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ITCHING FOR RELIEF: THE EVIDENCE OF FIXED DOSE CALCIPOTRIOL PLUS BETAMETHASONE DIPROPIONATE FOAM FOR PSORIASIS

Introduction

Psoriasis is a chronic immune-mediated skin disease with a variety of morphological presentations, distribution patterns and severities. Psoriasis can have a profound impact on health-related quality of life (HRQoL), almost equal to that seen in patients suffering from cardiovascular disease and cancer.[1] In Canada, it is estimated that approximately 3% of the population suffers from psoriasis, equating to over 1 million people.[2] The most common presentation is 'mild-to-moderate' plaque psoriasis characterized by well-defined silver scaly plaques on extensor surfaces.[3] However, classifying severity can be challenging. In 2020, the International Psoriasis Council recommended classifying psoriasis severity with a dichotomous definition: either candidates for topical therapy or candidates for systemic therapy.[4] Regardless of severity, all patients living with psoriasis will need a topical agent as part of their treatment regimen throughout the clinical course of their disease.

Topical treatments used to treat psoriasis in Canada include steroids, vitamin D analogues, retinoids, tar, keratolytic agents and fixed dose combination products. In 2001, the fixed dose combination of calcipotriol (Cal) 50 µg/g plus betamethasone dipropionate (BD) 0.5 mg/g was approved by Health Canada in ointment form, followed by a gel in 2012 and an aerosol ointment-based foam (Cal/BD foam) in 2016. Other combination products for psoriasis include topical steroids combined with either tazarotene or salicylic acid.

Fixed dose combination products have several advantages versus topical monotherapy agents including ease of use, increased efficacy, improved adherence, and potentially fewer adverse events.[5] Specifically for Cal/BD, Cal has been shown to reduce atrophy associated with BD; whereas, BD has been shown to reduce the irritation associated with Cal.[6]

The aim of this article is to review the evidence with regards to efficacy, onset of action, itch relief and patient-reported outcomes for Cal/BD foam.

Efficacy

Cal/BD foam is approved in Canada for the topical treatment of psoriasis vulgaris in adult and adolescent patients 12 years or older for up to 4 weeks.[8] All studies to be discussed hereafter include subjects with mild-to-severe disease severity. Head-to-head studies comparing Cal/BD foam to ointment[9] and gel[10] have demonstrated superiority of the foam in achieving physician global assessment as "clear" or "almost clear" (**Figure 1**) with at least a two-point improvement (PGA success), as well as superiority in the proportion of patients achieving at least a 75% reduction in modified psoriasis area severity index (mPASI75) (**Figure 2**). The PSO-LONG study also demonstrated ongoing proactive twice weekly use

beyond the initial daily 4 weeks resulted in patients in the proactive group having an additional 41 days in remission compared with the reactive group over a 1 year period (P < .001).[11] While there are no head-to-head studies comparing Cal/BD foam to the newer fixed dose combination of halobetasol plus tazarotene lotion (HP/TAZ lotion), an anchor-based, matching adjusted indirect comparison of the two products was performed. The indirect comparison found that 4 weeks of Cal/BD foam produced greater PGA success than 8 weeks of HP/TAZ lotion (**Figure 3**) (51.4 vs. 30.7%, p < .001).[12]

Onset of Action

The PSO-FAST study involving 426 subjects looked at the efficacy and safety of Cal/BD foam versus vehicle. At 4 weeks, 53.3% of subjects achieved PGA success in the Cal/BD foam group versus 4.8% in the vehicle group (OR 30.3, 95% CI 9.7,94.3; P < .001). Similarly, 52.9% of subjects achieved a mPASI75 in the Cal/BD foam group versus 8.2% on placebo (OR 14.9; 95% CI 6.5, 34.0; P < .001). Equally important, no major safety signals were identified. Incidence of adverse events were similar between active and placebo arms with most events rated as mild or moderate in

