis lesions.[8]

Thirty patients with mild psoriasis (defined as PASI score <10) who had a minimum of two 2 cm^2 symmetric lesions located on the elbows were randomized. Patients were randomized to apply either betamethasone foam, clobetasol propionate ointment, or placebo foam (emollient) to the elbows on one side of the body; all study participants applied Cal/BD aerosol foam to their elbows on the opposite side of their body. Topical therapies were applied to the same sites once daily for a 4-week period.[8] Photographic images of the lesions were obtained and evaluated using the targeted Psoriasis Area and Severity Index (t-PASI) score pre- and posttreatment. Punch biopsies were taken from non-lesional and lesional skin in each patient, and immunofluorescence was utilized to examine cellular infiltrate, interferon gama (IFN-γ), and interleukin (IL)-17. Changes in cutaneous inflammation were studied alongside changes in epidermal thickness and t-PASI scores.[8]

Observed characteristics of lesional skin included increased epidermal thickness and increased counts of IL-17 and IFN-γ producing CD8+ T cells, natural killer cells, and neutrophils.[8] While all topical therapies were found to reduce epidermal thickness and improve t-PASI scores, Cal/BD foam was the only treatment to completely suppress CD8+ T-cell influx in the epidermis and dermis. Cal/BD therapy was also unique in its ability to reduce CD8 + IFN-γ+ cell counts and significantly reduce the number of IL-17 expressing, myeloperoxidase (MPO)+ neutrophils. Thus, treatment with Cal/BD aerosol foam displayed superior efficacy in decreasing cellular influx into active psoriatic lesions compared to emollient or betamethasone alone.[8]

Errichetti et al investigated the clinical and dermoscopic features of psoriasis plaques pre-Cal/BD foam therapy and in treatment-respondent plaques. Investigators also characterized residual dermoscopic findings associated with clinically improved and post-treatment relapse lesions.[9] Patients ≥18 years old with moderate-to-severe psoriasis were treated with once-daily Cal/BD aerosol foam for 4 weeks and seen at baseline, week 4 (end of therapy), and week 8.

Patients refrained from applying anything other than emollient on the treated areas between week 4 and week 8.[9]

At baseline, 3 target psoriasis lesions were randomly selected from each participant and observed throughout the study. Investigators assessed clinical improvement using the Local Psoriasis Severity Index (LPSI) to grade lesional erythema, scaling, and induration.[9]

Dermoscopic evaluation of lesions was also performed. Upon completion of the 4-week treatment period, investigators assessed for clinical improvement, which was categorized as *limited response* (LPSI improvement<50%), *partial response* (LPSI improvement of 50%-75%), or *optimal response* (LPSI improvement>75%); therapeutic outcome was then correlated with clinical and dermoscopic features first observed at baseline.[9]

A total of 105 lesions were included in the study analysis. Poor treatment outcomes were associated with degree of lesion infiltration at baseline; lesions localized to the legs were also associated with diminished outcomes. The presence of globular vessels at baseline dermoscopy and no/limited treatment response was found to be significantly correlated.[9] Globular vessels were also significantly associated with psoriasis lesions localized to the legs. Analyses specific to leg lesions revealed that the presence of globular vessels was significantly more common in nonresponding plaques than in treatment-responding lesions. In contrast, the dermoscopic presence

of dotted vessels, which were significantly more common in truncal lesions, was associated with partial/optimal treatment response. Post-treatment follow-up at week 8 showed that 58.7% of lesions classified as treatment-respondent at week 4 had relapsed. Lesional recurrence was found to be significantly associated with dermoscopic vessel persistence at the end of therapy.[9]

Another IIS, led by Yelamos et al, evaluated the clinical and microscopic features in psoriasis target lesions treated with clobetasol cream compared to those treated with Cal/BD foam.[10] Patients were randomized in a 1:1 manner to receive either clobetasol cream 0.5 mg/g applied once daily for 2 to 4 weeks (depending on clinical response) or Cal/BD foam once daily for 4 weeks. Study visits occurred at baseline (week 0), week 2, week 4, and week 8 (1 month without treatment).[10]

Investigators employed high-resolution photography to document each patient's most severe plaque at baseline and throughout the study. The Total Clinical Score (TCS), was used to grade erythema, induration, and scaling from the high-resolution clinical images; dermoscopic images of the target lesion center were also taken. The study's primary objective was to attain a lesional TCS score ≤1 at week 4.[10] Investigators found that a significantly greater proportion of patients treated with Cal/BD foam achieved TCS ≤1 compared to those treated with clobetasol cream. Cal/BD treatment also resulted in significantly greater reductions in microscopic epidermal thickness by week 4 compared to clobetasol treatment. Furthermore, fewer telangiectasias were observed in Cal/BD-treated lesions than clobetasol-treated lesions.[10]

Special Considerations in Patient Outcomes

Patient Treatment Adherence

Patient adherence to topical therapies depends on multiple variables related to both the medication and patient. Lack of treatment adherence may contribute to unsatisfactory treatment outcomes. An open-label, prospective single-center study conducted by Navarro-Triviño et al examined adherence to treatment with Cal/BD foam of patients with psoriasis in addition to their satisfaction with the medication.[11] Eligible patients were diagnosed with psoriasis on the trunk and extremities and had affected body surface area (BSA) <10%, PASI score <10, and a Dermatology Life Quality Index (DLQI) score <10. Patients receiving psoriasis treatment prior to the study underwent a washout period.[11]

