H.6 Topical therapies for chronic plaque psoriasis – trunk and limbs

H.6.1 VITAMIN D OR VITAMIN D ANALOGUE VS POTENT CORTICOSTEROID

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
J. M. Camarasa, J. P. Ortonne, and L. Dubertret. Calcitriol shows greater persistence of treatment effect than betamethasone dipropionate in topical psoriasis therapy. J.Dermatol. Treat. 14 (1):8-13, 2003. REF ID:	Multicentre (20 centres in Europe) DESIGN Between patient Patient delivery ALLOCATION Random Method of randomisation: not reported Concealment: unclear BLINDING Double-blind (patient / investigator): no details given	N=258 **Drop-outs (don't complete the study):** N =15 6 (4.7%) calcitriol and 9 (6.9%) betamethasone **Reasons:** See below	**INCLUSION CRITERIA** Adults, **moderate to severe** chronic plaque psoriasis (≥ 2 on global severity score) **EXCLUSION CRITERIA** Systemic or intralesional therapy or photo(chemo)therapy in previous two mths; medications or conditions that might interfere with the assessment of study drugs; concomitant bacterial, fungal or viral skin conditions; clinically relevant abnormalities in laboratory parameters (calcium homeostasis and renal function); pregnancy or lactation; absence of adequate contraception, where appropriate	N=128 **Calcitriol** 3 µg/g **Formulation**: ointment **Frequency** twice daily Who administered not clear. --- **Both arms:** medication	N=130 0.05% **betamethasone dipropionate** **Formulation**: ointment **Frequency** twice daily	**Treatment duration**: 6 weeks (or until complete clearance) **Post-treatment follow-up**: 8 wk for those who were at least considerable improvement (not needing further therapy)	**Primary outcome**: IAGI (6-pt: worse to cleared) PASI Relapse rate Overall global severity of lesions (5pt: 0, none to 4,	Galderma Laboratories

CAMARASA 2003	• **Washout period**: 1 weeks using only emulsifying ointment and/or tar shampoo • **Sample size calculation**. 104 per arm to detect mean shift of 0.6 on IAGI at endpoint at 5% significance with 80% power • **ITT analysis** yes (LOCF)	Note: of responders 9 in calcitriol and 8 in betamethasone groups were lost to follow-up post-treatment	No explicit or implicit exclusion for face or scalp psoriasis. BC: Yes Age: 43.5 (14.3SD: range: 15 to 83) Gender (%M): 64.3% Duration of psoriasis (mths): mean: 199.2 (157.5SD: range: 1 to 745) %BSA: 25.5 (22.9SD: range: 1 to 95) PASI: 15.4 (10.6SD)	applied to all lesions except on the head Ointments to be left for at least 8 hours and washed off before each re-application (morning and night)			very severe) Proportion remaining in remission (non-randomised subgroup analysis)	

Effect Size

Outcomes

<u>Efficacy (ITT population)</u>

IAGI at end of treatment/6 weeks	**Calcitriol n=128**	**Betamethasone n=130**

IGAI marked improvement to clear (remission)	***67 (52.3%)***	***81 (62.3%)***
IGAI clear	12	26
IGAI considerable improvement	55	55
IGAI definite improvement	34	26
IGAI minimal improvement	18	14
IGAI no change	6	5
IGAI worse	3	4

PASI; mean±SD	**Calcitriol n=128**	**Betamethasone n=130**	**p-value (between group)**
Baseline	15.7±11.9	15.02±9.43	
Endpoint	5.4±5.06	3.67±3.79	
Absolute reduction	10.3±10.6	11.4±9.67	>0.05
% reduction	65.6%	75.9%	

Relapse: among those in remission (Calcitriol n=67; Betamethasone n=81)

	Calcitriol n=58	**Betamethasone n=73**	**p-value**
Relapse requiring re-treatment within 8 weeks of study endpoint	30 (52%) Mean: 25.3 days post-treatment	55 (75%) Mean: 23.4 days post-treatment	
Responders still in remission at 8 wks	28 (48%)	18 (25%)	<0.01

Withdrawals

	Calcitriol n=128	**Betamethasone n=130**
During treatment phase		
Withdrawal due to lack of efficacy	4	3
Withdrawal due to AEs	2	1
Withdrawal due to other reason	0	5
During post-treatment phase		
	Calcitriol n=67	**Betamethasone n=81**

Total withdrawal	9 (13.4%)	8 (9.9%)

Author's conclusion

- Twice-daily applications of either calcitriol 3 microg/g ointment or betamethasone dipropionate 0.05% ointment can be used to good effect in the treatment of chronic plaque psoriasis.
- The beneficial effect is likely to persist for longer following calcitriol treatment

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Molin, L; Cutler, TP; Helander, I; Nyfors, B; Downes, N; and the Calcipotriol study group. Comparative efficacy of calcipotriol (MC903) cream and betamethasone 17-valerate cream in the treatment of chronic plaque psoriasis. A randomised, double-blind, parallel group multicentre study. B J of Dermatolog	RCT – between subjects design. Multicentre study from 41 centres in Finland, Norway, Sweden and UK • **Setting:** outpatient • **Randomised**: Unclear method. • **Washout period**: 2 weeks • **Double blind.** Subjects and assessors (but no details of method given) • **Allocation concealment**	Total N: 421 **Drop-outs (don't complete the study):** Total = 21 n=14 from calcipotriol n=7 from betamethasone group. Full reasons not given, but 6 in calcipotriol group and 3 in betamethasone group left	**Inclusion criteria:** Outpatients aged 18 or over, of either sex, with a clinical diagnosis of stable, mild-to-moderate chronic plaque type psoriasis on the limbs and/or trunk **Exclusion criteria:** None reported. No explicit mention of face/scalp psoriasis being an exclusion criterion. **Baseline comparability**: Psoriasis comparable (similar PASI), demographics not reported (but states that groups were matched for age, sex and race)	**Calcipotriol** 50µg/g (N=210) **Formulation**: cream **Frequency** twice daily Who administered (patient or investigator) not described.	**Betamethasone 17-valerate** 1mg/g (0.1%) (N=211) **Formulation**: cream **Frequency** twice daily	**Treatment duration:** up to 8 weeks or until clearing. No long term FU described.	**1° outcome:** Patients and investigators gave assessment of response as cleared, marked or slight improvement (PAGI or IAGI) Adverse events **2° and other outcomes:** PASI – mean % reduction	Leo Pharmaceutical Products.

y 1997;136:89-93 **Ref ID: MOLIN1997A**	Not reported • **Sample size calculation** the study should allow detection of a difference of 10% between treatment groups with respect to mean change in PASI, and a SD of 35% for change in PASI from baseline. N=200 in each group needed. • **ITT analysis** not reported • **Drop-outs/withdrawals**. N=21	due to adverse events.					in PASI from baseline to end of treatment PASI (0 to 64.8) Severity scores Investigator global assessment of response (5 pt: worse to cleared) Patient global assessments of response (5 pt: worse to cleared) Laboratory assessment	
Effect Size								

Outcomes

Efficacy (available case)

Outcome	Calcipotriol cream (N=205)	Betamethasone cream (N=207)	p-value
% reduction in PASI at end of treatment	47.8%	45.4%	0.51
IAGI: marked improvement or clear at end of treatment	119 (58%)	116 (56%)	0.9

Time-to-remission/maximum effect

- Based on % change in PASI and change in thickness treatment effect for both interventions has not reached a plateau at 8 weeks

Adverse events (available case)

Outcome	Calcipotriol (N=207)	Betamethasone (N=210)	**P-value**
Withdrawal due to poor tolerability (skin irritation)	6	3	0.33
Skin atrophy/translucency of skin	0	3	-

Authors' conclusion

- Calcipotriol was effective and well-tolerated, and equal in effect to betamethasone.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Bruce S, Epinette WW, Funicella T, Ison A, Jones EL, Loss RJ, et al. Comparative Study of Calcipotriene (Mc 903) Ointment and Fluocinonide Ointment in the Treatment of Psoriasis. Journal of the American Academy of Dermatology 1994;31(5 Pt 1):755–9.	**RCT** **DESIGN** Between patient Patient delivery **ALLOCATION** Random Method of randomisation: not reported Concealment: Unclear **BLINDING** Double-blind (patient / investigator; not described) • **Washout period:** 2 weeks before study • **Sample size**	**Total N:** 114 (1 excluded for not meeting entry criteria) **Loss to follow up:** 15 (13.2%) **Drop-outs (don't complete the study):** Total = 14 (%) Noncompliance: 7 AEs: 3 (1 fluocinonide-related	INCLUSION CRITERIA Stable plaque psoriasis; adults (18 years or older); at least mild overall severity (2 of a possible 8); at least moderately severe plaque elevation (4 of a possible 8); 5-20% body surface area affected **(NB face and scalp excluded)** Women of childbearing potential were required to have a negative urine pregnancy test and agree to use an effective method of birth control. EXCLUSION CRITERIA Pregnancy; lactation; inadequate contraception; sensitivity to test medications; recent topical, UV or systemic treatment; recent involvement in other trials; planned sun exposure, erythrodermic or pustular psoriasis; plaque psoriasis that was spontaneously regressing or rapidly worsening	**n=** **Calcipotriol 0.005%** **Formulation:** ointment **Class:** vitamin D analogue **Frequency** twice daily **Amount used:** not stated	**n=** **Fluocinonide 0.05%** **Formulation**: ointment **Frequency** twice daily	**Treatment duration:** 6 weeks **Assessments at:** baseline and 2, 4 and 6 weeks **Follow-up after end of treatment:** none	Investigator global assessment on 7-point (0-6) ordinal scale ranging from "completely clear" to "worse" **Primary efficacy parameter:** not stated	Westwood Squibb Pharmaceuticals Inc

Ref ID: BRUCE1994	**calculation** not reported • **ITT analysis:** yes for AE and withdrawal (assumptions not stated) **Setting:** Outpatients	and 2 not treatment-related) 4 voluntary withdrawal	BC: Yes Age: 44.1 (14.6SD; range: 20 to 77) Gender (%M): 60.2% Severity: Mean duration of current episode (days): 142 (range: 0 to 601) Overall severity score, mean: 4.5 % body surface area treated: 9.61% (range 5-20%)					

Effect Size

Outcomes

<u>Efficacy</u>

Mean psoriasis scores shown graphically only: Table shows p values for Calcipotriol n=57 vs. Fluocinonide n=56

	Physician's global assessment
2 weeks	not stated
4 weeks	<0.05

6 weeks	<0.05 (90% Calcipotriol patients at least moderately improved vs. 72% with Fluocinonide

Time-to-effect

- Calcipotriol: significant change by 2 weeks and further improvement thereafter (no data for time to max effect)

Withdrawals: not stated by group

Adverse events related to treatment

	Calcipotriol n=57	**Fluocinonide n=56**
Total AE	12 AE in 10 people (7 mild; 5 moderate): burning sensation (5); pruritis (4); contact dermatitis (1); erythema (1); rash (1)	5 AE in 4 people (3 mild; 2 moderate): worsening or flare of psoriasis (2); pruritis (1); stinging (1); acne (1)
Withdrawal due to AEs	0	1

Authors' conclusion

Calcipotriol was superior to Fluocinonide in the treatment of plaque psoriasis.

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Kragballe K, Gjertsen BT, De Hoop D, Karlsmark T, van de Kerkhof PC, Larkö O, Nieboer C, Roed-Petersen J, Strand A, Tikjøb G. Lancet. 1991 26;337(8735):193-6.

REF ID:KRAGBALLE1991</td>
<td>Multicentre (Europe)

DESIGN

Within patient

Patient delivery

ALLOCATION

Random

Method of randomisation: not stated

Concealment: unclear

BLINDING

Double-blind (patient / assessor)

WITHDRAWAL / DROPOUT

Described</td>
<td>N=345

Drop-outs (don’t complete the study):

N=15 (4.3%)

Reasons: default, 6 (1.7%); voluntary, 4 (1.2%); adverse events, 3 (0.9%); unsatisfactory treatment response, 2 (0.6%). Information on which drug was</td>
<td>INCLUSION CRITERIA

Adult; symmetrical chronic plaque psoriasis; inpatients and outpatients

EXCLUSION CRITERIA

Unstable psoriasis; recent systemic or UV therapy; hypercalcaemia; impaired renal/ hepatic function; high dose calcium/Vitamin D intake; unresponsive to corticosteroids; concomitant medication

<table>
<tr><th></th><th>Calcipotriol side</th><th>Betamethasone side</th></tr>
<tr><td>Male/ female</td><td colspan="2">203/142</td></tr>
<tr><td>Mean age (range)</td><td colspan="2">45.2 (18-90) years</td></tr>
</table>
</td>
<td>N= 345

Calcipotriol ointment, 50 mcg/g

Formulation: ointment

Frequency: Twice daily, up to 50 g per week without occlusion to affected skin areas

Note: Both ointments were similar in appearance and texture. Patients were</td>
<td>N=345

Betamethasone valerate ointment, 1 mg/g, 0.1%)

Formulation: ointment

Frequency:

Twice daily, up to 50 g per week without occlusion to affected skin areas</td>
<td>6 weeks (evaluated every 2 weeks)</td>
<td>PASI

Patient assessment of response

Withdrawals</td>
<td>Not stated</td>
</tr>
</table>

	• **Setting:** Inpatients and outpatients • **Washout period**: 2 weeks (patients received an emollient to use as required) • **Sample size calculation**. Yes, protocol required 300 patients to allow detection of 5% difference between treatments in mean change in PASI (power 90%; alpha = 5%) • **ITT analysis:** Yes for safety (assumptions not sated). 3	associated with withdrawal was provided in case of withdrawals due to lack of efficacy or adverse events (see below)	Mean disease duration: 19.5 (0.5-76) years Pre-treatment PASIs: 8.36 (0.6-48.5); 8.33 (0.6-48.5)	not allowed to apply the study drugs to the face or scalp; in those regions an emollient or a low-strength corticosteroid was used				

	patients excluded from efficacy analysis (2 defaulted before first visit and didn't contribute any data; 1 had lesions that were not symmetrically distributed)							

Effect Size

Outcomes

Efficacy (ACA as reported)

	Calcipotriol-treated side (N=342)	Betamethasone-treated side (N=342)	95% CI for difference	p value
Mean % reduction in PASI at the end of treatment	68.6%	61.4%	5.1-9.8	<0.001
Proportion of patients who reported a pronounced improvement or psoriasis cleared at the end of treatment (PAGI)	82.1%	237 (69.3%)	-	-

Time to effect and time to max effect

- The PASI score was significantly ($p<0.001$) lower on the calcipotriol-treated side than on the betamethasone-treated side at all time-points. For

both treatments, the rate of decrease was greatest during the first two treatment weeks but the decline continued during the next four weeks

- The patients assessment of the response to treatment significantly ($p<0.001$) favoured calcipotriol at all visits

Toxicity (ITT)

	Calcipotriol-treated side	Betamethasone-treated side
Patients withdrawn due to adverse events	2 (redness and itching in 1 and erythematous papules in the other)	1 (eczema)
Patients withdrawn due to unsatisfactory treatment response	1 (one patient both sides)	2 (one patient both sides; one betamethasone-treated side only)

The investigators classified the reasons for withdrawal as default in 6 patients (1.7%); voluntary in 4 patients(1.2%); adverse events in 3 patients (0.9%) and unsatisfactory treatment response in 2 patients (0.6%) (1 on both sides and 1 on the betamethasone-treated side only).

Authors conclusion

- Calcipotriol ointment was superior to betamethasone valerate ointment in psoriasis vulgaris

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Cunliffe WJ, Berth-Jones J, Claudy A, Fairiss G, Goldin D, Gratton D, Henderson CA, Holden CA, Maddin WS, Ortonne JP, Young M. Comparative study of calcipotriol (MC 903) ointment and betamethasone 17-valerate ointment in patients with psoriasis vulgaris. Journal of the American	**RCT** multicentre (46 centres in Canada, England, France and Ireland). **DESIGN** Between patient design Delivery unclear Analysis found no centre effect, and so analysis was pooled. **ALLOCATION** Random Method of randomisation: balanced blocks of 10 according to	Total N: 409 (UK 238, Canada 89, France 63, Ireland 19) **Drop-outs (don't complete the study):** Total =38 (9.3%) withdrew from the study.; 21 (10.2%) received calcipotriol and 17 (8.3%) betamethasone valerate. In 6 patients from each group an **unsatisfactory treatment response** caused or contributed to withdrawal	**INCLUSION CRITERIA** Stable plaque psoriasis; adult; outpatients; psoriasis in any of: arms, legs or trunk. **EXCLUSION CRITERIA** Risk of pregnancy; pregnancy; lactation; recent systemic antipsoriatic treatment; acute guttate or pustular psoriasis; hypercalcaemia; significant hepatic or renal disease; patients taking vitamin d or calcium tablets; poor **Previous therapy**: Not reported, but washout period of 2 weeks given. **Baseline comparability: Yes (all NS)**	Calcipotriol ointment, 50mcg/g, BD None applied to face, scalp or genital region. Thin layer applied without occlusion to the affected skin, and a maximum of 100g of ointment per week was allowed. **n= 205** **Formulation**: ointment	Betamethasone- 0.1% 17-valerate 1 mg/g, BD None applied to face, scalp or genital region. Thin layer applied without occlusion to the affected skin, and a maximum of 100g of ointment per week was allowed. **n= 204**	**Treatment duration:** 6 weeks **Follow up:** 6 weeks (from start of treatment)	Outcomes assessed at 2,4 and 6 weeks. Primary outcome time point should be 6 weeks, as only this point measured the effects of a whole course of therapy. Also full data only given for 6 weeks. Change in PASI	Leo Pharmaceuticals

<table>
<tr>
<td>Academy of Dermatology 1992; 5:736-743. Ref ID: CUNLIFFE1992</td>
<td>a computer generated random

numbers table

Concealment: unclear

BLINDING

Double-blind (patient / investigator); adequate

Washout (from usual Rx): 2 weeks (emollient only)

Sample size calculation: 150 per group was the target based on sample size calculation, based on a PASI MD of 7%.</td>
<td>In the calcipotriol group the following adverse events caused or contributed to withdrawal : local irritation/burning (3 patients), eczema/pruritis on the scrotum (1 patient), and hypercalcaemia (1 patient). In the betamethasone valerate group skin infection caused withdrawal in 2 patients and marginal hypercalcaemia in one.

Follow up data was unavailable for 8 subjects (4 from each</td>
<td>
<table>
<tr><td></td><td>CP</td><td>BM</td></tr>
<tr><td>% men</td><td>55.1</td><td>56.4</td></tr>
<tr><td>Age mean (sd)</td><td>43.6 (16)</td><td>46.2 (14.9)</td></tr>
<tr><td>Duration of psoriasis (yrs)</td><td>15.6 (12.1)</td><td>16.8 (11.8)</td></tr>
<tr><td>% with 3 body regions affected</td><td>77.6 %</td><td>83.8%</td></tr>
<tr><td>PASI mean (sd)</td><td>8.7 (5.8)</td><td>9.4 (6.6)</td></tr>
</table>
</td>
<td>Frequency: 2 x per day

Concomitant therapies – other medication known to affect the course of the disease was not allowed.</td>
<td>Formulation : ointment

Frequency: 2 x per day</td>
<td></td>
<td>PAGI (described as patients overall assessment of improvement, on a 5 point scale)

Adverse events

withdrawal due to toxicity

Withdrawal due to lack of efficacy</td>
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	ITT analysis: Modified ITT for efficacy 38 did not complete the study but only 8 excluded from analysis (7 due to dispensing error and 1 protocol violation). For others lost to follow-up outcomes were assessed on withdrawal **ITT for withdrawals** Assumptions not stated	group). This was due to a dispensing error in 7 and 1 started systemic BM 2 weeks post randomisation. **Noncompliance:** Not reported						
Effect Size Outcomes **<u>Efficacy</u>** **<u>Change in PASI (2,4 and 6 weeks)</u>**								

Change from baseline	CP (n=201) mean (sd)	Betamethasone (n=200) mean (sd)
Change in PASI 2 weeks	3.19 (3.61)	3.39 (2.16)
Change in PASI 4 weeks	4.37 (4.70)	4.50 (5.33)
Change in PASI 6 weeks	5.5 (9.54)	5.32 (6.06)

PAGI (described as "patients overall assessment of improvement", on a 5 point scale, so very likely to be the PAGI, but unclear)

	CP	Betamethasone
Number cleared or marked improvement – 6 weeks	123/201	101/200

Time to effect and time to maximum effect

In both groups there was increasing reduction in PASI over 6 weeks, which was statistically significant at all time points; the greatest reduction was during the first 2 weeks.

ll adverse events

	CP	Betamethasone
lesional/perilesional irritation	40/205	8/204
irritation/eczema of face or scalp	4/205	0/204
erythema/infiltration/desquamation	8/205	3/204
skin infection	1/205	5/204
misc minor skin problems	11/205	2/204
Non dermatologic	6/205	3/204
nausea/vomiting	2/205	0/204
increased bronchospasm	1/205	0/204
headache	1/205	1/204
hot flushes/flue like symptoms	1/205	0/204
fatigue	1/205	0/204
upper abdominal pain	1/205	1/204
arthralgia	0/205	1/204

Withdrawal due to adverse events

	CP	Betamethasone
Adverse effects	**5/205**	**3/204**
local irritation/burning	3/205	0/204

eczema/pruritis of scrotum	1/205	0/204
hypercalceamia	1/205	1/204 (marginal)
skin infection	0/205	2/204

Withdrawal due to lack of efficacy

	CP	**Betamethasone**
Withdrawal because of lack of efficacy	6/205	6/204

Authors' conclusion: Calcipotriol ointment was as effective as betamethasone-17-valerate ointment as measured by the PASI and superior as measured by self assessment in patients with stable plaque psoriasis.

H.6.2 VITAMIN D OR VITAMIN D ANALOGUE VS PLACEBO

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
A. Langner, H. Verjans, V. Stapor, M. Mol, and M. Fraczykowska. 1alpha,25-Dihydroxyvitamin D₃ (calcitriol) ointment in psoriasis. J.Dermatol.Treat. 3 (4):177-180, 1992. Ref ID: **LANGNER1992**	DESIGN **Within patient** Patient delivery ALLOCATION Random Method of randomisation: Unclear Concealment: unclear BLINDING Double-blind (patient / investigator) – no details given **Washout**: 2 weeks **Sample size**	N: 29 **Drop-outs (don't complete the study): 0**	INCLUSION CRITERIA **Severe** chronic psoriasis; symmetrical lesions; adult; outpatients EXCLUSION CRITERIA Pregnancy or inadequate contraception. BC: Yes Age: mean: 40.5 (range: 16-77) Gender (%M): 69.0% **Note:** lesions to be treated were similar with respect to global severity and individual signs (selected lesions were on arms, legs or trunk)	n: 29 Calcitriol (3 µg/g) **Formulation**: ointment **Frequency:** Twice daily Who administered (patient or investigator): not stated. --- **Both arms:** 2	n: 29 Vehicle **Formulation**: ointment **Frequency:** Twice daily Who administered (patient or investigator): not stated. ---	Treatment duration up to 6 weeks – but less if at least one of the 2 selected lesions cleared. Longer term FU: none	Clear or marked improvement on Investigator global assessment (6-pt: worse to cleared) AEs	Not reported

	calculation: not stated **ITT analysis:** not relevant		No explicit mention that face and scalp lesions were excluded.	wk run in period when all lesions were treated with vehicle ointment	**Both arms:** all ointments washed off 8-12 hours after application			

Effect Size

Timing of assessment: There was still some improvement occurring in mean global improvement at week 6.

IAGI

IAGI: marked improvement or clear	**Calcitriol (N =29)**	**Vehicle (N=29)**
6 weeks/end of treatment	21 (72.4%)	9 (31.0%)

Withdrawals

Outcome	**Calcitriol (N =29)**	**Vehicle (N=29)**
Withdrawal due to AEs	0	0
Withdrawal due to lack of efficacy	0	0

Authors' conclusion

- Twice daily 3 µg/g calcitriol ointment appears to be a safe and effective topical treatment for severe chronic plaque psoriasis

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
A. Langner, H. Verjans, V. Stapor, M. Mol, and M. Fraczykowska. Topical calcitriol in the treatment of chronic plaque psoriasis: a double-blind study. Br.J.Dermatol. 128 (5):566-571, 1993. Ref ID: **LANGNER1993**	DESIGN Within patient Patient delivery ALLOCATION Random Method of randomisation: unclear Concealment: unclear BLINDING Double-blind (patient / investigator) – but not explained **Washout**: 2 weeks **Sample size**	N: 32 **Drop-outs (don't complete the study): 2** 1 due to AE due to calcitriol 1 due to lack of efficacy (treatment side not stated)	INCLUSION CRITERIA Bilateral; symmetrical; severe chronic plaque psoriasis; outpatients. EXCLUSION CRITERIA Pregnancy or inadequate contraception. Use of calcium; vitamin D or analogues; calcium-containing antacids; digitalis; thiazide diuretics or glucocorticosteroids. Age: mean: 42.4 (range: 16 to 77) Gender (%M): 62.5% Severity: global severity score (0 to 4): 3.5 Areas for Rx were arms legs and trunk, but no explicit exclusion for face and scalp psoriasis	n: 32 Calcitriol (15 µg/g) *Note: calcitriol is licensed at 3 µg/g* **Formulation**: ointment **Frequency:** Twice daily ---------- **Both arms:** 2 wk open run-in period when all lesions were treated with	n: 32 Vehicle **Formulation**: ointment **Frequency:** Twice daily ---------- **Both arms:** selected areas were located on the arms, legs and/or trunk and were similar, symmetrical and severe	Treatment duration up to 6 weeks – but less if at least one of the 2 selected lesions cleared. No longer term FU.	Clear or marked improvement on Investigator global assessment (6-pt: worse to cleared) AEs Lab values	Not reported

	calculation: not stated **ITT analysis:** yes (LOCF)			vehicle ointment (twice daily) Who administered (patient or investigator) not described.	All other psoriatic lesions were treated with vehicle twice a day. All ointments washed off 8-12 hours after application			

Effect Size

IAGI

IAGI: marked improvement or clear	**Calcitriol (N =32)**	**Vehicle (N=32)**
6 weeks/end of treatment	24 (75.0%)	13 (40.6%)

Time to max response

- Based on graphical data the maximum response to calcitriol based on mean IAGI was not seen within the 6 weeks treatment period; however, the increase in improvement was much more gradual after 4 weeks
- Similarly, based on graphical data of mean global severity scores, there was an initial rapid improvement over the first 2 weeks, and a continued gradual improvement between 2 and 6 weeks

Withdrawals

Outcome	Calcitriol (N =32)	Vehicle (N=32)
Withdrawal due to AEs	1	0
Withdrawal due to lack of efficacy	1	1

Authors' conclusion

- Twice daily 3 µg/g calcitriol ointment appears to be a safe and effective topical treatment for severe chronic plaque psoriasis

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
A. Highton and J. Quell. Calcipotriene ointment 0.005% for psoriasis: a safety and efficacy study. Calcipotriene Study Group. J.Am.Acad.Dermatol. 32 (1):67-72, 1995. Ref ID: **HIGHTON1995**	10 centres in USA DESIGN Between patient ALLOCATION Random Method of randomisation: not reported Concealment: unclear BLINDING Double-blind (patient / investigator) **Washout**: 2 weeks for topical treatments for psoriasis	N: 277 **Drop-outs (don't complete the study): 30 (10.8%)** **Note:** all patients were included in the safety population Reasons for withdrawal: 14 because of adverse events (6 calci group and 8 in veh group). Other reasons not	Severity: Mild-to-severe INCLUSION CRITERIA Moderately severe stable plaque psoriasis; plaque elevation score ? 4 (0 to 8); Not pregnant or nursing during the duration of the study. EXCLUSION CRITERIA Recent topical or systemic psoriasis treatment, prolonged exposure to sunlight, phototherapy; photochemotherapy; hypercalcaemia; erythrodermic or pustular psoriasis. Calcium, vitamin A or D supplements BC: Clinical severity comparable, demographics unclear	n: 139 Calcipotriol (0.005%) **Formulation**: ointment **Frequency:** Twice daily **Note:** Instructed to apple ointment to all plaques except on the face and scalp Who administered drug (patient or	n: 138 Vehicle **Formulation**: ointment **Frequency:** Twice daily Who administered (patient or investigator): no details given	Treatment duration up to 8 weeks. No longer term FU.	Investigator global assessment (7-pt: worse to completely clear) AEs and laboratory tests	Bristol Myers Squibb

	Sample size calculation: not stated **ITT analysis:** not for efficacy but all were evaluable for safety	reported.	TSS (0 to 8): 3.90 BSA: 9.1% No use to face or scalp allowed.	investigator): no details given				

Effect Size

IAGI

IAGI: marked improvement or clear (≥75% improvement)	**Calcipotriol (N =124)**	**Vehicle (N=123)**
Week 1	9.6%	0.0%
Week 2	27.8%	2.3%
Week 4	54.2%	5.6%
Week 6	65.1%	11.6%
8 weeks/end of treatment	87 (69.8%)	23 (18.6%)

Time to response

- After 1 week of treatment the calcipotriene treated group had already achieved statistically significantly lower mean scores for plaque elevation, erythema and scaling (p=0.043) and for IAGI (p<0.001); this difference was maintained at 2, 4, 6 and 8 weeks of treatment (p<0.001)

Time to max response

- Based on graphical presentation of overall disease severity over time the calcipotriene curve was beginning to plateaux after 6 weeks of treatment

Withdrawals

Outcome	Calcipotriol (N =139)	Vehicle (N=138)
Withdrawal due to AEs	6	8
(Aggravated psoriasis)	(3)	(6)

Authors' conclusion

- Calcipotriene is safe and effective for the treatment of moderate-to-severe plaque psoriasis

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Dubertret, L., Wallach, D., Souteyrand, P., Perussel, M., Kalis, B., Meynadier, J., Chevrant-Breton, J., Beylot, C., Bazex, J., Jessen Jurgensen, H. **Ref ID:** DUBERTRET 1992	RCT 8 centre study within-patient Recruitment October to April (1988-1989) to minimise effect of UV radiation DESIGN Within patient Patient delivery • **Setting:** not reported • **Randomised**: yes (method of randomisation not reported)	Total N: 65 **Drop-outs (don't complete the study):** Total = 8 During the initial 4 weeks of the study 4 patients were withdrawn; 3 patients defaulted and one patient left because of adverse events. During the	**Inclusion criteria:** People older than 18 years with bilateral, symmetric psoriasis of the arms, limbs, and/or trunk, which had remained stable in extent and severity during 2 weeks of treatment with an emollient only. **Exclusion criteria**: People with guttate psoriasis, pustular psoriasis, psoriasis of the scalp and/or face only, or which was restricted to the elbows and/or knees; people on systemic antipsoriatic treatment or UV therapy in the previous 10 weeks and concomitant therapy with calcium or more than 400IU of vitamin D daily; or any other medication that might affect the course of the disease; patients with hepatic or renal impairment and those intending to spend time in a sunny climate.	**N=65** **Calcipotriol (50 µg/gm)** **Formulation**: ointment **Frequency:** twice daily to all affected areas on half of body **Note:** no trial medication applied to face or scalp	**N=65** **Placebo** **Formulation:** ointment **Frequency:** twice daily to all affected areas on half the body	Treatment duration: 8 weeks – randomised treatment phase: 4 weeks Preferred treatment phase: 4 weeks	**1° outcome: severity rated using PASI score at end of 4 week randomised trial phase** **2° and other outcomes:** Adverse events, laboratory tests	Leo Pharmaceutical Products, Ballerup, Denmark

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Washout period: 2 weeks
Blinded: investigator and participant
Allocation concealment: not reported
Sample size calculation: to achieve 25% change in PASI from baseline to end of treatment, type I error=0.02, type II error=0.10, n=60 required
ITT analysis: no
Drop-outs/withdrawals: n=4, 3 defaulted, 1 withdrew due to adverse events

</td>
<td>preferred treatment phase 4 patients withdrew from the study: one patient was withdrawn at week 2 because of marginal hypercalcemia and three withdrew for ‘administrative’ reasons as they ran out of medication</td>
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Baseline comparability: Comparable.

