10-10-2021

# A pooled analysis of randomized, controlled, phase 3 trials investigating the efficacy and safety of a novel, fixed dose calcipotriene and betamethasone dipropionate cream for the topical treatment of plaque psoriasis

A Pinter

L J. Green

J Selmer

M Praestegaard

Linda F. Stein Gold
*Henry Ford Health*, lstein1@hfhs.org

*See next page for additional authors*



## Recommended Citation

Pinter A, Green LJ, Selmer J, Praestegaard M, Gold LS, and Augustin M. A pooled analysis of randomized, controlled, phase 3 trials investigating the efficacy and safety of a novel, fixed dose calcipotriene and betamethasone dipropionate cream for the topical treatment of plaque psoriasis. J Eur Acad Dermatol Venereol 2021.

Authors
A Pinter, L J. Green, J Selmer, M Praestegaard, Linda F. Stein Gold, and M Augustin

DOI: 10.1111/jdv.17734 JEADV

ORIGINAL ARTICLE

# A pooled analysis of randomized, controlled, phase 3 trials investigating the efficacy and safety of a novel, fixed dose calcipotriene and betamethasone dipropionate cream for the topical treatment of plaque psoriasis

A. Pinter,[1,*] L.J. Green,[2] J. Selmer,[3] M. Praestegaard,[3] L.S. Gold,[4] M. Augustin,[5] on behalf of the trial investigator group

[1]Department of Dermatology, University Hospital Frankfurt am Main, Frankfurt am Main, Germany
[2]George Washington University School of Medicine, Washington, DC, USA
[3]MC2 Therapeutics, Hørsholm, Denmark
[4]Dermatology Clinical Research, Henry Ford Health System, Detroit, MI, USA
[5]University Medical Center Hamburg-Eppendorf, Hamburg, Germany
*Correspondence: A. Pinter. E-mail: andreas.pinter@kgu.de

## Abstract

**Background** Plaque psoriasis is a common, chronic and relapsing inflammatory skin disease clinically characterized by erythema and scaling desquamation. As over 90% of psoriasis patients benefit from topical therapies, local treatments continue to play an eminent role in management strategies. One such topical treatment is the fixed dose combination of calcipotriol (CAL) and betamethasone dipropionate (BDP).

**Objectives** Pooled analysis of two different phase 3 clinical trails to compare superiority regarding efficacy, safety and quality of life (QoL) between CAL/BDP PAD-cream and CAL/BDP TS.

**Methods** The data from two phase 3, multicentre, randomized, investigator-blind, active and vehicle-controlled trials enrolling patients with psoriasis were pooled and analysed. Investigational products included a CAL/BDP cream based on PAD™ Technology (PAD-cream) designed for high skin penetration and increased patient preference, an active control (marketed CAL/BDP topical suspension/gel, in the following abbreviated as CAL/BDP TS) and cream vehicle, which were applied once daily for 8 weeks.

**Results** Efficacy and safety of the novel CAL/BDP PAD-cream formulation for the topical treatment of psoriasis demonstrated superiority for all efficacy end points after 8 weeks of treatment. PGA treatment success for CAL/BDP PAD-cream (43.2%) was greater than CAL/BDP TS (31.9%; $P < 0.0001$), the mean per cent reduction in mPASI for CAL/BDP PAD-cream was 64.6% compared to 56.4% for CAL/BDP TS ($P < 0.0001$) and DLQI 0/1 was obtained by 43.8% in the CAL/BDP PAD-cream group versus 34.2% in the CAL/BDP TS group ($P = 0.0005$). There was no adverse drug reaction reported with a frequency of >1%, associated with the CAL/BDP PAD-cream.

**Conclusions** The novel fixed dose combination CAL/BDP PAD-cream offers greater efficacy, superior patient QoL and equivalent favourable safety for the topical treatment of psoriasis, in comparison to the currently available topical suspension/gel.

Received: 21 May 2021; Accepted: 2 September 2021

## Conflict of interest

AP, LJG, LSG and MA received honoraria as investigator in Phase III clinical trial from MC2; JS and MP are employees of MC2.

## Funding sources

Trials presented herein were funded by MC2 Therapeutics, Hørsholm, Denmark.

This manuscript relates to two phase 3 studies, with the clinicaltrials.gov identifiers: NCT03308799 and NCT03802344.

## Introduction

Plaque psoriasis is a common, chronic and relapsing inflammatory skin disorder. The prevalence of diagnosed psoriasis is approximately 3% in the USA,[1] and between 2% and 3% in

Europe.[2] Clinically, psoriasis is characterized by erythema and scaling desquamation that most frequently appears on the scalp, elbows and/or knees; however, any area of the body can be affected.[3] While the armamentarium of different immunological targets for moderate-to-severe psoriasis has recently been expanding, topical steroid-based therapies still continue to play an eminent role in the majority of treatment for mild-to-moderate disease.[4] Most frequently prescribed topical treatment for adults is a fixed dose combination of calcipotriene (CAL; Vitamin D analogue) and betamethasone dipropionate (BDP; glucocorticoid steroid), which is recommended by European, Canadian and American psoriatic societies as first-line treatment in mild-to-moderate psoriasis.[5–8]The efficacy and safety of topical formulations containing fixed dose combinations of CAL and BDP has been shown in various clinical trials for more than 20 years.[9–13] However, the combination of CAL/BDP is not long-term stable in aqueous environments, as CAL requires basic conditions to maintain stability and BDP requires acidic conditions.[13] Therefore, currently marketed CAL/BDP fixed combinations are restricted to non-aqueous oil- or paraffin-based formulations (e.g. ointment, topical suspension (TS)/gel or foam)[14] that cause a greasy or sticky feeling that many patients do not like.[15] Patients prefer a topical formulation that dries quickly, without the sticky or greasy properties that affects skin/hair/clothing.[16] In a large international survey of non-adherence to topical psoriasis treatment, 73% of patients did not adhere to their topical treatment mainly because of product greasiness.[15] Thus, there is a need for a CAL/BDP fixed dose combination product that has high efficacy and is more patient friendly than current formulations. Such product could lead to increased adherence to treatment; a crucial aspect of any therapy for chronic conditions such as psoriasis.[5,16]

