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Topical Preparations for the Treatment of Psoriasis in Primary Care: A Systematic Review

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ABSTRACT

Context
There is clinical uncertainty about the appropriate use of first-line topical treatments for psoriasis.

Objective
To assess the relative effectiveness and tolerability of topical treatments for psoriasis in primary care.

Data sources
All major medical databases of published literature were searched electronically; references of trial reports and recent reviews were searched; authors and companies were contacted for missing data from published reports.

Study selection
(1) Randomised placebo-controlled trials of topical treatments for psoriasis and (2) randomised head-to-head studies of the new vitamin D3 derivative treatments for psoriasis, that reported clinical outcome using a Total Severity Score (TSS), Psoriasis Area Severity Index or Investigator Assessment of Global Improvement.

Data extraction
Eligibility and validity were assessed and data extracted independently by two authors.

Data synthesis
Clinical outcomes were pooled using a random effect standardised weighted mean difference (SWMD) metric, including 3,380 patients randomised in 41 placebo (vehicle) controlled trials and 4,898 patients randomised in 28 head-to-head studies.

There was a significant benefit in favour of active treatments against vehicle, SWMD: -1.06 (95%CI: -1.26 to -0.86), approximately a 2-point improvement on a 12-point TSS after 6 to 8 weeks of treatment. The only significantly different benefit was for very potent corticosteroids: SWMD: -1.51 (95%CI: -1.76 to -1.25), approximately a 3-point improvement on a 12-point TSS. Head-to-head studies support these findings, except that calcipotriol was estimated to be more effective than dithranol, coal tar and other vitamin D3 derivatives. Polytherapy, using a potent steroid and calcipotriol, was more effective than calcipotriol alone: SWMD 0.42, (95%CI: 0.12 to 0.72) approximately a 0.8 point improvement on a 12-point TSS. No important differences in withdrawal or reporting of adverse events were identified.

Conclusions
Trials of short duration neither adequately inform the management of chronic disease nor describe the sequelae of treatment. The evidence base for long-term care, reflecting the disease pathway, should be improved. Combination therapy with topical vitamin D analogues and steroids, and maintenance therapy following treatment response merit further investigation.

INTRODUCTION

Psoriasis is a chronic skin disease that involves thickening and scaling of the skin, commonly on the limbs and scalp. Plaque-type psoriasis, or psoriasis vulgaris, features circumscribed red patches of varying size covered with white scales. The degree of redness, scaling and surface area affected varies between patients and over time, most frequently affecting the elbows, knees, scalp and trunk. Other types of psoriasis include guttate (eruptive), inverse (flexural), erythrodermic and pustular (palmoplantar or generalised) [1]. Nail psoriasis is found in up to half of psoriasis patients, characterised by pitting, discoloration, onycholysis, subungual hyperkeratosis, nail crumbling and grooving, and splinter haemorrhages [2]. Psoriasis is associated with an increased risk of certain concomitant diseases such as arthritis: psoriatic arthropathy is found in 5 to 10% of patients [3]. However reported associations between psoriasis and cancers may be explained by exposure to carcinogenic agents, rather than by some underlying susceptibility [4].

Globally, the prevalence of psoriasis varies from nearly 5% in adult Scandinavians to negligible levels in South American Andeans and Eskimos [3,4]. In common with other European populations, it affects about 2% of people in the UK and USA [5].

Analyses of the risk factors suggest that psoriasis is multifactorial arising as a result of the interaction of multiple genes and environmental factors [3,4,6-9]. It has been estimated that a child with one affected parent has a 25% chance of developing the disease, rising to 60% if both parents are affected [10]. There has been a debate as to whether psoriasis is primarily a T-cell mediated disease or of epithelial origins. The chance discovery that patient's psoriasis improved while receiving cyclosporin (an immune suppressive drug) for the treatment of their arthritis supported the T-cell hypothesis [11]. However, several of the genetic loci that have been linked and associated with psoriasis contain groups of genes involved in the formulation of the epidermis [7,8]. It is probable that there are genetically determined changes in both the skin and immune system that interact to produce the psoriatic phenotype.

Understanding of the progression of the disease in individuals is complex and associated with many factors including local trauma, infections, certain drugs (such as beta-blockers), the duration of antipsoriatic treatments, endocrine factors, sunlight, alcohol, smoking and stress [12]. Streptococcal throat infections or upper respiratory tract infections have been recognised to trigger guttate psoriasis [12], but the effect of smoking or alcohol remains controversial. Evidence for stress leading directly to worsening psoriasis is inconclusive, although the effect of psoriasis on quality of life, including levels of stress, has been demonstrated [4].

Psoriasis was thought to be a variant of leprosy and regarded as contagious, until identified as a disease in its own right by von Hebra in 1841 [3]. The misconception persists: a survey of patients in 1997 revealed that 74% of respondents reported that others thought their condition was contagious. A similar proportion feared swimming and taking part in sporting activities [10]. Psoriasis is reported to lead to social isolation in sufferers [13].

Treatment for psoriasis

Despite an evolving comprehension of the disease, there remains no lasting cure for psoriasis. In mild and self-limiting episodes, emollient therapy and reassurance are often advocated. For more severe cases, a range of treatments are available including corticosteroids, salicylic acid, coal tar, vitamin D analogues, retinoids, dithranol and ultra-violet light. Topical treatments come in a range of ointments, gels, pastes, creams, and scalp solutions. Hospital treatment with oral preparations of acitretin, cyclosporin or methotrexate is indicated only for the most severe and resistant cases [14]. There is uncertainty about the value of available treatments or their appropriate sequencing in the progression of the disease.

The Greek physician, Hippocrates (circa 460-370BC), appears to have used tar to treat wounds [15]. Almost 300 years later, the Greek philosopher and surgeon, Dioscorides, described the use of tar as a treatment for skin disorders. This tar was probably asphalt, coal tar being first attributed to Becher and Serle in 1681 [16]. In 1925, Goeckerman demonstrated the effectiveness of crude coal tar and ultraviolet light for psoriasis. Uncertainty remains to this day about the potential for systemic adverse events from tar and its suitability in certain forms of psoriasis.

Dithranol (anthralin in the US) was introduced in 1916 to treat chronic plaque psoriasis [15]. In 1953, Ingram described his method of application: after soaking the patient in a warm bath containing coal tar solution, dithranol was applied to the dry skin and the patient then exposed to UV light to produce a slight erythema. Both tar and dithranol are associated with skin irritation, staining, odour and messiness and have in their turn been relegated to second-line therapy for most patients with psoriasis.

The introduction of topical corticosteroids in the 1960s provided a new approach to psoriasis treatment. Psoriasis is a relatively corticoid-resistant disease, which may therefore respond only to potent or very potent drugs [17]. In the UK, their recommended use for psoriasis is more restricted than in the US. In 1992, a survey revealed that about 85% of US dermatologists used topical corticosteroids first line in the treatment of patients with limited psoriasis. Second-line treatments included coal tar (40%), dithranol (28%) and keratolytics (17%) [18]. However, this practice may have been gradually changing in the last decade, with guidance recommending the use of topical corticosteroids only as an alternative or adjunctive treatment for psoriasis [19].

Although corticosteroids effectively suppress psoriasis in the short term, they are associated with relapse or vigorous rebound on withdrawal. Topical use of potent corticosteroids on substantial body surface areas, and over long periods of time, can lead to systemic as well as to local side-effects. Known adverse events include skin atrophy, pituitary-adrenal axis suppression, Cushing's syndrome, cutaneous striae and skin thinning, contact dermatitis, telangiectasia, and worsening of local infections [14]. Corticosteroids indicated for use in psoriasis vary between the UK and US, as does the classification of their potency (Appendix, Table A).

In 1985, a Japanese report of a striking improvement in psoriasis in a patient treated for osteoporosis with oral 1alpha-hydroxyvitamin D (alpha-calcidol) opened a new avenue of research into vitamin D derivatives [20]. Topical calcitriol was the first vitamin D3 analogue to be substantially investigated. Although effective in treating psoriasis, topical calcitriol was found to be associated with systemic adverse events and is no longer marketed in the US or UK. Systemic absorption of even small amounts can affect calcium metabolism, and the margin between efficacy and side effects appears narrow [21]. The synthetic analogue calcipotriol (calcipotriene in the US) was introduced to the UK market in 1992 and to the US in 1994. Calcipotriol ointment is rapidly transformed into inactive metabolites and is thought to retain antiproliferative activity against keratinocytes, whilst being unlikely to cause hypercalcaemia. Irritation, particularly on the face and intertriginous regions, is the most common reported side effect [11]. Tacalcitol is another synthetic vitamin D analogue [22], currently available in the UK, but not in the US. Compared with calcipotriol, tacalcitol has been less intensively investigated, but it has been suggested that tacalcitol has a similar safety profile [23]. In Europe, topical vitamin D3 analogue treatment is widely used for psoriasis. In both Europe and the US, it is not uncommon to find vitamin D3 analogue and topical steroids used in combination, the intention being to improve efficacy while minimising side effects [24,13].

Tazarotene was the first retinoid to be marketed as a topical preparation for mild-to-moderate plaque psoriasis [25]. Tazarotene, an acetylenic retinoid, is metabolised to therapeutically active tazarotenic acid after application to the skin [26]. Its action is purported to reduce inflammation and modulate the differentiation and proliferation of keratinocytes [27], the major reported side

effect being irritation, which affects between 13% and 30% of patients in a dose-related manner [11].

Changes in healthcare setting and delivery have accompanied changes in treatment: tar and dithranol have declined in use and modern treatments have lead to a shift from secondary to primary care. Even for severe psoriasis, there has been a shift from inpatient hospitalisation to outpatient treatment in the US, with dermatologists increasingly acting as a 'consultant to the primary care physician' [28]. In the UK primary care-led NHS, GPs might be expected to play an even more prominent role. Some treatments for the most severe cases of psoriasis remain marginal to, or outside the remit of primary care (phototherapies, oral retinoids and immunosuppressants); GPs generally take sole responsibility for the treatment of patients with mild or moderate psoriasis. This review addresses patients for whom appropriate management involves active topical treatment in the primary care setting.

Outcome measures in trials

Three kinds of investigator-assessed outcome measures are commonly used in clinical trials for treatment of psoriasis. The first involves assessing signs (redness or erythema, scaling or crusting, thickening or elevation or induration) and symptoms (pruritus) of psoriasis using 3 or 4 point scales (e.g. 0: none; 1: some; 2: extensive). These signs and symptoms are summed to obtain a Total Severity Score (TSS), typically scored 0 to 12. The second measure is an area-adjusted version of TSS called the Psoriasis Area Severity Index (PASI), the rationale being that reductions in area of psoriasis are as important as severity [29,30]. This index, like the TSS, is scored in several different ways in trials but was originally scored 0 to 72. The third measure involves an Investigator Assessment of Global Improvement (IAGI) or response of psoriasis. Typically this measure is scored on a 6 or 7 point scale scored, for example –1: worse through to 5: cleared. Less commonly used outcome measures include a variety of Patient Global Assessment scores. The independence of the patient and investigator assessments in many studies is unclear.

Summarising the results of trials is potentially problematic when different outcome measures are used. However, all of these measures feature ordered categorical scales and all assess the same underlying construct. Because of the number of points in each scale, these can reasonably be analysed as continuous measures, although scale and content differences in measures make a weighted mean difference (WMD) estimate to compare the results of trials inappropriate. An advantage of a standardised weighted mean difference (SWMD) estimate is that it adjusts for scale differences and allows most trials to contribute data. The disadvantage is the loss of physical interpretability, although it is possible to work back to a value to a natural scale from the SWMD.

A previous review reported response rates to treatments by dichotomising IAGI measures used in trials [31]. Trialists themselves often report, for example, patients substantially or completely cleared on different treatments. A difficulty with this approach is that quite modest differences between treatments on the original scales can be magnified by arbitrarily cutting the data into 'responders' and 'non-responders'. To this must be added the problem that often the choice of where to cut 'response' is made with sight of the data, rather than with reference to a protocol prescribed primary endpoint: this provides scope for substantial bias.

REVIEW METHODS

We retrieved placebo (vehicle) controlled trials of psoriatic treatments used in primary care: corticosteroids, vitamin-D derivatives, salicyclic acid, coal tar, dithranol and tazarotene. Additionally we retrieved head-to-head trials providing comparisons with the (relatively new) vitamin-D derivative treatments, to assess their performance directly against other established

treatments. Trials were included if they were randomised, without cross over, with two weeks or more duration of treatment. We excluded trials including patients primarily with other diseases (e.g. psoriatic arthritis, atopic dermatitis, eczema); adjunctive treatments for the iatrogenic effect of psoriasis therapies; studies pragmatically we were unable to translate; studies reporting biological or pharmokinetic markers, but not patient clinical outcomes; studies using healthy volunteers; psoriasis secondary to a particular co-morbid condition such as HIV.

We conducted sensitive electronic searches of the mainstream medical and grey literature: MEDLINE (1966-99), EMBASE (1974-99), BIOSIS (1985-99), Healthstar (1975-99), Sigle (1980-1999), IHTA (1990-1999), Cochrane Controlled Trials Register (-99), Conference Papers Index (1984-1999), Derwent Drug File (1992-1999), Dissertation Abstracts (1992-1999), Pascal (1992-1999), International Pharmaceutical Abstracts (1992-1999) and Science Citation Index (1981-1999). We also searched references of trial reports and recent reviews. We routinely contacted authors and companies for missing data from published reports.

We summarised the major attributes of trials including treatment forms, doses and duration, inclusion and exclusion criteria, level of blinding, within patient or parallel group design, concealment of allocation, numbers of patients randomised, baseline comparability, loss to follow up, primary and secondary outcomes, withdrawals and adverse events: full details are reported in the Appendix. Data were abstracted from trials on the three commonly reported clinical outcomes: TSS, PASI or IAGI and results were pooled using a standardised weighted mean difference metric. We used random effect estimates reflecting variations in content of the measures used. We also abstracted data on withdrawal due to any cause, to adverse events and to treatment failure, as well as adverse events due to local and systemic effects. These data were summarised using a risk reduction metric again using random effect estimates. Where estimates of variance were unobtainable for studies, these were imputed by pooling the standard deviations of treatment cohorts fully reported in trials. Separate imputations were made for each outcome and for within-patient and parallel group designs. Our intent was to explore consistency of treatment effect within and between classes of therapy. Corticosteroids were classified using the classification found in the British National Formulary (BNF) [14]. British and American classifications of potency show good correlation (Appendix, Table A).

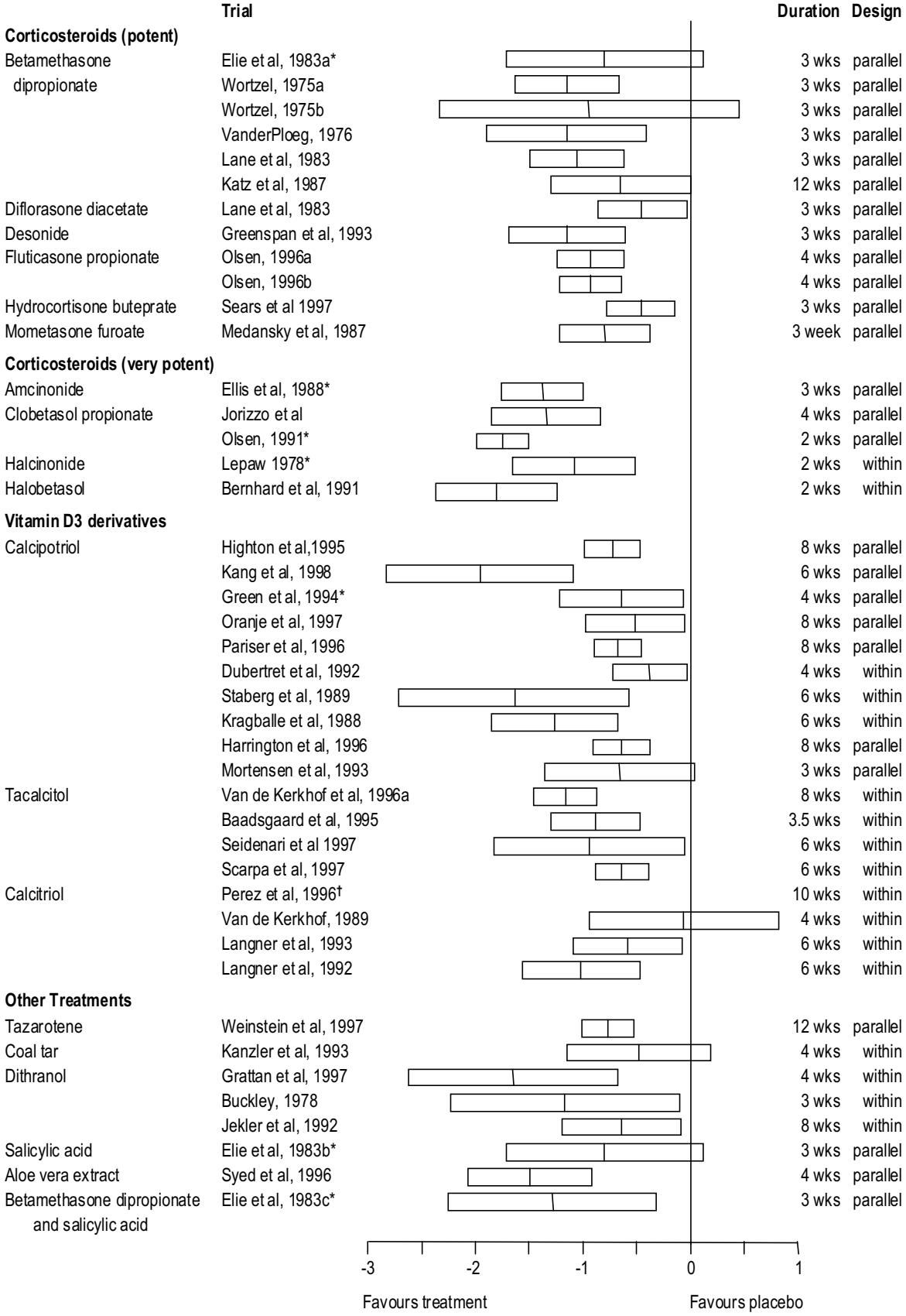
RESULTS

Placebo-controlled trials

We retrieved details of 52 randomised controlled trials comparing active treatments against placebo (Appendix, Table B) [34-85]. In all instances the placebo consisted of the emollient vehicle used by the active treatment or some similar emollient. Of these trials, 41 were able to provide summary data useful to the effectiveness analysis, either directly from the published report, by contact with authors or sponsors for additional data or by imputation (when variance estimates were absent). These 41 trials provided 49 comparisons against placebo and data on 3,830 patients (Appendix, Table C). With the exception of one small trial, [42] all were double-blinded. Duration of treatment in trials was typically 3 to 8 weeks. A within patient design was used in 17 trials and a parallel group design in 24 trials. Twenty-seven trials (66%) reported a Total Sign Score, 5 (12%) a PASI, and 24 (59%) an Investigator's Global Assessment of Improvement. Imputation of estimates of variance was necessary for 12 trials. Trials comparing steroids with placebo fell into either 'potent' or 'very potent' BNF categories.

