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A Phase 3, Randomized Trial Demonstrating the Improved Efficacy and Patient Acceptability of Fixed Dose Calcipotriene and Betamethasone Dipropionate Cream

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ABSTRACT

Background: The fixed dose combination of calcipotriene and betamethasone dipropionate (CAL/BDP) is a well-established, efficacious, and safe topical treatment of psoriasis.

Method: A Phase 3, multicenter, randomized, investigator-blind, active, and vehicle-controlled trial enrolling 796 patients with moderate to severe psoriasis according to the Physician Global Assessment (PGA) scale. Products were applied once daily for 8 weeks.

Results: The proportion of patients achieving PGA treatment success after 8 weeks was statistically significantly greater for CAL/BDP cream (37.4%) compared to CAL/BDP TS (22.8%, $P<0.0001$), and vehicle (3.7%, $P<0.0001$). A similar statistically significant difference in favor of CAL/BDP cream at week 8 was demonstrated for the percentage change in mPASI from baseline and the proportion of patients obtaining mPASI75. Patient reported treatment convenience for CAL/BDP cream was rated superior to CAL/BDP TS. Safety assessments during the trial demonstrated that CAL/BDP cream was well-tolerated with no adverse reactions with a frequency greater than 1%.

Conclusion: CAL/BDP cream is a novel topical treatment of psoriasis, which in a single product, offers a unique combination of high efficacy combined with favorable safety and excellent treatment convenience. For these reasons, CAL/BDP cream offers a distinctive advantage for the topical treatment of plaque psoriasis.

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INTRODUCTION

Psoriasis is an inflammatory skin disease that has a profound influence on all aspects of quality of life, including physical, psychologic, social, sexual, and occupational elements. Most psoriasis patients are candidates for topical treatments, and the fixed dose combination of calcipotriene (CAL) and betamethasone dipropionate (BDP) is a well established treatment option based on strong scientific rationale for the single agents having complementary efficacy and safety.

The CAL/BDP combination is recommended both by European guidelines[1-3] as a first line treatment of mild to moderate plaque psoriasis and is also recommended by the Canadian Dermatology Association,[4] and the American Academy of Dermatology.[5]

The currently marketed 0.005 w/w% CAL and 0.064 w/w% BDP fixed dose combinations are non-aqueous formulations containing petrolatum or mineral oil as the predominant excipient. Conversely, the CAL/BDP cream is an easily spreadable cream based on the proprietary PAD™ Technology (MC2Therapeutics), which has enabled development of a water-containing formulation of CAL and BDP, despite their known pH-related instability when combined in the presence of water.[6]

Treatment non-adherence is a well-known problem in dermatology and an important reason for treatment failure.[7,8] In a European survey of non-adherence of topical treatment in psoriasis, 73% of the patients did not adhere to the prescribed treatment regime. The principal reason for non-adherence was the greasiness of the product.[9] Other studies have also demonstrated that adherence is affected by treatments which are greasy or oily, stain clothes, are difficult to apply, or dosed more than once daily.[10,11]

CAL/BDP cream has the in-use characteristics of an easily spreadable cream, which absorbs rapidly and completely into the skin leaving no sticky feeling behind. It is anticipated that these qualities will result in increased patient adherence and consequently, improved real-world treatment outcomes.[12] The

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aim of the present trial was to evaluate the efficacy and safety of CAL/BDP cream as well as its patient treatment acceptability compared to CAL/BDP topical suspension (CAL/BDP TS) and cream vehicle.

MATERIALS AND METHODS

Study Design

This was a Phase 3 randomised, investigator-blind, multicentre, vehicle and comparator controlled, parallel-group trial. It was conducted at 55 study sites in the United States. The trial included a screening, 8-week treatment, and a 2-week follow-up period.

Subjects and Randomization

For inclusion, subjects could be of either gender, be 18 years or older and have plaque psoriasis with an Physcician Global Assessment (PGA) score of 2 (mild) or 3 (moderate), a modified psoriasis area and severity index excluding the scalp (mPASI) score of at least 2, and a treatment area between 2% to 30% of the body surface area (BSA). Eligible patients were randomly assigned in a 3:1:3 ratio to receive treatment with either CAL/BDP cream, vehicle, or CAL/BDP TS applied topically to the affected area once daily for 8 weeks. Areas of the face, scalp, and axillae or other intertriginous areas were not included or treated. Assessments were carried out at baseline and 1, 4, 6, and 8 weeks of treatment.

