Systematic literature review of long-term efficacy data for topical psoriasis treatments

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\textbf{ABSTRACT}

\textbf{Objective}: To identify long-term efficacy evidence that supports use of topical therapies as regular maintenance therapy in the prevention of psoriasis relapse.

\textbf{Methods}: A systematic literature review identified clinical trials and observational studies that reported efficacy outcomes for topical psoriasis treatments with treatment durations of at least 12 weeks. For therapies with long-term data, the approved treatment schedules in product labels were reviewed.

\textbf{Results}: Forty-six studies with at least 12-week efficacy outcomes were identified. Eight randomized controlled trials and six observational studies or single-arm open-label studies reported efficacy data for >12-week treatment periods. Most studies used treatment regimens that reflect current standard of care of repeated treatment of relapses. The PSO-LONG study is the only identified randomized controlled trial to have compared regular proactive maintenance use of a topical treatment (calcipotriol/betamethasone foam) with reactive management in response to psoriasis relapses.

\textbf{Conclusions}: Limited high-quality long-term efficacy data are available for topical psoriasis therapies. While some product labels mention clinical experience of up to 12 months, they do not provide specific recommendations on the optimal long-term regimen. Calcipotriol/betamethasone foam is the only treatment for which the approved label allows either reactive treatment of relapse or regular (twice weekly) maintenance use.

\section*{Introduction}

Psoriasis is a chronic inflammatory disease characterized by a fluctuating pattern of remission and flare (1). Plaque psoriasis accounts for \textasciitilde{}90\% of cases and manifests as sharply demarcated, scaly, erythematous lesions commonly affecting the knees, elbows, scalp and trunk (2). Psoriasis has an impact on the physical, psychological and social wellbeing of patients (3). Due to the chronic nature of psoriasis, long-term treatment strategies are needed to reach the treatment goals of achieving remission and maintaining clear, or almost clear, skin and restoring normal daily functional ability and quality of life (4).

Topical therapy is the standard of care for treatment of the majority of patients with mild to moderate disease (~88\% of all patients with psoriasis, (5)), whilst patients with more severe disease may use topical therapies in conjunction with conventional systemic treatments and biologics (6,7). Effective management with topical therapies offers several advantages over conventional systemic and biologic treatment including a more favorable side effect profile, significantly lower cost and the possibility for patients to manage their psoriasis without the need for specialist treatment (4,8). Vitamin D analogues (such as calcipotriol) and corticosteroids (such as betamethasone dipropionate and clobetasol propionate) are commonly used topical treatments and are often prescribed in combination.

While topical steroids play a key role in psoriasis treatment, potent and very potent agents are not recommended for periods of longer than 4–8 weeks because of potential adverse effects (3), this is reflected in approved labels. Current long-term management (>6 months) often follows a reactive approach in response to flares (9) without precise guidance on how or when to stop and re-start topical therapy, or the frequency and duration of treatment (8).

Alternative long-term management approaches include proactive maintenance treatment with long-term, low frequency (e.g. twice weekly) treatment. This proactive approach is well established for atopic dermatitis with topical calcineurin inhibitors for up to a year (8,10,11), and has been shown to reduce, prevent and delay disease exacerbations (12). There is a growing consensus amongst dermatologists for a proactive approach to long-term management of psoriasis with topical therapies in order to maintain remission, increase adherence and improve long-term outcomes (8,9,13).

In a recent review, Segaert et al. (8) described ‘long-term maintenance’ as aiming to maintain remission once achieved, with the possibility of continuous treatment on a less frequent basis. We use this terminology to distinguish between current, reactive long-term management approaches to treat relapse, and proactive treatment strategies to maintain remission.

Long-term maintenance with topical therapies has been recommended in psoriasis treatment guidelines, based on review of published literature and expert opinion. In France, twice weekly maintenance treatment with a vitamin D analogue and corticosteroid was recommended by a panel of experts (14). The
joint US guideline from the American Association of Dermatology and the National Psoriasis Foundation describes proactive management as treatment of quiescent areas (typically twice weekly) to reduce the frequency of flares (15). German and Swiss consensus guidelines agree that successful once daily induction therapy for 4-8 weeks may be followed by twice weekly proactive management to reduce the risk of relapse (16,17).

Previous reviews of topical psoriasis treatments have defined studies of <6 months duration as short-term and those >6 months as long-term (18,19). Long-term studies of topical psoriasis treatments have focused on demonstrating the safety and tolerability of treatments originally approved for short-term use (based on 4-12 week studies) when used over longer periods on a continuous basis, or intermittently in response to relapses (20,21). There is a lack of controlled evidence of high quality on the efficacy of topical treatments under a long-term maintenance regimen compared to the current standard of care (18,19). Such evidence is needed to support a change in product labeling and consequently clinical practice, and to provide patients with an alternative treatment strategy that could offer improved long-term disease control while also limiting the issues associated with continuous steroid use (3). Currently, only the fixed-dose combination of calcipotriol and betamethasone in foam formulation (Enstilar®) is indicated for long-term maintenance treatment in addition to short-term flare treatment (22).

The aims of this systematic review were to evaluate the available long-term efficacy evidence that supports the use of topical psoriasis treatments under long-term maintenance regimens, (i.e. alternative treatment strategies to the current practice of reactive treatment in response to flare), and to compare this evidence with recommendations on long-term use of topical treatments from the Summaries of Product Characteristics (SmPCs) of available topical treatments.

Materials and methods

A systematic literature review (SLR) was conducted to identify clinical trials and observational studies that assessed long-term efficacy of topical treatments for psoriasis in adult patients. PubMed, Embase and the Cochrane Library were searched from January 01, 2000 to November 05, 2020 for published articles, without language restriction. Search strategies included index and text terms for psoriasis, the relevant interventions, comparative outcomes and studies. The full search strategy is provided in Supplementary Table 1.

All identified titles and abstracts were assessed for inclusion by one reviewer. Full texts were then assessed, with a second reviewer checking those articles excluded by the first reviewer. Discrepancies were resolved by discussion.

Clinical trials and observational studies of vitamin D analogues, corticosteroids and other marketed topical therapies for psoriasis with a treatment period of at least 12 weeks that reported at least one efficacy outcome were eligible for inclusion. Details of inclusion and exclusion criteria are presented in Supplementary Table 2.

For studies meeting the eligibility criteria, details of the study design, patient population, interventions, treatment regimens and outcomes were extracted.

