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ORIGINAL ARTICLE

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Fixed Combination Calcipotriene/Betamethasone (Cal/BDP) Cream: Evaluating the Role of Polyaphron Dispersion (PAD) Technology in Psoriasis Treatment

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ABSTRACT

Most patients with plaque psoriasis exhibit mild-to-moderate disease and topical therapies remain the mainstay treatment option for these patients. The use of topical steroids in combination with vitamin D analogs can produce synergistic effects and minimize adverse effects. However, due to the incompatible pH ranges of topical steroids and vitamin D analogs, combination formulations can be difficult to manufacture. Until recently, only anhydrous formulations of these 2 agents were developed as foam, gel/suspension, and ointment. However, anhydrous vehicles can often result in greasy or oily skin, thus limiting treatment adherence. Recently, Polyaphron Dispersion (PAD) technology presents a new, more cosmetically appealing vehicle that allows for both topical steroids and vitamin D analogs to coexist in an aqueous environment, such as a cream formulation. The calcipotriene/betamethasone dipropionate (CAL/BDP) cream enhances drug delivery by reducing the greasy and oily side effects of anhydrous formulations. Phase 3 clinical trials have demonstrated CAL/BDP cream's superior efficacy in treating psoriasis over gel/suspension, and the clinical trials have also shown significantly improved patient satisfaction with the cream formulation.

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INTRODUCTION

Psoriasis vulgaris is a chronic, immune-mediated skin disease originating from a combination of environmental and genetic factors. Approximately 80% of psoriasis patients exhibit mild-to-moderate disease, for which topical therapies remain the cornerstone of psoriasis management.[2] The most common topical therapies include topical corticosteroids, vitamin D analogs (calcipotriene, calcipotriol), and retinoids (tazarotene). Current treatment guidelines have evolved to recommend the use of newer fixed-dose combinations of topical steroids (betamethasone dipropionate) and vitamin D analogs (calcipotriene) because the combination has demonstrated superior efficacy over monotherapy with either agent alone.[2] In addition, the combination of CAL/BDP exhibits a more favorable safety profile than topical corticosteroids alone. Furthermore, topical CAL/BDP combination therapies have become increasingly popular because they fulfill many requirements that patients and dermatologists alike look for in topical management of psoriasis including faster onset of action, maximal and longer duration of efficacy, less frequent application, and improved quality-of-life metrics.[3]

Until recently, the 2 ingredients (topical steroids and topical vitamin D analogs) have been limited to non-aqueous vehicles due to their distinctive pH environments.[4] The 2 are typically incompatible. To ensure compatibility, traditionally both agents have needed to coexist in non-aqueous environments. Currently, anhydrous formulations of CAL/BDP such as foam, gel/suspension, and ointment can result in undesired greasy or oily skin. PAD technology utilizes a newer vehicle to allow these two ingredients to coexist in an aqueous form. Thus, the PAD

technology presents a more cosmetically appealing alternative vehicle that allows for both ingredients to co-exist in aqueous solutions for a cosmetically elegant cream formulation. This manuscript describes the innovations in drug delivery vehicles for patients with mild-to-moderate psoriasis in evaluating a newer therapy that allows for delivery of topical vitamin steroids and topical vitamin D agents in an aqueous cream formulation.

Updates on the Mechanism of Action of Topical Corticosteroids and Calcipotriene

Psoriasis is thought to result from excess epidermal keratinocyte proliferation and differentiation. The significant increase in keratinocytes in psoriasis leads to skin thickening, which ultimately contributes to the development of the characteristic, well-demarcated plaques.[5] The increased keratinocyte proliferation also induces dermal angiogenesis, which encourages the flow of immune cells to the affected areas and exacerbates the inflammatory response of psoriasis.[6] Thus, topical corticosteroids remain a mainstay treatment option due to their anti-inflammatory effects. In particular, corticosteroids inhibit recruitment and migration of inflammatory cells, modulate cytokine and chemokine release, and interfere with transcriptional activity of cytokines.[6] However, long-term topical corticosteroid use, when used inappropriately, can produce undesirable side effects, such as thinning of the skin and striae.

