SUPPLEMENT ARTICLE

Fixed-dose combination calcipotriol/betamethasone dipropionate foam provides a rapid onset of action, effective itch relief and improves patient quality of life

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Abstract The physical symptoms of psoriasis vulgaris (chronic plaque psoriasis), such as itch and itch-related sleep loss, and the psychological impact of visible plaques on the body, all contribute to significantly reduced health-related quality of life (HRQoL) in patients with psoriasis. In fact, the deterioration of HRQoL in patients with psoriasis is similar to patients with other chronic conditions, such as cancer and cardiovascular diseases. Rapid and effective improvements in HRQoL and itch-related outcomes would therefore be highly valued by patients and may even improve adherence to treatment. In this article, we summarise previously published data assessing the impact of fixed-dose combination calcipotriol 50 μg/g plus betamethasone dipropionate 0.5 mg/g cutaneous foam (Cal/BD foam) on itch relief, quality of sleep, onset of action and HRQoL. Findings across multiple analyses indicate that Cal/BD foam provides significant improvements in itch, itch-related sleep loss and HRQoL compared with vehicle foam or Cal/BD gel comparators. Additionally, the benefits of Cal/BD foam were recorded earlier than these comparators, often within 1 week of treatment, indicating a rapid onset of action. With the published data to hand, it is clear that Cal/BD foam provides significant improvements in the outcomes that matter most to patients and should be considered an effective topical treatment for psoriasis.

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Conflicts of interest

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Introduction

Psoriasis vulgaris (chronic plaque psoriasis) is the most common psoriasis subtype and is characterised by scaly erythematous plaques on the skin.[1–3] The presence of these plaques, in addition to associated symptoms like itch, scaling and redness, has a significant negative impact on patients' health-related quality of life (HRQoL), reducing physical, psychological and social well-being.[4–6] Despite often being overlooked in the clinical setting, the debilitating effect of psoriasis on HRQoL should not be underestimated. The Global Burden of Disease project ranked skin and subcutaneous disorders, including psoriasis, as the 4th leading cause of non-fatal disease burden,[7,8] while patients with psoriasis have reported a similar deterioration in HRQoL as patients with other serious chronic diseases, including cancer and cardiovascular diseases.[2]

The factors associated with the decline in HRQoL in patients with psoriasis are well documented. Regardless of disease severity, itch is commonly reported in psoriasis and often regarded by patients as the most burdensome symptom: 64%–97% of patients with psoriasis suffer from itch[9–12] and around 75% regard freedom from itch as a primary need.[12,13] This is unsurprising, as psoriasis-related itch negatively impacts sleep and stress, and increases feelings of stigmatisation and depression.[14,15] Itch and itch-related sleep loss, in particular, have been

shown to decrease HRQoL and work productivity,[16,17] while sleep deprivation impacts psychological well-being through increased stress, anxiety and depression.[18]

Alongside the debilitating impact on HRQoL caused by physical symptoms like itch, the presence of visible plaques on patients with psoriasis can also lead to severe psychological stress and psychosocial disability.[3,19] Patients with psoriasis commonly report reduced self-esteem and emotional well-being,[3] as well as acute feelings of stigmatisation.[19] In fact, more than 5% of patients with psoriasis have reported depressive symptoms and suicidal ideation as a result of their disease.[1,20]

Given the dramatic burden of psoriasis on patients with the disease, it is therefore crucial for any successful psoriasis treatment to positively impact outcomes associated with HRQoL. Most clinical trials of new treatments focus on objective, physical markers of disease severity as efficacy endpoints, which by themselves might not resonate with patients in a real-life setting.[1] Noticeable improvements in HRQoL and outcomes such as itch relief may be far more meaningful to patients and prescribing physicians, as these are more likely to be associated with 'treatment success' by patients.[1]

In addition to improvements in HRQoL, speed of onset of action is also an important consideration for psoriasis treatments. Due to the significant impact of psoriasis symptoms on daily life, patients value rapid improvement in them in response to treatment.[13] However, many patients with psoriasis express frustration at the perceived ineffectiveness of their psoriasis treatment.[21] This is significant, as unrealistic expectations of the speed of onset of action have been shown to lead to poor adherence and treatment outcomes.[22,23] It is therefore plausible that adherence to a topical treatment, which is typically low, is likely to improve if patients are able to experience an early onset of action, with sustained improvement over time.[23]

