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ORIGINAL ARTICLE

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Efficacy, quality of life, and treatment satisfaction: an indirect comparison of calcipotriol/betamethasone dipropionate cream versus foam for treatment of psoriasis

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ABSTRACT

Objective: To assess how the use of calcipotriol and betamethasone dipropionate (Cal/BDP) cream impacted efficacy, patients' quality of life (QoL), and treatment satisfaction versus Cal/BDP foam.

Methods: Data from clinical trials of Cal/BDP cream and foam were analyzed, by applying the common anchor Cal/BDP gel. Efficacy was assessed by Physician Global Assessment (PGA) treatment success and $\geq 75\%$ reduction in Psoriasis Area and Severity Index (PASI75 response); QoL by Dermatology Life Quality Index (DLQI); treatment satisfaction by Psoriasis Treatment Convenience Scale (PTCS) and Topical Product Usability Questionnaire (TPUQ).

Results: Treatment with Cal/BDP cream was on par with foam on PGA treatment success (risk ratio (RR) for Cal/BDP cream versus foam: 0.80; 95%CI: 0.56, 1.14; $p = .21$) and PASI75 response (RR for Cal/BDP cream vs. foam: 0.85; 95%CI: 0.64, 1.13; $p = .27$) when assessed at the treatment duration of 8 weeks for Cal/BDP cream and 4 weeks for Cal/BDP foam. Treatment with Cal/BDP cream was associated with significantly greater treatment satisfaction versus foam on the domains: overall treatment satisfaction ($p = .01$), "ease of application" ($p < .001$), "lack of greasiness" ($p < .001$), "moisturizing effect" ($p = .01$), and almost significantly greater improvement on the domain "easily incorporated into daily routine" ($p = .07$). Furthermore, there was a trend for greater DLQI improvement with cream versus foam when assessed at recommended treatment duration [mean difference (MD) for Cal/BDP cream vs. foam: -1.00 ; 95%CI: -2.20 , 0.20 ; $p = .10$].

Conclusions: Indirect comparison analyses showed that Cal/BDP cream significantly improves treatment satisfaction and tends to improve QoL versus foam. Cal/BDP cream is on par with foam on efficacy.

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Indirect comparison; efficacy; quality of life; treatment satisfaction; calcipotriol and betamethasone dipropionate; cream; foam; gel; psoriasis; topical

Introduction

Psoriasis is a chronic immune-mediated inflammatory skin disease characterized by the formation of erythematous, scaly plaques in various regions of the body.¹ The prevalence of psoriasis in Western Europe varies from 1.1% to 3.5% with an average of $\sim 2\%$.² According to a Global Burden of Disease 2019 study, there were around 40.8 million prevalent cases of psoriasis worldwide in 2019.³ The negative impact of psoriasis on patients' quality of life (QoL) can be considerable.¹ Psoriasis poses a significant problem for affected subjects in everyday life, and studies have shown that patients with psoriasis are emotionally and physically impaired by their disease compared to what is seen with cancer, heart disease, rheumatoid arthritis, diabetes, or depression.⁴

There exists a wide range of therapeutic options for the treatment of psoriasis, e.g. various topical therapies, phototherapies, and systemic treatments. Besides current

treatment options, several new molecules and potential new therapeutic options are under investigation and pending approval. The choice of treatment typically depends on several factors, such as the age of the patient, disease severity, location, comorbidities, experience with psoriasis treatment, the cost of treatment, treatment satisfaction and adherence, the administration form, efficacy and safety of the therapeutic options, and impact on health-related quality of life^{5–11}.

Topical treatments are an essential part of the therapeutic options for psoriasis^{7,9,12,13}. Fixed combinations of calcipotriol and betamethasone dipropionate (Cal/BDP) are a cornerstone of treatment and are found to be efficacious and safe in the treatment of plaque psoriasis. Cal/BDP cream (Wynzora[®]) is a new topical treatment for plaque psoriasis which is based on a new proprietary PAD Technology and is recommended for up to 8 weeks of treatment¹⁴. Cal/BDP cream received US

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FDA approval in July 2020 and is approved in Europe through the decentralized procedure. The concentrations of Cal and BDP in Cal/BDP cream are identical to the concentrations in other Cal/BDP products (Cal 50 µg/g; BDP 0.64 mg/g).

The effect of a treatment is directly dependent on the patients' adherence to the therapy, which may be one of the largest barriers to treatment success¹⁵. The results of several studies on medication adherence in psoriasis show that 39–73% of patients do not use medication as prescribed¹⁶. Important factors for adherence are how practical and pleasant the formulation is, for instance, how easy it is to apply, how quickly it is absorbed into the skin, and whether it is pleasant to use. The treatment vehicle is, therefore, an important consideration in topical therapies. Cosmetic acceptability and ease of use affect treatment preference and adherence, with patients generally preferring less messy treatments that are easy to apply¹⁶. In a European survey of non-adherence to topical psoriasis treatment, 73% of patients did not adhere to their topical treatment, with product greasiness as the main reason for non-adherence¹⁷.

