Appendix H: Evidence tables – clinical studies

H.1 Tools for assessing disease severity and impact

H.1.1 Comparative data

H.1.1.1 Study 1

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
B. Kirby, H. Richards, P. Woo, E. Hindle, C. J. Main, and C. Griffiths. Physical and psychologic measures are necessary to assess overall psoriasis severity. *J.Am.Acad.Dermatol.* 45 (1):72-76, 2001.	**Observational:** cross sectional study Patients recruited from inpatient ward, psoriasis clinic and dermatology clinic at Hope Hospital, UK	N = 101	**Stage of disease journey:** unclear **Inclusion criteria:** Age ≥ 18 years **Exclusion criteria:** Suffering mental health problems **Parameter** / **All (n=101)** Mean age – years: 46 ± 1.7 Gender M/F (%): 56/44 Inpatients (n): 67	SPI, PDI, PASI, SAPASI, *HADS, IPQ* PASI assessed by one of three experienced clinicians SAPASI and self-report psychological	SPI, PDI, PASI, SAPASI, *HADS, IPQ*	N/A	Construct validity	None stated

Ref ID: KIRBY2001			Outpatients (n): 34 Mean PASI score: 14.7 ± 1.1		questionnaires completed by the patients Unclear how SPI score was obtained			

Effect size

Construct validity

Score 1	**Score 2**	**Correlation (Spearman's r)**	**p-value**	**Construct validity**	
				Convergent	**Divergent**
Signs score of SPI (derived from PASI)	Psychosocial disability score of SPI	0.46	<0.01		Adequate – measure different constructs
	PDI	0.51	<0.01		Adequate
	PASI	0.99	<0.01	Adequate	
	SAPASI	0.67	<0.01	Adequate	
PASI	**SAPASI**	**0.65**	**<0.01**	**Acceptable**	
Psychosocial disability score of SPI	PDI	0.69	<0.01	Acceptable	
	PASI	0.46	<0.01		Adequate

Interventions score of SPI (historical disease severity)	Any assessment of clinical severity or psychological impact		NS		
PDI	**Physical scores of psoriasis severity**	**0.50-0.52**	**<0.01**	**Poor**	
SAPASI	**PDI**	**0.52**	**<0.01**		**Adequate**
	Psychosocial disability score of SPI	0.49	<0.01		Adequate

In-patient vs out-patient groups

- There was no significant difference between the groups in terms of age
- Mean PASI, SAPASI and 'signs' score of SPI were significantly higher in the in-patients than out-patients ($p<0.001$)
- In-patients also had significantly higher score on PDI ($p<0.001$) and depression scale of HADS ($p<0.02$)

Summary/author's conclusion

- There is considerable discordance between the amount of physical disease and the degree of psychological disability; therefore, it is necessary to assess the patient holistically
- SPI provides information on clinical extent, psychosocial disability and historical severity

H.1.1.2 Study 2

It is unclear whether the assessments were given in Italian

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
F. Sampogna, F. Sera, E. Mazzotti, P. Pasquini, A. Picardi, D. Abeni, and IDI Multipurpose Psoriasis Research on Vital Experiences (IMPROVE) Study Group. Performance of the self-administered psoriasis area and severity index in evaluating clinical and sociodemographic subgroups of patients with psoriasis.[Erratum appears in Arch Dermatol. 2003 Jul;139(7):950].	**Observational:** cross sectional study Part of the IDI Multipurpose Psoriasis Research on Vital Experiences study, Feb-Aug 2000 In-patient wards of hospital in Italy	N = 351 (of 376 eligible and willing to participate)	**Stage of disease journey:** unclear **Inclusion criteria:** Specialist-confirmed diagnosis of psoriasis; age ≥ 18 years; absence of severe mental or physical illness; at least 5 years of education, ability to read Italian; and first hospitalisation for psoriasis since the data of the study beginning **Exclusion criteria:** Not stated **Parameter** / **All (n=351)** Age (years), n (%) 18-31: 92 (26.2) 32-45: 89 (25.4) 46-60: 90 (25.6) ≥61: 80 (22.8) Gender M/F (%): 63/37	PASI Measurement taken soon after admission before any medication was taken	SAPASI Given to patients after the visit and scored by an assessor who had not seen the patients and was blind to PASI scores	N/A	Construct validity	None stated

Arch.Dermatol. 139 (3):353-358, 2003. Ref ID: SAMPOGNA2003			Duration (years), n (%) 0-3 4-9 10-18 ≥19	 99 (28.2) 85 (24.2) 83 (23.7) 84 (23.9)					
			Clinical type						
			Palmoplantar	21 (6.2)					
			Pustular, localised	10 (2.9)					
			Guttate	52 (15.2)					
			Plaque, localised	73 (21.4)					
			Plaque, generalised	149 (43.7)					
			Psoriatic arthritis	22 (6.5)					
			Other	14 (4.1)					

Effect size

Construct validity (Pearson correlation coefficient)

- Overall correlation coefficient between lnPASI and lnSAPASI (log values used because frequency distributions were skewed) was 0.69 (acceptable construct validity)
- There was substantial variation in the agreement between PASI and SAPASI among different patient variables and among the subcomponents of the two tools (different body sites)

Variable	Difference between PASI and SAPASI	Correlation coefficient between lnPASI and lnSAPASI	Convergent construct validity
Overall	-6.26 ± 8.81	0.69	Acceptable
Head		0.55	Poor
Upper extremities		0.40	Poor
Trunk		0.68	Acceptable
Lower extremities		0.49	Poor
Sex			
Male	-5.74±8.56	0.68	Acceptable
Female	-6.99±9.24	0.70	Adequate
Clinical type			
Palmoplantar	-2.06±3.51	0.31	Poor
Pustular, localised	-1.97±2.49	0.50	Poor
Guttate	-11.16±9.92	0.60	Acceptable
Plaque, localised	-2.87±4.08	0.58	Poor
Plaque, generalised	-6.83±8.88	0.58	Poor
Psoriatic arthritis	-6.25±9.94	0.76	Adequate
Other	-9.16±16.69	0.91	Adequate
Physician rated severity score			
1	-3.14±4.27	0.45	Poor

2	-4.28±5.59	0.64	Acceptable
3	-7.36±8.22	0.56	Poor
4	-9.15±12.76	0.60	Acceptable
Duration (years)			
0-3	-6.04±8.07	0.64	Acceptable
4-9	-7.00±8.06	0.70	Adequate
10-18	-6.02±9.64	0.70	Adequate
≥19	-5.98±9.59	0.68	Acceptable

Summary/author's conclusion

- There was a high correlation between PASI and SAPASI scores
- SAPASI scores were higher and had wider scattering than the PASI values
- SAPASI could be used as a severity measure for psoriasis
- Caution is needed when using SAPASI to strictly estimate PASI measurements, especially for guttate psoriasis

H.1.1.3 Study 3

It is unclear whether the assessments were given in Italian

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
F. Sampogna, F. Sera, D. Abeni, and IDI Multipurpose Psoriasis Research on Vital Experiences (IMPROVE) Investigators. Measures of clinical severity, quality of life, and psychological distress in patients with psoriasis: a cluster analysis. *J.Invest.Dermatol.* 122 (3):602-607, 2004. Ref ID: SAMPOGNA20	**Observational:** cross sectional study Part of the IDI Multipurpose Psoriasis Research on Vital Experiences study, Feb 2000-July 2001 In-patient wards of hospital in Italy	N = 786 This relates to a participation rate of 88.5%	**Stage of disease journey:** a wide range of clinical presentations (including mild-to-moderate cases) **Inclusion criteria:** Specialist-confirmed diagnosis of psoriasis; age ≥ 18 years; absence of severe mental or physical illness; at least 5 years of education, ability to read Italian; and first hospitalisation for psoriasis since the date of the study beginning **Exclusion criteria:** Not stated **Parameter** / **All (n=786)** Mean age (years / 45.5 Gender M/F (%) / 59.2/41.8 Mean PASI score / 8.6 Mean age at onset / 33.6	**Clinical status:** PASI and SAPASI **QoL:** Skindex-29, DLQI, PDI, Impact of Psoriasis Questionnaire (IPSO) **Psychological distress index:** Psoriasis Life Stress Inventory (PLSI) PASI measurement taken soon after admission before any medication	All comparisons	N/A	Convergent and divergent construct validity	Italian Ministry of Health

04			(years)		was taken				
			Global severity as assessed by dermatologists (%)		Self-administered questionnaires completed before hospital discharge				
			Severe or very severe						
			Moderate	24.7					
			Mild	29.0					
				46.3					
			Clinical type (%)						
			Palmoplantar	7.3					
			Pustular, localised	2.0					
			Guttate	12.8					
			Plaque, localised	16.8					
			Plaque, generalised	47.1					
			Psoriatic arthritis	7.9					

Effect size

Note that log values were used for PASI and SAPASI because frequency distributions were skewed

Construct validity (Pearson's correlation coefficient)

- Correlation matrix:

	PLSI	PDI	DLQI	IPSO	Skindex			SAPASI
					Social functioning	Emotions	Symptoms	
PASI	0.258	0.198	0.190	0.175	0.122	0.116	0.175	0.647
SAPASI	0.354	0.269	0.261	0.286	0.175	0.189	0.223	
Skindex								
Social functioning	0.663	0.710	0.723	0.781	0.598	0.815		
Emotions	0.635	0.600	0.633	0.728	0.588			
Symptoms	0.433	0.489	0.542	0.512				
IPSO	0.738	0.798	0.758					
DLQI	0.627	0.805						
PDI	0.664							

- Cluster analysis revealed 2 main clusters: PASI and SAPASI in one and all of the QoL and psychological scales in another
- Correlations between QoL measures and SAPASI were slightly higher than those with PASI

Summary/author's conclusion

- The dissimilarity between clinical severity assessment and patient-centered measures stresses the need for a more comprehensive assessment of psoriasis severity

H.1.1.4 Study 4

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
M. B. Nichol, J. E. Margolies, E. Lippa, M. Rowe, and J. Quell. The application of multiple quality-of-life instruments in individuals with mild-to-moderate psoriasis. *Pharmacoeconomics* 10 (6):644-653, 1996. Ref ID: NICHOL1996	**Observational:** cross sectional study Clinical trial (US multicentre)	N = 644	**Stage of disease journey:** unclear, but 65% were on medication **Inclusion criteria:** Adults who met entry criteria for 2 multicentre trials for a new psoriasis medication; stable plaque psoriasis on trunk, legs or arms (≤20% BSA); 2 target lesions ≥2 cm in diameter (1 on elbow or knee and 1 on trunk arms or leg); **Exclusion criteria:** Not stated **Parameter** / **All (n=644)** Mean age (years), ±SD: 48.2±15.1 Mean gender M/F (%): 60.9/39.1 Mean age at onset of psoriasis (years), ±SD: 30.42±15.44 Mean duration of: 17.74±12.2	DLQI – 10-item questionnaire rated on a 0-3 scale considering the previous 7 days Self-administered at baseline Expressed as a % of maximum possible disability to improve comparability In the case of	PDI – 15 questions rated on a 7-point linear scale (transformed to 0-6 in this study) considering the past 4 weeks Self-administered at baseline Expressed as a % of maximum possible disability to improve comparability	N/A	Construct validity	Allergan Ltd.

			psoriasis (years), ±SD	3	missing values the maximum possible disability was based on the number of questions answered	Population mean substituted for missing values		
			Mean body involvement (%)±SD	7.19±5.02				
			Mean prescriptions (n)					
			Total population (n=644)	1.46				
			Patients on medication (n=362)	2.60				

Effect size

Construct validity

- PDI and DLQI were strongly and positively correlated with each other: adequate construct validity (r = 0.82; Pearson coefficient; p<0.001)
- PDI and DLQI both also correlated with 6 measured psoriasis characteristics. The PDI was most sensitive to % body involvement, while the DLQI was most influenced by pruritus and pain:

QoL scale	**Psoriasis characteristics**					
	Body involvement (% - estimated using palm = 1%)	Lesional severity (clinician rating)	Pain (self-rated)	Pruritus (self-rated)	Age at onset	Duration
PDI score (%)	**0.27**	0.08	0.20	0.21	-0.15	-0.08

DLQI score (%)	0.26	0.11	**0.30**	**0.32**	-0.14	-0.12

Summary/author's conclusion

- Patients averaged 16.5% of maximum possible disability as measured by the PDI and 23.4% as measured by DLQI
- Impairment in life quality in mild-to-moderate psoriasis has a strong psychosocial component

H.1.1.5 Study 5

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
R. Shikiar, M. K. Willian, M. M. Okun, C. Thompson, and D. A. Revicki. The validity and responsiveness of three quality of life measures in the assessment of psoriasis patients: results of a phase II study. *Health & Quality of Life Outcomes* 4:71, 2006. Ref ID: SHIKIAR2006	Within group comparison of data from an RCT (but focus on psychometric properties of tools and not on drug efficacy) Phase II, randomised, double-blind, parallel group, placebo controlled, multicentre clinical trial (adalimumab vs placebo); North America	N = 147	**Stage of disease journey:** unclear **Inclusion criteria:** Moderate-to-severe plaque psoriasis; BSA≥5% for at least 1 year; age ≥18 years; ability to self-inject medication/nurse or designee who can inject randomised assignment **Exclusion criteria:** Not stated **Parameter** / **All (n=147)** Mean age (years), ±SD: 44.2±12.7 Mean gender M/F (%): 67.3/32.7 Mean age at onset of psoriasis: 30.42±15.44	DLQI	PASI PGA: • Severe: very marked plaque elevation, scaling, and/or erythema • Moderate to Severe: marked plaque elevation, scaling, and/or erythema • Moderate: moderate plaque elevation, scaling, and/or erythema • Mild to moderate: intermediate between moderate and mild • Mild: slight plaque	12 weeks (30-day follow-up visit for patients not completing 12 weeks active treatment)	Sensitivity to change; construct validity; internal consistency	Abbot Laboratories

	7 patients lost to follow-up		(years), ±SD **Race (%)** White 90.5 Black 2.7 Asian 3.4 Other 3.4		elevation, scaling, and/or erythema • Almost clear: intermediate between mild and clear • Clear: no signs of psoriasis (post-inflammatory hypopigmentation or hyperpigmentation could be present).			

Effect size

Sensitivity to change (in a group including pooled placebo and active treatment groups)

DLQI vs PASI or PGA

- DLQI demonstrated acceptable sensitivity to clinically meaningful change (r = 0.69 vs PASI and 0.71 vs PGA)
- There was also a significant difference in improvement on DLQI between responders (PASI75) and non-responders (<PASI50); difference = -10.39 (p<0.0001)
- DLQI was able to demonstrate statistically significant differences between responders (PASI improvements ≥75%) and partial responders (PASI improvements 50-74%)

PASI vs PGA

- Acceptable sensitivity to clinically meaningful change (r = 0.75)
- Note: PASI showed a mean score reduction of 56.5% (from 15.69 to 6.84); while PGA showed a mean score reduction of 39.1% (from 5.48 to 3.36)

Construct validity (correlation coefficient not stated)

PASI vs PGA

- Adequate construct validity (r = 0.83) at trial end point, but poor construct validity (r = 0.59) at baseline

Internal consistency

- Adequate for DLQI: α = 0.89 at baseline and 0.92 at week 12

Summary/author's conclusion

- DLQI was the most responsive patient-reported outcome measure (compared with EQ-5D and SF-36) and was equally responsive to both PASI and PGA
- DLQI was correlated to clinical endpoints both at baseline and week 12

H.1.1.6 Study 6

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
L. Kotrulja, M. Tadinac, N. A. Joki-Begi, and R. Gregurek. A multivariate analysis of clinical severity, psychological distress and psychopathological traits in psoriatic patients. *Acta Derm.Venereol.* 90 (3):251-256, 2010. Ref ID: KOTRULJA2010	Case-control study Convenience sample Department of Dermatology and Venerology, University Hospital and School of Medicine, Croatia	N = 140 70 with psoriasis 70 with other (non-psychosomatic) dermatoses	**Stage of disease journey:** unclear **Inclusion criteria:** note stated **Exclusion criteria:** Age <18 years, severe mental or physical illness **Parameter** / **Cases (n=70)** / **Controls (n=70)** Mean age (years): Males: 48.7, Females: 51.4 / Males: 53.7, Females: 47.2 Mean gender M/F (%): 57.1/42.9 / 38.6/62.4 Mean age of onset (years±SD) -Early onset -Late onset: 25.8±7.2	PASI	Psoriasis Life Stress Inventory (PLSI) – 15-item version *(also used General Health Questionnaire, Beck Depression Index, State-Trait Anxiety Inventory, Minnesota Multiphasic Personality Inventory and Inventory of Stress Life Events)*	N/A	Construct validity	None stated

				52.0±8.93						
			Disease duration (years±SD) -Early onset -Late onset	 16.2±9.42 11.0±8.74						
			PLSI ≥10 (significant impact of disease-associated stress)	82.4%						

Effect size

Construct validity (divergent)

PASI vs PLSI – calculated in psoriatic patients

- Adequate divergent construct validity (Pearson's r = 0.30) – PASI and PLSI are not measuring the same construct (although the correlation was statistically significant; $p<0.05$)

Summary/author's conclusion

- PLSI showed a significant correlation with clinical extent of psoriasis, as measured by PASI; however, this was only moderate correlation and

demonstrated that they are likely to be measuring different constructs

H.1.1.7 Study 7

<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>S. P. McKenna. Development of the PSORIQoL, a psoriasis-specific measure of quality of life designed for use in clinical practice and trials. Br.J.Dermatol. 149 (2):323-331, 2003.

Ref ID: MCKENNA2003</td>
<td>Observational: within-group comparison

Development of the measure in 62 patients recruited through dermatology clinics (UK, Italy and the Netherlands)

Validation in a new sample of 148 UK patients recruited by postal survey of individuals randomly selected from a</td>
<td>N = 148

(of 445 mailed packages)

Second package sent to 119 of respondents and 88 (74%) were returned and adequately completed</td>
<td>Stage of disease journey: unclear; 78% on treatment; 80% experiencing a flare

Inclusion criteria: note stated

Exclusion criteria: not stated
<table>
<tr><th>Parameter</th><th>Postal sample (n=148)</th><th>Retest sample (n=88)</th></tr>
<tr><td>Mean age (years±SD)</td><td>45.1±14.9</td><td>46.2±15.5</td></tr>
<tr><td>Mean gender M/F (%)</td><td>50/50</td><td>44/56</td></tr>
<tr><td>Disease duration (years±SD)</td><td>20.9±13.5</td><td>21.6±13.6</td></tr>
<tr><td>On current</td><td>78</td><td>72</td></tr>
</table>
</td>
<td>PSORIQoL – 25-item version</td>
<td>DLQI (and General Well-Being Index)</td>
<td>2 weeks</td>
<td>Construct validity; internal consistency; test-retest reliability</td>
<td>None stated</td>
</tr>
</table>

	hospital database (Dermatology Clinic, Hope Hospital, Manchester)		treatment (%)							
			Current flare (%)	80	45					
			Parts of body affected (%)							
			Face	27	29					
			Hands	36	31					
			Other	51	51					
			None	1	1					

Effect size

Test-retest reliability

- **PSORIQoL:** acceptable (ICC = 0.89)

Internal consistency

- **PSORIQoL:** Adequate (α=0.94)
- **DLQI:** Adequate (α=0.88)

Convergent construct validity: PSORIQoL vs DLQI

- Adequate overall construct validity (Spearman's r = 0.70)
- Individual subscales of the DLQI showed lower correlation with PSORIQoL score
  - Symptoms and feelings: 0.55
  - Daily activities: 0.66
  - Leisure: 0.53
  - Work and school: 0.32
  - Personal relationships: 0.45

– Treatment: 0.47

Site-specific involvement

- PSORIQoL scores were related to whether or not patients had lesions on their face and/or hands

Area affected	Median PSORIQoL score	n	p-value
Not face or hands	9.0	67	<0.01
Face or hands	14.0	61	

Practicability

- 21 interviewees found the initial 45-item version easy to complete and relevant to their situation

Summary/author's conclusion

- PSORIQoL appears to be a practical, reliable and valid instrument for measuring the impact of psoriasis on QoL
- It is still necessary to test the instrument's responsiveness to change in QoL associated with treatment

H.1.1.8 Study 8

Data for PSORIQoL may not be relevant as it is a modified version for the US

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
S. P. McKenna. Development of the US PSORIQoL: A psoriasis-specific measure of quality of life. *Int.J.Dermatol.* 44 (6):462-469, 2005. Ref ID: MCKENNA2005	**Observational:** within-group comparison Validation by postal survey of a convenience sample of individuals from Mount Sinai School of Medicine	N = 72	**Stage of disease journey:** unclear (but 80% were receiving treatment) **Inclusion criteria:** note stated **Exclusion criteria:** not stated **Parameter** / **Postal sample (n=72)** Mean age (years±SD): 47.3±13.9 Mean gender M/F (%): 55.6/44.4 Mean duration of psoriasis (years±SD): 17.2±11.1 Currently: 80	PSORIQoL – 25-item US version	DLQI	2 weeks	Construct validity; internal consistency; test-retest reliability	None stated

			receiving treatment (%)					
			Current flare (%)	62				
			Face and/or hands affected	53.5				

Effect size

Test-retest reliability

- **PSORIQoL:** adequate (Spearman's r = 0.90)
- **DLQI:** acceptable (Spearman's r = 0.80)

Internal consistency

- **PSORIQoL:** Adequate ($\alpha \geq 0.88$)
- **DLQI:** Adequate ($\alpha \geq 0.88$)

Construct validity: PSORIQoL vs DLQI

- Adequate overall construct validity (Spearman's r = 0.81 at time 1 and r = 0.82 at time 2)

Summary/author's conclusion

- The US PSORIQoL appears to be a reliable and valid instrument for measuring the impact of psoriasis on QoL
- It is still necessary to test the instrument's responsiveness to change in QoL associated with treatment

H.1.1.9 Study 9

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
E. D. Dommasch, D. B. Shin, A. B. Troxel, D. Margolis, and J. Gelfand. Reliability, validity and responsiveness to change of the Patient Report of Extent of Psoriasis Involvement (PREPI) for measuring body surface area affected by psoriasis. *Br.J.Dermatol.* 162 (4):835-842, 2010.	**Observational :** Cross sectional study and prospective case series Patients presenting to University of Pennsylvania Department of Dermatology enrolled Oct 2004-Oct 2008	N = 140 (N=76 for follow-up study assessing responsiveness to change at second out-patient visit) Sample size calculation based on number needed to measure criterion validity with CIs of ±5%	**Stage of disease journey:** both new patients and patients in active follow-up for psoriasis in out-patient setting **Inclusion criteria:** Diagnosis of plaque psoriasis; ≥18 years old **Exclusion criteria:** unable to provide informed consent **Parameter** / **All (n=140)** Median age, years (IQR): 45.5 (33.5-57.0) Mean gender M/F (%): 55/45 **Baseline skin involvement (median palms; IQR)** Patient: 4 (1-10)	Body surface area (BSA) – patient report of extent of psoriasis involvement (PREPI) method This involves asking the patient to estimate how many palm areas it would take to cover up all the patches of psoriasis (the first 15 patients were asked to select from categorised scores (little or no visible psoriasis [<1 palm]; only a few patches [1-2 palms]; scattered patches [3-10 palms]; extensive psoriasis covering large areas of	Skindex -29 BSA assessed by dermatologist blinded to patients assessment	Median 2 days between test and re-test Median duration between visit 1 and 2 for sensitivity to change was 98 days	Test-retest reliability; construct validity; responsiveness to change; practicability	Grant from NIH and National Institute of Arthritis, Musculoskeletal and Skin Diseases

Ref ID: DOMMASCH2010			estimated		the body [>10 palms])				
			Physician-estimated	3.5 (1-10.5)	Subsequent patients were allowed to classify their psoriasis as a continuous variable, which was categorised by the investigators				
			Race (%)						
			White	80					
			Black	7.9					
			Asian	6.4					
			Hispanic	3.6					
			Other	2.1					

Effect size

Test-retest reliability (comparing the patients' two self assessments administered over the telephone and during visit 1)

- Patient-reported number of palms (n=22): adequate test-retest reliability (ICC = 0.99; 95% CI 0.97-0.99)
- Categorized score (n=37): adequate test-retest reliability (ICC = 0.98; 95% CI 0.96-0.99)

Inter-rater reliability

- Self-estimated vs physician estimated PREPI:
  - Visit 1 (n=140): number of palms ICC = 0.82 (95%CI 0.75-0.87)
    : categorized score ICC = 0.80 (95%CI 0.73-0.85)
  - Visit 2 (n=76): number of palms ICC = 0.68 (95%CI 0.54-0.74)
    : categorized score ICC = 0.71 (95%CI 0.58-0.80)

Sensitivity to change (measured by area under the ROC curve [AUC], which describes how well changes in PREPI discriminate between patients who have changed and those who have not based on patient judgements in response to the Global Rating of Change Questionnaire. Improvement on GRC = global rating ≥2; worsening = global rating ≥-2)

- Both physician and patient-reported assessments discriminated well between those who did and did not improve and those who did or did not worsen

Measure	**AUC (95% CI)**	
	Patients assessment (n=62)	Physician's assessment (n=72)
Delta number of palms - improvement	0.7(0.58-0.81)	0.78 (0.67-0.90)
Percentage change - improvement	0.7 (0.57-0.81)	0.76 (0.63-0.88)
Delta number of palms - worsening	0.7 (0.56-0.80)	0.76 (0.64-0.87)
Percentage change - worsening	0.73 (0.59-0.83)	0.81 (0.70-0.90)

Construct validity: BSA vs Skindex (does PREPI capture information on health-related quality of life)

- Number of palms: adequate divergent construct validity (**Patient** estimated: Spearman's r = 0.59; 95%CI: 0.45-0.69; p<0.0001; **Physician** estimated: r = 0.48; 95%CI: 0.34-0.60)
- Categorised score: adequate divergent construct validity (**Patient** estimated: Spearman's r = 0.50; 95%CI: 0.53-0.62; p<0.0001; **Physician** estimated: r = 0.48; 95%CI: 0.33-0.60)

Practicability

- PREPI instrument required 2-3 mins to administer

Summary/author's conclusion

- PREPI appears to be a responsive, reliable and valid instrument for measuring body surface area affected by psoriasis

H.1.1.10 Study 10

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
H. Iyatomi, H. Oka, M. Hagiwara, A. Miyake, M. Kimoto, K. Ogawa, and M. Tanaka. Computerized quantification of psoriasis lesions with colour calibration: preliminary results. *Clin.Exp.Dermatol.* 34 (7):830-833, 2009. Ref ID: IYATOMI2009	**Observational:** Prospective within-group comparison Patients volunteered	N = 5	**Stage of disease journey:** 3 on oral ciclosporine 2 on UVB phototherapy **Inclusion criteria:** mild psoriasis **Exclusion criteria:** none stated **No baseline data available**	Digital photograph (with colour reference marker – Casmatch® – assessed using Computer assisted Area and Severity Index (CASI; evaluates severity from size and redness of lesions)	PASI	28 days	Construct validity	Grant from Ministry of Education, Science, Sports and Culture (Japan)

Effect size

Construct validity: Photograph vs PASI

- Adequate construct validity (r = 0.922)

Summary/author's conclusion

- Although only erythema was evaluated, this method appears to be capable of quantifying psoriasis lesions

H.1.1.11 Study 11

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
D. Farhi, B. Falissard, and A. Dupuy. Global assessment of psoriasis severity and change from photographs : a valid and consistent method. *J.Invest.Dermatol.* 128 (9):2198-2203, 2008. Ref ID: FARHI2008	**Observational:** Prospective within-group comparison Consecutive patients between December 200 and February 2006 approached in out-patient and phototherapy clinics All photographic assessments were blinded to clinical data Sample size	N = 30	**Stage of disease journey:** varied (see table below) **Inclusion criteria:** clinical diagnosis of psoriasis; agreement to be photographed at 2 visits 1 month apart **Exclusion criteria:** none stated **Parameter** / **All N=30** Gender M/F (%): 60/40 Median age (range): 42(19-74) **Past treatments, n (%)** Hospitalisation: 7 (23) Retinoid,: 17 (57)	Dynamic and static physician global assessment (PGA) from photographs **Dynamic PGA:** global assessment of change between 2 photographs taken 1 month apart (+5) Very large improvement/cleared (+90 to 100%) (+4) Large improvement (+70 to 89%) (+3) Moderate to large improvement (+50 to 69%) (+2) Moderate improvement (+30 to +49%) (+1) Mild improvement	In-person clinical PGA rating Assessment made by a single clinician	1 month	Inter-rater reliability; test-retest reliability; construct validity; practicability	Wyeth France provided funding for the camera used

	calculation for number of patient sand assessors was performed		MTX, ciclosporine Biologics 8 (27) **Present treatments, n (%)** Retinoid, MTX, ciclosporine 6 (20) Biologics 15 (50) Topicals 8 (27)	(+10 to +29%) (0) No or minimal change (–10 to +10%) (–1) Mild deterioration (–2) Moderate deterioration (–3) Moderate to large deterioration (–4) Large deterioration (–5) Very large deterioration **Static PGA:** (6) Severe psoriasis (5) Moderate to severe psoriasis (4) Moderate psoriasis (3) Mild to moderate psoriasis (2) Mild psoriasis (1) Psoriasis almost cleared (0) Clear (no lesion) Photographs were				

				standardised and taken under artificial neon light 9 standardised poses were adopted Assessments made by a panel of experts				

Effect size

Practicability

- Time to take a full set of photographs was approximately 5 minutes

Construct validity:

ICC calculated from percentage of total variance that results from patient effect using static scores (photographic vs clinical assessment)

- Change in static photographic PGA from baseline vs change in static clinical PGA from baseline: acceptable construct validity (ICC = 0.64 [95% CI 0.51-0.79])
- Mean panel photographic static PGA vs clinical static PGA: adequate construct validity (ICC = 0.87 [95% CI 0.75-0.93])

Reliability

- **Photographic dynamic PGA (n=5)**
  - acceptable intra-rater (test-retest) reliability (ICC = 0.85; 95% CI: 0.74-0.92); note that this was over a period of 1 month but using the same set of

photographs
  – acceptable inter-rater reliability (ICC = 0.73; 95% CI: 0.56-0.87)

- **Photographic static PGA (n=5)**
  – acceptable intra-rater (test-retest) reliability (ICC = 0.84; 95% CI: 0.78-0.90); note that this was over a period of 1 month same set of photographs
  – acceptable inter-rater reliability (ICC = 0.80; 95% CI: 0.68-0.89)

Summary/author's conclusion

- Global assessment of psoriasis severity and change from photographs by a panel of experts was accurate and consistent

H.1.2 Study 12

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
J. Berth-Jones, J. Thompson, K. Papp, and Copenhagen Psoriasis Working Group. A study examining inter-rater and intrarater reliability of a novel instrument for assessment of psoriasis: the Copenhagen Psoriasis Severity Index. *Br.J.Dermatol.* 159 (2):407-412, 2008. Ref ID: BERTHJONES 2008	**Observational:** cross sectional study Volunteers with very mild to very severe chronic plaque psoriasis To minimise memory or recall bias (due to similar assessment of plaque quality in PASI and CoPSI a 2-sequence design was adopted: PGA, CoPSI,	N = 16	**Stage of disease journey:** unclear **Inclusion criteria:** not stated **Exclusion criteria:** pustular, erythrodermic or acute guttate psoriasis **Parameter** / **All N=16 (224 ratings)** Gender M/F (%): 75/25 Mean age (range): 55(42-75) Mean CoPSI ± SD: 32.6±14.3 Mean PASI± SD: 10.8±9.0 Mean PGA±SD: 3.7±1.3	Copenhagen Psoriasis Severity Index (CoPSI) Note that the genitalia were not scored in this study so the score range was restricted to 0-81 Assessed by 14 senior dermatologists in the morning and the afternoon. Dermatologists had a 2.5-h education session on the use of all 3	PGA, PASI Note the PGA score was based on the average intensity of the most prominent sign (thickness, erythema or scaling) and the proportion of skin involved was not considered. It was rated on a 7-point scale: • Clear • Almost clear • Mild	N/A	Inter-rater reliability; test-retest reliability; construct validity	Leo Pharma

	PASI or PGA, PASI, CoPSI – raters were randomly assigned to follow one sequence in the morning and the other in the afternoon			scales before the study Lighting and temperature were maintained at a consistent level Subjects remained in one examination room and raters moved between rooms in a pre-defined order	• Mild-to-moderate • Moderate • Moderate-to-severe • Severe			

Effect size

Responsiveness

- Half of the theoretical range of PASI (0-72) appears to be redundant, while the results obtained with CoPSI occupy a much larger part of the total range (0-81)
- PASI fails to separate out the subjects at the lower end of the severity spectrum but CoPSI separates these subjects out more effectively

Construct validity: using the mean of the two scores for each individual

- **CoPSI:** Adequate construct validity (r = 0.89 vs PASI and r = 0.75 vs PGA)

- **PASI vs PGA:** Adequate construct validity (r = 0.75)
- **For pairs of individual readings:**

Comparison	Correlation (Spearman's r)	
	Morning ratings	Afternoon ratings
PGA vs PASI	0.67	0.75
PGA vs CoPSI	0.68	0.73
PASI vs CoPSI	0.86	0.89

- Note: for all of the above correlations p<0.0001

Reliability

Score	Intra-rater reliability, ICC (95% CI)	Inter-rater reliability, ICC (95% CI)
CoPSI	0.95 (0.92-0.98)	0.83 (0.71-0.95)
PASI	0.96 (0.93-0.99)	0.91 (0.84-0.97)
PGA	0.81 (0.71-0.90)	0.61 (0.43-0.79)

Summary/author's conclusion

- The CoPSI and the PASI both provided reproducible psoriasis severity assessments, and they were both superior to PGA in terms of inter- and intra-rater reliability
- The CoPSI may overcome several of the problems of the PASI, including the ability to separate milder cases and avoiding the need to estimate the percentage skin involvement.
- The CoPSI also incorporates more meaningful weighting of different anatomical areas

Study 13

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
J. C. S. Szepietowski. Clinical evaluation of the self-administered psoriasis area and severity index (SAPASI). *Acta Dermatovenerologica Alpina, Panonica et Adriatica* 10 (3):79-83, 2001. Ref ID: SZEPIETOWSKI2001	**Observational:** cross sectional study Poland	N = 51	**Stage of disease journey:** unclear **Inclusion criteria:** not stated **Exclusion criteria:** not stated **Parameter** / **All N=51** Gender M/F (%) / 64.7/35.3 Mean age, years / 46.6±17.3 Disease duration / 17.8±11.9 Psoriasis vulgaris (n) / 40 Psoriatic arthritis (n) / 11 Mean PASI score / 16.1±11.9	SAPASI	PASI; extent score from SPI	N/A	Construct validity	Wroclaw University of Medicine

Effect size

Construct validity:

- SAPASI vs PASI: Acceptable construct validity (Spearman's r = 0.62; p<0.00001)
- SAPASI vs extent score from SPI: Acceptable construct validity (Spearman's r = 0.62; p<0.00001)
- There was no significant difference in the evaluation of skin lesions between those with and without PsA

Summary/author's conclusion

- There is a strong relationship between PASI and SAPASI assessments

H.1.2.1 Study 14

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
S. R. Feldman, A. B. Fleischer, D. M. Reboussin, S. R. Rapp, M. Exum, A. R. Clark, and L. Nurre. The self-administered psoriasis area and severity index is valid and reliable. *J.Invest.Dermatol.* 106 (1):183-186, 1996. Ref ID: FELDMAN1996	**Observational:** within-group comparison Wake Forest University Psoriasis and Skin Treatment Centre	N = 80	**Stage of disease journey:** new patients, patients returning for follow-up visits and patients returning for treatments **Inclusion criteria:** not stated **Exclusion criteria:** not stated **Parameter** / **All N=80** Gender M/F (%) / 47.5/52.2	SAPASI Patients received no training in the use of the instrument	PASI Assessed on the same day as the SAPASI by one of 3 clinicians blind to the SAPASI rating	2 days (for repeat observations)	Construct validity; sensitivity to change; test-retest reliability; inter-rater reliability	National Institute of Mental Health
Effect size								

Construct validity (Pearson's correlation coefficient):

- SAPASI vs PASI on first day: r = 0.58
- SAPASI vs PASI on second day: r = 0.70

- **SAPASI vs PASI for BSA determinations:**
  - Head: r = 0.62 (acceptable)
  - Upper extremities r = 0.75 (adequate)
  - Trunk: r = 0.73 (adequate)
  - Lower extremities: r = 0.69 (acceptable)

- **SAPASI vs PASI for erythema, induration and scale scores:**
  - Erythema: r = 0.39 (poor)
  - Induration: r = 0.24 (poor)
  - Scale: r = 0.38 (poor)

Test-retest reliability (n=19):

- **SAPASI:** Adequate test-retest reliability (Pearson's r = 0.82; p = 0.0001)
- **PASI:** Adequate test-retest reliability (r = 0.91; p = 0.0001)

Inter-rater reliability for BSA measurements (5 raters; 40 body silhouettes):

- Adequate inter-rater reliability (ICC = 0.953)
  - Head: ICC = 0.962
  - Upper extremity: ICC = 0.944
  - Trunk: ICC = 0.939
  - Lower extremities: ICC = 0.84

Sensitivity to change (n=38 with repeated paired observations)

- Acceptable sensitivity to change (over ≥2 days): change in SAPASI vs change in PASI score (r = 0.63)
- No significant difference in mean difference between SAPASI and PASI scores at two time points:
- First test: -3.47 ± 6.46; second test: -2.50 ± 8.5 (p =0.22)

Summary/author's conclusion

- Patients can accurately assess their psoriasis in a valid and reproducible fashion using the SAPASI, and it is responsive to changes over time

H.1.2.2 Study 15

<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>A. B. Fleischer, S. R. Feldman, and C. L. Dekle. The SAPASI is valid and responsive to psoriasis disease severity changes in a multi-centre clinical trial. J.Dermatol. 26 (4):210-215, 1999.

Ref ID: FLEISCHER1999</td><td>Observational: within group comparison

Population drawn from multicentre, double blind clinical trial of tazarotene</td><td>N = 182</td><td>Stage of disease journey: unclear

Inclusion criteria: not stated

Exclusion criteria: not all SAPASI items completed; not available at 12-week follow up; missing data

<table><tr><th>Parameter</th><th>All N=182</th></tr><tr><td>Gender M/F (%)</td><td>64.7/35.3</td></tr><tr><td>Mean age, years</td><td>48±14</td></tr></table></td><td>SAPASI</td><td>PASI-equivalent: (erythema + induration + scale)*BSA%</td><td>12 weeks</td><td>Construct validity</td><td>Not stated</td></tr>
<tr><td colspan="9">Effect size

Note that the population is a pooled group including those treated with tazarotene 0.1% gel alone or in combination with placebo cream, or low-, mid- or</td></tr>
</table>

high-potency corticosteroid cream

Construct validity:

- SAPASI vs PASI-equivalent: Poor construct validity (Pearson's r = 0.54 at baseline; r = 0.33 at endpoint; p=0.0001)

Sensitivity to change:

- SAPASI has poor sensitivity to change (Pearson's r = 0.16; p-0.04)
- SAPASI: 39% decrease in severity
- PASI: 62% decrease in severity

Summary/author's conclusion

- This study demonstrates the general validity of the SAPASI and demonstrate that it can detect changes in disease severity in a clinical trial

H.1.2.3 Study 16

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
A. B. Fleischer, S. R. Rapp, D. M. Reboussin, J. C. Vanarthos, and S. R. Feldman. Patient measurement of psoriasis disease severity with a structured instrument. *J.Invest.Dermatol.* 102 (6):967-969, 1994. Ref ID: FLEISCHER1994	**Observational:** within group comparison Wake Forest University Psoriasis and Skin Treatment Centre Development and assessment of a new scoring system	N = 43 (15 assessed for sensitivity to change)	**Stage of disease journey:** unclear **Inclusion criteria:** diagnosis of psoriasis vulgaris **Exclusion criteria:** not all SAPASI items completed; not available at 12-week follow up; missing data **Parameter** / **All N=43** Gender M/F (%): 46.5/53.5 Mean age, years: 44.7±13.4 Mean PASI: 8.1± 6.6 Mean SAPASI: 1.1±10.7	SAPASI	PASI Completed on the same day as the SAPASI by one of 2 clinicians blinded to the SAPASI rating	Mean: 18.4±9.1 days	Sensitivity to change	Glaxo Dermatology Research Fellowship

Effect size

Sensitivity to change:

- Mean decrease in score: PASI = 7.3±5.7; SAPASI = 5.9±4.7
- Both showed significant improvements: PASI $p<0.0003$; SAPASI $p<0.05$

Summary/author's conclusion

- Although the SAPASI may not allow for accurate prediction of clinical disease severity in an individual , the SAPASI facilitates prediction of disease severity in a population

H.1.2.4 Study 17

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
B. Kirby. The Salford Psoriasis Index: An holistic measure of psoriasis severity. *Br.J.Dermatol.* 142 (4):728-732, 2000. Ref ID: KIRBY2000	**Observational:** 3 separate cross sectional studies Consecutive patients seen in the Psoriasis Speciality Clinic, Hope Hospital, UK	N = 150 for SPI inter-observer reliability N= 100 for construct validity N=20 for PASI assessment	**Stage of disease journey:** unclear **Inclusion criteria:** diagnosis of psoriasis **Exclusion criteria:** not stated No baseline data available	Salford Psoriasis Index (SPI)	Psoriasis disability index (PDI), PASI, SAPASI	6 weeks	Inter-rater reliability; intra-rater reliability; construct validity; sensitivity to change	Novartis Pharmaceuticals Ltd.

Effect size

Inter-rater reliability (n=20; 6 trained clinical observers):

- PASI: Acceptable (Spearman's r= 0.71; 95% CI [0.51-0.86])
- SPI: Adequate for the historical disease severity score (r=0.86 [95% CI: 0.76-0.94) and acceptable for the extent score (r=0.70 [95% CI: 0.56-0.89)

Intra-rater reliability

- SPI: Adequate for the psychological impact score (r = 0.997[95% CI: 0.994-0.999])

Divergent construct validity (Spearman's correlation coefficient)

- PASI vs PDI: r = 0.45; p<0.001
- SPI (psychological impact score) vs PASI: r = 0.28; p<0.05
- SPI (psychological impact score) vs SAPASI: r=0.19; p = 0.1
- PDI vs SAPASI: r = 0.27; p<0.05

Convergent construct validity (Spearman's correlation coefficient)**:**

- SAPASI vs PASI: poor (r = 0.54)
- SPI (psychological impact score) vs PDI (n=100): r=0.59; p<0.001 (poor validity)

Sensitivity to change (n=20 treated with a number of different modalities)

- Statistically significant decrease for extent and psychological impact scores (p<0.0001), but not for the historical disease severity score, which wouldn't be expected to change

Summary/author's conclusion

- The SPI will be a more relevant real life categorization of psoriasis severity because it takes a holistic approach based not only on physician assessment but also psychological disability and treatment resistance

H.1.2.5 Study 18

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
A. Y. Finlay, G. K. Khan, D. K. Luscombe, and M. S. Salek. Validation of Sickness Impact Profile and Psoriasis Disability Index in Psoriasis. *Br.J.Dermatol.* 123 (6):751-756, 1990. Ref ID: FINDLAY1990	**Observational:** Cross sectional study Sequentially recruited at the University Hospital of Wales	N = 32	**Stage of disease journey:** 72% in-patients **Inclusion criteria:** diagnosis of psoriasis **Exclusion criteria:** not stated **Parameter** / **All N=32** Gender M/F (%): 46.9/53.1 Median age (range), years: 35 (14-73) Inpatients: 72% Median PASI (range): 5.5 (2-24) Median PDI (range): 38 (7-88)	*Sickness Impact Profile (SIP)*	PASI Psoriasis disability index (PDI) PDI: 15 questions answered on a 1-7 linear analogue scales The questions were grouped under 5 headings: daily activities (5 items); work/school (3 items); personal relationships (2 items); leaisure (4 items); and treatment (1 item)	N/A	Discriminant construct validity	Not stated

Effect size

Divergent construct validity:

- Adequate: Spearman's r = 0.40; p<0.05; therefore, PASI and PDI are not measuring the same construct

Summary/author's conclusion

- The PDI is an appropriate method to give a rapid overall measure of psoriasis disability

H.1.2.6 Study 20

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
J. Berth-Jones, K. Grotzinger, C. Rainville, B. Pham, J. Huang, S. Daly, M. Herdman, P. Firth, and K. Hotchkiss. A study examining inter- and intrarater reliability of three scales for measuring severity of psoriasis: Psoriasis Area and Severity Index, Physician's Global Assessment and Lattice System Physician's	**Observational:** cross sectional study Volunteers with very mild to very severe chronic plaque psoriasis Sample size selected to ensure coefficients were calculated with a standard error of 10%, given a false positive rate of 5%	N = 16	**Stage of disease journey:** unclear **Inclusion criteria:** diagnosis of psoriasis **Exclusion criteria:** pustular, erythrodermic or acute guttate psoriasis **Parameter** / **All N=16** Gender M/F (%): 56.3/43.7 Mean age, years (range): 50 (35-71)	PASI, Physician's Global Assessment (PGA), Lattice-System (LS)-PGA Assessed by 14 raters with a range of experience To minimise memory or recall bias (due to similar assessment of BSA in PASI and LS-PGA a 2-sequence design was adopted: PGA, LS-PGA,	PASI, Physician's Global Assessment (PGA), Lattice-System (LS)-PGA PGA was rated on a 7-point scale: • Clear • Almost clear • Mild • Mild-to-moderate • Moderate • Moderate-to-severe Severe	N/A	Construct validity; inter- and intra-rater reliability	Glaxo SmithKline

Global Assessment. *Br.J.Dermatol.* 155 (4):707-713, 2006. Ref ID: BERTHJONES 2006				PASI or PGA, PASI, LS-PGA – raters were randomly assigned to follow one sequence in the morning and the other in the afternoon Lighting and temperature were maintained at a consistent level Subjects remained in one examination room and raters moved between rooms in a pre-defined order				
Effect size **Construct validity** Adequate construct validity for all comparisons (Spearman's rank correlation coefficient)								

- LS-PGA vs PASI: r = 0.92 (p<0.001)
- LS-PGA vs PGA; r = 0.73 (p<0.001)
- PGA vs PASI; r = 0.79 (p<0.001)

Agreement for dichotomised scores

Outcome 1	Outcome 2	Agreement
PASI vs PGA		
PASI ≤4	PGA clear or nearly clear	K= 0.64 (0.53-0.74)
PASI ≥18	PGA very severe or severe	K= 0.18 (0.09-0.27)
PASI vs LS-PGA		
PASI ≤4	LS-PGA clear or nearly clear	K= 0.61 (0.50-0.73)
PASI ≥18	LS-PGA very severe or severe	K= 0.62 (0.55-0.69)
LS-PGA vs PGA		
LS-PGA clear or nearly clear	PGA clear or nearly clear	K= 0.67 (0.54-0.80)
LS-PGA very severe or severe	PGA very severe or severe	K= 0.08 (0.03-0.14)

Reliability

Score	Intra-rater reliability, ICC (95% CI)	Inter-rater reliability, ICC (95% CI)
PASI	0.94 (0.86-1.00) Adequate	0.90 (0.83-0.97) Adequate
LS-PGA	0.91 (0.77-1.00)	0.84 (0.73-0.95)

	Adequate	Adequate
PGA	0.88 (0.69-1.00) Acceptable	0.75 (0.61-0.88) Acceptable

Note: 99% of assessment scores on PASI were <40, whereas the PGA and LS-PGA scores spanned the majority of their scales (1-6 and 2-8, respectively)

Summary/author's conclusion

- The reliability of PGA and PASI are demonstrated
- LS-PGA shows similar reliability and good levels of correlation with PASI
- In terms of inter-rater reliability the scales can be ranked in order as: PASI, LS-PGA, PGA

H.1.2.7 Study 21

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
T. Henseler and K. Schmitt-Rau. A comparison between BSA, PASI, PLASI and SAPASI as measures of disease severity and improvement by therapy in patients with psoriasis. *Int.J.Dermatol.* 47 (10):1019-1023, 2008. Ref ID: HENSLER2008	**Observational:** within group comparison Patients with moderate-to-severe chronic plaque psoriasis at 18 dermatologic out-patient centres treated with 1 mg/kg/wk efalizumab (subcutaneous)	N = 33	**Stage of disease journey:** >60% had previously been treated with at least 4 different systemic treatments **Inclusion criteria:** not stated **Exclusion criteria** not stated **Parameter** / **All N=33** Gender M/F (%): 63.6/36.4 Mean age, years ±SD: 48.7 ±13.7 Median age of disease onset (years): 21.0 Median PASI score: 20.8 History of ≥4 systemic treatments: >60%	BSA, PASI, SAPASI **BSA:** mean of affected skin surface assuming that head = 10%; upper extremities = 20%; trunk = 30% and lower extremities = 40% of total body surface	BSA, PASI, SAPASI	12 weeks	Construct validity; sensitivity to change	Serono

			(most commonly PUVA, fumeric acid esters, MTX, retinoids and ciclosporine A)						

Effect size

Construct validity

Adequate construct validity for all comparisons (correlation coefficient)
- SAPASI vs PASI: r = 0.91 (p<0.0001)
- SAPASI vs BSA; r = 0.73 (p<0.0001)
- PASI vs BSA; r = 0.81 (p<0.0001)

Note: correlation between SAPASI and PASI significantly stronger than any correlation involving BSA

Sensitivity to change
- Relative change between baseline and follow-up: SAPASI = 70.6%; PASI = 67.3%; BSA = 48.6%

Summary/author's conclusion
- There is a high correlation between all measures
- The high correlation between SAPASI and PASI suggests that both measures, one administered by the patient and one by a dermatologist, are of equivalent value

H.1.2.8 Study 22

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
R. Shikiar, B. W. Bresnahan, S. P. Stone, C. Thompson, J. Koo, and D. A. Revicki. Validity and reliability of patient reported outcomes used in psoriasis: results from two randomized clinical trials. *Health & Quality of Life Outcomes* 1:53, 2003. Ref ID: SHIKIAR2003	**Observational:** Within group comparison Data from 2 RCTs – blinded examination of psychometric properties of patient-reported instruments in these studies (not treatment effects) Phase III, randomised, double-blind, parallel group, placebo controlled, multicentre clinical trial	N = 1095 Study A: n = 498 Study B: n = 597	**Stage of disease journey:** unclear **Inclusion criteria:** At least moderate psoriasis (BSA≥10%; PASI≥12) for at least 6 months; age 18-70 years **Exclusion criteria:** Concomitant diseases or allergies to medications used; pregnant or lactating females **Parameter** / **Study A (n=498)** / **Study B (n=597)** Mean age (years), ±SD: 44.1±12.0 / 45.6±12.7 Mean gender M/F (%): 72.3/27.7 / 64.8/35.2 Baseline PASI±SD: 18.84±7.05 / 20.01±8.35	DLQI	PASI, PGA **PGA:** Physician's global assessment of change compared to baseline condition (using photographs from baseline to aid in making the assessment) 'Cleared' = 100% improvement; 'excellent' = 75-99% improvement; 'good' = 50-74% improvement; 'fair' = 25-49% improvement; 'slight = 1-24%	12 weeks	Sensitivity to change; construct validity; internal consistency	Genentech Inc

	(efalizumab vs placebo); North America Analyses were performed on blinded data (separately for study A and study B)				improvement; 'unchanged'; 'worse'			

Effect size

Sensitivity to change

Correlation between change scores for DLQI and physician reported values

- Study A – Poor (r = 0.47 compared with PASI; 0.46 compared with PGA)
- Study A – Poor (r = 0.54 compared with PASI; 0.53 compared with PGA)

Classification into PASI-defined categories (ANOVA)

- Significant difference in improvement on DLQI between responders (PASI75 or PASI50) and non-responders (<PASI50)

	Study A				**Study B**			
	Mean change score				**Mean change score**			
	<50%	**≥50% and <75%**	**≥75%**	**p-value**	**<50%**	**≥50% and <75%**	**≥75%**	**p-value**
DLQI	2.48	5.33	9.57	<0.0001	2.49	6.83	10.03	<0.0001

Divergent construct validity (DLQI vs PASI; Pearson's product moment correlation coefficient**)**

Correlations were significantly stronger at the end of the study than at baseline

- Study A – Adequate (r = 0.20 at baseline; 0.51 at end point)
- Study B – Adequate (r = 0.25 at baseline; 0.59 at end point)

Internal consistency of DLQI

- Study A – Adequate: α = 0.871 at baseline and 0.921 at week 12
- Study B – Adequate: α = 0.869 at baseline and 0.919 at week 12

Summary/author's conclusion

- The DLQI is useful for the measurement of dermatological-related limitations of functional ability and the frequency, severity and impact of psoriasis symptoms on patients' lives and psoriasis-related QoL; it provides information about the change in the subjects symptoms that supplement the physicians clinical assessments

H.1.2.9 Study 23

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
R. G. Langley and C. N. Ellis. Evaluating psoriasis with Psoriasis Area and Severity Index, Psoriasis Global Assessment, and Lattice System Physician's Global Assessment. *J.Am.Acad.Dermatol.* 51 (4):563-569, 2004. Ref ID: LANGLEY2004	**Observational**: cross sectional study Recruited from out-patient departments, phototherapy unit and day treatment centre of the University of Michigan Department of Dermatology, USA (aiming to recruit a range of severities) Recall bias was minimised: patients randomly assigned to different rooms in the morning and	N = 35 **Note:** "patients were compensated for their time"	**Stage of disease journey:** unclear (but no medications were used during the study) **Inclusion criteria:** not stated **Exclusion criteria:** not stated **Parameter** / **All (n=35)** Median age, years (range): 42 (22-62) Mean gender M/F (%): 66/34 **Ethnicity, n (%)** White: 31	PASI, PGA, LS-PGA **PGA:** • Severe: very marked plaque elevation, scaling, and/or erythema • Moderate to Severe: marked plaque elevation, scaling, and/or erythema • Moderate: moderate plaque elevation, scaling, and/or erythema • Mild to moderate: intermediate between moderate and mild • Mild: slight plaque	All comparisons Each subject was evaluated twice by each of 17 physicians (who received 30 mins training on the day) 53% of physicians were experienced (previous involvement in 4 or more similar clinical trials); but none of them had previous experience with the LS-PGA	N/A	Construct validity; inter and intra-rater reliability; internal consistency	Biogen Inc

	afternoon; identical assessment rooms and patient gowns; no interaction between patient and physician		(89%) Black: 2 (6%) Asian American: 1 (3%) Hispanic: 1 (3%)	elevation, scaling, and/or erythema • Almost clear: intermediate between mild and clear • Clear: no signs of psoriasis (post-inflammatory hypopigmentation or hyperpigmentation could be present).				

Effect size

Construct validity (Spearman correlation coefficient)

	LS-PGA	PGA
PASI	0.86	0.87
PGA	0.83	

Internal consistency

- Adequate internal consistency (α=0.9 for each)

Reliability (all raters; n=17)

Assessed by ANOVA; lower σ values denote lower variation

	Intrarater	Intrarater	Corrected

	variation (σ by ANOVA)	**variation** (σ by ANOVA)	**intrarater variation** (relative σ by ANOVA)
PASI	2.5	8.8	2.7
PGA	0.2	1.2	2.3
LS-PGA	0.4	1.6	2.2

Summary/author's conclusion

- All three measures were highly correlated and had high internal consistency
- PGA and LS-PGA had lower intra-rater variation than PASI
- Experience was beneficial in reducing variation in PASI scores, but was not required with PGA or LS-PGA
- The LS-PGA does not require experience and is a reliable measure of the therapeutic effect in psoriasis, and would allow comparisons across different trials

H.1.2.10 Study 24

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
S. Krenzer, M. Radtke, K. Schmitt-Rau, and M. Augustin. Characterization of patient-reported outcomes in moderate to severe psoriasis. Dermatology 223 (1):80-86, 2011. Ref ID: KRENZER2011	**Observational**: case series Recruited from out-patient departments and dermatological practices in Germany (all receiving efalizumab in routine care)	N = 1787	**Stage of disease journey:** moderate to severe plaque psoriasis receiving efalizumab **Inclusion criteria:** not stated **Exclusion criteria:** not stated **Parameter** / **All (n=1787)** Median age, years (range): 46 (16-93) Mean gender M/F (%): 63.8/36.2 Mean height (cm): 174.3	PASI, BSA, DLQI (German version) **BSA:** • Total BSA calculated by adding percentages of affected areas of head, trunk, upper and lower extremities **PASI:** • Measures extent and severity on a range of 0-72	PASI vs BSA (at baseline, 3 months and 12 months) Change in PASI vs change in BSA (at 3 and 12 months)	1 year	Construct validity	Merck Serono

			Mean weight (kg)	84.1				
			Previous psoriasis phenotypes					
			Erythrodermic	39.4%				
			Pustular	28.4%				
			Palmoplantar	56.7%				

Effect size

Construct validity (Pearson correlation coefficient)

	Baseline (n=469)	**3 months (n=298)**	**6 months (n=109)**
PASI vs BSA	0.450	0.694	0.832

Sensitivity to change (Pearson correlation coefficient for change from baseline)

Change scores	**3 months (n=265)**	**6 months (n=94)**
PASI vs BSA	0.771	0.792

Summary/author's conclusion

- PASI and BSA, and change in these scores, were correlated

H.1.2.11 Study 25

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
V. Shankar, S. Ghosh, K. Ghosh, and U. Chaudhuri. PASI and PQOL-12 score in psoriasis: is there any correlation? Indian J.Dermatol. 56 (3):287-289, 2011. Ref ID: SHANKAR2011	**Observational**: Cross sectional study Department of Dermatology, MGM Medical College and LSK Hospital, Kishanganj, Bihar, India, from November 2008 to August 2009	N = 34	**Stage of disease journey:** unclear **Inclusion criteria:** all morphological variants of psoriasis with or without joint involvement, pre-treated or untreated. **Exclusion criteria:** psoriasiform dermatoses due to other etiologies; psoriatic arthropathy without skin involvement; nail psoriasis without skin involvement; generalized pustular psoriasis de novo without any associated or previous history of psoriatic plaque; and sebo-psoriasis, palmo-plantar pustulosis or inverse psoriasis presenting alone morphologically without any other classical clinical presentation of psoriasis elsewhere in the skin	**PQOL-12:** 12-item self-administered, disease-specific psychometric instrument **PASI:** Measures extent and severity on a range of 0-72	PASI vs PQOL-12	NA	Construct validity	None

			Baseline characteristics 47% male Age range: 8 to 55 years (median: 33.5 years) Duration of disease: 1 month to 20 years. PASI range: 0.8 to 32.8 PQOL-12 range: 4 to 120					

Effect size

Construct validity (correlation coefficient): PASI vs PQOL12

r = 0.422

Summary/author's conclusion

Disease severity has minimal correlation with quality of life in people with psoriasis.

Even psoriasis of limited objective severity, especially located on visible parts of the body, may induce great psychological trauma to the patients

H.1.3 Non-comparative data

H.1.3.1 Study 1

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
A. B. Fleischer, S. R. Feldman, S. R. Rapp, D. M. Reboussin, M. Exum, A. R. Clark, and V. Rajashekhar. Disease severity measures in a population of psoriasis patients: the symptoms of psoriasis correlate with self-administered psoriasis area severity index scores.	**Observational**: Case series Patients identified from electronic billing records from Wake Forest University, USA; had received clinical diagnosis of psoriasis between May 1992 and December 1993 Participants invited to complete a survey on demographics, therapeutics, co-	N = 578 (but only a random sample of 30 assessed for inter-rater reliability)	**Stage of disease journey:** 23% on intense treatment; 61% moderate treatment; 16% over-the-counter treatment **Inclusion criteria:** Age ≥ 18 years **Exclusion criteria:** not diagnosed with psoriasis; children **Parameter** / **All (n=101)** Mean age – years: 48.8 ± 14.6 Caucasian: 91% African American: 6% Native American: 1%	SAPASI – disease severity tool completed by the patients themselves	N/A	Inter-rater reliability Correlation of psoriasis symptoms with SAPASI score	NIMH grant number MH51552

J.Invest.Dermatol. 107 (1):26-29, 1996. Ref ID: FLEISCHER1996	existing conditions, psychological functioning, and quality of life		Gender M/F (%)	43/57					
			Time since psoriasis diagnosis (years)	14.4 ± 12.8					
			Mean age at psoriasis onset (years)	34.5 ± 17.1					
			Joint pain, n (%)	219 (69)					
			Psoriatic arthritis, n (%)	64 (20)					
			Comorbidities, n (%)						
			Hypertension	81 (25.5)					
			GI diseases	53 (16.7)					
			Arthritis	163 (51)					
			Heart disease	35 (11)					
			Thyroid disease	30 (9.4)					
			Urinary tract disease	26 (8.2)					
			Mental health conditions	18 (5.7)					
			Disease severity, n (%)						
			Remission (SAPASI = 0)	7 (2)					

			Mild (SAPASI >0 to 3	124 (39)				
			Moderate (SAPASI >3 to 15)	158 (50)				
			Severe (SAPASI >15)	29 (9)				

Effect size

Inter-rater reliability (scoring of self-administered form by 2 assessors)

- Adequate inter-rater reliability of SAPASI (97% agreement between 2 investigators)
- Body site specific inter-rater reliability ranged from 96-100% agreement

Correlation with patient-reported symptoms

- SAPASI predicted the severity of pruritus (p=0.004), burning (p=0.04) and skin soreness (p=0.0001) on regression analysis
- SAPASI correlated modestly with joint pain (r = 0.3; p = 0.0001) and psoriatic arthritis (r = 0.3; p = 0.0003) – this is not adequate for the criterion of convergent construct validity

Summary/author's conclusion

- The SAPASI is significantly associated with the severity of pruritus, burning, joint pain and psoriatic arthritis (as reported by patients)

H.1.3.2 Study 2

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>M. Morgan, R. McCreedy, J. Simpson, and R. J. Hay. Dermatology quality of life scales--a measure of the impact of skin diseases. Br.J.Dermatol. 136 (2):202-206, 1997.

Ref ID: MORGAN1997</td>
<td>Observational: Prospective case series

Questionnaire developed based on items derived from the responses of 50 dermatology out-patients attending St John’s Institute of Dermatology, UK, and factor analysis performed based on responses of 118 further patients, 41 of these (who had psoriasis and were attending for phototherapy) completed the form on a second occasion</td>
<td>N = 41</td>
<td>Stage of disease journey: Phototherapy

Inclusion criteria: Psoriasis out patients

Exclusion criteria: not stated

<table>
<tr><th>Parameter</th><th>All (n=101)</th><th>Psoriasis returning patients (n=41)</th></tr>
<tr><td>Mean age – years</td><td>38 (13-84)</td><td>Median: 38 (18-83)</td></tr>
<tr><td>Gender M/F (%)</td><td>54/46</td><td>59/41</td></tr>
</table></td>
<td>Dermatology quality of life scales (DQOLS)

Completed unaided by clinic attendees</td>
<td>7-10 days between tests</td>
<td>Internal consistency (for mixed population);

test-retest reliability</td>
<td>None stated</td>
</tr>
<tr><td colspan="8">Effect size</td></tr>
</table>

Test-retest reliability

- Consider that at the time of the second test the patients would have had an additional phototherapy session, which may have impacted their experience of the psoriasis; therefore, the difference may be due to improvement following the out-patient phototherapy session

Score	Intra-class correlation coefficient	Reliability
Psychosocial score	**0.84**	**Acceptable**
Embarrassment	0.85	Acceptable
Despair	0.77	Poor
Irritableness	0.76	Poor
Distress	0.79	Poor
Activity score	**0.84**	**Acceptable**
Everyday	0.80	Acceptable
Summer	0.66	Poor
Social	0.68	Poor
Sexual	0.86	Acceptable

Summary/author's conclusion

- There was good overall test-retest reliability for the psychosocial and activity scores (with variable reliability for the subscales)

H.1.3.3 Study 3 – nail psoriasis

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comaprison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>N. E. Kacar. The comparison of Nail Psoriasis Severity Index with a less time-consuming qualitative system. J.Eur.Acad.Dermatol.Venereol. 22 (2):219-222, 2008.

Ref ID: KACAR2008</td>
<td>Observational: Cross sectional study

Dermatology out-patient clinic, Turkey

NAPSI and Cannavo’s system carried out at time one by one investigator and NAPSI re-tested at time two by a second investigator</td>
<td>N = 45</td>
<td>Stage of disease journey: unclear

Inclusion criteria: Nail psoriasis

Exclusion criteria: Onychomycosis
<table>
<tr><th>Parameter</th><th>All (n=45)</th></tr>
<tr><td>Mean age – years
Men
Women</td><td>42.76 (11-65)
45.15 (11-66)</td></tr>
<tr><td>Gender M/F (%)</td><td>62.5/38.5</td></tr>
</table></td>
<td>NAPSI – involved nail quadrants evaluated for presence of nail matrix or nail bed disease (score 0-4 depending on number of quadrants involved)

Re-evaluated by second investigator on same day and under the same conditions</td>
<td>Cannavo’s qualitative system

Severity of pitting, oncholysis, nail plate crumbling, nail bed hyperkeratosis and oil drop discolouration scored from 0 (absent) to 3 (severe). The average score of all involved nails was considered as the severity of nail involvement</td>
<td>N/A</td>
<td>Inter-rater reliability</td>
<td>None stated</td>
</tr>
</table>

Effect size

Inter-rater reliability of NAPSI

- Pearson's r=0.768 (p<0.001); acceptable

Summary/author's conclusion

- There was good correlation between the NAPSI score of the 2 dermatologists, although the system was time consuming

H.1.3.4 Study 4 – nail psoriasis

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>S. Aktan, T. Ilknur, C. Akin, and S. Ozkan. Interobserver reliability of the Nail Psoriasis Severity Index. Clin.Exp.Dermatol. 32 (2):141-144, 2007.

Ref ID: ATKAN2007</td>
<td>Observational: Cross sectional study

Consecutive patients attending dermatology out-patient clinic, Turkey</td>
<td>N = 25</td>
<td>Stage of disease journey: None of the patients were receiving systemic therapy or topical therapy for their psoriatic nails at the time of assessment

Inclusion criteria: Nail psoriasis

Exclusion criteria: Onychomycosis, psoriatic arthritis and pustular psoriasis of the nails

<table>
<tr><th>Parameter</th><th>All (n=25)</th></tr>
<tr><td>Mean age – years</td><td>50.8 (range: 28-75)</td></tr>
<tr><td>Gender M/F (%)</td><td>64/36</td></tr>
<tr><td>PASI score</td><td>15.4±9.1</td></tr>
</table>
</td>
<td>NAPSI –nail quadrants evaluated for presence of nail matrix or nail bed disease (score 0-4 depending on number of quadrants involved)

Total NAPSI score: total nail score (matrix+bed) for all quadrants of 20 nails (0-160)

Nail score: sum of all matrix+bed scores for each nail (0-32)

Evaluated by 3 dermatologists on the same day, under the same conditions, in a well-illuminated room under direct vision using a standard NAPSI sheet</td>
<td>N/A</td>
<td>Inter-rater reliability</td>
<td>None stated</td>
</tr>
</table>

			(mean±SD)		All finger- and toe-nails were scored and each observer was blinded to the scoring of the others			
			Duration of psoriasis (mean±SD)	18.9±9.4				
			Disease phenotype					
			Chronic plaque	21 (84%)				
			Erythrodermic	3 (12%)				
			Palmoplantar	1 (4%)				

Effect size

Inter-rater reliability of NAPSI (intra-class correlation coefficients)

Total NAPSI

Score	**ICC**	**95% CI**	**Reliability**
Nail matrix	0.584	0.359-0.769	Poor
Nail bed	0.869	0.765-0.935	Adequate
Total NAPSI	0.781	0.625-0.888	Acceptable

Nail score

Score	All nails (n=500)			Fingernails (n=250)			Toenails (n=250)		
	ICC	**95% CI**	**Reliability**	**ICC**	**95% CI**	**Reliability**	**ICC**	**95% CI**	**Reliability**
Nail matrix	0.603	0.558-0.646	Acceptable	0.552	0.483-0.618	Poor	0.303	0.224-0.384	Poor
Nail bed	0.705	0.667-0.739	Acceptable	0.686	0.630-0.737	Acceptable	0.690	0.635-0.741	Acceptable
Nail	0.649	0.607-0.688	Acceptable	0.659	0.601-0.714	Acceptable	0.637	0.575-0.694	Acceptable

Summary/author's conclusion

- The inter-observer reliability appeared to be better for nail-bed scores than for nail matrix scores
- Moderate-to-good agreement of scoring with the NAPSI was found among the 3 observers

H.1.3.5 Study 5

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
T. Nijsten, D. Whalley, J. Gelfand, D. Margolis, S. P. McKenna, and R. S. Stern. The psychometric properties of the psoriasis disability index in United States patients. J.Invest.Dermatol. 125 (4):665-672, 2005. Ref ID: NIJSTEN2005	**Observational**: Cross sectional study Survey of US patients	N = 1196	**Stage of disease journey:** representative sample of all patients **Inclusion criteria:** Cutaneous psoriasis; age ≥18 years **Exclusion criteria:** Psoriatic arthritis **Characteristics** / **N=1196** Gender M/F (%): 40.5/59.5 Mean age, years, mean (SD): 47.4 (16.1) Race: White: 1050 (87.8%) Other: 146 (12.2%) Extent of disease (no. of palms):	PDI	N/A	Sensitivity to change, internal consistency	None stated

None or little	232 (19.4%)
<3 palms	372 (31.1%)
3-10 palms	430 (36.0%)
>10 palms	156 (13.0%)
Duration of disease, years, mean (SD)	17.1 (14.4)

Effect size

Sensitivity to change of PDI

- All subscales had small ceiling effects (≤5%) but substantial floor effects (≥49%)

Internal consistency

- Adequate internal consistency for subscales (Cronbach's α 0.77-0.81)

PDI and it's scales	Number of items (range of score)	% floor	% ceiling	Item-rest correlation (correlation of item with other items in subscale)	Cronbach's α
PDI	15 (0-45)	14.7	0.0	-	-
Daily activities	5 (0-15)	20.5	0.2	0.35-0.59	0.78

Work	3 (0-9)	63.8	0.3	0.45-0.56	0.81
Personal	2 (0-6)	67.6	1.0	0.52-0.53	0.80
Leisure	4 (0-12)	49.3	0.2	0.33-0.56	0.77
Treatment	1 (0-3)	52.9	4.5	-	-

Summary/author's conclusion

- The PDI lacks sensitivity for mild disease (shown by substantial floor effects)
- The PDI has good internal consistency
- Note that in a Rasch analysis the PDI and its subscales appeared to measure multiple constructs, which may compromise its validity to create an overall score
- Also note that there was differential item functioning for age and gender, suggesting that people with the same disease-related disability but of a different age or gender may score differently, implying that the PDI is not intrinsically generalisable in heterogeneous populations

H.1.3.6 Study 6

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>B. Ramsay and C. M. Lawrence. Measurement of involved surface area in patients with psoriasis. Br.J.Dermatol. 124 (6):565-570, 1991.

Ref ID: RAMSAY1991</td><td>Observational: Case series

In-patients selected over a 9 month period</td><td>N = 10</td><td>Stage of disease journey: unclear

Inclusion criteria: In-patients, chronic plaque psoriasis

Exclusion criteria: none stated

<table><tr><th>Characteristics</th><th>N=10</th></tr><tr><td>Gender M/F (%)</td><td>50/50</td></tr></table></td><td>BSA
• Rule of nines – 4 experienced observers rated the extent of psoriasis on 2 consecutive days (order of assessment of arms, legs and trunks randomized to minimise memory recall bias)
• Plaque tracings – only calculated once by a single observer
• Photographs – only calculated once by a single observer</td><td>1 day</td><td>Test-retest and inter-rater reliability</td><td>None stated</td></tr>
<tr><td colspan="8">Effect size (calculated using two-way within-subject analysis of variance)

Intra-rater reliability
• Acceptable intra-rater reliability between days 1 and 2 (differences of 1-2%; p>0.05 ANOVA)</td></tr>
</table>

Inter-rater reliability

- Poor inter-rater reliability among the 4 observers (significantly different mean percentage involvement estimations; range 14-33%; p<0.001 ANOVA)

Note that all observers using the rule of nines over-estimated the area involved compared with the plaque traced areas (and this was more than twice the plaque traced area on 62% of observations); there was a greater degree of error when assessing patients with less surface area involvement

Compared with plaque tracings analysis of clinical photographs underestimated the area of involvement by a mean of -2%.

Summary/author's conclusion

- Untrained observers using the rule of nines will over-estimate the extent of psoriasis
- Image analysis of whole body photographs is comparable to that of traced outlines

H.1.3.7 Study 7

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
Y. M. Yune, S. Y. Park, H. S. Oh, D. J. Kim, D. S. Yoo, I. H. Kim, J. S. Moon, M. K. Kim, and C. H. Oh. Objective assessment of involved surface area in patients	**Observational**: cross sectional study Department of dermatology, Korea University	N = 30	**Stage of disease journey:** unclear **Inclusion criteria:** not stated **Exclusion criteria:** not stated	BSA • visual grading (% area covered as assessed by 5 dermatologists) • digital image analysis (total % BSA affected)	N/A	Inter-rater reliability	None stated

with psoriasis. Skin Research & Technology 9 (4):339-342, 2003. Ref ID: YUNE2003	Hospital		**Characteristics** / **N=30** Gender M/F (%) / 56.7/43.3 Mean age, years, mean (SD) / 42.5 (13.6)		Seven photographs were taken of each patient (head, anterior trunk, posterior trunk, both anterior upper arms, both posterior upper arms, both anterior lower legs and both posterior lower legs) by one dermatologist using the same camera, lighting and posture for each patient		

Effect size

Inter-rater reliability

- Poor inter-rater reliability (statistically significantly different: $p<0.05$, Kruskal-Wallis test)

Note that the overall difference in estimations between the visual grading method and image analysis was statistically significant, with visual grading resulting in a higher percentage involvement being reported ($p < 0.05$, Wilcoxon signed rank sum test); although for the head and neck area there was no significant difference

Summary/author's conclusion

- Measuring the involved are of psoriasis using image analysis may overcome the inevitable differences between observers using the visual grading method.

H.1.3.8 Study 8

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>T. Nijsten. Refinement and reduction of the Impact of Psoriasis Questionnaire: Classical Test Theory vs. Rasch analysis. Br.J.Dermatol. 154 (4):692-700, 2006.

Ref ID: NIJSTEN2006</td>
<td>Observational: Prospective case series

Created 2 shortened versions of the instrument

Subjects taken from the PUVA follow-up study; 16 university centres in the USA</td>
<td>N = 792</td>
<td>Stage of disease journey: receiving PUVA and most had received systemic therapies

Inclusion criteria: not stated

Exclusion criteria: missing items on questionnaire

<table>
<tr><th>Parameter</th><th>N=792</th></tr>
<tr><td>Gender M/F (%)</td><td>62/48</td></tr>
<tr><td>Mean age (range)</td><td>56 (22-92)</td></tr>
</table></td>
<td>Impact of Psoriasis Questionnaire (IPSO): original version, classical test theory version (3 subscales – mental functioning, mental well-being and stigmatisation) and Rasch reduced version (unidimensional 11-item questionnaire)</td>
<td>N/A</td>
<td>Internal consistency</td>
<td>None stated</td>
</tr>
<tr><td colspan="8">Effect size</td></tr>
</table>

Internal consistency (α)

- **Original version**: Adequate internal consistency for physical and psychological scales (0.85 and 0.73); acceptable for social scale (0.63)
- **CTT version**: Adequate internal consistency for mental functioning and stigmatisation scales (0.85 and 0.75); poor for social scale (0.52)
- **Rasch version:** Adequate internal consistency overall (0.83)

Note that 7/16 items demonstrated differential item functioning for age and gender, particularly in the psychological and social subscales (e.g., older people were less likely to report high scores for feelings of being unattractive and/or sexually undesirable and sleeping problems)

Summary/author's conclusion

- The IPSO can be improved and shortened, and the Rasch reduced version is likely to assess the psychosocial impact of moderate-to-severe psoriasis on patients' lives best because it is short, reliable and unidimensional.

H.1.3.9 Study 9

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>M. A. Gupta and A. K. Gupta. The Psoriasis Life Stress Inventory: a preliminary index of psoriasis-related stress. Acta Derm.Venereol. 75 (3):240-243, 1995.

Ref ID: GUPTA1995</td>
<td>Observational: case series

In- and out-patients from Department of Dermatology, University of Michigan Hospitals, USA

Original development of the PLSI</td>
<td>N = 217</td>
<td>Stage of disease journey: in- and out-patients included to obtain patients with a wide range of psoriasis severity

Inclusion criteria: for out-patients: ≤30% total body surface area affected

Exclusion criteria: other concomitant dermatologic or medical disorders

<table>
<tr><th>Parameter</th><th>In-patients N=139</th><th>Out-patients N=78</th></tr>
<tr><td>Gender M/F (%)</td><td>51.8/48.2</td><td>52.9/47.7</td></tr>
<tr><td>Mean age (years) ± SE</td><td>47.2±1.4</td><td>49.4±1.8</td></tr>
<tr><td>Total body surface area affected (%)</td><td>52±2</td><td>≤30</td></tr>
</table>
</td>
<td>Psoriasis Life Stress Inventory (PLSI)

Global self-ratings of psoriasis severity on a 10-point scale also obtained (items: redness, scaling/shedding, plaque thickness, itching and overall severity). Therefore, the total stress score could be 0-45

For the in-patients the dermatologic assessments and psychological ratings were obtained within the first week of admission at the onset of treatment</td>
<td>N/A</td>
<td>Internal consistency</td>
<td>None stated</td>
</tr>
</table>

				Out-patients were recruited from a database			

Effect size

Internal consistency

- High degree of internal consistency within all 15 items: α= 0.90

Correlations between PLSI score and patient self-ratings:

Measure	**Correlation (Pearson's r)**	**p-value**
Redness	0.15	0.04
Scaling/shedding	0.20	0.008
Plaque thickness	0.17	0.02
Itching	0.24	0.001
Overall severity	0.19	0.01

Site-specific involvement

- There was a significant correlation between PLSI scores and self-reported psoriasis severity for the following body sites (which tended to be associated with greater cosmetic disfigurement):
  - Scalp (r=0.23; p=0.003)
  - Face (r=0.20; p=0.02)
  - Neck (r=0.23; p=0.006)
  - Chest (r=0.28; p=0.0002)
  - Right arm (r=0.26; p=0.0009)
  - Right forearm (r=0.31; p=0.0001)
  - Right hand (r=0.18; p=0.02)
  - Left arm (r=0.23; p=0.003)
  - Left forearm (r=0.29; p=0.0002)
  - Left hand (r=0.17; p=0.04)
  - Back (r=0.28; p=0.0003)
  - Abdomen (r=0.25; p=0.001)

- Psoriasis severity affecting the shoulder, hips, groin, thigh, legs and feet did not correlate significantly with PLSI scores

Note that none of the above correlations demonstrate acceptable construct validity

Summary/author's conclusion

- The PLSI represents an index of the psychosocial morbidity associate with psoriasis
- This preliminary questionnaire needs to be tested in patient samples from different samples and in prospective studies

H.1.3.10 Study 10

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
Joana Ribeiro Costa de Faria, Aline Rezende Aarao, Luiz Miguel Zabaleta Jimenez, Oscar Hernandez Silva, and Joao Carlos Regazzi Avelleira. Inter-rater concordance study of the PASI (Psoriasis Area and Severity Index). Anais Brasileiros de Dermatologia 85 (5):625-629, 2010. Ref ID: FARIA2010	**Observational**: cross-sectional study Patients attending a psoriasis ambulatory clinic (august-October 2007) 20 patients were randomly selected	N = 20	**Stage of disease journey:** attending a psoriasis ambulatory with a wide range of psoriasis severity **Inclusion criteria:** aged 15-70 years; mild, moderate or severe disease **Exclusion criteria:** none stated Baseline characteristics not available	PASI Assessed by 3 post-graduate students of dermatology with similar experience and knowledge	N/A	Inter-rater reliability	None stated

Effect size

Inter-rater reliability

Comparison	n	ICC (95% CI)	p-value

Observer 1 vs 2	20	0.729 (0.440-0.882)	0.00007
Observer 1 vs 3	20	0.753 (0.481-0.894)	0.00003
Observer 2 vs 3	20	0.817 (0.601-0.923)	<0.00001

- The raters showed greater differences (lower reliability) for more severe patients

Summary/author's conclusion

- PASI is a reliable indicator of psoriasis severity because it shows significant concordance when independent evaluations are performed

H.1.3.11 Systematic review

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Robinson A, Kardos M, Kimball AB. Physician Global Assessment (PGA) and Psoriasis Area and Severity	**Systematic review of RCTs** 30 studies of biologic agents in moderate to severe psoriasis	Unclear – 30 RCTs	**Stage of disease journey:** biologic treatment **Inclusion criteria:** RCTs of biologics, phototherapy, ciclosporin or methotrexate that record both PASI75 and PGA 0 or 1 (only biologic trials were found)	PASI75	PGA 0 or 1 PGA was rated on a 6 or 7-point scale: • Clear • *Almost clear*	Reported for 8-16, 17-24 and >24 weeks	Correlation – construct validity	National Psoriasis Foundation

Index (PASI): Why do both? A systematic analysis of randomized controlled trials of biologic agents for moderate to severe plaque psoriasis. *J. Am. Acad. Dermatol.* 66(3):369-75, 2012. Ref ID: ROBINSON2012A	(2001-2010)		No baseline characteristics for participants		• Mild • Mild-to-moderate • Moderate • Moderate-to-severe • Severe			

Effect size

Construct validity – correlation of PASI75 and PGA 0 or 1

Adequate construct validity (Pearson's correlation coefficient)

- 8-16 weeks: r = 0.9157 (p<0.01)
- 17-24 weeks; r = 0.892 (p<0.01)
- >24 weeks; r = 0.9559 (p<0.01)

Note: the tools correlate more tightly with more efficacious therapy during the early treatment period. For the 8-16 weeks period the correlation was 0.9201 for studies with ≥25% achieving PASI75 but 0.0612 for studies where <25% achieved this response. For 17-24 weeks the correlations were 0.9017 and 0.9925,

respectively

Summary/author's conclusion

The two assessment tools are substantially redundant and either alone is a sufficient tool for assessing psoriasis severity in patients with moderate to severe disease. Because the PASI is better validated and more detailed, it remains the score of choice for clinical trials, but the simpler PGA may be well suited for community-based outcomes projects

H.2 Diagnostic tools for psoriatic arthritis

H.2.1 ToPAS vs clinical diagnosis by rheumatologist

Reference	Study type	Number of patients	Patient characteristics	Index test	Reference standard	Outcome measures	Source of funding
D. D. Gladman, C. T. Schentag, B. D. Tom, V. Chandran, J. Brockbank, C. Rosen, and V. T. Farewell. Development and initial validation of a screening questionnaire for psoriatic arthritis: the Toronto Psoriatic Arthritis Screen (ToPAS). Ann.Rheum.Dis. 68 (4):497-501, 2009.	Diagnostic cohort study (following initial development of the questionnaire) Five clinics (PsA, psoriasis, general dermatology, general rheumatology (excluding PsA patients) and family medicine) • **Patient selection:** consecutive patients; some patients already had a known diagnosis when the index test was performed and so would not be directly applicable to our question regarding an initial screen for psoriasis patients to identify potential PsA for referral to a rheumatologist • **Index test:** post-hoc selection of threshold could have been	**N: 688** (257 relevant to our population) 134 patients from the PsA clinic, 123 with psoriasis, 118 from dermatology, 135 from rheumatology and 178 from family medicine	**Inclusion criteria:** Patients attending clinics for PsA, psoriasis (attending for phototherapy, other day therapy or education), general dermatology or rheumatology or family medicine **Exclusion criteria:** not stated **PsA clinic (n=134)** / **Psoriasis clinic (n= 123)** Mean age (years): 49.6 ± 13.1 / 48.6 ± 13.4 M/F: 59.7/4 / 64·2/35.	Toronto PsA Screening Questionnaire (ToPAS); not designed solely for a psoriasis population Based on simplified weighted scoring omitting questions 7,8 and 11: the questions are grouped into 3 domains: score calculated as: *(skin domain) + (nail domain) + (2× joint*	Clinical diagnosis by trained rheumatologists according to standard protocol: complete history, physical exam, routine lab tests, rheumatoid factor, anti-nuclear factor Radiographs performed in all in PsA clinic but only if a clinical suspicion of arthritis in other clinics (ie. Joint or back pain or limitation of movement, or joint deformities) Assessments performed by 4 rheumatologists	**Primary outcomes measures:** Sensitivity and specificity **Secondary outcomes measures:** PPV and NPV (only reported for the total patient group – not our population)	Krembil Foundation

Ref ID: GLADMAN2009	to maximise sensitivity and/or specificity and may lead to overoptimistic measures of test performance; also, post-hoc weighting and question selection used to optimise results • **Reference standard:** rheumatological assessment according to standard protocol; unclear if blinded to index test results • **Flow and timing:** index test prior to reference test; all patients analysed by index and reference test (but not all had radiographs); time between tests unclear but likely to be the same day as patients recruited during clinic visit		(%) 0.3 8	*domain)* **Domain scores** Skin: 0-3; joint: 0-3; nail: 0 or 1 Threshold of ≥8 for classifying as PsA means that a patient must score ≥2 on the joint domain	but the majority (77%) were conducted by a single rheumatologist **Diagnosis** of PsA: inflammatory arthritis in the presence of psoriasis **Note**: subsequent application of CASPAR criteria proved them to be sensitive and specific in these patients		

Effect Size

Clinical diagnosis, n	**PsA**	**No PsA**
PsA clinic (N=134)	134	0
Psoriasis clinic (N= 123)	30	93

Sensitivity and specificity of ToPAS in a combined patient group from PsA and psoriasis clinics (based on a threshold score of ≥8 for classifying as PsA):

- Sensitivity: 89.1 (83.0-93.2)% => 10.9% of those **with** PsA would not be detected
- Specificity: 86.3 (76.4-92.5)% => 13.7% of those **without** PsA would be inappropriately referred

2 x 2 table

	Reference test +ve	**Reference test -ve**
Index test +ve	TP: 146	FP: 13
Index test -ve	FN: 18	TN: 80

Summary statistic	
Pre-test probability/prevalence	0.64
PPV	91.8%
NPV	81.6% (18.4% probability of having PsA)
LR +	6.37
LR-	0.13

Authors' conclusion:

- The simplified ToPAS index is very good at classifying those who are and are not diagnosed with PsA

H.2.2 PASE vs clinical diagnosis by rheumatologist

Reference	Study type	Number of patients	Patient characteristics	Index test	Reference standard	Outcome measures	Source of funding
M. E. Husni, K. H. Meyer, D. S. Cohen, E. Mody, and A. A. Qureshi. The PASE questionnaire: pilot-testing a psoriatic arthritis screening and evaluation tool. *J.Am.Acad.Dermatol.* 57 (4):581-587, 2007. Ref ID: HUSNI2007	Diagnostic cohort study (following initial development of the questionnaire) • **Patient selection:** difficult diagnoses based on clinical assessment excluded from the study; unclear if patient selection method is appropriate; unclear if PsA diagnosis already known prior to selection for PASE testing • **Index test:** post-hoc selection of threshold to optimise sensitivity and/or specificity and may lead to overoptimistic measures of test performance • **Reference standard:** rheumatological assessment according to standard protocol; unclear if blinded to index test results • **Flow and timing:** all patients	**N: 69** Patients with missing data on >1 question excluded from analysis	**Inclusion criteria:** diagnosis of psoriasis **Exclusion criteria:** patients on systemic therapy; concomitant PsA and OA **Mean baseline** / **All (n=69)** Mean age (years): 51 M/F (%): 49/51	Psoriatic Arthritis Screening and Evaluation (PASE); self-administered Possible range 15-75 (each of 15 questions scored as either 1: strongly disagree; 2: disagree; 3: neutral; 4: agree; 5: strongly agree)	Clinical diagnosis on the basis of joint exam (including presence of dactylitis and/or synovitis and/or nail pitting), clinical history including history of morning stiffness and radiographs based on Moll and Wright Criteria; plus evaluation by a rheumatologist	**Primary outcomes measures:** Sensitivity and specificity **Secondary outcomes measures:** Median scores in subgroups	Bringham and Women's Hospital

	received index and reference test (but unclear if all results analysed/if all questionnaires were adequately completed); time between tests unclear (reference standard may have been performed at variable times prior to index test if diagnosis made before clinic visit)						

Effect Size

Clinical diagnosis	**N (%)**
PsA (N=69)	
PsA	17 (24.6%)
Non-PsA	52 (75.4%)
OA only	24 (34.8%)
Severe* PsA (n=17)	
PsA	10 (58.8%)
Severe PsA	7 (41.2%)

**Defined as PsA of the mutilans type or those who required immediate DMARD therapy based on erosions found on imaging*

There was a statistically significant difference in median scores (total, symptom and function) between:

- patients with and without PsA; all 3 scores were higher in PsA cases (p<0.001)
- patients with PsA and OA; all 3 scores were higher in PsA cases (symptom and function scores: p=0.01; total score: p=0.007)
- patients with non-severe PsA and severe PsA; all 3 scores were higher in severe PsA cases (symptom score: p=0.02; function score: p=0.051 (NS); total score: p=0.02)

Sensitivity and specificity of PASE in psoriasis population (based on a threshold score of 47 for classifying as PsA):

- **Sensitivity**: 82.4 (57-96)% => 17.6% of those **with** PsA would not be detected
- **Specificity**: 73.1 (59-84)% => 26.9% of those **without** PsA would be inappropriately referred
- **AUC** for *total* score = 0.84
- **AUC** for *function* score = 0.84
- **AUC** for *symptom* score = 0.80

	Reference test +ve	**Reference test -ve**
Index test +ve	TP: 14	FP: 14
Index test -ve	FN: 3	TN: 38

Summary statistic	
Pre-test probability/prevalence	0.25
PPV	50.0%
NPV	92.7% (7.3% probability of having

	PsA)
LR +	3.06
LR-	0.24

Authors' conclusion:

- The PASE questionnaire is a self-administered tool that can be used to screen for PsA among patients with psoriasis.
- PASE can distinguish between symptoms of PsA and osteoarthritis.
- A larger study is needed to validate PASE in dermatology clinics in the community.

H.2.3 PASE vs clinical diagnosis by rheumatologist using Moll and Wright criteria

Reference	Study type	Number of patients	Patient characteristics	Index test	Reference standard	Outcome measures	Source of funding
P. L. Dominguez, M. E. Husni, E. W. Holt, S. Tyler, and A. A. Qureshi. Validity, reliability, and sensitivity-to-change properties of the psoriatic arthritis screening and evaluation questionnaire. Archives of Dermatological Research 301 (8):573-579, 2009. Ref ID: DOMINGUEZ 2009	Diagnostic cohort study Brigham and Women's Hospital dermatology clinic, arthritis clinic, and a dermatology–rheumatology combined clinic (MA, USA) • **Patient selection:** unclear if patient selection method is appropriate (approached by study staff – may not be consecutive); PsA diagnosis new in the majority of participants and if not no Tx for PsA received (applicable) • **Index test:** post-hoc selection of threshold to optimise sensitivity and/or specificity and may lead to overoptimistic measures of test performance • **Reference standard:**	**N: 194** 4 patients with missing data on >1 question excluded from analysis (if one item left blank it was scored as 0)	**Inclusion criteria:** psoriasis or PsA; 18-85 years; **Exclusion criteria:** patients on systemic therapy; concomitant PsA and OA **Note**: concomitant diagnosis of other arthritides not excluded **Description** **Category** M/F (%) 57.8/42.1 Race/ethnicity (n) Caucasian 138 African–American 8	Psoriatic Arthritis Screening and Evaluation (PASE); self-administered while waiting to be seen by physician Possible range 15-75 (each of 15 questions scored as either 1: strongly disagree; 2: disagree; 3: neutral; 4: agree; 5: strongly agree) Usually	Clinical diagnosis by rheumatologist on the basis of Moll and Wright Criteria: the patient's history and clinical exam, including tender and swollen joint count, the presence of dactylitis, and/or nail pitting, as well as history of morning stiffness, and review of radiographs when available. A rheumatologist who employed the Moll and Wright criteria reviewed all cases to determine case from non-case. The majority of PsA	**Primary outcomes measures:** Sensitivity and specificity **Secondary outcomes measures:** Test-retest reliability; sensitivity to change	National Institute of Arthritis and Musculoskeletal and Skin Diseases

	rheumatological assessment according to standard protocol; unclear if blinded to index test results • **Flow and timing:** 4 patients with missing data on >1 question excluded from analysis; time between tests unclear (reference standard may have been performed at variable times prior to index test if diagnosis made before clinic visit)		Hispanic 3 Asian 1 Multiracial 3 Other 25 Unknown 12 PsA diagnosis (n) Non-PsA 153 PsA 37 Co-morbid conditions (n) Rheumatoid arthritis 7 Gout 13 Osteoarthritis 29	completed within 4-6 min	cases were new. Existing cases of PsA had not received therapy.		

Effect Size

- Total PASE score ranged from 15-74

There was a statistically significant difference in median scores (total, symptom and function) between:

- patients with and without PsA; all 3 scores were higher in PsA cases ($p<0.001$)

- patients with PsA and OA; all 3 scores were higher in PsA cases (symptom score: p=0.014; function score: p=0.082 (NS); total score: p=0.039) – *Note: 6 participants with **both** PsA and OS excluded from this analysis*

Sensitivity and specificity of PASE in psoriasis population (based on a threshold score of 44 for classifying as PsA):

- **Sensitivity**: 76 (59-88)% => 24% of those **with** PsA would not be detected
- **Specificity**: 76 (68-82)% => 24% of those **without** PsA would be inappropriately referred
- **AUC** for *total* score = 0.797
- **AUC** for *function* score = 0.759
- **AUC** for *symptom* score = 0.814

	Reference test +ve	**Reference test -ve**
Index test +ve	TP: 28	FP: 37
Index test -ve	FN: 9	TN: 116

Summary statistic	
Pre-test probability/prevalence	0.195
PPV	43.1%
NPV	92.8% (7.2% probability of having PsA)
LR +	3.13
LR-	0.32

Sensitivity and specificity of PASE in psoriasis population (based on a threshold score of 47 as determined in the Husni study for classifying as PsA):

- **Sensitivity**: 70 (53-84)% => 30% of those **with** PsA would not be detected
- **Specificity**: 80 (73-86)% => 20% of those **without** PsA would be inappropriately referred

	Reference test +ve	**Reference test -ve**
Index test +ve	TP: 26	FP: 31
Index test -ve	FN: 11	TN: 122

Summary statistic	
Pre-test probability/prevalence	0.195
PPV	45.61%
NPV	91.7% (8.3% probability of having PsA)
LR +	3.47
LR-	0.37

Sensitivity and specificity of PASE in psoriasis population excluding those with quiescent or asymptomatic PsA (n=180; 10 excluded) (based on a threshold score of 47 for classifying as PsA):

- **Sensitivity**: 93 (78-99)% => 7% of those **with** PsA would not be detected
- **Specificity**: 80 (73-86)% => 24% of those **without** PsA would be inappropriately referred

	Reference test +ve	Reference test -ve
Index test +ve	TP: 25	FP: 31
Index test -ve	FN: 2	TN: 122

Summary statistic	
Pre-test probability/prevalence	0.15
PPV	44.6%
NPV	98.4% (1.6% probability of having PsA)
LR +	4.57
LR-	0.09

Note: The PASE questionnaire missed nine participants with PsA because their total PASE score was below the 44 score cut-off for PsA. Of these nine participants, four had limited disease, two had quiescent disease, one had axial involvement, one participant received multiple intra-articular injections 10 days prior to PASE administration and another participant had been off systemic therapy for 5 months but began flaring at the time of PASE administration.

Another 37 participants were screening test-positive for PsA but did not have the disease. Of these 37 participants, 18 had a history of other musculoskeletal conditions such as severe osteoarthritis/degenerative joint disease, spinal stenosis, carpal tunnel syndrome, chondromalacia, muscle strain, and muscle sprain. Another seven participants had undifferentiated arthritis, four had gout, two had fibromyalgia, one had peripheral neuropathy, one had spondyloarthropathy, and one had lupus. The authors did not have access to the medical records of the three remaining individuals.

Authors' conclusion:

- Administration of a well-designed and validated screening tool can increase detection of PsA in psoriasis patients, determine the prevalence of PsA in a given population; capture clinical data for genotype–phenotype studies, and monitor response to therapy.
- The PASE questionnaire is a valid and reliable tool to screen for active PsA among individuals with psoriasis and may be used as a marker of therapeutic response after systemic therapy.

H.2.4 PAQ vs clinical diagnosis by rheumatologist

Reference	Study type	Number of patients	Patient characteristics	Index test	Reference standard	Outcome measures	Source of funding
G. M. Alenius, B. Stenberg, H. Stenlund, M. Lundblad, and S. R. Dahlqvist. Inflammatory joint manifestations are prevalent in psoriasis: prevalence study of joint and axial involvement in psoriatic patients, and evaluation of a psoriatic and arthritic questionnaire. J.Rheumatol. 29 (12):2577-2582, 2002. Ref ID: ALENIUS2002	Diagnostic cohort study Hospital and community-based population • **Patient selection:** patient selection appropriate (invited all eligible from register); patients with known arthritic disease excluded to assess relevant screening population • **Index test:** prior to reference standard; post-hoc selection of threshold to optimise sensitivity and/or specificity and may lead to overoptimistic measures of test performance	**N: 276** 74 patients (22.8%) dropped out (46 did not answer the questionnaire; 28 did not wish to participate in follow-up study)	**Inclusion criteria:** diagnosis of psoriasis by dermatologist or GP; >16 years **Exclusion criteria:** patients with known arthritic disease **Mean** / **Peripheral arthritis and/or axial disease (n=67)** / **Non-arthritic (n=135)** Age (years): 54.4 ± 14.4 / 50.4 ± 14.4 Duration of skin: 29.7 ± 14.3 / 24.8 ± 13.9	Psoriatic and Arthritic Questionnaire (PAQ); self-administered Question 3 removed because not relevant when selected patients known not to have diagnosed arthritis Possible range 0-8 Modified PAQ; weighted	Clinical diagnosis by rheumatologist : the patient's history and clinical exam Diagnostic criteria: Peripheral arthritis: tender and swollen joint >6 wk, located outside the spine and/or SI joints Sacroiliitus: radiological grading of SI joints according to New York Criteria (≥grade 2) **Note**: radiographic assessment	**Primary outcomes measures:** Prevalence, sensitivity and specificity **Secondary outcomes measures:** PPV, NPV	Swedish psoriasis association, Medial Faculty of University of Umea and King Gustav V 80-year foundation

	• **Reference standard:** rheumatological assessment according to standard protocol; unclear if blinded to index test results • **Flow and timing:** 74 patients (22.8%) dropped out (46 did not answer the questionnaire; 28 did not wish to participate in follow-up study); time between tests unclear (but index test appears to have been sent out by post so would have been some delay)		disease (years)			scoring giving the questions that most strongly predicted arthritis a double score Possible range 0-9	performed in patients with any history of back pain and/or decrease mobility of the spine; and those with peripheral arthritis (but not all consented to radiography) Axial disease: radiological sacroiliitis and/or syndesmophytes, ligamentous ossification, vertebral squaring and shining corners of the spine Undifferentiated SpA: inflammatory back pain and decreased mobility of the spine in at least 2 directions without fulfilling criteria for sacroiliitis or axial disease Enthesitits: signs of tenderness, swelling,		

					redness, warmth, loss of function, and/or radiographic destruction at the insertion site of the Achilles tendon, plantar fascia and lateral or medial epicondoyle Blood as collected to measure erythrocycte sedimentation rate, CRP, orosomucoid, haptoglobin and RF		

Effect Size

Clinical diagnosis

	All (N=202)	Active disease n (%)

	n (%)	
No joint disease	78 (38.6)	
Peripheral arthritis	45 (22.3)	23 (51.1)
Axial disease	9 (4.5)	4 (44.4)
Peripheral + axial disease	13 (6.4)	11 (84.6)
Undifferentiated SpA	12 (5.9)	5 (41.7)
Peripheral enthesitis/tenosynovitis	18 (8.9)	8 (44.4)
Other joint complaints	27 (13.4)	

Moll and Wright Classification

	All (N=202) n (%)	**Female (n=100)**	**Male (n=102)**	**Active disease n (%)**
DIP joint disease, exclusively	0	0	0	
Axial disease	15 (7.4)	15	15	10 (66.7)
Mono/oligoarthritis	30 (14.6)	12	15	15 (50)
Polyarthritis	21 (10.4)	0	9	12 (57.1)
Mutilans arthritis, exclusively	1	0	1	1 (100)

Sensitivity and specificity of PAQ in psoriasis population (based on a threshold score of ≥4 for predicting **peripheral arthritis and/or axial disease**):

- **Sensitivity**: 60% => 40% of those **with** PsA would not be detected
- **Specificity**: 62.2% => 37.8% of those **without** PsA would be inappropriately referred
- **AUC =** 0.640
- **OR =** 2.343 (1.224-4.482; p = 0.010)

Note: Only 30 of the 67 with PsA were newly diagnosed and included in analysis

	Reference test +ve	**Reference test -ve**
Index test +ve	TP: 18	FP: 51
Index test -ve	FN: 12	TN: 84

Summary statistic	
Pre-test probability/prevalence	0.182
PPV	26.09%
NPV	87.50% (12.5% probability of having PsA)
LR +	1.59
LR-	0.64

PAQ score	Sensitivity		Specificity		PPV (%)		NPV (%)	
	Population A	Population B	Population A	Population B	Population A	Population B	Population A	Population B
≥3	73.3	83.6	44.4	52.6	22.7	46.7	88.2	86.6
≥4	60.0	82.1	62.2	57.0	26.1	48.7	87.5	86.5
≥5	46.7	77.6	72.6	65.9	27.5	53.1	86.0	85.6
≥6	30.0	68.7	83.0	77.8	28.1	60.5	84.2	83.3
≥7	16.7	53.7	91.1	86.7	29.4	66.7	83.1	79.1
≥8	10.0	41.8	97.0	94.1	42.9	77.8	82.9	94.1

Population A: *PAQ score excluding patients with known arthritis and the third question*

Population B: *Total population including all patients and all questions*

Sensitivity and specificity of PAQ in psoriasis population (based on a threshold score of ≥4 for predicting **any inflammatory manifestation**):

- **Sensitivity**: 55% => 45% of those **with** PsA would not be detected
- **Specificity**: 65.7% => 34.3% of those **without** PsA would be inappropriately referred
- **AUC =** 0.647
- **OR =** 2.471 (1.100-5.548; p = 0.028)

	Reference test +ve	Reference test -ve

Index test +ve	TP: 33	FP: 36
Index test -ve	FN: 27	TN: 69

Summary statistic	
Pre-test probability/prevalence	0.364
PPV	47.83%
NPV	71.88% (28.12% probability of having PsA)
LR +	1.60
LR-	0.68

Sensitivity and specificity of **modified PAQ** (with weighted scoring giving the questions that most strongly predicted arthritis a double score) in psoriasis population (based on a threshold score of ≥5 for predicting **peripheral arthritis and/or axial disease**):

- **Sensitivity**: 50% => 50% of those **with** PsA would not be detected
- **Specificity**: 73.3% => 26.7% of those **without** PsA would be inappropriately referred
- **PPV**: 29.4%
- **NPV**: 86.8%

	Reference test +ve	**Reference test -ve**

Index test +ve	TP: 15	FP: 36
Index test -ve	FN: 15	TN: 99

Summary statistic	
Pre-test probability/prevalence	0.182
PPV	29.41%
NPV	86.84% (28.12% probability of having PsA)
LR +	1.88
LR-	0.68

Sensitivity and specificity of **modified PAQ** (with weighted scoring giving the questions that most strongly predicted arthritis a double score) in psoriasis population (based on a threshold score of ≥5 for predicting **any inflammatory manifestation**):

- **Sensitivity**: 45% => 55% of those **with** PsA would not be detected
- **Specificity**: 77.1% => 22.9% of those **without** PsA would be inappropriately referred
- **PPV**: 52.9%
- **NPV**: 71.1%

	Reference test +ve	**Reference test -ve**
Index test +ve	TP: 27	FP: 24
Index test -ve	FN: 33	TN: 81

Summary statistic	
Pre-test probability/prevalence	0.364
PPV	52.94%
NPV	71.05% (28.95% probability of having PsA)
LR +	1.97
LR-	0.71

Authors' conclusion:

- The PAQ did not discriminate for arthritis in this population with psoriasis.

H.2.5 PEST and PAQ vs clinical diagnosis by rheumatologist

Reference	Study type	Number of patients	Patient characteristics	Index test	Reference standard	Outcome measures	Source of funding
G. H. Ibrahim, M. H. Buch, C. Lawson, R. Waxman, and P. S. Helliwell. Evaluation of an existing screening tool for psoriatic arthritis in people with psoriasis and the development of a new instrument: the Psoriasis Epidemiology Screening Tool (PEST) questionnaire. *Clin.Exp.Rheumatol.* 27 (3):469-474, 2009.	Diagnostic cohort study plus extra pre-diagnosed cases Hospital and community-based populations • **Patient selection:** patient selection of main sample from GP database (all eligible were sent the questionnaire by post and 1 in 2 sample of respondents clinically examined); separate series of consecutive patients with known PsA also invited to complete the questionnaire • **Index test: PEST –** prior to reference standard; unclear method of selection of threshold • **Comparator test: PAQ –** no details of when administered or to whom	**N: 168** questionnaire returned (27% response rate) 1 in 2 sample of alternate respondents invited for hospital examination = **93** examined Plus separate sample of **21** known PsA cases	**Inclusion criteria:** diagnosis of psoriasis by dermatologist or GP **Exclusion criteria:** not stated **Mean** / **Newly diagnosed PsA (n=12)** Age (years): 54.9 ± 9.2 Duration of skin disease (years): 31.8 ± 17.9 Duration: 19.2 ± 15.1	Psoriasis Epidemiology Screening Tool (PEST) and the Alenius modified Psoriatic and Arthritic Questionnaire (PAQ); self-administered	Clinical diagnosis by rheumatologist : the patient's history and clinical exam (tender/swollen/damaged joint count) similar to CASPAR criteria Skin also assessed using PASI Blood as collected to measure CRP and RF, plus x-ray of hand, feet, pelvis and lumbar spine in first 20 patients found to be normal, so subsequent	**Primary outcomes measures:** Sensitivity and specificity **Secondary outcomes measures:** PPV, NPV	None stated

Ref ID: IBRAHIM2009	• **Reference standard:** rheumatological assessment according to standard protocol (similar to CASPAR criteria); unclear if blinded to index test results • **Flow and timing:** 168 sent questionnaire; 1 in 2 sample of alternate respondents invited for hospital examination = 93 examined Separate sample of 21 known PsA cases (used for assessment of diagnostic performance) also included; time between tests unclear (but index test sent out by post so would have been some delay); not all patients included in the analysis of PAQ (108/114) and unclear why the 6 were excluded	(unclear if these were just used for questionnaire design or also for assessment of diagnostic performance)	of joint disease (years) PASI 2.1 ± 2.0			participants only had these tests if thought to have PsA	

Effect Size

Clinical diagnosis

	All (N=93)
No joint disease	12
PsA	12

OA	26
Mechanical low back pain	18
Unclassified polyarthralgia	12
Hypermobility syndrome	3
Regional pain syndrome	5
Other	5

PEST manikin results

- Median number of joints ticked: PsA = 8; other diagnosis = 4

	AUC (95% CI)	**Sensitivity**	**Specificity**
Alenius modified PAQ (threshold ≥4)	0.76 (0.69-0.85)	0.63	0.72
PEST (threshold ≥3)	0.91 (0.86-0.97)	0.92	0.78

2 x 2 table for PEST (N=114)

	Reference test +ve	**Reference test -ve**
Index test +ve	TP: 30	FP: 19
Index test -ve	FN: 3	TN: 62

Summary statistic	
Pre-test probability/prevalence	0.289
PPV	61.22%
NPV	95.38% (4.62% probability of having PsA)
LR +	3.88
LR-	0.12

2 x 2 table for mPAQ (N=108)

	Reference test +ve	**Reference test -ve**
Index test +ve	TP: 20	FP: 21
Index test -ve	FN: 12	TN: 55

Summary statistic	
Pre-test probability/prevalence	0.296
PPV	48.78%
NPV	82.09% (17.91% probability of having PsA)

LR +	2.26
LR-	0.52

Authors' conclusion:

- A new screening tool for identifying people with psoriatic arthritis has been developed. Five simple questions demonstrated good sensitivity and specificity in this population but further validation is required.

H.3 Specialist referral for psoriatic arthritis

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
D. Kane, L. Stafford, B. Bresniham, O. FitzGerald. A prospective, clinical and radiological study of early psoriatic arthritis: an early synovitis clinic experience.	Inception cohort (prospective) Ireland/Scotland August 1994 – March 2000 Representative: Loss to follow-up:	1018 Patients presenting to Early Synovitis Clinic 129 (12/7%) diagnos	Patients referred to early arthritis clinic with joint tenderness in association with either active joint swelling or an elevated acute-phase response, **symptom duration <2 years**. RF factor titre < 1/80. Diagnosis of PsA confirmed by consultant rheumatologist using Moll & Wright criteria	Clinical assessment Baseline radiographs	2 years	RAI EULAR HAQ Pain	Not stated

Rheumatology. 42:1460-1468.2003 REF ID: KANE2003	10 patients (8%) at 1 year 31 patients (25%)at 2 years 119 patients followed up at 1 yr 97 patients followed up at 2 yr	ed with PsA	53% male, 47% female Mean age at presentation 41.2 ±15.1 years Mean duration of disease at presentation 9.9 ±15.1 months Median delay from symptom onset to rheumatology referral 5.75-7 months			DMARD use Swollen joints Radiological assessment – Sharp Remission: defined by absence of fatigue, stiffness <15 min, no joint pain, complete absence of joint tenderness or swelling (including dactylitis and enthesitis) on examination and ESR <20 mm/h (males) or ESR <30 mm/h (females)	

Effect size

At presentation 52 (40%) had olgioarticular PsA, 77 (60%) had polyarticular disease

ACR class at presentation: I: 39 (34%), II: 38 (32%), III: 33 (28%), IV 7 (6%)

Mean HAQ score at presentation 0.71 ±0.64, at 1 yr 0.4 ±0.6, 2 yr 0.4 ±0.6

Overall decrease in all clinical and lab parameters of inflammation at 1 and 2 yr.

	0 yr	**1 yr**	**2 yr**
No. of patients	*n* = 129	*n* = 119 (92%)	*n* = 97 (75%)
DMARD	15 (12%)	70 (59%)	54 (56%)
Corticosteroids	14 (11%)	6 (5%)	5 (5%)
VAS pain	4.8 (5) ± 2.7 (*n* = 122)	3.1 (2) ± 3 (*n* = 119)	3.4 (4) ± 2.7 (*n* = 97)
ACR class III/IV	40 (34%) (*n* = 117)	22 (19%) (*n* = 118)	16 (16%) (*n* = 97)
HAQ score	0.7 (0.6) ± 0.6 (*n* = 74)	0.4 (0.1) ± 0.6 (*n* = 65)	0.4 (0.1) ± 0.6 (*n* = 58)
Ritchie Index	5.6 (4) ± 6	2.4 (1) ± 3.8	1.9 (1) ± 3
Swollen joint count	6.9 (4) ± 8	2.9 (1) ± 5.2	2.4 (1) ± 4.1
ESR (mm/h)	24 (16) ± 27 (*n* = 124)	13 (7) ± 15 (*n* = 112)	12 (7) ± 14 (*n* = 94)
CRP (mg/l)	28 (10) ± 59 (*n* = 112)	10 (5) ± 14 (*n* = 111)	8 (4) ± 12 (*n* = 94)
Enthesopathy	29 (38%)	15 (13%)	25 (26%)
Dactylitis	37 (29%)	10 (8%)	16 (16%)

Remission	0	31 (26%)	20 (21%)

Remission in 26% of patients at 1 yr, 21% of patients at 2 yr

Spontaneous (DMARD-free) remission in only 11-12% of patients

Radiological:

At baseline, 32/117 (27%) of patients had erosions, 24 (19%) of patients had joint space narrowing and 22 (19%) of patients had periostitis

After median 24 months follow-up, 40/86 (47%) of patients had erosions (despite early DMARD use), 32 (37%) had joint space narrowing and 25 (29%) of patients had periostitis

Baseline (*n* = 117)	Follow-up (*n* = 86)	
Total number of joints with erosions		
Hands	75/3510 (2.1%)	100/2580 (3.9%)
Feet	26/1170 (2.2%)	53/860 (6.2%)
Mean no. of joints with erosions per patient ± S.D.		
Hands	0.7 ± 1.6	1.2 ± 2.5
Feet	0.2 ± 0.8	0.6 ± 1.6
Total number of joints with joint space narrowing		
Hands	71/3510 (2.0%)	62/2580 (2.4%)
Feet	14/1170 (1.2%)	35/860 (4.1%)

Mean no. of joints with joint space narrowing per patient ± S.D.

Hands	0.6 ± 2.3	0.7 ± 1.7
Feet	0.1 ± 0.5	0.4 ± 1.4

Mean sharp score at baseline 1.2 ±2.9, mean narrowing score (hands/feet) at baseline 1.4 ±5.3

Mean Sharp score increased to 3 ±5.2 (P=0.002), mean narrowing score increased to 3.2 ±7.5 (P=0.04)

Sacroileitis present in 16 (17%) of patients

Significant functional impairment at early stage

Author conclusion: PsA is a chronic disease with significant functional impairment and radiological damage at an early stage in the course of the disease

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

<table>
<tr>
<td>L. Punzi, M. Pianon, P. Rossini, F. Schiavon, P. F. Gambari. Clinical and laboratory manifestations of elderly onset psoriatic arthritis: a comparison with younger onset disease. Ann Rheum Dis. 58:226-229. 1999

REF ID: PUNZI1999</td>
<td>Prospective study

Italy

Elderly vs. younger onset disease</td>
<td>66 consecutive PsA patients</td>
<td>PsA patients with disease duration <1 year: 16 elderly onset PsA (>60 yrs), 50 younger onset PsA (≤60 yrs).

RF +ve patients excluded

<table>
<tr><td></td><td>EOPsA</td><td>YOPsA</td></tr>
<tr><td>M/F</td><td>8/8</td><td>23/27</td></tr>
<tr><td>Mean age at onset, y</td><td>65.1 ±6.7</td><td>44.2 ±11.1</td></tr>
</table>
</td>
<td>Disease duration</td>
<td>2 years</td>
<td>Clinical
Laboratory
Radiographic</td>
<td>Not stated</td>
</tr>
<tr>
<td colspan="8">Effect size
DMARD (SAARD) at 2 years: 42/50 (84%) in YOPsA patients, 15/16 (94%) EOPsA patients
Mean ±SD number of radiographic erosions in hands at presentation: 2.3 ±2.1 (EOPsA), 2.2 ±2.2 (YOPsA)
Mean ±SD number of radiographic erosions in hands after 2 years: 4.4 ±3.0 (EOPsA), 2.7 ±2.0 (YOPsA)

Mean ±SD number of radiographic erosions in feet at presentation: 2.7 ±1.2 (EOPsA), 1.1 ±1.1 (YOPsA)</td>
</tr>
</table>

Mean ±SD number of radiographic erosions in feet after 2 years: 4.7 ±2.2 (EOPsA), 2.1 ±1.2 (YOPsA)

Higher number of active joints in elderly vs young onset PsA at both baseline (12.2±6.3 vs 6.7±6.6; p<0.001) and 2-year follow-up (8.1±4.2 vs 4.7±3.6; NS)

Mean ESR decreased from 64.2 ±65.3 mm/h at baseline to 38.4 ±15.2 mm/h after 2 years' follow-up in Elderly Onset PsA patients and a more modest decrease from 3
±30.0 mm/h to 26.3 ±15.0 mm/h in Younger Onset PsA patients. Mean CRP levels also decreased in both groups: 3.9 ±2.0 mg/l to 2.2 ±1.0 mg/l in Elderly Onset PsA an
±1.3 mg/l to 0.9 ±0.9 mg/l in Younger Onset PsA patients.