Alternatively, calcipotriene, or calcipotriol, is a vitamin D derivative that offers another treatment option to patients with mild-to-moderate psoriasis. It inhibits keratinocyte proliferation, stimulates terminal keratinocyte differentiation, and regulates the release of pro-inflammatory cytokines.[6] However, calcipotriene can produce skin irritation. Multiple studies have shown that the efficacy of calcipotriene is comparable to that of topical corticosteroids. Furthermore, dual therapy with corticosteroids and calcipotriene demonstrated a synergistic effect in comparison to monotherapy with either agent in multiple studies.[2] In addition, the combination offers a more favorable safety profile as calcipotriene mitigates the atrophogenic effects of betamethasone and conversely betamethasone counteracts potential skin irritation of calcipotriene.[7] Given the superior efficacy and quick onset of action, the American Academy of Dermatology treatment guidelines recommend topical corticosteroids in conjunction with calcipotriene as the standard of care for mild-to-moderate plaque psoriasis.

On a molecular level, both corticosteroids and vitamin D analogs target the underlying inflammation in psoriasis. The inflammation in psoriasis is primarily driven by dendritic cells releasing cytokines (interleukin (IL)-23, IL-12, TNF-α), IL-17 inducing keratinocyte proliferation, and TH1 and TH17 cells promoting a pro-inflammatory feedback loop.[8,9] Corticosteroids and vitamin D analogs both independently inhibit the release of cytokines, specifically IL-17A, IL-23, and TNF-α, which prevents further activation and maturation of keratinocytes and dendritic cells.[8] Combination therapy has been shown to have additive effects in vitro cultures of primary human cells and ex vivo cultures of psoriatic skin, resulting in greater inhibition of cytokine release and initiation of the proinflammatory feedback loop in comparison to monotherapy with either agent alone.[9] Furthermore, corticosteroids and calcipotriene have synergistic effects on the adaptive immune system. Corticosteroids suppress immunomodulatory Th2-cell secretion while calcipotriene induces regulatory T-cell production.[9]

Challenges of Combining Topical Corticosteroids and Topical Vitamin D Analogs

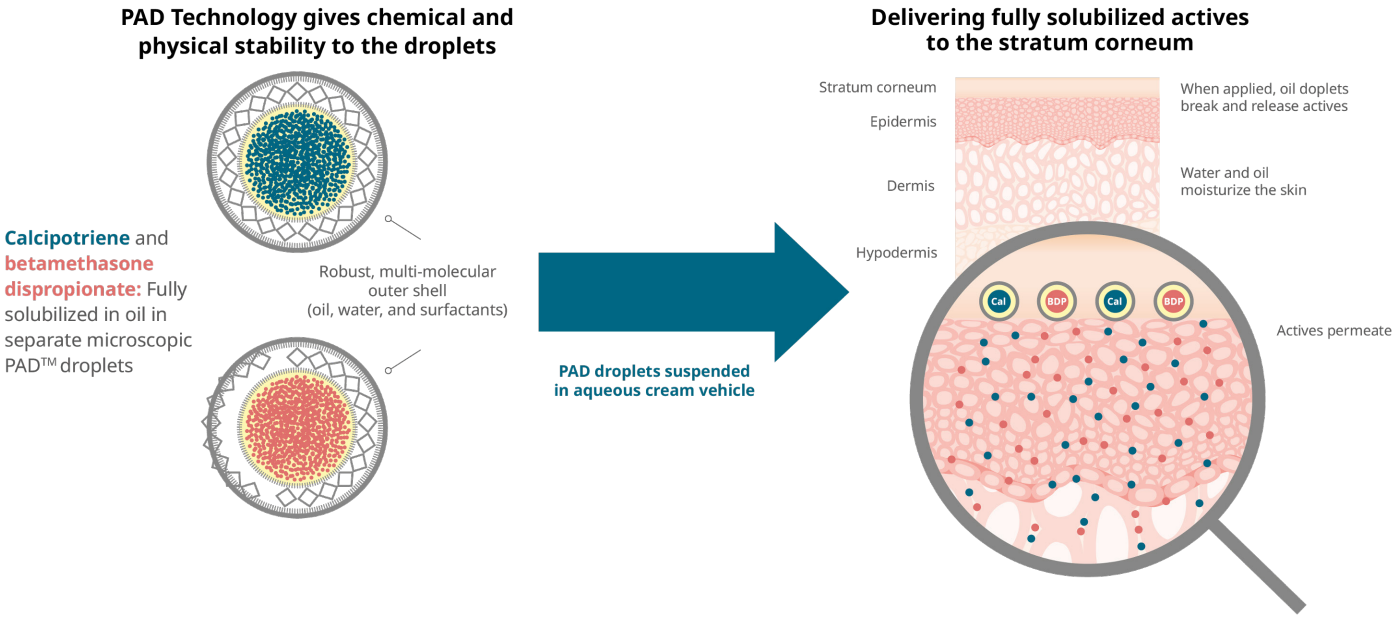
Topical corticosteroids and topical vitamin D analogs can be mixed and applied immediately after mixing onto the skin, applied serially, or used in combination from a specially formulated vehicle that allows for stable storage of the two active ingredients together.