Fixed-dose combination calcipotriol 50 μg/g plus betamethasone dipropionate 0.5 mg/g cutaneous aerosol foam (Cal/BD foam; Enstilar® [LEO Pharma, Ballerup, Denmark]) is a topical treatment which has previously demonstrated clinical efficacy and safety in the treatment of psoriasis (discussed in Tada Y, *et al.* and Stein Gold L, *et al.* of this supplement).[24–28] Accordingly, this article will highlight previously published and important findings on the impact of Cal/BD foam on itch relief, quality of sleep, onset of action and HRQoL.

Itch relief

The burden of itch and itch-related sleep loss are important contributors to the detrimental impact of psoriasis on patients and their HRQoL.[14–18] Despite this, and the numerous therapeutic options available that target psoriatic lesions, there is a distinct lack of options for managing itch as a symptom.[5] This may be attributed to the fact that the exact pathophysiology of itch in psoriasis is not fully understood, as it involves complex interactions between skin cells, immune cells, secreted factors and cutaneous neural networks. Research suggests an increase in certain itch-related substances and their receptors, such as nerve growth factor and substance P, and a decrease in itch/pain modulating substances, such as neuropeptide Y, may be associated with itch in psoriasis. Cytokines released from immune cells, such as IL-17A, IL-23A and IL-31, may also be key itch modulators, although this has yet to be confirmed.[5,29]

Cal/BD foam has demonstrated effective itch relief and improved itch-related sleep loss.[28] Although its antipruritic method of action is not fully understood,[5] it appears the topical combination of vitamin D and steroid improves barrier function and may attenuate immune function by inhibiting the cascade of key 'itch cytokines' noted above.[5,29,30] Previous studies have demonstrated that Cal/BD foam provides effective itch relief in the overall psoriasis patient population.[28] Recently, a *post hoc* pooled analysis of three Phase II/III trials examined the efficacy of Cal/BD foam at providing itch relief in patients with severe itch symptoms compared with vehicle foam.[12]

The pooled analysis included results from a 4-week Phase II study (NCT01536886),[31] the 4-week Phase III study PSO-FAST (NCT01866163)[28] and the 12-week Phase III study PSO-ABLE (NCT02132936).[26] An itch severity visual analogue scale (VAS) was used to identify patients ($N = 484$) with severe itch at baseline (itch severity VAS >40), who received either Cal/BD foam ($n = 362$) or vehicle foam ($n = 122$). This patient population was used to analyse itch relief over 4 weeks, with results starting from Week 1. A separate pool of patients from just the two Phase III studies was used to analyse itch relief results recorded earlier than Week 1, as the Phase II study did not record results at these early time points.[12]

Over 4 weeks, a greater proportion of patients receiving Cal/BD foam achieved an absolute itch reduction (itch VAS improvement >40 from baseline) compared with vehicle foam (Fig. 1a). This difference reached statistical significance by Day 5 (57.5% vs. 40.2%; $P < 0.01$) and continued to increase through to Week 4 (83.0% vs. 45.8%; $P < 0.001$).[12]

Similarly, a higher proportion of patients receiving Cal/BD foam achieved itch relief ≥70% VAS from baseline compared with vehicle foam (Fig. 1b). From as early as Day 3, 34.2% of patients receiving Cal/BD foam achieved ≥70% improvement in itch VAS compared with 22.5% of patients receiving vehicle foam ($P < 0.05$); by Week 4, this had increased to 79.3% and 38.1%, respectively ($P < 0.001$).[12]

In this study, the reduction in itch was also associated with significant improvements in itch-related sleep loss in patients receiving Cal/BD foam (Fig. 1c). In patients ($N = 218$) pooled from the two Phase III studies, who suffered from both severe itch (baseline itch VAS >40) and sleep loss (baseline sleep loss VAS >20), a higher proportion receiving Cal/BD foam reported improvements in itch-related sleep loss at Week 1 compared with vehicle foam (58.2% vs. 41.0%; $P < 0.05$). Sleep quality