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
B. J. Harrison, A. J. Silman, E. M. Barrett, D.G.I. Scottt, D.P.M. Symmons. Presence of psoriasis does not influence the presentation or short term outcome of patients with early inflammatory	Primary care inception cohort Norfolk, UK 1989	966 patients referred to Norfolk Psoriasis Registry 51 patients with psoriasis	Patients ≥16 years old with early inflammatory polyarthritis (swelling of at least 2 joint areas that has persisted for a minimum of 4 weeks) and psoriasis in a primary care population. 49% male, 51% female Median age at psoriasis onset 52 years Median duration of arthritis at	Clinical assessment Lab markers Radiographs	1 year	Total number of swollen joints DMARD use Remission	Not stated

polyarthrtitis. *J Rheumatol*. 24:1744-9.1997 REF ID: HARRISON1997			presentation 5.75 months Note: approximately 50% had RA not PsA			HAQ score Radiographs	

Effect size

	Baseline	1 year
Second line drugs/steroids		**21 (41%)**
Median HAQ	**0.63**	**0.44**
Median swollen joints	**7 (0-32)**	**4 (range: 0-16)**
Remission		**3 (6%)**
Radiological erosions		**7/32 (22%)**

Reference	Study type	Number of	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source

		patients					of funding
R. Queiro-Silva, J.C. Torre-Alonso, T. Tinture-Eguren, I. Lopez-Lagunas. A polyarticular onset predicts erosive and deforming disease in psoriatic arthritis. *Ann Rheum Dis*. 62:68-70.2003 REF ID: QUEIROSILVA2003	Prospective cohort – consecutive sample Spain 1991-2001	71 patients	Patients with PsA 44 men, 27 women Mean disease duration at presentation 12 ± months (without radiographical evidence of erosions at presentation) Mean age 47 ±12 years	Disease duration	10 years	ACR HAQ Lab values Radiographs	Not stated

Effect size

During first 6 months 5 patients (7%) had isolated DIP disease

30 (42%) oligoarthritis

20 (28%) polyarhtritis

16 (23%) axial disease

0 arthritis mutilans

At end of study (10 years)

28 (39%) showed oligoarthritis

24 (34%) polyarthritis

17 (24%) axial disease

2 (3%) arthritis mutilans

32/71 (45%) had developed erosive and deforming arthritis

Mean time to detect erosions or narrowing of joint spaces was 20±4 months (SD)

HAQ (unclear if at baseline or follow-up): 1.2 (0.3) in those with erosive (n=32) vs 0.6 (0.4) in non erosive (n=39) (p=0.012)

NS difference in between number of months duration of arthritis (8 ±7 months versus 10±6 months) for erosive and non-erosive disease

DMARD use in 68% of patients

Author conclusion: we support the use of DMARDs as early as possible, particularly in patients with polyarticular onset

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
N.J. McHugh, C. Balachrishnan, S.M. Jones. Progression of peripheral joint disease in psoriatic arthritis: a 5-year prospective study. *Rheumatology*. 42:778-783.2003 REF ID: MCHUGH2003	Prospective follow-up study Bath, UK Baseline information collected between 1987 and 1990 87% available for full follow-up	87 patients ; 13 patients with arthritis < 1 year duration	Patients attending a PsA clinic (established/new onset) 25% referrals from primary care, <10% from dermatology 49 females, 38 males Median age in years at follow-up (range) 53.5 (2-85) Median disease duration at baseline: 11 years (IQR 3.5-17 years), **subgroup analysed with arthritis within 1 year of baseline**	Disease duration	Median 65 months (range 39-90)	Rates of progression of peripheral joint score (0-70) Joint score PASI HAQ Radiographs	Jules Thor Charitable Trust Remedi U
Effect size **13 patients with <12 months duration of arthritis** Median joint score at baseline: 4 (IQR 2.3-10) Median joint score at follow-up: 7 (IQR 4.3-13)							

Rate of peripheral joint progression significantly higher in this group up to baseline assessment compared with the rate of the joint progression in the same patients ov
subsequent years of follow-up (4.0 vs. 0.32, P=0.003)

Highest rate of peripheral joint involvement appeared to be within 12 months of disease onset, but steady progression of peripheral joint involvement among those referred to a clinic – 0.4 joints per year)

Median rates of joint progression according to age of onset or stage of arthritis (interquartile ranges are given in parentheses)

	Total PsA group (*n*=87)	Arthritis within 1 yr of baseline (n=13)
Duration of arthritis at baseline (yr)	11 (3.5–17)	<12 months
Joint score at baseline	6 (2–15)	4 (2.3–10)
Change in joint involvement to baseline	0.88 (0.33–1.7)	4* (2.3–10)
Joint score at follow-up	11 (4.5–24)	7 (4.3–13)
Change in joint involvement to follow-up	0.76 ((0.28–1.3)	1.2 (0.6–2.4)
Change in joint involvement from baseline to follow-up	0.43 (0–1.3)	0.32 (0–1)

Full group (not just early onset; median duration at baseline = 11 years)

% of patients with erosions in hand or wrist increased from 53 to 68%, and erosive foot disease increased from 37 to 44%

% taking MTX: at baseline (referral) = 12% vs 15% at follow-up

4/87 patients in remission at follow-up Mean HAQ score at baseline 0.375, at follow-up 0.5 (p<0.001) Author conclusion: although a disproportionately high number of peripheral joints are involved in the first 12 months following disease onset, there is a steady progression of peripheral joint involvement in patients with PsA who are referred to a hospital clinic

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
S.J. Bond, V.T. Farewell, C.T. Schentag, D.D. Gladman. Predictors for radiological damage in psoriatic arthritis: results from a single centre. *Ann Rheum Dis*. 66:370-376. 2007	Prospective cohort Toronto 1978 – 2004 Analysis: corrected for within-patient correlation Adjusted for: Sex, age, arthritis duration, functional class, ESR, tender joint count, swollen	625 patients	Patients referred to University of Toronto PsA Clinic Baseline characteristics: Female/male 272/353 Median (range) age (years) 34 (9–86) Median (range) duration of arthritis (years) 4.5 (0–47.7) Median (range) number of tender	Disease duration	26 years	Change in number of permanently damaged joints between visits (clinically/radiographically) Radiological damage (Steinbrocker) hands and feet	Not stated

REF ID: BOND2007	joint count and drugs (order of increasing severity: no drug, NSAID, DMARD, steroids – none were taking biologics)		joints (all joints) 4 (0–43) Median (range) number of tender joints (hands and feet) 3 (0–35) Median (range) number of swollen joints (all joints) 2 (0–33) Median (range) number of swollen joints (hands and feet) 1 (0–28) Median (range) ESR rate 22.5 (0–105) Functional class Good (I) 29.3% (183) Medium (II) 59.2% (370) Poor (III, IV) 11.5% (72) Damaged joints (all joints) None 62.2% (389) 1–4 20.8% (130) 5–9 5.9% (37) >9 11.1% (69) Damaged joints (hands and feet) None 68.3% (427) 1–4 17.3% (108) 5–9 5% (31)				

			>9 9.4% (59) Drugs None 24.3% (152) NSAIDs 30.6% (191) DMARDs 40.5% (253) Steroids 4.6% (29)				

Effect size

Clinical damage: presence of a limitation of range of movement of >20% of the range not related to the presence of joint effusion, the presence of joint deformities, subluxation, loosening or ankylosis.

Radiological damage: Each joint is scored as 1, normal (with possible soft tissue swelling); 2, surface or pocket erosions; 3, erosion and joint space narrowing; and 4, disorganisation (including ankylosis, pencil-in-cup change or total joint destruction) or as requiring surgery. Radiological damage is assessed only in the joints of the hands (wrists, all metacarpophalangeals, PIPs and distal interphalangeals) and feet (MTPs and interphalangeal fist toes); 42 joints in total

Strong relationships were identified between clinical damage development and swollen joints, ESR and arthritis duration

PROGRESSION OF CLINICAL DAMAGE (outcome = change in clinically damaged joint count):

Factor	Single-factor analyses		All factors included	
	Relative damage rate (95% CI)	**p Value**	**Relative damage rate (95% CI)**	**p Value**
Functional class		<0.001		0.1
Good (I)	1		1	
Medium (II)	1.56 (1.24 to 1.96)		1.16 (0.89 to 1.5)	
Poor (III, IV)	1.37 (0.96 to 1.91)		0.87 (0.59 to 1.28)	
Tender joints		<0.001		0.2
None (0)	1		1	
Low (1–4)	1.45 (1.13 to 1.86)		1.15 (0.89 to 1.51)	
Medium (5–9)	1.63 (1.19 to 2.24)		1.27 (0.91 to 1.78)	
High (>9)	2.09 (1.54 to 2.85)		1.37 (0.97 to 1.95)	
Effusions		<0.001		<0.001
None (0)	1		1	
Low (1–4)	1.32 (1.07 to 1.63)		1.12 (0.89 to 1.42)	
Medium (5–9)	1.84 (1.33 to 2.55)		1.48 (1.02 to 2.13)	
High (>9)	2.95 (1.82 to 4.78)		2.6 (1.56 to 4.36)	
ESR		0.17		0.75

Low (<15)	1		1	
Medium (15–30)	1.05 (0.82 to 1.39)		0.99 (0.77 to 1.28)	
High (>30)	1.27 (0.94 to 1.73)		1.09 (0.8 to 1.48)	
Arthritis duration	0.67 (0.55 to 0.8) per extra decade in clinic	<0.001	0.73 (0.6 to 0.89)	<0.001
Drugs		0.143		0.044
None	1		1	
NSAIDs	0.72 (0.44 to 1.18)		1.11 (0.65 to 1.91)	
DMARDs	0.89 (0.6 to 1.32)		1.32 (0.84 to 2.07)	
Steroids	1.04 (0.68 to 1.6)		1.64 (1.02 to 2.68)	

DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; NSAID, non-steroidal anti-inflammatory drug.

Change in clinically damaged joint count for all joints

Before entry to the clinic, the longer the duration, the more damage caused by arthritis, but during duration the more damage in the clinic the effect is the opposite: t
longer the follow-up, the lesser the damage

Arthritis duration at first visit is a predictor for progression in patients who do not have damage at the first visit, but once a patient has a damaged joint the predictive
power of arthritis duration evaporates

Factor	Relative damage rate	Lower 95% CI	Upper 95% CI	p Value
Clinical damage				
Arthritis duration at first visit				
Damaged	1.06 per decade	0.92	1.22	0.39
Undamaged	1.54 per decade	1.22	1.96	<0.001
Radiological damage				
Arthritis duration at first visit				
Damaged	0.99 per decade	0.81	1.19	0.88
Undamaged	0.84 per decade	0.63	1.12	0.23

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

Gladman DD, Thavaneswaran A, Chandran V, Cook RJ. Do patients with psoriatic arthritis who present early fare better than those presenting later in the disease? *Ann Rheum Dis*. 70: 2152 – 2154 2011 REF ID: GLADMAN2011A	Prospective cohort University of Toronto PsA clinic 1978 – 2011 Analysis: multivariable analysis using a negative binomial model Adjusted for: Sex, age, arthritis duration, number of damaged joints at first visit, NSAID use at first visit; DMARD use at first visit; treatment with biologics after first visit; calendar effect (based on decade of entry into clinic)	1077 patients (436 within 2 years of diagnosis and 641 with disease duration >2 years	Patients referred to University of Toronto PsA Clinic; divided into those first seen within 2 years of diagnosis and those first seen with more than 2 years since diagnosis Baseline characteristics: See below	Disease duration	32 years	Change in number of permanently damaged joints between visits (clinically): defined as a limitation of movement of more than 20% of the range that is not related to a joint effusion, the presence of flexion contactures, fused or flail joints or evidence of surgery at a particular joint	None

Effect size

Demographic and disease characteristics at first visit

Variable	Early PsA (n=436)	Late PsA (n=641)	p-value

Sex F/M (%)	42.4/57.6	44.8/55.2	0.447
Age at PsA diagnosis	40.3	34.2	<0.0001
Age at first visit	41.1	45.2	<0.0001
Duration of PsA at first visit	0.92	11.0	<0.0001
Mean number of actively inflamed joints	10.5	11.7	0.239
Mean number of damaged joints	3.5	9.2	<0.0001
Mean PASI	6.2	5.5	0.254
Treatment at first visit	56.4%	61.6%	0.089
NSAID	28.0%	56.8%	<0.0001
DMARD biological agents	4.1%	6.7%	0.061

Multivariate analysis of progression of clinical damage

Relative rate of joint damage progression (>2 years vs <2 years disease duration at first visit): 1.38 (1.08-1.77); p=0.01

Stratification by duration of disease at clinic entry

Duration of disease at first visit	N	Relative rate of joint damage progression (95% CI)	P value
1-2 years vs <1 year	212	1.53 (0.99-2.36)	0.05
2-4 years vs <1 year	248	1.70 (1.11-2.62)	0.01

5-9 years vs <1 year	201	1.83 (1.16-2.88)	0.009
10-20 years vs <1 year	204	1.83 (1.14-2.96)	0.01
>20 years vs <1 year	86	2.96 (1.64-5.34)	0.0003

Authors' conclusions:

Disease progression is more marked in patients presenting with established disease of more than 2 years' duration; there is also a clear dose/exposure-response relationship with respect to the duration of disease. These results suggest that patients with PsA should be treated earlier in the course of their disease

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
J.A. Husted, B.D. Tom, V.T. Farewell, C.T. Schentag, D.D.Gladman. Description and prediction of physical functional disability in psoriatic arthritis: a	Prospective cohort Toronto 1993 – 2003 Markov model used to characterise disability process	341 patients	Patients attending University of Toronto PsA Clinic. Newly diagnosed and established PsA. 201 men, 140 women Mean age 45.9 ±12.4 years Mean duration of PsA 10.6 ±8.4 years	Disease duration	Mean ±SD follow-up 5.2 ±3.04 years	HAQ Disability state	Canadian Institute of Health Research and the Krembil Foundation

longitudinal analysis using a markov model approach. *Arthritis & Rheumatism*. 52(3):404-409.2005 REF ID: HUSTED2005	in PsA – transitions only between no disability (1) and moderate disability (2) and between moderate disability (2) and severe disability (3) The variables included were sex, age, duration of PsA, psoriasis severity as measured by the PASI, the number of clinically deformed or damaged joints, and the number of actively inflamed joints updated at each HAQ visit.		157 patients (46%) initial HAQ score <0.5 and thus assigned an initial disability state of 1 134 patients (39%) had a score between 0.5 and 1.5 inclusive and were assigned disability state 2 50 patients (15%) had a score > 1.5 and were assigned to disability state 3				

Effect size

Patients with duration of PsA less than 2 years were found to have more frequent transitions to different states (either to better or worse states).

Patients with duration of PsA 2-5 years and >5 years had a reduction in transition rates of 56-70% compared with those patients with PsA duration <2 years

Multivariate model of predictors of transitions between disability states:

RR transition from 1-2 or 2-3 (worsening)

< 2 years RR = 1

2-5 years RR = 0.42 (0.16-1.09)

>5 years RR 0.33 (0.14-0.76)

i.e. significantly lower rate of transition state worsening in patients with PsA duration >5 years compared to those with duration <2 years

RR transition from 2-1 or 3-2 (improving)

<2 years RR = 1

2-5 years RR = 0.33 (0.14-0.77)

>5 years RR = 0.44 (0.21-0.90)

i.e. significantly lower rate of transition state improvement in patients with PsA duration >2 years compared to those with duration <2 years

Mean length of follow-up with HAQ 5.2 years

Number and type of disability transition states (HAQ)

Of 341 patients, 95 (28%) were in state 1 (no disability) throughout follow-up

42 (12%) were in state 2

20 (6%) in state 3

91 patients (26.7%) encountered a single transition to either a lower or higher disability state.

93 patients (27.3%) experienced 2 or more observed transitions

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
U.R.C. Lindqvist, G.-M. Alenius, T. Husmark, E. Theander, G. Holmstrom, P.T. Larsson. The Swedish early psoriatic arthritis register – 2-year followup: a comparison with early rheumatoid arthritis. *J Rheumatol.* 35:668-7. 2008	Prospective cohort Sweden	135 patients	Patients with PsA (meeting CASPAR criteria) referred to rheumatology outpatients within 2 years of onset Assessed on inclusion and at follow-up after 2 years of conventional care. 58% female, 42% male Mean age ±SD: 47.3 ±15.2 years	Disease duration	2 years	Joint count PASI Lab values VAS HAQ Radiographs	Not stated

REF ID: LINDQVIST2008			Mean duration of psoriasis ±SD: 11.4 ±6.6 months DMARD on inclusion: 51 patients (38%)				

Effect size

Radiological examination performed in 120 patients on inclusion: proliferation/destruction indicating PsA found in 24 patients (20%). 79 patients examined radiographically at 2 year follow-up, 23 (32%) of patients exhibited radiological changes consistent with PsA.

60 patients classified as mono/oligoarthritis at inclusion, 36 of those classified as mono/olgi at 2 years, 8 as polyarticular, 1 as axial, 1 as DIP and 14 as remission

64 polyarticular at inclusion, 26 mono/oligo at 2 years, 28 poly, 0 axial, 1 DIP, 9 remission

Significant reduction in:

Number of swollen joints, no of tender joints, ESR/CRP, pain (VAS), PGA

No significant change in HAQ, PASI

Mean ±SD HAQ score at inclusion: 0.66 ±0.56, at 2 year follow-up 0.55 ±0.79

Outcome	Baseline	Follow-up	p-value (paired t-test)
N swollen joints	4.4±4.5	1.8±3.4	≤0.05
N tender joints	5.8±6.7	3.6±6.7	≤0.05
HAQ	0.43±0.26	0.25±0.29	NS
ESR (mm/h)	17.3±17.9	11.2±10.2	≤0.05
CRP (mg/l)	41.7±21.9	7.2±7.6	≤0.05
N with radiological damage compatible with PsA	24	33	NS
Pain VAS (mm)	44±24	34±26	≤0.05

17% in remission, radiological damage verified on inclusion or at follow-up in 31% of PsA patients

Reference	**Study type**	**Number of patients**	**Patient characteristics**	**Prognostic factors**	**Length of follow-up**	**Outcome measures**	**Source of funding**

F. Cantini, L. Niccoli, C. Nannini, E. Cassara, P. Pasquetti, I. Olivieri, C. Salvarani. Frequency and duration of clinical remission in patients with peripheral psoriatic arthritis requiring second-line drugs. *Rheumatology*. 47:872-876.2008 REF ID: 268	Prospective case-control (comparison with RA not relevant to question; therefore cohort data used) Consecutive series Italy	236 (6/251 lost to follow-up)	All consecutive outpatients with peripheral PsA requiring second-line drugs observed between Jan 2000 and Dec 2005 at Rheumatology Unit Mean disease duration: 13 ±7.1 months	Disease duration	Mean 38 months	Clinical remission DMARD/biologic use	None declared

Effect size

32.6% of patients were in remission after an average follow-up time of 38 months

68% were on DMARD therapy and 32% were on anti-TNF-α biologic therapy (plus methorexate) after an average follow-up time of 38 months

H.4 Identification of comorbidities

H.4.1 STUDY 1 Myocardial infarction

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
Gelfand et al. (2006) Risk of Myocardial infraction in patients with psoriasis Ref ID: GELFAND2006A	**Observational:** Prospective population-based cohort 1987-2002 **Representative population sample:** yes the data was collected from the electronic general Practice Research Database which has data on more than 8 million people. **Prognostic factor adequately measured:** yes **Confounders adjusted for:** age, diabetes, history of MI, hyperlipidemia,	N: 130976 psoriasis patients; 556995 corresponding control patients (127139 in mild psoriasis group and 3837 in severe psoriasis group)	**Inclusion criteria:** Patients with psoriasis aged 20 -90 years with at least 1 day of observation time. Each patient was matched to up to 5 control patients who did not have psoriasis diagnostic codes and were observed in the same practice on the latest date of when the psoriasis patient registered with the practice or when the practice was designated 'up to standard' within 60 days. **Exclusion criteria:** None stated. Mean age in years: Control: 45.72 Mild psoriasis:46.35	GPRD used. They either received a medical code consistent with the diagnosis or not. Severe psoriasis was based on history of having had systemic therapies, the majority of whom had MTX.	Mean 5.4 years **Note**: study ended due to: death, end of up to standard or transfer out.	Incidence of myocardial infarction	Grant from the National Institutes of Health/ National Institute of Arthritis and musculos keletal and Skin Diseases and an unrestricted grant to the Trustees of the University of Pennsylvania from Biogen Idec. Biogen Idec assisted in interpretin

	hypertension, sex, smoking. **Attrition bias:** No. Patients who died without MI were considered as censored for the primary analysis and they conducted sensitivity analyses for the composite outcome of the earlier of MI and death. **Outcomes adequately measured:** Yes **Appropriate statistical analysis:** yes		Severe psoriasis: 49.75 Note: all groups had <2% with a history of MI				g the data.

Effect size:

	Control	Mild	Severe
No. of new MI cases (%)	**11 194 (2.0)**	**2319 (1.8)**	**112 (2.9)**
Incidence of per 1000 person-years (95% CI)	**3.58 (3.52-3.65)**	**4.04 (3.88-4.21)**	**5.13 (4.22-6.17)**

Univariable and multivariable cox proportional hazard regression models of the risk of MI in patients

with mild and severe psoriasis compared with control patients*

	Model Hazard Ratio (95% CI)		**P value**
Covariate	**Mild psoriasis**	**Severe psoriasis**	**<0.001**
Psoriasis (unadjusted)	1.11 (1.07-1.17)	1.43 (1.18-1.72)	<0.001
Psoriasis	1.54 (1.24-1.91)**	7.08 (3.06-16.36)**	<0.001
Age per year	1.077 (1.076-1.079)	1.077 (1.076-1.078)	<0.001
Age x psoriasis (interaction term)	0.994 (0.991-0.997)	0.97 (0.96-0.99)	<0.001
Diabetes	1.61 (1.53-1.70)	1.62 (1.53-1.71)	<0.001
History of MI	3.24 (3.07-3.41)	3.31 (3.13-3.51)	<0.001
Hyperlipidemia	3.08 (2.93-3.23)	3.18 (3.02-3.36)	<0.001
Hypertension	1.11 (1.07-1.16)	1.12 (1.07-1.17)	<0.001
Male sex	2.12 (2.04-2.19)	2.14 (2.05-2.22)	<0.001
Smoking	1.15 (1.10-1.20)	1.16 (1.11-1.21)	<0.001

*Body mass index was not included in the primary model because it was available for only 61% of the patients.

** The point estimate of the hazard ratio for MI due to mild or severe psoriasis is not directly interpretable as this hazard ratio was modified by age (**ie age x psoriasis interaction term was significant**). Age was categorised in years.

Sensitivity analyses hazard ratio point estimates for patients aged 30 and 60 years:

	Hazard Ratio (95% CI)	
	Mild Psoriasis	Severe Psoriasis

	Age 30 years	Age 60 years	Age 30 years	Age 60 years
Primary analysis	1.29 (1.14 -1.46)	1.08 (1.03-1.13)	3.10 (1.98-4.86)	1.36 (1.13-1.64)
At least 6 months of follow-up (to ensure capture of incident, not prevalent MIs)	1.27 (1.12-1.45)	1.08 (1.03-1.14)	2.11 (1.95-4.94)	1.45 (1.20-1.76)
Last prescription or diagnosis as end date (to ensure that patients are actively followed up and censored for the same reason)	1.28 (1.13-1.44)	1.07 (1.02-1.13)	2.90 (1.86-4.54)	1.32 (1.09-1.59)
Inclusion of patients observed >/= time/y by the general practitioner (to ensure that patients are actively followed up)	1.20 (1.06-1.36)	1.04 (0.99-1.09)	2.82 (1.81-4.40)	1.29 (1.07-1.56)
Primary model but also adjusting for BMI (excluded approximately 40% of patients for whom there was no BMI)	1.36 (1.17-1.58)	1.07 (1.01-1.13)	2.65 (1.53-4.59)	1.56 (1.25-1.93)
Primary model excluding approximately 40% of patients for whom there was no BMI; in this model, BMI was not included	1.37 (1.18-1.59)	1.08 (1.02-1.14)	2.70 (1.56-4.66)	1.58 (1.27-1.96)
Exclusion of patients	NA	NA	4.12 (2.24-7.58)	1.45 (1.11-1.91)

treated with methotrexate				
Exclusion of patients treated with oral retinoids or ciclosporine*	NA	NA	2.06 (1.16-3.67)	1.28 (1.03-1.58)
Composite end point of MI or death	1.44 (1.34-1.55)	1.20 (1.17-1.24)	2.08 (1.54-2.82)	1.42 (1.27-1.58)

*Age x psoriasis interaction term was of borderline statistical significance (p=0.06).

Author's conclusion:

Psoriasis may confer an independent risk for MI. The risk was greatest in young patients with severe psoriasis, is attenuated with age and is still increased after controlling for traditional cardiovascular risk factors.

H.4.2 STUDY 2 MYOCARDIAL INFARCTION

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
Lin et al. (2011) Title: Increased risk of acute myocardial infarction in patients with	**Observational:** retrospective population-based cohort study from 1999-2005 **Representative population sample:**	N: 28,512. Psoriasis diagnosis n=4752; without Psoriasis diagnosis n=23,760.	**Inclusion criteria:** all patients who visited ambulatory care centres for treatment of psoriasis (International Classification of Disease, Ninth Revision, Clinical Modification codes 696, 696.0, 696.1, and 696.8) from January 1 1999 to December 31, 2001).	Longitudinal Health insurance database 2005 from the Taiwan National Health Research Institute (NHRI), released in 2006.	5 years.	Incidence of acute myocardial infarction;	None.

psoriasis: A 5-year population-based study in Taiwan Ref ID: LIN2011	Yes **Prognostic factor adequately measured:** yes **Confounders adjusted for:** stratified by sex and age and adjustments made for patient's hospital clustering, hypertension, diabetes, hyperlipidemia, monthly income, geographic region and urbanisation level **Attrition bias:** not reported. **Outcomes adequately measured:** yes **Appropriate statistical analysis:** yes – Pearson's X^2 tests for differences between two cohorts. 5-		**Exclusion criteria:** Younger than 18 years (n=2093); diagnosis of AMI (international classification of disease, ninth revision, clinical modification code 410 or 412) before their index ambulatory care visit (n=54).	They randomly selected patients and 5 control patients for every one patient diagnosed, matched by age (<30, 30-59, and >59 years) and sex.			

	year AMI-free survival estimated with Kaplan-Meier method. Stratified Cox proportional hazard regressions for clustering and confounders.						

Baseline:

	Patients with psoriasis	**Control group**	
Variable	**Number (%)**	**Number (%)**	**P value**
Male	2361 (49.7%)	11,805 (49.7%)	1.00
Aged 18-29	1568 (33%)	7840 (33%)	1.00
Aged 30-59	2429 (51.1%)	12,145 (51.1%)	1.00
>59	755 (15.9%)	3775 (15.9%)	1.00
Hypertension	1054 (22.2%)	4823 (20.3%)	0.003
Diabetes	567 (11.9%	2401 (10.1%)	<0.001
Hyperlipidemia	564 (11.9%)	2296 (9.7%)	<0.001

Effect size:

Crude and adjusted hazard ratios for psoriasis among patients during 5-year follow-up period starting from index ambulatory care visit (n=28,512)

			Psoriasis

Presence of AMI	Control group	Patients with psoriasis	Receiving systemic therapy* for >/= 90 days (n=590)	Receiving systematic therapy* for < 90 days (n=475)	Others (n=4162)
Yes	48 (0.2%)	22 (0.5%)	5 (0.8%)	0 (0%)	17 (0.4%)
Crude HR (95% CI)	1.00	2.30** (1.38-3.80)	4.22*** (1.68-10.65)	-	2.03**** (1.16-3.53)
Adjusted*** HR (95% CI)**	1.00	2.10 (1.27-3.43)	1.81 (0.69-4.74)	-	2.0 (1.13-3.54)

*Patients who receive systemic therapy in our study include those who received ultraviolet B phototherapy and systemic agents.

**P<0.001,

***p<0.01;

****p<0.05.

*****Stratified by patient's sex and age and adjustments were made for patient's hospital clustering, hypertension, diabetes, hyperlipidemia, monthly income, geographic region and urbanisation level.

Author's conclusion: Psoriasis may confer an independent risk of AMI in Asian populations.

H.4.3 STUDY 3 MYOCARDIAL INFARCTION AND STROKE

Reference	Study type	Number of	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source

		patients					**of** **funding**
Brauchli 2009 Psoriasis and risk of incident myocardial infarction, stroke or transient ischaemic attack: an inception cohort study with a nested case-control analysis. Ref ID: BRAUCHLI 2009A	**Observational:** inception cohort study with a nested case-control analysis **Representative population sample:** Yes - UK based General practice Research Database **Prognostic factor adequately measured:** yes **Confounders adjusted for:** Matched on calendar time, age (same year of birth), sex, general practice, and years of history in the GPRD. **Attrition bias:** not reported.	N: 73,404. 36,702 with psoriasis and 36,702 matched psoriasis-free.	**Inclusion criteria:** all patients with a first-time recorded diagnosis of psoriasis between 1st January 1994 and 31st December 2005 and a comparison group of the same number of psoriasis-free patients. **Exclusion criteria:** excluded those with <3 years of history in the database prior to the first-time psoriasis diagnosis (or the corresponding date in the comparison group); history of ischaemic heart disease or cerebrovasulcar diseases, cancer or human immunodeficiency virus (HIV) prior to the psoriasis diagnosis (or corresponding date in the control group).	The comparison group was matched to the psoriasis patients on date of psoriasis diagnosis, age (same year of birth), sex, general practice, and years of history in the GPRD. All patients with a recorded psoriasis diagnosis in the analyses. Validated all potential cases with a recorded code for incident MI, stroke or TIA using a computer-based algorithm and manual computer profile review. Validation process done blinded as to whether cases had psoriasis or not.	**Mean 4.6 years** **Note**: followed up until they developed a first-time diagnosis of MI, stroke or TIA, they died or follow-up in the medical record ended.	Incidence of MI; incidence of stroke; incidence of transient ischaemic attach	Funded by an unrestricted grant from Merck Serono International SA. One author was supported by a grant from the Senglet Foundation, Switzerland.

	Outcomes adequately measured: yes **Appropriate statistical analysis:** not multivariable/regression **Notes:** nested case-control analysis involved matching at random up to four control patients from the study population on age, sex and calendar time and applied same exclusion criteria to controls as did cases.						

Incidence rates of myocardial infarction (MI), stroke and transient ischaemic attack (ITA)

Outcome	Group	Events	Person-years	IR/1000 person-years (95% CI)	IRR (95% CI)
MI					
Psoriasis	All	238	150972.2	1.58 (1.39-1.79)	1.07 (0.89-1.29)
	Men	151	68503.1	2.20 (1.88-2.58)	1.06 (0.84-1.33)
	Women	82	82469.0	1.05 (0.86-1.30)	1.09 (0.80-1.48)

	Age 0-29 years	0	40383.7	NA	NA
	Age 30-59 years	76	70212.8	1.08 (0.86-1.35)	1.99 (1.37-2.88)
	Age 60-80+ years	162	40375.7	4.01 (3.44-4.68)	0.92 (0.75-1.14)
No psoriasis	All	211	143231.5	1.47 (1.29-1.69)	1.0
	Men	135	64707.2	2.09 (1.76-2.47)	1.0
	Women	76	78524.3	0.97 (0.77-1.21)	1.0
	Age 0-29 years	1	37068.7	0.03 (0.00-0.15)	1.0
	Age 30-59 years	36	66180.7	0.54 (0.39-0.75)	1.0
	Age 60-80+ years	174	39982.1	4.35 (3.75-5.05)	1.0
Stroke					
Psoriasis	All	264	156492.8	1.69 (1.50-1.90)	0.92 (0.77-1.09)
	Men	135	72208.3	1.87 (1.58-2.21)	1.02 (0.80-1.31)
	Women	129	84284.5	1.53 (1.29-1.82)	0.83 (0.65-1.05)
	Age 0-29 years	1	40392.1	0.02 (0.00-0.14)	NA
	Age 30-59 years	37	71800.5	0.52 (0.37-0.71)	0.75 (0.49-1.16)
	Age 60-80+ years	226	44300.3	5.10 (4.48-5.81)	0.98 (0.81-1.18)
No psoriasis	All	271	147287.7	1.84 (1.63-2.07)	1.0
	Men	123	67279.2	1.83 (1.53-2.18)	1.0
	Women	148	80008.5	1.85 (1.58-2.17)	1.0
	Age 0-29 years	0	37076.6	NA	NA

	Age 30-59 years	46	67094.7	0.69 (0.51-0.91)	1.0
	Age 60-80+ years	225	43116.3	5.22 (4.58-5.94)	1.0
TIA					
Psoriasis	All	205	156492.8	1.31 (1.14-1.50)	0.98 (0.81-1.19)
	Men	92	72208.3	1.27 (1.04-1.56)	0.88 (0.66-1.18)
	Women	113	84284.5	1.34 (1.12-1.61)	1.07 (0.82-1.40)
	Age 0-29 years	0	40392.1	NA	NA
	Age 30-59 years	28	71800.5	0.39 (0.27-0.56)	1.14 (0.66-1.97)
	Age 60-80+ years	177	44300.3	4.00 (3.45-4.63)	0.99 (0.80-1.22)
No psoriasis	All	197	147287.7	1.34 (1.16-1.54)	1.0
	Men	97	67279.2	1.44 (1.18-1.76)	1.0
	Women	100	80008.5	1.25 (1.03-1.52)	1.0
	Age 0-29 years	0	37076.6	NA	NA
	Age 30-59 years	23	67094.7	0.34 (0.23-0.51)	1.0
	Age 60-80+ years	174	43116.3	4.04 (3.48-4.68)	1.0

Author's conclusion: they did not find an increased risk for developing a cardiovascular outcome with early psoriasis. Subanalyses however found a suggestion of an increased (but low absolute) MI risk of patients with psoriasis aged <60 years.

H.4.4 STUDY 4 MYOCARDIAL INFARCTION

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
Kaye (2008) Incidence of risk factors for myocardial infarction and other vascular diseases in patients with psoriasis Ref ID: KAYE2008	**Observational:** retrospective cohort study. **Representative population sample:** Yes - General practice research database **Prognostic factor adequately measured:** yes **Confounders adjusted for:** Matched on age, sex and index date. **Attrition bias:** not reported	N: 44,164 with psoriasis and 219,784 without psoriasis.	**Inclusion criteria:** all patients with a first-time diagnosis of psoriasis after 1st January 1991 The psoriasis cohort was restricted to those with at least 1 year of medical history recorded in the database before their index date (the date of the first-time diagnosis of psoriasis). The index date defined the start of follow-up for estimating the cumulative incidences of the outcomes of interest in the psoriasis group. The comparison cohort was randomly selected and matched in a 5:1 ratio by year of birth, sex, general practice and index date. **Exclusion criteria:** none stated.	GPRD used. S standard OXMIS and READ codes for diagnosis.	**1, 3, 5 and 10 year follow-ups.** **Note**: follow-up ended when a patient developed an outcome of interest, transferred out of their practice or died.	Incidence of diabetes, hypertension, obesity, hyperlipidaemia, myocardial infarction, angina, atherosclerosis, peripheral vascular disease and stroke.	Amgen, Inc.

	Outcomes adequately measured: yes **Appropriate statistical analysis:** yes - Kaplan-Meier to estimate cumulative incidences for each of outcomes at specific times. Cox regression to estimate hazard ratio for each outcome comparing psoriasis cohort with comparison group.						

Baseline characteristics:

Variable	**Psoriasis**	**Comparison**
	N (%)	**N (%)**
Male	21,121 (47.8%)	105, 045 (48.8%)
Age (years)		
< 10	1887 (4.3%)	9418 (4.3%)

10-19	5058 (11.5%)	25,248 (11.5%)
20-29	5848 (13.2%)	29, 198 (13.3%)
30-39	7079 (16%)	35,363 (16.1%)
40-49	6415 (14.5%)	32,021 (14.6%)
50-59	6648 (15.1%)	33,193 (15.1%)
60-69	5740 (13%)	28,607 (13%)
70-79	3938 (8.9%)	19,520 (8.9%)
80-89	1389 (3.2%)	6679 (3.0%)
90+	162 (0.4%)	537 (0.2%)
Treatment	41,790 (94.6%)	N/A

Effect size:

Incident diabetes cases in the psoriasis and comparison cohorts

	Psoriasis n=44164	**Comparison n=219784**
	N (%)	**N (%)**
Total	1198 (2.7)	4482 (2.0)
Sex		
Male	661 (55.2)	2532 (56.5)

Female	537 (44.8)	1950 (43.5)
Age (years)		
< 10	4 (0.3)	13 (0.3)
10-19	7 (0.6)	27 (0.6)
20-29	24 (2.0)	91 (2.0)
30-39	86 (7.2)	264 (5.9)
40-49	191 (15.9)	638 (14.2)
50-59	325 (27.1)	1160 (25.9)
60-69	356 (29.7)	1357 (30.3)
70-79	168 (14.0)	774 (17.3)
80-89	35 (2.9)	151 (3.4)
90+	2 (0.2)	7 (0.2)

Estimated cumulative incidence of diabetes at specified time after the index date in the psoriasis and comparison cohorts

	Cases	**Cumulative incidence (per 1000)**	**95% CI (per 1000)**
Psoriasis			
1 year	**207**	**5.2**	**4.5-5.9**
3 years	**337**	**15.9**	**14.6-17.3**
5 years	**210**	**25.4**	**23.6-27.3**

10 years	**360**	**57.3**	**53.5-61.2**
Comparison			
1 year	**686**	**3.4**	**3.2-3.7**
3 years	**1169**	**10.9**	**10.4-11.4**
5 years	**886**	**19.0**	**18.3-19.7**
10 years	**1363**	**43.9**	**42.4-45.5**

Incident hypertension cases in the psoriasis and comparison cohorts

	Psoriasis n=44164	**Comparison n=219784**
	N (%)	**N (%)**
Total	**2765 (6.3)**	**12754 (5.8)**
Sex		
Male	**1332 (48.2)**	**6147 (48.2)**
Female	**1433 (51.8)**	**6607 (51.8)**
Age (years)		
< 10	**1 (0.0)**	**4 (0.0)**
10-19	**14 (0.5)**	**70 (0.6)**
20-29	**59 (2.1)**	**327 (2.)**
30-39	**206 (7.5)**	**955 (7.5)**
40-49	**515 (18.6)**	**2124 (16.7)**

50-59	**717 (25.9)**	**3340 (26.2)**
60-69	**724 (26.2)**	**3542 (27.8)**
70-79	**435 (15.7)**	**2003 (15.7)**
80-89	**93 (3.4)**	**368 (2.9)**
90+	**1 (0.0)**	**21 (0.2)**

Estimated cumulative incidence of hypertension at specified time after the index date in the psoriasis and comparison cohorts

	Cases	**Cumulative incidence (per 1000)**	**95% CI (per 1000)**
Psoriasis			
1 year	**501**	**14.0**	**12.9-15.3**
3 years	**796**	**42.2**	**39.9-44.5**
5 years	**521**	**68.2**	**65.2-71.4**
10 years	**732**	**138.5**	**132.7-144.6**
Comparison			
1 year	**2211**	**12.1**	**11.6-12.6**
3 years	**3440**	**36.1**	**35.2-37.1**
5 years	**2441**	**60.4**	**49.0-61.7**
10 years	**3610**	**129.4**	**126.9-132.1**

Incident obesity cases in the psoriasis and comparison cohorts

	Psoriasis n=44164	**Comparison n=219784**
	N (%)	**N (%)**
Total	**2760 (6.3)**	**11996 (5.5)**
Sex		
Male	**1183 (42.9)**	**5274 (44.0)**
Female	**1577 (57.1)**	**6722 (56.0)**
Age (years)		
< 10	**16 (0.6)**	**85 (0.7)**
10-19	**225 (8.2)**	**903 (7.5)**
20-29	**342 (12.4)**	**1560 (13.0)**
30-39	**415 (15.0)**	**2007 (16.7)**
40-49	**531 (19.2)**	**2307 (19.2)**
50-59	**561 (20.3)**	**2388 (19.9)**
60-69	**453 (16.4)**	**1856 (15.5)**
70-79	**191 (6.9)**	**785 (6.5)**
80-89	**25 (0.9)**	**103 (0.9)**
90+	**1 (0.0)**	**2 (0.0)**

*Obesity is defined as body mass index>/=30kgm^{-2}

Estimated cumulative incidence of obesity at specified time after the index date in the psoriasis and comparison cohorts

	Cases	Cumulative incidence (per 1000)	95% CI (per 1000)
Psoriasis			
1 year	**525**	**14.8**	**13.6-16.1**
3 years	**776**	**42.1**	**39.9-44.5**
5 years	**515**	**67.7**	**64.7-70.9**
10 years	**745**	**139.0**	**133.2-145.1**
Comparison			
1 year	**2191**	**11.8**	**11.3-12.3**
3 years	**3335**	**34.6**	**33.8-35.6**
5 years	**2299**	**57.0**	**55.7-58.3**
10 years	**3241**	**118.0**	**115.5-120.5**

*Obesity is defined as body mass index>/=30kgm^{-2}

Incident hyperlipidaemia cases in the psoriasis and comparison cohorts

	Psoriasis n=44164	Comparison n=219784
	N (%)	**N (%)**
Total	**1900 (4.3)**	**8111 (3.7)**
Sex		

Male	**978 (51.5)**	**4074 (50.2)**
Female	**922 (48.5)**	**4037 (49.8)**
Age (years)		
< 10	**0 (0.0)**	**3 (0.0)**
10-19	**1 (0.1)**	**13 (0.2)**
20-29	**35 (1.8)**	**126 (1.6)**
30-39	**112 (5.9)**	**539 (6.7)**
40-49	**319 (16.8)**	**1354 (16.7)**
50-59	**572 (30.1)**	**2337 (28.8)**
60-69	**580 (30.5)**	**2502 (30.9)**
70-79	**257 (13.5)**	**1105 (13.6)**
80-89	**21 (1.1)**	**130 (1.6)**
90+	**3 (0.2)**	**2 (0.0)**

Estimated cumulative incidence of hyperlipidaemia at specified time after the index date in the psoriasis and comparison cohorts

	Cases	**Cumulative incidence (per 1000)**	**95% CI (per 1000)**
Psoriasis			
1 year	**305**	**7.8**	**7.0-8.8**
3 years	**495**	**23.8**	**22.2-25.5**

5 years	**377**	**41.0**	**38.7-43.5**
10 years	**570**	**91.1**	**86.5-96.0**
Comparison			
1 year	**1223**	**6.2**	**5.9-6.6**
3 years	**2172**	**20.3**	**19.7-21.0**
5 years	**1526**	**34.4**	**33.5-35.4**
10 years	**2388**	**77.7**	**75.7-79.7**

Incident myocardial infarction cases in the psoriasis and comparison cohorts

	Psoriasis n=44164	**Comparison n=219784**
	N (%)	**N (%)**
Total	**596 (1.4)**	
Sex		
Male	**378 (63.4)**	**1596 (64.9)**
Female	**218 (36.6)**	**863 (35.1)**
Age (years)		
< 10	**0 (0.0)**	**0 (0.0)**
10-19	**1 (0.2)**	**3 (0.1)**
20-29	**3 (0.5)**	**4 (0.2)**
30-39	**21 (3.5)**	**55 (2.2)**

40-49	**52 (8.7)**	**187 (7.6)**
50-59	**128 (21.5)**	**472 (19.2)**
60-69	**176 (29.5)**	**744 (30.3)**
70-79	**164 (27.5)**	**719 (29.2)**
80-89	**42 (7.1)**	**262 (10.7)**
90+	**9 (1.5)**	**13 (0.5)**

Estimated cumulative incidence of myocardial infarction at specified time after the index date in the psoriasis and comparison cohorts

	Cases	**Cumulative incidence (per 1000)**	**95% CI (per 1000)**
Psoriasis			
1 year	103	2.6	2.1-3.1
3 years	177	8.2	7.3-9.2
5 years	113	13.3	12.0-14.7
10 years	165	27.7	25.2-30.4
Comparison			
1 year	440	2.2	2.0-2.4
3 years	719	6.7	6.3-7.1
5 years	459	10.9	10.4-11.5

10 years	679	22.6	21.6-23.7

Hazard ratios

Outcome	**HR (95% CI)**
Diabetes	1.33 (1.25-1.42)
Angina	1.20 (1.12-1.29)
Hypertension	1.09 (1.05-1.14)
Hyperlipidaemia	1.17 (1.11-1.23)
Obesity	1.18 (1.14-1.23)
Myocardial infarction	1.21 (1.10-1.32)
Atherosclerosis	1.28 (1.10-1.48)
Peripheral vascular disease	1.29 (1.13-1.47)
Stroke	1.12 (1.00-1.25)

Author's conclusion: risk factor for cardiovascular disease as well as myocardial infarction and other vascular disease occurred with higher incidence in patients with psoriasis than in the general population. Further investigations needed as to whether these associations involve causal factors related to psoriasis or its treatment.

H.4.5 STUDY 11 MYOCARDIAL INFARCTION – systemic therapy vs phototherapy for psoriasis

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
K. Abuabara, H. Lee, and A. B. Kimball. The effect of systemic psoriasis therapies on the incidence of myocardial infarction: a cohort study. Br.J.Dermatol. 165 (5):1066-1073, 2011. Ref ID: ABUABARA2011	**Observational:** population-based cohort study from May 2000 to Sept 2008. **Representative population sample:** yes – large database covering 50% of US hospitals **Prognostic factor adequately measured:** yes – at least one ICD code and at least 2 prescriptions a minimum of 30 days apart for systemic psoriasis treatment or UVB phototherapy **Confounders adjusted for:** Age and sex plus comorbid diagnoses of depression,	N 25,554: phototherapy group n=4220; systemics group (n=20094)	**Inclusion criteria:** open cohort of all patients aged ≥18 years with age and sex data available and moderate-to-severe psoriasis (defined as at least one ICD code and at least 2 prescriptions a minimum of 30 days apart for systemic psoriasis treatment or UVB phototherapy) **Exclusion criteria:** none reported. Note: Of the patients receiving systemic treatment 25% received traditional systemics (methotrexate or ciclosporin), 57% received a biologic (alefacept, efalizumab, adalimumab, etanercept or infliximab) and 18% received both	Data from medical and pharmacy administrative claims database – traditional or biologic systemic agents vs UVB phototherapy	Mean unclear Mean duration of treatment ranged from 243 to 591 days **Note**: follow-up began at first prescription and continued until patients developed the outcome of interest, left the health plan or reached the end of the study period.	Acute MI – ICD code in any position after the first prescription date for systemic or phototherapy	Abbot Inc and the American Academy of Dermatology (Minority Student Mentorship Program)

	hypertension, hyperlipidaemia and diabetes, history of MI **Attrition bias:** not reported **Outcomes adequately measured:** yes **Appropriate statistical analysis:** Cox adjusted models		93% of those receiving biologics took TNF-α inhibitors The mean duration of treatment ranged from 243 to 591 days				

Patient characteristics:

	Phototherapy group	**Systemic group**	**p-value**
N	**4220**	**20094**	
Follow-up data (mean ± SD)			
Age at enrolment	44.2 ± 14.0	44.1 ± 12.1	0.553
Duration of enrolment (years)	3.8 ± 2.2	3.6 ± 2.2	<0.001
Number of visits	96 ± 87	65 ± 69	<0.001

Demographics and comorbidities			
Male (%)	49%	53%	<0.001
PsA (%)	6%	42%	<0.001
Depression	12	15	<0.001
Hypertension	21	25	<0.001
Diabetes	7	11	<0.001
Hyperlipidaemia	27	33	<0.001
Obesity	8	11	<0.001
Tobacco use	10	12	0.003
Outcomes			
Acute MI	30 (0.7%)	187 (0.9%)	-
Total person years	7872	39,931	-
Incidence per 1000 person years (95% CI)	3.81 (2.57-5.44)	4.68 (4.04-5.40)	-

Effect size:

Adjusted hazard ratio (systemic therapy vs phototherapy)

	Cox model HR (95% CI)
Unadjusted	1.22 (0.83-1.80)
Adjusted for cardiovascular risk factors	1.33 (0.90-1.96)

Final model – primary analysis (treatment type)	0.18 (0.03-1.09)

There was a significant interaction between treatment type and age:

Adjusted hazard ratio under different assumptions (systemic therapy vs phototherapy)

	N	**All subjects aged 18-70 years**	**Subjects aged 18-49 years**	**Subjects aged 50-70 years**
Primary analysis	23,785	1.10 (0.74-1.64)	0.65 (0.32-1.34)	1.37 (0.79-2.38)
Exclusion of patients with a history of MI	23,466	1.20 (0.74-1.94)	0.60 (0.28-1.30)	1.61 (0.83-2.80)
Exclusion of patients with PsA	15,157	1.10 (0.70-1.73)	0.59 (0.28-1.24)	1.40 (0.79-2.49)

Author's conclusion: Overall, there appears to be a trend towards an increased risk of MI in patients with psoriasis receiving systemic therapy compared with a group undergoing phototherapy. The risk of MI may vary by age – risk reduction in younger people receiving systemics but risk increase in older people on systemics

H.4.6 STUDY 5 - STROKE

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
Gelfand et al (2009) The risk of stroke in patients with psoriasis Ref ID: GELFAND2009	**Observational:** population-based cohort study from 1987-2002. **Representative population sample:** yes - used GPRD (which has been validated). **Prognostic factor adequately measured:** yes **Confounders adjusted for:** age, sex, hypertension, diabetes, hyperlipidemia, atrial fibrillation, and smoking (current, former, none).	N: 129,143 with mild psoriasis; 3603 with severe psoriasis; 496,666 and 14,330 matched controls.	**Inclusion criteria:** all patients defined as having mild or severe psoriasis, aged >/=18 years old at index date and had at least 1 day of observation time. Up to 4 control subjects were randomly selected for each psoriasis patient, matched on practice, date of registration in the practice and psoriasis index date (so evaluated by same physicians during same time period). **Exclusion criteria:** not reported.	General Practice Research Database used. Mild psoriasis was those with a diagnostic code of psoriasis but no history of systemic therapy at any time point. Severe psoriasis was defined as those with a diagnostic code of psoriasis and a history of systemic therapy consistent with severe psoriasis. Index date first date on or after registration in practice in which a diagnosis was recorded. For severe the index date was first date on or after first diagnosis of	3-4.4 years mean and standard deviation 2-3.3 years. Notes: ended due to: death, end of UTS, transfer out.	Stroke occurring after the start date. Stroke identified using diagnostic codes (READ or OXMIS) entered by the GP into the medical record.	Grant from the National Institute of arthritis, musculos keletal, and skin diseases. Authors state that the funding sources had no role in the design and conduct of the study. The lead author receives grant support or is an investigat or for AMGEN, Centocor, and Pfizer and is a consultant

	Attrition bias: not reported. **Outcomes adequately measured:** yes **Appropriate statistical analysis:** yes - dichotomous variables tested with Fisher's exact test and continuous with t-test. Adjusted Cox models for overall HR of stroke in psoriasis patients. **Notes:** mild psoriasis patients defined as those with a diagnostic code of psoriasis, but no history of systemic therapy at any time point. Severe psoriasis patients were defined as those with a diagnostic code of psoriasis and a history of systemic therapy			psoriasis in which the patient received a code for treatment consistent with severe psoriasis. If psoriasis occurred before registration the registration date was the index date.			for Pfizer, Genentech, Celgene, AMGEN, Centocor and Luitpold.

	consistent with severe psoriasis. Systemic therapy included phototherapy, PUVA, methotrexate, azathioprine, ciclosporine, oral retinoids (etretinate, acitretin), hydroxyurea, and mycophenolate mofetil. It was noted that during the time period that the study was conducted, biological therapies were not approved for psoriasis in the UK. The control group had no history of a psoriasis diagnostic code.						

Patient characteristics:

	Mild group		**Severe group**	
Characteristics	**Control (n=496,666)**	**Psoriasis (n=129,143)**	**Control (n=14,330)**	**Psoriasis (n=3,603)**
Male	**198.498 (40%)**	**61,956 (48%)** **P<0.001**	**5,783 (40.4%)**	**1,750 (48.6%)** **P<0.001**

Age (years) mean+/- SD	**46.1 (19.1)**	**45.1 (17.8)**	**49.7 (19.3)**	**52.2 (16.7)**
Age (years) median (IQR)	43,30, 61	42,30, 59 P<0.001 Wilcoxon test	48, 33, 65	52, 39, 66 P<0.001 Wilcoxon test
Diabetes mellitus	22,296 (4.5%)	5,858 (4.5%) P=0.470	737 (5.1%)	270 (7.5%) P<0.001
History of stroke	7,401 (1.5%)	1,648 (1.3%) P<0.001	268 (1.9%)	89 (2.5%) P=0.023
History of TIA	5637 (1.1%)	1254 (1.0%) P<0.001	243 (1.7%)	68 (1.9%) P=0.432
History of stroke or TIA	11,883 (2.4%)	2,655 (2.1%) P<0.001	450 (3.1%)	140 (3.9%) P=0.028
Hyperlipidemia	22,839 (4.6%)	6,775 (5.2%) P<0.001	842 (5.9%)	250 (6.9%) P=0.019
Hypertension	88,397 (17.8%)	22,829 (17.7%) P=0.313	3,049 (21.3%)	858 (23.8%) P=0.001
Smoking never	383,824 (77.3%)	96,944 (75.1%)	10,465 (73%)	2,488 (69.1%)
Smoking current	19,839 (4%)	5,866 (4.5%)	755 (5.3%)	241 (6.7%)
Smoking former	93,003 (18.7%)	26,333 (20.4%) P<0.001	3,110 (21.7%)	874 (24.3%) P<0.001

BMI <25	166,470 (53.2%)	40,606 (49.6%)	5,057 (51.2%)	1,025 (42.1%)
BMI>/=25 & <30	100,551 (32.1%)	27,701 (33.8%)	3,291 (33.3%)	860 (35.4%)
BMI>/=30	45,977 (14.7%)	13,618 (16.6%) P<0.001	1,522 (15.4%)	548 (22.5%) P<0.001
Reason for study end				
Death	32,677 (6.6%)	7,302 (5.6%)	790 (5.5%)	297 (8.2%)
End of UTS	353,565 (71.2%)	95, 275 (73.8%)	11,247 (78.5%)	2,860 (79.4%)
Transfer out	110,424 (22.2%)	26,566 (20.6%) P<0.001	2,293 (16%)	446 (12.4%) P<0.001
Atrial fibrillation	12,861 (2.6%)	3,046 (2.4%) P<0.01	428 (3%)	99 (2.8%) P=0.507

BMI, body mass index (calculated as weight in kilograms divided by height in meters squared);

IQR, interquartile range, SD, standard deviation; TIA, transient ischemic attack; UTS, up-to-standard.

Data for BMI were available for 67% of the patients.

Unless noted otherwise, p-values are derived using Fisher exact test.

Systemic therapies received by patients with severe psoriasis (n=3603)

Systemic therapy	**No. of patients with severe psoriasis (%)***
Methotrexate	2,114 (58.7%)

Psoralen	607 (16.9%)
Azathioprine	582 (16.2%)
Ciclosporine	390 (10.8%)
Etretinate or acetretin	333 (9.2%)
Hydroxyurea	208 (5.8%)
Mycophenolate mofetil	9 (0.3%)

***percentages do not add up to 100 because patients could have received more than one systemic therapy.**

Effect size:

Incidence of stroke in patients with psoriasis compared with control patients

	Mild group		**Severe group**	
Variable	**Control (n=496,666)**	**Psoriasis (n=129,143)**	**Control (n=14,330)**	**Psoriasis (n=3,603)**
Follow up time (years) mean +/SD	4.2 (3.3)	4.4 (3.3)	3.4 (2.7)	3.4 (2.7)
Follow up time median (IQR)	3.5 (1.5, 6.6)	3.7 (1.6, 6.9)	2.6 (1.2, 5.0)	2.7 (1.2, 5.0)
No of person-years	2,108,718	570,814.5	48,248.4	12,222.1
No of new stroke	8,535 (1.72%)	2,100 (1.63%)	212 (1.48%)	74 (2.05%)

cases (%)				
Incidence per 1,000 person-years (95% CI)	4.05 (3.96, 4.13)	3.68 (3.52, 3.84)	4.39 (3.82, 5.03)	6.05 (4.76, 7.60)

CI, confidence interval; IQR, interquartile range; SD, standard deviation

Unadjusted and adjusted Cox proportional hazard regression models of the risk of stroke in patients mild and severe psoriasis compared with control patients

	Model hazard ratio (95% CI)	
Covariate	**Mild psoriasis**	**Severe psoriasis**
Unadjusted analysis Psoriasis	0.91 (0.86, 0.95)	1.38 (1.05, 1.80)
Adjusted for age and sex		
Psoriasis	1.07 (1.02, 1.12)	1.44 (1.10, 1.88)
Age per year	1.089 (1.087, 1.090)	1.09 (1.08, 1.10)
Sex (male)	1.27 (1.22, 1.32)	1.51 (1.20, 1.91)
Primary model (adjusted for major cardiovascular risk factors)*		
Psoriasis	1.06 (1.01, 1.11)	1.43 (1.10, 1.87)
Age per year	1.082 (1.081, 1.084)	1.08 (1.07, 1.09)
Diabetes	1.78 (1.69, 1.87)	1.60 (1.16, 2.19)
HX of Stroke	4.26 (4.01, 4.51)	3.65 (2.57, 5.18)
HX of TIA	2.01 (1.87, 2.16)	2.05 (1.40, 3.01)

Hyperlipidemia	1.12 (1.04, 1.20)	1.35 (0.92, 1.98)
Hypertension	1.49 (1.43, 1.55)	1.72 (1.35, 2.18)
Sex (male)	1.20 (1.16, 1.25)	1.42 (1.12, 1.80)
Smoking (current vs never)	0.97 (0.89, 1.06)	1.09 (0.71, 1.68)
Smoking (former vs never)	1.10 (1.03, 1.17)	1.24 (0.89, 1.73)

BMI, body mass index; CI, confidence interval; HR, hazard ratio; TIA, transient ischemic attack.

*BMI was not included in the primary analysis as these data are only available in about 65% of patients.

Atrial fibrillation was not included in the primary analysis as this is not a common stroke risk factor.

Interaction terms for sex and age were not statistically significant (p>0.05).

Author's conclusion: Patients with psoriasis, particularly if severe, have an increased risk of stroke that is not explained by major stroke risk factors identified in routine medical care.

H.4.7 STUDY 6 ACUTE ISCHAEMIC HEART DISEASE

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of

							funding
Wakkee (2010) Psoriasis may not be an independent risk factor for acute ischemic heart disease hospitalisations: results of a large population-based Dutch cohort. Ref ID: WAKKEE2010	**Observational:** prospective population-based cohort from 1997 to 2008. **Representative population sample:** yes – PHARMO record linking system which includes database of hospital discharge information, drug dispensing and clinical laboratory records for 2.5 million individuals in the Netherlands. **Prognostic factor adequately measured:** yes **Confounders adjusted for:** Matched for age and sex; adjusted for healthcare consumption proxy, metabolic drugs and an interaction term between psoriasis and healthcare consumption in IHD model	N: 15,820 (36.5%) psoriasis cohort; 25,577 (63.5%) reference cohort.	**Inclusion criteria:** An algorithm that categorised individuals by the likelihood of psoriasis diagnosis (none, possible, probable or definite) from which only those with definite were selected. Those with a hospital discharge diagnosis of psoriasis and/or psoriatic arthritis, dispensings for psoralen, calcipotriol, calcitriol or dithranol, fumaric acid, and/or efalizumab were considered as definite psoriasis patients. **Exclusion criteria:** patients were classified as possibly or probably having psoriasis if they did not meet any of the above criteria of definite but had prescriptions for topical corticosteroids, coal tar, systemic glucocorticosteroids, retinoids, methotrexate, ciclosporin, adalimumab,	Used data from the PHARMO record linkage system, which links various medical databases. Coded according to the international classification of diseases, ninth revision (WHO, 1987) – medical procedures, dates of hospital admission and discharge; The Anatomical Therapeutic Chemical Classification (WHO, 1999) – dispensing date, amount dispensed and prescription dose regimens and length.	Median follow-up 6 years in both cohorts. First available date of an active treatment or hospitalisation for psoriasis between 1998 and 2007. Matched controls followed from random drug dispensing or hospitalisation occurring within 30 days of the start of follow-up of their matched psoriasis patient. **Note**: follow-up ended with the last drug dispensing before 2008, an IHD or death, whichever was first.	Primary outcome was hospitalisation for acute IHD (acute MI, other acute IHD and angina pectoris); acute MI was also studied separately.	Grant from Wyeth Pharmaceuticals.

	Attrition bias: not reported. **Outcomes adequately measured:** yes **Appropriate statistical analysis:** yes – student t-test and Mann-Whitney for continuous variables. Incidence rates and 95% CIs from Byar's approximation. Kaplan-Meier and Cox proportional hazard analyses were used.		etanercept, and/or infliximab; definite psoriasis patients were excluded if hospitalised for skin conditions other than psoriasis, had < 6 months history before start of follow-up (which is twice the maximum prescription time allowed in the Netherlands) and/or were <18 years of age at index date; also those with a history of diseases that could, theoretically affect the development of psoriasis or its severity (HIV, immune disorders, inflammatory bowel diseases, hepatitis B and C, multiple sclerosis, rheumatoid arthritis, and status after organ transplant). Reference subjects selected and matched in a 1:2 ratio for age, gender, and presence of a database record within				

			30 days of cohort entry of a definite psoriasis patient. Excluded if < 6 months history was available or if they were hospitalised for dermatological diseases or other conditions above.				

Baseline characteristics

Variable	Psoriasis cohort	Reference cohort
Male (%)	7,583 (47.9%)	13,306 (48.3%)
Female (%)	8,237 (52.1)	14,271 (51.7
Age years Mean (SD)	48.9 (16.1)	48.1 (16.1)
Earlier hospitalisations[1]		
Yes (%)	1,130 (7.1)[2]	1,415 (5.1)[2]
Total	1,676	1,979
Unique	1,447	1,802
Medical history		
Lipid-lowering drugs (%)	1,102 (7.0)[3]	1,701 96.2)[3]
Antihypertensive	3,076 (19.4)[4]	4,519 (16.4)[4]

drugs (%)		
Antidiabetic drugs (%)	699 (4.4)[4]	993 (3.6)[4]
Psoriasis therapies		
Topicals only	13,851 (87.5)	
Systemic therapy and/or hospitalisation[5]	1,969 (12.5)	
Specific therapies ever used since start of follow-up[6]		
Topical antipsoriatic therapies[7]	15,646 (98.9)	
PUVA therapy	505 (3.2)	
Methotrexate	122 (0.8)	
Ciclosporin	424 (2.7)	
Acitretin	789 (5.0)	
Fumarates	14 (0.1)	
Biologics	84 (0.5)	

PUVA, psoralen plus ultraviolet light A; SD, standard deviation;

[1] In 6 months before cohort entry (excluding hospitalisations for cardiovascular diseases, n=100 and n=124 for the psoriasis and control cohorts, respectively).

[2] p<0.001.

[3] p=0.001.

[4] p<0.001.

[5] Systemic drugs include PUVA therapy, and hospitalisation should be specific for psoriasis.

[6] Total adds up to more than 100% because of the possibility of multiple therapies per patient.

[7] Coal tar, topical corticosteroids, dithranol, calcipotriol, calcitriol, tacrolimus, and pimecrolimus.

[8] Adalimumab (n=19), efalizumab (n=8), etanercept (n=65), infliximab (n=2).

Effect size:

Incidence rates of ischemic heart disease (IHD) and acute myocardial infarction (MI) in patients with psoriasis and the reference cohort, and the crude and adjusted hazard ratios (HRs)

Outcome	**Events**	**Person-years**	**Incidence rate[1]**	**95% CI**	**Crude HR[2]**	**95% CI**	**Adjusted HR[3]**	**95% CI**
IHD[4]								
Reference cohort	846	151,303	559	522,598	1		1	
Psoriasis cohort	583	95,437	611	562,663	1.10	0.99, 1.23	1.05	0.95, 1.17
Acute MI								
Reference cohort	360	153,514	235	211,260	1		1	
Psoriasis cohort	223	97,029	234	201,262	0.99	0.84, 1.17	0.94	0.80, 1.11

CI, confidence interval.

[1] Incidence rate per 100,000 person-years.

[2] HR adjusted for age and gender by matching.

[3] Adjusted for age, gender, earlier use of antihypertensive, antidiabetic, and lipid-lowering drugs, the number of earlier non-cardiovascular hospitalisations in 180 days before cohort entry, and significant interaction terms.

[4] IHD includes hospitalisations for acute myocardial infarction, angina pectoris, and other acute IHDs.

Author's conclusion: The risk of IHD tended to be increased in their study but the analyses of their data suggest that other factors, eg referral bias for other disease are important for interpreting the results. The age and gender-adjusted risk of IHD was comparable between the cohorts. Adjusting for the increased antihypertensive, antidiabetic and lipid-lowering drugs and more hospitalisations that the psoriasis group had the risk remained comparable between both groups. There was no difference between the subgroup that only used topicals versus those who received systemic therapies or inpatient care for psoriasis. Therefore they suggest that psoriasis is not a clinically relevant risk factor for IHD hospitalisations on the population level.

H.4.8 STUDY 6 VENOUS THROMBOEMBOLISM

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
O. Ahlehoff, G. H. Gislason, J. Lindhardsen, M. G. Charlot, C. H. Jorgensen, J. B. Olesen, D.-	**Observational:** retrospective Danish population-based cohort from 1997 to 2006 (data gathered prospectively). **Representative population sample:** yes	N: 38,664 (1%) psoriasis cohort (35,138 mild and 3526 severe); 4,126,075 (99%)	**Inclusion criteria:** age ≥18 years **Exclusion criteria:** prevalent psoriasis; history of previous VTE; receiving vitamin K	Used data from the Danish National Patient Register, National Prescription Registry, Central Population Register and National Causes of Death Register	Maximum follow-up 10 years in both cohorts. New-onset psoriasis **Note**: follow-up ended on	Primary outcome was first-time in-hospital discharge diagnosis of VTE (VTE diagnoses made in Emergency	Department of Cardiology, Copenhagen University Hospital

M. Bretler, L. Skov, C. Torp-Pedersen, and P. R. Hansen. Psoriasis carries an increased risk of venous thromboembolism: a Danish nationwide cohort study. PLoS ONE 6 (3), 2011. Ref ID: AHLEHOFF 2011	– entire adult Danish population (reduced surveillance bias [people with psoriasis being more likely to visit the GP and therefore be diagnosed with CVD] and avoids selection bias) **Prognostic factor adequately measured:** yes **Confounders adjusted for:** age, calendar year, concomitant medication, comorbidity, socioeconomic data, and gender. **Attrition bias:** not reported. **Outcomes adequately measured:** yes **Appropriate statistical analysis:** yes – Unadjusted event rates	reference cohort.	antagonist treatment **Note:** psoriasis patients were identified by claims of prescriptions for vitamin D analogues according to the comprehensive National Prescription registry and included on their second prescription Severe psoriasis was identified by hospitalisations (including out-patient visits) for psoriasis or psoriatic arthritis – this classification has been validated Note: unable to identify patients treated with topical corticosteroids alone and also unable to address the potential impact of various systemic treatment strategies Comorbidity at study	Individual-level linkage across all nationwide prospectively recorded registers was possible Coded according to the international classification of diseases, 8th-10th revision (WHO, 1987)	December 31st 2006 or death	Departments were not included) Secondary outcome was hospitalisations with the specific diagnosis of pulmonary embolism	

	are summarized as events per 1000 person-years. The rate ratios (RRs) and 95% confidence interval (CI) of VTE were estimated by time-dependent Poisson regression models adjusted for age, calendar year, concomitant medication, comorbidity (according to Charlton Comorbidity Index), socioeconomic data (surrogate for obesity and smoking), and gender. Psoriasis status was included as a time-dependent variable, i.e., patients were only considered at risk from the time they complied with the inclusion criteria. Age and calendar year were also included as time-dependent variables. Comorbidity, socioeconomics, and concomitant medication were included as fixed variables obtained at baseline.		entry was described by Charleson's Index (19 pre-specified diagnoses at study entry and up to 1 year previously) and modified to ICD-10				

Baseline characteristics

Characteristic	**Controls** **n = 4,126,075**	**Mild psoriasis** **n = 35,138**	**Severe psoriasis** **n = 3526**
Age, years (SD)	46.8 (18)	47.7 (16)	48.4 (16)
Men (%)	48.9%	50.0%	51.9%
No. of person-years	38,503,356	175,384	22,135
Comorbidity (%)			
Peripheral vascular disease	0.14%	0.12%	0.23%
Cerebrovascular disease	0.3%	0.26%	0.23%
Coronary heart disease	0.47%	0.54%	1.05%
Congestive heart failure	0.16%	0.11%	0.32%
Hepatic disease	0.06%	0.06%	0.88%
Chronic obstructive pulmonary disease	0.27%	0.16%	0.28%
Cardiac dysrhythmia	0.27%	0.19%	0.45%

Renal disease	0.06%	0.03%	0.14%
Cancer	0.6%	0.44%	0.99%
Rheumatological disease	0.09%	0.08%	0.26%
Treatment (%)			
Platelet inhibitor	2.32%	2.4%	2.01%
Beta-blocker	3.27%	4.27%	4.74%
ACEI/ARB	2.82%	3.54%	3.77%
Loop diuretic	2.98%	2.45%	4.28%
Statin	0.68%	1.06%	0.94%
Spironolactone	0.35%	0.29%	0.77%
Glucose-lowering drug	1.74%	1.83%	2.72%

Effect Size

Incidence rates of venous **thromboembolism (VTE)** in patients with psoriasis and the reference cohort, and the adjusted incidence rate ratios (RR)

Outcome	**Incidence rate per 1000 person years (95% CI)**[1]		**Adjusted RR (95% CI)**		
	< 50 years	**≥ 50 years**	**< 50 years**	**≥ 50 years**	**All ages**
Controls	0.58 (0.57-0.59)	2.03 (2.01-2.05)	1	1	**1**

Mild psoriasis	0.73 (0.56-0.95)	2.74 (2.45-3.06)	1.24 (0.97-1.58)	1.26 (1.13-1.42)	**1.35 (1.21-1.49)**
Severe psoriasis	2.10 (1.32-3.33)	3.93 (3.01-5.13)	3.14 (1.98-4.97)	1.74 (1.32-2.28)	**2.06 (1.63-2.61)**

Incidence rates of venous **pulmonary embolism** (PE) in patients with psoriasis and the reference cohort, and the adjusted incidence rate ratios (RR)

Outcome	**Adjusted RR (95% CI)**
	All ages
Controls	**1**
Mild psoriasis	**1.14 (0.95-1.37)**
Severe psoriasis	**1.88 (1.22-2.89)**

Sensitivity analyses for VTE risk

Outcome	**Adjusted RR (95% CI)**	
	Excluding those with a history of cancer or rheumatological disease	**Censoring patients undergoing a surgical procedure**
Controls	1	1
Mild psoriasis	1.34 (1.21-1.49)	1.20 (0.96-1.51)
Severe	1.99 (1.56-2.53)	2.55 (1.53-4.24)

psoriasis		

Note: results were not different if the diagnostic criteria for psoriasis were less restrictive (first Vit D prescription or first diagnosis); neither did exclusion of all patients with in- or out-patient hospital contacts up to 1 year prior to study start significantly alter the results

Author's conclusion:

- This first nationwide cohort study indicates that patients with psoriasis are at increased risk of VTE.
- The risk was highest in young patients with severe disease.
- Further prospective studies are needed to confirm this association, but physicians should be aware that patients with psoriasis may be at increased risk of both venous and arterial thromboembolic events

H.4.9 STUDY 7 CARDIOVASCULAR RISK

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
O. Ahlehoff, G. H. Gislason, M. Charlot, C. H. Jorgensen, J. Lindhardsen, J. B. Olesen, S. Z. Abildstrom, L. Skov, C. Torp-Pedersen, and P. R.	**Observational:** retrospective Danish population-based cohort from 1997 to 2006 (data gathered prospectively). **Representative population sample:** yes – entire adult Danish population (reduced surveillance bias and avoids selection bias)	N: 36,992 (1%) psoriasis cohort (34,371 mild and 2621 severe, including 607 with PsA); 4,003,265 (99%) reference cohort.	**Inclusion criteria:** age ≥18 years **Exclusion criteria:** prevalent psoriasis, diabetes mellitus or atherosclerotic disease (including prior stroke or MI) **Note:** psoriasis patients	Used data from the: Danish National Patient Register for mortality (records all hospital admissions, diagnoses, and invasive procedures according the World Health Organisations International Classification of	Maximum follow-up 10 years in both cohorts. New-onset psoriasis **Note**: follow-up ended on December 31st 2006 or death	All-cause mortality, cardiovascular mortality and hospitalisations for MI, stroke and coronary revascularisation (PCI and CABG)	Department of Cardiology, Copenhagen University Hospital

Hansen. Psoriasis is associated with clinically significant cardiovascular risk: A Danish nationwide cohort study. J.Intern.Med 270 (2):147-157, 2011. Ref ID: AHLEHOFF 2011D	**Prognostic factor adequately measured:** yes **Confounders adjusted for:** age, calendar year, concomitant medication, comorbidity, socioeconomic data, and gender. **Attrition bias:** not reported. **Outcomes adequately measured:** yes **Appropriate statistical analysis:** yes – Unadjusted event rates are summarized as events per 1000 person-years. The rate ratios (RRs) and 95% confidence interval (CI) were estimated by time-dependent Poisson regression models	In the adjusted analysis patients with psoriasis were matched for age and gender with 4 controls from the general population for sensitivity analyses	were identified by claims of prescriptions for vitamin D analogues according to the comprehensive National Prescription registry and included on their second prescription Severe psoriasis was identified by hospitalisations (including out-patient visits) for psoriasis or psoriatic arthritis – this classification has been validated Diabetes was identified by first prescription of glucose-lowering drugs or insulin Note: unable to identify patients treated with topical corticosteroids alone and also unable to address the potential impact of various systemic treatment strategies	Diseases (ICD), 8th-10th revision (WHO, 1987). Danish Registry of Medicinal Product Statistics (the National Prescription Registry), for medications (records all dispensed prescriptions since 1995) Central Population Register for mortality (records all deaths within 2 weeks). National Causes of Death Register for cause of death (records immediate, contributory, and underlying causes of death were recorded using ICD-10 codes) Individual-level linkage across all nationwide prospectively recorded registers was possible			

	adjusted for age, calendar year, concomitant medication, comorbidity (according to Charlton Comorbidity Index), socioeconomic data (surrogate for obesity and smoking), and gender. Psoriasis status was included as a time-dependent variable, i.e., patients were only considered at risk from the time they complied with the inclusion criteria. Age and calendar year were also included as time-dependent variables. Comorbidity and concomitant medication were included as fixed variables obtained at baseline.		Comorbidity at study entry was described by Charleson's Index (19 pre-specified diagnoses at study entry and up to 1 year previously) and modified to ICD-10				

Baseline characteristics

Characteristic	Controls	Mild psoriasis	Severe psoriasis

	n = 4,003,265	n = 34,371	n = 2621
Age, years (SD)	47.3 (15.8)	47.2 (15.9)	46.9 (15.4)
Men (%)	48.5%	49.4%	51.6%
No. of person-years	36,965,324	172,224	13,146
Comorbidity (%)			
Congestive heart failure	0.17%	0.1%	0.15%
Chronic obstructive pulmonary disease	0.24%	0.13%	0.23%
Cardiac dysrhythmia	0.27%	0.24%	0.38%
Renal disease	0.05%	0.03%	0.08%
Cancer	0.57%	0.46%	0.61%
Rheumatological disease	0.09%	0.06%	0.11%
Treatments			
Platelet inhibitor	0.17%	1.61%	1.34%
Beta-blocker	2.86%	3.83%	4.08%
ACEI/ARB	2.25%	2.88%	2.82%
Vitamin K antagonist	0.38%	0.38%	0.27%
Loop diuretic	2.43%	2.07%	3.24%
Statin	0.44%	0.67%	0.65%

Spironolactone	0.29%	0.26%	0.38%

Effect Size

Adjusted incidence rate ratios in patients with psoriasis compared with the reference cohort

Outcomes	**Mild psoriasis**				**Severe psoriasis**			
	Overall (n=43,371)	**18-50 yr (n=16,150)**	**51-70 yr (n=13,714)**	**>70 yr (n=4507)**	**Overall (n=2621)**	**18-50 yr (n=1296)**	**51-70 yr (n=1031)**	**>70 yr (n=294)**
All cause mortality								
RR (CI)	1.16 (1.11-1.20)	1.26 (1.08-1.47)	1.23 (1.15-1.31)	1.13 (1.08-1.19)	1.73 (1.54-1.94)	2.87 (2.04-4.02)	2.32 (1.96-2.74)	1.24 (1.05-1.48)
p-value	<0.001	0.003	<0.001	<0.001	<0.001	<0.001	<0.001	0.01
Cardiovascular death								
RR (CI)	1.14 (1.06-1.22)	1 (0.66-1.50)	1.2 (1.05-1.36)	1.14 (1.06-1.24)	1.57 (1.27-1.94)	2.98 (1.32-6.73)	2.22 (1.59-3.10)	1.18 (0.89-1.57)
p-value	<0.001	0.99	0.01	0.001	<0.001	0.001	<0.001	0.26
Composite end-point								
RR (CI)	1.2 (1.14-1.25)	1.4 (1.20-1.63)	1.21 (1.12-1.29)	1.16 (1.09-1.24)	1.58 (1.36-1.82)	2.04 (1.35-3.09)	1.85 (1.51-2.26)	1.19 (0.95-1.50)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	0.001	<0.001	0.13

Stroke								
RR (CI)	1.25 (1.16-1.33)	1.61 (1.32-1.97)	1.22 (1.10-1.35)	1.15 (1.05-1.20)	1.71 (1.39-2.11)	1.64 (0.88-3.07)	1.87 (1.41-2.49)	1.47 (1.07-1.26)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Myocardial infarction								
RR (CI)	1.22 (1.12-1.33)	1.17 (0.89-1.54)	1.12 (0.99-1.26)	1.3 (1.16-1.45)	1.45 (1.10-1.9)	2.32 (1.19-4.50)	1.44 (0.99-2.09)	1.00 (0.63-1.45)
p-value	<0.001	0.63	0.06	<0.001	0.01	0.01	0.05	0.97
Coronary revascularisation								
RR (CI)	1.37 (1.26-1.49)	1.62 (1.26-2.07)	1.26 (1.13-1.40)	1.45 (1.24-1.69)	1.77 (1.35-2.32)	2.27 (1.17-4.42)	1.63 (1.16-2.27)	1.58 (0.92-1.45)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	0.02	0.01	0.10

Adjusted incidence rate ratios in patients with psoriasis affecting the skin only or also the joints compared with the reference cohort

Note that there were no significant differences in baseline characteristics between these two subgroups

Outcome	**Severe psoriasis (skin only)** **N=2014**				**Psoriatic arthritis** **N=607**				**Wald Chi-square test between overall estimates**
	Overall	**18-50 yr**	**51-70 yr**	**>70 yr**	**Overall**	**18-50 yr**	**51-70 yr**	**>70 yr**	**P-value**
All cause mortality									
RR (CI)	1.81 (1.60-	3.33 (2.30-	2.59 (2.15-	1.27 (1.05-	1.74 (1.32-	2.23 (1.06-	1.87 (1.27-	1.43 (0.88-	0.79

	2.05)	4.84)	3.12)	1.54)	2.30)	4.69)	2.74)	2.34)	
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	0.03	0.001	0.15	
Cardiovascular death									
RR (CI)	1.56 (1.22-1.98)	3.58 (1.47-8.77)	2.18 (1.45-3.26)	1.25 (0.91-1.72)	1.84 (1.11-3.06)	1.87 (0.26-13.3)	2.68 (1.40-5.16)	1.19 (0.49-2.85)	0.55
p-value	<0.001	0.01	<0.001	0.16	0.02	0.53	0.003	0.7	
Composite end-point									
RR (CI)	1.56 (1.32-1.84)	1.77 (1.04-3.00)	1.93 (1.52-2.47)	1.24 (0.96-1.60)	1.79 (1.31-2.45)	3.27 (1.70-6.31)	1.79 (1.17-2.75)	1.20 (0.62-2.30)	0.44
p-value	<0.001	0.04	<0.001	0.1	<0.001	<0.001	0.01	0.59	

Sensitivity analyses

Note: results were not different if the diagnostic criteria for psoriasis were less restrictive (first Vit D prescription or first diagnosis); neither did exclusion of all patients with in- or out-patient hospital contacts up to 1 year prior to study start significantly alter the results. The results were also similar when using a control cohort matched for age and gender from the full population

Author's conclusion:

- Psoriasis is associated with increased risk of adverse cardiovascular events and all-cause mortality (independent of age, gender, comorbidity, concomitant medication and socio-economic status).
- Young age, severe skin affection and/or psoriatic arthritis carry the most risk.
- The risk was similar among those with severe skin psoriasis and PsA
- Patients with psoriasis may be candidates for early cardiovascular risk factor modification

H.4.10 STUDY 8 ATRIAL FIBRILLATION AND ISCHAEMIC STROKE

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
Ole Ahlehoff, Gunnar H. Gislason, Casper H. Jorgensen, Jesper Lindhardsen, Mette Charlot, Jonas B. Olesen, Steen Z. Abildstrom, Lone Skov, Christian Torp-Pedersen, and Peter Riis Hansen. Psoriasis and risk of atrial fibrillation and ischaemic stroke: a Danish Nationwide	**Observational:** retrospective Danish population-based cohort from 1997 to 2006 (data gathered prospectively). **Representative population sample:** yes – entire adult Danish population (reduced surveillance bias and avoids selection bias) **Prognostic factor adequately measured:** yes **Confounders adjusted for:** age, calendar year, concomitant medication, comorbidity, socioeconomic data, and gender.	N: 39,558 (0.9%) psoriasis cohort (36,765 mild and 2793 severe; 4,478,926 (99.1%) reference cohort. In a sensitivity analysis patients with psoriasis were matched for age and gender with 4 controls from the general populatio n	**Inclusion criteria:** age ≥18 years **Exclusion criteria:** prevalent psoriasis, AF and/or stroke **Note:** psoriasis patients were identified by claims of prescriptions for vitamin D analogues according to the comprehensive National Prescription registry and included on their second prescription (approximately 70% of psoriasis patients who require continuing topical treatment will receive vitamin D analogues)	Used data from the: Danish National Patient Register for mortality (records all hospital admissions, diagnoses, and invasive procedures according the World Health Organisations International Classification of Diseases (ICD), 8th-10th revision (WHO, 1987). Danish Registry of Medicinal Product Statistics (the National Prescription Registry), for medications (records all dispensed prescriptions since	Maximum follow-up 10 years in both cohorts. New-onset psoriasis **Note**: follow-up ended on December 31st 2006, emigration or death	First-time atrial fibrillation and ischemic stroke	Departme nt of Cardiolog y, Copenhag en University Hospital

Cohort Study. European Heart Journal, 2011. Ref ID: AHLEHOFF 2011E	A calculation was also made that showed that the estimated magnitude of any unmeasured confounder that could nullify the results would have to be greater than the effects and distribution of any of the measured confounders (e.g. valvular heart disease or prior MI) **Attrition bias:** <4% **Outcomes adequately measured:** yes **Appropriate statistical analysis:** yes – Unadjusted event rates are summarized as events per 1000 person-years. The rate ratios (RRs) and 95% confidence interval (CI) were estimated by time-dependent Poisson regression models adjusted for age calendar		Severe psoriasis was identified by hospitalisations (including out-patient visits) for psoriasis or psoriatic arthritis – this classification has been validated Diabetes was identified by first prescription of glucose-lowering drugs or insulin Note: unable to identify patients treated with topical corticosteroids alone and also unable to address the potential impact of various systemic treatment strategies Comorbidity at study entry was described by valvular heart disease and Charleson's Index (19 pre-specified diagnoses at study entry and up to 1 year previously) and modified to ICD-10	1995) Central Population Register for mortality (records all deaths within 2 weeks). National Causes of Death Register for cause of death (records immediate, contributory, and underlying causes of death were recorded using ICD-10 codes) Individual-level linkage across all nationwide prospectively recorded registers was possible			

	year, concomitant medication, comorbidity (according to Charlton Comorbidity Index), socioeconomic data (surrogate for obesity and smoking), and gender. Psoriasis status was included as a time-dependent variable, i.e., patients were only considered at risk from the time they complied with the inclusion criteria. Age and calendar year were also included as time-dependent variables. Comorbidity and concomitant medication were included as fixed variables obtained at baseline.						

Baseline characteristics

Characteristic	**Controls** **n = 4,478,926**	**Mild psoriasis** **n = 36,765**	**Severe psoriasis** **n = 2793**
Age, years (SD)	43.7 (19.7)	46.1 (16.9)	46.0 (16.4)

Men (%)	51.0%	50.4%	48.8%
Mean follow-up time (years)	9.2	5.0	4.7
No. of person-years	41,345,205	184,624	13,261

Effect Size

Adjusted incidence rate ratios in patients with psoriasis compared with the reference cohort

Outcomes	**Mild psoriasis**			**Severe psoriasis**		
	Overall (n=36,765)	**18-50 yr**	**≥50 yr**	**Overall (n=2793)**	**18-50 yr**	**≥50 yr**
Atrial fibrillation						
RR (CI)	1.22 (1.14-1.30)	1.50 (1.21-1.86)	1.16 (1.08-1.24)	1.53 (1.23-1.91)	2.98 (1.80-4.92)	1.29 (1.01-1.65)
Attributable risk percentage	18.0%			34.6%		
Ischaemic stroke						
RR (CI)	1.25 (1.17-1.34)	1.97 (1.66-2.34)	1.13 (1.04-1.21)	1.65 (1.33-2.05)	2.80 (1.81-4.34)	1.34 (1.04-1.71)
Attributable risk percentage	20.0%			39.4%		

Sensitivity analyses

Note: results were not different if the diagnostic criteria for psoriasis were less restrictive (first Vit D prescription or first diagnosis); neither did exclusion of all patients with prior MI or censoring of patients at the time of surgical procedure, valvular heart disease or anti-thyroid treatment significantly alter the results. The results were also similar when using a control cohort matched for age and gender from the full population

Author's conclusion:

- Psoriasis is associated with increased risk of adverse cardiovascular events
- Young age, and severe psoriasis carry the most risk.

H.4.11 STUDY 8 ALL-CAUSE MORTALITY AND CARDIOVASCULAR EVENTS (following first-time MI)

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
O. Ahlehoff, G. H. Gislason, J. Lindhardsen, J. B. Olesen, M. Charlot, L. Skov, C. Torp-Pedersen, and P. R. Hansen. Prognosis	**Observational:** retrospective Danish population-based cohort from 1997 to 2006 (data gathered prospectively). **Representative population sample:** yes (but indirect) – entire adult Danish population who experienced first-	N: 462 (0.9%) psoriasis cohort; 48935 (99.1%) reference cohort.	**Inclusion criteria:** first-time MI during 2002-2006; age ≥10 years **Exclusion criteria:** not stated	Used data from the: Danish National Patient Register for mortality (records all hospital admissions, diagnoses, and invasive procedures according the World	Short-term prognosis evaluated as 30-day outcome **Note**: follow-up ended on December 31st 2006, emigration, death or an event	Primary end-points: all-cause mortality and a composite of recurrent MI, stroke and cardiovascular death Invasive coronary revascularisat	Department of Cardiology, Copenhagen University Hospital

following first-time myocardial infarction in patients with psoriasis: A Danish nationwide cohort study. J.Intern.Med 270 (3):237-244, 2011. Ref ID: AHLEHOFF 2011B	time MI during 2002-2006 (reduced surveillance bias and avoids selection bias) **Prognostic factor adequately measured:** yes **Confounders adjusted for:** age, gender, year of inclusion, concomitant medication, comorbidity and socioeconomic data **Attrition bias:** <2% **Outcomes adequately measured:** yes **Appropriate statistical analysis:** yes – Unadjusted event rates are summarized as events per 1000 person-years. The hazard ratios (HRs) and 95% confidence interval (CI)		**Note:** psoriasis patients were identified by claims of prescriptions for vitamin D analogues according to the comprehensive National Prescription registry and included on their second prescription (approximately 70% of psoriasis patients who require continuing topical treatment will receive vitamin D analogues) Note: unable to identify patients treated with topical corticosteroids alone and also unable to address the potential impact of various systemic treatment strategies Comorbidity at study entry was assessed according to the Ontario acute MI mortality prediction rules	Health Organisations International Classification of Diseases (ICD), 8th-10th revision (WHO, 1987). Danish Registry of Medicinal Product Statistics (the National Prescription Registry), for medications (records all dispensed prescriptions since 1995) Central Population Register for mortality (records all deaths within 2 weeks). National Causes of Death Register for cause of death (records immediate, contributory, and underlying causes of death were recorded using ICD-10 codes) Individual-level linkage across all nationwide prospectively		ion was defined as percutaneous coronary intervention (PCI) or coronary artery bypass grafted (CABG)	

	were estimated by Cox regression models controlling for age, gender, year of inclusion, concomitant medication, comorbidity and socioeconomic data (surrogate for obesity and smoking).			recorded registers was possible			

Baseline characteristics

Characteristic	**Controls** **n = 48,935**	**Psoriasis** **n = 462**	**p-value for difference**
Age, years (SD)	70.6 (13.5)	69.5 (12.1)	0.06
Men (%)	61.3%	63.4%	0.35
Comorbidity (%)			
Shock	2.7	2.8	0.9
Pulmonary oedema	1.6	0.4	0.05
Cardiac dysrhythmia	13.9	13.4	0.78
Peripheral atherosclerosis	3.65	2.6	0.23
Congestive heart failure	15.4	16.5	0.52

Chronic obstructive pulmonary disease	7.8	8.9	0.41
Acute renal failure	1.7	1.5	0.75
Cancer	3.6	5.2	0.07
Treatments			
Platelet inhibitor	34.1	37.9	0.09
Beta-blocker	30.7	33.6	0.18
ACEI/ARB	**29.5**	**34.9**	**0.01**
Statin	**22.8**	**27.5**	**0.02**
Loop diuretic	22.9	25.5	0.18
Spironolactone	5.5	5.5	0.93
Glucose-lowering	11.8	13.2	0.35
Note: at baseline patients with psoriasis had a higher rate of ischemic heart disease other than MI (p=0.01)			

Effect Size

Adjusted hazard ratios in patients with psoriasis compared with the reference cohort

Outcomes	**Incidence rate per 1000**	**HR (95% CI)**
All cause mortality		
Complete follow-up	Psoriasis: 138.3 (114.1-167.7)	1.18 (0.97-1.43)

	Control: 119.4 (117.2-138.8)	
1 year follow-up	-	1.15 (0.95-1.40)
30-day follow-up	-	1.20 (0.99-1.46)
Sensitivity analysis – differences in post-MI treatment	-	1.15 (0.93-1.44)
Sensitivity analysis – less stringent classification of psoriasis	-	1.18 (1.03-1.34)
Composite outcome		
Complete follow-up	Psoriasis: 185.6 (155.8-221.0) Control: 149.7 (147.1-152.4)	1.26 (1.06-1.54)
1 year follow-up		1.24 (1.04-1.48)
30-day follow-up		1.24 (1.04-1.49)
Sensitivity analysis – differences in post-MI treatment		1.26 (1.03-1.53)
Sensitivity analysis – less stringent classification of psoriasis		1.25 (1.11-1.42)
Author's conclusion: • After first-time MI people with psoriasis have a significantly impaired prognosis		

H.4.12 STUDY 7 CARDIOVASCULAR DISEASE

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
N. N. Mehta, Y. Yu, R. Pinnelas, P. Krishnamoorthy, D. B. Shin, A. B. Troxel, and J. M. Gelfand. Attributable risk estimate of severe psoriasis on major cardiovascular events. Am.J.Med. 124 (8):775, 2011. Ref ID: METHA2011	**Observational:** cohort study from 1987-2002. **Representative population sample:** yes GPRD used. **Prognostic factor adequately measured:** yes **Confounders adjusted for:** cardiovascular risk factors including age, sex, hypertension, diabetes, hyperlipidaemia, and smoking (current, former, never). BMI calculated from the data available in medical record.	N: severe psoriasis group n=3603; control group n=14330)	**Inclusion criteria:** 18 years or older at index date and had at least 1 day of observation time; severe psoriasis patients their index date was first date on or after the first diagnosis of psoriasis in which they received a code for treatment consistent with severe disease. Patients without psoriasis the index date was date of medical record entry within 60 days of the psoriasis index date. Up to 4 unexposed subjects were randomly selected, matched on practice, date of registration in practice and psoriasis index date. **Exclusion criteria:** history of cardiovascular disease, defined as ischemic heart disease, MI, TIA, stroke or peripheral arterial disease on or before the start date	General Practice Research Database. Severe psoriasis defined as code of psoriasis and history of systemic therapy consistent with severe psoriasis (e.g., UVB, PUVA, MTX, azathioprine, CSA, retinoids, hydroxyurea and myconphenolate mofetil	Mean 3.4 ± 2.8 years for non-psoriasis and 3.4 ± 2.7 years for psoriasis group. For psoriasis cohort follow-up started at the latest date when they could be defined as having severe psoriasis For all groups follow-up ended at death, event, transfer out of practice or end of 'up-to-standard' status	First recorded major adverse cardiac event (nonfatal MI, nonfatal stroke or death due to CV cause)	National Psoriasis Foundation Award, Doris Duke Charitable Foundation grant, Psoriasis Research Foundation in honour of Herman Beerman and grant from the National Institute of Arthritis, Musculoskeletal, and Skin Diseases and the Heart Lung Blood Institute.

	Attrition bias: not reported **Outcomes adequately measured:** yes **Appropriate statistical analysis:** yes – age and sex adjusted Cox proportional hazards model						

Patient characteristics:

Characteristics	**Unexposed group(n=14330)**	**Psoriasis group (n=3603)**	**P values**
Sex (male)	5783 (40.4%)	1750 (48.6%)	P<0.001
Age (year)[1]		P<0.001	
Mean (SD)	49.7 (19.3)	52.2(16.7)	
Median (IQR)	48 (33-65)	52 (39-66)	
Diabetes mellitus	737 (5.1%)	270 (7.5%)	P<0.001
History of MI	375 (2.6%)	116 (3.2%)	P=0.052
History of stroke	268 (1.9%)	89 (2.5%)	P=0.023
History of TIA	243 (1.7%)	68 (1.9%)	P=0.432

Hyperlipidaemia	842 (5.9%)	250 (6.9%)	P=0.019
Hypertension	3049 (21.3%)	858 (23.8%)	P=0.001
Smoking			
Never	10465 (73%)	2488 (69.1%)	
Current	755 (5.3%)	241 (6.7%)	
Former	3110 (21.7%)	874 (24.3%)	P<0.001
BMI[2]			
<25	5057 (51.2%)	1025 (42.1%)	
>/=25 and <30	3291 (33.3%)	860 (35.4%)	
>/=30	1522 (15.4%)	548 (22.5%)	P<0.001
Reason for end of study			
Death	790 (5.5%)	297 (8.2%)	
End of UTS	11247 (78.5%)	2860 (79.4%)	
Transfer out	2293 (16%)	446 (12.4%)	P<0.001

MI, myocardial infarction; TIA, transient ischaemic attach; BMI, body mass index; SD, standard deviation; IQR, interquartile range.

[1] Wilcoxon test.

[2] Data for BMI were available for 69% of the patients.

Effect size:

Variable	Unexposed	Psoriasis
Mean follow-up, years (SD)	3.4 (2.8)	3.4 (2.7)
Number of person years	48661.8	12346.3
Number of MACEs	148 (2.9%)	384 (4.5%)
Incidence per 1000 person-years (95% CI)	11.6 (10.7-12.6)	16.4 (14.3-18.9)

Adjusted Cox proportional hazard regression models of the risk of MACE in severe psoriasis compared with unexposed patients (plus sensitivity analyses)

Covariate	N Psoriasis	N controls	Model hazard ratio (95% CI)	Attributable risk for 10-year incidence of MACE
Primary analysis	**14330**	**3603**	**1.53 (1.26-1.85)**	**6.2%**
Inclusion of patients with at least 1 GP visit per year on average	13643	3563	1.50 (1.23-1.81)	-
Primary model with exclusion of methotrexate	13289	1358	1.86 (1.44-2.41)	-
Primary model with exclusion of oral retinoids or ciclosporine	13253	2653	1.42 (1.14-1.77)	-
Primary model restricted to	13253	303	1.56 (1.05-2.32)	-

patients who received oral retinoids				
Primary model with exclusion of psoriatic arthritis	13289	1156	1.44 (1.16-1.78)	-
Inclusion of patients with at least 6 months of person time	11832	2963	1.60 (1.32-1.95)	-
Primary model with BMI included	9870	2433	1.71 (1.32-2.18)	-
Primary model without BMI included in those who had BMI measured[1]	9870	2433	1.70 (1.32-2.17)	-

[1] BMI is included in n=12303 or 69% of patients.

Author's conclusion:

- Severe psoriasis confers an additional 6.2% absolute risk of a 10-year rate of major adverse cardiac events compared with the general population.
- This potentially has important therapeutic implications for cardiovascular risk stratification and prevention in patients with severe psoriasis.

H.4.13 STUDY 7 CARDIOVASCULAR DISEASE

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
Mehta (2010)	**Observational:** cohort	N: severe psoriasis	**Inclusion criteria:** 18 years or older at index	General Practice	Mean 3.4 +/- 2.8	Cardiovascular death	Grant to the

Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database Ref ID: METHA2010	study from 1987-2002. **Representative population sample:** yes GPRD used. **Prognostic factor adequately measured:** yes **Confounders adjusted for:** cardiovascular risk factors including age, sex, hypertension, diabetes, hyperlipidaemia, and smoking (current, former, never). BMI calculated from the data available in medical record. **Attrition bias:** not reported **Outcomes adequately measured:** yes	group n=3603; control group n=14330)	date and had at least 1 day of observation time; severe psoriasis patients their index date was first date on or after the first diagnosis of psoriasis in which they received a code for treatment consistent with severe disease. Patients without psoriasis the index date was date of medical record entry within 60 days of the psoriasis index date. Up to 4 unexposed subjects were randomly selected, matched on practice, date of registration in practice and psoriasis index date. **Exclusion criteria:** not reported.	Research Database. Severe psoriasis was defined as those with a diagnostic code of psoriasis and history of systemic therapy consistent with severe psoriasis.	years for non-psoriasis and 3.4 +/- 2.7 years for psoriasis group.	defined as diagnoses consistent with MI, stroke, peripheral vascular disease, arrhythmia or left ventricular thrombus on or very close to the entry of death.	Trustees of the University of Pennsylvania from Centocor the Psoriasis Research Foundation in honour of Herman Beerman and grant K23AR0511125 from the National Institute of Arthritis, Musculoskeletal, and Skin Diseases and grant RO1HL089744 from the Heart Lung Blood Institute.

	Appropriate statistical analysis: yes **Blinding:** For every death the cause was determined by review of medical codes on or very near date of death by 2 physician reviewers blinded to exposure statues.						

Patient characteristics:

Characteristics	Unexposed group(n=14330)	Psoriasis group (n=3603)	P values
Sex (male)	5783 (40.4%)	1750 (48.6%)	P<0.001
Age (year)[1]		P<0.001	
Mean (SD)	49.7 (19.3)	52.2(16.7)	
Median (IQR)	48 (33-65)	52 (39-66)	
Diabetes mellitus	737 (5.1%)	270 (7.5%)	P<0.001
History of MI	375 (2.6%)	116 (3.2%)	P=0.052
History of stroke	268 (1.9%)	89 (2.5%)	P=0.023
History of TIA	243 (1.7%)	68 (1.9%)	P=0.432
Hyperlipidaemia	842 (5.9%)	250 (6.9%)	P=0.019

Hypertension	**3049 (21.3%)**	**858 (23.8%)**	**P=0.001**
Smoking			
Never	**10465 (73%)**	**2488 (69.1%)**	
Current	**755 (5.3%)**	**241 (6.7%)**	
Former	**3110 (21.7%)**	**874 (24.3%)**	**P<0.001**
BMI[2]			
<25	**5057 (51.2%)**	**1025 (42.1%)**	
>/=25 and <30	**3291 (33.3%)**	**860 (35.4%)**	
>/=30	**1522 (15.4%)**	**548 (22.5%)**	**P<0.001**
Reason for end of study			
Death	**790 (5.5%)**	**297 (8.2%)**	
End of UTS	**11247 (78.5%)**	**2860 (79.4%)**	
Transfer out	**2293 (16%)**	**446 (12.4%)**	**P<0.001**

MI, myocardial infarction; TIA, transient ischaemic attach; BMI, body mass index; SD, standard deviation; IQR, interquartile range.

[1] Wilcoxon test.

[2] Data for BMI were available for 69% of the patients.

Effect size:

Variable	**Unexposed**	**Psoriasis**

Follow-up time (year)		
Mean (SD)	3.4 (2.8)	3.4 (2.7)
Median (IQR)	2.6 (1.2-5.0)	2.7 (1.2-5.1)
Number of person years	48661.8	12346.3
Number of CBD mortality cases	301 (2.1%)*	108 (3%)*
Incidence per 1000 person-years (95% CI)	6.19 (5.51, 6.92)	8.75 (7.18, 10.56)

*p=0.002

Unadjusted and adjusted Cox proportional hazard regression models of the risk of cardiovascular disease mortality in severe psoriasis compared with unexposed patients

Covariate	**Model hazard ratio (95% CI)**
	Severe psoriasis
Unadjusted analysis – psoriasis	1.42 (1.14, 1.76)
Adjusted for age and sex	
Psoriasis	1.57 (1.26, 1.96)

Age per year	1.10 (1.09, 1.11)
Sex (male)	1.61 (1.32, 1.95)
Primary model (adjusted for major cardiovascular risk factors)*	
Psoriasis	1.57 (1.26, 1.96)
Age per year	1.10 (1.09, 1.11)
Sex (male)	1.54 (1.27, 1.88)
Hypertension	1.25 (1.01, 1.53)
Hyperlipidaemia	0.75 (0.42, 1.34)
HX of diabetes	2.25 (1.68, 3.02)
Smoking (current vs never)	1.33 (0.95, 1.86)
Smoking (former vs never)	1.31 (0.98, 1.74)

Interaction term for sex was not statistically significant (p=0.99), but was for age (p=0.07).

*Hypertension, hyperlipidaemia, diabetes, and smoking status.

Sensitivity analysis hazard ratio point estimates

Covariate	**N Psoriasis**	**N controls**	**Model hazard ratio (95% CI)**
Primary analysis	3603	14330	1.57 (1.26, 1.96)
Inclusion of patients with at least 1 GP visit per year on average	3563	13643	1.54 (1.23, 1.93)

Primary model excluding patients with history of myocardial infarction, stroke, and/or TIA or atherosclerotic disease	3310	13335	1.56 (1.20, 2.04)
Primary model with exclusion of methotrexate	1489	14330	2.04 (1.51, 2.74)
Primary model with exclusion of oral retinoids or ciclosporine	2914	14330	1.51 (1.18, 1.94)
Primary model restricted to patients who received oral retinoids	333	14663	1.59 (0.97, 2.60)
Primary model with exclusion of psoriatic arthritis	2375	14330	1.52 (1.19, 1.94)
Primary model with BMI included	2433	9870	1.66 (1.19, 2.30)
Primary model without BMI included in those who had BMI measured[1]	2433	9870	1.64 (1.18, 2.27)
Inclusion of patients with at least 6 months of person time	3246	12766	1.66 (1.30, 2.11)
Primary model after matching cases to controls by age (+/-5 years) and sex[2]	3603	7205	1.59 (1.23, 2.04)

[1] BMI is included in n=12303 or 69% of patients.

[2] Two-to-one matching using original controls.

Author's conclusion: patients with severe psoriasis have an increased risk of CV mortality that is independent of traditional CV risk factors. Additional studies are needed to determine the mechanism of this association and the impact that control of psoriasis has on CV risk.

H.4.14 STUDY 8 CARDIOVASCULAR DISEASE

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
Mallbris (2004) Increased risk for cardiovascular mortality in psoriasis inpatients but not outpatients Ref ID: MALLBRIS 2004	**Observational:** retrospective cohort study 1964-1995. **Representative population sample:** yes-used the Swedish inpatient registry. **Prognostic factor adequately measured:** yes **Confounders adjusted for:** yes	N: 8991 in-patients; 19,757 out-patients.	**Inclusion criteria:** all Swedish residents recorded in the Inpatient Registry with a discharge diagnosis of psoriasis (ICD-7 codes 70600 and 70609; ICD-8 codes 69600 and 69610; code ICD-9 codes 696A and 696B), during January 1964 to December 1995; Only in-patients treated at dermatological wards with psoriasis as the main diagnosis. **Exclusion criteria:** diagnosis of cardiovascular disease prior to index time.	Swedish inpatient registry used with ICD codes. Date of entry in cohort was set to 1st January 1987, the year the register was established. Inpatient cohort was followed up through the death registry and registry of population and population changes	**15 years+** **Note**: followed-up to the date of death, emigration or December 31st 1995, whichever occurred first. The outpatient cohort was followed with censoring at death, emigration or December 31st 1998.	Risk of mortality from ISH, cerebrovascular disease and pulmonary embolism	Swedish Heart Lung Foundation, the Swedish Psoriasis Association, the Swedish Medical Research Council, the Welander-Finsen Foundation and Karolinska Institutet.

	Attrition bias: not reported **Outcomes adequately measured:** not multivariable/regression **Appropriate statistical analysis:** yes comparisons within the cohort were performed with a Cox regression.		Notes: did not exclude members who had a history of hospitalisation. Date of entry into cohort.				

Patient characteristics of the cohort of patients

hospitalised with psoriasis as main diagnosis:

Variables	**Number (%)**
Total	**8991 (100%)**
Sex – male	**4708 (52%)**
Age at first hospital admission	
0-19	**927 (10.3%)**
20-39	**2362 (26.3%)**

40-59	**3069 (34.1%)**
60+	**2633 (29.3%)**
Years of follow-up	
0-1	**216 (2.4%)**
1-5	**1398 (15.6%)**
5-10	**1981 (22%)**
10-15	**1927 (21.4%)**
15+	**3469 (38.6%)**
Calendar year	
64-74	**3145 (35%)**
75-84	**3398 (37.8%)**
85-95	**2448 (27.2%)**

Effect size:

SMRs and 95%CIs for the association between at least one hospitalisation for psoriasis and cardiovascular death

Variables	Observed number of deaths	Expected number of deaths	SMR*	95% CI	p-value trend

Total	1529	1007	1.52	1.44-1.60	
Age at first hospital admission					
0-19	0	0.99	0.00	0.00-3.74	
20-39	46	18	2.62	1.91-3.49	
40-59	453	237	1.91	1.74-2.09	
60+	1030	750	1.37	1.29-1.46	<0.001
Years of follow up					
0-1	90	66	1.36	1.09-1.67	
1-5	349	260	1.34	1.21-1.49	
5-10	431	281	1.53	1.39-1.68	
10-15	304	192	1.58	1.41-1.77	
15+	355	207	1.71	1.54-1.90	<0.001
No. of hospital admissions					
One time	1529	1007	1.52	1.44-1.60	
Two times	851	501	1.70	1.58-1.81	
Three times or more	610	334	1.82	1.68-1.98	<0.001
Calendar year					
64-74	733	471	1.56	1.45-1.67	
75-84	590	403	1.46	1.35-1.59	
85-95	206	132	1.56	1.35-1.79	0.67

***The relative risk was calculated by SMRs and 95% CIs.**

SMRs and 95% CIs for the association between at least one hospitalisation for psoriasis and risk for death from different cardiovascular diseases

	Ischemic heart disease		**Cerbrovascular disease**		**Pulmonary embolism**	
Variable	**SMR**	**95% CI**	**SMR**	**95% CI**	**SMR**	**95% CI**
Total	1.86	1.76-1.96	1.63	1.47-1.80	1.64	1.12-2.31
Sex – male	1.89	1.76-2.03	1.74	1.49-2.01	1.43	0.76-2.45
Sex – female	1.80	1.65-1.97	1.54	1.33-1.77	1.82	1.10-2.84
Age at first hospitalisation						
20-39	2.91	1.98-4.14	1.85	0.68-4.02	5.18	0.63-18.7
40-59	2.22	2.00-2.46	1.92	1.52-2.40	2.24	1.07-4.12
60+	1.71	1.60-1.83	1.56	1.38-1.75	1.36	0.83-2.11

Stratified analysis of the joint effect of number of admissions and age at first admission

	Number of admissions				
	1	**2**		**3 or more**	
Variables	**Reference**	**HR**	**95% CI**	**HR**	**95% CI**
Age at first hospital admission					
0-39	1.00	2.71	1.15-6.41	3.13	1.55-6.32
40-59	1.00	1.11	0.84-1.47	1.43	1.16-1.77

60+	1.00	1.18	0.99-1.42	1.35	1.17-1.57

Observed and expected numbers of deaths from cardiovascular disease in a cohort representing outpatients treated for psoriasis with SMRs and 95% CIs

Variables	Number (%)	Obs	Exp	SMR	95% CI
Total	19,757	1302	1390	0.94	0.89-0.99
Age at start of follow-up					
0-19	758 (3.8%)	0	0.18	0.00	0.00-20.3
20-39	5298 (26.8%)	7	11	0.65	0.26-1.34
40-59	7732 (39.1%)	161	161	1.00	0.85-1.16
60+	5969 (30.2%)	1134	1218	0.93	0.88-0.99
Years of follow-up					
0-1	199	98	108	0.91	0.74-1.11
1-5	923	447	465	0.96	0.87-1.05
5-10	1307	616	667	0.92	0.85-1.00
10-15	17,328	141	150	0.94	0.79-1.11

Author's conclusion: A diagnosis of psoriasis per se does not appear to increase the risk for cardiovascular mortality. Severe psoriasis (repeated admissions, and early age at first admission) is associated with increased risk for cardiovascular risk.

H.4.15 STUDY 11 CARDIOVASCULAR DISEASE – systemic therapy vs phototherapy for psoriasis

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
H. Maradit-Kremers, M. Icen, F. C. Ernste, R. A. Dierkhising, and M. T. McEvoy. Disease severity and therapy as predictors of cardiovascular risk in psoriasis: a population-based cohort study. J.Eur.Acad. Dermatol.Venereol. 26 (3):336-343, 2012.	**Observational:** population-based cohort study from 1998-2007 Residents of Olmsted County – data from Rochester Epidemiology Project. **Representative population sample:** no – small sample from one US state only **Prognostic factor adequately measured:** yes – adequate record review	N 1905 with psoriasis (660 incident psoriasis and 1245 prevalent psoriasis)	**Inclusion criteria:** open cohort of all patients with psoriasis under observation between 1998 and 2007 **Exclusion criteria:** none reported. Baseline characteristics: Mean age: 48.8 ± 17.5 Male (%): 48% PsA: 96 (5%) – an additional 95 were diagnosed over the follow-up (191 with PsA in total)	Data from Rochester Epidemiology Project Psoriasis and PsA diagnoses validated through medical record review (confirmatory dermatologist diagnosis, lesion description or skin biopsy; CASPAR for PsA)	Mean: 6.3 ± 3.5 years	Composite score of cardiovascular events (MI, revascularisation, cerebrocascular events, heart failure and cardiovascular death)	National Institute of Aging and Amgen

Ref ID: MARADIT-KREMERS 2012	**Confounders adjusted for:** Age and sex plus cardiovascular risk factors (obesity, dyslipidaemia, hypertension, diabetes, total cholesterol, HDL cholesterol, LDL cholesterol, blood pressure) **Attrition bias:** not reported, but half did not have measurements of lipid data at baseline **Outcomes adequately measured:** yes **Appropriate statistical analysis:** Cox adjusted models						

Patient characteristics:

	Prevalence cohort (n=1905)

History of CVD (heart failure, stroke or MI/revascularisation)	12%
Hypertension	34%
Diabetes	13%
Dyslipidaemia	33%
Obesity	25%
History of treatment before baseline	
Phototherapy*	21 (1%)
Any systemic treatment*	82 (4%)

*Note: 157 additional patients received phototherapy (total 178) and 191 systemic therapy (total 273; 86 MTX; 73 biologics) during follow-up.