The estimates of effectiveness shown as standardised mean differences between treatment and placebo groups for each trial are presented in Figure 1. In dose-ranging studies, outcomes of patients at all doses of active therapy have been combined and shown against placebo, leaving 43 comparisons in total.

Figure 1: Placebo controlled trials of topical treatments for psoriasis: standardised weighted mean difference



* Trials of scalp psoriasis

† Not shown: -6.024 (95%CI: -5.312 to -6.735), see text for discussion

Performance of active treatment compared with placebo

The pooled results of the trials by treatment and by treatment class are shown in Figure 2. The pooled standardised weighted mean difference for all active treatments against vehicle was -1.06 (95%CI: -1.26 to -0.86), indicating a statistically significant benefit in favour of active treatment. On a 12-point Total Severity Score this approximates to an improvement of 2 points. We found evidence of heterogeneity confirming the need for a random effects approach, though a fixed effects approach provides a similar estimate of effect, with a standardised weighted mean difference of -0.94 (95%CI: -1.00 to -0.88). There were no significant differences between the findings of within patient and parallel group designs, or standardised estimates according to the outcome measure used: TSS, PASI or IAGI. Thus the heterogeneity appears to arise, at least in part, because of differences in effectiveness between the classes of treatments. The magnitude of benefit showed no marked differences comparing between classes of drugs with the exception of the very potent steroids. Topical very potent steroids were compared with a placebo vehicle in five trials providing effectiveness data from 646 patients. Overall, there was a statistically significant difference favouring very potent steroids -1.51 (95%CI: -1.76 to -1.25), approximately to a 3-point improvement on a 12-point Total Severity Score.

Twelve trials of topical potent steroids with 1,040 patients found a statistically significant difference favouring potent steroids: -0.84 (95% CI: -0.99 to -0.68), approximately a 1.6 point improvement on a 12-point Total Severity Score.

Trials of vitamin D3 treatments include calcitriol, which is no longer marketed in the UK or US because of its safety profile. One trial [71] reports spectacular improvement for calcitriol compared to placebo that is hard to interpret alongside the findings of other trials. Consequently, pooled results have been shown for all vitamin D3 derivative treatments and for those currently available. Fourteen trials of currently available vitamin D3 derivative treatments with 1,537 patients found a standardised weighted mean difference favouring active treatment of: -0.79 (95%CI: -0.95 to -0.63), a 1.6 point improvement on a 12-point Total Severity Score.

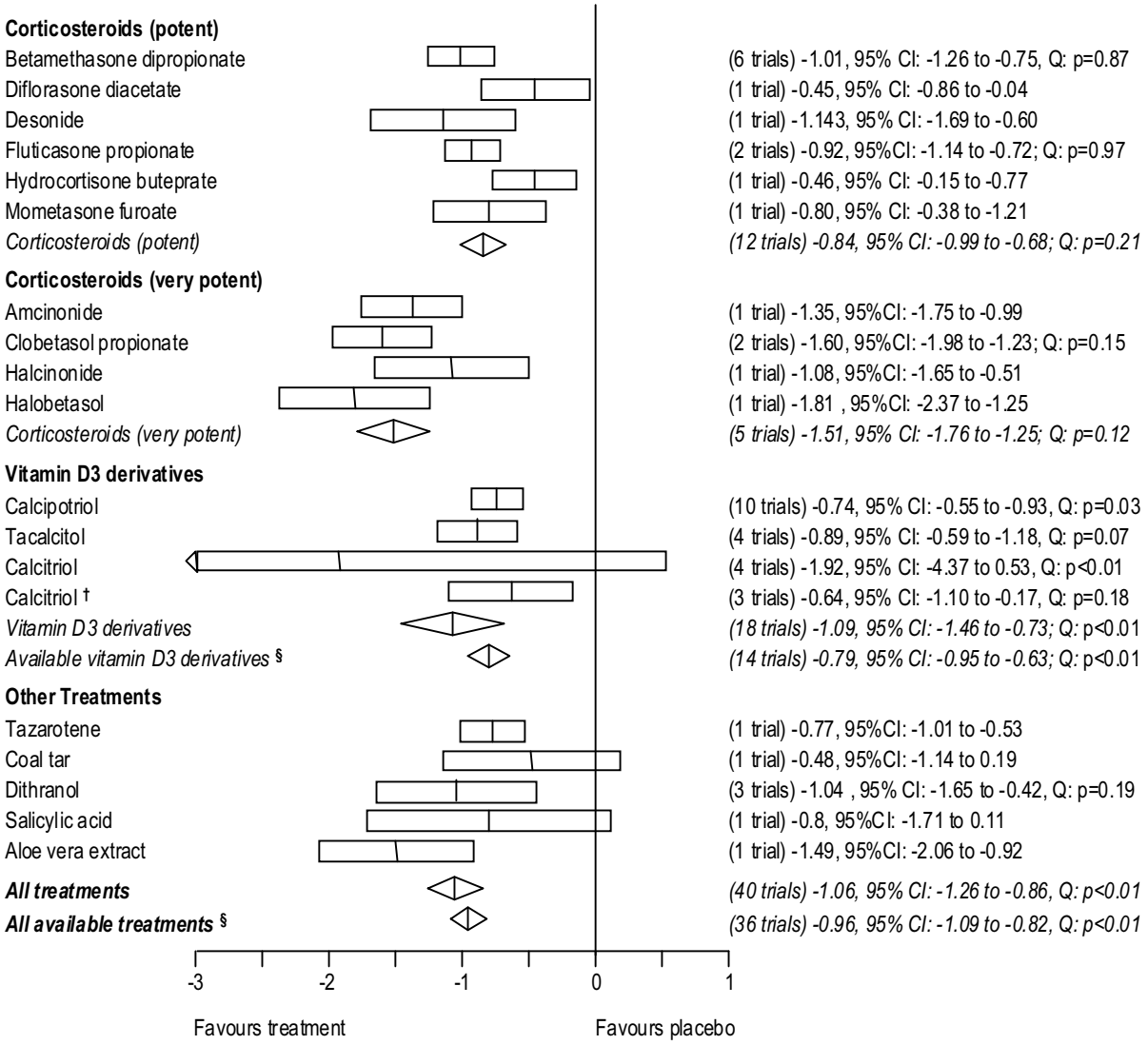
One placebo-controlled trial of tazoretene, providing data from 318 patients, provided a clinical effect favouring tazarotene: -0.77 (95%CI: -1.01 to -0.53), consistent with potent steroids and vitamin D3 derivative treatments. Estimates of benefits for other treatments are imprecise reflecting the small numbers enrolled in these trials. One small trial of Aloe Vera is included as a curio, although not clinically licensed for the treatment of psoriasis [78].

Thirty-six placebo-controlled trials provided data on at least one of the following: withdrawal for any reason, for adverse events or treatment failure, frequency of local or systemic adverse event rates. Within therapeutic classes, with few exceptions, there were no statistically significant differences between active treatment and vehicle in any of these measures (Table 1).

Head-to-head studies

We retrieved details of 34 randomised controlled trials comparing a vitamin D3 preparation with another active treatment (Appendix, Table D) [86-124]. Five of these studies were excluded on methodological grounds (Appendix, Table E). Of included trials, 28 were able to provide summary data useful to the effectiveness analysis, either directly from the published report, by contact with authors or sponsors for additional data or by imputation. These 28 trials provided 30 comparisons against vitamin D derivative treatment and data on 4,898 patients (Appendix, Table F). Fifteen trials feature double blinding, three single blinding and six an open design. In four studies, the level of blinding could not be ascertained. Duration of treatment in trials was typically 6 to 8 weeks. A within patient design was used in 10 trials and a parallel group design in 18 trials. Thirteen trials (46%) reported a Total Sign Score, 14 (50%) a PASI, and 14 (50%) an Investigator's Global Assessment of Improvement. Imputation of estimates of variance was necessary for five trials.

Figure 2: Summary of placebo controlled trials of topical treatments for psoriasis: standardised weighted mean difference ‡



† Excluding Perez et al, 1996.
§ Excluding calcitriol.
‡ Pooled estimates are calculated using a DerSimonian-Laird random effects model. Also shown is the 'Q' statistic for combinability.

The estimates of effectiveness are shown as standardised mean differences between vitamin derivative treatments and other active treatments for each trial in Figure 3. A meta analysis using random effects estimation and pooling the results for common treatment comparisons is shown in Figure 4.

Performance of vitamin D derivatives in head-to-head trials

Vitamin D derivative treatment was compared with a potent topical corticosteroid in 9 trials providing effectiveness data from 1,875 patients. Overall there was no statistically significant difference between treatments in clinical effect, withdrawal or adverse events consistent with placebo-controlled comparisons of the treatments.

Vitamin D derivative treatment was compared with dithranol in 5 trials providing effectiveness data from 972 patients. Overall, vitamin D derivative treatment performed better in terms of

clinical effect: -0.44, (95%CI: -0.72 to -0.16) and reporting of adverse events: -27% (95%CI: -36% to -17%). The clinical effect corresponds to nearly one point on a 12-point Total Severity Scale. However, there was no significant difference in overall withdrawal (Table 2).

Table 1: Withdrawal and adverse events in placebo-controlled trials

	No. of trials	Risk difference*	95% Confidence interval	Heterogeneity, Q (p)
Corticosteroids(potent)				
TW	3	-0.01	-0.08 to 0.05	0.70
WA	6	-0.01	-0.04 to 0.03	0.02
WF	3	-0.01	-0.02 to 0.01	0.70
AE	6	0.00	-0.05 to 0.00	0.57
SAE	1	0.00	(no events)§	
Corticosteroids (very potent)				
	5	-0.05	-0.15 to 0.05	0.001
WA	6	0.00	-0.01 to 0.00	0.99
WF	5	-0.03	-0.09 to 0.02	0.001
AE	4	0.00	-0.02 to 0.02	0.60
SAE	3	0.00	-0.01 0.01	1.00
Vitamin-d derivatives				
TW	15	0.00	-0.02 to 0.01	0.65
WA	15	0.01	0.00 to 0.01	0.98
WF	7	-0.03	-0.08 to 0.02	0.00
AE	11	0.00	-0.02 to 0.02	0.85
SAE	10	0.00	(no events)	
Tazarotene				
TW	1	0.01	-0.10 to 0.10	
WA	1	0.08	0.02 to 0.14	
WF	1	-0.01	-0.08 to 0.03	
AE	NR			
SAE	2	0.00		
Dithranol				
TW	4	0.00	-0.09 to 0.09	1.00
WA	3	0.00	(no events)	
WF	2	0.00	(no events)	
AE		0.26	-0.27 to 0.79	0.001
SAE	NR			
Salicyclic acid				
TW	NR			
WA	1	0.00	(no events)	
WF	NR			
AE	1	0.00	(no events)	
SAE	NR			
Aloe Vera extract				
TW	1	0.00	(no events)	
WA	1	0.00	(no events)	
WF	1	0.00	(no events)	
AE	1	0.00	(no events)	
SAE	NR			

Notes

TW: Total withdrawal

WA: Withdrawal due to adverse events

WF: Withdrawal due to treatment failure

AE: Local adverse events

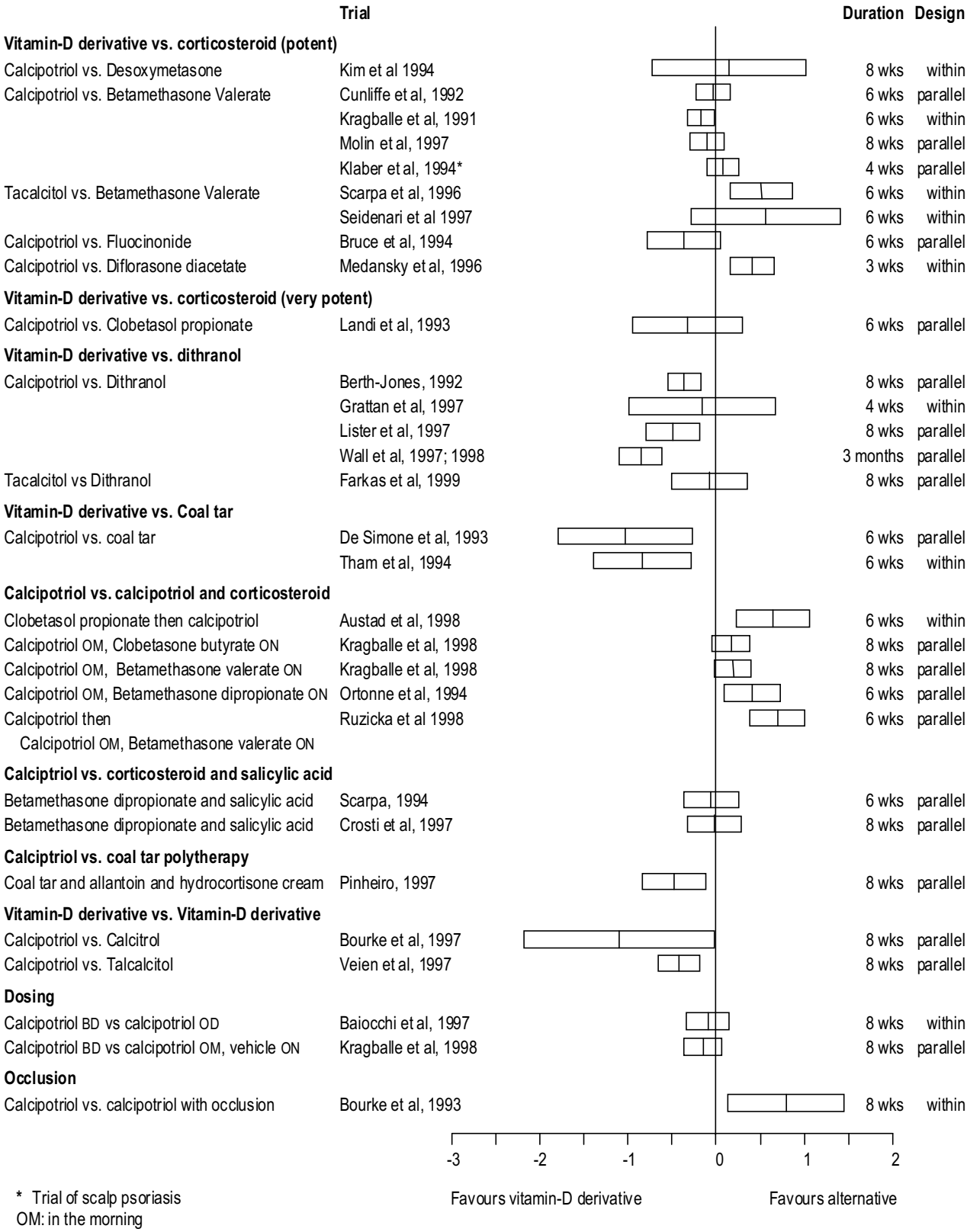
SAE: Systemic adverse events

* A random effects risk difference (DerSimonian-Laird) has been estimated. This is more appropriate than a fixed effect model since definitions of withdrawal and adverse events vary between studies. Positive risk difference: event more common on active therapy. Negative risk difference: event more common on placebo.

§ Where both arms of a trial recorded no events, the difference is given as zero but a confidence interval is not estimated

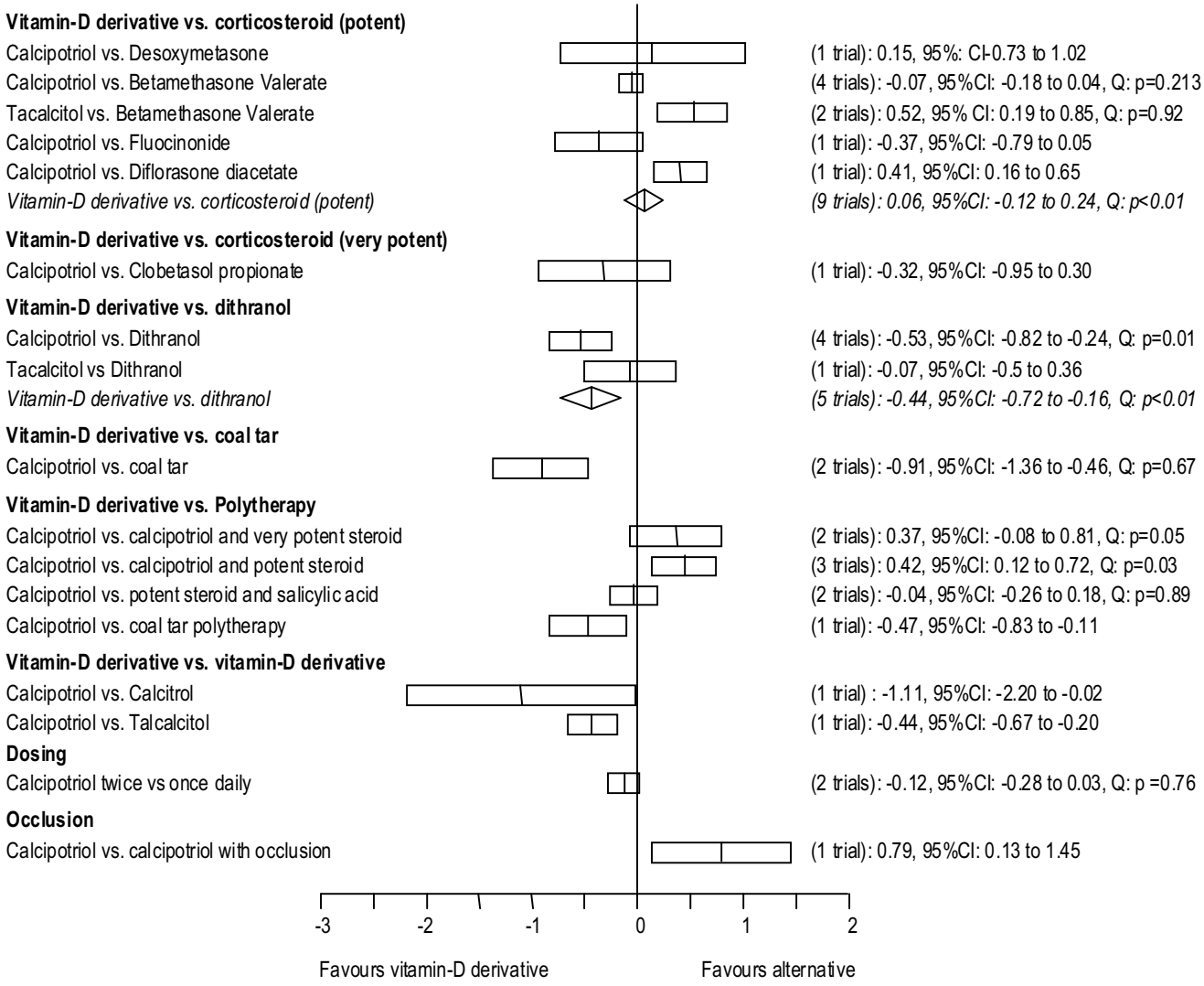
NR: Not recorded

Figure 3: Head-to-head RCTs including vitamin-D derivative treatments: standardised weighted mean difference



* Trial of scalp psoriasis
OM: in the morning
ON: at night
Calcipotriol is used twice daily unless indicated
Tacalcitol is used once daily

Figure 4: Summary of head-to-head RCTs including vitamin-D derivative treatments for the topical treatment of psoriasis: standardised weighted mean difference ‡



‡ Pooled estimates are calculated using a DerSimonian-Laird random effects model. Also shown is the 'Q' statistic for combinability

Vitamin D derivative compared with polytherapy

Comparison of calcipotriol treatment was made with combination therapy involving calcipotriol and a potent steroid in three trials providing effectiveness data for 671 patients. Overall, combination therapy achieved a better clinical effect: 0.42, (95%CI: 0.12 to 0.72) corresponding to a 0.8 point improvement on a 12-point Total Severity Score.