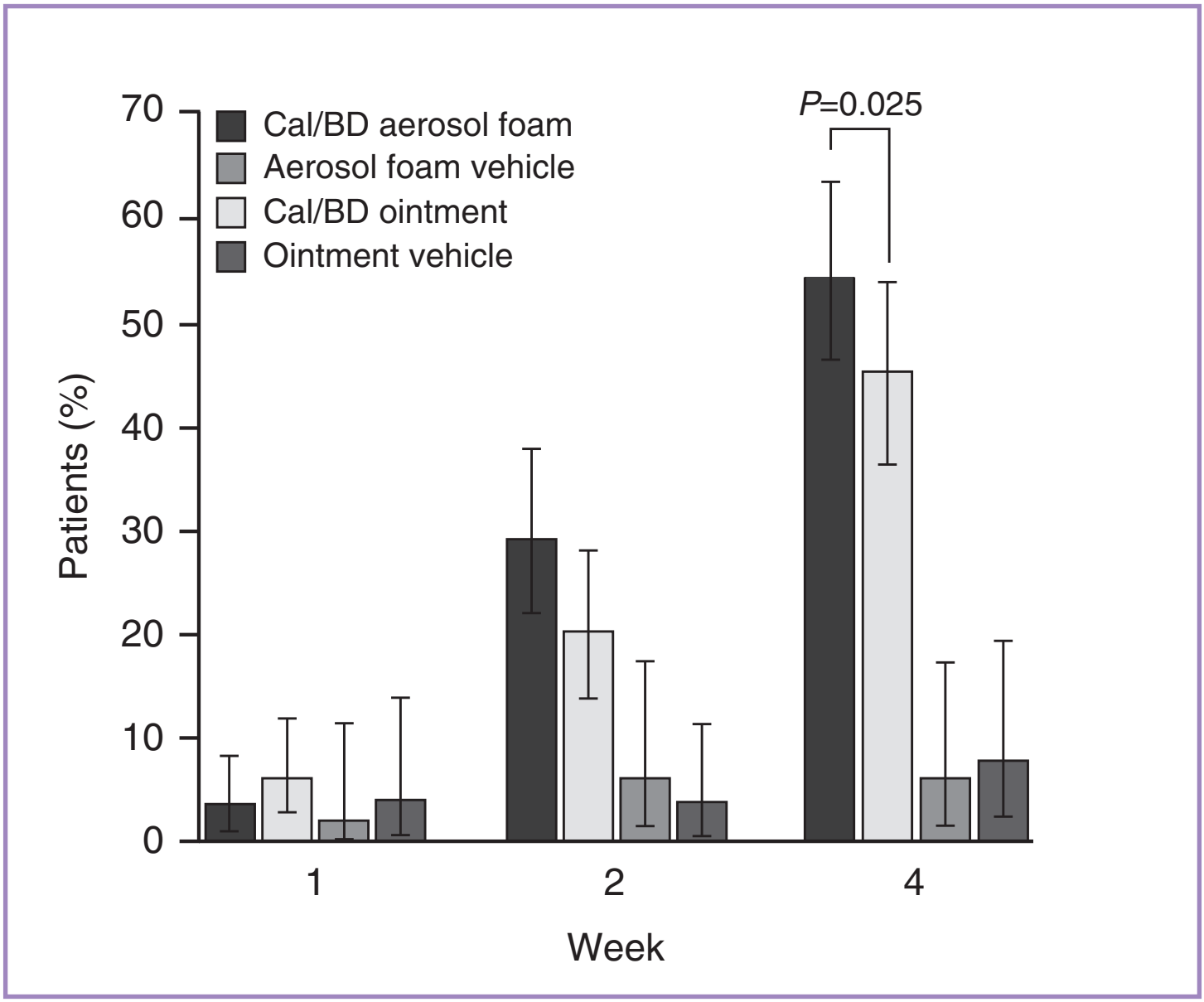


Figure 1. Proportions of patients experiencing treatment success as determined by InvestigatProportion of patients achieving PGA-assessed treatment success* over time. *Investigator assessment by PGA as ''clear'' or ''almost clear'' with at least a two-step improvement was defined as patient having achieved treatment success. Bars show 95% confidence interval. BD, betamethasone dipropionate 0.064%; Cal, calcipotriene 0.005%.