<u>Baseline characteristics:</u>
<table>
<tr><td>N total =66</td><td>Men = 46, Women = 20</td></tr>
<tr><td>Duration of psoriasis</td><td>13.3 years (range 0.3 to 40.0 years)</td></tr>
<tr><td>Antispsoriatic treatment given in previous three years</td><td>N=64 (97%)</td></tr>
<tr><td>Receiving treatment for their psoriasis (mainly topical steroids) at pre-study assessment</td><td>54.5%</td></tr>
<tr><td>Lesions widely distributed, affecting trunk and both upper and lower</td><td>Approximately 70% of cases</td></tr>
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			extremities					

Effect Size

Efficacy

PASI

PASI during initial 4-week randomised treatment phase	**Calcipotriol**	**Placebo**	**Difference between treatments***
Baseline (n=65)	14.2 ± 7.5	14.1 ± 9.9	-
After 2 weeks	8.6 ± 7.5	11.3 ± 9.1	-2.8 ± 4.3
% change from baseline (n=62)	41.2 ± 25.7	21.4 ± 24.5	-19.8 ± 24.4
After 4 weeks	6.3 ± 6.5	9.2 ± 8.3	-3.0 ± 4.6
% change from baseline (n=60)	58.6 ± 31.7	35.4 ± 37.2	-23.2 ± 30

Data are expressed as mean ± 1 standard deviation

*All difference between treatment are statistically significant at $p<0.001$ (paired t test)

IAGI

IAGI during initial 4-week randomised treatment phase	Calcipotriol (n=62)	Placebo (n=62)
Marked improvement or clear, n (%)	46 (74.2%)	11 (17.7%)

Time-to-remission/maximum effect

- Based on mean PASI over time *in those who preferred calcipotriol* the treatment effect for calcipotriol had not reached a plateau at 4 weeks, and in those who continued on calcipotriol during the preferred treatment phase, there was a continued but more gradual reduction in PASI score between 4 and 8 weeks

Safety at 8-weeks (randomised and non-randomised phase):

Adverse events	Calcipotriol	Placebo
Lesional or perilesional irritation	10	12
Eczematous reaction	1	
Burning sensation on both sides of body	1	
Withdrawal due to AEs	**2**	**1**

Preferred treatment phase (N=61 entered this phase, N=55 completed):

Calcipotriol applied on both sides of body	N=46
Placebo applied on both sides of body	N=5

Continued with assigned treatment as during initial randomisation phase	N=10

Authors conclusion

- Topical application of up to 50gm of calcipotriol ointment per week was found to be an effective and safe treatment of psoriasis vulgaris.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
P. C. van de Kerkhof, T. Werfel, U. F. Haustein, T. Luger, B. M. Czarnetzki, R. Niemann, and V. Planitz-Stenzel. Tacalcitol ointment in the treatment of psoriasis vulgaris: a multicentre, placebo-controlled, double-blind study on efficacy and safety. Br.J.Dermatol. 135 (5):758-765, 1996. **Ref ID:**	RCT Multicentre study DESIGN Within patient Patient delivery ALLOCATION Random Method of randomisation: not reported Concealment: unclear BLINDING Double-blind (patient / investigator) – no details given • **Washout period**: 2 weeks for all patients	Total N: 122 **Drop-outs (don't complete the study):** Total = 19 (15.6%) Withdrawal is not stratified according to treatment reasons for withdrawal: see table below. Other reasons were patients did not return (n=3),	INCLUSION CRITERIA Age 15-80 years; stable plaque psoriasis; Caucasian adults and adolescents EXCLUSION CRITERIA Increased serum calcium or serum phosphate level; recent systemic (2 months) or topical (1 month) 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 **Note:** psoriatic lesions chosen as test areas **could be located anywhere except the scalp**; they	**n=122** **Tacalcitol** (4µg/g) **Formulation**: ointment **Frequency** once daily Who administered unclear. Both arms: Concomitant therapies – test areas only treated with white petroleum or emollient during wash-	**n=122** **Vehicle** (paraffin oil, diisopropyl adipate and white petroleum) **Formulation**: ointment **Frequency** once daily	**Treatment duration:** up to 8 weeks (or until clear) **Post-treatment follow-up**: 4 weeks	**Primary outcome:** Time-to-clearance AEs and lab tests Relapse	Hermal Kurt Herrmann

VANDERKERKHOF1996	• **Sample size calculation** not reported • **ITT analysis:** yes; also analysed per protocol population	patient refused further participation (n=1) and unknown (n=1). Group breakdown unknown.	were required to have TSS >5 and at least moderate (score of 2) severity for erythema and desquamation. The difference in TSS between tacalcitol and placebo treated lesions had to be ≤1. The test lesion also had to be comparable for localisation and area **Note:** in 24.6% of patients test lesions were localised on the face or face and other parts of the body BC: Inadequately reported Age: 44.8 (13.69SD) Gender (%M): 62.3% Duration (mths): 233.5 (175.9SD) BSA: 5.6%	out and follow-up period Emollients, 2-3% salicylic acid in white petroleum or tar shampoos permitted for lesions **other than the test areas** throughout the whole study period				
Effect Size Outcomes								

Efficacy (ITT)

Time-to-remission/maximum effect

- Based on graphical data of mean TSS score over time the improvement in disease was most rapid over the first 4 weeks but had not reached a maximum by the end of treatment (wk 8) as gradual improvement was still apparent
- Time to complete healing could not be assessed as the duration of treatment was too short for most patients to become completely clear

Relapse

- An exact evaluation of relapses could not be made as the duration of treatment was too short for most patients to become completely clear
- 34/97 patients who were followed-up had an aggravation
    - This aggravation was bilateral in 28/34; on the tacalcitol side in 3/34; and on the placebo side in 3/34

Withdrawals

Outcome	Tacalcitol (n=94)	Vehicle (n=95)	Total (n = 33)
Total withdrawals	no data	no data	19
Withdrawal due to toxicity	no data	no data	1
Withdrawal due to lack of efficacy	no data	no data	13

Authors' conclusion

- Once daily application of a 4 µg/g tacalcitol ointment is an efficacious therapy for psoriasis vulgaris in Caucasian patients, and that its tolerance is good, wherever the lesion is located, including on the face

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Oranje AP; Marcoux D; Svensson A; Prendiville J; Krafchick B; Toole J; Rosenthal D; de Waard-van der Spek FB; Molin L; Axelsen M. "Topical calcipotriol in childhood psoriasis" J Am Acad Dermatol 1997;36:203-8 REF ID: ORANJE1997	Multicentre in Canada, Netherlands, Sweden and Denmark CHILDREN • **Setting:** patient/parent delivery • **Randomised** Computer-random generated number table • **Washout period**: 2 weeks using only emollient • **Double-Blinding stated** method unclear	N=77 **Drop-outs (don't complete the study):** N =9 (N=6; 14.0% Cal, N=3; 8.8% Placebo) **Reasons:** no details	**INCLUSION CRITERIA** **Mild to moderate** chronic plaque psoriasis (<30% BSA); children aged 2 to 14. **EXCLUSION CRITERIA** 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. BC: Yes Age: 10 (range: 2 to 14) Gender (%M): 46.8% Severity: Not reported	N=43 Calcipotriol ointment, 50 µg/g **Formulation**: ointment **Frequency** twice daily Who administered unclear. **Both arms:** medication applied to lesions on all body areas except face, scalp and	N=34 Placebo (vehicle) **Formulation**: ointment **Frequency** twice daily	Treatment duration 8 weeks or earlier if cleared - but still assessed at all points (assessed 2,4,6,8 wks). No longer term FU reported.	PASI: Severity: [redness; thickness; scaliness, area] Extent of disease Investigator global assessment Patient global assessment (by parent / guardian for those aged < 8)	Leo Pharmaceuticals

	• **Allocation concealment**. Unclear • **Sample size calculation**. Not reported • **ITT analysis** unclear (but numbers randomised presented in results)			genital region			Compliance	

Effect Size

Outcomes

<u>Efficacy</u>

IAGI at end of treatment/8 weeks	**Calcipotriol** **N=43**	**Placebo** **N=34**
IAGI marked improvement to clear	26 (60.5%)	15 (44.1%)

PAGI at end of treatment/8 weeks	**Calcipotriol** **N=43**	**Placebo** **N=34**

PAGI marked improvement to clear	21 (48.8%)	16 (47.1%)

% change in PASI at 8 weeks	**Calcipotriol N=43**	**Placebo N=34**
% change in PASI (no variance measures given for this continuous variable)	-52%	-37.1

MD of -14.9, p=0.14.

Time to maximum effect

- Based on graphical information of % change in PASI over time the maximum treatment effect with calcipotriol had not been reached by 8 wks, although the most rapid improvement was seen over the first 4 weeks

Adverse Events

	Calcipotriol N=43	**Placebo N=34**	**P value.**
Lesional/perilesional irritation	16%	24%	NS
Facial irritation	N=2	N=0	NS

Summary

- Calcipotriol ointment was more effective than its vehicle in terms of investigator's overall assessment . No significant difference was detected in adverse events.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Harrington CI, Goldin D, Lovell CR, Van De Kerkhof P, Nieboer C, Austad J, et al. Comparative Effects of Two Different Calcipotriol (Mc 903) Cream Formulations Versus Placebo in Psoriasis Vulgaris. A Randomised, Double-Blind, Placebo-Controlled, Parallel Group Multi-Centre Study 1. *Journal of the*	Multicentre (Europe) DESIGN Between patient Patient delivery ALLOCATION Random Method of randomisation: not reported Concealment: unclear BLINDING Double-blind (patient / investigator) WITHDRAWAL / DROPOUT Described • **Setting:** Not stated	N=413 **Drop-outs (don't complete the study):** N=47 (11.4%) **Reasons:** see below	**INCLUSION CRITERIA** Stable chronic plaque psoriasis on trunk or limbs; adult. **EXCLUSION CRITERIA** Recent systemic medication or phototherapy for psoriasis; hepatic or renal disease; raised serum calcium; calcium supplements or vitamin D. BC: Yes, except average age in placebo group higher than for A and B p = 0.02	N=165 Calcipotriol (50 µg/g) dissolved **Formulation**: cream **Frequency:** Twice daily **Note:** Face, scalp and flexural areas were excluded from treatment and the maximum permitted dose was 100 g/week. No concurrent antipsoriatic treatment was allowed except for treatment of the face and scalp Amount of medication	N=161 Calcipotriol (50 µg/g) suspended as fine particles **Formulation:** cream **Frequency:** Twice daily --- N=87 Vehicle control **Formulation:**	8 weeks (evaluated at 2, 5, 8 weeks)	PASI (modified to exclude head) Investigator global assessment (clinical success, improvement, no effect, relapse/deterioration) Patient global assessment (worse, no change, slight	Leo Pharmaceutical Products

European Academy of Dermatology & Venereology 1996;6(2):152–8. REF ID: HARRINGTON 1996	• **Washout period**: 2 weeks, during which only emollient was applied. 2 months for systemic antipsoriatic medications or phototherapy • **Sample size calculation**. Yes. 100 patients in each active group required to detect a 10% difference between the two creams and 25 patients required in the placebo group to detect a 20% difference between active and placebo with 80% power and a 5% significance level • **ITT analysis** No for efficacy yes for safety (assumptions not stated)		Age: 44.6 Gender (%M): 52.8% Severity: PASI (modified): 8.3 (range: 0.6 to 59.4) Duration (yrs): 17.7 (range: 0.04 to 70)	used: The mean use was 38.9 g/week (range 3.4 to 116.8) and 37.8 g/week (range 4.6 to 109.7) for Calcipotriol (dissolved) cream and Calcipotriol (suspended) cream and 44.9 g/week (range 3.7 to 98.1) for placebo.	cream **Frequency:** Twice daily		improvement, marked improvement, complete clearance except for residual discolouration) Withdrawal s Adverse events	

Baseline demographic and psoriasis data

	Calcipotriol (dissolved) cream (n = 165)	Calcipotriol (suspended) cream (n = 161)	vehicle (n = 87)	*p*
% Males	56.4	52.2	49.4	0.54
Age (years) mean (SD) range	44.0 (14.7) 17-79	43.0 (15.3) 18-84	48.7 (15.8) 17-77	0.02
Duration of psoriasis (years) mean (SD) range	18.1 (11.5) 0.09-50	17.7(13.9) 0.04-70	16.8 (12.4) 0.09-58	0.74
PASI mean (SD) range	8.3 (6.8) (1.0-59.4)	7.9 (5.0) (1.2-33.5)	9.2 (6.5) (0.6-38.4)	0.28

Effect Size

Outcomes

Efficacy

	Calcipotriol (dissolved) cream	Calcipotriol (suspended) cream	vehicle

Reduction in mean PASI from start to end of treatment*	4.4 (95% CI 3.5-5.3) (49.7% reduction)(n = not stated)	4.2 (95% CI 3.4-4.9) (48.7% reduction)(n = not stated)	0.8 (95% CI -0.5-2.0) (7.1%% reduction)(n = not stated)
Proportion of investigator's reporting clinical success or improvement at 8 weeks	79% (n = 148)	77% (n = 142)	44% (n = 71)
Proportion of patients reporting complete clearance or marked improvement at 8 weeks	53% (n = 148)	49% (n = 143)	18% (n = 71)

*There were no statistically significant differences between active creams, both of which were statistically superior to placebo at all visits (p<0.001)

Time to effect and time to max effect

Mean change in PASI from baseline was greatest for all treatment groups at 8 weeks (displayed graphically). Reductions from baseline for all treatment groups were apparent at 2 weeks (first evaluation)

Reasons for withdrawal from double-blind treatment

	Calcipotriol (dissolved) cream (n = 165)	Calcipotriol (suspended) cream (n = 161)	vehicle (n = 87)	*p*
Deterioration of psoriasis	5 (3.0%)	4 (2.5%)	11 (12.6%)	<0.001
Exclusion criteria emerging during study[a]	1 (0.6%)	0	0	
Voluntary	3 (1.8%)	4 (2.5%)	4 (4.6%)	0.42

Defaulted	3 (1.8%)	4 (2.5%)	1 (1.1%)	0.76
Unacceptable adverse events[c]	**6 (3.6%)**	**2 (1.2%)**	**4 (4.6%)**	**0.25**
Other[b]	0	0	2 (2.3%)	
Total number of patients	16 (9.7%)	14 (8.7%)	17 (19.5%)	0.03

[a]Patient continued to use betamethasone
[b]1: lack of effect. 2: Need of more than 100 g study cream per week
[c]7 patients withdrew from active treatment due to local skin irritation, 1 due to facial irritation, 1 due to possible allergic reaction; four patients withdrew from placebo group as a result of local irritation

Number of patients with clinical adverse events reported/observed during the treatment period

	Calcipotriol (dissolved) cream (n = 165)	Calcipotriol (suspended) cream (n = 161)	vehicle (n = 87)	p
Lesional/perilesional skin irritation	25 (15.2)	17 (10.6)	15 (17.2)	0.27
Face/scalp irritation	14 (8.5)	18 (10.6)	0 (0)	0.009
Exacerbation of psoriasis lesions (erythema/infiltration/desquamation	1(0.6)	3 (1.9)	5 (5.7)	0.03
Various dermatological	8 (4.8)	11 (6.8)	2 (2.3)	0.29
Dermatological	1 (0.6)	7 (4.3)	0 (0)	0.02
Non-dermatological	45 (27.3)	42 (26.1)	20 (26.1)	0.78

Authors conclusion

- Both calcipotriol creams were equally and statistically significantly more effective then vehicle in the treatment of psoriasis vulgaris.
- There was no statistically significant difference between the three treatment groups in the overall incidence of clinical adverse events.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Barker JN, Ashton RE, Marks R, Harris RI, Berth-Jones J. Topical maxacalcitol for the treatment of psoriasis vulgaris: a placebo-controlled, double-blind, dose-finding study with active comparator. *Br J Dermatol.* 1999;141(2):274-8.	RCT Multicentre (UK) DESIGN Within patient (between patient for placebo vs calcipotriol) Patient delivery Method of randomisation: unclear Concealment: unclear BLINDING	N=145 **Drop-outs (don't complete the study):** N=13 (1 withdrew immediately after randomisation) **Reasons:** see below	**INCLUSION CRITERIA** Chronic plaque psoriasis; stable bilateral lesions affecting < 20% total body surface area; adult (18 to 85) **EXCLUSION CRITERIA** Pregnancy; concomitant disease; known hypersensitivity to vitamin D derivatives; systemic treatments within previous 1 mth; systemic retinoids within previous 2 mths; plaques < 10 cm^2 or > 150 cm^2	Dose ranging study in which patients were randomised as follows: • Placebo vs maxacalcitol 6 mcg/g • Maxacalcitol 6 mcg/g vs Maxacalcitol 12.5 mcg/g • Maxacalcitol 12.5 mcg/g vs Maxacalcitol 25 mcg/g • Maxacalcitol 25 mcg/g vs Maxacalcitol 50 mcg/g • Maxacalcitol 25 mcg/g vs calcipotriol 50 mcg/g **Formulation**: All were	See intervention	8 weeks	IAGI (6-pt: worse, no change, minimal improvement, moderate improvement, marked improvement, cleared) PAGI (6-pt: worse to cleared, as above)	Chugai Pharma Europe

REF ID: BARKER1999A	Double blind (patient / assessor) WITHDRAWAL / DROPOUT Described • **Setting:** Not stated • **Washout period**: 2 weeks for topical antipsoriasis treatment (see also exclusion criteria) • **Sample size calculation**. Not stated • **ITT analysis.** Yes (assumptions not stated)		<table><tr><td></td><td>ITT population (n = 144)</td></tr><tr><td>Mean age (range)</td><td>47.2±14.5 (20-75)</td></tr><tr><td>M/F</td><td>86/58</td></tr></table> Clinical characteristics not reported BC: Demographics similar; clinical characteristics not reported Age: 47.2 (14.5SD, N = 144)(range: 20 to 75) Gender (%M): 59.7% (86/144) Severity: Not reported	ointments **Frequency:** All once daily **Note:** All ointments were applied without occlusion once daily: one to the target plaque on the left side, the other to the corresponding plaque on the right side. Non-target plaques received emollient or coal tar throughout			Withdrawals	

Effect Size

Outcomes

Efficacy

	Placebo n=26-29	Maxacalcitol 6 µg/g	Maxacalcitol 12.5 µg/g	Maxacalcitol 25 µg/g	Maxacalcitol 50 µg/g	Calcipotriol n=28-29
Investigator's global assessment – proportion of patients with marked improvement or clearance at the end of treatment (clearance alone)	1 (3.6% (0%))	34.5 (8.6)	42.9 (14.3)	54.7 (22.7)	52.2 (21.7)	13 (46.2% (11.5%))

Results for patient's overall assessment showed that all concentrations of maxacalcitol were significantly more effective than placebo, with greatest effect noted at 25 µg/g maxacalcitol.

Time to effect and time to maximum effect

- There was a progressive reduction in PSI with duration of therapy.
- A significant clinical effect was noted by week 2 and no effect plateau was observed, suggesting that prolongation of treatment would lead to further improvement.

Reasons for withdrawal from double-blind treatment

- In three patients (6/12.5 µg/g maxacalcitol, 25/50 µg/g maxacalcitol, 25/50 µg/g maxacalcitol) burning of the target plaque was severe enough to

require discontinuation of the study

- In one further patient (placebo/6 µg/g maxacalcitol) a general flare in the patients psoriasis occurred leading to withdrawal from the study
- One patient (6/12.5 µg/g maxacalcitol) was withdrawn from the study after developing symptoms suspected to be related to renal stones
- A further 7 patients were withdrawn for reasons thought to be unrelated to the study

Authors conclusion:

Results for investigator's and patient's overall assessment showed that all concentrations of maxacalcitol were significantly more effective than placebo, with greatest effect noted at 25 µg/g maxacalcitol

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Scarpa C, Kokelj F, Plozzer C, Lavaroni G, Torsello P. Efficacy and Tolerability of Tacalcitol Administered Once Daily in the Treatment of Psoriasis Vulgaris (Double-Blind, Randomized, Placebo Controlled Italian Multicenter Study). *Giornale Italiano di Dermatologia e Venereologia* 1997;132(5)	RCT DESIGN Within patient Patient delivery ALLOCATION Random Method of randomisation: Not reported; tubes labelled left or right and with patient ID number Concealment: unclear BLINDING Double-blind (patient / investigator; adequate) • **Washout period**: 2 weeks	Total N: 157 **Drop-outs (don't complete the study):** Total = 23 (14.6%); 1 had exclusion criteria, 1 dropped out for side effects (worsening of erythema around application area); 15 protocol deviation and 7 protocol violation	INCLUSION CRITERIA Stable chronic plaque psoriasis; symmetrical lesions; in- and out-patients; age 15-80 years EXCLUSION CRITERIA Pregnancy; lactation; inadequate contraception; recent systemic, light or topical therapy; severe renal failure; liver and cardiac dysfunction; hypercalcaemia; hyperphosphoraemia; AIDS; drug addiction; psoriasis guttata, erythrodermica, pustulosa, inversa (restricted to flexural areas) or psoriatic lesions showing worsening during 2 weeks prior to enrolment visit, vitamin D or calcium treatment or other drugs that could influence calcium and phosphate metabolism BC: Yes	**n=157** **Tacalcitol ointment, 4 mcg/g, OD** **Class:** vitamin D analogue **Formulation**: ointment **Frequency** once daily **Amount used:** not stated	**n=157** **Placebo (vehicle), OD** **Formulation**: ointment **Frequency** once daily	**Treatment duration:** 6 weeks **Assessments at:** unclear **Follow-up after end of treatment:** none	Withdrawals	not reported, but Istituto Gentili SpA provided medications and appears to have undertaken the randomisation

:335–8. **Ref ID: SCARPA1997**	• **Sample size calculation** not reported • **ITT analysis:** yes (assumptions not stated) **Setting:** Outpatients		Age: 49 (15SD; N = 134) Gender (%M):65.6% (N = 157) Severity: not stated					

Effect Size

Outcomes

<u>Time-to-effect</u>

A significant difference in symptom scores was seen after 2 weeks of treatment and at all subsequent visits.

<u>Adverse events</u>

1 erythema and itching; 1 ankle oedema; 1 itching with placebo; 1 burning with tacalcitol.

<u>Withdrawals</u>

Withdrawals not stated by treatment group.

Authors' conclusion

Tacalcitol was better than placebo on improvement in psoriasis symptoms (from day 15 and increasing throughout treatment); it was safe (especially with respect to calcium and phosphate metabolism).

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Perez A, Chen TC, Turner A, Raab R, Bhawan J, Poche P, et al. Efficacy and Safety of Topical Calcitriol (1,25-Dihydroxyvitamin D3) for the Treatment of Psoriasis. *British Journal Of Dermatology* 1996;134(2):238–46. **Ref ID: PEREZ1996**	**RCT** **DESIGN** Within patient Patient delivery **ALLOCATION** Random Method of randomisation: not reported Concealment: unclear **BLINDING** Double-blind (patient / investigator); not described • **Washout period:** 14 days • **Sample size calculation** not	**Total N:** 84 **Drop-outs (don't complete the study):** Total = 0 (0%) Noncompliance: 0 AEs: 0	INCLUSION CRITERIA Stable plaque or erythrodermic psoriasis; unsatisfactory response to at least one previous treatment (topical steroids / UVB / PUVA / MTX); adult; BSA≥10% EXCLUSION CRITERIA Pregnant, nursing or inadequate contraception; hepatic or renal impairment; recent systemic therapy or phototherapy or topical medications (excluding emollients) BC: Yes Age: 46 (range: 19 to 76) Gender (%M): 65.5% Severity: TSS (0 to 9): mean 7.6 at baseline	**n=84** **Calcitriol, 1.5 mcg/g OD** **Formulation:** ointment **Class:** vitamin D analogue **Frequency** once daily **Amount used:** 0.1g daily	**n=84** **Placebo (vehicle)** **Formulation**: ointment **Frequency** once daily	**Treatment duration:** 10 weeks **Assessments at:** every 2 weeks **Follow-up after end of treatment:** Uncontrolled follow up study (N = 22) involving large area administration of Calcitriol. Twelve month results based on N = 6	Investigator global assessment (5 pt, worse to excellent improvement) PASI (reported only for patients participating in follow up study) **Primary efficacy parameter:** not stated	NIH General Clinical Research Center

	reported • **ITT analysis:** not stated **Setting:** Outpatients							

Effect Size

Outcomes

<u>Efficacy</u>

<u>IAGI</u>:

	Calcitriol n = 84	**Placebo n=84**	**p-value**
Overall clinical assessment: response	96.5%	15.5%	
Excellent improvement	**37 (44.1%)**	**0**	
Moderate improvement	35.7%	0	
Slight improvement	16.7%	15.5%	
No benefit	3.5%	83.3%	
Deterioration	0	1.2%	

Time-to-effect

Only 2.4 month data point shown which shows effect.