Based on the review findings, studies were categorized based on treatment duration: 12 weeks, >12 weeks to 26 weeks and >26 weeks, which allowed for studies with a duration of ~6 months and studies with duration ~1 year to be clustered together. Within each treatment duration category, randomized controlled trials (RCTs) were considered separately from open-label and observational studies.

Results

Electronic database searches identified 3,586 articles. Following removal of duplicates, a total of 2,086 records were screened at title and abstract stage; of these 102 articles were assessed at the full text screening stage. The SLR included 55 articles reporting on 46 studies that included treatment periods of at least 12 weeks (Figure 1).

Studies reporting 12-week efficacy data

Thirty-two studies were identified that reported efficacy data following 12-week treatment with topical psoriasis treatment. Treatments evaluated were the vitamin D analogues calcipotriol (23–34), calcitriol (35–37) and tacalcitol (38) as monotherapy, vitamin D analogues in combination with topical corticosteroids (either clobetasol (39) or betamethasone (40–47)), tazarotene as monotherapy (48–54) or in combination with a topical corticosteroid (mometasone, clobetasol or betamethasone (55,56)), coal tar solution (57), dithranol (25,32,58), betamethasone monotherapy and mometasone in combination with salicylic acid (59,60).

Many of the trials reporting 12-week efficacy data were small (fewer than 100 patients), non-randomized, non-controlled studies. Twelve of the studies were RCTs including more than 100 patients (described in Table 1). These studies demonstrate that a range of treatments can be used safely and effectively for up to 12 weeks, but do not address the long-term management of psoriasis to prevent relapse.

Studies reporting >12–26 week efficacy data

One non-controlled, open-label trial and four RCTs reported efficacy data for treatment periods of between 16 and 26 weeks.

In the open-label study, patients were treated for 6 months with once daily tacalcitol used “as needed” in response to disease relapse (61). After 6 months treatment, mean Psoriasis Area and Severity Index (PASI) score was significantly improved compared to baseline and there was a reduction in total body surface involvement of 33%.

The four RCTs each included an initial treatment period of between 2 and 12 weeks for the induction of remission with a combination regimen of topical corticosteroid with either vitamin D analogue or tazarotene, and follow-on treatment period of between 8 and 24 weeks during which treatment was used either continuously (once daily or less frequently), or on an as needed basis – details of the regimens are provided in Table 2. In three studies, patients were required to have responded to initial treatment in order to progress to follow-on therapy (62–64). In the fourth study, this requirement was not stated but it was noted that all patients achieved at least 50% global improvement (i.e. “moderate” global response to treatment) at the end of the initial treatment phase (65).

Studies by Lebwohl et al. and Koo et al. showed respectively that tazarotene+clobetasol and calcipotriol+clobetasol could be used without steroid-specific side effects over 24 and 26 weeks and that combination treatment was more effective than monotherapy (with tazarotene (65) or either calcipotriol or...
clobetasol (63) during follow-on treatment. A comparison of once daily treatment with calcipotriol alone or calcipotriol + clobetasol reported by Katoh and Kishimoto (62) showed that switching from combination therapy during the initial phase to monotherapy with calcipotriol resulted in exacerbations of psoriasis during the long-term phase.

A multicenter, open-label RCT by Lee et al. (64) evaluated the optimal follow-on treatment regimen with calcipotriol/betamethasone gel following an initial eight week once daily treatment phase. In this trial, patients who responded to initial once daily treatment with calcipotriol/betamethasone gel were randomized to receive one of three follow-on calcipotriol/betamethasone gel regimens: once daily as needed, once daily every day and twice weekly (Saturday and Sunday, ‘weekend group’). At the end of the induction phase, patients who met the response criteria of a rating of ‘clear’ or ‘almost clear’ by Investigator’s Global Assessment of disease severity (IGA) progressed to follow-on treatment. At the end of the follow-on treatment phase (week 16), response rate was significantly lower in the twice weekly (‘weekend’) group compared to either the ‘as needed’ or ‘continuous daily’ treatment groups; 31% in the ‘weekend’ group compared with 64% in the ‘as needed’ group and 68% in the ‘continuous treatment’ group (p = .0109 and p = .0015).

Studies reporting >26-week efficacy data

One observational study, four open-label, non-controlled trials and four RCTs with efficacy data for treatment periods of between 52 weeks and 18 months were identified. (Results of an additional long-term open-label study of the fixed combination of tazarotene and halobetasol propionate used on an as-needed basis, which was excluded from the review as a research letter have recently been published in full).

The prospective, observational study (PRO-LONG) compared patient-reported outcomes with calcipotriol/betamethasone gel or calcipotriol/betamethasone ointment over a 52-week treatment period using a once daily, as needed regimen (66). The four open-label clinical trials were of vitamin D analogues (calcitriol, calcipotriol and tacalcitol) and all used an as needed treatment approach (67–71). The study designs are presented in Table 3.

Of the four RCTs, two studied once daily, as needed treatment regimens, in one study the treatment regimen was not