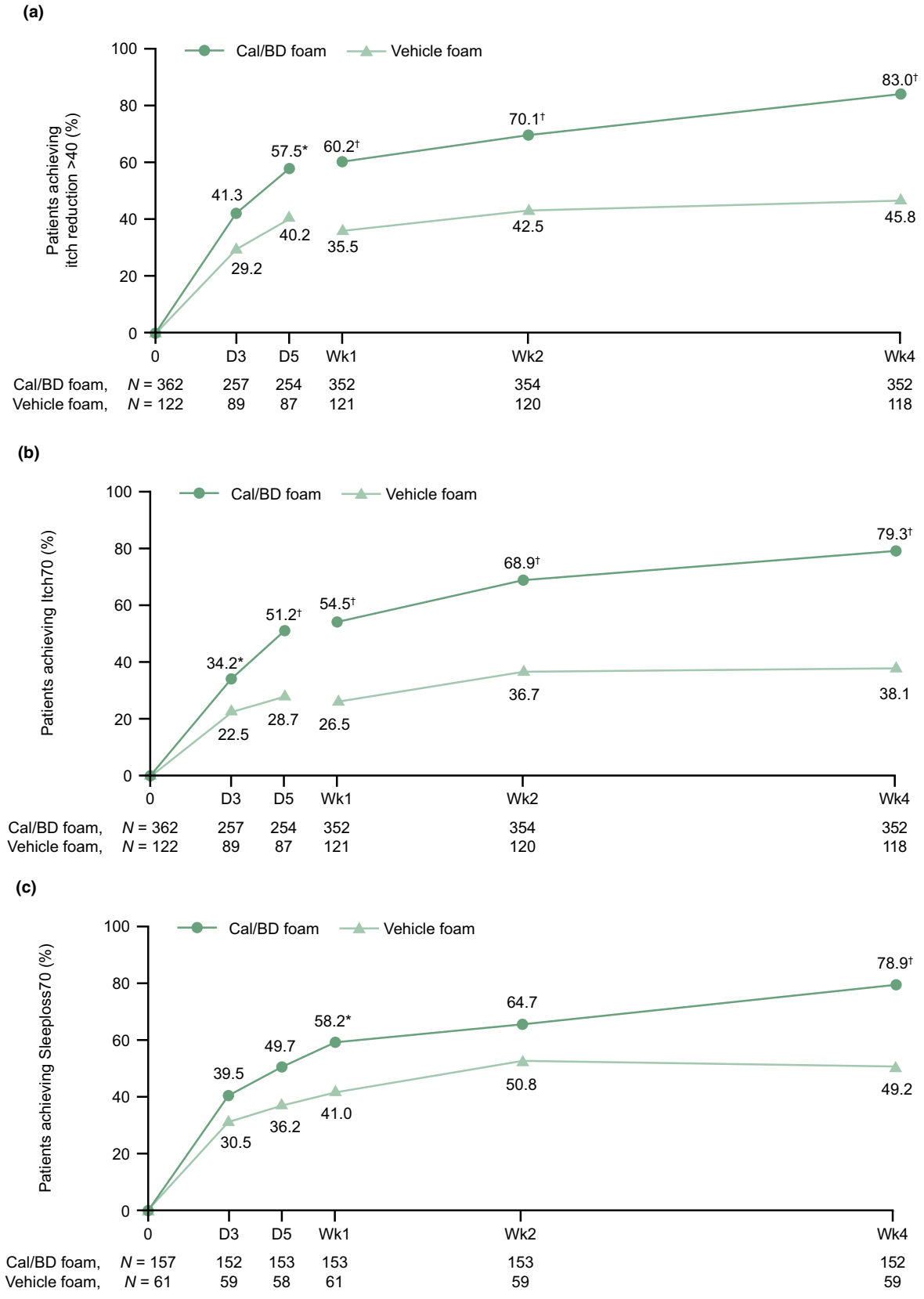

Figure 1 Proportion of patients achieving (a) absolute itch reduction >40 from baseline; (b) ≥70% improvement in itch and (c) ≥70% improvement in itch-related sleep loss. All patients in (a) and (b) had a baseline itch VAS >40; results for Days 3 and 5 were recorded from the Phase III pool, while results from Week 1 to 4 were recorded from the complete pool. All patients in (c) had a baseline itch VAS >40 and sleep loss VAS >20; all results were recorded from the Phase III pool. *$P < 0.05$; †$P < 0.001$ vs. vehicle foam. The absence of symbol indicates $P \geq 0.05$. The discontinuity in the figure lines in (a) and (b) indicates the use of the two different patient pools.[12] BD, betamethasone dipropionate (0.5 mg/g); Cal, calcipotriol (50 μg/g); D, day; Wk, week. Originally published in Jalili *et al.*[12] Reproduced with kind permission from John Wiley & Sons.

improvements continued throughout the study, with a statistically significant difference between the groups at Week 4 ($P < 0.001$).[12]

Although the lack of validated itch-related sleep-loss measurement tools and the lower patient numbers at early time points limit this pooled analysis, it does have several key strengths. The outcomes selected (an absolute itch VAS improvement >40 and the achievement of ≥70% improvement in itch VAS and itch-related sleep loss) were chosen by the authors as clinically relevant measures of itch improvement that would be meaningful to both patients and prescribing physicians. Furthermore, the patients included were those most affected by itch, rather than the overall patient population.[12] The results therefore provide evidence for the clinically meaningful antipruritic efficacy of Cal/BD foam in patients with the highest need for itch relief – a fact that will be significant to the large proportion of patients who list itch as their most burdensome symptom. The findings of this study also demonstrate that Cal/BD foam offers more rapid and effective itch relief compared with vehicle foam, as well as providing meaningful improvements in sleep loss.[12] This is significant, as itch-related sleep loss has rarely been investigated for topical psoriasis treatments. Patients with severe psoriasis often use systemic treatment options, which have been shown to improve sleep disturbances and HRQoL.[32] The results from this pooled analysis, along with those from PSO-FAST,[28] are amongst the first where topical treatments have demonstrated a positive impact on sleep loss in patients with severe itch, suggesting Cal/BD foam may be a viable treatment option for patients with more severe psoriasis.