Cal/BDP cream has demonstrated statistically significantly greater efficacy and improved QoL in comparison with Cal/BDP gel (Daivobetⁱⁱ gel) and the cream vehicle in two randomized phase 3 clinical trials (NCT03802344 and NCT03308799)^{14,18,19}. Efficacy was assessed by the Physician Global Assessment (PGA) scale as a PGA score of 0 (clear) or 1 (almost clear) with a minimum two-point improvement from baseline and by the Psoriasis Area and Severity Index as a reduction of at least 75% from baseline (PASI75 response), while QoL was assessed by improvement on the Dermatology Life Quality Index (DLQI). Moreover, the treatment satisfaction score in Cal/BDP cream-treated patients, using the Psoriasis Treatment Convenience Scale (PTCS), was superior compared with Cal/BDP gel-treated patients^{14,18,19}.

Similarly, Cal/BDP foam (Enstilarⁱⁱⁱ) has shown significantly greater efficacy and improved QoL in comparison with Cal/BDP gel in the randomized phase 3 clinical trial PSO-ABLE^{20–22}. The primary objective was to compare the efficacy of Cal/BD foam at week 4 to that of Cal/BD gel at week 8. Moreover, in the randomized phase 3b clinical trial PSO-INSIGHTFUL, treatment satisfaction scores, assessed by the Topical Product Usability Questionnaire (TPUQ), were high for both Cal/BDP foam and gel with significant differences in favor of Cal/BDP gel for many of the items²³. Treatment satisfaction with Cal/BDP foam has also been assessed in a real-life setting²⁴.

To date, no head-to-head clinical trials or published analyses have been conducted comparing Cal/BDP cream with Cal/BDP foam. An indirect treatment comparison between Cal/BDP cream and foam is important to real-world decision-making, as new topical treatments, such as Cal/BDP cream have advanced the psoriasis treatment landscape. It is common to undertake indirect comparison analyses, especially when relevant head-to-head data do not exist. Various health technology assessment (HTA) agencies, like in the UK, France, and Germany, accept indirect comparison analyses^{25–28}, and EUNETHTA has also provided clear guidance for using various indirect comparison methods²⁹.

Table 1. Literature search string in PubMed (July 2021).

Drug	Outcomes	Disease
Calcipotriene OR calcipotriol AND "betamethasone dipropionate" OR Enstilar	AND "Physician Global Assessment" OR PGA OR "Psoriasis Area and Severity Index" OR "Psoriasis Area Severity Index" OR PASI OR "Dermatology Life Quality Index" OR DLQI OR satisfaction OR preference	AND Psoriasis

Exact search string: ((calcipotriene OR calcipotriol AND "betamethasone dipropionate" OR Enstilar) AND ("Physician Global Assessment" OR PGA OR "Psoriasis Area and Severity Index" OR "Psoriasis Area Severity Index" OR PASI OR "Dermatology Life Quality Index" OR DLQI OR satisfaction OR preference)) AND (psoriasis).

Thus, the purpose of this analysis was to assess how the use of Cal/BDP cream impacted efficacy, patients' QoL, and treatment satisfaction compared with Cal/BDP foam in an indirect treatment comparison analysis among patients with psoriasis vulgaris. In accordance with the recommended treatment durations for Cal/BDP cream and foam, analyses comparing Cal/BDP cream at week 8 with Cal/BDP foam at week 4 were conducted as well as separate analyses for each available week (1, 4, 6, and 8), e.g. comparing 4 weeks of Cal/BDP cream treatment with 4 weeks of Cal/BDP foam treatment (with common comparator Cal/BDP gel, also assessed at 4 weeks).

Methods

Selection of studies and outcomes of interest

For Cal/BDP cream, two randomized, controlled clinical phase 3 studies were conducted in Europe (NCT03802344)¹⁸ and the US (NCT03308799)^{14,19} with a Cal/BDP cream and gel arm were included³⁰.

For Cal/BDP foam, a systematic review of the literature was conducted to identify studies eligible for the indirect comparison analyses. The search was conducted in the MEDLINE database through the PubMed platform in July 2021. The search string was constructed of three clusters including search terms relating to the drug, the outcomes of interest, and the disease (Table 1). Title and abstracts of all identified articles were reviewed for eligibility. Eligible articles proceeded to full-text review, and articles failing to meet the inclusion criteria were excluded. Articles were limited to English-language publications. References were also excluded if they did not report results on at least one of the defined outcomes of interest: PGA treatment success, PASI75 response, DLQI improvement, and a treatment satisfaction measure comparable with the PTCS applied in the Cal/BDP cream studies. In addition, references were excluded if they did not compare Cal/BDP foam with Cal/BDP gel or if the comparisons only included subgroups of patients.