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Figure 1. Prisma flow diagram.
| Study, publication | N   | Treatments compared | Overview of study design | Treatment regimen |
|-------------------|-----|---------------------|-------------------------|-------------------|
| Zhu et al. (37)   | 250 | Calcitriol vs calcipotriol | 12-week, parallel group RCT. Investigator blinded. | Calcitriol or calcipotriol ointment twice daily (AM and PM) |
| van de Kerkhof et al. De Korte et al. (25,32) | 106 | Calcipotriol vs dithranol | 12-week, parallel group RCT. Open-label. Patients visited a day care setting for treatment application 5 times during week 1 and twice-weekly thereafter, on other days treatment was applied at home. | Calcipotriol twice daily or dithranol once daily, following an intensification regimen with treatment exposure time increased over 9-day cycles, and then the concentration of dithranol cream increased (from 0.1% to a maximum of 5.0%). |
| Levine et al. (26) | 169 | Calcipotriene vs calcipotriene + nicotinamide | 12-week, bilateral RCT. Double blind. Patients were randomized to two of 7 treatments: placebo, calcipotriene alone, nicotinamide alone or one of 4 concentrations of calcipotriene/ nicotinamide combinations. Each treatment was applied to lesions on one side of the body, or to one of two lesions at least 5 cm apart. | Twice daily treatment (AM and PM) with either placebo, nicotinamide, calcipotriene or calcipotriene/ nicotinamide combination treatment. |
| Ortonne et al. (27) | 124 | Tacrolimus vs calcipotriol | 14-week (12-week treatment + 2-week follow up), parallel group RCT. Investigator blinded. | Tacrolimus gel or calcipotriol ointment twice daily (with interval of 10–14 h). |
| Wang et al. (34)  | 90  | Calcipotriol/betamethasone alternating treatment vs calcipotriol + betamethasone, sequential treatment vs calcipotriol alone | 12-week parallel group RCT. Blinding not stated. | Group 1: calcipotriol/betamethasone once daily for 4 weeks then alternate use of calcipotriol/betamethasone cream and calcipotriol ointment once daily for 2 weeks then calcipotriol alone once daily for 6 weeks. Group 2: topical betamethasone ointment once daily for 6 weeks then calcipotriol ointment once daily for 6 weeks. Group 3: topical calcipotriol ointment twice daily for 12 weeks. |
| PSO-ABLE (40,42–45) | 463 | Calcipotriol/betamethasone dipropionate foam vs calcipotriol/ betamethasone dipropionate gel | 12-week parallel group RCT. Investigator blinded. | Patients were randomized to once daily treatment with calcipotriol/ betamethasone aerosol foam, calcipotriol/betamethasone gel, foam vehicle or gel vehicle for 12 weeks. |
| Saraceno et al. (46) | 150 | Calcipotriol/betamethasone vs calcipotriol | 12-week parallel group RCT. Open-label. | Patients were randomized to two groups: Group A: once daily calcipotriol/betamethasone for 4 weeks followed by twice daily calcipotriol for 8 weeks, Group B: twice daily calcipotriol for 12 weeks. |
| Lahfa et al. (39) | 125 | Calcitriol vs calcipotriol | 12-week parallel group RCT. Investigator blinded. | Patients were randomized to calcitriol ointment or calcipotriol ointment once daily (PM). For the first two weeks, patients also received clobetasol propionate once daily in the morning – the steroid was discontinued if patients achieved a marked global improvement in their psoriasis (Grade 3). If not, the steroid was continued for a further 2 weeks before patients entered the monotherapy phase. |
| Weinstein et al. (52) | 1303 | Tazarotene vs placebo | 12-week parallel group RCT. Double blind. | Two RCTs with identical designs, Study A enrolled 668 patients in total and Study B enrolled 635. In both trials, patients were randomized to once daily treatment with either tazarotene 0.1%, tazarotene 0.05% or vehicle for 12 weeks. |
| Green and Sadoff (55) | 229 | Tazarotene + steroid vs tazarotene | 12-week parallel group RCT. Investigator blinded. | Patients were randomized to either tazarotene monotherapy once daily or tazarotene once daily (PM) + high potency corticosteroid (fluticasone) (continued) |
specified, and one studied a proactive twice weekly treatment regimen. Two of the studies evaluated the effects of non-pharmacological interventions aimed at improving patient adherence during long-term treatment when used in combination with calcipotriol/betamethasone or fluocinonide (72–74). The remaining two RCTs included an investigation of the safety of calcipotriol/betamethasone ointment over 52 weeks compared to alternating 4-week treatment periods with calcipotriol then betamethasone or calcipotriol alone (75), and a comparison of the efficacy and safety of twice weekly, proactive management with calcipotriol/betamethasone foam against vehicle foam for the prevention of psoriasis relapse (76). An overview of the RCT designs is provided in Table 4.

The first of the studies evaluating non-pharmacological interventions (PSO-TOP) compared standard of care treatment with calcipotriol/betamethasone gel with and without the addition of a topical treatment optimization program (TTOP; patient support including visit checklists for conversations between dermatologists, nurses and patients, patient information, telephone/e-mail helpdesks and treatment reminders) (73,74). Study medication was applied once daily for 8 weeks, followed by as needed application for 56 weeks. Greater improvement in mean

| Study, publication | N | Treatments compared | Overview of study design | Treatment regimen |
|-------------------|---|---------------------|-------------------------|-----------------|
| Goodfield et al. (57) | 338 | 1% coal tar solution vs 5% coal tar solution | 12-week parallel group RCT. Double-blind. | Patients were randomized to either 1% coal tar cream or 5% coal tar lotion three times daily. |
| Swinkels et al. (58) | 250 | Dithranol vs UVB | 12-week parallel group RCT. Open-label. | Patients were randomized to UVB three times per week for 12 weeks, short contact dithranol treatment (daily, either at home or outpatient clinic) for 12 weeks or inpatient dithranol treatment (daily) for up to 8 weeks. |

| Study, publication | N | Overview of study design | Initial treatment regimen | Long-term management regimen |
|-------------------|---|-------------------------|-------------------------|-----------------|
| Katoh & Kishimoto (62) | 61 | Patients randomized to initial 12-week treatment with either calcipotriol or calcipotriol + clobetasol therapy (blinding not described), responders in both groups progressed to 12-week maintenance treatment with calcipotriol alone. | Once daily calcipotriol ointment OR Once daily calcipotriol/clobetasol ointment | Continuous once daily calcipotriol ointment |
| Lebwohl et al. (65) | 50 | Six-week open-label treatment phase with tazarotene + clobetasol. Patients then randomized to one of three maintenance regimens for 20 weeks (double-blind). | Tazarotene gel + clobetasol propionate ointment, both applied once daily initially then tapered from week 3 to 3 times weekly for tazarotene and twice weekly for clobetasol by week 6 | Continuous tazarotene gel three times weekly + twice weekly clobetasol OR tazarotene three times weekly + vehicle twice weekly OR vehicle only |
| Koo et al. (63) | 86 | Patients randomized to single-blind two-week initial treatment with clobetasol + calcipotriene or either calcipotriene or clobetasol monotherapy. Patients in the combination group achieving remission then re-randomized to double-blind phase with either combination treatment or calcipotriene alone for twenty-four weeks. | Twice daily treatment with: clobetasol foam OR calcipotriene ointment OR clobetasol foam + calcipotriene ointment | Continuous weekday calcipotriene ointment + weekend clobetasol foam OR weekday calcipotriene ointment + vehicle foam. Medication was applied twice daily. |
| Lee et al. (64) | 201 | Eight-week open-label phase with calcipotriol/betamethasone gel. Responders then randomized to one of three maintenance regimens for 8 weeks (also open-label). | Once daily calcipotriol/betamethasone ointment | Calcipotriol/betamethasone gel in one of three regimens: Once daily, as needed Once daily, every day Twice weekly (Saturday and Sunday) |
Physician’s Global Assessment of psoriasis severity (PGA) during the ‘as needed’ period was achieved in the calcipotriol/betamethasone gel + TTOP arm compared to calcipotriol/betamethasone gel without TTOP \( (p = .0343) \).