Effect size: excluding those with a history of CVD prior to entry (n=221)

Adjusted hazard ratio (prognostic factors vs not having the prognostic factor in the psoriasis cohort)

Prognostic factor	**Cox model HR (95% CI)**	
	Age and gender adjusted	**Multivariate adjusted**
Phototherapy	3.76 (2.45-5.77)	1.28 (0.55-2.98)
Systemic therapy	2.17 (1.50-3.13)	0.93 (0.49-1.75)

Author's conclusion: Strong associations with phototherapy and systemic therapy suggest that the cardiovascular risk in psoriasis is confined to patients with severe disease. However, the small numbers treated with systemic therapy make it difficult to draw conclusions about the impact of this intervention on CVD risk

H.4.16 STUDY 9 DIABETES (type 2)

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
Wenqing Li, Jiali Han, Frank B. Hu, Gary C. Curhan, and Abrar A. Qureshi. Psoriasis and Risk of Type 2 Diabetes among Women and Men in the United States: A Population-Based Cohort	**Observational:** retrospective-prospective cohort study **Representative population sample:** no – predominantly women and all HCPs **Prognostic factor adequately measured:** yes – questionnaire report but conformed by	Total n: 184395; n=3074 reporting psoriasis.	**Inclusion criteria:** participants from Nurses Health Study (NHS), NHSII and Health Professionals Follow-up Study (HPFS) **Exclusion criteria:** not stated	Psoriasis determined by self-report of diagnosis and conformed by further self-completed questionnaire (Psoriasis Screening Tool Questionnaire – 99% sensitivity; 94% specificity)	Unclear	T2 diabetes - Identified by self-report of physician diagnosed T2D and confirmed in those reporting diabetes by a further questionnaire (had to meet at least one of the criteria of the National Diabetes Data Group)	None stated

Study. J.Invest.Dermatol., 2011. Ref ID: LI2011	validated tool **Confounders adjusted for:** time-varying covariates updated during follow-up: age, smoking status (never, current, past), body mass index, race, family history of diabetes, hypertension, hypercholesterolemia, current aspirin use, multivitamin use, menopausal status, post-menopausal hormone use alcohol intake and physical activity **Attrition bias:** not reported **Outcomes adequately measured:** yes – questionnaire report but conformed by validated tool **Appropriate statistical**						

	analysis: yes, Cox proportional hazards modelling stratified by age and 2-yr follow-up interval to estimate the age-adjusted and multivariate RRs of incident diabetes						

Baseline characteristics

	NHS		**NHS II**		**HPFS**	
	No psoriasis (n=62,738)	**Psoriasis (n=1189)**	**No psoriasis (n=94,437)**	**Psoriasis (n=1342)**	**No psoriasis (n=24,146)**	**Psoriasis (n=543)**
Mean age, years (SD)	60.9 (6.8)	61.2 (6.8)	36.2 (4.6)	39.7 (4.6)	50.5 (8.0)	50.8 (8.1)
Race, white (%)	95.7	96.6	95.3	96.7	96.0	95.8
BMI, kg/m^2 (SD)	26.2 (4.9)	27.1 (5.4)	24.5 (5.0)	25.4 (5.6)	24.8 (4.4)	25.2 (4.3)
Alcohol intake, g/day	4.6 (8.6)	5.0 (9.9)	2.9 (5.7)	2.9 (5.4)	11.1 (14.5)	11.9 (16.1)
Physical activity, metabolic equivalent hours per week	18.6 (22.4)	16.4 (19.1)	18.8 (26.2)	17.8 (26.2)	22.2 (29.4)	24.4 (34.7)
Current smoking (%)	10.6	14.5	11.5	15.2	6.9	9.2
Family history of diabetes (%)	26.5	28.0	16.3	18.9	14.0	14.7

Postmenopausal hormone (%)	59.0	60.9	2.6	3.7	NA	NA
Hypertension (%)	26.5	29.2	3.1	4.6	15.6	17.9
Hypercholesterolemia (%)	34.6	36.3	8.9	13.1	10.7	11.8
Aspirin use (%)	51.2	51.3	11.1	12.9	26.2	25.4
Multivitamin use (%)	49.2	46.7	38.7	40.2	40.8	41.4

Note that people with psoriasis were more likely to have higher BMI and be smokers

Effect size:

Multivariate relative risks (RRs) for the development of diabetes among people with psoriasis

Study	**Diabetes cases**	**Person-years**	**Multivariate RR[1]**	**Multivariate RR[2]**
NHS	4280	735664		
No psoriasis	4171	720650	1.00	1.00
Psoriasis	109	15014	1.14 (0.95-1.38)	1.01 (0.83-1.22)
NHSII	3968	1496867		
No psoriasis	3835	1470709	1.00	1.00
Psoriasis	133	26159	1.50 (1.26-1.78)	1.25 (1.05-1.49)
HPFS	1690	468427		

No psoriasis	1638	455263	1.00	1.00
Psoriasis	52	13163	0.94 (0.71-1.25)	0.91 (0.69-1.20)
NHS/NHSII/HPFS (pooled – no heterogeneity) – age <60 years during follow-up				
No psoriasis	5190	1881861	-	1.00
Psoriasis	179	35751	-	1.26 (1.08-1.46)

[1]Simultaneously adjusted for age, smoking status (never, current [1-14, 15-24 or ≥25 per day], past), alcohol intake (no, <4.9, 5.0-14.9 or ≥15 g/day) and physical activity in quintiles of metabolic equivalent hours per week, race (Caucasian, Asian, Hispanic or African American, family history of diabetes, hypercholesterolemia, current aspirin use, multivitamin use and post-menopausal hormone use (women only: pre-menopause, never, current or past users).

[2]Simultaneously adjusted for all variables above plus body mass index.

Sensitivity analysis: Multivariate relative risks (RRs) for the development of diabetes among people with *confirmed cases* of psoriasis

Study	**Diabetes cases**	**Person-years**	**Multivariate RR[1]**
NHS			
No psoriasis	4198	725208	1.00
Psoriasis	82	10456	1.14 (0.92-1.42)
NHSII			
No psoriasis	3891	1483100	1.00
Psoriasis	77	13768	1.46 (1.16-1.83)

[1]Simultaneously adjusted for age, BMI, smoking status (never, current [1-14, 15-24 or ≥25 per day], past), alcohol intake (no, <4.9, 5.0-14.9 or ≥15 g/day) and physical activity in quintiles of metabolic equivalent hours per week, race (Caucasian, Asian, Hispanic or African American, family history of diabetes, hypercholesterolemia, current aspirin use, multivitamin use and post-menopausal hormone use (women only: pre-menopause, never, current or past users).

Author's conclusion: Individuals developing psoriasis at a younger age are at significantly elevated risk of T2D

H.4.17 STUDY 9 DIABETES AND HYPERTENSION

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
Quereshi (2009) Psoriasis and the risk of diabetes and hypertension: a prospective study of US female	**Observational:** prospective cohort study from 1991 to 2005. **Representative population sample:** yes	Total n: 78061; n=1813 reporting psoriasis.	**Inclusion criteria:** registered nurses from 15 states in the US between ages of 25 and 42 when they completed and returned baseline questionnaire in 1989. **Exclusion criteria:** women with diabetes or	The nurses health study (NHS) II longitudinal study. Longitudinal study of female registered nurses in 15 states in the US.	14 years. Baseline questionnaire in 1989. Followed up from 1991 to 2005 (biennial questionnaires). **Note**: started in 1991 as this was first year that they	Diabetes and hypertension.	Partly supported by grants K07CA10897/NCI and CA050385/NCI from the National Cancer institute.

nurses Ref ID: QURESHI2009	**Prognostic factor adequately measured:** yes **Confounders adjusted for:** Simultaneously adjusted for age, smoking status (never, current, past), body mass index, alcohol intake and physical activity in quintiles of metabolic equivalent hours per week. **Attrition bias:** not reported **Outcomes adequately measured:** yes **Appropriate statistical analysis:** yes, Cox proportion hazards modelling to estimate the age-adjusted and multivariate RRs of incident diabetes and		hypertension at baseline.		had corresponding information on smoking and alcohol status.		One author has been a consultant and speaker for Abbott, Amgen and Genentech.

	hypertension.						

Baseline characteristics of women who self-reported a diagnosis

of psoriasis between 1991 and 2005

Characteristic	**Psoriasis no (n=76248)**	**Psoriasis yes (n=1813)**
Mean age, years	36.2	36.4
Mean BMI	23.6	24.4
Smoking status (%)		
Never	66	56
Current	22	26
Past	11	18
Mean alcohol intake, g/wk	3.2	3.7
Mean physical activity, METS/wk	21	20

BMI, body mass index; METS, metabolic equivalent hours

Effect size:

Age-adjusted and multivariate relative risks (RRs) for the development of diabetes and hypertension among women with psoriasis

	Psoriasis no	Psoriasis yes (95% CI)
Diabetes		
No. of cases[1]	1500	60
Person-years, millions	1.0	1.0
Age-adjusted RR	1.00	2.08 (1.60-2.69)
Multivariate RR[2]	1.00	1.63 (1.25-2.12)
Hypertension		
No. of cases[1]	15338	386
Person-years, millions	0.99	0.99
Age-adjusted RR	1.00	1.32 (1.19-1.45)
Multivariate RR[2]	1.00	1.17 (1.06-1.30)

[1]Excluding any individuals with concomitant diabetes and hypertension.

[2]Simultaneously adjusted for age, smoking status (never, current, past), body mass index, alcohol intake and physical activity in quintiles of metabolic equivalent hours per week.

To assess for any possible effect from age, BMI and smoking status multivariate models found the association between psoriasis and risk was not modified by BMI for diabetes (p=0.65) or hypertension (p=0.07). There was also no effect modification by smoking status for diabetes of hypertension (p>/=0.50). Additional analyses to limit population to those women who had at least 1 physical exam during follow-up to control for confounder that women with psoriasis may be more likely to see a physician and therefore diagnosed with diabetes or hypertension. There was no material change in the results.

Author's conclusion: Psoriasis was independently associated with an increased risk of diabetes and hypertension.

H.4.18 STUDY 10 ALCOHOL-RELATED DISEASES

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
Poikolainen (1999) Excess mortality related to alcohol and smoking among hospital-treated patients with psoriasis Ref ID: POIKOLAINAN1999	**Observational: cohort study from 1973 to 1984.** **Representative population sample:** yes **Prognostic factor adequately measured:** yes **Confounders adjusted for:**.	N: 3132 men and 2555 women.	**Inclusion criteria:** Identified all records of patients with psoriasis as main diagnosis in Hospital Discharge Register from January 1st 1973 to December 31st 1984 in Finland **Exclusion criteria:** not reported.	Used the Hospital discharge register which was then linked with the Population Central Register using personal identification codes. Underlying causes of death were based on official death certificates, coded to the Finnish modification of the International Classification of	**Mean length follow-up was almost 14 years. Length of study period was 22 years.** **Note**: follow-up started from month following earliest hospital discharge and follow-up ended on the date of emigration or death or December 31st 1995, whichever was	Date and underlying cause of death (standard mortality ratios).	Not reported.

	Attrition bias: not reported **Outcomes adequately measured:** yes **Appropriate statistical analysis:** not multivariable/regression **Notes:** Patients were hospitalised at least once so most were likely to have severe psoriasis than outpatients.			Diseases, Eighth and Ninth Revision. The causes selected related to alcohol only, smoking only and alcohol and smoking.	first.		

Effect size: 1918 observed deaths, whereas 1211 deaths were expected based on the national mortality rates.

Major causes of death among patients with psoriasis*

	Men		Women	
Cause of death	No. of observed deaths	SMR (95% CI)	No. of observed deaths	SMR (95% CI)

Alcohol-related	202	2.14 (1.84-2.44)	89	1.47 (1.16-1.77)
Directly**	94	4.46 (3.60-5.45)	13	5.60 (2.98-8.65)
Indirectly	108	1.47 (1.20-1.75)	76	1.31 (1.03-1.63)
Smoking-related	594	1.44 (1.33-1.56)	400	1.61 (1.45-1.77)
Both	13	1.92 (1.02-3.29)	8	2.52 (1.09-4.96)
Other	330	1.72 (1.54-1.91)	282	1.45 (1.28-1.62)
All	1139	1.62 (1.52-1.71)	779	1.54 (1.43-1.64)

*SMR indicates standardised mortality ratio; CI, confidence interval.

** Includes underlying causes with direct reference to alcohol in the diagnosis, ie alcohol-related psychosis, alcoholism, alcoholic polyneuropathy, alcoholic cardiomyopathy, alcoholic gastritis, alcoholic fatty liver, acute alcoholic hepatitis, alcoholic cirrhosis of the liver, unspecified alcoholic liver damage, alcoholic epilepsy, alcoholic pancreatitis, fetal alcohol syndrome, alcoholic withdrawal syndrome of the newborn, alcohol poisoning, and pregnancy, childbirth, or puerperium complicated by alcoholism.

Alcohol-and Tobacco-related causes of death among patients with psoriasis*

	Men		**Women**	
Cause of death	**No. of observed deaths**	**SMR (95%CI)**	**No. of observed deaths**	**SMR (95% CI)**
Alcohol-related				
Liver cancer	9	2.86 (1.31-5.42)	1	0.50 (0.01-2.79)
Female breast cancer	0	-	16	1.14 (0.65-1.85)

Alcohol psychosis	5	8.91 (2.89-20.70)	0	0 (0.00-71.70)	
Alcohol dependence	9	3.79 (1.73-7.19)	1	5.23 (0.13-29.20)	
Hypertension	10	2.23 (1.07-4.09)	10	1.33 (0.64-2.45)	
Hemorrhagic stroke	24	1.35 (0.87-2.01)	16	1.01 (0.57-1.63)	
Liver disease	61	6.98 (5.34-8.96)	13	5.06 (2.70-8.65)	
Alcoholic liver cirrhosis	20	2.88 (1.76-4.44)	6	5.77 (2.12-12.50)	
Acute pancreatitis	0	0	0	0 (0.00-5.86)	
Chronic pancreatitis	0	0	0	0 (0.00-40.70)	
Motor traffic injuries	12	1.40 (0.73-2.45)	4	1.27 (0.35-3.24)	
Alcohol poisoning	14	1.86 (1.02-3.12)	1	1.37 (0.03-7.61)	
Accidental falls	15	1.57 (0.88-2.58)	14	1.75 (0.96-2.93)	
Drowning	1	0.33 (0.01-1.86)	1	2.98 (0.08-16.60)	
Machine injuries	1	0.90 (0.02-5.00)	0	0 (0.00-38.40)	
Suicide	37	1.56 (1.10-2.15)	9	1.87 (0.86-3.55)	
Assault	5	2.15 (0.70-5.01)	3	4.54 (0.94-13.30)	
Smoking-related					
Pancreatic cancer	10	1.13 (0.54-2.08)	15	2.03 (1.14-3.34)	
Lung cancer	79	1.48 (1.17-1.83)	12	1.86 (0.96-3.24)	
Bladder cancer	11	2.56 (1.28-4.58)	2	1.42 (0.17-5.12)	

Stomach cancer	19	1.27 (0.77-1.98)	9	0.94 (0.43-1.77)
Coronary heart disease	354	1.49 (1.33-1.65)	235	1.70 (1.48-1.92)
Thromboembolic stroke	56	1.20 (0.91-1.55)	98	1.56 (1.27-1.90)
Atheroslerosis	12	0.70 (0.36-1.22)	15	1.03 (0.58-1.70)
Chronic obstructive pulmonary diseases	44	1.81 (1.31-2.42)	8	1.57 (0.68-3.09)
Peptic ulcer	9	2.31 (1.06-4.38)	6	1.96 (0.72-4.26)
Alcohol- and smoking-related				
Oropharyngeal cancer	1	2.69 (0.07-14.9)	1	2.45 (0.06-13.60)
Esophageal cancer	3	1.01 (0.21-2.94)	5	2.30 (0.75-5.35)
Laryngeal cancer	6	3.80 (1.40-8.27)	1	10.6 (0.27-59.20)
Fire injuries	3	1.64 (0.34-4.78)	1	2.28 (0.06-12.70)

*SMR indicates standardised mortality ratio; CI, confidence interval; and ellipses, not calculated.

Author's conclusion: patients with moderate to severe psoriasis are at increased risk for death. Alcohol is a major cause for this excess mortality**.**

H.4.19 STUDY 11 CAUSE-SPECIFIC MORTALITY

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
Abuabara (2010) Cause-specific mortality in patients with severe psoriasis Ref ID: ABUABARA2010	**Observational:** population-based cohort study from 1987 to 2002. **Representative population sample:** yes – used the general practice research database. **Prognostic factor adequately measured:** yes **Confounders adjusted for:** Age and sex. **Attrition bias:** not reported	N: severe psoriasis group n=3603; no psoriasis group (n=14330)	**Inclusion criteria:** all patients with severe psoriasis aged 18 years and above at their index date and had at least 1day of follow-up from 1987 and 2002. Severe psoriasis was defined if had a diagnostic code for psoriasis and a prescription consistent with severe disease on or after the first diagnosis date for psoriasis. Prescriptions included phototherapy, psoralen plus ultraviolet A, methotrexate, azathioprine, ciclosporin, oral retinnoids (etretinate, acitretin), hydorxyurea, and mycophenolate mofetil. For each patient they included four unexposed patients with no history of psoriasis diagnosis code at any time. They were matched	GPRD database used investigators performing cause of death coding were blinded to the study group. Cause of death assigned separately by two physicians. Each patient assigned a cause of death based on data in medical record.	3.4 (+/-2.8) for non-psoriasis and 3.4 (+/-2.7) **Note**: follow-up ended at the earliest: date of death, date of transfer out of practice or end of up-to standard designation.	Risk of death from CVDs.	Grant K23AR051125 and RC1AR058204 from the NIAMS. Grant R01HL089777 from the NHLBI. Grant F32AR056799 from the NIAMS, the Doris Duke Clinical Research Fellowship and the Psoriasis Research Foundation in honour of

	Outcomes adequately measured: yes **Appropriate statistical analysis:** cox adjusted models		on practice, date of registration in the practice (within 90 days if registration occurred after 1980 or within 5 years if registration before 1980), and index date. Index date for psoriasis patients was first date received a prescription for severe psoriasis on or after their first psoriasis diagnosis date. Non-psoriasis patients the index date was the date of any medical record within 60 days of the psoriasis index date. **Exclusion criteria:** none reported.				Herman Berman.

Patient characteristics:

	Control group	**Severe psoriasis group**	**p-value**
N	**14330**	**3603**	
Age, years			
Mean (SD)	49.73 (19.33)	52.19 (16.71)	<0.001[1]
Median (IQR)	48 (33-65)	52 (39-66)	
Sex, male (%)	5783 (40.36)	1750 (48.57)	<0.001[2]

Person time, years			
Mean (SD)	3.40 (2.76)	3.43 (2.73)	0.548[2]
Median (IQR)	2.63 (1.18-5.02)	2.69 (1.24-5.05)	
Cumulative	48662	12346	
No. of causes of death listed, mean (SD)	1.20 (0.47)	1.22 (0.47)	0.504[1]
No. of deaths (%)	862 (6.02)	321 (8.92)	
Death rate per 1000 patient-years (95% CI)	17.71 (16.55-18.94)	26.00 (23.23-29.01)	

[1] Student's t-test. [2] X^2 test. IQR, interquartile range; CI, confidence interval.

Effect size:

Cause and relative risk of death by treatment group

	Control group (%)	**Psoriasis group (%)[1]**	**P value[2]**	**Cox model HR (95% CI)[3]**
Accidents	7 (1%)	2 (1%)	1.000	1.03 (0.21-4.96)
Cardiovascular disease	301 (35%)	108 (34%)	0.002	**1.57 (1.26-1.96)**
Chronic lower respiratory disease	44 (5%)	22 (7%)	0.013	**2.08 (1.24-3.48)**
Dementia	10 (1%)	7 (2%)	0.060	**3.64 (1.36-9.72)**
Diabetes	10 (1%)	7 (2%)	0.060	**2.86 (1.08-7.59)**
Infection	195 (23%)	71(22%)	0.009	**1.65 (1.26-2.18)**

Kidney disease	17 (2%)	18 (6%)	0.000	**4.37 (2.24-8.53)**
Liver disease	4 (0%)	2 (1%)	0.347	2.03 (0.37-11.12)
Malignant neoplasms	190 (22%)	67 (21%)	0.019	**1.41 (1.07-1.86)**
Other	33 (4%)	17(5%)	0.02	**2.12 (1.19-3.88)**
Suicide	1 (0%)	1 (0%)	0.361	3.35 (0.21-53.77)
Unknown/missing	218 (25%)	70 (22%)	0.075	**1.43 (1.09-1.89)**
Total deaths	862	321		

[1]Percentages may not sum to 100 because each subject may have had more than one cause of death. [2]Two sided Fisher's exact test.

[3]Adjusted for age and sex.

HR, hazard ratio; CI, confidence interval. Significant HRs are shown in bold face.

Absolute and excess risk of death

Cause of death	Absolute risk[1]	Excess risk[1]
Cardiovascular disease	**61.9**	**3.5**
Infection	**40.1**	**2.6**
Unknown/missing	**44.8**	**1.9**
Malignant neoplasms	**39.0**	**1.6**
Kidney disease	**3.5**	**1.2**
Chronic lower respiratory disease	**9.0**	**1.0**

Other	**6.8**	**0.8**
Dementia	**2.1**	**0.5**
Diabetes	**2.1**	**0.4**
Liver disease	**0.8**	**0.1**
Suicide	**0.2**	**0.0**
Accidents	**1.4**	**0.0**

[1]Deaths per 1000 patient-years

Median age at death (years) by sex and cause

	Women			**Men**		
	Controls	**Psoriasis**	**p-value[1]**	**Controls**	**Psoriasis**	**p-value[1]**
Overall	82.85	75.49	**<0.001**	78.41	73.49	**<0.001**
Cardiovascular disease	83.71	76.94	**<0.001**	77.98	73.80	**0.018**
Malignant neoplasms	76.15	71.52	0.518	74.13	69.21	**0.034**
Chronic lower respiratory disease	72.38	72.74	0.507	80.98	73.23	0.107
Infection	82.22	76.56	**0.001**	83.11	75.10	**0.003**
Kidney disease	83.65	65.59	**0.003**	79.10	66.09	**0.026**
Other	79.91	72.43	0.393	80.86	64.13	**0.011**

Unknown/missing	85.40	80.20	**0.004**	80.27	74.38	**0.010**

[1]Wilcoxon rank-sum test. Significant p-values are shown in bold face.

Author's conclusion: Severe psoriasis is associated with an increased risk of death from a variety of cases, with cardiovascular death being the most common aetiology. These patients were also at increased risk of death from causes not previously reported such as infection, kidney disease and dementia.

H.4.20 STUDY 12 LYMPHOMA

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
Gelfand (2003) Lymphoma rates are low but increased in patients with psoriasis Ref ID: GELFAND 2003	**Observational:** retrospective population-based cohort study from 1988 to 1996 **Representative population sample:** yes GPRD used. **Prognostic factor adequately measured:** yes	N: 1718 with psoriasis; n=105203 without psoriasis.	**Inclusion criteria:** a random sample of 10% of the entire GPRD population who were 65 years or older because the incidence of cancer increases with age. **Exclusion criteria:** history of one of the outcome diseases prior to study entry or developed within 6 months of study entry.	OXMIS code used to define if patients had psoriasis or if they had no history of psoriasis consistent with OXMIS code. Any OXMIS code for lymphoproliferative disease (eg Hodgkin or non-Hodgkin lymphoma) occurring after the patient qualified for the	Median, months (25th, 75th percentile): 39.75 (19.1, 65.1) in psoriasis group and 46 (20.8, 73.1 in the non-psoriasis group. **Note**: for non-psoriasis patients follow-up time counted from patient's	Incidence of lymphoma and internal malignancy.	Grants F32-AR48100, R01-AR44695 and KK24-AR02212 from the National Institutes of Health, Bethesda, MD and from an unrestricted grant fro

	Confounders adjusted for: Age and sex. **Attrition bias:** not reported **Outcomes adequately measured:** yes **Appropriate statistical analysis:** yes, unadjusted Cox proportional hazards model. Then adjusted for age and sex for confounding. **Notes:** GPs unaware of the hypotheses to be tested.			study. Secondary analyses for incidence of interest.	registration with a GP and approval of GPs data as 'up to standard'. End of follow-up when patient experienced the outcome of interest, died or left the GPRD. For psoriasis patients follow-up was counted from the patient's diagnosis with psoriasis, registration with the GP and approval of GPs data as up to standard (whichever last) until outcome of interest, died or left the GPRD.		the Herzog Foundation to the Trustees of the University of Pennsylvania.

Patient characteristics:

Variable	With psoriasis	Without psoriasis
Patients	2718 (2.5)	105203 (97.5)

Median age, years (25th, 75th percentile)	60.63 (66.0, 76.6)	71.08 (65.5, 78.4)
Women	1540 (56.7)	61412 (58.4)
Men	1178 (43.3)	43791 (41.6)
Patients treated with methotrexate	42 (1.6)	185 (0.2)

Effect size:

Summary of follow-up time and incidence rate of lymphoma for patients with and without psoriasis

Variable	With psoriasis	Without psoriasis
Follow-up time, median, mo (25th, 75th percentile)	39.75 (19.1, 65.1)	46 (20.8, 73.1)
Person-years	9839	420008
Lymphoma, no.	18	258
Incidence rate of lymphoma per 10000 person-years	18.3	6.1
Attributable risk (excess no. of lymphoma cases related to psoriasis	122 per 100000 per year	-

Rates of lymphoma or internal malignancy in patients with psoriasis relative to rates for patients without psoriasis

	Relative risk (95% Confidence interval)	
Analysed malignancy	**Unadjusted**	**Adjusted for age and sex**
Lymphoma	2.95 (1.83-4.76)	2.94 (1.82-4.74)
Lymphoma, previous history of lymphoma excluded	3.39 (2.04-5.64)	3.38 (2.03-5.62)
Lymphoma, excluding patients diagnosed within 6 months of follow-up	3.04 (1.85-4.97)	3.02 (1.85-4.95)
Lymphoma, excluding patients treated with methotrexate	2.84 (1.74-4.64)	2.83 (1.73-4.64)
Lymphoma, excluding mycosis fungoides	2.26 (1.29-3.95)	2.26 (1.29-3.94)
Internal malignancy	1.08 (0.93-1.24)	1.09 (0.94-1.26)
Internal malignancy, previous history of malignancy excluded	1.04 (0.88-1.23)	1.05 (0.89-1.24)

Author's conclusion: patients with psoriasis are at increased risk of developing lymphoma.

H.4.21 STUDY 13 CANCER

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
Y. J. Chen, C. Y. Wu, T. J. Chen, J. L. Shen, S. Y. Chu, C. B. Wang, and Y. T. Chang. The risk of cancer in patients with psoriasis: A population-based cohort study in Taiwan. J.Am.Acad. Dermatol. 65 (1):84-91, 2011.	**Observational:** retrospective population based cohort study in Taiwan; 1996-2000 to 2007 **Representative population sample:** unsure – not UK population (Longitudinal Health Insurance Database 2000 [LHID 2000]– a randomly sampled subset of the National Health Insurance Database, which records 99% of the Taiwanese population)	N: 203,686	**Inclusion criteria:** all patients with a first time diagnosis of psoriasis (ICD-9 code 696.0, 696.1) made in a department of dermatology or rheumatology and a comparison group of people without psoriasis or a history of malignancies. **Exclusion criteria:** unclear baseline data e.g., conflicting gender or uncertain birth date; history of cancer before diagnosis of psoriasis or before first-time inclusion in this cohort	Data from National Health Insurance Database Note: ICD-9 codes used to define diseases in this study	From 1996/2000 to first-time diagnosis of cancer (except malignancy in situ, metastasis or secondary cancer), death, end of follow-up in medical records, end of observation period or end of 2007 Min 1.5 and max 10 years	Incidence of cancer Note: included cancers coded 140 to 208.91 in ICD-9 CM except metastatic cancers in lymph nodes and secondary cancers	Taichung Veterans General Hospital

Ref ID: CHEN2011	**Prognostic factor adequately measured:** yes **Confounders adjusted for:** age and gender, plus sub analysis for treatment modalities **Attrition bias:** not reported **Outcomes adequately measured:** yes – from Registry of Catastrophic Illness Patient Database (subpart of NHIRD) **Appropriate statistical analysis:** yes – hazard ratios using Cox proportional hazards model						

Patient characteristics:

Characteristic	Control (%)	Psoriasis (%)
Total	200000	3686
Gender – men	51.6%	60.8%
Duration of follow-up, mean±SD	6.68±1.23	4.58±1.68
Mean age±SD	32.93±20.56	44.00±19.62
Prior treatments for psoriasis		
PUVA	-	5.18%
UVB	-	15.2%
Systemics	-	14.4%
Phototherapy or systemics	-	24.4%

Effect size:

HR for specific cancer types adjusted for age and gender

Cancer types	N	HR (95% CI)
Any	116	1.66 (1.38-2.00)
Skin cancer	5	3.10 (1.24-7.71)
Lymphomatopoietic malignancies	6	2.21 (0.97-5.02)
Oropharynx and larynx	11	2.16 (1.17-3.96)
Digestive tract/liver/gall bladder	23	2.02 (1.33-3.07)

Colorectum	15	1.70 (1.01-2.86)
Stomach	4	0.95 (0.35-2.56)
Lung/mediastinum	14	1.46 (0.85-2.49)
Urinary bladder	8	3.18 (1.54-6.57)
Prostate	6	1.77 (0.78-4.00)
Other	9	1.55 (0.80-3.01)

Subgroup analyses

AGE: HR adjusted for gender only for risk of any cancer

Age (years)	HR (95% CI)	p-value
0-19	-	
20-39	2.16 (1.15-4.05)	0.0162
40-59	1.84 (1.36-2.50)	<0.0001
60-79	1.50 (1.16-1.95)	0.0022
>80	0.91 (0.34-2.46)	0.8538

TREATMENT MODALITIES: HR adjusted for age and gender and stratified by treatment modalities compared with control subjects for risk of any cancer

Treatment modalities	Adjusted HR (95% CI)	p-value
PUVA		
Yes	2.03 (1.06-3.91)	0.033
No	1.64 (1.35-1.99)	<0.0001
UVB		
Yes	1.01 (0.58-1.78)	0.98
No	1.80 (1.48-2.19)	<0.0001
Systemics		
Yes	2.08 (1.40-3.12)	0.0003
No	1.58 (1.28-1.94)	<0.0001
Phototherapy or systemics		
Yes (moderate-severe pso)	1.85 (1.33-2.57)	0.0002
No (mild psoriasis)	1.59 (1.27-1.98)	<0.0001

TREATMENT MODALITIES: HR adjusted for age and gender for comparisons within the psoriasis group for risk of any cancer

Comparison	Adjusted HR (95% CI)	p-value
PUVA vs no PUVA	1.15 (0.58-2.28)	0.6906
UVB vs no UVB	0.52 (0.29-0.95)	0.0324
Drugs vs no drugs	1.24 (0.79-1.95)	0.3511
Severe vs mild psoriasis	1.09 (0.74-1.63)	0.6583

Note: severe psoriasis = received phototherapy or systemics; mild = received neither

Author's conclusion:

- Psoriasis carries an elevated risk of malignancies, especially in younger and in male patients.
- This effect is independent of systemic treatment for psoriasis.
- Phototherapy with UVB did not increase, but rather reduced, the risk of cancer in psoriasis

H.4.22 STUDY 14 CANCER

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
A. E. Prizment, A. Alonso, A. R. Folsom, R. L. Ahmed, B. A. Virnig, E. M. Warshaw, and K. E. Anderson. Association between psoriasis and incident cancer: The Iowa's Women's	**Observational:** prospective population based cohort study in Iowa, USA with **retrospective** baseline data sources; 1991 to 2006 Linkage of data from 3 sources: Iowa Women's Health Study (IWHS), Medicare and the Iowa SEER cancer registry **Representative**	N: 33,266 (2.2% psoriasis)	**Inclusion criteria:** all cancer free women registered on IWHS **Exclusion criteria:** not in Iowa at start of follow-up; cancer at baseline or before start of follow-up	Data from Medicare claims data – psoriasis diagnoses identified using ICD-9 diagnosis code 696.1 Psoriasis was defined as: 2+ psoriasis claims from any Medicare file during 1991-2004 or 1+ psoriasis claim from a dermatologist (n = 719). Severe psoriasis	Prospective follow-up from 1991/2004 to disenrollment from Medicare; emigration from Iowa; cancer diagnosis; death or end of follow-up on 31 Dec 2006	Incidence of cancer	National Cancer Institute grant

Health Study. Cancer Causes Control 22 (7):1003-1010, 2011. Ref ID: PRIZMENT 2011	**population sample:** no – women over 65 only and limited to those who since 1991 were enrolled in at least 1 month of fee-for-service coverage after reaching 65 years. Derived from cohort of women aged 55-69 recruited by baseline questionnaire in 1986 (used only those over 65 because Medicare pays for health benefits for this group) **Prognostic factor adequately measured:** yes – Medicare claims **Confounders adjusted for:** age at start of follow-up, smoking status and pack use, body mass index, education, physical activity, and hormone therapy use (and number of live births for breast cancer) Note: alcohol intake, WHR, history of diabetes, oral contraceptive use			was defined as 4+ psoriasis claims from a dermatologist in any year (n=121). 4 visits were selected as a cut-off because patients receiving systemics or phototherapy are usually seen every 3 months by dermatologists			

	and start of follow-up did not materially change associations so these variables were not included in the final model **Attrition bias:** not reported (but 99% success in linkage) **Outcomes adequately measured:** yes – from SEER database using ICD-O codes (3rd edition) **Appropriate statistical analysis:** yes – hazard ratios using Cox proportional hazards model and psoriasis as a time-dependent variable						

Patient characteristics:

Characteristic	Control (%)	Psoriasis (%)
Total	32191	719
Mean age at start of follow-up, mean±SD	68.1±3.2	67.8±3.0
BMI (kg/m^2)		
<24.9	39.5	41.3
25-30	37.3	33.4
≥30	23.2	25.3
Education		
Less than high school	19.6	17.9
High school	42.2	38.2
More than high school	38.1	43.9
Smoking		
Never	67.6	53.1
Former	18.6	25.0
Current	13.8	22.0
Alcohol intake		
Never	56.9	52.8

<4g/day	23.6	22.4
≥4g/day	19.5	24.8

Effect size:

Adjusted HR for specific cancer types

	No psoriasis		**All psoriasis**		**Mild psoriasis**		**Severe psoriasis**	
Cancer types	**N**	**HR (95% CI)**	**N**	**HR (95% CI)**	**N**	**HR (95% CI)**	**N**	**HR (95% CI)**
Any	6381	1	107	1.1 (0.9-1.4)	85	1.1 (0.9-1.4)	22	1.2 (0.8-1.8)
Breast	2037	1	29	1.0 (0.7-1.5)	24	1.4 (0.8-2.2)	5	1.0 (0.4-2.7)
Lung	722	1	20	1.3 (0.8-2.0)	16	1.1 (0.7-1.6)	4	1.0 (0.4-2.3)
Colon	925	1	22	1.6 (1.0-2.4)	17	1.5 (0.9-2.4)	5	1.9 (0.8-4.7)

Trend across psoriasis group was tested by including psoriasis severity as a continuous variable (0-no psoriasis; 1-mild; 2-severe); p-value for total = 0.3; breast cancer = 0.4; lung cancer = 0.9 and colon cancer = 0.03

Note: after adjustment for confounders observed associations were attenuated and this was largely due to smoking

Author's conclusion:

- Psoriasis carries an elevated risk of colon cancer, particularly if severe.

H.4.23 STUDY 14 CANCER

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
X. Shu, J. Ji, J. Sundquist, K. Sundquist, and K. Hemminki. Survival in cancer patients hospitalized for psoriasis: A population-based cohort study in Sweden. Br.J.Dermatol. 165 (1):129-136, 2011. Ref ID: SHU2011	**Observational:** retrospective cohort study in Sweden; 1964 to 2006 Linkage of anonymous data **Representative population sample:** yes but indirect (all known to have cancer – survival rate) and also severe because all diagnosed following hospitalisation for psoriasis **Prognostic factor adequately measured:** yes – ICD codes **Confounders adjusted for:** gender, age at diagnosis of primary neoplasm and calendar year at diagnosis of	N: 1,011,757 control; 1746 psoriasis (0.2% psoriasis)	**Inclusion criteria:** psoriasis cohort: all patient diagnosed with psoriasis 1964-2006 in the Swedish Hospital Discharge Registry according to 7-10th edition of ICD Controls: cancer patients without psoriasis **Exclusion criteria:** not stated	Data from Swedish Hospital Discharge Registry – psoriasis diagnoses identified using ICD	Follow-up from cancer diagnosis to emigration; death or end of follow-up on 31 Dec 2006	Incidence of cancer mortality (primary neoplasms only)	Swedish Cancer Society, Swedish Council for Working Life and Social Research and the Deutsche Krebshilfe

	primary neoplasm Also explored in sensitivity analyses: COPD (surrogate for smoking), alcohol-related diseases (surrogate for alcohol intake) and obesity **Attrition bias:** not reported **Outcomes adequately measured:** yes –linkage to Swedish cancer registry (tumours ascertained with 4-digit ICD-7 code; records all new cases and most are cytologically or histologically confirmed; full national coverage) **Appropriate statistical analysis:** yes – hazard ratios using proportional hazards model						

Effect size:

Adjusted HR for mortality from specific cancer types in people diagnosed with cancer with psoriasis compared to people without psoriasis

		Cancer specific mortality		**Overall mortality**	
Cancer types	**Cases**	**N deaths**	**HR (95% CI)**	**N deaths**	**HR (95% CI)**
Upper aero-digestive tract	57	32	2.38 (1.68-3.37)	46	2.16 (1.62-2.89)
Oesophagus	33	29	1.78 (1.23-2.57)	32	1.69 (1.19-2.39)
Stomach	58	41	1.27 (0.94-1.73)	52	1.38 (1.05-1.81)
Colon	109	48	1.12 (0.85-1.49)	74	1.23 (0.98-1.54)
Rectum	67	31	1.16 (0.81-1.65)	45	0.97 (0.73-1.30)
Anus	11	1	0.48 (0.07-3.42)	3	0.68 (0.22-2.11)
Liver	70	52	1.43 (1.09-1.88)	68	1.50 (1.18-1.90)
Pancreas	56	51	1.23 (0.93-1.62)	56	1.24 (0.95-1.61)
Lung	190	147	1.11 (0.94-1.30)	170	1.11 (0.96-1.29)
Breast	199	31	0.71 (0.50-0.98)	86	1.09 (0.88-1.35)
Cervix	22	9	1.27 (0.66-2.45)	111	0.88 (0.49-1.58)
Endometrium	33	3	1.44 (0.46-4.45)	16	2.21 (1.35-3.61)
Ovary	25	16	1.11 (0.68-1.81)	21	1.10 (0.72-1.68)

Prostate	222	76	1.02 (0.81-1.27)	133	1.11 (0.94-1.32)
Kidney	50	31	1.58 (1.11-2.24)	41	1.44 (1.06-1.96)
Urinary bladder	89	28	1.22 (0.84-1.76)	51	1.10 (0.84-1.45)
Melanoma	46	10	1.85 (1.00-3.44)	20	1.63 (1.05-2.53)
Skin SCC	117	6	3.16 (1.41-7.07)	62	1.37 (1.07-1.76)
nervous system	51	21	1.12 (0.73-1.72)	32	0.95 (0.67-1.34)
Thyroid	11	2	0.54 (0.14-2.17)	5	0.67 (0.28-1.60)
Endocrine glands	30	0	-	15	1.27 (0.76-2.10)
Non-Hodgkin's lymphoma	72	35	1.10 (0.79-1.54)	49	1.03 (0.78-1.36)
myeloma	20	13	0.83 (0.48-1.43)	18	0.98 (0.62-1.56)
Leukaemia	49	28	1.48 (1.02-2.14)	39	1.49 (1.09-2.04)
Acute	16	13	1.15 (0.67-1.98)	14	1.13 (0.67-1.91)
Chronic	15	7	1.53 (0.73-3.21)	10	1.60 (0.86-2.97)
All	1746	754	1.26 (1.18-1.35)	1177	1.27 (1.20-1.35)

Adjusted HR for mortality from specific cancer types in people diagnosed with cancer with psoriasis compared to people without psoriasis, stratified by number of hospitalisations in the psoriasis group (as a surrogate for disease severity)

Cancer types	**One hospitalisation**		**Two or more hospitalisations**	
	N deaths	**HR (95% CI)**	**N deaths**	**HR (95% CI)**

Upper aero-digestive tract	24	2.86 (1.92-4.27)	8	1.73 (0.87-3.46)
Oesophagus	6	1.53 (0.69-3.40)	23	1.86 (1.23-2.80)
Stomach	25	1.17 (0.79-1.73)	16	1.50 (0.92-2.45)
Colon	31	1.06 (0.75-1.51)	17	1.28 (0.80-2.06)
Rectum	18	0.97 (0.61-1.53)	13	1.55 (0.90-2.67)
Anus	1	0.85 (0.12-6.06)	0	-
Liver	26	1.27 (0.86-1.86)	26	1.64 (1.12-2.42)
Pancreas	23	0.92 (0.61-1.39)	28	1.72 (1.19-2.50)
Lung	85	1.06 (0.85-1.31)	62	1.17 (0.91-1.50)
Breast	21	0.71 (0.47-1.10)	10	0.70 (0.38-1.30)
Cervix	4	0.91 (0.34-2.42)	5	1.86 (0.78-4.48)
Endometrium	2	1.33 (0.33-5.35)	1	1.56 (022-11.07)
Ovary	8	0.87 (0.44-1.74)	8	1.50 (0.75-3.01)
Prostate	42	0.85 (0.63-1.16)	34	1.34 (0.95-1.87)
Kidney	15	1.11 (0.67-1.84)	16	2.59 (1.59-4.22)
Urinary bladder	15	0.92 (0.55-1.52)	13	1.90 (1.11-3.28)
Melanoma	5	1.29 (0.54-3.11)	5	2.85 (1.19-6.82)
Skin SCC	2	2.14 (0.53-8.56)	4	3.96 (1.48-10.61)
nervous system	14	1.17 (0.69-1.97)	7	1.06 (0.51-2.23)

Thyroid	2	0.54 (0.14-2.18)	0	-
Endocrine glands	0	-	0	-
Non-Hodgkin's lymphoma	18	0.93 (0.58-1.47)	17	1.32 (0.82-2.13)
myeloma	7	0.71 (0.34-1.48)	6	1.00 (0.45-2.24)
Leukaemia	18	1.33 (0.84-2.11)	10	1.61 (0.87-2.99)
All	419	1.13 (1.03-1.23)	335	1.47 (1.33-1.63)

Adjusted HR for mortality from all cancer in people diagnosed with cancer with psoriasis compared to people without psoriasis, stratified by previously hospitalised for alcohol related diseases or non-alcohol related diseases

Cancer type	**Alcohol-related**		**Non alcohol-related**	
	N deaths	**HR (95% CI)**	**N deaths**	**HR (95% CI)**
All	**53**	**1.74 (1.35-2.24)**	**701**	**1.23 (1.15-1.32)**

Adjusted HR for mortality from specific cancer types in people diagnosed with cancer with psoriasis compared to people without psoriasis, stratified by age at diagnosis of cancer in the psoriasis group

Cancer types	**≤65 years**		**>65 years**	
	N deaths	**HR (95% CI)**	**N deaths**	**HR (95% CI)**

Upper aero-digestive tract	20	3.04 (1.96-4.71)	12	1.83 (1.04-3.22)
Oesophagus	16	1.88 (1.15-3.07)	13	1.78 (1.03-3.07)
Stomach	14	1.49 (0.88-2.51)	27	1.17 (0.80-)1.70
Colon	19	1.37 (0.87-2.14)	29	1.01 (0.70-1.46)
Rectum	11	1.35 (0.75-2.44)	20	1.09 (0.71-1.70)
Anus	1	0.76 (0.11-5.42)	0	-
Liver	17	2.45 (1.52-3.95)	35	1.22 (0.87-1.70)
Pancreas	18	1.42 (0.89-2.25)	33	1.15 (0.82-1.62)
Lung	51	1.04 (0.79-1.36)	96	1.16 (0.95-1.42)
Breast	16	0.78 (0.48-1.27)	15	0.65 (0.39-1.08)
Cervix	3	0.85 (0.27-2.64)	6	1.56 (0.70-3.49)
Endometrium	1	0.83 (0.12-5.91)	2	2.37 (0.59-9.51)
Ovary	4	2.28 (0.85-6.15)	12	1.01 (0.58-1.79)
Prostate	16	1.31 (0.80-2.14)	60	0.94 (0.73-1.21)
Kidney	15	1.61 (0.97-2.68)	16	1.58 (0.97-2.58)
Urinary bladder	3	0.63 (0.20-1.94)	25	1.39 (0.94-2.06)
Melanoma	6	1.77 (0.79-3.94)	4	1.85 (0.69-4.94)
Skin SCC	3	4.78 (1.52-15.02)	3	2.34 (0.75-7.30)
nervous system	15	1.60 (0.96-2.65)	6	0.66 (0.30-1.48)

Thyroid	1	2.01 (0.28-14.29)	1	0.35 (0.05-2.51)
Endocrine glands	0	-	0	-
Non-Hodgkin's lymphoma	22	1.44 (0.94-2.18)	13	0.79 (0.42-1.36)
myeloma	4	1.07 (0.40-2.87)	9	0.75 (0.39-1.45)
Leukaemia	9	1.21 (0.63-2.33)	19	1.62 (1.03-2.54)
All	288	1.39 (1.28-1.52)	466	1.18 (1.08-1.29)

Author's conclusion:

- A previous diagnosis of psoriasis worsens the prognosis of many cancers.
- A worse prognosis was more pronounced in psoriatic cancer patients diagnosed at an earlier age, previously hospitalized for alcohol-related diseases, or with severe symptoms

H.4.24 STUDY 13 CANCER

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
Boffetta (2001) Cancer risk in a population-based cohort of patients hospitalised for psoriasis in Sweden Ref ID: BOFFETTA 2001	**Observational:** population based cohort study 1965-1989 **Representative population sample:** yes. **Prognostic factor adequately measured:** yes **Confounders adjusted for:** Matched for age and sex. **Attrition bias:** not reported **Outcomes adequately measured:** yes	N: 9773	**Inclusion criteria:** all records in the in-patient register with a hospital discharge diagnosis of psoriasis (ICD-7 code 706; ICD-8 code 696) between 1965-83. **Exclusion criteria:** excluded the first year of observation following the index admission to reduce selection bias, which may occur if psoriasis patients who developed a cancer or died within 1 year are more likely hospitalised than other psoriasis patients and detection bias, if cancer was to be diagnosed during the diagnostic and therapeutic procedures involved in the management of psoriasis.	Swedish National Board of Health and Welfare in-patient register. Linked cohort to the cohort to the nationwide Registers of Total Population, Cause of Death, and Population Migration to identify all patients who lived in Sweden during the study period. Further linked to the Swedish cancer register.	15 years +, no mean given.	Incidence of cancer Standard mortality ratios	Not reported.

	Appropriate statistical analysis: not multivariable/regression						

Patient characteristics:

Characteristic	Patients	Person-years
Total	**9,773**	**93,775.6**
Gender – men	**5,306**	**49,138.3**
Duration of follow-up	**4,467**	**44,637.2**
1-4 years	**1,234**	**27,351.4**
5-9 years	**2,926**	**36,475.9**
10-14 years	**2,839**	**20,646.3**
15+years	**2,774**	**9,302.0**
Presence of other diagnoses		
Psoriasis as only diagnosis	**5,164**	**55,512.7**
Other diagnoses, psoriasis as primary	**1,652**	**14,755.0**
Other diagnoses, psoriasis as secondary	**2,957**	**23,,507.9**

Effect size:

Standardised incidence ratio of selected neoplasms among patients hospitalised for psoriasis[1]

Outcome	Men			Women			Both genders		
	N	SIR	95% CI	N	SIR	95% CI	N	SIR	95% CI
All cancers	444	1.34	1.22, 1.47	345	1.41	1.27, 1.57	789	1.37	1.28-1.47
Oral cavity, pharynx	25	2.60	1.68, 3.84	11	3.37	1.68, 6.04	36	2.80	1.96,3.87
Oesophagus	13	3.00	1.59, 5.13	4	3.03	0.82, 7.76	17	3.01	1.75, 4.81
Stomach	22	1.07	0.67, 1.62	10	0.99	0.47, 1.82	32	1.04	0.71, 1.47
Colon	26	1.08	0.71, 1.59	26	1.25	0.81, 1.83	52	1.16	0.87, 1.52
Rectum	19	1.10	0.66, 1.71	17	1.62	0.94, 2.60	36	1.29	0.91, 1.79
Liver	18	2.52	1.49, 3.98	11	1.36	0.68, 2.44	29	1.91	1.28, 2.74
Pancreas	14	1.34	0.73, 2.24	14	1.82	0.99, 3.05	28	1.56	1.02, 2.23
Larynx	6	1.55	0.57, 3.37	0	[0.32]	0,11.5	6	1.43	0.52, 3.12
Lung	65	1.91	1.48, 2.44	25	3.00	1.94, 4.43	90	2.13	1.71, 2.61
Connective tissue	1	0.47	0.01, 2.59	3	1.99	0.40, 5.81	4	1.09	0.29, 2.80
Melanoma	3	0.34	0.07, 1.00	2	0.29	0.03, 1.05	5	0.32	0.10, 0.74
SCC of the skin	35	2.75	1.92, 3.83	13	1.92	1.02, 3.28	48	2.46	1.82, 3.27
Breast	1	1.89	0.02, 10.5	78	1.27	1.00, 1.58	79	1.27	1.01, 1.58

Cervix	-	-	-	11	1.44	0.72, 2.57	11	1.44	0.72, 2.57
Endometrium	-	-	-	15	1.11	0.62, 1.84	15	1.11	0.62, 1.84
Ovary	-	-	-	19	1.38	0.83, 2.16	19	1.38	0.83, 2.16
Female genital organs	-	-	-	6	2.47	0.90, 5.37	6	2.47	0.90, 5.37
Prostate	77	0.96	0.76, 1.21	-	-	-	77	0.96	0.76, 1.21
Male genital organs	8	2.69	1.16, 5.30	-	-	-	8	2.69	1.16, 5.30
Bladder	33	1.37	0.95, 1.93	10		0.78, 2.98	43	1.43	1.03, 1.92
Kidney, pelvis	13	1.10	0.58, 1.88	15	1.62	1.37, 4.04	28	1.56	1.04, 2.25
Brain	4	0.49	0.13, 1.25	6	2.45	0.34, 2.00	10	0.68	0.33, 1.25
Thyroid	4	2.62	0.71, 6.71	3	0.92	020, 2.92	7	1.55	0.62, 3.19
Hodgkin's disease	1	0.58	0.01, 3.24	0	1.00	0,353	1	0.36	0.01, 2.02
Non-Hodgkin's lymphoma[2]	15	1.56	0.87, 2.57	7	[1.04]	0.48, 2.45	22	1.42	0.89, 2.15
Mycosis fungoides	5	26.7	8.60, 62.3	0	1.19	0, 51.3	5	19.3	6.22, 45.1
Multiple myeloma	5	0.92	0.30, 2.14	6	[0.07]	0.62, 3.69	11	1.22	0.61, 2.19
Lymphocytic leukaemia	2	0.44	0.05, 1.58	4	1.70	0.51, 4.84	6	0.90	0.33, 1.96
Non-	6	1.74	0.64, 3.79	5	1.89	0.70, 5.09	11	1.92	0.96, 3.43

lymphocytic leukaemia									

[1]N, number of observed cases; SIR, standardised incidence ratio; CI, confidence interval; SCC, squamous cell carcinoma. When no cases were observed, expected cases are reported in square brackets.

[2]Excluding mycosis fungoides.

Standardised mortality ratios for selected non-neoplastic causes among patients hospitalised for psoriasis[1]

	Whole cohort			Psoriasis as only diagnosis		
	N	SMR	95% CI	N	SMR	95% CI
All causes	3813	1.94	1.88,2.00	1392	1.56	1.48, 1.64
Infective diseases	28	2.25	1.49, 3.25	9	1.41	0.61, 2.77
Malignant neoplasms	611	1.48	1.36, 1.60	252	1.30	1.15, 1.47
Respiratory diseases	290	2.16	1.91, 2.42	94	1.58	1.27, 1.93
Pneumonia	169	2.02	1.73. 2.35	61	1.66	1.27, 2.14
Bronchitis	35	2.06	1.43, 2l86	8	1.05	0.46, 2.09
Emphysema	29	3.13	2.09, 4.49	6	1.44	0.53, 3.13
Asthma	24	2.46	1.58, 3.67	6	1.31	0.48, 2.85
Cardiovascular disease	2066	1.87	1.79, 1.95	715	1.45	1.35, 1.56
Isch. Heart disease	1357	1.97	1.87, 2.08	479	1.55	1.42, 1.70

Cerebrovasc. Disease	334	1.60	1.43, 1.78	123	1.33	1.11, 1.59
Arterial disease	134	1.83	1.54 2.17	43	1.34	0.97, 1.80
Diabetes mellitus	99	3.14	2.52, 3.87	24	1.88	1.20, 2.79
Neurological disease	33	1.77	1.22, 2.49	12	1.35	0.69, 2.35
Mental disorders	66	2.91	2.25, 3.70	33	3.03	2.08, 4.25
Alcoholism	51	7.19	5.35, 9.44	25	6.37	4.12, 9.39
Digestive diseases	246	3.86	3.39, 4.37	98	3.31	2.69, 4.03
Liver cirrhosis	133	8.13	6.81, 9.64	50	6.05	4.49, 7.97
Genito-urinary disease	74	2.54	2.00, 3.19	20	1.56	0.96, 2.42
Skin/subcutaneouse disease	20	17.7	10.8, 27.3	4	7.87	2.11, 20.1
Muscoloskeletal disease	27	3.34	2.20, 4.85	3	0.81	0.16, 2.35
External causes	213	2.29	2.00, 2.62	101	2.08	1.69, 2.53
Trauma to organs	21	7.13	4.42, 10.9	12	7.26	3.75, 12.7
Open wounds	66	2.19	1.69, 2.78	27	1.99	1.31, 2.89
Trauma of CNS	53	2.04	1.53, 2.67	28	1.91	1.27, 2.76
Adverse toxic effect	39	3.81	2.71, 5.21	15	2.53	1.42, 4.18

Author's conclusion: despite some limitations, they provide no evidence for an increased risk of melanoma among patients hospitalised for psoriasis. Indirect evidence that consumption of alcohol and tobacco is increased among patients with severe psoriasis**.**

H.4.25 STUDY 14 LYMPHOMA

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
Gelfand (2006) The risk of lymphoma in patients with psoriasis Ref ID: GELFAND2006	**Observational: population based** cohort study **Representative population sample:** yes, used GPRD **Prognostic factor adequately measured:** yes **Confounders adjusted for:** Age, gender and person time	N: 153,197 patients with psoriasis (149,203 mild psoriasis and 3994 severe psoriasis) and 765,950 without psoriasis.	**Inclusion criteria:** All psoriasis patients who had at least 1 day of observation time. They were matched to up to five control subjects on matched criteria who did not have psoriasis, who were seen in the same practice and had a date of observation in the practice within 60 days. **Exclusion criteria:** not stated	OXCMIS and Read codes were used to classify diseases. Those receiving systemic therapies were classified (according to treatment codes) as severe psoriasis and those who did not classified as mild psoriasis Classification of having a new lymphoma was determined if they	Mean time around 5 years. **Note**: follow-up time ended when they developed a lymphoma, died, transferred out of practice or practice no longer UTS.	Incidence of lymphoma, non-Hodgkin's' lymphoma, Hodgkin's lymphoma and T-cell lymphoma.	Funded by NIH/NIAMS K23AR051125-01 and an unrestricted grant to the Trustees of the University of Pennsylvania from Biogenide c.

	Attrition bias: not reported **Outcomes adequately measured:** yes **Appropriate statistical analysis:** yes, cox proportional hazards model **Notes:** psoriasis patients were older than control patients and mild psoriasis patients were slightly more likely to be females .			received a medical code after the start date and on or before the end date.			

Patient characteristics:

	Control	**Mild psoriasis**	**Severe psoriasis**
N (%)	**765, 950**	**149,203**	**3.944**
Gender – male	366,238 (48%)	70,742 (47.4%)	1,937 (48.5%)
Gender – female	399,712 (52%0	78,461 (52.6%)	2,057 (51.5%)
Odds ratio (95% CI)	-	0.98 (0.97, 1.00) P=0.0045	1.03 (0.97, 1.09) P=0.3912
Age – mean (median, 25th, 75th percentile)	35.76 (33, 18, 53)	41.51 (40, 26, 57) p=0.0045	48.51 (48, 35, 62) p=0.3912

History of lymphoma			
Yes	538 (0.07%)	179 (0.12%)	11 (0.28%)
No	765,412 (99.93%)	149, 024 (99.88%)	3,983 (99.72%)
Odds ratio (95% CI)	-	1.71 (1.44, 2.03) p<0.0001	3.93 (1.95, 7.09) p=0.0002
Systemic therapies (n%)			
Methotrexate	-	-	2,314 (57.94%)
Psoralen/phototherapy	-	-	681 (17.05%)
Azathioprine	-	-	659 (16.50%)
Ciclosporine	-	-	414 (10.37%)
Etretinate or acitretin	-	-	351 (8.79%)
Hydroxyurea	-	-	224 (5.61%)
Mycophenoalte mofetil	-	-	12 (0.30%)

Odds ratios and p-values refer to the comparison of the mild and severe psoriasis groups with the control group. Percentages for systemic therapies do not add to 100 because patients could have received more than one systemic therapy.

Effect size:

Incidence and relative risk (hazard) of lymphoma in psoriasis patients compared to controls

Variable	Control	Mild psoriasis	Severe psoriasis	All psoriasis
Mean follow-up time (media, 25th, 75th	5.61 (5.25, 2.18, 9.13)	4.50 (3.80, 1.64, 7.09)	5.77 (5.53, 2.70, 8.96)	4.54 (3.84, 1.67, 7.16)

percentile)				
Person years (n)	4,297,296	671,914	23,048	694,962
New lymphoma (n)	970	237	11	248
Incidence per 10,000 person years (95% CI)	2.26 (2.12, 2.40)	3.53 (3.09, 4.01)	4.77 (2.38, 8.54	3.57 (3.14 4.04)
Primary analysis				
Unadjusted hazard ratio	-	1.54 (1.33, 1.77) p<0.001	2.12 (1.17, 3.85) p=0.013	1.56 (1.35, 1.79) p<0.001
Adjusted hazard ratio	-	1.34 (1.16, 1.54) p<0.001	1.59 (0.88, 2.89) p=0.124	1.35 (1.17, 1.55) p<0.001
Attributable risk (excess number of lymphoma cases related to psoriasis)	-	-	-	7.9/100,000 per year
Sensitivity analysis				
New lymphoma	711	183	9	192
Unadjusted hazard ratio	-	1.71 (1.45, 2.01) p<0.001	2.37 (1.23, 4.57) p=0.010	1.73 (1.48, 2.03) p<0.001
Adjusted hazard ratio	-	1.48 (1.25, 1.74) p<0.001	1.78 (0.92, 3.44) p=0.085	1.49 (1.27, 1.75) p<0.001

[1]Adjusted for gender, age.

[2] Restricted to subjects with at least 6 months of follow-up time who did not have a history of lymphoma or a lymphoma in the first six months.

Incidence and relative risk (hazard) of NHL in psoriasis patients compared to controls

Variable	Control	Mild psoriasis	Severe psoriasis	All psoriasis
Mean follow-up time (median, 25th, 75th percentile)	5.61 (5.25, 2.18, 9.13)	4.51 (3.81, 1.65, 7.09)	5.77 (5.53, 2.70, 8.96)	4.54 (3.84, 1.67, 7.16)
Person years (n)	4,298,107	672,168	23,061	695,230
New NHL (n)	759	159	4	163
Incidence per 10,000 person years (95% CI)	1.77 (1.64, 1.90)	2.37 (2.01, 2.76)	1.73 (0.47, 4.44)	2.35 (2.00, 2.73)
Primary analysis				
Unadjusted hazard ratio	-	1.33 (1.12, 1.58) p=0.001	0.99 (0.37, 2.63) p=0.980	1.32 (1.11, 1.56) p=0.001
Adjusted hazard ratio	-	1.15 (0.97, 1.37) p=0.103	0.73 (0.28, 1.96) p=0.539	1.14 (0.96, 1.35) p=0.134
Sensitivity analysis				
New NHL (n)	581	128	4	132
Unadjusted hazard ratio	-	1.47 (1.21, 1.78) p<0.001	1.29 (0.48, 3.45) p=0.612	1.47 (1.21, 1.77) p<0.001
Adjusted hazard ratio	-	1.27 (1.05, 1.54) p=0.015	0.96 (0.36, 2.57) p=0.939	1.26 (1.04, 1.52) p=0.018

CI, confidence interval; NHL, non-Hodgkin's lymphoma.

[1] Adjusted for gender, age.

[2] Restricted to subjects with at least 6 months of follow-up time who did not have a history of lymphoma or a lymphoma in the first six months.

Incidence and relative risk (hazard) of HL in psoriasis patients compared to controls

Variable	Control	Mild psoriasis	Severe psoriasis	All psoriasis
Mean follow-up time (median, 25th, 75th percentile)	5.61 (5.25, 2.19, 9.13	4.51 (3.81, 1.65, 7.10)	5.77 (5.52, 2.70, 8.96)	4.54 (3.85, 1.67, 7.16)
Person years (n)	4,299,128	672,418	23,063	695,482
New Hodgkin's lymphoma (n)	160	39	3	42
Incidence per 10,000 person years (95% CI)	0.37 (0.32, 0.44)	0.58 (0.41, 0.79)	1.30 (0.27, 3.80)	0.60 (0.44, 0.82)
Primary analysis				
Unadjusted hazard ratio	-	1.48 (1.04, 2.10) p=0.029	3.50 (1.12, 10.96) p=0.032	1.54 (1.10, 2.17) p=0.012
Adjusted hazard ratio[1]	-	1.42 (1.00, 2.02) p=0.052	3.18 (1.01, 9.97) p=0.048	1.48 (1.05, 2.08) p=0.025
Attributable risk (excess number of lymphoma cases related to psoriasis)				1.8/100,000 per year
Sensitivity analysis[2]				
New HL (n)	98	24	1	25
Unadjusted hazard ratio	-	1.58 (1.01, 2.47) p0.045	1.91 (0.27, 13.68) P=0.521	1.59 (1.03, 2.47) P=0.038

Adjusted hazard ratio[1]	-	1.53 (0.98, 2.40) P=0.063	1.79 (0.25, 12.90) P=0.561	1.54 (0.99, 2.40) P=0.055

HI, Hodgkin's lymphoma; CTCL cutaneous T-cell lymphoma.

[1]Adjusted for gender, age.

[2]Restricted to subjects with at least 6 months of follow-up time who did not have a history of lymphoma or a lymphoma in the first 6 months.

Incidence and relative risk (hazard) of cutaneous T-cell lymphoma in psoriasis patients compared to controls

Variable	Control	Mild psoriasis	Severe psoriasis	All psoriasis
Mean follow-up time (median, 25th, 75th percentile	5.61 (5.25, 2.19, 9.13)	4.51 (3.81, 1.65, 7.10)	5.77 (5.53, 2.70, 8.96)	4.54 (3.85, 1.67, 7.16)
Person years (n)	4,299,563	672, 383	23,054	695,437
New CTCL (n)	51	39	4	43
Incidence per 10,000 person years (95% CI)	0.12 (0.09, 0.16	0.58 (0.41, 0.79)	1.74 (0.47, 4.44)	0.62 (0.45, 0.83)
Primary analysis				
Unadjusted hazard ratio	-	4.78 (3.15, 7.27) p<0.001	14.60 (5.28, 4.40 p<0.001	5.08 (3.38, 7.64) p<0.001
Adjusted hazard ratio	-	4.10 (2.70, 6.23) p<0.001	10.75 (3.89, 29.76) p<0.001	4.34 (2.89, 6.52) p<0.001
Attributable risk (excess number of lymphoma cases related to psoriasis)				4.0/100,000 per year

Sensitivity analysis				
New CTCL (n)	32	31	4	35
Unadjusted hazard ratio	-	6.37 (3.88, 10.46) p<0.001	23.21 (8.21, 65.62) p<0.001	6.89 (4.26, 11.15) p<0.001
Adjusted hazard ratio	-	5.42 (3.30, 8.89) p<0.001	17.18 (6.17, 48.58) p<0.001	5.84 (3.61, 9.44) p<0.001

Author's conclusion: psoriasis is associated with an increased risk of lymphoma. The strongest association is for Hodgkin's lymphoma and cutaneous T-cell lymphoma. Although patients with psoriasis have an increased relative risk of lymphoma, the absolute risk attributable to psoriasis is low as lymphoma is a rare disease and the magnitude of association is modest.

H.4.26 STUDY 15 CANCER

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
Olsen (1992) Malignant tumours in patients with psoriasis	**Observational:** population-based cohort discharged from hospital in Denmark between 1977 to 1987 **Representative**	N: 6910 patients with psoriasis.	**Inclusion criteria:** all discharge records for 1977 through 1987 that included a diagnosis of psoriasis and similar conditions (ICD-8: 696)	National Hospital Discharge Register for discharged psoriasis patients were linked to the Danish Central Population Register	On average 5.1 years. Maximum follow-up was 11 years.	Incidence of cancers.	Not reported

Ref ID: OLSEN1992	**population sample:** yes **Prognostic factor adequately measured:** yes **Confounders adjusted for:** Stratified by age and matched on sex and calendar time **Attrition bias:** not reported **Outcomes adequately measured:** yes **Appropriate statistical analysis:** not multivariable/regression		**Exclusion criteria:** not reported.	which has information on all Danish resident and information on date of emigration or death was obtained. The study cohort was linked to the Danish Cancer Registry. Matched on sex and year of birth at random from the cancer registry files.			
Effect size: **Observed (Obs) and expected (Exp) incidence of cancers among 6917 patients with a diagnosis of psoriasis included in their hospital discharge record, 1977-1987**							

Site	Obs	Exp	RR*	95% CI
All malignant neoplasms	401	296.4	1.35	1.22-1.49
Buccal cavity and pharynx	9	5.8	1.5	0.8-2.8
Oesophagus	1	2.6	0.4	0.0-1.92
Stomach	14	11.6	1.2	0.7-2.0
Colon	34	25.1	1.4	1.0-1.9
Rectum	12	14.4	0.8	0.4-1.5
Liver (primary)	4	3.0	1.3	0.4-3.2
Biliary tract	4	3.1	1.3	0.4-3.1
Pancreas	14	9.5	1.5	0.8-2.5
Larynx	7	3.0	2.4	1.0-4.6
Lung	58	40.6	1.4	1.1-1.8
Breast	24	28.3	0.9	0.5-1.3
Cervix uteri	2	5.6	0.4	0.1-1.2
Corpus uteri	7	7.4	1.0	0.4-1.9
Ovary	7	6.8	1.0	0.5-2.0
Prostate	24	18.4	1.3	0.8-1.9
Testis	1	1.6	0.6	0.0-3.1
Kidney	14	8.2	1.7	1.0-2.8
Bladder	17	16.8	1.0	0.6-1.6

Melanoma of skin	7	5.7	1.2	0.5-2.4
Other skin cancers	04	37.9	2.5	2.0-3.0
Brain and nervous system	5	6.2	0.8	0.3-1.8
Thyroid	1	1.2	0.9	0.0-4.1
Non-Hodgkin's lymphoma	8	5.6	1.4	0.7-2.7
Hodgkin's disease	1	1.0	1.0	0.1-4.9
Multiple myeloma	1	3.0	0.3	0.0-1.6
Leukaemia	8	6.8	1.2	0.5-2.2
Other specified sites	10	9.4	1.4	0.8-2.3
Secondary and unspecified sites	13	7.8	1.3	0.7-2.3

Sex-specific relative risks (RR) for cancers at selected sites among patients with psoriasis

Site	**Men**				**Women**			
	Obs	**Exp**	**RR**	**95% CI**	**Obs**	**Exp**	**RR**	**95% CI**
All malignant neoplasms	226	156.2	1.45	1.26-1.65	175	140.0	1.25	1.07-1.45
Melanoma of skin	0	2.5	-		7	3.2	2.2	1.0-4.3
Other skin cancers	55	20.8	2.6	2.0-3.4	39	17.0	2.3	1.6-3.1
Lung	42	30.3	1.4	1.0-1.9	16	10.3	1.6	0.9-2.5

Larynx	7	2.5	2.8	1.2-5.5	0	0.5	-	
Pharynx	4	1.0	3.9	1.2-9.3	0	0.4	-	
Pancreas	7	4.9	1.4	0.6-2.8	7	4.6	1.5	0.7-3.0
Colon	13	11.6	1.1	0.6-1.9	21	13.4	1.6	1.0-2.4
Kidney	6	4.7	1.3	0.5-2.7	8	3.5	2.3	1.1-4.4

Age-specific relative risks (RR) for nonmelanoma skin, lung and urinary bladder cancer among 7603 patients with psoriasis, 1977-1987

Age group (year)	**Nonmelanoma skin cancer**		**Lung cancer**		**Bladder cancer**	
	No.	**RR**	**No.**	**RR**	**No.**	**RR**
All ages	94	2.5	58	1.4	17	1.0
Up to 29	0	-	0	-	0	-
30-39	8	11.9	1	7.4	0	-
40-49	11	6.0	1	1.0	0	-
50-59	18	3.9	7	1.2	1	0.5
60-69	10	1.0	22	1.5	3	0.6
70-79	32	2.6	24	1.6	9	1.4
>/=80	15	1.9	4	0.9	4	1.4

Author's conclusion: the effect of cigarette smoking on the risk for noncutaneous cancer could not be assessed. Antipsoriatic treatment such as ionizing radiation and oral arsenicals must be considered as a possible cause of colon cancer**.**

H.4.27 STUDY 16 CANCER

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
Ji (2009) Cancer risk in hospitalised psoriasis patients: a follow-up study in Sweden Ref ID: JI2009	**Observational:** cohort study **Representative population sample:** yes **Prognostic factor adequately measured:** yes **Confounders adjusted for:** Rates standardised by age, gender, period, socioeconomic status and residential area.	N: 15858	**Inclusion criteria:** hospitalised one or more times for psoriasis. **Exclusion criteria:** not reported.	Using the Swedish Hospital Discharge Register and linking with the cancer registry. Psoriasis patients were retrieved from the registry according to ICD codes. The cancer registry used a four digit code according to ICD-7 to identify tumours. Additional linking to national census to obtain individual	Median follow-up 10 years, range 0 to 40 years. **Note**: follow-up ended after diagnosis of cancer, death, emigration or closing date (31st December 2004), whichever came first.	Incidence of cancer	Supported by Deutsche Krebshilfe, the Swedish cancer society, the Eu, LSHC-CT-2004-503465 and the Swedish council for working life and social research

	Attrition bias: not reported **Outcomes adequately measured:** yes **Appropriate statistical analysis:** not multivariable/regression			occupational status, national registry of causes of death to identify date of death, and emigration Registry to get date of emigration.			

Effect size:

Standardised incidence ratios (SIRs) for subsequent cancer in patients with hospitalised psoriasis by follow-up time

	Follow-up interval (years)															
	1-4				**5-9**				**>/=10**				**All 1+**			
Cancer site	**O**	**SIR**	**95% CI**		**O**	**SIR**	**95% CI**		**O**	**SIR**	**95% CI**		**O**	**SIR**	**95% CI**	
Upper aerodigestive tract	15	**2.38**	1.33	3.93	12	1.91	0.98	3.35	21	**1.79**	1.11	2.74	48	**1.97**	1.46	2.62
Oesophagus	10	**4.30**	2.05	7.94	6	2.52	0.91	5.52	12	**2.54**	1.31	4.45	28	**2.97**	1.97	4.30
Stomach	16	1.62	0.92	2.64	10	1.07	0.51	1.98	26	**1.57**	1.02	2.30	58	**1.45**	1.08	1.91
Colon	22	1.11	0.69	1.68	27	1.34	0.88	1.95	33	0.83	0.57	1.16	22	1.03	0.82	1.27

Rectum	13	1.16	0.61	1.98	17	1.49	0.87	2.40	24	1.05	0.67	1.56	54	1.18	0.89	1.55
Liver	15	**1.94**	1.08	3.21	13	1.71	0.91	2.93	29	**2.08**	1.39	2.99	57	**1.95**	1.47	2.52
Pancreas	15	**2.00**	1.12	3.31	6	0.82	0.29	1.80	20	1.49	0.91	2.30	41	**1.45**	1.04	1.97
Lung	42	**1.99**	1.43	2.69	37	**1.73**	1.22	2.38	71	**1.71**	1.33	2.15	150	**1.78**	1.51	2.09
Breast	35	1.02	0.71	1.42	42	1.22	0.88	1.65	85	1.15	0.91	1.42	162	1.13	0.97	1.32
Cervix	4	1.11	0.29	2.87	4	1.15	0.30	2.97	11	1.63	0.81	2.93	19	1.38	0.83	2.15
Endometrium	12	1.56	0.80	2.73	10	1.30	0.62	2.41	8	0.53	0.23	1.05	30	0.98	0.66	1.41
Ovary	8	1.27	0.54	2.52	5	0.82	0.26	1.93	8	0.68	0.29	1.35	21	0.87	0.54	1.33
Prostate	44	1.12	0.82	1.51	38	0.92	0.65	1.27	96	1.03	0.84	1.26	178	1.03	0.88	1.19
Kidney	18	**2.27**	1.34	3.59	9	1.16	0.53	2.21	18	1.25	0.74	1.99	45	**1.50**	1.09	2.00
Urinary bladder	20	1.52	0.93	2.36	18	1.35	0.80	2.13	43	**1.58**	1.14	2.13	81	**1.51**	1.20	1.88
Melanoma	9	1.05	0.47	2.00	5	0.56	0.18	1.32	21	1.09	0.67	1.67	35	0.95	0.66	1.32
Skin, squamous cell	26	**2.56**	1.67	3.76	25	**2.35**	1.52	3.47	40	**1.74**	1.24	2.37	91	**2.08**	1.67	2.55
Nervous system	7	0.89	0.35	1.84	8	1.03	0.44	2.03	29	**1.90**	1.27	2.73	44	**1.42**	1.03	1.91
Endocrine glands	4	0.83	0.22	2.16	7	1.46	0.58	3.02	16	1.71	0.98	2.78	27	1.42	0.94	2.08
Non-Hodgkin lymphoma	27	**2.44**	1.61	3.55	9	0.79	0.36	1.51	24	1.03	0.66	1.54	60	**1.31**	1.00	1.69

Leukemia	9	1.91	0.86	3.63	10	**2.15**	1.02	3.96	8	0.89	0.38	1.77	27	1.47	0.97	2.14
All	401	**1.54**	1.39	1.70	333	**1.26**	1.13	1.41	674	**1.26**	1.17	1.36	1408	**1.33**	1.26	1.40

Bold type, 95% confidence interval (CI) does not include 1.00; underline type, 99% CI does not include 1.00

Standardised incidence ratios (SIRs) for subsequent cancer in psoriasis patients by number of hospitalisations

	Number of hospitalisations						
	1		**2-3**		**>/=4**		
Cancer site	**O**	**SIR**	**O**	**SIRs**	**O**	**SIRs**	**Trend test p-value**
Upper aerodigestive tract	33	**2.18**	9	1.51	6	1.85	0.49
Oesophagus	6	1.03	13	**5.59**	9	**6.97**	**0.01**
Stomach	33	**1.48**	13	1.50	6	1.23	0.75
Colon	54	1.08	18	0.92	10	0.96	0.53
Rectum	35	1.23	12	1.08	7	1.18	0.88
Liver	33	**1.81**	17	**2.38**	7	1.81	0.72
Pancreas	21	1.19	7	1.02	13	**3.52**	0.06
Lung	92	**1.75**	37	**1.79**	21	**1.89**	0.78
Breast	104	1.10	41	1.23	17	1.13	0.66
Cervix	11	1.18	6	1.89	2	1.50	0.52

Endometrium	21	1.05	7	0.98	2	0.59	0.50
Ovary	11	0.69	6	1.07	4	1.59	0.12
Prostate	105	1.00	49	1.14	24	0.97	0.85
Kidney	28	1.48	10	1.38	7	1.81	0.76
Urinary bladder	51	**1.54**	16	1.21	14	**1.93**	0.74
Melanoma	24	1.00	8	0.92	3	0.73	0.62
Skin, squamous cell	34	1.26	29	**2.67**	18	**4.76**	**0.01**
Nervous system	29	1.44	8	1.10	7	2.01	0.68
Endocrine glands	16	1.30	6	1.35	5	2.31	0.31
Non-Hodgkin lymphoma	35	1.22	15	1.36	10	1.72	0.31
Leukaemia	15	1.29	9	2.04	3	1.32	0.60
All	835	**1.25**	358	**1.4**	215	**1.61**	**0.01**

Bold type, 95% CI does not include 1.00; underline type, 99% CI does not include 1.00.

Author's conclusion: a significant excess was noted for squamous cell skin cancer and for cancers of the upper aerodigestive tract, oesophagus, stomach, liver, pancreas, lung, kidney, and bladder as well as non-Hodgkin lymphoma. Many of these reflect the effects of alcohol drinking and tobacco smoking. Patients with multiple hospitalisations showed high risk, particularly for oesophageal and skin cancers.

H.4.28 STUDY 17 CANCER

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
Hannuksela-Svahn (2000) Psoriasis, its treatment, and cancer in a cohort of Finnish patients Ref ID: HANNUKSELA-SVAHN2000	**Observational:** retrospective cohort study with nested case-control discharged patients in Finland 1973-1984 **Representative population sample:** yes **Prognostic factor adequately measured:** yes **Confounders adjusted for:**. Stratified by sex and age. **Attrition bias:** not reported. **Outcomes adequately**	N: 5687	**Inclusion criteria:** all those hospitalised with a diagnosis of psoriasis in the Finnish Hospital Discharge register between 1973 and 1987. **Exclusion criteria:** those not found in the population central register due to an error in the personal identification code in the hospital discharge register;	Hospital patients from the Finnish hospital discharge register which was linked to the Population central register using personal identification codes. linked to the Finnish Cancer Registry. Dates of death and emigration obtained from the population central register .	Mean length of follow-up 14 years.	Incidence of cancers.	supported by the Finnish Psoriasis Association and the University of Oulu.

	measured: yes **Appropriate statistical analysis:** not multivariable/regression						

Effect size:

Number of patients with psoriasis under follow-up and number of person-years at risk in 1973-95, by sex and age

	Men		**Women**	
Age	**No ***	**Person years**	**No***	**Person years**
0-14	94	407	198	836
15-29	600	4591	629	7374
30-44	918	12559	419	8767
45-59	860	13165	534	6836
60-74	544	3919	573	8159
>/=76	116	3044	202	3921
Total	3132	41685	2555	35893

***age at the beginning of follow-up**

Observed and expected numbers of cancer and standardised incidence ratios (SIR) with 95% CI among 5687 Finnish patients with psoriasis in 1997-95, by site

Primary site	Obs	Exp	SIR	95% CI
All sites	533	425.8	1.3	1.2-1.4
Mouth	1	1.6	0.7	0.0-3.6
Pharynx	3	2.2	1.3	0.3-3.9
Oesophagus	7	5.7	1.2	0.5-2.5
Stomach	34	30.8	1.1	0.8-1.5
Colon	20	23.5	0.9	0.5-1.3
Liver	11	5.9	1.9	0.9-3.3
Pancreas	26	17.2	1.5	1.0-2.2
Larynx	12	4.2	2.9	1.5-5.0
Lung, bronchus	101	68.0	1.5	1.2-1.8
Breast	37	43.4	0.9	0.6-1.2
Kidney and renal pelvis	12	15.1	0.8	0.4-1.4
Bladder, urethra, and urethra	25	17.8	1.4	0.9-2.1
Skin melanoma	8	10.3	0.8	0.3-1.6
Non-melanoma skin ca*	40	12.4	3.2	2.3-4.4
Nervous system	14	12.7	1.1	0.6-1.9

Non-Hodgkin's lymphoma	21	9.6	2.2	1.4-3.4
Hodgkin's disease	8	2.5	3.3	1.4-6.4

*Excludes basal cell carcinoma: obs. 98; exp 81.1; SIR, 1.2; 95%CI 1.0-1.5.

Author's conclusion: an increased total incidence of cancer was found among the psoriasis patients, mainly attributable to squamous cell skin carcinoma, non-Hodgkin's lymphoma, and Hodgkin's lymphomas well as laryngeal cancer. The patients in the study were likely to have more severe psoriasis than in general because they needed dermatological consultation, which may result in potent therapies. The results are not necessarily applicable to all patients with psoriasis.

H.4.29 STUDY 18 CANCER

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
Brauchli (2009) Psoriasis and risk of incident cancer: an inception cohort study with a nested case-control	**Observational:** population-based inception cohort study with a nested case-control analysis **Representative population sample:** yes used the GPRD	N: 67,761 patients (33,760 with psoriasis and 34,001 psoriasis-free patients.	**Inclusion criteria: all patients with a first-time diagnosis of psoriasis between 1st January 1994 and 31st December 2005. A comparison group of the same number without psoriasis.** **Exclusion criteria:** history	Patients in the GPRD were matched with non-psoriasis patients. The non-psoriasis patients were matched by calendar time, age (same year of birth), sex, general practice, and years of	Mean follow-up 4.6 years. Maximum 11 years. **Note**: followed up until a first-time diagnosis of cancer (malignant or in situ, other than nonmelanoma skin	Incidence of cancer	Funded by an unrestricted grant from Merck Serono International. The first author was supported

analysis Ref ID: BRAUCHLI 2009	**Prognostic factor adequately measured:** yes **Confounders adjusted for:** Patients were stratified by type of cancer, duration of psoriasis, and treatment. Treatment further classified into amount of topical prescriptions and oral prescriptions. **Attrition bias:** not reported **Outcomes adequately measured:** yes **Appropriate statistical analysis:** not multivariable/regression		of cancer (except nonmelanoma skin cancer) or HIV. Patients with <3 years of history In the database before first-time psoriasis diagnosis (or the corresponding date in the comparison group)	history in the GPRD. All patients had a recorded code using on a computer-based algorithm and a computer profile review.	cancer); death; end of follow-up in the medical record; or end of the follow-up period.		by a grant from the Senglet Foundation, Switzerland.
Effect size:							

Cancer incidence rates stratified by cancer type in patients with or without psoriasis

	Non-psoriasis			**Psoriasis**		
	Cases	**IR/1,000 py**	**95% CI**	**Cases**	**IR/1,000 py**	**95% CI**
All cancer	776	5.18	4.83-5.55	927	5.83	5.47-6.22
Lymphohematopoietic malignancies	62	0.41	0.32-0.53	119	0.75	0.63-0.90
Lymphohematopoietic malignancies (excluding CTCL)	62	0.41	0.34-0.53	111	0.70	0.58-0.84
CTCL	0	NA	NA	8	0.05	0.03-0.10
Lymphoma overall	36	0.24	0.17-0.33	67	0.42	0.33-0.54
Lymphoma (excluding CTCL)	36	0.24	0.17-0.33	59	0.37	0.29-0.48
Leukemia/MD	26	0.17	0.12-0.25	52	0.33	0.25-0.43
Lung	101	0.67	0.55-0.82	85	0.53	0.43-0.66
Melanoma	33	0.22	0.16-0.31	29	0.18	0.13-0.26
Breast	130	1.71	1.45-2.02	153	1.79	1.53-2.10
Prostate	95	1.38	1.13-1.69	85	1.16	0.93-1.43
Digestive organs	107	0.71	0.59-0.86	159	1.00	0.86-1.17
Pancreas	12	0.08	0.05-0.14	28	0.18	0.12-0.25
Oesophagus	16	0.11	0.07-0.17	23	0.14	0.10-0.22
Colorectal	55	0.37	0.28-0.48	79	0.50	0.40-0.62

Others	24	0.16	0.11-0.24	29	0.18	0.13-0.26
Female genital organs	35	0.43	0.31-0.60	51	0.60	0.45-0.79
Bladder/kidney	43	0.29	0.21-0.39	57	0.36	0.28-0.46
Brain	16	0.11	0.07-0.17	22	0.14	0.09-0.21
Other cancers	97	0.65	0.53-0.79	126	0.79	0.67-0.94
Metastasis	48	0.32	0.24-0.42	41	0.26	0.19-0.35

Incidence rate ratios (IRRs) of cancer, stratified by type, sex, and age (reference group: patients without psoriasis)

Type	Overall IRR (95% CI)	Men IRR (95% CI)	Women IRR (95% CI)	<60 years IRR (95% CI)	>/=60 years IRR (95% CI)
All cancer	1.13 (1.02-1.24)	1.11 (0.97-1.28)	1.14 (1.00-1.30)	1.19 (0.99-1.43)	1.13 (1.02-1.27)
Lympho-hematopoietic malignancies	1.81 (1.35-2.42)	2.45 (1.67-3.59)	1.24 (0.79-1.94)	2.17 (1.25-3.78)	1.74 (1.24-2.45)
Excluding CTCL	1.69 (1.25-2.27)	2.23 (1.50-3.31)	1.21 (0.77-1.9)	1.98 (1.12-3.52)	1.64 (1.16-2.32)
Lymphoma overall	1.76 (1.19-2.58)	2.15 (1.27-3.63)	1.40 (0.79-2.48)	2.38 (1.19-4.75)	1.59 (1.00-2.53)
Lymphoma (excluding CTCL)	1.55 (1.03-2.31)	1.76 (1.01-3.08)	1.35 (0.76-2.41)	2.07 (1.00-4.28)	1.41 (0.87-2.28)
Leukemia/MD	1.89 (1.21-2.94)	2.88 (1.65-5.05)	1.02 (0.49-2.11)	1.86 (0.74-4.69)	1.95 (1.18-3.23)
Lung	0.79 (0.60-1.06)	0.80 (0.56-1.13)	0.78 (0.48-1.29)	0.74 (0.35-1.58)	0.83 (0.61-1.13)
Melanoma	0.83 (0.50-1.36)	0.73 (0.36-1.46)	0.95 (0.46-1.94)	0.83 (0.43-1.60)	0.84 (0.39-1.80)

Breast	1.04 (0.83-1.31)	NA	1.04 (0.83-1.31)	0.98 (0.68-1.40)	1.11 (0.82-1.49)
Prostate	0.84 (0.63-1.12)	0.84 (0.63-1.12)	NA	0.76 (0.32-1.83)	0.88 (0.65-1.20)
Digestive organs	1.40 (1.10-1.78)	1.25 (0.91-1.71)	1.64 (1.14-2.38)	1.80 (1.00-3.25)	1.38 (1.06-1.79)
Pancreas	2.20 (1.18-4.09)	2.43 (0.97-6.13)	2.03 (0.88-4.69)	NA	2.11 (1.12-3.99)
Oesophagus	1.36 (0.72-2.54)	1.40 (0.64-3.08)	1.27 (0.44-3.61)	2.48 (0.76-8.09)	1.13 (0.54-2.36)
Colorectal	1.35 (0.97-1.90)	1.30 (0.82-2.05)	1.42 (0.86-2.36)	1.21 (0.53-2.74)	1.43 (0.99-2.07)
Others	1.14 (0.67-1.95)	0.80 (0.42-1.52)	2.85 (1.07-7.59)	2.79 (0.70-11.17)	1.02 (0.57-1.83)
Female genital organs	1.38 (0.91-2.11)	NA	1.38 (0.91-2.11)	1.93 (1.04-3.59)	1.06 (0.60-1.90)
Bladder/kidney	1.25 (0.84-1.85)	1.11 (0.70-1.76)	1.71 (0.81-3.59)	0.78 (0.24-2.53)	1.37 (0.90-2.08)
Brain	1.30 (0.69-2.45)	1.74 (0.72-4.18)	0.95 (0.38-2.39)	1.70 (0.66-4.41)	1.07 (0.46-2.52)
Other cancers	1.23 (0.94-1.59)	1.14 (0.77-1.67)	1.31 (0.91-1.88)	1.06 (0.68-1.67)	1.35 (0.98-1.87)
Metastasis	0.81 (0.53-1.22)	1.25 (0.64-2.42)	0.60 (0.35-1.03	1.49 (0.50-4.42)	0.75 (0.48-1.17)

Author's conclusion: the findings suggest that patients with psoriasis seem to be at an increased risk of developing certain cancers, especially those with a long psoriasis duration and possibly severe disease.

H.4.30 STUDY 19 CANCER

Reference	Study type	Number of	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source

		patients					**of** **funding**
Frentz (1999) Malignant tumours and psoriasis: a follow-up study Ref ID: FRENTZ1999	**Observational:** prospective cohort study of patients discharged from Danish hospital between 1977 and 1993. **Representative population sample:** yes **Prognostic factor adequately measured:** yes **Confounders adjusted for:** Stratified for age and sex **Attrition bias:** not reported **Outcomes adequately measured:** yes	N: 6905 patients	**Inclusion criteria:** patients discharged from a Danish hospital during 1977-87 with a diagnosis of psoriasis. **Exclusion criteria:** those whose identity was questionable.	Psoriasis patients followed up in the Danish Cancer registry which has notified cases of NMSC and other cancers according to ICD-0.. Cohort matched against the central population register for updating information on vital status and migration.	9.3 years (range 0-17 years) **Note**: follow-up ended at date of emigration, date of death or 31st December 1993, whichever occurred first.	Incidence of cancers.	Grants from the Danish Psoriasis Association, Leo pharmaceuticals and the Aage Bang Foundation.

	Appropriate statistical analysis: not multivariable/regression Notes: only 62% of the patients had psoriasis as the primary diagnosis (admitted to hospital for treatment of psoriasis)						

Effect size:

Standardised incidence ratios (SIRs) for cancer in 6905 patients with psoriasis discharged from hospital, 1977-87 and followed up for cancer through 1993

	Men		**Women**		**Both sexes**			
Site	**Obs**	**SIR**	**Obs**	**SIR**	**Obs**	**Exp**	**SIR**	**95% CI**
All malignant neoplasms	**421**	**1.44**	**374**	**1.36**	**795**	**566.1**	**1.40**	**1.21-1.51**
Melanoma of skin	**4**	**0.8**	**12**	**1.8**	**16**	**12.1**	**1.3**	**0.8-2.1**
Non-melanoma skin cancer (190)	**101**	**2.36**	**95**	**2.58**	**196**	**79.6**	**2.46**	**2.13-2.83**
Sites other than skin	**316**	**1.30**	**267**	**1.16**	**583**	**474.4**	**1.23**	

Oral cavity	**18**	**2.3**	**1**	**0.3**	**19**	**11.0**	**1.7**	**1.0-2.7**
Pharynx	**8**	**4.1**	**0**	**0.0**	**8**	**2.7**	**2.9**	**1.3-5.8**
Stomach	**13**	**1.2**	**9**	**1.3**	**22**	**18/0**	**1.2**	**0.8-1.8**
Colon	**25**	**1.2**	**35**	**1.4**	**60**	**46.8**	**1.3**	**1.0-1.6**
Rectum	**18**	**1.2**	**6**	**0.6**	**24**	**25.8**	**0.9**	**0.6-1.4**
Larynx	**11**	**2.4**	**0**	**0.0**	**11**	**5.5**	**2.0**	**1.0-3.6**
Lung	**78**	**1.5**	**35**	**1.6**	**113**	**73.4**	**1.5**	**1.3-1.9**
Breast	**1**	**2.2**	**53**	**0.9**	**54**	**46.8**	**1.0**	**0.7-1.2**
Kidney	**10**	**1.1**	**8**	**1.2**	**18**	**15.3**	**1.2**	**0.7-1.9**
Bladder	**29**	**1.1**	**5**	**0.6**	**34**	**34.1**	**1.0**	**0.7-1.4**
Connective tissue	**2**	**2.2**	**3**	**4.4**	**5**	**1.6**	**3.2**	**1.0-7.4**
Non-Hodgkin's lymphoma	**10**	**1.6**	**6**	**1.1**	**16**	**11.7**	**1.4**	**0.8-2.2**
Leukaemia	**7**	**0.9**	**5**	**0.9**	**12**	**13.0**	**0.9**	**0.5-1.6**
Mycosis fungoides	**2**	**10.8**	**2**	**25.4**	**4**	**0.3**	**15.1**	**4.1-38**
Other specified sites **Secondary and unspecified**	**14**	**1.3**	**29**	**2.5**	**43**	**23.0**	**1.9**	

sites								

Standardised incidence ratios (SIRs) for selected cancer sites by time since first known discharge from hospital with a diagnosis of psoriasis

	Time since first known discharge (years							
	<1		**1.4**		**5-9**		**>/=10**	
Sex: cancer site	**Obs**	**SIR**	**Obs**	**SIR**	**Obs**	**SIR**	**Obs**	**SIR**
Both sexes								
Non-melanoma skin cancer	**18**	**2.6**	**48**	**1.8**	**74**	**2.6**	**56**	**2.6**
Lung	**12**	**1.6**	**34**	**1.3**	**47**	**1.8**	**20**	**1.5**
Bladder	**3**	**0.9**	**11**	**0.9**	**16**	**1.3**	**4**	**0.6**
Colon	**4**	**0.8**	**19**	**1.1**	**24**	**1.5**	**13**	**1.5**
Mycosis fungoides	**2**	**75.2**	**2**	**21.0**	**0**	**0**	**0**	**0.0**
Men								
Larynx	**2**	**4.1**	**2**	**1.2**	**5**	**3.2**	**2**	**2.5**
Pharynx	**0**	**0.0**	**4**	**5.7**	**2**	**2.8**	**2**	**5.4**
Oral cavity	**1**	**1.2**	**9**	**3.2**	**3**	**1.1**	**5**	**3.5**

Standardised incidence ratios (SIRs) for subtypes of skin cancer by gender and by age during follow-up, 1978-93.

	Basal cell carcinoma				Squamous cell carcinoma			
	Men		Women		Men		women	
	Obs	SIR	Obs	SIR	Obs	SIR	Obs	SIR
20-29	0	0.0	2	15.9	0	0.0	0	0.0
30-39	2	3.7	8	10.6	1	51.6	0	0.0
40-49	7	3.3	12	5.7	4	29.3	1	11.6
50-59	15	3.2	11	2.7	7	13.9	2	10.4
60-69	15	1.5	14	1.7	3	2.0	3	4.8
70-79	24	2.2	19	2.0	8	2.8	6	5.3
80	9	1.8	8	1.2	5	2.3	5	3.2
All age groups	72	2.16	74	2.33	28	3.86	17	4.7

Standardised incidence ratios (SIRs) for basal cell carcinoma in patients discharged from hospital with a diagnosis of psoriasis

	Total				Men		Women	
Body site	Obs (%)	Exp (%)	SIR	95% CI	Obs	SIR	Obs	SIR
Lip	1 (<1)	0.9 (1)	1.1	0.0-6.0	0	-	1	1.9
Eyelid	2 (1)	2.5 (4)	0.8	0.1-2.9	1	0.8	1	0.8
External ear	5 (3)	1.6 (2)	3.2	1.0-7.4	3	2.3	2	6.8
Face	41 (28)	19.9 (31)	2.1	1.5-2.8	20	2.0	21	2.1
Scalp/neck	8 (5)	3.0 (5)	2.7	1.1-6.2	3	2.1	5	3.2

Trunk	**22 (15)**	**5.6 (7)**	**4.0**	**2.5-6.0**	**8**	**3.9**	**14**	**5.1**
Arm/shoulder	**2 (1)**	**1.1 (2)**	**1.8**	**0.2-6.5**	**1**	**1.7**	**1**	**1.9**
Leg/hip	**3 (2)**	**1.2 (2)**	**2.4**	**0.5-7.1**	**3**	**6.8**	**0**	**-**
Multiple	**58 (40)**	**9.8 (15)**	**5.9**	**4.5-7.7**	**30**	**5.7**	**28**	**6.1**
Not otherwise specified	**4 (3)**	**0.7 (1)**	**5.4**	**1.4-13.7**	**3**	**8.1**	**1**	**2.7**
total	**146 (100)**	**65.1 (100)**	**2.24**	**1.9-2.6**	**72**	**2.16**	**74**	**2.33**

Standardised incidence ratios (SIRs) for squamous cell carcinoma in patients discharged from hospital with a diagnosis of psoriasis

	Total				**Men**		**Women**	
Body site	**Obs (%)**	**Exp (%)**	**SIR**	**95% CI**	**Obs**	**SIR**	**Obs**	**SIR**
Lip	**1 (2)**	**0.4 (4)**	**2.6**	**0.0-14.5**	**1**	**3.15**	**0**	**-**
Eyelid	**0 (0)**	**0.3 (3)**	**-**	**-**	**0**	**-**	**0**	**-**
External ear	**4 (9)**	**1.7 (16)**	**2.4**	**0.6-6.1**	**4**	**2.7**	**0**	**-**
Face	**5 (11)**	**2.9 (27)**	**1.8**	**0.6-4.1**	**3**	**2.0**	**2**	**1.5**
Scalp/neck	**3 (7)**	**0.7 (6)**	**4.4**	**0.9-12.8**	**0**	**-**	**3**	**14.7**
Trunk	**3 (7)**	**0.5 (5)**	**5.6**	**1.1-16.4**	**2**	**7.6**	**1**	**3.7**
Arm/shoulder	**7 (16)**	**1.2 (11)**	**5.7**	**2.3-11.8**	**5**	**6.6**	**2**	**4.3**
Leg/hip	**10 (22)**	**0.6 (6)**	**18.0**	**8.6-33.1**	**5**	**19.4**	**5**	**16.8**
Multiple	**11 (24)**	**0.9 (8)**	**11.7**	**5.8-21.0**	**8**	**12.4**	**3**	**10.3**

Not otherwise specified	**1 (2)**	**0.2 (2)**	**4.0**	**0.1-22.3**	**0**	**-**	**1**	**8.2**
total	**45 (100)**	**10.9 (100)**	**4.14**	**3.0-5.5**	**28**	**3.86**	**17**	**4.69**

Author's conclusion: There is a significantly increased risk of cancer in psoriasis patients. When monitoring patients extensively treated for psoriasis, the pattern of cancer should be taken in to account.

H.4.31 STUDY 20 DIABETES

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
Brauchli (2008) Psoriasis and the risk of incident diabetes Ref ID: BRAUCHLI 2008	**Observational:** cohort study with nested case-control. **Representative population sample:** yes, used the GPRD **Prognostic factor adequately measured:**	N: 73404; psoriasis patients: 36702; psoriasis-free patients: 36702. After excluding those with prevalent DM, cancer or HIV	**Inclusion criteria:** All patients with a first time diagnosis of psoriasis between 1st January 1994 and 31st December 2005; or matched comparison group. Cases with diabetes mellitus were included in the analyses if had a first-time diabetes mellitus code recorded plus at least one prescription for an antidiabetic drugs such as insulin,	Matched comparison group on calendar time, age, sex, general practice and years of history in the GPRD.	Followed all patients until they developed a first time diagnosis of diabetes mellitus, died or follow-up in the medical record ended, whichever was first.	Incidence rate and incidence rate ratio.	Unconditional grant from Merck Serono International SA, Switzerland. One author was supported by a grant from the

	Confounders adjusted for:. Matched on calendar time (date of the psoriasis diagnosis), age (same year of birth), sex, general practice and years of history in the GPRD. Stratified by age and sex in the cohort study the nested case-control was adjusted for smoking status, BMI, hypertension, hyperlipidaemia, infections and use of systemic steroids. **Attrition bias:** not reported **Outcomes adequately measured:** yes **Appropriate statistical analysis:** No statistical analysis of confounders in the cohort study.	population was 65449 (32593 psoriasis patients and 32856 controls).	sulphonylureas, biguanides, thiazolidinediones, acarbose, glinides or guar gum within 30 days prior to or at any time after the first diagnosis of diabetes. Also patients with a recorded diagnosis of diabetes who did not receive any drug treatment but who started on a diet were included. **Exclusion criteria:** prevalent diagnosis of diabetes mellitus as well as cancer or HIV prior to the psoriasis diagnosis (or the corresponding date in the comparison group). Also those who received antidiabetic drugs more than 30 days prior to the first recorded diagnosis of diabetes mellitus.				Senglet foundation, Switzerland.

Effect size:

	Person-years	Cases	IR per 1000 person-years (95%)	IRR (95% CI)
Psoriasis	154316.1	626	4.06 (3.75-4.39)	1.36 (1.20-1.53)
No psoriasis	145783.8	435	2.98 (2.92-3.28)	
Sex				
Male with psoriasis	71084.7	332	4.67 (4.20-5.20)	1.23 (1.04-1.44)
Male no psoriasis	66270.5	252	3.80 (3.36-4.30)	
Female with psoriasis	83231.3	294	3.53 (3.15-3.96)	1.53 (1.28-1.83)
Female no psoriasis	79513.4	183	2.30 (1.99-2.66)	
Age (years)				
0-29 psoriasis	40246.0	18	0.45 (0.28-0.71)	2.75 (1.24-6.13)
0-29 no psoriasis	36928.7	6	0.16 (0.07-0.35)	
30-59 psoriasis	70072.0	237	3.38 (2.98-3.84)	1.33 (1.09-1.61)
30-59 no psoriasis	65861.4	168	2.55 (2.19-2.97)	
60-79 psoriasis	37008.4	330	8.92 (8.01-9.93)	1.43 (1.21-1.69)
60-79 no psoriasis	36312.4	226	6.22 (5.47-7.09)	
80+ psoriasis	6989.7	41	5.87 (4.33-7.95)	1.12 (0.71-1.75)
80+ no psoriasis	6681.5	35	5.24 (3.77-7.28)	

Author's conclusion: The risk of incident diabetes mellitus was increased in the psoriasis patients compared to the psoriasis-free patients. The risk increased with psoriasis duration and severity and was not driven by BMI alone.

H.4.32 STUDY 21 DEPRESSION

Reference	Study type	Number of patients	Patient characteristics	Prognostic factors	Length of follow-up	Outcome measures	Source of funding
Kurd (2010) The risk of depression, anxiety and suicidality in patients with psoriasis Ref ID: KURD2010	**Observational:** population-based cohort study from 1987 to 2002. **Representative population sample:** yes GPRD used **Prognostic factor adequately measured:** yes	N: 146042 with mild psoriasis; 3956 with severe psoriasis and 766950 non-psoriasis patients.	**Inclusion criteria:** all patients with a diagnostic code for psoriasis and 5 random controls with at least one day of observation time. Controls were seen in the same practice and had a date of observation within 60 days of the psoriasis patient's entry. **Exclusion criteria:**	Patient received a diagnostic code for psoriasis . Patients were defined as having incident depression, anxiety or suicidality by a corresponding diagnostic code occurring after the start of follow-up time. Created an algorithm.	Not reported. **Note**: follow-up ended when both patients and controls when developed outcome of interest, transferred out of practice, or died or practice was not longer UTS.	Incidence of depression	Funded in part by a grant from the National Research Service Award from the National Institutes of Health, the Doris Duke Foundation, University

	Confounders adjusted for: Adjusted for age, sex. Sensitivity analyses for treatment, diabetes, hypertension, hyperlipidaemia, cancer and BMI **Attrition bias:** not reported **Outcomes adequately measured:** yes **Appropriate statistical analysis:** yes cox proportional regression used.		Fixed sample size of 150000 psoriasis and 765000 controls would have greater than 0.95 power to detect an effect size as small as 1.1, assuming baseline rates of 20, 15,and 5 per 1000 person-years for depression, anxiety and suicidality.	Severe psoriasis was defined by diagnosis code for psoriasis and a code for systemic treatment modality.			of Pennsylvania Center for Clinical Epidemiology and Biostatistics pharmacoepidemiology training grant and grant K23AR051125 from the National institute of arthritis and musculoskeletal and skin diseases. One author received grant support and is a consultant for Amgen, Centocor, Abbott, Genentech, Novartis and

							Pfizer.

Summary of baseline variables, follow-up time and incident outcomes by psoriasis severity

	Mild psoriasis			**Severe psoriasis**		
Variable	**Controls (n=746930; 81.44%)**	**Patients with mild psoriasis (n-146042; 15.94%)**	**P value**	**Controls (n=20020; 2.19%)**	**Patients with severe psoriasis (n=3956; 0.43%)**	**P value**
Male, sex. No. (%)	356669 (47.82)	69231 (47.40)	0.004	9569 (47.80)	1920 (48.53)	0.40
Age, median (IQR), year	33 (18-53)	40 (26-57)	0.001	34 (18-54)	48 (35-62)	0.001
History of depression, no. (%)	31984 (4.29)	14327 (9.81)	0.001	938 (4.69)	493 (12.46)	0.001
History of anxiety, no (%)	24152 (3.24)	10890 (7.46)		651 (3.25)	291 (7.36)	0.001
History of suicidality, no. (%)	2946 (0.39)	1041 (0.71)	0.001	76 (0.38)	40 (1.01)	0.001
Person-years, median (IQR)	5.24 (2.18-9.12)	6.18 (2.97-9.55)	0.001	5.62 (2.45-9.49)	7.59 (3.86-9.90)	0.001
Reason for censorship, no. (%)						
Death	39206 (5.26)	7334 (4.02)	0.001	1095 (5.47)	309 (7.81)	0.001
Practice no longer UTS	493810 (66.20)	108377 (74.21)	0.001	13143 (65.65)	3179 (80.36)	0.001

Transfer	212914 (28.54)	30331 (20.77)	0.001	5782 (28.88)	468 (11.83)	0.001
Unadjusted incidence rate per 1000 person-years (95% CI)						
Depression	17.4 (17.3-17.6)	25.7 (25.3-26.1)	NA	17.0 (16.2-17.7)	31.8 (29.5-34.3)	NA
Anxiety	14.7 (14.6-14.9)	20.9 (20.6-21.3)	NA	14.5 (13.8-15.2)	20.8 (18.9-22.8)	NA
suicidality	0.66 (0.63-0.68)	0.93 (0.85-1.00)	NA	0.66 (0.52-0.82)	0.92 (0.57-1.41)	NA

Systemic psoriasis therapy

Systemic psoriasis therapy	**Patients with severe psoriasis, no. (%)**
Methotrexate	2284 (57.74)
Psoralen or phototherapy	680 (17.19)
Azathioprine	625 (16.48)
Ciclosporine	412 (10.14)
Etretinate or acitretin	351 (8.87)
Hydroxyurea	222 (5.61)
Mycophonlate mofetil	12 (0.30)

Effect size:

Hazard ratios (HRs) for depression, anxiety and suicidality by psoriasis severity

	Mild psoriasis		**Severe psoriasis**		**All psoriasis**	
Variable	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Depression						
Adjusted for age and sex	1.38 (1.35-1.40)	0.001	1.72 (1.5-1.88)	0.001	1.39 (1.37-1.41)	0.001
Sex interaction term	NS	0.81	1.21 (1.00-1.46)	0.05	NS	0.51
Age interaction term	0.99 (0.99-0.99)	0.001	0.98 (0.98-0.99)	0.001	0.99 (0.99-0.99)	0.001
Age, years		NA		NA		NA
20	1.81 (1.59-1.65)		F: 2.51 (2.11-2.98); M: 2.91 (2.39-3.54)		1.83 (1.78-1.87)	
40	1.45 (1.42-1.47)		F: 1.85 (1.65-2.08); M: 2.15 (1.84-2.51)		1.46 1.44-1.49)	
60	1.16 (1.13-1.19)		F; 1.37 (1.21-1.55); M: 1.59 (1.34-1.88)		1.17 (1.14-1.20)	
Anxiety						
Adjusted for age and sex	1.31 (1.29-1.34)	0.001	1.29 (1.15-1.43)	0.001	1.31 (1.29-1.34)	0.001
Sex interaction term	NS	0.91	NS	0.16	NS	0.73

Age interaction term	0.99 (0.99-0.99)	0.001	0.98 (0.98-0.99)	0.001	0.99 (0.99-0.99)	0.001
Age, years		NA		NA		NA
20	1.61 (1.56-1.65)		2.11 (1.75-2.55)		1.61 (1.57-1.66)	
40	1.37 (1.34-1.40)		1.49 (1.33-1.67)		1.37 (1.34-1.40)	
60	1.17 (1.14-1.19)		1.06 (0.93-1.20)		1.16 (1.13-1.19)	
Suicidality						
Adjusted for age and sex	1.44 (1.32-1.57)	0.001	1.51 (0.92-2.49)	0.10	1.44 (1.32-1.57)	0.001
Sex interaction term	NS	0.96	NS	0.77	NS	0.91
Age interaction term	0.99 (0.9-0.99)	0.001	NS	0.43	0.99 (0.98-0.99)	0.001
Age, years		NA		NA		NA
20	1.83 (1.64-2.05)				1.83 (1.64-2.05)	
40	1.38 (1.26-1.51)				1.38 (1.27-1.51)	
60	1.04 (0.90-1.19)				1.04 (0.91-1.20)	

Attributable risk of diagnosis of depression, anxiety and suicidality attributable to psoriasis

Variable	**Mild psoriasis**	**Severe psoriasis**	**All psoriasis**
Depression			
Attributable risk per 1000 person	11.5	25.5	11.8

years			
Anxiety			
Attributable risk per 1000 person years	8.0	8.1	8.1
Suicidality			
Attributable risk per 1000 person years	0.4	0.4	0.4

Author's conclusion: patients with psoriasis have an increased risk of depression, anxiety and suicidality.

H.4.33 STUDY 22 Risk of mortality – mild versus severe psoriasis

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
Gelfand et al. (2007) The risk of mortality in patients with psoriasis Ref ID: GELFAND2007	**Observational:** population-based cohort from 1987-2002 **Representative population sample:** yes used the GPRD. **Prognostic factor adequately measured:** yes **Confounders adjusted for:** age and sex Smoking, BMI, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic	N:133,568 mild psoriasis patients; 2951 with severe psoriasis and 560,358 and 15,075 controls	**Inclusion criteria:** all patients defined as having mild or severe psoriasis (according to the author's definitions) who were 18 years or older at the study start date and who had at least 1 day of observation time. Up to 5 controls were included who were 18 years or older at start date, matched on practice and start date in the practice. **Exclusion criteria:** None stated.	GPRD used. They either received a medical code consistent with the diagnosis or not. Severe psoriasis was based on history of having had systemic therapies.	Mean 4-5 years **Note**: study ended due to: death, end of up to standard or transfer out.	Risk of mortality.	Supported by an unrestricted grant to the trustees of the university of pennsylvania from Centocor and grant from the national institute of arthritis and musculoskeletal and skin diseases

	disease, peptic ulcer disease, mild liver disease, moderate or severe liver disease, diabetes mellitus, diabetes with chronic complications, hemiplegia or paraplegia, renal disease, malignant neoplasm, metastatic solid tumour, and AIDS were all recorded and used in one analysis only **Attrition bias:** **Outcomes adequately measured:** Yes **Appropriate statistical analysis:** yes						

Patient characteristics:

Characteristics	Mild psoriasis		Severe psoriasis	
	Controls	Patients	Controls	Patients
Sex, no (%)	261710 (46.7)	64004 (47.9)	7023 (46.6)	1921 (48.6)

Male	298648 (53.3)	69564 (52.1)	8052 (53.4)	2031(51.4)	
Female	45.3 (42.0; 29.2-59.5)	46.9 (44.8; 31.4-61.3)	45.9 (42.8; 29.8-60.3)	52.4 (52.3;38.7-65.8)	
Age, mean (media, IQR), year	NA	NA	NA		
Systemic therapies, no. (%)					
Methotrexate				2302 (58.3)	
Psoralen or phototherapy				662 (16.8)	
Azathioprine				651 (16.5)	
Ciclosporine				408 (10.3)	
Etretinate or acitretin				350 (8.9)	
Hydroexyurea				224 (5.7)	
Mycophenolate mofetil				11 (0.3)	
Follow-up, mean (median, IQR), y)	5.6 (5.2; 2.2-9.2)	4.5 (3.8; 1.6-7.1)	5.9 (5.6; 2.4-9.5)	3.6 (2.8; 1.3-5.3)	
Cumulative person-years	3147693	600902	88391	14203	
Deaths, no.	38258	7198	1064	303	
Incidence rate of mortality per 1000	12.2 (12.0-12.3)	12.0 (11.7-12.3)	12.0 (11.3-12.8)	21.3 (19.0-23.9)	

person-years (95% CI)				

Effect size:

Hazard ratio of mortality in patients with psoriasis HR (95% CI)

Age, years	All patients with psoriasis	Patients with mild psoriasis	Patients with severe psoriasis
All ages >/=18	1.0 (0.99-1.04)	1.0 (0.97-1.02)	1.5 (1.3-1.7)
35			2.5 (1.7-3.7)
45			2.2 (1.6-2.9)
55			1.9 (1.5-2.3)
65			1.6 (1.4-1.9)
75			1.4 (1.3-1.6)
85			1.3 (1.0-1.5)
95			1.1 (0.8-1.5)

*data adjusted for age and sex.

Attributable risk (AR) and excess risk of death in patients with severe psoriasis

Age group, years	Mortality rate per 1000 patient-years in severe psoriasis	AR, no. of deaths per 1000 patients-years	Excess risk, no. of exposed deaths

	control group		
All ages >/=18	12.0	6.0	1/166 patients per year
30-39	0.8	1.8	1/856 patients per year
40-49	2.0	2.3	1/440 patients per year
50-59	6.4	5.6	1/179 patients per year
60-69	20.1	12.9	1/78 patients per year
70-79	48.5	20.9	1/48 patients per year
80-89	106.7	26.7	1/38 patients per year

*data adjusted for age and sex.

Sensitivity analyses

Analysis	Mortality in severe psoriasis patients HR (95% CI)
Patients with psoriatic arthritis excluded from severe psoriasis group	1.5 (1.3-1.8)
Patients with rheumatologic diseases excluded from psoriasis group	1.5 (1.3-1.8)

Person-time starts with first diagnosis of psoriasis during UTS time	1.1 (1.0-1.3)
Start date for severe psoriasis control group matched to start date for severe psoriasis group	1.7 (1.5-2.0)
Severe psoriasis group restricted to patients who received methotrexate sodium	1.3 (1.1-1.5)
Severe psoriasis group excluding patients treated with methotrexate	1.9 (1.6-2.2)
Severe psoriasis group restricted to patients who had been prescribed an oral retinoid	1.8 (1.3-2.3)

Author's conclusion: Severe but not mild psoriasis is associated with an increased risk of death.