Rapid onset of action

Due to the significant negative impact of psoriasis symptoms, particularly on HRQoL, patients value fast, noticeable improvement of symptoms in response to treatment.[13] A rapid onset of action is therefore a meaningful outcome to patients and may even increase their adherence to topical treatments.[22,23] Recent analyses have evaluated the efficacy of Cal/BD foam at early time points and provided evidence for its rapid onset of action.

In a pooled analysis ($N = 848$) of PSO-FAST, PSO-ABLE and a Phase II study (NCT01536886), the efficacy of Cal/BD foam ($n = 649$) and vehicle foam ($n = 199$) was compared over a 4-week period, with efficacy assessments beginning at Week 1.[23] The proportion of patients achieving various modified Psoriasis Area and Severity Index (mPASI) targets (mPASI 0, ≤1, ≤3 or ≤5) was compared between treatment groups for all patients. Additionally, the proportion of patients achieving these mPASI targets was assessed in a subgroup of patients with severe psoriasis (mPASI >10 at baseline), as well as the proportion of patients who achieved physician's global assessment (PGA) 'clear' or 'almost clear' despite being PGA 'severe' at baseline.[23]

Findings showed that Cal/BD foam demonstrated greater efficacy than vehicle foam and provided a faster onset of action.[23] At Week 1, a greater proportion of patients receiving Cal/BD foam versus vehicle foam achieved targets of mPASI ≤1 ($P < 0.01$), ≤3 ($P < 0.001$) and ≤5 ($P < 0.001$). These statistically significant improvements continued through to Week 4, where a greater proportion of patients receiving Cal/BD foam also achieved mPASI target of 0 compared with vehicle foam ($P < 0.001$) (Fig. 2a).[23] The fact that significantly more patients treated with Cal/BD foam achieved these stringent mPASI targets, as early as Week 1, is a strong indicator of its rapid onset of action. The statistical improvement over vehicle foam was observed even for lower mPASI targets, suggesting that patients treated with Cal/BD foam would be more likely to experience noticeable and meaningful improvements to their condition after a relatively short period of time. Furthermore, these improvements would likely be sustained over time, as Cal/BD foam provided significant improvements compared with vehicle foam over the entire 4 weeks of treatment.