CAL/BDP PAD cream (marketed under the brand name Wynzora® Cream) is a fixed dose combination of CAL and BDP formulated using the PAD™ Technology. PAD™ Technology formulations are oil-in-water dispersions but, in contrast to conventional emulsions, the PAD™ Technology droplets have relatively high robustness against coalescence and maintain their physical-chemical stability without needing a large excess of surfactant in the external phase. This high robustness is based on a multimolecular shell structure that limits any chemical interaction between active molecules solubilized in the internal oil phase with water molecules in the external phase. PAD™ Technology formulations are therefore characterized by having a very low level of surfactants compared to conventional emulsions and the physical-chemical robustness enables formulation of fully solubilized CAL and BDP, even in the presence of water, which otherwise would lead to significant degradation of the two active ingredients (Figure 1).

Data from two head-to-head phase 3 trials with essentially similar inclusion criteria have been pooled to increase the precision of estimates of the efficacy and safety profile of CAL/BDP PAD-cream. Both studies were randomized, multicentre, parallel-group and investigator-blinded studies comparing CAL/BDP PAD-cream to the active comparator [CAL/BDP gel/topical suspension (CAL/BDP TS)] and vehicle cream (CAL/BDP PAD-cream without active ingredients).

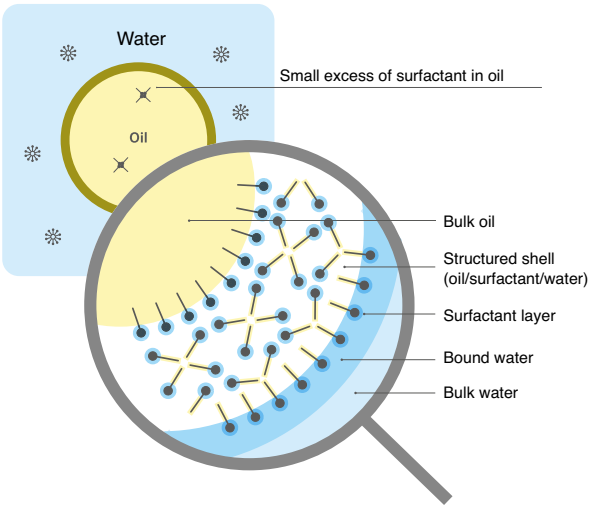


**Figure 1** Schematic Structure of a PAD™ Technology oil-in-water droplet. Multimolecular layer of organized surfactant, oil and water forms robust structure around oil droplets, limiting water contact and thereby protecting active ingredients in the oil phase against hydrolysis. PAD™ Technology oil-in-water dispersions can form with just a low level of surfactant in the water and oil phases, in contrast to conventional emulsions that require a large excess of surfactant in the water phase to maintain physical stability.

## Methods

### Trial design

In summary, two prospective, investigational, investigator-blind, vehicle and active- controlled, parallel-group, three-arm, randomized, phase 3 trials were conducted at multiple sites in the United States of America (MC2-01-C2) and the European Union (MC2-01-C7). The designs of both trials were almost identical (Figure 2), each including a screening and 8-week treatment period with application of topical agent once daily. Due to difference in formulation and packaging, the trials were investigator blinded. Numerous precautions were taken to ensure that this blinding was kept throughout the trials. The trial populations consisted of male and female subjects, above the age of 18 years, with mild-to-moderate psoriasis according to PGA and with a treatment area of 2%–30% of the body (trunk and/or limbs). Baseline-modified PASI was required to be at least 2 in trial MC2-01-C2 and at least 3 in trial MC2-01-C7. Subjects were randomly allocated to one of three parallel treatment groups in a 3 : 1 : 3 ratio (CAL/BDP PAD-cream, marketed

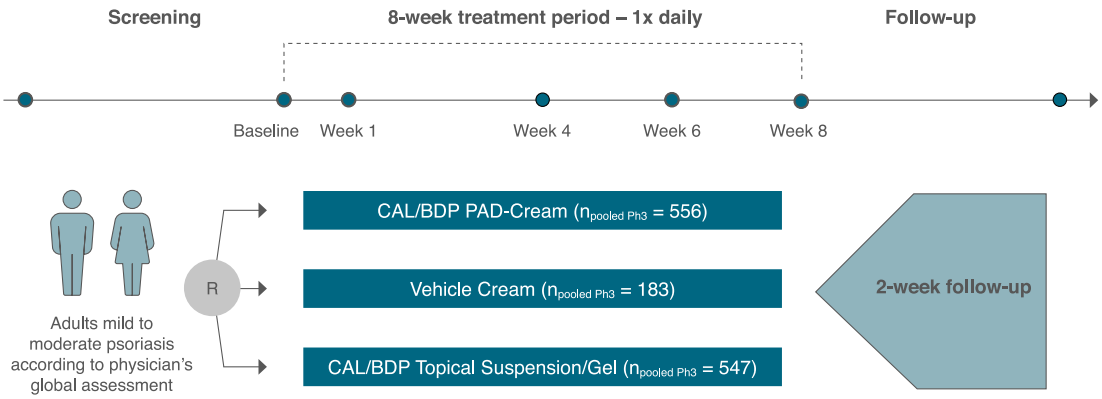


**Figure 2** Phase 3 trial design. Two prospective, investigational, investigator-blind, vehicle and active-controlled, parallel-group, three-arm, randomized, phase 3 trials enrolled 1286 subjects at multiple sites in the United States of America (MC2-01-C2; NCT03308799; *N* = 796) and the European Union (MC2-01-C7; NCT03802344; *N* = 490). The trial designs of the trials were almost identical, each including a screening and 8-week treatment period with application interval once daily. The trial populations consisted of male and female subjects, above the age of 18 years, with mild-to-moderate psoriasis according to PGA and with a treatment area of 2%–30% of the body (trunk and/or limbs). Baseline mPASI was required to be at least 2 in trial MC2-01-C2 and at least 3 in trial MC2-01-C7. Subjects were randomly allocated to one of three parallel treatment groups in a 3 : 1 : 3 ratio.