Physically mixing topical corticosteroids and vitamin D analogs together but not applied immediately to the skin can lead to inactivation of active ingredients due to their incompatible pH ranges. Serial application can also pose a challenge as absorption of the second agent may be limited if the first agent blocks the absorption of the second agent. In addition, serial application can often be inconvenient for patients, complicating treatment adherence.[10] Beyond frequent application, treatment formulation and speed of onset of action have been shown to impact treatment adherence. For example, a survey by the National Psoriasis Foundation found that although a majority of patients (74.6%) use topical therapies at least once weekly, most participants would consider discontinuation if they did not notice efficacy (80%) or did not like the treatment's formulation (74.7%).[11]

To increase treatment adherence, a fixed-dose combination product of betamethasone dipropionate and calcipotriene was desired. A combination of calcipotriene and betamethasone dipropionate was originally achieved only in anhydrous forms since both agents exhibit incompatible pH ranges. Anhydrous formulations are currently available as foam, gel/suspension, and ointment. CAL/BDP ointment gained approval by the Federal Drug Administration (FDA) in 2006 for the treatment of mild-to-moderate plaque psoriasis in patients 12 years and older.[4] The product is a fixed combination of 0.005% calcipotriene hydrate and 0.064% betamethasone dipropionate with recommended daily use of up to 4 weeks.

However, this combination CAL/BDP formulation is not stable in long-term aqueous environments. Topical corticosteroids are stable under acidic conditions (pH: 4–6) but are sensitive to alkaline residues and oxidizing agents. Calcipotriene requires a relatively alkaline pH (pH>8) for stability.[12] The 2 agents exhibit

FIGURE 1. Scanning electron microscopy of PAD technology-engineered oil droplets (taken with permission from MC2 Data on File).



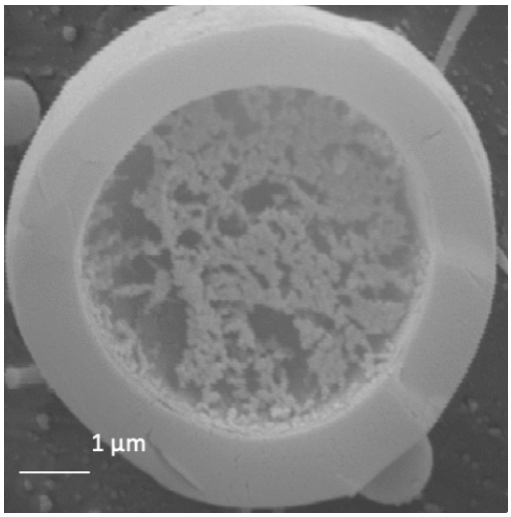
incompatible pH ranges and thus inactivate each other in the same setting. Consequently, producing a single formulation combining the 2 agents proves challenging. The earlier CAL/BDP formulations were restricted to non-aqueous, oil- or paraffin-based vehicles, often resulting in greasy or oily skin after application. Cosmetic characteristics of the earlier CAL/BDP formulations likely contributed to low treatment adherence, with one study demonstrating 73% of patients not adhering to treatment.[12] Despite the advances in delivering both topical agents simultaneously, treatment adherence with anhydrous formulations remains an area of concern.

Novel PAD Technology for Enhanced Drug Delivery

As discussed earlier, vitamin D analogs are stable under basic conditions (pH 8–10) and are sensitive to oxidizing agents and acidic residues. Topical corticosteroids are stable under acidic conditions (pH 4–6) and are sensitive to alkaline residues and oxidizing agents. Consequently, calcipotriene is inactivated at low pH, while betamethasone dipropionate is inactivated at high pH, proving a challenge to deliver the two agents in an aqueous vehicle. Traditionally, many emulsifiers are combined with oil and water to bind the two incompatible substances together found in anhydrous vehicles. However, too much emulsifier can result in stinging, burning, and disruption of the protective skin barrier, which may be exacerbated in psoriasis patients with increased skin sensitivity. In addition, these anhydrous vehicles utilize excess surfactants, which produce skin irritation, dryness, and fissuring of the skin. The increased levels of surfactants, emulsifiers, and wax in anhydrous vehicles contribute to their greasy and oily side effects.