In the subgroup of patients with baseline mPASI >10 (Fig. 2b), a greater proportion of patients receiving Cal/BD foam versus vehicle foam achieved mPASI ≤1 ($P < 0.05$), ≤3 ($P < 0.001$) and ≤5 ($P < 0.001$) at Week 4. Additionally, a significantly higher proportion of patients treated with Cal/BD foam achieved mPASI ≤5 by Week 2 ($P < 0.001$) versus those treated with vehicle foam, indicating a rapid onset of action even in the most severe patients. In patients with PGA 'severe' at baseline, there was a trend towards a greater proportion of patients treated with Cal/BD foam achieving PGA 'clear'/'almost clear' versus vehicle foam from as early as Week 1.[23]

As discussed earlier in this article, a separate pooled analysis of the same Phase II/III trials evaluated the itch relief efficacy of Cal/BD foam versus vehicle foam in patients severely affected by itch ($N = 484$). Compared with vehicle foam, a significantly higher proportion of patients treated with Cal/BD foam achieved from baseline: a ≥70% VAS improvement in itch by Day 3 ($P < 0.05$); a ≥70% VAS improvement in itch-related sleep loss

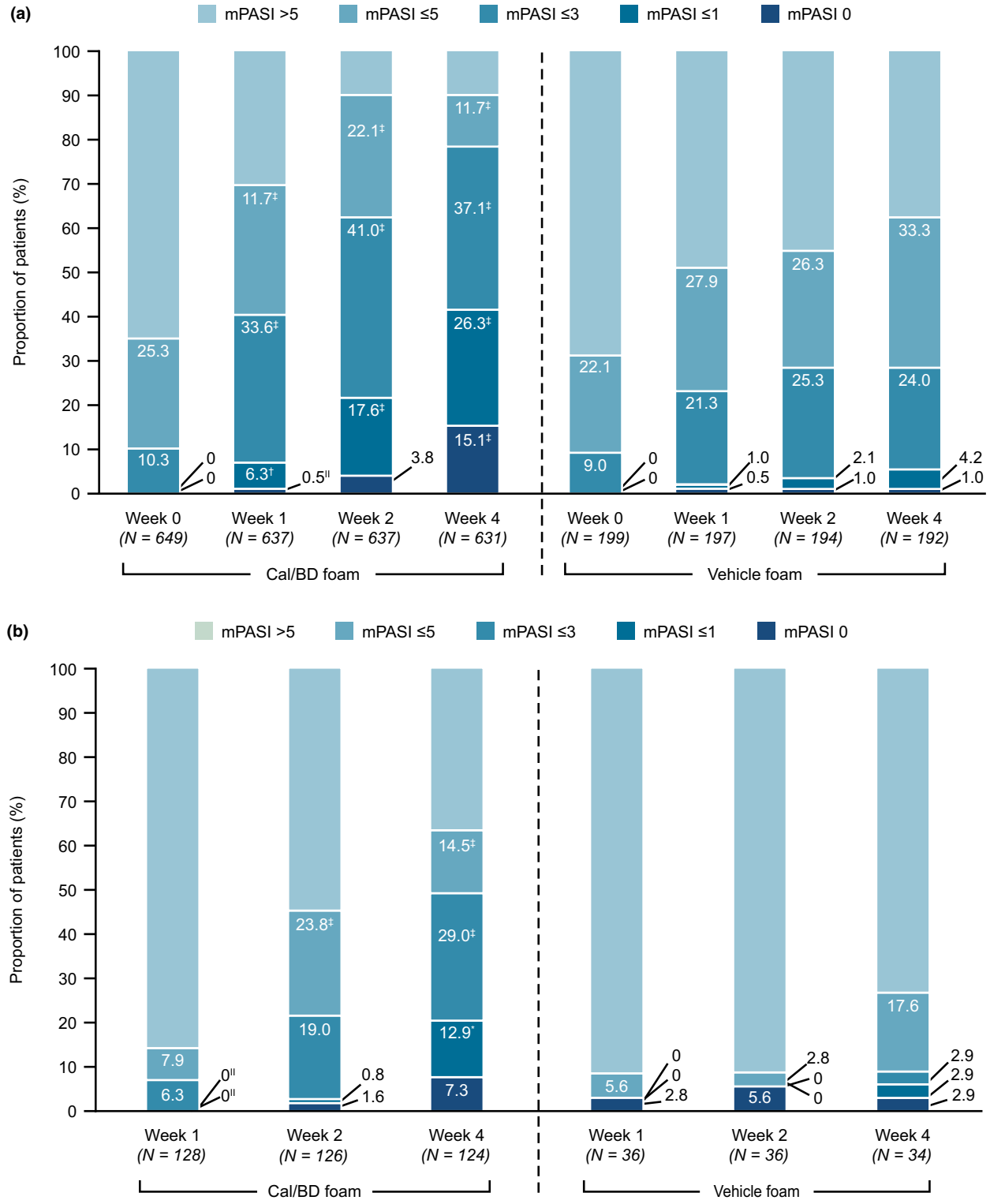

Figure 2 Patients in the complete pool achieving mPASI targets 0, ≤1, ≤3 and ≤5 at Week 4: (a) all patients or (b) severe patients with baseline mPASI >10. *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$ vs. vehicle foam. The absence of symbol indicates $P > 0.05$. ‖ indicates number was too small to calculate P value.[23] BD, betamethasone dipropionate (0.5 mg/g); Cal, calcipotriol (50 μg/g); mPASI, modified Psoriasis Area and Severity Index. Originally published in Pink *et al.*[23] Reproduced with kind permission from John Wiley & Sons.

by Week 1 ($P < 0.05$); and an absolute itch reduction (itch VAS improvement >40) by Day 5 ($P < 0.05$). Interestingly, these improvements in itch occurred before noteworthy clinical improvements in efficacy (assessed by mPASI) were observed.[12] As it is likely that many patients highly value noticeable improvements in symptoms such as itch, this extremely early onset of action for itch relief further highlights the efficacy of Cal/BD foam in terms of meaningful and relevant outcomes to the patient.

