

## ORIGINAL ARTICLE

# Calcipotriol plus betamethasone dipropionate aerosol foam vs. apremilast, methotrexate, acitretin or fumaric acid esters for the treatment of plaque psoriasis: a matching-adjusted indirect comparison

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## Abstract

**Background** Plaque psoriasis has significant impact on patients' quality of life. Topical therapy is considered the treatment mainstay for mild-to-moderate disease according to guidelines. Calcipotriol/betamethasone dipropionate (Cal/BD) [0.005%/0.05%] aerosol foam is indicated for psoriasis vulgaris treatment in adults. Cal/BD foam trials demonstrated improved efficacy and similar safety in this population. Psoriasis treatment is complicated by the broad range of disease presentation, variability and therapeutic options; particularly decisions on transition from topical to non-biologic systemic treatment are difficult. Assessing comparative effectiveness of treatment options provides meaningful value to treatment decisions.

**Objective** To compare efficacy of Cal/BD foam individual patient data from pooled trials with efficacy of non-biologic systemic treatments based on aggregated patient characteristics and treatment outcomes.

**Methods** Individual data from four Cal/BD foam trials in 749 psoriasis patients were pooled to conduct matching-adjusted indirect comparisons. Literature review identified non-biologic systemic treatment trials where methods, populations and outcomes align with Cal/BD foam trials. Of 3090 screened publications, four studies of apremilast, methotrexate, acitretin or fumaric acid esters (FAE) were included.

**Results** After baseline matching, patients treated with 4 weeks of Cal/BD foam had greater Physician's Global Assessment 0/1 response compared to those treated with 16 weeks of apremilast (52.7% vs. 30.4%;  $P < 0.001$ ). Patients treated with Cal/BD foam had significantly greater Psoriasis Area and Severity Index (PASI) 75 response at Week 4 compared to 16 weeks of apremilast treatment (51.1% vs. 21.6%;  $P < 0.001$ ). Cal/BD foam patients demonstrated significantly greater PASI 75 response improvements at Week 4 vs. 12 weeks of methotrexate (50.8% vs. 33.5%;  $P < 0.001$ ) or acitretin (50.9% vs. 31.7%;  $P = 0.009$ ), and comparable response to FAE (42.4% vs. 47.0%;  $P = 0.451$ ).

**Conclusions** Despite recent treatment advances, unmet needs for psoriasis patients remain. Cal/BD foam offers improved efficacy in baseline matched psoriasis patients compared to apremilast, methotrexate or acitretin, and comparable efficacy to FAE.

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## Conflicts of interest

AB reports no conflicts of interest. NHS and PCP have been paid by Leo Pharma for consulting services. JBH and MEN are employees of Leo Pharma. JS is an employee of Analysis Group Inc., which received funding from Leo Pharma for this research.

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## Introduction

Plaque psoriasis (PSO) is an immune-mediated inflammatory disease of uncertain aetiology with a worldwide prevalence ranging from 0.1% to 11.4%.<sup>1</sup> PSO has deleterious effects on patients' daily functioning, productivity and quality of life, and is associated with inflammatory arthritis, cardiovascular disease and depression.<sup>2,3</sup> As many as 80% of PSO patients may be characterized as having mild-to-moderate disease, for which topical therapy is considered the mainstay of treatment. This is followed by consideration of oral systemic therapy or phototherapy based on disease severity, success of prior therapy, or patient characteristics and preferences.<sup>2</sup>

Despite notable therapeutic advances over the past 15 years and robust use of non-biologic systemic treatments such as methotrexate, ciclosporin, acitretin and fumaric acid esters (FAE), there remains no cure for PSO and unmet needs persist for patients suffering from this chronic condition.<sup>4</sup> Systemic biologic treatments may be effective for severe disease but their use is often restricted due to cost. Many countries have adopted regulations that limit prescription of these expensive treatment options.<sup>5,6</sup> A recently introduced topical treatment, once-daily Enstilar® [Cal/BD; calcipotriol/betamethasone dipropionate aerosol foam (0.005%/0.05%)], is indicated for patients at least 18 years of age with PSO.<sup>7</sup> Cal/BD aerosol foam (Cal/BD foam) contains both Cal and BD in solution. In this vehicle, the excipients also function as solvents which evaporate after application. Both components enter a supersaturated state, yet crystals are absent for at least 26 h after application.<sup>8</sup> An *in vitro* model of skin penetration has shown higher levels of Cal/BD in the skin following aerosol foam application compared to ointment.<sup>9</sup> Cal/BD foam demonstrated significantly improved efficacy and safety in the four studies of the Cal/BD clinical trial program, compared to Cal/BD gel formulation in the PSO-ABLE study [12-week phase III randomized controlled trial (RCT)],<sup>10</sup> foam vehicle in the PSO-FAST study (4-week phase III RCT),<sup>11</sup> Cal/BD ointment in a 4-week phase II RCT,<sup>12</sup> and Cal or BD aerosol foams alone in a 4-week three-arm phase II RCT.<sup>13</sup> The increased skin penetration of Cal/BD foam based on its bioavailability and the supersaturated concentration of its active ingredients are likely to explain the improved clinical outcomes of Cal/BD foam compared to Cal/BD ointment and Cal/BD gel.<sup>8</sup>