Over the full 12 month period graphical presentation of PASI score over time showed that max response was achieved by 9 months (N<25)

Adverse effects

No local cutaneous side effects; no significant changes in urine or blood measures.

Withdrawals

None

Authors' conclusion

Topical calcitriol is safe and effective for patients with psoriasis

H.6.3 POTENT CORTICOSTEROID VS PLACEBO

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Medanski RS, Brody NI, Kanof NB, Russo GJ, Peets EA. Clinical Investigations of Mometasone Furoate – a novel, nonflourinated, topical corticosteroid.
Ref ID: MEDANSKY 1987A</td>
<td>RCT

DESIGN
Between patient
Patient delivery
ALLOCATION
Random
Method of randomisation: not reported
Concealment: unclear
BLINDING
Double-blind (patient / investigator); not described
WITHDRAWAL / DROPOUT</td>
<td>Total N: 121

Drop-outs (don’t complete the study):
Total = 6 (5%) at the first evaluation at 8 days; however by day 22 (end of treatment period) there was a loss of 26 patients [21.5%] (11 from mometasone and 15 from placebo group). No reasons for withdrawal given, except for 3 in the placebo group, who</td>
<td>INCLUSION CRITERIA
Aged≥12; chronic plaque psoriasis, stable or worsening; duration ≥ 1 year; Total Sign Score ≥ 6
EXCLUSION CRITERIA
Concomitant medication; recent systemic corticosteroids or antimetabolites; recent topical corticosteroids; pregnancy; lactation, those needing > 90 g/wk topical steroid, other forms of psoriasis.

Baseline characteristics [mean(range) or proportion unless stated]:
<table>
<tr><th></th><th>MF</th><th>Placebo</th></tr>
<tr><td>Age</td><td>55.5 (16-80)</td><td>52 (18-78)</td></tr>
<tr><td>male</td><td>36/58</td><td>42/57</td></tr>
</table>
</td>
<td>n= 58
Mometasone furoate ointment, 0.1% OD (M)

Formulation: ointment

Frequency: Once daily

Concomitant therapies – None</td>
<td>n= 57
Placebo Vehicle OD

Formulation: ointment

Frequency
Once daily</td>
<td>Treatment duration: 3 weeks

Follow up: day of treatment cessation.</td>
<td>Outcomes assessed on days 8, 15 and 22. Primary outcome time point should be 22 days, as only this point measured the effects of a whole course of therapy.

Investigator global assessment (6 pt: no change or worse to cleared or marked improvem</td>
<td>Schering Corporation</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td>Described

Sample size calculation: Not reported

ITT analysis: None reported; analyses all per protocol.</td>
<td>withdrew due to adverse events.

Noncompliance: Not reported</td>
<td>
<table>
<tr><td>Duration disease (yrs)</td><td>19.7 (1-50)</td><td>16 (2-52)</td></tr>
<tr><td>>25% body involved</td><td>15/58</td><td>11/57</td></tr>
<tr><td>Worsening</td><td>14/58</td><td>16/57</td></tr>
</table>
Only significant difference was for duration of disease.

Previous therapy:

Previous therapy was an exclusion criterion.</td>
<td></td>
<td></td>
<td></td>
<td>ent)

Adverse events – examined for irritation, folliculitsis, striae, skin atrophy, or telangiectasia and other adverse experiences</td>
<td></td>
</tr>
</table>

Effect Size

Outcomes

Efficacy

Global evaluation of change from baseline (exact test, and whether investigator or patient assessed, not specified)

IAGI	**Mometasone**	**Placebo**

proportion with global score change of 76% to 100% (marked improvement or cleared) at 8 days	4/58	0/57
proportion with global score change of 76% to 100% (marked improvement or cleared) at 15 days	12/55	2/56
proportion with global score change of 76% to 100% (marked improvement or cleared) at 22 days	18/50	7/45

Adverse events

	Mometasone	**Placebo**
Adverse events **(details unclear, but no skin atrophy)**	5/61	11/59

Withdrawal related to adverse events

	Mometasone	**Placebo**
mild urticaria, severe pruritis, mild burning	0/61	3/59

Authors' conclusion

- **Mometasone should have clinical utility in the treatment of patients with corticosteroid-responsive dermatoses.**

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Sears HW, Bailer JW, Yeadon A. A Double-Blind, Randomized, Placebo-Controlled Evaluation of the Efficacy and Safety of Hydrocortisone Buteprate 0.1% Cream in the Treatment of Psoriasis. *Advances In Therapy* 1997;14(3): 140–9. **Ref ID: SEARS1997**	RCT DESIGN Between patient Patient delivery ALLOCATION Random Method of randomisation: not reported Concealment: unclear BLINDING Double-blind (patient / investigator); not described • **Washout period**: 2 weeks • **Sample size calculation** not reported	Total N: 190 **Drop-outs (don't complete the study):** Total = 21 (11%): 10 intervention group and 11 placebo; failure to meet entry criteria (1 and 1);discontinuation due to AE (1 intervention); loss to follow up (3 and 4); use of prohibited concomitant medication (5 and 6) Noncomplia	INCLUSION CRITERIA Mild or moderate psoriasis not spontaneously remitting; adults aged 18 to 70; total sign score 3 to 8 of possible 9 EXCLUSION CRITERIA Acute systemic illness; hypothalamic-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. BC: Yes except gender (60.6% female in intervention group and 43.8% in placebo group,	**n=94** **Hydrocortisone buteprate 0.1% cream, BD** **Formulation**: cream **Class:** potent corticosteroid **Frequency** twice daily	**n=96** **Placebo (vehicle)** **Formulation**: cream **Frequency** twice daily	**Treatment duration:** 3 weeks **Assessments at:** baseline and day 7, 14 and 21 **Follow-up after end of treatment:** none	Investigator and patient evaluations of efficacy (4 pt: poor, fair, good, excellent) Investigator global assessmentof improvement (7 pt: exacerbation to cleared) **Primary efficacy parameter:** physician's end of study	not reported

	• **ITT analysis:** no **Setting:** Outpatients	nce (i.e. failed to apply medication for >3 days during trial): AEs: 1 hydrocortisone group	p=0.021; this was accounted for in analysis) Age: 44 (range: 19 to 73) Gender (%M): 47.9% Severity: moderately severe at baseline Duration (yrs): 17 (range: 1 to 56) TSS (0 to 9): 6.0				assessment of all treated areas (1=excellent, 2=good, 3=fair, 4=poor)	

Effect Size

Outcomes

<u>Efficacy</u>

Investigator's overall *static* assessment	**Hydrocortisone buteprate 0.1% cream, BD**		**Placebo (vehicle)**		**p**
Day 7: excellent or good	N=84	17.9%	N=84	2.4%	**0.001**
Day 14: excellent or good	N=84	28.2%	N=84	14.3%	**<0.001**
Day 21: excellent or good	N=78	41.3%	N=83	18.1%	**0.002**
Day 21: excellent	N=**78**	**15.0%**	N=**83**	**1.2%**	

Investigator's overall assessment of *improvement*	**Hydrocortisone buteprate 0.1% cream, BD**		**Placebo (vehicle)**		**p**
Day 21: cleared, excellent or good	N=78	39.8%	N=83	16.9%	**0.16**

Patient's overall static assessment	**Hydrocortisone buteprate 0.1% cream, BD**		**Placebo (vehicle)**		**p**
Day 21: excellent or good	78	42.5%	83	27.7%	**0.021**
Day 21: excellent	**78**	**15.0%**	**83**	**2.4%**	

No differences in cosmetic acceptability; >70% in both groups very satisfied.

Time-to-effect

Significant changes for erythema on day 21, scaling days 7, 14 and 21, total signs day 7, 14 and 21 and pruritis day 14 and 21.

Adverse effects

	Hydrocortisone buteprate 0.1% cream, BD	**Placebo (vehicle)**

Total AE (of which mild or moderate AE)	21 patients (23%); (of which mild or moderate AE 92%)	27 patients (29%); (of which mild or moderate AE 100%)
Headache	7%	9%
Upper respiratory infection	2%	4%
Severe AE	1 headache, 1 nasal congestion (neither considered drug related)	0

Withdrawals

	Hydrocortisone buteprate 0.1% cream, BD	**Placebo (vehicle)**
Total withdrawals	10	11
Failure to meet entry criteria	1	1
loss to follow up	3	4
use of prohibited concomitant medication	5	6
Withdrawal due to AEs	1	0

Authors' conclusion

Hydrocortisone buteprate 0.1% cream, BD was significantly more effective than its cream base in ameliorating psoriatic signs and symptoms and in improving overall disease and was well tolerated.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Stein LF, Sherr A, Solodkina G, Gottlieb AB, Chaudhari U. Betamethasone valerate foam for treatment of nonscalp psoriasis. *Journal of Cutaneous Medicine & Surgery* 2001;5(4):303–7. **Ref ID: STEIN2001**	RCT DESIGN Within patient Patient delivery ALLOCATION Random Method of randomisation: investigator undertook randomisation Concealment: inadequate BLINDING Double-blind (patient / investigator; not described) • **Washout period**: 2 weeks • **Sample size**	Total N: 40 **Drop-outs (don't complete the study):** Total = 3 (7.5%) due to stinging or itching when they applied foam Noncompliance: Compliance said to exceed 90% AEs: Temporary stinging, burning or itching described when first applying the foam by "a few" of the 40 patients	INCLUSION CRITERIA Mild to moderate symmetrical plaque, psoriasis; aged at least 18 **(NB scalp excluded)** EXCLUSION CRITERIA Systemic treatment within previous four wks; topical treatment within previous two wks; investigational medication within previous four wks; sunbathing/exposure to UV radiation; other topical treatment BC: unclear Age: range: 20 to 70 + Gender (%M): not reported Severity: TSS (elbows) (0 to 12): 7.0	**n=40** **Betamethasone valerate foam, 0.12% (Luxiq®), BD** **Class:** potent corticosteroid **Formulation**: foam **Frequency** twice daily **Amount used:** smallest amount to cover lesions	**n=40** **Placebo foam, BD** **Formulation**: foam **Frequency** twice daily	**Treatment duration:** 12 weeks **Assessments at:** At baseline and 2, 4, 8 and 12 weeks	IAGI (7 pt: 6=worse to 0=completely clear) Adverse events **Primary efficacy parameter:** composite severity score = difference scores for erythema, scaling and plaque thickness on elbows	Connetics Corporation

	calculation not reported • **ITT analysis:** unclear **Setting:** Outpatients							

Effect Size

Outcomes

<u>Efficacy</u>

Composite score for elbows at 12 weeks: intervention reduced from 7.0 to 4.0 ($p<0.001$ vs. baseline; $p<0.00004$ vs. placebo); placebo 7.0 to 6.3 (NS vs. baseline); for non-elbow/knee sites: 7.1 to 3.8 ($p<0.001$ vs. baseline and $p<0.00001$ vs. placebo) intervention vs. 7.1 to 6.0 placebo (NS vs. baseline).

Investigator's global assessment at 12 weeks: 2.9 intervention vs. 4.6 placebo ($p<0.001$)

Number of patients with >50% improvement (good to excellent) of elbows knees or torso: 70% intervention vs. 24% placebo. But only 15% achieved >90% improvement.

<u>Time-to-effect</u>

Some patients showed improvement after 2 weeks, especially those with small thickness plaques.

Adverse events:

Temporary stinging, burning or itching described when first applying the foam by “a few” of the 40 patients.

Withdrawals
3 (7.5%) due to stinging or itching when they applied foam

Authors’ conclusion

The Betamethasone valerate foam is effective against non-scalp psoriasis; twice daily applications are well tolerated; compliance exceeds 90% and the medication is cosmetically acceptable because it leaves no appreciable residue.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Katz HI, Prawer SE, Medansky RS, Krueger GG, Mooney JJ, Jones ML, et al. Intermittent corticosteroid maintenance treatment of psoriasis: a double-blind multicenter trial of augmented betamethasone dipropionate ointment in a pulse dose treatment regimen. *Dermatologi*	**RCT** **DESIGN** Between patient Patient delivery MAINTENANCE **ALLOCATION** Random Method of randomisation: computer generated code Concealment unclear **BLINDING** Double-blind (patient / investigator); not described • **Washout period:** none (straight after	**Total N:** 94 **Drop-outs (don't complete the study):** Total = 4 (4.3%) 2 from each group (protocol violations) Noncompliance: 0 AEs: no treatment-related AE	INCLUSION CRITERIA Initial severity ≤10% BSA Plaques psoriasis in remission after 3/4 weeks treatment with Betamethasone dipropionate (erythema score ≤ 1 (slight or minimal); induration = 0.5 (none-slight); scaling = 0 (none)) Note: 94/123 (76%) achieved remission during acute phase on ABD EXCLUSION CRITERIA Recent topical or systemic treatment; pregnant; nursing; intent to conceive; not achieving remission during acute phase treatment. BC: Yes	**n=46** **Betamethasone dipropionate (ABD),** intermittent maintenance (3 doses at 12 hour intervals once a week) **Formulation:** ointment **Class:** potent corticosteroid **Frequency** twice daily	**n=44** **Placebo (vehicle)** **Formulation**: ointment **Frequency** (3 doses at 12 hour intervals once a week)	**Treatment duration:** 24 weeks **Assessments at:** every 2 weeks **Follow-up after end of treatment:** none	Area adjusted clinical score Treatment failure (Adjusted clinical score ≥ 2.5, or overall disease status moderate or severe) Overall disease status Patient evaluation of	not reported, but corresponding author employed by the ScheringCorporation

ca 1991;183(4) :269–74. **Ref ID: KATZ1991**	acute phase therapy) • **Sample size calculation** not reported • **ITT analysis:** not stated **Setting:** Outpatients		Age: 46.0 (range: 21 to 86) Gender (%M): 67.8% Severity: overall score not reported	**Amount used:** given one 45g tube per month			effectiveness. Time to relapse **Primary efficacy parameter :** not stated	

Effect Size

Outcomes

<u>Efficacy for maintenance</u>

Clinical benefit: overall disease status

		Disease status			
	n	**Cleared/slight**	**Moderate/severe**	**Treatment failures** (moderate or severe	**p-value**

				disease or TSS ≥2.5 at 2 consecutive visits)	
Baseline: ABD (n=46) Placebo (n=44)	46 44	46 44	0 0	NA NA	0.4
2 weeks: ABD Placebo	44 44	44 40	0 4	0 0	0.01
6 weeks: ABD Placebo	45 43	35 23	7 12	3 8	<0.01
12 weeks: ABD Placebo	44 44	27 11	8 7	9 26	<0.001
18 weeks: ABD Placebo	44 43	24 6	5 3	15 34	<0.001
24 weeks: ABD Placebo	46 44	27 7	3 2	16 35	<0.001

Clinical benefit: target area lesion total sign scores

Time-to-relapse/duration of remission

Most of recurrences of disease with placebo occurred within first month of maintenance therapy; by day 84, only 34% (15/44) of placebo-treated patients remained in remission vs. 72% (33/46) on Betamethasone dipropionate (ABD). 65% (30/46) of the Betamethasone dipropionate (ABD) patients remained in remission for the whole of the 6-month treatment period vs. only 20% (9/44) on placebo.

By the end of the second week and throughout the remainder of the study there was a significant difference in favour of the ABD group (p=0.01) in the

number of patients in remission (i.e. cleared/slight).

The placebo patients in remission at week 6 had a lower quality remission (higher sign scores)

Time to treatment failure (KM curve given); p<0.001

AEs:

No treatment-related AEs; no changes in haematology, blood chemistry or urinalysis; no cutaneous atrophy; plasma cortisol levels showed no adverse effects.

Withdrawals

	Betamethasone dipropionate (ABD)	**Placebo (vehicle)**
Withdrawal due to non-compliance	not stated	not stated
Withdrawal due to AEs	none	none

Authors' conclusion

Betamethasone dipropionate (ABD) ointment was clinically beneficial and well tolerated in long-term (up to 6 months) maintenance therapy for psoriasis.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Wortzel MH. A new corticosteroid for moderate/ severe dermatoses. *Clinical medicine* 1975;**82**(3):23–6. **Ref ID: WORTZEL1975**	RCT DESIGN Between patient Delivery unclear ALLOCATION Random Method of randomisation: sequential admission number Concealment: adequate BLINDING Double-blind (patient / physician) • **Sample size calculation** not reported • **ITT analysis:** not stated	Total N: 76 **Drop-outs (don't complete the study):** 0 (0%)	INCLUSION CRITERIA Moderately severe to very severe psoriasis and atopic dermatitis; Inpatients EXCLUSION CRITERIA Not reported BC: not reported Age: not reported Gender (%M): not reported Severity: not reported	**n=39** Study 1: **Betamethasone dipropionate ointment 0.05, BD** **Formulation**: ointment **Class:** potent corticosteroid **Frequency** twice daily **Amount used:**	**n=37** : **Placebo, BD** **Formulation**: ointment **Frequency** twice daily	**Treatment duration:** Study 2: 3 weeks **Assessments at:** 3 weeks **Follow-up after end of treatment:** none	IAGI (5pt: worse to excellent) Physician opinion of drug effect (scale unclear, results not reported) **Primary efficacy parameter:** not stated	Not reported

	Setting: Outpatients							

Effect Size

Outcomes

Overall therapeutic response in psoriasis group

IAGI	**Betamethasone dipropionate ointment 0.05 (n=39)**	**Placebo (n=37)**
Excellent	15 (38%)	4 (11%)
Good	14 (36%)	4 (11%)
Fair	5 (13%)	10 (27%)
Poor	4 (10%)	15 (40%)
Exacerbation	1 (3%)	4 (11%)

Time-to-remission/maximum effect

Not stated

Adverse events

Serious side effects did not occur; 1/207 treated with Betamethasone dipropionate ointment 0.05, BD had itching as a side effect.

Withdrawals

None

Authors' conclusion

Betamethasone dipropionate ointment 0.05, BD highly effective in treating psoriasis.

H.6.4 TAZAROTENE VS PLACEBO

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Weinstein GD. Safety, Efficacy and Duration of Therapeutic Effect of Tazarotene Used in the Treatment of Plaque Psoriasis. *British Journal Of Dermatology* 1996;135 (Suppl 49):32–6. **AND** **Weinstein GD, Krueger GG, Lowe NJ, Duvic M, Friedman DJ,**	RCT DESIGN Between patient Patient delivery ALLOCATION Random Method of randomisation: not reported Concealment: unclear BLINDING Double-blind (patient / investigator); adequate • **Washout period**: 2 weeks • **Sample size**	Total N: 324 **Drop-outs (don't complete the study):** Total = 82: 39 (12%) administrative reasons (9 in 0.1% group, 12 in 0.05% group and 18 in placebo group); 15 (5%) lack of efficacy (4, 5 and 6); 27 (8%) AE (13, 11, 3); 1 (<1%)	INCLUSION CRITERIA Stable plaque psoriasis; BSA ≤ 20%; 2 target lesions with plaque elevation ≥ 2 (on a 0-4 scale) and ≥ 2cm in diameter; 1 on elbow/knee and 1 on trunk/limbs. EXCLUSION CRITERIA Pustular or exfoliative psoriasis, or spontaneously improving or rapidly deteriorating plaque 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	**n=105 (0.1%) and 106 (0.05%)** **Tazarotene gel, 0.1% OD** **Tazarotene gel, 0.05% OD** **Class:** retinoid **Formulation**: gel **Frequency** once daily each **Amount used:** thin layer to all	**n=107** **Placebo (vehicle)** **Formulation**: gel **Frequency** once daily	**Treatment duration:** 12 weeks **Assessments at:** weeks 4, 8, 12, 16, 20 and 24 **Follow-up after end of treatment:** 12 weeks	% clearance; number of patients achieving good (5-=74% improvement) or excellent (75%-99% improvement) or complete clearing. Patient assessment of cosmetic acceptability Adverse events	Allergan Inc.

Jegasothy BV, et al. Tazarotene gel, a new retinoid, for topical therapy of psoriasis: vehicle-controlled study of safety, efficacy, and duration of therapeutic effect. *Journal of the American Academy of Dermatology* 1997;37(1): 85–92. **Ref ID: WEINSTEIN 1996 AND WEINSTEIN 1997**	**calculation** reported • **ITT analysis:** yes but similar to analysis of evaluable patients and latter presented **Setting:** Outpatients	failed to meet entry criteria. Completion rates around 75% each group. 54 lost from T and27 from P	BC: Yes Age: 46.8 (range: 12 to 83) Gender (%M): 67% Severity: % BSA: 6.9 (5.2SD) Duration (yrs): 17.5 (12.7SD) TSS (0 to 12): 7.3	psoriatic lesions			**Primary efficacy parameter:** not stated	

Effect Size

Outcomes

Efficacy/Time-to-effect

Results shown graphically in WEINSTEIN1997 and success rates reported in WEINSTEIN1996.

During most weeks of the 12-week treatment period, tazarotene gel, 0.1% and 0.05% were **significantly more effective** ($p<0.05$) than placebo in reducing the severity of signs and symptoms: all treatment visits for plaque elevation; all from week 2 for scaling; and most treatment visits in the second half of treatment period for erythema; total TSS from week 1 for trunk/limb lesions and week 2 for knees/elbows "**treatment success" (good, excellent or cleared**) from week 2. For trunk/limbs target lesions, success rates at 12 weeks **70%** in 0.1% group, **59%** 0.05% group and **35%** with placebo; around 60% for both tazarotene groups at 12 weeks for elbows/knees (placebo not stated).

Remained significant (sustained within 20%) in all post-treatment visits for 12 weeks after treatment ($p<0.05$). No difference between 2 doses except "treatment success" had a dose-response relationship. No difference in use of emollient between groups. Assigned treatment rated cosmetically acceptable by 85% of patients.

The clinical response of 0.1% was more **rapid** than with 0.05% tazarotene (time to initial treatment success significantly different) but **maintenance of success** was greater for the 005% concentration (suggests higher concentration for induction and lower concentration for maintenance of remission).

Peak success rate seen at 12 weeks, and further improvement may have been seen if treatment was continued

Adverse events/ Withdrawals

	Tazarotene gel, 0.1%	Tazarotene gel, 0.05%	Placebo
Treatment related (mainly mild-moderate local irritation) including			
pruritis:	23%	17%	8%
burning:	19%	15%	6%
erythema:	8%	7%	1%
Treatment-related serious AE	0	0	0
Withdrawal due to AEs	13/108 (12%)	11/108 (10%)	3/108 (3%)
Withdrawal due to lack of efficacy	4	5	6
Skin atrophy	0	0	0

No significant drug effects on blood chemistry/urinalysis.

Authors' conclusion

Once daily tazarotene was effective and safe as a topical monotherapy for plaque psoriasis, providing rapid reduction in signs and symptoms.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Weinstein GD, Koo JY, Krueger GG, Lebwohl MG, Lowe NJ, Menter MA, et al. Tazarotene cream in the treatment of psoriasis: Two multicenter, double-blind, randomized, vehicle-controlled studies of the safety and efficacy of tazarotene creams 0.05% and 0.1% applied once daily for 12	RCT DESIGN Between patient Patient delivery ALLOCATION Random Method of randomisation: Randomised in blocks of 6 Concealment: unclear BLINDING Double-blind (patient / investigator; not described) • **Washout period**: 2 weeks	Total N: 1303 (668 study A and 635 study B) **Drop-outs (don't complete the study):** Total = 411 (31.5%)	INCLUSION CRITERIA Aged ≥18; BSA ≥ 2%; OLA (0 to 5) ≥ 3; acceptable blood or urinary test results EXCLUSION CRITERIA Pregnancy or risk thereof; lactation; UV or topical therapies within previous two wks; PUVA or systemic therapies within previous four wks; oral retinoid therapy within previous eight wks; expected prolonged exposure to UV light. BC: Yes Age: 48.2 (range: 18 to 84) Gender (%M): 62.6% Severity: OLA (0 to 5)(mean): 3.6 Duration (mean yrs):	**Tazarotene cream 0.05%, OD (T1)** **Tazarotene cream 0.1%, OD (T2)** **Class:** retinoid **Formulation**: cream **Frequency** once daily each **Amount used:** thin layer to all lesions	**Placebo** **Formulation**: cream **Frequency** once daily	**Treatment duration:** 12 weeks **Assessments at:** baseline and week 1, 2, 4, 8 and 12 **Follow-up after end of treatment:** Reports two trials, only study A reported follow up data after 12 weeks (N = 108) at weeks 16, 20 and 24	Overall lesion assessment (OLA; 0 = none to 5 = very severe), as applied to all treated lesions Clinical success (OLA ≤ 2 at 12 wks) Effectiveness (improvement in OLA from baseline of≥15%relative to placebo improvement score) Overall global response to treatment (7 pt: completely cleared to worsened) Target lesion response (7 pt:	Allergan Inc

weeks. Journal of the American Academy of Dermatology 2003;48(5): 760–7. **Ref ID: WEINSTEIN 2003**	• **Sample size calculation** not reported • **ITT analysis:** yes • **Setting:** Outpatients		18.4 BSA affected (mean): 10.5%				completely cleared to worsened) **Primary efficacy parameter:** clinical success (% patients with OLA score of none, minimal or mild) at 12 weeks	

Effect Size

Outcomes

<u>Efficacy</u>

Clinical success shown graphically.

Overall assessment score

<u>PGA</u>	**Tazarotene gel, 0.1%**		**Tazarotene gel, 0.05%**		**Placebo**	
	Study A (n=221)	**Study B (n=211)**	**Study A (n=218)**	**Study B (n=210)**	**Study A (n=229)**	**Study B (n=214)**

	Week 12	Week 24 (post Tx)	Week 12	Week 12	Week 24 (post Tx)	Week 12	Week 12	Week 24 (post Tx)	Week 12
None	0	0	6	1	1	2	0	1	1
Minimal	12	14	11	11	12	7	7	6	1
RESPONSE	**12**	**14**	**17**	**12**	**13**	**9**	**7**	**7**	**2**

Global response to treatment (IAGI): moderate or better (≥50% improvement) higher with both active treatments than vehicle at all time points; differences between doses not significant.

IAGI	**Tazarotene gel, 0.1%**			**Tazarotene gel, 0.05%**			**Placebo**		
	Study A (n=221)		**Study B (n=211)**	**Study A (n=218)**		**Study B (n=210)**	**Study A (n=229)**		**Study B (n=214)**
	Week 12	Week 24	Week 12	Week 12	Week 24	Week 12	Week 12	Week 24	Week 12
Success	48.9%	37.6%	58.8%	42.7%	38.5%	47.6%	30.1%	27.1%	36.9%

Time-to-effect

- In study A, success with Tazarotene gel, 0.1% was significantly higher than vehicle at weeks 1, 4, 8 and 12 ($p \leq 0.016$) and throughout follow up ($p \leq 0.029$), and with 0.05% gel at weeks 4 to 24 ($p \leq 0.034$).
- In study A, success with Tazarotene gel, 0.1% was significantly higher than vehicle at all visits and 0.05% at weeks 2 to 12 ($p \leq 0.038$)
- Differences between doses generally not significant
- **Most rapid effect seen over the first 4 weeks but maximum effect not reached by week 12**

Withdrawals

	Study A			Study B		
	Tazarotene gel, 0.1%	**Tazarotene gel, 0.05%**	**Placebo**	**Tazarotene gel, 0.1%**	**Tazarotene gel, 0.05%**	**Placebo**
Enrolled	221 (100%)	218 (100%)	229 (100%)	211 (100%)	210 (100%)	214 (100%)
Completed	145 (65.6%)	125 (57.3%)	155 (67.7%)	160 (75.8%)	144 (68.6%)	163 (76.2%)
Discontinued:	76 (34.4%)	93 (42.7%)	74 (32.3%)	51 (24.2%)	66 (31.4%)	51 (23.8%)
Lack of efficacy	5 (2.3%)	17 (7.8%)	15 (6.6%)	3 (1.4%)	15 (7.1%)	13 (6.1%)
AE	36 (16.3%)	25 (11.5%)	11 (4.8%)	20 (9.5%)	16 (7.6%)	9 (4.2%)
Other (non-compliance, personal reasons, concomitant therapy, relocation, improper entry, lost to follow up)	35 (15.8%)	51 (23.4%)	48 (21.0%)	28 (13.3%)	35 (16.7%)	29 (13.6%)

Authors' conclusion

Tazarotene creams were associated with significant reductions in the severity of the clinical signs of psoriasis are were safe with acceptable tolerability; 0.1% cream generally more effective although slightly less well tolerated than 0.05% cream.