Sixty-five study participants were enrolled and asked to apply Cal/BD foam on psoriasis plaques along the trunk and upper extremities once daily for no more than 4 weeks. Complete skin clearance was a criterion for treatment discontinuation; if psoriatic lesions relapsed, patients resumed treatment. Treatment adherence and medication satisfaction questionnaires were administered at week 4 and week 12. Strong patient adherence to treatment was observed, with 73.8% of patients demonstrating high adherence at week 12. Patients also notably reported high levels of satisfaction with Cal/BD therapy. By week 4, the majority of participants (70.8%) reported being *completely satisfied* with Cal/BD foam as their psoriasis treatment.[11] Additionally, enrolled patients experienced improvements in quality of life (QoL), as the average DLQI score of participants by week 4 was 2.41 (SD = 3.87) compared to the mean baseline score of 10.67 (SD = 4.96).[11]

Similarly, Svendsen et al investigated medication adherence by examining the impact of a smartphone application (app) in improving short-term adherence with once-daily Cal/BD foam therapy.[12] The study was a single-center, Phase IV randomized controlled trial; adult patients with mild-to-moderate psoriasis received once-daily treatment with Cal/BD foam and were randomized to no app or app study arms. Patient visits occurred at 4 weeks, 8 weeks, and 26 weeks. An electric monitor chip placed on the dispensed foam canisters registered the day and time the canister was used. Treatment adherence rates were collected at week 4 by measuring the number of treatment applications as recorded by the electronic monitor chip, change in medication canister weight before and after use, and patient self-reporting measures; adherence rates obtained by chip and medication weight that were above 80% were considered adherent. Secondary study outcomes were short-term (week 4) and long-term (weeks 8 and 26) disease severity based on Lattice System Physician's Global Assessment (LS-PGA) and DLQI scores.[12]

A total of 122 out of 134 patients completed the study. Intention-to-treat analyses showed that a statistically greater proportion of patients in the app treatment arm were adherent to Cal/BD cutaneous foam compared to those in the no-app group at week 4. At week 4, the app intervention group demonstrated a greater decrease in reported LS-PGA than the nonintervention group. A similar effect was observed at weeks 8 and 26, though it did not reach statistical significance.

Psoriasis Disease Burden and Impact on Patient Quality of Life

The signs and symptoms of psoriasis can contribute to profound physical and psychosocial disease burden, resulting in diminished patient QoL.[13] Two studies performed by da Silva et al investigated the impact of psoriasis disease burden on patient QoL. One study evaluated the degree and directionality of patient-physician (dis)agreement on psoriasis BSA ratings.[14] Patients utilized a high-resolution grid to document total psoriasis BSA and the regional BSA percentage affecting the head, trunk, arms, and legs; the regional BSA % was used

in PASI calculations. Patient-physician disagreement was calculated from the absolute difference between the patient's and physician's total BSA % reports. Directionality of the disagreement was determined by the difference between patient-assigned PASI regional BSA % and physician-assigned PASI regional BSA % (patient-report – physician-report).[14]

No significant differences between patients' and physicians' total BSA reports were detected; however, significant differences for the PASI regional scores for the head, trunk, arms, and legs were found to exist. Analyses examining the directionality of patient-physician (dis)agreement found that physicians were more likely to record a lower BSA percentage than patients. Additionally, a greater degree of patient-physician disagreement was significantly associated with greater QoL impairments and higher levels of depression.[14,15]

Another study conducted by da Silva et al assessed the effect of pruritus and anogenital psoriasis on disease burden and patient mental health.[15] Investigators also sought to identify variables associated with clinically significant depression/anxiety symptoms and body dysmorphia concerns. A total of 107 adult psoriasis patients completed the study. Approximately 40% of patient participants reported moderate-severe pruritus, and 29% reported anogenital involvement.[15] Patients with moderate-severe pruritus reported greater skin-related and pruritus-specific QoL impairment; they also reported more profound depression and anxiety symptoms along with greater concerns related to body dysmorphia. Moderate-severe pruritus patients also reported experiencing fewer treatment benefits than patients who reported no-mild pruritus. Additionally, moderate-severe pruritus had a detrimental effect on depression and perceived stigmatization for those without anogenital involvement. Patients who reported few treatment benefits were found to be more likely to experience clinically significant depression/anxiety symptoms.[15]

Sommer et al conducted a similar study to compare disease burden and patient needs between psoriasis patients with no-mild itch vs moderate-severe chronic pruritus.[16] This cross sectional, observational study also examined the effect of disease severity and intrapersonal burden on patients' sexual relationships and perceptions of stigmatization. Psoriasis patients ≥ 18 years completed questionnaires about pruritus severity, general skin-related and pruritus-specific QoL, anxiety/depression symptoms, body dysmorphia concerns, patient needs, treatment benefits, sexual dysfunction, and perceptions of stigmatization.[16]