Study Oversight

The trial was approved by the institutional review board of each participating center and was conducted in accordance with Good Clinical Practices, the Declaration of Helsinki, and all applicable local regulations. Written informed consent was obtained from each patient. The trial identifier on clinicaltrials.gov is NCT03308799.

Study Assessment

The primary endpoint was the proportion of patients in each treatment group with 'PGA treatment success' at week 8, which is defined as a PGA score of 0 (clear) or 1 (almost clear) with minimum 2-points improvement from baseline.

The secondary endpoints included: (1) the percentage change in modified (excluding the head) Psoriasis Area and Severity Index (mPASI) score at week 8; (2) the proportion of subjects with a 4-point improvement in itch based on an 11-point numerical rating scale (NRS) from Baseline to week 4 (CAL/BDP cream vs vehicle); and (3) patients assessment of treatment acceptability at week 8 using a Psoriasis Treatment Convenience Scale (PCTS) calculated as the sum of 5 treatment-specific questions rated on a 1–10 scale. Other endpoints included the proportion of subjects with mPASI75 (at least 75% reduction in mPASI from baseline) at week 8 and all efficacy assessments at week 4.

Information on reported and observed adeverse events (AEs) was obtained at each visit and reported using MedDRA version 20.1. The local safety and tolerability of the treatment area were assessed as local skin reactions (LSRs): perilesional erythema, scaling, edema, atrophy, vesicles, and erosion/ulceration and lesional vesicles, and erosion/ulceration. Subjects assessed the symptoms of application site burning or pain. Routine safety laboratory tests were performed at screening, week 4, and week 8.

Statistical Analysis

The superiority analyses of all efficacy endpoints (active treatments versus vehicle and CAL/BDP cream versus CAL/BDP TS) were based on multiple imputation of the intent-to-treat (ITT) population comprising all subjects who received study drug. Superiority analysis of itch intensity by the 11-point numeric rating scale (NRS) were based on the subset of subjects with minimum itch NRS of 4 at baseline (N=626). Categorial endpoints were analyzed by logistic regression, and continuous endpoints by ANCOVA with adjustment for treatment, disease severity at baseline, and analysis site. Superiority analysis of treatment convenience (PTCS) was based on the ITT population where missing data were imputed by last observation carried forward and analyzed by ANOVA with adjustment for treatment and analysis site. Quality of life endpoints were based on the ITT population without multiple imputation following the developer's instructions. Non-inferiority analyses (CAL/BDP cream vs CAL/BDP TS) were performed, based on the per-protocol (PP) population. Analyses were performed using SAS version 9.3.

All safety analyses were based on the safety population and summarized by frequency and severity for each treatment group.

RESULTS

Subject Disposition, Demographics, and Baseline Characteristics

Overall, 796 patients were randomized (343 patients treated with CAL/BDP cream, 338 patients treated with CAL/BDP TS and 115 patients treated with vehicle). Of the randomized patients 321 (93.6%), 319 (91.7%), and 94 (81.7%) completed the trial in the three groups, respectively. The main reason for discontinuation was lost to follow up (Table 1).

TABLE 1.

Summary of Subject Disposition (All Randomized Subjects, N=795)				
Characteristics	CAL/BDP cream	CAL/BDP Topical suspension	Vehicle	Total
Randomized, N	343	338	114	795
Adverse events, N (%)	2 (0.6%)	3 (0.9%)	4 (3.5%)	9 (1.1%)
Subject request	6 (1.7%)	15 (4.4%)	10 (8.7%)	31 (3.9%)
Lost to follow up	11 (3.7%)	8 (2.4%)	7 (6.1%)	26 (3.3%)
Protocol violation	1 (0.3%)	1 (0.3%)	0	2 (0.3%)
Other	2 (0.6%)	3 (0.9%)	2 (1.8%)	7 (0.9%)
Completed	321 (93.6%)	310 (91.7%)	94 (81.7%)	725 (91.2%)

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TABLE 2.