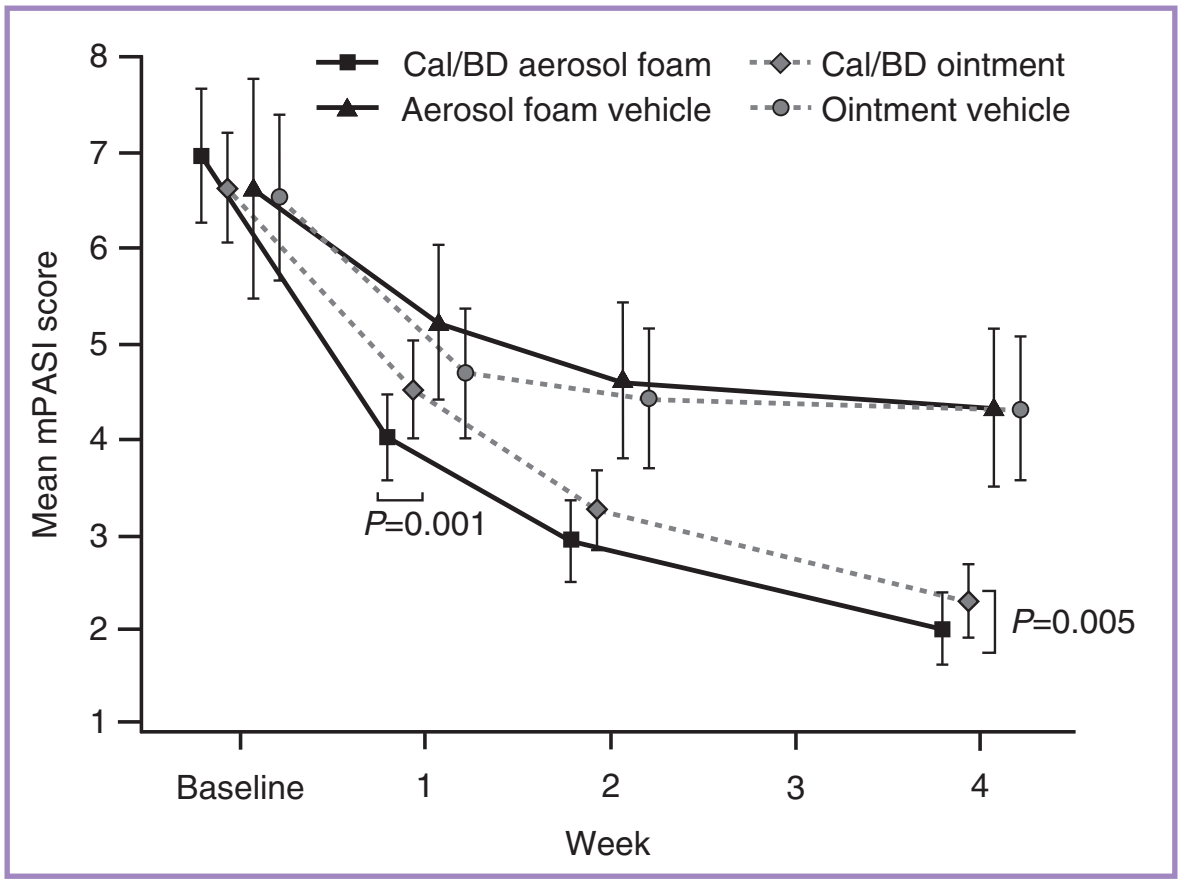


Figure 2. Change in mean mPASI over time. Bars show 95% confidence interval. BD, betamethasone dipropionate 0.064%; Cal, calcipotriene 0.005%; mPASI, modified psoriasis area severity index.