Out of 345 screened articles, two studies (published in three articles) met the inclusion criteria, referred to as the PSO-ABLE study and the PSO-INSIGHTFUL study^{20,22,23}. The PSO-ABLE study reported PGA treatment success, PASI75 response, and DLQI improvement, and was designed as a

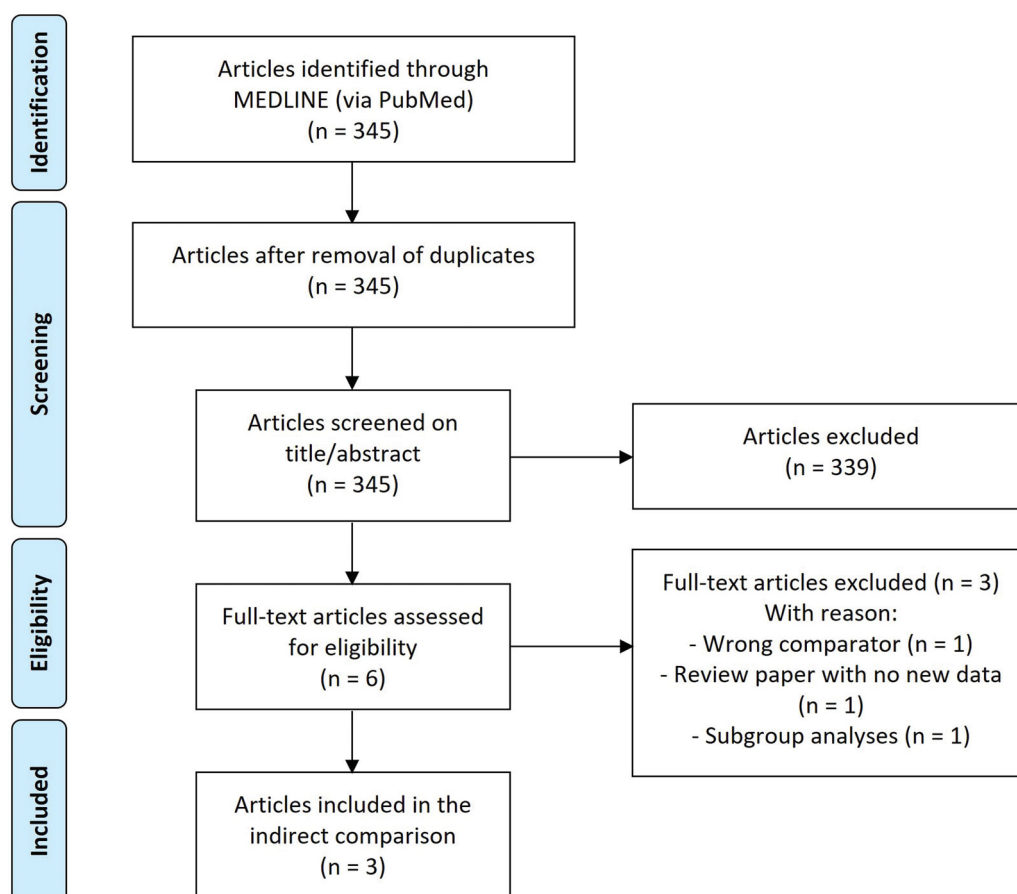


Figure 1. PRISMA flow diagram.

randomized, vehicle-controlled, investigator-blinded clinical phase 3 study with a Cal/BDP foam and gel arm^{20,22}. Patients were randomized to Cal/BDP foam, Cal/BDP gel, foam vehicle, or gel vehicle for up to 12 weeks. The PSO-INSIGHTFUL study was a randomized, open-label, two-arm crossover phase 3b study with a Cal/BDP foam and gel arm and reported results on treatment satisfaction measured by the TPUQ²³. Patients were randomized to Cal/BDP foam treatment for 1 week, followed by Cal/BDP gel treatment for 1 week, or vice versa²³. Figure 1 provides a PRISMA flow diagram showing the number of articles identified and the number of included and excluded articles.

The outcomes of interest for this analysis were PGA treatment success, PASI75 response, DLQI improvement, and treatment satisfaction. PGA treatment success, PASI75 response, and DLQI improvement were reported for Cal/BDP cream versus gel in the Cal/BDP cream studies^{14,18,19} and for Cal/BDP foam versus gel in the PSO-ABLE study²². Treatment satisfaction was measured with the PTCS for Cal/BDP cream versus gel in the Cal/BDP cream studies^{14,18,19} and with the TPUQ for Cal/BDP foam versus gel in the PSO-INSIGHTFUL study²³. PTCS questions were matched with relevant TPUQ questions covering five treatment satisfaction domains: ease of application, not greasy (measured with two questions on the PTCS), felt moisturizing, easily incorporated into daily routine, and overall treatment satisfaction (Table 2).

Statistical analyses

Indirect comparison analyses between Cal/BDP cream and foam were conducted by applying the common comparator Cal/BDP gel for all available timepoints. Where possible, indirect comparisons were also performed at 8 weeks, as the recommended treatment duration is up to 8 weeks for Cal/BDP cream and 4 weeks for Cal/BDP foam.

For PGA treatment success and PASI75 response, which are binary outcomes, the risk ratios (RRs) for Cal/BDP cream versus gel were estimated. Likewise, the RRs for Cal/BDP foam versus gel was estimated. Bucher's adjusted indirect comparison method was used to estimate RRs and absolute differences between Cal/BDP cream and foam. Bucher and co-authors suggested a simple method of adjusted indirect comparison. The indirect comparison of treatment A (Cal/BDP cream) and treatment B (Cal/BDP foam) is adjusted according to the results of their direct comparisons with a common intervention, treatment C (Cal/BDP gel)³¹. The application of multiple treatment comparison has become increasingly common since first being adopted in the late 1990s, and Bucher's method of adjusted indirect comparison is the most appropriate for the clinical start pattern network data we have available from this systematic literature review²⁹.