One small RCT \( (n = 40) \) evaluated adherence over a 52-week period in patients treated with topical fluocinonide with or without weekly self-reporting of the state of their psoriasis via an internet survey \( (72) \). Fluocinonide was applied in the intervention and control groups twice daily. The authors note that by month 12, 42.8% of patients had breaks in treatment of 7 days or longer and that missed dosing was common in patients who still had psoriasis. No clear statement was made on whether treatment was used continuously or as needed during the trial. The internet reporting intervention improved adherence (50% vs 35%, \( p = .08 \)) and there was an improvement in PASI at 52 weeks (3.32 vs 3.4, \( p = .038 \)) but no difference in IGA between the groups.

Kragballe et al. \( (75) \) reported on a randomized, double-blind safety study in which patients were randomized in a 1:1:1 ratio to either: 52 weeks of combination therapy with calcipotriol/betamethasone ointment, 52 weeks of alternating 4-week periods of calcipotriol ointment and calcipotriol ointment alone or calcipotriol ointment alone (calcipotriol group) during which subjects could discontinue treatment, “as needed,” without clear statement made on whether patients achieving an assessment of “minimal psoriasis” could discontinue treatment, and re-start if symptoms recurred or longer and that missed dosing was common in patients who still had psoriasis. No clear statement was made on whether treatment was used continuously or as needed during the trial.

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### Table 3. Summary of observational/open-label studies reporting > 26-week efficacy data on topical psoriasis treatments.

| Study, publication | N   | Overview of study design                                                                 | Treatment regimen                                                                 |
|--------------------|-----|-----------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| PRO-LONG \( (66,85) \) | 328 | Observational, prospective, multicenter study to compare patient’s perspectives on calcipotriol/ betamethasone gel and calcipotriol/betamethasone ointment for 52 weeks | Calcipotriol/ betamethasone ointment once daily as needed                           |
| Lebwohl et al \( (68,69) \) | 324 | Open-label, multicenter study to examine safety and efficacy of calcipotriol ointment for up to 52 weeks | Calcipotriol ointment twice daily; patients achieving an assessment of “minimal psoriasis” could discontinue treatment, and restart if symptoms recurred |
| Barnes et al. \( (67) \) | 202 | Open-label, multicenter study evaluating safety and efficacy of calcipotriol scalp solution and cream for up to 52 weeks | Calcipotriol scalp solution and calcipotriol cream (for psoriasis of the trunk and limbs) both treatments applied twice daily as needed |
| Miyachi et al. \( (70) \) | 160 | Open-label, multicenter study evaluating the safety and efficacy of tacalcitol ointment for 26 weeks. Based on the physicians’ judgment, treatment could be extended to 54 weeks | Tacalcitol ointment once daily as needed                                           |
| van de Kerkhof et al \( (71) \) | 157 | Open-label, multicenter study consisting of two phases. Patients received initial treatment with tacalcitol ointment for 3 months, those responding to treatment continued treatment for a maximum of 18 months in total | Tacalcitol ointment once daily as needed                                           |

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### Table 4. Summary of RCTs reporting > 26-week efficacy data on topical psoriasis treatments.

| Study, publication | N   | Overview of study design                                                                 | Initial treatment regimen | Long-term management regimen |
|--------------------|-----|-----------------------------------------------------------------------------------------|---------------------------|-------------------------------|
| Alinia et al. \( (72) \) | 40  | Patients were randomized to 52 weeks treatment with fluocinonide with or without an internet-based reporting intervention (patients reporting of psoriasis symptoms) aimed to support treatment adherence (investigator-blinded) | N/A                        | Twice daily fluocinonide with or without internet-based reporting of psoriasis symptoms No clear statement made on whether treatment was used continuously or on an as needed basis |
| PSO-TOP \( (73,74) \) | 1790 | Patients were randomized to receive (Cal/BD) gel with or without the Topical Treatment Optimization program patient support intervention. Responders after 8 weeks progressed to the 56-week maintenance phase (blinding not described) | Once daily calcipotriol/ betamethasone gel with or without Topical Treatment Optimization Program | Once daily, as needed calcipotriol/ betamethasone gel with or without Topical Treatment Optimization Program |
| Kragballe et al. \( (75) \) | 634 | Patients were randomized to 52 weeks treatment with two different Cal/BD regimens, or 4 weeks of Cal/BD combination treatment followed by 48 weeks of calcipotriol monotherapy (double-blind) | All patients received once daily Cal/BD ointment for 4 weeks | Once daily, as needed Cal/BD ointment (two-compound group) OR alternating 4-week periods of Cal/BD ointment then calcipotriol ointment (alternating group) OR calcipotriol ointment alone (calcipotriol group) |
| PSO-LONG \( (76) \) | 650 | Four-week open-label phase with Cal/BD foam. Responders randomized to 52 weeks double-blind maintenance treatment with Cal/BD foam or vehicle foam, with rescue Cal/BD foam upon relapse | Once daily Cal/BD foam | Twice weekly Cal/BD foam with rescue Cal/BD foam once daily for 4 weeks in case of relapse OR twice weekly vehicle foam with rescue Cal/BD foam once daily for 4 weeks in case of relapse |

Cal/BD: Calcipotriol/betamethasone.
group”, “alternating group”, “calcipotriol group”). Following the initial 4-week period, all treatments were used once daily as needed, to reflect usual clinical practice.

The primary objective of the study was to investigate the safety of two-compound therapy over 52 weeks. Secondary efficacy endpoints were also evaluated, and results showed a trend toward a difference in percentage of satisfactory responses by IGA (absent, very mild or mild disease) during the total study period, with a higher proportion of satisfactory responses in the two-compound and alternating groups compared to the calcipotriol group. After the first 4-week assessment the percentage of satisfactory treatment responses by IGA was similar across groups. At all subsequent visits, the proportion of patients with satisfactory responses was higher in the two-compound group than in the calcipotriol group. In the alternating group, the proportion of satisfactory responses after a two-compound treatment period was always higher than after a calcipotriol treatment period (75).

The recently published PSO-LONG study is the only long-term study identified to have compared usual clinical practice of intermittent reactive treatment with a regular twice weekly maintenance therapy (with an interval of 2-3 days between treatment) to evaluate whether proactive treatment can prevent or delay relapse and maintain time in remission (76). Following 4 weeks open-label, once daily treatment with a foam formulation of calcipotriol/betamethasone, patients who responded to treatment (defined as PGA 0/1 with at least a 2-grade improvement) were randomized to receive calcipotriol/betamethasone foam or vehicle foam twice weekly for 52 weeks (76). In case of relapse (defined as PGA ≥2), patients in both groups received rescue therapy with once daily calcipotriol/betamethasone foam for 4 weeks. Patients who regained a PGA score of “clear” or “almost clear” after 4 weeks of once daily treatment re-started twice weekly maintenance treatment according to prior randomization following the open-label treatment phase. Patients who did not regain response exited the trial.