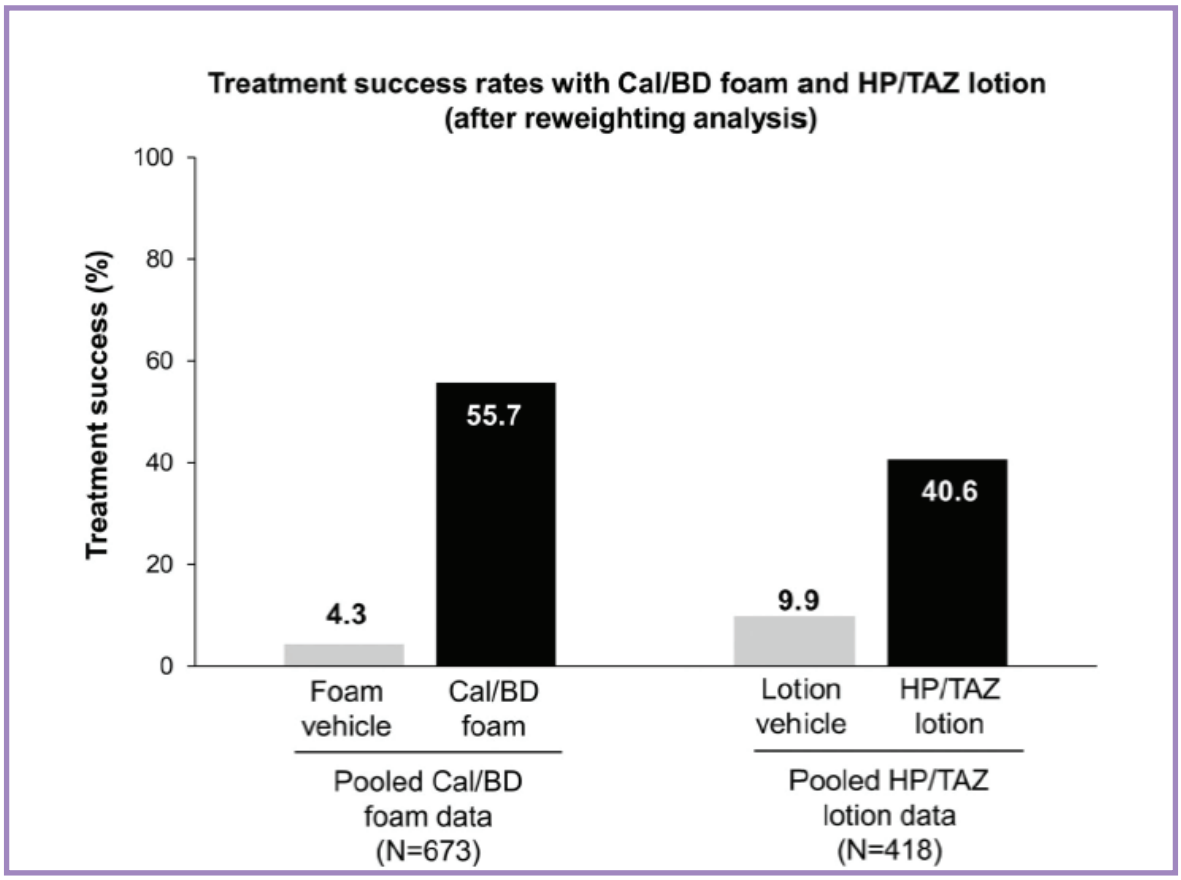


Figure 3. Matching-adjusted indirect comparison of PGA treatment success for patients treated with 4 weeks of Cal/BD foam or 8 weeks of HP/TAZ lotion. Abbreviations. Cal/BD, calcipotriene plus betamethasone dipropionate; HP/TAZ, halobetasol plus tazarotene.