The availability of new and more effective topical treatments such as Cal/BD foam and the improved safety profiles of newer systemic treatments such as apremilast have made the ability to make quantifiable distinctions among treatment options more complex, particularly for those patients who could be considered for either topical or non-biologic systemic treatment. Assessing the comparative effectiveness of treatment options provides meaningful, practical decision-making value to

clinicians and policy makers. In the absence of direct comparisons from head-to-head trials, indirect treatment comparisons offer opportunities to evaluate therapeutic options that have not been studied together. Such analyses often apply aggregated, summary-level findings which may be biased by differences in baseline characteristics across contributing studies. Matching-adjusted indirect comparison (MAIC) is a methodological approach for indirect comparisons where no appropriate common comparator is available, as required for a network meta-analysis, and individual patient-level data (IPD) are available for at least one intervention set. MAICs take advantage of individual IPD to align average study population characteristics with those from published comparator studies. This approach has been used to adjust for cross-trial differences in baseline characteristics, reduce sensitivity to effect measures, resolve differences in study outcome definitions, and to allow the comparison of clinically relevant doses.<sup>14–16</sup>

Indirect comparisons have been conducted among biologic therapies in psoriatic arthritis and have demonstrated their utility in decision support applications.<sup>17–20</sup> However, for clinicians making treatment recommendations, a broad range of clinical considerations is required (e.g. success of first-line therapy, patient characteristics, patient preferences), in particular for patients for whom both a topical or a non-biologic systemic treatment may be considered. A further crucial consideration impacting clinician decisions on appropriate therapeutic approaches is the association of systemic inflammation with development of comorbidities.<sup>21,22</sup> We conducted an indirect comparison to investigate the effectiveness of Cal/BD foam compared to non-biologic systemic therapies in adult matched PSO patients considered for either topical or non-biologic systemic treatment, with the aim to investigate some of the real-world challenges of treating this large patient population. While use of Cal/BD foam should always be restricted to patients with <30% affected body surface area, patient preferences and factors related to appropriate patient management decisions in real-world clinical practice may lend consideration to Cal/BD foam use before or in lieu of early non-biologic systemic treatment. Therefore, it is of interest to understand how a quantitative assessment of Cal/BD foam compared to non-biologic systemic therapies might contribute to treatment and policy decisions.

In the absence of a common comparator among studies of these PSO therapies, and because of the differences between oral placebo and topical vehicle, we conducted a MAIC analysis for the mentioned PSO therapies. This study used the MAIC approach to match the characteristics of the patient populations from the clinical trials of Cal/BD foam (based on pooled individual IPD) with those from the clinical trials of apremilast, methotrexate, acitretin or FAE.

## Materials and methods

### Selection of studies and parameters for analysis

In order to facilitate a robust comparison of Cal/BD foam with non-biologic systemic therapies for the matched PSO population, individual IPD were used from the four RCTs of Cal/BD foam that have been reported previously.<sup>10–13</sup> A comprehensive literature review was conducted to identify studies of non-biologic systemic therapies whose fundamental methods, patient populations, and reported outcome measures would align with those of the Cal/BD foam clinical program. Our literature search included RCTs and observational studies of apremilast, methotrexate, acitretin, FAE and ciclosporin monotherapy for the treatment of PSO. Studies were limited to English language publications.