Proactive management showed superior efficacy to the reactive management strategy based on prolonged time to first relapse (median time to first relapse from randomization was prolonged by 26 days for patients in the proactive group), greater number of days in remission (41 additional days over 1 year) and reduction in number of relapses (3.1 compared to 4.8 over 1 year). The incidence of adverse events was similar between treatment groups.

SmPC recommendations on use of topical psoriasis therapies for long-term management

The recommendations on long-term use of topical psoriasis therapies from the SmPCs for those treatments with long-term efficacy data are summarized in Table 5.

| SmPC | Treatment | Duration |
|------|-----------|----------|
| Calcipotriol/betamethasone ointment (Dovobet®/Daivobet® ointment) | 4 weeks | The recommended treatment period is 4 weeks. There is experience with repeated courses of Dovobet up to 52 weeks. If it is necessary to continue or restart treatment after 4 weeks, treatment should be continued after medical review and under regular medical supervision. |
| Calcipotriol/betamethasone gel (Dovobet®/Daivobet® gel) | 4 weeks | The recommended treatment period is 4 weeks for scalp areas and 8 weeks for “non-scalp” areas. If it is necessary to continue or restart treatment after this period, treatment should be continued after medical review and under regular medical supervision. |
| Calcipotriol (Dovonex® ointment) | 4 weeks | There is limited clinical experience available for the use of this dosage regimen of more than 6 weeks. |
| Calcitriol (Silkis® ointment) | 12 weeks | Normally duration of treatment depends on the severity of the lesions and should be decided by the physician. There is clinical trial experience with continuous and intermittent treatment in adults up to twelve months. |
| Tacalcitol (Curatoderm® ointment) | 12 weeks | No instruction provided on repeated courses. |
| Fluocinonide (Metosyn® ointment) | 12 weeks | Usually, the treatment period is up to 12 weeks. Clinical experience, particularly on tolerability, is available on periods of use of up to 12 months. |
| Tazarotene (Zorac® gel) | 12 weeks | Flare treatment: Enstilar foam should be applied to the affected area once daily. The recommended treatment period is 4 weeks. If it is necessary to continue or restart treatment after this period, treatment should be continued after medical review and under regular supervision. |
| Calcipotriol/betamethasone foam (Enstilar®) | 12 weeks | Long-term maintenance treatment: Patients who have responded at 4 weeks’ treatment using Enstilar once daily are suitable for long-term maintenance treatment. Enstilar should be applied twice weekly on nonconsecutive days to areas previously affected by psoriasis vulgaris. Between applications there should be 2-3 days without Enstilar treatment. |

If signs of a relapse occur, flare treatment, as described above, should be re-initiated.

Discussion

This SLR was intended to identify the available efficacy evidence for long-term maintenance treatment of psoriasis with topical therapies given the lack of standard approach to long-term management of psoriasis and interest in alternative strategies to the current practice of reactive treatment of relapses. We found 8 RCTs and 6 observational studies or non-controlled trials reporting >12-week efficacy outcomes. Most of these studies used treatment regimens that reflect current standard of care of repeated treatment of relapses.
The study by Lee et al. (64) compared proactive (weekend only treatment) and reactive (‘as needed’) follow-on regimens but only over an 8-week period. Long-term observational and open-label uncontrolled studies provide evidence of effectiveness of repeated treatment of relapses with vitamin D analogues (67–71) and two non-pharmacological intervention studies suggest different strategies to improve patient adherence and subsequently treatment outcomes (72,73), however none of these trials provide information on the optimal treatment regimen for long-term maintenance. While the study by Kragballe et al. indicates that combination therapy is favored over monotherapy as reactive long-term treatment, it does not provide information on whether a proactive or reactive strategy is more effective in the long-term maintenance of remission or frequency of relapse (75).

Relapse is common in psoriasis when using a reactive management approach. Some patients find that their relapse may be worse than their initial symptoms (83). Therefore, there is need to maintain skin clearance after flare treatment for as long as possible. A long-term proactive management approach, with maintenance treatment following initial treatment success, could help sustain disease remission and improve clinical and QoL outcomes for patients.

The PSO-LONG study is the only identified RCT to have compared regular maintenance use of a topical treatment with reactive management in response to psoriasis relapses (rescue therapy). While long-term data are available for other topical psoriasis treatments, this has not resulted in updates to SmPCs to provide specific recommendations on the optimal frequency of treatment during long-term use. In contrast, evidence from the 52-week PSO-LONG study has supported a recent update to the Enstilar® SmPC meaning that, in addition to reactive use for flare treatment, it can also be used twice weekly for proactive management, for which it is the only topical treatment with supporting efficacy data in the product label.

For completeness, 12-week studies were included in this review although they are not considered long-term from a regulatory perspective. Regulators indicate that studies of 8-12 weeks are usually required to demonstrate short-term efficacy (4 weeks for potent topical corticosteroids), and that one-year prolonged or intermittent use studies are recommended to demonstrate long-term safety and efficacy (84). In addition, previous SLRs of topical treatments for psoriasis included studies of at least 24 weeks as long-term (18,19) and have commented that long-term studies of topical treatments for psoriasis are lacking and studies such as PSO-LONG are needed to inform long-term management strategies (8,19). Such strategies have the potential to improve disease control and reduce the negative impact of psoriasis on patient’s lives, without the need for continuous daily treatment.

**Strengths and limitations**

This study covers a more recent time period compared to previous SLRs of topical treatments for psoriasis by Augustin et al. (18,19), and Mason et al. which cover time periods to 2013 and 2011, respectively. We identified and described relevant articles published between 1, January 2000 and November 2020. Articles published prior to this and data published in abstract form only at the time of review are not included within the scope of the study.

**Conclusion**

Despite the chronic nature of psoriasis, there are limited high-quality long-term efficacy data available for topical psoriasis therapies. Most studies have evaluated long-term reactive maintenance treatment of relapses and only the PSO-LONG study has compared regular, proactive maintenance use of a topical treatment with reactive management in response to psoriasis relapses. While some product labels mention clinical experience of up to 12 months, they do not provide specific recommendations on the optimal long-term treatment regimen. Calcipotriol/betamethasone foam is the only treatment for which the approved label allows either reactive treatment of relapse or regular (twice weekly) maintenance use.