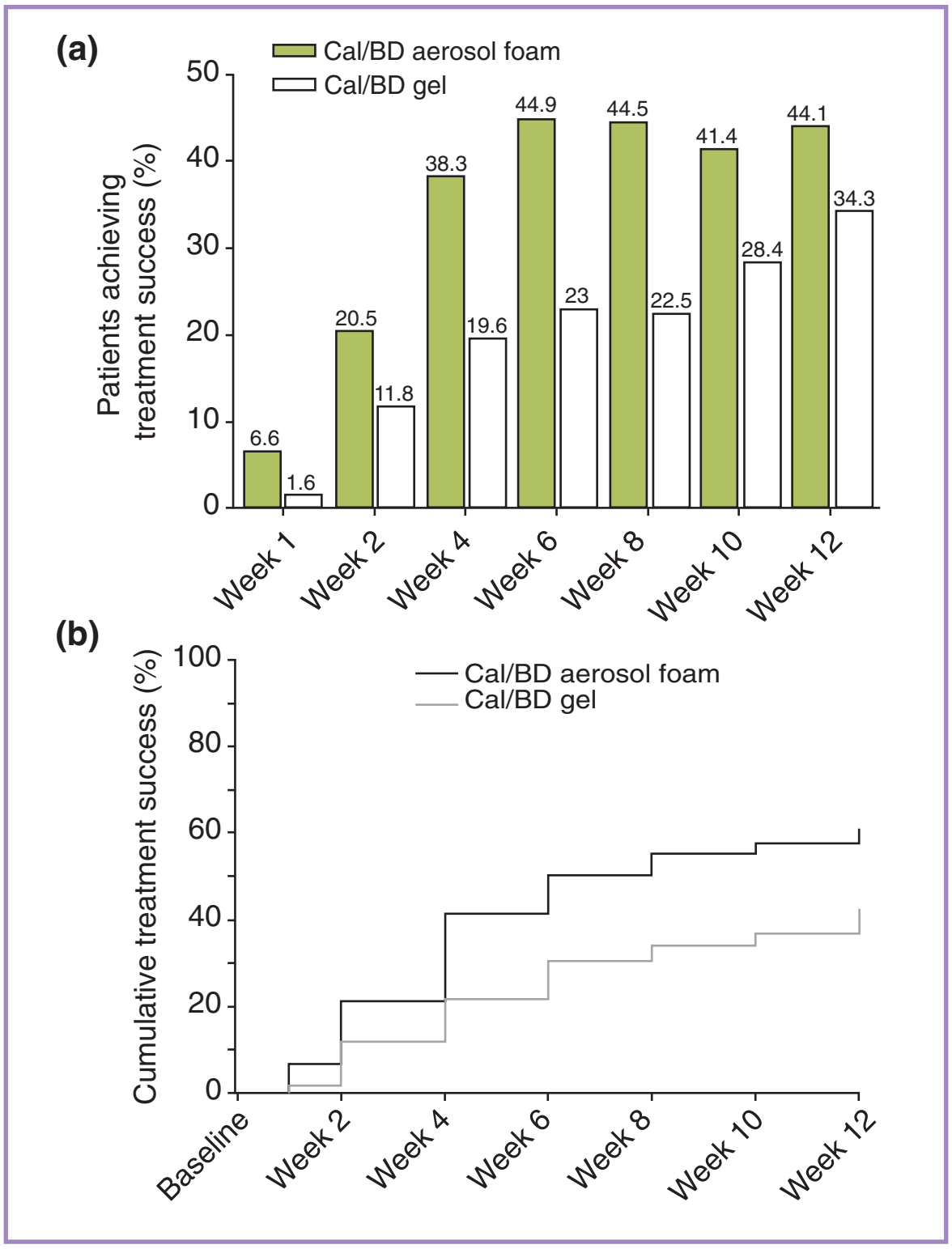
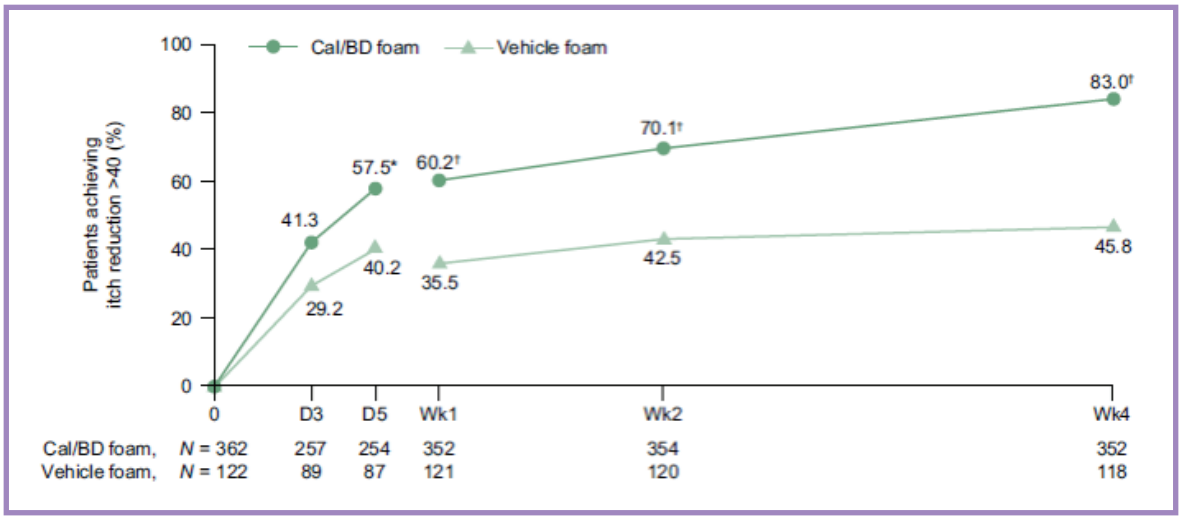