under the brand name Wynzora® Cream); cream vehicle and active comparator [a marketed CAL/BDP gel/topical suspension under brand names Taclonex® Topical Suspension (LEO Laboratories Ltd., Dublin 12, Ireland) and Dovobet®/Daivobet® Gel (EU and other territories)]. Randomization was performed using a validated system that automated the random assignment of treatment groups to randomization numbers. Treatment assignment was performed via a central interactive web response system (IWRS) in accordance with a pre-planned computer-generated randomization schedule and was stratified by trial site and country to ensure proper distribution into the three treatment arms. Subjects were at the sites instructed to topically apply their assigned product to the affected area(s) on the trunk (including the neck), limbs (i.e. arms, including the back of the hands) and legs (including the buttocks and the top of the feet), once daily for 8 weeks. The patient should apply sufficient product to treat the entire affected areas and rub in gently to ensure that the plaques were saturated with the medication. The patient should not apply product to the face, genital area or intertriginous areas. In the MC2-01-C7 trial, scalp psoriasis was treated, but disease severity or treatment efficacy on the scalp was not part of the PGA score reported in this publication.

### Study assessments

Efficacy and safety assessments were carried out at baseline and at Week 1, Week 4, Week 6 and Week 8. The primary objective of the pooled analysis was to evaluate the efficacy of CAL/BDP PAD-cream compared to active comparator, and the secondary objective was to characterize the safety profile CAL/BDP PAD-cream, the active comparator and the vehicle.

Prespecified selected efficacy end point variables included: (i) the proportion of patients in each treatment group with 'physician's global assessment (PGA) treatment success' [defined as a PGA score of 0 (clear) or 1 (almost clear) and with a minimum 2 points improvement from Baseline]; (ii) the percentage change in modified (excluding the head) Psoriasis Area and Severity Index (mPASI) score and the proportion of subjects with mPASI75 (at least 75% reduction in mPASI from Baseline); (iii) improvement in Dermatology Life Quality Index (DLQI) and (iv) patients' assessment of treatment acceptability using a Psoriasis Treatment Convenience Scale (PTCS) calculated as the sum of five treatment-specific questions rated on a 1–10 scale. The PTCS also included an additional question to assess overall satisfaction with treatment.

### Statistical analyses

Following the completion of the two phase 3 trials, the present pooled analyses were based on the combined data set and on primary and secondary end points defined in the two phase 3 trials. Efficacy analyses were based on the modified intention-to-treat (MITT) population ($n$ = 1271), which included all subjects randomly assigned to any investigational product, treated with the assigned investigational product and who had at least one assessment of efficacy after starting treatment. Safety analyses included all randomized subjects opening the medication ($n$ = 1283). Under the assumptions made for sample size calculation, the

two phase 3 trials had minimum 90% power to demonstrate superiority of CAL/BDP PAD cream comparison to vehicle.

Efficacy end points were analysed following a treatment policy strategy using all available data regardless of treatment and treatment adherence and imputing missing data by multiple imputation. For the PTCS end point, a while-on-treatment strategy was used requiring that treatment was followed within 7 days of the assessment.

Superiority analyses for end points (PGA treatment success, mPASI75, DLQI 'satisfaction' score 0 or 1) were analysed using a logistic model with effects of treatment, study and the baseline value of the end point as factors. Superiority analyses for continuous end points (mPASI, PTCS and DLQI) were performed using an ANCOVA model including treatment, study and baseline PGA as factors, and the baseline value of the respective end point as covariate. Efficacy and safety end points were summarized by frequency and severity for each treatment group. Analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

## Results

### Subject disposition, demographics and baseline characteristics

The MITT set included all subjects treated with CAL/BDP PAD-cream, the active comparator or the vehicle ($n$ = 1271). Overall, 551 patients were randomized to treatment with CAL/BDP PAD-cream, 542 patients were randomized to treatment with active comparator and 178 patients were randomized to treatment with vehicle. Of the randomized patients, 526 (94.6%), 513 (93.8%) and 149 (81.4%) completed the trial in the three groups respectively (Table 1).

Baseline demographics and disease characteristics were comparable across the treatment arms (Tables 1 and 2). At baseline, 228 (17.9%) and 1043 (82.1%) patients had mild and moderate disease, respectively, according to PGA of disease severity. Three-hundred and twenty-one (25.3%) subjects had at least moderate disease, defined as BSA > 10%.

### Efficacy

*PGA treatment success* The percentage of subjects achieving PGA treatment success at Week 8 was statistically significantly higher in the CAL/BDP PAD-cream group (43.2%) compared to the vehicle group (5.2%; $P < 0.0001$) and to the CAL/BDP TS group (31.9%; $P < 0.0001$). Moreover, statistically significant differentiation between CAL/BDP PAD-cream and CAL/BDP TS was observed as early as Week 4 ($P = 0.0001$) and maintained up to Week 8 (Figure 3a). PGA treatment success with CAL/BDP PAD-cream for subjects with BSA ≤ 10 and >10 was 41.7% and 48.3%, respectively, while the corresponding data for CAL/BDP TS were 33.0% and 28.7% (Table 3), demonstrating that the efficacy of CAL/BDP PAD-cream is maintained or even improves as baseline severity increases, while CAL/BDP TS loses efficacy as baseline severity increases. Figure 4 displays the results of a subject who underwent an 8-week, once-daily regimen of CAL/BDP PAD-cream application on the psoriatic skin of the elbows.