A total of 107 psoriasis patients were included in the final study analysis: 60% reported having no-mild itch while 40% reported moderate-severe pruritus. Like da Silva et al, investigators found that patients with moderate-severe pruritus reported greater QoL impairment, depression and anxiety symptoms, and concerns about body dysmorphia.[16] Moderate-severe pruritus patients also reported fewer treatment benefits than those with no-mild pruritus. Younger age, degree of disease involvement, increased scratching behaviors, body dysmorphia concerns, and perceived treatment benefits were factors significantly associated with higher levels of patient stigmatization.[16] Disease severity, difficulty sleeping, and general skin-related QoL impairments were shown to have a statistically significant positive association with sexual dysfunction. Finally, study participants in both the no-mild and moderate-severe pruritus groups most frequently rated be[ing] healed of all skin defects and be[ing] free of itching as very important and quite important.[16]

Treatment of Psoriasis Patients with Skin of Color

There is limited data on the efficacy of topical medications in treating patients with skin of color. Liu et al conducted a single-center, double-blinded study to examine the efficacy of fixed-dose Cal/BD aerosol foam as a treatment of psoriasis vulgaris in patients with Fitzpatrick skin types IV to VI.[17] Eligible adult psoriasis patients were randomized to Cal/BD foam or foam vehicle once-daily application for 4 weeks.

Approximately 21% (4/19) of patients randomized to the Cal/BD foam treatment arm reached *clear/almost clear* Investigator Global Assessment (IGA) status with ≥ 2 point improvement by week 4. In comparison, 0% (0/5) of vehicle patients reached clear/almost clear status at this time.[17] Investigators also found that a statistically greater proportion of Cal/BD foam patients achieved a 50% reduction in their PASI score at week 4 compared to vehicle patients (63% vs 0%; P=0.04). Average changes in melanin index observed at week 4 demonstrated a trend in increasing pigmentation in patients treated with Cal/BD foam. In contrast, decreased pigmentation was observed in patients treated with vehicle foam.[17]

Treatment in Palmoplantar Psoriasis

Mateu-Puchades et al led an observational, prospective study to investigate the effectiveness, and safety of Cal/BD foam as a treatment for non-pustular palmoplantar (PP) psoriasis.[18] Investigators evaluated the effect once-daily Cal/BD foam had on patient QoL and treatment satisfaction. Eligible adult patients diagnosed with PP psoriasis were enrolled in the 4-week clinical study. Palmoplantar Psoriasis Area Severity Index (PPASI) and PGA scores were used to assess treatment effectiveness and safety. The DLQI and the 14-item Treatment Satisfaction Questionnaire for Medication were administered to evaluate patient QoL and treatment satisfaction.[18]

A total of 19 patient participants were included in the final

analysis. All enrolled study individuals had a BSA < 10%. Notably, study participants experienced a statistically significant reduction in PPASI (median reduction: 3.6, *P*=0.0284) and PGA scores (median reduction:1.0, *P*=0.0047).[18] An improvement in QoL was observed in patients, though it did not reach statistical significance. No adverse reactions associated with treatment were recorded. Patient-reported treatment satisfaction with Cal/BD foam was high (score: 76.9/100, higher scores indicating greater satisfaction with treatment), implying patient satisfaction with the effectiveness, convenience, and side-effect profile of the medication.[18]

Treatment of Moderate-to-Severe Psoriasis

Efficacy of Cal/BD Aerosol Foam in Patients With Moderate Psoriasis

Topical treatments are the mainstay therapies used to treat mild and moderate psoriasis.[19] They are also commonly used as adjunctive therapies in patients with moderate-to-severe disease who are receiving treatment with phototherapy, oral systemic, or biologic agents.[20] Del Rosso et al conducted a 2-center, 4-week clinical study to examine the use of once-daily Cal/BD foam monotherapy to treat moderate-severity psoriasis.[20] The study also examined the efficacy of Cal/BD foam treatment on plaques localized to the knees and elbows, which were two sites that had not been previously evaluated and treated as target lesions. The study enrolled patients with psoriasis who were ≥ 18 years old with 3% to 20% BSA involvement and moderate disease (PGA score=3) at baseline. All participants had bilateral, symmetric psoriasis plaques along the knees and/or elbows that measured 2cm to 4 cm in diameter with a Target Lesion Severity Score ≥ 6.[20]

The study protocol required patient visits at baseline, week 2, and week 4 to assess efficacy, safety, and tolerability. The observed therapeutic responses related to clinical efficacy and medication-related adverse events were similar to findings observed in the pivotal studies.[5,6] Novel findings included statistically significant changes in absolute and percent target lesion size at week 4; significant reductions in target lesion erythema and induration from baseline to week 2 and from week 2 to week 4 were also observed.[20]

Adjunctive Cal/BD Foam with Oral Apremilast for Moderate Psoriasis

Apremilast is an oral small-molecule phosphodiesterase 4 (PDE4) inhibitor that may be used in the treatment of psoriasis. The medication has demonstrated a well-established safety and efficacy profile throughout various clinical studies.[21-22] Kircik et al conducted a 16-week, investigator-blinded study to better understand the efficacy and safety of using Cal/BD foam in combination with oral apremilast to treat moderate psoriasis.[23]