Table 2. PTCS questions matched with TPUQ questions covering five treatment satisfaction domains.

PTCS ^{14,18,19}		TPUQ ²³	
Q1	How easy was the treatment to apply to the skin?	Q1	Ease of application
Q2	How greasy was the treatment when applying it to the skin?	Q16	Not greasy
Q3	How moisturized did your skin feel after applying the treatment?	Q15	Felt moisturizing
Q4	How greasy did your skin feel after applying the treatment?	Q16	Not greasy
Q5	How much did your skin disrupt your daily routine?	Q9	Easily incorporated into daily routine
Q6	Overall, how satisfied were you with the medical treatment?	Q26	Overall satisfaction

PTCS: Psoriasis Treatment Convenience Scale; Q#: question number; TPUQ: Topical Product Usability Questionnaire.

Table 3. Patient demographics and baseline characteristics.

Treatment	Cal/BDP cream pooled studies ^{a30}		PSO-ABLE study ^{20,22}		PSO-INSIGHTFUL study ^{a23} All
	Cal/BDP cream	Cal/BDP gel	Cal/BDP foam	Cal/BDP gel	
<i>n</i>	551	542	185	188	212
Mean age, years (<i>SD</i>)	50.9 (14.1)	52.2 (14.2)	54.0 (14.5)	54.5 (14.9)	18–39 years: 48 (22.6%); 40–59 years: 92 (43.4%); ≥60 years: 72 (34.0%)
Female, <i>n</i> (%)	214 (38.8)	209 (38.6)	59 (31.9)	74 (39.2)	79 (37)
Mean BMI, kg/m ² (<i>SD</i>)	30.1 (6.9)	30.1 (6.3)	29.7 (6.1)	30.3 (6.6)	<25 kg/m ² : 37 (17.5%); 25–30 kg/m ² : 73 (34.4%); >30 kg/m ² : 102 (48.1%)
PGA, <i>n</i> (%)					
Mild	105 (19.1)	91 (16.8)	54 (29.2)	45 (23.9)	61 (28.8)
Moderate	446 (80.9)	451 (83.2)	109 (58.9)	124 (66.0)	122 (57.5)
Severe	0 (0.0)	0 (0.0)	22 (11.9)	19 (10.1)	29 (13.7)
Mean duration of psoriasis, years (<i>SD</i>)	17.9 (13.2)	16.6 (13.6)	19.3 (14.1)	19.0 (14.2)	<2 years: 4 (1.9%); 2–5 years: 30 (14.2%); >5 years: 178 (84.0%)
Mean BSA, % (<i>SD</i>)	8.0 (6.4)	8.7 (6.9)	7.1 (5.7)	7.0 (5.5)	<4%: 93 (43.9%); 4–6%: 56 (26.4%); 6–11%: 38 (17.9%); 11–15%: 11 (5.2%); ≥15%: 14 (6.6%)
Mean PASI (<i>SD</i>)	7.5 (3.9)	7.8 (4.0)	7.1 (4.5)	6.6 (3.6)	2–5: 86 (40.6%); 5.1–10: 91 (42.9%); >10: 35 (16.5%)

BMI: body mass index; BSA: body surface area; Cal/BDP: calcipotriene and betamethasone dipropionate; PASI: Psoriasis Area and Severity Index; PGA: Physician Global Assessment; *SD*: standard deviation.

^aMean age, BMI, duration of psoriasis, BSA and PASI not published.

The RR of the adjusted indirect comparison of treatments A and B can be estimated as:

$$RR'_{AB} = \exp(\ln RR'_{AC} - \ln RR'_{BC})$$

where $\ln RR'_{AC}$ and $\ln RR'_{BC}$ denote log RR of the study that compares treatment A with treatment C, and treatment B with treatment C, respectively. The absolute difference between treatments A and B can be estimated as:

$$AD'_{AB} = \text{event rate for treatment B} * (RR'_{AB} - 1)$$

For the continuous outcomes of DLQI improvement and treatment satisfaction, the mean difference (MD) between Cal/BDP cream and foam was estimated by the difference-in-differences method.

The Cal/BDP cream studies and the PSO-INSIGHTFUL study for Cal/BDP foam applied different scales for treatment satisfaction, PTCS and TPUQ, respectively. PTCS ranges from 1 to 10, and TPUQ ranges from −2 (very dissatisfied) to 2 (very satisfied), with higher scores indicating higher satisfaction. TPUQ mean and standard deviation values from the PSO-INSIGHTFUL study were converted to PTCS values, and PTCS mean and standard deviation values from the Cal/BDP cream studies were converted to TPUQ values. Both conversions

were conducted by multiplying with a factor taking the different scale ranges into account.