Figure 4. (a) Treatment success rates by visit (MI). (b) Time to treatment success, according to PGA (observed cases), in Cal/BD aerosol foam and gel groups. MI, multiple imputation.



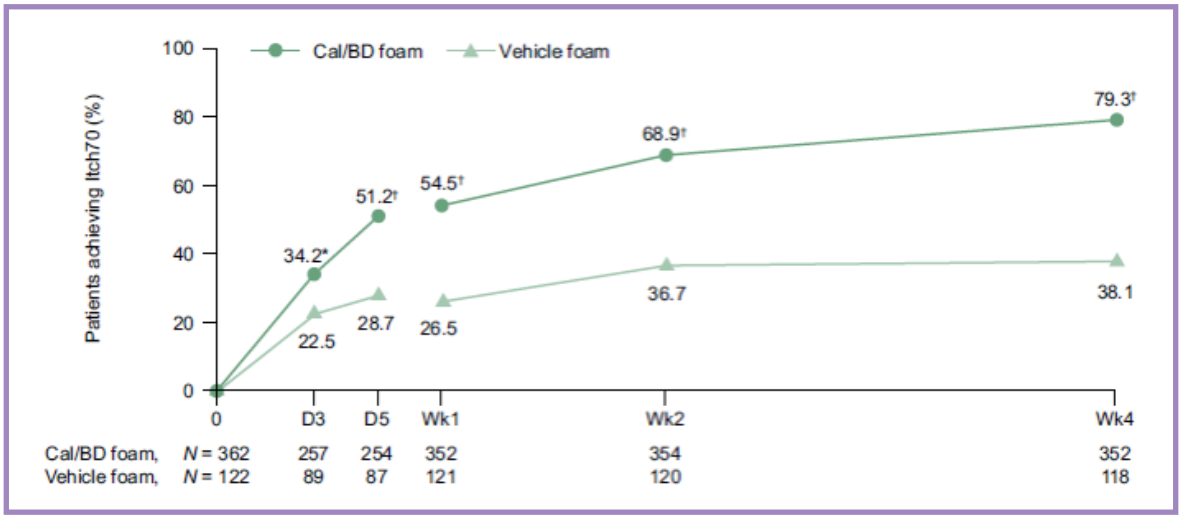


Figure 5. Proportion of patients achieving (a) absolute itch reduction >40 from baseline and (b) ≥70% improvement in itch. All patients in (a) and (b) had a baseline itch VAS >40; results for Days 3 and 5 were recorded from the Phase III pool, while results from Week 1 to 4 were recorded from the complete pool.*P < 0.05; †P < 0.001 vs. vehicle foam. The absence of symbol indicates P ≥ 0.05. The discontinuity in the figure lines in (a) and (b) indicates the use of the two different patient pools. BD, betamethasone dipropionate (0.5 mg/g); Cal, calcipotriol (50 µg/g); D, day; Wk, week.

severity. Adverse drug reactions were reported in ten Cal/BD foam patients (3.1%) and two vehicle patients (1.9%).[13] Due to the fast onset of action of Cal/BD foam, the PSO-ABLE study was designed based on the hypothesis that 4 weeks of Cal/BD foam was superior in efficacy to 8 weeks of Cal/BD gel, which was demonstrated (**Figure 4**).[10]

Itch Relief

Itch is a significant driver of health-related quality of life (HRQoL) deterioration related to psoriasis. As such, rapid and sustained improvement in itch is a valuable outcome for today's therapeutic treatments. A pooled analysis from three phase III studies examined the following outcomes: itch visual analogue scale (VAS) reduction >40 (**Figure 5a**), ≥70% improvement in itch (Itch70) (**Figure 5b**) or itch-related sleep loss, mPASI75 (excluding head) and Dermatology Life Quality Index (DLQI) scores 0/1 through 4 weeks. The results demonstrated that 57.5% of Cal/BD foam subjects achieved an itch VAS reduction of >40 from day 5 onwards versus 