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 ORIGINAL ARTICLE

Fixed Combination Calcipotriene and Betamethasone Dipropionate (Cal/BD) Foam for Beyond-Mild Psoriasis: A Possible Alternative to Systemic Medication

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ABSTRACT

Calcipotriene 0.005% plus betamethasone dipropionate 0.064% (Cal/BD) aerosol foam is a topical agent indicated for the treatment of plaque psoriasis. While topical treatments are typically reserved for milder disease, in clinical trials with Cal/BD foam, the vast majority of patients had beyond-mild psoriasis at baseline, and multiple studies (including subgroup analyses from randomized controlled trials and other small-scale studies) have demonstrated favorable outcomes with the use of Cal/BD foam in this population. The objective of this article is to review existing data on the efficacy, safety, and cost-effectiveness of Cal/BD foam used in patients with beyond-mild psoriasis, either alone as topical monotherapy or as adjunctive therapy. Practical recommendations for managing beyond-mild psoriasis with Cal/BD foam are also provided.

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INTRODUCTION

Psoriasis is a chronic, inflammatory condition characterized by the formation of erythematous, scaly plaques in various regions of the body.[1,2] Treatment strategies are typically guided by assessments of disease severity, with topical agents generally used to treat mild-to-moderate disease and photo, oral and biologic therapies reserved for moderate-to-severe disease.[1,3,4] Prior to initiating biologic therapy, quality-of-life (QOL) assessments and discussions with the patient about treatment costs are also recommended.[1] The recent development of novel topical medications has expanded the strategies that can be considered for managing patients with greater disease severity.[5,6] Given the complex nature of managing moderate-to-severe psoriasis, the availability of an efficacious, safe, easy-to-use, topical medication has the potential to improve treatment outcomes,[5] adherence,[7] and patient satisfaction[8] to deliver cost savings.[9]

Calcipotriene 0.005% (Cal) plus betamethasone dipropionate 0.064% (BD) foam (Cal/BD; Enstilar®) is an FDA-approved, once-daily topical agent indicated for the treatment of plaque psoriasis in patients 12 years and older.[10] The proprietary aerosol foam formulation enables supersaturation of Cal/BD that greatly enhances skin penetration and bioavailability.[11] While nominally a foam, the product is administered as an aerosol spray,[10] which can be applied to relatively large areas with ease. In pivotal Phase 2 and 3 trials, Cal/BD foam showed superior efficacy, together with favorable safety profiles, in comparisons with Cal/BD topical suspension (Taclonex® Topical Suspension; formulated as a gel), Cal/BD ointment (Taclonex® Ointment), Cal foam and BD foam, and foam vehicle.[12-15] Patients with psoriasis ranging from mild to severe, as defined by the Physician's Global Assessment (PGA) scale, were eligible for these studies; however, the majority (>70%) had moderate disease (PGA=3), and approximately 10% had severe disease (PGA=4).[12-15] This patient distribution differs from that of many other psoriasis clinical trials conducted in moderate-to-severe patients, in which baseline populations were weighted to more severe disease.[16] Therefore, we differentiate these patients in Cal/BD foam trials with baseline severity greater than mild as having "beyond-mild" psoriasis. Several post hoc analyses and small-scale studies have shown that beyond-mild psoriasis patients can benefit from treatment with Cal/BD foam, either alone or as adjunctive therapy.[5,17-20]

The purpose of this review is to (1) summarize Cal/BD foam efficacy and safety data for beyond-mild psoriasis, (2) summarize the cost-effectiveness of Cal/BD foam in comparison with systemic therapy, including biologic agents, and (3) provide practical recommendations for the use of Cal/BD foam in patients with beyond-mild psoriasis.

Definitions of Disease Severity

Body surface area (BSA), the PGA scale, and the Psoriasis Area and Severity Index (PASI) are commonly used assessments of psoriasis severity. They are continuous variables, reflecting a continuum of disease severity, that may be translated into distinct categories using predefined thresholds.[1,21-23] In terms of BSA, both the National Psoriasis Foundation and the American Academy of Dermatology define mild, moderate, and severe psoriasis as <3%, 3-10%, and >10% BSA involvement, respectively,[1] with 1% BSA estimated to equal the patient's full handprint (including the palm and fingers).[24] Regardless of the extent of BSA involvement, psoriasis that causes severe emotional consequences or that occurs on the scalp, face, hands, feet, or genitals may be classified as severe.[1] The PGA is a 5- (or 6-) point scale that evaluates lesion induration, scaling, and erythema; it indicates scores of clear (PGA=0), almost clear (PGA=1), mild (PGA=2), moderate (PGA=3), and severe (PGA=4).[25] The PASI is a composite score that evaluates BSA involvement, lesion sites, and lesion qualities.[21] Although PASI is considered the gold standard for measuring severity in clinical trials,[22,26] it is a complicated assessment that is time-consuming and thus impractical to use in daily practice.[27] PASI threshold scores of 7 and 12 have been proposed, whereby mild, moderate, and severe disease are defined as scores of <7, 7–12, and >12, respectively.[22] As no single tool is optimal for assessing psoriasis, it has become standard practice to perform all three assessments ⊢ PGA, BSA, and PASI ⊣ in clinical trials.[26]