Patients ≥ 18 years old diagnosed with moderate psoriasis (PGA score= 3) and who had been started on oral apremilast (30 mg twice daily) within 10 days of enrollment were deemed eligible. Study participants were randomized in a 1:1 manner to either once-daily Cal/BD foam and apremilast combination therapy or once-daily vehicle foam and apremilast combination therapy for 4 weeks. After the initial 4-week treatment period, those enrolled received 8 weeks of apremilast monotherapy, which was followed by re-initiation of once-daily Cal/BD foam or vehicle foam with apremilast for an additional 4 weeks.[23]

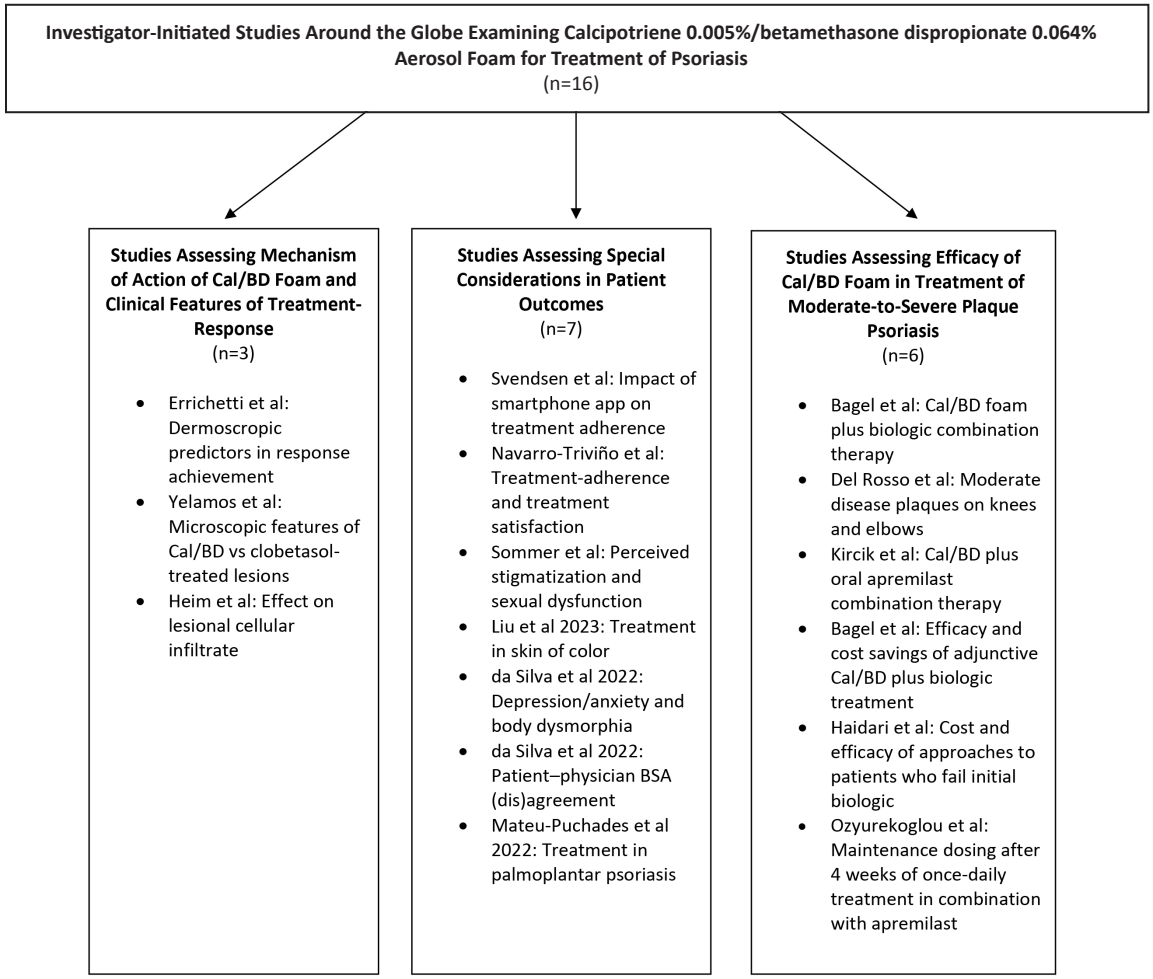
A total of 28 individuals completed the clinical study. At week 4, a statistically greater portion of patients in the Cal/BD foam plus apremilast treatment arm achieved improvement in skin clearance (≥ 75% reduction in PASI score and ≥ 2 PGA score improvement) than the vehicle foam plus apremilast arm.[23] The Cal/BD group also experienced statistically significant improvements in pruritus compared to the vehicle group. Disease severity (ie, PASI and PGA scores), pruritus, and patient QoL worsened after the 8-week Cal/BD foam treatment withdrawal period; however, improvements in these efficacy measures recovered after resuming Cal/BD foam therapy from week 12 to week 16.[23] Overall, investigators found that Cal/BD foam was effective in clearing patients' skin and improving their QoL when used as an adjunct therapy alongside apremilast. Thus, treatment regimen of Cal/BD foam and apremilast was found to be safe and well-tolerated in the management of moderate psoriasis.