Non-biologic systemic therapies are considered a close follow-up option to topical therapy and may even be considered for first-line treatment for some patients.<sup>23</sup> Biologic systemic therapies were excluded from this analysis, because they are indicated for patients with more advanced disease. We also excluded studies of combination systemic and non-systemic therapy, and those investigating phototherapy alone or in combination, due to the diversity of study methodology factors that would have precluded an appropriate indirect comparison analysis. We excluded studies with a sample size of fewer than 40 participants in order to preserve adequate statistical power. Studies were excluded if they did not measure treatment efficacy, did not specify the time points of efficacy measurements, or did not report baseline characteristics. Studies with a mean baseline Psoriasis Area and Severity Index (PASI) or body surface area (BSA)  $\geq 15$  (suitability range 3–15) were excluded in order to remain aligned with recent clinical study standards and ensure sufficient overlap with mean PASI score 7.3 (SD 4.6) from pooled Cal/BD trials populations.

Out of 3090 screened publications, four studies met the inclusion criteria, evaluating apremilast, methotrexate, acitretin or FAE (Fig. 1; Table 1).<sup>24–27</sup> No studies investigating ciclosporin met the inclusion/exclusion criteria. The four included studies were evaluated for suitability to align study methods, patient populations and outcome comparisons according with available baseline characteristics and endpoints in the pooled Cal/BD foam trials. Baseline age, sex, BMI, BSA, duration of psoriasis, PASI, BSA  $\times$  PASI, Dermatology Quality of Life Index (DLQI), previous topical treatment and previous systemic treatment were all considered potentially relevant due to clinical relevance and prevalence in PSO studies. Matching variables and outcomes were not consistently available across all studies (Table 1). The apremilast UNVEIL trial reported the most matching variable baseline characteristics that were reported for Cal/BD foam (previous systemic treatments was the only missing variable). The apremilast UNVEIL trial also reported physician's global assessment (PGA) as a secondary endpoint at Week 16. The only

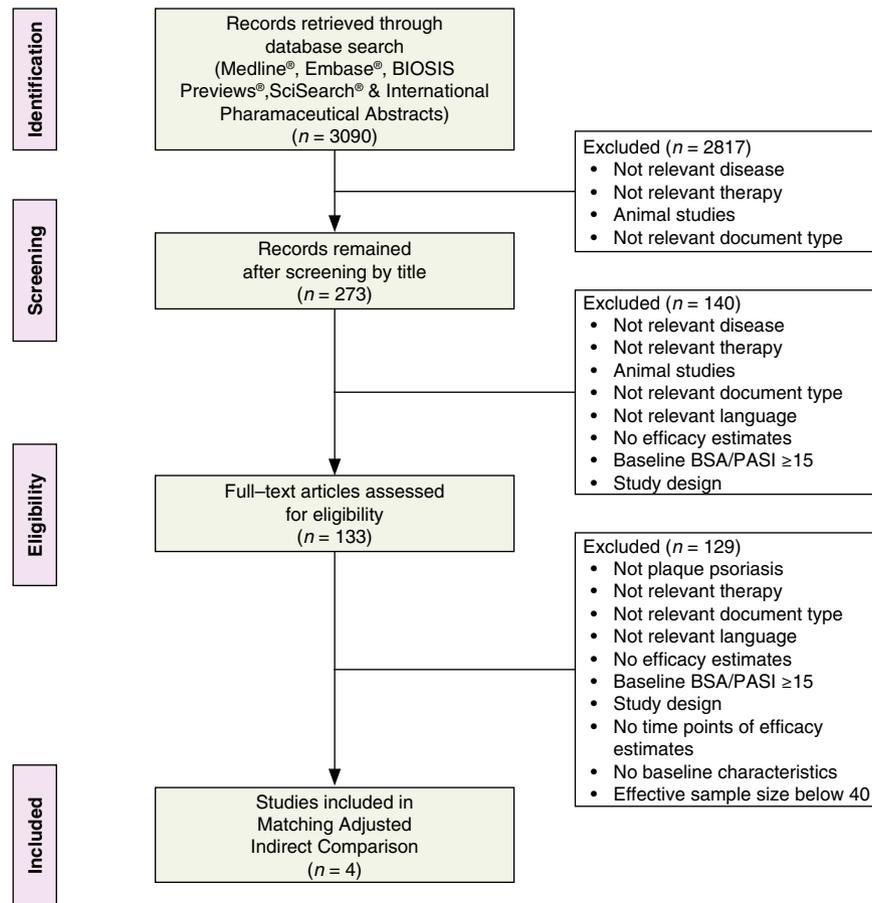
overlapping baseline characteristics from the methotrexate study were age, PASI and DLQI; from the acitretin study were sex, age, BMI, duration of psoriasis and PASI; and from the FAE study were age, duration of psoriasis and PASI. PASI 75 was the only overlapping outcome with Cal/BD foam trials from the methotrexate, acitretin and FAE studies.