The novel PAD technology, also referred to as colloidal liquid aphron and biliquid foams, improves upon greasy anhydrous vehicles by allowing calcipotriene and betamethasone to coexist in aqueous droplets, creating a novel, cosmetically appealing cream formulation (Figure 1).[10,13] An inner oil phase is surrounded by an aqueous layer with emulsifiers that are different from those found in conventional creams. While the inner core consists of a nonpolar solvent, it is encapsulated by an outer shell containing surfactants, oil, and water that stabilize and separate the inner core.[15] Consequently, the robust multimolecular shell structure of PAD-engineered oil droplets increases the chemical stability of the droplets and limits water contact, thereby protecting the active ingredients from hydrolysis (Figure 2).

FIGURE 2. Overview of the structure of PAD technology-engineered CAL/BDP cream formulation (taken with permission from Pinter et al. Poster 1447. 30TH EADV Virtual Congress, Sept 29 – Oct 2, 2021).



In contrast to conventional emulsions with multiple layers of surfactant, PAD technology creates oil droplets with <1% surfactants compared to >5% in conventional creams and lotions.[4,13] The low surfactant and minimal oil phases lessens skin irritation, promotes skin hydration, and is more tolerable for fissured skin by limiting interference with the skin barrier. The low level of emulsifier used in PAD creams makes it more convenient for patients to adapt into their regular routine because these creams are not greasy or sticky.[14] Lastly, the vehicle utilizes a light powder carbomer instead of greasy petroleum or wax, which lowers the oil content compared to other liquid or oil formulations and allows for easy, fast-acting, and non-greasy application on the skin.[14] Overall, PAD formulations enhance drug delivery by creating fully active solubilized molecules, optimizing thermodynamic forces to drive active ingredients into target tissue, and producing significant occlusion and surface contact with the stratum corneum and follicles. In particular, PAD technology has been shown to penetrate deeper into the epidermis when compared to an ointment vehicle.[15,16] Furthermore, Draelos et al demonstrated in 10 female volunteers with moderate plaque psoriasis that cream formulation of CAL/BDP resulted in higher deposition of BDP and its major active metabolite, betamethasone 17-propionate (B17P) up to 8 hours after administration in comparison to topical suspension. B17P specifically demonstrated deeper penetration into the upper skin layers, such as the stratum corneum.[15] These features of PAD technology make CAL/BDP cream desirable as the cream is fast-absorbing and easy to wash out of hair, thus improving adherence.

Emerging Evidence for the Use of CAL/BDP Cream Formulation in Psoriasis Treatment

Currently, most of the available data regarding the efficacy and safety profile of CAL/BDP cream for the treatment of psoriasis is from phase 3 clinical trials conducted in the United States and Europe. The pivotal clinical trials and their results are outlined below.

Pinter highlighted two identical phase 3, randomized, controlled, parallel-group, multicenter, investigator-blinded studies evaluating the efficacy and safety of CAL/BDP cream. 1271 patients were randomized to CAL/BDP PAD cream, CAL/BDP topical suspension (TS), or vehicle for once daily treatment over an 8-week study period. Efficacy was defined as percentage of subjects achieving Provider Global Assessment (PGA) treatment success and mean percent reduction in Psoriasis Area and Severity Index (mPASI) score. PGA treatment success for CAL/BDP PAD cream was significantly greater than CAL/BDPTS (43.2 vs 31.9%, $P<0.0001$) with improvement noted as early as week 4. CAL/BDP PAD cream exhibited significantly greater reductions in mPASI than the CAL/BDPTS (64.6% vs 56.4%, $P<0.0001$) with reductions observed as early as week 1.[4] CAL/BDP PAD cream demonstrated a favorable treatment profile with no adverse events reported. In addition, CAL/BDP PAD cream resulted in a significantly higher quality of life (6.5 points vs 5.6 points).[4] The authors also noted a favorable safety profile with no adverse events displaying a frequency of greater than 1%. A phase 3 randomized, multicenter, investigator-blind, parallel group trial of 796 adults with mild-to-moderate plaque psoriasis also noted faster onset of action, rapid improvement in both clinical (PGA scores) and patient-reported outcomes (DLQI, itch, convenience of use) in patients using the cream formulation in comparison to topical suspension.[17]

A European phase 3 sub-group analysis evaluated treatment efficacy and safety in patients with scalp psoriasis of at least 10% involvement and a PGA score of 2. Treatment success was defined as a 2-grade decrease in PGA score from baseline to week 8. CAL/BDP PAD cream demonstrated significant treatment success on the scalp compared to vehicle (50% vs 9.3%, $P<0.001$) as early as week 1.4 Safety assessment was similar to that of the previously noted studies.