**Disclosure statement**

Claire Bark is an employee of RJW & partners, as was Chloe Brown when the work was undertaken. Per Svangren is an independent consultant at Svangren Life Science Consulting. All were consultants to LEO Pharma for this study.

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**References**

1. Rendon A, Schakel K. Psoriasis pathogenesis and treatment. Int J Mol Sci. 2019;20(6):1475.
2. Boehncke WH, Schön MP. Psoriasis. Lancet. 2015; 386(9997):983–994.
3. National Institute for Health and Care Excellence. Psoriasis: assessment and management; 2012. [11 December 2020]. Available from: https://www.nice.org.uk/guidance/cg153
4. Girolomoni G, Calzavara Pinton P, Cristaudo A, et al. Back to the future: a new topical approach for mild-to-moderate psoriasis. G Ital Dermatol Venereol. 2018;153(3):375–382.
5. Yeung H, Takeshita J, Mehta NN, et al. Psoriasis severity and the prevalence of major medical comorbidity: a population-based study. JAMA Dermatol. 2013;149(10):1173–1179.
6. Kim WB, Jerome D, Yeung J. Diagnosis and management of psoriasis. Can Fam Physician. 2017;63(4):278–285.
7. Brandon A, Mufti A, Gary Sibbald R. Diagnosis and management of cutaneous psoriasis: a review. Adv Skin Wound Care. 2019;32(2):58–69.
8. Segart S, Calzavara-Pinton P, de la Cueva P, et al. Long-term topical management of psoriasis: the road ahead. J Dermatolog Treat. 2020:1–10.DOI:10.1080/09546634.2020.1729335
9. Carrascosa JM, Theng C, Thaci D. Spotlight on topical long-term management of plaque psoriasis. Clin Cosmet Investig Dermatol. 2020;13:495–498.
10. Wollenberg A, Ehmann LM. Long term treatment concepts and proactive therapy for atopic eczema. Ann Dermatol. 2012;24(3):253–260.
11. Reitamo S, Mandelin J, Remitz A. Long-term management of atopic dermatitis: evidence from recent clinical trials. Clinical Investigation. 2011;1(1):171–177.
12. Wollenberg A, Reitamo S, Girolomoni G, et al. Proactive treatment of atopic dermatitis in adults with 0.1% calcipotriol ointment. Allergy. 2008;63(7):742–750.
13. Mrowietz U. Implementing treatment goals for successful long-term management of psoriasis. J Eur Acad Dermatol Venereol. 2012;26(Suppl 2):12–20.
14. 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(Suppl 3):1–10.
15. 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(2):432–470.
16. Maul JT, Anzengruber F, Conrad C, et al. Topical treatment of psoriasis vulgaris: the Swiss treatment pathway. Dermatology. 2021;6:1–13.
17. Körber A, Wilsmann-Theis D, Augustin M, et al. Topische therapie bei psoriasis vulgaris - ein behandlungspfad. J Dtsch Dermatol Ges. 2019;17(Suppl 4):3–14.
18. Augustin M, Mrowietz U, Bonnekoh B, et al. Topical long-term therapy of psoriasis with vitamin D₃ analogues, corticosteroids and their two compound formulations: position paper on evidence and use in daily practice. J Dtsch Dermatol Ges. 2014;12(8):667–682.
19. Mason AR, Mason J, Cork M, et al. Topical treatments for chronic plaque psoriasis. Cochr Datab Syst Rev. 2013(3):Cd005028.
20. Gerritsen MJ, Van De Kerkhof PC, Langner A. Long-term safety of topical calcitriol 3 microg g⁻¹ ointment. Br J Dermatol. 2001;144(Suppl 58):17–19.
21. Ramsay CA, Berth-Jones J, Brundin G, et al. Long-term use of topical calcipotriol in chronic plaque psoriasis. Dermatology. 1994;189(3):260–264.
22. Medicines.org.uk. Enstilar Cutaneous Foam - Summary of Product Characteristics (SmPC). 2020. [08/12/20]. Available from: https://www.medicines.org.uk/emc/product/2139
23. Alora-Palli MB, Perkins AC, Van Cott A, et al. Efficacy and tolerability of a cosmetically acceptable coal tar tar solution in the treatment of moderate plaque psoriasis: a controlled comparison with calcipotriene (calcipotriol) cream. Am J Clin Dermatol. 2010;11(4):1–83.
24. Dahri GMM, Mughal SA, Qureshi MA, et al. Placebo controlled study on the efficacy and safety of calcipotriol in the treatment of mild to moderate psoriasis. Medical Forum Monthly. 2012;23(1):44–47.
25. De Korte JVDV, Sprangers PGM, Damstra MAG, et al. Comparison of twice-daily calcipotriol ointment with once-daily short-contact dithranol cream therapy: quality-of-life outcomes of a randomized controlled trial of supervised treatment of psoriasis in a day-care setting. British Journal of Dermatology. 2007;158(2):375–381.
26. Levine D, Even-Chen Z, Lipets I, et al. Pilot, multicenter, double-blind, randomized placebo-controlled bilateral comparative study of a combination of calcipotriene and nicotinamide for the treatment of psoriasis. J Am Acad Dermatol. 2010;63(5):775–781.
27. Ortonne JP, van de Kerkhof PC, Prinz JC, et al. 0.3% Tacrolimus gel and 0.5% Tacrolimus cream show efficacy in mild to moderate plaque psoriasis: results of a randomized, open-label, observer-blinded study. Acta Derm Venereol. 2006;86(1):29–33.
28. Roussaki-Schulze AV, Kouskoukis C, Klimi E, et al. Calcipotriol monotherapy versus calcipotriol plus UVAl versus calcipotriol plus narrow-band UVB in the treatment of psoriasis. Drugs Exp Clin Res. 2005;200531(5):169–174.
29. Sharma V, Kaur I, Kumar B. Calcipotriol versus coal tar: a prospective randomized study in stable plaque psoriasis. Int J Dermatol. 2003;42(10):834–838.
30. Siadat AH, Iraji F, Khodadadi M, et al. Topical nicotinamide in combination with calcipotriol for the treatment of mild to moderate psoriasis: A double-blind, randomized, comparative study. Adv Biomed Res. 2013;2:90.
31. Takahashi H, Tsuji H, Ishida-Yamamoto A, et al. Comparison of clinical effects of psoriasis treatment regimens among calcipotriol alone, narrowband ultraviolet B phototherapy alone, combination of calcipotriol and narrowband ultraviolet B phototherapy once a week, and combination of calcipotriol and narrowband ultraviolet B phototherapy more than twice a week. J Dermatol. 2013;40(6):424–427.
32. van de Kerkhof PC, van der Valk PG, Swinkels OQ, et al. A comparison of twice-daily calcipotriol ointment with once-daily short-contact dithranol cream therapy: a randomized controlled trial of supervised treatment of psoriasis vulgaris in a day-care setting. Br J Dermatol. 2006;155(4):800–807.
33. Vena GA, Cassano N, Alessandrini G, et al. Treatment of mild to moderate plaque psoriasis with calcitriol ointment applied with or without a dosing device. Eur J Inflamm. 2007;5(2):89–95.
34. Wang BL, Sun WB, Yang LW, et al. Sequential use of calcipotriol betamethasone cream and calcipotriol ointment for psoriasis. J Clin Dermatol. 2017;46(5):353–355.
35. Barker JN, Berth-Jones J, Groves R, et al. Calcium homeostasis remains unaffected after 12 weeks' therapy with calcitriol 3 microg/g ointment; no correlation with extent of stasis remains unaffected after 12 weeks.
36. Carboni I, de Felice C, Bergamin A, et al. Topical use of calcitriol 3 microg/g ointment in the treatment of mild-to-moderate psoriasis: results from an open-label study. J Eur Acad Dermatol Venereol. 2005;19(s3):11–13.
37. Zhu X, Wang B, Zhao G, et al. An investigator-masked comparison of the efficacy and safety of twice daily applications of calcitriol 3 microg/g ointment vs. calcipotriol 50 microg/g ointment in subjects with mild to moderate chronic plaque-type psoriasis. J Eur Acad Dermatol Venereol. 2007;427(6):466–472.
38. Katayama I, Ohkawara A, Ohkido M, et al. High-concentration (20 mug/g) tacalcitol ointment therapy on refractory psoriasis vulgaris with low response to topical corticosteroids. Eur J Dermatol. 2002;12(6):553–557.
39. Lahfa M, Mrowietz U, Köenig M, et al. Calcitriol ointment and clobetasol propionate cream: a new regimen for the treatment of plaque psoriasis. Eur J Dermatol. 2003;13(5):261–265.
40. Griffiths CE, Stein Gold L, Cambazard F, et al. Greater improvement in quality of life outcomes in patients using fixed-combination calcipotriol plus betamethasone.
dipropionate aerosol foam versus gel: results from the PSO-ABLE study. Eur J Dermatol. 2018;28(3):356–363.