Calcipotriol treatment was compared with combination therapy involving calcipotriol and a very potent steroid in 2 trials providing effectiveness data for 218 patients. These trials found a non-statistically significant trend in clinical effect favouring combination therapy 0.37, (95%CI: -0.08 to 0.81) corresponding to a 0.7 point improvement on a 12-point Total Severity Score.

Calcipotriol was compared with combination therapy involving a potent steroid and salicyclic acid in 2 trials providing effectiveness data for 320 patients. These trials found no difference in clinical effect between therapies: -0.04 (95%CI: -0.26 to 0.18)

One trial providing effectiveness data for 122 patients reported a favourable clinical effect for calcipotriol when compared to a coal tar, allantoin and hydrocortisone cream combination: -0.47 (95%CI: -0.83 to -0.11) corresponding to a 0.9 point improvement on a 12-point Total Severity Score.

Overall there was no significant difference in reported adverse events or withdrawal comparing single and combination therapy (Table 2).

Vitamin D derivative compared with vitamin D derivative
Calcipotriol treatment was compared with calcitriol in one small trial providing effectiveness data from 15 patients. This trial found a statistically significant difference favouring calcipotriol: -1.11 (95%CI: -2.20 to -0.02). Calcipotriol treatment was compared with tacalcitol in one trial providing effectiveness data from 287 patients. This trial similarly found a statistically significant difference favouring calcipotriol: -0.44 (95%CI: -0.67 to -0.20). No difference in adverse events or in withdrawal was reported in these trials. The results of the two head-to-head trials are inconsistent with the results of placebo-controlled trials, which suggest similar effectiveness for each treatment when compared with placebo. From the head-to head trial, the difference favouring calcipotriol over talcalcitol is a one point difference on a 12-point Total Sign Score.

Scalp and nail psoriasis
We retrieved seven placebo-controlled trials of topical treatments for scalp psoriasis. Results from these trials are consistent with trials involving treatment of the trunk or limbs (Figure 1). Similarly, one head-to-head trial in scalp psoriasis demonstrated no therapeutic difference between a vitamin D derivative and potent steroid consistent with other trials. The results of two pivotal trials of calcipotriol versus its vehicle in 235 and 204 patients were reported in abstract in 1996 [38, 55], but have not subsequently been fully reported and adequate data were unavailable.

Surprisingly, considering the prevalence of nail psoriasis, we retrieved only one trial comparing a vitamin D derivative treatment and a potent steroid in combination with salicylic acid [120]. Although the analysis was statistically flawed, the alternatives demonstrate no significant different in fingernail or toenail hyperkeratosis after three months consistent with the results of trials of the trunk or limbs.

Long-term outcomes
A number of randomised controlled trials continued following patients for periods beyond treatment. Qualitatively these studies show a common trend of gradually worsening psoriasis on cessation of treatment.

Two trials randomised potent steroid treatment responders to either an intermittent maintenance regime (three applications each weekend) or to no maintenance, and provided data on 128 patients [53, 54]. Taken together, these trials indicate over a six-month period that patients were more than three times as likely to stay in remission, Relative Risk = 3.28 (95% CI = 1.97 to 5.48): an absolute reduction in relapse of nearly half: 0.47 (95% CI = 0.32 to 0.62).

We identified no long-term studies involving substantial numbers of patients with psoriasis and that assessed the sequelae of long-term potent steroid use. Available studies demonstrate the association between prolonged topical steroid use and skin basal layer fragmentation, although this is demonstrably more marked after use in excess of six years [32]. Short-term studies have attempted to quantify the atrophogenic potential of topical steroids [33]. It is unclear how

Table 2: Withdrawal and adverse events in head-to-head trials

	No. of trials	Risk difference*	95% Confidence interval	Heterogeneity, Q (p)
vs. Corticosteroids (potent)				
TW	7	0.02	0.00 to 0.03	0.68
WA	7	0.01	-0.01 to 0.03	0.001
WF	4	0.00	-0.01 to 0.01	0.77
AE	6	0.10	-0.02 to 0.21	0.001
SAE	5	0.00	0.00 to 0.00	1.00
vs. Corticosteroids (very potent)				
TW	1	0.00	(no events)	
WA	1	0.00	(no events)	
WF	1	0.00	(no events)	
AE	2	-0.02	-0.09 to 0.06	0.27
SAE	1	-0.05	-0.24 to 0.12	
vs. Dithranol				
TW	3	-0.01	-0.10 to 0.08	0.97
WA	4	-0.04	-0.07 to -0.02	0.51
WF	2	0.00	-0.02 to 0.02	1.00
AE	5	-0.27	-0.36 to -0.17	0.02
SAE	2	0.00	-0.01 to 0.00	0.83
vs. Coal Tar				
TW	1	0.00	-0.17 to 0.17	
WA	1	0.03	-0.08 to 0.17	
WF	1	0.00	(no events) §	
AE	NR			
SAE	1	0.00	-0.14 to 0.14	
vs. polytherapy				
TW	6	0.02	-0.01 to 0.05	0.50
WA	6	0.02	0.00 to 0.04	0.25
WF	3	0.01	-0.01 to 0.02	0.34
AE	7	0.09	0.05 to 0.13	0.74
SAE	4	0.06	-0.07 to 0.20	0.001
vs. another vitamin-D3				
TW	1	0.00	-0.37 to 0.37	
WA	1	0.00	(no events)	
WF	1	-0.08	-0.39 to 0.23	
AE	2	-0.01	-0.09 to 0.07	
SAE	1	0.00	(no events)	
Dosing				
TW	2	0.01	-0.05 to 0.06	0.75
WA	2	0.01	-0.02 to 0.04	0.91
WF	2	0.00	-0.02 to 0.02	1.00
AE	1	-0.03	-0.13 to 0.07	
SAE	2	-0.01	-0.13 to 0.10	0.02
vs + occlusion				
TW	1	0.00	(no events)	
WA/WF/AE	NR			
SAE	1	0.00	(no events)	

Notes

TW: Total withdrawal

WA: Withdrawal due to adverse events

WF: Withdrawal due to treatment failure

AE: Local adverse events

SAE: Systemic adverse events

* Random effects risk difference. Positive risk difference: event more common on vitamin D derivative treatment. Negative risk difference: event more common on comparison treatment.

§ Where both arms of a trial recorded no events, the difference is given as zero but a confidence interval is not estimated

NR: Not recorded

common or marked such problems are in patients who make intermittent use of steroids with appropriate maintenance strategies.

We retrieved three long-term uncontrolled studies of calcipotriol and one of talcalcitol with up to a year and a half in follow-up [125-129]. Comparatively, they provide no useful information since it is not possible to say how enrolled patients would have faired under alternative treatment regimens. However, over more realistic treatment periods than the duration of most randomised trials, these studies indicate that initial gains from treatment can be maintained over longer periods in a majority of patients, with the most common adverse event being lesional irritation in about 20-25% of patients. Reasons for withdrawal have not been recorded consistently or in a blinded fashion in these studies, but between one quarter and one half of patients were lost to follow-up or withdrawn from treatment after enrolment. Hypercalcaemia was very rare: reports of its occurrence in these studies ranged from 0% to 0.6% of patients.

The economics of treatment

A number of studies have looked at economic aspects of psoriasis. These include cost-of-illness studies [130,131], quality-of-life [132,133], methodological issues [134,135] and cost-effectiveness analyses [136-143]. These analyses involve a range of modelling approaches and assumptions. Our review reveals no substantial variations in tolerability or effectiveness for most treatment comparisons, and no trials provide robust resource data on the consequences of managing treatment failure. Consequently, economic modelling beyond the duration of trials would be speculative and uninformative. In the light of available data, a 'cost and consequences' approach may be most informative to clinicians, at least when discussing first line treatment. The relative short-term clinical performance of topical anti-psoriatic therapies can be set against their reimbursed costs. While it is accepted that long-term sequelae in patients not responding to treatment may be very important when considering overall costs and benefits, there are no good comparative data on these costs with which to distinguish between treatments.

DISCUSSION

On the basis of short-term, randomised, placebo-controlled trials there are no therapeutic advantages for the newer treatments over the older ones, either in clinical effect, withdrawal of treatment or reporting of local or systemic adverse events. Head-to-head studies of vitamin D3 derivative treatments provide some evidence conflicting with this simple message.

When comparing trials both within and across therapeutic class, the summary estimates often demonstrate substantial heterogeneity. It would be tempting to try to find reasons for individual differences, but there are too many possible explanations and too few trials to do this: reasons might include differences in trial design, length of follow-up, patient selection, adequacy of concealment of allocation, adequacy of blinding, and source of funding. Concealment of allocation (preventing the investigator or clinician from having any influence, implicit or explicit, upon the treatment a patient is allocated to) is cited as a useful quality marker to categorise trials. Trials seldom provided adequate methodological detail to ascertain that concealment had been achieved. Similarly, many trials provided inadequate details of funding sources.

The duration of treatment in most trials is between 4 and 8 weeks, which appears an inadequate period either to reflect the management of many patients or to detect subcutaneous adverse effects. Some longer-term uncontrolled studies have been conducted. However, the outcome from a case series applies to that particular selection of patients with their own baseline characteristics and disease progression, as well as use of anti-psoriatic treatments and other health care. To choose between treatments on the basis of such data is not scientific. Prevention of relapse, after initial response with steroids, has been investigated experimentally:

intermittent therapy is an important bridging or step-down strategy [53, 54]. This research was in response to the awareness of the rebound phenomenon associated with steroids, but it is unclear to what extent rebound is caused by cessation of the steroid as opposed to the cessation of any treatment per se.

The importance of cosmetic acceptability upon compliance has implications for dithranol and tar. Dithranol showed significantly higher reporting of local adverse events than both placebo and vitamin D3 treatment although trial data on coal tar are inconclusive. The perceived clinical importance of cosmetic acceptability upon long-term compliance and outcome requires further research.

Comparative long-term outcome and disease progression associated with different treatments is under-researched, although maintenance dosing to prevent relapse and polytherapy for chronic psoriasis merit further investigation. Very few studies have enrolled children and the evidence base for this patient group is particularly sparse. Well-designed randomised trials could help to identify appropriate long-term care to both minimise harm and make best use of available resources.

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Appendix

A Systematic Review of Topical Preparations for the Treatment of Psoriasis in Primary Care

Table A: Availability and potency ratings of corticosteroids in the UK and USA

Drug Name	Strength	Potency Rating		Vehicle					
				Cream		Ointment		Other	
		UK	*US*	*UK*	*US*	*UK*	*US*	*UK*	*US*
Alclometasone dipropionate	0.05%	Moderate	Low	Y	Y	Y	Y	N	N
Amcinonide	0.1%	NA	High	NA	Y	NA	Y	NA	Lotion
Augmented betamethasone dipropionate	0.05%	NA	High	NA	Y	NA	Y[1]	NA	Gel; Lotion
Beclometasone dipropionate	0.025%	Potent	NA	Y	NA	Y	NA	N	NA
Betamethasone (as dipropionate)	0.05%	Potent	High	Y	Y	Y	Y	Lotion	Lotion[2]
Betamethasone (as valerate)	0.01%	NA	Mild	NA	Y	NA	N	NA	N
Betamethasone (as valerate)	0.025%	Moderate	NA	Y	NA	Y	NA	N	NA
Betamethasone (as valerate)	0.1%	Potent	Medium	Y	Y	Y	N	Lotion; Scalp application	N
Betamethasone benzoate	0.025%	NA	Medium	NA	Y	NA	N	NA	Gel; Lotion
Clobetasol propionate	0.05%	Very potent	Very high	Y	Y	Y	Y	Scalp application	Scalp application; Gel
Clobetasone butyrate	0.05%	Moderate	NA	Y	NA	Y	NA	N	NA
Clocortolone pivalate	0.1%	NA	Medium	NA	Y	NA	N	NA	N
Desonide	0.05%	NA	Low	NA	Y	NA	Y	NA	Y
Desoximetasone	0.05%	Moderate	Medium	N	Y	N	N	Oily cream	Gel[3]
Desoximetasone	0.25%	Potent	High	N	Y	N	Y	Lotion	N
Dexamethasone	0.01%, 0.04%	NA	Low	NA	N	NA	N	NA	Aerosol
Dexamethasone sodium phosphate	0.1%	NA	Low	NA	Y	NA	N	NA	N
Diflorasone diacetate	0.05%	NA	High	NA	Y	NA	Y[4]	NA	N
Diflucortolone valerate	0.1%	Potent	NA	Y	NA	Y	NA	Oily cream	NA
Diflucortolone valerate	0.3%	Very potent	NA	N	NA	Y	NA	Oily cream	NA
Fluocinolone acetonide	0.0025%	Mild	NA	Y	NA	N	NA	N	NA

[1] US potency rating for ABD ointment: very high
[2] US potency rating for betamethasone dipropionate lotion: medium
[3] US potency rating for desoximetasone gel: high
[4] US potency rating for diflorasone diacetate ointment with occlusive base: very high

Table A: Availability and potency ratings of corticosteroids in the UK and USA (continued).

Drug Name	Strength	Potency Rating		Vehicle					
				Cream		Ointment		Other	
		UK	*US*	*UK*	*US*	*UK*	*US*	*UK*	*US*
Fluocinolone acetonide	0.00625%	Moderate	NA	Y	NA	Y	NA	N	NA
Fluocinolone acetonide	0.01%	NA	Low	NA	Y	NA	N	NA	Solution; Shampoo; Oil
Fluocinolone acetonide	0.025%	Potent	Medium	Y	Y	Y	Y	Gel	N
Fluocinolone acetonide	0.2%	NA	High	NA	Y	NA	N	NA	N
Fluocinonide	0.05%	Potent	High	Y[5]	Y	Y	Y	Scalp Lotion	Gel; Solution
Fluocortolone	0.25%	Moderate	NA	Y	NA	Y	NA	N	NA
Flurandrenolide	0.025%	NA	Medium	NA	Y	NA	Y	NA	N
Flurandrenolide	0.05%	NA	Medium	NA	Y	NA	Y	NA	Lotion; Tape[6]
Flurandrenolone / Fludroxycortide	0.0125%	Moderate	NA	Y	NA	Y	NA	Tape[6]	NA
Fluticasone propionate	0.005%	Potent	Medium	N	N	Y	Y	N	N
Fluticasone propionate	0.05%	Potent	Medium	Y	Y	N	N	N	N
Halcinonide	0.025%	NA	NS	NA	Y	NA	N	NA	N
Halcinonide	0.1%	Very potent	High	Y	Y	N	Y	N	Solution
Halobetasol propionate	0.05%	NA	Very high	NA	Y	NA	Y	NA	N
Hydrocortisone	0.1%	Mild	NA	Y	NA	N	NA	N	NA
Hydrocortisone	0.25%	NA	Low	NA	N	NA	N	NA	Lotion
Hydrocortisone	1%	Mild	Low	Y	Y	Y	Y	Lipocream	Lotion; Solution; Gel; Pump spray; Stick; Roll-on
Hydrocortisone	2%	NA	Low	NA	N	NA	N	NA	Lotion
Hydrocortisone	2.5%	NA	Low	NA	Y	NA	Y	NA	Lotion
Hydrocortisone	0. 5%	Mild	Low	Y	Y	Y	Y	N	Lotion; Aerosol; Gel
Hydrocortisone acetate	0.1%	NA	Low	NA	N	NA	N	NA	Solution
Hydrocortisone acetate	0.5%	NA	Low	NA	Y	NA	Y	NA	N

[5] FAPG cream
[6] Dosage for tape: 4 mcg/cm^2

Table A: Availability and potency ratings of corticosteroids in the UK and USA (continued).