The primary endpoints of the Cal/BD foam trials were 'treatment success' or 'controlled disease' defined similarly as the proportion of patients who were scored 0/1 ('clear' or 'almost clear') with  $\geq 2$ -grade improvement in disease severity assessed by a 5-point PGA scale (scored using an ordinal rating system ranging from 0 to 4) at Week 4. This was the preferred efficacy outcome for the indirect comparison analysis, however, modified PASI 75 (mPASI 75; excluding the head, which was not treated) was also used due to its clinical relevance and consistency of reporting across studies. The UNVEIL trial defined treatment success similarly, but with a  $\geq 2$ -grade improvement on a 6-point PGA scale (scored using an ordinal rating system ranging from 0 to 5). Safety assessments were not included in this analysis due to inconsistency in reporting of data across included studies.

Baseline characteristics for matching were selected based on clinical input and by forward selection using a logistic model, with the relevant endpoint (PGA 0/1 or PASI 75, at Week 4) as the dependent variable and selection entry criteria  $P < 0.20$ . In addition, matching for analyses of acitretin or FAE included age and mean PASI score based on data availability and clinical relevance.

### Statistical analysis

We conducted a matching-adjusted indirect comparison (MAIC) according to the statistical methodology described by Signorovitch and colleagues.<sup>14,15</sup> Due to the absence of an appropriate common comparator, we performed an unanchored MAIC. The IPD from pooled Cal/BD foam trials was reweighted such that the average baseline characteristics from the Cal/BD foam treatment cohort matched with those from each of the comparator studies. All statistical analyses were performed using SAS version 9.4 or higher (SAS Institute Inc., Cary, NC, USA). The Newton–Raphson algorithm was applied to determine appropriate weighting of matching variables using the NLPNRA subroutine within the PROC IML. The distribution of weights for each analysis was inspected to check for the presence of any extreme weights. The weighted analyses of efficacy variables PGA and PASI 75 were conducted with the Cal/BD foam IPD and aggregated results from each of the other treatment studies using a logistic model and confidence intervals. We conducted sensitivity analyses to investigate results by: Week 12 for Cal/BD foam (only reported in the PSO-ABLE study) vs. Week 16 for apremilast, Week 12 for methotrexate, Week 12 for acitretin, or Week 12 for FAE; last observation carried forward (LOCF) vs. observed values in the PSO-ABLE study; and with imputation of



**Figure 1** PRISMA flow diagram. BSA, body surface area; PASI, Psoriasis Area Severity Index; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

baseline characteristics ( $\pm 10\%$  range) missing from apremilast, methotrexate, acitretin and FAE studies.

## Results

The MAIC analysis included individual patient data from 749 patients treated with Cal/BD foam and summary findings from 148 patients treated with apremilast in the UNVEIL trial, 218 patients treated with methotrexate in Zurita *et al.*, 41 patients treated with acitretin in Chiricozzi *et al.* and 115 patients treated with FAE in Inzinger *et al.* Pre- and postweighting comparisons for PGA 0/1 and PASI 75 between Cal/BD foam and apremilast are presented in Table 2. No extreme weights were identified. Patients from the pooled Cal/BD foam trials included in this comparison tended to have similar prematched BMI and BSA, slightly lower mean PASI score at baseline, and slightly more history of prior topical treatment than those in UNVEIL. After the matching adjustments, patients treated with 4 weeks of Cal/BD foam had greater PGA 0/1 response compared to those treated

with 16 weeks of apremilast in UNVEIL (52.7% vs. 30.4%;  $P < 0.001$ ; Table 2). Cal/BD foam patients had significantly greater PASI 75 response at Week 4 compared to 16 weeks of apremilast (51.1% vs. 21.6%;  $P < 0.001$ ; Table 2). Matched patients receiving Cal/BD foam demonstrated significantly greater improvements in PASI 75 response at Week 4 compared to 12 weeks of methotrexate (50.8% vs. 33.5%;  $P < 0.001$ ) or acitretin (50.9% vs. 31.7%;  $P = 0.003$ ), and comparable response to FAE (42.4% vs. 47.0%;  $P = 0.451$ ; Table 3).