Psoriasis can have profound impacts on a patient's psychosocial well-being, and none of the PGA, BSA, or PASI assessment methods account for QOL. Treatment adherence and outcomes may improve if management strategies are informed by patient perceptions, such as an individual's acceptance of potential life-altering side effects, treatment costs, and incomplete resolution of symptoms.[28,29] The patient-reported Dermatology Life Quality Index (DLQI) is often used in clinical studies to assess the impact of psoriasis and its treatment on patients' QOL, particularly for agents seeking regulatory approval in Europe.[30] It is incorporated in the Rule of Tens severity assessment tool where severe disease is defined as psoriasis with DLQI score >10, BSA involvement >10%, or PASI >10.[24]

The definitions of psoriasis severity discussed herein are not comprehensive. In 2019, the International Psoriasis Council proposed that, instead of severity categories, patients should be classified as candidates for either topical or systemic therapy, with systemic therapy candidates having BSA involvement >10%, disease involving special areas, or failed response to a topical therapy.[31] While definitions may continue to evolve as our understanding of psoriasis improves, it is clear that PGA, BSA, PASI, and DLQI, either as stand-alone or as composite tools, serve important functions in current assessments of disease severity. In the next section, we review data supporting the effectiveness of Cal/BD foam in patients with beyond-mild psoriasis defined using various measures of severity.

Cal/BD Foam for Patients With Beyond-Mild Psoriasis

The efficacy of Cal/BD foam in plaque psoriasis of all severities has been demonstrated in several randomized clinical trials (RCTs).[12-15] Across four RCTs, mean baseline BSA ranged from 6.7% to 8%, with overall baseline BSA ranging from 2% to 30%, and mean mPASI (modified PASI, excluding the head) scores ranged from 6.6 to 8.8. At baseline, >70% and <10% of patients had moderate and severe disease, respectively (Table 1).[12-15] Thus, the majority of patients in these four RCTs had beyond-mild psoriasis. Note that severity was defined according to the PGA; it is possible for patients with minimal or extensive BSA involvement (eg, <3% or >10%) to have been classified as moderate. Importantly, efficacy data from the overall population of more than 1300 patients showed consistent benefit with Cal/BD foam over Cal/BD topical suspension, Cal/BD ointment (mPASI75 and mPASI50, *P*=NS), Cal foam, BD foam, or foam vehicle (Table 2).[12-15] Adverse events (AEs) reported with Cal/BD foam have been mostly mild or moderate in severity, with similar incidence rates observed between groups.[12-15]

In patients with beyond-mild psoriasis, the efficacy of Cal/BD foam has been examined in several subgroup analyses and in a small, prospective study (Table 3).[5,12,17,18] Higher treatment success rates were observed with Cal/BD foam in patients with moderate or severe disease at baseline (per PGA) than with either Cal/BD topical suspension (PSO-ABLE)[12] or foam vehicle (PSO-FAST). Using data pooled from three Phase 2/3 RCTs, a post hoc analysis including 340 patients with 5-15% BSA and PGA=moderate/severe found statistically significant improvements in treatment success rates with Cal/BD foam vs foam vehicle as early as week 1, which continued to week 4 (Table 3).[17] Improvements were also observed in mPASI and pruritus outcomes. In a subgroup analysis of the PSO-ABLE trial, where beyond-mild psoriasis was defined according to the Rule of Tens, patients achieved numerically or statistically significant improvements at week 4 with Cal/BD foam vs Cal/BD topical suspension in treatment success rate, BSA, mPASI75, mPASI90, and DLQI, and these improvements continued through week 12 (Table 3).[5] Lastly, in 20 patients with moderate psoriasis involving the knees and elbows and 3-20% BSA at baseline, treatment with Cal/BD foam significantly improved PGA score, BSA involvement, and lesion qualities as early

TABLE 1.