H.6.5 VERY POTENT CORTICOSTEROID VS PLACEBO

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lowe N, Feldman SR, Sherer D, Weiss J, Shavin JS, Lin YL, Foley V, Soto P. Clobetasol propionate lotion, an efficient and safe alternative to clobetasol propionate emollient cream in subjects with moderate to severe plaque-type psoriasis. *J Dermatolog Treat.* 2005;16(3):1	**RCT** Multicenter Design: Between subjects. • **Randomised**: Subjects randomised into consecutive balanced blocks of seven • **Washout period**: Treatment-specific wash-out periods required for subjects taking	N: 192 **Drop-outs (don't complete the study):** 5 (6.1%): clobetasol propionate lotion 4 (4.9%): clobetasol propionate emollient cream 8 (27.6%): vehicle lotion	**Inclusion criteria:** Aged ≥18 years with stable moderate to severe plaque psoriasis, defined by a dermatological sum score (DSS) of ≥6 (out of 12). Subjects must have had lesions ≥3-4 cm in diameter, not located on the face, axillae, groin or on areas difficult to treat such as the scalp, hands or feet **Exclusion criteria:** none stated Demographics (see below)	n: 82 clobetasol propionate lotion 0.05% **Formulation**: lotion **Frequency:** Twice daily **Dose:** "thin coating" **Administration:** First dose	n: 81 clobetasol propionate emollient cream 0.05% **Formulation**: cream **Frequency:** Twice daily --- n: 29 vehicle	4 weeks (4-week treatment plus 4 week treatment free follow-up period). No longer term FU.	DSS (defined as sum of erythema, plaque elevation and scaling for target lesion. Component scores ranged from 0 [none] to 4 [very severe]) IAGI (rated by investigator from -1 [worse] to 5 [clear])	Not stated

58-64. Ref ID: **LOWE2005**	certain topical and systemic treatments • **Single blind** Investigator blind • **Allocation concealment** Not reported • **Sample size calculation** To detect with a 90% power a difference of 1 point in the mean DSS score between the two active treatments by a 2-sided t-test with alpha=0.05, a sample of 64 subjects per group was needed • **ITT analysis**			made under supervision.	**Formulation**: lotion **Frequency:** Twice daily **Dose:** "thin coating" **Administration:** First dose made under supervision		Safety (skin safety and adverse events. Evaluations of telangiectasia and skin atrophy from 0 [none] to 3 [severe]) Primary endpoints were: unclear	

	Yes for efficacy (LOCF) • **Drop-outs/withdrawals**. 17							

Subject demographics

	clobetasol propionate lotion (n = 82)	**clobetasol propionate emollient cream (n = 81)**	**Vehicle lotion (n=29)**
Mean age (range)	48.72 (19-76)	49.09 (21-77)	47.21 (26-78)
Gender			
Male	58 (70.7%)	52 (64.2%)	16 (55.2%)
Female	24 (29.3%)	29 (35.8%)	13 (44.8%)
Race			
White	69 (84.1%)	66 (81.5%)	24 (82.8%)
Black	2 (2.4%)	1 (1.2%)	2 (6.9%)
Hispanic	11 (13.4%)	14 (17.3%)	3 (10.3%)
Mean baseline DSS (SD)	7.55±1.61	7.78±1.58	7.21±1.49

Effect Size

Time to response

- From week 1 onwards, clobetasol propionate lotion was associated with a significantly superior mean percentage change in DSS compared to its vehicle

Time to max response

- The largest mean percentage change in DSS for clobetasol propionate lotion compared to its vehicle was observed at week 4. However the gradient of the lines suggested that further improvements may have occurred (the 8 week measure was taken after 4 weeks without the drugs).

IAGI

	Clobetasol propionate lotion	Clobetasol propionate emollient cream	Vehicle lotion
At 4 weeks			
Almost cleared or cleared psoriasis	45/82 (54.9%)	39/80 (48.8%)	0%
At 8 weeks (4 wk treatment free)			
Almost cleared or cleared psoriasis	33/81 (44%)	22/78 (28.2%)	Not stated

Adverse events

	Clobetasol propionate lotion	Clobetasol propionate emollient	Vehicle lotion

		cream	
Considered definitely related to study medication	1 (erythema)	0	0
Considered possibly or probably related to study medication			
Pruritus	1	0	2
Irritant dermatitis	1	1	0
Worsened treated disorder	1	0	0
Skin discomfort	1	0	0
Contact dermatitis	0	1	0
Paraesthesia	0	0	1
Withdrew due to adverse events	0	1 (irritant contact dermatitis)	0

- There were no significant differences between treatments (clobetasol propionate lotion vs vehicle lotion or clobetasol propionate lotion vs clobetasol propionate emollient cream) in telangiectasia score at any time during the study, nor was the worst telangiectasia score observed at any time during the study significantly different between groups
- Similar results were obtained for the skin atrophy score, except at week 4 where a statistically significant difference ($p = 0.05$) in favour of clobetasol propionate lotion over clobetasol propionate emollient cream could be shown

Authors' conclusion

- Clobetasol propionate lotion showed a better remission profile after 4 weeks of treatment-free follow-up period compared to an emollient cream formulation

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>J. Decroix, H. Pres, N. Tsankov, M. Poncet, and S. Arsonnaud. Clobetasol propionate lotion in the treatment of moderate to severe plaque-type psoriasis. Cutis 74 (3):201-206, 2004.

Ref ID: DECROIX2004</td>
<td>RCT

Multicentre study (Germany, Bulgaria, Belgium and France)

• Setting: unclear

• Randomised:
Unclear method
Ratio 3:3:1 (clobetasol propionate cream:lotion:vehicle)

• Washout period:
4 weeks for topicals and UV; 2-6 wk for systemics; and 2 wk for patients who had regular sun exposure</td>
<td>Total N: 222

Drop-outs (don’t complete the study):
Total = 9

n=2 (2.1%) from clobetasol cream

n=4 (4.3%) from clobetasol lotion

n=3 (9.1%) from vehicle

Reason for withdrawal: See table of</td>
<td>Inclusion criteria:
Aged 18 or over, of either sex, with a clinical diagnosis of stable, moderate-to-severe (at least 10% BSA) chronic plaque type psoriasis; target lesion 3-4 cm in diameter and not located on the scalp, face, hands or feet

Exclusion criteria:
Pregnancy

<table>
<tr><th>Mean baseline</th><th>Clobetasol lotion n=94</th><th>Clobetasol cream n=95</th><th>Vehicle lotion n = 33</th></tr>
<tr><td>Age (mean±SD)</td><td>48.71±14.08</td><td>47.29±15.90</td><td>50.94±14.61</td></tr>
<tr><td>Males %</td><td>50</td><td>58.9</td><td>63.6</td></tr>
<tr><td>Caucasians %</td><td>100</td><td>100</td><td>100</td></tr>
<tr><td>TSS±SD (scale: 0-12)</td><td>8.49±1.45</td><td>8.33±1.36</td><td>8.61±1.71</td></tr>
</table>
</td>
<td>n=94

Clobetasol propionate

Formulation: lotion

Frequency
once daily

Who administered drug unclear.</td>
<td>n=95

Clobetasol propionate

Formulation: cream

Frequency
once daily

———

n=33

Vehicle

Formulation: lotion

Frequency</td>
<td>Treatment duration: 4 weeks. No long term FU reported.</td>
<td>Erythema, plaque elevation, scaling, pruritus and global severity for target lesions on a 0 (none) to 4 (severe) scale

TSS: sum of erythema, thickness and scaling for target lesions (range: 0-12)

IAGI: 7-pt scale</td>
<td>Gladerma R&D</td>
</tr>
</table>

	• **Single blind.** Investigator ('appropriate procedures were applied to ensure investigator blinding') • **Allocation concealment** Not reported • **Sample size calculation** not reported • **ITT analysis:** yes for efficacy (LOCF)	adverse effects. For the 5 not included in that table, 2 in the clobetasol group and 3 in the lotion group withdrew "by request" (no further reasons given).			once daily		(worse to clear) Adverse events – skin atrophy a 0 (none) to 3 (severe) scale	
Effect Size Outcomes **Efficacy (ITT)** **TSS (data only presented graphically)**								

- TSS decreased over time in both active treatment groups and no difference could be demonstrated between the two formulations
- Clobetasol propionate resulted in statistically significantly lower mean TSS scores compared with vehicle at weeks 1, 2 and 4 ($p<0.001$ at all time points)

IAGI

Outcome	**Clobetasol lotion n=94**	**Clobetasol cream n=95**	**Vehicle lotion n = 33**	**p-value (active vs vehicle)**
IAGI: number clear or nearly clear at 4 weeks (or end of treatment)	70	74	5	<0.001

Time-to-remission/maximum effect

- Based on graphical data of mean TSS score over time the improvement in disease has not reached a maximum by the end of treatment (wk 4) as gradual improvement is still apparent

Adverse events

Outcome	**Clobetasol lotion (n=94)**	**Clobetasol cream (n=95)**	**Vehicle lotion (n = 33)**
Withdrawal due to toxicity	1	0	0
Withdrawal due to lack of efficacy	0	0	1
Withdrawal due to clearance	0	2	0
Skin atrophy	3	4	0

Authors' conclusion

- Clobetasol propionate lotion was efficient, safe and well tolerated and offers a cosmetic advantage over the cream formulation in the treatment of moderate-to-severe plaque-type psoriasis

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Beutner K, Chakrabarty A, Lemke S, Yu K. An intra-individual randomized safety and efficacy comparison of clobetasol propionate 0.05% spray and its vehicle in the treatment of plaque psoriasis. Journal of Drugs in Dermatology 2006; Vol. 5, issue 4:357–60.	**RCT** **DESIGN** Within patient Patient delivery **ALLOCATION** Random Method of randomisation: not stated Concealment: unclear **BLINDING** double-blind; not described • **Washout period:** 4 weeks • **Sample size calculation** not	**Total N:** 27 **Drop-outs (don't complete the study):** Total = 2 (7%) for administrative reasons Noncompliance: 0 AEs: 0 withdrawals	INCLUSION CRITERIA At least 18 years of age with 2 bilaterally distributed psoriasis plaques of equivalent size, each between 5cm^2 and 100cm^2. Overall target plaque severity score ≥5 (**moderate to severe**) on a scale of 0 (no evidence of disease) to 8 (very severe overall plaque elevation, scaling, and/or erythema of target plaque). Women of childbearing potential were required to have a negative urine pregnancy test and agree to use an effective method of birth control. EXCLUSION CRITERIA Not stated (no mention of difficult sites) Baseline comparability	**n=27** Clobatesol propionate 0.05% **Formulation:** spray **Frequency** twice daily **Amount used:** not stated	**n=27** vehicle **Formulation**: spray **Frequency** twice daily	**Treatment duration:** 4 weeks **Assessments at:** baseline and 1, 2, 3 and 4 weeks **Follow-up after end of treatment:** none	Collapsed 9-point scale: none (0-1), mild (2-3), moderate (4-5), severe (6-7) and very severe (8). **Primary efficacy parameter:** overall target plaque severity score at week 4, dichotomised to success or failure: the treatment with the	Dow Pharmaceutical Sciences and Galderma R&D

Ref ID: BEUTNER2006	reported • **ITT analysis:** no **Setting:** Outpatients		(BC): Yes Age (mean): 51.6 (range: 21 to 75) Gender (%M): 67% Ethnicity: White: 85%; Black: 4%; Hispanic/Latino: 7%; Other: 4%				lower (better) overall target plaque severity score was designated the success for that subject and the other treatment the failure.	

Effect Size

Outcomes

<u>Efficacy</u>

No or mild psoriasis

No or mild psoriasis	**Clobatesol propionate 0.05% spray n=25**	**Vehicle n=25**	**p-value**
Week 2	80%	16%	not stated

Week 4	25 (100%)	7 (28%)	p<0.001

Time-to-effect

- Clobatesol propionate: significant change seen at 1 week and maintained throughout 4 week

Withdrawals & AEs

	Calcipotriol n=25	**Tar n=25**
Skin atrophy	0	0
Withdrawal due to non-compliance	0	0
Withdrawal due to AEs	0	0

Authors' conclusion

Twice daily treatment with clobatesol propionate 0.05% spray over a period of 4 weeks was safe and effective in reducing the severity of overall target plaque psoriasis, scaling, erythema and plaque elevation from the first week of treatment.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Gottlieb AB, Ford RO, Spellman MC. "The efficacy and tolerability of clobetasol propionate foam 0.05% in the treatment of mild to moderate plaque-type **psoriasis** of nonscalp regions." J Cutan Med Surg. **2003** May-Jun;7(3):185-92. **Ref ID:** GOTTLIEB2003C	Multicenter • **Randomised**: 1:1 ratio • **Washout period**: Unclear • **Double blind.** Yes, but no details. • **Allocation concealment** not reported • **Sample size calculation** Not reported • **ITT analysis** They presented	Total N: 279 (N=139 with clobetasol foam and N=140 placebo) **Drop-outs (don't complete the study):** N=8 (4 each group) Clobetasol = request (1), non compliance (2), other (1) Placebo = request (1), AE (1), other (2).	**Inclusion criteria:** men or women, 18 yo+, good health with mild to moderate plaque-type psoriasis of non-scalp regions, if less than 20%BSA and a target lesion on the trunk or extremities with a score of 2-3 of erythema, scaling and plaque thickness; practicing adequate contraception **Exclusion criteria:** allergy to clobestal propionate or investigative formulations; use of systemic antipsoriatic therapy within preceding 8 weeks; use of topical corticosteroid or retinoid therapy for psoriasis within preceding 4 weeks; use of topical preparations within 2 weeks; UV or sun exposure during course of study; or any condition that may put them at risk; pregnant or lactating women. Demographics **Entire Sample N=279** Age: 19-82	Clobetasol propionate 0.05% **Formulation:** foam **Frequency** twice daily **Application** Administered by patients (am and pm) for 2 weeks. **Amount used:** Instructed to apply a max of 3.5g/each application	Placebo **Formulation:** foam **Frequency** twice daily	Baseline, wks 1, 2 (or end of treatment) and 4 wks (follow-up).	**1° outcome:** Proportion of patients with a PSGA score of 0 (no psoriasis) or 1 after 2 weeks of treatment. PSGA= Physicians static global assessment (6 point scale) **2° and other outcomes:** Mean change from	Connetics Corporation

<table>
<tr>
<td></td>
<td>per-protocol (PP) and non-per-protocol analysis (ITT)</td>
<td></td>
<td>
<table>
<tr><td>Male</td><td colspan="2">57%</td></tr>
<tr><td>Caucasian</td><td colspan="2">90%</td></tr>
<tr><td>Psoriatic involvement BSA mean</td><td colspan="2">6.7</td></tr>
<tr><td></td><td>Clobetasol
N=139</td><td>Placebo
N=140</td></tr>
<tr><td>High pruritus 4 or 5</td><td>14%</td><td>14%</td></tr>
<tr><td>Moderate pruritus 1-3</td><td>72%</td><td>76%</td></tr>
</table>
</td>
<td>All areas were treated except face and intertriginous sites.

Scalp only treated if sufficient quantities of foam remained.</td>
<td></td>
<td></td>
<td>baseline to week 2 (or end of treatment) and week 4.

Patients global assessment (PGA 6 point scale)

Patients preference for foam

Patients and investigator reported adverse events</td>
<td></td>
</tr>
<tr>
<td colspan="8">Effect Size
Outcomes</td>
</tr>
</table>

Efficacy

ITT Physicians static global assessment (PSGA) and Patients global assessment (PAGI)

Outcome	Clobetasol (N = 139)	Placebo (N = 140)	Placebo vs Clobetasol P value
PSGA (clear/minimal), wk 2 (or end of treatment)	94 (68%)	30 (21%)	<0.0001
PSGA (clear/minimal), wk 4 (follow-up)	75 (54%)	25 (18%)	<0.0001
PAGI (clear/80% improved), wk 2 (or end of treatment)	79 (57%)	36 (26%)	<0.0001
PAGI (clear/80% improved), wk 4 (follow-up)	68 (49%)	24 (17%)	<0.0001

PP Physicians static global assessment (PSGA)

Outcome	Clobetasol (N = 120)	Placebo (N = 125)	Placebo vs Clobetasol P value
PSGA (clear/minimal), wk 2 (or end of treatment)	85 (71%)	27 (22%)	<0.0001
PSGA (clear/minimal), wk 4 (follow-up)	68 (57%)	21 (17%)	<0.0001

0 = no psoriasis 1 = minimal psoriasis

Adverse events

	Clobetasol	Placebo
Adverse reaction – burning	5%	7%
Withdrew due to AE	N=0	N=1

Author's conclusion

- Clobetasol propionate foam 0.05% is safe and effective for the treatment of plaque-type psoriasis on scalp and non-scalp areas when applied twice daily for two weeks. The results of the patient's post study questionnaire suggest that there are multiple and integrated benefits for the use of clobetasol foam in the treatment of psoriasis of non-scalp sites.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lebwohl M, Sherer D, Washenik K, Krueger GG, Menter A, Koo J, Feldman SR. A randomized, double-blind, placebo-controlled study of clobetasol propionate 0.05% foam in the treatment of nonscalp psoriasis. *International Journal Of Dermatology* 2002;41 (5):269–274.	**RCT** **DESIGN** Between patient Patient delivery **ALLOCATION** Random Method of randomisation: not reported (but ratio 3:1 used) Concealment: unclear **BLINDING** Double-blind (patient / investigator) • **Washout period:** 2 weeks	**Total N:** 81 **Drop-outs (don't complete the study):** Total = 5 (6.2%): 3 (5%) clobetasol and 2 (10%) placebo Noncompliance: 2 in clobetasol group; 0 in placebo AEs: none in either group	INCLUSION CRITERIA **Mild to moderate** plaque type psoriasis; aged at least 18; TSS (0 to 12) ≥ 3; target lesions (>1cm^2) in at least one of 5 anatomical regions; BSA ≤ 20% **(NB Only non-scalp sites treated)** EXCLUSION CRITERIA Investigational medication within previous four wks; topical antipsoriatic treatment within previous two wks; systemic antipsoriatic treatment within previous four wks; concurrent UV treatment or sunbathing; pregnancy; lactation; inadequate contraception; men wishing to father children during the study; concurrent drug or alcohol abuse BC: Yes Age: mean 48.3 clobetasol (46 aged 18-59 and 15 aged 60 or over) and 45.9 placebo (16 aged 18-59 and 4 aged 60 or over) Gender (%M): 46 and 11 male	**n=61** **Clobetasol propionate foam, 0.05%** **Formulation:** foam **Class:** very potent corticosteroid **Frequency** twice daily **Amount used:** smallest amount to cover all lesions, maximum of 50 g/wk	**n=20** **Placebo** **Formulation**: foam **Frequency** twice daily	**Treatment duration:** 2 weeks **Assessments at:** baseline and week 1, week 2 and follow up at week 4 **Follow-up after end of treatment:** week 4	IAGI (7 pt: worse to completely clear) PAGI (7 pt: worse to completely clear) Adverse events Medicines consumption (compliance) **Primary efficacy parameter:** investigator's and patient's global assessmen	Conneticcs Corporation

Ref ID: LEBWOHL2002	• **Sample size calculation** not reported • **ITT analysis:** yes (assumptions not stated) **Setting:** Outpatients		(70%) Severity: pruritis (0 to 4): 2.11				t at all sites at week 2 and week 4 (low values indicate positive response)	

Effect Size

Outcomes

<u>Efficacy</u>

	Clobetasol propionate foam, 0.05% n=61	**Placebo n=20**	**p-value**
Investigator's global assessment at 2 weeks:			0.0005
Completely clear	3	0	
Almost clear	7	1	
Marked improvement	6	0	

Moderate improvement	19	2		
Slight improvement	14	5		
No change	9	9		
Worse	2	2		
Mean score	3.2	4.4		
Investigator's global assessment at 4 weeks (follow up):			0.015	
Completely clear	3	0		
Almost clear	4	1		
Marked improvement	8	0		
Moderate improvement	7	1		
Slight improvement	13	4		
No change	17	7		
Worse	6	5		
Mean score	3.7	4.7		
Patient's global assessment at 2 weeks:			0.0002	
Completely clear	3	0		
Almost clear	5	1		
Marked improvement	15	1		
Moderate improvement	17	1		
Slight improvement	12	6		

No change	6	8	
Worse	2	2	
Mean score	2.9	4.3	
Patient's global assessment at 4 weeks (follow up):			0.005
Completely clear	5	0	
Almost clear	5	1	
Marked improvement	13	0	
Moderate improvement	7	1	
Slight improvement	9	4	
No change	12	8	
Worse	7	4	
Mean score	3.3	4.7	

Time-to-effect

Mean composite psoriasis severity score shown graphically only; $p<0.05$ at weeks 1, 2 and 4

Adverse events

	Clobetasol propionate foam, 0.05% n=61	**Placebo n=20**

Total AE:	27 (44%) Application site reactions (17); Infection (4); Headache (2); Dry skin (2); Cellulitis, Viral infection, Dry mouth, Coagulation disorder, Arthritis, Insomnia, Contact dermatitis, Fungal dermatitis (1 each)	10 (50%) Application site reactions (6); Infection, Dry skin, Allergic reaction, Cyst, Flu syndrome and Sinusitis (1 each)
Severe AE:	1 Application site reaction	
AE possibly/probably/definitely related to drug	18 (30%) including 17 Application site reactions, 1 Contact dermatitis and 1 Dry skin	6 (30%) including 6 Application site reactions and 1 Dry skin

Withdrawals

= 5 (6.2%): clobetasol and placebo

	Clobetasol propionate foam, 0.05% n=61	**Placebo n=20**
Total withdrawals	3 (5%)	2 (10%)
Withdrawal due to non-compliance	2	0
Withdrawal due to protocol violation	1	2
Withdrawal due to AEs	0	0

Authors' conclusion

Clobetasol propionate foam, 0.05% is more effective than placebo in the treatment of non-scalp psoriasis; twice daily applications are well-tolerated; compliance exceeds 90%; and cosmetic characteristics are acceptable.

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Jarratt MT, Clark SD, Savin RC, Swinyer LJ, Safley CF, Brodell RT, Yu K.

“Evaluation of the efficacy and safety of clobetasol propionate spray in the treatment of plaque-type psoriasis.”

Cutis. 2006 Nov;78(5): 348-54.

Ref</td>
<td>Multicenter

(Finland)

• Randomised:
1:1 ratio. No other detail.

• Washout period:
Unclear

• Double blind.

• Allocation concealment
Unclear

• Sample size calculation
Yes, 53 deemed sufficient to detect a difference of</td>
<td>Total N: 120

Drop-outs (don’t complete the study): 0</td>
<td>Inclusion criteria:
Either sex, as least 18yo, plaque psoriasis covering at least 2% of body surface area (excluding face, scalp, groin, axillae) Overall severity score had to be as least 3 (moderate) on a scale of 0 to 4. Women of child bearing age had to use birth control, respect washout period.

Exclusion criteria: none stated.

Demographics
<table>
<tr><th></th><th>Clobetasol</th><th>Vehicle</th></tr>
<tr><td>N</td><td>60</td><td>60</td></tr>
<tr><td>Age</td><td>46.7±12.7</td><td>49.3±13.1</td></tr>
<tr><td>Sex M/F</td><td>38/22</td><td>34/26</td></tr>
<tr><td>Race White(%)</td><td>2 (3)</td><td>1 (2)</td></tr>
<tr><td>Black (%)</td><td>1 (2)</td><td>2 (3)</td></tr>
<tr><td>Hispanic/Latino</td><td>0 (0)</td><td>1 (2)</td></tr>
</table>
</td>
<td>Clobetasol propionate 0.05%

Formulation: spray

Frequency
twice daily

Application
Self-administered.
Allow 8 hours in between</td>
<td>Vehicle

Formulation: spray

Frequency
twice daily</td>
<td>Baseline, weeks 1,2, & 4 and at 8 weeks (=4 weeks follow-up)</td>
<td>1° outcome:
IAGI (investigator global assessment of improvement) on 5-point scale

2° and other outcomes:
Overall disease severity;
psoriasis signs and symptoms and calculated treatment success.</td>
<td>Dow pharma. And galderma R&D.</td>
</tr>
</table>

<table>
<tr>
<td>ID:JARRAT T2006</td>
<td>30% with power of 0.9 and type I error 0.05 (two-tailed)

• ITT analysis

Included ITT and per-protocol population (those whose visits were deemed evaluable; but figures not reported)</td>
<td></td>
<td>
<table>
<tr><td>BSA (%)</td><td>7.2±5.3</td><td>8.2±6.9</td></tr>
<tr><td colspan="3">Overall disease severity (%)</td></tr>
<tr><td>3 Moderate</td><td>56 (93)</td><td>53 (88)</td></tr>
<tr><td>4 Severe</td><td>4 (7)</td><td>7 (12)</td></tr>
</table>
</td>
<td></td>
<td></td>
<td></td>
<td>Adverse events</td>
<td></td>
</tr>
</table>

Effect Size

Outcomes

<u>Efficacy</u>
<u>Investigator's assessment of global improvement at 4 weeks (ITT)</u>

IAGI	Clobetasol	Vehicle	P value
Clear + Almost Clear, Week 4, N (%)	47 (78%)	2 (3%)	<0.001

Treatment success at 2 weeks was judged on a different level of success (achieving only mild disease or better).

4 weeks Follow-up (still in remission)

IAGI	Clobetasol	Vehicle	P value
Follow-up, clear + almost clear, N/total (%)	25/57 (44%)	2/54 (4%)	<0.001

Withdrawals and AEs

	Clobetasol	Vehicle
Skin atrophy	0	0
Withdrawal due to adverse reactions	0	0
Withdrawal due to treatment failure	0	0

Author's conclusion

- Clobetasol propionate spray 0.05% administered twice daily for 4 weeks was effective and safe in reducing scaling, erythema, plaque elevation, and overall disease severity.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Jorizzo Jl, Magee K,	**RCT** **DESIGN**	**Total N: 89**	INCLUSION CRITERIA **Moderate to severe** plaque	**n=44** **Clobetasol**	**n=45** **Placebo**	**Treatment duration:** 4	Investigator global	GlaxoWellcome

Stewart DM, Lebwohl MG, Rajagopalan R, Brown JJ. Clobetasol propionate emollient 0.05 percent: hypothalamic-pituitary-adrenal-axis safety and four-week clinical efficacy results in plaque-type psoriasis. *Cutis* 1997;60(1): 55–60. **Ref ID: JORIZZO1997**	Between patient Patient delivery **ALLOCATION** Random Method of randomisation: not reported Concealment: unclear **BLINDING** Double-blind (patient / investigator; not described) • **Washout period:** 2 weeks • **Sample size calculation** not reported • **ITT analysis:** yes for efficacy (assumptions not stated)	**Drop-outs (don't complete the study):** 9 (20%) clobetasol propionate and 7 (16%) vehicle Noncompliance: not stated AEs: 5 (11%) in each group of which 1 each were drug-related	type psoriasis (minimum 6 on 12-point scale); nonhospitalised men or nonpregnant; nonlactating women ≥ 12 yrs; baseline morning serum cortisol concentration of 5 to 18 mcg/100mL. **(NB face, axilla, perianal area, groin or scalp excluded)** EXCLUSION CRITERIA Recent topical anti-psoriatic medication or other drug that could alter psoriatic status. BC: Yes Age: 49.7 (range: 21 to 84) Gender (%M): 65% Severity: Duration of psoriasis (range, years): 1 to 57 Duration of exacerbation (range, wks): 3 to 2080 % BSA affected: 8.1%	**propionate emollient 0.05%** **Formulation:** emollient **Class:** very potent corticosteroid **Frequency** twice daily **Amount used:** "fingertip unit": 0.5gm in men and 0.43gm in women	**(vehicle)** **Formulation**: emollient **Frequency** twice daily	weeks **Assessments at:** day 4, 8, 15 and 29 and 2 weeks after end of treatment (day 43) **Follow-up after end of treatment:** 2 weeks after end of treatment (day 43)	assessment of improvement (6 pt: worse to cleared and %improvement of target lesion) Patient global assessment of improvement (5 pt: worse, poor, fair, good or excellent) **Primary efficacy parameter:** not stated	Inc.