H.5 Phototherapy, systemic therapy, tar and risk of cancer

H.5.1 Prospective cohorts

H.5.1.1 STUDY 1

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
R. S. Stern, L. A. Thibodeau, R. A. Kleinerman, J. A. Parrish, and T. B. Fitzpatrick. Risk of cutaneous carcinoma in patients treated with oral methoxsalen photochemotherapy for psoriasis. New Engl.J.Med. 300 (15):809-813, 1979. Ref ID:	**Observational:** Prospective cohort 1976-1979 **Representative population sample:** unclear (recruited from 16 university centres) – **94% of those eligible enrolled in the follow-up study** (and the other 7%were similar for age, sex, severity and exposure to ionising radiation) **Prognostic factor adequately measured:** yes	N: 1380	**Inclusion criteria:** PUVA treated **Exclusion criteria:** Not stated **Parameter** / **All (n=1380)** Mean age – years: 44 Male (%): 65% Mean BSA (%): 33 History of cutaneous carcinoma before PUVA: 3%	**Oral 8-MOP PUVA**	2.1 years	Incidence of SCC and BCC **Tumour counting** *Person counts*: if tumour of a given type developed that patient was removed from the at-risk set (effectively analysing time-to-first tumour; each patient only counted once for each tumour type even if multiple tumours – this would give a lower value than the federal survey data)	NIH and National Center for Health Services Research

STERN1979	**Confounders adjusted for:** age, sex and region (plus interactions of prior cancer, skin type and ionising radiation exposure) **Attrition bias:** 2% died **Outcomes adequately measured:** Yes (histological examination – diagnosis confirmed by one dermatopathologist across all centres) **Appropriate statistical analysis:** yes		**Psoriasis subtypes** Plaque 84% Guttate 12% Erythrodermic 4% **Skin type** I 5.4% II 22.1% III 56.3% IV 12.7% V 1.4% VI 2.0% **Prior therapy** Topical steroids 86% Coal tar 84% UV 61% MTX 45% Goekerman 38% x-ray 18%				

			Grenz ray 12% Most patients had severe psoriasis				

Effect Size

Outcomes

Observed vs expected incidence

- **Expected based on specific incidence rate for age-, sex- and geographic location-matched rate from federal survey**
- 30 patients had one or more cutaneous carcinomas (11.4 expected); **RR: 2.63 (1.91-3.90)**
- Total observed: 29 SCC in 18 patients; 19 BCC in 15 patients
- NOTE: 39 patients had a history of cutaneous carcinoma before PUVA (17% SCC and 83% BCC)

Risk group incidence

- Risk of cutaneous carcinoma is related to skin type, ionising radiation exposure, previous cutaneous carcinoma; but not to conventional sunlamp use, tar or immunosuppressive drugs

Risk factor (total N=1182)	**RR (observed/expected; age-sex-region adjusted)**	**95% CI**
Skin type		
I-II	4.73	2.12-9.16
III-IV	1.89	1.00-3.67
Ionising radiation exposure		
Yes	3.68	2.42-8.69

No	1.49	0.74-3.34
Previous cutaneous carcinoma		
Yes	10.22	4.78-37.1
No	1.99	1.13-3.51

Interactions (RR: observed/expected; age-sex-region adjusted):

Previous skin cancer	**Skin type I and II**		**Skin type III and IV**	
	Exposure to radiation		Exposure to radiation	
	Yes	No	Yes	No
Yes	11.13 (0.89-32.0)	22.20 (1.78-63.9)	9.47 (0.24-31.2)	5.13 (0.05-28.7)
No	5.95 (2.30-20.7)	1.64 (0.55-7.14)	2.74 (1.19-7.68)	0.95 (0.36-3.03)

Author's conclusion

- Patients with psoriasis and a previous history of cutaneous carcinoma or ionising radiation use and those with skin type I or II have a higher risk of skin cancer when using PUVA

H.5.1.2 STUDY 2

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
R. S. Stern, N. Laird, and J. Melski. Cutaneous squamous-cell carcinoma in patients treated with PUVA. New Engl.J.Med. 310 (18):1156-1161, 1984. Ref ID: STERN1984A AND R. S. Stern and K. Momtaz. Skin typing for assessment of skin cancer risk and acute response to UV-B and	**Observational:** Prospective cohort 1977-1982 **Representative population sample:** unclear (recruited from 16 university centres) – 94% of those eligible enrolled in the follow-up study **Prognostic factor adequately measured:** yes **Confounders adjusted for:** follow-up, tar and radiation in dose-risk analysis only **Attrition bias:** 94 died (similar to expected	N: 1380	**Inclusion criteria:** PUVA treated **Exclusion criteria:** Not stated **Parameter** / **All (n=1380)** Mean age – years: 44 Male (%): 65% Mean BSA (%): 33 **Psoriasis subtypes** Plaque: 84% Guttate: 12% Erythrodermic: 4% **Skin type**	**Oral 8-MOP PUVA** Note: to separate the effect of dose from time, dose was classified as low, medium or high the limits of which depended upon follow-up time (see below; approximate divisions made at 60th and 80th percentiles)	5.7 years (range: 1.3-8.3 years) Five cycles of follow-up (as well as pre-treatment examinations) – interviewed annually and examined periodically regardless of continued use of PUVA **Note**: for dose risk analysis tumours had to be detected at least 22 months after first PUVA treatment 98% of all patients had a dermatologic assessment performed at least 22 months	Incidence of SCC and BCC **Tumour counting** 1.*Person counts*: if tumour of a given type developed that patient was removed from the at-risk set (effectively analysing time-to-first tumour; each patient only counted once for each tumour type even if multiple tumours – this would give a lower value than the federal survey data) 2.*Population counts*: Federal survey rates are based on annual incidence so also computed observed rates by counting only the first tumour of a given type observed that year, but continuing individuals in the risk set after tumour occurrence	NIH and National Center for Health Services Research

oral methoxsalen photochemotherapy. Arch.Dermatol. 120 (7):869-873, 1984. Ref ID: STERN1984	figure); 82% of these had at least one follow-up visit **Outcomes adequately measured:** Yes (histological examination) **Appropriate statistical analysis:** yes		I: 5.4% II: 22.1% III: 56.3% IV: 12.7% V: 1.4% VI: 2.0% **Prior therapy** Topical steroids: 86% Coal tar: 84% UV: 61% MTX: 45% Goekerman: 38% x-ray: 18% Grenz ray: 12% Most patients had severe psoriasis		after first treatment		

PUVA dose classification

Time to tumour	Time to follow-up interview	PUVA exposure (number of treatments)

(months)	(months)	Low	Medium	High
22-27	24	<80	80-99	>99
28-39	35	<100	100-119	>119
40-57	47	<100	100-139	>139
58-69	60	<120	120-159	>159
>69	70	<120	120-159	>159

Effect Size

Outcomes

Observed vs expected incidence

- **Expected based on specific incidence rate for age-, sex- and geographic location-matched rate from federal survey**
- Numbers observed (at least 22 months after exposure and only counting one tumour of a given type each year): 89 SCC and 43 BCC
- Total observed: 169 SCC in 54 patients; 74 BCC in 50 patients
- In addition: SCC in situ observed in 12 patients with 24 lesions and keratoancanthoma in 18 patients with 23 lesions

PUVA dose	Person years	Population rates				Person counts			
		SCC		BCC		SCC		BCC	
		SMR	95% CI	SMR	95% CI	SMR	95% CI	SMR	95% CI
Low	3315	4.1	2.3-6.8	1.6	1.1-2.4	2.2	0.9-4.3	1.4	0.9-2.2
Medium	978	22.3	13.5-34.1	1.8	0.7-3.6	14.4	7.6-24.6	0.8	0.2-2.2

High	1219	56.8	42.7-74.2	4.5	2.8-6.9	31.6	21.3-45.1	3.2	1.8-5.3
Total	*5512*	*16.2*	*13.0-19.9*	*2.2*	*1.6-2.9*	*9.3*	*6.9-12.2*	*1.7*	*1.2-2.3*

SMR: ratio of observed to expected tumours

Risk group incidence: dose-risk relationship (person counts; adjusted for duration of follow-up, PUVA dose and prior exposure to ionising radiation and prior use of tar)

	Adjusted relative standard morbidity ratio					
	SCC			**BCC**		
	SMR	**95% CI**	**p-value**	**SMR**	**95% CI**	**p-value**
PUVA dose						
Medium:low	5.7	2.4-13.9		0.5	0.2-1.7	>0.1
High:low	12.8	5.8-28.5	<0.0001 (SS even after adjustment for tar and ionising radiation; χ^2 = 52.2)	2.0	1.0-4.1	<0.5
High: medium and low	-	-		2.2	1.2-4.4	<0.05
Tar dose						
High:low	1.8	1.0-3.3	<0.05 (χ^2 = 5.5)	1.3	0.6-2.6	>0.1
Ionising radiation						

Some:none	-	-		1.3	0.7-2.4	>0.5
Some:none (high tar)	0.7	0.3-1.6		-	-	-
Some:none (low tar)	2.3	1.1-4.8		-	-	-

Interactions:

- SCC: Ionising radiation interacted with dose of tar (χ^2 = 4.72; p<0.05)
- SCC: No interactions between PUVA and tar or ionising radiation

Note: 402 skin type I and II had SMR = 12 for SCC for high PUVA dose compared with low PUVA dose (SMR NS different from skin types III-VI; p>0.2)

Note: if first SCC was detected after high PUVA dose, patients had a significantly higher mean number of tumours than those who developed SCC at low PUVA dose (3.4 vs 1.5; p,0.05)

Risk group incidence: skin-type-risk relationship (STERN1984)

Skin type	N at risk	RR vs ref strata	p-value
I	90	3.2	<0.05
II	312	2.3	<0.05
III	735	1.2	NS
IV	178	1.0	-

Author's conclusion

- Risk of SCC greater with high vs low dose PUVA – this suggests that PUVA can act as an independent carcinogen
- No substantial dose-related increase for BCC

H.5.1.3 STUDY 3

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
R. S. Stern and R. Lange. Cardiovascular disease, cancer, and cause of death in patients with psoriasis: 10 years prospective experience in a cohort of 1,380 patients. J.Invest.Dermatol. 91 (3):197-201, 1988. STERN1988A	**Observational:** Prospective cohort 1976-1986 **Representative population sample:** unclear (recruited from 16 university centres) – 94% of those eligible enrolled in the follow-up study **Prognostic factor adequately measured:** yes **Confounders adjusted for:** age, sex and location only (but a comparable proportion of patients in the high and low dose strata	N: 1380	**Inclusion criteria:** PUVA treated **Exclusion criteria:** Not stated **Parameter** / **All (n=1380)** Mean age – years: 44 Male (%): 65% Mean BSA (%): 33 **Psoriasis subtypes** Plaque: 84% Guttate: 12% Erythrodermic: 4%	**Oral 8-MOP PUVA**	Mean >10 years **Note**: tumours had to be detected at least 58 months after first PUVA treatment 77% of surviving patients had a dermatologic assessment performed at least 9 years after first treatment; >90% had a dermatologic assessment performed at least 6 years after first treatment	Incidence of SCC and BCC **Tumour counting** 1.*Person counts*: if tumour of a given type developed that patient was removed from the at-risk set (effectively analysing time-to-first tumour; each patient only counted once for each tumour type even if multiple tumours – this would give a lower value than the federal survey data) **Note**: all patients with incident tumours occurring after 58 months are considered separately to those patients among whom the **first** incident tumour occurred at least 58	NIH

	were exposed to ionising radiation and high doses of tar and UVB; and the magnitude of increased risk for SCC associated with greater exposure to PUVA was comparable for both skin type groupings **Attrition bias:** Unclear **Outcomes adequately measured:** Yes (histological examination) **Appropriate statistical analysis:** not regression		**Skin type** I: 5.4% II: 22.1% III: 56.3% IV: 12.7% V: 1.4% VI: 2.0% **Prior therapy** Topical steroids: 86% Coal tar: 84% UV: 61% MTX: 45% Goekerman: 38% x-ray: 18% Grenz ray: 12% Most patients had severe psoriasis			months after first exposure to PUVA	

Effect Size

Outcomes

Observed numbers

Treatments	All pts with tumours (number of tumours)		All pts with first tumour ≥58 months after first treatment (number of tumours)	
	SCC	BCC	SCC	BCC
<160	30 (124)	37 (94)	21 (49)	26 (45)
160-199	13 (47)	8 (14)	10 (29)	7 (11)
200-259	22 (60)	14 (23)	17 (52)	13 (22)
260+	15 (61)	10 (30)	11 (28)	9 (19)
Total	**80 (292)**	**69 (161)**	**59 (158)**	**55 (97)**

Observed vs expected incidence

- **Expected based on specific incidence rate for age-, sex- and geographic location-matched rate from federal survey**

PUVA dose	All pts with tumours (number of tumours)				All pts with first tumour ≥58 months after first treatment (number of tumours)			
	SCC		BCC		SCC		BCC	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
<160	5.3	3.6-7.6	1.6	1.1-2.2	4.2	2.6-6.4	1.3	0.8-1.9

160-199	25.5	13.6-43.6	3.1	1.3-6.1	22.2	10.6-40.9	3.0	1.2-6.3
200-259	37.5	23.5-56.7	5.3	2.9-9.0	32.1	18.7-51.4	4.8	3.5-6.5
260+	62.5	35.0-103.1	7.0	4.1-11.2	50.1	24.9-89.5	6.9	3.2-13.1
Total	***11.4***	***9.1-14.2***	***2.3***	***1.8-2.9***	***9.5***	***7.2-12.3***	***2.1***	***1.6-2.7***

Risk group incidence: dose-risk relationship (not adjusted)

PUVA dose	**All pts with tumours (number of tumours)**				**All pts with first tumour ≥58 months after first treatment (number of tumours)**			
	SCC		**BCC**		**SCC**		**BCC**	
	RR	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
<160	1.0		1.0		1.0		1.0	
160-199	4.8	2.6-8.2	1.9	0.8-3.8	4.3	2.5-9.7	2.3	0.9-4.8
200-259	7.0	4.4-10.7	3.4	1.8-5.6	7.6	4.4-12.2	3.1	2.0-6.4
260+	11.8	8.1-16.7	3.7	2.1-8.0	11.9	5.9-21.3	5.3	2.4-10.1

Risk factors:

- A comparable proportion of patients in the high and low dose strata were exposed to ionising radiation and high doses of tar and UVB (p>0.2)
- Although the risk of SCC was higher than the expected rate for skin types I and II vs III and IV, the magnitude of increased risk for SCC associated with greater exposure to PUVA was comparable for both skin type groupings:

Risk group incidence: skin-type-risk relationship

PUVA dose	RR of SCC		RR of BCC	
	Skin type I-II	Skin type III-VI	Skin type I-II	Skin type III-VI
<160	1.0	1.0	1.0	1.0
160-199	6.1	4.4		
200-259	7.7	4.7		
260+	11.2	13.2	Nearly identical risk vs low dose	

NOTE: increase in RR for BCC vs that expected in general population is ~2.5-fold higher for skin type I-II vs types III and IV with comparable PUVA exposure

Author's conclusion

- Long-term exposure to PUVA substantially increases risk of SCC
- Risk of SCC greater with high vs low dose PUVA – this suggests that PUVA can act as an independent carcinogen
- Modest, but significant dose-related increase for BCC

H.5.1.4 STUDY 4

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>R. S. Stern, E. Abel, B. Wintroub, J. H. Epstein, J. Tschen, J. Wolf, T. P. Nigra, J. Voorhees, T. F. Anderson, R. Armstrong, L. Harber, S. Muller, J. R. Taylor, P. Frost, S. Horwitz, F. Urbach, K. A. Arndt, R. D. Baughman, and I. M. Braverman. Genital tumours among men with psoriasis exposed to psoralens and</td>
<td>Observational: Prospective cohort

1977-1989

and

1989-1998

Representative population sample: unclear (recruited from 16 university centres) – 94% of those eligible enrolled in the follow-up study

Prognostic factor adequately measured: yes

Confounders adjusted for: STERN1990: no; but also performed a nested</td>
<td>N: 892</td>
<td>Inclusion criteria: PUVA treated

Exclusion criteria: Not stated

<table>
<tr><th>Parameter</th><th>All (n=892)</th></tr>
<tr><td>Mean age – years</td><td>46±15</td></tr>
<tr><td>Male (%)</td><td>100%</td></tr>
<tr><td>White (%)</td><td>97%</td></tr>
<tr><td>BSA (%)</td><td>35±23</td></tr>
</table>
</td>
<td>Oral 8-MOP PUVA and UVB

Note: to separate the effect of dose from time, dose was classified as low, medium or high the limits of which depended upon follow-up time (see below; approximate divisions made at 60th and 80th percentiles)</td>
<td>12.3 years (1990)

>20 years (2002)

Interviewed annually and examined periodically regardless of continued use of PUVA

1990: 89% of surviving patients had a dermatologic assessment performed at least 6 years after first treatment</td>
<td>Incidence of genital tumours (SCC)

Tumour counting
1.Person counts (1990 and 2002 data): if tumour of a given type developed that patient was removed from the at-risk set (effectively analysing time-to-first tumour; each patient only counted once for each tumour type even if multiple tumours – this would give a lower value</td>
<td>NIH</td>
</tr>
</table>

ultraviolet A radiation (PUVA) and ultraviolet B radiation. New Engl.J.Med. 322 (16):1093-1097, 1990. Ref ID: STERN1990 R. S. Stern, S. Bagheri, K. Nichols, and Up Study PUVA Follow. The persistent risk of genital tumors among men treated with psoralen plus ultraviolet A (PUVA) for psoriasis. J.Am.Acad. Dermatol. 47 (1):33-39, 2002. Ref ID: STERN200	case-control analysis (1 case:4 controls) matched for age, site and time of enrolment – control for age, race and ethnicity, circumcision and variations between centres in genital shielding and in PUVA use and therapies before PUVA **STERN2002:** MVA adjusted for age, tumour site, tumour type, PUVA dose, combined PUVA/tar/UVB dose **Attrition bias:** **STERN1990** 160 (18%) died Of the remaining 732 men, 86% were interviewed at least 11 years after first treatment with PUVA **STERN2002** 336 (38%) died Of the remaining 556					than the federal survey data) 2.*Population counts (2002 data)*: Federal survey rates are based on annual incidence so also computed observed rates by counting only the first tumour of a given type observed that year, but continuing individuals in the risk set after tumour occurrence	

2	men, 82% were interviewed at last follow-up interview **Outcomes adequately measured:** Yes (histological examination by pathologists blinded to levels of exposure to PUVA) **Appropriate statistical analysis:** yes						

PUVA dose classification

Time to tumour (months)	**Time to follow-up interview (months)**	**PUVA exposure (number of treatments)**		
		Low	Medium	High
0-27	24	<80	80-99	>99
28-39	35	<100	100-119	>119
40-57	47	<100	100-139	>139
58-69	60	<120	120-159	>159
70-96	70	<120	120-159	>159
>96	121	<140	140-239	>239

Note: in the matched case-control analysis (1990) time to development of tumours varied among cases so annual number of treatments before development of first genital tumour was used as a measure of level of PUVA exposure:

- Low: <20 treatments per year
- Medium: 20-39 treatments per year
- High: ≥40 treatments per year

Other dose classifications

- High tar: topical tar for >90 months in STERN1990 and >44 months in STERN2002
- High UVB: >300 treatments

Effect Size

Outcomes

Observed vs expected incidence (1990)

- **Expected based on specific incidence rate for age- and sex-matched incidence rate from 3 population-based cancer registries**
- Numbers observed: 30 genital tumours in 14 patients

PUVA dose	Tumour					
	Invasive SCC of penis and scrotum		Invasive and in situ penile tumours		Invasive SCC of scrotum	
	SMR	95% CI	SMR	95% CI	SMR	95% CI
Low	17.5	0.4-97.7	23.0	2.8-83.0	No cases	
Medium	125.0	15.1-451.5	34.5	0.9-192.1	147.1	3.7-819.4
High	285.7	104.9-621.9	162.2	59.5-353.0	449.4	122.5-1150.7
Total	*95.7*	*43.8-181.8*	*58.8*	*26.9-111.7*	*131.6*	42.7-307.1

Number of tumours	*21*	*19*	9

SMR: ratio of observed to expected tumours

Observed vs expected incidence (2002)

- **Expected based on specific incidence rate for age- and sex-matched incidence rate from SEER registry**
- Numbers observed: 51 genital tumours in 24 patients (42 incident events and 28 person counts – including one BCC)

PUVA dose	**Tumour**					
	Invasive SCC of penis and scrotum			**All genital SCCs (including all sites and types)**		
	N	**SMR**	**95% CI**	**N**	**SMR**	**95% CI**
After 5/1/89						
Population counts						
Low	2	44.4	5.4-160.5	2	28.8	3.5-103.2
Medium	1	36.1	0.9-201.1	4	90.9	24.8-232.8
High	7	168.7	67.8-347-5	10	151.5	72.2-145.2
Total	*10*	*87.7*	*42.1-161.3*	*16*	*89.4*	*51.1-145.2*

Person counts						
Low	2	44.4	5.4-160.5	2	28.8	3.5-103.2
Medium	1	36.1	0.9-201.1	3	68.2	14.1-199.3
High	3	72.3	14.9-211.3	6	90.9	33.4-197.9
Total	*6*	*52.6*	*19.3-114.6*	*11*	*61.5*	*30.7-110.0*
Both periods						
Population counts						
Low	4	39.2	10.7-100.4	5	-	-
Medium	3	68.2	14.1-199.3	7	-	-
High	21	283.8	175.7-433.8	29	-	-
Total	*28*	*134.6*	*89.5-194.6*	41	-	-
Person counts						
Low	3	29.4	6.1-86.0	4	-	-
Medium	3	68.2	14.1-199.3	6	-	-
High	11	148.	74.2-	17	-	-

		6	266.0			
Total	*17*	*81.7*	*52.1-122.6*	27	-	-

SMR: ratio of observed to expected tumours

Risk group incidence: dose-risk relationship 1990 (not adjusted)

PUVA dose	**Tumour**					
	Invasive SCC of penis and scrotum		**Invasive and in situ penile tumours**		**Invasive SCC of scrotum**	
	SMR	**95% CI**	**SMR**	**95% CI**	**SMR**	**95% CI**
High:low	16.3	9.4-26.4	7.1	2.8-14.5	No cases in low dose group	
High:medium and low	-	-	-	-	13	24.1-48.3

Case-control analysis (controlling for confounders)

Characteristic	**Cases (N=14)**	**Age-matched controls (N=56)**	**p-value**
Age (years)	52±15	52±14	>0.2

BSA at enrolment (%)	41±22	35±20	>0.2
Number of PUVA treatments*	210±124	113±86	<0.02
PUVA treatments per year	41±22	23±17	<0.01
UVB treatments	712±640	202±343	<0.01
Exposure to x-ray therapy (%)	29	45	>0.2
Months of tar therapy	114±218	55±130	>0.2
PUVA dose			
Low	2	28	<0.002
Medium	4	20	
High	8	8	
Tar exposure			
Low	9	46	>0.2
High	5	10	

*In the period before development of first genital tumour, or during a similar period in the matched controls

Risk group incidence: dose-risk and site-risk relationship 2002

	Genital SCC	
	IRR (age-adjusted)	**95% CI**
Both periods		
Low PUVA	1	
Medium PUVA	1.8	0.7-4.5
High PUVA	8.8	4.5-17.2
All penile	1	
Invasive scrotal SCC	3.1	1.9-5.0

Multivariate (adjusted for age, tumour site, tumour type, PUVA dose, combined PUVA/tar/UVB dose); data only for after 1/5/1989 (to 1998)

NOTE: the distribution of skin type did not differ among those with and without genital SCCs

	Genital SCC	
	IRR	**95% CI**
Exposure		
Low PUVA	1	
High PUVA	2.8	0.5-15.5
Low PUVA, not high tar/UVB	1	
Medium	8.8	0.9-85.1

PUVA/high tar/UVB		
High PUVA, high tar/UVB	4.5	1.3-16.1
Site		
All penile	1	
Invasive scrotal SCC	4.7	1.4-15.2
In situ scrotal SCC	23.8	6.4-87.9

Author's conclusion

- The apparent high susceptibility of male genitalia to carcinogenic effects of UV light (PUVA and UVB) suggests that genital protection is prudent when people are exposed to therapeutic UV
- Although use of PUVA decreased and genital shielding in our cohort increased between the first and second reports, the dose-dependent increase in the risk of genital tumours in men treated with PUVA has persisted.
- Particularly high risks occur among those with high-dose exposures to both PUVA and topical tar/ultraviolet B.

H.5.1.5 STUDY 5

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>R. S. Stern and N. Laird. The carcinogenic risk of treatments for severe psoriasis. Photochemotherapy Follow-up Study. Cancer 73 (11):2759-2764, 1994.

Ref ID: STERN1994</td>
<td>Observational:
Prospective cohort

1977-1989

Representative population sample: unclear (recruited from 16 university centres) – 94% of those eligible enrolled in the follow-up study

Prognostic factor adequately measured: yes

Confounders adjusted for: yes – age, sex, ionising radiation, dosage of tar and UVB, dosage of MTX, duration of treatment</td>
<td>N: 1380</td>
<td>Inclusion criteria: PUVA treated

Exclusion criteria: Not stated

<table>
<tr><th>Parameter</th><th>All (n=1380)</th></tr>
<tr><td>Mean age – years</td><td>44</td></tr>
<tr><td>Male (%)</td><td>65%</td></tr>
<tr><td>Mean BSA (%)</td><td>33</td></tr>
<tr><td colspan="2">Psoriasis subtypes</td></tr>
<tr><td>Plaque</td><td>84%</td></tr>
<tr><td>Guttate</td><td>12%</td></tr>
<tr><td>Erythrodermic</td><td>4%</td></tr>
<tr><td colspan="2">Skin type</td></tr>
</table>
</td>
<td>Oral 8-MOP PUVA

Note: to separate the effect of dose from time, dose was classified as low, medium or high the limits of which depended upon follow-up time (see below; approximate divisions made at 60th and 80th percentiles)</td>
<td>13.2 years

Interviewed annually and examined periodically regardless of continued use of PUVA

This includes data to the end of 12th cycle of follow-up interviews and 7th cycle of physical examinations</td>
<td>Incidence of BCC and invasive SCC (SCC in situ excluded)

Tumour counting
1.Person counts: if tumour of a given type developed that patient was removed from the at-risk set (effectively analysing time-to-first tumour)

2.Population counts: Federal survey rates are based on annual incidence so also computed observed rates by counting only the first tumour of a given type observed that year as an incidence, but continuing</td>
<td>NIH</td>
</tr>
</table>

	Attrition bias: 227 (16%) died Of the remaining 1153, 93% were interviewed at final follow-up cycle and 83% had physical exam at least 10 years after first exposure **Note:** tumours occurring in patients who died are also counted **Outcomes adequately measured:** Yes (histological examination by pathologists) **Appropriate statistical analysis:** yes		I: 5.4% II: 22.1% III: 56.3% IV: 12.7% V: 1.4% VI: 2.0% **Prior therapy** Topical steroids: 86% Coal tar: 84% UV: 61% MTX: 45% Goekerman: 38% x-ray: 18% Grenz ray: 12% Most patients had severe psoriasis			individuals in the risk set after tumour occurrence	

PUVA dose classification

Time to tumour	Time to follow-up interview	Number of surviving patients	PUVA exposure (number of treatments)

(months)	(years)		Low	Medium	High
0-27	2	1358	<80	80-99	>99
28-39	3	1341	<100	100-119	>119
40-57	4	1321	<100	100-139	>139
58-69	5	1302	<120	120-159	>159
70-96	6	1286	<120	120-159	>159
94-136	10	1210	<140	140-239	>239
>136	13	1153	<160	160-299	>299

Other dose classifications (based on historical data collection)

- High tar: topical tar for >45 months
- High UVB: >300 treatments
- High MTX: ≥4 years use (approximately 3 g)

Effect Size

Outcomes

Observed vs expected incidence

- **Expected based on specific incidence rate for age-, sex- and geographic region-matched incidence rate from a federal survey**
- Numbers observed: 618 SCCs in 144 patients; 341 BCCs in 130 patients (41 patients had both BCC and SCC)
- Population counts: 326 incident cases of SCC and 217 incidence cases of BCC

PUVA	SCC	BCC

dose	N	SMR	95% CI	N	SMR	95% CI
Population counts (occurrence of one or more tumours of a given type in a given year = an incident event)						
Low	80	10.6	8.5-13.2	114	3.6	3.0-4.3
Medium	51	23.6	18.0-31.1	28	2.9	2.0-4.2
High	195	83.0	72.1-95.5	75	6.0	4.8-7.5
Total	*326*	*27.0*	*24.2-30.1*	*217*	*4.1*	*3.5-4.7*
Person counts (only the first tumour of a given type is counted)						
Low	38	5.0	3.6-6.9	66	2.1	1.6-2.7
Medium	29	13.4	9.3-19.3	19	1.9	1.2-3.0
High	77	32.8	26.2-41.0	45	3.8	2.8-5.1
Total	*144*	*11.9*	*10.1-14.0*	*130*	*2.5*	*2.1-3.0*

Risk group incidence: (person counts: adjusted for duration of follow-up, and prior exposure to ionising radiation, dosage of tar and UVB and dosage of MTX)

	Adjusted RR					
	SCC			BCC		
	RR	95% CI	p-value	RR	95% CI	p-value
PUVA dose						
Medium:low	2.6	2.0-3.3	-	0.9	-	>0.1

High:low	5.9	4.0-8.7	-	1.7	1.1-2.5	-
Skin type						
I-II:III-IV	~2-fold			~2-fold		

Note - interactions: none of the other risk factors (MTX, UVB or ionising radiation) modified the effect of PUVA.

Variable	**Adjusted RR** (adjusted for age, sex, residence, level of PUVA exposure)					
	SCC			**BCC**		
	RR	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**
High MTX	2.0	1.4-2.8	SS	-	-	NS
High UVB/tar	-	-	NS	-	-	NS
Exposure to ionising radiation	-	-	NS	-	-	NS

Note: no evidence that the association between prior MTX and SCC was **modified** by other exposures, including level of PUVA exposure

Note: the lack of independent carcinogenic effect of UVB, topical tar or ionising radiation conflicts with earlier findings in this cohort – this may be because PUVA is the main carcinogen and as more is received it outweighs the impact of other factors

Author's conclusion

- Long term exposure to PUVA and methotrexate significantly increases the risk of SCC in patients with psoriasis.
- The ultimate morbidity of these tumours is undetermined

H.5.1.6 STUDY 6

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
R. S. Stern, E. J. Liebman, and L. Vakeva. Oral psoralen and ultraviolet-A light (PUVA) treatment of psoriasis and persistent risk of nonmelanoma skin cancer. J.Natl.Cancer Inst. 90 (17):1278-1284, 1998. Ref ID: STERN1998A	**Observational:** Prospective cohort 1977-1996 **Representative population sample:** unclear (recruited from 16 university centres) – 94% of those eligible enrolled in the follow-up study **Prognostic factor adequately measured:** yes **Confounders adjusted for:** yes – age, sex, and all exposures that were significant predictors of risk in the univariate analysis	N: 1380	**Inclusion criteria:** PUVA treated **Exclusion criteria:** Not stated **Parameter** / **All (n=1380)** Mean age – years: 44 Male (%): 65% Mean BSA (%): 33 **Psoriasis subtypes** Plaque: 84% Guttate: 12% Erythrodermic: 4% **Skin type**	**Oral 8-MOP PUVA** 0.4-0.6 mg/kg psoralen orally, followed in 1.5-2.0 h by UVA (standing in an UV irradiation unit; fluorescent bulbs with emissions in the range of 320-400 nm). Initial UVA dose 1.5-5 J/cm^2 depending on photosensitivity. During the clearing phase, patients undergo two or three light treatments per week and UVA dose is gradually increased according to the degree of erythema or pigmentation.	20 years Interviewed annually and examined periodically regardless of continued use of PUVA This includes data to the end of 18th cycle of follow-up interviews and 8th cycle of physical examinations Separately assessed those with tumour development during the first decade and those surviving without tumour occurrence by the end of the first decade	Incidence of BCC and invasive SCC **Tumour counting** 1.*Person counts*: if tumour of a given type developed that patient was removed from the at-risk set (effectively analysing time-to-first tumour) 2.*Population counts*: Federal survey rates are based on annual incidence so also computed observed rates by counting only the first tumour of a given type observed that year as an incidence, but continuing individuals in the risk set after	NIH

	Attrition bias: 299 (21.7%) died **Outcomes adequately measured:** Yes (histological examination by pathologists) **Appropriate statistical analysis:** yes		I: 5.4% II: 22.1% III: 56.3% IV: 12.7% V: 1.4% VI: 2.0% **Prior therapy** Topical steroids: 86% Coal tar: 84% UV: 61% MTX: 45% Goekerman: 38% x-ray: 18% Grenz ray: 12% Most patients had severe psoriasis	Average max UVA dose = 8-15 J/cm^2. With disease improvement therapy slowly tapered off. If disease flared, patients treated again with PUVA or other therapies for psoriasis as determined by their physician. Note: for dose stratification the highest dose group was defined as the number of treatments received by the top decile who survived to 1986 without SCC		tumour occurrence	

PUVA dose stratification and number of patients followed after 1985 with SCC or BCC

Exposure	Number (%) of patients with cancers developing after 1985		
	Total	SCC	BCC
PUVA treatments up to 1986			
<100	435 (37%)	18 (13%)	29 (19%)
100-159	243 (21%)	15 (11%)	30 (20%)
160-336	373 (32%)	68 (50%)	58 (38%)
≥337	132 (11%)	34 (25%)	34 (23%)
Total	1183	135	151
PUVA treatments after 1985			
<50	877 (74%)	66 (49%)	99 (66%)
≥50	306 (26%)	69 (51%)	52 (34%)
Total	1183	135	151

Other dose classifications (based on historical data collection)

- High tar: topical tar for ≥45 months
- High UVB: >300 treatments
- High MTX: ≥4 years use (approximately 3 g)

Effect Size

Outcomes

Numbers observed: 1422 SCCs in 237 patients (17.2%); 1042 BCCs in 247 patients (17.9%)

Tumour type	**Total number of tumours by date of detection**		**Total**
	Before 1986	**Beginning 1986**	
SCC	**375**	**1047**	**1422**
BCC	**221**	**821**	**1042**

Tumour type	**Total number of patients with skin cancer by date of first detection and total number of cancers developed in these patients at any time**		**Total**
	Before 1986 (n=1380)	**Beginning 1986 (n=1081)**	
SCC			
• Number of patients	102	135	237
• Number of tumours	829	593	1422
BCC			
• Number of patients	96	151	247
• Number of tumours	NA	NA	1042

Observed vs expected incidence

- **Expected based on specific incidence rate for age-, sex- and geographic region-matched incidence rate from a federal survey**

Figures for 1st cancer after 1985

Total PUVA treatments to 1986	**SCC**		**BCC**	
	RR	**95% CI**	**RR**	**95% CI**
Population counts (occurrence of one or more tumours of a given type in a given year = an incident event)				
<100	5.1	3.5-7.2	1.7	1.2-2.3
100-159	8.4	5.6-12.1	3.9	3.0-5.0
160-336	26.5	22.2-31.4	4.5	3.5-5.7
≥337	68.5	54.9-84.5	11.7	9.3-14.5
All dosages	*17.6*	*15.6-19.8*	*4.1*	*3.7-4.6*

RR for all observed tumours after 1985 (including those who had experienced a first tumour before 1986) vs expected incidence

Total PUVA treatments to 1986	**SCC**	
	RR	**95% CI**
≥337	104	88.3-121.9

Risk group incidence: (person counts)

Univariate analysis showed the following regarding relation of potentially carcinogenic treatments to the risk of SCC and BCC (so the multivariate analysis was adjusted for those found to be SS predictors of risk, as well as age, sex, residence, and anatomic site)

Variable	**SCC**	**BCC**
PUVA exposure up to 1985	SS	SS
PUVA exposure after 1985	SS	*NS*
UVB/tar exposure	SS	SS
MTX exposure	SS	SS
Grenz ray/x-ray exposure	*NS*	SS

Exposure	**Multivariate adjusted OR for 1st cancer after 1985**			
	SCC		**BCC**	
	OR	**95% CI**	**OR**	**95% CI**
<100	1	-	1	-
100-159	1.6	0.9-3.1	2.0	1.3-3.1
160-336	4.5	2.7-7.4	2.1	1.4-3.1

≥337	8.6	4.9-15.2	4.7	3.1-7.3
≥50 vs <50	1.4	1.0-2.0	NA	-
UVB/tar (high vs low)	1.4	1.0-2.0	1.5	1.1-2.0
MTX (high vs low)	1.3	0.9-1.9	1.1	0.7-1.5
Grenz ray/x-ray (exposed vs not exposed)	NA	-	1.5	1.1-2.0

Author's conclusion

- High dose exposure to PUVA is associated with a persistent, dose-related increase in the risk of SCC, even among patients lacking substantial exposure to other carcinogens and among patients without substantial recent exposure to PUVA.
- The carcinogenic effects of PUVA are unlikely to solely reflect immunosuppressive effects on the skin (which diminish after treatment is stopped)
- Exposure to PUVA has far less effect on the risk of basal cell cancer.
- The use of PUVA for psoriasis should be weighed against the increased cancer risk.

H.5.1.7 STUDY 7

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
I. Marcil and R. S. Stern. Squamous-cell cancer of the skin in patients given PUVA and ciclosporin: Nested cohort crossover study. *Lancet* 358 (9287):1042-1045, 2001. Ref ID: MARCIL2001	**Observational:** Prospective cohort study 1977-1998 **Representative population sample:** unclear (recruited from 16 university centres) – 94% of those eligible enrolled in the follow-up study **Prognostic factor adequately measured:** yes **Confounders adjusted for:** follow-up time, PUVA and MTX exposure	N: 1380 (844 analysed)	**Inclusion criteria:** PUVA treated **Exclusion criteria:** Not stated **Parameter** / **CSA users (n=28)** / **Others (n=816)** Mean age – years: 53±11 / 55±14 Male (%): 71% / 61% **PUVA treatments to 1992** <200: 39% / 63% ≥200: 61% / 37% **UVB or tar** Less use: 39% / 63% >300 UVB or 45: 61% / 37%	**Oral 8-MOP PUVA and ciclosporin**	Average of 6 years for ciclosporin **Note**: 6/28 CSA users had <3 months of use Mean time for remaining 22 = 35±34 months (median = 20 months [IQR:12-53])	Incidence of SCC/keratoacanthoma and BCC	NIH

	Attrition bias: 396 died (29%); 55 (4%) withdrawn 91% of remaining participants were followed up **Outcomes adequately measured:** Yes (histological examination) **Appropriate statistical analysis:** yes		months **MTX use** <36 months: 61%, 85% ≥36 months: 39%, 15% PUVA exposure and MTX use SS higher in those who did receive CSA				

Effect Size

Outcomes

<u>Observed incidence</u>

14 of 28 CSA users developed BCC or SCC

Parameter	CSA users (n=28)	Others (n=816)

SCC		
Patients (n)	-	212
Tumours (n)	212	1736
BCC		
Patients (n)	-	-
Tumours (n)	55	

Incidence for patients who used CSA (nested cohort, N=28)

Treatment	Patients	Patients with SCC	Total SCC	Patient years	IRR	
					Univariate	Multivariate
Time						
5 years before CSA	28	6	20	140	1.0	1.0
After first CSA	28	13	169	172	6.9 (4.3-10.9)	6.9 (4.3-11.0)
PUVA treatments to 1992						
<200	11	4	15	123	1.0	1.0
≥200	17	9	174	187	7.8 (4.5-13.2)	5.1 (3.0-8.9)
MTX use						

<36 months	17	7	50	190	1.0	1.0
≥36 months	11	6	139	121	4.3 (3.1-6.0)	2.7 (2.0-3.8)

Incidence for full cohort (N=844)

Treatment	Patients	Total SCC	Patient years	IRR	
				Univariate	Multivariate
Time					
5 years before CSA	844	417	4220	1.0	1.0
After first CSA	844	1178	4853	2.5 (2.2-2.7)	2.1 (2.0-2.5)
CSA use					
No	816	1426	8901	1.0	1.0
Yes	28	169	172	6.1 (5.2-7.2)	3.1 (2.6-3.7)
PUVA treatments to 1992					
<200	525	514	5571	1.0	1.0
≥200	319	1081	3502	3.3 (3.0-3.7)	2.8 (2.6-3.2)

MTX use					
<36 months	710	1107	7653	1.0	1.0
≥36 months	134	488	1419	2.4 (2.1-2.6)	1.7 (1.5-1.9)

Note: the risk associated with long-term MTX was SS lower than that associated with any CSA use or high-dose PUVA (p<0.0001)

Incidence stratified by PUVA dose (adjusted by extent of MTX use)

Variable	**IRR**	
	Nested cohort (n=28)	**Full cohort (n=844)**
≥200 PUVA treatments		
Pre-use/non-user	1.0	1.0
CSA user	8.1 (4.8-13.5)	3.5 (2.9-4.2)
≤200 PUVA treatments		
Pre-use/non-user	1.0	1.0
CSA user	2.4 (0.9-7.8)	1.2 (0.7-2.2)

Note: SS increased risk of SCC for those using CSA only for those also having received high-dose PUVA

Author's conclusion

- The risk of SCC of the skin is increased by ciclosporin in patients with psoriasis who have been exposed to PUVA.
- Such risks should be balanced against the effectiveness of the drug and possible newer immunosuppressive agents.

H.5.1.8 STUDY 8

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
T. E. C. Nijsten and R. S. Stern. The increased risk of skin cancer is persistent after discontinuation of psoralen + ultraviolet A: A cohort study. J.Invest.Dermatol. 121 (2):252-258, 2003. Ref ID: NIJSTEN2003A	**Observational:** Prospective cohort study 1975-2001 **Representative population sample:** unclear (recruited from 16 university centres) – 94% of those eligible enrolled in the follow-up study **Prognostic factor adequately measured:** yes **Confounders adjusted for:** yes – IRR: calendar year plus all exposures that were significant predictors of risk in the univariate analysis; HR:	N: 1380	**Inclusion criteria:** PUVA treated **Exclusion criteria:** Not stated **No. of persons at last follow-up (%) (n=1380)** **Age (y)** <45: 129 (9.3%) 45–64: 565 (40.9%) >64: 686 (49.7%) Men: 892 (64.6%) **Skin type** I–II: 402 (29.1%) III–VI: 978 (70.9%) **Region**	**Oral 8-MOP PUVA** Note: for 85.3% of the person-years, no use of PUVA was recorded	>20 years Interviewed annually and examined periodically regardless of continued use of PUVA This includes data to the end of 19th cycle of follow-up interviews	Incidence of BCC and invasive SCC (ie only biopsy confirmed SCC not SCC in situ or keratacanthoma) **Tumour counting** All tumours counted (different method to other analyses of this cohort)	NIH and Fund for Scientific Research

	age, sex and PUVA dose **Attrition bias:** see table below **Outcomes adequately measured:** Yes (histological examination) **Appropriate statistical analysis:** yes (all incorporated time-dependent variables)		North	781 (56.6%)					
			Middle	233 (16.9%)					
			South	364 (26.4%)					
			Methotrexate exposure						
			Low	1039 (75.3%)					
			High	341 (24.7%)					
			Tar and/or UVB exposure						
			Low	877 (63.6%)					
			High	503 (36.5%)					
			X-ray therapy prior to entering study						
			No	1053 (76.3%)					
			Yes	327 (23.7%)					
			No. of PUVA treatments						
			<100	497 (36.0%)					
			100–199	371 (26.9%)					
			200–299	218 (15.8%)					
			300–399	121 (8.8%)					

400–499	70 (5.1%)
≥500	103 (7.5%)
Years since stopping PUVA	
<2	85 (6.2%)
2–5	235 (17.0%)
6–10	324 (23.5%)
11–15	268 (19.4%)
>15	468 (33.9%)

Status of 1380 patients originally enrolled by end of year

	Year				
	1979	**1984**	**1989**	**1995**	**2001**
Intervi ewed	1293	1152	988	860	609
Dead	59	134	223	395	510
Not intervi	28	94	169	125	261

			ewed									

Effect Size

Outcomes

Note: values for each patient for all variables determined for each calendar year (so were time-dependent)

Dose classifications (based on historical data collection)

- High tar: topical tar for ≥45 months
- High UVB: >300 treatments
- High MTX: ≥3 years use
- PUVA exposed year: ≥10 PUVA treatments per calendar year
- PUVA non-exposed year: ≤10 PUVA treatments per calendar year

TUMOUR RISK

SCC

- Incidence of SCC has increased over the 25 years of the study
- 2147 invasive SCC in 303 patients

BCC

- Average incidence has increased substantially over the last 10 y of the study
- 1363 BCC in 294 persons

Multivariate estimates of IRR and 95% CI for SCC and BCC adjusted for all other significant risk factors and for study year in members of the PUVA Follow-up Study (n=1380)

	SCC		BCC	
	IRR	95% CI	IRR	95% CI
Age (y)				
< 45	1		1	
45–64	2.08	1.63–2.65	2.19	1.64–2.92
>64	3.40	2.63–4.40	5.13	3.82–6.89
Men, compared with women	1.38	1.15–1.66	1.91	1.55–2.35
Skin type				
III–VI	1		1	
I–II	2.90	2.43–3.47	1.41	1.15–1.72
Region				
North	1		1	
Middle	0.74	0.58–0.95	1.18	0.91–1.52
South	2.19	1.79–2.68	1.79	1.43–2.25
Years since stopping PUVA				
< 2	1		1	

2–5	1.19	0.93–1.53	1.86	1.40–2.48	
6–10	1.25	0.92–1.70	2.74	1.95–3.85	
11–15	0.90	0.62–1.31	2.61	1.70–4.02	
>15	0.94	0.58–1.52	3.18	1.86–5.44	
High methotrexate exposure (36+mo) compared with low	2.18	1.79–2.66	1.46	1.17–1.81	
High tar (45+mo) and/or UVB exposure (300+treatments) compared with low	1.02	0.85–1.22	1.61	1.33–1.95	
X-ray therapy prior to entering study compared with none	2.87	2.40–3.44	2.13	1.75–2.60	
No. of PUVA treatments					
< 100	1		1		
100–199	3.20	2.27–4.51	2.35	1.64–3.38	
200–299	5.28	3.38–8.25	3.76	2.34–6.06	
300–399	8.18	4.95–13.53	4.63	2.68–7.98	
400–499	14.36	7.97–25.87	7.62	4.03–14.43	
≥500	18.67	10.23–34.07	12.69	6.34–25.40	
No. of PUVA treatments in first 5 y					
< 100	1		1		
100–199	1.10	0.83–1.46	0.86	0.63–1.17	

≥200	1.39	0.95–2.03	0.75	0.49–1.14
Period (adjusted for all variables except study year)				
1975–80	1		1	
1981–85	0.99	0.71–1.39	0.84	0.57–1.25
1986–90	1.28	0.88–1.87	0.90	0.58–1.41
1991–95	2.18	1.43–3.30	1.32	0.80–2.18
1996–2000	2.76	1.71–4.48	1.12	0.64–1.97

Summary:

SCC

- Level of PUVA exposure is the single factor most strongly associated with SCC risk
- Even 15 years after stopping PUVA the risk of SCC observed was not lower than that while still using PUVA
- Early intense therapy with PUVA was not significantly related to SCC risk.
- For most other significant predictors of risk for SCC, including methotrexate, X-ray, UVB and tar, the risk estimates from the multivariate analysis were somewhat lower than the univariate estimates

BCC

- BCC risk is significantly associated with increasing PUVA use, the years since first PUVA treatment and age.
- In the multivariate analysis, BCC risk increased greatly with very high levels of PUVA exposure
- For most significant predictors of risk for BCC, including years since stopping PUVA, there was little difference in the estimates obtained in the univariate and multivariate analysis
- The risk of BCC increases significantly with the passage of time since stopping PUVA and is about three times higher 10 y after stopping PUVA than during treatment.

RISK OF FIRST TUMOUR

Multivariate estimates of HR and 95% CI for a first SCC (n=303) and a first BCC (n=294) in members of the PUVA Follow-up Study (Each variable adjusted for the other two variables)

	SCC		BCC	
	HR	**95% CI**	**HR**	**95% CI**
Age (y)				
< 45	1		1	
45–64	1.37	0.98, 1.91	0.40	0.28, 0.57
>64	1.50	1.06, 2.14	0.74	0.57, 0.95
Men, compared with women	1.75	1.35, 2.28	1.45	1.12, 1.88
No. of PUVA treatments				
<100	1		1	
100–199	2.38	1.60, 3.54	1.52	1.09, 2.12
200–399	6.03	4.09, 8.88	2.26	1.62, 3.17
≥400	10.75	6.99, 16.54	3.17	2.13, 4.72

Summary:

SCC

- Total PUVA exposure significantly associated with risk of a first SCC
- Males had a modestly, but significantly, higher risk of developing a first SCC
- Risk of a first SCC and age were not significantly associated
- In 25 y, patients with fewer than 200 PUVA treatments have about 7% risk at least one SCC (Figure 3). After 25 y, more than half of the patients with 400 or more treatments develop at least one SCC.

BCC

- More than 100 PUVA treatments was significantly associated with an increased risk of a first BCC
- Risk of developing at least one BCC was higher in males.
- Risk of a first BCC was lower among patients older than 44 than younger patients.
- Risk of developing at least one BCC did not increase as sharply with increasing PUVA dose as did the risk of SCC.
- After 25 y, almost one-third of the patients with 200 treatments develop at least one BCC

Author's conclusion

- Substantial exposure to PUVA increases the risk of SCC and BCC
- The carcinogenic effects of PUVA increase over time, are independent of the intensity of the initial therapeutic regimen and persist for many years after stopping treatment
- The stabilization of SCC incidence after about 20 y of follow-up may reflect the death and/or loss of follow-up of highly susceptible patients or a stabilization of the SCC risk associated with PUVA therapy with the additional passage of time

H.5.1.9 STUDY 9

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>T. E. C. Nijsten and R. S. Stern. Oral retinoid use reduces cutaneous squamous cell carcinoma risk in patients with psoriasis treated with psoralen-UVA: A nested cohort study. J.Am.Acad. Dermatol. 49 (4):644-650, 2003.

Ref ID: NIJSTEN2003</td>
<td>Observational: Prospective nested cohort study

1985-2000

Representative population sample: unclear (recruited from 16 university centres) – 94% of those eligible enrolled in the follow-up study

Prognostic factor adequately measured: yes

Confounders adjusted for: yes – all factors that were significant predictors of risk in the univariate analysis</td>
<td>N: 135 (11.3% of surviving cohort)</td>
<td>Inclusion criteria: PUVA treated

Exclusion criteria: Not stated
<table>
<tr><th></th><th>Retinoid users at 1989 (n=135)</th><th>Non-users at 1989 (n=942)</th></tr>
<tr><td>Age (y)</td><td></td><td></td></tr>
<tr><td><45</td><td>34.1%</td><td>28.6%</td></tr>
<tr><td>45–64</td><td>41.5%</td><td>43%</td></tr>
<tr><td>>64</td><td>24.4%</td><td>28.4%</td></tr>
<tr><td>Men</td><td>65.2%</td><td>62.2%</td></tr>
<tr><td>Skin type</td><td></td><td></td></tr>
<tr><td>I–II</td><td>28.9%</td><td>30.9%</td></tr>
<tr><td>III–VI</td><td>71.1%</td><td>69.1%</td></tr>
</table></td>
<td>Retinoids 25-50 mg/day (year of use: at least 26 weeks of treatment

year of no use: < 26 weeks of treatment</td>
<td>≥1 year (mean >4 years)

Interviewed annually and examined periodically regardless of continued use of PUVA

This includes data to the end of 19th cycle of follow-up interviews (but only at each of the 1 interviews since 1985 was use of oral retinoids – isotretinoin, etretinate or</td>
<td>Incidence of BCC and SCC (including SCC in situ and keratacanthoma)

Tumour counting Categorised according to date of diagnosis (year of use or no use)

All tumours counted</td>
<td>NIH and Fund for Scientific Research</td>
</tr>
</table>

	Attrition bias: unclear **Outcomes adequately measured:** Yes (histological examination) **Appropriate statistical analysis:** yes		**Region**					acitretin – recorded; 95% aromatic retinoids)		
			North	60%	56.8%					
			Middle	21.5%	17.5%					
			South	18.5%	25.7%					
			No. of PUVA treatments							
			<200	44.4%	66%					
			200–499	41.5%	31.1%					
			>499	14.1%	3.4%					
			Methotrexate exposure							
			High (+3 y)	39.3%	17.4%					
			Tar and/or UVB exposure							
			High (+45 mo or +300)	29.6%	29.9%					
			X-ray therapy prior to entering study							
			Yes	31.1%	20.9%					
			History of SCC	14.1%	6.9%					

			before 1985					
			Retinoid users had higher PUVA exposure and MTX use and more had a history of SCC between enrolment and 1985					

Effect Size

Outcomes

TUMOUR RISK

SCC

- Incidence MD for years of use vs no use = 106 SCCs/1000 person-years (95%CI 173, 22)

BCC

- Incidence MD for years of use vs no use = 28 BCCs/1000 person-years (95%CI 79, -22)

Multivariate analysis (adjusted for retinoid use, age, sex, PUVA dose, radiograph, MTX, tar and UVB exposure and history of SCC before retinoid use)

	SCC		**BCC**	
	IRR	**95% CI**	**IRR**	**95% CI**
Retinoid use	**0.79**	**0.65-0.95**	**0.94**	**0.67-1.32**

Age (y)				
< 45	1		1	
45–64	1.03	0.81-1.31	1.25	0.68-2.31
>64	0.69	0.51-0.93	6.25	3.58-10.92
Men, compared with women	1.42	1.16-1.74	3.75	2.31-6.07
High tar (45+mo) and/or UVB exposure (300+treatments)	2.42	2.00-2.93	3.34	2.32-4.79
X-ray therapy prior to entering study compared with none	3.17	2.06-4.89	8.42	4.51-15.73
No. of PUVA treatments				
< 200	1		1	
200–499	3.36	2.34-4.85	1.17	0.78-1.78
>499	7.26	4.91-10.75	2.65	1.62-4.36
History of SCC >3 y before first retinoid use	4.51	3.61-5.64		
History of BCC >3 y before first retinoid use			3.44	2.28-5.21

Author's conclusion

- In patients with psoriasis treated with PUVA, systemic retinoid use reduced SCC risk but did not significantly alter basal cell carcinoma incidence.
- Level of exposure to PUVA and history of SCC were the strongest predictors of SCC risk

H.5.1.10 STUDY 10

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
J. L. Lim and R. S. Stern. High levels of ultraviolet B exposure increase the risk of non-melanoma skin cancer in psoralen and ultraviolet A-treated patients. J.Invest.Dermatol. 124 (3):505-513, 2005. Ref ID: LIM2005	**Observational:** Prospective cohort study 1975-2003 **Representative population sample:** unclear (recruited from 16 university centres) – 94% of those eligible enrolled in the follow-up study **Prognostic factor adequately measured:** yes **Confounders adjusted for:** yes – Univariate analyses adjusted for age and year only. Multivariate analyses: level of PUVA	N: 1380 (442 exposed to high UVB)	**Inclusion criteria:** PUVA treated **Exclusion criteria:** Not stated **Parameter** / **All (n=1380)** Mean age – years: 44 Male (%): 65% Mean BSA (%): 33 **Psoriasis subtypes** Plaque: 84% Guttate: 12% Erythrodermic: 4% **Skin type**	**Oral 8-MOP** **PUVA** **UVB (mostly BBUVB)** Note: UVB treatments outnumber PUVA by about 2:1	28 years (>15 years for UVB) Interviewed annually and examined periodically regardless of continued use of PUVA This includes data to the end of 21st cycle of follow-up interviews	Incidence of BCC and invasive SCC (excluding SCC in situ and keratacanthoma) **Tumour counting** To assess the risk of UVB, two primary endpoints used: (1) development of at least one SCC or BCC in a given year for a given patient (i.e., incident tumours) (2) total number of SCC or BCC in a given year for a given patient (i.e., total tumours).	NIH

	exposure, age, year since enrolment, gender, skin type, geographic residence, year, and use of methotrexate, tar, ciclosporin, and retinoids. **Attrition bias:** 609/1380 remained (521 died – consistent with number expected – and 250 lost to follow-up or withdrawn) **Outcomes adequately measured:** Yes (histological examination) **Appropriate statistical analysis:** yes RR/IRR = incidence rate among exposed divided by the incidence rate among non-exposed		I: 5.4% II: 22.1% III: 56.3% IV: 12.7% V: 1.4% VI: 2.0% **Prior therapy** Topical steroids: 86% Coal tar: 84% UV: 61% MTX: 45% Goekerman: 38% x-ray: 18% Grenz ray: 12% Most patients had severe psoriasis					

	Attributable risk = difference between observed incidence at the highest level of exposure compared with the lowest level, and gives an estimate of the absolute effect of the exposure.						

Dose classifications

- **<u>PUVA:</u>**

  1. <100 treatments

  2. 100-199

  3. 200-299

  4. 300-399

  5. 400-499

  6. ≥500 treatments

- **<u>UVB</u>**:

  High: ≥300 treatments

  Low <300 treatments

Effect Size

Outcomes

TUMOUR RISK

SCC

- 2528 SCCs in 329 patients

BCC

- 1566 SCCs in 305 patients

Variable	Person years (%)	Number of tumours (%)	Tumour incidence per 100,000 person years	Number of incident tumours (%)	Tumour incidence per 100,000 person years, if only including incident tumours
Squamous cell carcinoma (SCC)					
UVB					
Low (<300)	20,921 (74.9)	1538 (60.8)	7351	696 (63.0)	3327
High (≥300)	7007 (25.1)	990 (39.2)	14,129	408 (37.0)	5823
PUVA					
Low	11,922	197 (7.8)	1652	118 (10.7)	990

(<100)	(42.7)				
Not low (≥100)	16,006 (57.3)	2331 (92.2)	14,563	986 (89.3)	6160[b]
Basal cell carcinoma (BCC)					
UVB					
Low (<300)	20,921 (74.9)	880 (56.2)	4206	511 (61.8)	2443
High (≥300)	7007 (25.1)	686 (43.8)	9790	316 (38.2)	4510
PUVA					
Low (<100)	11,922 (42.7)	256 (16.3)	2147	148 (17.9)	1241
Not low (≥100)	16,006 (57.3)	1310 (83.7)	8184	679 (82.1)	4242

Univariate and multivariate analysis of potential risk factors associated with the development of at least one SCC (in a given year) for the entire cohort[a]

	Univariate model[b]	**Multivariate model[c]**

	IRR	95% CI	p-value for trend	IRR	95% CI	p-value for trend[d]
No. of lifetime UVB treatments			<0.001			<0.001
<300[e]	1			1		
≥300	1.42	1.08–1.86		1.37	1.03–1.83	
No. of lifetime PUVA treatments			<0.001			<0.001
<100[e]	1			1		
100–199	2.34	1.48–3.70		2.36	1.51–3.68	
200–299	4.15	2.59–6.66		4.14	2.64–6.50	
300–399	5.93	3.59–9.79		5.54	3.38–9.09	
400–499	10.25	6.26–16.78		11.05	6.88–17.76	
≥500	10.47	6.28–17.45		10.81	6.76–17.29	
Gender			0.007			0.005
Women[e]	1			1		
Men	1.57	1.13–2.19		1.62	1.19–2.20	
Skin type			0.010			<0.001
III–IV[e]	1			1		

I–II	1.46	1.09–1.95		1.76	1.33–2.31	
High methotrexate exposure (≥36 mo) compared with low	1.95	1.51–2.51	<0.001	1.66	1.32–2.08	<0.001
High tar exposure (≥45 mo) compared with low	1.21	0.89–1.65	0.216	1.02	0.75–1.39	0.926
High ciclosporin exposure (≥3 mo in a given year until 5 y after last use, compared with low exposure)	2.08	1.17–3.69	0.013	1.43	0.88–2.31	0.048
Year with high retinoid exposure (≥26 wk in a given year, compared with low exposure)	1.20	0.77–1.87	0.427	0.88	0.57–1.35	0.725

[a] Estimates of the incident rate ratios were obtained from univariate and multivariate negative binomial regression models.

[b] Univariate analysis adjusted for age and year.

[c] In addition to the variables listed, the multivariate model adjusted for age and year.

[d] The analysis for p for trend considered age, year, UVB, PUVA, and residence as continuous variables and gender, skin type, methotrexate, tar, ciclosporin, and retinoid use as categorical variables.

[e] This group served as the reference group.

Univariate and multivariate analysis of potential risk factors associated with the development of at least one BCC (in a given year) for the entire cohort

	Univariate model[b]			**Multivariate model[c]**		
	IRR	**95% CI**	**p-value for trend**	**IRR**	**95% CI**	**p-value for trend[d]**

No. of lifetime UVB treatments			0.024			0.025	
<300[e]	1			1			
≥300	1.53	1.15–2.03		1.45	1.07–1.96		
No. of lifetime PUVA treatments			<0.001			<0.001	
<100[e]	1			1			
100–199	1.87	1.23–2.82		1.80	1.21–2.70		
200–299	2.07	1.33–3.24		2.00	1.32–3.03		
300–399	3.07	1.90–4.95		2.81	1.75–4.51		
400–499	3.00	1.73–5.20		2.93	1.73–4.98		
≥500	3.73	2.21–6.30		3.65	2.21–6.03		
Gender			<0.001			<0.001	
Women[e]	1			1			
Men	1.80	1.35–2.40		1.80	1.35–2.40		
Skin type			0.993			0.485	
III–IV[e]	1			1			
I–II	1.00	0.74–1.36		1.15	0.85–1.55		
High methotrexate exposure (≥36 mo) compared with low	1.39	1.03–1.89	0.031	1.24	0.92–1.67	0.095	

High tar exposure (≥45 mo) compared with low	1.45	1.09–1.95	0.012	1.28	0.93–1.76	0.075
High ciclosporin exposure (≥3 mo in a given year until 5 y after last use, compared with low exposure)	1.88	0.87–4.04	0.108	1.38	0.64–2.99	0.284
Year with high retinoid exposure (≥26 wk in a given year, compared with low exposure)	1.45	0.89–2.36	0.131	1.28	0.80–2.04	0.261

[a] Estimates of the incident rate ratios were obtained from univariate and multivariate negative binomial regression models.

[b] Univariate analysis adjusted for age and year.

[c] In addition to the variables listed, the multivariate model adjusted for age and year.

[d] The analysis for p for trend considered age, year, UVB, PUVA, and residence as continuous variables and gender, skin type, methotrexate, tar, ciclosporin, and retinoid use as categorical variables.

[e] This group served as the reference group.

Note: Based on the IRR estimated in the multivariate analysis, among those patients who were exposed to high levels of UVB therapy, about 27% of SCC and 31% of BCC were attributable to receiving high levels of UVB (300 treatments).

Author's conclusion

- High UVB exposure levels (300 treatments) confer a modest but significant increase in NMSC risk in adults.
- The modest risks associated with UVB therapy must be weighed in the context of a patient's underlying skin cancer risk and against the benefits of therapy.
- Overall, UVB therapy is substantially less carcinogenic than PUVA therapy and so should continue to be considered a primary treatment option for patients with moderate-to-severe psoriasis

H.5.1.11 STUDY 11

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>C. F. Paul, V. C. Ho, C. McGeown, E. Christophers, B. Schmidtmann, J. C. Guillaume, V. Lamarque, and L. Dubertret. Risk of malignancies in psoriasis patients treated with cyclosporine: a 5 y cohort study. J.Invest. Dermatol. 120 (2):211-216,</td>
<td>Observational: Prospective cohort study

Representative population sample: unclear (recruited from 277 centres in 11 countries)

Prognostic factor adequately measured: yes

Confounders adjusted for: yes

Attrition bias: Median duration of follow-up = 4.5 y (Range: 0-8.6 y); 48% attended final 60 month visit</td>
<td>N: 1252</td>
<td>Inclusion criteria: severe psoriasis; ciclosporin treated for at least 1 month

Exclusion criteria: Not stated
<table>
<tr><th></th><th>Total (n=1252)</th><th>≤2 y of CSA (n=781)</th><th>>2 y of CSA (n=471)</th></tr>
<tr><td>Age (mean ±SD)</td><td>43.3 ± 14.0</td><td>44.0 ± 14.3</td><td>42.3 ± 13.4</td></tr>
<tr><td>Sex (% M/F)</td><td>68/32</td><td>70/30</td><td>65/35</td></tr>
<tr><td>Weight (kg)</td><td>76.9 ± 16.6</td><td>76.7 ± 16.4</td><td>77.3 ± 16.9</td></tr>
<tr><td>Duration of psoriasis (y)</td><td>16.2 ± 11.2</td><td>15.8 ± 11.5</td><td>16.8 ± 10.7</td></tr>
</table>
</td>
<td>Ciclosporin

Mean starting dose 3 mg/kg/d,

Mean daily dose decreased over time from 3.1 mg/kg/d at month 6 to 2.7 mg/kg/d at the end of month 54.

Approximately 40% of all patients received CSA intermittently</td>
<td>5 years (assessed every 6 months by a dermatologist)

Mean duration of CSA therapy was 1.9 y</td>
<td>Incidence of skin cancers (SCC, BCC and melanoma)

Tumour counting

Unclear</td>
<td>Novartis Pharma</td>
</tr>
</table>

2003. Ref ID: PAUL2003	**Outcomes adequately measured:** Yes **Appropriate statistical analysis:** yes RR/IRR = incidence rate among exposed divided by the incidence rate among non-exposed calculated separately for each year of exposure All models included three explanatory variables: exposure to ciclosporine, previous history of malignancy, and the respective exposure to previous treatments for psoriasis (PUVA, oral retinoids, methotrexate, other immuno-suppressants, phototherapy, tar)		Age at onset of psoriasis (y)	27.1 ± 14.3	28.2 ± 14.6	25.3 ± 13.6	The remaining 60% received it continuously. **Concomitant therapies during follow-up:** 34% of patients received other systemic therapy for psoriasis MTX and retinoids by 20% each; PUVA by 13% and phototherapy by 10%			
			Previous systemic therapy of psoriasis (% of patients receiving therapy)							
			PUVA	47	45	49				
			Retinoids	45	41	51				
			MTX	28	25	33				
			UVB/UVA	19	21	17				
			Tar	8	9	8				
			Ciclosporine	8	8	8				
			Immunosup. (excluding CSA).	6	4	8				
			Fumaric acid	2	2	1				

			Arsenic	< 1	< 1	< 1			

Effect Size

Outcomes

TUMOUR INCIDENCE

Cancer	Patients		Person-Years	Incidence rate	95% CI
	N	(%)			
All skin malignancies	23	1.8	4377	5.3	3.3–7.9
BCC	5	0.4	4426	1.1	0.4–2.6
SCC	15	1.2	4401	3.4	1.9–5.6
Melanoma	2	0.2	4431	0.5	0.1–1.6

Note: all patients with BCC and/or SCC had previously received PUVA therapy

Observed vs expected incidence

- **Expected based on specific incidence rate for age-, sex- and geographic location-matched rate**

	Overall			Low exposure ≤2 y of CSA (n=781)			High exposure >2 y of CSA (n=471)		
	person-years	**SIR**	**95% CI**	**Person years**	**SIR**	**95% CI**	**Person years**	**SIR**	**95% CI**
Any skin malignancy	4330	6.1	3.8–9.1	3300	4.8	2.6–8.1	1029	10.1	4.6–19.2
BCC	4379	1.8	0.6–4.1	3338	0.9	0.1–3.3	1041	4.6	0.9–13.3
SCC	4354	24.6	13.8–40.7	3317	19.2	8.8–36.5	1037	42.7	15.7–93.2
Malignant melanoma	4384	4.7	0.6–17.0	3336	6.2	0.8–22.5	1048	0.0	

Multivariate analysis of potential risk factors associated with the development of skin cancer (SIR as outcome variable and previous history of malignancy, exposure to ciclosporine, and exposure to respective previous therapy as explanatory variables; adjusted for all other factors in the model)

	RR	95% CI
All skin malignancies		

Exposure to ciclosporine (high/low)	2.7	1.1–6.4
Exposure to PUVA (some/none)	5.8	2.0–25.0
Exposure to retinoids (some/none)	4.5	1.5–19.5
Exposure to methotrexate (some/none)	2.1	0.9–5.3
Exposure to immunosuppressant (some/none)	2.9	1.2–6.8
Exposure to phototherapy (some/none)	0.7	0.2–1.8
Exposure to tar (some/none)	2.4	0.7–6.6
All nonmelanoma skin malignancies		
Exposure to ciclosporine (high/low)	3.3	1.3–8.4
Exposure to PUVA (some/none)	7.3	1.3–134.5
Exposure to retinoids (some/none)	4.6	0.9–86.1
Exposure to methotrexate (some/none)	2.7	1.1–7.3
Exposure to immunosuppressant (some/none)	3.5	1.4–8.4
Exposure to phototherapy (some/none)	0.5	0.1–1.5
Exposure to tar (some/none)	1.9	0.4–5.7
All BCC		
Exposure to ciclosporine (high/low)	4.9	0.8–36.9

Exposure to PUVA (some/none)	Not estimable	
Exposure to retinoids (some/none)	Not estimable	
Exposure to methotrexate (some/none)	2.5	0.4–18.7
Exposure to immunosuppressant (some/none)	3.3	0.4–19.6
Exposure to phototherapy (some/none)	2.3	0.1–24.0
Exposure to tar (some/none)	6.5	0.9–39.4
All SCC		
Exposure to ciclosporine (high/low)	3.3	1.0–10.6[b]
Exposure to PUVA (some/none)	4.4	0.7–84.7
Exposure to retinoids (some/none)	2.6	0.4–50.7
Exposure to methotrexate (some/none)	2.5	0.8–8.6
Exposure to immunosuppressant (some/none)	4.0	1.3–11.5
Exposure to phototherapy (some/none)	0.6	0.1–2.7
Exposure to tar (some/none)	1.5	0.1–9.3

Author's conclusion

- The risk of skin cancer associated with ciclosporine treatment in psoriasis appears to be significantly increased with more than 2 y of cumulative treatment as compared with less than 2 y.
- The contributing role of previous exposure to PUVA, methotrexate, and other immunosuppressants was demonstrated.

H.5.1.12 STUDY 12

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
R. S. Stern, K. T. Nichols, and L. H. Vakeva. Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet a radiation (PUVA). New Engl.J.Med. 336 (15):1041-1045, 1997. Ref ID: STERN1	**Observational:** Prospective cohort study **1975-1996** **Representative population sample:** unclear (recruited from 16 university centres) – 94% of those eligible enrolled in the follow-up study **Prognostic factor adequately measured:** yes **Confounders adjusted for: STERN1997:** inadequate (not adjusted for other treatments)	N: 1380	**Inclusion criteria:** PUVA treated **Exclusion criteria:** Not stated **Parameter** / **All (n=1380)** Mean age – years: 44 Male (%): 65% Mean BSA (%): 33 **Psoriasis subtypes** Plaque: 84% Guttate: 12% Erythrodermic: 4% **Skin type**	**Oral 8-MOP PUVA** 0.4-0.6 mg/kg psoralen orally, followed in 1.5-2.0 h by UVA (standing in an UV irradiation unit; fluorescent bulbs with emissions in the range of 320-400 nm). Initial UVA dose 1.5-5 J/cm^2 depending on photosensitivity. During the clearing phase, patients undergo two or three light treatments per week and UVA dose is gradually increased according to the degree of erythema or pigmentation.	Mean 20.2 years (+2.2 years for STERN2001) Interviewed annually and examined periodically regardless of continued use of PUVA	Incidence of malignant/invasive melanoma and melanoma in situ **Tumour counting** *Population counts*: Federal survey rates are based on annual incidence so also computed observed rates by counting only the first tumour of a given type observed that year as	NIH

997 AND R. S. Stern and Up Study PUVA Follow. The risk of melanoma in association with long-term exposure to PUVA. J.Am.Acad.Dermatol. 44 (5):755-761, 2001. Ref ID: STERN2001	**STERN2001:** yes (age, sex, year of follow-up and 'all other risk factors') **Attrition bias:** >90% interviewed in most years To 1996: 398 died; 160 lost to follow-up or withdrawn **Outcomes adequately measured:** Yes up to 1989 (but after 1991 no study-sponsored dermatological assessments and diagnosis based on patient report and medical records) Note: study-sponsored dermatological assessments took place between 1997 and 2001		I: 5.4% II: 22.1% III: 56.3% IV: 12.7% V: 1.4% VI: 2.0% **Prior therapy** Topical steroids: 86% Coal tar: 84% UV: 61% MTX: 45% Goekerman: 38% x-ray: 18% Grenz ray: 12% Most patients had severe psoriasis		Average max UVA dose = 8-15 J/cm^2. With disease improvement therapy slowly tapered off. If disease flared, patients treated again with PUVA or other therapies for psoriasis as determined by their physician.		an incidence, but continuing individuals in the risk set after tumour occurrence	

	Appropriate statistical analysis: yes						

Effect Size

Outcomes

Dose classifications (based on historical data collection)

- PUVA high: ≥200 or 250 PUVA treatments
- PUVA low: <200 or 250 PUVA treatments

STERN1997 data

Observed vs expected incidence

- **Expected based on specific incidence rate for age-, sex- and geographic location-matched rate**

Study period	**Number of invasive melanomas**		**RR (95% CI)**
	Observed	**Expected**	
1975-1990			
<250 treatments	2	2.9	0.7 (0.1-2.5)
≥250 treatments	2	0.6	3.1 (0.4-11.3)

All patients	4	3.5	1.1 (0.3-2.9)
1991-1996			
<250 treatments	3	0.8	3.5 (0.7-10.3)
≥250 treatments	4	0.4	8.9 (2.4-22.8)
All patients	7	1.3	5.4 (2.2-11.1)
1975-1996			
<250 treatments	5	3.7	1.3 (0.4-3.1)
≥250 treatments	6	1.1	5.5 (2.0-12.0)
All patients	**11**	**4.8**	**2.3 (1.1-4.1)**

Adjusted RR of PUVA dose and duration as potential risk factors associated with the development of skin cancer (adjusted for age, sex and increase in melanoma over time in USA, as well as the other factor in the model ie PUVA treatments or time to first tumour)

Variable	**IRR**	**95% CI**
Number of PUVA treatments (≥250 vs <250)	3.1	0.9–10.5
Years since first treatment (≥15 vs <15)	3.8	1.1–13.3

STERN2001 data

Study period	Number of melanomas					
	Invasive melanoma		In situ melanoma		All melanoma	
	Observed	Incidence (per 1000 person-years)	Observed	Incidence (per 1000 person-years)	Observed	Incidence (per 1000 person-years)
1975 to 1990	4	0.22	0	0	4	0.22
1991 to 29/2/96	7	1.73	3	0.74	10	2.47
29/2/96 to end	7	3.82	4	2.18	11	6.00
All years	18	0.69	7	0.35	25	1.04

Characteristics of cohort members with and without melanoma

	Melanoma (n=23)	No melanoma (n=1357)	p-value
Age	50±12	44±16	0.13
% male	78	65	0.17
Skin type (%)			
I	13	7	<0.005
II	44	23	<0.005

III	44	54	
IV or higher	0	17	

- Additionally:
  - Number of patients with exposure to ionising radiation and high dose MTX was nearly identical in those who did and did not develop melanoma
  - Proportion with high dose exposure to UVB and tar was NS lower among melanoma patients (p>0.2)

Adjusted RR of PUVA dose and duration as potential risk factors associated with the development of skin cancer (adjusted for age, sex and increase in melanoma over time in USA)

Study period	**Invasive melanomas**		**In situ**		**All melanoma**	
	IRR	**95% CI**	**IRR**	**95% CI**	**IRR**	**95% CI**
No. of PVUA treatments						
<200 treatments	1		1		1	
≥200 treatments	2.6	1.0-6.6	3.5	0.8-14.7	2.9	1.3-6.4
Period						
1975-1990	1		1		1	
1991-Feb 1996	4.7	1.4-16.1	8.1	0.8-77.6	5.4	1.8-15.7
March 1996-1999	7.4	2.2-25.1	16.8	1.9-150.5	9.3	3.2-26.6

Note: the 70% higher incidence of all melanoma after Feb 1996 did not reach significance (p=0.21)

Incidence of melanoma 6.9-times (95% CI 2.6-18.3) higher from 1991-1998 than from 1975-1990

Adjusted RR of PUVA dose and duration as potential risk factors associated with the development of skin cancer (adjusted for age, sex and increase in melanoma over time in USA, as well as significant predictors of risk in the univariate analysis)

Variable	Invasive melanoma		All melanomas	
	IRR	95% CI	IRR	95% CI
Number of PUVA treatments (≥200 vs <200)	1.9	0.7–4.9	2.0	0.9–9.5
Years since first treatment (≥15 vs <15)	5.0	1.6–15.5	5.9	2.2–15.9

Author's conclusion

- The increased risk of malignant melanoma that begins 15 years after the first PUVA treatment and is associated with a high level of exposure is a reason for caution in the long-term use of this therapy
- Neither the number of PUVA treatments at which the risk of melanoma begins to increase substantially, nor the relation between an increasing level of exposure and risk can be determined.
- Patients receiving substantial numbers of PUVA treatments should be followed carefully for the development of both melanoma and nonmelanoma skin cancer.

H.5.1.13 STUDY 13

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
K. A. Papp, Y. Poulin, R. Bissonnette, M. Bourcier, D. Toth, L. Rosoph, M. Poulin-Costello, M. Setterfield, and J. Syrotuik. Assessment of the long-term safety and effectiveness of etanercept for the treatment of psoriasis in an adult population. J.Am.Acad.Dermatol. 66 (2):e33-e45, 2012. Ref ID: PAPP2012A	**Observational:** Retrospective cohort study of prospectively studied participants **Representative population sample:** yes **Prognostic factor adequately measured:** yes **Confounders adjusted for:** inadequate (matched for age and sex only) **Attrition bias:** no (39% lost to follow-up)	N: 506 (307 completed: 39% attrition)	**Inclusion criteria:** from previous RCTs and open-label extension studies of etanercept Moderate-to-severe psoriasis **Exclusion criteria:** any anti-TNF other than etanercept, PUVA, UVA, UVB, systemic psoriasis therapy or corticosteroids within 14 days of first dose. Active guttate or **Parameter** / **All (n=506)** Mean age – years: 46.0±11.7 Male (%): 67.4% Mean BSA (%): 26.3±17.4 Mean: 11.1±6.5	**Etanercept** 50 or 25 mg once or twice weekly	Up to 4 years	Incidence of BCC and SCC **Tumour counting** Multiple tumours in one patient are counted as multiple tumours	Amgen and Pfizer

	Outcomes adequately measured: unclear **Appropriate statistical analysis:** not regression		DLQI **History of phototherapy** **71.9%** **Note:** any concomitant therapies necessary to provide adequate supportive care were permitted except PVUA, UVA/UVB, systemic psoriasis therapy and systemic or topical corticosteroids (except for mild facial/genital lesions)				

Effect Size

Observed vs expected incidence

- Expected based on specific incidence rate for age- and sex-matched rate based on 1305.4 years of patient exposure

Outcome	**General population registry**	**Number of NMSCs by completion**		**SIR (95% CI)**
		Observed	**Expected**	
BCC	Southeastern **Arizona** Skin Cancer Registry	8	15.3	0.52 (0.23-1.03)
SCC	Southeastern **Arizona** Skin Cancer Registry	4	3.71	1.08 (0.29-2.76)

	Rochester Epidemiology Project; **Minnesota**	4	1.49	2.68 (0.72-6.87)

Author's conclusion

- The majority of observed malignancies were NMSCs, but no significant difference in incidence was observed compared with the general population based on available registry data

H.5.1.14 STUDY 13

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
P. P. M. van Lumig, R. J. B. Driessen, M. A. M. Berends, J. B. M. Boezeman, P. C. M. Van de Kerkhof, and E. M. G. J. De Jong. Safety of treatment with biologics for psoriasis in daily practice: 5-year data. J.Eur.Acad.Dermatol.Venereol. 26 (3):283-291, 2012. Ref ID: VANLUMIG2012	**Observational:** Prospective cohort study Enrolled in registry between February 2005 and April 2010 **Representative population sample:** yes – consecutive sample of those starting biologic therapy **Prognostic factor adequately measured:** unclear **Confounders adjusted for:** inadequate (matched for gender and 10-year age group)	N: 173 (409 patient years)	**Inclusion criteria:** all those starting biological treatment for psoriasis at a Dermatology Outpatient clinic in The Netherlands **Exclusion criteria:** not stated **Parameter** / **All (n=173)** Mean age – years: 50.6±12.1 Male (%): 63.0% Duration of psoriasis, years (mean ±SD): 26.0±12.8 Psoriatic arthritis (%): 29% Total exposure to biologics: 2.7 ± 1.6	**Biologics** (etanercept, adalimumab, infliximab, ustekinumab, efalizumab, alefacept and onercept – note alefacept and onercept were only used pre-enrolment to the registry) Dose and interval changes were according to the opinion of the dermatologist and topical or systemic therapies could be added as required	Registry follow-up: mean 2.3 ± 1.6 years	Incidence of BCC and SCC according to ICD-10 **Tumour counting** Multiple tumours in one patient are counted as multiple tumours	Wyeth Pharmaceuticals

	Attrition bias: unclear **Outcomes adequately measured:** yes **Appropriate statistical analysis:** not regression – SMR compared with general incidence rate for Dutch general population from Dutch General Practice Registry (CMR)		years (mean ±SD) Number of different biologics One: 50.9% Two: 30.6% Three: 13.9% Four: 4.0% Five: 0.6%				

Treatment characteristics

Biologic	N	Treatment episode duration (years)		Patient-years	Mean weekly dose (mg)
		Mean ±SD	Median (range)		
Etanercept	150	2.0±1.5	1.7 (0.01-5.2)	319.8	67.6
Adalimumab	59	0.9±0.5	0.9 (0.02-1.9)	55.4	25.5
Efalizumab	27	0.9±0.9	0.5 (0.08-3.4)	24.8	Per label
Infliximab	7	0.6±0.5	0.5 (0.04-1.6)	5.3	Per label

Ustekinumab	8	0.5±0.4	0.4 (0.14-1.1)	4.0	Per label

Effect Size

Outcome	N malignancies	Treatment	Time to event (months)	Pre-treatment	Relevant medical history
BCC					
Patient 1	5	Etanercept	2, 2, 4, 30, 33	UVB, PUVA, CSA, MTX, azathioprine	-
Patient 2	2	Etanercept	5	UVB, PUVA, MTX	SCC, multiple BCCs
Patient 3	1	Etanercept	3	CSA, PUVA, MTX	-
Patient 4	2	Adalimumab	3	CSA, MTX, UVB, PUVA, etanercept	-
SCC					
Patient 1	3	Etanercept	4	UVB, PUVA, CSA, MTX	-
Patient 2	1	Etanercept	6	UVB, PUVA, MTX	SCC, multiple BCCs
Patient 3	1	Etanercept	17	UVB, PUVA, CSA, MTX, alefacept	-
Patient 4	5	Efalizumab	27	CSA, MTX	-

Observed vs expected incidence

- Expected based on specific incidence rate for age- and sex-matched rate

Outcome	Number of malignancies		SIR (95% CI)
	Observed	Expected	
BCC	10	0.8	12.2 (5.9-22.5)
SCC	10	0.1	81.4 (39.0-149.8)

H.5.2 Retrospective cohort

H.5.2.1 STUDY 1

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
R. M. Hearn, A. C. Kerr, K. F. Rahim, J. Ferguson, and R. S. Dawe. Incidence of skin cancers in 3867 patients treated with narrow-band ultraviolet B phototherapy. Br.J.Dermatol. 159 (4):931-935, 2008. Ref ID: HEARNE2008 I. Man, I. K. Crombie, R. S. Dawe, S. H. Ibbotson, and J. Ferguson.	**Observational:** Retrospective cohort **Representative population sample:** all TL-01 treated patients from departmental database **Prognostic factor adequately measured:** data from Tayside phototherapy database with linkage to the Scottish Cancer registry **Confounders adjusted for:** age, sex and location (insufficient cases to do regression analysis)	N:3867 (2130 [55%] with psoriasis)	**Inclusion criteria:** whole body NBUVB **Exclusion criteria:** Follow-up <6 months; first treated after 2002 **Characteristic** / **All (3867)** Gender (M/F %): 44/56 Median age at first treatment with NBUVB (range): 34 years (2.6–93.8) Median number of NBUVB treatments: 29 (19-53) **Skin type** I: 23% II: 47%	**TL-01**	Median: 5.5 (3.0-9.0) years	Incidence of malignant melanoma, BCC and SCC (at least 6 months after first NBUVB treatment) **Tumour counting** First registered tumour per person	None stated

The photocarcinogenic risk of narrowband UVB (TL-01) phototherapy: early follow-up data. Br.J.Dermatol. 152 (4):755-757, 2005. Ref ID: MAN2005	**Attrition bias:** all included in analysis but missing data for many **Outcomes adequately measured**: Cancer registry and case notes **Appropriate statistical analysis:** yes		III: 27% IV+: 3% **Other treatments** PUVA: 24% Psoriasis + PUVA: 707/2130 (33%) BBUVB: 4%				

Effect Size

Outcomes

Observed vs expected incidence (compared with age- and sex-matched Tayside population rates)

- Observed in total population (55% psoriasis): 27 first BCC; 7 first SCC; 6 first MM
- 15 BCC vs 7.9 expected among those with psoriasis treated with both NBUVB and PUVA

SIR among psoriasis subgroup

Cancer	Treatments	SIR (95% CI)*	p-value
BCC	TL-01 only	156 (57-339)	NS
	TL-01 + PUVA	190 (106-313)	<0.05
SCC	TL-01 only	0 (0-465)	NS

	TL-01 + PUVA	126 (15-454)	NS
MM	TL-01 only	105 (3-586)	NS
	TL-01 + PUVA	157 (32-460)	NS

*Note: A standardised incidence ratio (SIR) of 100 = no difference between observed and expected

Author's conclusion

- No significant association between NB-UVB treatment and BCC, SCC or melanoma.
- There was a small increase in BCCs amongst those also treated with PUVA.
- The early increase in skin cancers associated with PUVA treatment is not found with NBUVB.
- However, the cohort contained relatively few patients who had a high treatment number and the slow evolution of skin cancers may result in a delayed incidence peak.

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: CAMARASA2	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 No explicit or implicit exclusion	N=128 **Calcitriol** 3 µg/g **Formulation**: ointment **Frequency** twice daily Who administered not clear. **Both arms:** medication applied to all	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

003	• **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	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)	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 Dermatology 1997;136:89-	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** Not reported	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 due to adverse events.	**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 in PASI from	Leo Pharmaceutical Products.

93 **Ref ID: MOLIN1997 A**	• **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						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. **Ref ID:**	**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 calculation** not	**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 and 2 not	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

BRUCE1994	reported • **ITT analysis:** yes for AE and withdrawal (assumptions not stated) **Setting:** Outpatients	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.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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	Multicentre (Europe) DESIGN Within patient Patient delivery ALLOCATION Random Method of randomisation: not stated Concealment: unclear BLINDING Double-blind (patient / assessor) WITHDRAWAL / DROPOUT Described	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 associated with	**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 [illegible]	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	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	6 weeks (evaluated every 2 weeks)	PASI Patient assessment of response Withdrawals	Not stated

	Calcipotriol side	Betamethasone side
Male/female	203/142	
Mean age (range)	45.2 (18-90) years	
Mean disease	19.5 (0.5-76) years	

	• **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 patients excluded from efficacy analysis (2 defaulted	withdrawal was provided in case of withdrawals due to lack of efficacy or adverse events (see below)	duration 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				

	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 Academy of	**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 a computer	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 In the calcipotriol group the	**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 **Frequency:** 2 x	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** **Formulation:**	**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

Dermatology 1992; 5:736-743. **Ref ID: CUNLIFFE1992**	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%. **ITT analysis: Modified ITT for efficacy** 38 did not	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 group). This was due to a dispensing error in 7 and 1 started systemic BM 2 weeks		CP	BM	per day Concomitant therapies – other medication known to affect the course of the disease was not allowed.	ointment **Frequency:** 2 x per day		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	
			% men	55.1	56.4				
			Age mean (sd)	43.6 (16)	46.2 (14.9)				
			Duration of psoriasis (yrs)	15.6 (12.1)	16.8 (11.8)				
			% with 3 body regions affected	77.6 %	83.8%				
			PASI mean (sd)	8.7 (5.8)	9.4 (6.6)				

	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	post randomisation. **Noncompliance :** Not reported						

Effect Size

Outcomes

Efficacy

Change in PASI (2,4 and 6 weeks)

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 calculation**: not	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

	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 calculation**: not	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

	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 reported.	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 TSS (0 to 8): 3.90	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 investigator):	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		BSA: 9.1% No use to face or scalp allowed.	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:** DUBERTRET1992	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 preferred treatment phase 4 patients	**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. **Baseline comparability**:	**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

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

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	N=10

during initial randomisation phase	

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), patient	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 were required to have TSS >5 and at least moderate	**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	refused further participation (n=1) and unknown (n=1). Group breakdown unknown.	(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 **<u>Efficacy (ITT)</u>**								

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 • **Allocation concealment**. 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) Compliance	Leo Pharmaceuticals

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

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 European Academy of Dermatology*	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 Age: 44.6 Gender (%M): 52.8% Severity:	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 used: The mean use was 38.9 g/week (range 3.4	N=161 Calcipotriol (50 µg/g) suspended as fine particles **Formulation:** cream **Frequency:** Twice daily --- N=87 Vehicle control **Formulation:** cream	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 improvement, marked improveme	Leo Pharmaceutical Products

& 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)		PASI (modified): 8.3 (range: 0.6 to 59.4) Duration (yrs): 17.7 (range: 0.04 to 70)	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.	**Frequency:** Twice daily		nt, complete clearance except for residual discolouration) Withdrawals 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)

<u>Reasons for withdrawal from double-blind treatment</u>

	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 ITT	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 ointments	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) Withdrawals	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>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	**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				

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): 335–8.	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 Age: 49 (15SD; N = 134)	**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

Ref ID: SCARPA1997	• **Sample size calculation** not reported • **ITT analysis:** yes (assumptions not stated) **Setting:** Outpatients		Gender (%M):65.6% (N = 157) Severity: not stated					

Effect Size

Outcomes

Time-to-effect

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

Adverse events

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

Withdrawals

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

	Setting: Outpatients							

Effect Size

Outcomes

Efficacy

IAGI:

	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

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Medanski RS, Brody NI, Kanof NB, Russo GJ, Peets EA. Clinical Investigations of Mometasone Furoate – a novel, nonflourinated, topical corticosteroid. **Ref ID: MEDANSKY1987A**	**RCT** **DESIGN** Between patient Patient delivery **ALLOCATION** Random Method of randomisation: not reported Concealment: unclear **BLINDING** Double-blind (patient / investigator); not described **WITHDRAWAL / DROPOUT**	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 withdrew due to adverse	**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]**: MF / Placebo Age: 55.5 (16-80) / 52 (18-78) male: 36/58 / 42/57 Duration disease: 19.7 (1-50) / 16 (2-52)	**n= 58** Mometasone furoate ointment, 0.1% OD (M) **Formulation**: ointment **Frequency:** Once daily Concomitant therapies – None	**n= 57** Placebo Vehicle OD **Formulation:** ointment **Frequency** Once daily	**Treatment duration:** 3 weeks **Follow up:** day of treatment cessation.	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 improveme	Schering Corporation

	Described **Sample size calculation:** Not reported **ITT analysis:** None reported; analyses all per protocol.	events. **Noncompliance:** Not reported	(yrs)					nt) Adverse events – examined for irritation, folliculitsis, striae, skin atrophy, or telangiectasia and other adverse experiences
			>25% body involved	15/58	11/57			
			Worsening	14/58	16/57			
			Only significant difference was for duration of disease. **Previous therapy**: Previous therapy was an exclusion criterion.					

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%	4/58	0/57

(marked improvement or cleared) at 8 days		
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) Noncompliance (i.e. failed	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, p=0.021; this was accounted for in analysis)	**n=94** **Hydrocortisone buteprate 0.1% cream, BD** **Class:** potent corticosteroid **Formulation**: cream **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 assessment of improvement (7 pt: exacerbation to cleared) **Primary efficacy parameter:** physician's end of study assessment of all	not reported

	• **ITT analysis:** no **Setting:** Outpatients	to apply medication for >3 days during trial): AEs: 1 hydrocortisone group	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				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

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 calculation** not	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

	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. *Dermatologica* 1991;183(4): 269–74.	**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 effectivene	not reported, but corresponding author employed by the Schering Corporation

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			ss. 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 disease or TSS ≥2.5 at 2 consecutive visits)	**p-value**

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, Jegasothy BV, et al.**	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 calculation** reported	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%) failed to meet entry criteria.	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 BC: Yes	**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 psoriatic lesions	**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 **Primary**	Allergan Inc.

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: WEINSTEIN1996 AND WEINSTEIN1997**	• **ITT analysis:** yes but similar to analysis of evaluable patients and latter presented **Setting:** Outpatients	Completion rates around 75% each group. 54 lost from T and27 from P	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				**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	RCT DESIGN Between patient Patient delivery ALLOCATION	Total N: 1303 (668 study A and 635 study B) **Drop-outs (don't complete**	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	**Tazarotene cream 0.05%, OD (T1)** **Tazarotene cream 0.1%, OD (T2)**	**Placebo** **Formulation**: cream **Frequency**	**Treatment duration:** 12 weeks **Assessments at:** baseline and	Overall lesion assessment (OLA; 0 = none to 5 = very severe), as applied to all treated lesions Clinical success (OLA ≤ 2 at 12 wks)	Allergan Inc

treatment of psoriasis: Two multicenter, double-blind, randomized, vehicle-controlled studies of the safety and efficacy of tazarotene creams 0.05% and 0.1% applied once daily for 12 weeks. Journal of the American Academy of Dermatology 2003;48(5):760–7. **Ref ID: WEINSTEIN2003**	Random Method of randomisation: Randomised in blocks of 6 Concealment: unclear BLINDING Double-blind (patient / investigator; not described) • **Washout period**: 2 weeks • **Sample size calculation** not reported • **ITT analysis:** yes • **Setting:** Outpatients	**the study):** Total = 411 (31.5%)	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): 18.4 BSA affected (mean): 10.5%	**Class:** retinoid **Formulation**: cream **Frequency** once daily each **Amount used:** thin layer to all lesions	once daily	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	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: completely cleared to worsened) **Primary efficacy parameter:** clinical success (% patients with OLA score of none, minimal or mild) at 12 weeks	
Effect Size								

Outcomes

Efficacy

Clinical success shown graphically.

Overall assessment score

PGA	**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**	**Study A (n=218)**	**Study B**	**Study A (n=229)**	**Study B**

			(n=211)			(n=210)			(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≤0.016) and throughout follow up (p≤0.029), and with 0.05% gel at weeks 4 to 24 (p≤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≤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	35 (15.8%)	51 (23.4%)	48 (21.0%)	28 (13.3%)	35 (16.7%)	29 (13.6%)

reasons, concomitant therapy, relocation, improper entry, lost to follow up)						

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):158-64.	**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 certain topical	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 made under	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

Ref ID: **LOWE2005**	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**			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 cream	Vehicle lotion

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

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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**	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	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 adverse effects. For the 5 not	**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 **Mean baseline** Age (mean±SD): Clobetasol lotion n=94: 48.71±14.08; Clobetasol cream n=95: 47.29±15.90; Vehicle lotion n = 33: 50.94±14.61 Males %: 50; 58.9; 63.6 Caucasians %: 100; 100; 100 TSS±SD (scale: 0-12): 8.49±1.45; 8.33±1.36; 8.61±1.71	**n=94** **Clobetasol propionate** **Formulation**: lotion **Frequency** once daily Who administered drug unclear.	**n=95** **Clobetasol propionate** **Formulation**: cream **Frequency** once daily **n=33** **Vehicle** **Formulation**: lotion **Frequency**	**Treatment duration:** 4 weeks. No long term FU reported.	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 (worse to clear)	Gladerma R&D

	• **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)	included in that table, 2 in the clobetasol group and 3 in the lotion group withdrew "by request" (no further reasons given).			once daily		Adverse events – skin atrophy a 0 (none) to 3 (severe) scale	

Effect Size

Outcomes

<u>Efficacy (ITT)</u>

<u>TSS (data only presented graphically)</u>

- 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. **Ref ID:**	**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 reported • **ITT analysis:** no	**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 (BC): Yes	**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

BEUTNER2006	**Setting:** Outpatients		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 per-protocol	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; Male 57%}	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 baseline to week 2 (or	Conneticcs Corporation

	(PP) and non-per-protocol analysis (ITT)		Caucasian: 90% Psoriatic involvement BSA mean: 6.7 **Clobetasol N=139** / **Placebo N=140** High pruritus 4 or 5: 14% / 14% Moderate pruritus 1-3: 72% / 76%	All areas were treated except face and intertriginous sites. Scalp only treated if sufficient quantities of foam remained.			end of treatment) and week 4. Patients global assessment (PGA 6 point scale) Patients preference for foam Patients and investigator reported adverse events	

Effect Size

Outcomes

<u>Efficacy</u>
<u>ITT Physicians static global assessment (PSGA) and Patients global assessment (PAGI)</u>

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. **Ref ID:**	**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 assessment at all sites	Connetics Corporation

LEBWOHL2002	• **Sample size calculation** not reported • **ITT analysis:** yes (assumptions not stated) **Setting:** Outpatients		(70%) Severity: pruritis (0 to 4): 2.11				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.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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 ID**:JARRATT 2006	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 30% with power	Total N: 120 **Drop-outs (don't complete the study):** 0	**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 (see table below)	Clobetasol propionate 0.05% **Formulation**: spray **Frequency** twice daily **Application** Self-administered. Allow 8 hours in between	Vehicle **Formulation**: spray **Frequency** twice daily	Baseline, weeks 1,2, & 4 and at 8 weeks (=4 weeks follow-up)	**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.	Dow pharma. And galderma R&D.

	Clobetasol	**Vehicle**
N	60	60
Age	46.7±12.7	49.3±13.1
Sex M/F	38/22	34/26
Race White(%)	2 (3)	1 (2)
Black (%)	1 (2)	2 (3)
Hispanic/Latino	0 (0)	1 (2)

	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)		BSA (%) 7.2±5.3 8.2±6.9 Overall disease severity (%) 3 Moderate 56 (93) 53 (88) 4 Severe 4 (7) 7 (12)				Adverse events	

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).

<u>4 weeks Follow-up (still in remission)</u>

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, Stewart DM, Lebwohl MG, Rajagopalan	**RCT** **DESIGN** Between patient Patient delivery	**Total N: 89** **Drop-outs (don't complete the study):**	INCLUSION CRITERIA **Moderate to severe** plaque type psoriasis (minimum 6 on 12-point scale); nonhospitalised men or	**n=44** **Clobetasol propionate emollient 0.05%**	**n=45** **Placebo (vehicle)**	**Treatment duration:** 4 weeks	Investigator global assessment of improvement (6 pt:	GlaxoWellcome Inc.

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**	**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) **Setting:** Outpatients	9 (20%) clobetasol propionate and 7 (16%) vehicle Noncompliance: not stated AEs: 5 (11%) in each group of which 1 each were drug-related	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%	**Formulation:** emollient **Class:** very potent corticosteroid **Frequency** twice daily **Amount used:** "fingertip unit": 0.5gm in men and 0.43gm in women	**Formulation**: emollient **Frequency** twice daily	**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)	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	

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 reported	**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 **Primary efficacy parameter:**	not reported

	Setting: Outpatients						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	11%	1%	3%	0
Excellent/good	60%	33%	66%	34%

End of treatment: Clear	10/88 (11%)	1/90 (1%)	3/105 (3%)	0
Excellent/good	50/88 (57%)	25/90 (28%)	69 (66%)	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 with once-	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 • **Blinding**: Not reported	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 calcipotriol or dithranol cream; unable to comply with study	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>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>• 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 a % point superiority of calcipotriol over dithranol and an SD of 30% of %</td>
<td></td>
<td>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 instructions.</td>
<td></td>
<td></td>
<td>Adverse events</td>
<td></td>
</tr>
</table>

	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.			**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**	**Calcipotriol**	**Dithranol**	**Dithranol**

	ITT n = 54	PP n = 46	ITT N=52	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 • **ITT analysis:** yes	**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 very severe	**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 **Primary**	not reported

	Setting: Outpatients		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%)				**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.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Wall AR, Poyner TF,	Multicentre	Total N: 306	**Inclusion criteria:** Over 18 years of age with stable, mild to moderate chronic	Dovon	Dithrocream	3 months	**1° outcome:**	Leo Pharmac

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	• **Randomised**: Yes, but no detail • **Washout period**: Unclear • **Open study** Not blinded • **Allocation concealment** Unclear • **Sample size calculation** Unclear • **ITT analysis** Unclear	(n=161 calcipotriol, 145 dithranol) **Drop-outs (don't complete the study):** N=11 defaulted and N=9 allocated incorrect treatment	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 [see table below]	ex (0.005 % calcipotriol) **Formulation**: ointment **Frequency**: Twice daily	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 decreased step by step.		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)	euticals

	Calcipotriol N=161	Dithrocream N=145
Sex M/F	75/86	69/76
Age (mean ±SD)	47±15.8	46.3±15
Duration of psoriasis	18±12	19±13
Previous calcipotriol use	73%	57%
Previous	69%	49%

			dithranol use							
			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 = 0.05

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 below head and next	**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)		except flexures.			

Effect Size

Efficacy

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 Mean duration of psoriasis:	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 to increase to 3%	**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	18.5 (range: 1 to 58) No explicit or implicit exclusion of face or scalp psoriasis.	exposure	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. 2010;11(4):275-83.	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 consent	**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) / Calcipotriene (n=30) Males: 15 / 19 Females: 15 / 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:** Changes in: PASI	NeoStrata

Ref ID:ALORAPALLI2010	• **ITT analysis** Performed to determine efficacy at 12 wks of treatment (modified ITT – those with at least one post baseline assessment)	n=3) 8 on Calcipotrine (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	Age: 48.2 (19-77); 48.7 (21-74) Duration of practice: 18.9 (4-62); 14 (1-46) Baseline PASI: 7.07 ± 3.13; 7.11 ± 3.14					(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 psoriasis symptoms.	

							ITT population. 75% or 50% reduction in psoriasis severity and area index, **PASI50 PASI75**	

Effect Size

Outcomes

Efficacy

Treatment phase (12 weeks)

Primary outcome. Change in PASI (0-64.8) from baseline

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 treatment	Week 12: 3.8 Week 18: 2.6	Week 12: 4.7 Week 18: 5.4	0.009 (between groups)

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 **Sample size**	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

	calculation: not stated **ITT analysis:** not stated		Baseline comparisons (stated as well matched but no useful variance measures given)					

	calcipotriol	comparison Rxs
male	41/69	37/63
age	45.8	50.9
duration of psoriasis	16.2	17.4
severe grade of psoriasis	16/69	11/63
area of psoriasis (cm2)	100-800	100-6000

Effect Size

IAGI

IAGI: marked improvement or clear	**Calcipotriol (N =65)**	**Comparison Rxs (N=57)**	**p-value**
8 weeks	47 (72.3%)	28 (49.1%)	<0.02

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: calcipotriol 1	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: 2 to 20)	**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		**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* 36.9±25.0%	*5.9±4.5* 9.4±15.9%	<0.001

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

	Not reported • **ITT analysis** no – 2 withdrawals due to lack of efficacy therefore included in ACA analysis		Age (mean±SD): 40.3±13.4 / 42.4±12.8 Males %: 60.7 / 63.3 PASI±SD (scale: 0-12): 17.1±2.9 / 17.7±3.8	lesions on upper and lower extremities and trunk; no facial or flexural lesions were treated				

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-blind, randomized study."	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 • **Sample size calculation**	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 or non-medical	**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 **Application**	6 wks Monotherapy Calcipotriol ointment 0.005% **Formulation** ointment **Application** Twice daily BOTH ARMS: Exacerbation during first 2 weeks =	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) assessment of global improvement	None provided.

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

Effect Size

Outcomes

<u>Efficacy</u>
<u>ITT for PASI at baseline, 2, 6 or 14 weeks</u>

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	

<u>ITT for IAGI at end of treatment</u>

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 randomised, parallel group, double-blind,	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 allowed.	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	**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. Does not explicitly exclude face and scalp lesions. May be included as they are mentioned with reference to the wash-out period.	**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 once daily for up to 8 weeks	**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.	Leo Pharma A/S.

exploratory study" Eur J Dermatol, 2010;40(4):465-71 Ref ID: FLEMING2010A	• **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** Yes. Efficacy analysis was performed on all 364 patients	withdrew at or just after baseline **Reasons** No reasons given		Unclear who administered the interventions. ---------- **ALL ARMS:** **Frequency:** once daily **Formulation:** gel			PASI 75% patients obtaining at least 75% improvement. Adverse events	

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

	(LOCF) • **Drop-outs/withdrawals** N=20							

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 gel**
% 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 funding
Guenther L; Cambazard F; VanDeKerkoff; Snellman E; Kragballe K; Chu AC; Tegner, E; Garcia-Diez A; Sprinborg,J "Efficacy and	RCT International multicenter (Europe and Canada) Between subjects trial • **Setting:** out-	Total N: 828 **Drop-outs (don't complete the study):** N=77 (but provided efficacy data).	**Inclusion criteria:** 18-86 years, psoriasis vulgaris at least 10% of one or more body parts (arms, legs, trunk). **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	**Combined formulation (Dovobet)** Calcipotriol 50µg/g + Betamethasone 0.5mg/g plus vehicle	**Vehicle** **Formulation**: ointment **Frequency:** twice daily	TD: 4 weeks. No log terms FUs.	**1° outcome:** Investigators gave assessment of response as cleared, marked or slight improvement (IAGI)	Leo Pharmaceutical Products.

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 Dermatology 2002;147:316-323

Ref ID: **GUENTHER2002**

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 identical appearance)

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

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.

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

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

No details on who administered (patient or

Combined formulation (Dovobet)

Calcipotriol 50µg/g + Betamethasone 0.5mg/g

Formulation: ointment

Frequency:

twice daily

Calcipotriol (Dovonex)

50µg/g

Formulation: ointment

Frequency:

twice daily

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

	• **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			investigator) drug.			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	

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

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 treatment of psoriasis.	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 (range: 1 to 36) **Duration: 18.7 years**	**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.

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%		**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: calci/veh: 1, calci/calci: 1,**	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) + **clobetasone17-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) Patient	Leo Pharmaceutical Products.

	Washout: 2 weeks (emollient only) No sample size calculation reported **ITT analysis: Modified ITT (figures from CR)**	**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			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. REF ID: KAUFMANN2	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 maximum	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 vehicle	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 that time	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, very mild, mild, moderate,	Leo Pharmaceuticals

002	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 no study	the calcipotriol group and 12 (7.6%) in the vehicle group. Rest not stated		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)	ointment **Formulation:** ointment **Frequency:** once daily N=157 Placebo (vehicle) ointment **Formulation:** ointment **Frequency:** once daily		severe, very severe) Patient's global assessment of disease severity (6 pt: worse, unchanged, slight improvement, moderate improvement, marked improvement, cleared) Compliance Withdrawal due to adverse events	

	medication							

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. Ref ID: **DOUGLAS200**	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 65)	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: worse to cleared)	Leo Pharmaceuticals

<table>
<tr>
<td>2</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>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 therapy with calcipotriol BD</td>
<td>Formulation: ointment

Frequency: Twice daily</td>
<td></td>
<td>Patient’s assessment of treatment response (6-pt: worse to cleared)

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

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	Calcipotriol

		(N=363)	(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. **Ref ID:**	**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 3)	**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; 65.8% group 2;	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: Duration (yrs): 18.5 (range: 0 to 70)	**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 formulation: calcipotriol	**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 parameter:**	Leo Pharmaceuticals

KRAGBALLE2004	• **Washout period:** not stated • **Sample size calculation** not reported • **ITT analysis:** yes (assumptions not stated) **Setting:** Outpatients	55.2% group 3	PASI: 10.5 (range: 2 to 49) % with moderate disease: 64.3%	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			% 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 • **ITT analysis:** 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 (6.8%) in group A; 11 (5.2%) group B; 16 (7.8%)	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, duration of psoriasis,	**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	**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: KRAGBALLE2006A**	**Setting:** Outpatients	group C	duration of previous topical corticosteroid use and disease severity	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 (6.8%) in group A; 11 (5.2%) group B; 16	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, duration of psoriasis, duration of previous topical corticosteroid use and	**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 **Frequency**	**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 **Primary efficacy**	Leo Pharma A/S

vulgaris. Dermatology 2006; Vol. 213, issue 4:319–26. **Ref ID: KRAGBALLE2006**	• **Sample size calculation** reported • **ITT analysis:** yes **Setting:** Outpatients	(7.8%) group C	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	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, alternating and calcipotriol.			**parameter:** not stated	
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 • **ITT analysis:** no **Setting:** Outpatients	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 dermatitis; 4 for concomitant diseases	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

			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
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
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

Efficacy

PASI: 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): 308–13.	**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: AEs: 6 in	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 BC: Yes	**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 **Class:** vitamin D	**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

Ref ID: ORTONNE2004	• **ITT analysis:** yes (assumptions not stated) **Setting:** Outpatients	TCP group and 11 in tacalcitol group	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)	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 randomiz	RCT Multicenter (Canada) Between subjects trial • **Randomised**: Method unclear Ratio of 2:2:1 2=interventions 1=vehicle • **Washout period**: See exclusion criteria. • **Single blind.**	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. Demographics (see table below)	**Combined formulation (Dovobet)** **N=183** Calcipotriol 50µg/g + Betamethasone dipropionate 0.5mg/g p **Formulation**: gel **Frequency:** once daily **ALL ARMS:** If a patient cleared before week 8	**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:** Clear or nearly clear on IGA at	Leo Pharmaceutical Products.

Demographics

	All **N=458**	**TCF** **N=183**	**Tacalcitol** **N=184**	**Vehicle** **N=91**
Mean	51.6±1	50.9±1	51.7±1	52.8±1

ed, controlled clinical trial. Dermatology 222 (2):148-156, 2011. Ref ID: **LANGLEY 2011A**	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 non-responder imputation as sensitivity analysis for categorical endpoints – no difference		age (yrs)	4.0	4.3	3.4	4.9	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		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 with daily life Adverse events Relapse (reduction in	
			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				

	found as only one IGA responder withdrew but data not given) • **Drop-outs/withdrawals**. N=60						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)	

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.