Taken together, these analyses demonstrate that Cal/BD foam provides a rapid onset of action for clinically important outcomes in patients with psoriasis, which may translate into increased patient satisfaction and continued treatment adherence with Cal/BD foam.

Quality of life

The negative impact of psoriasis symptoms dramatically decreases HRQoL, which is a significant factor in the burden of disease.[2–8] As such, it is important that HRQoL outcomes are included in clinical studies of psoriasis treatments.[1] The Dermatology Life-Quality Index (DLQI) is commonly used to track changes in HRQoL during psoriasis treatment,[33] and several studies have examined the effect of Cal/BD foam treatment on HRQoL by tracking changes in DLQI.[3,23,34,35]

One such study compared Cal/BD foam versus vehicle foam, using results from the 4-week, Phase III PSO-FAST study.[3] DLQI scores were assessed at baseline and Weeks 1, 2 and 4.[3] At Week 1, a greater mean improvement in DLQI from baseline was observed for Cal/BD foam compared with vehicle foam ($P < 0.001$). This improvement was sustained to Week 4, where a greater mean improvement from baseline was observed in patients using Cal/BD foam versus vehicle foam (−7.0 vs. −4.4; $P < 0.001$).[3]

An improvement in DLQI score of ≥5 from baseline was used to define a minimal clinically significant difference in HRQoL. In patients with baseline DLQI scores ≥5, 81.2% of patients receiving Cal/BD foam achieved a ≥5-point improvement compared with 57.3% of patients receiving vehicle foam ($P < 0.001$).[3] By the end of the study, more than twice the proportion of patients receiving Cal/BD foam reported no impairment on HRQoL (DLQI = 0/1) compared with vehicle foam (48.1% vs. 21.2%; $P < 0.001$).[3]

Similar HRQoL results were reported from the Phase III PSO-ABLE study.[34] Significantly more patients treated with Cal/BD foam 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 those treated with Cal/BD gel. However, mean DLQI score improvements were similar for both patient groups at Weeks 4 and 12.[34]