A phase 3 randomized, multicenter, vehicle-controlled study randomized 796 patients to CAL/BDP PAD cream, CAL/BDP TS, or vehicle for once daily application over an 8-week study period. This trial yielded similar results to those described by Pinter et al, with a significant improvement in PGA and mPASI scores in the CAL/BDP PAD cream group compared to the CAL/BDPTS group (PGA 37.4 vs 22.8, $P<0.0001$; mPASI 42.3% vs 29.7, $P=0.0027$).[7] In addition, patients using CAL/BDP PAD cream exhibited a significantly greater quality of life ($P=0.016$). Lastly,

TABLE 1.

Summary of Studies Examining CAL/BDP Cream in the Treatment of Psoriasis		
Author	**Study Type**	**Findings**
Pinter et al	Pooled analysis of two randomized, controlled phase 3 trial	PGA treatment success for CAL/BDP PAD-cream was greater than CAL/BDPTS (topical suspension) (43.2% vs 31.9%; *P*<0.0001) The mean percent reduction in mPASI for CAL/BDP PAD-cream was 64.6% versus 56.4% for CAL/BDPTS (*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/BDPTS group (*P*=0.0005)
Gold et al	Two randomized, controlled phase 3 trials	Proportion of patients achieving PGA treatment success after 8 weeks was statistically significantly greater for CAL/BDP PAD cream (37.4%) versus CAL/BDPTS (22.8%, *P*<0.0001), and vehicle (3.7%, *P*<0.0001)
Han et al	Phase 3 randomized, controlled trial	PGA improved at least 1-grade after one week of treatment in 34.7% of patients with CAL/BDP cream compared to 26.2% in the CAL/BDPTS (topical suspension) group (*P*=0.0122) and 13.7% in the vehicle group (*P*<0.0001) mPASI score decreased more in the CAL/BDP group (25.4% change from baseline) after 1 week compared to the CAL BDPTS group (18.7%; *P*=0.0013) and the vehicle group (9.8%, *P*<0.0001) More patients in the CAL/BDP cream group (44.8%) achieved clinically relevant 4-point improvement in DLQI at week 1 than with CAL/BDPTS (40.4%; *P*= 0.0476) or vehicle (29.7%)

Patient Treatment Convenience Scores (PTCS) demonstrated significant ease of treatment use for CAL/BDP PAD cream.[7] The PTCS evaluated for (1) ease-of-treatment application on the skin, (2) how greasy the skin felt during application, (3) how moisturized the skin felt after application, (4) how greasy the skin felt after application, (5) if treating the skin disrupted daily routine, and (6) overall satisfaction with medical treatment. CAL/BDP PAD cream demonstrated significant improvement compared to anhydrous formulations in all PTCS questions.[7] Thus, the data presented in this trial not only demonstrates excellent treatment efficacy, but also highlight the product's convenience and patient satisfaction for regular, long-term use.

CONCLUSION

Combination CAL/BDP therapy is desired given their synergistic effect in treating mild-to-moderate psoriasis and favorable safety profile. Currently, available formulations produce unwanted side effects, thereby limiting treatment adherence. Thus, the innovative PAD-technology creates a cosmetically elegant vehicle that enhances drug delivery and improves treatment adherence. The clinical trials discussed above demonstrate the superior efficacy, safety, and tolerability of the CAL/BDP PAD cream in comparison to the currently available alternatives. Thus, the success of the CAL/BDP PAD cream in clinical trials highlights the growing utility of PAD technology in advancing topical drug design and delivery for management of psoriasis and potentially other inflammatory diseases within the field of dermatology.

DISCLOSURES

April W. Armstrong MD MPH has served as a research investigator and/or scientific advisor to AbbVie, Almirall, Arcutis, ASLAN, Beiersdorf, BI, BMS, EPI, Incyte, Leo, UCB, Janssen, Lilly, Nimbus, Novartis, Ortho Dermatologics, Sun, Dermavant, Dermira, Sanofi, Regeneron, Pfizer, and Modmed.