	Setting: Outpatients							

Effect Size

Outcomes

Efficacy

Total signs/symptoms: score shown graphically: p≤0.006 by day 4, erythema and skin thickening by day 8, and pruritis by day 15; mean reduction were greater than vehicle throughout the rest of the treatment period.

Physician's gross assessment: good, excellent or cleared

	Clobetasol propionate emollient 0.05% n=44	**Placebo (vehicle) n=45**	**p-value**
Day 4	7%	7%	
Day 8	30%	7%	p<0.02
Day 15	48%	13%	p<0.02
Day 29	69%	12%	p<0.02
Day 43	69%	6%	p<0.02

Patient's gross assessment: good, excellent or cleared

	Clobetasol propionate emollient 0.05% n=44	**Placebo (vehicle) n=45**	**p-value**
Day 4	51%	44%	
Day 8	67%	44%	p≤0.05
Day 15	71%	37%	p≤0.05
Day 29	85%	35%	p≤0.05
Day 43	72%	28%	p≤0.05

Time-to-effect

Total signs/symptoms: by day 4, erythema and skin thickening by day 8, and pruritis by day 15; physician's and patient's assessment by day 8. Differences between groups increased over time (except pruritis score same at day 29 as at day 15). 2 weeks after the end of treatment (day 43) differences similar to day 29.

Adverse events

	Clobetasol propionate emollient 0.05% n=44	**Placebo (vehicle) n=45**
Total AE	5 (11%) people (all mild to moderate): burning/stinging (5); tenderness in elbow (1); pruritis (1)	5 (11%) people (all mild to moderate): burning/stinging (4); worsening of psoriasis (1)
Withdrawal due to AEs	1	1

No skin atrophy; subnormal serum cortisol concentrations (<5µg/100mL): 1 Clobetasol propionate emollient 0.05% and 0 Placebo (vehicle); ≥50% decrease in serum cortisol concentrations form baseline: 2 (5%) Clobetasol propionate emollient 0.05% and 3 (8%) Placebo (vehicle); p=0.664.

Authors' conclusion

Clobetasol propionate emollient 0.05% more effective than Placebo (vehicle) emollient in reducing total signs/symptoms: by day 4, erythema and skin thickening by day 8, and pruritis by day 15; and physician's and patient's assessment by day 8.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Olsen EA. Efficacy and Safety of Fluticasone Propionate 0.005% Ointment in the Treatment of Psoriasis. *Cutis* 1996;57(2 Suppl): 57–61. **Ref ID: OLSEN1996**	**2 RCTs** **DESIGN** Between patient Patient delivery **ALLOCATION** Random Method of randomisation: not reported Concealment: unclear **BLINDING** Double-blind (patient / investigator) • **Washout period:** not reported • **Sample size calculation :** not reported **ITT analysis:** not	**Total N: Study 1: 181; study 2: 207** **Drop-outs (don't complete the study):** Total = 3 (1.7%) Noncompliance: not stated AEs: not stated	INCLUSION CRITERIA Moderate to severe psoriasis; TSS ≥6/9; stable or worsening disease EXCLUSION CRITERIA Not stated BC: Yes Age: study 1: 49 (range: 15 to 76) years; study 2: 45 (12-87) years Gender (%M): study 1: 66.9%; study 2: 52% Severity: Duration (yrs): study 1: 19 (range: 1 to 60) years; study 2: 16 (0.8-50) years % BSA affected: study 1: 12.0% (range: 1 to 80%); study 2: 13 (1-45) % BSA treated: study 1: 11% (range: 1 to 80%); study 2: 12 (1-80%)	**n=** study 1: 88; study 2: 105 **Fluticasone propionate 0.005% ointment** **Formulation:** ointment **Class:** synthetic fluorinated topical corticosteroid **Frequency:** twice daily **Amount used:** max. 100 g/wk	**n=** study 1: 90; study 2: 100 **Placebo (vehicle)** **Formulation**: ointment **Frequency:** twice daily	**Treatment duration:** 4 weeks **Assessments at:** baseline and 1, 2, 3 and 4 weeks **Follow-up after end of treatment:** none	Investigator global assessment (6 point: 1=cleared to 6=worse) Severity: [erythema; induration; scaling; pruritis] 0 absent to 3 severe. Patient subjective assessment [treatment effect: 1 = excellent to 4 = poor]; adverse events	not reported

	reported **Setting:** Outpatients						**Primary efficacy parameter:** not stated	

Effect Size

Outcomes

Efficacy

Investigator global assessment:

	Study 1		Study 2	
	Fluticasone propionate 0.005% ointment (n=88)	**Placebo (vehicle, n=90)**	**Fluticasone propionate 0.005% ointment (n=105)**	**Placebo (vehicle, n=100)**
Week 1: Clear	0	0	0	0
Excellent/good	55%	17%	29%	11%
Week 2: Clear	4%	1%	0	0
Excellent/good	60%	27%	50%	21%
Week 3: Clear	4%	1%	0	0
Excellent/good	65%	34%	65%	30%

Week 4: Clear Excellent/good	11% 60%	1% 33%	3% 66%	0 34%
End of treatment: Clear Excellent/good	10/88 (11%) 50/88 (57%)	1/90 (1%) 25/90 (28%)	3/105 (3%) 69 (66%)	0 30/100 (30%)

% Patient assessment of treatment as excellent or good:

	Study 1		Study 2	
	Fluticasone propionate 0.005% ointment (n=88)	**Placebo (vehicle, n=90)**	**Fluticasone propionate 0.005% ointment (n=105)**	**Placebo (vehicle, n=100)**
Week 1: Excellent/good	66%	39%	68%	42%
Week 2: Excellent/good	65%	24%	65%	35%
Week 3: Excellent/good	63%	26%	66%	34%
Week 4: Excellent/good	62%	27%	64%	34%
End of treatment: Excellent/good	52/88 (59%)	21/90 (23%)	65/105 (62%)	31/100 (31%)

Time-to-effect: Fluticasone propionate 0.005% ointment significantly better than vehicle at all post-baseline visits for investigator global assessment and patient assessment, and better than vehicle in each of the signs and symptoms at week 2 and thereafter ($p \leq 0.01$) except pruritis week 4 study 2 ($p=0.05$).

Adverse events:

	Fluticasone propionate 0.005% ointment (n=193)	Placebo (vehicle, n=190)
Drug-related AE	13/193 (6.7%)	12/190 (6.3%)
Burning/pruritis at application site	11/193 (6%)	11/190 (6%)
AE not resolved at end of study	1 hypertrichosis	0

Withdrawals: Total = 3 (1.7%); not stated which group.

Authors' conclusion

Fluticasone propionate 0.005% ointment is superior to vehicle in the treatment of psoriasis.

H.6.6 DITHRANOL VS VITAMIN D OR VITAMIN D ANALOGUE

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Van de Kerkhof, P.C.M; Van der Valk, P.G.M; Kucharekova, S.M; de Rie, M.A; de Vries, H.J.C; Damstra, R; Ornaje, A.P; de Waard-van der Spek, F.B; Van Neer, P; Lijnen, R.L.P; Kunkeler, A.C.M; Van Hees, C; Haertlein, N.G.J; Hol, C.W " A comparison of twice-daily calcipotriol ointment	RCT Multicentre study (6 centres in the Netherlands). • **Setting:** Day care centre (daily visits during the first week and twice weekly visits subsequently for up to 12 weeks) • **Randomised** Computer generated system. • **Washout period**: Unclear	Total N: **106** **Drop-outs (don't complete the study):** N= 21 Reasons; **Unacceptable side effects** (calcipotriol n = 7, dithranol n = 3) **Unacceptable treatment efficacy** (calcipotriol n = 7, dithranol n =4)	**Inclusion criteria:** clinical diagnosis of psoriasis vulgaris, amenable to treatment with topical medications; area should be treatable with 100g max ointment/wk; min PASI score ≥ 2 in at least one body region; written consent; negative urine pregnancy test and agree to use contraception; capability/willingness to attend the day-care centre. **Exclusion criteria:** acute guttate, generalized pustular or erythrodermic exfoliative psoriasis, atopic dermatitis; seborrhoeic dermatitis or other inflammatory skin disease; systemic antipsoriatic treatment or phototherapy <6 wks; topical antipsoriatic treatment <2 wks (except for emollients); removal of scales <1 day of study or during study; treated with corticosteroids <6wks; planned changes in medication that could affect psoriasis; pregnant or breast feeding or wished to be pregnant during study; with or suspected hypercalcaemia; hypersensitivity to	N=54 Calcipotriol,, 50µg/g in 100g tubes Day 1-3, 0.1% for 15min, then washed off. Day 4-6, 30min Day 7-9, 45 min Increased to 0.2% and repeat cycle	N=52, Dithranol, 0.05%, 0.1%, 0.2%, 0.3%, 0.4%, 0.6%, 0.8%, 1.0%, 2.0%, 3.0% and 5.0% in 50-g tubes **Formulation:** cream **Frequency:** Once daily	Treatment duration: Treated for 12 weeks or until cleared Follow-up: 12 weeks	Outcomes assessed after 2, 4, 8 and weeks of treatment. **1° outcome:** PASI Treatment response (6 point scale) Overall treatment response **2° and other outcomes:**	Leo Pharma

<table>
<tr>
<td>with once-daily short-contract dithranol cream therapy: a randomized controlled trial of supervised treatment of psoriasis vulgaris in a day-care setting" B J of Dermatology. 2006: 155; 800-7

Ref ID:

VANDEKERKHOF2006</td>
<td>• Blinding: Not reported

• Allocation concealment: Yes, assignment was carried out by means of a telephone voice response system to ensure that the investigators decision to randomized the patients preceded knowledge of the randomized system.

• Sample size calculation Yes. Calculated on a noninferiority design – limit -10%. Assumed</td>
<td></td>
<td>calcipotriol or dithranol cream; unable to comply with study protocol; treatment with investigational drug <3 months; participating in another clinical trial; exposed to excessive sun or UV radiation during study; known to be unresponsive to treatment; require more than 100g of treatment/wk.

<table>
<tr><th>Mean baseline</th><th>Calcipotriol N=54</th><th>Dithranol N=52</th></tr>
<tr><td>Age (range)</td><td>51.5 (29-78)</td><td>50.9 (25-83)</td></tr>
<tr><td>PASI (range)</td><td>9.8 (3.2-27)</td><td>10.1 (2.7-20.9)</td></tr>
</table>
</td>
<td>Formulation:
Ointment

Frequency:
Twice daily

Note: At the day care unit, the nurse had to apply the study medication as appropriate. At home, the patient, preferably with the assistance of another person, had to apply the study medication himself or herself, according to the</td>
<td></td>
<td></td>
<td>Adverse events</td>
<td></td>
</tr>
</table>

	a % point superiority of calcipotriol over dithranol and an SD of 30% of % reduction in PASI from baseline to end of treatment. With a sample size of 51, a two-group 0.05 one sided t-test would have 80% power to reject null-hypothesis. • **ITT analysis** Yes, all 106 patients.			instructions. **Amount of medication used:** The mean amount of calcipotriol used during treatment was 387.8 g vs. 1017.5 g dithranol.				
Effect Size Outcomes								

Efficacy

Percent change in Psoriasis area and severity index (PASI) from baseline to the end of treatment by intention to treat (ITT) and per protocol analysis set (PP).

Outcome	**Calcipotriol ITT n = 54**	**Calcipotriol PP n = 46**	**Dithranol ITT N=52**	**Dithranol PP N=40**
% Change in PASI index (Mean ± SD)	-56.1 ± 37.2	-57.0 ± 35.4	-63.3 ± 29.7	-63.6 ± 29.1

Percentage change in Psoriasis Area and Severity Index from baseline (per-protocol analysis)

	Week 2	**Week 4**	**Week 8**	**Week 12**	**End of treatment**
Calcipotriol group	**35.0**	**47.3**	**55.2**	**59.8**	**57.0**
Dithranol group	**19.5**	**33.9**	**46.0**	**63.8**	**63.6**

Overall assessment of treatment response (per protocol analysis): assessments of percent of patients reaching clearance

Outcome - clear	**Patient assessment**	**Investigator assessment**
Calcipotriol **n = 46**	19.6%	12.5%
Dithranol **N=40**	25.0%	25.0%

Safety

- A significantly greater number of patients reported adverse events in the dithranol group (50/52 patients, 96%) compared with the calcipotriol group (37/53 patients, 70%) (P<0.001)
  The odds ratio for the calcipotriol group relative to the dithranol group was 0.09(95% CI: 0.02 to 0.43)
- A significantly greater number of patients reported application-related skin and subcutaneous tissue disorders in the dithranol group (37/53 patients, 71%) compared with the calcipotriol group (21/53 patients, 40%). (p=0.001)
  The odds ratio for the calcipotriol group relative to the dithranol group was 0.27 (95% CI: 0.12 to 0.60).

The safety analysis set comprised all ITT patients except one. This patient randomised to calcipotriol, failed to attend after visit 1 and provided no safety information.

Withdrawal

Outcome	**Calcipotriol** **n = 54**	**Dithranol** **N=52**
Due to unacceptable AEs	7	3
Due to unacceptable treatment efficacy	7	4

Authors' conclusion:

- NS difference between the calcipotriol and dithranol treatment on the PASI index, in the PP analysis (-6.0%, 95% CI: -19.0 to 7.9%) or the ITT analysis (-6.9%, 95% CI: -19.8 to 6.0%)
- Significantly greater number of adverse events reported in the dithranol group compared with the calcipotriol group.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hutchinson PE, Marks R, White J. The efficacy, safety and tolerance of calcitriol 3 µg/g ointment in the treatment of plaque psoriasis: a comparison with short-contact dithranol. *Dermatology* 2000;201(2):139–45. **Ref ID: HUTCHINSON2000**	**RCT** **DESIGN** Between patient Patient delivery **ALLOCATION** Random Method of randomisation: not reported Concealment: Unclear **BLINDING** Open • **Washout period:** 1 week • **Sample size calculation** reported	**Total N:** 114 **Drop-outs (don't complete the study):** Total = 28 (24.6%): 12 calcitriol and 16 dithranol Noncompliance: not stated Withdrawal due to intolerance: calcitriol 0; dithranol 2	INCLUSION CRITERIA Chronic plaque psoriasis of **at least moderate** (grade 2) severity, aged over 18 years; Caucasian or Asian origin **(NB head excluded)** EXCLUSION CRITERIA Other forms of psoriasis; systemic or intralesional therapy or photo-chemotherapy within previous two months; topical antipsoriatics within previous wk or concomitant; other medications that could affect psoriasis; pregnancy; inadequate contraception BC: Yes Age: 42.3years Gender (%M): 74.4% Severity: moderate to	**n=60** **Calcitriol ointment, 3 mcg/g** **Formulation:** ointment **Class:** vitamin D analogue **Frequency** twice daily **Amount used:** not stated	**n=54** **Short contact dithranol, 0.25 to 2%** **Formulation**: cream **Frequency** once daily for 30 minutes only	**Treatment duration:** 8 weeks **Assessments at:** weeks 1, 2, 4, 6 and 8 **Follow-up after end of treatment:** none	PASI (erythema, induration and scale assessed on arms, trunk and legs) IAGI (6 pt: worse to clearing) Overall global severity (5 point: 0=none, 1= slight; 2= moderate; 3= severe; 4= very severe) Adverse events	not reported

	• **ITT analysis:** yes **Setting:** Outpatients		very severe Duration of psoriasis, months, (mean): 185.1 (range: 1 to 85) PASI (mean): 11.8 Mean body surface area involved around 18% (range 1-85%)				**Primary efficacy parameter :** global improvement score (-1 = worse; 0= no change; 1=minimal improvement; 2= definite improvement; 3= considerable improvement; 4= clearing	
Effect Size Outcomes **<u>Efficacy</u>**								

Global improvement score of 2= definite improvement; 3= considerable improvement or 4= clearing: 72% calcitriol vs. 70% dithranol patients.

Global severity score distribution (p=0.35)

	Calcitriol n=60	**Dithranol n=54**
0=none	**4 (7%)**	**9 (17%)**
1= slight	**19 (32%)**	**15 (28%)**
2= moderate	31 (52%)	22 (41%)
3= severe	6 (10%)	8 (15%)
4= very severe	0	0

PASI scores (shown graphically only) very similar at all time points except at week 1 when a difference in favour of calcitriol was recorded (p=0.049). At the last assessment, scores had fallen from a baseline of 11.6 to 4.2 for calcitriol (64% reduction) and 12.0 to 5.2 for dithranol (57% reduction).

Time-to-effect

- Global improvement at 1 week and continued throughout treatment period for both treatments (had not reached max effect)
- Reduction in PASI score beginning to plateaux between 6-8 weeks in both groups

Withdrawals

	Calcitriol n=60	**Dithranol n=54**
Withdrawal due to non-compliance	not stated	not stated
Withdrawal due to AEs (intolerance) Intolerance not due to study medication	0 1	2 2
Missing	1	0
Inefficacy	1	2
Recovered	3	6
Unrelated	0	2
Other	6	2
Total	12	16

Adverse events:

3 patients on calcitriol and 4 on dithranol reported AE of the skin and appendages (pruritis, erythema, rash, dry skin, eczema). No significant changes in blood chemistry parameters.

Authors' conclusion

Twice daily calcitriol ointment is equally as effective as short-contact dithranol cream but is better tolerated and provides better quality of life and greater patient acceptability.

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>Wall AR, Poyner TF, Menday AP.

“A comparison of treatment with dithranol and calcipotriol on the clinical severity and quality of life in patients with psoriasis.”

Br J Dermatol. 1998 Dec;139(6):1005-11.

Ref ID: WALL1998</td>
<td>Multicentre
• Randomised:
Yes, but no detail

• Washout period:
Unclear

• Open study
Not blinded

• Allocation concealment
Unclear

• Sample size calculation
Unclear

• ITT analysis
Unclear</td>
<td>Total N: 306 (n=161 calcipotriol, 145 dithranol)

Drop-outs (don’t complete the study): N=11 defaulted and N=9 allocated incorrect treatment</td>
<td>Inclusion criteria: Over 18 years of age with stable, mild to moderate chronic plaque psoriasis of at least 100cm2 surface area, less than 40% of body surface, attended GP in last 6 months for psoriasis

Exclusion criteria: acute guttate or pustular psoriasis, chronic plaque affecting face and scalp only, prescribed topical antipsoriatic treatment in 2 weeks before visit 1, systemic treatment in last 8 weeks, pregnant or breast feeding, receiving >400 iu of VitD daily, Ca tablets or other medication that would affect course of disease, hypersensitive to trial medication, and likely to be non-compliant.

Demographics
<table>
<tr><th></th><th>Calcipotriol N=161</th><th>Dithrocream N=145</th></tr>
<tr><td>Sex M/F</td><td>75/86</td><td>69/76</td></tr>
<tr><td>Age (mean ±SD)</td><td>47±15.8</td><td>46.3±15</td></tr>
</table>
</td>
<td>Dovonex (0.005% calcipotriol)

Formulation: ointment

Frequency:
Twice daily</td>
<td>Dithrocream containing 0.1%, 0.25%, 0.5%, 1.0% or 2.0% dithranol

Formulation: cream

Application
Concentration was increased at weekly intervals until either clearance or adverse side effects, in which case concentration was</td>
<td>3 months</td>
<td>1° outcome:
IAGI (investigator) and PAGI (patient) assessment of global improvement (5 point scale)

2° and other outcomes:
Quality of life using Psoriasis Disability Index (PDI) and sickness impact profile (SIP)</td>
<td>Leo Pharmaceuticals</td>
</tr>
</table>

			Duration of psoriasis	18±12	19±13			decreased step by step.			
			Previous calcipotriol use	73%	57%						
			Previous dithranol use	69%	49%						
			Extent 0-10%	N=60	N=60						
			Extent 31-40%	N=12	N=9						

Effect Size

Outcomes

Efficacy

Investigator and patient assessment of global improvement at 3 months.

Outcome	Calcipotriol N=153	Dithrocream N=131	Odds Ratio
IAGI (% with cleared or marked improvement)	60.1%	51.1%	1.44 (95%CI: 0.9, 2.31) NS
PAGI (% with cleared or marked improvement)	60.8%	49.6%	1.57 (95%CI 0.98, 2.52) p = 0.059

Adverse events

None reported

Author's conclusion

- The response to treatment was similar in the calcipotriol and dithrocream treatment groups.
- Patients with plaque psoriasis who are treated with calcipotriol or dithrocream have significantly improved quality of life, with calcipotriol treatment tending to have an advantage over dithranol.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Berth-Jones, J., Chu, A.C., Dodd, W.A.H., Ganpule, M., Griffiths, W.A.D., Haydey, R.P., Klaber, M.R., Murray, S.J., Rogers, S., Jurgensen, H.J. **Ref ID:** BERTHJONES 1992	RCT Multicentre study from United Kingdom, Canada and Ireland. **DESIGN** Between patient Patient delivery • **Setting:** outpatient • **Randomised**: balanced blocks of four using computer generated random numbers • **Washout period**: 2 weeks • **Blinded:** no	Total N: 478 **Drop-outs (don't complete the study):** Total = 58 (16.7% in dithranol and 11.3% in calcipotriol groups) See table below	**Inclusion criteria:** Out-patients attending dermatology clinics for treatment of chronic stable plaque psoriasis. **Exclusion criteria**: Patients known not to respond to dithranol or calcipotriol; people receiving systemic treatment, including PUVA, during two months preceding the study; hypercalcaemia; abnormal renal or hepatic function; intake of more than 400 units daily of vitamin D, or calcium tablets; sensitivity to any component of Dithrocream or calcipotriol ointment; concurrent medication likely to affect the outcome of the trial; pregnant women or women not using adequate contraception. No explicit or implicit exclusion of scalp/face	**N=239** **Calcipotriol** 50µg/g (Dovonex) **Formulation**: ointment **Frequency:** twice daily to all lesions below head and next except flexures. Who administered unclear.	**N=239** **Dithranol (Dithrocream)** Commenced at highest concentration patient known to tolerate, or 0.1% in people new to dithranol. Concentration increased each week to 0.25, 0.5, 1 and 2%. **Formulation:** cream **Frequency:** once daily to all lesions	**Treatment duration:** 8 weeks. No longer time FU.	**1° outcome:** Response to treatment measured using severity of psoriasis (PASI) scoring system **2° and other outcomes:** Changes to full blood count Adverse events	Leo Pharmaceutical Products, Ballerup, Denmark.

	• **Allocation concealment:** unclear • **Sample size calculation:** 10% difference between groups with power of 80% at significance level of 5%. N=200 each group. • **ITT analysis:** no • **Drop-outs/withdrawals**:58 before end of 8 weeks' treatment (see below).		psoriasis. **Baseline comparability**: comparable at baseline. Age: 44 (range: 18 to 85) Gender (%M): 55% Severity: PASI: 9.3 Duration (yrs): 18 (12SD)		below head and next except flexures.			

Effect Size

<u>Efficacy</u>

Outcome	**Dithranol** (n=227)	**Calcipotriol** (n=231)	MD (95% CI)
IAGI (marked improvement/completely cleared)	116 (51%)	180 (78%)	28 (19-36)%
PAGI (marked improvement/completely cleared)	123 (54%)	180 (78%)	

PASI

During the 8 weeks of the study the mean PASI score fell from 9.1 (SD 6.1, n=239) to 4.7 (4.4, n=208) in patients on dithranol (p<0.001) and from 9.4 (6.5, n=239) to 3.4 (2.7, n=214) in those on calcipotriol (p<0.001). The difference between the groups was significant in favour of calcipotriol at 2 weeks (p<0.001) and remained so at each subsequent assessment. At 8 weeks, this difference was 1.6, 95% CI 0.5 to 2.7.

Time-to-remission/maximum effect

- Based on mean PASI over time treatment effect had not reached a plateau at 8 weeks in any group, but the response was more gradual between 4 and 8 weeks

Safety:

Adverse events	N=239	N=239	P
Burning or irritation of lesional or perilesional skin (%)	115 (48)	48(20)	<0.001
Facial erythema or rash	1(0.4)	10(4)	0.006
Other cutaneous symptoms at sites remote from treatment	11(5)	26(11)	0.01
Total	127(53)	84(35)	<0.001

Withdrawals

Reason	Dithranol (n=239)	Calcipotriol (n=239)	p-value
Complete clearing of psoriasis	**2**	**2**	**NS**
Voluntary	7	4	NS
Deterioration of psoriasis	**3**	**3**	**NS**
Medical deterioration unrelated to study	0	2	NS
Cutaneous adverse effects	**12**	**4**	**0.04**
Exclusion criteria	1	1	NS
Hypercalcemia	1	0	NS
Non-compliance	**11**	**11**	**NS**
Other	3	0	NS

Authors conclusion

- Calcipotriol is more effective and better accepted than short-contact dithranol.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
O. B. Christensen, N.-J. Mork, R. Ashton, F. Daniel, and S. Anehus. Comparison of a treatment phase and a follow-up phase of short-contact dithranol and calcipotriol in outpatients with chronic plaque psoriasis. J.Dermatol.Treat. 10 (4):261-265, 1999. REF ID: CHRISTENSE	Multicentre (19 centres in Europe; Sweden, England, Norway and France) DESIGN Between patient Patient delivery ALLOCATION Random Method of randomisation: not reported Concealment: unclear BLINDING Single-blind at inclusion only (investigator); not described • **Washout period**:	N=171 **Drop-outs (don't complete the study):** N =5 during treatment phase All in dithranol group **Reasons:** unclear Note: during the full 16 weeks a	**INCLUSION CRITERIA** Outpatients with **mild to severe** chronic stable chronic plaque psoriasis, not more than 10% BSA, total severity score (0 to 9)≥4, involving all three signs (erythema, scaling, infiltration) **EXCLUSION CRITERIA** Systemic treatment within previous 4 weeks; topical treatment within previous 2 weeks; receipt of oral retinoids within previous 2 months BC: Yes (except more males in calcipotriol group) Age: 47.4 (range: 17 to 88) Gender (%M): 62.6% Severity: Mean TSS (0 to 9): 6.24	N=89 **Calcipotriol** 50 µg/g **Formulation**: ointment **Frequency** twice daily (without washing off) Who administered drug unclear. --- **Both arms:** all patients approaching treatment end-point advised to avoid sun	N=82 **Dithranol** (1 and 3%) **Formulation**: cream **Frequency** once daily – left in contact for 30 mins before being washed off NOTE: patients started on 1% dithranol and instructed	**Treatment duration**: 8 weeks **Post-treatment follow-up**: 8 wk for those who were at least 50% improved and willing to continue OTC moisturisers allowed	IAGI (7-pt: worse to cleared) TSS (scaling, erythema, thickness); 0-12 Initially done separately for A: elbows and/or knees; and B: arms, thighs or trunk Relapse rate (at least 25% exacerbation)	Not reported

N1999	See exclusion criteria • **Sample size calculation**. no • **ITT analysis** no	total of 76 patients were withdrawn	Mean duration of psoriasis: 18.5 (range: 1 to 58) No explicit or implicit exclusion of face or scalp psoriasis.	exposure	to increase to 3% between wk 1-4 if able to tolerate 1% (62/77 completers escalated dose)		AEs	

Effect Size

Outcomes

Efficacy (PP population)

IAGI	**Dithranol n=77**	**Calcipotriol n=89**	**p-value**
Clear	4	6	
At least moderate (50%) improvement	48 (62%)	71 (80%)	0.013

Time to max response

- Based on graphical information of change in TSS over time the maximum treatment effect with dithranol and calcipotriol had not been reached by 8 wks, although the most rapid improvement was seen over the first 4 weeks, with much more gradual reduction in mean TSS between 4-8 wk

Follow-up phase

<u>Relapse:</u> among those at least 50% improved and willing to continue (Calcipotriol n=62 (70%); dithranol n=33 (43%))

TSS (0-12)	Area A		Area B		Area A+B	
	Dithranol n=33	**Calcipotriol n=62**	**Dithranol n=33**	**Calcipotriol n=62**	**Dithranol n=33**	**Calcipotriol n=62**
Start of follow-up	2.5	2.1	2.0	1.6	2.26	1.88
Post-treatment endpoint	3.6	4.1	3.1	3.3	3.30	3.72
Change	+1.1	+2.0	+1.1	+1.7	+1.04	+1.84
					p=0.0114 (favouring dithranol)	

Relapse during 8 wk follow-up	Dithranol n=33	Calcipotriol n=62	p-value
Total relapse (at least 25% exacerbation)	19 (58%)	50 (81%)	0.0053
Relapse among those at least 90% cleared	3/10 (30%)	16/24 (67%)	0.068
Relapse among those at least 50-75% cleared	16/23 (70%)	34/38 (90%)	0.084

Time-to-relapse

- A survival curve shows that time-to-relapse was shorter with calcipotriol than with dithranol
- 86% of relapses following response to calcipotriol occurred within the first 4 weeks
- **Approximate median time to relapse (from graphical data): Calcipotriol = 29 days; dithranol = 56 days**

Withdrawals

	Calcipotriol n=89	Dithranol n=82
During treatment and post-treatment phase		
Withdrawal due to lack of efficacy	16	26
Withdrawal due to AEs	2	6
Voluntary withdrawal	6	9
Total withdrawal	76	

Author's conclusion

- Calcipotriol and dithranol both proved to be efficacious, but calcipotriol was more efficacious
- However, a significantly greater percentage of patients relapse following successful treatment with calcipotriol compared with dithranol (indicating a longer remission period following response to treatment with dithranol)

H.6.7 COAL TAR VS VITAMIN D OR VITAMIN D ANALOGUE

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Alora-Palli MB, Perkins AC, Van Cott A, Kimball AB. "Efficacy and tolerability of a cosmetically acceptable coal tar solution in the treatment of moderate plaque psoriasis: a controlled comparison with calcipotriene (calcipotriol) cream." Am J Clin Dermatol.	RCT • **Randomised**: Computer generated • **Washout period**: Unclear. • **Single blind.** Investigator • **Allocation concealment** Unclear • **Sample size calculation** Unclear	Total N: 60 **Drop-outs (don't complete the study):** Treatment phase N=13 (5 [16.7%]in LCD and 8 [26.7%] in calcipotriol) 5 on LCD (1 = lost to follow-up; discontinued intervention n=1, withdrew	**Inclusion criteria:** Men and women aged 18 or older with chronic plaque affecting 3-15% of their body surface area (excluding the head, groin, palms and soles). **Exclusion criteria:** pregnant or breast feeding; used topical anti-psoriatic therapy (including retinoids, corticosteroids, or vit D analogues) and/or received UVB phototherapy within 2 weeks of baseline; received psoralen+UVA, laser phototherapy, or systemic psoriasis therapy with corticosteroids or retinoids within 4 weeks of baseline; or received systemic immunomodulatory therapy within 12 wks of visit. Demographics N: **LCD (n=30)**: Males 15, Females 15; **Calcipotriene (n=30)**: Males 19, Females 11	Liquor carbonis distillate (LCD_ 15%, equivalent to 2.3% coal tar **Formulation:** solution **Application** Self administered - 2x day at home to all areas except head.	Calcipotriene (calcipotriol), 0.005% **Formulation:** cream **Frequency**: Twice daily	12 weeks + 6 weeks follow-up	Blinded investigator evaluated patients. **1° outcome:** Difference in % change in baseline and 12 weeks in the Psoriasis Area and Severity Index (PASI) score **2° and other outcomes:**	NeoStrata

<table>
<tr>
<td>2010;11(4): 275-83.