*Change from Baseline in mPASI* The mean per cent reduction in mPASI score from baseline to Week 8 was statistically greater for CAL/BDP PAD-cream (64.6%) than CAL/BDP TS (56.4%; $P < 0.0001$) and vehicle (20.0%; $P < 0.0001$). The difference in treatment effect between CAL/BDP PAD-cream and CAL/BDP TS was statistically significant as early as Week 1 ($P = 0.0009$) and maintained at Weeks 4 ($P < 0.0001$) and 6 ($P < 0.0001$; Figure 3b). In addition, the proportion of subjects obtaining mPASI75 was greater in the CAL/BDP PAD-cream group than in the CAL/BDP TS group at Week 4 (22.1% vs. 13.7%; $P = 0.0004$) and at Week 8 (44.3% vs. 34.5%; $P = 0.0011$; Figure 3c). mPASI75 with CAL/BDP PAD-cream for subjects with BSA ≤ 10 and >10 was 43.6%, and 46.5%, respectively, while the corresponding data for CAL/BDP TS were 35.2% and 32.5%.

*Improvement in Dermatology quality life index (DLQI)* The mean DLQI improvement from baseline, at Week 8, was significantly greater for CAL/BDP PAD-cream (6.5 points) compared

**Table 1** The modified intention-to-treat (MITT) set included all subjects randomly assigned to any investigational product, treated with the assigned investigational product and who had at least one assessment of efficacy after starting treatment

| | CAL/BDP PAD-cream *N* = 551 | Active comparator *N* = 542 | Cream vehicle *N* = 178 | Total randomized *N* = 1271 |
|---|---|---|---|---|
| Number of subjects randomized | 556 | 547 | 183 | 1286 |
| Number of subjects treated with an investigational drug (safety set) | 555 | 546 | 182 | 1283 |
| Number of subjects in modified intention to treat | 551 | 542 | 178 | 1271 |
| Number of subjects prematurely discontinued trial, *n* (%) | 30 (5.4) | 34 (6.2) | 24 (18.6) | 98 (7.6) |
| Number of subjects completed trial, *n* (%) | 526 (95.5) | 513 (94.6) | 149 (83.7) | 1188 (93.5) |

'CAL/BDP PAD-cream' represents patients treated with a fixed dose of calcipotriene and betamethasone dipropionate topical cream, 'Active Comparator' represents patients treated with a fixed dose of calcipotriene and betamethasone dipropionate topical suspension/gel and 'Cream Vehicle' represents patients treated with a topical cream comprised of inactive ingredients identical to CAL/BDP PAD-cream.

**Table 2** The modified intention-to-treat (MITT) population included all subjects randomly assigned to any investigational product, treated with the assigned investigational product and who had at least one assessment of efficacy after starting treatment

| | CAL/BDP PAD-cream *N* = 551 | CAL/BDP TS *N* = 542 | Cream vehicle *N* = 178 | Total *N* = 1271 |
|---|---|---|---|---|
| Study, *n* (%) | | | | |
| MC2-01-C2 | 338 (61.3) | 334 (61.6) | 112 (62.9) | 784 (61.7) |
| MC2-01-C7 | 213 (38.7) | 208 (38.4) | 66 (37.1) | 487 (38.3) |
| Country, *n* (%) | | | | |
| USA | 338 (61.3) | 334 (61.6) | 112 (62.9) | 784 (61.7) |
| Germany | 94 (17.1) | 90 (16.6) | 28 (15.7) | 212 (16.7) |
| Czech Republic | 64 (11.6) | 63 (11.6) | 20 (11.2) | 147 (11.6) |
| Poland | 55 (10.0) | 55 (10.1) | 18 (10.1) | 128 (10.1) |
| Sex, *n* (%) | | | | |
| Female | 214 (38.8) | 209 (38.6) | 65 (36.5) | 488 (38.4) |
| Male | 337 (61.2) | 333 (61.4) | 113 (63.5) | 783 (61.6) |
| Age, *n* (%) | | | | |
| 18–64 years | 456 (82.8) | 434 (80.1) | 145 (81.5) | 1035 (81.4) |
| 65 years or more | 95 (17.2) | 108 (19.9) | 33 (18.5) | 236 (18.6) |
| Race, *n* (%) | | | | |
| White | 498 (90.4) | 500 (92.3) | 163 (91.6) | 1161 (91.3) |
| Black or African American | 34 (6.2) | 20 (3.7) | 12 (6.7) | 66 (5.2) |
| Other | 19 (3.4) | 22 (4.1) | 3 (1.7) | 44 (3.5) |
| Ethnic origin, *n* (%) | | | | |
| Hispanic or latino | 99 (18.0) | 91 (16.8) | 30 (16.9) | 220 (17.3) |
| Not hispanic or latino | 452 (82.0) | 451 (83.2) | 148 (83.1) | 1051 (82.7) |
| PGA, *n* (%) | | | | |
| Mild (2) | 105 (19.1) | 91 (16.8) | 32 (18.0) | 228 (17.9) |
| Moderate (3) | 445 (80.8) | 451 (83.2) | 145 (81.5) | 1043 (82.1) |
| Severe (4) | 1 (0.2)[†] | | 1 (0.6) | |
| BSA, *n* (%) | | | | |
| Less or equal 10% | 422 (76.6) | 396 (73.1) | 132 (74.2) | 950 (74.7) |
| More than 10% | 129 (23.4) | 146 (26.9) | 46 (25.8) | 321 (25.3) |

BSA, Body surface area, PGA, Physician's global assessment.
'CAL/BDP PAD-cream' represents patients treated with a fixed dose of calcipotriene and betamethasone dipropionate topical cream, 'CAL/BDP TS' represents patients treated with a fixed dose of calcipotriene and betamethasone dipropionate topical suspension/gel and 'Cream Vehicle' represents patients treated with a topical cream comprised of inactive ingredients identical to CAL/BDP PAD-cream.
[†]Two subjects with severe psoriasis was by mistake included in the trials. These subjects were categorized as moderate in all calculations.

to CAL/BDP TS (5.6 points, $P < 0.0001$) and vehicle (2.5 points, $P < 0.0001$). A statistically significant difference between CAL/BDP PAD-cream and CAL/BDP TS was also observed at Week 4 ($P = 0.0002$; Figure 5). A DLQI score of 0 or 1 (meaning that the psoriasis disease had no effect at all on patient's life) at Week 8 was obtained by 43.8% in the CAL/BDP PAD-cream group and 34.2% in the CAL/BDP TS group ($P = 0.0005$).