Ozyurekoglou et al sought to build upon Kircik et al's findings and examined the efficacy of twice-weekly maintenance dosing following treatment with 4 weeks of standard once-daily Cal/BD foam application in combination with apremilast.[24] Twice-weekly application has been shown to prolong disease remission and reduce relapses in patients initially treated with standard once-daily Cal/BD foam dosing.[7] However, previous studies had not evaluated the use of Cal/BD foam as a maintenance therapy used alongside apremilast.

A single-center, open-label pilot study was conducted and enrolled adult patients with moderate psoriasis who began treatment with oral apremilast (30 mg twice daily) within 10 days of their baseline visit. Study visits and assessments were performed at baseline, week 4, week 16, and week 20. Individuals who reached *clear*/*almost clear* PGA status at week 4 were instructed to reduce Cal/BD application to twice-weekly maintenance dosing through week 16 while continuing apremilast treatment. Treatment was stopped at week 16, and safety follow-up was conducted at week 20.[24]

At week 4, 95% of patients treated with the combination regimen of apremilast plus Cal/BD achieved *clear*/*almost clear*

FIGURE 1. Schematic depicting the investigator-initiated studies around the globe examining calcipotriene 0.005%/betamethasone dipropionate 0.064% aerosol foam for the treatment of psoriasis.



PGA status.[24] Though the greatest reduction in PGA occurred at week 4, significant PGA score reductions were observed at each subsequent visit after baseline. A majority of patients (74%) were still *clear*/*almost clear* at week 16. Additionally, 90% of patients reported being *somewhat* to *extremely satisfied* with treatment overall at week 16, with the most common patient responses to the week-16 patient satisfaction questionnaire being *mostly satisfied* to *extremely satisfied* with Cal/BD foam's efficacy in treating and preventing symptoms. No adverse events were suspected to be due to the study medication, and no serious adverse events were reported.[24]

Adjunctive Cal/BD Foam Therapy Plus Biologic Treatment for Moderate-to-Severe Psoriasis

Despite their high levels of efficacy, biologic agents do not always result in rapid and complete clearance in patients with moderate-to-severe psoriasis; topical treatments are commonly added as adjunct therapies in these instances.[25] Bagel et al conducted two trials to obtain real-world data related to the safety and efficacy of Cal/BD foam as an adjunctive therapy to biologic treatment for moderate-to-severe psoriasis. One of the studies assessed the tolerability and effectiveness of once-daily Cal/BD foam in patients with psoriasis who may have failed to obtain adequate treatment responses with biologic therapy.[26] The study employed a prospective, single-arm design; enrolled individuals were adult patients with psoriasis, a BSA ≤ 5%, and had been treated with a biologic ≥ 24 weeks. All patients were asked to continue their biologic regimen and apply Cal/BD foam once daily for 4 weeks; this was followed by a 12-week maintenance dosing period where individuals applied Cal/BD foam on 2 consecutive days weekly.[26]

Combination therapy of biologic plus Cal/BD foam resulted in significant clinical improvement in disease. Over one-quarter of participants achieved total clearance (defined as 0% BSA and PGA=0) as early as week 4.[26] Whereas only 12% reached

TABLE 1.

Studies Assessing the Mechanism of Action of Cal/BD Foam and Clinical Features of Treatment-Response

Investigator and Publication Year (Country)	Title	Objective	Study Findings
Errichetti et al 2020 (Italy)	Plaque-Type Psoriasis Treated with Calcipotriene Plus Betamethasone Dipropionate Aerosol Foam: A Prospective Study on Clinical and Dermoscopic Predictor Factors in Response Achievement and Retention	• Assess correlation between baseline clinical/dermoscopic features of psoriasis plaques and therapy-respondent lesions • Examine residual dermoscopic findings in lesions exhibiting clinical improvement and post-treatment relapse	• Poor treatment outcomes correlated with lesions located on legs and degree of lesion infiltration at baseline • Presence of globular vessels at baseline dermoscopy more commonly associated with no/limited treatment response • Dotted vessels on baseline dermoscopic examination associated with good outcomes
Yelamos et al 2021 (Spain)	Non-invasive clinical and microscopic evaluation of the response to treatment with clobetasol cream vs calcipotriol/ betamethasone dipropionate foam in mild to moderate plaque psoriasis: an investigator-initiated, phase IV, unicentric, open, randomized clinical trial	• Compare clinical and microscopic features in psoriasis target lesions treated with clobetasol cream or Cal/BD foam	• More patients treated with Cal/BD foam achieved TCS ≤ 1 than with clobetasol at week 4 • Cal/BD foam induced significantly greater reduction in epidermal thickness at week 4
Heim et al 2022 (France)	Impact of topical emollient, steroids alone or combined with calcipotriol, on the immune infiltrate and clinical outcome in psoriasis.	• Examine effect of topical therapies on cellular infiltrate and cytokine profile in psoriasis lesions	• Cal/BD foam was the only topical treatment to completely suppress CD8+ T-cell influx in epidermis and dermis • Cal/BD therapy was the only topical to reduce CD8 + IFN-γ+ and IL-17 expressing, MPO+ neutrophils

TABLE 2.