Ref ID:ALORAPALLI2010</td>
<td>• ITT analysis

Performed to determine efficacy at 12 wks of treatment (modified ITT – those with at least one post baseline assessment)</td>
<td>consent n=3)

8 on Calcipotriene (2=lost to follow-up; worsening of psoriasis n=3, cancer n=2, withdrew consent n=1)

Follow-up phase N=4

2 in each group</td>
<td>
<table>
<tr><td>Age</td><td>48.2 (19-77)</td><td>48.7 (21-74)</td></tr>
<tr><td>Duration of practice</td><td>18.9 (4-62)</td><td>14 (1-46)</td></tr>
<tr><td>Baseline PASI</td><td>7.07 ± 3.13</td><td>7.11 ± 3.14</td></tr>
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<td></td>
<td><u>Changes in:</u> PASI (modified bc head was not included, score ranged 0-64.8)

Physician’s global assessment (PGA) 6point scale.

Pruritus scale

Dermatology Life Quality Index (DLQI)

Patient reported</td>
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							psoriasis symptoms. ITT population . 75% or 50% reduction in psoriasis severity and area index, **PASI50 PASI75**	

Effect Size

Outcomes

<u>Efficacy</u>

<u>Treatment phase (12 weeks)</u>

<u>Primary outcome. Change in PASI (0-64.8) from baseline</u>

Outcome	**Mean PASI score (% change)**		
	LCD (n=27)	Calcipotriene (n=28)	**P value**
Baseline (N=55)	7.3	7.07	
4 weeks (N=55)	4.69 (-35.4%)	5.09 (-30.2%)	0.3498

8 weeks (N=55)	3.70 (-48.9%)	4.71 (-34.2%)	0.0584
12 weeks (N=55)	3.24 (-58.2%)	4.66 (-36.5%)	0.0151
6 week follow-up (N=43)	N=23 3.15 (-52.5%)	N=20 4.85 (-22.2%)	0.0196

PGA (clear/minimal)

PGA response	LCD (n=27)	Calcipotriene (n=28)	**P value**
12 weeks (N=55)	14	6	<0.05

Time to max effect

Based on change in PASI score, the psoriasis was still gradually improving in response to treatment at 12 weeks.

Post-treatment follow-up phase (6 weeks)

Outcome	**LCD**	**Calcipotriene**	**P value**
Relapse (loss of PASI50) by week 18	4/16	7/9	<0.05
PGA > pre-treatment by week 18	5/22	14/20	<0.01
Change in DLQI from end of	Week 12: 3.8	Week 12: 4.7	0.009 (between groups)

treatment	Week 18: 2.6	Week 18: 5.4	

Withdrawals

	LCD	Calcipotriene
Withdrawal due to AEs	0	0

Author's conclusion

- The new formulated LCD solution, applied twice daily for 12 weeks, was more effective and as well tolerated as the calcipotriene cream.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
N. Pinheiro. Comparative effects of calcipotriol ointment (50 micrograms /g) and 5% coal tar/2% allantoin/0.5% hydrocortisone cream in treating plaque psoriasis. British Journal of Clinical Practice 51 (1):16-19, 1997. Ref ID: **PINHEIRO1997**	DESIGN Multicentre Between patient Patient delivery ALLOCATION Random Method of randomisation: not reported Concealment: unclear BLINDING Open **Washout**: not stated	N: 132 **Drop-outs (don't complete the study): 10** Calcipotriol: 4 (5.8%) Tar: 6 (9.5%) Reasons for withdrawal: Not given, apart from those withdrawing due to adverse events (1 calci and 3 in comparison group).	INCLUSION CRITERIA Chronic plaque psoriasis; Adult; BSA ≥100 cm² EXCLUSION CRITERIA Hypersensitivity to trial medications; concomitant treatment with Vitamin D/calcium/other relevant agent; pregnancy; risk of pregnancy; lactation; unable to comply with protocol BC: Yes Age: 48.2 (range: 17 to 90) Gender (%M): 59.1% Severity: Duration (yrs): 16.9 (range: 0.5 to 60) % severe: 13.6% No exclusion for face/scalp psoriasis explicity stated.	n: 69 Calcipotriol (50 µg/g) **Formulation**: ointment **Frequency:** Twice daily	n: 63 Coal tar 5%/allantoin 2%/hydrocortisone cream 0.5% (Alphosyl HC) **Formulation**: cream **Frequency:** Twice daily	Treatment duration up to 8 weeks. A longer FU was termed "end of treatment" but was not described in detail.	Primary outcome: Clear or marked improvement on Investigator global assessment (5-pt: worse to cleared) Total sign score (0 to 12) AEs	Leo Pharmaceuticals

<table>
<tr>
<td></td>
<td>Sample size calculation:
not stated

ITT analysis:
not stated</td>
<td></td>
<td>Baseline comparisons (stated as well matched but no useful variance measures given)
<table>
<tr><td></td><td>calcipotriol</td><td>comparison Rxs</td></tr>
<tr><td>male</td><td>41/69</td><td>37/63</td></tr>
<tr><td>age</td><td>45.8</td><td>50.9</td></tr>
<tr><td>duration of psoriasis</td><td>16.2</td><td>17.4</td></tr>
<tr><td>severe grade of psoriasis</td><td>16/69</td><td>11/63</td></tr>
<tr><td>area of psoriasis (cm2)</td><td>100-800</td><td>100-6000</td></tr>
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<tr>
<td colspan="9">Effect Size

<u>IAGI</u>

<table>
<tr><th>IAGI: marked improvement or clear</th><th>Calcipotriol (N =65)</th><th>Comparison Rxs (N=57)</th><th>p-value</th></tr>
<tr><td>8 weeks</td><td>47 (72.3%)</td><td>28 (49.1%)</td><td><0.02</td></tr>
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TSS

- Both treatments resulted in a significant reduction in total sign score ($p<0.001$) at 4 and 8 weeks
- The reduction was significantly greater in the calcipotriol group after 4 wk ($p=0.001$), 8 weeks ($p=0.01$) and at the end of treatment ($p=0.002$)

Time to max response

- Based on graphical data the maximum response based on mean TSS was seen at 4 weeks, with negligible further improvement up to 8 weeks

Withdrawals

Outcome	Calcipotriol (N =65)	Vehicle (N=57)
Withdrawal due to AEs	1	3

Note: one patient in each group suffered a flare of psoriasis

Authors' conclusion

- Up to 8 weeks treatment calcipotriol is significantly more effective than a similar course of therapy with coal tar 5%/allantoin 2%/hydrocortisone cream in the treatment of general practice patients with plaque psoriasis

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

S. N. Tham, K. C. Lun, and W. K. Cheong. A comparative study of calcipotriol ointment and tar in chronic plaque psoriasis. Br.J.Dermatol. 131 (5):673-677, 1994. **Ref ID: THAM1994**	RCT DESIGN Within patient Patient delivery ALLOCATION Random Method of randomisation: computer generated random numbers Concealment: unclear BLINDING Single-blind (investigator); no details given • **Washout period**: 2 weeks using twice daily white soft paraffin • **Sample size calculation** not reported	Total N: 30 **Drop-outs (don't complete the study):** Total = 3 (10%) Noncompliance: 2 AEs: calcipotriol1	INCLUSION CRITERIA Stable symmetrical chronic plaque-type psoriasis including one or more areas of the trunk, upper or lower limbs; adult EXCLUSION CRITERIA Unstable psoriasis during washout period; recent systemic or UV therapy; hypercalcaemia; high calcium or vitamin D intake; impaired renal or hepatic function; previous poor response to tar; concomitant medications; pregnancy No explicit or implicit exclusion of scalp/face psoriasis. BC: Yes Age: 40 (range: 20 to 74) Gender (%M): 56.7% Ethnicity: Chinese (70.0%), Indian (16.7%), Malay (10.0%) and Sikh (3.3%) Severity: PASI: 6.65 Duration (years): 9.7 (range:	**n=30** **Calcipotriol** (μg/g) **Formulation**: ointment **Frequency** twice daily Who administered unclear. --- Both arms: Concomitant therapies – low potency topical steroids permitted for lesions on face and scalp (applied after trial medications to avoid contamination)	**n=30** **coal tar solution BP in aqueous cream 15% (LPC)** **Formulation**: cream **Frequency** once daily (plus emollient in the morning)	**Treatment duration:** 6 weeks **Preferred treatment phase**: 4 weeks	Modified PASI (excluding head) IAGI: 6-pt – worse to cleared	Leo Pharma

	• **ITT analysis:** yes		2 to 20) **Previous therapy**: Topicals:100% UVB 60% PUVA 10% Re-PUVA 10% MTX 26.7%					

Effect Size

Outcomes

Efficacy

PASI: ITT population

Mean PASI (italics) and % change in PASI score from baseline; mean±SD	**Calcipotriol n=27**	**Tar n=27**	**p-value (between group for change score)**
Baseline	*6.6±4.9*	*12.95±3.4*	
2 weeks	*4.1±3.4*	*5.9±4.5*	<0.001

	36.9±25.0%	9.4±15.9%	
4 weeks	*2.8±2.2* 57.5±19.4%	*5.1±4.2* 22.3±24.2%	<0.001
6 weeks	*2.0±2.1* 69.8±20.4%	*4.5±3.6* 30.9±24.6%	<0.001

IAGI	**Calcipotriol n=27**	**Tar n=27**
Clear or marked improvement	13	3

Time-to-effect

- Calcipotriol: significant change in PASI score seen at 2 weeks ($p<0.05$); improvement slowed between 2 and 4 wk; and improvement between 4 and 6 weeks was not significant
- Tar: less rapid onset of action – significant difference in PASI score from baseline only seen after 4 weeks of treatment

Withdrawals

	Calcipotriol n=27	**Tar n=27**

Withdrawal due to non-compliance	2	
Withdrawal due to AEs	1	0

Authors' conclusion

- For limited plaque psoriasis topical calcipotriol is superior to topical tar and has the advantages of being odourless and non-staining, although irritation may occur in some patients

H.6.8 POTENT CORTICOSTEROID VS COAL TAR

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
P. Thawornchaisit and K. Harncharoen. A comparative study of tar and betamethasone valerate in chronic plaque psoriasis: a study in Thailand. J Med Assoc Thai 90 (10):1997-2002, 2007. REF ID: THAWORNCHAISIT2007	Single centre in Thailand (2001-2006) • **Setting:** unclear • **Randomised** Unclear method • **Washout period**: 2 weeks using only 10% urea cream twice daily • **Blinding:** unclear • **Allocation concealment**. Unclear • **Sample size calculation**.	N=58 **Drop-outs (don't complete the study):** N =2 (both in tar group) **Reasons:** Lack of efficacy	**Inclusion criteria: Mild to moderate** psoriasis; adults; plaque psoriasis on the body for at least 6 months **Exclusion criteria:** Pregnancy, only scalp or drug-induced psoriasis; severe psoriasis (>50% involvement); systemic anti-psoriasis or UV treatment within the previous 8 weeks; ingestion of medications known to influence psoriasis. Face or scalp psoriasis not explicitly excluded. **Mean baseline** — **Coal tar n=28** — **Betamethasone n=30**	N=28 10% liquor carbonis detergens coal tar (LCD) **Formulation**: cream **Frequency** twice daily Who administered is unclear. **Both arms:** medication applied to	N=30 0.1% betamethasone valerate **Formulation**: cream **Frequency** twice daily	Treatment duration 6 weeks . No long term FU reported.	PASI: Severity: [redness; thickness; scaliness, area] IAGI Compliance All patients assessed by the same physician	None stated

<table>
<tr>
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<td>Not reported

• ITT analysis
no – 2 withdrawals due to lack of efficacy therefore included in ACA analysis</td>
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<table>
<tr><td>Age (mean±SD)</td><td>40.3±13.4</td><td>42.4±12.8</td></tr>
<tr><td>Males %</td><td>60.7</td><td>63.3</td></tr>
<tr><td>PASI±SD (scale: 0-12)</td><td>17.1±2.9</td><td>17.7±3.8</td></tr>
</table>
</td>
<td>lesions on upper and lower extremities and trunk; no facial or flexural lesions were treated</td>
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Effect Size

Outcomes

<u>Efficacy</u>

<u>Time to maximum effect: PASI scores still improving at 6 weeks, so time to remission is likely to be >6 weeks.</u>

IAGI at end of treatment/6 weeks	**Coal tar n=28**	**Betamethasone n=30**
IAGI marked improvement to clear	7 (24.99%)	23 (76.67%)

Mean PASI (in italics) and % change in PASI score from baseline; mean±SD	**Coal tar n=28**	**Betamethasone n=30**	**p-value (between group)**

2 weeks (p-value for within group change)	*14.83±3.0* 13.56±8.5% (<0.001)	*12.95±3.4* 27.23±10.6% (<0.001)	<0.001
4 weeks (p-value for within group change)	*12.31±3.3* 28.18±16.5% (<0.001)	*8.68±3.8* 51.41±18.2% (<0.001)	<0.001
6 weeks (p-value for within group change)	*10.60±4.1* 38.39±21.1% (<0.001)	*5.52±4.5* 69.36±23.3% (<0.001)	<0.001

Withdrawals

	Coal tar n=28	**Betamethasone n=30**
Withdrawal due to lack of efficacy	2	0

Author's conclusion

- The investigator's overall assessment of the treatment response at completion of the trial demonstrated that the betamethasone valerate group achieved significantly greater clearance and marked improvement compared with the coal tar group
- Betamethasone valerate cream was safe, effective, and well-tolerated while the coal tar cream was described as messy, malodorous, and with a tendency to staining clothes

H.6.9 COMBINED OR CONCURRENT VITAMIN D OR VITAMIN D ANALOGUE AND POTENT CORTICOSTEROID VS MONOTHERAPIES/PLACEBO

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Ruzicka T, Lorenz B. "Comparison of calcipotriol monotherapy and a combination of calcipotriol and betamethasone valerate after 2 weeks' treatment with calcipotriol in the topical therapy of **psoriasis** vulgaris: a multicentre, double-	Multicentre, Germany • **Randomised**: Yes, but no details • **Washout period**: 2 week wash-out, could apply ointment base • **Double blind.** Yes, but no details **Allocation concealment** Unclear	Total N: 169 (monotherapy n=87, combination N=82) **Drop-outs (don't complete the study):** N=11 (5 monotherapy, 6 combination) Laboratory values at beginning (n=2), insufficient healing, AE (n=2), healing of psoriasis	**Inclusion criteria:** Men and women 18 + yrs with chronic plaque-type psoriasis with lesions on the lower and/or upper extremities and/or trunk, with an affected area not exceeding 30% of total body surface. Serum calcium, renal and liver function were normal. **Exclusion criteria:** No systemic antipsoriatic treatment or UV therapy had been administered during previous 2 months. Pregnant or nursing. Exacerbated disease during first 2 week treatment phase. **Demographics** Minimal data provided **Entire sample (n=169)**	2 wks Calcipotriol ointment 0.005% BD THEN 4 wks Calcipotriol ointment 0.005% (applied once AM)+ betamethasone valerate 0.1% (applied once PM) **Formulation** ointment	6 wks Monotherapy Calcipotriol ointment 0.005% **Formulation** ointment **Application** Twice daily BOTH ARMS: Exacerbation	2, 6 (or early remission) and 14 weeks (8-week post-treatment follow-up)	**1° outcome:** Psoriasis area and severity index (PASI) **2° and other outcomes** Investigator (IAGI, 6 point scale) and patient (5 point scale) assessme	None provided.

blind, randomized study." Br J Dermatol. **1998** Feb;138(2): 254-8. **Ref ID:** Ruzicka1998	• **Sample size calculation** Not reported • **ITT analysis** Yes (modified ITT – for all patient data available after beginning treatment – not all randomised; assumptions not stated)	or non-medical reasons.	Age (mean, range): 42 yrs (18-80) Men: 94 Women: 75	**Application** Twice daily – concurrent use	during first 2 weeks = excluded Complete remission before end of study = treatment terminated		nt of global improvement Safety evaluation (serum markers) Adverse events	

Effect Size

Outcomes

Efficacy

ITT for PASI at baseline, 2, 6 or 14 weeks

Outcome	Monotherapy N=86	Combination N=78	P value
PASI score at baseline → 2 and 6 weeks	6.2 →3.5 and 1.9	5.7→3.2 and 1.0	P<0.001
PASI score at 8 weeks after therapy (follow-up)	2.6	2.4	

ITT for IAGI at end of treatment

Outcome	Monotherapy N=86	Combination N=78	P value
IAGI responders (complete or distinct improvement), 6 wks – or at premature withdrawal (includes only patients with at least 4 weeks therapy, but this means just 2 weeks randomised)	52 (60.5)%	60 (77%)	

ITT for IAGI for initial low responders (moderate or slight improvement, no change or exacerbation)

Outcome	Monotherapy N=86	Combination N=78	P value
Low responders at week 2 (all on monotherapy)	50 (57.5)%	41 (50.0%)	
High responders during randomised phase among those who initially did not respond to monotherapy at 2 weeks	N=49 22 (44.9%)	N=39 27 (69.2%)	

Time to max effect

- Based on PASI score over time neither the monotherapy nor the combination group had reached a plateau by 4 weeks of treatment in the randomised phase (following 2 weeks of calcipotriol treatment)

Adverse events

	Monotherapy N=86	Combination N=78
Adverse reactions	23%	16%
Withdrew due to adverse events	N=1	N=1

Author's conclusion

- Combination therapy was more effective.
- Patients showing insufficient response to calcipotriol alone after 2 weeks showed a regression of psoriatic lesions using combination therapy
- Combination therapy is recommended as a first choice for patients who do not respond to treatment within 2 weeks of calcipotriol alone.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Fleming,C; Ganslandt, C; Guenther, L; Buckley, C; Simon J.C; Stegmann, H; Vestergaard Tingleff, L "Calcipotriol plus betamethasone dipropionate gel compared with its active components in the same vehicle and the vehicle alone in the treatment of psoriasis vulgaris: a	RCT 19 centre in Germany, Sweden, Ireland, UK and in Canada • **Between subjects design** • **Randomised** Randomised in a 4:2:2:1 ratio according to a pre-planned, computer generated, randomisation schedule • **Washout period**: No details, except use of emollients was	Total N: **364** **Drop-outs (don't complete the study):** Total 10%: 8% withdrew from two-compound group; 6% from betamethasone dipropionate gel group; 7.6% in calcipotriol group. N=10 withdrew after washout period; N=2 withdrew at or just after baseline **Reasons** No reasons given	**Inclusion criteria:** either sex aged 18 years or older with a clinical diagnosis of psoriasis vulgaris involving trunk and/or arms and/or legs amenable to treatment with a max of 100 g of tropical medication per week; IGA of at least mild was required. **Exclusion criteria:** patients with guttate, erythrodermic, exfoliative or pustular posriasis; used biological therapies with a possible effect on psoriasis vulgaris within 6 months prior to randomization, other systemic antipsoriatic therapies, PUVA or Grenz ray therapies within 4 weeks prior to randomization, and UVB therapy with topical treatment within 2 weeks prior to randomization.	**Calcipotriol gel** 50µg/g and **Betamethasonedipropionate gel** 0.5 mg/g N=162 <u>Monotherapy</u> **Calcipotriol** (50µg/g) N= 79 **Betamethasonedipropionate gel (DB)** (0.5 mg/g) N=83 All treatments	**Vehicle** N=40	Treated up to 8 weeks. No longer term FU.	**1° outcome:** Psoriasis area and severity index (PASI_ (6 point scale) IGA – Investigators global assessment of disease severity (=IAGI) **2° and other outcomes:** % change in PASI from baseline to wk 4 and 8. PASI 75% patients obtaining at least 75%	Leo Pharma A/S.

randomised, parallel group, double-blind, exploratory study" Eur J Dermatol, 2010;40(4): 465-71 Ref ID: FLEMING2010A	allowed. • **Blinding**: Double-blind (adequate) • **Allocation concealment** Unclear (no details) • **Sample size calculation** Yes. Total of 360 patients was calculated to provide 80% power if the comparison achieving controlled disease was 485 in the two-compound gel arm and not more than 28% in the comparator arms • **ITT analysis**		Does not explicitly exclude face and scalp lesions. May be included as they are mentioned with reference to the wash-out period.	once daily for up to 8 weeks Unclear who administered the interventions. ---------- **ALL ARMS:** **Frequency:** once daily **Formulation:** gel			improvement. Adverse events	

	Yes. Efficacy analysis was performed on all 364 patients (LOCF) • **Drop-outs/withdrawals** N=20							

Demographics

Mean baseline	**Two compound n=162**	**Betamethasone n=83**	**Calcipotriol n = 79**	**Vehicle n=40**
Age (mean±SD)	50.1±14.9	51.4±14.5	52.6±15.2	51.4±13.4
Males %	57.4	57.8	60.8	62.5
Caucasians %	97.5	100	97.5	97.5
Duration of psoriasis±SD, yrs	18.5±13.8	18.8±14.0	19.5±14.8	19.2±11.5
IGA, No of patients, %, Range				
Mild	31 (19.1) (1-8)	25 (30.1) (1-10)	17 (21.5) (2-8)	9 (22.5) (3-6)
Moderate	95 (58.6) (2-23)	43 (51.8) (2-19)	50 (63.3) (1-16)	26 (65) (3-22)
Severe	34 (21) (3-25_	14 (16.9) (6-21)	12 (15.2) (6-23)	5 (12.5) (9-18)

Very severe	2 (1.2) (6-11)	1 (1.2) (14)	0 (0)	0 (0)
Mean PASI±SD	7.7±4.6	7.8±4.4	7.9±3.9	7.9±4.7

Effect Size

Outcomes

Efficacy

Time to maximum effect – not clear, as no plateau of effect seen at end of trial.

Outcome	**Two compound gel**	**Betamethasone dipropionate**	**vs 2 compound gel**	**Calcipotriol**	**vs 2 compound gel**	**Gel vehicle**	**vs 2 compound g**
% responders* by IGA at **4 wks**	26/162 (16.0%)	8/83 (9.6%)	p=0.11	3/79 (3.8%)	p=0.006	1/40 (2.5%)	p=0.027
% responders* by IGA at **8 wks**	44/162 (27.2%)	14/83 (16.9%)	p=0.027	9/79 (11.4%)	p=0.006	0/40 (0%)	P<0.001
Mean % change in PASI **4 wks**[$]	-48.1%	-40.9%	p=0.04; MD: -7.85 (-15.2, -0.5)	-32.7%	p<0.001; MD: -15.4 (-22.8, -7.9)	-16.9%	p<0.001; MD 30.8 (--40.4 21.2)
Mean % change in PASI **8 wks**[$]	-55.3%	-49.8%	NS; MD: -6.16 (-14.2,+1.9)	-41.2%	p<0.001; MD: -13.9 (-22.0, -5.7)	-11.9%	p<0.001; MD 43.1 (-53.6, 32.6)
PASI 75 at **8 wks**	35.8%	28.9%	NS	17.7%	p=0.003	0%	p<0.001

* responders = proportion of those experiencing a change from at least moderate at baseline to clear or minimal; or as a change from mild at baseline to clear.

[$] no measure of variance provided for this continuous measure, but ORs and 95% CIs for the comparison are given.

Safety

- The proportion of patients with at least one adverse event was not statistically different in the two-compound gel group (96/162 or 42.5%) compared with the betamethasone dipropionate gel group (40/83 or 48.2%), the calcipotriol gel group (28/79 or 35.4%) and gel vehicle group (22/40 or 55%).
- Most adverse events were considered not related to study treatment and were of mild or moderate intensity.
- Lesional/perilesional adverse events on the trunk or limbs occurred in 12/162 (7.5%) patients in the two-compound group, 7/83 (8.4%) in the betamethasone dipropionate gel group, 8/79 (10.1%) in the calcipotriol gel group versus 10/40 (25.0%) in the gel vehicle group.
- No serious adverse events related to the study treatment were reported.

Authors' conclusion

- The percentage of patients who disease was clear or very mild and who had at least a two-step improvement in the Investigators Global Assessment of disease severity at 8 weeks, was significantly higher with calcipotriol plus betamethasone dipropionate than with betamethasone dipropionate, calcipotriol or gel vehicle.