*Improvement in Psoriasis Treatment Convenience Score (PTCS)* The mean psoriasis treatment convenience score (PTCS) at Week 8 for CAL/BDP PAD-cream (40.4) was statistically significantly greater than CAL/BDP TS (37.0; $P < 0.0001$). Similar significant level between CAL/BDP PAD-cream and CAL/BDP TS was seen at Week 1 and Week 4. Review of the individual responses to the PTCS questions made clear that the greater preference for CAL/BDP PAD-cream was mainly due to CAL/BDP TS being a greasier formulation. Finally, the sixth question 'Overall, how satisfied were you with the medical treatment' was highly significant in favour of CAL/BDP PAD-cream compared to the topical suspension ($P < 0.0001$).

## Safety

There were no statistically significant differences between the treatment arms in relation to the proportion of subjects experiencing a TEAE. Adverse drug reactions during the trial were seen in 4.1%, 2.6% and 6.6% of subjects in the CAL/BDP PAD-cream arm, the CAL/BDP TS arm and the vehicle arm respectively (Table 4). The highest frequency of adverse drug reactions was in System Organ Class Preferred Term 'General disorders and

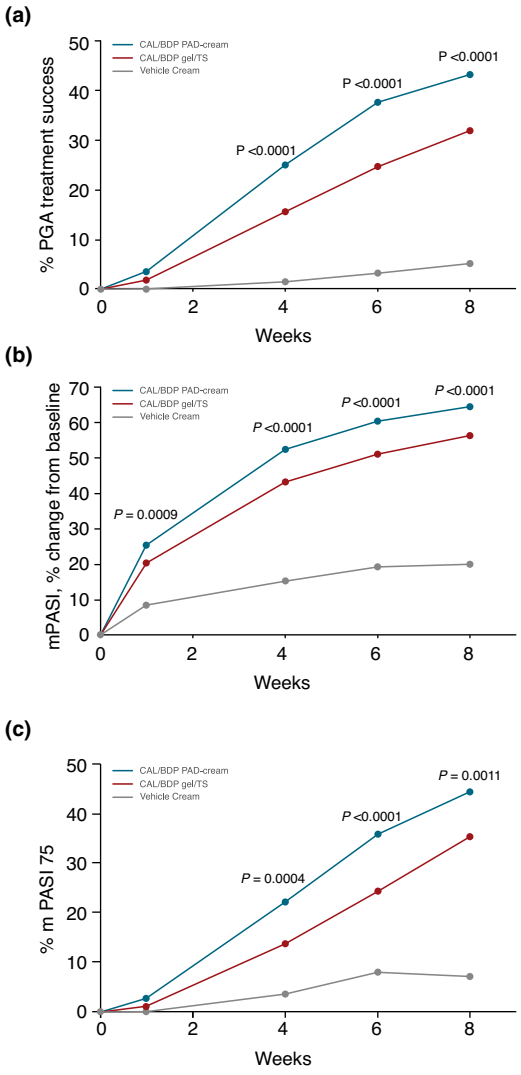


**Figure 3** (a) Proportion of patients obtaining PGA treatment success improvement by trial visit. (b) Percentage change in mPASI from baseline. (c) Proportion of patients obtaining mPASI75 by trial visit. A response to active treatment could already be noted after 1 week. All data based on the MITT population using multiple imputation.

administration site conditions', but there were no local site reactions above 1%. In the CAL/BDP PAD-cream arm, the most frequent local site reactions were application site pain, irritation, and pruritus, each with a frequency of 0.7%.

There were 15 AEs reported in 9 subjects leading to discontinuation. In the CAL/BDP PAD-cream group, three (0.5%) subjects were discontinued due to AEs with two events (insomnia and urticaria) deemed to be probably related, whereas the third event (renal cell carcinoma) was deemed unrelated.

**Table 3** CAL/BDP PAD-cream represents patients treated with a fixed dose of calcipotriene and betamethasone dipropionate topical cream, 'CAL/BDP TS' represents patients treated with a fixed dose of calcipotriene and betamethasone dipropionate topical suspension/gel and 'Cream Vehicle' represents patients treated with a topical cream comprised of inactive ingredients identical to CAL/BDP PAD-cream

| | CAL/BDP PAD-cream *N* = 551 | CAL/BDP TS *N* = 542 | Cream Vehicle *N* = 178 |
|---|---|---|---|
| All, *n* (%) | 551 (43.2) (0.391, 0.474) | 542 (31.9) (0.279, 0.359) | 178 (5.2) (0.017, 0.082) |
| PGA severity, *n* (%) | | | |
| Mild | 105 (10.6) (0.047, 0.166) | 91 (15.6) (0.081, 0.231) | 32 (0.0) |
| Moderate | 446 (50.9) (0.462, 0.556) | 451 (35.2) (0.306, 0.397) | 146 (6.3) (0.021, 0.106) |
| BSA severity | | | |
| BSA ≤ 10% | 422 (41.7) (0.369, 0.465) | 396 (33.0) (0.283, 0.378) | 132 (4.5) (0.006, 0.083) |
| BSA > 10%, *n* (%) | 129 (48.3) (0.395, 0.570) | 146 (28.7) (0.211, 0.363) | 46 (7.3) (−0.006, 0.151) |

BSA, Body surface area; PGA, Physician's global assessment; mPASI, Modified psoriasis area and severity index.
95% Confidence intervals in parentheses. The significance level for comparison of CAL/BDP PAD-cream to CAL/BDP TS was $P < 0.0001$ for patients with moderate Baseline PGA. No statistical difference was observed between the two active treatments for mild patients. The significance level for comparison of CAL/BDP PAD-cream to CAL/BDP TS was $P = 0.0044$ for patients with baseline BSA ≤ 10% and $P = 0.0012$ for patients with baseline BSA > 10%.