Patient Demographic and Disease Baseline Data (ITT Population)				
Characteristics	**CAL/BDP cream N=342**	**CAL/BDP TS N=337**	**Vehicle N=115**	**Total N=794[1]**
Mean age ± SD	52±14.4	52.8±13.7	50.4±14.3	52.0±14.1
Gender (%)				
Female	40.6	34.4	38.3	37.7
Male	59.6	65.6	61.7	62.3
Ethnicity (%)				
Latino	29.5	27.9	27.0	28.5
Non-Latino	70.5	72.1	73.0	71.5
Race (%)				
White/Caucasian	84.8	88.7	88.7	87
Black/African Americans	9.6	5.9	9.6	8.2
Asian	2.9	3.0	0.9	2.6
Other	2.4	2.4	0.9	2.2
Duration of psoriasis ± SD (years)	17.7±13.4	15.0±12.7	16.2±13.7	16.3±13.2
Baseline PGA (%)				
Mild	19.9	16.9	17.4	18.3
Moderate	80.1	83.1	82.6	81.7
Baseline mPASI±SD	7.3±3.9	7.7±4.1	7.1±4.1	7.4±4.0
Baseline mPASI >12 (%)	12.4	12.9	13.4	12.8
Baseline mean BSA ± SD (%)	7.3±6.0	8.4±7.0	7.5±6.1	7.8±6.5
Baseline BSA>10	18.9	24.9	18.8	21.4

[1]Two patients (one in each active arm) were excluded from the ITT population since they did not apply treatment

Baseline demographics and disease characteristics were comparable across the treatment arms (Table 2). At baseline, 81.7% subjects had moderate and 18.3% mild disease according to PGA disease severity. The mean BSA was 7.8% (SD 6.5%) with 64 subjects having severe disease defined as BSA>10%. Mean mPASI was 7.4% (SD 4.0%) with 42 subjects having severe disease defined as mPASI>12% (Table 2).

Efficacy

PGA treatment success

The percentage of patients achieving PGA treatment success at week 8 was statistically significantly higher in the CAL/BDP cream group (37.4%) compared to the cream vehicle group (3.7%) (*P*<0.0001) and to the CAL/BDP TS group (22.8%) (*P*<0.0001). Statistically significant differentiation between CAL/BDP cream and CAL/BDP TS was observed already at week 4 (*P*=0.0001) and week 6 (*P*<0.0001) (Figure 1). PGA treatment success with MC2-01 cream for subjects with mPASI≤12 and >12 was 37.3% and 48.0%, respectively, whilst the corresponding data for CAL/

FIGURE 1. (A) PGA Treatment Success improvement over time. *P* values represent comparison of CAP/BDP_cream to CAL/BDP TS analyzed by logistic regression (B) Percentage change in mPASI from Baseline. *P* values represent comparison of CAP/BDP_cream to CAL/BDP TS analyzed by an ANCOVA model. (C) Proportion of subjects obtaining mPASI75 over time. *P* values represent comparison of CAP/BDP_cream to CAL/BDP TS analyzed by logistic regression. All data based on the ITT population using multiple imputation.