Reference	**Study type**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of fundin g**
Guenther L; Cambazard F; VanDeKerkoff; Snellman	RCT International multicenter (Europe	Total N: 828 **Drop-outs (don't complete the study):**	**Inclusion criteria:** 18-86 years, psoriasis vulgaris at least 10% of one or more body parts (arms, legs, trunk).	**Combined formulation (Dovobet)**	**Vehicle** **Formulation**:	TD: 4 weeks. No log terms	**1° outcome:** Investigators gave assessment of	Leo Pharm aceuti cal Produc

E; Kragballe K; Chu AC; Tegner, E; Garcia-Diez A; Sprinborg,J "Efficacy and safety of a new combination of calcipotriol and betamethasone diproprinate (one or twice daily) compared to calcipotriol (twice daily) in the treatment of psoriasis vulgaris: a randomized, double-blind, vehicle-controlled clinical trial" B J of Dermatolog	and Canada) Between subjects trial • **Setting:** out-patient • **Randomised**: In the ratio of 2:2:2:1 2=intervention/s 1=vehicle Used a computer generated random numbers table. • **Washout period**: Not stated. • **Double blind.** All study personnel and subjects were blinded (identical tubes and ointments of	N=77 (but provided efficacy data). **Combined (1x):** 9 (6%) **Combined (2x)**: 16 (7%); **Calcipotriol**: 19 (8%); **placebo**: 33 (16%) The most common reason was the emergence of various exclusion criteria which affected all treatment groups equally	**Exclusion criteria:** Received systemic antipsoriatic treatment within previous 6 weeks or topical antipsoriatic treatment within 2 weeks. Need for concurrent use of type II or IV topical corticosteroids, recent exposure to sun or ultraviolet treatments, current diagnosis of unstable psoriasis, atopic dermatitis, seborrhoeic dermatitis, or other inflammatory skin disease, pregnancy or breast-feeding and use of any other medications that could affect psoriasis. Not explicitly stated that the face and scalp were excluded.	Calcipotriol 50µg/g + Betamethasone 0.5mg/g plus vehicle **Formulation**: ointment **Frequency:** once daily active treatment (plus vehicle in the evening to maintain blinding) **Note:** Scalp and facial psoriasis were not treated nor assessed. **ALL ARMS:** Parallel	ointment **Frequency:** twice daily **Combined formulation (Dovobet)** Calcipotriol 50µg/g + Betamethasone 0.5mg/g **Formulation**: ointment **Frequency:** twice daily **Calcipotriol (Dovonex)** 50µg/g **Formulation**:	FUs.	response as cleared, marked or slight improvement (IAGI) on 6 point scale Lesion thickness, redness and scaliness **2° and other outcomes:** PASI at (0,1,2 and 4 wks) + Speed of response - % change in PASI from baseline to 2nd visit. Patient assessment of overall efficacy	ts.

y 2002;147:316-323 Ref ID: **GUENTHER2002**	identical appearance) • **Allocation concealment** adequate • **Sample size calculation** N= 160 patients in the combined groups and N=80 in vehicle, will give each comparison 95% power to detect a difference in 15% in % change in PASI. Assumes the SD is 30 and uses a two-group t-test with 0.05 two-sided significance. **Note:** there was an error in the initial packing procedure so medication packaged in 2 batches (1:2:2:2 erroneously followed in first batch; 2:2:2:1 correctly followed			No details on who administered (patient or investigator) drug.	ointment **Frequency:** twice daily		Patients gave assessment of response as cleared, marked or slight improvement (PAGI) on 6 point scale Laboratory assessment PASI (head excluded) IAGI (6 pt: worse to clearance) PAGI (6 pt: worse to clearance) Percentage change in thickness score Speed of response (PASI) at one week Adverse events Quality of life: Psoriasis Disability Index	

	in second batch) • **ITT analysis** Efficacy analysis was performed on ITT (assumptions not stated) • **Drop-outs/withdrawals**. N=77						EQ-5D and EQ-VAS (reported in van de Kerkhof 2004)	

Demographics

	All N=828	Combined (1x) N=152	Combined (2x) N=237	Calcipotriol N=231	Vehicle N=208
Mean age (yrs)	48.5	47.9	49.3	49.0	47.3
Gender (% males)	64	59.2	69.9	61.9	63.5
Mean PASI	**10.5**	9.9	10.6	10.8	10.4
Mean duration of psoriasis (yrs)	18.3	18.3	18.3	18.5	17.9

Effect Size

Outcomes

MEDICATION USED OVER TRIAL: Combined 1x per day: 76.2 g combined plus 72.1g vehicle; Combined 2x daily: 156g; calcipotriol: 166.8g; vehicle 152.8g

Efficacy at 4 weeks

Outcome	Combined 1 x (n=150)	Combined 2x (n=234)	Calcipotriol (n=227)	Vehicle (n=206)	P value
% change in PASI to end of treatment (no measures of variance given. NB these results differ from graph in terms of Combined 1x and combined 2x regimes)	68.6	73.8	58.8	26.6	1x vs 2x: 0.052; 1x vs calcipotriol: <0.001; 1x vs vehicle: <0.001; 2x vs calcipotriol: <0.001; 2x vs vehicle: <0.001
IAGI 'marked improvement' or 'clearance'	95 (63.3%)	172 (73.5%)	115 (50.7%)	19 (9.2%)	Combined (1x,2x) vs Calcipotriol p=0.033; Combined (1x,2x)vs Vehicle p<0.001
PAGI 'marked improvement' or 'clearance'	98(65.3%)	164(70.1%)	117(51.5%)	26(12.6%)	
IAGI 'clearance'	21 (14%)	47 (20.1%)	22 (9.7%)	0(0%)	

Time to maximum effect (based on change in PASI):

- All active arms still improving at 4 wk

Adverse events at 4 weeks

Outcome	Combined 1 x (n=151)	Combined 2x (n=235)	Calcipotriol (n=227)	Vehicle (n=208)
Withdraw due to unacceptable adverse events	0	0	4	2
Withdraw due to unacceptable treatment efficacy	0	1	2	19
Skin Atrophy	1	0	1	1

Authors' conclusion

- Safety data showed the frequency of adverse events to be less in the combined formulation groups than in both the calcipotriol and vehicle groups.
- Combined treatment (either 1x or 2x daily) showed a greater marked improvement or clearance in psoriasis than calcipotriol or vehicle.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
K. A. Papp, L. Guenther, B. Boyden, F. G. Larsen, R. J. Harvima, J. J. Guilhou, R. Kaufmann, S. Rogers, P. C. van de Kerkhof, L. I. Hanssen, E. Tegner, G. Burg, D. Talbot, and A. Chu. Early onset of action and efficacy of a combination of calcipotriene and betamethasone dipropionate in the	DESIGN Multicentre (75 centres in Europe and Canada) Between patient Patient delivery ALLOCATION Random Method of randomisation: computer generated random code (3:3:3:1) Concealment: Unclear (treatments identified by a code number and assigned in chronologic order) BLINDING Double-blind (patient / assessor) – same vehicle, identical tubes, similar appearance, taste and smell	Total N: 1043 **Drop-outs (don't complete the study): 72.** **Combination: 16 (5%)** **Calcipotriol: 27 (9%)** **Betamethasone: 17 (5%)** **Vehicle: 12 (11%)** **Reasons not stated**	**Inclusion criteria:** Chronic plaque psoriasis; aged at least 18; BSA ≥10% **Exclusion criteria:** Other types of psoriasis or skin diseases; hypercalcaemia; systemic antipsoriatic treatment or UV therapy within previous six wks; topical antipsoriatic therapy within previous two wks; other concomitant medication that might affect psoriasis; contraindications for corticosteroid treatment; planned exposure to UV light; pregnancy; lactation **Baseline comparability**: **Yes** Age: 47.1 Gender (%M): 58.4% Severity: mean PASI: 10.8	**Calcipotriol** 50µg/g + **betamethasone dipropionate** 0.5 mg/g combination, (n=301) **Formulation**: ointment **Frequency** twice daily No information on method of who administered (patient or investigator) drug.	**Calcipotriol** 50µg/g + vehicle (n=308) **Betamethasone dipropionate** + vehicle 0.5 mg/g (n=312) **Placebo** (combination vehicle) (n=107) **Formulation**: ointment	**Treatment duration:** 4 weeks	**1° outcome:** PASI (head excluded; % change from baseline) **2° outcomes** Total severity score (9 pt, absent to very severe) IAGI (response = marked improvement or	Leo Pharmaceutical Products.

treatment of psoriasis. *J.Am.Acad.Dermatol.* 48 (1):48-54, 2003. **Ref ID: PAPP2003**	**ITT analysis:** all analyses based on all patients with at least one post-randomisation efficacy assessment (called ITT – assumptions not stated) **Sample size calculation**: 270 per active arm and 90 in vehicle for 98% power to detect a mean difference in % change in PASI of 14.7%		(range: 1 to 36) **Duration: 18.7 years** **Note: face and scalp psoriasis not treated or assessed**		**Frequency** twice daily		clearance)	

Effect Size

Outcomes

Efficacy

Outcome	Combination (N=301)	Calcipotriol (N=308)	Betamethasone (N=312)	Placebo (N=107)	**MD (CI)**
% change in PASI at 4 weeks. (**Values estimated from a figure**, and no variance given; however the comparison data are given in final column)	-72%	-49.5%	-63.5%	-28.5%	comb v calcipotriol: 24.4% (20, 28.9); Comb v betamethasone: 10.3% (5.8-14.7); comb v placebo: 44.6% (38.4 – 50.8)

					Odds ratio for proportion of responders
IAGI: marked improvement or clear at 4 weeks	229 (76.1%)	103 (33.4%)	174 (55.8%)	8 (7.5%)	P<0.001 for all compared to combination
Combination vs calcipotriol					0.14 (0.10-0.20)
Combination vs betamethasone					0.37 (0.26-0.53)
Combination vs vehicle					0.02 (0.01-0.04)
PAGI : marked improvement or clear at 4 weeks (**estimated from figure only)**	223 (74%)	99(32%)	195(62.5%)	13 (12%)	Not given

Time-to-remission/maximum effect

- Based on change in PASI and change in thickness treatment effect has not reached a plateau at 4 weeks in any active group (although the initial largest effect had occurred by 2 weeks)
- The combination treatment produced a more rapid onset of action

Adverse events

Outcome	Combination (N=304)	Calcipotriol (N=308)	Betamethasone (N=313)	Placebo (N=108)

Skin atrophy (mild and reversible)	1	0	2	0

Authors' conclusion

- A combination product of calcipotriene 50 microg/g and betamethasone dipropionate 0.5 mg/g in the new vehicle shows superior efficacy with a more rapid onset of action than the new vehicle containing either constituent alone in the treatment of psoriasis vulgaris.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
K. Kragballe, L. Barnes, K. J. Hamberg, P. Hutchinson, F. Murphy, S. Moller, T. Ruzicka, and P. C. van de Kerkhof. Calcipotriol cream with or without concurrent topical corticosteroid in psoriasis: tolerability and efficacy. *Br.J.Dermatol.* 139 (4):649-654, 1998. **Ref ID: KRAGBALLE1998**	53 centres in 6 countries DESIGN Between patient Patient delivery ALLOCATION Random Method of randomisation: not stated Concealment: not stated BLINDING Double-blind (patient / assessor) WITHDRAWAL / DROPOUT Described	Total N: 699 **Drop-outs (don't complete the study):** 59 **Calcipotriol + vehicle: 19 (10.9%)** **Calcipotriol: 17 (9.8%)** **Betamethasone: 11 (6.3%)** **Reasons for leaving:** **20 left because of adverse events, mainly skin irritation (see results below for details);** **6 left for lack of efficacy (see results below);** **17 lost to follow up: calci/veh: 6, calci/calci: 3, Calci/clob: 3, calci/betameth: 5;** **4 left voluntarily (no other reasons given): calci/veh: 1, calci/calci: 2, Calci/clob: 0, calci/betameth: 1;** **other reasons/unknown:**	INCLUSION CRITERIA Adult; stable chronic plaque psoriasis on trunk and limbs EXCLUSION CRITERIA Pregnancy; risk of pregnancy; lactation; recent systemic or UV therapy; concomitant medication; hypercalcaemia or renal disease; planned exposure to sun. BC: Psoriasis comparable, demographics	**Calcipotriol** 50µg/g (morning) + **clobetasone 17-butyrate**, 0.5 mg/g (evening) (n=175) **Calcipotriol** 50µg/g (morning) + **betamethasone 17-valerate**, 1mg/g (evening) (n=176) **Formulation**: cream method of	**Calcipotriol** 50µg/g (morning and evening) (n=174) **Calcipotriol** 50µg/g (morning) plus vehicle (evening) (n=174) **Formulation**: cream	**Treatment duration:** 8 weeks. A final follow up occurred at "end of trial" which was beyond 8 weeks, but no further details given.	Assessed at weeks 2,4 and 8 PASI IAGI (6 pt: worse to clearance) Adverse events PASI Investigator overall assessment of response (6 pt: worse to clearance)	Leo Pharmaceutical Products.

	Washout: 2 weeks (emollient only) No sample size calculation reported **ITT analysis: Modified ITT (figures from CR)**	**calci/veh: 1, calci/calci: 1, Calci/clob: 5, calci/betameth: 1**	unclear Age: not stated Gender (%M): not stated Severity: not stated	who administered (patient or investigator) not given --- **All arms:** Scalp and face not treated; patients allowed to use tar/dithranol or low-to-medium potency corticosteroids			Patient overall assessment of response (6 pt: worse to clearance)	

Effect Size

Outcomes

Total use of medication: mean of 36g per week used in calcipotriol/calcipotriol group.

Efficacy

Outcome	C + vehicle (N=172)	C + C (N=172)	C + clobetasone	C + betamethasone

			(N=172)	(N=174)
IAGI: marked improvement or clear at 8 weeks / end of treatment	49 (28.5%)	69 (40.2%)	73 (42.5%)	94 (54.0%)
PAGI: marked improvement or clear at 8 weeks / end of treatment	46 (26.6%)	69(40.1%)	69(40.1%)	89(51.2%)
% change in PASI (estimate taken from graph, as the text only gives the raw changes, and gives no baseline values from which to perform a calculation). No variance measures available for this continuous variable.	-43%	-52%	-55%	-58%

Time-to-remission/maximum effect

- Based on change in PASI treatment effect had not reached a plateau at 8 weeks in any group

Withdrawals

Outcome	C + vehicle (N=174)	C + C (N=174)	C + clobetasone (N=175)	C + betamethasone (N=176)
Withdrawal due to AEs	8	6	3	3
Withdrawal due to lack of efficacy	2	3	0	1
Withdrawal due to	1	0	1	0

medical deterioration				

Authors' conclusion

- Calcipotriol applied twice daily was as effective as calcipotriol/clobetasone 17-butyrate, but slightly less effective than calcipotriol/betamethasone 17-valerate. The incidence of skin irritation was less for patients using concurrent corticosteroids, whereas treatment with calcipotriol/vehicle did not reduce the incidence of skin irritation when compared with calcipotriol twice daily

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Kaufmann R, Bibby AJ, Bissonnette R, Cambazard F, Chu AC, Decroix J, Douglas WS, Lowson D, Mascaro JM, Murphy GM, Stymne B. A new calcipotriol/ betamethasone dipropionate formulation (Daivobet) is an effective once-daily treatment for psoriasis vulgaris. *Dermatology* 2002;205(4):389-93.	Multicentre (Europe, Canada) PSORIASIS OF THE TRUNK AND/OR LIMBS DESIGN Between patient Patient delivery ALLOCATION Random Method of randomisation: computer generated randomisation schedule Concealment: unclear BLINDING	N=1603 **Drop-outs (don't complete the study):** 2.6%: combination; 4.6%: betamethasone; 8.1%: calcipotriol; 15.9%: vehicle **Reasons:** Adverse events: 3 (0.6%) in combination group; 5 (1.1%) in betamethasone group; 15 (3.1%) in	**INCLUSION CRITERIA** Patients aged 18 and over with chronic plaque psoriasis; BSA at least 10% **EXCLUSION CRITERIA** Unstable psoriasis in treatment areas; other skin diseases that could confound treatment assessments; concomitant antipsoriatic therapy; hypercalcaemia; application of study corticosteroid to untargeted lesion; pregnancy; lactation BC: Yes Age: 48.4 (range: 17 to 90) Gender (%M): 60.5% Severity: PASI mean: 10.0 (range: 1.2 to 49.5) Duration: 19.2 (range: 0 to 75)	N=490 Calcipotriol 50 mcg/g + betamethasone dipropionate 0.5 mg/g combination ointment **Formulation**: ointment **Frequency:** once daily **Note:** All medications were used to treat psoriasis of the trunk and/or limbs up to a	N=480 Calcipotriol, 50 mcg/g, in combination vehicle ointment **Formulation:** ointment **Frequency:** once daily --- N=476 Betamethasone dipropionate 0.5 mg/g, in combination	4 weeks (evaluate at 1, 2, 4 weeks). Patients who were considered by the investigator to require no further treatment for their psoriasis before the end of the 4-week treatment completed the study at	PASI, modified to exclude assessment of the head, since this area was not treated with any study medication; its possible range was 0–64.8. Investigator's global assessment of disease severity (6-pt: disease absent,	Leo Pharmaceuticals

REF ID: KAUFMANN 2002	Double-blind (patient / assessor) WITHDRAWAL / DROPOUT Described • **Setting:** Not stated • **Washout period**: Not stated • **Sample size calculation**: Not stated • **ITT analysis:** Yes for efficacy analysis (assumptions not sated). 14 patients were excluded from safety analysis as they provided no data after visit 1 and/or used	the calcipotriol group and 12 (7.6%) in the vehicle group. Rest not stated		maximum of 100g/week. Amount of medication used: The mean weight of medication used per patient during the study was 134 g (combination group), 140 g (betamethasone group), 142 g (calcipotriol group) and 133 g (vehicle group)	vehicle ointment **Formulation:** ointment **Frequency:** once daily --- N=157 Placebo (vehicle) ointment **Formulation:** ointment **Frequency:** once daily	that time	very mild, mild, moderate, severe, very severe) Patient's global assessment of disease severity (6 pt: worse, unchanged, slight improvement, moderate improvement, marked improvement, cleared) Compliance Withdrawa	

	no study medication						l due to adverse events	

Demographics and baseline characteristics

	Combination	Betamethasone	Calcipotriol	Vehicle
Age, years				
Mean	47.6	48.2	48.9	49.8
Range	19-83	18-83	17-90	18-87
Males %	62.9	61.1	59.0	56.1
Caucasians %	96.5	97.7	96.0	97.5
PASI				
Mean	9.9	9.8	10.4	9.5
Range	1.2-42.8	1.2-49.5	1.2-44.5	2.3-36.9
Patients with moderate disease activity, %	63.5	62.4	62.5	63.1
Duration of psoriasis, years				
Mean	18.3	19.4	20.3	18.3
range	0-66	0-75	1-67	1-56

Effect Size

Outcomes

Compliance

Compliance with once daily application of the study medication for the total treatment period was reported by 81.4% of patients in the combination group, 80.3% in the betamethasone group, 77.5% in the calcipotriol group and 73.9% in the vehicle group

Efficacy

	Combination	Betamethasone	Calcipotiol	Vehicle	MD
mean % change in PASI from baseline to end of treatment	-71.3	-57.2	-46.1	-22.7	TCF vs betamethasone -14.2 (-17.6 to -10.8; p<0.001) TCF vs vit D -25.3 (-28.7 to -21.9 p<0.001)
Investigator's global assessment – proportion of patients with absent or very mild disease at the end of treatment	276 (56.3%)	176 (37.0%)	107 (22.3%)	16 (10.2%)	
Patient's global assessment – marked improvement or cleared at the end of treatment	316 (64.9%)	216 (45.7%)	137 (29.0%)	15 (9.7%)	

Time to effect

Speed of response was assessed by the mean percentage change in PASI after 1 week of treatment

	Combination	Betamethasone	Calcipotriol	Vehicle
mean % change in PASI from baseline after 1 week of treatment	-39.2	-33.3	-23.4	-18.1

Time to max effect

Mean % change in PASI from baseline was greatest for all treatment groups at 4 weeks (displayed graphically).

Toxicity

	Combination	Betamethasone	Calcipotriol	Vehicle
Reported adverse events	118 (24.3%)	117 (24.7%)	157 (33.1%)	53 (34.4%)
Local cutaneous events where investigator has not excluded relationship to study medication	29 (6.0%)	23 (4.9%)	54 (11.4%)	21 (13.6%)
Adverse events associated with withdrawal	3 (0.6%)	5 (1.1%)	15 (3.1%)	12 (7.6%)

Authors conclusion

- Calcipotriol/betamethasone dipropionate combination ointment used once daily is well tolerated and more effective than either active constituent used alone.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
W. S. Douglas, Y. Poulin, J. Decroix, J. P. Ortonne, U. Mrowietz, W. Gulliver, A. L. Krogstad, F. G. Larsen, L. Iglesias, C. Buckley, and A. J. Bibby. A new calcipotriol/betamethasone formulation with rapid onset of action was superior to monotherapy with betamethasone dipropionate or calcipotriol in psoriasis vulgaris. Acta Derm.Venereol. 82 (2):131-135, 2002.	79 centres in 10 countries DESIGN Between patient Patient delivery ALLOCATION Random Method of randomisation: computer generated randomisation schedule Concealment: unclear BLINDING Double-blind (patient / investigator)	N: 1106 **Drop-outs (don't complete the study):** 28 (7.5%): combination 21 (5.8%): betamethasone 37 (10%): calcipotriol **Note:** 5 patients were excluded from the safety population and 9 from ITT population as they provided no data after visit 1.	INCLUSION CRITERIA Chronic plaque psoriasis; aged at least 18 years; use of systemic antipsoriatic treatment/phototherapy in previous 6 weeks; treatment of lesions contraindicated for topical corticosteroid therapy EXCLUSION CRITERIA Pregnancy; lactation; current participation in other trial; abnormality of calcium metabolism; hypercalcaemia. LF: 86 (7.8%) BC: Yes Age: mean: 47.1 (range: 18 to 89) Gender (%M): 59.8% Severity: PASI: 10.7 (range: 2.1 to 39.6) Duration: mean 18.4 (range: 0 to	n: 372 Calcipotriol (50 µg/g) + betamethasone (0.5 mg/g) combination (Daviobet®), **Formulation**: ointment **Frequency:** Twice daily **Note:** All groups received 4 weeks of maintenance therapy with calcipotriol (twice daily)	n: 369 Calcipotriol ointment (Daivonex®), 50 µg/g **Formulation**: ointment **Frequency:** Twice daily ---------- n: 365 Betamethasone dipropionate ointment (Diprosone®) 0.5 mg/g	Treatment duration up to 4 weeks (plus 4 week maintenance therapy with calcipotriol at 4 wk or clearing, but this additional phase was not double blinded and no ITT analysis was done in this phase)	IAGI (rated by investigator from worse to clear; 6-pt scale) Response = marked improvement or clear AEs PASI (modified) (0 to 64.8) Redness, thickness, scaling (0 to 8 each) Investigator global assessment (6-pt:	Leo Pharmaceuticals

<table>
<tr>
<td>Ref ID: DOUGLAS2002</td>
<td>Washout: 6 weeks for systemic and 2 weeks for topical treatments for psoriasis

Sample size calculation: yes – 270 per arm to give 90% power to detect difference in mean change of 8.4% on PASI

ITT analysis: for efficacy in blinded phase (assumptions not stated)</td>
<td>No reasons for withdrawal given.</td>
<td>65)

NO implicit or explicit mention whether face/scalp psoriasis was included or excluded.

Baseline characteristics
<table>
<tr><th></th><th>Combo</th><th>Beta</th><th>Calci</th></tr>
<tr><td>Mean age</td><td>47.6</td><td>46</td><td>47.6</td></tr>
<tr><td>males (%)</td><td>58.1</td><td>60.8</td><td>60.4</td></tr>
<tr><td>caucasian (%)</td><td>99.2</td><td>96.4</td><td>99.5</td></tr>
<tr><td>Baseline PASI</td><td>10.8</td><td>10.5</td><td>10.9</td></tr>
<tr><td>Duration psoriasis (yrs)</td><td>19</td><td>17.7</td><td>18.6</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
</table></td>
<td>Note: treatment only applied to trunk/limbs

Calcipotriol (50 mcg/g) /betamethasone (0.5 mg/g) combination ointment (Daviobet®),

BD (D)

Calcipotriol ointment (Daivonex®), 50 mcg/g, BD (C)

Betamethasone dipropionate ointment (Diprosone®), 0.5 mg/g, BD (B)

All groups then received four weeks of maintenance</td>
<td>Formulation: ointment

Frequency: Twice daily</td>
<td></td>
<td>worse to cleared)

Patient’s assessment of treatment response (6-pt: worse to cleared)

Adverse events</td>
<td></td>
</tr>
</table>

				therapy with calcipotriol BD				

Effect Size

IAGI at 4 weeks

Outcome	Combination (N=369)	Betamethasone (N=363)	Calcipotriol (N=365)
IAGI: marked improvement or clear	251 (68%)	169 (46.4%)	142 (38.9%)
PAGI: marked improvement or clear	248 (67.2%)	183 (50.4%)	140 (38.4%)

% change in PASI at 4 weeks

Outcome	Combination (N=369)	Betamethasone (N=363)	Calcipotriol (N=365)	pair wise MDs (95% CIs)
% change in PASI (no variances given for this continuous measure)	-74.4%	-61.3	-55.3	Combo v Beta: -13.1(-16.9, -9.3) Combo v Calci: -19.0 (-22.8, -15.2)

Time to response

- The combined product has a more rapid onset of action.