A total of 26 (2.0%) subjects reported a serious adverse event with similar frequency in the three treatment groups. None was assessed by the investigator to be related to trial medication. Laboratory data did not suggest CAL-mediated changes in calcium metabolism in any of the three arms during the trial.

## Discussion

Results from the present meta-analysis of pooled data from two randomized, controlled phase 3 trials investigating the efficacy and safety of CAL/BDP PAD-cream for the topical treatment of psoriasis demonstrated superiority in comparison to CAL/BDP TS for all efficacy end points including PGA treatment success, mPASI and PASI75. Superiority was also demonstrated for patient-reported DLQI and PTCS.

Overall, these trials demonstrated that CAL/BDP PAD-cream was significantly more effective than CAL/BDP TS after 8 weeks of once-daily use. The achievement of PGA treatment success at Week 8 was greater for CAL/BDP PAD-cream (43.2%) than for CAL/BDP TS (31.9%) ($P < 0.0001$), and the reduction in mPASI from baseline to Week 8 was greater for CAL/BDP PAD-cream (64.6%) compared to CAL/BDP TS (56.4%; $P < 0.0001$).

These findings were confirmed by significantly more subjects obtaining mPASI75 at Week 8 in the CAL/BDP PAD-cream group than in the CAL/BDP TS (44.3% vs. 34.5%, respectively).

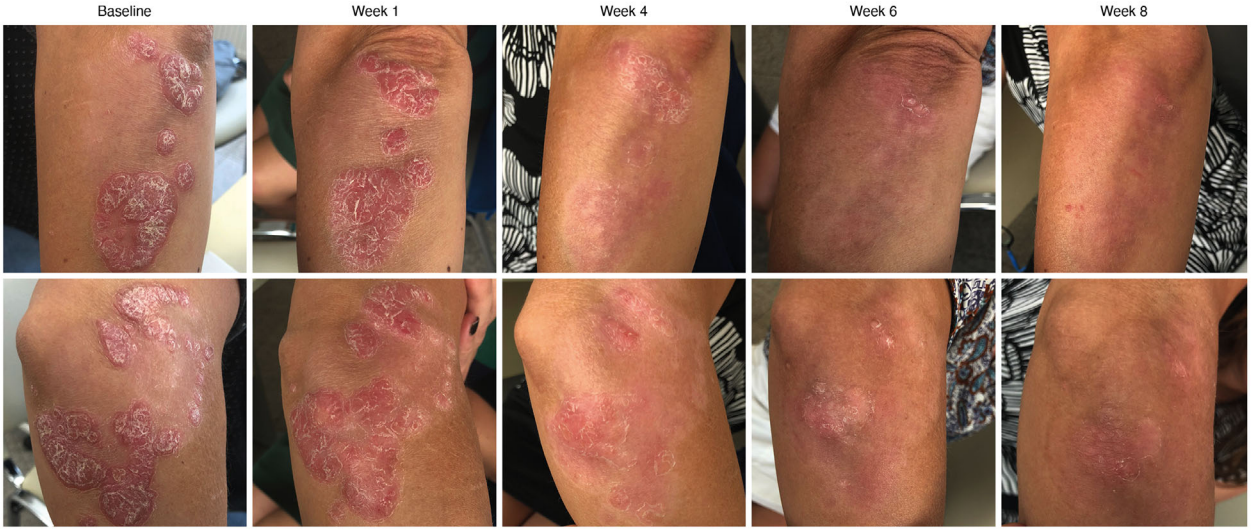


**Figure 4** Images depict an adult female with psoriasis vulgaris on the elbows, at baseline and after a 1, 4, 6 and 8 weeks of once-daily application of CAL/BDP PAD-cream.

The CAL/BDP PAD-cream had a faster onset of action than CAL/BDP TS. With respect to treatment efficacy measured by reduction in mPASI, there was a statistically significant difference in favour of CAL/BDP PAD-cream already at Week 1 (mean percentage reduction: 25.5% vs. 20.5%, $P = 0.0009$), which continued with significant difference at all subsequent visits ($P < 0.0001$).

PGA treatment success at week 8 in subjects using CAL/BPD cream with BSA >10% increased to 48.3% (compared to 43.2% in subjects with <10% BSA), while PGA treatment success at week 8 for CAL/BDP TS subjects with >10% BSA decreased to 28.7% (compared to 31.9% in subjects with <10% BSA).

For subjects with BSA > 10% treated with CAL/BDP PAD-cream, mPASI75 increased from 44.3% to 46.5%, whereas efficacy of CAL/BDP TS decreased from 34.5% to 32.5%. The increase in treatment efficacy in subjects with BSA > 10% treated with CAL/BDP PAD-cream was seen for all efficacy parameters including mPASI and DLQI, whereas a decrease was seen for subjects treated with CAL/BDP TS.

At all visits throughout the trial, patient assessed QoL was higher in patients having received CAL/BDP PAD-cream than in those treated with the CAL/BDP TS. A significantly greater proportion of subjects treated with CAL/BDP PAD-cream reported that the psoriasis had no effect at all on their life (DLQI 0 or 1) compared to CAL/BDP TS (43.8% vs. 34.2%, $P = 0.0005$) after 8 weeks of treatment.

Types and incidences of AEs were on par with the safety profile of currently available CAL/BDP products. The majority of adverse drug reactions were local site reactions, with no adverse drug reaction reported at a frequency >1%.