40.2% in the vehicle group (P < 0.05) and by week 4 this increased to 83% in the Cal/BD arm vs 45.8% in the vehicle arm (P < 0.001). A statistically significant difference in those achieving ≥70% improvement in itch was demonstrated in the Cal/BD foam group vs the vehicle group as early as day 3 (34.2% vs 22.5%, P < 0.05) and by week 4 this increased to 79.3% vs 38.1% (P < 0.001).[14]

Patient-reported Outcomes

The PSO-ABLE study also examined HRQoL wholistically in addition to itch specifically. Subjects enrolled in the study completed the Dermatology Life Quality Index (DLQI), EuroQoL-5D-5L-PSO (EQ-5D), and Psoriasis QoL (PQoL-12) questionnaires at baseline, Weeks 4, 8 and 12. At the 4-week study time point Cal/BD foam demonstrated meaningful improvement in HRQoL measures. Significantly more Cal/BD foam patients achieved DLQI scores of 0/1 at Weeks 4 (45.7% vs 32.4%; p = 0.013) and 12 (60.5% vs 44.1%; p = 0.003) than Cal/BD gel patients (**Figure 6**). Cal/BD foam significantly improved EQ-5D utility index (0.09 vs 0.03; p<0.001) and PQoL-12 scores (-2.23 vs -2.07; p = 0.029) from baseline to Week 4 versus Cal/BD gel. Itch, itch-related sleep loss, and work impairment improved more with Cal/BD foam than gel.[15]

Conclusion

Psoriasis is a chronic, relapsing, and unpredictable inflammatory disease. All patients can benefit from a safe, effective, and fast treatment whether they are candidates for topical treatments only or if they are also candidates for systemic therapies. The use of Cal/BD foam has demonstrated efficacy, quick onset of action, itch relief and overall improvement in HRQoL measures in various peer-reviewed studies of mild-to-severe plaque psoriasis. Thus, Cal/BD foam should be considered a valuable therapeutic tool for clinicians to use with psoriasis patients across all disease severities.