H.7 Topicals: high impact and difficult to treat sites

H.7.1 VITAMIN D OR VITAMIN D ANALOGUE + POTENT CORTICOSTEROID VS MONOTHERAPIES/PLACEBO

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
G. B. Jemec, C. Ganslandt, J. P. Ortonne, Y. Poulin, A. D. Burden, P. de Unamuno, B. Berne, A. Figueiredo, and J. Austad. A new scalp formulation of calcipotriene plus betamethasone compared with its active ingredients	RCT (4-arm) Multicentre (international) SCALP PSORIASIS • **Randomised** Computer-generated. Subjects were randomised in a ratio of 4:4:2:1 • **Washout period**: see exclusion	Total N: **1505** **Drop-outs (don't complete the study): n= 77** **Reasons** Adverse events (n = 8 in combined group, n = 9 betamethasone group; n=20 in calcipotrie	**Inclusion criteria:** aged > 18years; scalp psoriasis involving >10% of the scalp surface area; amenable to topical treatment with a maximum of 100 g medication/wk. clinical signs or previous diagnosis of psoriasis vulgaris on trunk and/or limbs. Investigator assessment of clinical signs moderate on at least one sign and other signs at least slight. **Mild to very severe** disease according to investigator's global assessment. **Exclusion criteria:** PUVA or grenz ray therapy within 4 wks before randomisation; UVB therapy within 2 wks before randomisation; systemic biologic therapies with possible effect on scalp psoriasis within 6 months before randomisation; other systemic therapies with possible effect on scalp psoriasis within 4 weeks before randomisation; any topical treatment of the scalp (except medicated shampoos and emollients) within 2 wks before randomisation; topical	Calcipotriene 50 µg/g plus betamethasone 0.5 mg/g (N=541) Betamethasone 0.5 mg/g (N=556) Calcipotriene 50 µg/g (N=272) All in the same	Vehicle alone (N=136) **Formulation**: scalp gel **Frequency:** once daily ---------- **BOTH ARMS:** study treatments	Treated for 8 weeks	**1° outcome:** Proportion with absence of disease or very mild disease according to static Investigators Global Assessment **2° and other outcomes:**	LEO Pharma

and the vehicle in the treatment of scalp psoriasis: a randomized, double-blind, controlled trial. J.Am.Acad.Dermatol. 59 (3):455-463, 2008. Ref ID: JEMEC2008	criteria • **Double blind** – adequately described • **Allocation concealment**. Unclear (pre-planned computer-generated sequence) • **Sample size calculation**. Yes. 90% power and a two-sided 5% significance level (N= 540m 540, 270 and 135 in each group). • **ITT analysis** Yes for efficacy, but not AEs. • **Drop-outs/withdraw**	ne group; n=7 in vehicle group) Lack of efficacy (n = 2 in combined group, n = 9 betamethasone group; n=19 in calcipotriene group; n=16 in vehicle group) Exclusion criteria (n = 3 in combined group, n = 3 betamethasone group; n=2 in calcipotriene group;	treatment of face, trunk or limbs with very potent corticosteroids within 2 wks before randomisation, planned initiation or changes to concomitant medication that could affect scalp psoriasis, planned exposure to the sun, current diagnosis of erythrodermic, exfoliative or pustular psoriasis, presence of viral lesions, fungal or bacterial skin infections, parasitic infections or atrophic skin on the scalp, known or suspected anomaly of calcium homeostasis associated with clinically significant hypercalcaemia, severe renal insufficiency or severe hepatic disorders. **Note:** Patients who were using or recently used biologics were not eligible as these required a washout of >1 month **Mean baseline** / **Calcipotriene + betamethasone N = 541** / **Betamethasone N = 556** / **Calcipotriene N = 272** / **Vehicle N = 136** Age, years (mean± SD): 47.9±15.4 / 49.5±15.9 / 50.1±16.6 / 49.6±15.8 Gender M/F: 47.9/52.1 / 41.9/58.1 / 44.5/55.5 / 44.9/55.1 Race: 95.7% / 96.8% / 97.4% / 94.9	vehicle **Formulation**: scalp gel **Frequency:** once daily **Amount of medication used**: The average weight of study medication used for the entire study period was 139.1 g for the two-compound scalp formulation group, 159.5g for the betamethasone dipropionate group, 155.4 g for the	applied topically to affected areas of scalp once daily		IAGI (worse to cleared); Adverse events, serum calcium and serum albumin; compliance	

	als Combination: 61 (11.3%) Betamethasone: 47 (8.5%) Calcipotriene: 57 (21.0%) Vehicle: 30 (22.1%)	n=3 in vehicle group) Other (n = 49 in combined group, n = 33 betamethasone group; n=25 in calcipotriene group; n=10 in vehicle group)	(Caucasian%)				%	calcipotriene group, and 176.0 g for the vehicle group. The average weight of the study medication used per week was approximately 17 to 22 g/week.				
			Duration of scalp psoriasis, years (mean± SD)	15.4±13.5	17.4±13.5	16.7±14.0	16.3±13.1					
			TSS (mean ± SD)	6.7±1.9	6.9±1.8	6.8±1.8	7.0±1.9					
			Investigators global assessment of disease severity (%)									
			Mild	8.7	4.5	5.9	7.4					
			Moderate	56.2	57.0	57.4	50.7					
			Severe	28.8	32.9	32.0	36.0					
			Very severe	6.3	5.6	4.8	5.9					

Effect Size

Outcomes

<u>Efficacy & time to effect</u>

Patients achieving absent or very mild disease on IAGI (%)	**Calcipotriene + betamethasone** **N = 541**	**Betamethasone N = 556**	**Calcipotriene** **N = 272**	**Vehicle** **N = 136**
Week 2	311 (57.5%)	262 (47.1%)	51 (18.8%)	16 (11.6%)
Week 4	362 (66.9%)	304 (54.7%)	64 (23.5%)	20 (14.7%)
Week 8 (primary outcome)	385 (71.2%)	356 (64.0%)	100 (36.8%)	31 (22.8%)

Patients overall assessment of treatment response at week 8 (name of scale not reported)

	Calcipotriene + betamethasone **N = 541**	**Betamethasone N = 556**	**Calcipotriene** **N = 272**	**Vehicle** **N = 136**
Proportion of patients who rated their scalp psoriasis as 'cleared' or 'almost clear' at week 8 (PAGI)	371 (68.6%)	348 (62.5%)	104 (38.3%)	28 (20.7%)

The two compound scalp formulation was significantly more effective than calcipotriene (OR 3.54; 99.3% CI, 2.28 TO 5.50; P<0.0001) and the vehicle alone (OR 8.45; 99.3% CI, 4.49 to 15.91; p<0.0001). The difference versus betamethasone dipropionate was not statistically significant (OR 1.38; 99.3% CI, 0.95 to 1.99; p=0.2)

Withdrawals

	Calcipotriene + betamethasone **N = 541**	**Betamethasone N = 556**	**Calcipotriene** **N = 272**	**Vehicle** **N = 136**
Total	61	47	57	30
Adverse events	8	6	20	7
Treatment failure	2	9	19	16

Compliance

	Calcipotriene + betamethasone **N = 541**	**Betamethasone N = 556**	**Calcipotriene** **N = 272**	**Vehicle** **N = 134**
Study medication used as instructed	37.9%	47.5%	42.6%	49.3%
Absence of disease recorded so allowed to miss applications	33.5%	25.9%	11.0%	4.4%

Summary

- Calcipotriene plus betamethasone dipropionate scalp formulation was more effective than either of the individual components or the vehicle alone

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
P. C. van de Kerkhof, V. Hoffmann, A. Anstey, L. Barnes, C. Bolduc, K. Reich, S. Saari, S. Segaert, and L. Vaillant. A new scalp formulation of calcipotriol plus betamethasone dipropionate compared with each of its active ingredients in the same vehicle for the treatment of scalp psoriasis: a randomized,	RCT Multicentre International Parallel group (3 arm) SCALP PSORIASIS • **Setting:** out-patient • **Randomised** Computer-generated (ratio 2:2:1). • **Washout period**: 2 wk to 1 month depending on previous	Total N: **1418** **Drop-outs (don't complete the study):** **TCF:** 48 (8.5%) **Betamethasone:** 66 (11.7%) **Calcipotriol:** 38 (13.3%)	**Inclusion criteria:** aged ≥ 18 years; **mild-to-very severe** scalp psoriasis on PGA (affecting at least 10% of scalp area) amenable to topical treatment with a max of 100 g medication per week. Clinical signs or previous diagnosis of psoriasis vulgaris on trunk and/or limbs. One or more clinical signs at least moderate and the others at least slight. **Exclusion criteria**: any topical treatment of the scalp (except medicated shampoos and emollients), topical treatment of face, trunk or limbs with very potent corticosteroids or UVB within 2 weeks of randomisation. PUVA or grenz ray therapy within 4 wks before randomisation; systemic biologic therapies with possible effect on scalp psoriasis within 6 months before randomisation; planned initiation or changes to concomitant medication that could affect scalp psoriasis, planned exposure to the sun, current diagnosis of erythrodermic, exfoliative or pustular psoriasis, presence of viral lesions, fungal or bacterial skin infections, parasitic infections or atrophic skin on the scalp, known or suspected anomaly of calcium homeostasis associated	Cacipotriol 50 µg/g plus betamethasone 0.5 mg/g (Xamiol) (N=568) **Formulation**: scalp gel **Frequency:** once daily	Betamethasone 0.5 mg/g (N=563) Cacipotriol 50 µg/g (N=286) **Formulation**: same vehicle as TCF **Frequency:** once daily ---------- **BOTH**	Treated for up to 8 weeks	IGA (clear/very mild) Patient's global assessment (clear or nearly clear) Withdrawals	Leo Pharma

double-blind, controlled trial. Br.J.Dermatol. 160 (1):170-176, 2009. Ref ID: VANDEKERKHOF2009	therapy • **Double blind** – states double blind but no details • **Allocation concealment**. Unclear • **Sample size calculation**. No stated • **ITT analysis** Yes (LOCF).		with clinically significant hypercalcaemia, severe renal insufficiency or severe hepatic disorders. **Mean baseline** / **TCF N = 568** / **Betamethasone N = 563** / **Calcipotriol N=286** Age, years (mean±SD): 48.5±16.4 / 47.9±16.4 / 48.7±16.2 Gender M/F%: 41.9/58.1 / 46.2/53.8 / 47.9/52.1 Race – white, n (%): 559 (98.4%) / 545 (96.8%) / 274 (95.8) TSS 0-15 (mean): 6.8±1.9 / 6.9±1.8 / 6.8±1.8 **Note:** the majority of patients had moderate-to-severe disease		**ARMS:** patients with 'absence of disease' on PGA could stop treatment at investigators discretion but were required to attend visits (could restart treatment if required)			
Effect Size Outcomes								

Mean weight of study medication used: 163.8 g for TCF; 177.2 g for betamethasone; 192.3 g for calcipotriol

Efficacy & time-to-effect

Investigators assessment

IGA week 8	**TCF** **N = 567**	**Betamethasone** **N = 562**	**Calcipotriol** **N=286**
Absence of disease (discontinued applications)	149 (26.2%)	123 (21.8%)	34 (11.9%)
Very mild	197 (34.7%)	193 (34.3%)	80 (28.0%)

IGA (absent/very mild)	**TCF** **N = 567**	**Betamethasone** **N = 562**	**Calcipotriol** **N=286**
Week 2	278 (49.0%)	216 (38.4%)	45 (15.7%)
Week 4	311 (54.9%)	287 (51.1%)	74 (25.9%)
Week 8 (primary	388 (68.4%)	343	124

outcome)		(61.0%)	(43.4%)

Patients assessment

Week 8	**TCF** **N = 567**	**Betamethasone** **N = 562**	**Calcipotriol** **N=286**
Clear/nearly clear	395 (69.6%)	337 (59.9%)	128 (44.7%)

Withdrawals

	TCF **N = 568**	**Betamethasone** **N = 563**	**Calcipotriol** **N=286**
Withdrawal due to adverse events	4	7	8
Withdrawal due to lack of efficacy	7	9	8

Author's conclusion

- The two-compound scalp formulation was well tolerated and more effective in the treatment of scalp psoriasis than either of its individual components in the same vehicle

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

								of funding
C. Buckley, V. Hoffmann, J. Shapiro, S. Saari, F. Cambazard, and M. Milsgaard. Calcipotriol plus betamethasone dipropionate scalp formulation is effective and well tolerated in the treatment of scalp psoriasis: a phase II study. Dermatology 217 (2):107-113, 2008. Ref ID: BUCKLEY2008	RCT (2-arm) Multicentre (international) SCALP PSORIASIS • **Randomised** Unclear • **Washout period**: see exclusion criteria • **Double blind** – not described • **Allocation concealment**. Unclear • **Sample size calculation**. No	Total N: **218**	**Inclusion criteria:** aged ≥18years; scalp psoriasis involving >10% of the scalp surface area; amenable to topical treatment with a maximum of 100 g medication/wk. **Mild to very severe** disease according to investigator's global assessment. **Exclusion criteria:** PUVA therapy within 4 wks before randomisation; UVB or grenz ray therapy or topical treatment of scalp psoriasis or other relevant skin disorder within 2 wks before randomisation; systemic therapies with possible effect on scalp psoriasis within 4 weeks before randomisation; erythrodermic or pustular psoriasis, known or suspected severe renal insufficiency or severe hepatic disorders. **Mean baseline** / **Calcipotriene + betamethasone N = 108** / **Betamethasone N = 110** Age, years (mean±SD): 48.4±16.5 / 48.4±14.4 Gender M/F: 43.5/56.5 / 46.4/53.6	**N=108** Calcipotriene 50 µg/g plus betamethasone dipropionate 0.5 mg/g **Formulation**: scalp gel **Frequency:** once daily **Amount of medication used:** The average weight of medication used was similar between the groups (17.3 g/week for the two	**N=110** Betamethasone dipropionate 0.5 mg/g **Formulation**: scalp gel (same vehicle) **Frequency:** once daily ---------- **BOTH ARMS:** study treatments applied topically to	Treated for up to 8 weeks (mean duration 6.1 weeks in combined and 6.8 weeks for mono-therapy)	IAGI (worse to cleared); treatment success measured by patient Adverse events and adverse drug reactions; compliance	LEO Pharma

	• **ITT analysis** Yes for efficacy, but not AEs. Primary outcome assessed ITT and PP • **Drop-outs/withdrawals** Combination: 47 (43.5%) Betamethasone: 33 (30.0%) **Note:** of these the number withdrawing according to the protocol owing to 'absence of disease' were Combination: 33 (30.6%) Betamethasone: 24 (21.8%) So the		Race (Caucasian%) 97.2% 98.2% Duration of scalp psoriasis, years (mean±SD) 16.0±15.5 13.2±12.0 TSS (mean ± SD) 6.79±1.53 6.81±1.63		compound group and 17.1g/week for the betamethasone group) and remained fairly constant throughout the trial.	affected areas of scalp once daily in the same vehicle			

	unplanned withdrawals were Combination: 14 (12.9%) Betamethasone : 9 (8.2%)							

Effect Size

Outcomes

Efficacy

	Calcipotriol + betamethasone **N = 108**	**Betamethasone** **N = 110**	Mean difference	95% CI	p-value
Treatment success (at least marked improvement on PAGI)	100 (92.5%)	91 (82.6%)	9.9%	1.3-18.7%	0.027

- The distribution of IGA at the end of treatment was in favour of the two compound scalp formulation, with 8.8% more patients achieving controlled disease in the two compound group than in betamethasone dipropionate group (95% CI: -2.0, 19.5; p=0.11)

Time to effect

- Both products showed a rapid onset of action, with an effect registered by change in TSS after 1 week of treatment
- Based on absolute change in TSS maximal effect was not achieved by the trial endpoint with either treatment

Withdrawals

	Calcipotriol + betamethasone **N = 108**	**Betamethasone** **N = 110**
Total	47	33
Total (not including due to absence of disease)	14	9
Adverse events	1	2
Treatment failure	0	2

Compliance

	Calcipotriene + betamethasone **N = 107**	**Betamethasone** **N = 110**
Fully compliant or missed <20% of applications	93 (86.1%)	103 (93.6%)

Authors conclusion

- The two-compound scalp formulation provided clinically significant improvements after 2 weeks and remained throughout the study period.
- The two-compound scalp formulation was well-tolerated and compliance was high.
- Calcipotriene plus betamethasone dipropionate scalp formulation was superior to betamethasone dipropionate alone

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Kragballe K et al. Efficacy and safety of calcipotriol plus betamethasone dipropionate scalp formulation compared with calcipotriol scalp solution in the treatment of scalp psoriasis: a randomized controlled trial. Br J Dermatol 2009; 161: 159-166.	RCT 17 centres in Belgium, Canada, Denmark, France and Sweden. SCALP PSORIASIS • **Setting:** out-patient • **Randomised** Assigned an exclusive randomisation code in ascending order (generation of code not stated); randomised 2:1 **Washout period**: 2-4 weeks	N= 312 **Drop-outs (don't complete the study): 40 (12.8%)** Group 1: 17 (8.2%) Group 2: 23 (21.9%) **Reasons:** not stated for all	**Inclusion criteria:** Scalp psoriasis amenable to topical treatment; 18 years old or over; clinical signs or prior diagnosis of psoriasis vulgaris on trunk and/or limbs; 10% or more of total scalp area involved; clinical signs (redness, thickness, scaliness) of at least "moderate" on one sign and at least "slight" on each of the other 2 signs; investigator's global assessment of disease **at least "moderate".** **Exclusion criteria:** Psoralen and ultraviolet A or Grenz ray therapy within 4 weeks; ultraviolet B within 2 weeks; biological therapies that could affect scalp psoriasis within 6 months; other systemic therapy that could affect scalp psoriasis within 4 weeks; topical treatment on the scalp within 2 weeks; or very potent (WHO group IV) corticosteroids elsewhere on body within 2 weeks; unstable forms of psoriasis or other skin diseases confounding psoriasis assessment; skin infections, infestations or atrophy or the scalp; abnormalities in calcium homeostasis; severe renal or hepatic disorders; concomitant use of medications	Group 1: 2-compound scalp formulation of calcipotriol 50 µg/g + betamethasone 0.5mg/g; maximum 100g per week (Xamiol) **Formulation**: scalp gel **Frequency:** once daily **Concomitant therapy:** No other topical treatments or emollients	Group 2: Calcipotriol scalp solution twice daily 60ml (50µg/ml) per week (Dovonex) **Formulation**: scalp solution **Frequency:** twice daily **Concomitant therapy:** No other topical treatments or emollients were allowed	Phase 1 = 8 weeks of treatment; then phase 2 = observation phase (entered if "clear" or "minimal" disease) of further 8 weeks	**Primary outcome:** clear or minimal disease at wk 8 on IGA scale: clear, minimal, mild, moderate, severe, very severe). **Secondary outcomes:** *Relapse* = recurrence of at least moderate disease according to IGA.	LEO Pharma

ID KRAGBALLE2009	• **Single blind** (investigator) • **Allocation concealment** – not stated • **Sample size calculation** Estimated sample size 160-185 patients in group 1 and 80-93 in group 2 for 90% power • **ITT analysis** Yes (LOCF) • **Drop-outs/withdrawals** 312 patients randomised (207 group 1 and 105 group 2); 190 + 82 completed treatment phase; 135 + 29 entered observation phase;		with a possible effects on scalp psoriasis; pregnant or breastfeeding. Group 1 / Group 2 Age (yr) mean (SD) range: 50.8 (15.3) 18-91 / 51.4 (15.6) 24-85 Men n (%): 90 (43.5%) / 44 (41.9%) Caucasian n (%): 205 (99.0%) / 104 (99.0%) Duration of psoriasis (yr): 18.4 (13.8) 0-62 / 19.3 (16.0) 1-70 Investigator's global assessment Moderate Severe: 113 (54.6%) / 64 (61.0%) Very severe: 78 (37.7%) / 34 (32.4%) 1`6 (7.7%) / 7 (6.7%) SF-36 score Physical: 51.4 (8.4 (22-67) / 52.3 (7.8) 30-63	were allowed			*Rebound* = 1-category increase in IGA from baseline. Adverse events	

	115 + 27 completed observation phase		Mental	50.2 (9.4) 22-69	51.0 (8.4) 26-67						
			Skindex-16 score	51.5 (23.6) 0-100	49.6 (21.0) 2-91						

Effect Size

Efficacy & time-to-effect

Treatment phase

	Group 1: 2-compound scalp formulation of calcipotriol + betamethasone	**Group 2: Calcipotriol scalp solution**	**Odds ratio (CI), p value**
Proportion of patients with 'clear' or 'minimal' disease according to IGA at week 2	125/207 (60.4%)	11/105 (10.5%)	-
Proportion of patients with 'clear' or 'minimal' disease according to IGA at week 4	114/207 (55.1%)	19/105 (18.1%)	-
Proportion of patients with 'clear' or 'minimal' disease according to **IGA** at week 8 (primary endpoint)	142/207 (68.6%)	33/105 (31.4%)	OR 5.4, 95% CI 3.1 to 9.4;p<0.001
Proportion of patients with 'clear' or 'very mild disease according to **patient's** assessment at week 8	170/207 (82.1%)	36/105 (34.3%)	OR 9.4, 95% CI 4.3 to 20.3;p<0.001
Withdrawals due to AE in treatment phase	2/207 (1.0%)	9/105 (8.6%)	
Skin atrophy	0/207	0/105	

Compliance (missed ≤10% of applications)	170/206 (82.5%)	82/102 (80.4%)	*Note: compliance data not available for all patients*

Time to maximum effect (based on mean TSS):

- Mean TSS plateaux after 2 wks for calcipotriol vs 4 wks for two-compound formulation
- Over the first 2 weeks of treatment , the mean TSS for the two compound formulation decreased more rapidly than for the calcipotriol scalp solution and remained below that of the calcipotriol scalp solution throughout the treatment period to week 8

Observation phase

	Group 1: 2-compound scalp formulation	**Group 2: Calcipotriol scalp solution**	**Odds ratio (CI), p value**
Relapse:			Not calculated (groups not randomised; far fewer entered from group 2)
number of patients	73/135 (54.1%)	10/29 (34.5%)	
median time to relapse	35 days	58 days	
meeting criteria for rebound	2 (1.5%)	0	

Authors conclusion

- Once daily 2-compound scalp formulation of calcipotriol + betamethasone significantly more effective than twice daily calcipotriol scalp solution with fewer adverse effects and a low rate of withdrawals for patients with moderate to severe scalp psoriasis, although it is not a cure and relapse may be expected.

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

								funding
Tyring S et al. A calcipotriene / betamethasone diproprionate two-compound scalp formulation in the treatment of scalp psoriasis in Hispanic/ Latino and Black/ African American patients: results of the randomized, 8-week, double-blind phase of a clinical trial. Int J Dermatol 2010; 49: 1328-1333.	**RCT** **DESIGN** Between patient Patient delivery **ALLOCATION** Random Method of randomisation: computer generated Concealment: unclear **BLINDING** double-blind • **Washout period:** 2 weeks • **Sample size calculation:** reported • **ITT analysis:** yes **Setting:** Outpatients	**Total N: 177** **Drop-outs (don't complete the study):** Total = 19 (10.7%): 14 in two-compound group and 5 vehicle group excluded for failure to apply medication correctly, no post-baseline data or use of excluded treatments; 7 and 4 provided no data on AEs; 27 (15.3%) withdrew: 19 (14.1%)	INCLUSION CRITERIA Age 18 or above; psoriasis involving at least 10% of the scalp and trunk/limbs; an investigator's global assessment of moderate, severe or very severe scalp psoriasis; participants who self-report their ethnicity as Hispanic or Latino, and their race as Black or African American; females of child-bearing potential must have a negative result for a urine pregnancy test before randomisation and must agree to use an adequate method of contraception during the study. EXCLUSION CRITERIA Erythrodermic, exfoliative or pustular psoriasis; skin infections/diseases; disorders of calcium metabolism; pregnancy/ breastfeeding; concurrent antipsoriatic treatment; chemical treatments of the hair BC: yes Mean age around 45 years (range 18-76) 44% male 99 Hispanic/ Latino (75 in two-	**n=135** **Calcipotriene / betamethasone diproprionate two-compound scalp formulation** **Formulation:** scalp gel **Class:** vitamin D analogue plus corticosteroid **Frequency:** once daily **Amount used:** maximum 40g/week; mean 12.5g/week (range 0.1 to 34.9) in the two-compound	**n=42** **Vehicle** **Formulation**: scalp gel **Frequency:** once daily	**Treatment duration:** 8 weeks **Assessments at:** every 2 weeks	Investigator global assessment (6-point scale where 1=absence of disease to 6=very severe disease); Investigator assessment of redness, thickness and scaliness, each on 0-4 scale (0=none to 4=very severe); adverse events; patient's global assessment (5-point scale where n=clear and 4=severe); compliance	

Ref ID: TYRING2010		in two-compound group and 8 (19.0%) in vehicle group Non-compliance: 78.5% of patients applied scalp formulation on at least 90% of days vs. 73.8% in vehicle group	compound group and 24 in vehicle group) and 78 Black/ African American (60 in two-compound group and 18 in vehicle group) Mean duration psoriasis around 11 years (range 1-50) Around 80% moderate and 20% severe/very severe scalp psoriasis Mean TSS around 6.3 (range 4-11)	group and 11.8g/week (range 0.0 to 28.8) in vehicle group; mean duration of exposure 7.6 weeks (range 0.1-15.6) in two-compound group and 7.4 weeks (0.0 to 14.0) in vehicle group			(returned medication bottles weighed); TSS ≤1 **Primary efficacy parameter:** proportion of patients with cleared/minimal disease by Investigator global assessment at week 8	
Effect Size Outcomes **<u>Efficacy</u>**								

ITT analysis	Calcipotriene / betamethasone dipropionate two-compound scalp formulation n=135	Vehicle n=42	Odds ratio (95% CI), p value
Proportion of patients with cleared/minimal disease by Investigator global assessment at week 8: Hispanic/ Latino Black/ African American	97 (71.9%) 49 (65.3%) of 75 patients 48 (80.0%) of 60 patients	17 (40.5%) 8 (33.3%) of 24 9 (50.0%) of 18	3.30 (1.62 to 6.72), p<0.001
Cleared/very mild disease by patient's global assessment	84 (62.2%)	15 (35.7%)	2.97 (1.11 to 7.93), p=0.004*

PP analysis	Calcipotriene / betamethasone dipropionate two-compound scalp formulation n=121	Vehicle n=37
Proportion of patients with cleared/minimal disease by Investigator global assessment at week 8:	97 (80.2%)	16 (43.2%)

* p values <0.01 considered significant for secondary criteria to account for multiplicity

Adverse events/ Withdrawals:

	Calcipotriene / betamethasone dipropionate two-compound scalp formulation n=135	Vehicle n=42	Odds ratio (95% CI), p value

ADR = adverse events possibly/probably related to treatment (none severe)	9 (7.0%) patients with 11 events	3 (7.9%) pts with 4 events	0.88 (0.23 to 3.44), p=1.00
Constipation	1 (0.8%)	0	
Dizziness	1 (0.8%)	0	
Dry skin	1 (0.8%)	0	
Dysgeusia	0	1 (2.6%)	
Folliculitis	1 (0.8%)	0	
Headache	1 (0.8%)	1 (2.6%)	
Hyperaesthesia	1 (0.8%)	0	
Hyperhidrosis	1 (0.8%)	0	
Hypoesthesia	1 (0.8%)	0	
Paraesthesia	2 (1.6%)	1 (2.6%)	
Skin irritation	1 (0.8%)	1 (2.6%)	
Serious AE unrelated to treatment	1 CVA; 1 nausea (withdrew); 1 nausea, tremor and depression (withdrew)	0	

No clinically significant changes in blood chemistry.

Time-to-effect: week 8 data only

Authors' conclusion

The two-compound calcipotriene / betamethasone dipropionate scalp formulation was safe and effective in the treatment of scalp psoriasis in Hispanic/ Latino and Black/ African American patients.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Luger TA, Cambazard F, Larsen FG, Bourcier M, Gupta G, Clonier F, et al. A Study of the Safety and Efficacy of Calcipotriol and Betamethasone Dipropionate Scalp Formulation in the Long-Term Management of Scalp Psoriasis. Dermatology 2008; Vol. 217, issue 4:321–8. **Ref ID: LUGER2008**	**RCT** **DESIGN** Between patient Patient delivery **ALLOCATION** Random Method of randomisation: computer generated Concealment: unclear **BLINDING** double-blind • **Washout period:** up to 28 days • **Sample size calculation :** not reported • **ITT analysis:** not stated	**Total N: 869** **Drop-outs (don't complete the study):** Total = 267 (30.7%); 92/429 (21.4%) of patients in two compound group and 175/440 (39.8%) in calcipotriol group, p<0.001 Noncompliance: 70.9% of patients in two compound	INCLUSION CRITERIA Age 18 or over; scalp psoriasis amenable to topical treatment with a maximum of 100g study medication per week; also clinical signs/previous diagnosis of psoriasis on trunk/limbs; psoriasis involving at least 10% of the scalp; an investigator's global assessment of moderate, severe or very severe scalp psoriasis. EXCLUSION CRITERIA Concurrent antipsoriatic treatment; disorders of calcium metabolism BC: yes Mean age around 49 years (range 18-86) 44% male 97% Caucasian Mean duration psoriasis around 17.5 years (range 1-72 years) Investigator assessment of disease severity: moderate: 55.5%; severe: 37.8%; very severe: 6.7%	**n=429** **Calcipotriol and Betamethasone Dipropionate Scalp Formulation** **Formulation:** Scalp gel **Class:** vitamin D analogue plus corticosteroid **Frequency:** once daily when required **Amount used:** mean weekly weight used 10.6g in two	**n=440** **Calcipotriol** **Formulation**: Scalp gel **Frequency:** once daily when required	**Treatment duration:** 52 weeks **Assessments at:** baseline and every 4 weeks	Adverse drug reactions (ADRs); any type of adverse event Investigator global assessment (6-point scale where 1=absence of disease to 6=very severe disease); patient's assessment (satisfactory or not satisfactory); compliance (medication used once or twice	LEO Pharma

	Setting: Outpatients	group >90% compliant vs. 58.9% in calcipotriol group		compound group and 12.8g in calcipotriol group; mean weight used over whole study period 470.8g and 440.0g; mean duration treatment 44 weeks and 37 weeks.			daily at all visits, or not used because not needed; weighing returned tubes) **Primary efficacy parameter:** Adverse drug reactions (ADRs); any type of adverse event	
Effect Size Outcomes								

Efficacy
Investigator global assessment: patients with absent/very mild/mild disease – only shown graphically

	Calcipotriol and Betamethasone Dipropionate Scalp Formulation **n=429**	**Calcipotriol** **n=440**	**p value**
median number of visits per patient with satisfactorily controlled disease (absent/very mild/mild disease)	92.3% of assessments	80.0%	p<0.001
Patient assessment satisfactory at every visit	76.2%	50.2%	p<0.001

Time-to-effect: number of patients with absent/very mild/mild disease started at each 4-week assessment displayed graphically but unclear

Adverse events:

No skin atrophy reported.

Withdrawals

	Calcipotriol and Betamethasone Dipropionate Scalp Formulation **n=429**	**Calcipotriol** **n=440**	**p value**

Withdrawal due to unacceptable treatment efficacy	14 (3.3%)	51 (11.6%)	
Withdrawal due to AEs	9 (2.1%)	44 (10.0)	
Death	1 (0.2%)	1 (0.2%)	
Exclusion criteria	5 (1.2%)	15 (3.4%)	
Lost to follow up	26 (6.1%)	29 (6.6%)	
Other reasons (personal/dissatisfaction with cosmetic appeal/unable to attend visits)	24 (5.6%)	47 (10.7%)	
Voluntary	17 (4.0%)	18 (4.1%)	
Total withdrawals (patients could have >1 reason)	92 (21.4%)	175 (39.8%)	p<0.001

Authors' conclusion

The Calcipotriol and Betamethasone Dipropionate Scalp Formulation demonstrated high levels of safety and efficacy in long-term management of scalp psoriasis.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Jemec GBE et al. Significant one week efficacy of a calcipotriol plus betamethasone dipropionate scalp formulation. JEADV 2011; 25: 27-32 **Ref ID: JEMEC2011**	**Pooled data from 2 phase III RCTs** **DESIGN** Between patient Patient delivery **ALLOCATION** Random Method of randomisation: not stated Concealment: unclear **BLINDING** Double-blind • **Washout period:** 2 weeks • **Sample size calculation** not reported • **ITT analysis:** not stated	**Total N: 2920** **Drop-outs (don't complete the study):** Total = 40 (1.4%): 15 two-compound group; 14 betamethasone group; 10 calcipotriol group; 1 vehicle group plus withdrawal due to AEs in first week: two-compound group 5 (0.5%); betamethasone group	INCLUSION CRITERIA Adults with >10% of the scalp affected by mild to very severe psoriasis; scalp psoriasis amenable to topical treatment with maximum 100g/week; 1 or more clinical signs (redness, thickness or scaliness) with a score of at least 2 (moderate) and a score of at least 1 (slight) for the remaining 2. EXCLUSION CRITERIA Very potent corticosteroids and, in study 1, vitamin D analogues BC: Yes Age: median around 50 years (range: 18 to 97) Gender (%M): around 45% Ethnicity: around 97% Caucasian Severity: around 8% mild; 55% moderate; 31% severe; 6% very severe; mean TSS around 6.8 at baseline Duration (median around 12 years):	**n=1108** **Calcipotriol 50µg/g and Betamethasone 0.5mg/g as dipropionate** **Formulation:** scalp formulation **Class:** vitamin D analogue plus corticosteroid **Frequency** once daily **Amount used:** mean in first week: 21.6g in	**a) Betamethasone 0.5mg/g as dipropionate: n=1118; b) Calcipotriol 50µg/g: n=558; c) vehicle: n=136** **Formulation**: scalp formulation **Frequency** once daily Study 1: all 4 groups; study 2: no vehicle	**Treatment duration:** 8 weeks **Assessments at:** 1 week and 8 weeks **Follow-up after end of treatment:** none	Investigator global assessment (6-point scale where 1=absence of disease to 6=very severe disease); endpoint absent or very mild disease. Patient's overall assessment of treatment response on a 7-point scale from 1=cleared to 7=worse; endpoint cleared or almost	Leo Pharma A/S

	Setting: Outpatients	2 (0.2%); calcipotriol group 13 (2.4%); vehicle group 2 (1.5%)	(range: 0 to 72)	two-compound group; 22.9g betamethasone group, 23.4g calcipotriol group and 24.4g in vehicle group	group		clear. **Primary efficacy parameter:** not stated	

Effect Size

Outcomes

<u>Efficacy</u>

At 1 week:

	two-compound group (n=1108)	betamethasone group (n=1118)	calcipotriol group (n=558)	vehicle group (n=136)
Absent/very mild disease (Investigator global assessment)	331 (30.6%) p<0.001 vs. all other groups	262 (24.1%)	54 (10.0%)	9 (6.9%)
Clear/almost clear (patient assessment)	200 (18.5%) p<0.001 vs. all other groups	148 (13.6%)	22 (4.1%)	5 (3.8%)

Time-to-effect (TCF)

Effect seen at week 1; almost 90% of total response seen by week 2 (64.0% reduction in TSS in two-compound group) with small additional improvement up to week 8 (73.3% reduction in TSS in two-compound group) – data not shown for other groups.

Adverse events Withdrawals:

	two-compound group (n=1108)	betamethasone group (n=1118)	calcipotriol group (n=558)	vehicle group (n=136)
Pruritis	15 (1.4%)	4 (0.4%)	22 (4.0%)	3 (2.2%)
Burning sensation	2 (0.2%)	4 (0.4%)	5 (0.9%)	0
Skin burning sensation	2 (0.2%)	0	1 (0.2%)	0
Skin irritation	1 (0.1%)	1 (0.1%)	6 (1.1%)	1 (0.7%)
Paraesthesia	1 (0.1%)	1 (0.1%)	2 (0.4%)	0
Alopecia	0	3 (0.3%)	1 (0.2%)	0
Psoriasis	0	1 (0.1%)	2 (0.4%)	0
Erythema	0	0	6 (1.1%)	0
Dermatitis contact	0	0	2 (0.4%)	1 (0.7%)
Total number of patients with lesional/perilesional AE	27 (2.5%)	22 (2.0%)	53 (9.7%)	5 (3.7%)
Withdrawal due to AEs	5 (0.5%)	2 (0.2%)	13 (2.4%)	2 (1.5%)

Authors' conclusion

The two-compound group demonstrated efficacy at week 1 with a faster onset of effect than either of the individual components in the same vehicle in the treatment of scalp psoriasis.

H.7.2 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
P. Reygagne, U. Mrowietz, J. Decroix, de Waard-van der Spek FB, L. O. Acebes, A. Figueiredo, R. Caputo, M. Poncet, and S. Arsonnaud. Clobetasol propionate shampoo 0.05% and calcipotriol solution 0.005%: a randomized comparison of efficacy and safety in subjects with scalp psoriasis. J.Dermatol.Treat. 16	RCT Multicentre SCALP PSORIASIS • **Randomised** Computer-generated. • **Washout period**: not stated • **Single blind** – investigator (adequately described) • **Allocation concealment**. Unclear	Total N: **151** **Drop-outs (don't complete the study): 14** 3 (3.9%) on clobetasol and 11 (14.7%) on calcipotriol **Reasons** 7 in calcipotriol group due to AEs **Protocol deviations:** 9 in clobetasol	**Inclusion criteria:** aged ≥ 12 years; **moderate-to-severe** scalp psoriasis (GSS at least 3/5 and affected area at least 2 cm^2 of scalp. **Exclusion criteria:** Very severe scalp psoriasis requiring systemic treatment, known allergy to any study intervention; immunosuppression; history of adverse response to topical or systemic steroid therapy **Mean baseline** / **Clobetasol propionate N = 76** / **Calcipotriol N = 75** Age, years (mean±SD): 44.9±16.8 / 45.7±17.4 Gender M/F: 49/51 / 45/55 TSS (mean ± SD): 4.86±1.95 / 4.95±1.49	Clobetasol propionate shampoo 0.05% (N=76) **Formulation**: shampoo **Frequency:** once daily (to a dry scalp – rinse off after 15 mins)	Calcipotriol solution 0.005% (N=75) **Formulation**: scalp solution **Frequency:** twice daily (to a dry scalp – without rinsing) ---------- **BOTH ARMS:** concomitant use of	Treated for 4 weeks	Assessed at baseline, week 2 and week 4 **1° outcomes:** Global and total severity scores (GSS and TSS) GSS: 0 (none) to 5 (very severe) **2° and other outcomes:** IAGI (worse	Galderma R&D

(1):31-36, 2005. Ref ID: REYGAGNE2005	• **Sample size calculation**. Yes. 50 per group gives 90% power to detect a 1.5 point difference on TSS at a two-sided 5% significance level • **ITT analysis** Yes for efficacy, but not AEs.	group and 14 in calcipotriol group excluded from per protocol analysis	GSS (mean ± SD) 3.49±0.60 3.51±0.60 % scalp area affected (mean ± SD) 46±28 44±28			topical or systemic psoriasis treatments (except emollients, tars or salicylic acid for other sites) or drugs that could aggravate psoriasis (b-blockers, lithium, anti-malarials or NSAIDs) not permitted		to cleared); Adverse events	

Effect Size

Outcomes

Efficacy (ITT population: clobetasol propionate N = 76 calcipotriol N = 75)

	Clobetasol propionate **N = 76**	**Calcipotriol** **N = 75**	**p-value**
% clear or nearly clear at wk 4 on	38 (50%)	21 (28.4%)	0.003

IAGI			
% clear or nearly clear at wk 4 on **PAGI**	36 (47.3%)	23 (31.1%)	0.009

Time to effect

- Graphical representation of mean TSS over time shows that clobetasol propionate acts more quickly, with a large effect by week 2 which begins to slow between weeks 2-4. Calcipotriol has a more constant reduction in mean TSS, which has not reached a plateau by the end of the trial (4 weeks)

Withdrawals

	Clobetasol propionate **N = 76**	**Calcipotriol** **N = 75**
Withdrawal due to adverse events	0	7

Adverse events

Skin atrophy, n (%)	**Clobetasol propionate**	**Calcipotriol**
Baseline	**N = 76**	**N = 75**

Edge of scalp	3 (3.9%)	**0**
Face	5 (6.6%)	**0**
Neck	1 (1.3%)	**2 (2.7%)**
Week 4 *	**N = 74**	**N = 64**
Edge of scalp	1 (1.4%)	0
Face	4 (5.4%)	0
Neck	1 (1.4%)	1 (1.6%)

Authors conclusion

- Short contact therapy of scalp psoriasis with this new shampoo formulation of clobetasol propionate was significantly more effective and better tolerated than calcipotriol solution for the treatment of scalp psoriasis.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Klaber MR, Hutchinson PE, Pedvis-Leftick A, Kragballe K, Reunala TL, Van de Kerkhof PC, Johnsson MK, Molin L, Corbett MS, Downess N. Comparative effects of calcipotriol solution (50 micrograms/ml) and betamethasone 17-valerate solution (1 mg/ml) in the treatment of scalp psoriasis. *Br J Dermatol*. 1994;131(5):	Multicentre (Canada, Denmark, Finland, the Netherlands, Norway, Sweden, UK) SCALP PSORIASIS DESIGN Between patient Patient delivery ALLOCATION Random Method of randomisation: (method unclear) Concealment: unclear BLINDING	N=474 **Drop-outs (don't complete the study):** N=29 (6.1%): 20 (8.3%) calcipotriol; 9 (3.8%) betamethasone **Reasons:** N=13 Adverse events (N=11 calcipotriol; N=2 betamethasone) N=6 unacceptable treatment	**INCLUSION CRITERIA** Adults; stable, mild-to-moderate scalp psoriasis; history of psoriasis on body **EXCLUSION CRITERIA** More extensive, severe or infected psoriasis; recent systemic antipsoriatic treatment or UV; concurrent vitamin D, calcium or other relevant medication; significant hepatic or renal disease; hypercalcaemia; risk of pregnancy; pregnancy; lactation [illegible]	N=240 Calcipotriol solution (50 µg/ml) **Formulation**: scalp solution **Frequency:** Twice daily (maximum amount allowed was 60 ml) **Amount of medication used:** Patients used a mean (±SD) of 31.5 (±16.9) ml per week in the calcipotriol	N=234 Betamethasone 17-valerate solution (1 mg/ml) **Formulation** scalp solution **Frequency:** Twice daily (maximum amount allowed was 60 ml)	Double-blind treatment duration: 4 weeks (evaluated at 1, 2, 4 weeks). After this time, patients who required no further treatment were observed for 4 weeks for relapse. Retreatment for further 6 weeks	Assessment of extent of scalp psoriasis (graded 0-5) Total sign score (erythema, thickness, scaliness [each graded 0-4 for overall score of 0 to 12]) Investigator global assessment (5-pt: worse to cleared)	Leo Pharmaceutical Products, Denmark

	Calcipotriol (n=240)	Betamethasone (n=234)
Age (years) Mean (SD) Range	45.2 (15.9) 18 – 90	42.9 (15.5) 18 – 83
Sex Males (%) Females (%)	53.3 46.7	49.6 50.4

678-83. REF ID: KLABER1994	Double-blind (patient / assessor) WITHDRAWAL / DROPOUT Described • **Setting:** Not stated • **Washout period**: 2 weeks • **Sample size calculation** Yes. Study designed to detect an absolute difference of 10% with a power of 80% and a significance level of 5% between the two treatment arms with respect to the proportion of	response (N=4 calcipotriol; N=2 betamethasone) N=10 default (N=5 calcipotriol; N=5 betamethasone)	Duration of scalp psoriasis (years) Mean (SD) Range 13.1 (11.0) 0.1 – 52.0 13.1 (11.3) 0.1 – 67.0 Score for extent Mean (SD) Range 2.7 (1.3) 1 – 5 2.8 (1.3) 1 – 5 Total sign score* Mean (SD) Range 6.4 (1.7) 3 – 12 6.6 (1.7) 2 – 12 *Sum of scores for erythema, thickness and scaliness	group, and 27.1 (±17.5) ml per week in the betamethasone group (p=0.014).		was offered to patients who relapsed and who were originally in the calcipotriol-treated group	Patient global assessment (5-pt: worse to cleared) Adverse events Compliance Relapse rate	

	patients who attain either clearance or marked improvement according to investigators overall assessment • **ITT analysis** Yes (adverse events); No (efficacy)							

Effect Size

Outcomes

<u>Efficacy</u>

	Calcipotriol (n = 236)	Betamethasone (n = 232)	95% CI of difference	P value
Investigator global assessment at week 4 'marked improvement or cleared'	138 (58.5%)	175 (75.4%)	25.3 – 8.6	<0.001
Patient global assessment at week 4 'marked improvement or cleared'	136 (57.6%)	171 (73.7%)	24.6 – 7.6	<0.001

Time to effect

Score for extent and total sign score decreased significantly from baseline at week one (and all subsequent time points) for both treatment groups (displayed graphically).

Time to max effect

TSS had not reached a minimum for either treatment group at week 4

Compliance

Compliance was good in both groups and >90% of patients were fully compliant at each follow-up visit. Patients used a mean of 31.5 (±16.9) ml per week in the calcipotriol group and 27.1 (±17.5) ml per week in the betamethasone group (p = 0.014)

Toxicity

Prematurely discontinued treatment

	Calcipotriol (n = 240)	Betamethasone (n = 234)
Adverse event s	11 (4.6%)	2 (0.85%)
Unacceptable treatment response	4 (1.7%)	2 (0.85%)
Default	5 (2.1%)	5 (2.1%)

Adverse events

	Calcipotriol (n = 240) No. of adverse events (%)	Betamethasone (n = 234) No. of adverse events (%)	P
Lesional or perilesional irritation	62 (25.8)	19 (8.1)	<0.001
Facial irritation	27 (11.3)	1 (0.4)	<0.001
Various skin reactions	6 (2.5)	9 (3.08)	NS
Non-cutaneous	3 (1.2)	6 (2.5)	NS
No. of patients reporting ≥1 adverse event	87 (36.3)	31 (13.2)	<0.001

There were no consistent or clinically important differences between the calcipotriol- and betamethasone-treated groups with regard to haemopoietic, liver or renal function. In particular there was no change in the mean serum total calcium in either group during the double-blind treatment.

Post treatment follow-up and re-treatment

	Calcipotriol (n = 99)	Betamethasone (n = 129)	95% CI of difference	P value
Relapse rate after 4 weeks observation (defined as an increase in the total sign score to at least 50% of the score at the start of double-blind treatment)	75 (75.8%)	102 (79.1%)		NS
Received retreatment with calcipotriol for 6 weeks	n = 69			
Patient global assessment at end of retreatment 'marked improvement or cleared'	82.6%			
TSS Mean % reduction in score from relapse to end of	60.1%		51.8 – 68.4	<0.001

retreatment				

There was no change in serum calcium during retreatment

Summary

- Calcipotriol solution was effective in treating mild to moderate scalp psoriasis. However, betamethasone solution was significantly more effective, and was associated with statistically significantly less local irritation on the scalp and face

H.7.3 VITAMIN D OR VITAMIN D ANALOGUE VS TAR

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Klaber MR, McKinnon C. "Calcipotriol (DovonexR) scalp solution in the treatment of scalp psoriasis: Comparative efficacy with 1% coal tar/1% coconut oil/0.5% salicylic acid (CapasalR) shampoo, and long-term experience." *Journal Of Dermatologi*	Multicentre SCALP PSORIASIS • **Setting:** hospital out-patients and primary care patients • **Randomised** method unclear • **Washout period**: not stated • **Blinding** No. Open study	N: 475 **Drop-outs (don't complete the study):** N =141: 72 (30.3%) calcipotriol ; 69 (29.1%) tar **Reasons:** N=32 Loss to follow-up (N=12 Calcipotriol ; N=20 Coal tar). N=20 stopping medication	**INCLUSION CRITERIA** **Mild or moderate** scalp psoriasis; ≥18 years old **EXCLUSION CRITERIA** Other forms of psoriasis; topical antipsoriatic treatment within previous 2 wks; systemic antipsoriatic treatment or UV therapy within previous 4 wks; concomitant vitamins, calcium or other medications that could affect the course of psoriasis; known hypersensitivity to study medications; pregnancy; inadequate contraception; lactation; hypercalcaemia; significant renal or hepatic disease **Mean baseline** / **Calcipotriol N = 238** / **Coal Tar N = 237** Age, years (mean±SD): 45.8±15.6 / 44.7±16.1	N=238 Calcipotriol solution, 50 µg/g, (Dovonex®) **Formulation**: scalp solution **Frequency:** twice daily (to a dry scalp after washing)	N=237 Coal tar,1%, coconut oil, 1%, salicylic acid, 0.5%, shampoo (Capasal®) **Formulation** : shampoo **Frequency:** once daily (leave for a few minutes before washing out) **Note:** Alphosyl HC	Treatment duration: 8 weeks. + 16 weeks further treatment for those who received calcipotriol scalp solution and showed at least slight improvemen t	IAGI (6 pt: worse to cleared) Patients global assessment of disease severity (VAS) AEs	Leo Pharmac euticals

cal Treatment 2000;**11**(1):21–8. REF ID:MCKINNON2000	• **Allocation concealment**. Unclear • **Sample size calculation**. Unclear • **ITT analysis** No	for >7 days (N=16 Calcipotriol; N=4 Coal Tar) Plus 35 and 16 for calcipotriol and coal tar respectively for adverse events (Note: may be classified under >1 reason)	Gender M/F% 52/48 52/48 TSS (mean ± SD) (0-12) 5.1±1.4 5.0±1.6 Caucasian 98.3% 98.3%			was applied twice daily to any psoriasis on the trunk and limbs in this group			

Effect Size

Outcomes

Efficacy (available case analysis)

0-8 weeks	**Calcipotriol (n=210)**	**Coal Tar (n=213)**	**OR (95% CI)**	**p-value**
IAGI (at least moderate improvement) (6 pt: worse to cleared)	120 (57%)	79 (37%)	3.2 (2.0-5.2)	<0.001

- N = 166 Calcipotriol-treated patients, who had shown at least slight improvement entered the long-term treatment phase. For these patients, the mean change in TSS from baseline to 8 weeks was -2.2 and week 8 to 24 was -1.0. p<0.05 16 versus 8 weeks.

Time to effect

- During the 8 wk comparative phase graphical information shows that based on change in TSS both treatments had not reached maximum effect by the end of 8 weeks
- Over the long-term treatment phase graphical information shows that based on change in TSS calcipotriol reaches maximal effect by 12 weeks, with only slight further improvement up to 24 wks (<0.5 point reduction on TSS over 12 weeks)

Toxicity

	Calcipotriol (8wks) **N=230** (during comparative treatment)	**Coal Tar** **N=215** (during comparative treatment)	**Calcipotriol (16wks)** **N=166** (long-term treatment)
Withdrawal due to adverse events	35 (15.2%)	16 (7.4%)	6 (3.6%)

Summary

- Calcipotriol scalp solution is more effective than a coal tar-based shampoo and shows continued efficacy and good tolerability with long-term use.

H.7.4 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
Green C, Ganpule M, Harris D, Kavanagh G, Kennedy C, Mallett R, et al. Comparative Effects of Calcipotriol (Mc903) Solution and Placebo (Vehicle of Mc903) in the Treatment of Psoriasis of the Scalp. *British Journal Of Dermatology* 1994;130(4): 483–7. **Ref ID: GREEN1994**	**RCT** **DESIGN** Between patient Patient delivery **ALLOCATION** Random Method of randomisation: not reported Concealment: unclear **BLINDING** Double-blind (patient / investigator) • **Washout period:** 2 weeks • **Sample size calculation** not stated • **ITT analysis:** yes	**Total N:** 49 **Drop-outs (don't complete the study):** Total = 3 (6.1%) 1 active group had local side effects of erythema, itching and scalp flaking; 2 in placebo group withdrew due to inadequate response	INCLUSION CRITERIA Mild to moderate scalp psoriasis and a history of psoriasis elsewhere on the body; adult. EXCLUSION CRITERIA Excessively thick scalp psoriasis. Other scalp disease; marked deterioration of scalp psoriasis at entry; recent systemic or UV therapy; concurrent topical corticosteroid use; vitamin D or calcium supplement; medications which could affect the course of the disease; hypercalcaemia; hepatic or renal disease; at risk of pregnancy BC: unclear (not reported in full; only reported as "well matched at baseline for age, sex, history of psoriasis and extent and severity of scalp psoriasis) Age: not reported Gender (%M): not reported	**n=25** **Calcipotriol solution, 50mcg/ml, BD** **Formulation:** solution **Class:** vitamin D analogue **Frequency:** twice daily **Amount used:** not stated	**n=24** **Placebo (vehicle)** **Formulation**: solution **Frequency:** twice daily	**Treatment duration:** 4 weeks **Assessments at:** week -2, 0, 1, 2 and 4 **Follow-up after end of treatment:** none	Investigator global assessment (Extent of psoriasis: 0=none to 5=80-100%; treatment response: -1 worse, no change, slight improvement, marked improvement, cleared)) Patient global assessment and scalp flaking/ itching (0-3 scale)	Leo Pharmaceutical Products

	Setting: Outpatients		Severity: mean TSS (0 to 12): 6.7				**Primary efficacy parameter:** not stated	

Effect Size

Outcomes

<u>Efficacy</u>
Results presented graphically

	Calcipotriol N=25	**Placebo N=24**	**95% CI for difference**	**p value**
Investigator global assessment			19.0 to 67.6	<0.001
Patient global assessment			18.3 to 68.0	<0.001
IAGI (Clearance or marked improvement)	15 (60%)	4 (17%)		
PAGI (Clearance or marked improvement)	Only reported graphically			

Time-to-effect: Mean TSS still reducing at week 4

Withdrawals

Withdrawal due to inadequate response	2 in placebo group
Withdrawal due to AEs	1 active group had local side effects of erythema, itching and scalp flaking

Authors' conclusion

Calcipotriol was superior to Placebo in reducing redness, thickness, scaliness, extent of psoriasis, and scalp flaking and itching.

H.7.5 PIMECROLIMUS VS PLACEBO

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
C. Gribetz, M. Ling, M. Lebwohl, D. Pariser, Z. Draelos, A. B. Gottlieb, N. Zaias, D. M. Chen, A. Parneix-Spake, T.	RCT Multicentre (7 centres in USA) INVERSE/FLEXURAL	Total N: **57** **Drop-outs (don't complete the study): 6** 2 (7.1%) on pimecrolim	**INCLUSION CRITERIA** Stable, chronic plaque psoriasis; **moderate to severe** inverse psoriasis affecting axillae, inguinal, inframammary or gluteal cleft regions (duration ≥ 6 months); PGA ≥ 3; erythema ≥2; aged ≥ 18 **EXCLUSION CRITERIA**	(N=28) **Pimecrolimus** 1% (Elidel®) **Formulation**: cream	(N=29) **Placebo/vehicle of identical appearance** **Formulation**	Treated for 8 weeks	IGA score : recorded at each visit using a 5 point scale: 0(clear)=no signs of inverse psoriasis	Novartis Pharmaceuticals Group

Hultsch, and A. Menter. Pimecrolimus cream 1% in the treatment of intertriginous psoriasis: a double-blind, randomized study. J.Am.Acad.Dermatol. 51 (5):731-738, 2004. Ref ID: GRIBETZ2004	PSORIASIS DESIGN Between patient Patient delivery ALLOCATION Random Method of randomisation: 'validated system that automates the random assignment of treatment codes'. Concealment: Adequate (randomisation code kept confidential) BLINDING Double-blind (patient / investigator); adequately defined • **Washout period**: 'appropriate' washout period of other medications	us and 4 (13.8%) on placebo **Reasons** See below	Clinically significant laboratory abnormalities; hypersensitivity to study drug or vehicle; systemic, phototherapy or immuno-modifying agents within previous 30 dys; topical therapies within previous 14 dys; unstable plaque psoriasis, pustular, drug associated or erythrodermic psoriasis BC: Yes Age: 47.8 (range: 21 to 88) Gender (%M): 50.9% Severity: PGA, % moderate: 72% PGA, % severe: 29.8% TSS: 5.34 (range: 3.0 to 9.0)	**Frequency:** twice daily (~12h apart)	: cream **Frequency:** twice daily (~12h apart) ---------- **BOTH ARMS:** study medication applied to all study sites areas; no concomitant medications in intertriginious areas (except bland emollients) **Concomitant** use of existing topical therapies		except for residual discolouration; 1 (almost clear)=just perceptible erythema, no induration, and no scaling; 2 (mild disease)=mild erythema, no induration, and mild or no scaling; 3 (moderate disease)=moderate erythema, mild induration, and mild or no scaling; and 4 (severe disease)= severe erythema,	

	(see exclusion criteria) • **Sample size calculation**. No • **ITT analysis** Yes – LOCF (including all randomised patients who took at least one dose of study medication and had at least one post-baseline efficacy assessment).				(low-to-mid potency corticosteroids, tazarotene and calcipotriene) allowed to non-study sites		moderate to severe induartion, and mild or no scaling; and 4 (severe disease)= severe erythema, moderate to severe induartion and scaling of any degree. Adverse events (including skin atrophy) and withdrawals	
Effect Size Outcomes								

Efficacy (ITT population)

IGA (Investigators Global Assessment) & time to effect

Percentage of patients with IGA score 0 or 1 at each visit (0=clear, 1=almost clear)	**Pimecrolimus** **N=28**	**Vehicle** **N=29**	**p-value**
baseline	**0**	**0**	
Day 3	**14.3**	**0**	**p=0.04**
Day 7	**35.7**	**13.8**	**P=0.07**
Week 2	**53.6**	**20.7**	**P=0.01**
Week 4	**64.3**	**20.7**	**p=0.001**
Week 6	**67.9**	**17.2**	**P<0.0001**
Week 8	**71.4**	**20.7**	**P<0.0001**

Withdrawals

	Pimecrolimus (N=28)	**Placebo** **N=29**

Withdrawal due to adverse events	0	0
Withdrawal due to lack of efficacy	1	2
Withdrawal (other)	1	2

Adverse events

	Pimecrolimus (N=28)	**Placebo** **N=29**
Skin atrophy, n (%)	**0**	**0**

Authors conclusion

- Pimecrolimus cream 1% is an effective treatment for inverse psoriasis with a rapid onset of action, and is safe and well-tolerated.

H.7.6 TACROLIMUS VS PLACEBO

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lebwohl M, Freeman AK, Chapman MS, Feldman SR, Hartle JE, Henning A; Tacrolimus Ointment Study Group. Tacrolimus ointment is effective for facial and intertriginous psoriasis. *J Am Acad Dermatol.* 2004;51(5):723-30. REF ID: LEBWOHL2004	Multicentre (USA) FACIAL AND INTERTRIGINOUS PSORIASIS DESIGN Between patient Patient delivery ALLOCATION Random Method of randomisation: not reported Concealment: unclear BLINDING Double-blind	N=167 **Drop-outs (don't complete the study):** N=30 (18%): 14 (12.5%) tacrolimus; 16 (29.1%) vehicle **Reasons:** N=1 adverse event – non-treated area (N=1 vehicle). N=6 lack of efficacy (N=6 vehicle).	**INCLUSION CRITERIA** Age limit unclear (stated as ≥2 and ≥16); chronic plaque psoriasis affecting intertriginous and facial skin; disease stable or slowly worsening for ≥1 wk; target lesion of moderate erythema and TSS (0 to 12) ≥4 **EXCLUSION CRITERIA** Systemic therapy or phototherapy within previous four wks; topical therapy within previous two wks; inhaled / intranasal corticosteroids within previous two wks; other topical agents (excluding sunscreen)within previous one day; recently diagnosed (< six months) or recent exacerbation of inverse psoriasis; uncontrolled chronic co-morbidity; pregnancy; lactation; previous use of tacrolimus ointment for facial or intertriginous psoriasis [illegible] | Tacrolimu | Vehicle	N=112 0.1% tacrolimus ointment **Formulation**: Ointment **Frequency:** Twice daily (thin layer of ointment to all areas of active disease on the face or intertriginous areas as defined by the investigator at baseline)	N=55 Vehicle **Formulation** Ointment **Frequency:** Twice daily (thin layer of ointment to all areas of active disease on the face or intertriginous areas as defined by the investigator at baseline)	Treatment duration: 8 weeks (evaluated: days 1, 8, 15, 29, 43, 57 or end of treatment)	Inverse psoriasis severity score (Static Severity Score; SSS) (6 pt: clear to very severe) IAGI ('PGA')(7 pt: exacerbation to clear) Adverse events Withdrawals	Fujisawa Healthcare, Inc

	(patient / investigator) WITHDRAWAL / DROPOUT Described • **Setting:** Not stated • **Washout period**: see exclusion criteria • **Sample size calculation**. Not stated • **ITT analysis** Yes. All patients received at least one dose of study drug and had ≥1 follow-up visit and were included in analysis	N=11 Lost to follow-up (N=7 tacrolimus; N=4 vehicle). N=12 Other reasons(including patient decision, non-compliance and ineligibility) (N=7 tacrolimus; N=5 vehicle)		s ointment (n = 112)	(n = 55)	**Note:** Patients were instructed to continue topical treatment of their plaque-type psoriasis in other body-sites with their current treatment regimen The use of lithium, tricyclic antidepressants, beta-blockers and oral antihistimines was permitted during study if patient was receiving stable dose at baseline.				
			Gender Male Female	70 (62.5%) 42 (37.5%)	28 (50.9%) 27 (49.1%)					
			Race White African America Other	96 (85.7%) 8 (7.1%) 8 (7.1%)	46 (83.6%) 6 (10.9%) 3 (5.5%)					
			Age (y) Mean ± SD	48.0±15.7	48.0±15.6					
			Static severity score Median range	3 (1.5–5)	3 (1.5–4.5)					
			Concurrent plaque-type lesions	96 (85.7%)	46 (83.6%)					

Effect Size

Outcomes

Efficacy

	Tacrolimus ointment (n = 112)	Vehicle (n = 55)	P value
PGA Clinical improvement ≥90% (excellent improvement or clearing) at day 57	66.7%	36.8%	= 0.002
SSS Clear or almost clear at day 57	73 (65.2%)	17 (31.5%)	<0.0001
Total disease signs and symptoms score of 0 at day 57	45.5%	11.1%	<0.0001

Disease signs and symptoms score for the target lesions at the end of the study

	Tacrolimus ointment (n = 112)	Vehicle (n = 54)	P value
Erythema	0.5	1.8	<0.0001

Induration	0	1.0	<0.0001
Desquamation	0	1.0	<0.0003
Overall severity	0.5	1.5	<0.0001

Time to effect

Tacrolimus ointment was associated with significant improvements on the PGA and SSS at day 8 (first evaluation after baseline) in 24.8% compared with 6% in vehicle group.

	Tacrolimus ointment (n = 112)	Vehicle (n = 55)	P value
PGA Clinical improvement ≥90% (excellent improvement or clearing) at day 8	24.8%	6%	= 0.004
SSS	Not stated	Not stated	= 0.001

Time to max effect

Percentage of patients with rating of 'excellent improvement' or 'clearing' for PGA was highest for both vehicle and tacrolimus ointment at day 57 (displayed graphically); although there was only modest improvement (<5% increase in numbers achieving success) from day 29.

Toxicity

Prematurely discontinued treatment

	Tacrolimus ointment (n = 112)	Vehicle (n = 55)
Adverse event – treated area	0	0
Adverse event – non-treated area	0	1 (1.8%)
Lack of efficacy	0	6 (10.9%)
Lost to follow-up	7 (6.3%)	4 (7.3%)
Other*	7 (6.3%)	5 (9.1%)

*Other reasons include patient decision, non-compliance and ineligibility

Incidence rate of reported or observed drug-related adverse events occurring in >2% of the study population

	Tacrolimus ointment (n = 112)	Vehicle (n = 55)	P value
Burning or stinging	9 (8.0%)	4 (7.3%)	1.00
Hyperesthesia	5 (4.5%)	0	0.17
Itching	8 (7.1%)	1 (1.8%)	0.27

These three adverse events occurred on average within the first three days of treatment for both treatment groups, excluding burning/stinging in the tacrolimus ointment-treated group, which had a mean time to onset of 10 days.
There were no reports of cutaneous infections or systemic adverse events

Authors conclusion

- Tacrolimus ointment (0.1%) is an effective treatment for psoriasis of the face or intertriginous areas

H.7.7 TACROLIMUS 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
Y. H. Liao, H. C. Chiu, Y. S. Tseng, and T. F. Tsai. Comparison of cutaneous tolerance and efficacy of calcitriol 3 microg g(-1) ointment and tacrolimus 0.3 mg g(-1) ointment in chronic plaque psoriasis involving facial or genitofemoral areas: a double-blind, randomized controlled trial. Br.J.Dermatol. 157	RCT Single centre Parallel group FACIAL or GENITOFEMORAL PSORIASIS • **Setting:** out-patient • **Randomised** Computer-generated (ratio 1:1). • **Washout period**: 1 wk for topicals; 2 wk for UV; 4 wk for systemics	Total N: **50** **Drop-outs (don't complete the study):** **Calcitriol:** 3 (12%) **Tacrolimus**: 0% Reasons: non-medical	**Inclusion criteria:** aged ≥ 18 years; diagnosis of chronic plaque psoriasis affecting the face and/or gentiofemoral area. **Exclusion criteria**: Underlying conditions requiring systemic calcium or vitamin D supplements; use of systemic treatments known to worsen psoriasis **Mean baseline** / **Calcitriol N = 24** / **Tacrolimus N = 25** Age, years (mean±SD): 41.6±14.0 / 37.7±11.5 Gender M/F%: 79.2/20.8 / 68/32 **Target lesion** Face: 22 (91.7%) / 22 (88%) Gentiofe: 2 (8.3%) / 3 (12%)	**Calcitriol** 3 µg/g (Silkis) (N=25) **Formulation**: ointment **Frequency:** twice daily	**Tacrolimus** 0.3 mg/g (Protopic) (N=25) **Formulation**: ointment **Frequency:** twice daily ---------- **BOTH ARMS:** no concomitant topical agents (including emollients) Only lesions in facial or gentiofemoral	Treated for up to 6 weeks	**IAGI:** 7-pt scale Clear (100% improvement); nearly clear (90%); marked improvement (75%); moderate improvement (~50%); minimal improvement (~25%); no change; worse Withdrawals	Galderma

(5):1005-1012, 2007. Ref ID: LIAO2007	• **Double blind** – adequately described • **Allocation concealment**. Unclear • **Sample size calculation**.Not stated • **ITT analysis** Yes (LOCF).		moral TSS 0-12 (mean±SD)	 6.88±1.88	 5.76±2.68		areas were treated using the investigational product Standard topical regimens on other body areas were permitted Irritancy sufficient to interfere with usual activity resulted in reduction in dose frequency to once daily (severe irritancy lead to discontinuation of study medication)			
Effect Size Outcomes									

Efficacy

IAGI ITT population (LOCF)	Calcitriol N = 24	Tacrolimus N = 25	p-value for difference
Clear or nearly clear	8 (33.3%)	15 (60%)	<0.05

Time to effect

- Graphical representation of % change in TSS over time shows that both treatments reached maximum effect by week 4, with negligible further improvement between wk 4 and 6)

Author's conclusion

- Both calcitriol and tacrolimus are safe and well tolerated in the treatment of psoriasis in sensitive areas
- Tacrolimus demonstrated better clinical efficacy

H.7.8 TAR VS CORTICOSTEROID

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
C. E. Griffiths, A. Y. Finlay, C. J. Fleming, J. N. Barker, F. Mizzi, and S. Arsonnaud. A randomized,	RCT Multicentre Parallel group SCALP PSORIASIS	Total N: **162** **Drop-outs (don't complete the study):** unclear	**Inclusion criteria:** aged ≥ 18 years; **moderate-to-severe** scalp psoriasis (affecting at least 15% of scalp area). **Exclusion criteria:** immunosuppression; pregnancy; lactation; history of allergic reactions or contraindications to studied medications	Clobetasol propionate shampoo 0.05% (N=121) **Formulation**:	Tar blend shampoo (Polytar Liquid®: arachis oil extract of coal tar 0.3%, cade	Treated for 4 weeks	**1° outcome:** TSS: sum of scores for erythema, desquamated and	Not stated

investigator-masked clinical evaluation of the efficacy and safety of clobetasol propionate 0.05% shampoo and tar blend 1% shampoo in the treatment of moderate to severe scalp psoriasis. J.Dermatol.Treat. 17 (2):90-95, 2006. Ref ID: GRIFFITHS2006A	• **Setting:** unclear • **Randomised** Method not stated (ratio 3:1). • **Washout period**: 'subjects were asked to avoid excessive UV exposure and yo respect specified wash-out periods for systemic therapies for psoriasis' • **Single blind** – investigator (no details) • **Allocation concealment**. Unclear • **Sample size calculation**. Yes. 90% power to detect a 1.5 point		**Mean baseline** **Clobetasol propionate N = 121** **Tar blend shampoo N = 41** Age, years (mean±SD): 46.7±14.9 / 45.4±13.2 Gender M/F: 48.8/51.2 / 65.9/34.1 Race – white, n (%): 116 (95.8%) / 38 (92.7%) TSS 0-9 (mean): 6.1 / 6.3		shampoo **Frequency:** once daily (to a dry scalp – rinse off after 15 mins)	oil 0.3%, coal tar solution 0.1%, oleyl alcohol 1%, tar 0.3%) (N=41) **Formulation**: shampoo **Frequency:** twice weekly (to a wet scalp – followed by rinsing) ---------- **BOTH ARMS:** concomitant use of systemic psoriasis treatments or drugs that could		thickness (each on a 0-3 scale); range: 0-9 **2° and other outcomes:** Skin atrophy	

	difference on TSS at a two-sided 5% significance level • **ITT analysis** Yes.				aggravate psoriasis not permitted			

Effect Size

Outcomes

Efficacy

TSS (0-9) **ACA population (evaluable patients)**	**Clobetasol propionate** **N = 121**	**Tar blend shampoo** **N = 41**	**ANCOVA 95% CI**
Mean TSS at wk 4	3.1±1.9	5.3±1.9	-2.73, -1.41
TSS reduction at wk 4	50%	14.5%	

Sign score (0-3) **ITT population (LOCF)** **Mean±SD**	**Clobetasol propionate** **N = 121**	**Tar blend shampoo** **N = 41**	**p-value between groups**
Erythema			

Baseline Week 4	1.9±0.6 1.2±0.8	1.9±0.6 1.7±0.7	0.0001
Thickening			
Baseline Week 4	2.0±0.7 0.9±0.8	2.1±0.6 1.6±0.9	0.0001
Desquamation			
Baseline Week 4	2.2±0.6 1.1±0.8	2.3±0.5 1.9±0.8	0.0001

Time to maximum effect

- A small amount of continued improvement was seen between weeks 2 and 4 based on improvement in subjects' global assessment of improvement from baseline for both treatments (with greater continued improvement for the clobetasol propionate group)

Withdrawals

	Clobetasol propionate **N = 121**	**Tar blend shampoo** **N = 41**
Withdrawal due to adverse events	1	0

Adverse events

	Clobetasol propionate	**Tar blend shampoo**

	N = 121	N = 41
Skin atrophy, n	**0**	**0**

Author's conclusion

- Clobetasol propionate shampoo is superior to tar blend shampoo in the treatment of moderate-to-severe scalp psoriasis in terms of both efficacy and cosmetic acceptability

H.7.9 POTENT CORTICOSTEROID VS PLACEBO

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparisons	Length of follow-up	Outcome measures	Source of funding
Franz TJ, Parsell DA, Halualani RM, Hannigan JF, Kalbach JP, Harkonen WS. Betamethasone valerate foam 0.12%: a novel vehicle with enhanced delivery and efficacy. *Int J Dermatol.* 1999;38(8):628-32. REF ID: FRANZ1999	Multicentre (USA) SCALP PSORIASIS DESIGN Between patient Patient delivery ALLOCATION Random Method of randomisation: unclear Concealment: unclear BLINDING Double-blind (patient / investigator)	N=190 **Drop-outs (don't complete the study):** N=18 **Reasons:** no details	**INCLUSION CRITERIA** Moderate to severe scalp psoriasis (each of 3 primary signs ((erythema, scaling, plaque thickness) ≥ 2); scalp involvement ≥10%; adults **EXCLUSION CRITERIA** Systemic psoriatic therapy within previous four wks; topical scalp preparations within previous two wks	N= 57 Betamethasone valerate (BMV) foam (0.1%) **Formulation**: foam **Frequency:** Twice daily to the entire scalp for 28 consecutive days **Note:** Patients were instructed to apply the study	N=58 BMV lotion (0.1%) **Formulation:** lotion **Frequency:** Twice daily N=28 Placebo foam **Formulation:** foam	28 days (evaluated at 2 and 4 weeks)	Erythema, scaling, thickness, pruritus IAGI (7 pt: worse to completely clear) PAGI (7 pt: worse to completely clear)	Connetics Corporation

	WITHDRAWAL / DROPOUT Described • **Setting:** No details • **Washout period**: see exclusion criteria • **Sample size calculation**: Not stated • **ITT analysis** Not stated			medication to the entire scalp; all patients were required to use DHS shampoo during the treatment phase. No other therapy to the scalp was allowed	**Frequency:** Twice daily N=29 Placebo lotion **Formulation:** lotion **Frequency:** Twice daily			

Baseline demographics

	BMV foam (n = 57)	BMV lotion (n = 58)	Placebo foam (n = 28)	Placebo lotion (n = 29)
Age				
Mean	46.6	48.6	50.8	48.5
18-59 (%)	70	78	68	69

>60(%)	30	22	32	31
Gender (%)				
Male	44	55	50	48
Female	56	45	50	52
Race (%)				
Caucasian	95	93	100	100
Hispanic	4	3	0	0
Other	1	4	0	0
Mean severity of disease (score 0-4)				
Scaling	2.75	2.67	2.93	2.83
Erythema	2.49	2.48	2.79	2.59
Plaque thickness	2.63	2.55	2.61	2.66

Effect Size

Outcomes

<u>Efficacy</u>

For each sign of psoriasis (scaling, plaque thickness, erythema), patients in the BMV foam group demonstrated significantly greater improvement after 28 days of treatment

than did patients in the BMV lotion, placebo lotion or placebo foam groups (displayed graphically). The same trend was seen in the pruritus score, though the difference between BMV foam and BMV lotion was not statistically significant (displayed graphically)

% of patients completely clear or almost clear of disease at the end of treatment	BMV foam (n = 57)	BMV lotion (n = 58)	Placebo foam (n = 28)	Placebo lotion (n = 29)
IAGI	41 (72%*†)	27 (47%§)	6 (21%)	6 (21%)
PAGI	44 (77%*†)	27 (47%§)	6 (21%)	4 (14%)

*BMV foam vs placebo foam: p<0.05
†BMV foam vs BMV lotion: p<0.05
§BMV lotion vs placebo lotion: p<0.05

Time to max effect

Maximum effect was not reached for scaling, plaque thickness, pruritus and erythema scores by 28 days for all treatment groups (displayed graphically), with exception of placebo foam which was reached after 15 days for the scaling score.

Toxicity

No patients discontinued treatment during the study due to local skin reactions
Drug related complaints were burning, stinging, or itching at the site of application. Majority of these reactions were classified as mild. By the end of the treatment period, reports of local reactions at the site of application had diminished in both active treatment groups relative to the placebo groups. No patient discontinued treatment during the study due to local skin reactions.

Summary

- BMV foam was associated with significantly greater improvement after 28 days of treatment for scaling, erythema and plaque thickness scores of psoriasis compared to BMV lotion, placebo lotion or placebo foam

H.7.10 VERY 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>Olsen AE, Cram DL, Ellis CN, Hickman JG, Jacobsen C, Jenkins EE, Lasser AE, et al. A double-blind, vehicle-controlled study of clobetasol propionate 0.05% (Temovate) scalp application in the treatment of moderate to severe scalp psoriasis. Journal of the American Academy of</td>
<td>DESIGN
Between patient
Patient delivery
SCALP
ALLOCATION
Random
Method of randomisation: not reported
Concealment: unclear
BLINDING
Double-blind (patient / investigator)
WITHDRAWAL /</td>
<td>N: 378
Drop-outs (don’t complete the study):
1 did not complete one week of therapy (no reasons given and no group allocation reported).
27 did not attend the 1 week post treatment visit (5 in Clobetasol and 22 in placebo). Of the 5 Clobetasol patients not attending the post treatment session, 2 dropped out because of treatment failure, 2 due to unrelated medical problems and one because of non-compliance. Of the 22 not attending the post treatment session, 17 dropped out because of</td>
<td>INCLUSION CRITERIA
Moderate to severe scalp psoriasis (TSS (0 to 9) ≥ 6); stable or worsening; adult.
EXCLUSION CRITERIA
Recent systemic, topical or UV treatment for psoriasis.
Baseline characteristics [mean(range) or proportion unless stated]:
<table>
<tr><th></th><th>Clobetasol</th><th>Placebo</th></tr>
<tr><td>Age</td><td>47 (19-88)</td><td>46 (18-88)</td></tr>
<tr><td>male</td><td>79/188</td><td>89/189</td></tr>
<tr><td>duration of psoriasis (yrs)</td><td>12.3 (0.4-50)</td><td>11.7 (1-55)</td></tr>
<tr><td>Severe disease</td><td>41/188</td><td>33/189</td></tr>
</table></td>
<td>Clobetasol propionate 0.05% BD, scalp application. A maximum of 50ml of study drug could be applied per week.
n= 188
Formulation:
solution
Frequency: Twice daily</td>
<td>Placebo (vehicle)
n= 189
Formulation: unclear
Frequency: Twice daily</td>
<td>Treatment duration: 2 weeks
Follow up: 3 weeks.</td>
<td>Outcomes assessed at 3,7, 14 days. Primary outcome time point should be 14 days, as only this point measured the effects of a whole course of therapy.
Investigator global assessment (6 pt: worse to cleared)
Patient</td>
<td>Glaxo Inc. Scalp trial</td>
</tr>
</table>

Dermatology 1991; 24:443-7 Ref ID: OLSEN1991	**DROPOUT** Described **Sample size calculation:** Not reported **ITT analysis:** Not reported	treatment failure, 1 due to local irritation from the vehicle, 3 because of non-compliance and 1 was lost to follow-up. **Noncompliance:** 1 in the clobetasol group and 3 in the placebo group.	**Previous therapy**: Must have ceased systemic treatments for at least 4 weeks, and topical therapy for at least 2 weeks, prior to study entry.	**Concomitant therapies –** none reported			global assessment (4 pt: poor to excellent) Adverse events Withdrawal due to adverse vents Withdrawal due to lack of efficacy	

Effect Size

Outcomes

Efficacy
IAGI

	Clobetasol	**Placebo**
End of treatment – cleared or excellent	129/188	16/189

1 week post-treatment – cleared or excellent	114/183	13/167
End of treatment – good to excellent	152/188	42/189
1 week post-treatment – good to excellent	142/183	32/167

Adverse events

	Clobetasol	**Placebo**
Adverse events		
burning or stinging	21/188	18/189
scalp/ear papules	3/188	0/188
Increased pruritis	1/188	4/189
scalp tingling, tightness and hair loss	1/188	1/189
eye irritation	1/188	0/189
tightness	0/188	1/189
soreness	0/188	1/189
worsening of psoriasis	0/188	1/189
dryness	0/188	1/189

Withdrawals

	Clobetasol	Placebo
Withdrawal related to adverse events	0/188	1/189
Withdrawals due to lack of efficacy	2/188	17/189

Authors' conclusion: Clobetasol propionate 0.05% scalp application appears to be a safe and an effective treatment for scalp psoriasis.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Franz TJ, Parsell DA, Myers JA, Hannigan JF. Clobetasol propionate foam 0.05%: a novel vehicle with enhanced delivery. International Journal of dermatology 2000; 39: 521-538. **Ref ID: FRANZ2000**	**DESIGN** Between patient Patient delivery Multicentre **SCALP PSORIASIS** **ALLOCATION** Random Method of randomisation: not reported Concealment: unclear **BLINDING** Double-blind (patient / investigator)	Total N: 188 **Drop-outs (don't complete the study):** Total = 0 (0%) **Noncompliance:** Not reported	**PATIENT CHARACTERISTICS** N: 188 Baseline comparability: unclear; stated that groups well matched for age, gender and baseline severity. Age: not reported; all adult Gender (%M): 49.5% Severity: Mean TSS (0 to 12): 7.25 **INCLUSION CRITERIA** Moderate to severe scalp psoriasis (each of 3 primary signs [erythema, scaling, plaque thickness] ≥ 2); scalp involvement ≥10%; adults **EXCLUSION CRITERIA** Not reported	**Clobetasol propionate foam, 0.05% BD, or** **Clobetasol propionate lotion, 0.05% BD.** **Both manually applied to the whole scalp.** **n= 125** **Formulation**: Foam or solution **Frequency** twice daily Concomitant	**Placebo** **n= 63** **Formulation** Foam or lotion **Frequency** twice daily	**Treatment duration:** 2 weeks **Follow up:** 4 weeks (from start of treatment)	Taken at 7, 14 and 28 days from start of treatment. Primary outcome point is 14 days, as that is when main outcomes data are presented. IAGI PAGI Adverse events withdrawal due to toxicity Withdrawal due	Connectics Corporation

	Sample size calculation: Not reported **ITT analysis:** Not applicable		**Previous therapy**: Not reported	therapies – They were required to use DHS shampoo. No other scalp therapy allowed.			to lack of efficacy	

Effect Size

Outcomes

Efficacy

IAGI and PAGI at 14 days: Number completely clear or almost clear

	CP –foam or solution (n=125)	**Placebo – foam or solution (n=63)**	CP foam (n=62)	CP solution (n=63)	placebo foam (n=31)	placebo solution (n=32)
IAGI	**86/125**	**5/63**	46/62	40/63	3/31	2/32
PAGI	**77/125**	**4/63**	41/62	36/63	2/31	2/32

Time to max effect

Maximum effect was not reached for scaling, plaque thickness, pruritus and erythema scores by 14 days for all treatment groups (displayed graphically); the mean severity score increased during the 14 days following removal of treatment

Adverse events

No difference between groups reported; no actual data given.

Withdrawal due to toxicity

None in either group

Withdrawal due to lack of efficacy

None in either group

Authors' conclusion

No conclusion was stated relating to CP versus placebo; however the improved efficacy of foam compared to solution was stated.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Poulin Y et al. Clobetasol propionate shampoo 0.05% is efficacious and safe for long-term control of moderate scalp psoriasis. J Dermatol Treat 2010; 21: 185-192. **Ref ID: POULIN2010**	**RCT** **DESIGN** Between patient Patient delivery **ALLOCATION** Random Method of randomisation: not stated Concealment: unclear **BLINDING** Open-label initial treatment phase (up to 4 weeks); then if GSS ≤2 (clear, very mild or mild) randomised to double-blind maintenance phase • **Washout period:**	**Total N: 168 entered treatment phase; 141 eligible for maintenance phase; 136 randomised** **Drop-outs (don't complete the study):** Total = (%): 9 (13.4%) active group and 17 (24.6%) vehicle group (5 [7.5%] and 16 [23.2%] due to "patient's	INCLUSION CRITERIA Moderate scalp psoriasis (global severity score 3 on a 0-5 scale) EXCLUSION CRITERIA Pregnant, nursing or planning a pregnancy Baseline comparability: yes Mean age 50 years 50% male 91.2% Caucasian; 6.6% Asian; 1.5% Hispanic; 0.7% other Global severity score: 15.4% clear; 47.8% very mild; 36.8% mild Erythema: 85.3% none-mild; 14.7% moderate-severe Scaliness: 88.9% none-mild; 11.1% moderate	**n=67** **Clobetasol propionate shampoo 0.05%** **Formulation:** short-contact shampoo formulation **Class:** super potent corticosteroid **Frequency:** once daily for initial treatment phase (4 weeks) and relapses (for 4 weeks); twice-weekly (3 days apart) in long-term remission/ maintenance **Amount used:** applied to scalp as a thin film; left in place for 15	**n=69** **Vehicle** **Formulation**: short-contact shampoo formulation **Frequency:** twice-weekly in long-term remission/ maintenance	**Treatment duration:** initial treatment phase (up to 4 weeks); then if GSS ≤2 (clear, very mild or mild) randomised to double-blind maintenance phase up to 6 months **Assessments at:** every 4 weeks in maintenance phase **Follow-up after end of treatment:**	Relapse: GSS >2 (moderate, severe or very severe scalp psoriasis); investigator extent of disease (6-point scale) and individual sign scores (scaliness, erythema, plaque thickness) on a 5-point scale; patient assessment of pruritus intensity on 4-point scale; safety assessment (burning sensation, skin atrophy, telangiectasia, adverse events), morning serum cortisol, patient satisfaction questionnaire; time to first	Galderma

	not applicable • **Sample size calculation :** not reported • **ITT analysis:** yes **Setting:** Outpatients	request"; 2 [3.0%] and 0 due to AE; 1 [1.5%] and 0 lost to follow up; 1 [1.5%] and 1 [1.4%] "other")	Plaque thickness: 97.1% none-mild; 2.9% moderate Extent of disease: 85.3% none to <20%; 14.7% 20-100% Pruritus: 96.4% none-mild; 3.6% moderate-severe	minutes before lathering and rinsing. During whole study (treatment + maintenance phase), clobetasol propionate shampoo 0.05% applied for 79.3 days in the CP group and 59.5 days in the vehicle group Note: during maintenance phase evaluation for relapse was every 4 weeks, if after 4 more weeks of once daily treatment disease control was not regained patients left the study, if control was regained the twice weekly maintenance schedule was re-instituted (further relapses were treated in the same manner)		none	relapse; 5 of patients who had no relapse at each visit; total relapses in maintenance phase **Primary efficacy parameter:** not stated	

Effect Size

Outcomes

Efficacy during maintenance phase (for those achieving clear, very mild or mild during induction)

% patients with no relapse (GSS response maintained: mild, very mild or clear)

ITT (worst case population; those who discontinued before relapse were considered as having relapse at the next visit)	**Clobetasol propionate shampoo 0.05%** **n=67**	**Vehicle** **n=69**	**p value**
Baseline	100%	100%	-
1 month	71.6%	44.1%	p<0.01
2 months	61.2%	29.0%	p<0.01
3 months	58.2%	19.1%	p<0.01
4 months	50.0%	15.9%	p<0.01
5 months	44.8%	14.5%	p<0.01
6 months	40.3%	11.6%	p<0.01

Number of relapses by 6 months

	Clobetasol propionate shampoo 0.05%	**Vehicle**	**p value**

	n=67	n=69	
% patients who relapsed with only 1 relapse	73.2%	34.1%	p<0.001
2 relapses	16.8%	38.3%	
3 relapses	10.0%	27.6%	

	Clobetasol propionate shampoo 0.05% **n=67**	**Vehicle** **n=69**	**p value**
% patients with <20% of scalp affected at time of relapse	54.3%	38.6%	not stated
No pruritus at relapse	17.1%	3.5%	not stated
Median time to relapse	**141 days**	**30.5 days**	**<0.0001**

Patient satisfaction questionnaire

	Clobetasol propionate shampoo 0.05% **n=67**	**Vehicle** **n=69**	**p value**
Regime easy to incorporate into daily routine	100%	83.1%	not stated
Preferred twice-weekly treatment for a long period to daily treatment	72.7%	47.4%	p=0.004
Willing to continue treatment in the same way	86.0%		
Could adopt regimen for as long as a year	57.1%		

Treatment enough to control disease	73.7%	39.7%	p<0.001
Not bothered by side effects	93%	79.7%	p<0.05
Satisfied or very satisfied with overall treatment	84.2%	59.7%	p=0.006

Compliance: >95% both groups

Time-to-effect: 89% (141/168) of those entered into the induction phase achieved clear, mild or very mild disease after 4 weeks of treatment

Adverse events:

	Clobetasol propionate shampoo 0.05% **n=67**	**Vehicle** **n=69**	p value
Burning: 0 none 1 mild 2 moderate	 58 (86.6%) 7 (10.4%) 2 (3.0%)	 56 (81.2%) 9 (13.0%) 4 (5.8%)	0.063
Skin atrophy 0 none 1 mild	 66 (98.5%) 1 (1.5%)	 69 (100%) -	0.527
Telangiectasia			0.806

0 none 1 mild (transient or already present at baseline)	65 (97.0%) 2 (3.0%)	68 (98.6%) 1 (1.4%)	
Total AE (total 84 events in 57 people)	34 events (no. of people not stated)	50 events (no. of people not stated)	
Treatment-related AE	3 (1 asthma – severe treatment-related AE)	5	

No notable hypothalamic-pituitary-adrenal (HPA) axis suppression

Withdrawals

	Clobetasol propionate shampoo 0.05% **n=67**	**Vehicle** **n=69**
Withdrawal due to AEs	2 (3.0%)	0
Withdrawal due to “patient’s request”	5 (7.5%)	16 (23.2%)
Withdrawal due to loss to follow up	1 (1.5%)	0
Withdrawal other	1 (1.5%)	1 (1.4%)

Authors’ conclusion

The regimen of Clobetasol propionate shampoo 0.05% once daily for initial treatment phase (4 weeks) and relapses (for 4 weeks) and twice-weekly (3 days apart) in long-term remission/ maintenance is efficacious and safe for long-term control of moderate scalp psoriasis.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Jarratt M, Breneman D, Gottlieb AB, Poulin Y, Liu Y, Foley V. Clobetasol propionate shampoo 0.05%: a new option to treat patients with moderate to severe scalp psoriasis. *J Drugs Dermatol.* 2004;3(4):367-73 REF ID: JARRATT2004	Multicentre (USA and Canada) SCALP PSORIASIS DESIGN Between patient Patient delivery ALLOCATION Random Method of randomisation: Computer generated list Concealment: unclear BLINDING Double-blind (patient / investigator)	N=142 **Drop-outs (don't complete the study):** N=1 (not stated which arm they were allocated to) **Reason:** Applied a group III potent corticosteroid during washout period	**INCLUSION CRITERIA** Aged 12 or over; moderate to severe scalp psoriasis (global severity score ≥ 3); compliance with washout periods for systemic therapies (details not reported) **EXCLUSION CRITERIA** Pregnancy or risk thereof; known allergy to test products; need for systemic therapy or other concomitant antipsoriatics; excessive UV exposure [illegible]	N=95 Clobetasol propionate shampoo, 0.05% **Formulation**: shampoo **Frequency:** Once daily **Note:** Treatments applied once a day and left on the dry scalp for 15 minutes, before lathering and rinsing The use of	N=47 vehicle shampoo **Formulation** shampoo **Frequency:** Once daily	treatment duration: 4 weeks, followed by treatment free 2 week follow-up (patients told to avoid study medication and all psoriasis medications previously excluded)	The primary endpoint was the success rate after 4 weeks of treatment, defined as the proportion of subjects with a GSS of 0 or 1. Failure was defined as GSS of ≥2 Global severity score (GSS) (6 pt: clear to very severe) IAGI (5 pt:	Galderma R&D Inc

	Clobetasol propionate shampoo (n =95)	Clobetasol propionate shampoo vehicle (n=47)
Male/female (n)	38/57	22/25

	WITHDRAWAL / DROPOUT Unclear • **Setting:** Not stated • **Washout period**: 2 weeks for systemic anti-psoriatic medications • **Sample size calculation**. Yes. 132 subjects were planned to be enrolled to collect sufficient safety data and to detect a significant difference in success rates of 60% vs 20% with 90% power at the 0.05 significance		Caucasian (n)	88	43	topical emollients, coal tars, vitamin D derivatives, tazarotene or salicylic acid to treat body psoriasis during the course of the study was allowed			worse to clear) PAGI (5 pt: worse to clear)	
			Black (n)	2	1					
			Hispanic (n)	4	3					
			Other (n)	1	0					
			Mean age ± SD (years)	45.1±15.3	45.1±15.7					
			Global severity score (full scaled							
			Moderate	70	32					
			Severe	20	10					
			Very severe	5	5					
			Total severity score ± SD	6.5±1.1	6.7±1.2					

	level for the 2-tailed alternative, adjusting for a 10% dropout rate. • **ITT analysis** For efficacy endpoints							

Effect Size

Outcomes

<u>Efficacy</u>

	Clobetasol propionate shampoo (n = 95)	**Vehicle shampoo (n = 47)**	**P value**
Proportion of patients achieving 'success' (GSS clear or minimal) at 4 weeks	40 (42.1%)	1 (2.1%)	<0.001
Proportion of patients achieving 'success'(GSS clear or minimal) at 6 weeks	Significantly more patients in clobetasol propionate shampoo arm achieved 'success' compared to vehicle arm (no further details)		=0.003

- About 50% of subjects in the clobetasol propionate shampoo arm who achieved success at week 4 remained a treatment 'success' at the 2 week follow-up
- There was no observation of rebound, defined as having achieved 'success' during treatment and then deteriorated to worse than pre-treatment levels.

	Clobetasol propionate shampoo (n = 95)	**Vehicle shampoo (n = 47)**	**P value**
GSS at 4 weeks – Proportion mild or better	68 (71.6%)	7 (14.9%)	<0.001
GSS at 4 weeks – Proportion clear	10 (10.5%)	0	<0.001
Investigator assessment at 4 weeks	Significantly better with clobetasol propionate shampoo compared to vehicle (depicted graphically)		<0.001
Subject assessment at 4 weeks	Significantly better with clobetasol propionate shampoo compared to vehicle (depicted graphically		<0.001

Time to effect

Score for TSS decreased significantly from baseline at week two (first evaluation after baseline) for clobetasol propionate shampoo subjects compared to vehicle control (displayed graphically).

Time to max effect

Score for TSS was most reduced for both treatment groups at week 4 (displayed graphically).

<u>Toxicity</u>

	clobetasol propionate shampoo (n = 94)	vehicle (n = 47)	
Proportion of patients with ≥1 study drug related AE	13 (13.8%)	10 (21.3%)	

Skin discomfort which included stinging and burning (this was the most frequently reported dermatologic AE)	10.6%	17%	

- One subject treated with clobetasol propionate shampoo reported conjunctivitis, resolving in one day, not requiring treatment and not causing the patient to discontinue the study
- No case of skin atrophy, telangiectasia, acne, serious adverse events or deaths were reported during the study

Summary

- Results after 4 weeks demonstrated that clobetasol propionate shampoo, 0.05% was with a similar safety profile significantly more effective than its vehicle

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
H. Sofen, C. P. Hudson, F. E. Cook-Bolden, N. Preston, L. E. Colon, S. W. Caveney, and R. W. Gottschalk. Clobetasol propionate 0.05% spray for the management of moderate-to-severe plaque psoriasis of the scalp: Results from a randomized controlled trial. Journal of Drugs in Dermatology 10 (8):885-892, 2011.	Multicentre (4 centres in the USA) SCALP PSORIASIS DESIGN Between patient Patient delivery ALLOCATION Random Method of randomisation: sequential numbering Concealment: unclear BLINDING Double-blind (patient / investigator)	N=81 **Drop-outs (don't complete the study):** N=10 **Clobetasol**: 8 – 4 clear at 2 weeks; 4 other **Vehicle**: 2 – 1 adverse event; 1 other	**INCLUSION CRITERIA** Aged 18 or over; moderate to severe scalp psoriasis (global severity score 3-4 on a scale of 0-5) **EXCLUSION CRITERIA** Systemic treatment for body psoriasis; >20% BSA psoriasis that required >50g/wk of study product; history of adverse response to topical or systemic steroid therapy; chemical process on the hair within 14 days of baseline visit; use of any of the following within 14 days prior to baseline visit: steroid, UVB, vitamin D3, anthralin, coal tar, any other topical anti-psoriasis medications; anticipated intensive exposure to UV during study period; UVA within 4 weeks, biologics within 12 weeks, systemics within 4 weeks from baseline; women who were pregnant, nursing or planning to become pregnant **Clobetasol propionat** / **Vehicle (n=40)**	N=41 Clobetasol propionate spray, 0.05% **Formulation**: spray **Frequency:** Twice daily (at least 8 hours apart) **Note:** Treatments applied directly onto clean, dry scalp lesions followed by gentle rubbing to ensure a thin film was present on the	N=40 Vehicle **Formulation** spray **Frequency:** Twice daily (at least 8 hours apart)	Treatment duration: 4 weeks	**Primary endpoint:** Global severity score (GSS) (6 pt: clear to very severe) at week 4 **Secondary endpoints:** GSS at 2 weeks; Skin atrophy	Galderma

REF ID: SOFEN2011	• **Setting:** Not stated • **Washout period**: see exclusion criteria • **Sample size calculation**. Yes. • **ITT analysis** Yes (LOCF)			**e spray (n =41)**		lesions **Dose:** not to exceed 50g/wk The use of topicals to treat body psoriasis during the course of the study was allowed **Note:** if GSS 0 after 2 weeks subjects completed study at that point				
			Mean age (years ±SD)	46.0±15.4	41.3 ±13.7					
			Male (%)	39%	40%					
			Race (%)							
			Caucasian	78	78					
			Black/African-American	15	13					
			Asian	2	5					
			Native Hawaiian/Pacific Islander	2	0					
			Other/mixed	2	5					
			Fitzpatrick skin type (%)							
			I	2	5					
			II	12	20					
			III	39	38					
			IV	29	28					
			V	17	8					
			VI	0	3					
			Duration of	13.5±12.8	8.6±7.5					

			psoriasis (years)							
			GSS							
			Moderate	66	70					
			Severe	34	30					

Effect Size

Outcomes

<u>Efficacy</u>

GSS score	**Week 2**		**End of treatment (week 4 or week 2 if GSS = 0 at that time)**	
	Clobetasol propionate (n = 41)	**Vehicle (n = 40)**	**Clobetasol propionate (n = 41)**	**Vehicle (n = 40)**
Clear	5	0	21	1
Almost clear	28	3	14	4
Mild	5	11	4	11
Moderate	2	22	1	18
Severe	1	4	1	6
p-value (between groups)	<0.001		<0.001	

Time to max effect

Of those who achieved clear/nearly clear status at week 4, the majority had done so by week 2

Toxicity

	Clobetasol propionate shampoo (n = 41)	**Vehicle (n = 40)**
Skin atrophy	0	1
Withdrawal due to adverse events	0	1

Summary

- Treatment with clobetasol propionate 0.05% spray for up to four weeks is effective and well tolerated for moderate-to-severe plaque psoriasis of the scalp

H.8 Phototherapy

H.8.1 Narrow-band UVB vs broad-band UVB (between-patient randomisation)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Sou of fun
S. M. Kirke, S. Lowder, J. J. Lloyd, B. L. Diffey, J. N. Matthews, and P. M. Farr. A randomized comparison of selective broadband UVB and narrowband UVB in the treatment of psoriasis. *J.Invest.Dermatol.* 127 (7):1641-1646, 2007. Ref ID: KIRKE2007	RCT Single-centre (phototherapy unit), UK Recruited May 2003 – Nov 2004 • Randomised (permuted blocks within strata) • No explicit 'washout' or run-in period (but see exclusion criteria) • Observer blinded • Allocation	Total N: 100 **Drop-outs (don't complete the study):** N=6 drop-outs in TL01 arm: 3 failed to attend for treatments and 3 withdrew because of side effects N=9 drop-outs in UV6 arm: 8 failed to attend for	**Inclusion criteria:** Plaque psoriasis; ≥18 years of age, **Exclusion criteria:** received phototherapy or systemic agents for psoriasis in the preceding 3 months **Note:** allocation stratified by: • plaque size (small <3 cm diameter) or large (>3 cm diameter) • involvement of skin around or below the knees • skin type (I/II or III/IV) **Mean baseline** / **TL01 (n=50)** / **UV6 (n=50)** Mean age – years (range): 42 (19-76) / 39 (17-77)	N=50 **Selective broadband UVB (UV6 – little emission below 290 nm), three-times weekly** Administered using whole-body exposure units fitted with 40 fluorescent lamps Dose determined by minimal erythematic dose (MED) measurement by	N=50 **Narrow-band UVB (TL-01), three-times weekly** Administered using whole-body exposure units fitted with 40 fluorescent lamps Dose determined by minimal erythematic dose (MED) measurement by testing on the	6 months (plus unclear Tx duration – at least 5.5 weeks)	**1° outcome:** median number of treatments to clear Clearance = no residual psoriasis or psoriasis only remaining in areas shaded from UV exposure, e.g., flexures **2° and other outcomes:** clearance of psoriasis, PASI scores for non-	Nor sta

	concealment using opaque, sealed, sequentially number envelopes • Sample size calculation based on 80% power to detect change in 1° outcome of 25% at 5% significance • ITT analysis – assumptions not stated • N=4 drop-outs/withdrawals due to AEs (n=3 TL01, N=1 UV6)	treatments and 1 withdrew because of side effects	Gender M/F: 50%/50%; 40%/60% Mean baseline PASI (range): 7.5 (2.1-27.9); 6.1 (2.7-21.7) The 2 groups were similar for baseline characteristics	testing on the forearm and judged visually 24 h after irradiation. ---------- **BOTH ARMS: stepped Tx strategy** Initial dose 70% MED, increased 40% after alternate treatments, decreasing stepwise to 5% by the 18th treatment (dose increments postponed if erythema developed)	forearm and judged visually 24 h after irradiation. ---------- **BOTH ARMS:** Emollients only permitted Planned withdrawal permitted after 16 treatments; treatment was continued until psoriasis cleared or no further improvement was made		clearing participants, patients remaining clear, adverse events	

Effect Size

Outcomes (ITT population - included all patients)

Outcome	TL01	UV6	Ratio of medians (95% CI)	p-value

	(N=50; ITT)	(N=50; ITT)		
1° outcome: number of exposures for clearance (median adjusted for stratification variables; based on Weibull distribution)	28.4	30.4	0.93 (0.80-1.09)	0.39
Outcome	**TL01** **(N=50; ITT)**	**UV6** **(N=50; ITT)**	**Odds ratio (adjusted for stratification factors; 95% CI)**	**p-value**
Clearance of psoriasis – time of assessment not reported	28	20	2.00 (0.87-4.62)	0.10

Effect of stratifying factors:

Comparison	**Odds of clearance**	**95% CI and p-value**
Plaque size: large relative to small	0.71	0.30, 1.68 P=0.43
Skin type: III/IV relative to I/II	3.22	1.40, 7.43 P=0.006
Involvement of skin around or below knees: No relative to	1.11	0.41, 3.02 P=0.84

yes		

Mean PASI scores in non-clearing patients

	Mean TL-01 (*n*)	Mean UV6 (*n*)	Difference and 95% CI	*P*-value
Score at baseline				
All patients failing to clear	7.4 (22)	6.8 (30)	0.6 (-2.6, 3.9)	0.69
Patients failing to clear who made a planned exit from the trial	8.3 (16)	5.8 (21)	2.5 (-1.4, 6.4)	0.20
Last PASI available				
All patients failing to clear	3.8 (22)	3.9 (30)	0.0 (-2.1, 2.1)	0.99
Patients failing to clear who made a planned exit from the trial	3.8 (16)	3.0 (21)	0.7 (-1.5, 2.9)	0.50
Change in PASI				

All patients failing to clear	3.6	2.9	0.7	
Patients failing to clear who made a planned exit from the trial	4.5	2.8	1.7	

Number remaining clear

	TL-01	**UV6**
3 months		
Number assessed	25	18
Number clear (% of those who cleared) (% of those assessed)	4 (14.3) (16)	8 (40) (44.4)
6 months		
Number assessed	19	13
Number clear (% of those who cleared) (% of those assessed)	1 (3.6) (5.3)	0

Withdrawal due to toxicity

Side effect	**TL01 (n=50)**		**UV6 (n=50)**	
	Occurrence	**Withdrawal**	**Occurrence**	**Withdrawal**
Erythema	43	0	42	0
Polymorphic light eruption	3	2	1	0

Pruritus	0	0	2	1
Inflammatory psoriasis	1	1	1	1

- **TL-01: 2** missed treatments because of erythema
- **UV6:** 3 missed treatments because of erythema

Summary

- No significant difference was found in the proportion of patients achieving clearance and side effects, including the development of erythema during phototherap were similar for the two lamp types.

H.8.2 Narrow-band UVB vs broad-band UVB (within-patient randomisation)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Sou of fun
E. Picot, L. Meunier, M. C. Picot-Debeze, J. L. Peyron, and J. Meynadier. Treatment of	RCT – within patient design (vertical side of the body) Single-centre,	Total N: 21 **Drop-outs (don't complete the study):** 6	**Inclusion criteria:** Widespread and symmetrical psoriasis **Exclusion criteria:** history of photo-aggravated psoriasis	N=15 **Selective broadband UVB (TL-12), three-times weekly**	N=15 **Narrow-band UVB (Tl-01), three-times weekly**	Tx max 10 weeks	**1° outcome:** change in PASI (from baseline to 10th and 20th exposure)	Nor sta

psoriasis with a 311-nm UVB lamp. *Br.J.Dermatol.* 127 (5):509-512, 1992. Ref ID: PICOT1992	France Jan-June 1990 • Randomised (method unclear) • No explicit 'washout' or run-in period (but see exclusion criteria) • Observer blinded • Allocation concealment not mentioned • Sample size calculation not mentioned • ITT analysis not mentioned • Drop-outs/withdrawals due to AEs: unclear		**Note:** none had received UVB, PUVA or retinoids in the preceding 3 months **Mean baseline** / **All (n=15)** Mean age – years (range): 46.5 (24-81) Gender M/F: 53.3%/46.7% Psoriasis phenotype - Plaque: 6 - plaque/guttate: 5 - guttate: 4 Mean duration of disease; years (range): 11.8 (4 months – 28 years)	Administered using whole-body exposure units fitted with 12 fluorescent lamps (untreated side of the body covered with thick material preventing UV penetration) Dose determined by minimal erythematic dose (MED) measurement ---------- **BOTH ARMS: stepped Tx strategy** Initial dose 70% MED with TL-12, increased exposure time by	Administered using whole-body exposure units fitted with 12 fluorescent lamps (untreated side of the body covered with thick material preventing UV penetration) Dose determined by minimal erythematic dose (MED) measurement with TL-12 lamps Thus, the applied doses in each cabin were *not associated with the same risk of erythema* ---------- **BOTH ARMS:**		**2° and other outcomes:** burning (arbitrary 0-3 scale), pruritus, cumulative dose	

				40% if previous exposure produced no perceptible effect. Increases were reduced if erythema occurred Maximum exposure time 16 mins	The only topicals permitted were pure Vaseline or 1% salicylic acid in petroleum permitted			

Effect Size

Outcomes

Outcome	TL01 (N=15)	UV6 (N=15)	p-value
Mean PASI at baseline	27.9	27.6	NS
Mean PASI (after 10 exposures)	12.9	12.5	NS
Mean PASI (after 20 exposures)	6.6	7.8	<0.01
Mean change in PASI	21.3	19.8	

Mean score burning	0.33	2.1	<0.001

Summary

- TL01 lamps have superior efficacy and tolerance to TL-12

H.8.3 PUVA vs UVB (between-patient randomisation)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Sou of fun
S. S. P. Yones. Randomized double-blind trial of the treatment of chronic plaque psoriasis: Efficacy of psoralen-UV-A therapy vs narrowband	RCT Single-centre (hospital phototherapy unit), UK Recruited April	Total N: 93 **Drop-outs (don't complete the study):** N=6 drop-outs in PUVA arm: 1 had inadequate	**Inclusion criteria:** Chronic plaque psoriasis, moderate-to-severe disease (PASI >7; BSA rule of nines ≥8%); ≥18 and ≤70 years of age **Exclusion criteria:** pregnant or breastfeeding women, history of skin malignancies or photosensitivity; renal or hepatic disease; photosensitising agents in previous 4 weeks; topical antipsoriatic treatments in previous 4 weeks or	N=43 **PUVA (oral 10 mg 8-MOP tablets – total dose 25 mg/m^2 total BSA; in case of nausea switched to 20-mg 5-MOP tablets**	N=45 **NB-UVB (+placebo tablet), twice weekly** Administered	Max 30 Tx + 12 months	**1° outcome:** PASI; Physician's Global Evaluation (0-6; clear, almost clear, mild, mild-to-moderate, moderate, moderate-to-severe, severe)	Nor sta

UV-B therapy. *Arch.Dermatol*. 142 (7):836-842, 2006. Ref ID: YONES2006	2002 – March 2004 • Randomised (sequentially-numbered list) • "Washout" for systemic and topical anti-psoriatic agents (see exclusion criteria) • Assessor and patient blinded • Allocation concealment (unclear) • Sample size calculation based on 80% power to detect change in number of exposures of 25% at 5% significance • Reported as ITT analysis • N=5 drop-outs/withdra	response; 3 for logisitic reasons; 2 for adverse events N=16 drop-outs in NB-UVB arm: 9 had inadequate response; 3 for logisitic reasons; 3 for adverse events; 1 lost to follow-up (unknown reason)	systemic antipsoriatic treatments in previous 3 months; phototherapy up to 3 months before study entry or >150 sessions in lifetime. **Note:** allocation stratified by: • skin type (I/II, III/IV or V/VI) **Mean baseline** / **PUVA (n=43)** / **NB-UVB (n=45)** Median age – years (range): 44 (18-70) / 40 (21-70) Gender M/F (%): 72/28 / 73/27 Previously treated with PUVA, BB or NB UVB (%): 44 / 26 Median baseline PASI (range): 11.0 (8.0-30.0) / 10.6 (8.0-27.9) **Skin type, n (%)** I-II: 26 (60) / 17 (38) III-IV: 11 (26) / 17 (38) V-VI: 6 (14) / 11 (24)	**at dose of 50 mg/m^2), twice weekly** Administered using cabin fitted with 40 (100W UVA) fluorescent tubes Dose determined by minimal erythema dose (MED) and minimum phototoxic dose (MPD) measurement judged visually 96 h after irradiation of unaffected upper buttock skin surfaces. In 3 patients initial dose determined using a skin-type based method	using UV5000 cabin fitted with 24 100W NB-UVB fluorescent tubes (emitting 311-313 nm) Dose determined by minimal erythema dose (MED) and minimum phototoxic dose (MPD) measurement judged visually 24 h after irradiation of unaffected upper buttock skin surfaces. In 3 patients initial dose determined using a skin-type based method ----------		**2° and other outcomes:** DLQI, visual analogue scale (0-10; "At the moment how would you rate your psoriasis?"); relapse Relapse: recurrence of psoriasis with a PASI of 50% or more of baseline	

	wals due to AEs (n=2 PUVA, N=3 NB-UVB)		The 2 groups were similar for baseline characteristics	---------- **BOTH ARMS: stepped Tx strategy** Initial dose 70% MED or MPD, increased 20% at each visit (if tolerated) up to 5 J/cm^2 (UVB)or 15 J/cm^2 (PUVA); dose increments postponed if erythema developed	**BOTH ARMS:** all patients used aqueous cream twice daily and a bath emollient daily throughout therapy and follow-up. All wore eye protection for 12 h after treatment. Unaffected skin was covered with clothing during therapy Treatment terminated at clearance; minimal improvement after 16 Tx; very slow progress after 16 treatments; intolerance to therapy; completion of 30 Tx			

					Those who cleared followed-up every month for 1 year or until relapse (recurrence of psoriasis with PASI ≥50% of baseline)			

Effect Size

Outcomes (ITT population - included all patients)

Outcome	**PUVA (N=43; ITT)**	**NB-UVB (N=45; ITT)**	**All**	**p-value**
Clearance (%)				
Skin types				
I-II	81	65	74%	
III-IV	91	65	75%	
V-VI			24%	
Clearance (n)				
Skin type I-IV (ITT)	31/37	22/34		

Skin type V-VI (ITT)	3/6	1/11		
Skin type I-VI (ACA)	34/38	23/38		
Median treatments to clearance	17.0	28.5		<0.001
Median change in PASI (among those with skin type I-IV; ITT) Baseline After 8 treatments Change	N=37 11 (8.0-30.0) 4.2 (0-9.3) -6.8	N=34 9.6 (8.0-27.9) 5.7 (0-21.5) -3.9		0.001
Change in DLQI	Data given graphically (greater reduction for PUVA)			0.02
Cumulative dose (J/cm^2)	126	41.3		ND

Note: superiority of PUVA did not vary according to initial severity of psoriasis (dichotomised as PASI <10.8 vs ≤10.8)

Adverse events

Erythema (any grade)	**PUVA (N=43; ITT)**	**NB-UVB (N=45; ITT)**	**All**
Skin types, n (%)			

All I-II III-IV V-VI	21 (49%) 65% 27% 17%	10 (22%) 29% 12% 27%	35%
Grade 2 erythema	14%	7%	

2 patients changed from 8-MOP to 5-MOP due to nausea

Relapse rate (57/88 who cleared followed-up until relapse or max of 12 months; 3 lost to follow-up)

	PUVA (N=34)	**NB-UVB (N=23)**	**All p-value**
Still in remission at 6 months	23/34	8/23	0.02
Median time to relapse (months)	8	4	0.03

Withdrawal due to toxicity

- **PUVA:** 1 erythema; 1 itch
- **NB-UVB:** 2 erythema; 1 polymorphic light eruption

Summary

- Patients with skin types V and VI had a lower rate of clearance than those with skin types I through IV.
- In patients with skin types I through IV,PUVA was significantly more effective than NB-UVB at achieving clearance.
- The median number of treatments to clearance was significantly lower in the PUVA group.
- Six months after the cessation of therapy, 68% of PUVA-treated patients were still in remission vs 35% of NB-UVB–treated patients.
- **PUVA achieves clearance in more patients with fewer treatment sessions and results in longer remissions than NB-UVB**

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Sou of fur
P. S. Chauhan, I. Kaur, S. Dogra, D. De, and A. J. Kanwar. Narrowband ultraviolet B versus psoralen plus ultraviolet A therapy for severe plaque psoriasis: an Indian perspective. Clin.Exp.Dermatol. 36 (2):169-173, 2011.	RCT India • Randomised (computer-generated random numbers) • "Washout" for systemics 4 wk and topicals 2 weeks • Unclear	Total N: 51 **Drop-outs (don't complete the study): 7** 4 in NBUVB and 3 in PUVA group (reasons unclear)	**Inclusion criteria:** plaque psoriasis, (BSA >20%); skin types IV and V **Exclusion criteria:** those recommended for PUVA or NBUVB plus pustular psoriasis or erythroderma. **Mean baseline** / **NBUVB (n=26)** / **PUVA (n=25)** Age – years: 33.3 ±14 / 38.1 ± 12.1	N=25 **PUVA (oral methoxsalen 0.6 mg/kg), three-times weekly** Administered on non-consecutive days with UVA exposure 2h after methoxsalen	N=26 **NB-UVB, three-times weekly** Administered on non-consecutive days No minimal erythema dose (MED) estimation performed.	Maximum 4 months on treatment (+1-6 months post treatment)	**1° outcome:** PASI **2° outcomes:** relapse (50% of baseline PASI)	No sta

Ref ID: CHAUHAN2011	blinding • Allocation concealment (no) • Sample size calculation: no • Reported as ACA		(±SD)			No minimum phototoxic dose (MPD) measurement was performed Initial dose determined using a skin-type based method; 2.0 J/cm^2 for skin type IV and 2.5 J/cm^2 for skin type V UVA dose increased by 1-1.5 J/cm^2 at every second visit ---------- **BOTH ARMS:** No concomitant treatment allowed except emollients and anti-histamines	Standard starting dose of 280 mJ/cm^2 and dose increased 20% at each visit, depending on erythema, pruritus and burning sensation ---------- **BOTH ARMS:** Treatment terminated at PASI75 or after 4 months; if no improvement in severity seen after 6 weeks treatment was terminated early and considered a treatment failure After completion of active treatment period, followed-up for 1-6 months to assess time to relapse (recurrence of psoriasis with PASI ≥50% of baseline)			
			Gender M/F (%)	80/20	81.8/18.2				
			Duration – years (±SD)	7.9±5.2	7.4±5				
			PASI (±SD)	15.8±2.9	16.9±4.7				

Effect Size

Outcomes (ACA population)

Efficacy at end of treatment

Outcome	**NB-UVB (N=21)**	**PUVA (N=22)**	**p-value**
PASI75	17 (80.9%)	18 (81.1%)	NS
Mean time to PASI75, weeks	9.9 ± 3.3	9.9 ± 3.5	NS
Mean treatments required to PASI75	29.6 ± 9.8	29.8 ± 10.6	
Total UV dose required for PASI75 (J/cm^2)	30.1 ± 19.5	93.8 ± 51.8	

Relapse rate by 6 months

Outcome	**NB-UVB (N=15)**	**PUVA (N=14)**	**p-value**
No longer in remission	11 (73.3%)	8 (57.1%)	NS

Summary

- PUVA and NBUVB seem to be equally effective in achieving clearance and maintaining remission of severe chronic plaque psoriasis in patients with Fitzpatrick ski type 4 and 5

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
S. Dayal, Mayanka, and V. K. Jain. Comparative evaluation of NBUVB phototherapy and PUVA photochemotherapy in chronic plaque psoriasis. *Indian J.Dermatol.Venereol.Leprol.* 76 (5):533-537, 2010. Ref ID: DAYAL2010	RCT Single-centre (outpatient), India Recruited Feb 2004 – May 2005 • Randomised (day of the week) • "Washout" for anti-psoriatic agents (see exclusion criteria)	Total N: 60 **Drop-outs (don't complete the study):** unclear	**Inclusion criteria:** Chronic plaque psoriasis, BSA rule of nines ≥25%); ≥16 and ≤60 years of age **Exclusion criteria:** pregnant or breastfeeding women, history of skin malignancies or photosensitivity; renal or hepatic disease; previous failure or intolerance of phototherapy; any antipsoriatic treatments in previous 4 weeks **Note:** local population skin type IV or V: **Mean baseline** / **PUVA (n=30)** / **NB-UVB (n=30)**	N=30 **PUVA (oral 8-MOP tablets 2h before light – total dose 0.6 mg/kg) twice weekly (non-consecutive days)** Administered using V-care UVA unit Standard initial dose: 2 J/cm^2	N=30 **NB-UVB/TL-01, twice weekly (non-consecutive days)** Administered using V-care NBUVB unit Standard initial dose:	3 months (or until PASI75)	**1° outcome:** PASI75 (remission) **2° and other outcomes:** cumulative clearance dose; number of treatments for clearance; grade I or II erythema; pruritus PASI measures at	None stated

	• Blinding unclear • Allocation concealment (unclear) • No sample size calculation • ITT analysis unclear • Dropouts unclear		Mean age (years): 32.45 / 32.1 Gender M/F (%): 73/27 / 60/40 BSA 25-50%, n: 19 / 21 BSA 50-75%, n: 11 / 9 Disease duration (range): 6 months – 30 years / 6 months-27 years The 2 groups were similar for baseline characteristics	---------- **BOTH ARMS: stepped Tx strategy** Initial dose increased 20% at each visit; if symptomatic erythema developed dose decreased by 50% and then increased by 10% at each subsequent visit	280 mJ/cm^2		baseline, 4, 8 and 12 weeks	

Effect Size

Outcomes

Outcome	PUVA (N=30)	NB-UVB (N=30)	p-value

Change in PASI Baseline (mean ± SD; range) After 3 months (mean ± SD; range) Mean change	 21.6 ± 4.42 (16.4-34.8) 1.39±0.78 (0-2.6) -20.21	 16.82±3.90 (12.2-30.6) 1.6 ± 1.2 (0-3.2) -15.22	 >0.05 >0.05
PASI75 (n)	30	30	<0.05
Days to clearance (mean ± SD; range)	49.2±20.8 (35-80)	65.6±14.59 (45-86)	<0.05
Mean cumulative dose to clearance (J/cm^2)	7.4	1.16	
Mean number of treatments ± SD (range)	12.7±4.99 (6-26)	16.4±4.13 (10-32)	

Adverse events	**PUVA (N=30)**	**NB-UVB (N=30)**
Grade 1 erythema	100%	100%
Grade 2 erythema	70%	40%
Pruritus	80%	
Nausea and vertigo	75%	30%
Diffuse hair fall	70%	30%
Headache	90%	45%

Summary

- Patients of both NBUVB and PUVA groups achieved >75% clearance or complete clearance at the end of 3 months of therapy
- PUVA group achieved faster clearance, required significantly fewer number of treatment sessions and fewer number of days to clear
- However, the mean cumulative clearance dose and adverse effects were lower in the NBUVB group than in the PUVA group.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
T. Markham, S. Rogers, and P. Collins. Narrowband UV-B (TL-01) phototherapy vs oral 8-methoxypsoralen psoralen-UV-A for the treatment of chronic plaque psoriasis. *Arch.Dermatol*. 139 (3):325-	RCT Single-centre (phototherapy unit), Ireland Recruited Jan 1999 – June 2000 • Randomised (unclear	Total N: 54 **Drop-outs (don't complete the study):** N=5 drop-outs in TL01 arm: 4 defaulted and 1 withdrawn because of flaring and required in-	**Inclusion criteria:** Chronic plaque psoriasis affecting trunk and limbs, extent on trunk and limbs by rule of nines ≥8%); no antipsoriatic treatment within 2 weeks prior to study or phototherapy 4 months beforehand; ≥16 years of age; skin types I-III **Exclusion criteria:** pregnant or breastfeeding women; active systemic therapy for psoriasis within previous 8 weeks; abnormal photosensitivity; renal or hepatic disease; previous failure or intolerance of phototherapy; any antipsoriatic treatments in previous 4 weeks	N=25 **PUVA (oral 8-MOP crystalline tablets 2h before light – total dose 0.6 mg/kg; those who could not tolerate 8-MOP were given 5-MOP 1.2 mg/kg) twice weekly (non-consecutive days)**	N=29 **NB-UVB/TL-01, three-times weekly** Administered using whole-body cabin with 24 TL01 fluorescent lamps (311-313 nm)	Tx + 12 months	**Outcomes:** number of treatments to clear, number of days in treatment, number of days in remission, and adverse effects. The end	None stated

<table>
<tr>
<td>328, 2003.

Ref ID: MARKHAM2003</td>
<td>method)
• “Washout” for anti-psoriatic agents (see exclusion criteria)
• Observer blinded
• Allocation concealment (unclear)
• Sample size calculation based on 80% power to detect change in number of exposures of 25% at 5% significance (2 groups of 50 patients required – power not reached)
• No ITT analysis (only available cases analysed)
• Dropouts due to AEs: unclear</td>
<td>patient admission

N=4 drop-outs in PUVA arm: 2 defaulted and 2 withdrawn because of flaring and required in-patient admission</td>
<td>
<table>
<tr><th>Mean baseline</th><th>PUVA (n=25)</th><th>NB-UVB (n=29)</th></tr>
<tr><td>Mean age, years (range)</td><td>39 (28.5-52)</td><td>36 (27-50)</td></tr>
<tr><td>Gender M/F (%)</td><td>52/48</td><td>58.6/41.4</td></tr>
<tr><td>Skin type
I
II
III</td><td>
4
11
10</td><td>
3
13
13</td></tr>
<tr><td>Extent, mean (range), %</td><td>15 (10-25.5)</td><td>13.9 (12.2-17.5)</td></tr>
<tr><td>PASI score, mean (range)</td><td>15.2 (10.8-18.9)</td><td>13.9 (12.2-17.5)</td></tr>
<tr><td>Previous phototherapy</td><td>18</td><td>17</td></tr>
</table>
The 2 groups were similar for baseline characteristics
</td>
<td>Administered using whole-body cabin with 40 UVA fluorescent lamps (315-400 nm)

Dose determined by minimal phototoxic dose (MPD) measurement judged visually 72 h after irradiation of 8 unaffected regions of the upper back.