In the indirect comparison between treatment A and treatment B, the MD can then be estimated as:

$$\mu_{AB} = (\mu_{AAC} - \mu_{CAC}) - (\mu_{BBC} - \mu_{CBC})$$

where $(\mu_{AAC} - \mu_{CAC})$ denotes the MD of the outcome of treatment A in the study that compares treatment A and treatment C, and $(\mu_{BBC} - \mu_{CBC})$ denotes the MD of the outcome of treatment B, in the study that compares treatment B and treatment C.

Results

Baseline demographics

A total of 1,093 patients from the two studies with Cal/BDP cream (pooled Cal/BDP cream: $n = 551$; pooled Cal/BDP gel: $n = 542$), 373 patients from the Cal/BDP foam PSO-ABLE study (Cal/BDP foam: $n = 185$; Cal/BDP gel: $n = 188$) and 212 patients from the Cal/BDP foam and gel PSO-INSIGHTFUL study were included in the indirect comparison analyses. Baseline demographics are presented in Table 3. Most of the

Table 4. PGA treatment success and PASI75 response per week.

	Cal/BDP cream ³⁰	Cal/BDP gel ³⁰	Cal/BDP foam ²⁰	Cal/BDP gel ²⁰
Observations (N)	551	542	185	188
PGA treatment success (%)				
Week 1	3.60	2.00	6.60	1.60
Week 4	25.20	15.60	38.30	19.60
Week 6	37.70	24.60	44.90	23.00
Week 8	43.20	31.90	44.50	22.50
Recommended treatment duration ^a	43.20	31.90	38.30	22.50
PASI75 response (%)				
Week 1	2.70	1.20	7.20	1.60
Week 4	22.10	13.70	52.10	24.30
Week 6	36.00	24.20	59.00	33.40
Week 8	44.30	34.50	59.30	34.60
Recommended treatment duration ^a	44.30	34.50	52.10	34.60

Cal/BDP: calcipotriene and betamethasone dipropionate; PASI75: 75% reduction in Psoriasis Area and Severity Index; PGA: Physician Global Assessment.

^a8 weeks for Cal/BDP cream and gel and 4 weeks for Cal/BDP foam.

Table 5. Indirect comparison of PGA treatment success and PASI75 response between Cal/BDP cream and foam with the common comparator Cal/BDP gel.

PGA	Cal/BDP cream vs. gel ³⁰	Cal/BDP foam vs. gel ²⁰	Cal/BDP cream vs. foam				
			Relative difference			Absolute difference assuming event rate for Cal/BDP foam	
			RR ^b	95%CI	p-Value	Difference	95%CI
treatment success							
Week 1	1.80	4.13	0.44	0.10; 1.85	.26	−3.72%	−5.92%; 5.60%
Week 4	1.62	1.95	0.83	0.54; 1.26	.37	−6.64%	−17.49%; 9.88%
Week 6	1.53	1.95	0.79	0.55; 1.12	.18	−9.65%	−20.22%; 5.45%
Week 8	1.35	1.98	0.68	0.48; 0.97	.03	−14.03%	−22.97%; −1.38%
Recommended treatment duration ^a	1.35	1.70	0.80	0.56; 1.14	.21	−7.83%	−17.00%; 5.28%
PASI75 response							
Week 1	2.25	4.50	0.50	0.11; 2.32	.38	−3.60%	−6.43%; 9.52%
Week 4	1.61	2.14	0.75	0.51; 1.11	.15	−12.90%	−25.56%; 5.79%
Week 6	1.49	1.77	0.84	0.62; 1.14	.26	−9.31%	−22.18%; 8.04%
Week 8	1.28	1.71	0.75	0.57; 0.99	.04	−14.87%	−25.52%; −0.86%
Recommended treatment duration ^a	1.28	1.51	0.85	0.64; 1.13	.27	−7.67%	−18.61%; 6.85%

Cal/BDP: calcipotriene and betamethasone dipropionate; PASI75: 75% reduction in Psoriasis Area and Severity Index; PGA: Physician Global Assessment; RR: risk ratio; vs.: versus; 95%CI: 95% confidence interval.

^a8 weeks for Cal/BDP cream and gel and 4 weeks for Cal/BDP foam.

^bRR < 1 imply more events (PGA treatment success and PASI75 response) for Cal/BDP foam than Cal/BDP cream.

characteristics were considered similar across the studies. The distribution of PGA in terms of mild, moderate, and severe disease varied between the studies; in the Cal/BDP cream studies, patients with “severe disease” were excluded, but fewer patients had a “mild disease” than in the PSO-ABLE and PSO-INSIGHTFUL studies. Duration of psoriasis, body surface area (BSA), and PASI at baseline also varied between the studies.

Efficacy

In Table 4, we have provided the efficacy outcomes on PGA treatment success and PASI75 response from the two studies with Cal/BDP cream and from the PSO-ABLE study on Cal/BDP foam^{20,30}. The percentage of subjects achieving PGA treatment success as well as PASI75 response at weeks 1, 4, 6, and 8 are provided. PGA treatment success and PASI75 response from the respective studies were used to undertake the indirect comparison of Cal/BDP cream versus Cal/BDP foam.