Study Designs and Baseline Characteristics from Cal/BD Foam Phase 2 and 3 RCTs in Patients With Mild-to-Severe Psoriasis

	PSO-FAST[13]		PSO-ABLE[12]		Koo J, et al. (2016)[15]		Lebwohl M, et al. (2016)[14]		
Study Design	Phase 3 RCT (NCT01866163) Patients randomized 3:1 to Cal/BD foam or foam vehicle		Phase 3 RCT (NCT02132936) Patients randomized 4:1:1:1 to Cal/BD foam, Cal/BD topical suspension, foam vehicle, or topical suspension vehicle*		Phase 2 RCT (NCT01536886) Patients randomized 3:3:1:1 to Cal/BD foam, Cal/BD ointment, foam vehicle, or ointment vehicle†		Phase 2 RCT (NCT01536938) Patients randomized 1:1:1 to Cal/BD foam, Cal foam, or BD foam		
Baseline Characteristics									
	Cal/BD foam (n=323)	**Foam vehicle (n=103)**	**Cal/BD foam (n=185)**	**Cal/BD topical suspension (n=188)**	**Cal/BD foam (n=141)**	**Cal/BD ointment (n=135)**	**Cal/BD foam (n=100)**	**Cal foam (n=101)**	**BD foam (n=101)**
Sex, male, n (%)	204 (63.2)	49 (47.6)	126 (68)	114 (60.6)	87 (61.7)	87 (64.4)	53 (53.0)	61 (60.4)	56 (55.4)
Age, y (range or SD)	52 (18-87)‡	46 (19-79)‡	54.0 (14.5)§	54.5 (14.9)§	51.0 (21-84)‡	52.0 (21-88)‡	47.4 (14.8)§	50.7 (14.7)§	49.0 (14.4)§
Mean duration of psoriasis, y (range or SD)	16.3 (1-67)	14.9 (1-53)	19.3 (14.1)	19.0 (14.2)	16.1 (1-51)	16.3 (1-52)	14.6 (13.8)	18.4 (14.6)	16.2 (13.3)
Mean BSA, % (range or SD)	7.4 (6.4)	8.0 (7.0)	7.1 (5.7)	7.0 (5.5)	7.7 (2-30)	7.4 (2-30)	6.7 (4.9)	7.2 (5.6)	7.6 (6.3)
Mean mPASI, score (range or SD)¶	7.4 (2-37)	7.9 (2-47)	7.1 (4.5)	6.6 (3.6)	7.0 (4.2)	6.7 (3.3)	8.8 (4.6)	8.6 (4.4)	8.1 (4.0)
PGA severity, n (%)									
Mild	50 (15.5)	15 (14.6)	54 (29.2)	45 (23.9)	22 (15.6)	22 (16.3)	9 (9.0)	13 (12.9)	10 (9.9)
Moderate	244 (75.5)	75 (72.8)	109 (58.9)	124 (66.0)	112 (79.4)	106 (78.5)	77 (77.0)	75 (74.3)	81 (80.2)
Severe	29 (9.0)	13 (12.6)	22 (11.9)	19 (10.1)	7 (5.0)	7 (5.2)	14 (14.0)	13 (12.9)	10 (9.9)

*Baseline characteristics in foam and topical suspension vehicle arms not shown.
†Baseline characteristics in foam and ointment vehicle arms not shown.
‡Median (range).
§Mean (SD).
¶Modified PASI (excluding the head).

TABLE 2.

Efficacy of Cal/BD Foam in the Overall Population of Phase 2 and 3 RCTs

	PSO-FAST[13] (Week 4)	PSO-ABLE[12] (Week 4 vs week 8)*	Koo J, et al. (2016)[15] (Week 4)	Lebwohl M, et al. (2016)[14] (Week 4)	
	Cal/BD foam (n=323) vs foam vehicle (n=103)	**Cal/BD foam (n=185) vs Cal/BD topical suspension (n=188)†**	**Cal/BD foam (n=141) vs Cal/BD ointment (n=135)†**	**Cal/BD foam (n=100) vs Cal foam (n=101)**	**Cal/BD foam (n=100) vs BD foam (n=101)**
Treatment success rate‡	53.3% vs 4.8% (*P* < .001)	38.3% vs 22.5% (*P* < .001)	54.6% vs 43.0% (*P* = .025)	45.0% vs 14.9% (*P* < .001)	45.0% vs 30.7% (*P* = .047)
Mean mPASI§	2.0 vs 5.5	2.18 vs. 2.77	1.82 vs 2.46	2.37 vs 4.39	2.37 vs 3.37
Difference (95% CI)	–3.3 (–3.9, –2.7)	–0.59 (–1.11, –0.06)	–0.6 (–1.1, –0.2)	–2.03 (–2.63, –1.43)	–1.19 (–1.80, –0.59)
P value	*P* < .001	*P* = .028	*P* = .005	*P* < .001	*P* < .001
mPASI75§	52.9% vs 8.2% (*P* < .001)	52.1% vs 34.6% (*P* < .001)	50.4% vs 40.7% (*P* = .052)	49% vs 18% (*P* < .001)	49% vs 34%
mPASI50§	82.3% vs 28% (*P* < .001)		80.9% vs 74.8% (*P* = 0.17)	80% vs 44% (*P* ≤ .003)	80% vs 59% (*P* ≤ .003)