Drug Name	Strength	Potency Rating		Vehicle					
				Cream		Ointment		Other	
		UK	*US*	*UK*	*US*	*UK*	*US*	*UK*	*US*
Hydrocortisone acetate	1%	Mild	Low	Y	Y	Y	Y	N	N
Hydrocortisone butyrate	0.1%	Potent	Medium	Y	N	Y	Y	Lipocream; Scalp lotion; Lotion	Solution
Hydrocortisone valerate	0.2%	NA	Medium	NA	Y	NA	Y	NA	N
Methylprednisolone acetate	0.25%	NA	NS	NA	N	NA	Y	NA	N
Methylprednisolone acetate	1%	NA	NS	NA	N	NA	Y	NA	N
Mometasone furoate	0.1%	Potent	Medium	Y	Y	Y	Y	Lotion	Scalp Lotion
Prednicarbate	0.1%	NA	NS	NA	Y	NA	N	NA	N
Triamcinolone acetonide	0.025%	NA	Medium	NA	Y	NA	Y	NA	Lotion
Triamcinolone acetonide	0.1%	Potent	Medium	Y	Y	Y	Y	N	Lotion
Triamcinolone acetonide	0.5%	NA	High	NA	Y	NA	Y	NA	N

Table B: Description of placebo controlled trials

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Design	Enrolment*	Reported Outcome measures
Agrup et al, 1981	Budesonide ointment 0.025% BD Placebo (vehicle)	Psoriasis vulgaris; stable symmetrical lesions of the same morphology; adult	Pregnancy; receiving steroid preparations	Double blind Within patient Patient delivery	N: 11 TD: 3 wks LF: 0 (0%) BC: Not reported	Investigator's preference Patient's preference
Baadsgaard et al, 1995	Tacalcitol ointment, (7 concentrations – 0.25-16 µg/g) OD Placebo (vehicle) Untreated area	Psoriasis vulgaris; TSS ≥5 on 9-pt scale.	Acute guttate psoriasis; pregnancy; lactation; recent systemic treatment; poor response to steroids	Double blind Within patient Nurse delivery	N: 58 TD: 3.3 wks LF: 8 (13.8%) BC: Yes	Signs [erythema; infiltration; scaling] Total Sign Score Degree of Healing
Bernhard et al, 1991	Halobetasol 0.05% ointment, BD Placebo (Vehicle)	Bilateral, comparable psoriasis of at least moderate severity; adult; at least 2 signs or symptoms ≥2 on a 4-pt scale.	None reported	Double blind Within patient Delivery unclear	N: 100 TD: 2 wks LF: 4 (4%) BC: Inadequately reported	Signs [erythema; plaque elevation; scaling; overall lesion severity] Patient global assessment
Bernhard et al, 1991	Halobetasol 0.05% ointment, BD Placebo (Vehicle)	Plaque psoriasis of at least moderate severity; adult; signs ≥4 on a 7-pt scale. BSA 1-20%	None reported	Double blind Parallel group Delivery unclear	N: 72 TD: 2 wks LF: 0 (0%) BC: Inadequately reported	Signs: [erythema; induration; scaling] Investigator global assessment
Buckley, 1978	Dithranol 0.1% in a carbamide (17% urea) base (Psoradrate), BD Placebo (Vehicle)	Active chronic psoriasis; lesions approximately symmetrically distributed.	None reported	Double blind Within patient Patient delivery	N: 10 TD: 3 wks LF: 2 (20%) BC: Not reported	Jacoby assessment score (0-7 score transformed to % clinical improvement) Photographic evaluation Overall patient assessment
Callen, 1996	Fluticasone propionate 0.05%, BD Vehicle, BD	Moderate-to-severe psoriasis	Patients with a history of alcoholism, drug abuse, psychosis, poor motivation, emotional problems; antagonistic personality	Double blind Parallel group Patient delivery	N: Unclear TD: 4 wks LF: Not reported BC: Not reported	Investigator global assessment Patient assessment of effectiveness Severity [erythema; induration; scaling; pruritus]

* **Enrolment definitions**

N: Number of patients randomised
TD: Treatment duration and length of follow up (FU) if the study continued beyond cessation of treatment; FU includes the treatment period
LF: Loss to follow up, defined as patients randomised, not contributing to primary outcome measure
BC: Baseline comparability

Table B: Description of placebo controlled trials (continued)

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Design	Enrolment*	Reported Outcome measures
Dubertret et al, 1992	Calcipotriol ointment 50 µg/gm BD Placebo (vehicle)	Bilateral stable symmetric psoriasis vulgaris of the arms, limbs or trunk; adult	Guttate or pustular psoriasis; psoriasis restricted to the scalp, face, elbows or knees; recent systemic or UV therapy in the previous; calcium, vitamin D daily or other medications; hepatic or renal impairment;planned exposure to sun.	Double blind Within patient Patient delivery	N: 66 TD: 4 wks ; FU: 8 wks LF: 6 (9%) BC: Yes	Severity [erythema, infiltration, desquamation] Modified PASI Preferred treatment Patient and Investigator global assessments
Elie et al, 1983	Betamethasone-17,21-dipropionate, 0.05% BD Salicylic acid 2%BD Betamethasone-17,21-dipropionate, 0.05% + Salicylic acid 2% BD Placebo (vehicle)	Moderate to severe psoriasis, seborrhoeic dermatitis or neurodermatitis of the scalp; adult.	None reported	Double blind Parallel group Patient delivery	N: 40 (55% psoriasis) TD: 3 wks LF: Not reported BC: Inadequately reported	Investigator global assessment Severity [redness; scaling; pruritus] Area of lesion (cm^2)
Ellis et al, 1988	Amcinonide lotion 0.1% OD Placebo (vehicle)	Psoriasis of the scalp; adult; total sign score ≥ 6 on 12 point scale; patients were required to have psoriatic lesions elsewhere.	Acute systemic illness; active skin infection; concomitant antihistamine, topical or systemic corticosteroid, antimetabolites, PUVA, or other dermatologic treatment; recalcitrant psoriasis; intolerance or hypersensitivity to topical corticosteroids; pregnant or lactating.	Double blind Parallel group Patient delivery	N: 165 TD: 3 wks LF: 33 (20%) BC: Yes	Severity: [erythema; excoriation; scaling; induration, pruritus] Total sign score [erythema; scaling; induration, pruritus] Investigators' Overall Evaluation Patient's Overall Evaluation Patient Acceptability Evaluation.
Grattan et al, 1997	Dithranol in aqueous gel, (dose titration 0.1-2.0%), BD. Placebo (vehicle)	Bilateral stable chronic plaque psoriasis; adult; hospitalised for routine dithranol treatment.	Intolerance of dithranol; unstable or pustular psoriasis; calcium metabolism disorders; systemic psoriasis treatment; recent UVB or PUVA therapy; pregnancy or lactation.	Open Within patient Delivery unclear	N: 12 TD: 4 wks: FU: 16 wks LF: 0 (0%) BC: Yes	Severity: [erythema; scaling; palpability] Total severity score Patient assessment of irritation (VAS) Investigator assessment of skin staining

Table B: Description of placebo controlled trials (continued)

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Design	Enrolment*	Reported Outcome measures
Green et al, 1994	Calcipotriol solution, 50µg/ml, BD. Placebo (vehicle)	Mild to moderate scalp psoriasis and a history of psoriasis elsewhere on the body; adult.	Excessively thick scalp psoriasis. Other scalp disease; marked deterioration of scalp psoriasis at entry; recent systemic or UV therapy; concurrent topical corticosteroid use; vitamin D or calcium supplement; medications which could affect the course of the disease; hypercalaemia; hepatic or renal disease; Susceptible to pregnancy.	Double blind Parallel group Patient delivery	N: 49 TD: 3 wks LF: 3 (6%) BC: Inadequately reported	Signs: [erythema; thickness; scaliness; flaking; itching] Total Sign Score [redness, thickness, scaliness] Investigator and patient global assessments
Greenspan et al, 1993	Desonide lotion, 0.05% TID Desonide cream, 0.05% TID Placebo (vehicle lotion)	Mild to moderate psoriasis	Recent systemic or topical treatment for psoriasis; contraindiaction to low-potency corticosteroids; pregnant, nursing or planning pregnancy.	Double blind Parallel group Patient delivery	N: 80 TD: 4 wks LF: 9 (11%) BC: Inadequately reported	Severity: [erythema; scaling; induration; pruritus] Investigator global assessment
Harrington et al, 1996	Calcipotriol cream, 50 µg/g as: Cream A (dissolved), Cream B (suspended) Placebo (Vehicle of A)	Stable psoriasis vulgaris on trunk or limbs; adult.	Recent systemic medication or phototherapy for psoriasis; hepatic or renal disease; raised serum calcium; calcium supplements or vitamin D.	Double blind Parallel group Patient delivery	N: 413 TD: 8 wks LF: 47 (11.4%) BC: Yes, except age p=0.02	PASI Investigator and patient global assessments
Highton et al, 1995	Calcipotriene ointment 0.005%, BD. Placebo (vehicle)	Moderately severe stable plaque psoriasis; plaque elevation score ≥ 4 (0-8); Not pregnant or nursing during the duration of the study.	Recent topical or systemaic psoriasis treatment, prolonged exposure to sunlight, phototherapy; photochemotherapy; hypercalcemia; erythrodermic or pustular psoriasis. Calcium, vitamin A or D supplements	Double blind Parallel group Patient delivery	N: 277 TD: 8 wks LF: 30 (10.8%) BC: Psoriasis comparable, demographics inadequately reported.	Severity: [erythema; plaque elevation; scaling; overall disease severity] Investigator global assessment
Jansen et al, 1986	Lonapalene 0.5% ointment, TDS Fluocinolone acetonide, 0.025% ointment, TDS Vehicle, TDS No treatment	Symmetrical psoriasis	None reported	Double blind Parallel group Delivery unclear	N: 60 TD: 6 wks LF: Not reported BC: Not reported	Unclear

Table B: Description of placebo controlled trials (continued)

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Design	Enrolment*	Reported Outcome measures
Jekler et al, 1992	Dithranol 2% ointment one minute therapy, OD Placebo (vehicle)	Chronic plaque-type psoriasis vulgaris with bilateral lesions of equal clinical severity; adult.	Topical or systemic corticosteroids; recent phototherapy.	Double blind Within patient Patient delivery	N: 30 TD: 8 wks LF: 3 (10%) BC: Not reported	Severity: [pruritus; erythema; scaling; infiltration; overall result] Degree of clearing Investigator and patient global assessments
Jorizzo et al, 1997	Clobetasol propionate emollient 0.05% BD Placebo (vehicle)	Moderate to severe plaque type psoriasis. Men or nonpregnant, nonlactating women ≥ 12 years in age; baseline morning serum cortisol concentration of 5 to 18 µg/100mL.	Recent topical anti-psoriatic medication or other drug that could alter psoriatic status.	Double blind Parallel group Patient delivery	N: 89 TD: 4 wks; FU: 6 wks LF: Unclear BC: Yes	Severity [erythema; skin thickening; scaling; pruritus] Total Severity Score Patient evaluation Investigator global assessment
Kang et al, 1998	Calcipotriene ointment 0.005%, BD Placebo (vehicle)	Mild to moderate stable plaque-type psoriasis; adult.	Recent systemic therapy, UV or topical therapy for psoriasis (excluding emollient). Pregnant or breast-feeding women.	Double blind Parallel group Patient delivery	N: 30 TD: 6 wks LF: 0 (0%) BC: Psoriasis comparable, demographics inadequately reported.	Signs: [erythema; thickness; scaling] Investigator global assessment
Kanzler et al, 1993	Tar (liquor carbonis detergens) 5%, BD Placebo (vehicle)	Bilaterally similar chronic stable plaque psoriasis vulgaris.	Recent topical or systemic therapy.	Double blind Within patient Patient delivery	N: 18 TD: 4 wks LF: 0 (0%) BC: Not reported	Severity: [erythema; induration; scaling; pruritus] Total severity score Investigator global assessment
Katz et al, 1987	Betamethasone dipropionate, intermittent maintenance (3 doses at 12 hour intervals each weekend). Placebo (vehicle)	Plaques psoriasis in remission (>85% resolution) after 2/3 weeks treatment with Betamethasone dipropionate Note: 38/59 (64%) achieved remission during the acute phase	Not achieving remission during acute phase treatment.	Double blind Parallel group Patient delivery	N: 38 TD: 12 wks LF: 0 (0%) BC: Yes	Signs: [erythema; induration; scaling] Area adjusted clinical score Relapse (adjusted clinical score >35% of baseline score)

Table B: Description of placebo controlled trials (continued)

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Design	Enrolment*	Reported Outcome measures
Katz et al, 1991a	Betamethasone dipropionate, intermittent maintenance (3 doses at 12 hour intervals once a week). Placebo (vehicle)	Plaques psoriasis in remission after 3/4 weeks treatment with Betamethasone dipropionate (erythema score ≤1; induration ≤0.5; scaling =0) Note: 94/123 (76%) achieved remission during acute phase	Recent topical or systemic treatment; pregnant; nursing; intent to conceive; not achieving remission during acute phase treatment.	Double blind Parallel group Patient delivery	N: 94 TD: 24 wks LF: 4 (4.3%) BC: Yes	Signs: [erythema; Induration; Scaling] Area adjusted clinical score Treatment failure (Adjusted clinical score ≥ 2.5, or overall disease status moderate or severe). Overall disease status Patient's evaluation of effectiveness. Time to relapse
Katz et al, 1991b	Halobetasol propionate cream, 0.05% BD Placebo (vehicle)	Comparable bilateral lesions of moderate or greater severity of plaque psoriasis; adult; at least 2 signs or symptoms of at least moderate severity; lesions at least 10cm^2.	Pustular or erythodermic psoriasis; recent topical or systemic medication; women susceptible to pregnancy.	Double blind Within patient Patient delivery	N: 110 TD: 2 wks LF: 2 (1.8%) BC: Inadequately reported	Severity: (0-3) [erythema; plaque elevation; scaling pruritus] Total severity score (0-12) Patient global assessments of effectiveness and overall rating
Kiss et al, 1996	Calcipotriene solution 0.005% BD Placebo (vehicle)	Moderate scalp psoriasis; adult; overall disease severity ≥4	None reported	Double blind Parallel group Patient delivery	N: 235 TD: 8 wks LF: 31 (13.2%) BC: Not reported	Severity: [Scaling; erythema; plaque elevation; pruritus] Overall severity Investigator's global assessment
Kiss et al, 1996; Carder et al, 1996	Calcipotriene solution 0.0025% and 0.005% BD Placebo (vehicle)	Moderate scalp psoriasis; adult; overall disease severity ≥4	None reported	Double blind Parallel group Patient delivery	N: 239 TD: 8 wks LF: 29 (12.1%) BC: Not reported	Severity: [Scaling; erythema; plaque elevation; pruritus] Overall severity Investigator's global assessment
Kragballe et al, 1988	Calcipotriol cream, 10 µg/g, 33 µg/g or 100 µg/g, BD Placebo (vehicle)	Stable symmetrically distributed moderate; chronic plaque-type psoriasis; outpatients; adult. Women above child bearing age or using adequate contraception.	Recent topical, systemic, intralesional or UV radiation therapy (excluding bland emollients); non-normal serum levels of calcium and creatinine; taking calcium tablets.	Double blind Within patient Patient delivery	N: 30 TD: 6 wks LF: 3 (10%) BC: Yes	Severity: [erythema; thickness; scaling] Investigator and patient global assessments
Krueger et al, 1998	Tazarotene gel 0.01% or 0.05% BD Placebo (vehicle)	Mild to moderate bilateral psoriatic plaques; adult; total severity score ≤6.	Pregnant; nursing or of likely to conceive; recent use of certain topical agents; recent systemic retinoids, UV phototherapy or systemic anti psoriasis drugs.	Double blind Within patient Patient delivery	N: 45 TD: 6 wks LF: 0 (0%) BC: Not reported	Severity: [erythema; plaque elevation; scaling] Investigator global assessment

Table B: Description of placebo controlled trials (continued)

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Design	Enrolment*	Reported Outcome measures
Lane et al, 1983	Betamethasone dipropionate ointment, 0.05% OD Diflorasone diacetate ointment, 0.05% OD Placebo (vehicle)	History and physical finding compatible with psoriasis including scaling erythema, epidermal thickening and/or crusting; all ages >1 year; stable disease.	Recent topical or systemic corticosteroid treatment; oral antihistamine; antipruritic therapy, UV or X-ray therapy or any medication affecting the study; pregnant.	Double blind Parallel group Patient delivery	N: 157 TD: 3 wks LF: 18 (11%) BC: Yes	Severity: [Scaling; erythema; pruritus; thickening; crusting; overall condition] Total severity score
Langner et al, 1993	Calcitriol ointment 15 µg/g BD Placebo (vehicle)	Bilateral; symmetrical; severe chronic plaque psoriasis; outpatients.	Pregnancy or inadequate contraception. Use of calcium; vitamin D or analogues; calcium-containing antacids; digitalis; thiazide diuretics or glucocorticosteroids.	Double blind Within patient Patient delivery	N: 32 TD: 6 wks LF: 2 (3%) BC: Yes	Severity: [erythema; scaling; induration; pruritus} Investigator global assessment
Langner et al, 1992	Calcitriol ointment, 3 mcg/g BD Placebo (vehicle)	Severe chronic psoriasis; symmetrical lesions; adult; outpatients	Pregnancy or inadequate contraception.	Double blind Within patient Patient delivery	N: 29 TD: 6 wks LF: 0 (0%) BC: Yes	Severity: [erythema; pustules, desquamation, ncrustation, vesiculation and pruritus] Investigator global assessment
Lepaw 1978	Halcinonide solution 0.1%, TID Placebo (vehicle)	Bilaterally similar psoriatic lesions of the scalp; adults or adolescents.	Systemic therapy, topical scalp treatments	Double blind Within patient Patient delivery	N: 29 TD: 2 wks LF: 2 (6.9%) BC: Inadequately reported	Overall therapeutic response Overall comparative response
Medansky et al, 1987	Mometasone furoate ointment, 0.1% OD Vehicle OD	Aged ≥ 12; psoriasis vulgaris stable or worsening; duration ≥ 1 year; Total Sign Score ≥ 6	Concomitant medication; recent systemic corticosteroids or antimetabolites; recent topical corticosteroids; pregnancy; lactation	Double blind Parallel group Patient delivery	N: 121 TD: 3 wks LF: 6 (5.0%) BC: Yes, except duration of disease (p=0.04).	Signs: erythema; induration; scaling Total sign score Investigator global assessment
Mortensen et al, 1993	Calcipotriol ointment 50µg/g BD Placebo (vehicle)	Stable plaque-type psoriasis vulgaris; adult outpatients; normal hepatic and renal function.	Recent UV or other psoriasis treatments; disease or medication influencing calcium or bone metabolism.	Double blind Parallel group Patient delivery	N: 34 TD: 3 wks LF: 0 (0%) BC: Psoriasis comparable, demographics inadequately reported.	PASI Investigator and patient global assessments
Olsen, 1991	Clobetasol propionate 0.05% BD Placebo (vehicle)	Moderate to severe scalp psoriasis (sign score ≥6/9); stable or worsening; adult.	Recent systemic, topical or UV treatment for psoriasis.	Double blind Parallel group Patient delivery	N: 378 TD: 2 wks; FU: 3 wks LF: 1 (0.3%) BC: Yes	Severity: [erythema; induration; scaling, pruritus] Investigator and patient global assessments

Table B: Description of placebo controlled trials (continued)