The sensitivity analysis of 12-week outcomes from 185 patients who received Cal/BD foam in the PSO-ABLE trial showed results consistent with the pooled analysis vs. comparators (Table S1). Improvements in efficacy outcomes from Week 12 of the PSO-ABLE study remained significantly greater than apremilast at Week 16 for PGA 0/1 (Cal/BD foam 45.6% vs. apremilast 30.4%;  $P = 0.011$ ) and PASI 75 (60.4% vs. 21.6%;  $P < 0.001$ ), than methotrexate at Week 12 (PASI 75, 59.8% vs. 33.5%;  $P < 0.001$ ), than acitretin at Week 12 (PASI 75, 77.5%

**Table 1** Design and characteristics of included studies

Study characteristic/Matching variable	Cal/BD foam Pooled analysis <sup>10–13</sup>	Apremilast <sup>24</sup>	Methotrexate <sup>25</sup>	Acitretin <sup>26</sup>	Fumaric acid esters <sup>27</sup>
Study design	Randomized, double-blind, active control clinical trials	Randomized, double-blind, active control clinical trial	Retrospective observational cohort analysis	Retrospective observational cohort analysis	Retrospective observational cohort analysis
Active treatment administration	Once daily Cal/BD aerosol foam	Twice daily apremilast 30 mg	As prescribed, mean 12 mg/week	As prescribed, mean 25 mg/day	30 mg
Active treatment, <i>N</i>	749	148	218	41	115
Sex, male, <i>n</i> (%)†,‡	470 (62.8)	74 (50.0)	NR	29 (70.7)	NR
Age, mean (SD), years†,§,¶,††,‡‡	51.4 (14.1)	48.6 (15.4)	45.8 (15.0)	62.9 (12.4)	40.4 (13.3)
Duration of psoriasis, mean (SD), years	16.8 (14.0)	17.5 (13.9)	NR	17.8 (NR)	17.3 (12.4)
BMI, kg/m <sup>2</sup> , mean (SD)†,‡,§,¶,†††	31.2 (7.2)§§§	30.5 (7.4)	NR	27.1 (3.8)	NR
BSA, m <sup>2</sup> , mean (SD)‡,¶¶	7.3 (6.1)	7.2 (1.6)	NR	NR	NR
PASI, mean (SD)†,‡,§,¶,†††,‡‡‡	7.3 (4.6)¶¶¶	8.2 (4.0)	7.4 (6.7)	11.9 (10.4)	11.6 (5.0)
DLQI, mean (SD)¶¶,‡‡‡	NR	11.0 (6.5)	8.2 (5.1)	NR	NR
BSA × PGA, mean (SD)‡	21.9 (20.5)	21.8 (5.3)	NR	NR	NR
Previous topical treatment, <i>n</i> (%)‡,§,§§,†††	637 (85.1)	122 (82.4)	NR	NR	NR
Previous systemic treatment, <i>n</i> (%)	233 (31.1)	NR	NR	11 (26.8)	NR

Matching variables identified based on responder analysis to be potentially associated with outcomes, depending on visit and endpoint for each of the comparisons to comparator studies, are shown in the following footnotes a–j.

†Pooled data, Week 4 vs. acitretin (Week 12), PASI 75.

‡PSO-ABLE data, Week 12 vs. apremilast (Week 16), PGA 0/1.

§Pooled data, Week 4 vs. apremilast (Week 16), PASI 75.

¶Pooled data, Week 4 vs. methotrexate (Week 12), PASI 75.

††Pooled data, Week 4 vs. FAE (Week 12), PASI 75.

‡‡PSO-ABLE data, Week 12 vs. FAE (Week 12), PASI 75.

§§Pooled data, Week 4 vs. apremilast (Week 16), PGA 0/1.

¶¶PSO-ABLE data, Week 12 vs. apremilast (Week 16), PASI 75.

†††PSO-ABLE data, Week 12 vs. acitretin (Week 12), PASI 75.

‡‡‡PSO-ABLE data, Week 12 vs. methotrexate (Week 12), PASI 75.

§§§748/749 patients included where BMI used for matching/reweighting – BMI value missing for one patient.

¶¶¶Modified (excluding the head) PASI was used in Cal/BD foam trials.

BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; NR, not reported; PASI, Psoriasis Area Severity Index; PGA, Physician's Global Assessment; SD, standard deviation.

vs. 31.7%;  $P < 0.001$ ), and comparable to PASI 75 at Week 12 for FAE (58.5% vs. 47.0%;  $P = 0.11$ ). Comparisons were also consistent with the analysis for the use of LOCF vs. observed values based on the PSO-ABLE study, and for reweighted treatment responses based on imputed missing baseline characteristic values for comparator studies based on the primary pooled analysis.