*Cal/BD foam week 4 results are compared with Cal/BD topical suspension week 8 results.
†Topical suspension, foam, and/or ointment vehicle arms not shown.
‡Defined as percent of patients who had ratings of "clear" (PGA=0) or "almost clear" (PGA=1), with at least a 2-grade improvement in PGA.
§Modified PASI (excluding the head).

TABLE 3.

Efficacy and Safety of Cal/BD Foam in Patients With Beyond-Mild Psoriasis		
Severity	**Results at Week 4 (except where stated otherwise)**	
Study: PSO-ABLE (Cal/BD foam at Week 4 vs Cal/BD topical suspension at Week 8)[12]		
PGA=3 (moderate)		**Cal/BD foam (n=105) vs Cal/BD topical suspension (n=117)**
	Treatment success*	44.8% vs 31.6%
	mPASI75†	47.6% vs 35.9%
PGA=4 (severe)	Treatment arms	**Cal/BD foam (n=22) vs Cal/BD topical suspension (n=19)**
	Treatment success*	50.0% vs 15.8%
	mPASI75†	63.6% vs 21.1%
Study: PSO-FAST [unpublished data]		
PGA=3 (moderate)		**Cal/BD foam (n=235) vs foam vehicle (n=72)**
	Treatment success*	60.0% vs 4.2%
PGA=4 (severe)		**Cal/BD foam (n=29) vs foam vehicle (n=13)**
	Treatment success*	37.9% vs 7.7%
Study: Post-hoc analysis of pooled data from PSO-FAST, PSO-ABLE, and NCT01536886[17]		
BSA=5-15% and PGA≥3 (moderate/severe)		**Cal/BD foam (n=254) vs foam vehicle (n=86)**
	Treatment success*	*Week 1*: 8.8% vs 2.4% ($P = .044$) *Week 4*: 58.1% vs 3.6% ($P < .001$)
	Mean mPASI†	2.3 vs 6.0 ($P < .001$)
	Mean itch score‡	10.0 vs 30.8 ($P < .001$)
	Safety assessment	• No significant differences in the percent of patients experiencing AEs between Cal/BD foam and foam vehicle • No serious AEs • Treatment-related AEs occurred in 3.9% and 2.3% of patients in the Cal/BD foam and foam vehicle groups, respectively; the most common treatment-related AE was pruritus
Study: Post-hoc analysis of PSO-ABLE in moderate-to-severe psoriasis patients defined by the Rule of Tens[5§]		
Moderate-to-severe (Rule-of-Tens)		**Cal/BD foam (n=77) vs Cal/BD topical suspension (n=82)**
	Treatment success*	*Week 4*: 32.0% vs 19.0% *Week 12*: 38.0% vs 31.6%
	Percent change from baseline in BSA	*Week 4*: –30.1% vs –18.6% *Week 12*: –50.2% vs –39.2% ($P = .04$)
	mPASI75†	*Week 4*: 40.3% vs 17.1% ($P = .001$) *Week 12*: 57.1% vs 35.4% ($P = .006$)
	mPASI90†	*Week 4*: 11.7% vs 2.4% ($P = .02$) *Week 12*: 15.6% vs 12.2% (P = ns)
	DLQI 0/1	*Week 4*: 33.8% vs 14.1% ($P = .004$) *Week 12*: 55.7% vs 29.3% ($P = .001$)
Study: Open-label, single-arm, 4-week study of Cal/BD foam in moderate psoriasis involving the elbows and knees[18]		
PGA=3 (moderate) and BSA=3-20%		**Cal/BD foam (n=20)**
	Patients with PGA=3/2/1/0	*Baseline*: 100% / 0 / 0 / 0 *Week 2*: 5% / 65% / 30% / 0 ($P < .0001$) *Week 4*: 5% / 20% / 45% / 30% ($P < .002$)
	Mean BSA	*Baseline*: 9.8% *Week 2*: 9.2% (P=.02 vs baseline) *Week 4*: 6.9% (P=.002 vs week 2)
	Erythema, induration, scaling	Significant reductions at week 2 ($P < .03$ vs baseline) and week 4 ($P < .03$ vs week 2) with exception of scaling at week 4 ($P = .07$ vs week 2)
	Safety assessment	No treatment-related AEs and no serious AEs were reported