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Design	Enrolment*	Reported Outcome measures
Olsen, 1996 (two trials)	Fluticasone propionate 0.005% ointment Placebo (vehicle)	Moderate-to-severe psoriasis; adolescent or adult	None reported	Double blind Parallel group Patient delivery	[1] N: 181; [2] 207 TD: 4 wks [1] LF:3 (2%) [2] 2 (1%) BC: Partial, clinical comparability reported	Investigator global assessment Severity: [erythema; induration; scaling; pruritus] Patient's subjective assessment
Oranje et al, 1997	Calcipotriol ointment, 50 µg/g BD Placebo (vehicle)	Mild to moderate psoriasis vulgaris; children aged 2-14.	Acute guttate; pustular, erythrodermic or worsening psoriasis; psoriasis mainly on the face; scalp or diaper area; systemic treatment; recent phototherapy; concurrent Vitamin D, calcium or other intercurrent medication; renal; hepatic or osteoarthritic disease.	Double blind Parallel group Patient delivery	N: 77 TD: 8 wks LF:0 (0%) BC: Yes	PASI: Severity: [redness; thickness; scaliness, area] Extent of disease Investigator and patient global assessments
Ormerod et al, 1997	Betamethasone Valerate ointment, 0.1% BD White soft paraffin, BD	Bilaterally similar chronic; stable plaque psoriasis.	Recent systemic or UV therapy.	Double blind Within patient Patient delivery	N: 12 TD: 2 wks LF: Unclear BC: Inadequately reported	Signs: [erythema; elevation; scaling] Total sign score
Pariser et al, 1996	Calcipotriene ointment, 0.005% OD Placebo (vehicle)	Stable plaque-type psoriasis; otherwise healthy, non-pregnant patients; at least 4/9 for plaque elevation. BSA 5-20%	None reported	Double blind Parallel group Patient delivery	N: 235 TD: 8 wks LF: Unclear BC: Psoriasis comparable, demographics not reported.	Severity: [scaling; erythema; plaque elevation] Investigator global assessment
Perez et al, 1996	Calcitriol, 1.5µg/g OD Placebo (vehicle)	Stable plaque or erythrodermic psoriasis; not response to previous treatment; adult; BSA ≥10%	Pregnant, nursing or inadequate contraception; hepatic or renal impairment; recent systemic therapy or phototherapy or topical medications (excluding emollients)	Double blind Within patient Patient delivery	N: 84 TD: 10 weeks: FU: 12 months LF: 0 (0%) BC: Yes	PASI Severity [erythema; plaque thickness; scaling] Total severity score Investigator global assessment
Scarpa et al, 1997	Tacalcitol ointment, 4 mcg/g, OD Vehicle, OD	Stable psoriasis vulgaris; symmetrical lesions; in- and outpatients	Pregnancy; lactation; inadequate contraception; recent systemic, light or topical therapy; severe renal failure; liver and cardiac dysfunction; hypercalcemia; hyper phosphoremia; AIDS; drug addiction	Double blind Within patient Patient delivery	N: 157 TD: 6 wks LF: 23 (14.6%) BC: Yes	Signs: Scaling; erythema; scaling

Table B: Description of placebo controlled trials (continued)

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Design	Enrolment*	Reported Outcome measures
Sears et al 1997	Hydrocortisone buteprate 0.1% cream, BD Placebo (vehicle)	Mild or moderate psoriasis not spontaneously remitting; adults; total sign score 3-8	Acute systemic illness; hypothamic-pituitary-adrenal system disorder, severe hepatic or renal disorder; psoriatic infection; lactation, pregnancy or inadequate contraception; recent use of any corticosteroid, long-acting antihistamines, retinoids; drugs exacerbating or influencing psoriasis; antimetabolic therapy; PUVA; ACE inhibitor; intolerant of topical corticosteroids or study medication.	Double blind Parallel group Patient delivery	N: 190 TD: 3 wks LF: 21 (11%) BC: Yes, except gender, p=0.021	Signs: [erythema; skin thickening; scaling] Total sign score Pruritus Investigator and patient evaluations of efficacy Investigator global assessment
Sefton et al 1984	Hydrocortisone valerate 0.2% ointment BD Placebo (vehicle)	Bilaterally symmetrical mild to moderate, stable, chronic plaque psoriasis; adult.	Acute flare; rebound from cessation of previous therapy; "atypical" psoriasis; disease limited to hands and feet; recent use of topical or parenteral steroids, oral or topical therapy with phototherapy; sensitivity to study medication; secondary infection; pregnancy	Double blind Within patient Patient delivery	N: 58 TD: 3 wks LF: 6 (10%) BC: Inadequately reported	Investigator global assessment
Seidenari et al 1997	Tacalcitol ointment 4 µg/g OD Placebo (vehicle)	Symmetrical, stable psoriatic plaques;adult; in- or out- patients.	Recent topical steroids, UV light, systemic or PUVA therapy. Inadequate contraception.	Double blind Within patient Patient delivery	N: 12 TD: 6 wks; FU: 8 wks LF: 1 (8%) BC: Yes	Signs: [erythema; thickening; scaling] Total sign score
Staberg et al, 1989	Calcipotriol cream, 1200 µg/g BD Placebo cream	Symmetrical chronic plaque psoriasis; inpatients; adult	None reported	Double blind Within patient Patient delivery	N: 10 TD: 6 wks LF: 1 (10%) BC: Yes	Signs: [infiltration; erythema;scaling] Total sign score
Sudilovsky et al, 1981	Halcinonide cream 0.1% OD + vehicle cream BD Placebo (vehicle) TD	Bilateral lesions of similar severity and chronicity	Recent corticosteroid medication; history of poor response to corticosteroids; concomitant local or systemic therapy that could affect psoriasis.	Double blind Within patient Patient delivery	N: 78 (57% psoriasis) TD: 3 wks LF: 0 BC: Inadequately reported	Comparative therapeutic response Absolute therapeutic response Investigator global assessment
Syed et al, 1996	Aloe vera extract 0.5% hydrophilic cream, TDS Placebo cream, TDS (Treatments given 5 days a week)	Mild-to-moderate chronic plaque-type psoriasis vulgaris; water washable emollients permitted	Pregnancy; lactation; cytotoxic drugs; beta-blockers; recent systemic medication, UV therapy; epilepsy	Double blind Parallel group Patient delivery	N: 60 TD: 4 wks LF: 0 (0%) BC: Yes	PASI Cure rate Significant clearing

Table B: Description of placebo controlled trials (continued)

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Design	Enrolment*	Reported Outcome measures
Van de Kerkhof 1989	Calcitriol solution 2 µg/ml, BD Placebo (vehicle)	Patients with symmetrical chronic stable plaque psoriasis	Recent topical therapy	Double blind Within patient Patient delivery	N: 10 TD: 4 wks LF: 0 (0%) BC:	Severity [erythema; thickness; scaling]
Van de Kerkhof et al, 1996a	Tacalcitol 4 µg/g OD Placebo (vehicle)	Stable plaque psoriasis; not localised on the scalp; Score ≥ 2 for erythema and desquamation and Score sum >5); Caucasian adults and adolescents	Increased serum calcium or serum phosphate level; recent systemic or topical antipsoriatic treatment; serious disease; known allergy to study medication; recent participation in another clinical trial; expected poor compliance; calcium supplements; drugs influencing calcium metabolism; corticosteroids; barbiturates; phenytoin; NSAIDs; pregnancy	Double blind Within patient Patient delivery	N: 122 TD: 8 wks; FU: 12 wks LF: 19 (16%) BC: Inadequately reported	Signs [erythema; infiltration; desquamation] Total sign score Severity Preference assessment Area of test lesions Investigator and patient global assessments Assessment of benefit Post-treatment relapse
Van de Kerkhof et al, 1996b	Hydrocortisone17-butyrate 0.1% emulsion BD Placebo (vehicle)	Psoriasis vulgaris	None reported	Double blind Within patient Patient delivery	N: 20 TD: 4 wks LF: Not reported BC: Not reported	Severity [erythema; induration; scaling; pruritus; lichenification; overall severity]
VanderPloeg, 1976	Betamethasone dipropionate ointment, 0.05%, BD Vehicle, BD	Psoriasis or atopic dermatitis	Recent systemic or topical steroids; concomitant medications	Double blind Parallel group Patient delivery	N: 72 (50% psoriasis) TD: 3 wks LF: 3 of 36 (8.3%) BC: Yes	Signs: Scale; erythema; pruritus; thickness; crusting Total sign score Investigator global assessment
Volden et al, 1992	Dithranol 1% in petrolatum Placebo (vehicle)	Symmetrical plaque-type psoriasis; adult outpatients	Recent active treatment for psoriasis	Double blind Within patient Patient delivery	N: 10 TD: 4 wks LF: 1 (10%) BC: Yes	Signs: [erythema; infiltration; scaling] Total sign score
Weinstein et al, 1997 Weinstein 1996	Tazarotene gel, 0.1% Tazarotene gel, 0.05% Placebo (vehicle)	Stable plaque psoriasis; BSA≤20%; 2 target lesions with plaque elevation ≥2 and ≥2cm in diameter; 1 on elbow/knee and 1 on trunk/limbs.	Pustular or exfoliative psoriasis; sensitivity to study medication; other confounding skin conditions; recent use of tar shampoos; topical/ systemic/light therapies; topical corticosteroids/UVB; PUVA/systemic therapy; oral retinoids; uncontrolled systemic disease; pregnant; lactating; inadequate contraception	Double blind Parallel group Patient delivery	N: 324 TD: 12 wks; FU: 24 wks LF: 6 (1.9%) BC: Yes	Signs: [plaque elevation; scaling; erythema] Total Sign Score % clearance Patient assessment of cosmetic acceptability

Table B: Description of placebo controlled trials (continued)

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Design	Enrolment*	Reported Outcome measures
Wortzel, 1975 (2 trials)	Betamethasone dipropionate ointment 0.05, BD Placebo, BD	Moderately severe to very severe psoriasis and atopic dermatitis [1] Outpatients [2] Inpatients	Not reported	Double blind Parallel group Delivery unclear	[1] N: 130 (58% psoriasis) [2] N: 15 (60% psoriasis) TD: 3 wks [1] LF: 0 (0%), [2] LF:0 (0%) BC: Not reported	Investigator global assessment

Synonyms:

Thickness=elevation =induration? (hardness, callous), Erythema =redness

Scaling; erythema; pruritus; thickening of epidermis; crusting

Table C: Summary findings from placebo controlled trials

Trial	Comparisons	Reported Outcome measures	Withdrawal and Adverse Events*
Agrup et al, 1981	Budesonide ointment (B) 0.025% BD Placebo (P)	At 3 weeks: No useful outcomes recorded	TW: B: 0/11; P: 0/11 WA: B: 0/11; P: 0/11 WF: B: 0/11; P: 0/11 AE: NR
Baadsgaard et al, 1995	Tacalcitol ointment (T) 4 µg/g OD. Placebo (P)	At 24 days: Total Sign Score: (0-9) T: 4.4 (1.8SD); P: 6.0 (1.8SD); N=50	TW: T: 1/58; P: 1/58 WA: T: 0/58; P: 0/58 WF: T: 0/58; P: 0/58 AE: T(L): 0/58; P(L): 3/58; (S): NR
Bernhard et al, 1991	Halobetasol (H) 0.05% ointment, BD Placebo (P)	At 2 weeks: No adequate data reported or available from author or sponsor	TW: NR WA: H: 0/100; P: 0/100 WF: H: 0/100; P: 0/100 AE: H: 0/100; P: 0/100
Bernhard et al, 1991	Halobetasol (H) 0.05% ointment, BD Placebo (P)	At 2 weeks: Investigator global assessment (5-pt: 0=worse, 4=clear) H: 2.97 (0.97SD, N=36); P:1.30 (0.85SD, N=33)	TW: H: 0/72; P: 0/72 WA: H: 0/72; P: 0/72 WF: H: 0/72; P: 0/72 AE: NR
Buckley, 1978	Dithranol (D) 0.1% in a carbamide (17% urea) base, BD Placebo (P)	At 3 weeks: Jacoby assessment score, % improvement D: 53.75% (29.08%SD); P: 26.44% (13.78%SD); N=8	TW: D: 2/10; P: 2/10 WA: NR WF: NR AE: D(L): 5/7; P(L): 2/7; (S): NR
Callen, 1996	Fluticasone propionate cream 0.05%, BD Placebo (P)	At 4 weeks: Investigator global assessment (6- pt) Total severity score (0-12): No adequate data reported or available from author or sponsor	TW: NR WA: NR WF: NR AE: NR
Dubertret et al, 1992	Calcipotriol ointment (C) 50 µg/gm BD Placebo (P)	At 4 weeks: PASI: C: 6.30 (6.45SD); P: 9.16 (8.34SD); N=65 PASI, % reduction: C: -58.6% (31.7%SD); P: -35.4% (37.2%SD); N=63 PASI, adjusted for baseline: C: -7.75 (6.2SD): P: -4.82 (5.7SD); N=63 Total severity score: C: 3.15; P: 4.68; N=61 Investigator global assessment: (5pt: 4=cleared, 0=worse) C: 2.66 (0.87SD); P: 1.84 (0.75SD), N=62	TW: C: 4/66; P: 4/66 WA: C(L): 2/66; P(L): 1/66 WF: NR AE: C(L): 14/66; P(L): 16/66; C(S): 0/66; P(S): 0/66
Elie et al, 1983	Betamethasone (B) -17,21-dipropionate, 0.05% Salicylic acid 2% (S) Betamethasone (BS) -17,21-dipropionate, 0.05% + Salicylic acid 2% Placebo (P)	At 3 weeks: Total Severity Score: (0-12) B: 2.18 (N=10); S: 2.18 (N=10); BS: 1.15 (N=10); P: 3.87 (N=10) Investigator global assessment: (5-pt rescaled as 0=very severe, 4=clear) B: 1.80 (N=10); S: 1.80 (N=10); BS: 2.55 (N=10); P: 0.80 (N=10)	TW: NR WA: B(L): 0/10; S(L): 0/10; BS(L): 0/10; P(L): 0/10 WF: NR AE: B(L): 0/10; S(L): 0/10; BS(L): 0/10; P(L): 0/10; (S): NR

* **Withdrawal and adverse event definitions**

TW: Total withdrawal
WA: Withdrawal reported due to adverse events (deterioration of symptoms, treatment failure or inadequate treatment response)
WF: Withdrawal due to treatment failure
AE: Number of patients with reported adverse events: (L) local and (S) systemic side effects if reported separately; exacerbation of symptoms; excluding discoloration of skin or clothing
NR (not reported) indicates that patient data for each treatment group was incomplete or unreported

Table C: Summary findings from placebo controlled trials (continued)

Trial	Comparisons	Reported Outcome measures	Withdrawal and Adverse Events*
Ellis et al, 1988	Amcinonide lotion (A) 0.1% OD Placebo (P)	At 3 weeks: Investigator global assessment: (7-pt: re-scaled as 0=worse; 6=clear) A:4.60 (1.29SD, N=65); P: 2.8 (1.31SD, N=67) Total Severity Score (0-12) adjusted for baseline: A: -6.31 (N=59); P: -2.7 (N=67)	TW: A: 13/83; P: 13/82 WA: A: 1/83; P: 0/82 WF: A: 0/83; P: 1/82 AE: NR
Grattan et al, 1997	Dithranol (D) in aqueous gel, (dose titration 0.1-2.0%), BD. Placebo (P)	At 4 weeks: Total severity score (0-9) D: 1.2 (1.77SD); P: 4.1 (1.59SD); N=11	TW: D: 0/12; P: 0/12 WA: D: 0/12; P: 0/12 WF: D: 0/12; P: 0/12 AE: NR
Green et al, 1994	Calcipotriol solution (C) 50µg/ml, BD. Placebo (P)	At 4 weeks: Total sign score (0-12) C: 3.6 (2.7SD, N=25); P: 5.3 (2.5SD, N=24) Investigator global assessment (5-pt re-scaled as worse = 0, cleared = 4) C: 2.52 (1.08SD, N=25); P: 1.25 (1.22SD, N=24)	TW: C: 1/25; P: 2/24 WA: C(L): 1/25; P: 0/24 WF: C: 0/25; P: 2/24 AE: C(L): 5/25; P(L): 7/24 (S): NR
Greenspan et al, 1993	Desonide lotion (DL) 0.05% TID Desonide cream (DC) 0.05% TID Placebo (P)	At 3 weeks: Overall Severity (10-pt)): DL: 3.07 (1.048SD, N=27); DC: 3.07 (0.868SD, N=29); P: 4.11 (0.65SD, N=20) Investigator global assessment (5-pt, re-scaled as worse = 0, cleared = 4) DL: 2.8 (N=27); DC: 2.8 (N=29); P: 2.0 (N=20)	TW: DL: 2/30; DC: 2/30; P: 5/20 WA: DL: 0/30; DC: 0/30; P: 2/20 WF: DL: 0/30; DC: 0/30; P: 0/20 AE: DL(L): 1/30; DC(L): 2/30; P(L): 1/20; (S): NR
Harrington et al, 1996	Calcipotriol cream, 50 µg/g as: Cream A (dissolved) (CA), Cream B (suspended) (CB), Placebo (P) of A	At 8 weeks: PASI, adjusted for baseline: CA: -4.4 (5.6SD; N=149); CB: -4.2 (4.6SD; N=147); P: -0.8 (5.4SD; N=70) Investigator's global assessment (4-pt: 0=worse, 3=clinical success): CA: 2.08 (0.76SD, N=148); CB: 2.04 (0.84SD, N=142); P: 1.37 (0.91SD, N=71)	TW: CA: 16/165; CB: 14/161; P: 17/87 WA: CA(L): 6/165; CB(L): 2/161; P(L): 4/87 WF: CA(L): 5/165; CB(L): 4/161; P(L): 11/87 AE: CA(L): 44/165 ; CB(L): 37/161; P(L): 20/87; CA(S): 0/165 ; CB(S): 0/161; P(S): 0/87
Highton et al, 1995	Calcipotriene ointment (C) 0.005% BD. Placebo (P)	At 8 weeks: Overall severity score (0-8): C: 1.70 (N=124); P: 3.15 (N=123) (N approximated) Investigator's global assessment (7-pt) No adequate data reported or available from author or sponsor	TW: C: NR; P: NR WA: C: 6/139; P: 8/138 WF: C: NR; P: NR AE: C(L): 28/139; P(L): 21/138; (S): NR
Jansen et al, 1986	Lonapalene, TDS Fluocinolone acetonide, TDS Vehicle, TDS No treatment	At 6 weeks: No useful data reported	TW: NR WA: NR WF: NR AE: (L): NR L(S): 0%; F(S): 0%; P(S): 0%
Jekler et al, 1992	Dithranol 2% ointment (D) one minute therapy, OD Placebo (P)	At 8 weeks: Severity: (0-3: mean score) D: 0.99 (0.47SD); P: 1.30 (0.42SD); N=27 Investigator's global assessment: (5-pt) No adequate data reported or available from author or sponsor	TW: D: 3/30; P: 3/30 WA: D: 0/30; P: 0/30 WF: NR AE: D(L): 0/30; P(L): 0/30; (S): NR

Table C: Summary findings from placebo controlled trials (continued)