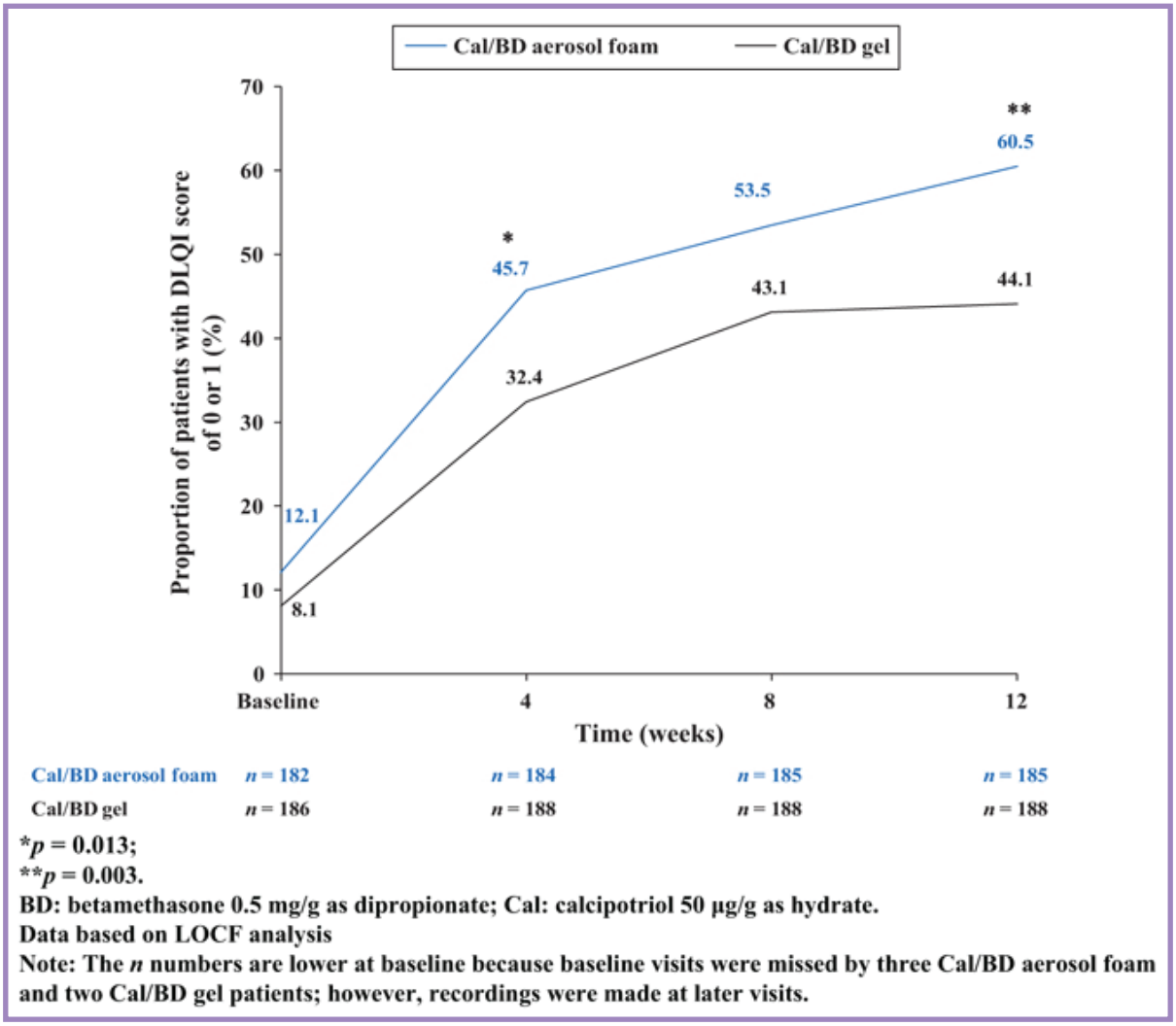


Figure 6. Proportion of patients with a Dermatology Life Quality Index score of 0 or 1 with Cal/BD aerosol foam versus Cal/BD gel at baseline and Weeks 4, 8 and 12; adapted from Griffiths et al, 2018.

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