Wore UVA protective glasses for 24 h after treatment

BOTH ARMS: stepped Tx strategy

Initial dose 70%</td>
<td>Dose determined by minimal erythematic dose (MED) measurement judged visually 24 h after irradiation of 8 unaffected regions of the upper back.

BOTH ARMS:

Aqueous cream allowed as required; Vioform HC cream applied twice daily to flexural psoriasis and tar pomade was applied to the scalp</td>
<td></td>
<td>point of the study was complete clearance of psoriasis.</td>
<td></td>
</tr>
</table>

				MED or MPD, increased 20% at each treatment (dose increments postponed if erythema developed; grade 2 or 3 erythema = next exposure postponed)	Patients were reviewed once weekly during the study and monthly after clearance for 12 months Relapse was defined as 50% of the original extent.			

Effect Size

Outcomes (for 45 who completed treatment)

Outcome	**PUVA** **(N=21)**	**NB-UVB** **(N=24)**	**p-value**
Median number of treatments to clearance (95% CI)	19 (14.6-25.0)	25.5 (18.0-32.5)	0.03
Median days to clearance (95% CI)	66 (52.0-92.6)	67 (47.9-81.7)	0.46
	N=19	**N=24**	
Median duration of remission/ time to relapse (days) (95% CI)	231 (162.7-365.0)	288.5 (170.6-365.0)	0.40

Months in remission; n (%)			
3	18 (95)	23 (96)	
6	13 (68)	16 (67)	
9	8 (42)	23 (96)	
12	10 (42)	7 (37)	

Adverse events	**PUVA (N=21)**	**NB-UVB (N=24)**
Grade 1 erythema	80%	75%
Grade 2 erythema	40%	0%
Pruritus	"Equal"	
Polymorphic light eruption	"Equal"	
Nausea	~15% (presented graphically)	0%

Summary

- Those in the PUVA group required significantly fewer treatments to clear.
- There was no significant difference in the number of days to clear or number of days in remission.
- A similar percentage of patients in the TL-01 and PUVA groups developed minimal perceptible erythema, showing that the regimens were equally

erythemogenic. Asymptomatic, well-defined erythema occurred only in the PUVA group.

- **Narrowband UV-B phototherapy, used 3 times weekly, is as effective for the treatment of CPP as oral 8-MOP PUVA used twice weekly**

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
A. B. Serwin and B. Chodynicka. Soluble tumour necrosis factor-alpha receptor type 1 as a biomarker of response to phototherapy in patients with psoriasis. *Biomarkers* 12 (6):599-607, 2007. Ref ID: SERWIN2007	RCT (plus control group) Single-centre, Poland Recruited Jan–Sept 2005 • Randomised (unclear method) • No washout period • Blinding not stated • Allocation concealment (unclear)	Total N: 50 **Drop-outs (don't complete the study):** 0	**Inclusion criteria:** Early onset (before 40 years of age) plaque-type psoriasis; skin type II or III **Exclusion criteria:** concomitant systemic disorders **Mean baseline** / **PUVA (n=25)** / **NB-UVB (n=25)** Mean age, years±SD (range): 43.40±12.18 (22-59) / 38.21±11.40 (21-60) Gender M/F (%): 56/44 / 44/56 Mean age of onset of psoriasis, years±SD: 22.93±8.71 (10-40) / 18.89±11.11 (4-40)	N=25 **PUVA (oral 8-MOP soft gelatine capsules 1h before light – total dose 0.6 mg/kg; three-times weekly (up to 20 irradiations); non-consecutive days** Administered using Arimed	N=25 **NB-UVB three-times weekly (up to 20 irradiations); non-consecutive days** Administered using TL01 lamps (311-313 nm) Initial dose: 50% MED	20 Tx + 1 month follow-up	**1° outcome:** serum concentration sTNF-R1 (including from 20 controls – healthy volunteers) **2° and other outcomes:** PASI75 and change in PASI	None stated

	• No sample size calculation • ITT analysis • Dropouts due to AEs: 0		(range) PASI score (range) 11.40-24.61 7.11-23.40 The 2 groups were similar for baseline characteristics		PUVA lamps (320-340 nm) Initial dose: 70% MPD	---------- **BOTH ARMS:** Only topical emollients permitted			

Effect Size

Outcomes (ITT analysis)

PASI score (mean±SD)	**PUVA (N=25)**	**NB-UVB (N=25)**	**p-value**
Baseline	17.22±3.48	16.32±5.26	NS
After 10 treatments	11.23±3.39	8.57±3.33	<0.01
After 20 treatments	5.55±2.10	4.42±1.67	<0.05
1 month after end of treatment	4.85±1.79	4.50±1.60	NS
PASI75 after 20 treatments, n (%)	**19 (76%)**	**21 (84%)**	**p>0.05**

Summary

- Narrowband UV-B and PUVA gave similar therapeutic results after 20 treatments

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
A. Akman, O. Dicle, F. Yilmaz, M. Coskun, and E. Yilmaz. Discrepant levels of vascular endothelial growth factor in psoriasis patients treated with PUVA, Re-PUVA and narrow-band UVB. *Photodermatol.Photoimmunol.Photomed.* 24 (3):123-127, 2008. Ref ID: AKMAN2008	RCT Single-centre (dermatology out-patient clinic), Turkey • Randomised (unclear method) • No washout period • Blinding not stated • Allocation concealment (unclear) • No sample size calculation • No ITT analysis (only available	Total N: 40 **Drop-outs (don't complete the study):** 2 – due to side effects or lost to follow-up PUVA: 2 NB-UVB: 0	**Inclusion criteria:** Topical or systemic therapy for at least 2 months **Exclusion criteria:** not stated **Mean baseline** / **PUVA (n=18)** / **NB-UVB (n=20)** Mean age, years±SD: 38.8±15.0 / 42.6±14.0 Gender M/F (%): 28/72 / 40/60 Mean PASI ±SD: 15.8±8.2 / 10.5±6.5	N=20 **PUVA three-times weekly** **Initial dose:** determined by Fitzpatrick skin type **Dose escalation:** increased by 30% of initial dose at each session	N=20 **NB-UVB three-times weekly** **Initial dose:** 70% MED **Dose escalation:** 20% increment at each session N=20	8 weeks (24 sessions)	**1° outcome:** Change in PASI **2° and other outcomes:** Serum VEGF	None stated

	cases analysed) • Dropouts due to AEs: unclear							

Effect Size

Outcomes (ACA)

PASI score (mean±SD)	**PUVA (n=18)**	**NB-UVB (n=20)**
Baseline	15.8±8.2	10.5±6.5
After 10th day of treatment	12.6±1.6	9.23±1.33
After 12 treatments	8.71±1.59	7.1±1.0
After 24 treatments	3.4±0.7	3.9±0.7
Mean change (all P<0.001)	**-12.4**	**-6.6**

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
P. M. Gordon, B. L. Diffey, J. N. Matthews, and P. M. Farr. A randomized comparison of narrow-band TL-01 phototherapy and PUVA photochemotherapy for psoriasis. *J.Am.Acad.Dermatol.* 41 (5 Pt 1):728-732, 1999. Ref ID: GORDON1999	RCT Single-centre (referred to PUVA clinic), UK Referred July 1996-Sept 1997 • Randomised (randomised permuted blocks within strata) • Washout period (emollient alone in 4 weeks before treatment) • Assessor blinded • Allocation concealment (sealed	Total N: 100 **Drop-outs (don't complete the study):** TL01: 4 4 = failure to attend PUVA: 5 2 = failure to attend; 2 = withdrew due to nausea; 1 = general health problem	**Inclusion criteria:** Chronic plaque psoriasis (moderate-to-severe) **Exclusion criteria:** current systemic therapy for psoriasis; any UV therapy within the preceding 6 months **Note:** allocation stratified by: • plaque size (small <3 cm diameter) or large (>3 cm diameter) • skin type (I/II or III/IV) **Mean baseline** / **PUVA (n=49)** / **TL01 (n=51)** Mean age (SD): 41.0 (11.2) / 43.3 (12.9) **Skin phototype (n)**	N=49 **Oral PUVA twice weekly** Psoralen: microcrystalline methoxsalen; 25 mg/m^2 total BSA (range 30-60 mg; median 40 mg) Administered using whole-body units fitted with 40 fluorescent PUVA lamps Minimal phototoxic dose (MPD) measurement 2 h after psoralen ingestion judged	N=51 **NB-UVB (TL01) twice weekly** Administered using whole-body units fitted with 40 fluorescent TL01 lamps Dose determined by minimal erythematic dose (MED) measurement judged visually 24 h after irradiation of forearm (10 test doses)	Tx + 6 months in those who cleared Patients withdrawn if no improvement after 16 Tx	**1° outcome:** clearance of plaques at all sites above knees (nearly clear) **2° and other outcomes:** number of treatments for clearance; UV dose for clearance; adverse effects; relapse rate Assessments made by clinician after every 8 Tx (or sooner if nurses suspected clear)	None stated

	envelopes) • Sample size calculation based on 80% power to detect change in median exposure of 25% at 5% significance (2 groups of 50 patients required • ITT analysis • Dropouts due to AEs: PUVA: 2; TL01: 0		I II III IV	 8 18 16 7	 5 21 24 1	visually 72 h after irradiation of the forearm (4 test doses); initial dose on same day as phototesting 1-2.5 J/cm^2 based on PUVA history, skin type, and experience of sunburn. Dose then increased stepwise to MPD if tolerated or to a maximum of 6 J/cm^2; subsequently weekly dose increments used starting with 40%, reducing stepwise to 10% by sixth week ---------- **BOTH ARMS:** dose increments postponed or treatments missed in case of erythema	**Initial dose:** 70% MED **Dose escalation:** increased by 30-40% each week, reducing stepwise to 5-10% by 6th week (max dose 2066 mJ/cm^2)			
			Small plaque psoriasis	28	29				
			Large plaque psoriasis	21	22				
Effect Size									

Outcomes (ITT analysis n=100)

Outcomes	PUVA (n=49)	TL01 (n=51)	OR (95% CI)	p-value
Clear (n)	41 (84%)	32 (63%)	3.04 (1.18-7.84)	0.018
Treatment stopped owing to poor response (after 16 Tx), n	3	15		
Median number of exposures for clearance (based on Weibull distribution)	16.7	25.3	Ratio of medians: 1.52 (1.24-1.86)	<0.001
Erythema	17	37		
Erythema requiring missed Tx	6	1		
Nausea	2	0		

Relapse rate (no longer clear)/time to relapse of those cleared (after stopping UV treatment)

	TL-01	PUVA
Failed to clear	19 (38%)	8 (18%)
Clear but relapsed at 3 months	19 (38%)	14 (32%)
Clear at 3 months but relapsed at 6 months	5 (10%)	5 (11%)

Clear at 6 months	7 (14 %)	17 (39%)
Total	50	44

- Cumulative proportional odds model showed a significant difference between the treatments
- Odds of failing to clear at each of the trial assessment points (end of Tx; 3 moths and 6 months) were 3.69 times higher for TL01 than PUVA (95% CI: 1.61-8.47)

Conclusion

- Twice weekly oral PUVA is more efficacious than twice weekly TL01; clearance of psoriasis achieved in a significantly greater proportion of patients treated with PUVA than TL01 and significantly fewer treatments were needed for clearance with PUVA

H.8.4 PUVA vs UVB (within-patient randomisation)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
R. S. Dawe, H. Cameron, S. Yule, I. Man, N. J. Wainwright, S. H. Ibbotson, and J. Ferguson. A randomized controlled trial of narrowband ultraviolet B vs bath-psoralen plus ultraviolet A photochemotherapy for psoriasis. *Br.J.Dermatol.* 148 (6):1194-1204, 2003. Ref ID: DAWE2003	RCT – **within-patient randomisation** Single-centre (referred from general dermatology clinics), Scotland Referred September 1996-May 1999 • Randomised (random number generation) • Washout period • Assessor	Total N: 28 **Drop-outs (don't complete the study):** 10 4 = inadequate response on PUVA side 1=inadequate response on NBUVB 2 = PLE requires topical steroids 1 = illness 1 = PUVA itch 1 = pregnancy	**Inclusion criteria:** Chronic plaque psoriasis **Exclusion criteria:** age <18 years, history of skin cancer or keratoses; phototherapy, PUVA or systemic therapy for psoriasis within the preceding 3 months **Mean baseline** / **All (n=28)** Age (range): 22-71 Gender M/F (%): 61.7/39.3 **Skin phototype (n)** I: 6 II: 12 III: 10	N=28 **Bath PUVA twice weekly** Psoralen: TMP 50 mg in 100ml ethanol mixed in 150 l 37C bathwater to make a concentration of 0.33 mg/l. Patient soaked in bathwater for 10 minutes followed by immediate exposure to UVA Administered using Dixwell cabinet fitted with 47 R-UVA tubes	N=28 **NB-UVB (TL01) three-times weekly** Administered using either Waldmann UV5000 cabinet fitted with 24 100W TL01 lamps or Ninewells Medical Physics department cabinet fitted with 50 100W TL01 lamps This side	Tx + 1 year (or until relapse) in those who cleared/had MRA on both sides End points: clearance (no palpable psoriasis) or minimal residual activity (MRA; trace disease, below knees or on sacrum only); or 30 treatments on both sides Relapse: return of psoriasis of	**1° outcome:** days and number of Tx to clear **2° and other outcomes:** Adverse events, duration of remission Severity of psoriasis assessed before Tx and at each Tx visit on 0-4 scale for each of scaling, erythema and induration of	None stated

	blinded (assessment of AEs by unblinded nurse) • Allocation concealment (sequentially numbered allocation list held by independent administrator) • Sample size calculation (power of 80% to detect either a difference of 2 Tx or of 7 days to clearance = need 22 patients; **underpowered** because only 18 completed) • Per protocol comparison for those who reached clearance or	1 = fail to attend	Previous UVB or PUVA (n): 24 Previous UVB only: 11 Previous PUVA only: 13* Previous systemic retinoid: 2 Previous methotrexate: 1 *High proportion; not representative of psoriasis population	Light dose determined by minimal phototoxic dose (MPD) measurement judged visually 72 h after irradiation of 8 unaffected regions of the upper back. Wore half-body suits that allowed transmission of no UVB and negligible UVA (0.6% transmission at 365 nm) **Initial dose:** 40% MPD **Dose escalation:** increased by 20% at each session, reducing to 10% increments (max dose 15 J/cm^2)	treated first Dose determined by minimal erythematic dose (MED) measurement judged visually 24 h after irradiation of 8 unaffected regions of the upper back. **Initial dose:** 70% MED **Dose escalation:** increased by 20% at each session, reducing to 10% increments (max dose 2066 mJ/cm^2)	sufficient severity that patient was unwilling to proceed with emollient alone or increase in global score to 50% that of baseline	3 symmetrical plaques chosen at baseline on upper limbs, trunk and lower limbs A 0-4 global score was also used (no psoriasis to severe) based on PASI	

	MRA • ITT analysis (using Cox's proportional hazards – assumes outlook for those who withdrew was the same as for those who did not withdraw) • Dropouts due to AEs: 3			---------- **BOTH ARMS:** decision to stop treatment made by masked observer Facial protection offered if no facial psoriasis; males wore genital protection Adjunctive therapy restricted to emollients known not to significantly impede UV transmission and standard topicals for scalp, face and flexures Tx stopped when patient clear or after 4th exposure following first documentation of				

				minimal residual activity				

Effect Size

Outcomes (available case analysis)

Outcomes	**PUVA side**	**NB-UVB side**	**95% CI; p-value**
Clear/MRA at completion (n)	15/22	21/23	

Outcomes (ITT analysis n=28)

Outcomes	**Hazard ratio (TL01 vs PUVA)**	**TL-01 (n=28)**	**PUVA (n=28)**	**95% CI; p-value**
Clear/MRA at completion – modelled against days to clear	3.53			1.99-6.26; <0.001
Median days to clear		61	86	
Clear/MRA at completion – modelled against Tx to clear	1.03			0.58-1.83; 0.92
Median Tx to clear		25	21	
Clear/MRA at completion (n)		**21**	**15**	6-37%; p = 0.02

Mean time to relapse among those who cleared		**N=21** **106.72 (SD 62.71)**	**N=15** **67.45 (SD 65.62)**	**MD: 39.27 days**

Adverse events	**TL-01** **(N=28)**	**PUVA** **(N=28)**	**95% CI; p-value**
Grade 1 erythema	16 (57%)	21 (75%)	-2 to 38%; p=0.10
Grade 2 erythema	10 (36%)	8 (29%)	-12 to 27%; p=0.48
Grade 3 erythema	4 (14%)	4 (14%)	-17 to 17%; p >0.99
Polymorphic light eruption	2 (71.4%)	2 (71.4%)	
Itch	0	1 (3.6%)	

Duration of remission

No difference between treatments in duration of remission (data presented graphically)

Conclusion

- TL01 is more efficacious than TMP bath PUVA to treat chronic plaque psoriasis

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
E Snellman, T. Klimenko, T. Rantanen Randomized Half-side Comparison of Narrowband UVB and Trimethylpsoralen Bath plus UVA Treatment for Psoriasis *Acta Derm Venereol.* 84: 132-137, 2004 Ref ID: SNELLMAN2004	RCT (right/left comparison; **within-patient randomisation**) Single-centre (referred to Dermatology Department), Finland Referred September 2001- March 2002 • Right/Left side of the body comparison of TL01 and PUVA • Randomised (automatically computed random number table) • Washout period (2 months for	Total N=18 **Drop-outs (don't complete the study): 3** PUVA side: 1 (exacerbation of psoriasis) Remaining 2 not related to treatment	**Inclusion criteria:** Chronic over 2 years duration, symmetric and mostly plaque type, > 18 years of age, suitable for and in need of phototherapy, skin type II-IV. **Exclusion criteria:** Systemic therapy or any UV therapy within the preceding 2 months or topical treatment in the previous 2 weeks. Scalp and face psoriasis was excluded from being assessed during the study. No individual group baseline data apart from skin type/MED/MPD.	N=17 **Bath PUVA three times a week** Half side irradiations: patients wore a double brown cotton material UV protective suit Psoralen: Trioxysalen alcohol solution; 50mg/100ml diluted in 150L of tap water. 0.33mg/l bath concentration. Bathing time was 10 mins. Skin Type II: Dose 0.05 J/cm^2. 20-30% increases initially, then 10%. Skin Type III & IV: Dose 0.07 J/cm^2. Each dose	N=17 **NB-UVB (TL01) three times a week** Half side irradiations: patients wore a double brown cotton material UV protective suit UVB was given first to avoid any interaction with the Trioxysalen. Administered using a cabin	10 week treatment during the trial with a 6 month follow up period in those who cleared If treatment was unsatisfactory at the end of the 10 weeks, patients could withdraw.	**1° outcome:** Improvement in the PASI (modified PASI excluding the palms, soles, and head), GIS (Global Improvement Score) and TLS (Target Lesion Score) **2° and other outcomes:** Time to 100% relapse in the PASI or time to start another treatment (2 month interval recordings in post treatment phase) Cumulative	None stated

	systemic/phototherapy and 2 weeks for topicals) • Assessor blinded • Allocation concealment (sealed envelopes) • Sample size calculation based on 80% power to detect 10% difference in PASI at 5% significance (minimum 12 patients required) • ITT **but note :** One patient dropped out after randomisation so did not receive their allocated treatment or have their data collected. • **Drop out due to AEs : PUVA : 1 ; TL01 : 0**		For the 17 patients who undertook the trial: • 4 females, 13 males • Mean age 46 +/- 12 years • Severity ranged from mild to severe • Skin phototype: II n=9 , III n=5 , IV n=3 .	repeated at least twice. Administered using cabinets fitted with 27 fluorescent PUVA tubes Minimal phototoxic dose (MPD) and minimal erythema dose (MED) were assessed at the beginning using geometric dose series increasing by √2. MPD measurement read at 72hrs. Maximum 30 exposures. Emollient or Salicylic acid were permitted for concurrent use (not to be applied before the irradiations). In adverse events such as skin burn topical glucocorticoid	with 40 TL01 tubes. **Initial dose:** 50% MED **Dose escalation:** increased by 20-30% each time until erythema appeared or 1.0J/cm^2. Then increases were by 10 or 20%. Erythema development would result in reducing, keeping constant or not giving the dose. Minimal phototoxic dose (MPD)		UVB and UVA dose Adverse events Assessments made by a blinded observer at the start of the trial, then weekly for the 10 weeks. During the post-treatment follow up it was every 2 months.	

				formulation was permitted for 1-2 days.	and minimal erythema dose (MED) were assessed at the beginning using geometric dose series increasing by √2. MPD measurement read at 72hrs. Maximum 30 exposures. Emollient or Salicylic acid were permitted for concurrent use (not to be applied before the irradiations). In adverse events such as skin burn			

					topical glucocorticoid formulation was permitted for 1-2 days.			

Effect Size

Outcomes (ITT n=17)

Outcomes	**PUVA (n=17)**	**TL01 (n=17)**	**p-value**
Improvement in the PASI (modified PASI), median (range)	Initial: 8.6 (1.8-14.4) Final: 3.5 (0-9.6) Difference: 45%↓ (8-100%↓)	Initial: 8.5 (1.8-15.2) Final: 1.0 (0-6.6) Difference: 77%↓ (24-100%↓)	Initial: p>0.05 Final: p<0.001
Mean change in PASI	**4.44 SD: 3.83** **N=14**	**7.15 SD: 4.07** **N=14**	
Clear - 100% improvement in modified PASI (n)	1 (5.9%)	5 (29.4%)	
2 month relapse (100% PASI relapse)	7/13[1]	6/13[2]	

[1] Two patients had bilateral relapse, 4 patients used other treatments (PUVA or TL01 sides not stated) and 1 patient had a relapse on their PUVA treated side

Relapse in 2 months to ≤ 4 months follow up	6/6 (100%)[3]	6/6 (100%)	
Median cumulative dose of UV (J/cm^2), range	8.06 (3.31-12.51)	39.92 (13.95-81.56)	
Median number of UV treatments[4], range	30 (23-30)	30 (22-30)	
Erythema	11	17	

Conclusion

- NBUVB was more effective and safer than PUVA

[2] Two patients had bilateral relapse, 4 patients used other treatments (PUVA or TL01 sides not stated)
[3] 1 patient had a bilateral relapse at < 4months, 4 patients used other treatments and one patient relapsed at 4 months.
[4] Calculations exclude two patients who withdrew early from the study (moved house, deteriorated on the PUVA side)

H.8.5 Different frequencies of narrowband UVB (TL01) – between patient randomisation

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Z. Hallaji, M. Barzegari, K. Balighi, P. Mansoori, A. Taheri, P. Mansoori. 2010 A comparison of three times vs. five times weekly narrowband ultraviolet B phototherapy for the treatment of chronic plaque psoriasis. *Photodermatology, Photoimmunology & Photomedicin*	RCT Single-centre (referred to Dermatology clinic), Iran Referred April 2003- October 2004 • Randomised (Weighted randomization (minimization) • Assessor blinded • No allocation concealment • Sample size	Total N=65 **Drop-outs (don't complete the study):** 3 times/wk TL01: N=9 1= lost to f/u 8= withdrawal due to repeated failure to attend or inability to attend the clinic for >2wks 5 times/wk TL01: N=11 11= withdrawal	**Inclusion criteria:** Patients with chronic plaque psoriasis affecting >10% of their body surface area **Exclusion criteria:** Patients aged <10 years old, pregnancy, history of skin cancer/solar keratoses, history of immunosuppressive therapy or phototoxic drugs, history of abnormal photosensitivity, history of previous failure or intolerance to phototherapy and patients who have had topical psoriasis therapy in the last 2 weeks, systemic treatment in the last 2 months or phototherapy in the last 4 months. Emollients or mild/mod glucocorticoids on the scalp or	N=32 **NB UVB - TL01 three times a week** Petrolatum was applied to the psoriatic lesions prior to treatment. TL01 fluorescent lamps were used in the cubicles. First dose: 75mJ/cm^2	N=33 **NB UVB -TL01 five times a week** Petrolatum was applied to the psoriatic lesions prior to treatment. TL01 fluorescent lamps were used in the cubicles. First dose:	Tx until clearance occurred (range 4.7-23 weeks) Treatment continued until clearance (above the knees) or unacceptable side effects. Treatment was stopped if deemed no further improvement could be made. Poor clearance withdrawal only after ≥16	**1° outcome:** Proportion of patients who reached clearance[5] **2° and other outcomes:** Cumulative UVB dose Number of treatments Length of treatment period PASI score Skin erythema during treatment, postlesional hypopigmentation or hyperpigmentation at the site of healed psoriatic	None stated

[5] Clearance: When all exposed psoriatic lesions above the knees had healed (flat, without scale or erythema)

e26; 10-15. 2010 Ref ID: HALLAJI2010	calculation based on 80% power to detect >30% difference in treatment success (clearance) at 5% significance (2 groups of 28 patients required) • ITT for clearance. For all other outcomes available cases were analysed.	due to repeated failure to attend or inability to attend the clinic for >2wks	photoprotected areas was allowed pre and during the study. Two groups were matched for PASI, age and sex. **Mean baseline** / **TL01 3 times/wk** / **TL01 4 times/wk** Sex (M%): 60.9% / 54.5% Mean age (range): 32.6 (13-75) / 36.1 (20-58) **Skin phototype (n)** I: 0 / 0 II: 6 / 3 III: 13 / 16 IV: 4 / 3 No significant differences were	Incremental dose increase: 20% of previous dose Effect of erythema on next dose: Grade 1: repeat previous dose, thereafter 10% increases Grade 2: postpone until erythema resolved. 80% previous dose, thereafter 10% increases. Grade 3: postpone until erythema and pain resolved. 50% previous dose, thereafter 10% increases. Missed treatments: 5-7 days: repeat previous dose 8-14 days: 75% of previous dose >14 days: withdraw	75mJ/cm^2 Incremental dose increase: 20% of previous dose Effect of erythema on next dose: Grade 1: repeat previous dose, thereafter 10% increases Grade 2: postpone until erythema resolved. 80% previous dose, thereafter 10% increases. Grade 3: postpone until erythema and pain resolved. 50% previous dose, thereafter 10% increases.	exposures.	lesions Patient satisfaction with the treatment Assessments made by clinician after 12 Tx and when the patient was clear (end of the treatment period)	

			found between the two groups in their baseline/demographic variables. **Note: Adult and Child mixed population**	patient from the study MED used was the lowest MED reported in previous papers: 75mJ/cm^2 Male patients wore genital protection. All patients were given UV protective goggles. No limit for the number of exposures.	Missed treatments: 5-7 days: repeat previous dose 8-14 days: 75% of previous dose >14 days: withdraw patient from the study MED used was the lowest MED reported in previous papers: 75mJ/cm^2 Male patients wore genital protection. All patients were given UV protective goggles.			

					No limit for the number of exposures.			

Effect Size

Outcomes (ITT analysis n=65, ACA N=45)

Outcomes	**TL01 3 times a week** **(ITT n=32 , ACA n=23)** **(95% CI)**	**TL01 5 times a week** **(ITT n=33, ACA n=22)** **(95% CI)**	**p-value**
Clearance of psoriasis - ITT (non-responder imputation (n,%)	18 (56.3%)	15 (45.5%)	0.38
Clearance of psoriasis - ACA (n,%)	18 (78%) (61-95%)	15 (68%) (48-88%)	0.44
Mean number of treatments to clearance (95% CI)	35.1 (30.2-39.9) **N=18**	36.5 (31.2-41.8) **N=15**	
Mean time to clearance, weeks (95% CI)	13.7 (11.4-15.9)	7.9 (6.7-9.0)	

	N=18	N=15	
Mean cumulative UVB dose (J/cm^2) (95% CI) – ACA	43.0 (34.4-51.7)	46.3 (34.5-58.0)	0.51
Mean number of treatments (95% CI)– CA	37.6 (32.6-42.6)	37.8 (33.5-42.2)	0.95
Mean length of treatment (weeks) (95% CI) – ACA	14.7 (12.5-16.9)	8.9 (7.6-10.1)	<0.001
Mean Baseline PASI score - ACA	16.4	16.4	0.02
Mean end of treatment PASI score-ACA	1.9	4.9	
Erythema[6] Mild (Grade1-2) Moderate (Grade 3)	 15 (65%) 0	 16 (73%) 0	 0.59

Conclusion

- **There is no significant difference for the clearance of psoriasis between TL01 3 times a week and TL01 five times a week**
- **There is a significant reduction in the number of weeks of treatment for TL01 five times a week compared to TL01 3 times a week**
- **TL01 three times a week significantly reduces the PASI score compared to TL01 five times a week**

[6] No other complication or side-effect was recorded in the study

H.8.6 Different frequencies of narrowband UVB (TL01) – within-patient randomisation

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
R. S. Dawe, N. J. Wainwright, H. Cameron, J. Ferguson. Narrow-band (TL-01) ultraviolet B phototherapy for chronic plaque psoriasis: three times or five times weekly treatment? *British Journal of Dermatology.* 138; 833-839. 1998 Ref ID:	Paired (within patient) **right/left comparison** RCT Single-centre (referred to the dermatology outpatient clinic), UK Referred November 1995 – June 1996 • Randomised (random number table) • Unclear allocation concealment	Total N: 21 **Drop-outs (don't complete the study): 2** 1= failure to attend (intercurrent illness) 1=declined to continue as satisfied with a modest improvement	**Inclusion criteria:** Chronic plaque psoriasis **Exclusion criteria:** history of skin cancer/ solar keratoses, on systemic immunosuppressive therapy, age <18 years old, phototherapy PUVA or any systemic therapy for psoriasis within the preceding 3 months, guttate psoriasis, known abnormal photosensitivity and any expressed hesitation about ability to attend daily treatment.	N=21 **NB-UVB (TL01) three times a week** Either a UV5000 Waldmann cubicle with 24 100W TL01 lamps or a 50 100W TL01 lamps were used. ---------- **Both arms:**	N=21 **NB-UVB (TL01) five times a week** Either a UV5000 Waldmann cubicle with 24 100W TL01 lamps or a 50 100W TL01 lamps were used.	Treatment was stopped when the patient was clear of psoriasis or in a state of minimal residual activity (MRA) for 4 treatments. Treatment given until clearance is reached. The patient is then followed up until relapse/ for one year.	**1° outcome:** clearance of psoriasis **2° and other outcomes:** Psoriasis Severity Scores (SEI) number of treatments for clearance; UV dose for clearance; number of days to clearance Relapse[7] Adverse events	None stated

[7] Relapse definition: Increase in Global Score to 50% of the baseline value or an increase in the psoriasis severity that the patient is no longer willing to solely use emollient.

DAWE1998	• Assessor blinded • No sample size calculation reported in the paper • ACA analysis and those who cleared • There were no dropouts due to adverse events		**Mean baseline** / **N=21** Sex (M%) / 61.9% Mean age (SD) / 43 years (13.6) **Skin phototype (n)** I / 2 II / 14 III / 5 IV / 0	MED was done on the upper back skin. MED was the lowest dose that produced a just perceptible erythema. **Initial dose**: 70% of MED Max. Exposure dose: 2066mJ/cm^2 Each side was treated independently: Mon, Wed, Fri for 3x week and Mon-Fri for 5x week. Patients wore a half body suit. **Dose escalation:** No erythema- 20% increase. Mild- repeat previous dose and reduce to 10% increments. Mod- postpone 1 treatment, repeat previous dose, then 10% increments. Sever- no treatment.			Assessments were made at each appointment for UVB. Assessments were made by monthly telephone calls or appointments at the department for relapses.	

				Further treatment at the doctors discretion. Maximum 30 exposures. All patients were offered facial photo-protection (faceshield) or topical sunscreen if no facial psoriasis. Emollients, aqueous cream, diprobase, coconut oil were allowed. Standard topical treatments for scalp, face and flexures were also permitted.				
Effect Size **Outcomes (ITT analysis n=21, those that cleared analysis CLA n=16)**								

Outcomes	TL01 3 times a week (ITT N=21 CLA N=16)	TL01 five times a week (ITT N=21 CLA N=16)	Difference between the two treatment groups	OR (95% CI)	p-value
Clearance of psoriasis* – ITT Clearance of psoriasis* - ACA	16/21 16/19	16/21 16/19			
Median number of days to clear (range) - CLA	40 (23-63)	35 (19-43)	5 95% CI 2-11		0.007
Median UVB dose (multiples of individuals MED) to clear (range) - CLA	64 (23-125)	94 (27-164)	95% CI 5-33		0.010
Median number of treatments to clear (range) - CLA	17	23.5	95% CI 3.5-8		0.001
Erythema – Grade 2 - CLA	3/16	15/16			<0.001
Adverse events: Polymorphic light eruption (PLE)	1	2			
Time to Relapse (topical therapy other than emollients required or fall to 50% of baseline)	Graphical representation – median = 165 days	No data given. Graphical representation - median = 174 days	9 days		0.73

*Note – this was defined as clearance on both sides (unclear if any participants cleared on one side only and were not counted)

Conclusion

- TL01 five times a week has significantly fewer number of days required to clear psoriasis however, three times a week TL01 requires significantly lower median UVB doses, number of treatments and has fewer Grade 2 erythema.

H.8.7 Different frequencies of narrowband UVB (TL01) – between-patient randomisation

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
H. Cameron, R. S. Dawe, S. Yule, J. Murphy, S. H Ibbotson, J. Ferguson. A randomized, observer-blinded trial of twice vs. three times weekly narrowband ultraviolet B phototherapy for chronic plaque psoriasis. *British Journal of Dermatology*. 147;973-978. 2002 Ref ID:	RCT Single-centre (referred to the phototherapy general dermatology clinic), UK Referred May 1998 to December 2000 • Randomised (computer generated random allocation) • Assessor blinded • Sample size calculation: 5% level of	Total N: 113 **Drop-outs (don't complete the study): 29** TL01 twice a week N= 18 4= poor progress 9= poor attendance 2= polymorphic light eruption 1= withdrew as wanted to be in the other group 1= moved house 1=treated	**Inclusion criteria:** Chronic (present or recurring psoriasis for at least 1 year) plaque psoriasis (clinical diagnosis by a Dermatologist) **Exclusion criteria:** Those on immunosuppressive therapy or with a history of skin cancer, patients who had phototherapy/PUVA or systemic psoriasis therapies in the previous 3 months, <16 years of age or were unable to attend reliably. Median age: 41 years (range 17-80) Sex: 70 male (62%), 43	N=58 **NB-UVB (TL01) twice a week** ---------- **Both arms:** Either a UV5000 Waldmann cubicle or one built by a medical physics department. Both used100W TL01 lamps. MED was done on	N=55 **NB-UVB (TL01) three times a week**	Treatment was stopped when the patient was clear of psoriasis or in a state of minimal residual activity (MRA) for 4 treatments. Followed up for time to relapse in the following year.	**1° outcome:** number of treatments, dose and time (days) to the clearance of psoriasis **2° and other outcomes:** Psoriasis Severity Scores (SEI) Erythema Remission (psoriasis requiring treatment other than emollients) duration	None stated

CAMERON2002	significance and an 80% completion rate, 44 patients were needed in each group • ITT and competers analysis • There were 3 drop outs for polymorphic light eruption	with 3xweek by error TL01 three times a week N=11 4=poor progress 4= poor attendance 1= polymorphic light eruption 1= wanted to attend 2xweek 1=used self prescribed topical therapy	female (38%) Skin phototypes I-III: no significant difference between the two groups; p=0.27 No other baseline data reported.	the upper back skin. MED was the lowest dose that produced a just perceptible erythema in 24 hrs. **Initial dose**: 70% of MED No limit to number of exposures. Treatment days: Mon and Fri. Patients were assessed prior to treatment by an independent assessor. Erythema recorded by nurse phototherapists (not blinded). **Dose escalation:** 20% increase followed by 10% dose increments. All male patients wore genital			Assessments were made by monthly telephone calls or appointments at the department for relapses.	

				protection. All patients wore a face shield unless they had facial psoriasis. Only approved emollients, or scalp, facial and flexural therapies were permitted.				

Effect Size

Outcomes (ITT analysis n=113, Completers analysis (CA) n=84)

Outcomes	**TL01 twice a week (ITT N=58, CA N=40)**	**TL01 three times a week (ITT N=55, CA N=44)**	**Difference (95% CI)**	**p-value**
Number of patients cleared of psoriasis	40	44	10% fewer (25% fewer to 7% more)	0.21
Mean number of days to clearance-CA (range)	88 (48-150)	58 (32-112)		<0.0001

Mean number of treatments to clearance- CA (range)	24.4 (11-41)	23.0 (14-38)		0.15
Mean UVB dose (total dose in multiples of each individual's MEDs) to clearance- CA (range)	125 (17-923)	95 (36-357)		0.062
Relapse (topical therapy other than emollients required) in the year post clearance - CA	Only graphical representation – median = 4.7 months	Only graphical representation median = 3.8 months		0.53
Relapse (further phototherapy or other second line therapy required) in the year post clearance - CA	Only graphical representation median = 21.3 months	Only graphical representation median = 17 months		0.73
Erythema[8] (ITT) Grade 2 Grade 3	 31% 17%	 56% 21%	 25% (7-43%) 4% (-10-19%)	 0.007 0.57

Conclusion

- Three times a week TL01 requires significantly fewer number of days to clear chronic plaque psoriasis.A higher percentage of grade 2 erythema was found in the three times a week TL01. There were no other significant associations found. A non significant association was demonstrated with TL01 three times a week having a lower total UVB dose than TL01 twice a week.

[8] One patient in the twice weekly group had a single episode of blistering erythema (grade 4). It was localized and suggested to be due to a misplacement of genital protection exposing skin not previously exposed.

H.8.8 Home vs out-patient UVB (PLUTO Study)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
M. B. Koek, E. Buskens, H. van Weelden, P. H. Steegmans, C. A. Bruijnzeel-Koomen, and V. Sigurdsson. Home versus outpatient ultraviolet B phototherapy for mild to severe psoriasis: pragmatic multicentre randomised controlled non-inferiority trial (PLUTO study). *Br.Med.J.* 338:b1542, 2009.	RCT 'Pragmatic' design: treatments applied under the conditions they usually would be in clinical practice (treatment regimen not imposed) Multi-centre (14 hospital dermatology departments), The Netherlands 2002-2005	Total N: 196 **Drop-outs (don't complete the study):** **Total** lost to follow-up (including those who did not start therapy) Home: 7 (4 did not start therapy) Hospital: 11 (3 did	**Inclusion criteria:** Plaque or guttate psoriasis (mild to severe) clinically eligible for TL01; UVB prescribed by patient's dermatologist; willing to undergo treatment according to randomisation **Exclusion criteria:** age below 18 years; not willing to accept one of the two treatments offered; not able to receive one of the two treatments offered (e.g. lack of space at home/living too far from hospital etc.); analphabetism (unable to read the patient information and the questionnaires, unable to provide written answers and written informed consent); lack of command of the Dutch language; not in possession of a telephone. Expected non-compliance:	N=98 **TL01 home phototherapy unit, 3 or 4 times a week (every other day)** (Waldmann UV 100) Prescribed in units of time (patients given Tx schedule) Patients given 30-60 min training in use of the unit	N=98 **TL01 hospital phototherapy unit, 2 or 3 times a week** Administered according to local hospital's own schedule prescribed in either dose or unit of time Dose determined by minimal erythematic dose (MED) only if	Tx (mean 11.4 and 14.1 weeks for home and hospital, respectively) + 1 year in first 105 recruited	**1° outcome:** PASI50, 50% improvement in SAPASI **2° and other outcomes:** % reduction in median PASI or SAPASI; PASI75, SAPASI75; PASI90; SAPASI90; short-term side effects; SF-36, PDI, EQ-5D	Netherlands Organisation for Health Research and Development

Ref ID: KOEK2009 M. B. Koek, E. Buskens, P. H. Steegmans, H. Weelden, C. A. Bruijnzeel-Koomen, and V. Sigurdsson. UVB phototherapy in an outpatient setting or at home: a pragmatic randomised single-blind trial designed to settle the discussion. The PLUTO study. *BMC Med.Res.Meth*. 6:39, 2006. Ref ID: KOEK2006	• Randomised (computer generated list – minimisation method considering recruiting hospital and previous UV therapy) • No washout period (starting out-patient phototherapy while waiting for home unit was permitted) • Assessor blinded • Allocation concealment (central co-ordination centre) • Sample size calculation based on 80% power to detect change	not start therapy) Protocol violation: 5 patients switched therapy (4 from hospital to home) No difference in severity of psoriasis at baseline between patients who did and did not complete	lack of understanding of what the study/treatment is about, and its potential consequences. Medical contraindications: Malignancy of the skin in the past/at present; known UVB-allergy or chronic polymorphic photodermatosis; use (at time of inclusion) of medication with known phototoxic or photoallergic properties; use (at time of inclusion) of systemic antipsoriatic medication (ciclosporin, methotrexate, neotigason, fumaric acid); history of exposure to ionising radiation. **Mean baseline** / **Home (n=98)** / **Hospital (n=98)** Mean age (SE): 41.2 (1.38) / 45.0 (1.37) M/F%: 67 / 67 Mean duration of psoriasis: 16.1 (1.37) / 16.0 (1.36)	No MED calculated ---------- **BOTH ARMS:** no exclusion on grounds of any concomitant treatment initiated after inclusion Adjuvant topical therapy allowed Cut-off of 46 Tx to establish effectiveness	standard practice for hospital			

	of -15% in proportion of patients(2 groups of 90 patients required); 50 per group was considered sufficient for cumulative costs • Available case analysis • Dropouts due to AEs: 0		±SE (years)						
			SAPASI, mean (SE)	7.2 (0.38)	7.3 (0.32)				
			PASI, mean (SE)	9.7 (0.71)	8.6 (0.56)				
			No (%) with experience of phototherapy	50 (51)	50 (51)				

Effect Size

Outcomes (ITT analysis n=196)

Variables, % (n)	Home phototherapy	Outpatient phototherapy	Difference (95% CI)
Effectiveness			
SAPASI 50, 75, and 90*:	(n=94)	(n=91)	—
SAPASI 50	81.9 (77)	79.1 (72)	2.8 (−8.6 to 14.2)

SAPASI 75	69.1 (65)	59.3 (54)	9.8 (−4.0 to 23.6)
SAPASI 90	43.6 (41)	29.7 (27)	13.9 (0.002 to 27.8)
PASI 50, 75, and 90†:	(n=91)	(n=84)	—
PASI 50	70.3 (64)	72.6 (61)	−2.3 (−15.7 to 11.1)
PASI 75	40.7 (37)	41.7 (35)	−1.0 (−15.6 to 13.6)
PASI 90	19.8 (18)	19.0 (16)	0.8 (−10.9 to 12.5)
Safety			
Irradiations:	(n=98)	(n=98)	—
Mean No of irradiations	34.4	28.6	5.8 (2.7 to 9.0)
Mean cumulative dose (J/cm^2):	(n=85)	(n=68)	—
At 23 irradiations	21.2	26.9	−5.7 (−10.3 to −1.1)
	(n=91)	(n=93)	
At end of therapy	51.5	46.1	5.4 (−5.2 to 16.0)
Proportion of side effects per irradiation (%):	(n=93)	(n=92)	—
Severe erythema	5.5	3.6	1.9 (−1.1 to 4.9)
Blistering	0.3	0.6	−0.3 (−0.9 to 0.3)
Burning sensation	7.1	10.0	−2.9 (−7.1 to 1.2)
Mild erythema	28.8	28.6	0.3 (−7.4 to 8.0)

Use of adjuvant drugs, % (n)			
During waiting time (between inclusion and Tx start):	(n=94)	(n=95)	—
Topical steroids	25.5 (24)	6.3 (6)	19.2 (8.8 to 29.6)
Vitamin D derivatives	18.1 (17)	6.3 (6)	11.8 (2.5 to 21.1)
During phototherapy:	(n=92)	(n=92)	
Topical steroids	31.5 (29)	52.2 (48)	−20.7 (−35.0 to −6.4)
Vitamin D derivatives	19.6 (18)	40.2 (37)	−20.6 (−33.8 to −7.4)
Duration of therapy			
	(n=93)	(n=95)	—
Mean duration of therapy (weeks)	11.4	14.1	−2.7 (−4.1 to −1.2)
Mean time from inclusion to end of therapy (weeks)	17.2	16.2	1.0 (−0.6 to 2.5)

- Treatment effect (mean decline in SAPASI and PASI scores) was statistically significant in both treatment groups
- Treatment effect (mean decline in SAPASI and PASI scores) was not significantly different between the 2 groups (p>0.3)

Conclusion

- UV B phototherapy at home is equally effective and equally safe as ultraviolet B phototherapy in an outpatient department when applied in a setting that precludes non-prescribed irradiations.
- Treatment at home also led to a lower burden of treatment and greater patients' satisfaction than did ultraviolet B phototherapy in an outpatient setting,

despite waiting times sometimes being considerably longer.

- Home ultraviolet B phototherapy is a worthy alternative to standard outpatient ultraviolet B phototherapy for patients with psoriasis.

H.8.9 PUVA: 2- vs 3-times weekly (between patient randomisation)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
M. El-Mofty, H. El Weshahy, R. Youssef, M. Abdel-Halim, H. Mashaly, and M. El Hawary. A comparative study of different treatment frequencies of psoralen and ultraviolet A in psoriatic patients with darker skin types (randomized-controlled study). *Photodermatol .Photoimmunol.Photomed.* 24 (1):38-42,	RCT Single-centre (outpatient clinic), Egypt Recruited May-Nov 2005 • Randomised (computer generated random number tables) • 4 wk washout period for topicals and systemics • Blinding of senior (but not junior) observer	Total N: 20 **Drop-outs (don't complete the study):** 2x weekly: 0 3x weekly: 1	**Inclusion criteria:** Chronic plaque psoriasis **Exclusion criteria:** age <12 years; psoriasis extent <30% or >70%; pregnancy or lactation; liver or kidney disease; photosensitive disorders **Baseline** / **Twice weekly (n=10)** / **Three times weekly (n=10)** Mean age: 41.95±14.17 M/F%: 40/60 / 50/50 **Skin type** III: 3 / 3 IV: 6 / 6 V: 1 / 1	N=10 **Oral PUVA, 2 times a week** (0.7 mg/kg 8-MOP 2 h before irradiation) Sessions 2-3 days apart Max number of Tx: 24 ---------- **BOTH ARMS:** Administered using Waldman PUVA	N=10 **Oral PUVA, 3 times a week** (0.7 mg/kg 8-MOP 2 h before irradiation) Sessions 1 day apart Max number o Tx: 36 ---------- **BOTH ARMS:**	Complete clearance or 12 weeks max treatment	**1° outcome:** PASI **2° outcomes:** total number of sessions and total cumulative UV dose Clinical response graded as Complete clearance: 100% improvement Excellent response: 85-100% improvement Very good response: 70-85%	None stated

2008. Ref ID: ELMOFTY2008	• Allocation concealment (not reported) • Sample size calculation (not reported) • ITT analysis not reported • Dropouts due to AEs: unclear		Mean duration of psoriasis ±SD (months): 53.80±73.36 / 105.10±86.45 Extent of lesions (%): 56.00±11.73 / 51.00±14.49 PASI: 24.16±20.07 / 21.61±15.40			1000 cabin containing 26 F85/100W lamps (315-400 nm) Initial dosage determined by skin type (1-2 J/cm^2) Increments of 0.5 J/cm2 every other session until mild erythema occurred and then the dose was fixed	Adjuvant topical keratolytics used for thick scales Instructed to use sunscreen and wear eye protection during the sessions and for the rest of the day		improvement Good response: 60-70% improvement Fair response: 50-60% improvement Poor response: <50% improvement	

Effect Size

Outcomes (available case analysis n=19)

Treatment result	2 x a week (n=10)	3 x a week (n=9)
Complete clearance	3	2
Excellent response	6	2
Very good response	1	3

Good response	0	2
Dropped out	0	1

End of Tx outcomes	**2 x a week (n=10)**	**3 x a week (n=9)**	**p-value**
Total UV dose (J/cm^2)	54.57 ± 20.42	99.20 ± 19.48	<0.001
Total sessions	18.70 ± ±5.61	35.33 ± 2.00	<0.001
Final PASI	5.16 ± 6.88	5.88 ± 5.24	0.497
% reduction in PASI	**82.31 ± 18.22**	**66.88 ± 29.31**	**0.356**

Conclusion

- **Reducing PUVA frequency and the cumulative UVA dose does not compromise the efficacy of PUVA, but it may improve its benefit/risk ratio.**

H.8.10 PUVA: 2- vs 3-times weekly (within patient randomisation)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
M. C. Valbuena, O. Hernandez, M. Rey, G. Sanchez, and L. P. de Quintana. Twice- vs. thrice-weekly MPD PUVA in psoriasis: a randomized-controlled efficacy study. *Photodermatol.Photoimmunol.Photomed.* 23 (4):126-129, 2007. Ref ID: VALBUENA2007	RCT – within patient randomised Single-centre (outpatient clinic), Colombia Recruited Feb 2003-Jan 2005 • Randomised (random number tables) • 4 wk washout period for systemics; 2 wk for topicals • Blinded assessor • Allocation concealment (not reported)	Total N: 28 **Drop-outs (don't complete the study):** 5	**Inclusion criteria:** Clinical diagnosis of psoriasis; ≥20% BSA involvement (rule of nines) **Exclusion criteria:** age <18 years; pregnancy or lactation; liver or kidney disease; photosensitive disorders; history of adverse reaction to psoralens; systemic treatment within 4 wks of study entry or topicals within 2 wks; phototherapy within 3 months of study entry **Baseline** / **All (n=23)** Mean age / 41.9 ± 15.1 M/F% / 78.3/21.7 **Skin type** / II / 6	N=28 **Oral PUVA, 2 times a week** (0.6 mg/kg 8-MOP 2 h before irradiation) Sessions on Mondays, and Fridays (half body covered on Wednesdays with protective suit) ---------- **BOTH ARMS:** Administered	N=28 **Oral PUVA, 3 times a week** (0.6 mg/kg 8-MOP 2 h before irradiation) Sessions on Mondays, Wednesdays and Fridays ---------- **BOTH ARMS:**	Up to 25 exposures	**1° outcome:** decrease PASI (excluding assessment of the head) **2° outcomes:** treatments for clearance; cumulative doses	None stated

	• Sample size calculation (based on 80% power and 95% confidence = need 44 body halves) • Available case analysis • Dropouts due to AEs: 3		III-IV	17	using Daavlin 305/350 cabinet containing 24 TL-100W lamps Initial dosage determined by MPD Increments of 40%, 20%, 10% or no increment depending on erythema	Adjuvant topical treatment only for scalp lesions Wore UV protective goggles			
			Ostraceous psoriasis, n (%)	7 (30.4)					
			Mean extent of lesions (%)	48.7 (20-80)					
			PASI	Twice weekly: 31.8±7.3 Thrice weekly: 31.9±7.3 (p=0.758)					

Effect Size

Outcomes (Available case analysis n=23)

Treatment result	**n**	**2 x a week (n=23)** **Median (IQR)**	**3 x a week (n=23)** **Median (IQR)**	**p-value**
% PASI decrease				
Skin type I	6	91.5 (89.9-97.1)	93.2 (91.8-94.0)	0.673
Skin type III-IV	17	93.1 (91-94.9)	95.5 (93.0-96.8)	0.079

Vulgaris type	16	93.6 (92.6-96.4)	95.2 (79.1-99.2)	0.972
Ostraceous subtype	7	90.5 (87.3-91.1)	94.0 (92.8-96.0)	0.043
Total group	*23*	*92.9 (89.9-96.1)*	*94.8 (91.8-96.8)*	*0.179*
Total number of exposures				
Skin type I	6	17.5 (17-25)	25 (25-25)	0.049
Skin type III-IV	17	14 (10-17)	20 (15-25)	0.000
Vulgaris type	16	13 (10-17)	19 (15-24)	0.001
Ostraceous subtype	7	25 (17-25)	25 (25-25)	0.180
Total group	*23*	*15 (11-25)*	*22 (17-25)*	*0.000*
Cumulative dose (J/cm^2)				
Skin type I	6	130.1 (113.0-381.2)	238.9 (167.0-366.3)	0.173
Skin type III-IV	17	144.2 (106.1-238.6)	241.4 (172.3-292.4)	0.003
Vulgaris type	16	120.9 (95.4-146.8)	195.8 (159.5-258.2)	0.000
Ostraceous subtype	7	344.8 (238.6-394.1)	366.3 (257.0-421.9)	1.000
Total group	*23*	*142.5 (106.1-316.0)*	*241.4 (169.7-366.3)*	*0.001*

Adverse events	**2 x a week (n=23)**	**3 x a week (n=23)**

Grade 3 erythema	0	1
Grade 2 erythema	1	1
Mild pruritus	15	16
None	5	1

Conclusion

- **The treatment of psoriasis patients with twice- or thrice-weekly PUVA in this study was equally effective, the number of sessions required and the cumulative doses of UVA were lower with the twice-weekly regimen.**
- **Reducing the frequency of PUVA sessions should enhance adherence and reduce risk of skin cancer and cost of treatment**
- **Ostraceous psoriasis is better treated with the thrice-weekly regimen**

H.8.11 Hand and foot PUVA vs no treatment for palmoplantar pustulosis – within patient randomisation

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
D. Murray, M. F. Corbett, and A. P. Warin. A controlled trial of photochemotherapy for persistent palmoplantar pustulosis. *Br.J.Dermatol.* 102 (6):659-663, 1980. Ref ID: MURRAY1980	RCT Single-centre (referred from outpatient department of St John's Hospital), UK • Randomised (unclear method) • 2 wk washout period for topicals and systemics • Blinding not reported • Allocation concealment (not reported) • Sample size calculation (not reported) • ITT analysis	Total N: 22 **Drop-outs (don't complete the study):** **0**	**Inclusion criteria:** Bilaterally symmetrical palmoplantar pustulosis of at least 1 year duration **Exclusion criteria:** Not stated **Mean baseline** / **All (n=22)** Mean age (SE): Males: 47.8 (2.09); Females: 52.9 (2.47) M/F%: 27.3/72.7 Mean age of onset of psoriasis ±SE (years): 46.1 (2.1) Mean duration of psoriasis: 5.3 (0.94)	N=22 **Oral PUVA, 4 times a week (Mon, Tues, Thurs, Fri)** (10 mg 8-MOP tablets taken with food 2 h before irradiation; total dose related to body weight e.g., 30-50 kg = 20 mg; 80-90 kg = 50 mg) Administered using Waldman UVA 200 hand unit containing 14 F8T5/BL tubes (320-400 nm) Initial dosage	N=22 **No treatment** Body side covered during irradiation ---------- **BOTH ARMS:** Adjuvant emulsifying ointment BP applied equally to both sides at least twice daily	30 Tx (7.5 weeks)	**1° outcome:** Visual analogue scale from 0-100 (0= worse; 25= no change; 50 = improved; 75 = much improved; 100 = cleared)	None stated

	Dropouts due to AEs: 0		±SE (years) Hands only affected: 2 Feet only affected: 13 Feet and hands affected: 7	determined by skin type (0.5-2 J/cm^2) Increments of 0.5-1 J/cm2 made at ≥48-h intervals until clinical improvement and then maintained (or until 1 h of radiation had been given) End point = 30 Tx	Patients seen weekly by a single observer (but similar results obtained by an independent observer using photographs)			

Effect Size

Outcomes (ITT analysis n=22)

Treatment result	**Treated side (n=22)**	**Untreated side (n=22)**
Cleared	12	0
Much improved	5	0
Improved	5	13
No change	0	6
Worse	0	3

- The treated side did better in every case except one where there was modest and similar improvement on both sides ($p<0.001$)
- Mean (SE) Tx dose at clearing: soles = 12 ± 1.20 J/cm^2; palms 10.5 ± 1.44 J/cm^2
- Mean Tx to clear: 26 (range: 18-30)

Duration of remission (number clear and off Tx; note this was after gradual reduction in Tx frequency until it could be stopped)

Duration	PUVA	Untreated
1 month	1	0
2 months	3	0
6 months	1	0
10 months	1	0

Adverse events

Effect	PUVA	Untreated
Burn	1	0
Nausea	4	0
Ankle swelling	4	0
Brief non-purulent conjunctivitis	6	0

Conclusion

- **Oral PUVA is effective in clearing palmoplantar pustlosis, but at least 20 treatments may be required (more than for chronic plaque psoriasis)**

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
K. Rosen, H. Mobacken, and G. Swanbeck. PUVA, etretinate, and PUVA-etretinate therapy for pustulosis palmoplantaris. A placebo-controlled comparative trial. *Arch.Dermatol*. 123 (7):885-889, 1987. Ref ID: ROSEN1987	RCT Single-centre, Sweden • Randomised (treatment side according to date of birth) • 4 wk washout period for topicals and systemics • Blinding of second assessor • Allocation concealment (not reported) • Sample size calculation (not reported) • Available case analysis • Dropouts due to AEs: 1	N: 14 **Drop-outs (don't complete the study):** 2 (1 psoralen reaction; 1 logistical); both with feet to be treated	**Inclusion criteria:** Bilaterally symmetrical palmoplantar pustulosis with lesions of comparable severity and morphology on each body side; of at least 6 months duration; previous treatment without satisfactory response; no topical or systemic treatment for PPP for 4 weeks before trial start (except emollients) **Exclusion criteria:** pregnancy; liver or kidney disease; hypertriglyceridemia; alcohol abuse; inability to co-operate/follow instructions **Mean baseline** / **All (n=14)** Mean age (range): 56 (39-71) M/F%: 21.4/78.6 Mean duration of: 7 (0.5-22)	N=14 **Oral PUVA, 3 times a week (Mon, Tues, Thurs, Fri)** (0.6 mg/kg 8-MOP tablets taken 1.5 h before irradiation) Administered using Waldmann PUVA 180+200 unit (200 U placed behind the feet) Initial dosage 20 kJ/m^2 Increments of 20 kJ/m^2 made at	N=14 **No treatment** ---------- **BOTH ARMS:** Adjuvant therapy not mentioned Patients seen every 3 weeks during TX by a single observer observer (but similar results obtained by an independent/	12 weeks max treatment	**1° outcome:** Global severity evaluation by physician (cleared = no desquamation or pustulation; much improved = some residual desquamation, pustulation and infiltration; somewhat improved = substantial/easily recognised improvement; unchanged/worse) Assessment of desquamation, pustlation, erythema, infiltration on a 0 = none to 3 = severe scale	None stated – drugs provided by AB Draco and AB Hoffmann-La Roche

			psoriasis (years; range) Mean (SE) combined severity score Feet treated Hands treated Psoriasis Previous PUVA Previous etretinate	 Treated side: 9.2 ± 0.5 Untreated side 9.2 ± 0.4 11 3 5 6 3	each treatment (5 kJ/m^2 increments between 40 and 60 kJ/m^2) to a max of 150 kJ/m^2 No increment if erythema, edema or severe itch occurred Instructed to wear UVA protective glasses during day of Tx End point = clearance or max 12 wks **Note**: treated *either* hand *or* foot (foot if most severely affected and hand if lesions here caused most distress)	blinded observer using photographs)			

Effect Size

Outcomes (ITT analysis n=22)

Treatment result	**Treated side (n=12)**	**Untreated side (n=12)**
Cleared	3	0
Much improved	6	2
Somewhat improved	1	2
No change/worse	2	8
Mean combined severity score at end of Tx	*4.8*	*8.0*

- Of the 3 who cleared 2 were hand PUVA and 1 was foot PUVA; all **relapsed** after ~1 month

Treatment duration for PUVA side

	Total	**At clearance**
Mean (range) number of sessions	29 (16-40)	24 (16-29)
Mean (range) duration of Tx (days)	83 (43-135)	65 (43-86)
Mean (range) total UV dose	1990 (1140-3630)	1990 (1170-2500)
Mean (range) max UV dose (kJ/m^2)	115 (7-150)	130 (120-140)

Adverse events

Effect	PUVA	Untreated
Symptomatic erythema	4	0
Nausea	3	0
Ankle swelling	1	0
Dermatitis	1	0
Polymorphic light eruption	1	0

Conclusion

- **The choice of treatment for PPP should be individualised according to disease severity and medical background**
- **There is a high relapse rate and patients should be monitored for potential long-term risks**

H.8.12 Hand and foot PUVA vs NBUVB for palmoplantar pustulosis – within patient randomisation

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
E. Sezer, A. H. Erbil, Z. Kurumlu, H. B. Tastan, and I. Etikan. Comparison of the efficacy of local narrowband ultraviolet B (NB-UVB) phototherapy versus psoralen plus ultraviolet A (PUVA) paint for palmoplantar psoriasis. *J.Dermatol.* 34 (7):435-440, 2007. Ref ID: SEZER2007	RCT – within patient (right/left) Single-centre, Turkey • Randomised (computer-based programme) • 2 wk washout period for topicals and 4 wk for systemics • Assessor blinded • Allocation concealment (not reported) • Sample size calculation (not reported) • No ITT analysis • Dropouts due to AEs: 1 (PUVA)	Total N: 25 **Drop-outs (don't complete the study):** **4** 1 = phototoxic reaction to 8-MOP 3 = non-compliance	**Inclusion criteria:** Biopsy-diagnosed PPP of >6 months duration in which conventional therapies (other than phototherapy) proved ineffective **Exclusion criteria:** topical treatment with corticosteroids within 2 weeks or systemic treatment with immunosuppressants and retinoids within the last 4 weeks, unilateral disease, pregnancy, inability to meet follow-up consultations **Mean baseline** / **All (n=25)** Age (range) / 19-75 years	N=25 **Local NBUVB 3-times a week** Administered using local NB-UVB unit fitted with TL01 bulbs Initial dosage (0.15 J/cm^2) Increments of 20% made at each session until a final dose of 2 J/cm^2 reached	N=25 **PUVA paint 3-times a week** Administered using local UVA unit Initial dosage (1.0 J/cm^2) Increments of 0.5 J/cm^2 made at every second session until a final dose of 7.5 J/cm^2 reached	9 weeks Tx +10 wk follow-up of completers	**1° outcome:** Severity index scores based on separate scores (0, absent; 1, slight; 2, moderate; 3, marked; 4, very marked) of erythema, scaling, pustulation and infiltration for palms and soles (complete clearance = SI of 0; marked clinical improvement = reduction of 70% or more from baseline) **2° outcome:** Relapse at	None stated

			M/F% 56/44 Mean duration of PPP (range), years 5.3 (0.94)		Hand and/or foot painted with 1% 8-MOP in hydrophilic water/oil emulsion 15 min before UVA exposure (patiets were advised to wash treated sides after the session) ---------- **BOTH ARMS:** Only topical emollients permitted between treatment sessions; eye shielding employed during irradiation		10 weeks (severe = >70% pre-treatment scores; moderate = 30-70% pre-treatment scores; mild = <30% pre-treatment scores) Clinical assessment every 3 weeks by blinded assessor	

Effect Size

Outcomes (available case analysis n=21)

Treatment result (n)	NBUVB (n=21)	PVUA (n=21)
Cleared	0	5
Marked clinical improvement	9	15
Mean cumulative dose (J/cm^2)	34.9	111.5

Relapse at 10 weeks

Relapse	NBUVB (n=21)	PUVA (n=21)
Severe	2	1
Moderate	8	3
Mild	2	3
No relapse	9	14

Adverse events

Effect	NBUVB	PUVA

Phototoxic reaction	0	1
Palmar hyperpigmentation	0	11

Conclusion

- **Although some clinical improvement was observed with local NBUVB, the results were better with local PUVA.**

H.9 Dithranol, coal tar and vitamin D analogues combined with UVB

H.9.1 Calcipotriol + NB-UVB versus Calcipotriol

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Sour of func
A.V. Roussaki-Schulze, C. Kouskoukis, E. Klimi, E. Zafirou, A. Galanous, E. Rallis. Calcipotriol monotherapy versus calcipotriol plus UVA1 versus calcipotriol plus narrow-band UVB in the treatment of psoriasis. *Drugs Exptl. Clin. Res*, 31(5/6):169-174.2005 REFID: ROUSSAKISCHULZE2005	**RCT** Single centre, Greece **Randomised:** Method not stated **Allocation concealment:** Not mentioned **Blinding:** Not mentioned	**Total N = 45** Pts randomised to three groups: A, B &C. Group B not relevant (UVA+calcipotriol)	**Inclusion criteria:** Patients with plaque psoriasis **Exclusion criteria:** Pregnant women, history of skin cancer **Baseline characteristics of randomised patients:** [illegible]	Group A N=15 Calcipotriol ointment (Dovonex; 50 µg/g, b.d.)	Group C N=15 Calcipotriol ointment (Dovonex 50 µg/g, b.d.) + NB-UVB* (twice weekly) NB-UVB starting dose 80% MED and inc. by	3 months	**1º Outcome:** PASI reduction PASI 50 **Other outcomes:** Clear Non-responder	Not state

	Calcipotriol	Calcipotriol + NB-UVB
M/F	12/3	12/3
Age	44.93±6.48	49.53±22.01

	Washout period: 90 days if using systemic therapy, 30 days if using topicals **Sample size calculation:** Not stated **ITT Analysis**: Yes **Drop outs:** None		Skin type I/II/III/IV: 0/11/3/1 / 2/5/6/2		20% every 3 sessions *Cosmetico, 10 lamps Helarium B1, 100 W each. 311-313 nm			

Effect size

PASI

	Calcipotriol (n=15)	**Calcipotriol + NB-UVB (n=15)**	
Number of patients achieving PASI 50	6	12	**(p<0.05)**

Mean PASI at baseline	2.51 ±1.89	5.73 ±2.89
Mean PASI after treatment	1.27 ±1.25	2.51 ±2.34
Mean change in PASI	-1.24 ±1.54	-3.22 ±1.70
Relapse at 3 months		2

Clear

	Calcipotriol (n=15)	Calcipotriol + NB-UVB (n=15)
Clear	4	2

Author conclusion

The response to narrow-band UVB with calcipotriol was superior to calcipotriol monotherapy

H.9.2 Calcipotriol + BB-UVB versus Calcipotriol

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

K. Kragballe. Combination of topical calcipotriol (MC 903) and UVB for psoriasis vulgaris. *Dermatologica*. 181:211-214.1990 REFID: KRAGBALLE1990	**RCT** Single centre Denmark **Randomised:** Right/left comparison: patients randomised to have UVB on right/left side **Allocation concealment:** Not stated **Blinding:** Open **Washout:** No systemic therapy for 2 months or topical therapy for at least 2 weeks prior to study	**Total N =** 20 patients, 40 body halves	**Inclusion criteria:** Patients 18 years or older with symmetrically distributed chronic plaque psoriasis. **Exclusion criteria:** Patients intolerant of UV light, patients whose psoriasis worsens with UV light exposure **Baseline characteristics of randomised patients:** Sex: M/F 10/10 Mean Age, y 47 Disease duration, y 19 BSA involved, % 17	**Calcipotriol** N=20 halves Calcipotriol ointment 50 µg/g twice daily	**Calcipotriol + BB-UVB** N=20 halves Calcipotriol ointment 50 µg/g twice daily + BB-UVB radiation 3 times a week UVB 280-350 nm (TL 60), suberythemogenic starting at 50% MED	12 weeks total: 8 weeks of therapy, 4 week post-therapy (emollient only)	**1º Outcome:** Clearance **Other outcomes:**	Not stated, however ointment provided by Leo Pharmaceu Products

	Sample size calculation: Not performed **ITT Analysis**: No **Drop outs:** 2 patients							

Effect size

Clearance at week 8

	Calcipotriol + BB-UVB	**Calcipotriol**
Number of halves cleared	7	3
Excellent improvement	9	12

17% of patients in calcipotriol alone group and 39% of patients in calcipotriol + UVB group (NS)

2 patients developed mild facial dermatitis with slight erythema and scaling around the mouth (group not stated) which disappeared during continue treatment

After a 4 week post-therapy follow-up with emollient use only, i.e. study week 12, 12/13 patients were relapse-free

No other outcomes of interest

Author conclusion

These results show that the combination of topical calcipotriol and UVB radiation is well tolerated

H.9.3 Calcitriol + BB-UVB versus Placebo + BB-UVB

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
J. Ring, L. Kowalzick, E. Christophers, W.B. Schill, E. Schopf, M. Stander, H.H. Wolff, P. Altmeyer. Calcitriol 3 µg g^{-1} ointment in combination with ultraviolet B phototherapy for the treatment of plaque psoriasis: results of a	**RCT** **Multicentre,** **Germany** **Randomised:** Method not stated **Allocation concealment:** Not stated **Washout:**	**Total N =** 104	**Inclusion criteria:** Patients over 18 years of age with chronic plaque-type psoriasis and global severity classification of ≥2 (moderate) and skin type I, II, II or IV **Exclusion criteria:** Pregnant & breast-feeding women, use of topical treatments other than emulsifying ointments or tar shampoos during study period, sensitisation to calcitriol or phototherapy,	N= 49 Calcitriol ointment (Silkis; 3 µg/g, b.d.) + BB-UVB (290-320 nm) Max. 24 sessions of UVB therapy	N= 53 Placebo (vehicle) + BB-UVB (290-320 nm) Max. 24 sessions of UVB therapy	8 weeks	**1º Outcome:** Global severity score PASI **Other outcomes:** Adverse events	Grant fro Galderm Laborato

comparative study. *Br J Dermatol*. 144:495-499. 2001 REF ID: RING2001	2 months (intralesional therapy or photochemotherapy) **Blinding:** Double-blind **Sample size calculation:** Not stated **ITT Analysis**: Modified ITT (patients who used study medication for at least 1 day, had a at least 1 UVB treatment and had at least 1 postbaseline assessment) **Drop outs:** 2 patients – outcomes not reported		concomitant bacterial, fungal or viral skin conditions **Baseline characteristics of randomised patients:** Stated no significant difference in demographic data between groups					
Effect size								

	Calcitriol + UVB (n=49)	Placebo + UVB (n=53)
Considerable improvement or clearing	22	11
% change in PASI	65%	43%

Adverse events

	Calcitriol + UVB	Placebo + UVB
Adverse events	11 (22%)	13 (25%)
Withdrawal due to adverse events	2 (rash, suspected diverticulitis)	1 (rash)

Number of UVB treatments

	Calcitriol + UVB (n=49)	Placebo + UVB (n=53)
Range of number of UVB treatments	4-29	3-35

However, combination group exposed to 34% less radiation than placebo + UVB group.

PASI scores decreased for both groups – scores for calcitriol treated patients significantly lower than those for vehicle group from week 4 onwards (P<0.05)

Author conclusion:

High levels of clinical efficacy and local tolerance demonstrated in this study indicate that calcitriol in combination with UVB has considerable potential for the management of patients with chronic plaque psoriasis, particularly on a long-term basis

H.9.4 Calcipotriol + NB-UVB versus Placebo + NB-UVB

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Sour of fund
W.K. Woo, K.E. McKenna. Combination TL01 ultraviolet B phototherapy and topical calcipotriol for psoriasis: a prospective randomized placebo-controlled clinical trial. *Br J Dermatol*. 149:146-150. 2003 REFID WOO2003	**RCT** Single centre N. Ireland **Randomised:** Computer-generated randomisation **Allocation concealment:** Randomisation codes concealed by pharmacy until end of trial **Blinding:** Double-blinded: Patients blinded, assessor blinded	**Total N =** 50	**Inclusion criteria:** Patients aged ≥18 years with psoriasis (chronic plaque and/or guttate psoriasis) **Exclusion criteria:** Standard contraindications for phototherapy; history of photosensitivity, skin carcinomas, cataracts, epilepsy, known hypercalcaemia, hypersensitivity to calcipotriol, hypersensitivity to cetomacrogol, cetostearyl, alcohol or paraffin **Baseline characteristics of randomised patients:** Calcipotriol / Placebo +	**Calcipotriol + NB-UVB** N=25 TL01 phototherapy + topical calcipotriol Calcipotriol cream 50 µg/g applied twice daily, max 100 g per week. Applied 2 hrs prior to UVB.	**Placebo + NB-UVB** N=25 TL01 phototherapy + emollient (placebo) Emollient cream applied twice daily TL01 three times a week starting at 70% MED with 20%	10 weeks post-treatment	**1º Outcome:** PASI **Other outcomes:** PDI Adverse events	Not state

	Washout: 2 months – phototherapy/systemic antipsoriatic therapy **Sample size calculation:** Not stated **ITT Analysis**: Yes **Drop outs:** 6 in active group, 8 in control			TL01 three times a week starting at 70% MED with 20% increments as tolerated, max. 20 sessions	increments as tolerated, max. 20 sessions			

	+ TL01	Tl01
Mean age, y	38.2	43.3
Sex: M/F	12/13	16/9
Mean duration of disease, y	14.2	20.6
Mean baseline PASI	12.4	14.1

Stated no significant differences in demographic characteristics/baseline PASI

Effect size

Outcome

Mean PASI score

	TL01 + calcipotriol	**TL01 + placebo**	**P-value (active vs. placebo)**

Baseline	12.4	14.1	-
8th treatment session	4.8	11.6	P<0.01
14th session	2.5	6.5	P<0.01
20th session	1.3	2.3	NS
Week 5 post-treatment	*2.6*	*4.4*	*NS*
Week 10 post-treatment	*3.1*	*4.3*	*NS*

Mean difference in PASI score

	TL01 + calcipotriol	**TL01 + placebo**	**Difference (95% CI)**	**P-value (active vs. placebo)**
8th treatment session	6.2	2.6	3.6 (1.0-6.2)	0.008
14th session	9.1	7.4	1.7 (-2.2-5.6)	0.4
20th session	9.8	11.8	-2.0 (-5.9-1.9)	0.3

Adverse events

	Tl01 + calcipotriol	**Tl01 + placebo**	**P-value (active vs. placebo)**
Number of adverse events	9	4	NS

Withdrawal due to adverse events

	Tl01 + calcipotriol	Tl01 + placebo
Number of withdrawals due to adverse events	0	1

Mean number of UVB exposures

	Tl01 + calcipotriol	Tl01 + placebo
Mean number of UVB exposures	18.7	20.4

Author conclusion

Combing TL01 phototherapy with topical calcipotriol cream has a UVB-sparing effect

H.9.5 Calcipotriol + BB-UVB versus Placebo + BB-UVB

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Sour of fund
C.A. Ramsay, B.E. Schwartz, D. Lowson, K. Papp, A. Bolduc, M. Gilbert, and other members of the Canadian Calcipotriol and UVB Study Group. Calcipotriol cream combined with twice weekly broad-band UVB phototherapy: a safe, effective and UVB-sparing antipsoriatic combination treatment. *Dermatology*. 200:17-24. 2000 REFID: RAMSAY2000	**RCT** Multicentre Canada **Randomised:** Computer-generated **Allocation concealment:** Not stated **Blinding:** Single-blind (investigator) **Sample size calculation:** No **ITT Analysis**:	**Total N** = 164 159 included in ITT population	**Inclusion criteria:** Out-patients with a clinical diagnosis of extensive body psoriasis (20-40% body surface area) with skin types I, II, III, or IV **Exclusion criteria:** Hypercalcaemia, impaired renal function, previous or current carcinoma of the akin or actinic keratosis. **Baseline characteristics of randomised patients:** Calcipotriol + BBUVB (n=84) / Placebo + BBUVB (n=80) Mean Age, y: 45.7 / 43.2 Sex: M/F: 53/31 / 46/34 Skin type I/II/III/IV: 3/27/42/12 / 7/29/31/13	**Calcipotriol + BB-UVB** N=80 Calcipotriol cream (50 µg/g, twice daily, max. 100 g/week) + BB-UVB twice weekly	**Placebo + BB-UVB** N=79 Vehicle cream (Placebo) + BB-UVB three times a week	Treatment phase 12 weeks, post-treatment follow-up 12 weeks During post-treatment follow-up only emollient cream permitted	**1º Outcome:** 80% reduction in modified PASI (excludes head) **Other outcomes:** Clearance Number of UVB treatments Relapse % change in PASI	Leo

	Yes **Washout:** 1 week washout. No systemic antipsoriatic treatment or phototherapy within 2 months. Patients not permitted to take any other topical/systemic medication that could affect their psoriasis **Drop outs:** 5 patients (2 lost to follow-up, 1 exclusion criteria emerging, 1 other and 1 erysipelas) 29 patients did not complete treatment (14 group A, 15 group B), 5 patients withdrawn during follow-up phase		Mean Baseline PASI: 11.6 / 11.7						
Effect size **PASI at 12 weeks**									

	Group A (n=80)	Group B (n=79)	P-value
Baseline (mean ±SD)	11.6 ±4.9	11.7 ±4.5	
Mean % reduction in PASI at end of treatment	77% ±39.4%	80.1% ±25.2%	=0.554 (NS)
Number of patients achieving modified PASI 80	61	58	

Clearance at 12 weeks

	Group A	Group B	P-value
Clearance or marked improvement (investigator)	58	61	=0.432 (NS)
Clearance or marked improvement (patient)	56	59	=0.157 (NS)
Clearance	48	51	

Number of UVB treatments at 12 weeks

	Group A	Group B	P-value
Median number of UVB treatments to achieve modified PASI-80	12	19	<0.001 (SS)
Median number of UVB treatments to achieve clearance	22 (8-25)	25 (14-35)	<0.001 (SS)
Cox hazards model of number of treatments to clear	Median Tx to clear: 22	Median Tx to clear: 25	RR 2.59 (1.71-3.92)

Cox hazards model of number of treatments to achieve modified PASI-80	Median Tx to PASI80: 12	Median Tx to PASI80: 19	RR 3.66 (2.16-6.20)

Adverse events

	Group A (n=80)	**Group B (n=79)**
Adverse events	46	53
Burn, erythema, pruritus	22	33

Relapse during post-treatment follow-up of those who cleared

	Group A	**Group B**	**OR**	**p-value**
Relapse (requiring treatments other than emollients)	n=47	n=48	0.81 (0.29-2.21)	0.677

Author conclusion

Calcipotriol cream + twice weekly broad-band UVB phototherapy is an effective and safe anti-psoriatic treatment, resulting in fewer UVB exposures, lower cumulative irradiance and a saving of time.

H.9.6 Dithranol + BB-UVB versus Placebo + BB-UVB

Reference	**Study type**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Comparison 2**	**Length of follow-up**	**Outcome measures**	**Sourc of**

									fundi
M-J.P. Gerristen, J.B.M. Boezeman, M.E. Elbers, P.C.M. van de Kerkhof. Dithranol Embedded in crystalline monoglycerdides combined with phototherapy (UVB): a new approach in the treatment of psoriasis. *Skin Pharmacol Appl Skin Physiol*. 11:133-139.1998 REFID: GERRISTEN1998	**RCT** Single centre Netherlands **Randomised:** Randomised left-right body comparison **Allocation concealment:** No **Blinding:** Part open, part double-blind **Sample size calculation:** No	**Total N** = 36 patients, 72 body halves	**Inclusion criteria:** Patients with stable psoriasis and between 5 and 35% whole body surface involved, symmetrical distribution of lesions, severity scores of ≥3 for each symptom for at least one compartment of one body half **Exclusion criteria:** Any concomitant disease which may interfere with the evaluation of efficacy/accomplishment of study, concomitant therapy with (e.g. lithium, b-blockers, antimalaria drugs, systemic corticosteroids, NSAIDs, cytostatics), inability to follow instructions, alcohol and drug abuse, known intolerance or unresponsiveness to dithranol or UVB, pregnancy **Baseline characteristics of randomised patients:** Left-right body comparisons Mean age 46.9 years	**Dithranol** N=24 body halves Group A: Dithranol (Micanol)	**Dithranol + BB-UVB** N=24 body halves Group B: Dithranol (Micanol)+ UVB UVB (Voltarc F71T12/2072 285-350 nm) three times a week Micanol starting dose 0.25%, titrated up to 0.65, 1, 2 and 3% if no irritation	**Plaecbo + BB-UVB** N=24 body halves Group C: Placebo + UVB	8 weeks treatment 27 weeks follow-up of patients in complete remission on four post-treatment visits	**1º Outcome:** Number of weeks taken to obtain a reduction in lesions of one body half to 1% or less of whole body surface area together with a severity score of 1 or less for each symptom for all lesions on one body half **Other outcomes:**	Zyma nethe Zyma Nyon

	ITT Analysis: Yes **Washout:** Systemic treatment not permitted within 4 weeks, topical treatment not permitted within 2 weeks. **Drop outs:** 9 patients during follow-up		Mean PASI scores comparable across body halves Group A: **13.1** Group B: **13.2** Group C: **12.1** (Mean baseline PASI score)		UVB started at 50% MED			Remission period	

Effect size

	Dithranol (n=24 halves)	**Dithranol + BB-UVB (n=24 halves)**	**Plaecbo + BB-UVB (n=24 halves)**
Number achieving healing (≤1% BSA, ≤1 on all severity scores)	7 halves	15 halves	11 halves
Duration of treatment for healing (weeks)	Mean: 6.4	Mean: 6.1	Mean: 5.9

	Median: 5.7	Median: 6.4	Median: 6.4
Marked improvement	7 halves	13 halves	7 halves
Median number of weeks to severity score ≤1 (remission)	3.7 weeks	3.7 weeks	3.6 weeks
Irritation requiring adjustment of Micanol	4 halves	2 halves	Not reported
Still in remission during 27 weeks follow-up of patients in complete remission on four post-treatment visits	33%	23%	20%

Author conclusion

The safety and tolerability of Micanol make this active substance an important tool in the management of psoriasis

H.9.7 Calcipotriol + NB-UVB versus NB-UVB

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

S. Brands, M. Brakman, J.D. Bos, M.A. de Rie. No additional effect of calcipotriol ointment on low-dose narrow-band UVB phototherapy in psoriasis. *J Am Acad Dermatol*. 41:991-5.1999 REFID: BRANDS1999	**RCT** Multicentre Netherlands **Randomised:** By odd/even numbers **Allocation concealment:** **Blinding:** Single blind **Washout:** Systemic therapy 3 weeks, topical therapy 1 week **Sample size calculation:** Yes, 80% power to detect difference of at least 15% reduction in PASI with n=30	**Total N** = 53	**Inclusion criteria:** Outpatients with plaque psoriasis, skin phototypes II, II, and IV. **Exclusion criteria:** History of photoaggravated psoriasis or cutaneous malignancy, use of phototoxic drugs or drugs that might influence psoriasis, natural or artificial phototherapy **Baseline characteristics of randomised patients:** Stated no significant differences between study groups with respect to age, initial PASI and skin phototypes however detailed information by group not given	**Calcipotriol + NB-UVB** N=25 Calcipotriol ointment 50 µg/g (Daivonex) twice daily + NB-UVB (TL01) three times a week ---------- **Both Groups** Emollients, tar-containing shampoo and desoximetasone lotion 0.25% for the scalp region allowed in both groups	**NB-UVB** N=28 NB-UVB (TL01) three times a week	No follow-up time given	**1º Outcome:** 'complete cure' or nor longer no further improvement PASI **Other outcomes:**	LEO Pharmaceu Products

	ITT Analysis: Yes **Drop outs:** 11 patients							

Effect size

PASI

	Calcipotriol + NB-UVB (n=25)	**NB-UVB (n=28)**	**p-value**
Mean PASI pre-treatment (range)	13.2 (3.5-27.3)	12.5 (0.7-19.2)	
Mean PASI post-treatment (range)	3.0 (0.7-19.2)	3.1 (0.7-24.0)	
% reduction	79.3%	75.5%	0.77

Number of NB-UVB treatments

	Calcipotriol + NB-UVB (n=25)	**NB-UVB (n=28)**	**P-value**
Mean number of UVB treatments	31.0	31.7	0.81 (NS)

Withdrawal due to adverse events

	Calcipotriol + NB-UVB (n=25)	NB-UVB (n=28)
Withdrawal due to adverse events	2	0

H.9.8 Tar oil + low dose BB-UVB versus Placebo + high dose BB-UVB

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Sour of fund
A. Menkes, R.S. Stern, K.A. Arndt. Psoriasis treatment with suberythrogenic ultraviolet B radiation and a coal tar extract.	**RCT** Single centre USA **Randomised:**	**Total N =** 49	**Inclusion criteria:** Outpatients with stable plaque psoriasis **Exclusion criteria:**	**Tar oil + low dose BB-UVB** N=30	**Placebo + high dose BB-UVB** N=19	Until clear or up to 36 UVB treatments (12 weeks)	**1º Outcome:** Clearance (complete resolution of >90% of original	Not state

J Am Acad Dermatol. 12:21-25.1985 REF ID: MENKES1985	Random numbers, 3:2 **Allocation concealment:** Not stated **Blinding:** No **Washout:** All patients only used bland emollients 4 weeks prior to study, no PUVA or methotrexate for 12 weeks prior **Sample size calculation:** Not stated **ITT Analysis**: No – available case		None stated **Baseline characteristics of randomised patients:** [table below]	Tar oil (twice daily) and suberythemogenic UVB (three times a week) BB-UVB Westinghouse FS40 280-320 nm UVB starting dose = 50% MED	Maximally erythemogenic UVB (three times a week) and emollients (white petrolatum) UVB starting dose = MED		affected areas exposed to UVB) **Other outcomes:**

	Tar oil	Control
%Male	53	53
Age of enrolment	39	34
% of skin affected by psoriasis <11/11-25/>25	37/50/13	56/11/33

	Drop outs: 10 patients (compliance failures)							

Effect size

Clearance

	Tar oil + BB-UVB (n=30)	**Placebo + BB-UVB (n=19)**	**P-value**
Number of patients achieving clearance	19	14	0.08 (NS)

Number of UVB treatments

	Tar oil + BB-UVB	**Placebo + BB-UVB**	**P-value**
Mean number of UVB treatments for clearance	17	21	**<0.05 (SS)**

Author Conclusion

For most patients with moderate psoriasis, suberythemogenic UVB and tar oil is an effective, low-cost and acceptable outpatient therapy

H.9.9 Calcipotriol + NB-UVB versus NB-UVB

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Sour of fund
J.H. Rim, Y.B. Choe, J.I. Youm. Positive effect of using calcipitriol ointment with narrow-band ultraviolet B phototherapy in psoriatic patients. *Photodermatol Photoimmunol Photomed*. 18:131-134.2002 REF ID: RIM2002	**RCT** Single centre Korea **Randomised:** Method not stated **Allocation concealment:** Not stated **Blinding:** Open	**Total N =** 28	**Inclusion criteria:** Outpatients with chronic plaque psoriasis affecting >5% BSA **Exclusion criteria:** Patients with a history of photosensitive disease or cutaneous malignancy or who had used phototoxic drugs or arsenic, pregnant women **Baseline characteristics of randomised patients:**	**Calcipotriol + NB-UVB** N=10 Calcipotriol (50 µg/g, Daivonex, twice daily) + NB-UVB (TL01 three times a week) ---------- **Both Groups:**	**NB-UVB** N=18 NB-UVB (TL01 three times a week)	Around 6 weeks (not precisely defined)	**1º Outcome:** Grade I-IV I minimal improvement, II definite improvement, III considerable improvement, IV clearing (>95% improvement) **Other outcomes:**	

	Washout: No systemic/UV therapy 4 weeks prior to study **Sample size calculation:** Not performed **ITT Analysis**: Yes **Drop outs:** 4 overall		Stated no significant difference in baseline characteristics	NB-UVB Started at the lower of: 70% MED or 0.3 J/cm^2 for type III skin, 0.4 J/cm^2 for type IV/V skin			Number of phototherapy sessions	

	Calcipotriol + UVB	UVB
Mean age, y	39.7	39.7
Sex: M/F	7/11	3/7
Initial PASI score	17.6	16.3

Effect size

Clearance

	Calcipotriol + NB-UVB (n=10)	**NB-UVB (n=18)**
Number of patients clearing (Grade IV)	9	11

PASI

Change in PASI given graphically – not extractable

Difference in PASI reductions of the two groups was significant at week 2 (P<0.05) but difference not maintained at weeks 4, 6, and 8

Number of UVB treatments

	Calcipotriol + NB-UVB (n=10)	NB-UVB (n=18)
Mean number of UVB treatments – trunk	14.3 ±5.8	15.7 ±4.1
Mean number of UVB treatments – extremities	16.0 ±4.3	18.5 ±4.8

Withdrawal due to adverse events

	Calcipotriol + NB-UVB (n=10)	NB-UVB (n=18)
Number of patients	1	1

Mild to moderate burn

	Calcipotriol + NB-UVB (n=10)	NB-UVB (n=18)
Number of patients	2	2

Author conclusion:

Higher percentage of patients attained grade IV at the end of therapy in the combination group and this therapy was more effective in reducing PASI early in treatmen

H.9.10 Tacalcitol + NB-UVB versus Tacalcitol

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Sour of fund
M. Rocken, G. Messer, G. Plewig. Treatment of psoriasis with vitamin D_3 derivatives and 311-nm UVB. *J Derm Treatment*. 9(3):537-540.1998 REF ID: ROCKEN1998	**RCT** Single centre Germany **Randomised:** By body halves. Method not given **Allocation concealment:** Not stated **Blinding:** Open **Washout:** Not stated	**Total N =** 24 patients recruited, 22 included	**Inclusion criteria:** Patients 18 years age and older with either plaque or guttate psoriasis **Exclusion criteria:** **Baseline characteristics of randomised patients:** Mean PASI 14.09 at baseline Stated no difference observed between right and left sides at baseline	**Tacalcitol** Tacalcitol (once daily)	**Tacalcitol + NB-UVB** Tacalcitol (once daily) + NB-UVB (3 to 5 times a week) UVB started at 0.2 or 0.3 J/cm^2	3 weeks	**1º Outcome:** PASI **Other outcomes:**	

	Sample size calculation: Not performed **ITT Analysis**: No **Drop outs:** 4 patients							

Effect size

	Tacalcitol (n=22)	**Tacalcitol + NB-UVB (n=22)**	**P-value**
Mean PASI at baseline	14.09	14.09	-
Mean PASI at 3 weeks	7.03	4.25	P<0.001
Withdrawal due to adverse events	0/24	1/24	

No vitamin D-related side effects reported. One patient interrupted treatment because of UVB-induced erythema.

Author conclusion

As both treatment modalities seem to be associated with little long-term side effects, the combination of tacalcitol and NB-UVB seems to be an effective therapy for patients with mild to intermediate severe psoriasis, including young adults

H.9.11 LCD + NB-UVB versus NV-UVB

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
J. Bagel. LCD plus NB-UVB reduces time to improvement of psoriasis vs. NB-UVB alone. *J Drugs in Derm*. 8(4):351-357. 2009 REF ID: BAGEL2009	**RCT** Single centre USA **Randomised:** Side of body randomised, method not stated **Allocation concealment:** Not stated **Blinding:** Investigator blinded to which side received topical therapy	**Total N = 12 patients, 24 halves**	**Inclusion criteria:** Adults in good general health with chronic symmetrically distributed plaque psoriasis **Exclusion criteria:** Excluded if receiving any other psoriasis treatment or couldn't tolerate coal tar and/or ultraviolet radiation. **Baseline characteristics of randomised patients:** Sex: M/F — 7/5 Mean Age, y — 44 Race: White/Black/Asian — 8/1/3	**LCD + NB-UVB** N=12 halves NB-UVB 3 times a week + Topical LCD applied twice daily (Psorent: liquor carbonis distillate 15%, equivalent to 2.3% coal tar USP) solution Both Arms: Patients applied Cetaphil moisturiser	**NB-UVB alone** N=12 halves NB-UVB phototherapy 3 times a week	12 weeks	**1º Outcome:** Time to minimal disease/clearance **Other outcomes:** PGA Adverse events	NeoSt Compa Inc.

	Washout: None, however patients on other treatments excluded **Sample size calculation:** Not performed **ITT Analysis**: Yes **Drop outs:** None		Skin type: I/II/III/IV/V: 1/3/4/1/3 Mean psoriasis duration, y: 25 Baseline psoriasis severity: mild/moderate/severe: 3/6/3	immediately prior to light therapy and in between sessions as needed Treatment continued until 100% clearing or 36 NB-UVB sessions completed				

Effect size

Time to minimal disease or clearance

	NB-UVB + LCD	**NB-UVB**	**P-value**
Median number of weeks	4 weeks	7 weeks	0.187 (NS)

Number of patients achieving minimal disease (PGA 1)/clearance (PGA 0)

	NB-UVB + LCD (n=12 halves)	**NB-UVB (n=12 halves)**	**P-value**

Number of patients at 2 weeks	3	3	-
Number of patients at 4 weeks	9	4	0.025 (sig)
Number of patients at 6 weeks	9	6	-
Number of patients at 8 weeks	10	7	<0.10
Number of patients at 10 weeks	10	7	<0.10
Number of patients at 12 weeks	11	11	-

Complete clearance (PGA 0) at week 12

	NB-UVB + LCD	**NB-UVB**	**P-value**
Number of patients	7	6	NS

Burn (12 weeks)

One report of mild and two reports of moderate post-UVB erythema, uniformly distributed across both sides of the body

No severe adverse events (12 weeks)

Author conclusion:

Incorporating an at-home regimen with a novel LCD solution into outpatient NB-UVB light therapy is safe, convenient, effective, and can improve psoriasis more quickl
than NB-UVB light therapy alone.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison 1	Comparison 2	Length of follow-up	Outcome measures	Source of fundin
J.F. Bourke, S.J. Iqbal, P.E. Hutchinson. The effects of UVB plus calcipotriol on systemic calcium homeostasis in patients with chronic plaque psoriasis. *Clin Exp Derm*. 22:259-261.1997 REF ID: BOURKE1997	**RCT** Single centre UK **Randomised:** Method not stated **Allocation concealment:** No **Blinding:** Open **Washout:** All topical medications other than emollients	**Total N = 30**	**Inclusion criteria:** Patients with chronic plaque psoriasis aged between 18 and 75 years **Exclusion criteria:** Pregnant or lactating females and patients receiving systemic psoriasis therapy, taking vitamin D, calcium supplements or thiazide diuretics excluded **Baseline characteristics of randomised patients:** Stated groups matched for age and sex	**NB-UVB** N=10 NB-UVB therapy 3 times a week	**Calcipotriol** N=10 100 g calcipotriol 50 µg/g ointment per week	**NB-UVB + Calcipotriol** N=10 NB-UVB therapy 3 times a week + 100 g calcipotriol 50 µg/g ointment per week	4 weeks	**1º Outcome:** Serum calcium/phosphate **Other outcomes:** PASI	Leo Labora Ltd.

	stopped 1 week prior to study entry **Sample size calculation:** Not performed **ITT Analysis**: Yes **Drop outs:** None								

Effect size

PASI

Mean PASI	**NB-UVB alone (A)**	**Calcipotriol alone (B)**	**UVB + Calcipotriol (C)**
Baseline	12.0	11.7	14.6
4 weeks	7.5 (P=0.013)	6.3 (P=0.013)	3.4* (P=0.009)

*improvement in UVB + calcipotriol group significantly (P=0.045) greater than in the other two groups

Author conclusion:

Combination of UVB plus maximum recommended amount of calcipotriol is a safe and effective treatment for chronic plaque psoriasis and has little adverse effect on systemic calcium homeostasis

H.9.12 Broadband UVB triple combination versus short contact dithranol

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Sour of fund
Y. Paramsothy, M. Collins, C.M. Lawrence. Effect of UVB therapy and a coal tar bath on short contact dithranol treatment for psoriasis. *Br J Dermatol.* 118:783-789.1988 REF ID: PARAMSOTHY1988A	**RCT** Single centre UK **Randomised:** Patients randomised after SCDT, method not stated **Allocation concealment:** No **Blinding:**	**Total N = 53**	**Inclusion criteria:** Patients with stable chronic plaque psoriasis requiring inpatient treatment. Patients divided into either 35% or less and 36% or more body surface area involvement **Exclusion criteria:** Not reported **Baseline characteristics of randomised patients:** SCDT+UVB / SCDT	**Triple combination** N=27 Short contact dithranol + coal tar bath + BB-UVB (285-350 mm wavelength, five times a week) UVB started at 50% MED	**Dithranol only** N=26 Short contact dithranol emollient (placebo)	Unclear, however some outcomes reported up to 69 weeks	**1º Outcome:** Clearance (point at which patient had <3% of their skin involved by psoriasis) ****EXCLUDES FACE, SCALP, AND FLEXURES**** **Other outcomes:** Relapse	Not state

	Open **Washout:** Not stated **Sample size calculation:** Not reported **ITT Analysis**: No **Drop outs:** 5 patients withdrew from study – reasons not given (SCDT alone group)				Both Arms: Dithranol started at 1% and increased every 2nd/3rd day if no inflammation of surrounding skin Dithranol inflammation treated with 0.25% fluocinalone acetonide cream Other topical agents used on areas not suitable for SCDT (flexures, scalp, face) – these areas were excluded from study				

	(n=27)	(n=26)
Age, y	46.9	42.5
Sex: M/F	15/12	17/9
Mean %BSA	30.8%	28%
Mean disease duration, months	6.1	7.6

Effect size

5 patients withdrew from study (reasons not stated) therefore ITT analysis used

Clear (excluding scalp, face, flexures)

	SCDT+UVB (n=27)	SCDT (n=26)	P-value
Number of patients	20	16	>0.05 (NS)

Time to clearance

	SCDT + UVB	SCDT
Mean number of days	20.3±1.6	19.5±2.6

Relapse

	SCDT + UVB	SCDT
Mean number of weeks to relapse	18.9 (5-48 weeks)	10.6 (1-26 weeks)
Relapse rate	14/20	13/16

Adverse events

20 patients who cleared developed erythema on at least one occasion with (mean 3, range 1-8 episodes). 5 patients who failed to clear (mean 4.4, range 2-8 episodes) Therefore, overall 25/27 patients developed erythema with UVB therapy.

Author conclusion:

This study shows that UVB therapy does not improve the clearance of psoriasis in SCDT, but does significantly postpone relapse.

H.10 Systemic therapy (second line, non-biologic therapy)

H.10.1 INDUCTION OF REMISSION

H.10.1.1 Methotrexate vs placebo

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
J. H. Saurat, G. Stingl, L. Dubertret, K. Papp, R. G. Langley, J. P. Ortonne, K. Unnebrink, M. Kaul, A. Camez, and Champion Study Investigators. Efficacy and safety results from the randomized controlled comparative	RCT **CHAMPION trial** Multi-centre, 28 centres in Europe and Canada • Randomised (2:1) by central computer-generated scheme stratified by centre (block	Total N: **163** for our comparison (plus 108 receiving adalimumab) **Drop-outs (don't complete the study):** 11 (plus 4 using ADA) MTX: 6 due to AEs Placebo: 5 (1 AE; 4 lack of efficacy)	**Inclusion criteria:** ≥18 years of age; moderate-to-severe psoriasis (BSA ≥10% and PASI ≥10); plaque psoriasis for at least 1 year and stable plaque psoriasis for at least 2 months; candidate for systemic or phototherapy; active psoriasis despite topical treatment **Exclusion criteria:** previous treatment with TNF-antagonist or MTX; Patients with a history of clinically significant haematological, renal or liver disease/abnormal laboratory values; with a history of demyelinating disease, cancer, or other lymphoproliferative disease (other than successfully treated nonmetastatic cutaneous squamous	N=110 **MTX** **Encapsulated tablets** **7.5 mg –** increased as needed and as tolerated to **25 mg/wk** Administered as a single weekly	N=53 **Placebo encapsulated tablets (or injection for adalimumab control – data not given separately for the 2 placebo groups)** Administered as a single weekly dose	16 weeks (plus 70 days after last treatment for adverse events)	**1° outcome:** PASI75 **2° and other outcomes:** AEs; PASI50; PASI90; PASI100; PGA PASI and PGA measured at weeks 1,	Abbott laboratories

<table>
<tr>
<td>study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br.J.Dermatol. 158 (3):558-566, 2008.

Ref ID: SAURAT2008</td>
<td>size = 4)
• Washout period: 2 weeks for topical therapies and phototherapy , 4 weeks for nonbiologic systemic therapies, and 12 weeks for biologic therapies
• Double blind (patients, investigators, study site personnel and Abbott unaware of assignments)
• Allocation concealment (centrally assigned)
• Sample size calculation for PASI75 at 16 wks (for comparisons with adalimumab not placebo);</td>
<td></td>
<td>cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix); or who were immunocompromised

Note: Patients with evidence of latent TB were permitted to enrol if they had received prophylactic treatment for TB, or if prophylactic treatment was initiated before administration of study drug

<table>
<tr><th>Mean baseline</th><th>Placebo (N=53)</th><th>MTX (N= 110)</th></tr>
<tr><td>Age (years)</td><td>40·7 ± 11·4</td><td>41·6 ± 12·0</td></tr>
<tr><td>Age ≥ 65 years (%)</td><td>1·9</td><td>4·5</td></tr>
<tr><td>Gender M/F</td><td>66/44</td><td>66·4/43.6</td></tr>
<tr><td>Caucasian (%)</td><td>92·5</td><td>95·5</td></tr>
<tr><td>Weight (kg)</td><td>82·6 ± 19·9</td><td>83·1 ± 17·5</td></tr>
</table>
</td>
<td>dose

BOTH ARMS: concomitant therapies

Concomitant psoriasis therapies were not permitted during the study except shampoos free of corticosteroids; bland emollients; and low-potency topical corticosteroids for the palms, soles, face, infra-mammary areas and groin only, provided they were not used within 24 h of a study visit.</td>
<td></td>
<td></td>
<td>2 ,4 , 8, 12 and 16

AEs assessed up to 70 days after last treatment</td>
<td></td>
</tr>
</table>

	recruitment achieved this • ITT analysis for efficacy analyses (using non-responder imputation or LOCF for continuous variable) • Drop-outs/withdrawals due to AEs: MTX = 6; placebo = 1		Duration of psoriasis (years)	18·8 ± 8·7	18·9 ± 10·2		All received dietary supplement of oral folate (~5 mg weekly) beginning 48 h after ingestion of oral medication				
			BSA affected by psoriasis (%)	28·4 ± 16·1	32·4 ± 20·6						
			Patients with psoriatic arthritis (%)	20·8	17·3						
			Previous systemic and/or phototherapy (%)	90·4	87·2						
			PASI (range)	19·2 ± 6·9 (6·5–38·1)	19·4 ± 7·4 (9·3–46·6)						
			Physician's global assessment (%)								

			Very severe psoriasis	3·8	5·5						
			Moderate to severe psoriasis	58·5	41·8						
			Moderate psoriasis	37·7	52·7						

Effect Size

Outcomes

NOTE: 89 of 95 (94%) patients in the MTX group received a MTX dosage of ≥ 15 mg at week 12. Six patients (6%) received a dosage of < 15 mg at week 12 because of elevations of alanine aminotransferase or aspartate aminotransferase concentrations > 1·5 times the upper limit of normal value, which necessitated decreasing the methotrexate dosage.

NOTE: Treatment compliance (mean ± SD) was high for MTX (99·7 ± 2·5%).

NOTE: The use of low-potency (grade VI or VII) topical corticosteroids was roughly balanced between groups (8% placebo, 11% methotrexate).

Efficacy

Outcome	MTX (% patients) (N= 110)	Placebo (% patients) (N=53)
Week 16		
PASI 100	7.3 (n=8)	1.5 (n=1)
PASI 90	13.6 (n=15)	11.3 (n=6)
PASI 75	35.5 (n=39)	18.9 (n=10)
PASI 50	61.8 (n=68)	30.2 (n=16)
Change in PASI	-10.9± 8.3	-4.6± 9.9
Mean % PASI improvement (based on LOCF)	54.3	21.5
PGA (clear or minimal)	30% (n=33)	11.3 (n=6)
Week 12		
PASI 100	0.9	0.0
PASI 90	9.1	7.5
PASI 75	15.1	24.5
PASI 50	54.5	26.4
Mean % PASI improvement	48.6	21.0

Safety

Outcome	**Placebo (N= 53)**	**MTX (N= 110)**
Total adverse events	42 (79·2%)	90 (81·8%)
Serious adverse events	**1 (1·9%)** ***Hepatitis***	**1 (0·9%)** ***Calculus***
Serious infections	0	0
Adverse events leading to discontinuation	**1 (1·9%)**	**6 (5·5%)**
Adverse events		
Infections, nonserious	23 (43·4%)	46 (41·8%)
Nasopharyngitis	11 (20·8%)	26 (23·6%)
Headache	5 (9·4%)	12 (10·9%)
Pruritus	6 (11·3%)	2 (1·8%)
Rhinitis	4 (7·5%)	4 (3·6%)
Nausea	4 (7·5%)	8 (7·3%)
Rhinorrhea	3 (5·7%)	0
Viral infection	1 (1·9%)	6 (5·5%)

Arthralgia	1 (1·9%)	5 (4·5%)	
Liver function tests			
Glutamyltransferase elevation	**3 (5·7%)**	**0**	
Alanine aminotransferase > 2·5 times the ULN	**1 (1·9%)**	**4 (3·6%)**	
Aspartate aminotransferase > 2·5 times the ULN	**0**	**2 (1·8%)**	
Total bilirubin > 1·5 times the ULN	**0**	**4 (3·6%)**	
Total elevated liver enzyme concentrations	**4 (7.5%)**	**10 (9.1%)**	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
S. G. Ho, C. K. Yeung, and H. H. Chan. Methotrexate versus traditional Chinese medicine in psoriasis: a randomized, placebo-controlled trial to determine efficacy, safety and quality of life. *Clin.Exp.Dermatol.* 35 (7):717-722, 2010. Ref ID: HO2010	RCT Two centres, Hong Kong • Randomised (1:1) by drawing random cards • Washout period: 4 weeks for topical corticosteroids, phototherapy, systemic therapies and Traditional Chinese medicine (TCM); 2 weeks for moderate potency topical corticosteroids, vit D analogues, keratolytics and coal tar	Total N: **40** for our comparison (plus 21 on TCM) **Drop-outs (don't complete the study):** 4 (plus 7 using TCM) MTX: 1 Placebo: 3 Reasons unclear	**Inclusion criteria:** ≥18 years of age; chronic plaque psoriasis (BSA ≥20%); psoriasis for at least 1 year **Exclusion criteria:** renal or liver disease, active infection, immunosuppression or other serious concomitant illness; pregnant or lactating women **Mean baseline** / **MTX (N=20)** / **Placebo (N=20)** Age (range): 38.45 (21-68) / 43.45 (27-61) Gender M/F: 90/10 / 90/10 PASI (mean ± SD): 22.82 ± 13.36 (4.1–61.2) / 21.35 ± 9.17 (7.2–42·6) PDI (mean ± SD): 52.6 ± 20.6 / 48.1± 18.8	N=20 **MTX** **Initial doses 2.5-5.0 mg/wk** – if parameters of complete blood count were within normal limits dose increased to **10 mg/wk**, followed by further increases of 2.5 mg/wk (up to a max of **30 mg/wk**) until a good clinical response was seen Folic acid 5 mg/day also	N=20 **Placebo encapsulated tablets**	Treated for 6 months (assessed at monthly intervals)	**1° outcome:** PASI, PGA, PDI **2° and other outcomes:** AEs	None stated

	• Single blind (assessors only) • Allocation concealment (not stated) • Sample size calculation not reported • ITT analysis not performed • Drop-outs/withdrawals due to AEs: unclear			given ---------- **BOTH ARMS: concomitant therapies** Concomitant psoriasis therapies were not permitted during the study except fluocinolone 0.0125% cream and aqueous cream				
Effect Size Outcomes **<u>Efficacy</u>**								

Note: the difference between placebo and MTX was significant at 2, 4 and 6 months (p<0.01; p<0.001; p<0.01)

Outcome	**MTX (N= 19)**	**Placebo (N=17)**	**p-value**
At end of study (6 months)			
Baseline PASI (mean ± SD)	22.0 ± 11.3	20.4 ± 10.8	
Final PASI (mean ± SD)	5.7 ± 8.5	13.9 ± 10.1	<0.01
Mean % PASI improvement	73.9%	32%	
PASI 75	12 (63%)	3 (18%)	
PASI 50	15 (79%)	4 (24%)	
Improvement in PDI	34.8%	21.4%	NS

Safety

AEs reported by 65% of MTX group and 30% of placebo group

No serious AEs reported and no numerical data for specific AEs in each group

Summary

- The results verify the therapeutic effect of methotrexate for the management of psoriasis

H.10.1.2 Methotrexate vs ciclosporin

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
I. Flytstrom, B. Stenberg, A. Svensson, and I. M. Bergbrant. Methotrexate vs. ciclosporin in psoriasis: effectiveness, quality of life and safety. A randomized controlled trial. *Br.J.Dermatol.* 158 (1):116-121, 2008.	RCT Multi-centre (Sweden) Recruitment Sept-Feb 2002/3 and 2004/5 (to avoid sunny seasons) • Randomised (1:1) by central computer-generated random	Total N: **84** **Drop-outs (don't complete the study):** 20 **MTX**: 4 - withdrawn before first dose (2 due to laboratory abnormalities and 2 withdrew consent) **CSA**: 16 – 12 withdrawn before first dose (7 due to laboratory abnormalities	**Inclusion criteria:** ≥18 years of age; moderate-to-severe psoriasis (classified by physician and patient); chronic plaque psoriasis; insufficient response to topical and/or UV treatment; **Exclusion criteria:** Patients with haematological, renal or liver disease; with a history of cancer; immunocompromised; medication contraindicated by MTX or ciclosporin; problems of abuse, planned or ongoing pregnancy, breastfeeding or non-compliance **Mean baseline** | **MTX** | **CSA (N= 31)**	N=37 **MTX** **Initial dose** **7.5 mg/wk (3-divide dose at 12-h intervals) –** increased gradually if response inadequate (<PASI50) and no considerable AEs to a max	N=31 **Ciclosporin** **Initial dose 3 mg/kg daily (divided into 2 doses) –** increased gradually if response inadequate (<PASI50) and no considerable AEs up to a max of **5**	12 weeks (examined monthly)	**1° outcome:** PASI (assessors given 2-day training in using PASI) **2° and other outcomes:** DLQI; AEs	Swedish Psoriasis Association; Welander Foundation

Ref ID: FLYTSTROM2008	numbers • Washout period: 2 weeks for phototherapy, 4 weeks for nonbiologic systemic therapies • Assessor blind • Allocation concealment (centrally assigned) • Sample size calculation to detect a difference of one Tx producing PASI75 and the other PASI50 (need 35 in each group); • ITT analysis of all who began treatment • Drop-outs/withdrawals due to AEs: MTX = 0;	and 5 withdrew consent); 4 discontinued treatment (due to AEs)		**(N=37)**		of **15 mg/wk** Folic acid (5 mg) give daily except MTX days ---------- **BOTH ARMS: concomitant therapies** Concomitant psoriasis therapies were not permitted during the study except topicals	**mg/kg** daily			
			Age (years), mean (range)	48 (23-78)	45 (18-70)					
			Gender M/F	75.7/24.3	87.1/12.9					
			Weight (kg), mean (range)	85 (56-132)	87 (61-130)					
			PASI mean ± SD (range)	14.1 ± 7.0 (3.8-35.0)	15.5 ± 6.3 (4.3-26.2)					
			DLQI mean ± SD	7.9 ± 5.8	9.3 ± 6.0					
			Previous therapies (n)							
			UVB	33	25					
			PUVA	3	5					
			Acitretin	2	1					
			MTX	2	1					
			CSA	0	2					
			Topical only	3	6					
			Current therapy (n)							
			Topical (calcipotriol/steroids (group	22	20					

	CSA = 4 (fatigue and GI symptoms)		I-IV)							
			Emollients only	10	7					
			No topicals	5	4					

Effect Size

Outcomes (**ITT**)

<u>Efficacy</u>

PASI

Outcome	**MTX (N=37)**	**CSA (N= 31)**	**p-value**
Baseline PASI mean ± SD	14.1 ± 7.0	15.5 ± 6.3	
Week 12			
PASI mean ± SD	5.6 ± 3.8	3.6 ± 3.0	
Mean % PASI improvement	58	72	0.0028
Percentage achieving (n):			
PASI 90	11% (4)	29% (9)	NS
PASI 75	24% (9)	58% (18)	0.0094

PASI 50	65% (24)	87% (27)	NS

DLQI

Mean change from baseline in DLQI	**MTX (N=37)**	**CSA (N= 31)**	**p-value**
Week 12			NS
Week 8	42%	71%	0.0078

Safety

No serious AEs reported (but 2 patients on CSA developed mild hypertension – no anti-HT treatment was needed)

Temporary discontinuation of treatment occurred in 4 MTX and 1 CSA patients due to infections (2 MTX and 1 CSA patient required antibiotics)

Outcome	**MTX (N=37) n (%)**	**CSA (N= 31) n (%)**	**p-value**
Total adverse events	29 (78%)	30 (97%)	0.03
Serious adverse events	**0**	**0**	**NS**
Adverse events leading to discontinuation	**0**	**4 (12.9%)**	
Adverse events			

Fatigue	6 (16)	15 (48)	0.008
GI	13 (35)	12 (39)	0.80
Infections	11 (30)	11 (35)	0.80
Headache	5 (14)	9 (29)	0.14
Paraesthesia	0	11 (35)	<0.0001
Arthralgia	4 (11)	5 (16)	0.72
Myalgia	0	5 (16)	0.02
Muscle cramp	0	4 (13)	0.04
Hypertrichosis	0	4 (13)	0.04
Urgency	1 (3)	4 (13)	0.17
Elevation in liver enzymes	**7 (19%)**	**0**	**0.01**
Elevated creatinine	**0**	**6 (19%)**	**0.007**

Summary

- Treatment with methotrexate or ciclosporin for chronic plaque psoriasis brings satisfactory disease control, improved quality of life and tolerable side-effects.
- A statistically significant difference in effectiveness between treatment groups was recorded, showing ciclosporin to be more effective than methotrexate in a short-term perspective.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
V. M. Heydendael, P. I. Spuls, B. C. Opmeer, C. A. De Borgie, J. B. Reitsma, W. F. Goldschmidt, P. M. Bossuyt, J. D. Bos, and M. A. de Rie. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. *New England Journal of Medicine* 349 (7):658-665, 2003. Ref ID: HEYDENDAEL2003 R. J. Rentenaar, V. M. Heydendael, F. N. van Diepen, M. A. de Rie, and I. J. ten Berge. Systemic treatment with either cyclosporin A	RCT Multi-centre (The Netherlands) Recruitment Oct 1998-June 2000 • Randomised (1:1) by central computer-generated random numbers (block size of 8) • Washout period: 2 weeks for topicals, 4 weeks for UVB, PUVA or systemic	Total N: **88** **Drop-outs (don't complete the study):** 35 (16 in primary analysis) **Primary analysis** **MTX**: 13 - 1 withdrew consent before first dose; 12 discontinued owing to abnormal laboratory values **CSA**: 3 – 2 found to be ineligible; 1 discontinued owing to abnormal laboratory bilirubin values	**Inclusion criteria:** ≥18 years of age; moderate-to-severe chronic plaque psoriasis (≥PASI of 8); chronic plaque psoriasis; insufficient response to topical and/or UVB treatment; not previously treated with either methotrexate or ciclosporin **Exclusion criteria:** liver or renal impairment; insulin-dependent diabetes mellitus; a high risk of liver-function abnormalities; a positive serologic test for hepatitis B virus; uncontrolled hypertension; a history of cancer, including skin cancer or severe cardiovascular, pulmonary, cerebral, neurologic, or hematologic disease; or acute infection requiring antimicrobial therapy or associated with human immunodeficiency virus infection. Patients were also excluded if they were pregnant, breast-feeding, or noncompliant with an effective regimen of contraception. Patients with moderate or severe steatohepatitis (as established by ultrasonography of the liver) **Mean baseline** | **MTX** | **CSA (N= 42)**	N=44 **MTX** **Initial dose** **15 mg/wk (3-divide dose at 12-h intervals)** – if <25% reduction in PASI, dose increased up to **22.5 mg/wk** after 4 wks of treatment ---------- **BOTH ARMS:**	N=44 **Ciclosporin** **Initial dose 3 mg/kg daily (divided into 2 doses)** – if <25% reduction in PASI, dose increased up to **5 mg/kg** daily after 4 wks of treatment ----------	16 weeks treatment (examined twice during the first month and then monthly); plus 36-wk off treatment follow-up	**1° outcome:** PASI **2° and other outcomes:** PGA; SF-36; AEs; time to relapse **Relapse**: PASI > 50% of the base-line score or the need for UVB or systemic therapy.	Dutch Health Authorities

or methotrexate does not influence the T helper 1/T helper 2 balance in psoriatic patients. *Journal of Clinical Immunology* 24 (4):361-369, 2004. Ref ID: RENTENAAR2004	therapies • Assessor blind • Allocation concealment (centrally assigned) • Sample size calculation to rule out a difference of 2 points or more in mean PASI at 95% power (need 42 in each group); • ITT analysis (LOCF) • Drop-outs/withdrawals due to AEs (abnormal laboratory values): MTX = 12 (liver enzymes); CSA = 1 (bilirubin)	**Lost to follow-up post Tx** **MTX**: 2 at wk 32; 10 at wk 52 **CSA**: 1 at wk 32; 6 at wk 52		**(N=43)**		Dose decreased according to guidelines in case of AEs **Concomitant therapies** Concomitant psoriasis therapies were not permitted during the study except emollients	**BOTH ARMS:** During the follow-up period, active therapy for psoriasis was allowed if necessary. Drugs known to interfere with psoriasis and/or with the systemic treatments were not allowed.			
			Age (years), mean ±SE	41.6 ± 13.0	38.3 ± 12.4					
			Gender M/F	65.1/34.9	69.0/31.0					
			PASI mean ± SE	13.4 ± 3.6	14.0 ± 6.6					
			Age at onset, mean ± SE	41.6 ± 13.0	38.2 ± 12.4					
			PsA (n)	3	1					
			Previous therapies (n)							
			UVB	28	25					
			PUVA	10	8					
			Acitretin	5	5					
			Fumaric acid	3	0					
			Topical only	8	14					

Effect Size

Outcomes (**ITT**)

Note: an increase in dose was needed in 4 MTX patients and 6 CSA patients

Efficacy

PASI

Outcome	**MTX** **(N=43; 21 completed)**	**CSA (N= 42; 41 completed)**	**p-value**
Week 16			
Initial PASI (mean ± SE)	13.4 ± 3.6	14.0 ± 6.6	
Final PASI (mean ± SE)	5.0 ± 0.7	3.8 ± 0.5	
Mean difference in PASI (adjusted for baseline by ANCOVA)		1.3 points lower	0.09 (95% CI: -0.2 to 2.8)
Mean % change in PASI	64%	72%	0.14 (95% CI: -2 to 18)
Number achieving:			
PASI 90	17	14	0.55
PASI 75	26	30	0.29
Time-to-remission (PASI75)	-	-	NS: p = 0.07 (log rank test)

Time-to-remission (PASI90)	-	-	NS: p = 0.70 (log rank test)
Duration of remission (PASI75)			p = 0.43 (log rank test)
Duration of remission (PASI90)			p = 0.34 (log rank test)
Median time to relapse (requiring active therapy)	4 weeks	4 weeks	

Safety

Note: 2 in CSA group were given anti-**hypertensive** treatment

No serious or irreversible AEs reported

Outcome	**MTX (N=43)**	**CSA (N= 42)**
Total adverse events	29	35

Summary

- No significant differences in efficacy were found between methotrexate and ciclosporin for the treatment of moderate-to-severe psoriasis.
- As the effectiveness and tolerability of methotrexate are similar to those of ciclosporin in patients with moderate-to-severe psoriasis differences between the treatments in terms of side effects, long-term adverse effects, ease of administration (once-daily vs. twice-daily treatment), and costs can be used to guide treatment decisions in individual cases.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
K. Sandhu, I. Kaur, B. Kumar, and A. Saraswat. Efficacy and safety of cyclosporine versus methotrexate in severe psoriasis: a study from north India. *J.Dermatol.* 30 (6):458-463, 2003. Ref ID: SANDHU2003	RCT Single-centre (India) 30 consecutive patients • Randomised (method not stated) • Washout period not stated • Blinding not stated • Allocation concealment (not stated) • Sample size calculation not stated • ITT analysis not stated • Drop-	Total N: **30** **Drop-outs (don't complete the study):** Not stated	**Inclusion criteria:** severe psoriasis (>40% BSA **Exclusion criteria:** Patients with renal or liver disease; with a history of cancer; uncontrolled hypertension; epilepsy; gout; alcoholism; pregnant or lactating women **Mean baseline** / **MTX (N=15)** / **CSA (N= 15)** Age (years), mean ± SE: 39.3±3.0 / 46.2±2.5 Gender M/F (%): 80/20 / 87.5/12.5 PASI mean ± SE: 27.6 ± 2.3 / 29.6 ± 2.1 Duration (months) mean ± SE: 65.4 ± 14.2 / 62.5 ± 14.9 Duration (years) mean ± SE: 33.5±3.0 / 41±2.5 BSA (%)mean ± SE: 70.6% / 72%	N=15 **MTX** **Initial dose** **0.5 mg/kg/wk–** ---------- **BOTH ARMS: concomitant therapies** No concomitant psoriasis therapies (topical or systemic) were not permitted during the study; neither was concomitant	N=15 **Ciclosporin** **Initial dose 3 mg/kg daily (divided into 2 doses) –** increased up to a max of 4 **mg/kg** daily if no change or a rise in PASI after 2 weeks of therapy ---------- **BOTH ARMS:** Consensus guidelines followed in cases	12 weeks (examined fortnightly)	**1° outcome:** PASI75 **2° and other outcomes:** clearance; AEs	None stated

	outs/withdrawals due to AEs: not stated		Nail involvement (%) 8 (53.5%) 7 (46.6%) Joint involvement (%) 1 (6.6%) 2 (13.3%) **Type of psoriasis** Plaque (%) 11 (73.3%) 11 (73.3%) Erythroderma (%) 4 (26.6%) 4 (26.6%)		therapy with nephrotoxic compounds nor drugs known to interact with MTX or CSA **Dose tapering** Tapering initiated once PASI75 achieved	of persistent abnormal laboratory values After 4 weeks on optimum dose all patients reassessed and those with <25% reduction on PASI were regarded as non-responders			

Effect Size

Outcomes (**ITT**)

<u>Efficacy</u>

To achieve satisfactory results the initial dose of CYA had to be increased in 7/15 (46.6%) – the response then became comparable to the rest of the group

During tapering 13/15 CSA-treated patients experienced a gradual rise in PASI score (which was not seen in the MTX group)

Change in PASI

Outcome	MTX (N=15)	CSA (N= 15)	p-value
Week 12			
Baseline PASI (mean ± SE)	27.6 ± 2.3	29.6 ± 2.1	NS
Final PASI (mean ± SE)	0.4 ± 0.2	4.3 ± 1.7	-
Mean % PASI improvement	98.5%	85.6%	<0.05
Week 10			
Baseline PASI (mean ± SE)	27.6 ± 2.3	29.6 ± 2.1	NS
Week 10 PASI (mean ± SE)	1.1 ± 0.94	2.4 ± 0.8	-
Mean % PASI improvement	95.8%	91.7%	NS

Time to remission/PASI/clear

Outcome	MTX (N=15)	CSA (N= 15)	p-value
Time-to-PASI75 (mean; range)	5.3 (2-12) weeks	6.8 (4-8) weeks	<0.05
Complete clearance	13 (86.6%)	6 (40%)	-
Remaining clear at 12 weeks (after tapering)	13/13	2/6	-

Safety

No abnormal biochemical parameters (except slight rises in serum creatinine below the 30% threshold for dose reduction in CSA group)

Outcome	MTX (N=15)	CSA (N= 15)
Diastolic hypertension	0	4

Author's summary

- Patients on methotrexate were found to have more rapid and complete clearance than those on ciclosporin.
- Both drugs were well tolerated.
- Side effects in both the treatment groups were minor, transient, and manageable.
- At doses with comparable short-term safety profiles, methotrexate resulted in more rapid and cost effective clearance of patients with severe psoriasis. Ciclosporin can provide an effective and safe alternative.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
M. Gumusel, M. Ozdemir, I. Mevlitoglu, and S. Bodur. Evaluation of the efficacy of methotrexate and cyclosporine therapies on psoriatic nails: a one-blind, randomized study. Journal of the European Academy of Dermatology & Venereology 25 (9):1080-1084, 2011. Ref ID: GUMUSEL2011	RCT Single-centre (Turkey) Consecutive in- and out-patients in Dermatology Department (recruited Jan-Nov 2007) • Randomised (roll of a die - inadequate) • Washout period: topicals 4 weeks; systemics 6 months • Blinding unclear • Allocation concealment	Total N: **37** **Drop-outs (don't complete the study):** 3	**Inclusion criteria:** moderate-to-severe psoriasis; nail involvement; BSA >10% and PASI ≥10 and NAPSI >10 (or less severe disease but distressed by condition) Note: only 2 patients had BSA<10 and PASI<10, and they had severe, resistant nail psoriasis **Exclusion criteria:** Age <18 years, renal or liver disease; history of skin cancer or other systemic malignancy; uncontrolled hypertension; pregnant or lactating women or plans to conceive; haematological problems; hyperlipoproteinamia; severe cardiac or neurological disease; risk of abuse of treatment; fungal infection; current systemic therapy for psoriasis or UV and acitretin in the last 2 years; guttate, erythrodermic, pustular or localised palmoplantar psoriasis	N=18 MTX Initial dose **15 mg weekly** (plus 5 mg folic acid on day not taking MTX) for 3 months, reduced to **10 mg/wk** for second 3 months ---------- **BOTH ARMS: concomitant therapies** No concomitant psoriasis	N=19 Ciclosporin **Initial dose 5 mg/kg daily (divided into 2 doses) –** decreased to **2.5-3.5 mg/kg daily** for second 3 months	6 months	**1° outcome:** NAPSI **2° and other outcomes:** clearance of nails; AEs	None stated

	(adequate) • Sample size calculation performed • ITT analysis not performed • **Drop-outs/withdrawals due to AEs: 1 MTX; 2 CSA**			therapies were not permitted during the study; only once daily emollients				

Mean baseline	MTX (N=17)	CSA (N= 17)
Age (years), mean ± SD	42.5±12.5	34.8±10.2
Gender M/F (%)	58.8/41.2	47.1/52.9
PASI mean ± SD	10.7 ± 6.0	12.9 ± 6.4
Duration (years) mean ± SD	12.6 ± 8.4	13.6 ± 10.8
NAPSI (mean ± SD)	39.1±19.9	42.1±26.4
BMI (kg/m^2)mean ± SD	27.8±4.1	26.7±5.8

Note: no statistically significant difference in any characteristic

Effect Size

Outcomes (**ACA**)

Efficacy

Outcome	MTX (N=17)	CSA (N= 17)	p-value
Baseline NAPSI (mean ± SD)	39.1±19.9	42.1±26.4	0.9

Final NAPSI (6 months; mean ± SD)	18.0 ± 11.5	25.8 ± 19.2	-
Mean NAPSI improvement	21.1	16.3	0.27
Mean % NAPSI improvement	43.3%	37.2%	0.49
Moderate improvement (>50-99%)	7 (41.1%)	7 (41.1%)	-
Complete improvement (100%)	0	1 (5.8%)	-

Time to remission/PASI

- Graph of PASI over time shows the maximum response is achieved at 8 weeks for MTX and 12 weeks for CSA

Safety

All 3 patients withdrawn

Outcome	**MTX (N=18)**	**CSA (N= 19)**
Increased transaminase	1	0
Elevated serum creatinine	0	2

Author's summary

- Moderate effectiveness on psoriatic nail was found in the two treatment agents and there were no significant differences in efficacy between the groups.
- Both drugs were well tolerated.