Studies Examining Special Considerations in Patient Outcomes

Investigator and Publication Year (Country)	Title	Objective	Study Findings
Svendsen et al 2018 (Denmark)	A smartphone application supporting patients with psoriasis improves adherence to topical treatment: a randomized controlled trial	• Evaluate impact of a smartphone app on treatment adherence and psoriasis symptoms	• Statistically greater proportion of patients in the app treatment arm were adherent to Cal/BD cutaneous foam compared to the no-app group • App intervention group had greater reductions in LS-PGA than the non-intervention group
Navarro-Triviño et al 2021 (Spain)	Calcipotriol/Betamethasone Dipropionate Aerosol Foam for Plaque Psoriasis: A Prospective, Observational, Non-Interventional, Single-Center Study of Patient Adherence and Satisfaction in Daily Use	• Assess patient adherence to Cal/BD aerosol foam treatment • Assess patient satisfaction with efficacy, safety, and impact on QoL	• 73.8% of patients showed high adherence at week 12 • 70.8% of participants reported being completely satisfied with Cal/BD foam as their psoriasis treatment
Sommer et al 2021 (Germany)	Significance of chronic pruritus for intrapersonal burden and interpersonal experiences of stigmatization and sexuality in patients with psoriasis	• Compare psoriasis disease burden and patient needs between patients with none/mild vs moderate/severe pruritus • Examine impact of disease severity and intrapersonal burden on patients' perceived stigmatization and sexual relationships	• Moderate-severe pruritus patients reported greater QoL impairment, depression and anxiety symptoms, concerns about body dysmorphia, and fewer treatment benefits • Younger age, degree of disease involvement, increased scratching behaviors, body dysmorphia concerns, and perceived treatment benefits significantly associated with higher levels of patient stigmatization • Disease severity, difficulty sleeping, and general skin-related QoL impairments have significant positive association with sexual dysfunction
Liu et al 2023 (USA)	Efficacy and Safety of Cal/BD Foam in the Treatment of Plaque Psoriasis Patients with Skin of Color: A Single-Center, Double-Blinded, Placebo-Controlled Study	• Investigate the efficacy of Cal/BD foam compared to vehicle in treatment of psoriasis in skin of color	• 21% of Cal/BD patients achieved *clear/almost clear* IGA status at week 4 vs 0% of vehicle patients • Statistically greater proportion of Cal/BD foam patients achieved PASI 50 at week 4 compared to vehicle
da Silva et al 2022 (Germany)	Psychological (co)morbidity in patients with psoriasis: the impact of pruritus and anogenital involvement on symptoms of depression and anxiety and on body dysmorphic concerns – a cross-sectional study	• Examine effects of pruritus severity and anogenital psoriasis on disease burden and psychological comorbidity • Identify variables associated with clinically significant depression, anxiety, and body dysmorphia concerns	• Patients with moderate-severe pruritus reported greater skin-related, pruritus-specific QoL impairment, more profound depression/anxiety symptoms, and body dysmorphia concerns • Patients who reported few treatment benefits were more likely to experience clinically significant depression/ anxiety symptoms
da Silva et al 2022 (Germany)	Patient–physician (dis)agreement on their reports of body surface area affected by psoriasis and its associations with disease burden	• Investigate the degree and directionality of patient–physician (dis)agreement on BSA affected by psoriasis	• No significant differences between patients' and physicians' total BSA reports observed • Significant differences for PASI area categories for the head, trunk, arms, and legs found • Greater degrees of patient-physician disagreement significantly associated with QoL impairments and higher levels of depression
Mateu-Puchades et al 2022 (Spain)	Effectiveness, safety, quality of life and satisfaction of patients with palmo-plantar psoriasis treated with calcipotriol and betamethasone foam	• Evaluate effectiveness, safety, QoL and patient satisfaction with Cal/BD foam in PP psoriasis patients	• Patients experienced a statistically significant reduction in PPASI and PGA • No adverse reactions associated with treatment were recorded • High patient-reported treatment satisfaction with Cal/BD foam

TABLE 3.

Studies Assessing Efficacy of Cal/BD Foam in Treatment of Moderate-to-Severe Plaque Psoriasis