41. Khandpur S, Sahni K. An open label prospective randomised trial to compare the efficacy of coal tar-salicylic Acid ointment versus calcipotriol/betamethasone dipropionate ointment in the treatment of limited chronic plaque psoriasis. Indian J Dermatol. 2014;59(6):579–583.

42. Paul C, Leonardi C, Menter A, et al. Erratum to: calcipotriol plus betamethasone dipropionate aerosol foam in patients with moderate-to-severe psoriasis: sub-group analysis of the PSO-ABLE study. Am J Clin Dermatol. 2017;18(4):591.

43. Paul C, Leonardi C, Menter A, et al. Calcipotriol plus betamethasone dipropionate aerosol foam in patients with moderate-to-severe psoriasis: sub-group analysis of the PSO-ABLE study. Am J Clin Dermatol. 2017;18(3):405–411.

44. Paul C, Stein Gold L, Cambazard F, et al. Calcipotriol plus betamethasone dipropionate aerosol foam provides superior efficacy vs. gel in patients with psoriasis vulgaris: randomized, controlled PSO-ABLE study. J Eur Acad Dermatol Venereol. 2017;31(1):119–126.

45. Paul C, Stein Gold L, Cambazard F, et al. More rapid improvement in quality of life with fixed-combination calcipotriene plus betamethasone dipropionate aerosol foam vs. topical suspension (PSO-ABLE study in patients with psoriasis vulgaris) [Journal: Conference Abstract]. British Journal of Dermatology. 2016;175:213–214.

46. Saraceno R, Andreassi L, Ayala F, et al. Efficacy, safety and quality of life of calcipotriol/betamethasone dipropionate (Dovobet) versus calcipotriol (Daivonex) in the treatment of psoriasis vulgaris: a randomized, multicentre, clinical trial. J Dermatolog Treat. 2007;18(6):361–365.

47. Sardar Singh H, Narayana S, Vijayarangam S. Comparison of efficacy of calcipotriol and betamethasone combination with betamethasone alone in plaque psoriasis. Nat J Physiol Pharm Pharmacol. 2017;7(1):99–102.

48. Afreen H, Islam A, Alam M, et al. A comparative study of once daily tazarotene versus combination of tazarotene and betamethasone valerate in the treatment of plaque psoriasis. J Pak Assoc Dermatol. 2019;29(1):93–100.

49. Angelo JS, Kar BR, Thomas J. Comparison of clinical efficacy of topical tazarotene 0.1% cream with topical clobetasol propionate 0.05% cream in chronic plaque psoriasis: a double-blind, randomized, right-left comparison study. Indian J Dermatol Venereol Leprol. 2007;73(1):65.

50. Kumar U, Kaur I, Dogra S, et al. Topical tazarotene vs. coal tar in stable plaque psoriasis. Clin Exp Dermatol. 2010;35(5):482–486.

51. Mehta BH, Amladi ST. Evaluation of topical 0.1% tazarotene cream in the treatment of palmoplantar psoriasis: an observer-blinded randomized controlled study. Indian J Dermatol. 2011;56(1):40–43.

52. Weinstein GD, Koo JY, Krueger GG, et al. Tazarotene cream in the treatment of psoriasis: two multicenter, double-blind, randomized, vehicle-controlled studies of the safety and efficacy of tazarotene creams 0.05% and 0.1% applied once daily for 12 weeks. J Am Acad Dermatol. 2003;48(5):760–767.

53. Cuyun D. Evaluating the potential clinical benefits of switching patients with plaque psoriasis from calcipotriene to tazarotene treatment. Cutis. 2000;66(6 Suppl):19–24.

54. Tanghetti EA. An observation study evaluating the treatment of plaque psoriasis with tazarotene gels, alone and with an emollient and/or corticosteroid. Cutis. 2000;66(6 Suppl):4–11.

55. Green L, Sadoff W. A clinical evaluation of tazarotene 0.1% gel, with and without a high- or mid-high-potency corticosteroid, in patients with stable plaque psoriasis. J Cutan Med Surg. 2002;6(2):95–102.

56. Koo JY, Martin D. Investigator-masked comparison of tazarotene gel q.d. plus mometasone furoate cream q.d. vs. mometasone furoate cream b.i.d. in the treatment of plaque psoriasis. Int J Dermatol. 2001;40(3):210–212.