Treatment with Cal/BDP cream was on par with Cal/BDP foam on PGA treatment success (RR for Cal/BDP cream vs. foam: 0.80; 95%CI: 0.56, 1.14; $p = .21$) and PASI75 response (RR for Cal/BDP cream vs. foam: 0.85; 95%CI: 0.64, 1.13; $p = .27$) when assessed at the treatment duration of 8 weeks for Cal/BDP cream and 4 weeks for Cal/BDP foam (Table 5). Likewise, treatment with Cal/BDP cream was on par with Cal/BDP foam on PGA treatment success and PASI75 response at weeks 1, 4, and 6. At week 8, Cal/BDP foam was significantly in favor compared with Cal/BDP cream on both PGA treatment success (RR for Cal/BDP cream vs. foam: 0.68; 95%CI: 0.48, 0.97; $p = .03$) and PASI75 response (RR for Cal/BDP cream vs. foam: 0.75; 95%CI: 0.57, 0.99; $p = .04$).

Quality of life

In Table 6, we have provided the quality of life outcomes on DLQI improvement from the two studies with Cal/BDP cream and from the Cal/BDP foam PSO-ABLE study^{22,30}. Changes in DLQI from baseline at weeks 4 and 8 are provided. DLQI

Table 6. Change in DLQI from baseline—DLQI improvement.

	Cal/BDP cream ³⁰	Cal/BDP gel ³⁰	Cal/BDP foam ²²	Cal/BDP gel ²²
DLQI improvement				
Week 4	−5.7	−5.0	−4.3	−3.8
Week 8	−6.5	−5.6	−4.5	−4.4
Recommended treatment duration ^a	−6.5	−5.6	−4.3	−4.4

Cal/BDP: calcipotriene and betamethasone dipropionate; DLQI: Dermatology Life Quality Index.

Data on DLQI improvement is measured as change in DLQI from baseline.

^a8 weeks for Cal/BDP cream and gel and 4 weeks for Cal/BDP foam.

Table 7. Indirect comparison of DLQI improvement between Cal/BDP cream and foam with the common comparator Cal/BDP gel.

	Cal/BDP cream vs. gel ³⁰	Cal/BDP foam vs. gel ²²	Cal/BDP cream vs. foam		
DLQI improvement	MD	MD	MD ^b	95%CI	p-Value
Week 4	−0.70	−0.50	−0.20	−1.37; 0.97	.74
Week 8	−0.90	−0.10	−0.80	−2.04; 0.44	.21
Recommended treatment duration ^a	−0.90	0.10	−1.00	−2.20; 0.20	.10

Cal/BDP: calcipotriene and betamethasone dipropionate; DLQI: Dermatology Life Quality Index; MD: mean difference; vs.: versus; 95%CI: 95% confidence interval.

^a8 weeks for Cal/BDP cream and gel and 4 weeks for Cal/BDP foam.

^bMD values with negative sign imply greater DLQI improvement for Cal/BDP cream than Cal/BDP foam.

improvement from the respective studies was used to undertake the indirect comparison of Cal/BDP cream versus Cal/BDP foam.

Treatment with Cal/BDP cream was associated with a trend for greater DLQI improvement than Cal/BDP foam when assessed at the treatment duration of 8 weeks for Cal/BDP cream and 4 weeks for Cal/BDP foam (MD for Cal/BDP cream vs. foam: −1.00; 95%CI: −2.20, 0.20; $p = .10$) (Table 7). Cal/BDP cream was on par with Cal/BDP foam on DLQI improvement at week 4 (MD for Cal/BDP cream vs. foam: −0.20; 95%CI: −1.37, 0.97 $p = .74$) and week 8 (MD for Cal/BDP cream vs. foam: −0.80; 95%CI: −2.04, 0.44; $p = .21$).

Treatment satisfaction

Treatment satisfaction analyses at week 1 showed significant differences in favor of Cal/BDP cream compared with Cal/BDP foam on the treatment satisfaction domains “ease of application” (MD on PTCS for Cal/BDP cream vs. foam: 1.10; 95%CI: 0.61, 1.59; $p < .001$), “not greasy” (MD on PTCS for Cal/BDP cream vs. foam: 1.58; 95%CI: 0.88, 2.27; $p < .001$) and “felt moisturizing” (MD on PTCS for Cal/BDP cream vs. foam: 0.62; 95%CI: 0.14, 1.11; $p = .01$), and an almost significant difference in favor of Cal/BDP cream compared with Cal/BDP foam on the domain “easily incorporated into daily routine” (MD on PTCS for Cal/BDP cream vs. foam: 0.43; 95%CI: −0.03, 0.88; $p = .07$) (Table 8). For overall treatment satisfaction, Cal/BDP cream showed significantly greater improvement compared with Cal/BDP foam (MD on PTCS for Cal/BDP cream vs. foam: 0.62; 95%CI: 0.13, 1.12; $p = .01$).