A pooled analysis of the PSO-FAST and PSO-ABLE studies demonstrated that a significantly greater proportion of patients with baseline DLQI >10 achieved target DLQI ≤1 ($P = 0.001$) or 0 ($P = 0.006$) at Week 4 with Cal/BD foam versus vehicle foam.[23]

In addition to clinical studies, the positive effect of Cal/BD foam on HRQoL is also reflected in a real-world setting. In a patient global assessment of psoriasis undertaken in Germany ($N = 410$), 43% of patients stated that their psoriasis had no negative influence on QoL (DLQI = 0/1) after 4 weeks of Cal/BD foam treatment compared with just 10% at inclusion.[35]

DLQI scores are a reliable and well-used metric for tracking changes in HRQoL during psoriasis treatment. Taken separately and pooled together, DLQI results from the PSO-FAST and PSO-ABLE studies indicate that treatment with Cal/BD foam is likely to improve patient HRQoL,[3,23,34] a key goal in psoriasis treatment given the severe burden of disease felt by many patients. This is further supported by real-world evidence of improvement in patient HRQoL,[35] indicating that Cal/BD is likely to provide very real and tangible benefits to patients with psoriasis. Further real-world evidence in support of Cal/BD foam is discussed in more detail in Armstrong A, *et al.* of this supplement.[36]

Although DLQI is most commonly used, it is not the only HRQoL tool that can be used to evaluate response to psoriasis treatment. The EuroQoL-5D-5L (EQ-5D) is a generic HRQoL questionnaire, with utility index scores ranging from 0 to 1 (1 indicating perfect health) for five domains (mobility, self care, usual activities, pain/discomfort and anxiety/depression).[37] EQ-5D results from the PSO-FAST analysis showed that the mean improvement in EQ-5D utility index scores from baseline to Week 4 was significantly greater with Cal/BD foam versus vehicle foam ($P = 0.05$). This improvement was most noticeable in the pain/discomfort domain, where the proportion of patients treated with Cal/BD foam who reported no pain/discomfort increased from baseline (30.1%) to Week 4 (68.4%). At Week 4, this proportion was significantly higher for Cal/BD foam compared with vehicle foam (68.4% vs. 43.0%; $P < 0.001$).[3] EQ-5D results were similar in PSO-ABLE, where Cal/BD foam significantly improved EQ-5D utility index scores at Week 4 compared with Cal/BD gel ($P \leq 0.001$).[35] The psoriasis-specific psoriasis quality of life questionnaire-12 (PQoL-12)[38] comprises 12 questions to assess how psoriasis affects a range of QoL measures, including itch, pain/discomfort, embarrassment and emotional well-being, with scores for each question ranging from 0 (not at all) to 10 (very much).[39] PQoL-12 was used in PSO-ABLE, where mean PQoL-12 scores for patients using Cal/BD foam improved significantly from baseline to Week 4 compared with Cal/BD gel ($P = 0.029$).[34] These results, using both generic and disease-specific measures of HRQoL, are further indication that treatment with Cal/BD foam significantly improves quality of life in patients suffering from psoriasis.

Conclusion

Patient-reported outcomes, such as itch relief and HRQoL, are important factors in the treatment of psoriasis given the dramatic impact they have on patients' daily life and disease

burden. Improvement in these aspects, as well as a rapid onset of action, should be key goals for any potential psoriasis treatment. In this review, we examined the data from previously published studies on the efficacy of Cal/BD foam, focussing on itch relief, onset of action and HRQoL, and clearly highlight the significant improvements Cal/BD foam can offer patients with psoriasis across all three domains. While the efficacy of Cal/BD foam has already been demonstrated in several studies, evidence presented in this review goes further – Cal/BD foam effectively and rapidly improves patient quality of life in the outcomes that matter most to them. In a patient population with a HRQoL burden similar to those with cancer and cardiovascular disease, these improvements are vital and therefore strongly support the use of Cal/BD foam in the treatment of patients with psoriasis vulgaris.

What does this mean for clinical practice in psoriasis?

- Cal/BD foam provides improvements to HRQoL and outcomes such as itch relief and itch-related sleep loss, all of which are meaningful for the patient.
- Cal/BD foam has a rapid onset of action. This may increase adherence to treatment, particularly in patients who are not satisfied with their existing topical treatment.

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