*Defined as percent of patients who were "clear" (PGA=0) or "almost clear" (PGA=1), with at least a 2-grade improvement in PGA.
†Modified PASI (excluding the head).
‡Itch score assessed by visual analogue scale of 0-100.
§Mean baseline BSA, mPASI, and DLQI score (expressed as mean ± standard deviation) were 10.9% ± 6.8%, 10.2 ± 5.2, and 10.4 ± 5.7, respectively, in the Cal/BD foam group and 10.4% ± 6.4%, 8.9 ± 4.0, 12.0 ± 6.4, respectively, in the Cal/BD topical suspension group.

as week 2 (Table 3).[18] These results show that Cal/BD foam is effective in treating beyond-mild psoriasis regardless of how baseline disease severity is assessed. Additionally, existing safety data are consistent with the general safety profile of Cal/BD foam (Table 3).[17,18]

Oral treatments are frequently used to treat moderate-to-severe psoriasis.[1-3] There are no high-quality, head-to-head trials comparing Cal/BD foam with oral agents in psoriasis. In the absence of randomized comparative studies, matching-adjusted indirect comparison (MAIC) analyses have been used.[32,33] The analyses involved matching the baseline characteristics of individual patient-level (IPL) data from Cal/BD foam clinical trials with aggregate data from published studies of oral agents so that treatment outcomes may be indirectly compared. In one such MAIC analysis comparing pooled data from four Cal/BD foam trials with published data of apremilast, acitretin, and fumaric acid esters (FAE), variable matching resulted in an increase in mean baseline PASI of the Cal/BD foam group (from 7.3 to 8.2, 11.9, and 11.6 in the MAICs with apremilast, acitretin, and FAE, respectively), reflecting patient populations with greater disease severity (Table 4).[32] Importantly, Cal/BD foam efficacy following matching adjustment was significantly greater than that of apremilast and acitretin and comparable to that of FAE.[32]

Combination Therapy With Cal/BD Foam

Use of Cal/BD foam as adjunctive treatment was investigated in two studies involving patients with beyond-mild psoriasis.[19,20] In 28 patients with moderate psoriasis, Cal/BD foam plus apremilast significantly improved PASI75, PGA, and pruritus at week 4 compared with apremilast alone; numerical improvements were also observed in BSA and DLQI (Table 5).[19] Discontinuing Cal/BD foam at week 4 dramatically reduced efficacy, but the efficacy was restored upon reintroduction of Cal/BD foam. Notably, improvements in BSA, PGA, and PASI75 at week 16 were equal to or greater than those observed at week 4, suggesting no loss in the level of response when Cal/BD foam was reinitiated after discontinuation. The combination therapy was considered well tolerated.[19] In a study of 25 adults with

TABLE 4.

Matching Variable Alignment and PGA 0/1 and PASI75 Responder Outcomes in MAIC Analyses of Pooled Cal/BD Foam Trials vs Apremilast, Acitretin, and Fumaric Acid Esters[32]

	Cal/BD foam, pooled analysis		Comparator¶
	Before matching	After matching	
Pooled Cal/BD foam, Week 4 vs apremilast Week 16 (UNVEIL trial)*			
Sample size, n	748	640	148
Mean PASI	7.3†	8.2†	8.2
PGA 0/1 responders, % (95% CI)‡	56.4 (51.9, 60.9)	52.7 (44.9, 60.4)	30.4 (23.6, 38.2)
P value			< .001
Pooled Cal/BD foam, Week 4 vs acitretin Week 12§			
Sample size, n	748	102	41
Mean PASI	7.3†	11.9†	11.9
PASI75, % (95% CI)	51.4 (51.2, 51.5)†	50.9 (50.1, 51.6)†	31.7 (17.5, 46.0)
P value			.009
Pooled Cal/BD foam, Week 4 vs fumaric acid esters Week 12‖			
Sample size, n	749	224	115
Mean PASI	7.3†	11.6†	11.6
PASI75, % (95% CI)	51.4 (51.3, 51.5)†	42.4 (35.0, 50.2)†	47.0 (37.9, 56.1)
P value			.451