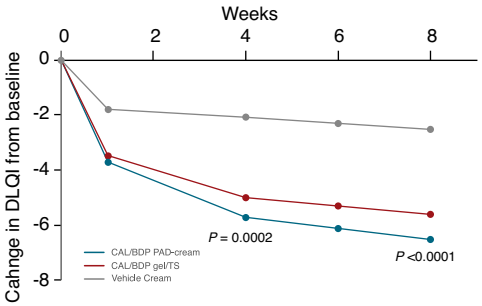


**Figure 5** DLQI improvement by trial visit. Data based on the MITT population using multiple imputation.

Topical fixed dose combinations of CAL and BDP have in the last 20 years proven very effective and safe both for acute treatment and for long-term maintenance therapy. However, until now CAL/BDP combination products have been restricted to non-aqueous oil- or paraffin-based formulations resulting in formulations that by many are perceived as greasy or sticky. Such formulations take a long time to dry, interfere with clothing and other daily activities. The result can for many patients be lack of adherence to treatment leading to suboptimal treatment outcomes in the real-world setting.[17,18]

The robust oil-in-water dispersion structure resulting from the PAD™ Technology eliminated the inherent lack of CAL/BDP stability in water. In addition, PAD™ Technology creams offer unique advantages with respect to solubility of actives and high penetration into the skin. The physical appearance of the CAL/

**Table 4** CAL/BDP PAD-cream represents patients treated with a fixed dose of calcipotriene and betamethasone dipropionate topical cream, 'CAL/BDP TS' represents patients treated with a fixed dose of calcipotriene and betamethasone dipropionate topical suspension/gel and 'Cream Vehicle' represents patients treated with a topical cream comprised of inactive ingredients identical to CAL/BDP PAD-cream

| | CAL/BDP PAD-cream *N* = 555 | CAL/BDP TS *N* = 546 | Cream Vehicle *N* = 182 |
|---|---|---|---|
| Subjects with any adverse drug reactions, *n* (%) | 23 (4.1) | 14 (2.6) | 12 (6.6) |
| Adverse drug reactions leading to discontinuation of trial regime, *n* (%) | 3 (0.5) | 5 (0.9) | 7 (3.8) |
| Drug-related serious adverse events, *n* (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **System Organ Class (Preferred Term)** | | | |
| **General disorders and administration site conditions** | 15 (2.7) | 8 (1.5) | 7 (3.8) |
| Application site dermatitis | 0 (0.0) | 2 (0.4) | 1 (0.5) |
| Application site eczema | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| Application site erosion | 2 (0.4) | 0 (0.0) | 2 (1.1) |
| Application site exfoliation | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| Application site hypersensitivity | 0 (0.0) | 0 (0.0) | 1 (0.5) |
| Application site irritation | 4 (0.7) | 0 (0.0) | 1 (0.5) |
| Application site pain | 4 (0.7) | 1 (0.2) | 1 (0.5) |
| Application site pruritus | 4 (0.7) | 4 (0.7) | 1 (0.5) |
| Application site telangiectasia | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| Application site vesicles | 0 (0.0) | 1 (0.2) | 0 (0.0) |
| **Infections and infestations** | 2 (0.4) | 4 (0.7) | 1 (0.5) |
| Application site folliculitis | 2 (0.4) | 1 (0.2) | 0 (0.0) |
| Herpes zoster | 0 (0.0) | 1 (0.2) | 0 (0.0) |
| Nasal abscess | 0 (0.0) | 1 (0.2) | 0 (0.0) |
| Upper respiratory tract infection | 0 (0.0) | 1 (0.2) | 1 (0.5) |
| **Injury, poisoning and procedural complications** | 0 (0.0) | 0 (0.0) | 1 (0.5) |
| Overdose | 0 (0.0) | 0 (0.0) | 1 (0.5) |
| **Investigations** | 1 (0.2) | 2 (0.4) | 2 (1.1) |
| Blood parathyroid hormone increased | 1 (0.2) | 2 (0.4) | 2 (1.1) |
| **Nervous system disorders** | 1 (0.2) | 1 (0.2) | 0 (0.0) |
| Dysgeusia | 0 (0.0) | 1 (0.2) | 0 (0.0) |
| Headache | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| **Psychiatric disorders** | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| Insomnia | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| **Skin and subcutaneous tissue disorders** | 4 (0.7) | 1 (0.2) | 2 (1.1) |
| Dermatitis contact | 0 (0.0) | 1 (0.2) | 0 (0.0) |
| Pruritus | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| Psoriasis | 0 (0.0) | 0 (0.0) | 2 (1.1) |
| Rash | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| Skin erosion | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| Urticaria | 1 (0.2) | 0 (0.0) | 0 (0.0) |

TEAE, Treatment-emergent adverse events.

BDP PAD-cream is a white, easily spreadable cream that absorbs rapidly and completely into the skin leaving no sticky feeling behind.

The increased patient acceptability of the CAL/BDP PAD-cream is demonstrated by the significantly increased treatment preference (PTCS) at Week 8 compared to the CAL/BDP TS. A similar statistically significant difference between CAL/BDP PAD-cream and CAL/BDP TS was observed at Week 1 and Week 4. Analysis of single treatment acceptability questions clarified that the higher preference for CAL/BDP PAD-cream was mainly due to the cream being a less greasy formulation than to CAL/BDP TS.

As previous studies have demonstrated that treatment adherence is affected by greasy or oily, sticky topical products that stain clothes or are difficult to apply,[16,17] factors related to physical characteristics of the topical product are of importance for the level of adherence of the medication.[19,20] An important benefit of the PAD™ Technology formulation is its resulting high

penetration/efficacy profile, which presumably have contributed to the superior treatment efficacy of CAL/BDP PAD-cream compared to CAL/BDP TS.

The CAL/BDP fixed combination is approved and marketed in three formulations worldwide, and the combination of CAL/BDP is recommended as first-line treatment by disease management guidelines in Europe, Canada and in the US.[5–8,10,21] In the recently published AAD-NFP Guidelines,[8] there is a class A recommendation of use of CAL/BDP products for psoriasis up to 52 weeks. Furthermore, this guideline emphasizes the importance of selecting topical formulations accepted and preferred by the patient. This is in line with the conclusion in a 2016 consensus paper[22] that a key research priority for topical psoriasis therapy is to develop agents with higher efficacy, fewer side-effects and potential for long-term use. Limitations of this pooled analysis are missing data on scalp psoriasis, prolonged efficacy after intermittent use as well as data on efficacy and safety in adolescent patients with CAL/BDP PAD-cream. For these purposes, further data should be collected.