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REFERENCES

1. Armstrong AW, Read C. Pathophysiology, Clinical Presentation, and Treatment of Psoriasis: A Review. *JAMA*. 2020;323(19):1945-1960.
2. Patel NU, Felix K, Reimer D, Feldman SR. Calcipotriene/betamethasone dipropionate for the treatment of psoriasis vulgaris: an evidence-based review. *Clin Cosmet Investig Dermatol*. 2017;10:385-391.
3. Armstrong AW et al, Consensus statements on the use of corticosteroid-containing topical medications in psoriasis. *J Drugs Dermatol*. <in press>
4. Pinter A, Green LJ, Selmer J, et al. 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*. 2022;36(2):228-236.
5. Saraceno R, Gramiccia T, Frascione P, Chimenti S. Calcipotriene/betamethasone in the treatment of psoriasis: a review article. *Expert Opin Pharmacother*. 2009;10(14):2357-2365.
6. Purvis CG, Balogh EA, Heron CE, Feldman SR. Topical calcipotriol plus betamethasone dipropionate for the treatment of plaque psoriasis: a drug evaluation. *Expert Opin Pharmacother*. 2021;22(9):1107-1118.
7. Stein Gold L, Green LJ, Dhawan S, et al. A phase 3, randomized trial demonstrating the improved efficacy and patient acceptability of fixed dose calcipotriene and betamethasone dipropionate cream. *J Drugs Dermatol*. 2021;20(4):420-425. doi:10.36849/JDD.2021.5653
8. Lovato P, Norsgaard H, Tokura Y, et al. Calcipotriol and betamethasone dipropionate exert additive inhibitory effects on the cytokine expression of inflammatory dendritic cell-Th17 cell axis in psoriasis. *J Dermatol Sci*. 2016;81(3):153-164.
9. Segaert S, Shear NH, Chiricozzi A, et al. Optimizing anti-inflammatory and immunomodulatory effects of corticosteroid and vitamin d analogue fixed-dose combination therapy. *Dermatol Ther (Heidelb)*. 2017;7(3):265-279.
10. Kragballe K, Barnes L, Hamberg KJ, et al. Calcipotriol cream with or without concurrent topical corticosteroid in psoriasis: tolerability and efficacy. *Br J Dermatol*. 1998;139(4):649-654.
11. Curcio A, Kontzias, C, Feldman,SR. Improving Patient Acceptability and Adherence in Psoriasis Treatment. *SKIN The Journal of Cutaneous Medicine*. 2022;6(6): s59. doi:10.25251/skin.6.supp.59
12. Molin L, Cutler TP, Helander I, et al. Comparative efficacy of calcipotriol (MC903) cream and betamethasone 17-valerate cream in the treatment of chronic plaque psoriasis. A randomized, double-blind, parallel group multicentre study. Calcipotriol Study Group. *Br J Dermatol*. 1997;136(1):89-93.
13. Vakirlis E, Kastanis A, Ioannides D. Calcipotriol/betamethasone dipropionate in the treatment of psoriasis vulgaris. *Ther Clin Risk Manag*. 2008;4(1):141-148.
14. Barrea L, Savanelli MC, Di Somma C, et al. Vitamin D and its role in psoriasis: An overview of the dermatologist and nutritionist. *Rev Endocr Metab Disord*. 2017;18(2):195-205.
15. Praestegaard M, Steele F, Crutchley N. Polyaphron Dispersion Technology, A Novel Topical Formulation and Delivery System Combining Drug Penetration, Local Tolerability and Convenience of Application. *Dermatol Ther (Heidelb)*. 2022;12(10):2217-2231.
16. Draelos, Z. D., Draelos, M. M., & Praestegaard M. Enhanced Skin Deposition of Betamethasone Dipropionate into the Skin of Human Volunteers from Calcipotriene/Betamethasone Dipropionate Cream Compared to Topical Suspension. *SKIN The Journal of Cutaneous Medicine*. 2022;6(6):s54. doi:10.25251/skin.6.supp.54.
17. Han et al. Calcipotriene (CAL) and betamethasone dipropionate (BDP) cream (CAL 0.005%/BDP 0.064% W/W) improves plaque psoriasis at one week in a phase 3 trial. Poster presented at: Fall Clinical Dermatology Conference 2022; October 20–23, 2022; Las Vegas, NV.

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