Trial	Comparisons	Reported Outcome measures	Withdrawal and Adverse Events*
Jorizzo et al, 1997	Clobetasol propionate (C) emollient 0.05% BD Placebo (P)	At 4 weeks: Total severity score (0-12), adjusted for baseline: C: -4.3 (N=35); P: -1.6 (N=39) Investigator global assessment (5-pt): No adequate data reported or available from author or sponsor	TW: C: 6/44; P: 15/45 WA: C(L): 1/44; P(L): 1/45 WF: C: 1/44; P: 6/45 AE: C(L): 5/44; P(L): 5/45; C(S): NR; P(S): 3/45
Kang et al, 1998	Calcipotriene ointment (C) 0.005%, BD Placebo (P)	At 6 weeks: Investigator global assessment (7-pt: rescaled as 0=worse, 6=clear) C: 3.87 (1.36SD, N=15); P: 1.47 (0.99SD, N=15) Total sign score (0-24): C: 4.53 (N=15); P: 10.8; (N=15)	TW: C: 0/15; P: 0/15 WA: C: 0/15; P: 0/15 WF: NR AE: C(L): 2/15; P(L): 0/15; C(S):0/15; P(S): 0/15
Kanzler et al, 1993	Tar (T) 5%, BD Placebo (P)	At 4 weeks: Total severity score(0-12), adjusted for baseline: T: -3.25 (SD: 2.03); P: -2.36 (SD: 1.86); N=18 Investigator global assessment (mean % improvement) T: 48.72% (28.38%SD); P: 35.33% (26.04%SD); N=18	TW: NR WA: NR WF: NR AE: NR
Katz et al, 1987	Betamethasone dipropionate (B) intermittent maintenance therapy Placebo (P)	At 12 weeks: Total sign score (0-9), baseline area adjusted: B: 0.83 (N=19); P: 2.12 (N=19) Remission: B: 14/19 (74%); P: 4/19 (21%)	TW: B: 6/20; P: 16/20 WA: B: 0/20; P: 0/20 WF: B: 5/20; P: 15/20 AE: B: 0/20; P: 0/20
Katz et al, 1991a	Betamethasone dipropionate 0.05% (B) intermittent maintenance therapy Placebo (P)	At 24 weeks: Total sign score, baseline area adjusted (0-9): No adequate data reported or available from author or sponsor Remission: B: 30/46 (65%); P: 9/44 (20%)	TW: B: 0/48; P: 0/46 WA: B: 0/48; P: 0/46 WF: B: 16/46; P: 35/44 AE: B: 0/48; P: 0/46
Katz et al, 1991b	Halobetasol propionate (H) cream, 0.05% BD Placebo (P)	At 2 weeks: Total severity (0-12) No adequate data reported or available from author or sponsor	TW: NR WA: H: 0/110; P: 0/110 WF: NR AE: H(L): 7/110; P(L): 7/110; H(S): 0/110; P(S): 0/110
Kiss et al, 1996	Calcipotriene (C) solution 0.005% BD Placebo (P)	At 8 weeks: Overall severity Investigator's global assessment No adequate data reported or available from author or sponsor	TW: NR WA: NR WF: NR AE: NR
Kiss et al, 1996; Carder et al, 1996	Calcipotriene (C) solution 0.0025% and 0.005% BD Placebo (P)	At 8 weeks: Overall severity Investigator's global assessment No adequate data reported or available from author or sponsor	TW: C: 3/30; P: 3/30 WA: C: 0/30; P: 0/30 WF: NR AE: C: 0/30; P: 0/30

Table C: Summary findings from placebo controlled trials (continued)

Trial	Comparisons	Reported Outcome measures	Withdrawal and Adverse Events*
Kragballe et al, 1988	Calcipotriol cream (C), 10 µg/g, 33 µg/g or 100 µg/g, BD Placebo (P)	At 6 weeks: Total sign score (0-9): C(10):5.4 (1.7SD); P: 6.8 (1.7SD); N=9 C(33):4.1 (2.2SD); P: 5.7 (1.4SD); N=9 C(100):4.4 (1.7SD); P: 7.7 (0.9SD); N=9 Investigator global assessment: (5-pt: rescaled as 0: worse, 4 clear) C(10): 1.8 (0.7SD); P: 0.9 (0.8SD); N=9 C(33): 2.6 (1.1SD); P: 1.6 (0.5SD); N=9 C(100): 2.8 (0.8SD); P: 1.0 (0.5SD); N=9	TW: NR WA: NR WF: NR AE: NR
Krueger et al, 1998	Tazarotene gel (T) 0.01% or 0.05% BD Placebo (P)	At 6 weeks: Total SeverityScore (0-12) [erythema; plaque elevation; scaling] Investigator's global assessment (6-pt) No adequate data reported or available from author or sponsor	TW: NR WA: NR WF: NR AE: (L): NR; T(S): 0/45; P(S): 0/45
Lane et al, 1983	Betamethasone dipropionate (B) ointment, 0.05% OD Diflorasone diacetate ointment (D), 0.05% OD Placebo (P)	At 3 weeks: Total severity score (0-20) B: 4.5 (N=46); D: 5.7 (N=46); P: 6.6 (N=47)	TW: NR WA: NR WF: NR AE: NR
Langner et al, 1993	Calcitriol ointment (C) 15 mcg/g BD Placebo (P)	At 6 weeks: Investigator global assessment: (6-pt; 0=worse, 5=clear) C: 4.00 (1.33SD); P: 3.28 (1.14SD); N=32	TW: C: 1/32; P: 1/32 WA: C: 1/32; P: 0/32 WF: C: 0/32; P: 1/32 AE: C(L): 2/32; P(L): NR; C(S): 3/32; P(S): NR
Langner et al, 1992	Calcitriol ointment (C) 3 mcg/g BD Placebo (P)	At 6 weeks: Investigator global assessment: (6-pt; 0=worse, 5=clear) C: 4.10 (1.05SD); P: 3.00 (1.04SD); N=29	TW: C: 0/29; P: 0/29 WA: C: 0/29; P: 0/29 WF: AE: C(L): 0/29; P(L): 0/29; C(S): NR; P(S): NR
Lepaw 1978	Halcinonide solution (H) 0.1%, TID Placebo (P)	At 2 weeks: Overall therapeutic response (4-pt, 0=poor 3 excellent) H: 2.30 (0.95 SD); P: 1.30 (0.82 SD); N=27	TW: H: 2/29; P: 2/29 WA: H(L): 0/29; P(L): 0/29 WF: NR AE: H(L): 0/29; P(L): 1/29; (S): NR
Medansky et al, 1987	Mometasone furoate ointment (M), 0.1% OD Vehicle (P) OD	At 3 weeks: Total sign score (0-9): M: 2.7 (N=50); P: 4.2 (N=45) Investigator global assessment (6 pt: rescaled as 4 pt: 0=no change or worse; 3=cleared or marked improvement) M: 1.96 (0.90SD, N=50); P: 1.24 (1.00SD, N=45)	TW: NR WA: M: 0/61; P: 3/59 WF: NR AE: M(L): 5/61; P(L): 11/59; M(S): 0/61; P(S): 0/59
Mortensen et al, 1993	Calcipotriol ointment (C) 50µg/g BD Placebo (P)	At 3 weeks: PASI: C: 6.53 (2.49SD, N=17); P: 9.04 (4.71SD, N=17);	TW: C: 0/17; P: 0/17 WA: C: 0/17; P: 0/17 WF: NR AE: C(L): NR; P(L): NR; C(S): 0/17; P(S): 0/17
Olsen, 1991	Clobetasol propionate (C) 0.05% BD Placebo (P)	At 2 weeks: Investigator's global assessment (6-pt, re-scaled as worse = 0, cleared =5) C: 3.65 (1.24SD, N=188); P:1.70 (1.09SD, N=189) Total sign score (0-12) C: 2.4 (N=188); P: 6.3 (N=189)	TW: C: 5/189; P: 22/189 WA: C(L): 0/189; P(L): 1/189 WF: C: 2/189; P: 17/189 AE: C(L): 21/189; P(L): 18/189; C(S): 4/83; P(S): 4/85

Table C: Summary findings from placebo controlled trials (continued)

Trial	Comparisons	Reported Outcome measures	Withdrawal and Adverse Events*
Olsen, 1996 (two trials)	Fluticasone propionate (F) 0.005% ointment Placebo (P)	At 4 weeks: Investigator global assessment (6 pt): 1=cleared, 6=worse, estimated from 3 points) [1]: F: 2.9 (1.37SD, N=88); P: 1.7, (1.18SD, N=90) [2]: F: 2.8 (1.22SD, N=105); P: 1.7, (1.15SD, N=100)	TW: NR WA: NR WF: NR AE: Both Studies together: F(L): 13/193; P(L): 12/190 (S): NR
Oranje et al, 1997	Calcipotriol ointment (C) 0 50 µg/g BD Placebo (P)	At 8 weeks: PASI, % reduction: C: -52.0% (45%SD, N: 43); P: -37.1% (39.6%SD, N=34) Investigator global assessment (5-pt; 0 worse, 4 clear) C: 2.53 (1.05SD, N=43); P: 1.91 (1.19SD, N=34),	TW: C: 6/43; P: 3/34 WA: NR WF: NR AE: C(L): 7/43; P(L): 8/34; C(S): 0/43; P(S): 0/34
Ormerod et al, 1997	Betamethasone Valerate (B) ointment 0.1% BD White soft paraffin (P)	At 2 weeks: Total sign score (0-24): B: 4.92 (2.53SD); P: 7.75 (2.45SD); N=11 (Data received after analysis and not included)	TW: NR WA: NR WF: NR AE: NR
Pariser et al, 1996	Calcipotriene (C) ointment 0.005% OD Placebo (P)	At 8 weeks: Total severity score (0-9): C: 2.27 (N=167); P: 3.63 (N=168) (N estimated) Investigator global assessment (0-9): No adequate data reported or available from author or sponsor	TW: NR WA: NR WF: NR AE: NR
Perez et al, 1996	Calcitriol (C) 1.5µg/g OD Placebo (P)	At 10 weeks: Investigator global assessment (5pt, re-scaled as 0=worse, 4=excellent improvement) C: 3.20(0.85SD); P: 1.14 (0.38SD); N=84 Total severity score (0-9) C: 2.8 (1.0SD), P: 7.1 (0.1SD); N=84	TW: C: 0/84; P: 0/84 WA: C: 0/84; P: 0/84 WF: C: 0/84; P: 0/84 AE: C(L): 0/84; P(L): NR; C(S): 0/84; P(S): 0/84
Scarpa et al, 1997	Tacalcitol ointment (T) 4 mcg/g, OD Vehicle (P) OD	At 6 weeks: Total sign score(0-12) T: 3.44; P: 4.34; N=134	TW: T: 23/157; P: 23/157 WA: T: 1/157; P: 0/157 WF: T: 0/157; P: 0/157 AE: T(L): 1/134; P(L): 2/157; (S): NR
Sears et al 1997	Hydrocortisone buteprate (H) 0.1% cream, BD Placebo (P)	At 3 weeks: Total sign score (0-9), adjusted for baseline: H: -2.0 (1.69SD, N=78); P: -1.3 (1.32SD, N=83) Investigator global assessment: No adequate data reported or available from author or sponsor	TW: H: 10/84; P: 11/96 WA: H: 1/94; P: 0/96 WF: H: 0/94; P: 0/96 AE: H(L+S): 21/94; P(L+S): 27/96;
Sefton et al 1984	Hydrocortisone valerate (H) 0.2% ointment BD Placebo (P)	At 3 weeks: Investigator global assessment (7-pt): No adequate data reported or available from author or sponsor	TW: NR WA: NR WF: NR AE: NR
Seidenari et al 1997	Tacalcitol (T) ointment 4 µg/g OD Placebo (P)	At 6 weeks: Total sign score (0-12) T: 2.92 (1.93SD); P: 4.52 (1.38SD), N=11	TW: T: 1/12; P: 1/12 WA: T: 0/12; P: 0/12 WF: NR AE: NR
Staberg et al, 1989	Calcipotriol (C) cream 1200 µg/g BD Placebo cream	At 6 weeks: Total sign score (0-9) C: 1.3 (1.6SD); P: 4.6 (2.2SD); N=9	TW: C: 0/10; P: 0/10 WA: C: 0/10; P: 0/10 WF: C: 0/10; P: 0/10 AE: C(L): 1/10; P(L): 1/10; C(S): 0/10; P(S): 0/10

Table C: Summary findings from placebo controlled trials (continued)

Trial	Comparisons	Reported Outcome measures	Withdrawal and Adverse Events*
Sudilovsky et al, 1981	Halcinonide (H) cream 0.1% OD + vehicle cream BD Placebo (P) TD	At 3 weeks: Investigator global assessment: No adequate data reported or available from author or sponsor	TW: NR WA: NR WF: NR AE: (L): NR; H(S): 0/78; P(S): 0/78
Syed et al, 1996	Aloe vera extract 0.5% (A) hydrophilic cream, TDS Placebo cream, TDS (P)	At 4 weeks: PASI: Mean PASI at 4 weeks: A: 2.2 (N=30); P: 8.2 (N=30)	TW: A: 0/30; P: 0/30 WA: A: 0/30; P: 0/30 WF: A: 0/30; P: 0/30 AE: A(L+S): 0/30; P(L+S): 0/30
Van de Kerkhof 1989	Calcitriol (C) solution 2 µg/ml, BD Placebo (P)	At 4 weeks: Total Sign Score (0-9) C: 6.0; P: 6.1; N=10	TW: C: 0/10; P: 0/10 WA: C: 0/10; P: 0/10 WF: C: 0/10; P: 0/10 AE: C(L+S): 0/10; P(L+S): 0/10
Van de Kerkhof et al, 1996a	Tacalcitol (T) ointment 4 µg/g OD Placebo (P)	At 8 weeks: Total sign score (0-12), adjusted for baseline: T: -4.0; P: -2.3, N=103 Investigator global assessment (4-pt; re-scaled as 0=poor, 3=very good) T: 1.66 (0.88SD); P: 0.75 (0.72SD); N=103	TW: T: 19/122; P: 19/122 WA: T: 1/122; P: 0/122 WF: NR AE: (L): NR; T(S): 0/122; P(S): 0/122
Van de Kerkhof et al, 1996b	Hydrocortisone17-butyrate 0.1% emulsion BD Placebo (P)	At 4 weeks: Overall assessment: No adequate data reported or available from author or sponsor	TW: NR WA: NR WF: NR AE: NR
VanderPloeg, 1976	Betamethasone dipropionate (B) ointment, 0.05%, BD Vehicle, BD (P)	At 3 weeks: Total sign score (0-20) B: 3.2 (N=17); P: 5.4 (N=16) Investigator global assessment (5-pt: re-scaled as 0=exacerbation; 4=excellent) B: 3.24 (0.97SD, N=17); P: 2.06 (0.93SD, N=16)	TW: B+P: 3/36; B: NR; P: NR WA: B: 0/17; P: 0/16 WF: NR AE: B: 0/17; P: 0/16
Volden et al, 1992	Dithranol (D) 1% in petrolatum Placebo (P)	At 4 weeks: Total sign score: No adequate data reported or available from author or sponsor	TW: D: 1/10; P: 1/10 WA: D: 0/10; P: 0/10 WF: D: 0/10; P: 0/10 AE: D: 4/10; P: 0/10
Weinstein et al, 1997 Weinstein 1996	Tazarotene (T1) gel, 0.1% Tazarotene (T2) gel, 0.05% Placebo (P)	At 12 weeks: Total Sign Score: T1: 3.66 (N=105); T2: 3.86 (N=106); P=5.28 (N=107)	TW: T1: 27/108; T2: 28/108; P: 27/108 WA: T1: 13/108; T2: 11/108; P: 3/108 WF: T1: 4/108; T2: 5/108; P: 6/108 AE: (L): NR; T1(S): 0/108; T2(S): 0/108; P(S): 0/108
Wortzel, 1975 (2 trials)	Betamethasone dipropionate (B) ointment 0.05, BD Placebo, BD (P)	At 3 weeks Investigator global assessment (5pt: 0=worse, 4=excellent) [1]: B: 2.97 (1.09SD, N=39); P: 1.70 (1.15SD, N=37) [2]: B: 2.20 (1.10SD, N=5); P: 1.25 (0.5SD, N=4)	[1] and [2] TW: NR WA: NR WF: NR AE: NR

Table D: Description of head-to-head trials involving vitamin-D derivative preparations

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Design	Enrolment*	Reported Outcome measures
Austad et al, 1998	Clobetasol propionate ointment, 0.05% BD (2/52), followed by calcipotriol 50 µg/g BD (4/52) Calcipotriol 50µg/g BD (6/52)	Adults; symmetrical plaque psoriasis, total severity score ≥ 6	Widespread psoriasis; hypercalcemia; liver or renal disease; risk of pregnancy; pregnancy; relevant concomitant medication or conditions; previous adverse response	Double blind Within patient Patient delivery	N: 49 TD: 6 wks; FU: 10wks LF: 3 (6.1%) BC: Yes	Total severity score Treatment preference: physician and patient Investigator global assessment
Baadsgaard et al, 1995	Tacalcitol (7 concentrations: 0.25-16 µg/g) OD Hydrocortisone butyrate 0.1% OD Betamethasone dipropionate 0.05% OD Calcipotriol 50 µg/g OD	Adults; stable psoriasis vulgaris; sign score ≥ 5 on 9-pt scale.	Acute guttate psoriasis; pregnancy; lactation; recent systemic treatment; poor response to steroids	Double blind Within patient Nurse delivery	N: 58 TD: 24 days LF: 8 (13.8%) BC: Yes	Signs: [erythema; infiltration; scaling] Total sign score Degree of healing
Baiocchi et al, 1997	Calcipotriol ointment, 50 mcg/g, OD Calcipotriol ointment, 50 mcg/g, BD	Adult; symmetrical mild-to-moderate psoriasis vulgaris	Recent topical or systemic antipsoriatic therapy; rapidly worsening psoriasis; concurrent vitamin D; renal or hepatic disease; pregnancy; lactation	Open Within patient Patient delivery	N: 132 TD: 8 wks LF: 2 (1.5%) BC: Yes	PASI
Berth-Jones, 1992	Calcipotriol ointment, 50 mcg/g BD Dithranol cream, (dose titration 0.1 – 2%) OD	Outpatients; adults; chronic stable plaque psoriasis	Previous non-response to study medications; recent systemic treatment; hypercalcaemia; abnormal renal/hepatic function; calcium or vitamin D intake; relevant concomitant medication; pregnancy; risk of pregnancy	Open Parallel group Patient delivery	N: 478 TD: 8 wks LF: PASI: 56 (11.7%) Response: 20 (4.2%) BC: Yes	PASI Investigator and patient global assessments Cosmetic acceptability