57. Goodfield M, Kownacki S, Berth-Jones J. Double-blind, randomised, multicentre, parallel group study comparing a 1% coal tar preparation (Exorex) with a 5% coal tar preparation (Alphosyl) in chronic plaque psoriasis. J Dermatolog Treat. 2004;15(1):14–22.

58. Swinkels OJJ, Prins M, Veenhuis RT, et al. Effectiveness and side effects of UVB-phototherapy, dithranol inpatient therapy and a care instruction programme of short contact dithranol in moderate to severe psoriasis. Eur J Dermatol. 2004;14(3):159–165.

59. Asbati M, Lugo AR, Reyes E, et al. Topic treatment of psoriasis: efficacy and safety of mometasone-salicilic acid ointment. Informe Medico. 2003;5(5):191–197.

60. Stein LF, Sherr A, Solodkina G, et al. Betamethasone valerate foam for treatment of nonscalp psoriasis. J Cutan Med Surg. 2001;5(4):303–307.

61. Lambert J, Trompke C. Tacalcitol ointment for long-term control of chronic plaque psoriasis in dermatological practice. Dermatology. 2002;204(4):321–324.

62. Katoh N, Kishimoto S. Combination of calcipotriol and clobetasol propionate as a premixed ointment for the treatment of psoriasis. Eur J Dermatol. 2003;13(4):382–384.

63. Koo J, Blum RR, Lebwohl M. A randomized, multicenter study of calcipotriene ointment and clobetasol propionate foam in the sequential treatment of localized plaque-type psoriasis: short- and long-term outcomes. J Am Acad Dermatol. 2006;55(4):637–641.

64. Lee JH, Park CJ, Kim TY, et al. Optimal maintenance treatment with calcipotriol/betamethasone dipropionate gel in Korean patients with psoriasis vulgaris: a multicentre randomized, controlled clinical trial. J Eur Acad Dermatol Venereol. 2017;31(3):483–489.

65. Lebwohl M, Lombardi K, Tan MH. Duration of improvement in psoriasis after treatment with tazarotene 0.1% gel plus clobetasol propionate 0.05% ointment: comparison of maintenance treatments. Int J Dermatol. 2001;40(1):64–66.

66. 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(12):2349–2355.

67. Barnes L, Altmeyer P, Forstrom L, et al. Long-term treatment of psoriasis with calcipotriol scalp solution and cream. European Journal of Dermatology. 2000;10(3):199–204.

68. Lebwohl M, Ortonne JP, Andres P, et al. Calcitriol ointment 3 microg/g is safe and effective over 52 weeks for the treatment of mild to moderate plaque psoriasis. J Am Acad Dermatol. 2003;48(5):760–767.

69. Lebwohl M, Preston N, Gottschalk RW. Impact of baseline disease severity over 26 and 52 weeks of treatment with calcitriol ointment 3 microg/g in patients with mild-to-
70. Miyachi Y, Ohkawara A, Ohkido M, et al. Long-term safety and efficacy of high-concentration (20 microg/g) tacalcitol ointment in psoriasis vulgaris. Eur J Dermatol. 2002;12(5):463–468.

71. Van de Kerkhof PCM, Berth-Jones J, Griffiths CEM, et al. Long-term efficacy and safety of tacalcitol ointment in patients with chronic plaque psoriasis. H+G Zeitschrift Fur Hautkrankheiten. 2002;77(9):424–432.

72. Alinia H, Moradi Tuchayi S, Smith JA, et al. Long-term adherence to topical psoriasis treatment can be abysmal: a 1-year randomized intervention study using objective electronic adherence monitoring. Br J Dermatol. 2017;176(3):759–764.

73. Reich K, Zschocke I, Bachelez H, et al. A Topical Treatment Optimization Programme (TTOP) improves clinical outcome for calcipotriol/betamethasone gel in psoriasis: results of a 64-week multinational randomized phase IV study in 1790 patients (PSO-TOP). Br J Dermatol. 2017;177(1):197–205.

74. Reich K, Zschocke I, Bachelez H, et al. Efficacy of a fixed combination of calcipotriol/betamethasone dipropionate topical gel in adult patients with mild to moderate psoriasis: blinded interim analysis of a phase IV, multicenter, randomized, controlled, prospective study. J Eur Acad Dermatol Venereol. 2015;29(6):1156–1163.

75. Lebwohl M, Kirck L, Lacour JP, et al. Twice-weekly topical calcipotriene/betamethasone dipropionate foam as proactive management of plaque psoriasis increases time in remission and is well tolerated over 52 weeks (PSO-LONG trial). J Am Acad Dermatol. 2020;84(5):1269–1277.

76. Medicines.org.uk. Silkis 3 micrograms per g ointment - Summary of Product Characteristics (SmPC); 2020. Available from: https://www.medicines.org.uk/emc/product/1602

77. Medicines.org.uk. Metosyn Ointment - Summary of Product Characteristics (SmPC); 2020. Available from: https://www.medicines.org.uk/emc/product/11392

78. Medicines.org.uk. Dovobet gel - Summary of Product Characteristics (SmPC); 2020. Available from: https://www.medicines.org.uk/emc/product/5690

79. Medicines.org.uk. Dovobet Ointment - Summary of Product Characteristics (SmPC); 2020. Available from: https://www.medicines.org.uk/emc/product/1609

80. Medicines.org.uk. Curatoderm 4lg/g Ointment - Summary of Product Characteristics (SmPC); 2020. Available from: https://www.medicines.org.uk/emc/product/6389

81. Medicines.org.uk. Zorac 0.05% Gel (tazarotene) - Summary of Product Characteristics (SmPC); 2020. Available from: https://www.medicines.org.uk/emc/product/6762

82. Lebwohl M, Thaci D, Warren RB. Addressing challenges associated with long-term topical treatment and benefits of proactive management in patients with psoriasis. J Eur Acad Dermatol Venereol. 2021;35 (Suppl 1):35–41.

83. European Medicines Agency. CHMP Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis. 2004.

84. Lambert J, Hol CW, Vink J. Real-life effectiveness of once-daily calcipotriol and betamethasone dipropionate gel vs. ointment formulations in psoriasis vulgaris: 4- and 12-week interim results from the PRO-long study. J Eur Acad Dermatol Venereol. 2014;28(12):1723–1731.

85. Medicines.org.uk. Dovonex Ointment - Summary of Product Characteristics (SmPC); 2020. Available from: https://www.medicines.org.uk/emc/product/981