H.10.2 INDUCTION OF REMISSION

H.10.2.1 Actitretin dosing schedules

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
P. Berbis, J. M. Geiger, C. Vaisse, C. Rognin, and Y. Privat. Benefit of progressively increasing doses during the initial treatment with acitretin in psoriasis. *Dermatologica* 178 (2):88-92, 1989. Ref ID: BERBIS1989	RCT • Randomised (method not stated) • Washout period (see exclusion criteria) • Double blind • Allocation concealment (not stated) • Sample size calculation not stated • ITT analysis not	Total N: **66** **Drop-outs (don't complete the study):** 8 Group I: 1 (cleared at 2 wks) Group II: 4 (2 abnormal LFTs; 1 mucocutaneous AEs; 1 non-treatment related) Group III: 3 (1 abnormal LFTs; 1 mucocutaneous AEs; 1 non-treatment related) **Note:** 7	**Inclusion criteria:** severe psoriasis **Exclusion criteria:** Impaired renal or hepatic function; severe cardiological or neurological disease; female of childbearing potential not willing to use effective contraception; received MTX, etretinate, PUVA, UVB, topical corticosteroids, tar derivatives, or anthralin 4 weeks before entry into the study **Mean baseline** / **Group I - increasing (n=21)** / **Group II - constant (n=23)** / **Group III - decreasing (n=22)** Age (years), mean ± SD: 38.9±14.5 / 50.3±12.4 / 46.7±14.3 Gender M/F (%): 81/19 / 65.2/34.8 / 68.2/31.8 Weight (kg) mean ± SD: 66.0± 12.4 / 70.0 ± 12.3 / 71.1 ± 12.2 PASI (mean ± SEM): 22.0±1.9 / 22.0±2.1 / 21.8±1.8	N=21 **Acitretin** **Group I: low initial dose increased at 2-wk intervals (10, 30, 50 mg/day) (n=21)** ---------- **BOTH ARMS: concomitant therapies**	N=45 **Acitretin** **Group II: constant dose (30 mg/day) (n=23)** **Group III: high initial dose decreased at 2-wk intervals (50, 30, 10 mg/day) (n=22)**	12 weeks (6 wk double blind phase; 6 wk open phase)	**1° outcome:** change in PASI **2° and other outcomes:** clinical and laboratory AEs	None stated

	performed • Drop-outs/withdrawals due to AEs: Group I: 0; Group II: 3; Group III: 2	additional patients dropped out during the open phase (6 due to clearance and 1 pregnancy)	**Type of psoriasis (n)** Psoriasis vulgaris (plaque, nummular): 14, 18, 12 Guttate psoriasis: 2, 1, 3 Psoriasis vulgaris (partim pustulosa): 3, 1, 5 Erythrodermic psoriasis: 0, 1, 1 Palmoplantar pustular psoriasis: 1, 1, 1 Acrodermatitis continua (Hallopeau): 1, 1, 0	Topical corticosteroid allowed after week 8 on limited areas (32 patients received moderately strong preparations). No other antipsoriatic therapy permitted 19 patients received drugs for concomitant diseases	---------- **BOTH ARMS:** Daily dose dispensed in a blister pack containing 5 identical capsules (10 mg acitretin and placebo). Boxes dispensed for 2-weeks at each visit During open phase dose adjusted to 10, 30 or 50 mg/day according to improvement and AEs (mean dose = 33.9 mg/day)			

Effect Size

Outcomes

Efficacy

- An improvement of >80% was obtained in 42/58 patients by the end of the open trial phase

Outcome	**Group I (n=21)**	**Group II (n=23)**	**Group III (n=22)**	**p-value**
Initial PASI (mean ± SEM)	22.0±1.9	22.0±2.1	21.8±1.8	
PASI at 2 wk	Dose dependent improvement (presented graphically)			0.07
% change in PASI at end of double blind phase (6 wk)	(n=20) 62.7%	(n=19) 55.9%	(n=19) 67.1%	0.42
% change in PASI; mean ± SEM (12 wk – end of open phase) note that numbers in each group are unclear at 12 wks	81±4	87±4	88±3	

Safety

- The adverse reactions were dose dependent: their frequency and intensity increased progressively with increasing dose in group I and decreased with decreasing dose in group 3

Outcome	During double blind phase			During whole treatment (n=65)
	Group I (n=21)	Group II (n=23)	Group III (n=21)	
Experienced side effects	21	23	21	65
Mucous membrane				
Dry lips/cheilitis	21	23	21	65
Dry mouth	13	18	14	54
Dry nose	11	16	10	45
Epistaxis	1	1	0	2
Rhinorrhea	0	0	0	1
Conjuntivitis/dry eyes	2	6	8	29
Skin				
Dry skin	16	16	16	51
Scaling (palms/soles)	18	18	18	57
Scaling (elsewhere)	13	12	15	48
Pruritis	0	4	1	7
Facial dermatitis	2	0	3	5
Localised erythroderma	0	0	0	1
Phototoxicity	0	1	0	2
Sticky skin	0	1	0	1

Folliculitis	0	0	0	2
Hair and nails				
Hair loss	1	2	6	13
Nail fragility	3	5	2	16

Severe clinical adverse reactions

Treatment period	**Group I**		**Group II**		**Group III**	
	Dose (mg/day)	**N'/n**	**Dose (mg/day)**	**N'/n**	**Dose (mg/day)**	**N'/n**
Week 0-2*	10	0/21	30	7/23	50	9/21
Week 3-4	30	3/20	30	7/22	30	5/20
Week 5-6**	50	8/20	30	9/21	10	2/19

*Group I vs group II and group I vs III: p<0.01

** Group III vs group I: p =0.06; group III vs group II: p<0.05

Author's summary

- Acitretin is efficacious at doses between 10-50 mg/day and the 3 therapeutic schemes appeared to have similar efficacy
- The undesirable effects on skin and mucous membranes are dose-dependent
- The number of severe adverse reactions was lower in the group with increasing dosage and no patient in this group had to interrupt treatment because of adverse reactions in this group
- The acceptability of acitretin is better when treatment is started at a low dose and progressively increased

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
T. P. Kingston, L. H. Matt, and N. J. Lowe. Etretin therapy for severe psoriasis. Evaluation of initial clinical responses. *Arch.Dermatol.* 123 (1):55-58, 1987. Ref ID: KINGSTON1987	RCT • Randomised (method not stated) • Washout period 1 month for systemic treatments for psoriasis • Double blind • Allocation concealment (not stated) • Sample size calculation not stated • ITT analysis not performed • Drop-outs/withdrawals due to AEs: 0	Total N: **21** **Drop-outs (don't complete the study):** 6 Placebo: 3 switched to high dose acitretin because of increased disease severity at 4 weeks 3 due to administrative reasons	**Inclusion criteria:** psoriasis affecting 21-95% of the body **Exclusion criteria:** Fertile women **Mean baseline** / **All (n=21)** Age (years), range: 31-74 Gender M/F (%): 81/19 **Note:** unclear if suitably matched at baseline	N=15 (5 in each group) **Acitretin** **10, 50 or 75 mg/day (mean doses 0.14, 0,66 or 0.85 mg/kg/day)** ---------- **BOTH ARMS: concomitant therapies** 1% hydrocortisone ointment permitted on local areas	N=6 **Placebo** ---------- **BOTH ARMS:** During open phase dose adjusted to clinical response	8 months (2 months double blind phase; 6 month open phase)	**1° outcome:** extent of psoriasis involvement (0-100%) and scaling, erythema, thickness and pustulation on 0-6 scale (0 = absent) Excellent responders >75% clearing; good responders = 50-75% reduction in % BSA; minimal reposnders = <50% clearing **2° and other outcomes:** clinical and laboratory AEs	None stated

				(≤5% BSA) but no other anti-psoriatic treatment permitted				

Effect Size

Outcomes

Efficacy (8-wk double blind period)

- Patients who received 50 or 75 mg/day showed significant improvement on every parameter, whereas those receiving 0 or 10 mg/day did not
- The group receiving 75 mg/day did not show greater improvements than 50 mg/day
- Most patients needed daily doses of 0.66 mg/kg or more to initiate remission

Safety

- There were more side effects at higher doses
- 3 patients required dose adjustment because of transient increases in liver enzymes and hypertriglyceridaemia (group not stated)

Outcome	% of those receiving ≥0.66 mg/kg with the outcome
Cheilitis and mucosal dryness	89
Palmoplantar peeling	86
Alopecia	58

Sticky skin	32
Paronychia and other nail problems	31
Skin fragility	62

Author's summary

- Acitretin is an effective treatment for severe recalcitrant psoriasis

H.10.3 INDUCTION & MAINTENANCE OF REMISSION

H.10.3.1 Acitretin 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>A. Lassus, J. M. Geiger, M. Nyblom, T. Virrankoski, M. Kaartamaa, and L. Ingervo. Treatment of severe psoriasis with etretin (RO 10-1670). Br.J.Dermatol. 117 (3):333-341, 1987.</td>
<td>RCT

Volunteers from the Finnish Psoriasis Association

Recruitment Dec 1984-Jan1985

• Randomised (method not stated)
• Washout period not stated
• Double blind (details not stated)</td>
<td>Total N: 80

Drop-outs (don't complete the study): 7

3 for protocol violation (group not stated)

Group I: 1 due to lack of efficacy

Group II: 1 due to side effects</td>
<td>Inclusion criteria: long-standing severe psoriasis

Exclusion criteria: not stated

Note: baseline severity not reported
<table>
<tr><th>Mean baseline</th><th>Acitretin 10 mg/day (n=20)</th><th>Acitretin 25 mg/day (n=20)</th><th>Acitretin 50 mg/day (n=20)</th><th>Placebo (n=20)</th></tr>
<tr><td>Age (years), mean ± SD</td><td>48.5±11.2</td><td>52.7±11.3</td><td>45.9±13.2</td><td>47.5±11.9</td></tr>
<tr><td>Gender M/F (%)</td><td>55/45</td><td>50/50</td><td>50/50</td><td>55/45</td></tr>
<tr><td>Duration (years) mean ± SD</td><td>23.7 ± 14.5</td><td>20.1 ± 21.3</td><td>17.9 ± 10.6</td><td>19.2 ± 12.2</td></tr>
<tr><td>Weight (kg) mean ± SD</td><td>73.2 ± 10.4</td><td>78.5 ± 18.1</td><td>75.8 ± 17.9</td><td>71.7 ± 11.7</td></tr>
<tr><td>Height (cm) mean ± SD</td><td>172 ± 11</td><td>171 ± 10</td><td>172 ± 11</td><td>170 ± 9</td></tr>
<tr><td colspan="5">Type of psoriasis (n)</td></tr>
</table>
</td>
<td>N=60

Acitretin

Group I: 10 mg/day (n=20)

Group II: 25 mg/day (n=20)

Group III: 50 mg/day (n=20)

After 2</td>
<td>N=20

Placebo</td>
<td>6 months (examined monthly)

Induction of remission

(8-week phase) and maintenance treatment

(26-week phase)

Note: final evaluation at 6 months was during the summer when there may have</td>
<td>1° outcome: PASI

2° and other outcomes: AEs, g-GT, SGOT, SGPT, cholesterol, triglycerides</td>
<td>None stated</td>
</tr>
</table>

Ref ID: LASSUS1987	• Allocation concealment (not stated) • Sample size calculation not stated • ITT analysis not performed • Drop-outs/withdrawals due to AEs: 1 in group II	Group III: 1 due to lack of efficacy Group IV: 1 due to lack of efficacy	Psoriasis vulgaris: 15, 18, 17, 20 Psoriasis pustulosa: 1, 1, 2, 0 Erythrodermic psoriasis: 4, 1, 1, 0	months (induction) the dose was reduced owing to AEs or good clinical response ---------- **BOTH ARMS: concomitant therapies** 0.1% diflucortolone valerate ointment permitted on request		been partial spontaneous remission		
Effect Size Outcomes **INDUCTION** (2 months – during this time 2 in group I; 3 in group II, 2 in group III and 1 in group IV did not take the dosage stated)									

Efficacy

- There was a significantly greater reduction in PASI in the groups receiving 25 mg/day and 50 mg/day compared with placebo ($p<0.05$)
- There was no significant difference between the 25 and 50 mg groups
- The mean percentage decrease in PASI score in the 10 mg group was greater than in the placebo group, but did not differ significantly from any other group

Outcome	**Acitretin 10 mg/day (n=20)**	**Acitretin 25 mg/day (n=20)**	**Acitretin 50 mg/day (n=20)**	**Placebo (n=20)**
PASI75 (n)	8	12	14	5
Requiring topical steroid	6	7	4	12

Safety

In patients in whom the initial dose was maintained

Outcome	**Acitretin 10 mg/day (n=18)**	**Acitretin 25 mg/day (n=17)**	**Acitretin 50 mg/day (n=18)**	**Placebo (n=19)**
Experienced side effects	15	16	17	9
Mucous membrane				
Dry lips	15	13	16	5
Dry mouth	1	1	2	1
Dry nose	3	4	4	1

Conjuntivvitis	5	2	2	1
Skin				
Dry skin (palms/soles)	0	1	1	0
Dry skin (elsewhere)	7	6	10	4
Scaling (palms/soles)	0	0	2	0
Scaling (elsewhere)	1	2	3	1
Skin thinning	0	0	0	0
Pruritis	3	5	3	1
Retinoid dermatitis	1	0	4	0
Vesicular lesion	0	0	0	0
Hair and nails				
Hair loss	0	0	6	0
Paronychia	0	0	3	0
Nail fragility	0	0	0	0

Outcome (increase in lab values to above ULN when previously normal)	**Acitretin 10 mg/day (n=18)**	**Acitretin 25 mg/day (n=17)**	**Acitretin 50 mg/day (n=18)**	**Placebo (n=19)**
Gamma GT > 50 U/l	1	0	0	0

SGOT > 40 U/l	2	0	0	0
SGPT > 40 U/l	0	0	0	0
Cholesterol > 6.9 mmol/l	2	5	3	3
Triglycerides >1.7 mmol/l	2	2	2	1

Dose

Daily doses used during whole treatment period

- Group I: 9.0 ± 1.5 mg
- Group II: 21.4 ± 4.0 mg
- Group III: 37.4± 7.7 mg

MAINTENANCE (subsequent 4 month phase)

Efficacy

- After 6 months there was no significant difference in PASI between the 4 groups, and all were markedly improved

Outcome	**Acitretin 10 mg/day (n=20)**	**Acitretin 25 mg/day (n=20)**	**Acitretin 50 mg/day (n=20)**	**Placebo (n=20)**
Requiring topical steroid during	13	12	13	18

whole study				

Safety

Outcome	Acitretin 10 mg/day (n=20)	Acitretin 25 mg/day (n=20)	Acitretin 50 mg/day (n=20)	Placebo (n=20)
Experienced side effects	17	19	20	11
Mucous membrane				
Dry lips	16	17	19	6
Dry mouth	1	2	3	1
Dry nose	3	6	7	1
Conjuntivvitis	5	3	2	1
Skin				
Dry skin (palms/soles)	0	2	7	0
Dry skin (elsewhere)	8	6	15	5
Scaling (palms/soles)	0	0	2	0
Scaling (elsewhere)	1	3	4	1
Skin thinning	0	1	0	0
Pruritis	3	6	5	4
Retinoid dermatitis	1	1	5	0

Vesicular lesion	0	1	0	0
Hair and nails				
Hair loss	3	3	15	2
Paronychia	1	0	4	1
Nail fragility	0	0	1	0

Outcome (increase in lab values to above ULN when previously normal)	**Acitretin 10 mg/day (n=18)**	**Acitretin 25 mg/day (n=17)**	**Acitretin 50 mg/day (n=18)**	**Placebo (n=19)**
Gamma GT > 50 U/l	0	1	1	1
SGOT > 40 U/l	1	2	1	0
SGPT > 40 U/l	1	3	2	0
Cholesterol > 6.9 mmol/l	2	0	Value missing	1
Triglycerides >1.7 mmol/l	1	1	0	1

Author's summary

- The optimal initial dose seems to be approximately 25 mg/day and the maintenance dose somewhat lower.
- Six months after the start of treatment there were no significant differences between the four groups; the last follow-up examination took place during the summer and some of the patients probably experienced spontaneous improvement.
- Although clinical adverse effects were frequent in all groups, severe side effects, namely hair loss and paronychia, occurred frequently only among patients treated with an initial dose of 50 mg of etretin daily.
- The effect of treatment on liver enzymes, cholesterol and triglycerides was minimal.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
M. T. Goldfarb, C. N. Ellis, A. K. Gupta, T. Tincoff, T. A. Hamilton, and J. J. Voorhees. Acitretin improves psoriasis in a dose-dependent fashion. *J.Am.Acad.Dermatol.* 18 (4 Pt 1):655-662, 1988. Ref ID: GOLDFARB1988	RCT • Randomised (method not stated) • Washout period: 1 month for systemics; 2 weeks for topicals • Blinding (not stated) • Allocation concealment (not stated) • Sample size calculation not stated • ITT analysis not performed • Drop-outs/withdrawals due to AEs: 6 (group not specified)	Total N: **38** **Drop-outs (don't complete the study):** 5 to end of 8-wk DB phase – had to enter open phase early due to flaring of psoriasis (3 in placebo; 1 on 10 mg 1 on 25 mg); 12 to end of 24-wks acitretin (6 clinical or lab side effects; 2 failure to improve; 2 clearance of psoriasis; 2 noncompliance)	**Inclusion criteria:** adults; 10-70% BSA or disabling disease; **Exclusion criteria:** women of childbearing potential **Note:** baseline characteristics not reported but states that there was no significant difference in mean weight age or sex distribution	N=26 **Acitretin** **10 mg/day (n=5)** **25 mg/day (n=5)** **50 mg/day (n=11)** **75 mg/day (n=5)** ----------	N=12 **Placebo**	8 weeks double-blind phase then open phase of 24 wk for placebo and 16 for acitretin groups (second phase non-comparative) Evaluated monthly **Note**: daily doses of acitretin during the open phase could be 10, 25, 30, 50 or 75 mg determined by the investigator based on response to therapy, side effects and lipid levels; all placebo patients started on 50 mg **Note**: after 24 weeks of acitretin therapy patients were required	**1° outcome:** global severity scale: % skin involvement and overall scaling, erythema, thickness and global extent on 0-6 scale (0 absent/clear to 6 severe) After 8 weeks, overall improvement ranked as worse (>10% worse); unchanged (10% worse to 10% better); fair (11-50% improvement); good (51-75% improvement); or excellent (>75% improvement) **2° and other outcomes:** AEs, blood count, urinalysis, LFTs, cholesterol,	None stated

				BOTH ARMS: concomitant therapies No topicals except bland emollients and limited amounts of 1% hydrocortisone cream		to stop treatment for at least 1 month, but could receive additional 1 month courses if psoriasis recurred (worsening of global score by 2 points)	triglycerides	

Effect Size

Outcomes

8-wk DB period

Efficacy

- Overall improvement scores and individual parameters showed a dose-response relationship (p=0.002)
- NS difference between 10 or 25 mg acitretin and placebo on any parameter
- At the initial 2-wk evaluation 19% of all patients experienced an initial expansion in extent of psoriasis

Outcome (change from baseline – positive numbers indicate improvement)	Placebo (n=12)	Acitretin 10 mg/day (n=5)	Acitretin 25 mg/day (n=5)	Acitretin 50 mg/day (n=11)	Acitretin 75 mg/day (n=5)
Scaling	0.6±0.5	-0.8±0.5	1.2±0.4	2.2±0.4	3.2±0.6
Erythema	0.5±0.5	-0.2±0.5	0.6±0.4	1.5±0.5	3.0±0.6
Thickness	0.6±0.3	-0.4±0.2	1.4±0.2	2.1±0.4	4.2±0.4
Global improvement	0.5±0.3	0.0±0.0	1.0±0.3	1.6±0.4	3.0±0.8
% improvement	-0.8±6.1	-0.3±1.2	-3.2±4.3	5.5±2.5	17.4±5.9
>75% improvement in global score (n)	1	0	0	2	2
Clearance	1	0	0	0	0

Safety during 8 wk double-blind phase

Symptom	% showing the symptom					
	Placebo (n=12)	Acitretin 10 mg/day (n=5)	Acitretin 25 mg/day (n=5)	Acitretin 50 mg/day (n=11)	Acitretin 75 mg/day (n=5)	During first 24 wk (average 50 mg/day)
Cheilitis	25 (n=3)	40 (n=2)	100 (n=5)	100 (n=11)	80 (n=4)	95
Peeling palms and soles	17	0	50	64	20	78
Alopecia	8 (n=1)	0	25 (n=1)	18 (n=2)	40 (n=2)	73

Dry nose	0	0	50	36	60	41
Dry eyes	17	0	50	18	60	35
Chills	0	0	25	27	0	27
Pruritis	0	0	50	18	20	22
Muscle pain	0	0	25	18	0	22
Joint pain	8	0	0	9	20	22
Fatigue	8	0	0	0	40	19
Sticky skin	0	0	0	0	0	16
Xerosis	17	0	25	9	0	14
Tender skin	8	0	0	18	0	11
Fragile skin	0	0	0	9	20	8
Granulation tissue	0	0	0	0	20	8
Headaches and edema	8	0	0	9	0	3

Full 24-wk period (includes DB and open phase); n=37- completed by 25

- Average patient achieved 51-75% improvement in psoriasis
- On average 13.3 ± 2.4 wks without acitretin elapsed before psoriasis returned strongly enough to require treatment

Author's summary

- After the double-blind period, patients continued treatment in an open fashion until they had received a total of 24 weeks of acitretin therapy. Most patients received 50 mg of acitretin daily, which adequately cleared their psoriasis.
- After approximately 3 months without acitretin, most patients required retreatment. Subsequent 24-week courses of therapy were generally effective and well tolerated.
- The most common laboratory abnormalities were elevations of triglyceride, cholesterol, and liver transaminase levels.
- The efficacy and side effects of acitretin appear to be similar to those of etretinate; the principal advantage of acitretin is its shorter half- life. Although acitretin is a potent teratogen, its rapid elimination makes it a viable treatment for psoriasis among women of childbearing potential.

H.10.4 INDUCTION OF REMISSION

H.10.4.1 ciclosporin vs placebo

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
C.N. Ellis, M. S. Fradin, J.M. Messana, M.D. Brown, M.T. Siegel, T.A. Hamilton, T.G. Parish, M. Ellis-Madu, E. Duell, T.N. Annesley, K.D. Cooper, J.J. Voorhees. Cyclosporine for plaque-type psoriasis results of a multidose	RCT USA Randomised: computer generated random code in blocks of 17 Blinding: Double-blinded: Patients blinded & patients	Total N=85 **Drop-outs (don't complete the study):** 4 withdrawals due to AEs, 3 withdrawals due to protocol violation,	**Inclusion criteria:** Outpatients with chronic plaque psoriasis affecting >25% BSA, or disabling psoriasis (mainly hands) Patients had not responded to at least one of the major agents for psoriasis i.e. UVB, pUVA, etretinate, or methotrexate Washout: Patients stopped receiving systemic therapy/phototherapy 30 days prior to enrolment, 14 days prior for topicals (except emollients) **Exclusion criteria:** Women of childbearing potential **Baseline characteristics**	**Ciclosporin (CSA)** N=60 Three groups given 8 weeks of fixed dose oral ciclosporin 7.5 mg/kg (n=15) 5 mg/kg (n=20) 3 mg/kg (n=25)	**Placebo** N=25 Placebo followed by 8 week period of crossover (i.e. to CSA 3 mg/kg/day started) titrated according to clinical response further increases at	8 weeks Placebo comparison only valid at 8 weeks due to crossover of placebo group (trial 16 weeks in total however)	**1° outcome:** Clear/almost clear **2° and other outcomes:** Global severity scale PASI BSA AEs	Sandoz Research Institute, Babcock Dermatologic Endowment, NIH Clinical Research Center Grant

<table>
<tr>
<td>double-blind trial. NEJM. 324(5):277-284,1991.

Ref ID: ELLIS1991</td>
<td>directly evaluated by blinded physicians. Lab results reviewed by unblinded physician who adjusted dosage of CSA

Allocation concealment: not mentioned

Sample size calculation: to provide 95% power to detect ‘dose-response relation’ by 8th week of study

ITT analysis:</td>
<td></td>
<td>Stated baseline characteristics similar; slightly higher %male in 3mg CSA group
<table>
<tr><td></td><td colspan="3">Ciclosporin</td><td>Place bo</td></tr>
<tr><td></td><td>3mg</td><td>5mg</td><td>7.5mg</td><td></td></tr>
<tr><td>No. Of pts</td><td>25</td><td>20</td><td>15</td><td>25</td></tr>
<tr><td>Sex – M/F</td><td>23/2</td><td>15/5</td><td>12/3</td><td>16/9</td></tr>
<tr><td>Mean age</td><td>46</td><td>42</td><td>46</td><td>43</td></tr>
<tr><td>Mean weight</td><td>87</td><td>82</td><td>84</td><td>84</td></tr>
<tr><td>Mean %BSA involving</td><td>41</td><td>46</td><td>46</td><td>38</td></tr>
<tr><td>Mean global severity score</td><td>6.2</td><td>6.5</td><td>6.5</td><td>6.1</td></tr>
</table></td>
<td>followed by 8 week period of dose adjustment

according to clinical response

further increases at 12 weeks to max 10 mg/kg/day

dose reduction if: rise in creatinine or bilirubin or uncontrollable rise in DBP >90 mmHg, CSA trough blood level >800</td>
<td>12 weeks

dose reduction if: rise in creatinine or bilirubin or uncontrollable rise in DBP >90 mmHg, CSA trough blood level >800 ng/ml, marked reduction in renal function, serious clinical side effects</td>
<td></td>
<td>Renal function

Blood pressure changes

Uric acid

LFTs</td>
<td></td>
</tr>
</table>

	Yes			ng/ml, marked reduction in renal function, serious clinical side effects				

Effect Size

Clear/nearly clear

	CSA 3 mg/kg/day	CSA 5 mg/kg/day	CSA 7.5 mg/kg/day	Placebo
Clear/nearly clear at 8 weeks	36%	65%	80%	0%
PASI75	7/25	12/20	NA	1/25

PASI

PASI data not extractable: PASI improved significantly in all groups receiving CSA compared to placebo at 8 weeks (P<0.001 for each), no sig difference in score between 5 and 7 mg/kg (P>0.4), but each better than the response in the group receiving the lowest dose (P<0.01 for each comparison).

Withdrawal due to adverse events

4 patients withdrawn in CSA group due to adverse events at **16 weeks**

Severe adverse events

1 high creatinine requiring dose reduction (CSA 7.5 mg/kg)

Renal function

	CSA 3 mg/kg/day	CSA 5 mg/kg/day	CSA 7.5 mg/kg/day	Placebo	*P* value
Median % decrease in GFR at 8 weeks	6%	15%	19%	2%	**CSA 7.5mg vs. Placebo = 0.05**
decrease ≥15% in GFR during first 8 weeks	4/12	5/10	9/12	0/9	

18/34 patients had decrease ≥15% in GFR during first 8 weeks (

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
C.N. Ellis, D.C. Gorsulowsky, T.A. Hamilton, J.K. Billings, M.D. Brown, J.T. Headington, K.D. Cooper, O. Baadsgaard, E.A. Duell, T.M. Annesley, J.G. Turcotte, J.J. Voorhees. Cyclosporine improves psoriasis in a double-blind study. *JAMA*.256(22):3110-3116. 1986 Ref ID: ELLIS1986	RCT USA Randomised: random number tables Blinding: Double-blinded: Patients blinded & patients directly evaluated by blinded physicians. Lab results reviewed by unblinded physician who adjusted dosage of	Total N=21 **Drop-outs (don't complete the study):** Nil	**Inclusion criteria:** Outpatients aged ≥18 years with severe chronic large plaque-type psoriasis vulgaris and >20% BSA involvement, failed to improve with UVB, pUVA, or methotrexate. Patients selected who were 'thought to be reliable' Washout:No systemic / intralesional / UV / topicals (other than emollients) for 4 weeks prior **Exclusion criteria:** Patients with other types of psoriasis Women of childbearing potential **Baseline characteristics** CSA / Placebo	**Ciclosporin (CSA)** N=11 Oral ciclosporin 14 mg/kg per day (single dose) For 4 weeks then stopped Dose adjusted according to trough ciclosporin levels if >350 ng/ml	**Placebo** N=10 Placebo for 4 weeks, then switched to ciclosporin 14mg/kg/day open-label	4 weeks (double-blinded)	**1° outcome:** Clear/almost clear **2° and other outcomes:** Global severity scale Improvement AEs Renal function Blood pressure changes	Babcock Dermatologic Endowment

	CSA. Open-label crossover after 4 weeks. Allocation concealment: not stated Sample size calculation: Not stated ITT: Yes		Age: 36 yrs / 36 yrs Sex: M/F: 9/2 / 7/3 Other baseline characteristics not detailed				LFTs	

Clear

	CSA (n=11)	Placebo (n=10)
Clear	2	0

Hypertension

	CSA (n=11)	Placebo (n=10)
Hypertension (DBP >90 mmHg or SBP >150 mmHg)	7	7

No withdrawals due to adverse events

No withdrawals due to deranged lab values

Number of patients with creatinine above normal range in ciclosporin group: at baseline 1, at end of therapy 4, 2 weeks after end of therapy 0

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
H. Meffert, M. Brautigam, L. Farber, G. Weidinger. Low-dose (1.25 mg/kg) cyclosporin A: treatment of psoriasis and investigation of the influence on lipid profile. Acta Derm Venereol (Stockh). 77:137-141.1997 Ref ID: MEFFERT1997	RCT Multi-centre Germany Randomised: method not stated Blinding: Double-blind Allocation concealment: not stated Sample size calculation: not stated ITT analysis:	Total N=133 Drop-outs (don't complete the study): 6	**Inclusion criteria:** Patients 18-70 years with psoriasis vulgaris with an indication for systemic therapy, starting PSI score of 8-25 (mean 16) **Exclusion criteria:** Creatinine > 10% above upper limit of normal, cholesterol >350 mg/dl, bilirubin and liver enzymes >150% of upper lab normal value, hyperkalaemia, hyperuricaemia, hypertension (DBP >95 mmHg), leucopaenia, thrombocytopaenia, concomitant therapy with potentially nephrotoxic drugs Drug-induced psoriasis, erythrodermia, Rx with MTX, retinoids, PUVA or CSA in 4 weeks prior, specific topical Rx in previous week	**Ciclosporin** N= 85 Period 1 CSA 1.25 mg/kg/day PO (n=41) or CSA 2.50 mg/kg/day PO (n=44) Period 2 Dose inc. up to 5 mg/kg/day PO if inc. in PASI >50%	**Placebo** N=43 In period 2 patients given CSA 2.5 mg/kg/day inc. to 5 mg/kg/day if PASI reduction <10% in week 13, or <30% in week 16	10 weeks Period 1 10 weeks (DB phase) Period 2 12 week open label study Period 3 4 week no treatment follow-up period Total 26 weeks	**1° outcome:** PASI change **2° and other outcomes:** Adverse events	Not stated

	No		Pregnant/breastfeeding women **Note:** 85 men, 48 women Mean age 38.2±11.6 years No significant difference between groups with respect to age, sex, BMI, severity of psoriasis					

Effect Size

PASI scores

	Placebo (n=39)		**CSA 1.25 mg/kg (n=40)**		**CSA 2.5 mg/kg (n=41)**	
	Mean	SD	Mean	SD	Mean	SD
Baseline	15.6	5.1	16.7	5.7	15.1	5.0
% change						
1 week	-3.2	6.5	-4.3	9.8	-10.2	15.3

3 weeks	-7.3	19.2	-11.7	22.3	-22.9	26.3
6 weeks	-11.0	28	-22.1	29.0	-39.3	28.8
10 weeks	**-5.9**	**36.1**	**-27.2**	**34.6**	**-51.0**	**30.9**
End of period 1	14.9	7.9	11.8	6.8	7.6	6.2
PASI75	2/43		4/41		12/44	

Creatinine

11/133 patients serum creatinine increased by 30% or more from baseline on at least 1 occasion

No discontinuations due to renal side effects

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
T.H. van Joost, J.D. Bos, F. Huele, M.M.H.M. Meinardi. Low-dose cyclosporin A in severe psoriasis. A double-blind study. *Br J Dermatol*. 118:183-190. 1988 REF ID: VANTOOST1988A Data also reported in: F. Huele, M.M.H.M. Meinardi, T. van Joost, J.D. Bos. Low-dose cyclosporine effective in severe psoriasis: A double-blind study.	**RCT** Two centre , Netherlands Randomisation: 'Randomly treated', no further information Blinding: Double-blind Allocation concealment: Not mentioned	Total N=20 Drop-outs (don't complete the study): None during 4 weeks	**Inclusion criteria:** Chronic plaque psoriasis of a progressive character over more than 10 years, no effect from conventional therapy. Starting PASI score of 20 or above. Active antipsoriatic treatment (MTX, retinoids, PUVA) stopped four weeks prior, topically applied agents (two weeks) **Exclusion criteria:** Pregnancy or acutre uncontrolled infections, impaired renal function with a serum creatinine >100 umol/L, bilibrubin or liver enzymes >2 x upper limit of normal, uncontrolled HTN, epilepsy, malabsorption syndrome, past or present malignancies, pharmacokinetic interactions **Baseline characteristics:** [table below]	**Ciclosporin** N=10 Divided doses Phase 1 – Dosing by body weight: ≤59 kg: 300 mg 60-80 kg: 400 mg >80 kg: 500 mg CSA dose reduced by 1 ml if: rise in serum creatinine >50% above baseline, rise	**Placebo** N=10 Partial crossover: Placebo patients switched to CSA in open-label outpatient trial	4 weeks (for this comparison) (24 weeks in total 12 weeks treatment + post-treatment observation for 12 weeks)	**1° outcome:** PASI **2° and other outcomes:** Relapse: increase in PASI ≥50% baseline score AEs	

	CSA	Placebo
Mean age	54.6 yrs	45.6 yrs
Sex – M/F	8/2	5/5

Transplantation Proceedings. 20(3):32-41. 1988 Ref ID: HEULE1988	Sample size calculation: Not performed ITT:		Mean weight: 70.2 kg / 72.6 kg Mean duration of disease, yr: 27.2 / 22.7			in potassium, raise in LFTs, hypertension unresponsive to treatment, or CSA trough levels >900 ng/ml Dose reduced by 1 ml (100 mg) if increase in creatinine, potassium, LFTs, hypertension unresponsive to therapy, or whole blood CSA trough levels >900 ng/ml Phase 2 – patients who responded with >50% improvement after 4 weeks continued for another 2				

				months (5-12 weeks) – double-blinded, doses tapered. If relapse during tapering test med stopped Phase 3 Post-treatment observation period for 12 weeks				

Effect Size

PASI

	CSA (n=10)	Placebo (n=10)
Mean PASI score at baseline	36.5	30.0
Mean PASI score at 4 weeks	9.6	29.1
Mean PASI score at 12 weeks (responders, n=9)	6.9	n/a
Mean % reduction in PASI score at week 4	72%	3% (P<0.001)

Mean % reduction in PASI score at week 12 (responders, n=9)	82%	n/a	
PASI50 at week 4	9	0	

No withdrawals due to adverse events

No dose reductions due to clinical or biochemical side-effects

Hypertension

Mild hypertension in 5 patients/18 receiving CSA

Creatinine

Non-significant increase in creatinine in placebo versus CSA (P=0.08)

Slight increase in creatinine in 7 patients (< 40% above respective individual baselines), returned to normal in all patients on stopping CSA

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
L. Guenther, D.M. Wexler. Inducing remission of severe psoriasis with low-dose cyclosporin A. *Canad. J. Dermatol.* 163-167. 1991 REF ID: GUENTHER1991	RCT Multicentre, Canada Randomisation: Method not stated Blinding: Double-blinded Allocation concealment: No Sample size calculation: Not stated	N=23 9 drop-outs (1 in CSA group due to concomitant therapy and 8 in placebo group due to treatment failure)	**Inclusion criteria** Patients with extensive and disabling large plaque psoriasis involving ≥25% BSA and a PASI ≥12. Washout period: no systemic, intralesional, or UV therapy for at least 3 weeks, no topical therapy at least 1 week prior **Exclusion criteria** Patients with hepatic or renal impairment, or patients with DBP >95 mmHg Comparable baseline demographics: CSA group slightly older than	**Ciclosporin** N=12 2.5 mg/kg/day in divided doses Increased at week 2 to 5 mg/kg/day Dose adjusted if trough levels outside range: 50-275 ng/ml	**Placebo** N=11	10 weeks	**1º outcome** PASI 50 **2º outcomes** Pruritus AEs	

	ITT: Modified ITT		placebo group (42.5 years vs. 37 years).					

Effect Size

PASI 50 (Mod ITT)

	CSA (n=12)	**Placebo (n=11)**
Number of patients achieving PASI 50 at week 4	**9**	**0**
Number of patients achieving PASI 50 at week 6	**11**	**0**
Number of patients achieving PASI 50 at week 10	**11**	**1**

Stated no alteration in kidney function or hepatic function

Increased BP in 2 patients (CSA) and 1 patients (placebo)

H.10.5 INDUCTION OF REMISSION

H.10.5.1 Ciclosporin dose-finding studies

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Christophers E et al. Cyclosporine in psoriasis: a multicenter dose-finding study in severe plaque psoriasis. J Am Acad Dermatol 1992; 26: 86-90. Ref ID CHRISTOPHERS1992	**RCT** **Randomisation:** not stated **Allocation concealment:** not stated **Blinding:** no **Sample size calculation:** not stated	285 randomised; this paper reports on 217 patient who had completed study (but some patients re-entered the study more than once at different dosage so n's in table 1 for example add up to more than 285, while outcomes are not	**Inclusion:** 18-70 years; severe generalised chronic plaque psoriasis; Psoriasis Area Severity Index (PASI) at least 15. **Exclusion:** treatment with methotrexate, retinoids, glucocorticoids or PUVA in last 2 weeks; treated with compounds known to	Ciclosporin 1.25mg/kg/day (n=109 excluding drop-outs and those still in trial). After 2 weeks, patients with a reduction of >10% of baseline PASI, and after 6 weeks reduction of >30%, continued with unchanged dose until week 12. Patients not achieving a reduction of >10% of	Ciclosporin 2.5mg/kg/day (n=108 excluding drop-outs and those still in trial). After 2 weeks, patients with a reduction of >10% of baseline PASI, and after 6 weeks reduction of >30%, continued with unchanged dose until week 12. Patients not achieving a reduction of >10% of	12-36 weeks	"Success" = PASI declined by >75% of baseline (i.e. to <25% of baseline) or to below 8. Severity of lesions: erythema, infiltration and desquamation rated (0=complete absence, 4=most severe involvement). Involvement of nails (4-	Sandoz AG

	ITT analysis: no; patients moved between dosage groups and not all patients analysed (only completers, some still in trial) **Drop outs:** 18/109 on 1.25mg/kg/day dropped out (2 adverse events, 1 concomitant disease, 5 noncompliance, 9 lack of efficacy, 1 other). Unclear how many dropped out of 2.5mg/kg/day initial randomisation group as data presented for drop-outs while on 2.5mg/kg/day (i.e. from the initial 2.5 mg/kg/day group or those in initial 1.25mg/kg/day group who had had dosage increased; 32 dropped out: 6 adverse events, 1 concomitant disease, 8 noncompliance, 14 lack of efficacy, 3 other) and while on 5mg/kg/day (i.e. from initial	given for all patients as some still in the trial)	interact with ciclosporin metabolism; pregnant or nursing women; impaired renal or liver function; infectious or neurological disorders; history of malignancy; alcohol abuse. **Baseline characteristics:** Ciclosporin 1.25mg/kg/day: 29 female, 80 male; Ciclosporin 2.5mg/kg/day: 28 female, 80 male. Mean age of both groups 42 years. No other details given.	baseline PASI at 2 weeks or reduction of >30% after 6 weeks re-entered study at double dose. Patients whose PASI declined by >75% of baseline (i.e. to <25% of baseline) or to below 8 = success; if not, re-entered study at double dose. Dose halved if 1) increase in serum creatinine >30%; 2) increase of serum potassium above upper limit of normal; 3) increase in serum total bilirubin or liver enzymes of >100% above baseline	baseline PASI at 2 weeks or reduction of >30% after 6 weeks re-entered study at double dose. Patients on 5mg/kg/day who failed to show these reductions were withdrawn from study. Dose halved if 1) increase in serum creatinine >30%; 2) increase of serum potassium above upper limit of normal; 3) increase in serum total bilirubin or liver enzymes of >100% above baseline or above three-fold upper limit of normal, or 4)		point scale), severity of arthropathy (intensity of inflammation, pain, swelling and impairment of daily activities each on a 4-point scale), pruritis (4-point scale). Laboratory values.	

	1.25mg/kg/day group who had had 2 dose increases or from initial 2.5mg/kg/day group who had had 1 dose increase; 11 dropped out: 1 adverse events, 1 concomitant disease, 1 noncompliance, 7 lack of efficacy, 1 other).			or above three-fold upper limit of normal, or 4) ciclosporin trough level >250ng.mL on 2 consecutive measurements.	ciclosporin trough level >250ng.mL on 2 consecutive measurements.			

Effect size

	Initial dose 1.25mg/kg/day (n=109)				**Initial dose 2.5mg/kg/day (n=108)**		
	Stayed on 1.25mg/kg/day	Increased to 2.5mg/kg/day	Increased again to 5mg/kg/day	Total number of responders in the 1.25mg/kg/day randomisation group	Stayed on 2.5mg/kg/day	Increased to 5mg/kg/day	Total number of responders in the 2.5mg/kg/day randomisation group
Number of responders	19 (18%)	27 (25%)	22 (20%)	68 (62%)	60 (56%)	18 (17%)	78 (72%)

In all other analyses, the patient groups were combined into a) 1.25mg/kg/day; 2) 2.5mg/kg/day and 3) 5mg/kg/day, i.e. the doses that the patients ended up on, not the groups of randomisation. Outcomes were given as percentages but the denominators were sometimes unclear due to patients moving between dosage groups.

	Patients on 1.25mg/kg/day (n=109)*	Patients on 2.5mg/kg/day (n=183)*	Patients on 5mg/kg/day (n=60)*
Decrease in pruritis score at end of treatment	27.8%	61%	42.8%
Percentage of patients with creatinine level >130micromol/L (none discontinued treatment)	1%	5%	13%
Number of patients in whom dose of ciclosporin reduced because of increased serum creatinine	1	2	2
Blood urea nitrogen >8.3mmol/L	4%	13%	18%
Uric acid >400micromol/L	19%	28%	43%
Cholesterol>6.7mmol/L	12%	21%	25%
Triglyceride >2.0mmol/L	20%	40%	53%
Serum glutamic-oxaloacetic transaminase (SGOT=Aspartate transaminase [AST]) >20U/L	11%	15%	33%
Bilrubin level >17 micromol/L	8%	20%	31%
Alkaline phosphatise >180U/L	11%	13%	20%
Blood pressure >160mmHg systolic and/or >95mmHg diastolic on two consecutive visits	11%	21%	26%
Adverse events (%)	10%	20%	32%
Gastrointestinal (n)	4†	8	3
Common cold	1	7†	2
Viral infections	2	3	1

Headache	0	1	3†
Tremor	2	1	1
Fatigue	0	2	1
Gingival hyperplasia	1	1	1
Oedema of lower limbs	0	3	0
Hypertrichosis	1	1	1
Parasesthesia	0	2	0
Also single reports of the following adverse effects but not stated which group the patient was in: photoallergic eczema, haematuria†, swelling of lymph nodes†, alopecia, diabetes mellitus†, arthralgia†, squamous cell carcinoma†, lumbago† and extrasystoles†. † = the drug was withdrawn because of the side effect.			

* NB numbers of patients add up to more than the number originally randomised because patients moved between groups and some were therefore counted more than once

Author's conclusion

- We recommend 2.5mg/kg/day as the initial dosage for treatment of severe psoriasis; in case of insufficient response this can be increased to 5mg/kg/day.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
C. Laburte, R. Grossman, J. Abi-Rached, K.H. Abeywickrama, L. Dubertret. Efficacy and safety of oral cyclosporine A (CyA; Sandimmun) for long-term treatment of chronic severe plaque psoriasis. *Br J Dermatol*.130:366-375. 1994 REF ID: LABURTE1994	RCT Three-part multinational multicentre study Part 1: induction – open, randomised 2.5 vs. 5 for 3 months 2.5 mg non-responders switched to 5 mg. Part 2: Pts achieving remission entered open 12 month maintenance study at 2.5 mg or 5 mg (tapering over 3 months to	N=251 Drop-outs: 88 patients discontinued Rx at end of Part II 163 patients treated for 16-22 months	**Inclusion criteria** Patients with severe chronic plaque psoriasis (PASI ≥18) resistant to topical therapy and requiring systemic treatment. 2 week washout period for systemic Rx and 1 week washout period for topical Rx **Exclusions** Patients with 'abnormal screening lab values', patients with serum creatinine > 100 µol/L, patients with pre-existing hypertension or hx of malignancy, concomitant Rx with nephrotoxic medications **Baseline characteristics:** Differences in mean body weight [illegible] 2.5 mg (n=119) 5 mg (n=132)	N=119 CSA 2.5 mg/kg/day Induction and maintenance Maintenance Responders: 62 pts exposed to mean dosage of 2.7 mg/kg/day for mean 12.2 months Non-responders:	N=132 CSA 5 mg/kg/day Maintenance 132 pts exposed to mean dose of 4.0 mg/kg/day for mean duration of 11.3 months	12 weeks (part 1 – open, randomised phase) 21 months in total	PASI - ≥75% reduction of baseline PASI, or PASI ≤8 at week 12 Overall assessment of efficacy 5-point scale Simple severity scoring system (0-4) used Relapse defined as increase in PASI ≥50% of baseline	Sandoz Pharma

	2.5 mg) inc. to 5 mg if relapse. Dose tapered in last 3 months in all pts. Part III 3 month post-treatment observation period (inc.pts who discontinued) Randomisation: Method not stated Blinding: Open Allocation concealment: no		Age	42.0±12.6	40.7±12.3	57 pts exposed to mean dose of 3.7 mg/kg/day for mean duration 11.2 months			Safety
			Weight	77.4±15.5	72.9±13.4				
			%Male	72%	68%				
			Disease duration, years	18.4±11.0	17.7±11.1				
			Baseline PASI	24.9±7.0	25.1±8.0				
			Previous treatment %						
			MTX	32%	28%				
			Retinoids	58%	54%				
			PUVA	73%	67%				

	Sample size calculation: not stated ITT: No							

Effect Size

Induction of remission

	2.5 mg group (n=119)	**5 mg group (n=132)**	**P-value**
Mean reduction in PASI score, %	69%	89%	0.0001
Success (PASI 75 or a PASI score ≤8)	57 patients	117 patients	0.001
Median time to first success	3 months	6 weeks	

Maintenance of remission – Mean PASI score

	2.5 mg group	**5 mg group**	**2.5 mg non-responders**
Beginning of maintenance	4.2 (n=52)	3.6 (n=116)	3.9 (n=41)
End of maintenance	5.9 (n=40)	6.3 (n=79)	8.3 (n=25)

Safety

	2.5 mg group	**5 mg group**

Serious adverse events related to CSA Rx	2	17	
Development of hypertension (DBP ≥95 mmHg on two consecutive visits)	17 patients	20 patients	
High uric acid level (≥625 µmol/l in males, ≥506 µol/l in females)	5	8	

Hypertension

Hypertension developed in 41 patients during treatment with CSA: 17 patients in 2.5 mg group, 20 in 5 mg group, 4 receiving a mean dose of 3.6 mg

50 patients received antihypertensive therapy

10 CSA discontinuations due to hypertension

Creatinine

Maximum % increase in creatinine above baseline by month 12: 10% (2.5 mg group), 14% (5 mg group)

Increase in serum creatinine >30% above baseline seen at least once in:

22% of patients (2.5 mg group): decreasing to 2 patients (3%) having persistently raised creatinine 3 months after discontinuation of CSA

55% of patients (5 mg group): decreasing to 9 patients (9%) having persistently raised creatinine 3 months after discontinuation of CSA

Discontinuation due to raised serum creatinine in 24 patients (10%)

Withdrawal due to AEs: 16 patients

H.10.6 MAINTENANCE OF REMISSION

H.10.6.1 Ciclosporin regimens: continuous vs intermittent

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
A. Ozawa, J. Sugai, M. Ohkido, M. Ohtsuki, H. Nakagawa, H. Kitahara, K. Tamaki, K. Urabe, J. Nakayama, T. Horikoshi, Y. Morimoto, and K. Jimbow. Cyclosporin in psoriasis: continuous monotherapy versus intermittent long-term therapy. *Eur.J.Dermatol*. 9 (3):218-	RCT Multicentre (4 medical school hospitals in Japan) • Randomised (envelope method) • Washout period: 2 months for MTX, retinoid or PUVA • Blinding (not stated) • Allocation concealment (not stated)	Total N: **94** **Drop-outs (don't complete the study):** 29 **Note:** data from all 94 analysed for adverse reactions **Continuous (n=16)**: 1 AEs; 2 aggravation of complications; 3 lost to follow-up; 1 change of location; 1 relapse; **8 remission**	**Inclusion criteria:** psoriasis vulgaris with PASI >20; psoriatic arthritis; generalised pustular psoriasis; erythrodermic psoriasis **Exclusion criteria:** treated with MTX, retinoid or PUVA within the past 2 months; use of drug with renal toxicity; hypertension (BP>95/160); acute or chronic bacterial or viral infections; malignant tumours; severe hepatic function abnormality; pregnant women **Mean baseline** / **Continous CSA (N=17)** / **Intermittant CSA (N= 20)** PASI mean ± SD: 29.9 ± 2.19 / 35.08 ± 3.54 **Type of psoriasis in the full sample**	N=50 **Continuous CSA** Initial dose 3-5 mg/kg/day After remission: reduced by 0.5-1.0 mg/kg/day **every week** Maintenance treatment	N=44 **Intermittent CSA** Initial dose 3-5 mg/kg/day After remission: dose reduced by 0.5 -1.0 mg/kg/day **every other week** followed by **withdrawal**.	48 months **Remission** = a decrease in PASI by 80% from baseline **Relapse** = an increase in PASI by 50% from baseline	**1° outcome:** Change in PASI; time-to-remission; time-to relapse **2° and other outcomes:** AEs, laboratory tests: blood pressure, peripheral blood counts, serological tests (GOT, GPT, gamma-GTP,	None stated

223, 1999. Ref ID: OZAWA1999	• Sample size calculation not stated • ITT analysis not performed • Drop-outs/withdrawals due to AEs: 1 in continuous; 2 in intermittent	**Intermittent (n=13)**: 2 AEs; 2 change of location; 4 relapse; **5 remission**	**(n=94)** Psoriasis vulgaris (n): 85 Psoriatic arthritis (n): 4 Generalised pustular psoriasis (n): 2 Erythrodermic psoriasis (n): 3	continued at a dose ranging from 0.5 to 3 mg/kg/day at as low a dose as possible If a relapse was noted, the dose was increased to 3 to 5 mg/kg/day until remission was achieved, and the same procedure was repeated.	During withdrawal period, topical steroids (10 g/day or less) of strong or medium class were applied to the lesion. If any relapse was noted, the dose was increased to 3-5 mg/kg/day until remission was achieved. Oral ciclosporine was withdrawn on remission and the treatment depended on topical steroids only.		creatinine, BUN, uric acid, Na, K, Cl, Mg, glucose, total cholesterol and triglyceride), qualitative urinalysis, and serum ciclosporine trough level	

Effect Size

Outcomes

Dose

The mean daily dose was 3.20 ± 0.21 mg/kg/day in the continuous monotherapy group and 3.06 ± 0.21 mg/kg/day in the intermittent therapy group. There was no significant difference between the groups.

Efficacy

- Remission was not observed in one patient in the continuous group and four patients in the intermittent therapy group

Outcomes	**Continuous CSA (N=17)**	**Intermittent CSA (N= 20)**	**p-value**
Baseline PASI; mean ± SD	29.9 ± 2.19	35.08 ± 3.54	
48 month PASI; mean ± SD	9.93 ± 1.79	9.96 ± 2.12	
48 month mean PASI improvement rate ± SD	61.96 ± 4.80%	71.16 ± 5.27%	NS
Time to remission			

Mean time to first remission (months)	4.7 (n=16)	3.0 (n=16)	
Mean time to second remission after relapse (months)	4.4 (n=4)	6 (n=13)	
Mean time to third remission after relapse (months)	-	7 (n=6)	
Mean time to fourth remission after relapse (months)	-	12 (n=2)	
Mean time to fifth remission after relapse (months)	4.4 (n=2)		
Time to relapse			
Mean time to first relapse (months)	20±4.2 (n=11)	10 (n=15)	
Mean time to relapse after second remission (months)	13.4±4.3 (n=6)	8 (n=8)	
Mean time to relapse after second remission (months)	11.95 (n=1)	3.0 (n=6)	

Safety

No difference in incidence between the 2 groups

Symptom	Full sample (n=94)
BUN	17
Creatinine	9
Hypertension	21
Infection	29

Author's summary

- The PASI score evaluated at each visit was maintained between 5 and 10 by both treatment methods and the improvement rate was more than 70%, while there was no difference in the daily dose between the two treatment methods
- The period required to achieve remission tended to be prolonged by intermittent therapy, while no change was observed with continuous monotherapy
- The period up to relapse tended to become shorter with both treatment methods but this tendency was more marked with intermittent therapy
- E-PAP(evaluation for prognosis with averaged PASI) was lower in the continuous monotherapy group and the patients were more satisfied
- The incidence of adverse reactions was similar to that reported in previous studies, with no difference between the two treatment methods in this regard
- A significant increase in BUN levels was observed in elderly patients
- There were only three cases in which the drug was discontinued due to exacerbation and adverse reactions.
- Based on the above findings, continuous monotherapy seems to be of greater clinical usefulness than intermittent therapy.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Ohtsuki M et al. Long-term continuous versus intermittent cyclosporine: therapy for psoriasis. J Dermatol 2003; 30: 290-298. Ref ID OHTSUKI2003	**RCT** **Randomisation:** "by the envelope method" **Allocation concealment:** see above **Blinding:** no **Sample size calculation:** not stated **ITT analysis:** not stated.	122 recruited (111 psoriasis vulgaris, 5 psoriatic arthropathy, 3 generalised pustular psoriasis, 3 psoriatic erythroderma)	**Inclusion:** PASI score >20 and meeting eligibility criteria specified in the Japanese Guidelines for Ciclosporin Therapy in Psoriasis **Exclusion:** Treatment with methotrexate, retinoids or PUVA in previous 2 months; absolute need for concomitant therapy with any nephrotoxic drug; hypertension (BP ≥160/95mmHg); acute or chronic active bacterial or viral infection; malignancy; severe hepatic dysfunction; pregnancy **Baseline** / **Intermittent (N=61)** / **Continuous (N=61)** PASI mean (range): 35.54 (13.6) / 29.17 (10.6)	n=61 **Intermittent ciclosporin** 3-5mg/kg/day; once remission (decrease of PASI score by at least 80% from baseline) achieved, **dose reduced by 0.5-1mg/kg/day every 2 weeks until tapered off**. While ciclosporin being withdrawn, topical application of "strong" or less potent corticosteroi	n=61 **Continuous ciclosporin** 3-5mg/kg/day; once remission (decrease of PASI score by at least 80% from baseline) achieved, **dose reduced by 0.5-1mg/kg/day every 2 weeks until lowest dose that could maintain remission reached** (range 0.5-3mg/kg/day). If relapse (return to	Planned for 5 years; only 25% of patients followed for >48 months; this paper reports these patients followed >48 months (mean follow up for these patients 55.9 SD 4.6 months)	PASI score, itching, pustules, articular symptoms, local/systemic adverse events; routine laboratory tests; trough ciclosporin level; blood pressure; mean ciclosporin dose; Evaluation for Prognosis with Averaged PASI [E-PAP] score calculated by dividing the PASI score versus time curve	not stated

	Paper states that "most of the patients in the intermittent group suffered from recurrence of psoriasis soon after withdrawal of ciclosporin; ciclosporin was resumed in the patients who violated the study protocol at their strong request before the PASI score returned to ≥50% of baseline, especially after the second relapse" i.e. many patients restarted ciclosporin earlier than in the protocol (so regimen more like the		Groups reported to be similar also with respect to sex ratio, age, diagnosis and concomitant illness.	ds allowed. If relapse (return to 50% or more of baseline PASI), ciclosporin restarted and dose escalated to 3-5mg/kg/day until remission obtained again. Ciclosporin dose reduced if serum creatinine increased by 30% or more from baseline. Mean daily dose 2.78 (0.26) mg/kg/day	50% or more of baseline PASI), dose gradually escalated to 3-5mg/kg/day until remission obtained again. Ciclosporin dose reduced if serum creatinine increased by 30% or more from baseline. Mean daily dose 3.24 (0.27) mg/kg/day		integrated over follow up period divided by time period (i.e. average severity of psoriasis during treatment).	

	continuous treatment than planned) **Drop outs:** 53 failed to revisit or changed hospital; 14 had sustained remission; 11 had adverse events or exacerbation of complications (of whom **4 withdrawn due to adverse reactions** – 1 back pain, 1 hyperuricaemia, 1 gum hyperplasia, 1 increase in blood urea nitrogen and serum creatinine); 6 changed therapy because of relapse; 3							

	changed therapy because of **lack of efficacy**; 3 withdrew consent; 1 withdrawn for other reasons, i.e. **75% drop out.**							

Effect size

	Intermittent ciclosporin (n=16)		Continuous ciclosporin (n=15)		p value
Mean PASI score at 54 months	9.59 (2.22)		6.03 (0.95)		NS
Adverse events:	Total over 5 years N=18	Total at 1 year N=61	Total over 5 years	Total at 1 year N=19	NS

increase in blood urea nitrogen (BUN)	23	5	26	4	
hypertension	**19**		**17**		
increase in serum creatinine	**15**	10	**15**	6	
hyperuricaemia	**16**		**13**		
hyperlipidaemia	**11**	3	**8**	2	
bilirubinaemia	9		0		
ALP increased	**7**	6	**1**	3	
hyperglycaemia	5		2		
gastric cancer	1	1	0	3	
hepatocellular carcinoma	1		0		
		4		0	
		3		0	
		0		1	

Author's conclusion

The intermittent and continuous regimens were found to be equally effective for the long-term management of psoriasis, with a slightly better response obtained with continuous therapy, but malignancy developed in 2 patients on continuous therapy. Our conclusions may have been influenced by the inclusion of patients with good tolerance and better follow up (i.e. acknowledging potential bias due to large loss to follow up).

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Chaidemenos GC et al. Intermittent vs. continuous 1-year cyclosporine use in chronic plaque psoriasis. JEADV 2007; 21: 1203-8. Ref ID: CHAIDEMONAS2007	**RCT** Single centre (Greece) **Randomisation:** Quasi-randomised (alternate allocation) **Allocation concealment:** inadequate **Blinding:** no **Sample size calculation:**	51 enrolled in induction phase; 3 patients non-compliant in induction phase so excluded from entry into maintenance phase; 3 did not achieve 50% reduction in PASI from baseline during induction phase so not eligible for randomised maintenance phase.	**Inclusion:** over 18 years; moderate to severe chronic plaque psoriasis (CPP) i.e. PASI 8 or more; insufficient response to topical (corticosteroids, calcipotriol and dithranol) and/or UVB therapy; effective contraception for women of child-bearing potential; stop other treatment for 3 weeks (apart from emollients); 1st phase of study – all patients received ciclosporin 2.5-2.7mg/kg daily, increased to a maximum of 5mg/kg/day if <30% response in 1st 3 weeks; had to achieve >50% reduction in PASI from baseline to enter maintenance phase **Exclusion:** history of malignancy, abnormal renal and liver function **Baseline at start of induction phase for the participants going on to maintenance phase** — **A (N=21)** — **B (N=24)**	**N=21** **Intermittent ciclosporin** for maintenance (Group A); i.e. **abruptly stopped** ciclosporin after induction, then received additional 12-week course "when investigator and patient considered that their disease had deteriorated adequately in order for	**N=24** **Continuous ciclosporin** for maintenance (Group B); i.e. **dose tapered** by 0.5mg/kg/day bi-monthly down to maintenance level, i.e. the dose considered marginally effective for that individual i.e. not a standard regimen for all patients	9 months maintenance phase (after achieving >50% reduction in PASI from baseline in induction phase of 3 months)	PASI; endpoints were improvement by 50%, 75% and 90% from baseline and Dermatology Life Quality Index DLQI: at end of induction phase, 1 year, and prior to and after each repeat course of treatment	Not stated

	none reported **ITT analysis:** yes **Drop outs:** 3 patients non-compliant in induction phase so excluded from entry into maintenance phase; 3 did not achieve 50% reduction in PASI from baseline during induction phase so not eligible for randomised maintenance phase. **No drop-outs reported in maintenance**		Age (years), mean (range)	40 (18-73)	51 (18-75)	ciclosporin to be re-instituted" i.e. not objective criteria for re-treatment	Both arms received 2.5-2.7 mg/kg/day CSA for induction initially (up to a max of 5 mg/kg/day if PASI reduction <30%)		Relpase: further treatment required	
			Gender M/F	15 (62.5%)/ 9 (37.5%)	15 (50%)/ 12 (50%)					
			Duration of psoriasis (years) mean (range)	15 (15-40)	12 (1-41)					
			PASI median (range)	10.2 (8-35)	10.12 (8-47)					
			DLQI median (range)	9.5 (3-23)	9 (3-22)					

	phase							

Effect size

- **Improvement under ciclosporin therapy was significant at the end of the induction phase; PASI decreased by 77.8%, achieving a median value of 2.7 (range 0-25.5), p=0.003 from baseline; DLQI dropped by 89%, median 1 (range 0-14), p=0.002**

Treatment period	**Outcome**	**Overall**	**Group A (Intermittent ciclosporin)**	**Group B (Continuous ciclosporin)**	**p value**
12 weeks (i.e. end of induction phase when all patients treated with ciclosporin)	PASI 50	45/48 (94%)			
	PASI 75	31/48 (65%)			
	PASI 90	14/48 (29%)			
12 months (i.e. end of 9-month randomised maintenance phase)	PASI 50	43/45 (96%)	20/21 (95%)	23/24 (96%)	0.348
	PASI 75	35/45 (78%)	13/21 (62%)	22/24 (92%)	0.008
	PASI 90	18/45 (40%)	4/21 (19%)	14/24 (58%)	0.006
	DLQI median (range)	1 (0-9)			
	Median (range) maintenance dose (mg/kg/day)		3 (2.5-3.8)	1.8 (0.7-3)	

	Number of courses of intermittent ciclosporin given		1 course: 7/21 (33%) 2 courses: 9/21 (43%) 3 courses: 5/21 (24%)	NA	
	Mean (SD) PASI at relapse		59 (13%) of initial value	NA	
	Median PASI at relapse		62% (35-79%) of initial value (i.e. variability of disease severity perceived as “relapse”)	NA	
	Increase in serum creatinine to 30% above baseline value		2/21	2/24	
	Increase in blood pressure necessitating treatment adjustment (not stated what criteria of increase were)		0	1/24	
	Gingival hyperplasia		1/21	0	
	Gastrointestinal disturbance		0	1/24	

Author’s conclusion

- Despite the high efficacy and safety of continuous ciclosporin in the trial, these patients received 139% of the mean cumulative dose used for the intermittent schedule. Effectiveness and safety are known to be time- and dose-dependent, so although it appears that continuous dosing offers greater PASI improvement without compromise in tolerability, this option should be reserved for patients who do not respond to, or are uncooperative with, intermittent ciclosporin use.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
INTERMITTENT TREATMENT STUDY V.C. Ho, C.E.M. Griffiths, G. Albrecht, F. Vanaclocha, G. Leon-Dorantes, N. Atakan, S. Reitamo, A. Johannesson, N.J. Mork, P. Clarke, P. Pfister, C. Paul. Intermittent short courses of cyclosporine (Neoral) for psoriasis unresponsive to topical therapy: a 1-year multicentre, randomized study. *Br J Dermatol*. 141:283-291.1999 PISCES study REF ID: HO1999	RCT Multicentre Europe/N. America Randomised: After 12 weeks of treatment, method not stated Blinding: Open Allocation concealment: No	N=400, 365 eligible for randomisation at end of 1st treatment period Drop-outs: 39 (before randomisation)	**Inclusion criteria:** Patients 17-81 years with plaque psoriasis unresponsive to topical therapies Washout period: stopped systemic therapy 14 days prior to enrolment; 30 days for PUVA Topical therapy continued throughout **Exclusion criteria:** Abnormal renal function (serum creatinine above 10% of upper limit of ref range), abnormal liver function, hyperkalaemia or hyperuricaemia, received >12 weeks of systemic therapy with corticosteroids, immunomodulating or cytotoxic drugs or retinoids, history of malignancy, acute uncontrolled bacterial, viral or fungal	Ciclosporin (Neoral): Abrupt cessation N=192 Ciclosporin 2.5 mg/kg/day titrated to max 5 mg/kg/day Treatment continued until clearance or for a maximum of 12 weeks Stop ciclosporin or abruptly	Ciclosporin (Neoral) Tapering dose N=173 Ciclosporin 2.5 mg/kg/day titrated to max 5 mg/kg/day. Treatment continued until clearance or for a maximum of 12 weeks Tapering	1 year	**1° outcome:** Time to relapse after first treatment period (Relpase: when investigator or patient deemed CSA should re-start or recurrence of psoriasis affecting ≥75% surface area) **2° and other outcomes:** %BSA Global	Novartis Pharma A.G.

	Sample size calculation: Not mentioned ITT: yes		infection, uncontrolled hypertension, clinically significant impairment of haematopoietic, cardiovascular and/or cerebral function and concomitant therapy with nephrotoxic medications. Baseline characteristics similar: CSA Abrupt / CSA Tapered Mean age: 41 years / 40 years Mean weight: 77 kg / 77 kg Psoriatic area %: 24 / 25 Modified PASI: 13 / 14	On relapse patients given another course of ciclosporin At end of treatment period, patients stop ciclosporin according to treatment plan specified at randomisation. Up to 4 treatment courses during the year	dose (1 mg/kg daily each week) until stopping within 4 weeks On relapse patients given another course of ciclosporin At end of treatment period, patients stop ciclosporin according to treatment plan specified at randomisation. Up to 4 treatment courses during the year		response Modified PASI (0-54) Time to relapse Time to clinical response Safety	

Median time to relapse

	Abrupt stopping	Tapered stopping	P-value
After ciclosporin cessation (first treatment)	109 days	113 days	**0.04**
After second treatment	60 days	95 days	-
After third treatment	52	63	-

Median time to achieve satisfactory clinical response in 1st treatment period 68 days using a mean ±SD daily dose of 3.3 ± 1.1 mg/kg, 70 days after second period, 74 days after third period, 63 days after fourth period

Serious adverse events

15 events in 11 patients

Withdrawals due to adverse events

33 patients

3 patients withdrawn due to hypertension, 2 due to serum creatinine increase

Creatinine

% of patients with serum creatinine increase >30% from baseline =10% during first treatment period, 18% during second treatment period, 20% during third treatment period, 27% during fourth treatment period

32 patients 3 or more rises in serum creatinine of more than 30% above baseline in 1 year period

Number of patients with elevation of serum creatinine >30% above baseline during treatment = 120, off treatment = 37

New onset hypertension

45 patients (12%), one patient experience severe hypertension, initiation on antihypertensive medication in 21 patients (5%)

Dose reduction due to hypertension in 26 patients (7%)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
V.C.Y. Ho, C.E.M. Griffiths, J. Berth-Jones, K.A. Papp, F. Vanaclocha, E. Dauden, A. Beard, L. Purvanarjan, C. Paul. Intermittent short courses of cyclosporine microemulsion for the long-term management of psoriasis: A 2-year cohort study. *J Am Acad Dermatol*. 44:643-51. 2001 REF ID: HO2001	RCT Multicentre, Europe and N. America Randomised: Method not stated Blinding: Open Allocation concealment: No Sample size calculation:	N=76	**Inclusion criteria** Patients with plaque psoriasis unresponsive to topical therapies and requiring systemic therapy Washout period: no systemic therapy within 2 weeks prior to entry/PUVA 4 weeks prior Exclusion History of >12 weeks systemic therapy with corticosteroids and immunomodulating or cytotoxic drugs or retinoids. Concomitant therapy with nephrotoxic drugs/pharmacokinetic interactors, history of malignancy, acute uncontrolled bacterial, viral or fungal infection, abnormal renal function/LFTs, hyperkalaemia, hyperuricaemia, clinically significant imapairment of haematopoietic, cardiovascular, and/or cerebral function, psychotic disorders or mental	Ciclosporin: Abrupt cessation N=46 Ciclosporin 2.5 mg/kg/day titrated to max 5 mg/kg/day (divided doses) Dosage reductions according to guidelines (rise in creatinine or hypertension) Treatment continued until clearance or for a	Ciclosporin: Tapering dose N=30 Ciclosporin 2.5 mg/kg/day titrated to max 5 mg/kg/day. Dosage reductions according to guidelines (rise in creatinine or hypertension) Treatment continued until clearance or for a maximum of 12 weeks	2 years	Median time to relapse (Relpase: when investigator or patient deemed CSA should re-start or recurrence of psoriasis affecting ≥75% surface area) %BSA Global assessment Modified PASI (0-54: excludes head)	

	Not stated ITT:		instability Similar baseline patient characteristics: <table><tr><td></td><td>Abrupt</td><td>Tapered</td></tr><tr><td>Mean age</td><td>41.9</td><td>38.2</td></tr><tr><td>M/F ratio</td><td>24:22</td><td>17:13</td></tr><tr><td>Weight kg</td><td>77.9</td><td>78.7</td></tr><tr><td>Psoriasis duration</td><td>14.71 years</td><td>14.70 years</td></tr><tr><td>Psoriatic area %</td><td>16.05</td><td>17.87</td></tr></table>	maximum of 12 weeks **Stop ciclosporin or abruptly** On relapse patients given another course of ciclosporin At end of treatment period, patients stop ciclosporin according to treatment plan specified at randomisation. Up to 8 treatment courses during the 2 years	**Tapering dose (1 mg/kg daily each week) until stopping within 4 weeks** On relapse patients given another course of ciclosporin At end of treatment period, patients stop ciclosporin according to treatment plan specified at randomisation. Up to 8 treatment courses during the 2 years		DLQI	
Effect Size								

Median time to relapse (days)

	Abrupt	Tapered
1	115	119.5
2	87	104
3	64	112
4	59	110
5	58	62
6	45	63
7	34	56

DLQI

Overall reduction – data not reported for each group

Hypertension

18 patients had elevated blood pressure on 2 or more occasions. no patients experienced severe hypertension. Reduction in ciclosporin dose due to raised BP in 8 patients. 7 patients required initiation of antihypertensive therapy. No discontinuations due to hypertension.

%patients with increase in creatinine >30% & >50% baseline

18 patients had 3 or more rises in serum creatinine >30% above baseline. No discontinuations due to elevated serum creatinine.

8 serious adverse events reported (1 meningitis, 2 cataract, 2 requiring surgical intervention not related to study medication), 1 fever, 1 severe arthralgia.

5 patients discontinued study due to adverse events

H.10.7 MAINTENANCE OF REMISSION

H.10.7.1 Ciclosporin 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>C.N. Ellis, M.S. Fradin, T.A. Hamilton, J.J Voorhees. Duration of remission during maintenance cyclosporine therapy for psoriasis. Arch Derrmatol.131:791-795. 1995

REF ID: ELLIS1995</td>
<td>RCT

USA

Randomised:

To three groups, method not stated

Blinding:

double-blinded, patients and investigators</td>
<td>N=61

Drop-outs:

3</td>
<td>Inclusion criteria

Follow-on maintenance study from ELLIS1991. Patients who had cleared/nearly cleared with induction CSA (3/5/7.5 mg/kg/day) continued on in low-dose CSA for maintenance.

Comparable for baseline demographic characteristics:
<table>
<tr><th></th><th>CSA 1.5 mg</th><th>CSA 3 mg</th><th>Placebo</th></tr>
<tr><td>Mean age</td><td>43 (19-74)</td><td>42 (22-65)</td><td>48 (21-64)</td></tr>
<tr><td>Sex – m/F</td><td>12/8</td><td>17/4</td><td>17/3</td></tr>
<tr><td>Mean PASI at end of Induction</td><td>2±0</td><td>2±0</td><td>2±0</td></tr>
<tr><td>Average daily dose during induction</td><td>4.3 mg/kg</td><td>4.4 mg/kg</td><td>3.9 mg/kg</td></tr>
</table></td>
<td>Ciclosporin (CSA)

N=41

Group 1:

1.5 mg/kg/day (N=20)

Group 2:

3 mg/kg/day (n=21)

No dose adjustment</td>
<td>Placebo

N=20</td>
<td>4 months

However, patients removed from study earlier if relapse</td>
<td>1° outcome:

Clear/nearly clear

2° and other outcomes:

PASI

Cumulative relapse rate

Creatinine

AEs</td>
<td>Sandoz Research Institute, Babcock Dermatologic Endowment, Alumni of Univ. Of Michigan Dermatology Department, NIH grant</td>
</tr>
</table>

	Allocation concealment: Not stated Sample size calculation: Not stated ITT: modified							

Relapse

	CSA 1.5 mg/kg (N=20)	CSA 3 mg/kg (N=21)	Placebo (N=20)
Relapse	14 patients	8 patients	18 patients
Mean time to relapse ±SE	9±1 weeks	12±1 weeks	7±1 weeks
Mean time to relapse ±SD	9±4.47 weeks	12±4.58 weeks	7±4.47 weeks

Stated no significant difference between CSA 1.5 mg group and placebo (P=.3), significant difference between CSA 1.5 mg and CSA 3 mg (P=0.04) and CSA 3 mg and placebo group (P=0.002)

PASI

Not reported

No severe adverse events

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Shupack J et al. Cyclosporine as maintenance therapy in patients with severe psoriasis. J Am Acad Dermatol 1997; 36: 423-32. Ref ID SHUPACK 1997	**RCT** **Randomisation:** Method not stated **Allocation concealment:** Not stated **Blinding:** yes double blind **Sample size calculation:** yes, minimum 36 patients needed to provide 80% power to detect therapeutically meaningful and statistically significant	181 enrolled in 16-week induction phase (ciclosporin 5mg/kg/day; increased to 6mg/kg/day if 25% clearing or more or exacerbation after 6 weeks at 5mg/kg/day; decreased in steps of 1mg/kg/day to minimum 3mg/kg/day if adverse event, abnormal laboratory value [high drug levels i.e. trough >600ng/mL or renal dysfunction i.e. serum	**Inclusion:** History of either extensive psoriasis (88% of patients) involving >25% of body surface area or disabling psoriasis (12% of patients) that impaired their ability to carry out daily activities; plus responded poorly or not appropriate for treatment with conventional therapy; achieving 70% reduction in involved body surface area for 2 weeks **Exclusion:** History of pustular or erythrodermic psoriasis; significant hepatic, renal or bone marrow disease; history of malignancy; concurrent use of other immunosuppressants; significant infection; clinically significant laboratory abnormalities including elevated serum creatinine or uncontrolled hypertension; systemic therapy for psoriasis within last 30 days; topical medications for psoriasis within 2 weeks; any previous therapy with ciclosporin.	Ciclosporin 3mg/kg/day (n=86) or 1.5mg/kg/day (n=7, randomisation to this arm discontinued when other data published suggesting this dose ineffective and higher dose used instead for people randomised to this group)	Placebo (n=49)	16 week induction phase + 24 week maintenance phase	% body surface area involved with psoriasis (relapse = the point at which BSA returned to 50% or more of baseline). Overall change compared with baseline (1=cleared through to 8=markedly worsened). Global evaluation (1=totally	Sandoz Research Institute

	difference in relapse rates between groups (based on relapse rate of 60% with ciclosporin 3mg/kg/day and 95% for placebo **ITT analysis:** not stated **Drop outs:** 13/181 discontinued in induction phase due to adverse event (includes **8 serious AE** including 3 considered drug-related: hypertension, gout/fluid retention, diarrhoea), i.e. leaving 168 patients. Other patients	creatinine 50% or more over baseline or absolute value >1.8mg/dL or liver dysfunction i.e. ASAT/ALAT increased by more than twice the upper normal limit or total bilirubin >2mg/dL] or increased blood pressure defined as "uncontrollable hypertension"); 142 entered maintenance phase	Baseline characteristics at beginning of induction phase: **Baseline** / **All (n=181)** Mean age: 44.9 years (range 21-78) Gender (M/F%): 85/15 Mean weight (kg): 85.9 (range 46.8-138.8) Mean duration psoriasis (years): 17.5 (range 1.1-51.0) Mean % BSA affected: 42.3% (SD22.6%) Mean PASI score: 23.2 (SD 12.7) Mean indicator lesion severity score: 5.9 (SD 1.0) Mean global evaluation score: 6.1 (SD 1.0) Previous treatment with: Photochemother: 48%				clear to 7=severe). PASI (range 0-72; 18 or higher represents moderately severe to severe). Severity of 3 selected indicator lesions for scaling erythema, pustules, thickness and overall severity (1=totally clear to 7=severe).	

	were to be discontinued if they did not achieve 70% clearance by end of induction phase (number this applied to not stated) or presumably if they withdrew consent (not stated) – a further 26 patients withdrew for some reason (not stated) as only **142 entered maintenance phase**. **9**/86 on ciclosporin 3mg/kg/day dropped out of maintenance phase due to **adverse effects** (7 clearly related to study drug i.e. decreased renal function 5 [increased serum creatinine 3,		apy Etretinate 30% Methotrexate 49% None of these 30% Previous treatment with: Tar 89% Anthralin 46% Corticosteroids 96% UVB 73%					

	decreased urine creatinine clearance 1 and decreased GFR 1]; laboratory abnormality 1; worsening gynaecomastia/ hypertension 1; and a further 2 uncertain relation to study drug i.e. 1 squamous cell carcinoma of skin and 1 flare of pustular psoriasis). Also 1 dropped out for **illness unrelated to study drug**. Drop-outs in placebo or 1.5mg/kg/day ciclosporin groups not stated.							

Effect size

Outcome	**Induction phase**	**Maintenance phase**		
	Ciclosporin 5mg/kg/day	**Placebo**	**Ciclosporin 3mg/kg/day**	

	No. of patients	Mean % improvement from baseline	No. of patients	Start % of baseline	End % of baseline	No. of patients	Start % of baseline	End % of baseline	p value for difference between groups
Body surface area	181	81	49	89	39	85	89	64	p<0.001
Global evaluation	181	73 (mean rating 2.4, representing "almost clear to mild")	49	81	18	85	82	50	p<0.001
PASI score	181	86	47	91	29	76	91	59	p<0.001
Indicator lesions	181	83 (mean lesion severity rating 1.9 reflecting "absent to trace")	49	85	39	85	88	67	p<0.001

Median time in **induction** phase to achieve 70% reduction in BSA was 8 weeks and to achieve 90% reduction was 12 weeks. 84% of patients were clear of psoriasis or markedly improved by end of induction phase; 95% achieved moderate or marked improvement. Adverse events in induction phase reported by 88% of patients: headache (30%), paraesthesia (18%) and hirsutism (17%) the most frequent. New onset hypertension (i.e. systolic BP >150mmHg and/or diastolic >90mmHg) in 8.8% of sample.

In **maintenance** phase, percentage of patients who had a **relapse** (defined as BSA returned to 50% or more of baseline) in ciclosporin 3mg/kg/day group was 42% (n=83) vs. 84% on placebo (n=48), p<0.001. Median **time to relapse** for placebo group or ciclosporin 1.5mg/kg/day group was 6 weeks vs. >24 weeks (i.e. not seen in duration of study) for ciclosporin 3mg/kg/day group. The most frequently noted adverse events during maintenance phase were headache and hirsuitism; most rated as mild to moderate in severity (numbers of patients affected not stated). 3 patients on ciclosporin 3mg/kg/day had a **fall in GFR** to 33% or more below baseline. New or worsening **serum creatinine** abnormalities (defined as new elevations or increases of 15% or more above abnormal baseline) in 17% of those on ciclosporin 3mg/kg/day and 10% of placebo group (denominators unclear as not all patients had all investigations).

Author's conclusion

- Ciclosporin 3mg/kg/day adequately and safely maintained 58% of patients with psoriasis for a 6-month period after clearing their psoriasis with doses of around 5mg/kg/day.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Maintenance study (weekend maintenance schedule) Colombo et al., Psoriasis relapse evaluation with week-end cyclosporine A treatment: results of a randomized, double-blind, multicenter study. Int J Immunol & Phamacol. Vol. 23, no.4,1143-1152 (2010) PREWENT Trial REF ID: COLOMBO2010	RCT Multicenter Italy Randomised: 2:1, method not stated Blinding: Double-blind Allocation concealment: Not mentioned Sample size calculation: Yes, power 88%	N=243 (randomised) 4 patients (2 in each group) did not take drug/placebo – excluded from ITT	**Inclusion** Patients 18-65 years with chronic plaque psoriasis on continuous treatment with any dose regimen for 8-16 weeks (**induction treatment**) and who had achieved remission (i.e. PASI reduction ≥75% from pre-treatment) CSA washout period **Exclusion** Body weight >110 kg, uncontrolled hypertension, malignancies, infections and severe haematological, immunological, cardiovascular metabolic or neurological disorders. Patient baseline characteristics	**Ciclosporin** N=160 CSA microemulsion 5mg/kg/day PO Two divided daily doses 2 consecutive days per week (weekends)	**Placebo** N =79	24 weeks	**1° outcome** Relapse rate at 24 weeks – worsening of psoriasis PASI ≥75% of baseline **2° outcome** Time to relapse Change in baseline PASI score BSA Itch intensity Safety AEs, lab values	Funding from Novartis Farma SpA

	to detect 20% risk reduction with α5% (N=264) ITT: Primary analysis per-protocol, supplementary ITT for primary and secondary outcomes. ITT safety analysis. 30% drop-out rate		similar: CSA / Placebo Mean Age: 41.8 (11.0) / 41.8 (12.7) %Male: 65.6 / 59.5 Caucasian (%): 158 (98.8) / 78 (98.7) Asian: 1 (0.6) / 0 Other: 1 (0.6) / 1 (1.3) Mean disease duration, years: 14.9 (10.3) / 13.9 (11.0) Mean PASI ratio (% of baseline score at end of induction): 8.5 / 8.1				Clinical success rate (proportion of patients with no clinical worsening – no relapse or PASI <75% of pre-treatment PASI) Time to first relapse Creatinine BP	
Effect Size **PASI 75 (PP)**								

	CSA 5 mg/kg (n=127)	Placebo (n=62)
PASI 75	85	33

Final Mean PASI (PP)

	CSA 5 mg/kg (n=127)	Placebo (n=62)
Final Mean PASI ±SD	7.3±8.5	8.8±8.8

Time to relapse – not extractable (K-M curve)

Relapse rates: 33.1% CSA and 46.8% placebo

Serious adverse events

CSA 1 (0.6%) – breast mass (considered unrelated), Placebo 0

Rise in creatinine >30% above baseline (ITT)

	CSA 5 mg/kg (n=160)	Placebo (n=79)
Rise in creatinine >30% above baseline	8	3

Stated no significant difference in mean blood creatinine levels between treatment groups at any time during the study

Withdrawal due to AEs (ITT)

	CSA 5 mg/kg (n=160)	Placebo (n=79)
Withdrawal due to AEs	8	2

Hypertension

No significant differences in systolic and diastolic BP reported in either group

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
D. Thaçi, M. Brautigam, R. Kaufmann, G. Wiedinger, C. Paul, E. Cristopher s. Body-weight-independent micro-emulsion and three time weekly	RCT Multicentre Germany Randomised: computer generated list Blinding:	N=122 3 patients excluded due to lack of creatinine data 15 drop-outs	Inclusion criteria Patients with chronic plaque type psoriasis requiring systemic treatment. One or more conventional systemic therapies failed or inappropriate. Psoriasis stable for at least 3 weeks prior to entry. Minimum PASI of 12. Washout: no methotrexate, sulphasalazine, retinoids, UVB or PUVA 3 weeks prior. No topical	Ciclosporin N=42 Maintenance phase following achievement of PASI75 Twice daily in divided doses	Placebo N=51 Maintenance phase following achievement of PASI75 Patients achieving remission	Period 2: 12 weeks Treatment stopped if relapse (inc. in PASI >50% of baseline)	1º outcomes Increase in serum creatinine Relapse rate 2º outcomes	

maintenance regimen in severe psoriasis. *Dermatology.*205:383-388.2002 REF ID THACI2002	Period 1 Open Period 2 DB Allocation concealment: not stated Sample size calculation: ITT: Modified ITT	N=93 responders in Period I randomised to Period II	therapy at time of entry. Exclusion: Pregnant/breast feeding women, patients thought to be 'non-compliant'. Patients with malignancy, uncontrolled bacterial, viral or fungal infections, hypertension or generalised erythrodermic, pustular, or drug-induced psoriasis. Patients with abnormal creatinine or LFTs, intolerant of CSA, previous failed CSA. Those receiving investigational drug within 4 weeks of entry, or taking nephrotoxic drugs or drugs with pharmacokinetic interactions with CSA. Baseline characteristics at start of maintenance phase similar apart from slightly higher body weight in CSA group CSA / Placebo Mean age: 43.1 yrs / 44.6 yrs Weight: 85.5 / 78.1 Sex – M/F: 30/12 / 35/16	Period 1: open, randomised to body-weight-dependent dosing or body-weight-independent dosing. BWI 200 mg/day starting dose (to max 300 mg/day), BWD 2.5 mg/kg/day starting dose (to max 5 mg/kg/day). Doses increased if PASI had not dec. >40% by wk 4, or >60% by wk 6, or ≥75% by wk Period 2 Lowest effective dose CSA continued	randomised to double-blind trial: CSA maintenance dose or placebo		PASI score BP Global assessment	

			PASI	2.7±1.9	3.0±2.2					
			Creatinine	88.4±19.4	86.6±18.6					
			Previous systemic psoriasis Rx	88.1%	86.3%					

Effect Size

15 dose modifications for increased BP or serum creatinine in Period I

3 dose adjustments for increased creatinine (>30% baseline at two consecutive visits)

13 increases in blood pressure reported as adverse events

Withdrawal due to serious increases in BP in 3 patients

Increased serum creatinine in 4 patients

Period II

Relapse rate: 17/42 vs 29/51 with placebo (p=0.15)

Time to relapse 98 days (intermittent CSA) 69 days (placebo) – log-rank test p = 0.09

PASI increased from 2.7 to 9.9 with CSA, from 3.0 to 11.9 with placebo (n/s)

Mild disease or better: 14/31 CSA vs 5/22 placebo

No creatinine increases >30% on two consecutive visits during period II

H.10.8 INDUCTION OF REMISSION

H.10.8.1 Ciclosporin vs placebo for palmoplantar pustulosis

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

<table>
<tr>
<td>Reitamo S et al. Cyclosporine in the treatment of palmoplantar pustulosis. Arch Dermatol 1993; 129: 1273-1279.

Ref ID: REITAMO1993</td>
<td>RCT

Randomisation: given numbers 1-40 in consecutive order (each number preassigned to ciclosporin or placebo)

Allocation concealment: no

Blinding:

yes for phase 1 of study

Washout period: Retinoids and PUVA had to be withdrawn 4 and 2 weeks prior to study, respectively; no</td>
<td>40</td>
<td>Inclusion: 18-70 years; clinically defined palmoplantar pustulosis of the palms and/or soles with at least 20 whitish-yellow pustules of diameter at least 2mm.

Exclusion: Abnormal hepatic or renal function; malignancy; active or chronic infection; pregnancy or lactation; drugs known to interact with ciclosporin. Retinoids and PUVA had to be withdrawn 4 and 2 weeks prior to study, respectively; no topical treatments other than emollients allowed in last 2 weeks.
<table>
<tr><th></th><th>Ciclosporin (n=20)</th><th>Placebo (n=20)</th></tr>
<tr><td>Gender (M/F%)</td><td>30/70</td><td>30/70</td></tr>
<tr><td>Mean age (yr) range</td><td>40.80 (11.49) 24-69</td><td>41.65 (10.41) 29-62</td></tr>
<tr><td>Mean weight (kg) range</td><td>66.90 (9.26) 52-91</td><td>70.65 (14.76) 50-104</td></tr>
<tr><td>Smoking</td><td>20</td><td>20</td></tr>
<tr><td>Mean age at</td><td>34.3 (21-</td><td>34.3</td></tr>
</table>
</td>
<td>n=20

Ciclosporin

2.5mg/kg/day

Both arms: intervention administered twice daily as capsules of 25 and 100 mg</td>
<td>n=20

Placebo (vehicle without CSA)</td>
<td>1 month double blind phase; 3 month open, dose-finding phase; 2 months off treatment

Also, 38/40 seen 4-12 months after termination of treatment</td>
<td>Total number of fresh pustules compared with baseline; success = “responder” = 50% or more reduction in number of pustules; others = failure = “nonresponder”; relapse defined as nonresponse after earlier response.

Number of fresh pustules averaged across right and left palm and right and left soles; indexes of severity of affected areas (palms or soles separately, or composite index for palms and soles together) based on erythema, infiltration and scaling (all scored 0= absent through 3 =severe, for total of 18 maximum, then divided by 18 to get percentage (max score 100 = all areas</td>
<td>Sandoz Pharma, Finska Läkaressällskapet, Paulo Foundation.</td>
</tr>
</table>

	topical treatments other than emollients allowed in last 2 weeks **Sample size calculation:** yes – sample size of 20 for 80% power to detect a difference of 50% of patients improving with treatment compared with 30% improving on placebo. **ITT analysis:** not stated **Drop outs:** 1 from each group – 1 moved away and 1 not willing to come in for evaluation		onset of PPP (yr) range	67)	(21-61)				severely affected by each symptom). Overall efficacy of treatment scored by patient and investigator individually (1=very good through 5=very poor). Adverse events (occurrence, severity, frequency), vital signs, laboratory and physical examinations. Overall tolerance to treatment.	
			Mean number of fresh pustules (range)	76.5 (21-338)	72.5 (21-282)					
			Location: Palmar Plantar	 19 20	 18 20					
			Mean duration PPP (yr)	7	8					
			Previous systemic therapy: Methotrexate PUVA Retinoids	 0 10 8*	 0 7 2*					
			* p<0.001							

Phase 1 of study: double-blind placebo-controlled trial (n=40).

Effect size at week 4:

	Ciclosporin (n=19)	Placebo (n=19)	p value between groups
Responders Nonresponders	17 (89%) 2 (11%)	4 (21%) 15 (79%)	p<0.001
Overall efficacy score	1.9 (1=very good, 2=good)	4.5 (4=poor, 5=very poor)	p<0.001
Number of patients with adverse events	7 (4 headache [of whom 1 stopped treatment], 2 weakness, stiffness or tenderness of feet, 1 cold feet, 1 common cold, 1 diarrhoea, 1 nausea, 1 dry mouth)	6 (2 tiredness, 1 arthralgia, 1 paronychia, 1 maxillar sinusitis, 1 urticaria [who stopped treatment])	not stated

Mean serum creatinine levels increased in ciclosporin but not placebo group but all remained **within normal range**; no patient had to terminate study due to high serum creatinine. No patient stopped therapy due to hypertension and no patients received antihypertensive therapy.

Phase 2 of study – open dose-finding study: nonresponders in placebo group given 1.25mg/kg/day ciclosporin at week 4 and if still did not respond, dose increased at monthly intervals in steps of 1.25mg/kg/day up to maximum of 3.75mg/kg/day until week 16; responders in ciclosporin group continued previous treatment; nonresponders in ciclosporin group had dose increased to 3.75mg/kg/day.

Effect size at week 12:

	Ciclosporin (n=19)	Placebo - (n=13)	p value between groups
Responders Relapse	10 0	10 (1 required >1.25 mg/kg/day) 2	not stated
Number of patients with adverse events	12 (3 headache, 3 weakness , stiffness or tenderness of feet, 3 common cold, 1 nausea, 1 paronychia, 1 maxillar sinusitis, 1 hypertension, 1 hypertrichosis, 1 vaginitis, 1 mucous secretion of eyes, 1 increased sweating, 1 dizziness, 1 abdominal pain, 1 paraesthesia)	4 (1 common cold)	not stated

Phase 3 of study: 8-week post-treatment observation period.

Of those succeeding at the start of phase 3

	Ciclosporin (n=10)	Placebo (n=12)	p value between groups
Relapsed Did not relapse	6 4	8 4	not stated

Number of patients with adverse events	7 (2 headache, 2 weakness , stiffness or tenderness of feet, 1 skin infection, 1 eczema)	4 (1 headache, 1 weakness , stiffness or tenderness of feet, 1 urticaria)	not stated

Once CSA was withdrawn, among the 14 who relapsed the time-to relapse was 2 weeks for 13/14 (weeks 17 and 18)

Of the 6 in the CSA group who relapsed, 3 relapsed at week 17 and three at week 18

Additionally, 38 patients seen between 4 months and 1 year after end of official 3-phase study.

27/38 patients in remission and had only minor signs of palmoplantar pustulosis that required no specific treatment.

Author's conclusion

- Ciclosporin at a dose of 1.25-2.5mg/kg/day in an effective treatment for most patients with palmoplantar pustulosis, a disease that is usually resistant to treatment.
- The clinical appearance of palmoplantar pustulosis is of a cyclic nature in many individuals, who can show a wide variation in the number of pustules from day to day; this variation may have accounted for the placebo response rate.

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

								funding
Erkko P et al. Double-blind placebo-controlled study of long-term low-dose cyclosporin in the treatment of palmoplantar pustulosis. Br J Dermatol 1998; 139: 997-1004. Ref ID ERKKO1998	**RCT** Multicentre (Sweden) **Randomisation:** given numbers in consecutive order (each number preassigned to ciclosporin or placebo) **Allocation concealment:** not stated **Blinding:** yes phase 1 **Washout period:** Retinoids, PUVA and	58	**Inclusion:** 18-70 years; clinically defined palmoplantar pustulosis of the palms and/or soles with at least 20 whitish-yellow pustules (not showing any brownish colour) of diameter at least 1mm. **Exclusion:** Abnormal hepatic or renal function; malignancy; active or chronic infection; pregnancy or lactation; drugs known to interact with ciclosporin; hypertension (diastolic BP >95mmHg treated or untreated). Retinoids, PUVA and antimicrobial treatment had to be withdrawn 4 weeks prior to study; no topical treatments other than emollients allowed in last 2 weeks. **Ciclosporin (n=27)** / **Placebo (n=31)** Gender (M/F%): 14.8/85.2 / 38.7/61.3 Mean age (yr) range: 45.2 (12.1) 25-70 / 43.0 (13.3) 21-65 Mean: 74.5 / 72.2	n=27 **Ciclosporin** Sandimmun® 1mg/kg/day for 1 month ---------- Both arms: intervention administered twice daily as capsules of 25 and 100 mg	n=31 **Placebo** for 1 month	12 months Tx (monthly visits): Part 1: randomised, double blind 4 wks Part 2: open continuation of part 1 (11 months) Part 3: followed for 1 year after completion of study	Total number of fresh pustules compared with baseline; success = "responder" = 50% or more reduction in number of pustules; others = failure = "nonresponder"; relapse defined as nonresponse after earlier response. Erythema, infiltration and scaling (all scored 0= absent through 3 =severe) and area of skin affected. Overall efficacy of treatment scored by patient and	Novartis Pharma Ltd

	antimicrobial treatment had to be withdrawn 4 weeks prior to study; no topical treatments other than emollients allowed in last 2 weeks. **Sample size calculation:** not stated **ITT analysis:** not stated **Drop outs:** none in phase 1; 6/58 phase 2 (3 AEs, 1 lost to FU, 1 lack of efficacy and 1 protocol violation)		weight (kg) range	(14.2) 56-130	(12.3) 46-97					investigator individually (1=very good through 5=very poor). Adverse events (occurrence, severity, frequency), vital signs, laboratory and physical examinations. Overall tolerance to treatment.	
			Mean age at onset of PPP (yr) range	37.0 (10.1) 25-61	37.6 (12.8) 20-65					
			Mean number of fresh pustules (range)	56.2 (40.4) 21-178	70.0 (38.3) 21-186					
			Location: Palmar Plantar	 23 24	 23 31					
			Mean duration PPP (yr)	7.2 (7.5)	5.4 (6.0)					
			Previous systemic therapy: Methotrexate PUVA Retinoids	 1 11 5	 0 10 9					

Phase 1 of study: double-blind placebo-controlled trial (n=58, all completed).

Effect size at week 4:

	Ciclosporin (n=27)	Placebo (n=31)	p value between groups
Responders	13 (48%)	6 (19%)	p<0.02
Number of patients with adverse events	6 (2 headache, 1 gastrointestinal symptoms [nausea, vomiting, abdominal pain, diarrhoea], 1 musculoskeletal pain, 1 hypertension, 1 paraesthesia)	8 (1 upper respiratory tract infection, 2 gastrointestinal symptoms [nausea, vomiting, abdominal pain, diarrhoea], 3 fatigue, 1 paraesthesia, 1 other)	NS
Hypertension	1	0	

No serious adverse events or malignancies.

Phase 2 – open continuation of Phase 1: code broken if no response to treatment at initial dose level. Patients initially randomised to placebo received ciclosporin 1mg/kg/day; all nonresponders had dose increased in steps of 1mg/kg/day (adjusted every 2 months) until response or to a maximum of 4mg/kg/day. In cases of treatment response, dose reduced by 12mg/kg/day to minimum of 1mg/kg/day. Treatment continued for 12 months. Treatment stopped if no response to maximum dose after 2 months. (52 completed phase 2; 6 discontinued: 1 each for lost to follow up, hypertension, severe pruritis, diarrhoea, lack of efficacy and protocol violation).

Effect size at 12 months:

	Ciclosporin group (n=27)	**Placebo group (n=31)**	**p value between groups**
Mean duration of blinded treatment	5.1 months	2.1 months	p<0.01
Patients in **remission** throughout 12 months of treatment (i.e. not unblinded)	7	2	p<0.05
Number of patients with adverse events	166 (53 upper respiratory tract infection , 15 headache, 10 gastrointestinal symptoms [nausea, vomiting, abdominal pain, diarrhoea], 10 skin infections, 9 musculoskeletal pain 6 fatigue, 7 hypertension, 4 paraesthesia, 6 hypertrichosis, 6 swelling of fingers or feet, 5 herpes simplex, 2 herpes zoster, 4 dizziness, 3 conjunctivitis, 2 vaginitis, 24 other)	11 (7 upper respiratory tract infection, 2 headache, 1 gastrointestinal symptoms [nausea, vomiting, abdominal pain, diarrhoea], 1 fatigue)	NS
Serum creatinine increased by >30% over baseline	2	0	
Diastolic BP increased to >95mmHg	7 (5 needed anti-hypertensives; 1 stopped ciclosporin)		

No serious adverse events or malignancies.

Phase 3: patients follow up for 12 months after completing treatment.

A reduction in activity of disease was seen at 6 and 12 months; 2 patients totally free of lesions 12 months after stopping treatment and 11 had only minor symptoms (erythema and/or scaling without pustulation).

Author's conclusion

- Ciclosporin was well tolerated and side effects were mainly mild and reversible. We recommend treating with 1-2mg/kg/day for 1-2 months; if this does not show a satisfactory response, dose may be increased stepwise up to 4mg/kg/day.