*Matching variable alignment also included BMI and previous topical treatment.
†Modified PASI (excluding the head) was used in Cal/BD foam trials.
‡Defined in Cal/BD foam trials as the percent of patients who scored "clear" (PGA=0) or "almost clear" (PGA=1), with at least a 2-grade improvement in a 5-point PGA scale; defined similarly in UNVEIL except using a 6-point PGA scale.
§Matching variable alignment also included sex, age, and BMI.
‖Matching variable alignment also included age.
¶Population characteristics and responder outcomes are from published comparator studies.

TABLE 5.

Efficacy and Safety of Apremilast Plus Cal/BD Foam vs Apremilast Plus Foam Vehicle in Patients With Moderate Psoriasis[19]

Study Design			
Population	Adult patients (n=28) with moderate plaque psoriasis (PGA=3), who were initiated on commercial apremilast within the previous 10 days, randomized 1:1 to receive apremilast + Cal/BD foam vs apremilast + vehicle foam		
Treatment Regimen	Week 0-4	Week 4-12[§]	Week 12-16
Group A	Apremilast + Cal/BD foam	Apremilast monotherapy	Apremilast + Cal/BD foam
Group B	Apremilast + vehicle foam	Apremilast monotherapy	Apremilast + vehicle foam
Efficacy			
	Week 4 Group A vs Group B	**Week 12** Group A vs Group B	**Week 16** Group A vs Group B
PASI75, %	50 vs 7 (*P* = .003)	29 vs 14	50 vs 14
Change from baseline in BSA, %	–32 vs –11	–32 vs –18	–58 vs –23
Patients achieving PGA "clear" or "almost" clear, %	43 vs 7 (*P* = .001)	14 vs 21 (*P* = .002)	64 vs 14 (*P* = .02)
Mean itch score*	2 vs 5 (*P* = .0079)	4 vs 4	3 vs 4
Mean DLQI score[†]	2 vs 5	5 vs 5	3 vs 6 (*P* = .007)
Safety Assessments			
• 36 AEs occurred in 15 subjects: 18 AEs in 6 subjects in the apremilast + Cal/BD foam group (Group A) and 18 AEs in 9 subjects in the apremilast + foam vehicle group (Group B)[‡] • 4 treatment-related AEs: 3 in Group A (nausea, diarrhea, abdominal cramping) and 1 in Group B (rash); all were considered related to apremilast[‡] • 1 subject discontinued in each group[‡]			

*Based on visual analogue scale of 0-10; mean baseline score was 7 for the apremilast + Cal/BD foam group and 6 for the apremilast + foam vehicle group.
[†]Baseline mean DLQI score was 9 for both treatment groups.
[‡]Unpublished data.
[§]Cal/BD foam and vehicle foam were temporarily discontinued from week 4 to week 12.

moderate-to-severe psoriasis who had inadequate response to a biologic therapy, the addition of Cal/BD foam to the biologic significantly improved PGA, BSA, and PGAxBSA at weeks 4 and 16 compared with baseline (Table 6).[20] Response was rapid, with 76% of patients reaching the National Psoriasis Foundation's treat-to-target goal of BSA ≤1% at week 4 compared with 12% at baseline (*P*<.001). These results suggest that adding Cal/BD foam to either apremilast or a biologic can confer quick and lasting benefits in patients with beyond-mild psoriasis.

Cost-Effectiveness

The use of Cal/BD foam in patients conventionally treated with biologic or oral medication has the potential to significantly reduce the cost of therapy. The cost per PASI75 response of Cal/BD foam ($3770) in moderate psoriasis has been estimated to be more than 17-fold lower than that of apremilast ($66,671).[33,34] In the setting of adjunctive therapy, the addition of Cal/BD foam to remove residual disease in patients receiving biologic therapy was estimated to substantially reduce treatment cost compared with either dose escalation or switching to another biologic agent (Table 7).[35] These calculations suggest that adding Cal/BD foam to the treatment options for beyond-mild psoriasis would be associated with significant cost savings. In a budget impact model of moderate-to-severe psoriasis in a hypothetical US healthcare plan of 1 million plan lives, formulary adoption of Cal/BD foam was estimated to reduce the annual costs of treatment by more than $36 million and the per-member per-month cost by $3.00 (Table 8).[9]

Practical Recommendations for Managing Beyond-Mild Psoriasis With Topical Agents

It has been estimated that ~32% of insured patients in the United States with moderate or severe psoriasis are not currently being treated.[36] Adverse effects, lack of response, and cost are among the most common reasons why patients discontinue treatment.[37,38] In psoriasis, for which there are a limited number of options, finding the optimal management strategy requires that all avenues of treatment, topical, oral, or biologic, be considered. As the data described in this review have demonstrated, topical therapy with Cal/BD foam is potentially

TABLE 6.