## Discussion

This matching-adjusted indirect comparison utilized individual IPD from Cal/BD foam clinical trials to match baseline characteristics with similar studies of non-biologic systemic treatment options for PSO with the aim to compare efficacy of treatment with Cal/BD foam vs. treatment with non-biologic systemic comparators. Patients who may be considered for either topical treatment or non-biologic systemic treatment present with a broad range of symptoms and factors, complicating clinical and policy treatment decisions. Determining the most effective treatment in a decision process that includes personalized care

considerations and patient preferences will often lead to consideration of topical, oral and injectable systemic treatments for overlapping clinical scenarios. This MAIC analysis sought to address some of the gaps in comparative efficacy that are relevant to real-world decision-making.

Participants who received apremilast in the UNVEIL trial shared the most commonality in reported baseline characteristics and outcome measures with those in Cal/BD foam clinical trials. This analysis showed consistently improved PGA and PASI 75 with Cal/BD foam at 4 and 12 weeks compared to 16 weeks of apremilast which was supported by the sensitivity analyses. Cal/BD foam also showed greater efficacy in matched analyses compared to methotrexate or acitretin, and similar results to FAE. These treatment comparisons are important to real-world decision-making, particularly for the matched patient group, as newer topical therapies such as Cal/BD foam and non-biologic systemic treatments such as apremilast have advanced the PSO treatment landscape in this population.<sup>10,23</sup> From a clinical perspective, reasons for discontinuation of traditional

**Table 2** Matching variable alignment and PASI 75/sPGA outcomes from pooled Cal/BD foam trials vs. apremilast (UNVEIL)

Response outcome/matching variable	Cal/BD foam, pooled analysis <sup>10–13</sup>		Apremilast <sup>24</sup>
	Before reweighting	After reweighting	
<b>sPGA 0/1 LOCF analysis: pooled Cal/BD foam Week 4 vs. apremilast Week 16</b>			
Sample size, <i>n</i>	748	640†	148
BMI, mean, kg/m <sup>2</sup>	31.2‡	30.5	30.5
PASI, mean	7.3§	8.2§	8.2
Previous topical treatment, %	85.1	82.4	82.4
PGA 0/1 responders, % (95% CI)	56.4 (51.9–60.9)	52.7 (44.9–60.4)	30.4 (23.6–38.2)
<i>P</i> value			< 0.001¶
<b>PASI 75 LOCF analysis: pooled Cal/BD foam Week 4 vs. apremilast Week 16</b>			
Sample size, <i>n</i>	748	651†	148
Age, mean, years	51.3	48.6	48.6
BMI, mean, kg/m <sup>2</sup>	31.2‡	30.5	30.5
Previous topical treatment, %	85.1	82.4	82.4
PASI 75 responders, % (95% CI)	51.4 (51.2–51.5)§	51.1 (50.5–51.7)§	21.6 (15.8–28.9)
<i>P</i> value			<0.001¶

†Effective sample size after reweighting.

‡748/749 patients included where BMI used for matching/reweighting – BMI value missing for one patient.

§Modified (excluding the head) PASI was used in Cal/BD foam trials.

¶*P* values are for Cal/BD foam vs. apremilast.

BMI, body mass index; BSA, body surface area; CI, confidence interval; FAE, fumaric acid esters; LOCF, last observation carried forward; PASI, Psoriasis Area Severity Index; sPGA, Static Physician's Global Assessment.

non-biologic systemic treatments have been studied for some time, with adverse events cited most frequently.<sup>28,29</sup> Patients receiving methotrexate stop treatment due to the burden of treatment monitoring such as liver biopsy, for pregnancy, and child-bearing reasons, and are more likely to discontinue methotrexate due to side effects than those receiving biologics.<sup>28</sup> Patients receiving acitretin are even more likely to discontinue therapy due to side effects than those receiving methotrexate.<sup>28</sup> Acitretin and ciclosporin have shown nearly double the risk of discontinuation as FAE.<sup>29</sup> Although analysis of the side effects was not included in the present study, insights into the challenges of historical treatment options may also be of interest to policy and population health managers as the comparative effectiveness of Cal/BD foam with other treatment options for patients qualifying for either treatment can have important implications for cost-effectiveness evaluations. Cal/BD foam may improve the effectiveness of early and progressive treatment approaches for managed disease, extending the time to more expensive treatment approaches, and merits further research to elucidate the potential of this approach.