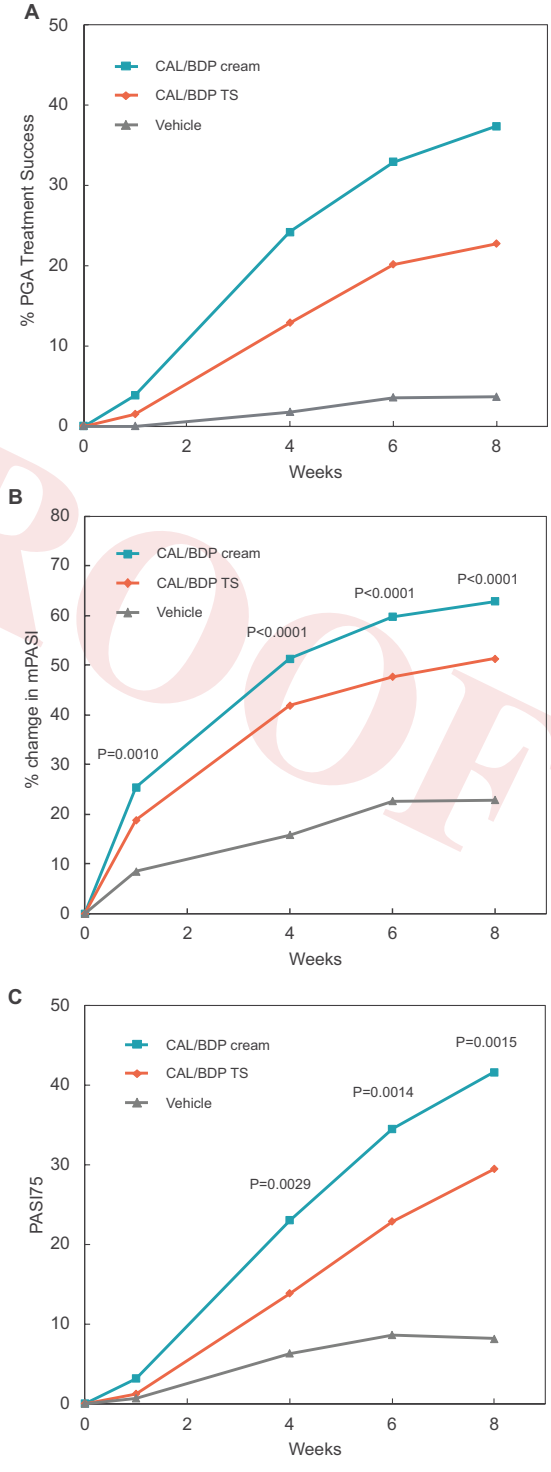

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TABLE 3.

PGA Success Rate as a Function of Baseline Severity Measured by BSA and mPASI

Characteristics	CAL/BDP cream	CAL/BDP TS	Vehicle	Comparison CAL/BDP cream to TS
BSA≤10	38.0% (274)	26.0% (251)	4.9% (91)	*P*=0.0018
BSA>10	41.5% (64)	23.3% (83)	5.5% (21)	*P*=0.0549
mPASI≤12	37.3% (296)	25.6% (291)	5.6% (97)	*P*=0.0011
mPASI>12	48.0% (42)	23.3% (43)	0.9% (15)	*P=0.0387*

Number in parenthesis reflects the number of subjects.
Statistical comparison: Logistic regression model including randomized treatment and baseline PGA as independent variables. *P* values are for test of difference

BDP TS was 25.6% and 23.3%. For subjects with BSA≤10 and >10, PGA treatment success was was 38.0% and 41.5% for CAL/BDP cream and 26.0% and 23.3% for CAL/BDP TS, suggesting that PGA treatment success increases for CAL/BDP cream and decreases for CAL/BDP TS by increasing severity (Table 3).

Change from Baseline in mPASI

The mean percentage reduction in mPASI score from baseline to week 8 was statistically greater for CAL/BDP cream (62.9%) than for CAL/BDP TS (51.3%) *P*<0.0001) and vehicle (22.9%) (*P*<0.0001). The difference in treatment effect between CAL/BDP cream and CAL/BDP TS was statistically significant already at week 1 (*P*=0.0010) and maintained at week 4 (*P*<0.0001), and week 6 (*P*<0.0001) (Figure 1).

The proportion of subjects obtaining mPASI75 was statistically greater in the CAL/BDP cream group than in the CAL/BDP TS group at week 8 (41.7% vs 29.5%; *P*=0.0015) and at week 4 (23.1% vs 13.9%; *P*=0.0029) (Figure 1).