Efficacy and Safety of Adjunctive Cal/BD Foam With Biologic Medication in Patients Who Had Inadequate Response to Biologic Therapy[20]

	Baseline Biologic	Week 4 Biologic + Cal/BD foam*	Week 16 Biologic + Cal/BD foam*
Study Design			
Open-label, single-arm study of patients (n=25) with chronic plaque psoriasis of ≤5% BSA involvement and inadequate response with biologic therapy† for ≥24 weeks			
Efficacy Assessments			
Median PGA (IQR)	3 (2-3)	1 (0-1), *P* < .01	1 (1-2), *P* < .01
Patients with PGA ≤1, %	4	76, *P* < .001	68, *P* < .001
Median BSA, % (IQR)	3 (2-4)	1 (0-1), *P* < .01	1 (1-2), *P* < .01
Patients with BSA ≤1%, %	12	76, *P* < .001	68, *P* < .001
Median PGA X BSA (IQR)‡	8 (6-12)	1 (0-2), *P* < .01	1 (1-3), *P* < .01
DLQI (IQR)	3 (1-4)	1 (1-2), *P* < .01	1 (0-3)
Safety Assessments			
• AEs in ≥1% of patients: bone fracture, fatigue, headache, melasma, muscle weakness, pruritus, pulled knee tendon, renal hematoma§ • No treatment-related AE • No serious AE • No discontinuation due to any AE			

*All *P* values compared with baseline.
†Biologic agents included ustekinumab, adalimumab, secukinumab, etanercept, and ixekizumab.
‡The product of PGA and BSA.
§Grade 1 severity for all AEs except bone fracture and renal hematoma (1 each), which were grade 2.

TABLE 7.

Estimated Cost per PASI100 or PGA 0 Response in Patients Who Failed to Achieve Complete Clearance With a Biologic Agent[35]

Treatment Approach	Duration, weeks	Patients achieving PASI100 or PGA 0, %	Number needed to treat to achieve clearance in 1 additional patient	Estimated additional cost to achieve clearance in 1 additional patient
Adding Cal/BD foam to current biologic therapy* (n=25)	16	28	3.6	$3,780
Switching to infliximab from etanercept (n=179)	26	15.8	6.3	$88,225
Switching to guselkumab from ustekinumab (n=135)	36	20	5.0	$108,590
Adalimumab dose escalation (n=334)	24	24.9	4.0†	$581,800‡
Ustekinumab dose escalation (n=397)	28	18.6	5.4†	$473,200‡
Ixekizumab dose escalation (n=195)	28	49.50	2.0†	$195,200‡
Guselkumab dose escalation (n=329)	24	44.4	2.2†	$146,740‡

*Biologic therapy included ustekinumab (52%), adalimumab (20%), secukinumab (20%), etanercept (4%), ixekizumab (4%).
†Number needed to treat to achieve clearance in one biologic therapy-naïve subject with standard biologic dosing.
‡Calculated as 2 times the cost of effectively clearing one biologic therapy-naïve subject with standard biologic dosing.

TABLE 8.

Estimated Annual Treatment Costs for Moderate-to-Severe Psoriasis Before and After Formulary Adoption of Cal/BD Foam[9]

	Patients, n*		Total annual cost, $	
	Before Cal/BD foam	After Cal/BD foam	Before Cal/BD foam	After Cal/BD foam
Etanercept 50 mg	600	520	20,361,280	17,646,443
Adalimumab	600	400	43,463,757	31,873,422
Infliximab	600	400	16,342,880	11,984,779
Ustekinumab 90 mg	600	400	35,269,524	25,864,318
Secukinumab	600	400	54,651,678	40,077,897
Apremilast	600	400	9,208,243	6,752,712
Ixekizumab	400	480	22,323,856	26,788,627
Cal/BD foam (moderate-to-severe)	0	800	0	4,520,450
Total annual budget†	4000	4000	201,621,219	165,508,647
Cost per member per month			16.80	13.80