* **Enrolment definitions**

N: Number of patients randomised
TD: Treatment duration and length of follow up (FU) if the study continued beyond cessation of treatment; FU includes the treatment period
LF: Loss to follow up, defined as patients randomised, not contributing to primary outcome measure
BC: Baseline comparability

Table D: Description of head-to-head trials involving vitamin-D derivative preparations (continued)

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Design	Enrolment*	Reported Outcome measures
Bourke et al, 1993	Calcipotriol, BD Calcipotriol, BD plus polythene film at night	Adult; symmetrical chronic plaque psoriasis; outpatients	UV or systemic antipsoriatic therapy.	Single blind Within patient Patient delivery	N: 19 (evaluable) TD: 8 wks LF: not reported BC: Yes	Signs: [erythema; induration; scale] Total sign score
Bourke et al, 1995 and 1997	Calcitriol, 3 mcg/g, BD Calcipotriol 50 mcg/g, BD	Adults; symmetrical chronic moderate plaque psoriasis vulgaris	Pregnancy; lactation; drugs affecting systemic calcium homeostasis; recent systemic anti-psoriatic or UVB therapy	Double blind Parallel group Patient delivery	N: 24 TD: 8 wks LF: 4 (16.7%) BC: Yes	PASI
Bruce et al, 1994 & Siskin, 1993	Calcipotriol ointment (C) 0.005%, BD Fluocinonide ointment (F) 0.05%, BD	Stable plaque psoriasis; adults; at least mild overall severity; at least moderately severe plaque elevation;	Pregnancy; lactation; inadequate contraception; sensitivity to test medications; recent topical, UV or systemic treatment; recent involvement in other trials; planned sun exposure	Double blind Parallel group Patient delivery	N: 114 TD: 6 wks LF: 15 (13.2%) BC: Yes	Signs [scaling; eythema; plaque elevation] Overall severity (total sign score and % involvement) Investigator global assessment
Crosti et al, 1997	Calcipotriol ointment, 50mcg/g, BD Betamethasone dipropionate + salicylic acid, BD	Mild, stable psoriasis vulgaris; adult;	Recent topical or systemic treatments; pregnancy; lactation; concomitant vitamin D or systemic steroids; hepatic or renal failure	Blinding unclear Parallel group Delivery unclear	N: 160 TD: 6 wks; FU: 10 wks LF: 8 (5%) BC: Yes	PASI Investigator and patient global assessments
Cunliffe et al, 1992	Calcipotriol ointment, 50mcg/g, BD Betamethasone-17-valerate 1 mg/g, BD	Stable plaque psoriasis; adult; outpatients	Risk of pregnancy; pregnancy; lactation; recent systemic antipsoriatic treatment;	Double blind Parallel group Delivery unclear	N: 409 TD: 6 wks LF: 8 (2.0) BC: Yes	PASI Patient overall assessment
De Simone et al, 1993	Calcipotriol ointment, 50mcg/g, BD Coal tar (T) 5% in Lassar's paste	Psoriasis vulgaris; PASI score 2.7-24.3	Pregnancy, lactation, hepatic or renal disease; recent systemic or topical therapy; high intake of vitamin D or calcium	Blinding unclear Parallel group Patient delivery	N: 30 TD: 6 wks; FU: 10 wks LF: 0 (0%) BC: Not reported	Investigator global assessment (estimated from PASI score)

Table D: Description of head-to-head trials involving vitamin-D derivative preparations (continued)

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Design	Enrolment*	Reported Outcome measures
Farkas et al, 1999 and Farkas, 1995	Tacalcitol ointment, 4 mcg/g, OD Dithranol stick, 1.5% or 3%, OD	Chronic stable plaque psoriasis; adults; Caucasian patients ≤ 30% BSA; mPASI>10; in- and outpatients	Recent topical, systemic or UV therapies; sensitivity to study medications; concurrent medication; abnormal hepatic or renal function; risk of pregnancy; pregnancy; lactation; serious co-morbidity	Open Parallel group Delivery unclear	N: 84 TD: 8 wks; FU: 12 wks LF: 0 (0%) BC: Yes	PASI Total sign score [erythema, infiltration and desquamation] Investigator global assessment
Grattan et al, 1997	Calcipotriol ointment, 0.005% BD Dithranol in aqueous gel, (dose titration 0.1-2.0%), BD	Bilateral stable chronic plaque psoriasis; adult; hospitalised for routine dithranol treatment.	Intolerance of dithranol; unstable or pustular psoriasis; calcium metabolism disorders; systemic psoriasis treatment; recent UVB or PUVA therapy; pregnancy or lactation.	Open Within patient Delivery unclear	N: 25 TD: 4 weeks; FU: 16 weeks LF: not reported BC: Yes	Severity: [erythema; scaling; palpability] Total severity score Patient assessment of irritation Investigator assessment of skin staining
Kim et al, 1994	Calcipotriol ointment 50mcg/g, BD Desoxymetasone ointment 2.5mg/g, BD	Psoriasis	Not identifiable	Double blind Between patient Patient delivery	N: 10 TD: 8 wks LF: 0 (0%) BC: Yes	PASI
Klaber et al, 1994	Calcipotriol solution 50mcg/ml, BD Betamethasone 17-valerate solution 1mg/ml BD	Adults; stable, mild-to-moderate scalp psoriasis; history of psoriasis on body	More extensive, severe or infected psoriasis; recent systemic antipsoriatic treatment or UV; concurrent vitamin D, calcium or other relevant medication; significant hepatic or renal disease; hypercalcaemia; risk of pregnancy; pregnancy; lactation	Double blind Parallel group Patient delivery	N: 474 TD: 4 wks LF: Assessment: 6 (1.3%) TSS: 29 (6.1%) BC: Yes	Investigator and patient overall assessments Total sign score [erythema, thickness, scaliness] Assessment of extent of scalp psoriasis: Assessment of acceptibility
Kragballe et al, 1991	Calcipotriol ointment, 50 mcg/g, BD Betamethasone valerate ointment, 0.1%, BD	Adult; symmetrical psoriasis vulgaris	Unstable psoriasis; recent systemic or UV therapy; hypercalcaemia; impaired renal/ hepatic function; high dose calcium /Vitamin D intake; unresponsive to corticosteroids; concomitant medication	Double blind Within patient Patient delivery	N: 345 TD: 6 wks LF: 3 (0.9%) BC: Yes	PASI Total sign score [erythema, thickness, scaliness] Patient assessment of response

Table D: Description of head-to-head trials involving vitamin-D derivative preparations (continued)

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Design	Enrolment*	Reported Outcome measures
Kragballe et al, 1998; Glade et al, 1996	Calcipotriol cream, 50 mcg/g BD Calcipotriol cream, 50 mcg/g OM plus clobetasone17-butyrate cream, 0.5mg/g ON Calcipotriol cream, 50 mcg/g OM plus betamethasone 17-valerate cream, 1mg/g ON Calcipotriol cream, 50 mcg/g OM plus vehicle ON	Adult; stable psoriasis vulgaris on trunk and limbs	Pregnancy; risk of pregnancy; lactation; recent systemic or UV therapy; concomitant medication; hypercalcaemia or renal disease; planned exposure to sun	Double blind Parallel group Patient delivery	N: 699 TD: 8 wks LF: 8 (1.1%) BC: Psoriasis comparable, demographics inadequately reported	PASI Investigator and patient overall assessments of response
Landi, 1993; Landi et al, 1993	Calcipotriol ointment, 50 mcg/g, BD Clobetasol propionate 0.05% ointment, BD	Adult; mild and moderate psoriasis	None reported	Blinding not reported Parallel group Delivery unclear	N: 40 TD: 6 wks; FU: 10 wks LF: 0 (0%) BC: Psoriasis comparable, demographics not reported	PASI Note Landi, 1993 reports the findings of a single centre, one of three centres reported in Landi et al, 1993 (120 patients)
Lister et al, 1997	Dithranol cream 1-3%, OD Calcipotriol, BD	Psoriasis	Not stated	Single (investigator) blind Parallel group Patient delivery	N: 171 TD: 8 wks; FU: 16 wks LF: not reported BC: Psoriasis comparable, demographics inadequately reported	Total sign score [erythema, scaling, induration] Investigator and patient global assessments
Medansky et al, 1996	Diflorasone diacetate ointment, 0.05%, BD Calcipotriene ointment 0.005%, BD	Mild-to-moderate symmetrical psoriasis vulgaris; adult; TSS ≥ 6	Recent topical or systemic antipsoriatic therapy; recent lithium, NSAIDs or beta-blockers	Double blind Within patient Patient delivery	N: 134 TD: 3 wks LF: (4.5%) BC: Inadequately reported	Signs: [erythema, scaling, induration] Total sign score Physician overall evaluation Physician comparative evaluation Patient comparative evaluation

Table D: Description of head-to-head trials involving vitamin-D derivative preparations (continued)

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Design	Enrolment*	Reported Outcome measures
Molin et al, 1996 and 1997	Calcipotriol cream 50 mcg/g, BD Betamethasone 17-valerate cream, 1mg/g, BD	Adult outpatients; mild-to-moderate stable and chronic plaque psoriasis of limbs and trunk	None reported	Double blind Parallel group Patient delivery	N: 421 TD: 8 wks LF: 4 (1%) BC: Psoriasis comparable, demographics not reported	PASI Severity scores Investigator and patient global assessments of response
Ortonne et al, 1994	Calcipotriol ointment, BD Calcipotriol ointment OM, plus Betamethasone dipropionate ointment ON	Psoriasis vulgaris; stable or worsening; BSA 10-40%; PASI 1-30	Pregnancy; lactation; concurrent disease; concomitant therapy; hypersensitivity to Vitamin D or analogues; planned exposure to sun	Double blind Parallel group Patient delivery	N: 188 TD: 6 wks LF: 32 (17.0%) BC: Yes	PASI: Investigator global assessment
Pinheiro, 1997	Calcipotriol ointment, 50 mcg/g BD Coal tar 5%/allantoin 2%/hydrocortisone cream 0.5% BD	Chronic plaque psoriasis; Adult;BSA ≥100 cm^2	Hypersensitivity to trial medications; concomitant treatment with Vitamin D/calcium/other relevant agent; pregnancy; risk of pregnancy; lactation; unable to comply with protocol	Open Parallel group Patient delivery	N: 132 TD: 8 wks LF: 10 (7.6%) BC: Yes	Signs: [redness; thickness; scaliness] Total sign score Investigator global assessment Area of affected skin (area scales) Patient's evaluation of overall response (VAS)
Ruzicka et al 1998 and 1996	Calcipotriol 0.005% ointment BD, 6 weeks (C) Calcipotriol 0.005% ointment BD, 2 weeks, then Calcipotriol ointment 0.005% OM plus Betamethasone valerate ointment ON, 4 weeks (CB)	Adults; chronic plaque-type psoriasis; BSA ≤ 30%; calcium levels, renal and liver function within normal range	Pregnancy; lactation; recent systemic or UV therapy	Double blind Parallel group Patient delivery	N: 178 TD: 2+4 wks; FU: 14 wks LF: 7 (3.9%) BC: Psoriasis comparable, demographics not reported	PASI Investigator global assessment Patient evaluation of overall response

Table D: Description of head-to-head trials involving vitamin-D derivative preparations (continued)

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Design	Enrolment*	Reported Outcome measures
Scarpa et al, 1996 and Scarpa, 1996	Tacalcitol ointment, 4 mcg/g, OD Betamethasone-17-valerate ointment 0.1%, OD	Psoriasis vulgaris	Concomitant medications (except emollients, tar shampoo and salicylic acid); topical or systemic steroids; calcium or vitamin D intake; antipsoriatic medications	Double blind Within patient Delivery unclear	N: 76 TD: 6 wks; FU: 8 wks LF: 13 (17.1%) BC: Yes	Severity [erythema; thickness; scaling] Total severity score Comparison of lesions, based on difference in TSS Investigator global assessment
Scarpa, 1994	Calcipotriol ointment, 50 mg/g, BD Betamethasone dipropionate ointment, 0.05% + salicylic acid, 3%, BD	Plaque-type psoriasis	Not reported	Blinding unclear Parallel group Delivery unclear	N: 160 TD: 6 wks; FU: 10 wks LF: not reported BC: Demographics comparable, psoriasis not reported	Investigator global assessment Patient's overall acceptance
Seidenari et al 1997	Tacalcitol ointment 4 µg/g OD Betamethasone valerate ointment 0.1%, OD	Symmetrical, stable psoriatic plaques; adult; in- or outpatients.	Recent topical, UV or systemic therapy. Inadequate contraception.	Double blind Within patient Patient delivery	N: 14 TD: 6 wks; FU: 8 wks LF: 3 (21.4%) BC: Yes	Signs [erythema; thickening; scaling] Total sign score (0-12)
Tham et al, 1994	Calcipotriol ointment 50 mcg/g, BD White soft paraffin, OM plus coal tar solution BP in aqueous cream 15% ON	Stable symmetrical chronic plaque-type psoriasis; adult	Recent systemic or UV therapy; hypercalcaemia; high calcium or vitamin D intake; impaired renal or hepatic function; previous poor response to tar; concomitant medication	Single blind (investigator) Within patient Patient delivery	N: 30 TD: 6 wks LF: 3 (10%) BC: Yes	PASI Severity: [erythema; infiltration; desquamation] Investigator and patient global assessments
Tosti et al, 1998	Calcipotriol ointment 50 mcg/g, BD Betamethasone dipropionate, 64 mg/g + salicylic acid, 0.03g/g, ointment, BD	Nail bed psoriasis with severe subungual hyperkeratosis; adult	Onchymycosis; pregnancy; lactation; severe renal or hepatic insufficiency; hypersensitivity to study medication; concomitant vitamin D, or antipsoriatic therapy.	Double blind Parallel group Patient delivery	N: 58 [29 pts with 129 fingernails; 44 pts with 270 toenails] TD: 3 mths; FU: 6 mths LF: 5 (8.6%) BC: Psoriasis comparable, demographics inadequately reported	Nail thickness (nail plate + hyperkeratotic nail bed, mm) Nail thickness, % reduction from baseline Patient's assessment of acceptability (5-pt: 0=nil; 4=excellent)

Table D: Description of head-to-head trials involving vitamin-D derivative preparations (continued)

Trial	Comparisons	Inclusion Criteria	Exclusion Criteria	Design	Enrolment*	Reported Outcome measures
Van der Verleuten et al, 1995	Calcipotriol ointment, 50 mcg/g, BD Dithranol in paste or petroleum, 0.05%-4%, 24 hour application on alternate days	Adult; inpatient; severe, disabling psoriasis; resistant to topical therapy	Recent or concomitant oral antipsoriatic therapy, no topical or systemic treatments except corticosteroids for the scalp and face	Open Within patient Delivery unclear	N: 10 TD: 2 wks LF: 0(0%) BC: Inadequately reported	PASI
Vladimirov et al, 1994	Calcipotriol cream 50 mcg/g, BD Betamethasone 17-valerate ointment 0.1%, BD	Adult; mild to moderate psoriasis	None reported	Double blind Parallel group Patient delivery	N: 60 TD: 6 wks LF: 0 (0%) BC: Inadequately reported	PASI Investigator global assessment
Veien et al, 1997	Tacalcitol ointment, 4mcg/g, OD plus Tacalcitol vehicle OD Calcipotriol ointment, 50 mcg/g, BD	Adult; stable plaque psoriasis; TSS>5; erythema ≥ 2, scaling ≥ 2	Pregnancy; lactation; high serum calcium, serum phosphate, serum creatinine; unresponsive to calcipotriol; intolerant to study ingredients; serious morbidity	Double blind Parallel group Patient delivery	N: 287 TD: 8 wks FU: 12 wks LF: 0 (0%) BC: Psoriasis comparable, demographics inadequately reported	Severity: [erythema; infiltration; scaling; pruritus] Total sign score (TSS): (0-12) Investigator and patient global assessments Patient's evaluation of global usefulness (VAS) Patient's evaluation of cosmetic acceptability
Wall et al, 1997 and 1998	Calcipotriol ointment, 50 mcg/g, BD Dithranol 0.1%-2%, OD	Adult; stable mild-to-moderate chronic plaque psoriasis; BSA ≥100cm^2 but <40%; Recent GP attender	Acute guttate or pustular psoriasis; psoriasis of scalp or face only; recent topical or systemic antipsoriatic therapy; pregnancy; lactation; concomitant vitamin D or calcium intake; hypersensitivity to study medication; unlikely to comply with protocol	Open Parallel group Patient delivery	N: 306 TD: 3 mths LF: 28 (7.2%) BC: Yes	Overall clinical response Quality of Life: Psoriasis Disability Index (PDI) Sickness Impact Profile (SIP)

Table E: Excluded head-to-head trials involving vitamin-D derivative preparations

Trial	Comparisons	Reason for exclusion
Kragballe et al, 1994	KH1060 (20-epi-vitamin D3 analogue) ointment 0.2 µg/g OR 0.4 µg/g, BD [1]	Dose ranging study of an unlicensed product not subsequently marketed
	KH1060 ointment 0.2 µg/g OR 1 µg/g, BD [2]	
Kragballe, 1989	Calcipotriol ointment 25 mcg/g, BD *OR* Calcipotriol ointment 50 mcg/g, BD [1]	Patients were randomised to the two substudies but within the substudies treatments were applied without randomisation
	Calcipotriol ointment 50 mcg/g, BD *OR* Calcipotriol ointment 100 mcg/g BD [2]	
Lebwohl et al, 1998	Halobetasol ointment BD weekends, Calcipotriene ointment BD weekdays *OR* Halobetasol ointment BD weekends, placebo ointment BD weekdays	The study doesn't provide a simple comparison against a vitamin D3 derivative treatment
Meyrat, 1996	Calcipotriol ointment, BD	The study does not provide a comparison of interest
	Calciptoriol cream OM, calcipotriol ointment ON	
Sander et al, 1998	Dithranol ointment, titrated, BD	The study doesn't provide a simple comparison against a vitamin D3 derivative treatment
	Calcipotriol ointment 0.005%, OM, Dithranol ointment titrated ON	
	Mometasone furoate ointment, 0.1% OM, Dithranol ointment titrated ON	