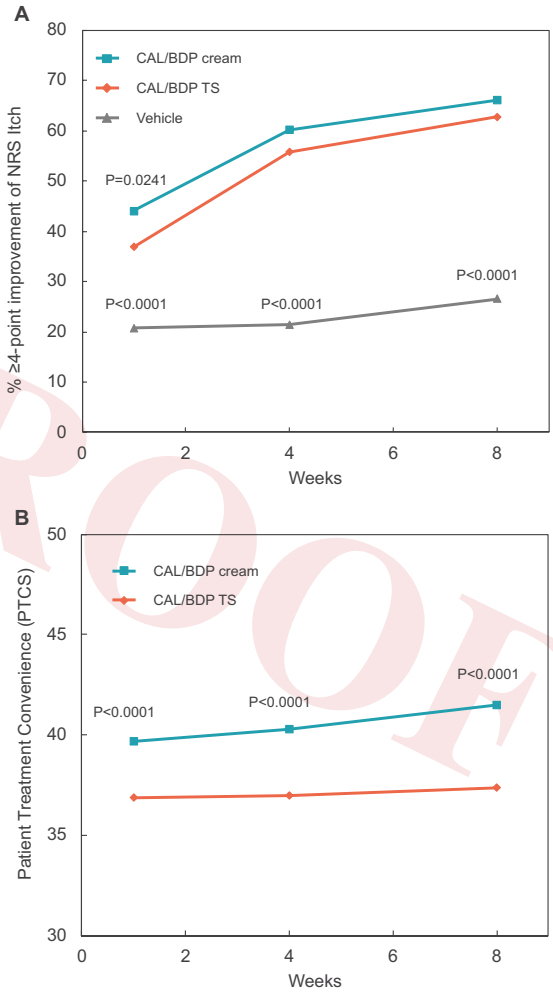
Itch by NRS

The proportion of subjects with a 4-point or greater improvement in itch using the 11-point NRS at week 4 was statistically significantly greater in the CAL/BDP cream group (60.2%) compared to the vehicle group (21.4%) (*P*<0.0001). The onset of reduction of itch was rapid with most of the reduction already occuring in the first week after initiating treatment. At week 1, the proportion of subjects obtaining improvement in itch was greater for CAL/BDP cream (44.0%) than for CAL/BDP TS (36.9%) (*P*=0.0241). At week 4, there was only a marginal difference between the two active treatments in improvement of itch (60.3% versus 55.8% for CAL/BDP cream and CAL/BDP TS, respectively).

Patient treatment acceptability

The mean patient treatment convenience score (PTCS) at week 8 for CAL/BDP cream (41.5) was statistically significantly superior to CAL/BDP TS (37.5) (*P*<0.0001). A similar statistically significant difference between CAL/BDP 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 cream was mainly due to the cream being a less greasy formulation compared to CAL/BDP TS.

FIGURE 2. (A) Proportion of subjects obtaining minimum 4-point improvement in itch intensity rated by patients on the 11-point numerical rating scale (NRS). Data based on the subset of subjects in the ITT population with minimum itch NRS of 4 at Baseline (N=626). *P* values were analyzed by logistic regression and represent either CAP/BDP_cream comparison to vehicle or CAL/BDP TS as indicated. (B) Patient reported acceptabilty of treatment assessed by the patient treatment convenience scale over time. *P* values represent comparison of CAP/BDP_cream to CAL/BDP TS analyzed based on the ITT population where missing data were imputed by last observation carried forward by an ANOVA model.



Safety

Overall, 311 AEs were reported by 198 of 794 (24.9%) patients. The incidence and type of AEs were similar in the 3 treatment groups with 90 (26.3%) patients in the CAL/BDP cream group, 76 (22.6%) in the CAL/BDP TS group, and 32 (27.8%) in the vehicle group. The majority of AEs were of mild or moderate intensity and only few were severe.

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In total, 35 treatment related AEs in 28 (3.5%) patients were reported, showing an even distribution between the three treatment arms. The related AEs for the CAL/BDP cream group were benign in nature and essentially similar to those described for existing CAL/BDP products. Most treatment related AEs were located at the application site, eg, irritation, pain, and pruritus. In the CAL/BDP cream group, 6 subjects reported such events (1.8%). No single related AE, including application site reactions, was greater than 1% in frequency.

Local skin reactions (LSR) occurred with similar frequency in the 3 treatment groups and were mostly mild or moderate. All LSRs decreased in intensity and frequency during the trial – especially in the two active treatment arms. The subject-assessed LSR (application site burning or pain) also decreased in frequency and intensity during the trial.

There were 12 AEs reported in 9 subjects leading to discontinuation. In the CAL/BDP cream group, 2 (0.6%) subjects were discontinued due to AEs with 1 event (insomnia) deemed to be probably related.