Clinical practice guidelines estimate 80% of patients with psoriasis have mild-to-moderate disease, with the majority well served by the efficacy and safety profile of topical treatment, according to individual patient needs and preferences.<sup>2</sup> Consideration of adjunctive topical therapy is also recommended with systemic or phototherapy options in patients with more extensive or resistant disease.<sup>2</sup> Combining topical preparations such as corticosteroids and calcipotriol is also recommended, with a caution to consider potential compatibility issues, in further

combination with systemic or phototherapy based on patient needs and preferences.<sup>2</sup> Cal/BD foam may be expected to find an important role in future clinical practice recommendations, with the opportunity to deliver the potency of combination therapy from proven ingredients while alleviating concerns of compatibility issues inherent in patients' mixed application of stand-alone preparations. The comparative effectiveness of combination therapy in a unified Cal/BD foam can offer clinicians, patients and payers more solidified expectations for use. The manageable safety profile of Cal/BD foam may also be less likely to contribute to frequent treatment switching observed with traditional non-biologic systemic therapy.

This analysis should be interpreted in the context of certain considerations. A limited number of publications were identified in the literature review for included treatment options. No studies provided sufficient relevant information about ciclosporin to justify inclusion in the MAIC due to severity of PSO of the sample population and duration of treatment and follow-up, despite the flexibility granted to study designs and availability of information for other included treatments. The scope of systemic therapy was limited to non-biologic medications because symptoms and prior treatment history are markedly more advanced in appropriate patient candidates for biologic treatment, as reflected in clinical and health technology assessment recommendations.<sup>30,31</sup> Phototherapy was not included in this analysis though it is an available option for these patients, despite being cited as too expensive to initiate or continue, and often prescribed intermittently for several months at a time.<sup>28</sup> The variability of patient populations, baseline characteristics and

**Table 3** Matching variable alignment and PASI 75 outcomes from pooled Cal/BD foam trials vs. methotrexate, acitretin, or FAE

Response outcome/matching variable	Cal/BD foam, pooled analysis <sup>10–13</sup>		
	Before reweighting	After reweighting	Methotrexate <sup>25</sup>
<b>PASI 75 LOCF analysis: pooled Cal/BD foam Week 4 vs. methotrexate Week 12</b>			
Sample size, <i>n</i>	749	633†	218
Age, mean, years	51.4	45.8	45.8
PASI 75 responders, % (95% CI)	51.4 (51.3–51.5)‡	50.8 (50.3–51.3)‡	33.5 (27.2–39.8)
<i>P</i> value			<0.001§
	Before reweighting	After reweighting	Acitretin <sup>26</sup>
<b>PASI 75 LOCF analysis: pooled Cal/BD foam Week 4 vs. acitretin Week 12</b>			
Sample size, <i>n</i>	748	102†	41
Sex, male, %	62.7	70.7	70.7
Age, mean, years	51.4	62.9	62.9
BMI, mean, kg/m <sup>2</sup>	31.2¶	27.1	27.1
PASI, mean	7.3‡	11.9‡	11.9
PASI 75 responders, % (95% CI)	51.4 (51.2–51.5)‡	50.9 (50.1–51.6)‡	31.7 (17.5–46.0)
<i>P</i> value			0.009††
	Before reweighting	After reweighting	Fumaric acid esters <sup>27</sup>
<b>PASI 75 LOCF analysis: pooled Cal/BD foam Week 4 vs. FAE Week 12</b>			
Sample size, <i>n</i>	749	224†	115
Age, mean, years	51.4	40.4	40.4
PASI, mean	7.3‡	11.6‡	11.6
PASI 75 responders, % (95% CI)	51.4 (51.3–51.5)‡	42.4 (35.0–50.2)‡	47.0 (37.9–56.1)
<i>P</i> value			0.451‡‡

†Effective sample size after reweighting.

‡Modified (excluding the head) PASI was used in Cal/BD foam trials.

§*P* value is for Cal/BD foam vs. methotrexate.

¶748/749 patients included where BMI used for matching/reweighting – BMI value missing for one patient.

††*P* value is for Cal/BD foam vs. acitretin.

‡‡*P* value is for Cal/BD foam vs. FAE.

BMI, body mass index; CI, confidence interval; FAE, fumaric acid esters; LOCF, last observation carried forward; PASI, Psoriasis Area Severity Index.

outcome measures was determined as too high to justify inclusion of phototherapy or biologic systemic therapy in this analysis. Lastly, as with any comparison of non-randomized treatment groups, the results may be confounded by unobserved differences between patient populations; only a well-controlled head-to-head randomized trial can avoid unobserved confounding. Future work may find methodological approaches that would address these concerns.