Investigator and Publication Year (Country)	Title	Objective	Study Findings
Bagel et al 2018 (USA)	A Prospective, Open-Label Study Evaluating Adjunctive Calcipotriene 0.005%/ Betamethasone Dipropionate 0.064% Foam in Psoriasis Patients With Inadequate Response to Biologic Therapy	• Evaluate effectiveness and safety of Cal/BD foam with biologic therapies for patients with plaque psoriasis who have not obtained adequate response with biologic monotherapy	• Significantly greater proportion of patients achieved treat-to-target goal of ≤1% BSA after receiving adjunctive treatment with Cal/BD foam • Significantly more patients achieved PGA ≤ 1 with Cal/BD foam at both week 4 and week 16 compared to those treated with biologics alone at baseline
Del Rosso et al 2019 (USA)	The Effect of Calcipotriene-Betamethasone Dipropionate Aerosol Foam versus Vehicle on Target Lesions in Moderate Severity Plaque Psoriasis: Focus on Elbows and Knees	• Assess clinical response to once-daily Cal/BD foam on the elbows and knees in adults with moderate psoriasis	• Statistically significant changes in absolute and percent lesion size found at week 4 • Significant reductions in lesional erythema and induration from baseline to week 2 and from week 2 to week 4 observed
Kircik et al 2020 (USA)	Efficacy and Safety of Calcipotriene 0.005%/ Betamethasone Dipropionate 0.064% Foam With Apremilast for Moderate Plaque Psoriasis	• Assess efficacy and safety of Cal/BD plus oral apremilast combination therapy as treatment for moderate plaque psoriasis	• Statistically greater portion of patients in the Cal/BD foam plus apremilast arm achieved improvement in skin clearance than vehicle foam plus apremilast group • Cal/BD group experienced statistically significant improvements in pruritus compared to the vehicle group • Disease severity, pruritus, and patient QoL worsened after withdrawing Cal/BD foam for 8 weeks; improvements recovered after resuming Cal/BD foam from week 12 to week 16
Bagel et al 2020 (USA)	Adjunctive Use of Calcipotriene/ Betamethasone Dipropionate Foam in a Real-World Setting Curtails the Cost of Biologics Without Reducing Efficacy in Psoriasis	• Investigate efficacy and safety of adjunctive Cal/BD therapy in patients who failed to clinically respond to stable etanercept or adalimumab therapy • Determine the potential cost savings of adjunctive treatment approach vs switching to a different biologic agent	• Clinical improvements observed within 4 weeks of initiating Cal/BD adjunct therapy; improvements maintained for additional 12 weeks of Cal/BD every-other-day dosing combination therapy • Cal/BD foam adjuvant therapy costs less than switching biologic agents
Haidari et al 2020 (USA)	Management of Residual Psoriasis in Patients on Biologic Treatment	• Determine efficacy, cost, and safety of three treatment approaches in psoriasis patients who failed to achieve complete clearance from initial biologic	• Cal/BD foam plus initial biologic therapy (28%), switching to guselkumab (20%), and switching to infliximab (15.8%) found to be therapeutic approaches most likely to induce complete clearance in patients who failed to reach clearance with initial biologic • Addition of Cal/BD foam to initial biologic treatment less costly than dose escalation or switching to the lowest cost alternative biologic
Ozyurekoglou et al 2022 (USA)	The Maintenance Effect of Calcipotriene 0.05% and Betamethasone Dipropionate 0.064% (Cal/BD) Aerosol Foam in Combination With Apremilast	• Assess effect of twice-weekly Cal/BD maintenance dosing after 4 weeks of once-daily treatment in combination with apremilast	• 95% of patients treated with the combination regimen of apremilast plus Cal/BD achieved *clear* or *almost clear* PGA status at week 4 • 74% of patients were still *clear*/*almost clear* at week 16

the study's treat-to-target goal of ≤1% BSA from biologic monotherapy at baseline, 76% and 68% of patients achieved this status at weeks 4 and 16 respectively after receiving adjunctive treatment with Cal/BD foam (P<0.001). Significantly more patients achieved PGA ≤ 1 status with Cal/BD foam at both week 4 and week 16 compared with those treated with biologics alone at baseline.[33] Furthermore, no serious adverse events or medication-related adverse events were reported throughout the duration of the study.[26]

Bagel et al conducted another 16-week, open-label study to assess the efficacy of Cal/BD foam in patients who failed to clinically respond to treatment with stable etanercept or adalimumab therapy.[27] The clinical study had an additional aim of evaluating the potential cost savings of treatment with adjunctive Cal/BD compared to switching treatment to a different biologic therapy. Patient visits occurred at baseline and weeks 4, 8, 12, and 16. Failed clinical response to biologic therapy was defined as having BSA involvement of 2% to 10% and a PGA rating ≥ 2 despite treatment with etanercept or adalimumab for ≥ 24 weeks. Enrolled participants were treated with 4 weeks of once-daily Cal/BD foam adjunct therapy, followed by every-other-day Cal/BD foam dosing for an additional 12 weeks. Maintenance biologic dosing with either etanercept or adalimumab was continued throughout the duration of the 16-week study. For pharmacoeconomic evaluation, investigators calculated the cumulative cost of adjuvant Cal/BD therapy by adding the cost of 4 weeks of once-daily Cal/BD foam dosing followed by 12 weeks of once-every-other-day therapy to the cost of 16 weeks of maintenance etanercept or adalimumab dosing. This was compared to the cost of switching to a new biologic, which was determined by averaging the wholesale prices for commonly prescribed biologics multiplied by the FDA-approved induction and maintenance doses for up to 16 weeks of treatment.[27]

The study demonstrated clinical improvements in BSA involvement, PGA scores, and composite BSA×PGA scores within 4 weeks of initiating Cal/BD adjunct therapy.[27] These improvements were maintained for an additional 12 weeks of Cal/BD every-other-day dosing combination therapy. Additionally, 75% of patients achieved treat-to-target status of BSA ≤1%. Investigators were less inclined to switch biologics by week 16, as their reported likelihood to switch decreased from 90.0% at baseline to 7.1%. Finally, pharmacoeconomic evaluation revealed that Cal/BD foam adjuvant therapy resulted in lower costs than switching biologic agents.[27]