A total of 21 (2.6%) subjects reported a serious adverse event with similar frequency in the 3 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 3 arms during the trial.

DISCUSSION

Results from the present trial demonstrated that CAL/BDP cream was significantly more effective than CAL/BDP TS. The achievement of PGA treatment success at week 8 was greater for CAL/BDP cream (37.4%) than for CAL/BDP TS (22.8%) (P<0.0001), and the reduction in mPASI from baseline to week 8 was greater for CAL/BDP cream (62.9%) compared to CAL/BDP TS (51.3%) (P<0.0001). This finding was confirmed by significantly more subjects obtaining mPASI75 in the CAL/BDP cream group.

The CAL/BDP 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 favor of CAL/BDP cream already at week 1 (mean percentage reduction: 25.4% vs 18.8%, P=0.0010), which continued with significant difference at all subsequent visits (P<0.0001). The PGA treatment success rate was found to be statistically significantly greater in the CAL/BDP cream group compared to CAL/BDP TS at week 4 (24.2 vs 12.9, P=0.0001) and at week 6 (P<0.0001). The level of PGA success and reduction in mPASI from baseline for CAL/BDP cream at week 4 was similar to that obtained with CAL/BDP TS after 8 weeks of treatment. Most of the reduction in itch took place within the first week of treatment where more patients obtained 4-point itch improvement in the CAL/BDP cream group (44.0%) than in the CAL/BDP TS (36.9%) group (P=0.0241). Further comparisons demonstrated only marginally greater improvement of itch for CAL/BDP cream at week 4 and week 8 compared to CAL/BDP TS.

The treatment efficacy measured as PGA treatment success at week 8 of CAL/BDP cream increased in subjects with severe psoriasis (defined by BSA>10% or mPASI>12), whereas efficacy of CAL/BDP TS decreased in these subjects (Table 3).

At all visits throughout the trial, patient treatment convenience was significantly (P<0.0001) higher in patients having received CAL/BDP cream than in those treated with the CAL/BDP TS.

Types and incidences of related AEs with CAL/BDP cream were as expected based on the known safety profile of marketed CAL/BDP products. The majority of the related AEs for CAL/BDP cream were application site reactions, with no AE frequency above 1%. There were 12 AEs reported in 9 subjects leading to discontinuation. In the CAL/BDP cream group, 2 (0.6%) subjects were discontinued due to AEs and only 1 event (insomnia) was deemed probably related.

Topical formulations containing fixed dose combinations of CAL and BDP with 0.005 w/w% CAL and 0.064 w/w% BDP have over the last decades confirmed their clinical efficacy and favorable systemic and dermal safety.[1,13-18] However, for stability reasons, all marketed CAL/BDP combination products have until now been based on non-aqueous petrolatum or mineral oil as the predominant ingredient. Consequently, these formulations are perceived by many patients as inconvenient since they are greasy, sticky, take a long time to dry and stain clothes, consequently interfering with daily routines and persistently reminding the patient about their disease condition. The result may be lack of adherence to treatment leading to suboptimal treatment outcomes in the real-world setting.[19]

The CAL/BDP cream has been designed to create a novel and unique topical formulation of CAL/BDP, combining excellent patient acceptability, high efficacy and favorable safety in one product. Development of CAL/BDP cream is enabled by PAD™ technology, which, by its robust oil-in-water dispersion structure, offers unique advantages with respect to solubility of actives, high penetration into the skin, and increased drug stability. These features have overcome the inherent pH-dependent stability problem associated with formulation of CAL/BDP in the presence of water.[9] Moreover, formulations based on PAD™ technology are appealing creams of high cosmetic quality and patient acceptability.

CONCLUSION

In conclusion, the CAL/BDP cream is a novel topical treatment of psoriasis that in a single product has the unique combination of high efficacy, favorable safety, and excellent patient acceptability. CAL/BDP cream thus offers a distinctive advantage for topical treatment of psoriasis.

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DISCLOSURES

Johan Selmer, Birgitte Vestbjerg, Morten Praestegaard are employees of MC2 Therapeutics. Linda Stein Gold is an investigator/advisor/or speaker for MC2, Leo Pharma, Dermavant, Arcutis, Ortho Dermatologics, and Sun Pharma.

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