Discussion

Based upon a systematic literature review, efficacy, QoL, and treatment satisfaction were compared in indirect comparison analyses of Cal/BDP cream and Cal/BDP foam with the common comparator Cal/BDP gel *via* Bucher’s method of adjusted indirect comparison and the difference-in-differences method. This analysis showed that treatment with Cal/BDP

cream was on par with Cal/BDP foam on PGA treatment success and PASI75 response when assessed at the treatment duration of 8 weeks for Cal/BDP cream and 4 weeks for Cal/BDP foam. Treatment with Cal/BDP cream was associated with significantly greater overall treatment satisfaction versus Cal/BDP foam. Moreover, treatment satisfaction analyses at week 1 showed significant differences in favor of Cal/BDP cream compared with Cal/BDP foam on the treatment satisfaction domains “ease of application”, “not greasy”, and “felt moisturizing”, and an almost significant difference in favor of Cal/BDP cream compared with Cal/BDP foam on the domain “easily incorporated into daily routine”. Furthermore, treatment with Cal/BDP cream showed a trend for greater improvement in DLQI compared with Cal/BDP foam when assessed at the recommended treatment duration.

Overall, the indirect comparison analyses showed that Cal/BDP cream tends to improve QoL and significantly improves overall treatment satisfaction compared with Cal/BDP foam. Moreover, Cal/BDP cream is on par with Cal/BDP foam on efficacy measured by PGA treatment success and PASI75 response. Considering that a major European survey found that greasiness was the main reason for non-adherence¹⁷, and that we found a significant difference in favor of Cal/BDP cream compared with foam on the treatment satisfaction domain “not greasy” in addition to improved overall treatment satisfaction, it is likely that we will see a greater treatment adherence to Cal/BDP cream in real life. The efficacy of a Cal/BDP treatment is directly dependent on the patient’s adherence to the therapy; therefore, we will probably see greater real-life efficacy with Cal/BDP cream compared to foam. This highlights the importance of taking the patient’s preferences into account when choosing the right treatment for the specific patient to ensure adherence and, as a result of this, efficacy.

Indirect treatment comparisons are important to real-world decision-making, as new topical treatments, such as Cal/BDP cream have advanced the psoriasis treatment landscape. Undertaking indirect treatment comparisons is an opportunity to compare treatment options that have not

Table 8. Indirect comparison of treatment satisfaction^a in week 1 between Cal/BDP cream and foam with the common comparator Cal/BDP gel.

	Cal/BDP cream vs. gel ^b	Cal/BDP foam vs. gel ^{23,38}	Cal/BDP cream vs. foam		
	MD	MD	MD ^c	95%CI	p-Value
Ease of application					
PTCS Q1	0.20	−0.90	1.10	0.61; 1.59	<.001
TPUQ Q1	0.09	−0.40	0.49	0.27; 0.71	<.001
Not greasy v1					
PTCS Q2	0.90	−0.68	1.58	0.88; 2.27	<.001
TPUQ Q16	0.40	−0.30	0.70	0.39; 1.01	<.001
Not greasy v2					
PTCS Q4	0.90	−0.68	1.58	0.88; 2.27	<.001
TPUQ Q16	0.40	−0.30	0.70	0.39; 1.01	<.001
Felt moisturizing					
PTCS Q3	0.40	−0.22	0.62	0.14; 1.11	.01
TPUQ Q15	0.18	−0.10	0.28	0.06; 0.49	.01
Easily incorporated into daily routine					
PTCS Q5	0.20	−0.23	0.43	−0.03; 0.88	.07
TPUQ Q9	0.09	−0.10	0.19	−0.01; 0.39	.07
Overall treatment satisfaction					
PTCS Q6	0.40	−0.22	0.62	0.13; 1.12	.01
TPUQ Q26	0.18	−0.10	0.28	0.06; 0.50	.01

Cal/BDP: calcipotriene and betamethasone dipropionate; MD: mean difference; PTCS: Psoriasis Treatment Convenience Scale; Q#: question number; TPUQ: Topical Product Usability Questionnaire; v#: version number; vs.: versus; 95%CI: 95% confidence interval.

^aTreatment satisfaction measured with PTCS in the Cal/BDP cream studies³⁰ and TPUQ in the Cal/BDP gel PSO-INSIGHTFUL study.

^bData on file.

^cMD values with positive sign imply greater treatment satisfaction for Cal/BDP cream than Cal/BDP foam.

been studied in head-to-head clinical trials. In the absence of direct evidence, indirect treatment comparisons can be performed to evaluate the difference in, for example, efficacy, QoL, and treatment satisfaction, and are often used in health technology assessments to authorities in various countries—e.g. in the UK, Germany, France, Norway and Denmark^{25,26,28,29,32–34}.

Limitations of the study

There are several limitations to this study that should be considered when interpreting the results. One limitation relates to the indication of heterogeneity across study populations. For example, patients with “severe disease” were excluded in the Cal/BDP cream studies, but not in the PSO-ABLE and PSO-INSIGHTFUL studies. However, fewer patients in the Cal/BDP cream studies had a “mild disease” than in the PSO-ABLE and PSO-INSIGHTFUL studies, and the study population in the Cal/BDP cream studies also seemed to have higher baseline BSA and PASI than the study populations in both the PSO-ABLE and PSO-INSIGHTFUL studies. These differences could be potential effect modifiers and add bias to the results.