Outcome	Combination (N=369)	Betamethasone (N=363)	Calcipotriol (N=365)
PASI: mean % improvement at week 1	47.4%	39.8%	31.0%

Time to max response

- The mean percentage change in thickness was beginning to plateaux after 2 weeks of treatment in all groups (but more so for betamethasone and the combination)
- The mean percentage change in PASI had not reached a plateaux after 4 weeks of treatment in all groups (although the largest portion of the response occurred over the first 2 weeks)

Withdrawal

Outcome	Combination (N=369)	Betamethasone (N=363)	Calcipotriol (N=365)
Withdrawal due to adverse effects (toxicity)	1/369 (0.27%)	0	0

Authors' conclusion

- The combination product is more effective and has a more rapid onset of action than either of its active constituents used alone.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Kragballe K, Noerrelund KL, Lui H, Ortonne JP, Wozel G, Uurasmaa T, et al. Efficacy of once-daily treatment regimens with calcipotriol/ betamethasone dipropionate ointment and calcipotriol ointment in psoriasis vulgaris. *British Journal of Dermatology* 2004; 150(6):1167–73.	**RCT** **DESIGN** Between patient Patient delivery **ALLOCATION** Random Method of randomisation: Computer generated randomization schedule, using centralized telephone voice response system Concealment: unclear **BLINDING** Double-blind (patient / investigator)(Groups 1 and 2) Single-blind (investigator) (Group	**Total N:** 972 **Drop-outs (don't complete the study):** Total = 99 (10.2%); 9.3% group 1; 6.5% group 2; 14.4% group 3 Noncompliance: compliance for total treatment period: 63.4% group 1;	INCLUSION CRITERIA Aged 18 and over; chronic plaque psoriasis (at least mild severity) amenable to topical treatment; BSA ≥ 10% of at least one body region (arms, trunk, legs) EXCLUSION CRITERIA Pregnancy or risk thereof; lactation; unstable psoriasis or other inflammatory skin disease; concurrent systemic or UV therapy; concurrent topical therapy for trunk or limbs; abnormal calcium homeostasis BC: Yes Age: 47.7 (range: 18 to 97) Gender (%M): 63.8% Severity:	**n=322 group 1** **TCF** OD for 8 wks then**: calcipotriol ointment 50 mcg/g OD for 4 wks (group 1);** **N=323 group 2:** **TCF** OD for 4 wks then**: calcipotriol** ointment 50 mcg/g OD (weekdays) and **TCF** OD (weekends) for 8 wks **"**TCF"= Two compound	**n=327** **Calcipotriol ointment 50 mcg/g BD for 12 wks (group 3)** **Formulation**: ointment **Frequency** twice daily	**Treatment duration:** 12 weeks **Assessments at:** baseline, 1, 2, 4, 5, 8 and 12 weeks **Follow-up after end of treatment:**	PASI Investigator's global assessment of severity (PGA) (6pt: absence of disease, very mild, mild, moderate, severe or very severe disease) Self reported compliance with trial medication Adverse events **Primary efficacy**	Leo Pharmaceuticals

Ref ID: KRAGBALLE 2004	3) • **Washout period:** not stated • **Sample size calculation** not reported • **ITT analysis:** yes (assumptions not stated) **Setting:** Outpatients	65.8% group 2; 55.2% group 3	Duration (yrs): 18.5 (range: 0 to 70) PASI: 10.5 (range: 2 to 49) % with moderate disease: 64.3%	formulation: calcipotriol ointment 50 mcg/g, plus betamethasone dipropionate 0.5 mg/g ointment **Formulation:** ointment **Class:** vitamin D analogue plus corticosteroid **Frequency** once daily **Amount used:** not stated			**parameter:** % change in PASI from baseline to end of 8 weeks' treatment and proportion of patients with absent/ very mild disease by investigator's global assessment at 8 weeks	
Effect Size								

Outcomes

Efficacy

	Group 1	Group 2	Group 3	Estimated treatment difference, 97.5% CI and p-value (Group 1 vs. group 2)	Estimated treatment difference, 97.5% CI and p-value (Group 1 vs. group 3)	Estimated treatment difference, 97.5% CI and p-value (Group 2 vs. group 3)
Mean % change in PASI score from baseline to 8 weeks	73%	68.2%	64.1%	-4.8% (-9.3 to -0.3), p=0.016	-9.2% (-13.7 to -4.7), p<0.001	-4.4% (-8.9 to +0.1), p=0.029
At 12 weeks	no significant differences between groups					

	Group 1	Group 2	Group 3	Estimated odds ratio, 97.5% CI and p-value (Group 1 vs. group 2)	Estimated odds ratio, 97.5% CI and p-value (Group 1 vs. group 3)	Estimated odds ratio, 97.5% CI and p-value (Group 2 vs. group 3)
Number of patients with absent/very mild disease at 8 weeks (IGA)	178/322 (55.3%)	154/323 (47.7%)	133/327 (40.7%)	1.37 (0.95 to 1.99), p=0.057	1.94 (1.33 to 2.83), p<0.001	1.37 (0.94 to 1.99), p=0.063
At 12 weeks	not reported					1.45 (1.04 to 2.01), p=0.026

Time-to-effect

Groups 1 and 2 superior to 3 at each of the following weeks: 1 ($p<0.02$), 2 ($p<0.001$), 4 ($p<0.001$) and 5 ($p<0.001$)

Atrophy

Reversible skin atrophy: group 1: 1 (mild)/322; group 2: 0/322; group 3: 0/327

Withdrawals

30 (9.3%) group 1; 21 (6.5%) group 2; 14.4% group 3 (mostly lost to follow up)

Authors' conclusion

The two regimens using the two compound product provided rapid and marked clinical efficacy and were safe for psoriasis.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Kragballe K, Austad J, Barnes L, Bibby A, de la Brassinne M, Cambazard F, et al. A 52-week randomized safety study of a calcipotriol/ betamethasone dipropionate two-compound product (Dovobet/Daivobet/Taclonex) in the treatment of psoriasis vulgaris. British Journal of Dermatology 2006; Vol.	**RCT** **DESIGN** Between patients Patient delivery **ALLOCATION** Random Method of randomisation: computer generated random numbers Concealment: unclear **BLINDING** Double-blind - unclear • **Washout period:** not stated • **Sample size calculation** reported	**Total N:** 634 **Drop-outs (don't complete the study):** Total = 190 (30%): 64 (30.2%) in group A; 56 (26.3%) group B; 70 (33.5%) group C Noncompliance: not stated AEs: 14 (6.8%) in group A; 11 (5.2%)	INCLUSION CRITERIA Patients aged 18 or over with a clinical diagnosis of psoriasis vulgaris of trunk and/or limbs with investigator's assessment of at least moderate severity (on a scale of absent, very mild, mild, moderate, severe or very severe). Difficult sites not mentioned EXCLUSION CRITERIA Pregnancy or lactation; erythrmodermic, exfoliative and pustular psoriasis, skin infections; concurrent systemic or topical or UV therapy; need for treatment of >30% body surface area; abnormal calcium metabolism BC: Yes Well balanced for age,	**n=212** **Calcipotriol /betamethasone dipropionate two compound product** for 52 weeks (two compound group [A]); **n=213:** 52 weeks of **alternating two compound product and calcipotriol** (alternating group [B]) **Formulation:** ointment	**n=209** 4 weeks of **two compound product** then 48 weeks of **calcipotriol (calcipotriol group[C])** **Formulation**: ointment **Frequency** once daily	**Treatment duration:** 52 weeks **Assessments at:** every 4 weeks **Follow-up after end of treatment:** none	Safety **Primary efficacy parameter:** Adverse drug reactions (ADRs) and corticosteroid reactions	Leo Pharma A/S

154, issue 6:1155–60. **Ref ID: KRAGBALLE 2006A**	• **ITT analysis:** not stated **Setting:** Outpatients	group B; 16 (7.8%) group C	gender, ethnic origin, duration of psoriasis, duration of previous topical corticosteroid use and disease severity	**Class:** vitamin D analogue plus corticosteroid **Frequency** once daily (only when required) **Amount used:** maximum 100g/week (mean 898.8g in group A; 892.5g group B; 1044.0g group C				
Effect Size Outcomes **<u>Safety</u>**								

	group A	group B	group C	group A vs. group B	group A vs. group C	group B vs. group C
ADR	45 (21.7%)	63 (29.6%)	78 (37.9%)	OR 0.66 (0.42 to 1.03, p=0.066).	OR 0.46 (95% CI 0.30 to 0.70, p<0.001)	OR 0.69 (0.46 to 1.04, p=0.073)
These ADR included worsening/flare of psoriasis	5.3%	3.8%	6.8%			
Adjudicated corticosteroid reactions	10 (4.8%)	6 (2.8%)	6 (2.9%)	OR 1.75 (0.62 to 4.91, p=0.317)	OR 1.69 (0.60 to 4.74, p=0.445)	OR 0.97 (0.31 to 3.05, p=1.000)
Median time to onset of reaction	13 weeks	25 weeks	20 weeks			
Adjudicated corticosteroid reactions included: skin atrophy folliculitis	4 (1.9%) 3 (1.4%)	1 (0.5%) 1 (0.5%)	2 (1.0%) 0			
Serious AE related to treatment	1 flare of psoriasis causing hospitalisation		1 flare of psoriasis causing hospitalisation; 1pustular psoriasis			
Withdrew due to AE	14 (6.8%)	11 (5.2%)	16 (7.8%)			

Authors' conclusion

Treatment with the two compound preparation for up to 52 weeks appears safe and well tolerated whether used on its own or alternating every 4 weeks with calcipotriol treatment.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Kragballe K, Austad J, Barnes L, Bibby A, de la Brassinne M, Cambazard F, et al. Efficacy results of a 52-week, randomised, double-blind, safety study of a calcipotriol/ betamethasone dipropionate two-compound product (Daivobet/Dovobet/ Taclonex) in the treatment of psoriasis	**RCT** **DESIGN** Between patients Patient delivery **ALLOCATION** Random Method of randomisation: computer generated random numbers Concealment: unclear **BLINDING** Double-blind - unclear • **Washout period:** not stated	**Total N:** 634 **Drop-outs (don't complete the study):** Total = 190 (30%): 64 (30.2%) in group A; 56 (26.3%) group B; 70 (33.5%) group C Noncompliance: not stated AEs: 14	INCLUSION CRITERIA Patients aged 18 or over with a clinical diagnosis of psoriasis vulgaris of trunk and/or limbs with investigator's assessment of at least moderate severity (on a scale of absent, very mild, mild, moderate, severe or very severe). Difficult sites not mentioned EXCLUSION CRITERIA Pregnancy or lactation; erythrmodermic, exfoliative and pustular psoriasis, skin infections; concurrent systemic or topical or UV therapy; need for treatment of >30% body surface area; abnormal calcium metabolism BC: Yes Well balanced for age, gender, ethnic origin,	**n=212** **Calcipotriol /betamethasone dipropionate two compound product** for 52 weeks (two compound group [A]); **n=213:** 52 weeks of **alternating two compound product and calcipotriol** (alternating group [B]) **Formulation:** ointment **Class:** vitamin D analogue plus corticosteroid	**n=209** 4 weeks of **two compound product** then 48 weeks of **calcipotriol** (calcipotriol group[C]) **Formulation**: ointment **Frequency** once daily	**Treatment duration:** 52 weeks **Assessments at:** every 4 weeks **Follow-up after end of treatment:** none	Investigator global assessment of disease severity on a 6-point scale (absent, very mild, mild, moderate, severe, very severe. Patients' global assessment: satisfactory, not satisfactory, or not applicable /not used	Leo Pharma A/S

vulgaris. Dermatology 2006; Vol. 213, issue 4:319–26. **Ref ID: KRAGBALLE 2006**	• **Sample size calculation** reported • **ITT analysis:** yes **Setting:** Outpatients	(6.8%) in group A; 11 (5.2%) group B; 16 (7.8%) group C	duration of psoriasis, duration of previous topical corticosteroid use and disease severity Mean age: 48.8 (14.2) years % male: 61.0% Caucasian: 97.3% Disease severity: moderate: 69.1%; severe: 27.9%; very severe: 3.0% Median duration psoriasis: 17.0 (range 1-65) years	**Frequency** once daily (only when required) **Amount used:** maximum 100g/week (mean 898.8g in group A; 892.5g group B; 1044.0g group C during total study period; mean usage did not change greatly over the course of the study: per 4-week period usage ranged 84.6-99.3 g in TCF group, 83.3-99.0 in alternating group and 95.8-118.5 in calcipotriol group) Note: the proportion in each group with 52 or more weeks of exposure was 52.8%, 54.9% and 45.9%, respectively for TCF,			**Primary efficacy parameter :** not stated	

				alternating and calcipotriol.				

Effect Size

Outcomes

Efficacy – LOCF 52 wk

	TCF (n=212)	Alternating (n=213)	TCF then calcipotriol (n=209)
IGA: clear, very mild or mild	134	132	117

Efficacy – Observed cases 52 wk

	TCF (n=104)	Alternating (n=104)	TCF then calcipotriol (n=89)
IGA: clear, very mild or mild	80	78	62

Time-to-effect

At visit 2, when all patients had had two compound product, efficacy was similar between groups (69.0-80.0% satisfactory response by investigator's assessment); at all subsequent visits, the proportion of patients with satisfactory responses was higher in the two compound group than in the calcipotriol group. In the alternating group, the proportion of patients with satisfactory responses was higher after the two compound group treatment

period (weeks 4, 12, 20 etc) than after a calcipotriol period (weeks 8, 16, 24 etc). Responses using patient's assessment were similar.

Withdrawals

	TCF (n=212)	Alternating (n=213)	TCF then calcipotriol (n=209)
Withdrawal due to lack of efficacy	32 (15.1%)	31 (14.6%)	42 (20.1%)
Withdrawal due to AEs	14 (6.8%)	11 (5.2%)	16 (7.8%)

Authors' conclusion

There was a trend towards the efficacy of the two compound product used for up to 52 weeks being better than that of 4 weeks of two compound product followed by 48 weeks of calcipotriol.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Salmhofer W, Maier H, Soyer HP, Honigsmann H, Hodl S. Double-blind, placebo-controlled, randomized, right-left study comparing calcipotriol monotherapy with a combined treatment of calcipotriol and diflucortolone valerate in chronic plaque psoriasis. *Acta Dermato Venereologica. Supplementum* 2000;**211**:5–8. **Ref ID: SALMHOFER2000**	RCT DESIGN Within patient Patient delivery ALLOCATION Random Method of randomisation: not reported Concealment: BLINDING Double-blind (patient / assessor; not described) • **Washout period**: 1 week • **Sample size calculation** not reported	Total N: 63 **Drop-outs (don't complete the study):** Total = 5 (7.9%) Noncompliance: 58 completers: compliance excellent (>90%) and course not interrupted >5 days; 1 withdrawn for lesional and perilesional contact	INCLUSION CRITERIA Stable chronic plaque psoriasis; aged over 19; symmetrical lesions EXCLUSION CRITERIA Other types of psoriasis; BSA affected > 30%; concurrent systemic antipsoriatic therapy; pregnancy; lactation; concurrent infectious disease; other concurrent dermatoses; hypercalcaemia; severe hepatic / renal disease BC: Yes Age: 47 (15.4SD, range: 19 to 83) Gender (%M): 54.0% Severity: Duration (months):	**n=63** **Calcipotriol ointment, 0.005%, morning plus diflucortolone valerate ointment, 0.1%, night** **Class:** vitamin D analogue + potent corticosteroid **Formulation**: ointment **Frequency** once daily each element	**n=63** **Calcipotriol ointment, 0.005%, BD** **Formulation**: ointment **Frequency** twice daily	**Treatment duration:** 4 weeks **Assessments at:** 1, 2 and 4 weeks **Follow-up after end of treatment:** week 6 and week 8 (i.e. 2 and 4 weeks after end of treatment)	PASI IAGI (7 point: extreme deterioration to complete healing) PAGI (3 pt: good, satisfactory or bad) **Primary efficacy parameter:** PASI	Schering Wien GmbH

	• **ITT analysis:** no **Setting:** Outpatients	dermatitis ; 4 for concomitant diseases	141 (124SD) PASI: 5.5 (2.65SD)	**Amount used:** not stated				

Effect Size

Outcomes

Efficacy

Final PASI: ITT population: mean (SD)

	Pre-treatment	**Baseline**	**Treatment phase**			**Follow-up**	
Week:	**-1**	**0**	**1**	**2**	**4**	**6**	**8**
Calcipotriol ointment, 5 mcg/g, morning plus diflucortolone valerate ointment, 0.1%, night	5.5 (2.7)	5.7 (2.9)	3.3 (2.1)	2.4 (1.6)	1.9 (1.4)	3.5 (2.4)	3.8 (2.4)
Calcipotriol ointment, 5 mcg/g, morning and night	5.5 (2.6)	5.7 (2.9)	3.0 (1.8)	2.1 (1.3)	1.8 (1.2)	3.5 (2.2)	3.8 (2.3)
p	NS	NS	0.039	0.0077	NS	NS	NS

Individual criteria (eryhtema, infiltration, scaling) not significantly different. No difference in subjective measures.

Time-to-effect

The greatest improvement was observed in the first 2 weeks; a significantly different effect seen between groups at weeks 1 and 2 (but not at week 4).

Adverse events/ Withdrawals

Slight to moderate itching and burning at lesional sites observed with both treatments (8 combination + 6 monotherapy); NS.

1 patient (monotherapy) **withdrawn** for severe contact dermatitis; no contact dermatitis with combination therapy. No abnormal laboratory parameters.

Authors' conclusion

The combination treatment achieved a more rapid clinical response and was as effective as calcipotriol alone.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Saraceno R, Andreassi L, Ayala F, Bongiorno MR, Giannetti A, Lisi P, et al. Efficacy, safety and quality of life of calcipotriol/ betamethasone dipropionate (Dovobet) versus calcipotriol (Daivonex) in the treatment of psoriasis vulgaris: a randomized, multicentre, clinical trial. Journal of Dermatological	RCT DESIGN Between patient Patient delivery ALLOCATION Random Method of randomisation: computer-generated Concealment: not stated BLINDING open • **Washout period**: 2 weeks • **Sample size calculation** not reported	Total N: 150 **Drop-outs (don't complete the study):** in first 4 weeks: Total = 18; 5 group A and 13 group B; week 12: 25 group A and 29 group B	INCLUSION CRITERIA 18 years or older; mild-to-moderate plaque psoriasis EXCLUSION CRITERIA severe forms of plaque-type psoriasis, guttate, erythrodermic and pustular psoriasis, cutaneous atrophy, suspected abnormality in calcium homeostasis, recent systemic therapy or phototherapy or topical treatment; pregnant or breast-feeding women BC: Yes Age: mean 49 group A and 46 group B Gender (%M): 45/75 group A and 54/75 group B Severity: 19% BSA affected group A and 18% group B Duration (years): 11.9 group A and 15.7 group B	**n=75** Calcipotriol 50 mcg/g/ betamethasone dipropionate 0.5mg/g **(Dovobet)** for 4 weeks then **calcipotriol (Daivonex)** 50mcg/g cream for 8 weeks (Group A) **Class:** vitamin D analogue plus potent corticosteroid **Formulation**: ointment/ cream **Frequency**	**n=75** **calcipotriol (Daivonex)** 50mcg/g cream for 12 weeks (Group B) **Formulation**: cream **Frequency** twice daily	**Treatment duration:** 12 weeks **Assessments at:** baseline and 2, 4, 8 and 12 weeks **Follow-up after end of treatment:** none	PASI Safety Quality of life (Skindex-29: 3 sclaes scoring burden of symptoms, social functioning and emotional state) **Primary efficacy parameter :** PASI at 4 weeks	PRODOTTI FORMENTI srl, Milano, Italy

Treatment 2007; Vol. 18, issue 6:361–5. **Ref ID: SARACENO2007**	• **ITT analysis:** yes • **Setting:** Outpatients		PASI: 9.44 group A and 8.93 group B	once daily first 4 weeks then twice daily next 8 weeks **Amount used:** not stated				

Effect Size

Outcomes

<u>Efficacy</u>

<u>PASI</u>: ITT population

Mean PASI (SD)	**Calcipotriol 50 mcg/g/ betamethasone dipropionate 0.5mg/g (Dovobet) for 4 weeks then calcipotriol (Daivonex) 50mcg/g cream for 8 weeks (Group A)**	**calcipotriol (Daivonex) 50mcg/g cream for 12 weeks (Group B)**	**p-value**
Baseline	9.49 (5.39)	9.11 (4.09)	NS
2 weeks	3.81 (3.27)	5.47 (3.47)	p<0.001
4 weeks	2.50 (2.50)	4.07 (3.33)	p<0.001

8 weeks	2.29 (2.27)	3.45 (3.77)	not stated
12 weeks	2.11 (2.56)	3.04 (3.76)	NS

Time-to-effect

Significant improvement from baseline for both groups at week 2 for PASI and Skindex-29(but group A higher; maintained at week 4); both groups improved in weeks 5-12 and no difference between them at week 12.

Adverse effects

7 group A (none severe) and 8 group B (1 in group B severe exacerbation of psoriasis considered an adverse drug reaction; 2 severe AE not considered drug-related).

Withdrawals

	Group A	**Group B**
loss to follow up	2	4
complete resolution	11	12
exacerbation of psoriasis	4	4
lack of efficacy	1	3
non-compliance	0	1

burning/contact dermatitis	3	2
other	4	3
Total	25	29

Authors' conclusion

Higher efficacy and more rapid onset of action with two-compound ointment than calcipotriol cream alone in short-term treatment, but sequential application of calcipotriol cream allows maintenance of results.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Ortonne JP, Kaufmann R, Lecha M, Goodfield M. Efficacy of treatment with calcipotriol/ betamethasone dipropionate followed by calcipotriol alone compared with tacalcitol for the treatment of psoriasis vulgaris: A randomised, double-blind trial. *Dermatology (Basel)* 2004;209(4)	**RCT** **DESIGN** Between patient Patient delivery **ALLOCATION** Random Method of randomisation: Computer generated randomisation schedule Concealment: unclear **BLINDING** Double-blind (patient / investigator; adequate) • **Washout period:** 2 weeks • **Sample size calculation** reported	**Total N:** 501 **Drop-outs (don't complete the study):** Total = 37 (15.7%) in TCP group and 51 (20.2%) in tacalcitol group Loss to follow up: 21 (4.2%); 5 in TCP group and 16 in tacalcitol group Noncompliance:	INCLUSION CRITERIA Stable chronic plaque psoriasis amenable to topical treatment; aged 18 and over EXCLUSION CRITERIA Pregnancy or risk thereof; lactation; unstable psoriasis or other inflammatory diseases; abnormality of calcium metabolism or hypercalcaemia; systemic or phototherapy within previous four wks; topical therapy within previous two wks; other topical therapy for trunk or limbs during study period; corticosteroid treatment of scalp (WHO: class IV) or facial area (WHO: class III/IV) during study period	**n=249** **TCP ointment** ON for 4 wks then: **calcipotriol** ointment 50 mcg/g ON for 4 wks (A) TCP: two compound product: calcipotriol 50 mcg/g, plus betamethasone dipropionate 0.5 mg/g ointment **Formulation:** ointment	**n=252** **Tacalcitol** ointment 4 mcg/g ON for 8 wks (T) **Formulation**: ointment **Frequency** once daily	**Treatment duration:** 8 weeks **Assessments at:** baseline and 2, 4, 6 and 8 weeks **Follow-up after end of treatment:** none	PASI: mean % reduction IAGI (6 pt: worse to clearance) PAGI (6 pt: worse to clearance) Adverse events **Primary efficacy parameter:** % reduction in PASI at 4 weeks	Leo Pharmaceutical Products

:308–13. **Ref ID: ORTONNE2004**	• **ITT analysis:** yes (assumptions not stated) **Setting:** Outpatients	AEs: 6 in TCP group and 11 in tacalcitol group	BC: Yes Age: 51.2 (15.0 SD, N = 501) Gender (%M): 54.9% Severity: Mean baseline PASI: 9.8 (6.1 SD, N = 501) Duration (yrs): 19.4 (14.6 SD, N = 501)	**Class:** vitamin D analogue plus corticosteroid **Frequency** once daily **Amount used:** not stated				

Effect Size

Outcomes

<u>Efficacy</u>

<u>PASI</u>: ITT population

Mean % reduction in PASI score from baseline; mean±SD	**TCP group**	**Tacalcitol group**	**Mean difference (95% CI) p-value**
2 weeks	50.5%	24.5%	p<0.001

4 weeks	65.0%	33.3%	31.5 (25.5 to 37.4), p<0.001
End of treatment	59.0%	38.4%	20.4 (13.1 to 27.6(, p<0.001

Responders (investigator's assessment – marked improvement or clear)	**TCP group**	**Tacalcitol group**	**Mean difference (95% CI) p-value**
4 weeks	57.6%	17.0%	p<0.001
8 weeks	50.8%	23.5%	p<0.001

Responders (patient's assessment– marked improvement or clear)	**TCP group**	**Tacalcitol group**	**Mean difference (95% CI) p-value**
4 weeks	58.4%	17.4%	p<0.001
8 weeks	52.4%	27.0%	p<0.001

Time-to-effect

Much of the reduction in PASI seen in first 2 weeks.

Withdrawals

	TCP group	**Tacalcitol group**
Total withdrawals	32	35
Withdrawal due to voluntary withdrawal	4	2
Withdrawal due to inefficacy	3	8
Withdrawal due to medical deterioration	0	8
Withdrawal due to AEs	6 patients	11 patients
Withdrawal due to clearance of lesions	16 (6.4%)	3 (1.2%)
Withdrawal due to other reason	3	3

Authors' conclusion

A regimen of a two compound product: calcipotriol 50 mcg/g, plus betamethasone dipropionate 0.5 mg/g ointment for 4 weeks followed by calcipotriol ointment 50 mcg/g for 4 weeks is superior to tacalcitol for 8 weeks in patients with psoriasis.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
R. G. Langley, A. Gupta, K. Papp, D. Wexler, M. L. Osterdal, and D. Curcic. Calcipotriol plus betamethasone dipropionate gel compared with tacalcitol ointment and the gel vehicle alone in patients with psoriasis vulgaris: a randomized, controlled clinical trial. Dermatology 222 (2):148-156, 2011. Ref ID: **LANGLEY2011**	RCT Multicenter (Canada) Between subjects trial • **Randomised**: Method unclear Ratio of 2:2:1 2=interventions 1=vehicle • **Washout period**: See exclusion	Total N: 458 **Drop-outs (don't complete the study):** N=60 (13%) for treatment phase. **Dovobet:** 12 (6.6%) **Tacalcitol:** 21 (11.4%) **Placebo**: 27 (29.7%)	**Inclusion criteria:** >18 years, clinical diagnosis of psoriasis vulgaris involving trunk and limbs (at least 10% of arms, and/or legs, and/or trunk); severity at least moderate on IGA **Exclusion criteria:** Received systemic treatment with biologics within previous 3 months; systemic treatment with retinoids, corticosteroids or other immunosuppressants within 4 weeks; systemic treatment with vitamin D preparations>500IU/day; UVA or grenz ray therapy within 4 weeks; UVB within 2 weeks. Pregnant or breast-feeding women Head not assessed.	**Combined formulation (Dovobet)** **N=183** Calcipotriol 50µg/g + Betamethasone dipropionate 0.5mg/g p **Formulation**: gel **Frequency:** once daily **ALL ARMS:** If a patient	**Vehicle** **N=91** **Formulation**: gel **Frequency:** once daily **Tacalcitol** 4 µg/g + **N=184** **Formulation**: ointment	TD: 8 weeks. Post Tx observation: 8 weeks for those clear/nearly clear on IGA at wk 8	**1° outcome:** Investigators static Global Assessment on 6 point scale (clear, nearly clear, mild, moderate, severe, very severe; based on morphological characteristics of lesions) Clear or nearly clear on IGA at week 8 **2° and other outcomes:**	Leo Pharmaceutical Products.

A	criteria. • **Single blind.** Investigators (performing clinical assessment) blinded (handling of products performed by third party) • **Allocation concealment** unclear • **Sample size calculation** N= 180 patients in the active groups and N=90 in vehicle, will give 81% power. • **ITT analysis** Yes (LOCF) performed			cleared before week 8 treatment was stopped but they remained in the study (treatment restarted if psoriasis reappeared) No details on who administered (patient or investigator) drug.	**Frequency:** once daily		Clear or nearly clear on IGA at week 4 Modified PASI (excluding head; 0-64.8) Patient global static assessment (5-point scale: clear to severe; based on subjective symptoms and quality of life) Clear/nearly clear = no psoriatic symptoms or only slight symptoms that do not interfere	

	non-responder imputation as sensitivity analysis for categorical endpoints – no difference found as only one IGA responder withdrew but data not given) • **Drop-outs/withdrawals**. N=60						with daily life Adverse events Relapse (reduction in PASI improvement from baseline of at least 50% in those achieving clear/nearly clear at week 8) Time-to-relapse (from date of last under-treatment visit to relapse)	

Demographics

	All **N=458**	**TCF** **N=183**	**Tacalcitol** **N=184**	**Vehicle** **N=91**

Mean age (yrs)	51.6±14.0	50.9±14.3	51.7±13.4	52.8±14.9
Gender (% males)	62.2	63.9	62.5	58.2
% Caucasian	93.9	94.5	92.9	94.5
Mean PASI (range)	9.39 (2.4-59.4)	8.93 (2.4-36.9)	9.86 (2.4-59.4)	9.38 (4.4-22.6)
IGA (%)				
Moderate	63.8	71.0	64.7	70.3
Severe	29.5	27.3	31.5	29.7
Very severe	2.2	1.6	3.8	0.0

Effect Size

Outcomes

MEDICATION USED OVER TRIAL (8 wk):

Combined: 27.5 g; Tacalcitol: 33.2 g; vehicle 26.2 g

Efficacy at 4 & 8 weeks (8 weeks is the primary end point); ITT (LOCF); note: all but one who dropped out were non-responders

Outcome	**Combined (n=183)**	**Tacalcitol (n=184)**	**Vehicle (n=91)**	**OR (P value)**	
				TCF vs vit D	**TCF vs vehicle**

Clear/nearly clear (IGA) Week 4	34 (18.6%)	12 (6.5%)	1 (1.1%)	3.51 (p<0.001)	32.9 (p<0.001)
Clear/nearly clear (IGA) Week 8	73 (39.9%)	33 (17.9%)	5 (5.5%)	3.42 (p<0.001)	13.9 (p<0.001)
Clear/nearly clear (patient rating) Week 4	52/175 (29.7%)	21/175 (12.0%)	7/81 (8.6%)	-	-
Clear/nearly clear (patient rating) Week 8	69/171 (40.4%)	35/163 (21.5%)	14/64 (21.9%)	-	-
	The reasons for fewer patients having data available are unclear			-	-
% change in PASI week 4	-53.1	-37.3	-13.3	MD: -15.5 (p<0.001)	MD: -39.8 (p<0.001)
% change in PASI week 8	-57.0	*-41.9*	*-17.9*	MD: -14.7 (p<0.001)	MD: -39.1 (p<0.001)

Time to maximum effect (based on change in PASI):

- A faster response was observed in the TCF group
- Graph of % change in PASI over time show s that the TCF begins to plateau after 6 weeks, while there is a slight increase in PASI in the tacalcitol group between 6 and 8 weeks

Withdrawals at 8 weeks

Outcome	**Combined (n=182)**	**Tacalcitol (n=184)**	**Vehicle (n=91)**
Withdraw due to unacceptable adverse events	3 (1.6%)	4 (2.2%)	4 (4.4%)
Excoriation	0	2	0

POST-TREATMENT OBSERVATION PHASE (those clear/nearly clear at 8 weeks entered this phase; n=103/398 completers)

Outcome	Combined (n=67)	Tacalcitol (n=31)	Vehicle (n=5)
Relapse rate	28 (41.8%)	7 (22.6%)	3 (60%)
Median time to relapse	63 days	61 days	61 days
Rebound (PASI >125% relative to baseline)	**0**	**0**	**0**

Authors' conclusion

- Once-a-day treatment with the 2-compound Dovobet gel is a safe and efficacious therapeutic regimen for individuals with psoriasis on the body.