The MAIC approach was successfully applied in this analysis, with the most robust comparison between the Cal/BD foam and apremilast trials due to their overall similarity in design and conduct. Matching baseline variables from these trials were consistently reported and well-aligned following the reweighting procedure; efficacy outcomes were also similarly measured. The UNVEIL trial reported primary efficacy for apremilast at Week 16, while the Cal/BD foam primary endpoints were at Week 4, each designed to evaluate timeframes of expected effectiveness. To account for this difference as closely as possible, this MAIC included the Week 12 time point from PSO-ABLE as a sensitivity analysis. PGA and PASI 75 results were in favour of Cal/BD

Week 4 and Week 12 vs. apremilast Week 16 assessments. More rapid and effective demonstration of efficacy is likely to be a benefit for patients with symptomatic disease. Fewer matching baseline characteristics and fewer similar efficacy outcomes were available from studies of methotrexate, acitretin or FAE to align with those of pooled Cal/BD foam trials. The primary pooled analysis and sensitivity analyses conducted to account for these differences showed consistent results.

Further consideration of the variability in study designs, patient populations and outcomes is also warranted. The Cal/BD foam trials included patients with a PGA  $\geq 2$  on a 5-point scale (scored 0–4) and UNVEIL included patients with PGA 3 on the 6-point scale (scored 0–5);<sup>10,24</sup> these patient populations may be considered to be generally well-aligned, with a conceivably narrow 10% difference in the threshold for study inclusion (60th vs. 50th percentiles of severity, respectively). In this respect, Cal/BD foam trials may have included some patients with slightly less severe disease, however, the reweighting of baseline characteristics related to disease severity should have addressed this slight imbalance. Treatment success in both

studies was defined as a minimum two-step improvement in PGA score. Cal/BD patients had to achieve a PGA 0/1 score (defined as 'clear' or 'almost clear') with  $\geq 2$ -grade improvement in disease severity assessed by the 5-point PGA by Week 4 in pooled Cal/BD foam trials or Week 12 in the PSO-ABLE study used for sensitivity analysis, and apremilast patients had to achieve PGA 0/1 from a score of 3 assessed by the 6-point PGA scale by Week 16.<sup>10</sup> Cal/BD foam trials also used a modified PASI 75 score that did not include the head, a difference vs. other studies PASI 75 measures (that did include the head), which might introduce bias. The comparison of pooled Cal/BD foam and apremilast was based on RCTs. The methotrexate and acitretin studies were retrospective observational analyses of medical charts from several years of clinical experience that offered more modern, comparable patient populations than the initial clinical studies.<sup>25,26</sup> The FAE study was based on 8 years of clinical experience from a psoriasis registry.<sup>27</sup> The inherent differences between randomized, controlled trials and observational analyses must be acknowledged. However, the general tendency observed for real-world data to show lower effectiveness compared to head-to-head trial efficacy data was not observed for Cal/BD foam, for which real-world data are in line with results reported from clinical trials.<sup>32</sup> Though the use of individual IPD for Cal/BD foam offered meaningful advantages over naïve, unadjusted indirect comparisons, the MAIC could not account for unknown confounders or differences among patient populations that were not measured or available. An unanchored MAIC was conducted in the absence of an appropriate common comparator among the included interventions. This approach requires the assumption that all effect modifiers and prognostic factors have been accounted for in the analysis, which would be difficult to demonstrate. The definition of treatment response also varied across studies, which may have introduced some inherent variability in outcome measures.

## Conclusion

Despite advances in psoriasis treatment over the past decade, unmet needs for patients remain. This matching-adjusted indirect comparison took advantage of IPD to account for differences in patient populations between Cal/BD foam clinical trials and studies of new and traditional non-biologic systemic therapies. In this analysis, Cal/BD foam demonstrated comparable results to FAE and greater efficacy compared to apremilast, methotrexate or acitretin. This is of the highest relevance for psoriasis patients considered for non-biologic systemic treatment, unresponsive to systemic treatments or cannot be treated because of contraindications, previous toxicity or concurrent treatments.

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### Supporting information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Sensitivity analyses – matching variable alignment and PASI 75/sPGA outcomes from Cal/BD foam 12-week data (PSO-ABLE) vs. apremilast (UNVEIL), methotrexate, acitretin, or FAE.