Regarding the treatment duration, the recommended treatment duration of Cal/BDP cream is up to 8 weeks, but we compare 8 weeks of Cal/BDP cream and gel with 4 weeks of Cal/BDP foam according to what was measured in the clinical trials. While the compared treatment durations are in accordance with the recommended treatment duration for each Cal/BDP treatment and their respective regulatory approved regimens in the US and the EU^{35–37}, and thus their comparisons appear to align with current real-world clinical practice (for Cal/BDP gel and foam), there is inherent variability associated with different treatment durations that can influence the analyses. Therefore, separate analyses for each

available week were also conducted, e.g. comparing 4 weeks of Cal/BDP cream treatment with 4 weeks of Cal/BDP foam treatment (with common comparator Cal/BDP gel, also assessed at 4 weeks).

The treatment satisfaction analysis is associated with several uncertainties. The PSO-INSIGHTFUL study was designed as a crossover study with 1 week of Cal/BDP foam treatment followed by 1 week of Cal/BDP gel treatment, or vice versa, while the Cal/BDP cream studies were randomized clinical trials with 8 weeks of follow-up. This implied that it was only possible to assess treatment satisfaction between Cal/BDP cream and foam after 1 week of treatment, which may be too short given the longer recommended treatment duration of both Cal/BDP cream and foam. Moreover, an obvious limitation is the comparison of two different questionnaires to assess treatment satisfaction: the PTCS and the TPUQ. The PTCS questionnaire was developed by MC2 Therapeutics, while the TPUQ was developed by LEO Pharma. Both questionnaires were used for the first time in the respective studies, and there is thus a lack of experience with the questionnaires. Furthermore, the six questions from the PTCS questionnaire were matched with five similar items from the 26-item TPUQ questionnaire. Others might argue for another matching of questions, which could have an impact on the results of the analysis. Lastly, the PTCS values were converted to TPUQ values, and vice versa, by multiplying with a factor taking the different scale ranges into account. There might be issues with this approach, and the results of the treatment satisfaction analysis should therefore be interpreted with caution.

Nevertheless, while this indirect comparison analysis cannot replace a head-to-head randomized clinical trial, it may be the best option to provide additional insights into the comparative effect, QoL, and treatment satisfaction of Cal/BDP cream versus foam.

Conclusions

The indirect comparison analyses showed that Cal/BDP cream significantly improves most domains and overall treatment satisfaction and tends to improve QoL compared with foam. Moreover, Cal/BDP cream is on par with Cal/BDP foam with regards to efficacy. Treatment satisfaction seems to depend on the Cal/BDP formulation, and the patient's satisfaction with treatment might be an important factor for adherence and, as a result of this, efficacy. It is therefore important to take patients' preferences into account when choosing the right treatment for the specific patient. Future direct and indirect comparisons, including population-adjusted indirect comparisons, will be important to provide additional evidence on the relative treatment effects of Cal/BDP cream versus foam.

Notes

- i. Wynzora is a registered trademark of MC2 Therapeutics.
- ii. Daivobet is a registered trademark of LEO Pharma A/S.
- iii. Enstilar is a registered trademark of LEO Pharma A/S.

Transparency

Declaration of funding

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Declaration of financial/other relationships

Sandra Elkjaer Stallknecht and Anne Danø are employees of Incentive, a paid vendor to Almirall and MC2 Therapeutics. Johan Selmer and Paw Trebbien are employees of MC2 Therapeutics. Jordi Galván and Aina Pi-Blanca are employees of Almirall S.A. Adam Reich is an employee at the Department of Dermatology, University of Rzeszow, Poland and Anthony Bewley is an employee at the Whipps Cross University Hospital and The Royal London Hospital (Barts Health) NHS Trust, London, UK.

Adam Reich has worked as a consultant or speaker for AbbVie, Bioderma, Celgene, Chema Elektromet, Eli Lilly, Galderma, GlaxoSmithKline, Janssen, LEO Pharma, Medac, Menlo Therapeutics, Novartis, Pierre-Fabre, Sandoz, Sanofi Aventis, and Trevi Therapeutics; participated as principal investigator or sub-investigator in clinical trials sponsored by AbbVie, AnaptysBio, Argenx, Corbus, Drug Delivery Solutions Ltd, Galderma, Genentech, Janssen, Kymab Limited, LEO Pharma, Menlo Therapeutics, MetrioPharm AG, MSD, Novartis, Pfizer, and Trevi Therapeutics.

Anthony Bewley has served as a consultant for AbbVie, Almirall, Celgene, Galderma, Janssen, LEO Pharma, Lilly, Novartis, Sanofi, and UCB; has participated in advisory boards for the Psoriasis Association, Changing Faces, ISG and NES; has received grants from EADV and travel grants from Janssen, LEO Pharma, and Almirall; has participated in guidelines committees of BAD; is working as an editor for the journal Practical Psychodermatology, as a treasurer for BAD, as a secretary for ESDaP and as a chair for APPGOS.

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Author contributions

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility

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All authors contributed to the study concept and manuscript design. Material preparation, data collection, and analysis were performed by Sandra Elkjaer Stallknecht and Anne Danø. All authors interpreted the data and provided critical feedback on the analyses and the manuscript. All authors read and approved the final manuscript for submission and are accountable for the accuracy and integrity of the manuscript.

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Data availability statement

The datasets generated and/or analyzed during the current study are not publicly available due to privacy reasons.

Ethical approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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