The overall findings of the two clinical studies conducted by Bagel et al provided real-world evidence demonstrating the efficacy and cost-effectiveness of adjunctive Cal/BD foam therapy in patients who experience lack of clinical response despite treatment with biologics. Information related to the pharmacoeconomic considerations associated with biologic plus Cal/BD combination therapy was further examined by Haidari et al.[28] Investigators conducted a systematic literature review using MEDLINE to identify articles discussing treatment approaches for moderate-to-severe psoriasis patients who failed to attain complete skin clearance (defined as 100% improvement in PASI score and/or PGA score=0) despite treatment with a biologic. The efficacy, cost, and safety associated with each therapeutic approach were reviewed.[28]

Of the treatment regimens reported in the literature, the therapeutic approaches most likely to induce complete clearance in patients who failed to reach clearance on a biologic were addition of Cal/BD foam to initial biologic therapy (28%), switching biologic therapy to guselkumab (20%), and switching to treatment with infliximab (15.8%).[28] The cost of adjuvant therapy with Cal/BD foam plus existing biologic treatment was found to be $3,780 per patient cleared; this was less costly compared to the lowest-cost biologic dose escalation (guselkumab; $73,370 per patient cleared) or switching to the least expensive alternative biologic agent (infliximab; $88,250 per patient cleared).[28]

CONCLUSION

The efficacy and safety of Cal/BD foam as a treatment for psoriasis has been well-studied in large-scale clinical trials and several IISs. Data from these studies add to the body of clinical evidence that aids physicians in selecting efficacious, cost-effective therapeutic approaches to improve patient treatment outcomes in psoriasis.

The results reported by Errichetti et al and Yelamos et al confirmed the efficacy of once-daily Cal/BD therapy in treating psoriasis.[9,10] Their novel findings provide dermoscopic characteristics associated with treatment improvement (ie, lesions localized to the trunk and dermoscopic presence of dotted vessels) to aid physicians in clinical management. Svendsen et al and Navarro-Triviño et al examined medication adherence with once-daily Cal/BD foam; the real-world data obtained from their studies highlight the impact of treatment adherence and clinical efficacy of once-daily Cal/BD dosing.[11-12] These findings demonstrate the need for clinicians to counsel patients on the importance of treatment adherence for clinical improvement. Navarro-Triviño et al's work also highlighted the high levels of patient satisfaction with Cal/BD foam, as most patients reported high levels of overall satisfaction in addition to satisfaction with the cosmetic quality and ease of application of the drug. Given the importance of patient treatment satisfaction on treatment adherence and overall treatment outcomes, this finding suggests that Cal/BD foam is an easy-to-use medication that psoriasis patients may be more likely to apply regularly and thereby improve their disease.

Additional studies provided insight into special treatment considerations. For example, the findings provided by da Silva et al and Sommer et al brought attention to the need to account for patients' perceived stigmatization and disease burden to better care for patients and increase treatment compliance.[14-16] Their findings exhibit the importance of shared decision-making practices given the burden that visible areas of disease can have on psoriasis patients. Liu et al's clinical study also presented novel findings, documenting Cal/BD foam's safety and efficacy as a psoriasis treatment in patients with skin of color.[17] The increased pigmentation of lesional skin observed in the Cal/BD treatment group may be due to pigmentary changes associated with clinical improvement of psoriasis in skin of color. Thus, clinicians may consider the therapeutic benefit of Cal/BD for psoriasis patients with skin of color. Finally, Mateu-Puchades et al's examination of Cal/BD foam as a potential treatment for PP psoriasis found that the medication is well-tolerated and clinically effective with high levels of patient satisfaction.[18]

Clinicians also investigated the role of Cal/BD foam in therapeutic management of moderate-to-severe psoriasis. Del Rosso et al notably documented the effectiveness and tolerability of once-daily Cal/BD aerosol foam as a treatment for moderate-severity plaques affecting the elbows and knees, which were target lesion sites that had not been previously studied.[20] These findings suggest that patients with moderate-to-severe psoriasis plaques involving these anatomic sites would benefit from Cal/BD therapy. Other studies conducted by Kircik et al and Ozyurekoglou et al confirmed the safety and efficacy of Cal/BD plus apremilast combination therapy in treating moderate psoriasis while also substantiating the effectiveness of twice-weekly maintenance Cal/BD maintenance dosing.[23-24] Furthermore, the studies led by Bagel et al and Haidari et al highlighted the efficacy and cost-effectiveness of

adjunct Cal/BD therapy.[26-28] Given the clinical improvements and economic savings associated with biologic plus Cal/BD foam treatment reported in these studies, physicians may consider this regimen in patients with inadequate response to stable biologic treatment.

This report summarizes the real-world data regarding the unique clinical and therapeutic considerations of Cal/BD foam as presented in the IISs that have been conducted around the globe and have been published to date. These studies provide an abundance of strong, real-world evidence to guide clinicians' everyday practice.

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AUTHOR CORRESPONDENCE

April W. Armstrong MD MPH
E-mail:..... armstrongpublication@gmail.com

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