Table F: Summary findings from head-to-head trials

Trial	Comparisons	Reported Outcome measures	Withdrawal and Adverse Events*
Austad et al, 1998	Clobetasol propionate 0.05% ointment BD (2/52), followed by calcipotriol 50µg/g BD (4/52) (CP) Calcipotriol (C) 50µg/g BD (6/52)	At 6 weeks: Total severity score (0-9) CP: 1.7 (1.2SD); C: 2.5 (1.3SD); N=46 Investigator global assessment: (5-pt 0=poor to 4=cleared) CP: 2.67 (0.84SD); C: 2.2 (0.84SD); N=46	TW: CP: 3/49; C: 3/49 WA: CP: 0/49; C: 0/49 WF: CP: 0/49; C: 0/49 AE: CP(L): 3/49; C(L): 4/49
Baadsgaard et al, 1995	Tacalcitol (T) 4 µg/g OD Hydrocortisone butyrate (HB) 0.1% OD Betamethasone dipropionate (BD) 0.05% OD Calcipotriol (C) 50 µg/g OD	No adequate data available	TW: NR WA: NR WF: NR AE: NR
Baiocchi et al, 1997	Calcipotriol ointment, (C1) 50 mcg/g, OD Calcipotriol ointment, (C2) 50 mcg/g, BD	At 8 weeks: PASI: C1: 1.1 (1.4SD); C2: 0.97 (1.3SD); N=130	TW: C1: 34/132; C2: 33/132 WA: C1: 6/132; C2: 7/132 WF: C1: 1/132; C2: 1/132 AE: (L): NR; C1(S): 0/132; C2(S): 0/132
Berth-Jones, 1992	Calcipotriol ointment (C) 50 mcg/g BD Dithranol cream (D) (dose titration 0.1 – 2%) OD	At 8 weeks: PASI: D: 4.7 (4.4SD, N=208); C: 3.4 (2.7SD, N=214) Investigator global assessment: 5-pt; (0=worse to 5=clear): D: 2.29 (0.95SD, N=227); C: 2.80 (0.61SD, N=231)	TW: NR WA: C(L): 4/239; D(L): 12/239; C(S): 0/239; D(S): 1/239 WF: C: 3/239; D: 3/239 AE: C(L): 84/239; D(L): 127/239; C(S): 0/239; D(S): 1/239
Bourke et al, 1993	Calcipotriol, BD (C) Calcipotriol, BD (O) Plus polythene film at night.	At 8 weeks: Total severity score (0-12): change from baseline C: -3.1 (2.6SD); O: -5.2 (2.6SD); N=19	TW: NR WA: NR WF: NR AE: (L): NR; C(S): 0/19; CO(S): 0/19
Bourke et al, 1995; 1997	Calcitriol (CL) 3 mcg/g, BD Calcipotriol (C) 50 mcg/g, BD	At 8 weeks: PASI: CL: 8.8 (4.2SD, N=8); C: 4.7 (2.4SD; N=7)	TW: CL: 4/12; C: 4/12 WA: CL: 0/12; C: 0/12 WF: CL: 2/12; C: 1/12 AE: NR
Bruce et al, 1994; Siskin, 1993	Calcipotriol ointment (C) 0.005%, BD Fluocinonide ointment (F) 0.05%, BD	At 6 weeks: Overall severity (total severity score [0-8], adjusted for surface area) C: 1.92 (N=44); F: 2.66 (N=45) (Numbers in groups approximated) Investigator global assessment: (7pt: 0=worse to 6=clear) C: 4.04 (1.31SD; N=52) F: 3.30 (1.20SD; N=47) (Data received after analysis and not included)	TW: NR WA: C: 0/57 ; F: 1/573 WF: C: 0/57; F: 0/56 AE: C(L): 10/573; F(L): 4/563; (S): NR

* **Withdrawal and adverse event definitions**

TW: Total withdrawal
WA: Withdrawal reported due to adverse events (deterioration of symptoms, treatment failure or inadequate treatment response)
WF:Withdrawal due to treatment failure
AE: Number of patients with reported adverse events: (L) local and (S) systemic side effects if reported separately; exacerbation of symptoms; excluding discoloration of skin or clothing
NR (not reported) indicates that patient data for each treatment group was incomplete or unreported

Table F: Summary findings from head-to-head trials (continued)

Trial	Comparisons	Reported Outcome measures	Withdrawal and Adverse Events*
Crosti et al, 1997	Calcipotriol ointment (C) 50mcg/g, BD Betamethasone dipropionate + salicylic acid, (B) BD	At 6 weeks: PASI: C: 2.6 (N=80); 2.7 (N=80) Investigator global assessment: (5-pt, -1 worse, 3 healing): No adequate data available	TW: C: 20/80; B: 17/80; WA: C: 4/80; B: 0/80; WF: C: 1/80; B: 3/80; AE: C(L): 7/80; B(L): 0/80; C(S): 0/80; B(S): 0/80
Cunliffe et al, 1992	Calcipotriol ointment, (C) 50mcg/g, BD Betamethasone-17-valerate (B) 1 mg/g, BD	At 6 weeks: (adjusted for baseline) PASI: C: -5.50 (5.84SD, N=201) B -5.32 (6.02SD, N=200)	TW: C: 21/205; B: 17/204; WA: C(L): 4/205; B(L): 2/204; C(S): 1/205; B(S): 1/204 WF: C: 6/205; B: 6/204; AE: C(L): 64/205; B(L): 18/204; C(S): 1/205; B(S): 1/204
De Simone et al, 1993	Calcipotriol ointment, (C) 50mcg/g, BD Coal tar (T) 5% in Lassar's paste	At 6 weeks: Investigator global assessment: (5-pt: 0=worse, 4=remission) C: 2.73 (0.88SD, N=15); T: 1.80 (0.86SD, N=15)	TW: NR WA: NR WF: NR AE: NR
Farkas et al, 1999; Farkas, 1995	Tacalcitol ointment (T) 4 mcg/g, OD Dithranol stick (D) 1.5% or 3%, OD	At 8 weeks PASI: T: 4.16 (3.22SD, N=42); D: 4.38 (3.05SD, N=42) Total sign score (0-12) (adjusted for baseline): T: -6.1 (2.4SD, N=42); D: - 5.7 (2.1SD, N=42) Investigator global assessment: (6-pt: -1=worse, 4 =clear) No adequate data available	TW: T: 4/42; D: 5/42 WA: NR WF: NR AE: T(L): 2/42; D(L): 17/42; T(S): 0/42; D(S): 0/42
Grattan et al, 1997	Calcipotriol ointment (C) 0.005% BD Dithranol in aqueous gel, (D) (dose titration 0.1-2.0%), BD.	At 4 weeks: Total severity score (0-9) C: 1.8 (2.2SD); P: 2.2 (2.7SD); N=11	TW: D: 3/25; C: 3/25 WA: NR WF: NR AE: D(L): 11/22; C(L): 1/22; (S): NR
Kim et al, 1994	Calcipotriol ointment C) 50mcg/g, BD Desoxymetasone ointment (D) 2.5mg/g, BD	At 8 weeks: PASI C: 3.69 (1.9SD, N=10): D: 3.4 (1.93SD, N=10)	TW: NR WA: NR WF: NR AE: NR
Klaber et al, 1994	Betamethasone 17-valerate (B) solution 1mg/ml BD Calcipotriol (C) solution 50mcg/ml, BD	At 4 weeks: Investigator global assessment: (5-pt, 1=worse, 5=cleared, re-scaled as 0 to 4) C: 2.51 (1.14SD, N=236); B: 2.93 (1.02SD, N=232) Total sign score (0-12) C: 3.29 (0.36SE, N=220); B: 2.71 (0.29SE, N=225)	TW: C: 20/240; B: 9/234 WA: C(L): 11/240; B(L): 2/234 WF: C: 4/240; B: 2/234 AE: C(L): 84/240; B(L): 26/234; C(S): 0/240; B(S): 0/234
Kragballe et al, 1991	Calcipotriol ointment (C) 50 mcg/g, BD Betamethasone valerate (B) ointment 0.1%, BD	At 6 weeks: PASI: C: 2.5 (2.86SD, N=316); B: 3.06 (3.38SD, N=316) Total sign score (0-12) TSS: C: 2.31 (N=342); B: 2.82 (N=342)	TW: C: 15/345; B: 15/345 WA: C(L): 2/345; B(L): 1/345 WF: C: 1/345; B: 2/345 AE: C(L): 37/345; B(L): 35/345; C(S): 0/345; B(S): 0/345

Table F: Summary findings from head-to-head trials (continued)

Trial	Comparisons	Reported Outcome measures	Withdrawal and Adverse Events*
Kragballe et al, 1998	Calcipotriol cream(CV) 50 mcg/g OM plus vehicle ON Calcipotriol cream (CC) 50 mcg/g BD Calcipotriol cream(CL) 50 mcg/g OM plus clobetasone17-butyrate cream, 0.5mg/g ON Calcipotriol cream(CB) 50 mcg/g OM plus betamethasone 17-valerate cream, 1mg/g ON	At 8 weeks: PASI: CV: 4.58 (3.93SD, N=173); CC: 4.04 (3.39SD, N=172); CL: 3.50 (2.86SD, N=172); CB: 3.42 (3.05SD, N=174) PASI, adjusted for baseline: CV: -3.86 (4.63SD, N=173); CC: -4.61 (5.40SD, N=172); CL: -4.61 4.39SD, N=172), CB: -4.61 (4.12SD, N=174); Investigator global assessment: (6 pt: re-scaled as 0-5) CV: 2.63 (1.34SD, n=172); CC: 2.98 (1.23SD, N=172); CL: 3.04 (1.15SD, N=172); CB: 3.29 (1.09SD, N=174)	TW: C: 19/174; CC: 17/174; CL: 12/175; CB: 11/176 WA: C: 8/174; CC: 6/174; CL: 3/175; CB: 3/176 WF: C: 3/174; CC: 3/174; CL: 1/175; CB: 1/176 AE: C(L): 54/173; CC(L): 59/172; CL(L): 41/172; CB(L): 30/175; C(S): 54/173; CC(S): 59/172; CL(S): 41/172; CB(S): 30/175
Landi et al, 1993	Calcipotriol ointment (C) 50 mcg/g, BD Clobetasol propionate (CP) 0.05% ointment, BD	At 6 weeks: PASI: C: 1.33 (1.4SD: N=20); CP: 2.02 (2.6SD, N=20) No useful data available from Landi et al, 1993 (120 patients)	TW: NR WA: NR WF: NR AE: C(L): 0/20; CP(L): 1/20; C(S): 0/20; CP(S): 1/20
Lister et al, 1997	Dithranol cream (M) 1-3%, OD Calcipotriol, BD (C)	At 8 weeks: Total sign score: M: 3.35 (N=82); C: 2.37 (N=89) Investigator global assessment: No adequate data available	TW: NR WA: D(L): 6/82; C(L): 2/89 WF: NR AE: D(L): 23/82; C(L): 11/89; (S): NR
Medansky et al, 1996	Diflorasone diacetate ointment, (P) 0.05%, BD Calcipotriene ointment (C) 0.005%, BD	At 3 weeks: Total sign score (0-9): P: 2.1; C: 2.7; N=128 Investigator global assessment: (7 pt: rescaled as 0: worse, 6=clear) P: 4.4; C:4.1; N=128	TW: D: 6/134; C: 6/134 WA: NR WF: NR AE: NR
Molin et al, 1996; 1997	Calcipotriol cream (C) 50 mcg/g, BD Betamethasone (B) 17-valerate cream, 1mg/g, BD	At 8 weeks: PASI: C: 3.1 (2.8SD, N=205); B: 3.5 (4.3SD, N=207) PASI, adjusted for baseline: C: -3.3 (2.9SD, N=201); B -2.8 (3.7SD, N=196) PASI: mean % reduction C: 47.9% (33%SD, N=201); B: 45.4% (34%SD, N=196) Investigator global assessment: (5 pt: 0=worse, 4=cleared) C: 2.41 (0.94SD, N=205); B: 2.39 (0.92SD, N=207)	TW: C: 14/210; B: 7/211 WA: C(L): 6/210; B(L): 3/211 WF: NR AE: C(L): 49/207; B(L): 21/210; C(S): 0/207; B(S): 0/210
Ortonne et al, 1994	Calcipotriol ointment (C) BD Calcipotriol ointment (CB) OM, plus Betamethasone dipropionate ointment ON	At 6 weeks: PASI: C: 25.63 (22.38SD, N=81); CB: 17.45 (16.41SD, N=75) Investigator global assessment: (6 pt: 0=worse, 5=cleared) C: 3.56 (1.00SD, N=80): B: 4.05 (0.76SD, N=74)	TW: NR WA: C(L): 6/97; B(L): 3/91 WF: NR AE: C(L): 24/94; B(L): 11/88; (S): NR
Pinheiro, 1997	Calcipotriol ointment (C) 50 mcg/g, BD Coal tar 5%/allantoin 2%/hydrocortisone cream (H) 0.5% BD	At 8 weeks: Investigator global assessment: (5-pt: 0=worse, 4=cleared) C: 2.66 (0.67SD, N=65); H: 2.28 (0.92SD, N=57) Total sign score (0-12): C: 2.7 (N=69); H: 3.8 (N=63)	TW: C: 4/69; T: 6/63 WA: C(L): 1/65; T(L): 3/57 WF: NR AE: C(L): 15/65; T(L): 10/57; (S): NR

Table F: Summary findings from head-to-head trials (continued)

Trial	Comparisons	Reported Outcome measures	Withdrawal and Adverse Events*
Ruzicka et al 1998; 1996	Calcipotriol 0.005% ointment BD, 6 weeks (C) Calcipotriol 0.005% ointment BD, 2 weeks, then Calcipotriol ointment 0.005% OM plus Betamethasone valerate ointment ON, 4 weeks (CB)	At 6 weeks: PASI : C: 1.9 (1.59SD, N=87); CB: 1.0 (0.82SD, N=82) Investigator global assessment: (6-pt: 0=worse, 5=cleared): C: 3.34 (1.40SD, N=86); CB: 4.00 (1.23SD, N=78)	TW: C: 5/87; CB: 6/82 WA: C(L): 1/87; CB(L): 1/82; (S): NR WF: NR AE: C(L): 13/87; CB(L): 6/82; C(S): 11/87; CB(S): 7/82
Scarpa et al, 1996; Scarpa, 1996	Tacalcitol ointment (T) 4 mcg/g, OD Betamethasone-17-valerate (B) ointment 0.1%, OD	At 6 weeks: Total severity score (0-12) T: 3.06 (N=63), B: 2.3 (N=63) Investigator global assessment (6-pt): No adequate data available	TW: T: 13/76; B: 13/76 WA: T(L): 0/76; B(L): 0/76; T(S): 1/76; B(S): 1/76 WF: T: NR; B: NR AE: T(L): 2/76; B(L): 3/76; T(S): 7/76; B(S): 7/76
Scarpa, 1994	Calcipotriol ointment (C) 50 mg/g, BD Betamethasone dipropionate (B) ointment, 0.05% + salicylic acid, 3%, BD	At 6 weeks: Investigator global assessment: (5 pt: 0=null, 4=excellent): C: 2.71 (1.27SD, N=80); B: 2.64 (1.19SD, N=80)	TW: NR WA: NR WF: NR AE: NR
Seidenari et al 1997	Tacalcitol (T) ointment 4 µg/g OD Betamethasone valerate (B) ointment, 0.1% OD	At 6 weeks: Total sign score (0-12) T: 2.77 (1.48SD); B: 1.92 (1.43SD); N=11	TW: T: 3/14; B: 3/14 WA: T: 0/14; B: 0/14 WF: NR AE: NR
Tham et al, 1994	Calcipotriol ointment (C) 50 mcg/g, BD White soft paraffin, OM, (T) plus coal tar solution BP in aqueous cream 15% ON	At 6 weeks: PASI: C: 2.0 (2.1SD); T: 4.5 (3.6SD, N=27); N=27 PASI: % change from baseline C: 69.8 (20.4SD); T: 30.9 (24.6SD); N=27 Investigator global assessment: (6-pt:- re-scaled as 0=worse; 5=cleared) C: 3.44 (0.89SD, N=27); T: 2.11 (0.85SD, N=27)	TW: C: 3/30; T: 3/30 WA: C(L): 1/30; T(L): 0/30 WF: C: 0/30; T: 0/30 AE: (L): NR; C(S): 1/30; T(S): 1/30
Tosti et al, 1998	Calcipotriol ointment (C) 50 mcg/g, BD Betamethasone dipropionate (B) 64 mg/g + salicylic acid, 0.03g/g, ointment, BD	At 3 months: Nail thickness (nail plate + hyperkeratotic nail bed, mm) Fingernails: C:1.5 (0.1SEM, N=13); B: 1.6 (0.1SEM, N=16) Toenails: C: 2.1 (0.1SEM, N=20); B: 2.3 (0.1SEM, N=24) The unit of analysis is 'nails' rather than 'patients', consequently the variance estimates are over-precise	TW: C: 6/29; B: 8/29 WA: NR WF: NR AE: C(L): 3/29; B(L): 3/29; (S): NR
Van der Verleuten et al, 1995	Calcipotriol ointment (C) 50 mcg/g, BD Dithranol in paste or petroleum (D) 0.05%-4%, 24 hour application on alternate days	At 2 weeks: PASI No adequate data available	TW: C: 0/10; D: 0/10 WA: C: 0/10; D: 0/10 WF: C: 0/10; D: 0/10 AE: C(L): 4/10; D(L): NR; (S): NR
Veien et al, 1997	Tacalcitol ointment (T) 4mcg/g, OD plus tacalcitol vehicle OD Calcipotriol ointment (C) 50 mcg/g, BD	At 8 weeks: TSS, adjusted for baseline: T: -4.03 (2.33SD; N=142); C: -5.05 (2.32SD; N=145) TSS: T: 3.61 (N=142); C: 2.40 (N=145) Investigator global assessment: (6-pt: re-scaled as 0=worse; 5=clear) T: 3.30 (1.14SD, N=115); C: 3.85 (0.95SD, N=112)	TW: NR WA: NR WF: NR AE: T(L): 18/142; C(L): 17/145; T(S): 0/142; C(S): 0/145

Table F: Summary findings from head-to-head trials (continued)

Trial	Comparisons	Reported Outcome measures	Withdrawal and Adverse Events*
Vladimirov et al, 1994	Calcipotriol cream (C) 50 mcg/g, BD Betamethasone (B) 17-valerate ointment 0.1%, BD	At 6 weeks: PASI: C: 0.97 (N=32); B: 1.54 (N=28)	TW: NR WA: NR WF: NR AE: NR
Wall et al, 1997 and 1998	Calcipotriol ointment (C) 50 mcg/g, BD Dithranol (D) 0.1%-2% (Dithrocream®), OD	At 3 months: Investigator global assessment: (5 pt: 0=worse; 4=clear) C: 2.48 (0.88SD, N=153); D: 1.69 (0.96SD, N=131)	TW: NR WA: C(L): 9/161; D(L): 20/145 WF: NR AE: C(L): 28/161; D(L): 71/145; (S): NR