## Conclusions

The present analysis of pooled data from two randomized, controlled phase 3 trials investigating the efficacy and safety of a CAL/BDP PAD-cream for the topical treatment of psoriasis demonstrated statistically significant efficacy in favour of CAL/BDP PAD-cream for all efficacy end points including PGA treatment success, mPASI and PASI75. Superiority was also demonstrated for patient-reported dermatology life quality index and treatment preference. Based on this unique combination of high efficacy combined with favourable safety and excellent treatment preference in a single product, CAL/BDP PAD-cream can be considered a first-line topical therapy of psoriasis.

## Acknowledgements

The patients in this manuscript have given written informed consent to publication of their case details.

## Data availability statement

The data that support the findings of this study are available on request from the sponsor of that clinical trials. The data are not publicly available due to privacy or ethical restrictions.

## References

1 Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the United States. *J Am Acad Dermatol* 2014; **70**: 512–516.
2 Parisi R, Iskandar IYK, Kontopantelis E *et al*. National, regional, and worldwide epidemiology of psoriasis: systematic analysis and modelling study. *BMJ (Clinical Research ed)* 2020; **369**: m1590.
3 Chiricozzi A, Pimpinelli N, Ricceri F *et al*. Treatment of psoriasis with topical agents: recommendations from a Tuscany Consensus. *Dermatol Ther* 2017; **30**: e12549.
4 Lebwohl M. Psoriasis. *Ann Intern Med* 2018; **168**: ITC49.
5 Dauden E, Bewley A, Lambert J *et al*. Expert recommendations: the use of the fixed combination calcipotriol and betamethasone dipropionate gel for the topical treatment of psoriasis. *J Eur Acad Dermatol Venereol* 2014; **28**: 22–32.
6 Paul C, Gallini A, Archier E *et al*. Evidence-based recommendations on topical treatment and phototherapy of psoriasis: systematic review and expert opinion of a panel of dermatologists. *J Eur Acad Dermatol Venereol* 2012; **26**: 1–10.
7 Papp K, Gulliver W, Lynde C, Poulin Y, Ashkenas J. Canadian guidelines for the management of plaque psoriasis: overview. *J Cutan Med Surg* 2011; **15**: 210–219.
8 Elmets CA, Korman NJ, Prater EF *et al*. Joint AAD-NPF Guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures. *J Am Acad Dermatol* 2021; **84**: 432–470.
9 Kragballe K, van de Kerkhof P. Pooled safety analysis of calcipotriol plus betamethasone dipropionate gel for the treatment of psoriasis on the body and scalp. *J Eur Acad Dermatol Venereol* 2014; **28**: 10–21.
10 Augustin M, Mrowietz U, Bonnekoh B *et al*. Topical long-term therapy of psoriasis with vitamin D(3) analogues, corticosteroids and their two compound formulations: position paper on evidence and use in daily practice. *J Dtsch Dermatol Ges* 2014; **12**: 667–682.
11 Vakirlis E, Kastanis A, Ioannides D. Calcipotriol/betamethasone dipropionate in the treatment of psoriasis vulgaris. *Ther Clin Risk Manag* 2008; **4**: 141–148.
12 van de Kerkhof P, de Peuter R, Ryttov J, Jansen JP. Mixed treatment comparison of a two-compound formulation (TCF) product containing calcipotriol and betamethasone dipropionate with other topical treatments in psoriasis vulgaris. *Curr Med Res Opin* 2011; **27**: 225–238.
13 Kragballe K, Austad J, Barnes L *et al*. Efficacy results of a 52-week, randomised, double-blind, safety study of a calcipotriol/betamethasone dipropionate two-compound product (Daivobet/Dovobet/Taclonex) in the treatment of psoriasis vulgaris. *Dermatology* 2006; **213**: 319–326.
14 Simonsen L, Hoy G, Didriksen E *et al*. Development of a new formulation combining calcipotriol and betamethasone dipropionate in an ointment vehicle. *Drug Dev Ind Pharm* 2004; **30**: 1095–1102.
15 Fouere S, Adjadj L, Pawin H. How patients experience psoriasis: results from a European survey. *J Eur Acad Dermatol Venereol* 2005; **19**: 2–6.
16 Eastman WJ, Malahias S, Delconte J, DiBenedetti D. Assessing attributes of topical vehicles for the treatment of acne, atopic dermatitis, and plaque psoriasis. *Cutis* 2014; **94**: 46–53.
17 Bewley A, Page B. Maximizing patient adherence for optimal outcomes in psoriasis. *J Eur Acad Dermatol Venereol* 2011; **25**: 9–14.
18 Svendsen MT, Andersen F, Hansen J, Johannessen H, Andersen KE. Medical adherence to topical corticosteroid preparations prescribed for psoriasis: A systematic review. *J Dermatol Treat* 2017; **28**: 32–39.
19 Brown KK, Rehmus WE, Kimball AB. Determining the relative importance of patient motivations for nonadherence to topical corticosteroid therapy in psoriasis. *J Am Acad Dermatol* 2006; **55**: 607–613.
20 Lambert J, Hol CW, Vink J. Real-life effectiveness of once-daily calcipotriol and betamethasone dipropionate gel vs. ointment formulations in psoriasis vulgaris: final analysis of the 52-week PRO-long study. *J Eur Acad Dermatol Venereol* 2015; **29**: 2349–2355.
21 Nast A, Boehncke WH, Mrowietz U *et al*. German S3-guidelines on the treatment of psoriasis vulgaris (short version). *Arch Dermatol Res* 2012; **304**: 87–113.
22 Wu JJ, Lynde CW, Kleyn CE *et al*. Identification of key research needs for topical therapy treatment of psoriasis - a consensus paper by the International Psoriasis Council. *J Eur Acad Dermatol Venereol* 2016; **30**: 1115–1119.