*Based on a hypothetical 1,000,000-population US healthcare plan; 2% with psoriasis and 0.4% (ie, 4000 plan members) with moderate-to-severe psoriasis.
†Based on market share distribution as shown in the preceding rows. Etanercept is the most widely used biologic and its use was projected to decrease disproportionately with the introduction of Cal/BD foam. Ixekizumab use was projected to increase over time as it was a new product.

a safe and effective alternative for patients with beyond-mild psoriasis. By various definitions of severity (PGA, BSA, and/or Rule-of-Tens), Cal/BD foam has consistently been shown to improve treatment outcomes in patients with beyond-mild psoriasis. In MAIC comparisons, Cal/BD yielded higher response rates compared with either apremilast or acitretin. Cal/BD foam also demonstrated lower costs per responder compared with apremilast. In the absence of formal comparative trials, claims of superiority cannot be made. However, together, these data for Cal/BD foam challenge conventional recommendations that limit the use of topical monotherapy to milder forms of psoriasis.[1] Cal/BD foam may be considered among the first-line therapies for beyond-mild psoriasis. Specifically, Cal/BD foam may be preferable to oral agents such as apremilast or acitretin.

The practicality of applying topical agents in psoriasis involving a large BSA is an important issue. However, the administration of Cal/BD foam via an aerosol spray allows it to be applied to large surface areas with relative ease. Moreover, Cal/BD foam is administered once daily,[10] unlike many other topical agents that require twice-daily application.[2] Therefore, having a high BSA involvement at presentation should not preclude the use of Cal/BD foam in patients who are otherwise deemed candidates for this medication. Additionally, Cal/BD foam is associated with a rapid onset of action; the median time to mPASI50 in the PSO-FAST trial was 2.1 weeks, with 65.5% and 82.3% of patients treated with Cal/BD foam achieving mPASI50 by week 2 and week 4, respectively.[39] This suggests that use of Cal/BD foam in patients with extensive disease has the potential to quickly reduce BSA involvement to a more mild to moderate range. At that point, patients have the option to switch treatment or continue with Cal/BD foam, if they desire to avoid oral and biologic medications.

For patients with psoriasis that cannot be effectively managed with oral or biologic medication alone, existing data suggest that adjunctive therapy with Cal/BD foam may improve treatment outcomes with minimal AEs. Adjunctive therapy may offer several advantages that should be considered before switching oral or biologic therapy, including quick symptom relief while patients await laboratory results and/or insurance approval, as well as avoidance of complications that may potentially result from new therapies (eg, lack of response, systemic AEs, development of neutralizing antibodies, worsening of symptoms). Additionally, the ability to discontinue and reinitiate Cal/BD foam without apparent loss of efficacy is conducive to a more flexible treatment plan.

DISCUSSION AND CONCLUSIONS

Despite decades of research, the availability of effective, safe, and affordable treatment options remains an unmet need for many patients with psoriasis. For those with beyond-mild psoriasis, who may be burdened with greater discomfort and comorbidities, higher cost of treatment, and adverse reactions

associated with less tolerable agents, it is crucial that a wide range of options be accessible so that treatment may be tailored to suit individual needs. Cal/BD foam has been shown to be an effective treatment option with potential for cost savings and a role in adjunctive therapy for appropriate patients. Cal/BD foam cannot replace orals and biologics in the management of psoriasis. However, its inclusion among the list of available options for beyond-mild psoriasis can confer benefits to patients who seek fast symptom relief and/or prefer the convenience of a once-daily, user-friendly, and easily applied spray foam.

DISCLOSURES

Leon Kircik has served either as an investigator, consultant, or an advisor for LEO Pharma. Linda Stein Gold is a consultant/investigator/advisor for LEO Pharma, Dermavant, Arcutis, Ortho Derm, Novartis, AbbVie, Lilly, and Celgene. Joyce Teng is an investigator for LEO Pharma. Angela Moore has received funds as an investigator, advisory board member, and speaker for LEO Pharma. Wendy Cantrell has nothing to disclose. Javier Alonso-Llamazares is an investigator for LEO Pharma, speaker for Eli Lilly, Celgene (Amgen), Dermira (Eli Lilly), Ortho Derm and UCB, and serves on Advisory Boards for LEO Pharma. John Koo is a consultant, speaker, and advisor for LEO Pharma, Novartis, Eli Lilly, Janssen, AbbVie, Ortho Dermatologic, Sun Pharma, Pfizer, Regeneron/Sanofi, and UCB.

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