H.11 Methotrexate and risk of hepatotoxicity

H.11.1 Liver enzyme tests

H.11.1.1 STUDY 1

Reference	Study type	Number of patients	Patient characteristics	Index test	Reference standard	Source of funding
M. Newman, R. Auerbach, H. Feiner, R. S. Holzman, J. Shupack, P. Migdal, M. Culubret, P. Camuto, and H. Tobias. The role of liver biopsies in psoriatic patients receiving long-term methotrexate treatment. Improvement in liver abnormalities after cessation of treatment. Arch.Dermat	**Observational:** Case series and within-group comparison **Retrospective** • **Patient selection:** New York University Hospital and office records; attempted to identify **all** those undergoing biopsy 1968-1986 • **Index tests: LFTs –** within 3 days of reference standard; unclear method of selection of threshold (may have been post-hoc) • **Reference standard:**	N: 168 Total of 364 biopsies (85 before treatment) 49% had biopsies before starting methotrexate (279/346 biopsies were from	**Inclusion criteria:** Patients who have diagnosed psoriasis unresponsive to previous treatment; liver biopsy before and/or during therapy with MTX **Exclusion criteria:** none stated **Parameter** / **All (n=168)** Mean age (at biopsy) – years: 47.7 Gender M/F (%): 52/48 Pre-MTX biopsy (%): 49% Median monthly MTX dose before: 67.3 (7.5-205.6) mg	**Liver function tests:** Alanine aminotransferase Aspartate aminotransferase Bilirubin Alkaline phosphatase Prothrombin time Albumin	**Histological techniques:** Biopsy by Menghini technique; fixed and embedded in paraffin; staining with H&E, reticulin and trichrome stains Diagnosis made by blinded assessor according to Roenigk grading: Grade 1: normal tissue, no/mild fatty change, no/mild nuclear pleomorphism, no fibrosis, mild portal inflammation	Honors Research Program of New York State University School of Medicine; partial funding from Lederle Laboratories

ol. 125 (9):1218-1224, 1989. Ref ID: NEWMAN1989	biopsy classification according Roenigk grading (grade IIIA-IV = abnormal); blinded to clinical data Reviewed by 3 pathologists (experience unclear); inter-reader agreement periodically checked (questionable specimens reviewed by all and consensus made) • **Flow and timing:** Max 3 days between tests (index test second); unclear if all patients included in the analysis/if all received LFTs because raw data/2x2 table not available	those with at least 1 months MTX)	biopsy (range) | Duration of treatment (median) | 48 months IBD or gallbladder disease | 0 History of high alcohol intake | 14 (8 of whom received MTX) Diabetes | 16 Obese | 67 (40%) **Methotrexate schedule:** Most received oral administration in either a single weekly or a divided weekly dose MTX treatment stopped when biopsy specimen was grade IIIB or greater		Grade 2: moderate/severe fatty changes, moderate/severe nuclear pleomorphism, no fibrosis, moderate/severe portal inflammation Grade 3a: mild fibrosis, portal fibrotic, septa, extending in the lobuli, portal tract enlargement Grade 3b: moderate/severe fibrosis Grade 4: cirrhosis, regenerating noduli and bridging of the portal tracts	

Effect Size

Outcomes

Pre-test probability/prevalence

17/83 patients had abnormal biopsy before taking MTX

2/31 patients with biopsy before and after MTX had abnormal biopsy at both time points

Pre-test probability not available for group with biopsy after MTX and not before

Note: raw data not available (based on both those taking methotrexate and those who had biopsy before methotrexate, but unclear if analysed on a per patient basis – taking the most severe biopsy sample for each patient – or if multiple biopsies per patient were included)

Test	Abnormal range	Sensitivity	Specificity	Predictive value	
				Positive test	Negative test
Alanine aminotransferase	≥40 U/L	0.05 (0.006-0.17)	0.85 (0.72-0.94)	0.22 (0.03-0.48)	0.52 (0.40-0.63)
Aspartate aminotransferase	≥40 U/L	0.20 (0.13-0.30)	0.90 (0.84-0.93)	0.49 (0.33-0.65)	0.70 (0.62-0.76)
Bilirubin	≥2 µmol/l	0.19 (0.12-0.29)	0.86 (0.80-0.90)	0.41 (0.26-0.57)	0.60 (0.63-0.75)
Alkaline phosphatase	≥100 U/L	0.38 (0.28-0.49)	0.71 (0.63-0.77)	0.39 (0.28-0.49)	0.70 (0.63-0.77)
Prothrombin time	≥14.5 s	0.01 (0.00-0.05)	0.99 (0.94-0.99)	0.25 (0.06-0.80)	0.66 (0.61-0.72)
Albumin	≥35 g/l	0.19 (0.11-0.29)	0.76 (0.68-0.83)	0.33 (0.19-0.48)	0.61 (0.52-0.68)

Author's conclusion

- No single test was a good predictor of liver damage; although the specificity for prothrombin time was high, the prevalence of abnormal values was such that the predictive values were low for both a positive and negative test

H.11.1.2 STUDY 2

Reference	Study type	Number of patients	Patient characteristics	Index test	Reference standard	Outcome measures	Source of funding
G. T. O'Connor, E. M. Olmstead,	**Observational:** Retrospective case series and within-group comparison	N: 78 (147 biopsies;	**Inclusion criteria:** Psoriasis patients who had undergone biopsy associated with MTX	**Liver function tests:** total bilirubin, aminotransferas	**Liver biopsy** Graded by the Roenigk	Hepatotoxicity by biopsy and LFTs -sensitivity,	None stated

K. Zug, R. D. Baughman, J. R. Beck, J. L. Dunn, P. Seal, and J. F. Lewandowski. Detection of hepatotoxicity associated with methotrexate therapy for psoriasis. Arch.Dermatol. 125 (9):1209-1217, 1989. Ref ID: OCONNOR 1989	• **Patient selection:** Patients who had undergone MTX treatment for psoriasis at Dartmouth-Hitchcock Medical Centre, USA between 1972-1986 (unclear if included all/consecutive sample) • **Index tests: LFTs –** obtained during week prior to reference standard; obtained using standard methods during regular clinical care threshold selection based on normal ranges that were in effect at the time the test was performed (note that this changes during the study period for AST and ALP) • **Reference standard:** biopsy classification according Roenigk grading (grade IIIA-IV = abnormal); single pathologist blinded to clinical data **Note:** the specimens were obtained during regular care but re-graded for this analysis (biopsy sample method unclear) • **Flow and timing:** Max 1 week between tests (index test first); not all biopsies were included in the analysis (2 of the pre-Tx and 9 of the post-Tx biopsies were excluded because	52 before and 95 after treatment) Analysis restricted to 50 before and 86 after Tx with full lab and Tx data	therapy **Exclusion criteria:** Not stated No baseline data presented **Methotrexate**: Dosing schedules not stated	e, alkaline phosphatase Abnormal levels in effect at the time of assessment	classification by blinded assessor **Histological techniques:** Biopsy by Menghini technique; staining with H&E, and Masson trichrome	specificity, PPV and NPV	

	complete laboratory and demographic data were not available Excluded from analysis if from patient with abnormal pre-Tx biopsy or if incomplete data set						

Effect Size

Outcomes

Pre-test probability: 28/147 (19%)

Biopsy grade	**Overall**	**Pre-treatment**	**Post-treatment**
I	96	41	55
II	23	6	17
IIIa	20	3	17
IIIb	7	1	6
IV	1	1	0
Total 'abnormal'	**28**	**5**	**23**

Note: 2 and 9 from the pre- and post-treatment groups respectively were not included in the analysis due to incomplete data sets (unclear what biopsy grade they had). For the 2 pre-treatment biopsies, laboratory and/or demographic data were not available. For the 9 post-treatment biopsies complete laboratory and treatment data were not available and/or there were abnormal findings before treatment

Pre-treatment test accuracy

Test	Biopsy specimens *before* treatment (n=50)					
	Sensitivity	**Specificity**	**PPV**	**NPV**	**LR+**	**LR-**
AST	0.40 (0.05-0.85)	0.89 (0.76-0.96)	0.29 (0.04-0.71)	0.93 (0.81-0.99)	3.76 [0.97,15]	0.67 [0.33,1.38]
ALP	0.40 (0.05-0.85)	0.77 (0.60-0.87)	0.15 (0.02-0.45)	0.92 (0.83-0.97)	1.71 [0.52,5.63]	0.78 [0.38,1.63]
TB	0.20 (0.07-0.72)	0.96 (0.85-0.99)	0.33 (0.01-0.91)	0.91 (0.80-0.98)	4.7 [0.51,43]	0.84 [0.54,1.30]
AST or ALP	0.60 (0.15-0.95)	0.71 (0.56-0.84)	0.19 (0.04-0.46)	0.94 (0.80-0.99)		
AST, ALP or total bilirubin	0.60 (0.15-0.95)	0.71 (0.56-0.84)	0.19 (0.04-0.46)	0.94 (0.80-0.99)		

2 x 2 table – based on definition of abnormal biopsy as fibrosis or cirrhosis combined

	Reference test +ve	**Reference test -ve**
Index test +ve	**TP:** AST = 2 ALP = 2 TB = 1	**FP:** AST = 5 ALP = 11 TB = 2
Index test -ve	**FN:**	**TN:**

	AST = 3 ALP = 3 TB = 4	AST = 42 ALP = 36 TB = 45

Post-treatment test accuracy

Test	Biopsy specimens *after* treatment (n=86)					
	Sensitivity	**Specificity**	**PPV**	**NPV**	**LR+**	**LR-**
AST	0.43 (0.22-0.66)	0.86 (0.75-0.93)	0.50 (0.26-0.74)	0.82 (0.71-0.91)	3.13 [1.49,6.56]	0.66 [0.45,0.95]
ALP	0.57 (0.34-0.78)	0.72 (0.60-0.83)	0.40 (0.23-0.59)	0.84 (0.72-0.92)	2.03 [1.21,3.41]	0.6 [0.37,0.98]
TB	0.10 (0.02-0.30)	0.95 (0.87-0.99)	0.40 (0.05-0.85)	0.76 (0.65-0.85)	1.57 [0.31,8.00]	0.97 [0.84,1.11]
AST or ALP	0.81 (0.58-0.95)	0.60 (0.47-0.72)	0.40 (0.25-0.56)	0.91 (0.78-0.95)		
AST, ALP or total bilirubin	0.86 (0.64-0.97)	0.58 (0.46-0.71)	0.40 (0.26-0.56)	0.93 (0.80-0.98)		

2 x 2 table – based on definition of abnormal biopsy as fibrosis or cirrhosis combined

	Reference test +ve	**Reference test -ve**
Index test +ve	**TP:** AST = 10	**FP:** AST = 10

	ALP = 13 TB = 2	ALP = 20 TB = 4
Index test -ve	**FN:** AST = 13 ALP = 10 TB = 21	**TN:** AST = 62 ALP = 52 TB = 68

Test	**Association of abnormal LFT and biopsy specimen grade III or IV**					
	Crude analysis			**Adjusted analysis (age and history of cholecystitis)**		
	OR	X^2	**p-value**	**OR**	X^2	**p-value**
AST	4.7	7.98	0.005	14.7	12.83	<0.001
ALP	3.5	5.99	0.014	2.1	1.58	0.209
TB	2.2	0.69	0.406	5.1	2.38	0.123
AST or ALP	6.4	10.50	0.001	5.5	6.78	0.009
AST, ALP or total bilirubin	8.4	12.27	<0.001	14.7	8.00	0.005

Author's conclusion

- The benefit of performing liver biopsies serially is markedly reduced in the absence of clinical suspicion of hepatotoxicity and/or abnormal liver

function test results

H.11.1.3 STUDY 3

Reference	Study type	Number of patients	Patient characteristics	Index test	Reference standard	Source of funding
M. S. Ho, E. Cheah, S. N. Tham, L. B. Teh, H. S. Ng, and S. Thirumoorthy. Liver biopsies from psoriatics treated with methotrexate. Ann.Acad. Med.Singapore 15 (2):210-214, 1986. Ref ID: HO1986	**Observational:** Case series **Prospective** • **Patient selection:** Study conducted in Singapore Limited to those indicated for biopsy investigation (indication of potential liver damage according to cumulative dose or SGPT/ALT) Consecutive patients meeting the inclusion criteria • **Index tests: LFTs –** time between tests unclear; unclear method of selection of threshold (may have been post-hoc) • **Reference standard:** biopsy classification according Robinson grading; all specimens assessed by 2 independent pathologists with no prior knowledge of clinical	N: 18	**Inclusion criteria:** Patients who have diagnosed psoriasis unresponsive to topical treatment and requiring systemic MTX; either minimum total dose of 1500 mg or SGPT/ALT more than twice normal values **Exclusion criteria:** none stated **Parameter** / **All (n=18)** Mean age (years): 55 (39 – 77) Gender M/F (%): 66.7/33.3 Cumulative MTX dose (mean, range): 1808 (20-3500) mg Duration of treatment (mean, range): 88 months (2 weeks to 208	**Liver function tests:** Alanine aminotransferase (ALT/SGPT)	**Liver biopsy** **Histological techniques:** Biopsy by Menghini technique; fixed and embedded in paraffin; staining with H&E, reticulin and trichrome stains, Perl's stain and periodic acid Schiff Diagnosis made by independently by 2 blinded assessors according to the following grading based on degree of fatty change, parenchymal cell necrosis, portal inflammation, nuclear vacuolation, periportal and septal	None stated

	or biochemical details of patients (experience unclear); biopsy sample size unclear • **Flow and timing:** Unclear time between tests; all patients included in the analysis and all received LFTs				fibrosis and cirrhosis): 1. Minimal change 2. None-specific hepatitis 3. Fibrosis (septum formation) 4. Cirrhosis	

	months)
History of high alcohol intake	0
PsA	1 (5.6%)
Diabetes	0
Obese	0

Methotrexate schedule:

Not stated

Effect Size

Outcomes

Pre-test probability/prevalence

5/18 had fibrosis or cirrhosis (27.8%)

Summary of findings

Biopsy grade	**Number of biopsies**	**Number of ALT tests (using threshold of approx 32 U/l)**		**Number of ALT tests (using threshold of approx 40 U/l)**	
		Normal	**Abnormal**	**Normal**	**Abnormal**

Normal	2	2	0	2	0
Minimal change	3	3	0	3	0
Non-specific hepatitis	8	6	2	5	1
Fibrosis	4	2	2	2	2
Cirrhosis	1	1	0	1	0

Note: failed to detect the one case of cirrhosis

2 x 2 table – based on definition of abnormal biopsy as fibrosis or cirrhosis combined and ALT threshold of >32

	Reference test +ve	**Reference test -ve**
Index test +ve	TP: 2	FP: 2
Index test -ve	FN: 3	TN: 11

Summary statistic	
Pre-test probability/prevalence	27.8%
Sensitivity	40 (79-71.3)%
Specificity	84.6 (72.3-96.7)%
PPV	50 (9.8-89.2)%

NPV	78.6 (67.1-89.8)%
LR +	2.60 [0.49,14]
LR-	0.71 [0.33,1.50]

2 x 2 table – based on definition of abnormal biopsy as fibrosis or cirrhosis combined and ALT threshold of >40

	Reference test +ve	**Reference test -ve**
Index test +ve	TP: 2	FP: 1
Index test -ve	FN: 3	TN: 12

Summary statistic	
Pre-test probability/prevalence	27.8%
Sensitivity	40 (8.0-58.9)%
Specificity	92.3 (80.0-99.6)%
PPV	66.7 (13.4-98.2)%
NPV	80.0 (69.3-86.3)%
LR+	5.20 [0.60,45]
LR-	0.65 [0.31,1.35]

Author's conclusion

- SGPT was not a good predictor of liver damage

H.11.1.4 STUDY 4

Reference	Study type	Number of patients	Patient characteristics	Index test	Reference standard	Source of funding
P. Lenler-Petersen, H. Sogaard, K. Thestrup-Pedersen, and H. Zachariae. Galactose tolerance test and methotrexate-induced liver fibrosis and cirrhosis in patients with psoriasis. Acta Derm.Venereol. 62 (5):448-449, 1982. Ref ID: LENLERPETERSEN 1982	**Observational:** Case series **Retrospective** • **Patient selection** Setting = out-patient clinic Limited to those known to have developed fibrosis or cirrhosis Consecutive patients meeting the inclusion criteria during 1972-1981 (investigated previous paired test results) • **Index tests: LFTs –** time between tests unclear; pre-defined selection of threshold • **Reference standard:** biopsy grading unclear; all specimens assessed by one of 2 pathologists (experience and blinding unclear); biopsy sample size unclear • **Flow and timing:** Unclear time between tests; all patients included in the	N: 45 151 concurrent biopsy and tests	**Inclusion criteria:** Patients who have diagnosed psoriasis and MTX-induced liver fibrosis **Exclusion criteria:** none stated **Parameter** / **All (n=45)** Fibrosis: 22 Cirrhosis: 23 **Methotrexate schedule:** Not stated	**Liver function tests:** Galactose tolerance test (abnormal >3 g galactose excretion per litre of urine) 40 g galactose given orally to fasting patient and urine collecting during ensuing 8-h period	**Liver biopsy** **Histological techniques:** Biopsy by Menghini technique Assessed by one of 2 pathologists Tested at approximately 1-year intervals for biopsy and GTT Unclear how biopsies were classified/categorised	None stated

	analysis and all received LFTs					

Effect Size

Outcomes

Pre-test probability/prevalence
All had fibrosis or cirrhosis by last follow-up (100%)
At first comparative investigation 10 had fibrosis and 6 had cirrhosis (35.5%)

Summary of findings

Biopsy grade	**Number of biopsies**	**Galactose tolerance test**	
		Normal	**Abnormal**
Normal	46	43	3
Fibrosis	64	57	7
Cirrhosis	41	33	8

2 x 2 table – based on definition of abnormal biopsy as fibrosis or cirrhosis combined

	Reference test +ve	**Reference test -ve**
Index test +ve	TP: 15	FP: 3
Index test	FN: 90	TN: 43

-ve		

Summary statistic	
Pre-test probability/prevalence	69.5%
Sensitivity	14.3 (10.2-16.4)%
Specificity	93.5 (84.1-98.3)%
PPV	83.3 (59.5-95.5)%
NPV	32.3 (29.1-34.0)%
LR +	2.19 [0.67,7.20]
LR-	0.92 [0.82,1.02]

Author's conclusion

- Oral GTT is not sensitive enough to reveal methotrexate-induced liver fibrosis or cirrhosis

H.11.1.5 STUDY 5

Reference	Study type	Number of patients	Patient characteristics	Index test	Reference standard	Source of funding
J. Paramsothy, R. Strange, H. Sharif, M. Collins, P. Shaw, and C. M. Lawrence. The use of antipyrine clearance to measure liver damage in psoriatic patients receiving methotrexate. Br.J.Dermatol. 119 (6):761-765, 1988. Ref ID: PARAMSOTHY1988	**Observational:** Case control study (included group not receiving MTX, but they did not receive a biopsy) **Prospective** • **Patient selection** Unclear • **Index tests: LFTs –** time between tests unclear; pre-defined selection of threshold based on normal ranges • **Reference standard:** biopsy grading according to extent of fat, inflammatory cells per portal tract, fibrosis and liver cell necrosis; all specimens assessed blind by one pathologists (experience unclear); biopsy sample size unclear • **Flow and timing:** Unclear time between tests; all	N: 15	**Inclusion criteria:** Patients who have diagnosed psoriasis receiving MTX **Exclusion criteria:** none stated **Parameter** / **All (n=15)** % male: 60% Age, mean years: 48.3 (31-64) Cumulative MTX dose (mean): 2194 (992-4450) mg Alcohol consumption (mean, range): 3.5 (0-16) units/week On other medicines: 53.3%	**Liver function tests:** Plasma concentration of albumin and bilirubin and the activities of alkaline phosphatase (AP), aspartate aminotransferase (AST) and γ-glutamyl transferase (GGT) measured with a Sequential Multiple Analyser with Computer System	**Liver biopsy** **Histological techniques:** Biopsy technique unclear Examined and scored blind by a pathologist Assessment of fat, inflammatory cells per portal tract, fibrosis and liver cell necrosis (each graded 0-3 depending on severity)	None stated

	patients included in the analysis and all received LFTs except one for whom no GGT value was available		**Methotrexate schedule:** Not stated			

Effect Size

Outcomes

Pre-test probability/prevalence
Cases of fibrosis = 7/15 (46.7%)
Summary of findings

Patient number	**Liver biopsy score**					**Liver function tests**				
	Fatty change	**Infiltrate**	**Fibrosis**	**Necrosis**	**Total**	**Albumin (g/l)** *Ref range: 39-150*	**AP (u/l)** *Ref range: 45-120*	**AST (u/l)** *Ref range: 0-40*	**GGT (u/l)** *Ref range: 0-35*	**Bilirubin (µmol/l)** *Ref range: 0-17*
13	0	0	0	0	0	44	54	29	**77**	10
15	0	0	0	0	0	45	87	25	29	7
5	0.5	0	0	0.5	0.5	46	**151**	26	**142**	7
6	0.5	0	0	0.5	0.5	47	66	18	15	8
14	0.5	0	0	0	0.5	45	78	19	23	3
7	1	0	0	0	1	47	68	26	28	5

9	2	0	0	2	4	47	87	26	27	**19**
1	2	0.5	1	1	4.5	45	113	**44**	-	9
10	2	0	0.5	2	4.5	44	**168**	24	23	12
8	2	1	0	2	5	42	**208**	28	**162**	6
11	0	1	2	2	5	43	78	23	33	8
4	2	0.5	1	2	5.5	51	59	**57**	21	15
3	3	0	1	2	6	42	95	20	10	5
12	2	0.5	2	3	7.5	**30**	**225**	25	**85**	4
2	2	1	3	2	8	**36**	**186**	32	**38**	6

Note: no cases of cirrhosis were observed

ALB

2 x 2 table – based on definition of abnormal biopsy as any fibrosis or cirrhosis combined

	Reference test +ve	**Reference test -ve**
Index test +ve	TP: 2	FP: 0
Index test -ve	FN: 5	TN: 8

Summary statistic	
Pre-test probability/prevalence	46.7%
Sensitivity	29%
Specificity	100%
PPV	100 (21-100)%
NPV	62%
LR +	Infinity [0.31,101]
LR-	0.71 [0.44,1.19]

AP

2 x 2 table – based on definition of abnormal biopsy as fibrosis or cirrhosis combined

	Reference test +ve	**Reference test -ve**
Index test +ve	TP: 3	FP: 2
Index test -ve	FN: 4	TN: 6

Summary statistic	

Pre-test probability/prevalence	46.7%
Sensitivity	42.9 (14.1-65.6)%
Specificity	75.0 (49.9-94.9)%
PPV	60.0 (19.8-91.9)%
NPV	60.0 (39.9-75.9)%
LR +	1.71 [0.39,7.48]
LR-	0.76 [0.36,1.62]

AST

2 x 2 table – based on definition of abnormal biopsy as fibrosis or cirrhosis combined

	Reference test +ve	**Reference test -ve**
Index test +ve	TP: 2	FP: 0
Index test -ve	FN: 5	TN: 8

Summary statistic	
Pre-test probability/prevalence	46.7%
Sensitivity	29%

Specificity	100%
PPV	100 (21-100)%
NPV	62%
LR +	Infinity [0.31,101]
LR-	0.71 : [0.44,1.19]

GGT

2 x 2 table – based on definition of abnormal biopsy as fibrosis or cirrhosis combined

	Reference test +ve	**Reference test -ve**
Index test +ve	TP: 2	FP: 3
Index test -ve	FN: 4	TN: 5

Summary statistic	
Pre-test probability/prevalence	42.9%
Sensitivity	33.3 (6.7-65.8)%
Specificity	62.5 (42.5-86.8)%
PPV	40 (8.0-79.0)%

NPV	55.6 (37.8-77.2)%
LR +	0.89 [0.21,3.76]
LR-	1.07 [0.49,2.33]

Bilirubin

2 x 2 table – based on definition of abnormal biopsy as fibrosis or cirrhosis combined

	Reference test +ve	**Reference test -ve**
Index test +ve	TP: 0	FP: 1
Index test -ve	FN: 7	TN: 7

Summary statistic	
Pre-test probability/prevalence	46.7%
Sensitivity	0%
Specificity	88%
PPV	0 (0-87)%
NPV	50 [41%,58%]
LR +	0
LR-	1.14 [0.80,1.58]

Author's conclusion

- Standard liver function tests are a poor marker for histological liver damage

Liver scintigraphy and ultrasound scans

H.11.1.6 STUDY 6

Reference	Study type	Number of patients	Patient characteristics	Index test	Reference standard	Source of funding
R. G. Geronemus, R. Auerbach, and H. Tobias. Liver biopsies upsilon liver scans in methotrexate-treated patients with psoriasis. Arch.Dermatol. 118 (9):649-651, 1982. Ref ID: GERONEMUS1982	**Observational:** Retrospective case series • **Patient selection:** Psoriasis patients receiving long-term MTX therapy (unclear if included all relevant individuals/consecutive sample) • **Index tests: Liver scintigraphy: Tc 99m sulphur colloid liver scan –** Evaluated for commonly accepted pre-specified abnormalities • **Reference standard:** biopsy classification according Roenigk grading (grade IIIA-IV =	N: 24	**Inclusion criteria:** Psoriasis patients receiving long-term MTX therapy (at least 1 year) **Exclusion criteria:** concomitant diseases that might affect liver or reticuloendothelial system Baseline data: **% male**: 54% **Mean age**: 53 years (range 27-70)	**Liver scintigraphy:** Tc 99m sulphur colloid liver scan Evaluated for commonly accepted abnormalities each of which have been shown to correlate with histologically proved liver diseases: **heterogeneous uptake** (irregular distribution of Tc), **hepatomegaly** (width >18 cm and height >17cm), **extra hepatic uptake** (increased Tc distribution in spleen, bone marrow or lungs relative to liver),	**Liver biopsy** Graded by the Roenigk classification **Histological techniques:** Biopsy by Menghini technique Biopsy graded (according to Roenigk) 1. Normal or mild fatty infiltration,	None stated

	abnormal); unclear if blinded, who made the classification and size of biopsy sample • **Flow and timing:** Time between tests: 23/24 pairs performed within 2 weeks and one within a 2-month period while MTX therapy was continued (test order unclear); data available for all		**Methotrexate**: Administered in a 1-5 year period either once weekly intramuscular or orally (either once weekly or in divided doses during a 24-h period). Total MTX dose per patient: 800mg-4g	**focal defects** (areas of absent or minimal radioactive colloid uptake with surrounding tissue concentration) Positive = presence of any of the above abnormalities	nuclear variability and portal inflammation 2. Moderate to severe fatty infiltration, nuclear variability and portal inflammation and focal necrosis 3. Fibrosis (septum formation) 4.Cirrhosis	

Effect Size

Summary of findings

Biopsy grade	**Number of biopsies**	**Number of liver scans**		**Specific abnormalities**
		Normal	**Abnormal**	
1	13	8	5	1 hepatomegaly

				3 extra-hepatic uptake 1 extra-hepatic uptake, hepatomegaly and heterogeneous uptake
2	4	3	1	1 heterogeneous uptake
3	5	3	2	1 heterogeneous uptake 1 extra-hepatic uptake
4	2	0	2	2 extra-hepatic uptake and heterogeneous uptake

Note: both cases of cirrhosis were identified correctly

2 x 2 table – based on definition of abnormal biopsy as grade 3 or 4 (fibrosis or cirrhosis) combined

	Reference test +ve	**Reference test -ve**
Index test +ve	TP: 4	FP: 6
Index test -ve	FN: 3	TN: 11

Summary statistic	
Pre-test probability/prevalence	29.2%
Sensitivity	57.1 (22.7-86.7)%
Specificity	64.7 (50.5-76.9)%
PPV	40.0 (15.9-60.7)%

NPV	78.6 (61.3-93.3)%
LR +	1.62 [0.65,4.02]
LR-	0.66 [0.26,1.67]

Authors' conclusion:

Hepatotoxic reactions from long-term methotrexate use in psoriasis cannot be reliably evaluated by the Tc 99m sulphur colloid liver scan

H.11.1.7 STUDY 7

Reference	Study type	Number of patients	Patient characteristics	Index test	Reference standard	Source of funding
P. M. McHenry, E. A. Bingham, M. E. Callender, P. B. Delvin, M. D. O'Hara, W. R. Ferguson, J. D. Laird, and D. Burrows. Dynamic hepatic scintigraphy in the screening of psoriatic patients for	**Observational:** Retrospective case series • **Patient selection:** All psoriasis patients about to receive or receiving MTX therapy since 1981 (consecutive sample) • **Index tests:** Liver scintigraphy: Tc 99m sulphur colloid liver	N: 63 (23 had data while on MTX) 87 paired biopsy and DHS scans (49 prior to MTX and 38 during therapy)	**Inclusion criteria:** psoriasis patients about to receive or receiving MTX therapy with both biopsy and DHS since 1981 (max interval 4 weeks) **Exclusion criteria:** not stated Baseline data:	**Liver scintigraphy:** Tc 99m sulphur colloid liver scan Sequence of images taken (using gamma camera operated in conjunction with nuclear medicine computer) over an 80-s interval following Tc99 injection showing uptake of colloid in liver and spleen	**Liver biopsy** **Histological techniques:** Biopsy by Tru-Cut needle stained with H7E, reticulin, Masson trichrome, Perl's and orcein Fibrosis graded as none, very mild, mild (sparse	None stated

methotrexate-induced hepatotoxicity. Br.J.Dermatol. 127 (2):122-125, 1992. Ref ID: MCHENRY1992	scan – Evaluated for portal contribution (threshold <50%) • **Reference standard:** biopsy classification according Warin grading by a single independent pathologist, unclear size of biopsy sample • **Flow and timing:** Time between tests: max 4 weeks (test order unclear); data available for all		**% male**: 65% **Mean age**: 52 years (range 21-84) **Methotrexate**: Schedule unclear Mean cumulative MTX dose in 23 patients: 1.5 g (60mg-7g) and mean duration of MTX 32 months (1 month-9 years)	Analysis of time activity curves allows estimation of the proportion of the total colloid uptake represented by the portal venous contribution Positive = portal contribution of <50% of total hepatic uptake of colloid at 30s Threshold chosen based on reference range in 50 patients with no liver disease (mean portal contribution 64.4±11.7%)	interlobular), moderate (just bridging portal tracts) or severe (bridging portal tracts Abnormal = at least moderate Abnormal cut-off chosen because MTX may be continued in the presence of sparse intra-lobular fibrosis Biopsy performed prior to MTX and after every 1-1.5 g MTX (or at approximately yearly intervals)	
Effect Size **Summary of findings** • Sensitivity: 83.3% • Specificity: 81.5%						

- NPV: 98.5%
- PPV: 25%

2 x 2 table – based on definition of abnormal biopsy as grade 2 or 3 (portal fibrosis) and DHS threshold of <50% portal contribution

	Reference test +ve	**Reference test -ve**
Index test +ve	TP: 5	FP: 15
Index test -ve	FN: 1	TN: 66

Note: the one false negative result had a portal contribution of 51% so a 2% increase in the threshold would have allowed all patients with portal fibrosis to have been detected by DHS

Summary statistic	
Pre-test probability/prevalence	6.9%
Sensitivity	83.3 (38.0-99.1)%
Specificity	81.5 (78.1-82.6)%
PPV	25.0 (11.4-29.7)%
NPV	98.5 (94.4-99.9)%
LR +	4.50 [2.52,8.04]
LR-	0.20 [0.03,1.23]

Authors' conclusion:

Dynamic hepatic scintigraphy may therefore offer a means to reduce the number of liver biopsies necessary in patients receiving methotrexate for

psoriasis

H.11.1.8 STUDY 8

Reference	Study type	Number of patients	Patient characteristics	Index test	Reference standard	Source of funding
D. Mitchell, R. J. Johnson, H. J. Testa, N. Y. Haboubi, and R. Chalmers. Ultrasound and radionuclide scans - Poor indicators of liver damage in patients treated with methotrexate. Clin.Exp.Dermatol. 12 (4):243-245, 1987. Ref ID: MITCHELL1987	**Observational:** Prospective case series • **Patient selection:** Psoriasis patients receiving long-term MTX therapy (unclear if included all relevant individuals/consecutive sample) • **Index tests:** assessed without prior knowledge of liver histology or duration of MTX treatment **Liver scintigraphy: Tc 99m sulphur colloid liver scan –** Evaluated for pre-specified abnormalities by consultant in nuclear medicine **Ultrasound:** assessed by either a radiologist or a qualified ultrasound radiographer for signs of abnormality according to standard proforma • **Reference standard:** biopsy classification by one observer (experience unclear); unclear if blinding and size of biopsy sample	N: 49	**Inclusion criteria:** Psoriasis patients receiving long-term, low dose, once weekly oral MTX therapy requiring biopsy **Exclusion criteria:** not stated **Baseline data** **% male**: 53.1% **Median age**: 46 years (range 22-69) **Cumulative dose** MTX: median 2.8 g (0.5-10 g) **Median duration of MTX therapy**: 5.3	**A. Liver scintigraphy:** Tc 99m sulphur colloid liver scan (Tc99 given intravenously 10 min before scan) Consultant in nuclear medicine evaluated anterior, posterior and lateral views for: size of liver and spleen, pattern of uptake in these organs and degree of extrahepatic uptake Positive = presence of any of the above abnormalities **B. Ultrasound** Examination carried out by one of two operators (radiologist or a qualified ultrasound radiographer);	**Liver biopsy** **Histological techniques:** Biopsy by Menghini technique; staining with H&E, periodic acid Schiff, Perl's stain for iron, reticulin fibre stain and haematoxylin picrosirus red Biopsy graded as: 1.Normal 2.Fatty change (steatosis) alone	None stated

	• **Flow and timing:** Time between tests: scans performed 1 day prior to biopsy; data available for all		years (range: 1-13) **Methotrexate**: long-term, low dose, once weekly oral MTX therapy	scan images obtained at 1-cm intervals through the liver in 2 planes Assessed for liver size, shape, echo pattern and information about the biliary and vascular system according to a standard proforma	3.Inflammatio n 4. Fibrosis (graded mild, moderate or severe) 5. Cirrhosis	

Effect Size

Summary of findings: ultrasound

Biopsy grade	**Number of biopsies**	**Number of liver scans**	
		Normal	**Abnormal**
Normal	13	12	1
Steatosis alone	7	6	1
Inflammation	17	14	3
Fibrosis	9	9	0
Cirrhosis	3	3	0

Note: ultrasound failed to detect any of those with fibrosis or cirrhosis

2 x 2 table – based on definition of abnormal biopsy as fibrosis or cirrhosis combined

	Reference test +ve	**Reference test -ve**
Index test +ve	TP: 0	FP: 5
Index test -ve	FN: 12	TN: 32

Summary statistic	
Pre-test probability/prevalence	24.5%
Sensitivity	0%
Specificity	86%
PPV	0%
NPV	73%
LR +	0
LR-	1.16 [0.95,1.33]

Summary of findings: scintigraphy

Biopsy grade	Number of biopsies	Number of liver scans		Specific abnormalities detected on scan
		Normal	Abnormal	
Normal	13	9	4	Mostly patchy tracer uptake No splenomegaly or extra-hepatic uptake
Steatosis alone	7	6	1	
Inflammation	17	12	5	-
Fibrosis	9	5 – mild fibrosis	4 – moderate fibrosis	5 splenomealy 3 patchy tracer uptake 2 increased extra-hepatic uptake
Cirrhosis	3	1	2	

2 x 2 table – based on definition of abnormal biopsy as fibrosis or cirrhosis combined

	Reference test +ve	Reference test -ve
Index test +ve	TP: 6	FP: 10
Index test -ve	FN: 6	TN: 27

Summary statistic	

Pre-test probability/prevalence	24.5%
Sensitivity	50.0 (24.2-74.9)%
Specificity	73.0 (64.6-81.1)%
PPV	37.5 (18.2-56.2)%
NPV	81.8 (72.4-90.9)%
LR +	1.85 [0.85,4.02]
LR-	0.69 [0.38,1.25]

Authors' conclusion:

Hepatotoxic reactions from long-term methotrexate use in psoriasis cannot be reliably evaluated by the Tc 99m sulphur colloid liver scan or by ultrasound scan, so these cannot replace biopsy

H.11.1.9 STUDY 9

Reference	Study type	Number of patients	Patient characteristics	Index test	Reference standard	Source of funding
I. H. Coulson, J. Mckenzie, V. S. Neild, A. E. Joseph, and R. A. Marsden. A comparison of liver ultrasound with liver biopsy histology in psoriatics receiving long-term methotrexate therapy. Br.J.Dermatol. 116 (4):491-495, 1987. Ref ID: COULSON1987	**Observational:** Prospective case series • **Patient selection:** Psoriasis patients receiving or about to receive MTX (unclear if included all relevant individuals/consecutive sample) • **Index test** **Ultrasound:** assessed by experienced radiologist for signs of fatty change and fibrosis (according to pre-defined echo pattern) Assessed blind to clinical details • **Reference standard:** biopsy classification by one observer (experience unclear);performed before scans so no need for blinding; 5µm sections	N: 28 54 paired observations (7/54 were pre-MTX)	**Inclusion criteria:** Severe psoriasis patients receiving or about to receive MTX **Exclusion criteria:** not stated **Baseline data** **% male**: 71.4% **Age**: range 30-74 **Methotrexate schedule:** once-weekly oral dose	**Ultrasound** Examination carried out by an experienced radiologist; scan images obtained using a 3.5 or 5 mHz transducer by a single experience operator unaware of clinical details Graded as normal or abnormal (fatty change and/or fibrosis) **Fatty change** identified by hyper-echoic liver tissue with fine packed echoes **Fibrosis without fatty change** = coarse echo	**Liver biopsy** at least 5 days after last MTX dose **Histological techniques:** Biopsy by Tru-Cut needle; 5µm sections cut and stained with haematoxylin and van Gieson stain **Grading** Subjective microscopic assessment based on method of Warin et al of fat, inflammation, fibrosis (each graded 0, 0.5, 1, 2, or 3) and cirrhosis (not graded)	None stated

	sampled • **Flow and timing:** Time between tests: scans performed within 1 month of biopsy; data available for all			pattern **Fibrosis with fatty change** (difficult to identify) = coarse echoes (pin-head echoes) within the fine echo pattern of fatty change		

Effect Size

Summary of findings: ultrasound

Biopsy grade	**Number of biopsies**	**Number of liver scans**		
		Normal	**Steatosis**	**Fibrosis**
Normal	11	9	2	0
Steatosis ± inflammation	17	5	12	0
Mild fibrosis (intralobular)	6	4	2	0
Marked fibrosis	20	0	15	5

(portal)				
Cirrhosis	0	0	0	0

Note: no cases of cirrhosis

2 x 2 table – based on definition of abnormal biopsy as any degree of fibrosis or cirrhosis combined and abnormal ultrasound as showing fibrosis (not fatty change)

	Reference test +ve	**Reference test -ve**
Index test +ve	TP: 5	FP: 0
Index test -ve	FN: 21	TN: 28

Summary statistic	
Pre-test probability/prevalence	48.2%
Sensitivity	19.0%
Specificity	100%
PPV	100 (39-100)%
NPV	57%
LR +	Infinity [0.69,204]
LR-	0.81 [0.67,0.99]

2 x 2 table – based on definition of abnormal biopsy as portal fibrosis (in accordance with Roenigk criteria) or cirrhosis combined and abnormal ultrasound as showing fibrosis (not fatty change)

	Reference test +ve	**Reference test -ve**
Index test +ve	TP: 5	FP: 0
Index test -ve	FN: 15	TN: 34

Summary statistic	
Pre-test probability/prevalence	37.0%
Sensitivity	25.0%
Specificity	100.0%
PPV	100% (39-100)%
NPV	69%
LR +	Infinity [1.07,315]
LR-	0.75 [0.58,0.97]

Authors' conclusion:

- No patient with a normal ultrasound scan showed significant fibrosis and thus such patients may be spared liver biopsy and safely continue with methotrexate therapy.
- Ultrasound cannot reliably distinguish between fatty change and fibrosis, so all patients with abnormal scans require liver biopsy

H.11.2 PIIINP

H.11.2.1 STUDY 10

Reference	Study type	Number of patients	Patient characteristics	Index test	Reference standard	Source of funding
M. J. Boffa, A. Smith, R. Chalmers, D. Mitchell, B. Rowan, T. W. Warnes, M. Shomaf, and N. Y. Haboubi. Serum type III procollagen aminopeptide for assessing liver damage in methotrexate-treated psoriatic patients. Br.J.Dermatol. 135 (4):538-544, 1996. Ref ID: BOFFA1996	**Observational:** Prospective case series and case control study • **Patient selection:** Unclear if a random or consecutive sample was taken • **Index tests: PIIINP –** serum sample immediately prior reference standard (unclear when analysed); unclear method of selection of threshold) • **Reference standard:** biopsy classification; 2 observers blinded to MTX dose (experience unclear); biopsy sampling unclear	N: 87 147 paired liver biopsies and serum samples	**Inclusion criteria:** Long-term low-dose once weekly oral MTX for severe psoriasis; 1 or more biopsies with simultaneous serum sampling **Exclusion criteria:** Not stated **Parameter** / **Treated (n=87)** Median age – years at first biopsy: 50 (22-75) Cumulative MTX dose at first biopsy, median (range): 2.2 (0.3-10.0) g Duration of treatment at	PIIINP (^{125}I) – Orion Diagnostica Serum samples collected at least 5 days after last dose of MTX and immediately prior to liver biopsy Samples stored at -20°C until analysis Abnormal values of PIIINP >4.2 ng/ml **BUT** in 3 control groups (normal enzyme levels and no history/clinical features of liver disease the reference ranges were:	Hepatotoxicity by histology score – assessed blind to MTX dose by 2 assessors **Histological techniques:** Biopsy by Menghini technique; staining with H&E, periodic acid Schiff, Perl's stain for iron, orcein, Hep B surface antigen and metallothionein, untoned reticulin and haematoxylin/picrosirius red for collagen **Grading**: 1. Normal histology 2. Steatosis alone 3. Inflammation (±steatosis) without fibrosis 4. Fibrosis (±steatosis ± inflammation)	Skin disease research fund

	• **Flow and timing:** Tests taken immediately after each other (index test first); all received both index and reference tests		first biopsy, median weeks (range) **Methotrexate**: Long-term low-dose once weekly oral MTX	1. 17 healthy patients with non-inflammatory skin disorders: 1.6-4.9 ng/ml 2. 18 people with moderate-severe psoriasis with no history of systemic treatment: 2.1-4.7 ng/ml 3. 11 PsA with no MTX use: 2.2-4.6 ng/ml	5. Cirrhosis	

Effect Size

Outcomes

Summary of findings

Pre-test probability/prevalence: 21/87 (24.1%)

Biopsy grade	**Number of biopsies**	**Number with raised PIIINP**
Normal	28	5 (18%)

Steatosis	12	5 (42%)
Inflammation	26	14 (54%)
Fibrosis	18	14 (78%)
Cirrhosis	3	3 (100%)

Note: all cases of cirrhosis were identified correctly; proportion with raised PIIINP increased with increasing severity of histological damage

Based on single biopsy specimen – **fibrosis**: sensitivity = 81%; specificity = 62%

Based on all 147 paired observations – **fibrosis**: sensitivity = 77%; specificity = 66%

2 x 2 table – based on definition of abnormal biopsy as fibrosis or cirrhosis combined (data from time of first biopsy only)

	Reference test +ve	**Reference test -ve**
Index test +ve	TP: 17	FP: 24
Index test -ve	FN: 4	TN: 42

Summary statistic	
Pre-test probability/prevalence	24.1%
Sensitivity	81.0 (60.3-93.5)%

Specificity	63.6 (57.1-67.6)%
PPV	41.5 (30.9-47.9)%
NPV	91.3 (81.9-97.0)%
LR +	2.23 [1.52,3.26]
LR-	0.30 [0.12,0.74]

Authors' conclusion:

PIIINP-O is of value in detecting liver damage and, particularly if measured serially, may reduce the need for liver biopsy in MTX-treated patients. Although the test does not detect all patients with fibrosis, it would appear that the risk of missing significant liver damage in patients with persistently normal PIIINP-O is low

H.11.3 STUDY 11

Reference	Study type	Number of patients	Patient characteristics	Index test	Reference standard	Source of funding
H. Zachariae, L. Heickendorff, and H. Sogaard. The value of amino-terminal propeptide of type III procollagen in routine screening for methotrexate-induced liver fibrosis: a 10-year follow-up. Br.J.Dermatol. 144 (1):100-103, 2001. Ref ID: ZACHARI	**Observational:** Retrospective case series (follow-up 1-11 years) • **Patient selection:** Unclear if a random or consecutive sample was taken; psoriasis patients on MTX in 1989-90 • **Index tests: PIIINP –** all had at least 2 assays prior to or at time of biopsy and all but one had at least 3 analyses within a year around the time of the biopsy (unclear when analysed); unclear method of selection of threshold) • **Reference standard:** biopsy classification; unclear who assessed and unclear if blind to ref standard (experience unclear); biopsy sampling unclear • **Flow and timing:**	N: 70 189 biopsies and 329 PIIINP analyses	**Inclusion criteria:** psoriasis patients on MTX in 1989-90; studied with both biopsy and PIIINP; initial biopsy and PIIINP normal and continued to take MTX **Exclusion criteria:** Not stated **Parameter** / **All (n=70)** % male: 55.7% Cumulative MTX dose at latest biopsy, mean (range): 3.5 (0.6-16.8) g Duration of treatment at first biopsy, mean years (range): 4 (1-20) PsA: 27 (38.6%)	PIIINP (^{125}I) – Orion Diagnostica Abnormal values of PIIINP >4.2 ng/ml **Note**: serial analyses of PIIINP were performed; therefore not a 1:1 relationship with biopsies. Those who tested positive on both tests could also have had several negative PIIINP tests within a year of a positive biopsy	Fibrosis on biopsy **Histological techniques:** Biopsy by Menghini technique; staining with H&E, van Gieson and Masson's trichrome stain **Grading**: Unclear classification system, only fibrosis reported	None stated

AE2001	all received both index and reference tests, but order unclear and all received more index test analyses than reference standards 1 patient excluded after finding a positive biopsy result had been found prior to 1989		**Methotrexate**: Dosing regimen not stated			

Effect Size

Outcomes

Only 2/6 showed increased PIIINP without either biopsy verified liver fibrosis or verified PsA (one of the false positives had PsA)

2 x 2 table –fibrosis (note: a positive result on the index test was based on at least 1 elevated PIIINP reading, but among the serial analyses at least one could also have been normal, but data on this are not reported, although the 4 true positives all had 2 elevated PIIINP tests)

	Reference test +ve	**Reference test -ve**
Index test +ve	TP: 4	FP: 2
Index test -ve	FN: 0	TN: 63

Summary statistic	
Pre-test probability/prevalence	5.8%
Sensitivity	100%
Specificity	97%
PPV	66% [30%,84%]
NPV	100%
LR +	32 (6.80,83)
LR-	0 (0.01,1.44)

Authors' conclusion:

As long as PIIINP is consistently normal in serial investigations there is minimal risk of development of substantial liver fibrosis

H.11.3.1 STUDY 12

Reference	Study type	Number of patients	Patient characteristics	Index test	Reference standard	Source of funding
P. D. Maurice, A. J. Maddox, C. A. Green, F. Tatnall, J. K. Schofield, and D. J. Stott. Monitoring patients on methotrexate: hepatic fibrosis not seen in patients with normal serum assays of aminoterminal peptide of type III procollagen. Br.J.Derm	**Observational:** Retrospective case series • **Patient selection:** All dermatology patients in 3 adjacent dermatology departments undergoing MTX treatment entered into a database established in 1999 (consecutive sample) • **Index tests: PIIINP –** serial analyses before and after biopsy; unclear if blinded to biopsy grade but should be objective; prior selection of threshold according to laboratory normal range) • **Reference standard:**	N: 34 70 biopsies and 306 PIIINP analyses	**Inclusion criteria:** dermatology patients on MTX before or after the database was established who had both serial PIIINP assays and at least one liver biopsy **Exclusion criteria:** Not stated **Parameter** / **All (n=34)** % male: 68% Median age at latest biopsy: 50.5 (21-81) years Weekly MTX dose at latest biopsy, median (range): 2740 (150-23,955) mg Cumulative MTX dose at latest biopsy, median (range): 15 (0-30) mg/wk	PIIINP (^{125}I) – Orion Diagnostica Abnormal values of PIIINP >4.2 ng/ml Serum samples sent to biochemistry laboratory where PIIINP assays were performed using the radioimmunoassay Laboratory normal range is 1.2-4.2 ug/l **Note**: serial analyses of PIIINP were performed; therefore not a 1:1 relationship with biopsies. PIIINP assays performed at 3-mothnly intervals	Fibrosis on biopsy **Histological techniques:** Biopsy by percutaneous route using ultrasound control with an 18 gauge Biopince needle; staining with H&E and van Gieson for fibrosis; reticulin for liver architecture; Perl's stain, periodic acid –Schiff and orcein stain used on most biopsies **Grading**: According to Roenigk classification (abnormal = Grade IIIA-IV) Assessed by one	R&D group of West Hertfordshire Hospitals NHS trust

atol. 152 (3):451-458, 2005. Ref ID: MAURICE 2005	biopsy classification according to Roenigk grade; single blinded pathologist (experience unclear); biopsy sampling by 18 gauge needle • **Flow and timing:** all received both index and reference tests, and all received more index test analyses than reference standards (some before and some after ref test); some biopsies excluded if not within right time frame relative to assays		Duration of treatment, mean years (range): 0.5-20 y Psoriasis: 33 (97%) Pemphigus foliaceus: 1 (3%) Mean (SD) body weight: Male: 87.6 (18.2) kg; Female: 70.3 (14.5) kg No alcohol intake: 71% (the median intake for 29% was 5 units/week (range: 1-21) Inflammatory arthritis: 22% **Methotrexate**: Oral once weekly dosing	Selected data on all biopsies where PIIINP assays had been performed within 12 months (6 months preceding and 6 months following) of biopsy to compare assay levels with biopsy grade Note: not all 70 biopsies included because some were not at the mid-point of the series of assays	pathologist blind to MTX dose and PIIINP values	

Effect Size

Outcomes

Summary of findings

Pre-test probability/prevalence: 8/70 biopsies (11.4%); 5/34 patients (14.7%)

Biopsy grade	Number of biopsies	Number with raised PIIINP
I	91	16 (18%)
II	60	33 (55%)
Fibrosis	15	24 (62%)
Cirrhosis	0	0

Note: Some biopsies counted more than once as paired with more than one PIIINP assay

Numbers of biopsies and contemporaneous PIIINP assays

Proportion PIIINP abnormal	Roenigk grade

	I	II	IIIA/B
None	15	5	20
<50%	4	2	8
≥50%	5	2	8
All	0	7	10
Total	24	16	46

Note: 3 liver biopsies in 2 morbidly obese patients who also had maturity-onset diabetes were graded II on Roenigk classification but showed signs of NASH (rather than portal fibrosis which is more often associated with MTX)

Note: 6 grade II biopsies were from 4 patients with inflammatory arthritis; 4 of these biopsies had elevated PIIINP in **all** associated readings; the other two biopsies had **some** abnormal PIIINP readings

2 x 2 table –fibrosis (note: PIIINP and biopsy not matched 1:1 and more than one result per patient; based on 46 biopsies with contemporaneous PIIINP assays [number of PIIINP assays per biopsy ranged from 2 to 6])

	Reference test +ve	**Reference test -ve**
Index test +ve	TP: 15	FP: 49
Index test -ve	FN: 9	TN: 102

Summary statistic	
Pre-test probability/prevalence	13.7%

Sensitivity	62.5 (42.1-79.8)%
Specificity	67.5 (64.3-70.3)%
PPV	23.4 (15.8, 29.9)%
NPV	91.9 (87.5, 95.6)%
LR +	1.93 (1.31,2.83)
LR-	0.56 (0.33,0.94)

Authors' conclusion:

- Follow-up liver biopsies for patients on long-term low-dose methotrexate can be avoided if PIIINP levels are consistently normal.
- The PIIINP assay will also be helpful in the management of patients on methotrexate in whom liver biopsy is contraindicated, and in patients with nonalcoholic steatohepatitis

H.11.3.2 STUDY 13

Reference	Study type	Number of patients	Patient characteristics	Index test	Reference standard	Source of funding
J. Risteli, H. Sogaard, A. Oikarinen, L. Risteli, J. Karvonen, and H. Zachariae. Aminoterminal propeptide of type III procollagen in methotrexate-induced liver fibrosis and cirrhosis. Br.J.Dermatol. 119 (3):321-325, 1988. Ref ID: RISTELI1988 H. Zachariae, H. Sogaard, and L. Heickendorff. Serum aminoterminal propeptide of type III procollagen. A non-invasive test for liver fibrogenesis in methotrexate-treated psoriatics. Acta Derm.Venereol. 69 (3):241-244, 1989. Ref ID: ZACHARIAE1989	**Observational:** Prospective case control study (included untreated group with no biopsy measurement) • **Patient selection:** Unclear if a random or consecutive sample was taken (state it represents their total experience with PIIINP) • **Index tests: PIIINP –** unclear if performed blind but should be objective; prior selection of threshold • **Reference standard:** biopsy classification; assessed by single pathologist blind to clinical and laboratory data (experience unclear); biopsy sampling unclear • **Flow and timing:**	N: 24 for pilot and 73 for full study (including the original 24)	**Inclusion criteria:** psoriasis patients on MTX for at least 6 months, no more than slight fibrosis before MTX **Exclusion criteria:** Not stated **Parameter** / **Pilot group (n=24)** Median age (range): 50 (32-75) % male: 56.3% Duration of treatment, mean years (range): 7.6 (0.5-20) PsA: 11 (45.8%) PP: 3 (12.5%)	PIIINP Stored at -20°C and measured by radioimmunoassay based on human propeptide Abnormal values of PIIINP >4.2 ng/ml (based on 88 Finnish blood donors) Serial PIIINP performed in 11 patients (one in pilot study)	Hepatotoxicity on biopsy Biopsies taken at 1-2 year intervals while on MTX (used biopsy closest to time of PIIINP measurement) **Histological techniques:** Biopsy by Menghini technique; staining with H&E, periodic acid Schiff, van Gieson and Masson's trichrome stain, Perl's stain for iron, reticulin fibre stain **Grading**: Unclear classification system, included normal, pronounced steatosis, slight fibrosis, fibrosis, cirrhosis	None stated

	all received both index and reference tests (except one in full study who refused biopsy), but order unclear and time between tests unclear (used biopsy closest to time of PIIINP measurement)		**Note:** baseline data not available for full group **Methotrexate**: Weekly divided oral dose of 5 mg with 12-h intervals once weekly			

Effect Size

Outcomes

Summary of findings in pilot study (N=24)

Diagnosis	**PIIINP (ug/l)**	**Liver histology**
PsA	**7.6**	Steatosis
Pustular psoriasis	**7.4**	Fibrosis
Psoriasis	**7.2**	Fibrosis
PsA	**5.9**	Fibrosis
PsA	**?**	Cirrhosis

	PsA	**4.8**	Fibrosis
	PsA	**4.6**	Fibrosis
	Psoriasis	**4.5**	Fibrosis
	PsA	**4.3**	Cirrhosis
	Psoriasis	4.1	Fibrosis
	Pustular psoriasis	4.1	Fibrosis
	PsA	3.9	Normal
	Psoriasis	3.7	Slight fibrosis
	Pustular psoriasis	3.5	Slight fibrosis
	Psoriasis	3.5	Normal
	Psoriasis	3.4	Cirrhosis
	PsA	3.4	Normal
	Psoriasis	3.4	Normal
	Psoriasis	3.1	Fibrosis
	PsA	3.1	Normal
	PsA	3.0	Normal
	Psoriasis	3.0	Normal
	Psoriasis	2.8	Normal
	PsA	2.7	Normal

2 x 2 table –fibrosis and cirrhosis combined

	Reference test +ve	**Reference test -ve**
Index test +ve	TP: 9	FP: 1
Index test -ve	FN: 6	TN: 9

Pre-test probability/prevalence	60%
Sensitivity	60.0 (41.0-66.3)%
Specificity	90.0 (61.6-99.5)%
PPV	90.0 (61.6, 99.5)%
NPV	60.0 (41.0, 66.3)%
LR +	6.0 (0.89, 40)
LR-	0.44 (0.23, 0.85)

Subgroup analysis for PsA and non-PsA populations

2 x 2 table –fibrosis and cirrhosis combined - no PsA

	Reference test +ve	Reference test -ve
Index test +ve	TP: 3	FP: 0
Index test -ve	FN: 6	TN: 4

Pre-test probability/prevalence	69.2%
Sensitivity	33.0%
Specificity	100%
PPV	100 (33-100)%
NPV	40%
LR +	Infinity
LR-	0.67

2 x 2 table –fibrosis and cirrhosis combined - PsA

	Reference test +ve	Reference test -ve
Index test +ve	TP: 4	FP: 1
Index test -ve	FN: 0	TN: 5

Pre-test probability/prevalence	40%
Sensitivity	100%
Specificity	83%
PPV	80 (40-92)%
NPV	100%
LR +	6.00 [0.99,18]
LR-	0.00 [0.01,1.82]

Summary of findings in full study (N=72 including original 24)

2 x 2 table –fibrosis and cirrhosis combined

	Reference test +ve	**Reference test -ve**
Index test +ve	TP: 19	FP: 1
Index test -ve	FN: 6	TN: 46

Summary statistic	
Pre-test probability/prevalence	34.7%
Sensitivity	76.0 (61.8-79.8)%
Specificity	97.9 (90.3-99.9)%
PPV	95.0 (77.2, 99.7)%
NPV	88.5 (81.6, 90.3)%
LR +	36 (5.07,251)
LR-	0.25 (0.12,0.49)

Authors' conclusion:

The study indicates that PIIINP can be utilized as a valuable non-invasive marker of fibrogenesis in the liver. This analysis is not specific for the liver, but it seems that the number of liver biopsies probably can be reduced in people with psoriasis on methotrexate who have normal levels of PIIINP

H.11.4 Fibrotest and Fibroscan

H.11.4.1 STUDY 14

Reference	Study type	Number of patients	Patient characteristics	Index test	Reference standard	Source of funding
M. A. Berends, J. Snoek, E. M. de Jong, J. H. Van Krieken, R. J. de Knegt, M. G. van Oijen, P. C. van de Kerkhof, and J. P. Drenth. Biochemical and biophysical assessment of MTX-induced liver fibrosis in psoriasis patients: Fibrotest predicts the presence and Fibroscan predicts the absence of significant liver	**Observational:** Retrospective case series • **Patient selection:** unclear, only 34 contacted and 24 agreed • **Index tests:** **Fibrotest–** Measurements were performed immediately on fresh obtained samples using validated methods; pre-defined selection of threshold) **Fibroscan –** performed on the same day as the	N: 24	**Inclusion criteria:** of all 60 psoriasis patients on MTX treatment at the end of 2005 those who had biopsy and fibrotest and fibroscan within 18 months as part of their regular MTX monitoring **Exclusion criteria:** Not stated **Parameter** / **All (n=24)** % male / 45.8% Mean age / 55 (34-73) Cumulative MTX dose (range) / 3352 (314-	**Fibrotest and Fibroscan** **Fibrotest** is an artificial intelligence alogorithm consisting of a biochemical fibrosis index using inputs from 5 serum markers (g-GT, bilirubin, a2-macroglobulin apolipoprotien A1 and heptoglobin) and is corrected for age and sex leading to a composite value between 0 and 1 to determine the presence of significant liver fibrosis Measurements performed immediately on fresh	Hepatotoxicity by histology score – all biopsies assessed blind by 2 investigators and verified by an experienced pathologist (disagreements resolved by consensus) **Histological techniques:** Biopsy by Menghini technique (1.6 mm needle); staining with H&E, von Gieson **Grading**: Metavir system F0 = no fibrosis F1 = portal fibrosis without septa F2 = portal fibrosis with few septa F3 = numerous septa without cirrhosis	None stated

fibrosis. Liver International 27 (5):639-645, 2007. Ref ID: BERENDS2007B	biological parameters input to Fibrotest; used the median value of successful measurements • **Reference standard:** biopsy classification; 2 independent observers and verified by an experienced pathologist (disagreements resolved by consensus = difficult to diagnose cases included); biopsy sampling by 1.6 mm needle • **Flow and timing:** Time between tests up to 18 months; all received Fibrotests and Fibroscan but only 20 had evaluable scans; it failed in four people with obesity			20235) mg Follow-up, median weeks (range): 346 (111-2162) Median BMI (range): 26 (20-38) kg/m^2 N overweight (BMI>25): 14 N alcohol consumption: 10 (1 excessive >14U/wk) Diabetes: 4 Note: all patients underwent a liver biopsy after a median dosage of 1635 mg MTX (range 162–2354 mg). Only one patient had elevated liver enzymes more than twice the ULN. Sixteen patients were biopsied before treatment. **Methotrexate**:	obtained samples using validated methods The quantitative output estimate of liver fibrosis stage corresponds to stages F0-F4 of metavir scale Based on the literature a cut-off of 0.31 was chosen to identify Metavir ≥F2 **Fibroscan** measures liver elasticity using 1 dimensional transient elastography, as the liver stiffness roughly correlates with the degree of hepatic fibrosis (a fine correlation has been established between significant fibrosis (Metavir F2) and Fibroscan outcome It uses an ultrasound transducer that generates vibrations that cause a slow elastic shear wave. The propagation and velocity of	F4 = cirrhosis	

			Dosing unclear	the wave in the liver are tracked by pulse-echo ultrasound and correlate to tissue stiffness. Measurements were performed on the right lobe of the liver, at the same target area for liver biopsy. The procedure was performed through the intercostals space while the patients were lying on their backs with their arms in maximal abduction behind their heads. Conducted by an experienced physician blinded to histological outcome Each patient underwent a series of 10 validated electrographic measures. A cut-off value of 7.1 kPa was chosen to identify significant fibrosis (≥F2) Only procedures with 10 validated measurements and a success rate of at		

				least 60% were considered to be reliable.		

Effect Size

Outcomes

Summary of findings

Pre-test probability/prevalence (at least F2): 6/24 (25%)

Biopsy grade	**Number of people**
F0	5
F1	13
F2	4
F3	1
F4	1

Test accuracy as reported in study (not possible to derive 2x2 table for Fibroscan from the text)

	Fibrotest **≥F2**	**Fibroscan** **≥F2**

Optimal cut-off	0.31	7.1 kPa
Sensitivity (%)	83	50
Specificity (%)	61	88
Negative predictive value (%)	92	86
Positive predictive value (%)	42	33

Note: 16 people had more than one biopsy and unclear if analysed on a per-patient basis

Fibrotest 2 x 2 table – (at least F2)

	Reference test +ve	**Reference test -ve**
Index test +ve	TP: 5	FP: 7
Index test -ve	FN: 1	TN: 11

Summary statistic	
Pre-test probability/prevalence	25%
Sensitivity	83.3 (40.8-99.1)%
Specificity	61.1 (46.9-66.4)%
PPV	41.7 (20.4-49.6)%

NPV	91.7 (70.4-99.6)%
LR +	2.14 [1.08,4.23]
LR-	0.27 [0.04,1.69]

Discordance between fibrotest and fibroscans

- In nine patients, Fibroscans and Fibrotest resulted in different Metavir scores with a discordance of two stages. In four of them, the total Fibroscans procedure failed because of the presence of obesity. In the remaining five, biopsy length was significantly shorter compared with the biopsy length of the remaining patients. There was no significant difference in BMI between those patients. Other potential confounders for failure of Fibrotest such as Gilbert, haemolysis and acute inflammation were ruled out.

Authors' conclusion:

Fibrotest seems to be good in detecting and the Fibroscans seems to be good in excluding significant MTX-induced liver fibrosis (FZ2) in patients with psoriasis treated with MTX. This suggests that the combined use of Fibrotest and Fibroscans may be beneficial in establishing the grade of liver fibrosis in MTX-induced liver fibrosis in psoriasis patients

H.12 Methotrexate and monitoring for hepatotoxicity

H.12.1 Case Series

H.12.1.1 STUDY 1

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
R. E. Ashton, G. H. Millward-Sadler, and J. E. White. Complications in methotrexate treatment of psoriasis with particular reference to liver fibrosis. J.Invest.Dermatol. 79 (4):229-232, 1982. Ref ID: ASHTON19	**Observational:** Retrospective case series	N: 38	**Inclusion criteria:** Patients taking MTX for psoriasis **Exclusion criteria:** No follow-up biopsy, any signs of fibrosis on pre-treatment biopsy **Parameter** / **All (n=38)** Mean age – years: 53 Gender M/F (%): 45/55 Cumulative MTX dose (MG), mean (range): 1928 (800-5500)	**Methotrexate**: Oral or intramuscular, up to 30 mg weekly, fortnightly or every 10 days Mean total cumulative dose: 1928 mg (range: 800-5500 mg) **Histological techniques:** Biopsy by a right lateral technique; staining with H&E, Pearl's Prussian blue, periodic acid-Schiff, orcein	Mean treatment duration: 32.7 weeks (range: 12-102 weeks)	Hepatotoxicity: **fatty change** (1-4 scale), **fibrosis** (mild: foci of reticulin proliferation scattered throughout the lobules or occasionally adjacent to portal tracts; moderate: more extensive enlargement of portal tracts seen by reticulin or presence of	Not mentioned

82			Duration of treatment (mean): 32.7 months Oral MTX: 25 Intramuscular MTX: 7 Oral then intramuscular route: 6 Heavy alcohol intake (n): 8	and non-gold-toned reticulin (trichrome and Van Giesen preparations did not detect all fibrosis) Each biopsy initially assessed blind, further assessment included comparison with previous biopsies **Definitions** Alcohol intake 1. Occasional: <25 g/week 2. Moderate: 25-100 g/week 3. Heavy: >100 g/week **Prognostic factors:** alcohol, cumulative dose **Confounders** In those who developed hepatotoxicity: - duration of treatment mean 28.3 (range 16-38) months;		mature collagen; or severe: linking of portal tracts usually with extension of fibrous spurs) or **cirrhosis**	

				- mean MTX dose 1954 mg (range 1060-3375 mg); - average monthly dose 70 (range 41-112.5 mg) - mean age 57.4 (range 30-77) years			

Effect Size

Outcomes

Summary

- **Alcohol consumption is a risk factor for hepatotoxicity**
  - Of 8 heavy drinkers, 4 developed fibrosis or cirrhosis (50%); none of these had evidence of significant fibrosis on initial biopsy
  - Of 30 non-heavy drinkers 5 developed fibrosis or cirrhosis (16.7%)
  - Of the 9 patients who developed hepatotoxicity, 4 showed significant progression of fibrosis; of these 4 only one developed cirrhosis, and this patient had moderate/heavy alcohol intake
  - Of the 9 patients who developed hepatotoxicity, 3 showed classical features of alcoholic hepatitis
  - Of the 9 patients who developed hepatotoxicity 4 were heavy drinkers and 1 was a moderate drinker:

Age (years)	Alcohol	Route	Duration of	MTX dose (mg)

	consumption		treatment (months)	Total	Mean/month
77	1	Oral	16	1060	66.2
56	3	Oral-IM	26	1300	50.0
66	1	Oral	31	1300	41.9
54	1	Oral	21	1367	65.1
66	2	Oral	36	1950	54.2
54	3	Oral	38	2080	54.7
56	3	Oral	30	2500	83.3
58	1	IM	26	2655	102.1
30	3	Oral	30	3375	112.5

Cumulative dose of MTX

Group	N	Total MTX dose (mg)	Mean dose per month
Total	38	1928	59.0
Fibrosis	9	1955	69.3
No fibrosis	29	1920	56.5

Author's conclusion

- MTX should be used only:
  - If satisfactory control of psoriasis cannot otherwise be achieved
  - In the absence of other hepatotoxic factors or any regular alcohol intake
  - If a pre-treatment biopsy does not show any pre-existing liver disease
  - If follow-up liver biopsies do not contra-indicate further therapy

H.12.1.2 STUDY 2

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
M. J. Boffa, R. J. Chalmers, N. Y. Haboubi, M. Shomaf, and D. M. Mitchell. Sequential liver biopsies during long-term methotrexate treatment for psoriasis: a reappraisal. *Br.J.Dermatol.* 133 (5):774-778, 1995. Ref ID: BOFFA199	**Observational:** Prospective case series	N: 49	**Inclusion criteria:** Long-term low-dose once weekly oral MTX for severe psoriasis; 2 or more biopsies **Exclusion criteria:** Not stated **Parameter** / **Treated (n=49)** Mean age – years: 54.8 (at last biopsy) Gender M/F (%): 61/39 Cumulative MTX dose (mg), mean (range): At first biopsy: 2743 (315-10,024 mg) plus mean of 2362 mg during FU Duration of treatment weeks, 275 (26-738)	**Methotrexate**: Long-term low-dose once weekly oral MTX (mean weekly dose 10.5 mg; range 3.9-19.2 mg) **Histological techniques:** Biopsy by Menghini technique; staining with H&E, periodic acid Schiff, Perl's stain for iron, orcein, Hep B surface antigen and metallothionein, untoned reticulin and haematoxylin/picrosirius red **Prognostic factors:** alcohol, cumulative dose	10-years	Hepatotoxicity by histology score **Grading**: 1. Normal histology 2. Steatosis alone (not abnormal) 3. Inflammation (±steatosis) without fibrosis 4. Fibrosis (±steatosis ± inflammation) 5. Cirrhosis	None stated

5			mean (range)	**Confounders** Histology score at initial biopsy, cumulative dose and mean weekly MTX dose presented (no multivariate analysis)			

Effect Size

Outcomes

Patient group	**First biopsy**		**Interval (weeks)**	**Last biopsy**						
	Histology score	Alcohol (units/week)		Age (years)	Alcohol (units/ week)	Change in alcohol intake (units/week)	Cumulative MTX dose (mg)	Durati on of MTX	Histology score	Change in histology score
Improved (n=12)	3.4	8.2	301	55.0	3.7	-4.5	7082	613	1.9	-1.5
No change (n=28)	2.2	5.6	190	53.5	4.0	-1.6	4265	441	2.2	0
Deteriorated (n=9)	1.6	2.1	233	55.8	1.3	-0.8	5078	535	3.4	+1.8

Summary

- **Alcohol consumption not a risk factor for hepatotoxicity**
  - Histology score at end point greater in those with lowest alcohol consumption
- But, reduction in alcohol intake is associated with improved histology score
- No significant correlation between liver histology group (improved, no change or deteriorated) and cumulative MTX dose (r = -0.013; p = 0.46) or duration of treatment (r = -0.036013; p = 0.40)

Cumulative MTX dose not a risk factor for hepatotoxicity

- Change in histological group and the dose of methotrexate (cumulative at the time of the last biopsy or doses between biopsies) were not statistically significant (Spearman correlation coefficient = 0.11, p=0.23 and r = 0.23, p=0.06 respectively).
- At the last biopsy, cumulative dose and duration of treatment were also not correlated with the liver histology groups (r = -0.013, p=0.46 and r = -0.036, p=0.40 respectively).

Author's conclusion

- Although no correlation between stated alcohol consumption and likelihood of histological deterioration was demonstrated, alcohol restriction should be advised during long-term treatment with MTX because alcohol is a well-known hepatotoxin
- Liver biopsy near the start of treatment may be justified where there is doubt about previous alcohol consumption, to exclude hepatic pathology not apparent on enzyme tests

STUDY 3

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
A. Nyfors. Liver biopsies from psoriatics related to methotrexate therapy. 3. Findings in post-methotrexate liver biopsies from 160 psoriatics. Acta Pathologica et Microbiologica Scandinavica - Section A, Pathology 85 (4):511-518, 1977. Ref ID: NYFORS1977	**Observational:** Retrospective case series	N: 160 (92 in part A and 68 in part B)	**Part A – single liver biopsies** **Inclusion criteria:** Patients who have had: severe psoriasis unresponsive to previous treatment; MTX therapy; one post-MTX liver biopsy >5 mm; willingness to co-operate **Part B – serial liver biopsies** **Inclusion criteria:** Patients who have had: severe psoriasis unresponsive to previous treatment; MTX therapy; at least 2 post-MTX liver biopsy >5 mm; willingness to co-operate **Exclusion criteria:** none stated **Parameter** / **Part A (n=92)** / **Part B (n=68)** Mean age – years: 57 / 57 Gender M/F: 50/50 / 49/51	**Methotrexate**: **Part A** – Single weekly oral 25-mg dose maximum in 23 patients; 69 had MTX therapy discontinued after clearing of psoriasis **Histological techniques:** Biopsy by Menghini technique; staining with H&E and van Gieson; in cases of suspected fibrosis/cirrhosis a reticulin stain was also used **Definitions** **Alcohol intake** 1. Occasional 2. 1-3 drinks/week 3. 1-3 drinks/day 4. >3 drinks/day	Mean treatment duration: 52 months (range: 2-105 months) Part B: mean time between biopsies = 19 months	Hepatotoxicity: cirrhosis (diffuse nodular regeneration with fibrosis, with lobular architecture disturbed), fibrosis (portal fibrosis: enlarged portal tracts with preservation of lobular architecture), mixed changes, non-specific reactive hepatitis, fatty change (all but cirrhosis graded as 0, +, ++, or +++)	Research grant from Lederle

			(%)			**Prognostic factors:** alcohol, obesity, cumulative dose **Confounders:** not controlled for but individual patient data presented on age, obesity, alcohol intake, cumulative MTX dose for those with fibrosis/cirrhosis			
			Cumulative MTX dose (mg), mean (range)	2287 (50-5075)	3940 (325-8355) at last biopsy				
			Duration of treatment (mean)	52 months	52 months				
			Previous jaundice	12	11				
			Gallstones	14	8				
			Diabetes	0	5				
			Obese	29	23				

Effect Size

Outcomes

Study	**Alcohol intake**	**Pre-MTX (n)**		**During MTX (n)**	
		Total	**Fibrosis or cirrhosis, n (%)**	**Total**	**Fibrosis or cirrhosis, n (%)**
Part A	Occasional	40	3 (7.5)	44	2 (4.5)
	1-3 a week	14	0 (0.0)	33	1 (3.0)

	1-3 a day	23	2 (8.7)	19	3(15.8)
	>3 a day	15	2 (13.3)	6	1(16.7)
Part B	Occasional	27	3 (11.1)	28	4 (14.3)
	1-3 a week	20	5 (25.0)	26	7 (26.9)
	1-3 a day	18	5 (27.8)	11	3 (27.3)
	>3 a day	3	1 (33.3)	3	0 (0.0)

Part A

- **Alcohol** intake significantly decreased in the group as a whole during MTX therapy (p<0.01), but was unchanged in the 7 patients who had cirrhosis or fibrosis
- When comparing the 13 patients with normal histology and the 7 with fibrosis or cirrhosis:
  - No significant difference between **total MTX dose** (p<0.45)
  - Those with hepatic damage were significantly older (p<0.002) and had consumed more **alcohol** during therapy (p<0.016)
  - No significant difference in the number of patients with **obesity**

Patients with cirrhosis or fibrosis

Age	**Obesity**	**Ethanol intake***		**Cumulative MTX dose (mg)**	**Diagnosis**
		Pre-MTX	**During MTX**		
75	0	3	3	1895	Fibrosis, moderate
79	0	1	1	305	Fibrosis, mild
63	+	3	3	1642	Fibrosis, mild
85	0	4	4	1612	Cirrhosis

59	0	1	1	2718	Fibrosis, mild
84	+	1	3	1015	Fibrosis, mild
54	0	4	2	2640	Fibrosis, mild
Mean: 71.3				Mean: 1689.6	

*1: occasionally; 2: 1-3 drinks a week; 3: 1-3 drinks a day; 4 >3 drinks a day

Part B

- **Alcohol** intake significantly decreased in the group as a whole during MTX therapy (p<0.01)
- When comparing the 9 patients with normal histology and 14 with cirrhosis:
  - No statistically significant difference between MTX **cumulative dose**: 3000 mg vs 3061mg (p=0.245)
  - Patients with cirrhosis had significantly higher **alcohol** intake during MTX therapy (p=0.041)
  - A significantly higher number of patients with cirrhosis were also **obese** (p=0.033) and were older (p=0.058)
- No significant correlation between histological subgroups with respect to sex of intake of hepatotoxic medicine

Patients with cirrhosis

Age	**Ethanol intake***		**Cumulative MTX dose (mg)**	
	Pre-MTX	**During MTX**	**First biopsy**	**Latest biopsy**
56	3	3	2994	4469
71	1	1	2378	2378
67	3	1	2510	2610
66	2	2	3260	3850

72	2	2	2500	2500
58	2	2	2345	2595
59	3	3	2205	2580
58	2	2	3408	3423
70	1	2	1755	1790
64	1	1	2748	5798
65	2	1	328	4065
60	4	2	325	325
61	3	2	3633	4045
66	3	3	2415	2430
Mean: 63.8			Mean: 2343.1	Mean: 3061.3

*1: occasionally; 2: 1-3 drinks a week; 3: 1-3 drinks a day; 4 >3 drinks a day

Summary

- **Alcohol consumption is a risk factor for hepatotoxicity**
  - A – Those who developed fibrosis or cirrhosis consumed statistically more alcohol during therapy than those with normal histology
  - B – Those who developed cirrhosis consumed statistically more alcohol during therapy than those with normal histology (p=0.041)

Author's conclusion

- The liver damage seen suggests a multifactorial aetiology produced by: MTX, alcohol, age, obesity and potentially hepatotoxic medicine

H.12.1.3 STUDY 4

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
M. Newman, R. Auerbach, H. Feiner, R. S. Holzman, J. Shupack, P. Migdal, M. Culubret, P. Camuto, and H. Tobias. The role of liver biopsies in psoriatic patients receiving long-term methotrexate treatment. Improvement in liver abnormalities after cessation of treatment. Arch.Dermatol. 125 (9):1218-1224, 1989.	**Observational:** Case series and within-group comparison New York University Hospital and office records; all those undergoing biopsy 1968-1986	N: 168	**Inclusion criteria:** Patients who have diagnosed psoriasis unresponsive to previous treatment; liver biopsy before and/or during therapy with MTX **Exclusion criteria:** none stated **Parameter** / **All (n=168)** Mean age (at biopsy) – years: 47.7 Gender M/F (%): 52/48 Pre-MTX biopsy (%): 49% Median monthly MTX dose before biopsy (range): 67.3 (7.5-205.6) mg Duration of treatment: 48 months	**Methotrexate**: Most received oral administration in either a single weekly or a divided weekly dose MTX treatment stopped when biopsy specimen was grade IIIB or greater **Histological techniques:** Biopsy by Menghini technique; fixed and embedded in paraffin; staining with H&E, reticulin and trichrome stains Diagnosis made by blinded assessor **Definitions**	Median treatment duration: 48 months (range: 1-218 months)	Hepatotoxicity: grading by Roenigk classification	Honors Research Program of New York State University School of Medicine; partial funding from Lederle Laboratories

Ref ID: NEWMAN1989			(median)		**Obesity:** 40% increase above ideal body weight **High alcohol intake:** >200g pure alcohol (>14 drinks) per week **Moderate alcohol intake:** 1-7 fluid oz pure alcohol (2-14 drinks) **Prognostic factors:** alcohol, obesity, diabetes, cumulative dose **Confounders:** States univariate and bivariate analyses performed but combined factors for bivariate not specified in methods - Oral therapy less likely to result in abnormal biopsy independent of cumulative dose			
			IBD or gallbladder disease	0				
			History of high alcohol intake	14 (8 of whom received MTX)				
			Diabetes	16				
			Obese	67 (40%)				
Effect Size								

Outcomes

Summary

Cumulative dose analysis: calculated the actuarial probability of a normal (grade I or II) biopsy as a function of cumulative MTX dose

The probability of a normal liver biopsy result dropped to below 50% when the cumulative dose of methotrexate was 3115 mg (for those who had a pre and post methotrexate biopsy).

Cumulative dose (mg)	**Probability ±SE**	**N still at risk**
Patients with paired biopsies before and after MTX (N=31)		
1000	0.88 ± 0.06	21
2000	0.65 ± 0.10	15
3000	0.51 ± 0.11	8
4000	0.25 ± 0.10	4
5000	0.13 ± 0.13	1
Patients without biopsies before MTX (N=137)		
1000	0.93 ± 0.03	62
2000	0.77 ± 0.05	41
3000	0.68 ± 0.06	33
4000	0.63 ± 0.07	25

5000	0.54 ± 0.07	18
6000	0.48 ± 0.08	15
7000	0.32 ± 0.09	6
8000	0.24 ± 0.09	3

Risk factor analysis performed on all patients (not all of whom had post-MTX data)

Alcohol

- No significant association between high or moderate alcohol consumption before MTX treatment (patients instructed to cease intake during therapy) and biopsy grade. Therefore, despite evidence that alcohol intake correlates with biopsy grade, a history of pre-treatment alcohol consumption may not.

Obesity

- Obesity increased the risk of hepatotoxicity
  - Significant association between biopsy grade and obesity in the MTX-treated group (but not in untreated; p=0.003)

Diabetes

- No association between diabetes and hepatotoxicity

Liver function tests

- Liver function tests were not predictive of liver histology findings

H.12.1.4 STUDY 5 – study in children (included although N<30)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
B. Collin, A. Vani, M. Ogboli, and C. Moss. Methotrexate treatment in 13 children with severe plaque psoriasis. Clin.Exp.Dermatol. 34 (3):295-298, 2009. Ref ID: COLLIN2009	**Observational:** Retrospective case series Birmingham Children's hospital; 1997-2007	N: 13	**Inclusion criteria:** Severe plaque psoriasis, recalcitrant to topical therapy, treated with MTX **Exclusion criteria:** none stated **Parameter** / **All (n=13)** Mean age (years) - presentation: 8.1 - MTX initiation: 12.1 Gender M/F (%): 31/69 Family history of psoriasis (n): 11 Cumulative MTX dose (mg), mean (range): 993.1 (45.0-3637.5) Duration of: 71 weeks	**Methotrexate**: Initial: 2.5-10 mg oral once weekly, increased to 7.5-20 mg according to response **Histological techniques:** Biopsy technique not stated; staining not defined **Prognostic factors:** obesity **Confounders**: Treatment duration and cumulative dose presented for each patient	Mean treatment duration: 71 weeks	Treatment response Hepatotoxicity: disturbed liver function tests (aspartate transaminase, alanine transaminase)	None declared

			treatment (mean)				
			Full blood count, urea, electrolytes and creatinine and liver function tests were all normal at baseline				

Effect Size

Outcomes

- **Obesity may increase the risk of hepatotoxicity in children**
  - 3/13 cases were obese and 2 of these 3 had disturbed liver function tests (but no fibrosis on histology in one biopsied) vs 0 of the 10 non-obese children
  - Those with disturbed liver function tests had low cumulative doses of MTX (45 and 432.5 mg) compared with the mean (993.1 mg)

Author's conclusion

- MTX treatment is efficacious in severe childhood psoriasis and can be safe when closely monitored; obesity may be a relative contra-indication as associated NAFLD is likely to increase hepatotoxicity

H.12.1.5 STUDY 6

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>P. Rosenberg, H. Urwitz, A. Johannesson, A. M. Ros, J. Lindholm, N. Kinnman, and R. Hultcrantz. Psoriasis patients with diabetes type 2 are at high risk of developing liver fibrosis during methotrexate treatment. J.Hepatol. 46 (6):1111-1118, 2007.

Ref ID:</td>
<td>Observational: Retrospective case series

Karolinska Hospital or out-patient clinic (Stockholm); 1975-2003</td>
<td>N: 71</td>
<td>Inclusion criteria: At least one liver biopsy for monitoring during MTX treatment for psoriasis

Exclusion criteria: none stated
<table>
<tr><th>Parameter</th><th>No risk factors (n=45)</th><th>Risk factors (n=26)</th></tr>
<tr><td>Median age (years)
First biopsy
Start of treatment</td><td>48
47</td><td>52
49</td></tr>
<tr><td>Gender M/F (%)</td><td>68.9/31.1</td><td>57.7/42.3</td></tr>
<tr><td></td><td colspan="2">All (n=71)</td></tr>
<tr><td>Cumulative</td><td colspan="2">0-17.2 g</td></tr>
</table>
</td>
<td>Methotrexate:

Dosage schedule not stated

Histological techniques:

Biopsy technique not stated; staining not defined

Assessed by blinded evaluators

Prognostic factors: alcohol, diabetes, hepatitis B/C

Confounders: no apparent controlling in analyses (but survival analysis performed – fibrosis vs cumulative dose)</td>
<td>N/A</td>
<td>Hepatotoxicity: biopsy – inflammation, fibrosis, steatosis and ballooning according to Kleiner and Brunt; disturbed liver function tests (aspartate transaminase, alanine transaminase, gamma-glutamyl transferase)

Fibrosis staged as 0:none; 1:perisinusoidal or periportal; 2:perisinusoidal and periportal; 3: bridging fibrosis; 4:</td>
<td>Swedish Research Council, The Bengt Ihre Foundation and Karolinska Institutet</td>
</tr>
</table>

ROSENBERG2007			MTX dose, range		**Definitions:** **Alcohol overconsumption:** >30g daily **Diabetes mellitus**: fasting blood glucose >6.0 mmol/l or blood glucose >11 mmol 2 h after intake of 75 g glucose		cirrhosis
			Maximum weekly dose: ≤12.5 mg 15-20 mg >20mg	 46 30 2			

Effect Size

Outcomes

Summary

Data presented in Kaplan-Meier curves

Risk factor	**% developing fibrosis**		**p-value**	**% developing severe fibrosis**		**p-value**
	With risk factor	**Without risk factor**		**With risk factor**	**Without risk factor**	
Alcohol	100% (9/9)	66% (41/62)	-	22% (2/9)	18% (11/62)	0.599
Overweight	93% (14/15)			33% (5/15)		0.0132

Diabetes	100% (7/7)	52% (37/64)		57% (4/7)	14% (9/64)	0.003
Viral hepatitis	100% (3/3)			33% (1/3)		
Any of the above	96%	58%				

- Alcohol, overweight, diabetes and hepatitis increased the risk of fibrosis
- Risk for severe fibrosis dependent on the presence of at least one of the risk factors (p=0.002)
- Serum ALT, AST and γGT before treatment did not significantly predict hepatotoxicity

Author's conclusion

- There is a correlation between the presence of a risk factor for steato-hepatitis, particularly diabetes, and development of severe liver fibrosis in MTX-treated psoriasis patients, even when lower cumulative doses of MTX are given
- It is important to thoroughly assess risk factors for liver disease before and during MTX therapy

STUDY 7

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
Anonymous. Psoriasis-liver-methotrexate interactions. Arch.Dermatol. 108 (1):36-42, 1973. Ref ID: ANON1973	**Observational:** Case series and within-group comparison Multicentre	N: 550 (212 pre-MTX, 38 pre- and post-MTX, 356 post-MTX)	**Inclusion criteria:** Psoriatic patients with liver biopsies prior to or after MTX therapy **Exclusion criteria:** none stated **Parameter** / **All (n=550)** Mean age (years): 46.9±15.4 Gender M/F (%): 57/43 Mean duration of psoriasis (years): 16.8±12.2 Mean cumulative dose MTX (g): 1.84 Diabetes (n): 33 Obesity (n): 108 Previous systemic therapy	**Methotrexate**: 4 main dosage schedules: 1. Daily oral administration of low doses interspersed with rest periods 2. Weekly oral administration of a single dose 3. Weekly intra-oral or intramuscular administration of a single dose 4. Weekly oral administration of divided dosage; 3-4 dosages over a 36-h periods weekly **Histological techniques:** Biopsy technique not stated; staining with H&E, trichrome or Van Gieson stains – graded by blinded pathologists	Mean treatment duration: 2.8±2.0 years	Hepatotoxicity: biopsy – fatty changes, nuclear variability, periportal inflammation, focal necrosis and fibrosis (all graded 1-4; not present-severe), cirrhosis (present,1, or absent, 2) Disturbed liver function tests (BSP retention, SGOT, SGPT, alkaline phosphatase)	None stated

			Corticosteroids 127 Anti-metabolites 111 Alcohol intake Non-drinkers 197 1-3 drinks/week 190 1-3 drinks/day 79 4+ drinks/day 68	Assessed by blinded evaluators **Prognostic factors:** alcohol, diabetes, obesity, cumulative dose **Confounders:** states matching for cumulative MTX dose and drug schedule in analysis of alcohol intake as a risk factor			

Effect Size

Outcomes

Summary

- In 338 post-MTX patients, increasing alcohol intake significantly correlated with presence of periportal inflammation, fibrosis and cirrhosis (even after correction for confounders)
- Obesity significantly correlated with presence of fatty metamorphosis
- Diabetes significantly correlated with presence of fatty metamorphosis and fibrosis

Morphologic variable	**Post MTX (mean histologic grade)**		
	No diabetes (n=360)	**With diabetes (n=24)**	**p-value (less than)**

Fatty metamorphosis	1.99	2.62	0.001
Nuclear variability	2.31	2.58	0.088
Periportal inflammation	1.70	2.00	0.086
Necrosis	1.92	2.00	0.550
Fibrosis	1.55	1.96	0.029
Cirrhosis	1.96	1.96	0.888

- In 38 patients with pre- and post-MTX biopsies, there were significant increases in fatty change and fibrosis
- Increasing BSP retention significantly associated with abnormal morphologic findings in both pre- and post-MTX patients ($p < 0.001$), but ~50% of patients with fibrosis or cirrhosis did not have elevated BSP
- Increasing total cumulative dose of MTX correlates with periportal inflammation ($p<0.001$), fibrosis ($p<0.001$) and cirrhosis ($p<0.002$)
- Daily oral dose schedule significantly increases nuclear variability, necrosis and fibrosis (independent of cumulative dose)
- No correlation of sex, extent of psoriasis or history of systemic corticosteroids on body surface with liver changes

Authors' conclusion

- Factors found to be significantly associated with histologic liver damage include increased alcohol intake, daily oral MTX doing, obesity and diabetes

STUDY 8

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

<table>
<tr>
<td>M. A. Berends, J. Snoek, E. M. de Jong, P. C. van de Kerkhof, M. G. van Oijen, J. H. Van Krieken, and J. P. Drenth. Liver injury in long-term methotrexate treatment in psoriasis is relatively infrequent. Aliment.Pharmacol.Ther. 24 (5):805-811, 2006.

Ref ID: BERENDS2006</td>
<td>Observational: Retrospective chart review (1976-2005)

Department of dermatology, Nijmegen Medical Centre, The Netherlands</td>
<td>N: 125</td>
<td>Inclusion criteria: Psoriatic patients receiving a weekly dosage of MTX who underwent at least one liver biopsy

Exclusion criteria: none stated

<table>
<tr><th>Parameter</th><th>All (n=125)</th></tr>
<tr><td>Mean age (years)</td><td>45.0</td></tr>
<tr><td>Gender M/F (%)</td><td>54/46</td></tr>
<tr><td>Cumulative dose MTX (mg), median (range)</td><td>2113 (180-20,235)</td></tr>
<tr><td>Diabetes (n)</td><td>9</td></tr>
<tr><td>Overweight</td><td>39</td></tr>
<tr><td colspan="2">Alcohol intake</td></tr>
<tr><td>Non-drinkers</td><td>64 (51.2%)</td></tr>
<tr><td>Any intake</td><td>61 (49%)</td></tr>
<tr><td>Excessive intake (>14 units/week)</td><td>11 (8%)</td></tr>
</table>
</td>
<td>Methotrexate:

Dosage schedule not stated

Histological techniques:

Biopsy by right intercostals approach, fixed with paraffin; staining with H&E, and von Gieson stains

Monitoring: complete blood cell count and liver chemistry every 4-8 weeks; follow-up liver biopsy after every 1.5 g MTX

Prognostic factors: alcohol, diabetes, obesity, cumulative dose

Confounders: cumulative MTX dosage did not affect the association</td>
<td>Median treatment duration: 228 weeks (range: 16-1763)</td>
<td>Hepatotoxicity: biopsy – graded according to Roenigk classification

Disturbed liver function tests (alanine transaminase, aspartate transaminase, alkaline phosphatase, γ-GT, total bilrubin)</td>
<td>None</td>
</tr>
<tr><td colspan="8">Effect Size</td></tr>
</table>

Outcomes

Summary

Characteristics of patients with no histologic abnormalities during treatment:

Risk factor	**Patients without histologic injury (n=88)**
Alcohol	37
Alcohol >14 U/week	5
Diabetes	8

Association between liver function tests and higher Roenigk score:

- More patients with Roenigk ≥2 had g-GT above normal (OR: 1.80; 95%CI: 1.30-2.49)
- ASAT and ALAT concentrations did not correlate with Roenigk scores
- Patients with Roenigk ≥2 had significantly higher AP and ASAT compared with those with Roenigk = 1, but values were well within the normal range.

Association between risk factors and progression to higher Roenigk score:

- Obesity and/or diabetes led to progression to higher Roenigk score (>1) at earlier cumulative MTX dose, while alcohol did not
- Histologic progression to a Roenigk grade 2 or higher most likely when the methotrexate cumulative dose was between 1500mg-6000mg, with limited

progression rate below 1500mg

- Progression to higher Roenigk score levelled out above 6000mg, and higher exposure was not associated with any further increase in liver damage.

Distribution of Roenigk score per risk factor

- In comparison to those without risk factors, those with overweight and/or diabetes had higher Roenigk scores, and there was a modest adverse effect of alcohol use on histological scores. The effect of these risk factors was most apparent when considering fibrosis and cirrhosis (grades 3a, 3b and 4):

Patients	**Roenigk n, (%)**						
	1	**2**	**3a**	**3b**	**4**	**Grades 2-4**	**p-value (Roenigk = 1 vs Roenigk >1)**
No risk factors (n=34)	29 (85%)	5 (15%)	0	0	0	15%	0.19
Overweight (n=38)	24 (63%)	10 (26%)	2 (5%)	1 (3%)	1 (3%)	37%	0.01
Alcohol use (n=62)	49 (79%)	8 (13%)	4 (6%)	0	1 (2%)	21%	0.67
Diabetes (n=9)	6 (67%)	1 (11%)	0	1 (11%)	1 (11%)	33%	0.42

Authors' conclusion

- At any given cumulative MTX dosage, patients with obesity and/or diabetes had a significantly worse liver histology compared with those without risk factors
- Histological monitoring of MTX toxicity could be tailored to obese patients with or without diabetes
- Normal liver enzyme tests do not exclude progression of liver injury, although γ-GT levels may be an exception
- Liver histology deterioration is mostly seen at cumulative MTX doses of 1500-6000 mg.

H.12.1.6 STUDY 9

Reference	Study type	Number of patients	Patient characteristics	Intervention/Prognostic factors	Length of follow-up	Outcome measures	Source of funding
Lindsay K, et al. Liver fibrosis in patients with psoriasis and psoriatic arthritis on long-term, high cumulative dose methotrexate therapy. *Rheumatology (Oxford).*48 (5):569-72, 2009 Ref ID: LINDSAY 2009	**Observational:** Prospective case series Leeds General Infirmary and Harrogate District Hospital (Oct 2002-May 2004) •	N=54 (47 PsA – 32 of whom also had skin involvement)	**Inclusion criteria:** Patients with PsA and psoriasis alone on long-term MTX therapy with full assessment of risk factors **Exclusion criteria:** None stated **Parameter** / **Mean ±SD** / **Range** Age, years: 54.4±11: 30–78 Disease duration, years: 27.3±15: 3–68 Skin disease duration, years: 25.8±16: 0–68 Arthritis duration,	**Methotrexate**: Schedule not stated, but 14 on subcutaneous MTX **Techniques:** • Liver biopsy under ultrasound guidance. • Liver biopsy was performed if >1 g of MTX had been taken cumulatively in keeping with dermatology guidelines • Two days prior to liver biopsy, patients were assessed clinically for signs of cutaneous and joint psoriasis, liver disease, obesity (BMI >30), diabetes for chronic renal impairment. **Prognostic factors:**	Not stated	Hepatic fibrosis detected by liver biopsy (grade 3 according to Roenigk classification)	None stated

			years			Alcohol, diabetes (type I/II), obesity (BMI >30), cumulative dose **Confounders:** not controlled for **Definitions:** Current or previous excess alcohol consumption was arbitrarily defined as greater than the recommended weekly amounts in the UK (14U of alcohol for women and 21U for men)			
			MTX duration, years	6.59±4.22	1.33–30				
			Weekly dose, mg	15.5±6.17	0–25				
			Cumulative dose, mg	4396±3140	1020–19657				
			Swollen joint count	2.51±3.69	0–12				
			Tender joint count	4.75±6.69	0–24				
			Leeds enthesial tender count	3.55±6.12	0–25				
			Diabetes	4					
			Obese	15					
			Previous excess alcohol intake	9					

Demographic data and methotrexate cumulative dose for patients having liver biopsy

Psoriatic disease characteristics

Ps or PsA	Ps alone	PsA alone	Both PsA and Ps	PsA
54	7	15	32	47

Effect Size

- Study showed a prevalence of mild and clinically insignificant fibrosis of 20% and no clinical liver disease or cirrhosis
- Post-liver abdominal pain within 2 hours was present in all to varying degree. This continued up to 24 hours in 21 patients

Significance of risk factors for hepatic fibrosis in long-term MTX treatment for psoriatic disease

	Median (Range)		Mann–Whitney U-test
Parameter	No fibrosis (n=43)	Fibrosis (n=11)	P
Age, years	53 (30–78)	59 (47–78)	NS
Units of alcohol/week	5 (0–40)	0 (0–42)	0.02
BMI	29 (19.3–40)	32.3 (26–46.6)	NS
Disease duration, years	28 (4–68)	24 (3–53)	NS
MTX dose, mg	15 (0.0–25.0)	15 (0.0–25.0)	NS
Duration on MTX, years	6.58 (1.3–30.0)	5.5 (2.0–10.3)	NS
Cumulative dose of MTX, mg	3839 (1020–19657)	3541 (1000–5908)	NS
Diabetic	3	3	NS
Renal impairment	3	1	NS

Number of risk factors[a]	0 (0–3)	1 (0–2)	0.01

[a]The number of risk factors for hepatotoxicity or liver fibrosis was calculated for each patient, with history of excessive alcohol consumption in the past or current consumption over the recommended weekly amount counting as one risk factor; diabetes, renal impairment or obesity counting as others.

Authors' conclusion

- The sample size in this study is too small to demonstrate an effect of each individual risk factor. However, mild liver fibrosis appears to be more likely the greater the total number of pre-disposing factors for hepatotoxicity.
- None of the individual risk factors predicted the presence of early fibrosis (but the total number of risk factors was linked to the likelihood of fibrosis)
- No link was established between weekly dose, duration of treatment and cumulative dose of MTX

H.12.1.7 STUDY 10

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
Malatjalian DA, et al. Methotrexate hepatotoxicity in psoriatics: report of 104 patients from Nova Scotia, with analysis of risks from obesity, diabetes and alcohol consumption during long term follow-up. *Can J Gastroenterol*.10(6):369-75. 1996 Ref ID: MALATJALIAN1996	**Observational:** Retrospective case series Victoria General Hospital, Canada 1979-1990 •	104	**Inclusion criteria:** patients with psoriasis who had a pre-MTX liver biopsy and who had regular annual follow-up biopsies while on MTX **Exclusion criteria:** Patients with psoriasis receiving MTX <1 year; patients for whom baseline or regular annual follow-up biopsies were not available for histological evaluation **Parameter** / **Mean ±SD** Age, years: 42.8 Gender M/F (%): 57/43 Mean follow-up (years): 3.8	**Methotrexate**: MTX was given in 5–25 mg weekly doses, either as a single dose or as one-third of the dose every 12 h once per week The estimated annual dose was 1–1.5 g MTX was discontinued in patients with histological grades IIIB or IV **Histological techniques** Annual liver biopsies serially cut to 5 µm; had a minimum of three hematoxylin and eosin stained sections, one Masson's trichrome stained section for connective tissue and one section stained for iron using Perls' reaction; where appropriate, periodic acid Schiff ± pretreatment with diastase, Shikata orcein stain for hepatitis B virus surface antigen and van	Mean: 3.81 (range 1–11)	Histological grade of liver biopsies (according to the Roenigk classification)	Not stated

				Gieson stain for connective tissue were done Histological slides were reviewed unblinded by an author **Histological variables assessed** • Degree of steatosis • Amount and cellular distribution of stainable iron • Presence of centrilobular sinusoidal fibrosis • Amount of portal inflammation • Extent of portal fibrosis • Presence of periportal inflammation • Presence of periportal fibrosis • Presence of bridging fibrosis • Degree of hepatocellular nuclear availability • Presence and extent of hepatocellular degeneration • Presence and extent of hepatocellular necrosis • Presence and extent of lobular inflammation • Presence of cirrhosis **Definitions:** **Alcohol use** (≤3 drinks/week)			

				Obesity: unclear definition (28/35 obese had BMI ≥20% above normal) **Prognostic factors:** Obesity, diabetes, alcohol consumption, pre-existing disease **Confounders**: see results section			

Effect Size

Patients with risk factors: obesity, diabetes and alcohol consumption*

Risk factor	Females	Males	Total
Obesity	7	7	14
Diabetes	2	0	2
Alcohol consumption	4	16	20
Obesity + diabetes	5	0	5
Obesity + alcohol consumption	7	7	14
Diabetes + alcohol consumption	1	0	1
Diabetes + obesity + alcohol consumption	1	1	2

*No greater than three drinks per week (a drink constitutes 30 ml of hard liquor, 118 ml of wine or 355 ml of beer); patients advised against drinking alcohol prior to MTX administration

Effect of initial (pre-MTX) biopsy grade on final biopsy grade

- 62.5% of patients with pre-MTX grade IIIA liver biopsies (5/8) progressed to bridging fibrosis or cirrhosis (compared with 3/16 (18.8%) from grade II and 16/80 (20.0%) from grade I)

Initial grade	**Final grade**				
	I	**II**	**IIIA**	**IIIB**	**IV**
I	37	10	17	14	2
II	3	2	8	3	0
IIIA	0	1	2	4	1

- Increased biopsy grade progression was associated with obesity; but not with alcohol and diabetes
- Progression to final grades IIIB and IV was associated with diabetes but not with obesity or alcohol use

Effect of diabetes, obesity and alcohol on disease progression and final grade of liver biopsies

Risk factor	Odds ratio	95%CI	P
Progression of liver pathology to higher grade			
Diabetes	2.07	0.35–12.35	0.42
Obesity	8.85	3.14–25.00	0.001
Alcohol	0.96	0.38–2.46	0.93
Progression of liver pathology to grades IIIB and IV			
Diabetes	5.68	1.34–24.39	0.02

Obesity	2.23	0.82–6.06	0.12
Alcohol	2.23	0.81–6.10	0.12

Confounders:

- Age and years of follow-up were initially used as covariates and found to be nonsignificant. They were therefore omitted from model producing final estimates
- None of the biopsies showed evidence of alcoholic hepatitis, chronic viral hepatitis or increased accumulation of sustainable iron
- There were no statistically significant differences in the initial biopsy grade by sex (p=0.67), or alcohol use status (p=0.82) but the obese (p=0.006) and the diabetes group (p=0.004) had a higher percentage of grades II and IIIA biopsies, and the initial biopsy grade was positively correlated with age (p=0.003)

Of note: there was unpredictable rapid histological deterioration in 3 patients associated with obesity, pre-exisiting mild hepatic fibrosis and re-exposure to MTX after MTX was discontinued because of high-grade fibrosis

Authors' conclusion

- Significant risk of severe hepatotoxicity is related to diabetes (p = 0.02) but not to obesity (p = 0.12) or occasional alcohol consumption (p = 0.12)
- There may be an increased risk for severe hepatotoxicity on MTX when a patient has pre-existing liver pathology

H.12.1.8 STUDY 11

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
Tobias H and Auerbach R. Hepatotoxicity of long-term methotrexate therapy for psoriasis. Arch Intern Med. 132(3):391-6. 1973 Ref ID: Tobias 1973	**Observational:** Case series New York University Medical Centre •	88 (69 treated with MTX)	**Inclusion criteria:** Patients with severe psoriasis involving ≥80% of the body. **Exclusion criteria:** None stated **Parameter** / **All (n=88)** Average duration of psoriasis (years): 14.7 Average age (years): 48.3 Gender % (M/F): 48/40 No large difference between MTX-treated and untreated patients with regard to age	**Methotrexate**: • Various dosing schedules (no further details) **Histological techniques** Menghini liver biopsy technique Sections studied by hematoxylin-eosin and trichrome connective tissue strains Biopsy findings were reviewed by two observers without knowledge of patient identity, history or treatment **Prognostic factors:** diabetes, alcohol, obesity, cumulative dose **Alcohol use:** categorised as 0,	Duration of treatment: 0.1-10 years	Hepatotoxicity Biopsy findings: fibrosis, fatty change, portal inflammation, nuclear variability and focal necrosis (all graded 1-4; none to marked) and cirrhosis (present or absent) Disturbed liver function tests (BSP, SGOT, SGPT, alkaline phosphatase, bilirubin)	Not stated

			and severity or duration of psoriasis	28–85, or >88 g/week **Confounders:** Total dose, duration of treatment, method of administration, alcohol intake and diabetes presented in individual patient data			

Effect Size

MTX-treated

Alcohol intake	**Hepatotoxicity**			
	Cirrhosis	**Marked-to-moderate fibrosis**	**Slight fibrosis**	**No fibrosis**
0 gm/week	2 (4.9%)	6 (14.6%)	6 (14.6%)	27 (65.9%)
28–85 gm/week	1 (20%)	4 (25.0%)	2 (12.5%)	9 (56.3%)
>85 gm/week	2 (16.7%)	3 (25.0%)	1 (8.3%)	6 (50.0%)

No MTX

Alcohol intake	**Hepatotoxicity**			
	Cirrhosis	**Marked-to-moderate fibrosis**	**Slight fibrosis**	**No fibrosis**
0 gm/week	0	3	4	7
28–85 gm/week	0	1	0	1
>85 gm/week	0	0	1	2

- Note that cirrhosis was only seen in patients who had received >2 g MTX

- **Fatty change –** increased alcohol consumption and diabetes were associated with increased fat
- **Portal inflammation –** associated with MTX dose
- **Nuclear variability –** associated with high MTX dose
- **Focal necrosis –** not associated with MTX dose or alcohol intake (appears to occur independent of therapy)
- Physical findings (e.g., hepatomegaly), and liver function tests were not dependable indicators of liver abnormalities

Cumulative dose

Biopsy grade	N	Mean cumulative dose (mg)
Cirrhosis	5	4140
Marked fibrosis	3	2933
Moderate fibrosis	10	2760
Slight fibrosis	9	2864
No fibrosis	42	1479

Authors' conclusion

- Fatty change and fibrosis occurred to a greater extent in MTX-untreated non-alcohol consuming psoriatic patients than in the normal population.
- Cirrhosis is related to MTX dose and alcohol intake may have an additive or synergistic effect
- Alcohol intake and diabetes are associated with fatty change; however, fatty infiltration alone is not considered to be a contra-indication for MTX therapy in the absence of considerable fibrosis and portal inflammation or cirrhosis
- Liver enzyme elevations may be transient and do not reflect changes in histopathology

H.12.1.9 STUDY 12

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
A. Nyfors and H. Poulsen. Liver biopsies from psoriatics related to methotrexate therapy. 2. Findings before and after methotexate therapy in 88 patients. A blind study. Acta Pathol.Microbiol.Scand.[A]. 84 (3):262-270, 1976. Ref ID: NYFORS1976	**Case series** •	N: 88	**Inclusion criteria:** Patients who have had: typical and severe psoriasis unresponsive to previous treatment; at least 2 liver biopsies, including an initial one; willingness to co-operate; no evidence of cirrhosis or fibrosis in pre-MTX biopsy; MTX given in a single, weekly, oral dose of 25 mg maximum **Exclusion criteria:** None stated Note that patients were warned to avoid alcohol and not to take acetylsalicyclic acid-containing analgesics, barbiturates, thiazides, sulphonamides and other possible hepatotoxic medications **Parameter** / **All (n=88)** Mean duration / 26 (2-72)	**Methotrexate**: Therapy usually started within 2 days of pre-MTX biopsy with initial oral dose of 25 mg Single, weekly, oral dose of 25 mg maximum **Histological techniques** Menghini liver biopsy technique Staining not mentioned Histological evaluation was performed blindly to treatment period (Pre- or post-) and biopsies from other skin diseases were intermingled **Prognostic factors:** alcohol, pre-existing liver disease, cumulative dose	Average duration of treatment 26 months	Hepatotoxicity Biopsy findings: Hepatotoxicity: cirrhosis (diffuse nodular regeneration with fibrosis, with lobular architecture disturbed), fibrosis (portal fibrosis: enlarged portal tracts with preservation of lobular architecture), mixed changes, non-specific reactive	Not stated

			of MTX therapy: months Mean cumulative MTX dose at time of last biopsy (mg): 1733 (175-4590) Mean age (years): 50 (range: 21-78) Gender % (M/F): 47.7/52.3 Potentially hepatotoxic medicine history (n): 25 Jaundice history (n): 13 Gall stones history (n): 9 Diabetes mellitus (n): 2 Obese (n): 28	**Confounders:** Multivariate analysis including: chief histological diagnoses of pre-MTX liver biopsy, MTX cumulative dose, admitted alcohol intake during MTX therapy, age and obesity (but not clear if these confounders were controlled for when assessing the impact of individual risk factors)		hepatitis, fatty change (all but cirrhosis graded as 0, +, ++, or +++) Liver function tests (SGOT, alkaline phosphatase, bilirubin, gamma-globulin, creatinine)	
Effect Size							

Pre-existing liver disease

Laboratory tests	Number of abnormal tests		
	2 days before first biopsy	**During MTX therapy (number of patients)**	**2 days before latest biopsy**
Serum aspartate aminotransferase	2	60	4
Serum bilirubin	0	2	1
Alkaline phosphatase	0	9	4
Serum gamma globulin	32	73	48

Biopsy diagnosis (pre-MTX)	Post-MTX diagnosis				
	Cirrhosis/fibrosis	Mixed changes*	Non-specific reactive hepatitis	Fatty change	Normal
Cirrhosis/fibrosis	0	0	0	0	0
Mixed changes[a]	3	0	0	0	0
Non-specific reactive hepatitis	1	1	2	2	0*
Fatty change	4	3	0	23	2*
Normal	3	0	6	12	26

[a]Mixed changes = on-specific reactive hepatitis and fatty change

*p<0.05

- **No significant difference between development of increased histological changes from normal or abnormal pre-MTX biopsies;** although, cirrhosis and fibrosis developed more frequently in patients with abnormal (8/41) than with normal (3/47) pre-MTX biopsies (p = 0.062)

Alcohol intake

Alcohol intake	**Pre-MTX (n)**		**During MTX (n)**	
	Total	**With fibrosis/cirrhosis, n (%)**	**Total**	**With fibrosis/cirrhosis, n (%)**
Occasional	46	4 (8.7)	56	6 (10.7)
1-3 a week	12	2 (16.7)	23	3 (13.0)
1-3 a day	22	2 (9.1)	6	1 (16.7)
>3 a day	8	3 (37.5)	3	1 (33.3)

- The 11 patients who developed fibrosis or cirrhosis did not have significantly higher alcohol intake during therapy (p>0.05) or significantly higher cumulative dose MTX (p = 0.19) than the 28 whose liver pathology remained normal
- The three subjects who had cirrhosis diagnosed within the first 3 years of MTX therapy had relatively low cumulative MTX doses but later admitted to an intake of >4 alcoholic drinks a day; therefore, alcohol consumption may contribute to the development of cirrhosis

	Chief histologic diagnosis		**Time between biopsies (years)**	**Age (years)**	**Ethanol intake**		**MTX total dose (mg)**	**SGOT at last biopsy**
	Pre-MTX	Post-MTX			Before MTX	During MTX		
1	Moderate fatty	Cirrhosis	1.5	44	d	b	925	Elevated

	change							
2	Mild mixed changes	Cirrhosis	2.2	56	d	b	1395	Normal
3	Normal	Cirrhosis	2.3	71	b	c	1405	Elevated
4	Moderate fatty change	Cirrhosis	3.3	57	a	a	3010	Normal
5	Mild fatty change	Cirrhosis	4.8	68	c	b	2253	Elevated
6	Mild mixed changes	Possible cirrhosis	2.0	50	d	d	525	Normal
7	Mild non-specific reactive hepatitis	Fibrosis	3.5	46	a	a	3588	Normal
8	Normal	Fibrosis	3.7	71	a	a	845	Normal
9	Mild fatty change	Fibrosis	3.8	62	a	a	2819	Normal
10	Moderate mixed changes	Fibrosis	4.0	53	c	a	2165	Normal
11	Normal	Fibrosis	4.5	52	b	a	4590	Normal

Ethanol intake – a: occasionally; b: 1-3 drinks a week; c: 1-3 drinks a day; d: more than 3 drinks a day

Cumulative methotrexate dose is not a risk factor for hepatotoxicity

- No significant correlation between the cumulative methotrexate dose and the number of pathological post methotrexate liver biopsies.
- No significant difference in mean cumulative does between the 11 who developed fibrosis or cirrhosis and those whose liver histology remained normal (p = 0.19)

Combination risk factors

- Highly statistically significantly more frequent development of cirrhosis or fibrosis in patients with combinations of the following: pathological pre-MTX

liver histology, high total MTX dose, daily alcoholic intake during MTX therapy, advanced age and obesity (p<0.001)

Authors' conclusion

- There was a statistically significant increase in the number of pathological findings in liver biopsies during MTX therapy
- Individually, none of the following risk factors (cumulative MTX dose, duration of MTX therapy, admitted alcohol intake during MTX therapy or obesity) were significantly correlated with increasing liver changes
- There was a highly statistically significant association between the number of patients with fibrosis or cirrhosis and the following factors grouped together: pathological pre-MTX liver histology, high MTX dose, regular daily alcohol intake during MTYX therapy, advanced age and obesity
- Tendency for cirrhosis and fibrosis to develop more frequently in patient swith pathological pre-MTX biopsies (p = 0.062)

H.12.1.10 STUDY 13

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
G. T. O'Connor, E. M. Olmstead, K. Zug, R. D. Baughman, J. R. Beck, J. L. Dunn, P. Seal, and J. F. Lewandowski. Detection of hepatotoxicity associated with methotrexate therapy for psoriasis. Arch.Dermatol. 125 (9):1209-1217, 1989. Ref ID: OCONNOR1989	**Observational:** Retrospective case series Dartmouth-Hitchcock Medical Centre, USA	N: 78	**Inclusion criteria:** Psoriasis patients who had undergone biopsy associated with MTX therapy **Exclusion criteria:** Not stated No baseline data presented	**Methotrexate**: Dosing schedules not stated **Histological techniques:** Biopsy by Menghini technique; staining with H&E, and Masson trichrome **Prognostic factors:** alcohol, obesity **Confounders** Logistic regression analysis controlling for confounders performed to compare liver function tests with biopsy results	N/A	Hepatotoxicity by biopsy: graded by the Roenigk classification by blinded assessor Liver function tests: total bilirubin, aminotransferase, alkaline phosphatase	None stated

				Age, gender, obesity, alcohol use, cholecystitis also assessed			

Effect Size

Outcomes

Summary

Data from those not known to have abnormal pre-treatment liver biopsy specimen

Variable	**Liver biopsy specimen results after treatment by grade, % (95% CI)**		
	I	**II**	**III-IV**
BMI	30.5 (45.8-51.8)	34.1 (29.7-38.6)	28.3 (25.7-30.9)
Alcohol consumption (% >1 drink/day)	17.6 (8.4-30.9)	16.7 (2.1-48.4)	11.1 (1.4-34.7)

- Alcohol consumption and obesity showed no significant association with abnormal findings from liver biopsy post-MTX
- Patient age and history of cholecystitis significantly positively associated with biopsy grade III or IV
- Abnormal liver function tests and biopsy specimen grade III or IV significantly correlated

Test	**Association of abnormal LFT and biopsy specimen grade III or IV**	
	Crude analysis	**Adjusted analysis (age and history of cholecystitis)**

	OR	X^2	p-value	OR	X^2	p-value
AST	4.7	7.98	0.005	14.7	12.83	<0.001
ALP	3.5	5.99	0.014	2.1	1.58	0.209
TB	2.2	0.69	0.406	5.1	2.38	0.123
AST or ALP	6.4	10.50	0.001	5.5	6.78	0.009
AST, ALP or total bilrubin	8.4	12.27	<0.001	14.7	8.00	0.005

H.12.1.11 STUDY 14

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
H. H. Roenigk, Jr., W. F. Bergfeld, R. St Jacques, F. J. Owens, and W. A. Hawk. Hepatotoxicity of methotrexate in the treatment of psoriasis. Arch.Dermatol. 103 (3):250-261, 1971. Ref ID: ROENIGK1971	**Observational:** Retrospective case series	N: 50 (37 treated)	**Inclusion criteria:** psoriasis patients with at least one liver biopsy **Exclusion criteria:** Not stated **Parameter** / **All (n=50)** Mean age – years: Pre-MTX group: 40; Post-MTX group: 45 Gender M/F (%): 56.8/43.2 Cumulative MTX dose (mg), mean (range): Range: 25-10,000 mg	**Methotrexate**: Dosing usually 25 mg/week orally **Histological techniques:** Biopsy with Menghini technique; staining with H&E, Masson's trichrome Specimens reviewed by blinded assessor **Definitions** Alcohol intake 0 No intake 1+ One drink/week (beer or hard liquor)	N/A	Hepatotoxicity by biopsy: fatty infiltration, hepatocellular damage, anisonucleosis, periportal inflammatory infiltrate, nuclear glyconeogenesis, fibrosis or cirrhosis **Grading**: 1 (normal); 2 (mild fatty infiltration); 3 (moderate-to-severe fatty infiltration, anisonnucleosis, nuclear changes, glycogenosis); 4 (periportal inflammation, early fibrosis); 5 (cirrhosis)	None stated

				2+ One drink per day (beer or hard liquor) 3+ More than one drink/day (beer or hard liquor; but <1/5 of liquor) 4+ One or more pints of hard liquor/day **Prognostic factors:** alcohol, obesity, diabetes, cumulative dose **Confounders** Alcohol, MTX dose, MTX duration, obesity, diabetes (no multivariate analysis or adjustment but data presented for individual patients) pre-MTX data not available for all		Liver function tests: bilirubin, alkaline phosphatase, SGOT, SGPT, LDH, total proteins	
Effect Size Outcomes							

Incidence of abnormal liver results:

- 7/13 (53.8%) pre-MTX patients
- 29/37 (78.4%) post-MTX patients

Post-MTX group – risk factors:

- AGE: Those with abnormal liver biopsy results were significantly (mean 15 years) older than those with normal results (this difference was only 5 years in the pre-MTX group)
- DIABETES AND OBESITY: of 6 diabetics 5 had liver damage (mild-to-severe fatty change, plus early fibrosis in two), but all of these 5 were also obese and had relatively high cumulative MTX dose (2500-5000 mg); compared with the one diabetic who didn't develop liver damage, who was not obese and not a heaver drinker and had received only 50 mg MTX

Obesity level	**Liver biopsy classification (n)**				
	1	**2**	**3**	**4**	**5**
0	5	7	4	0	3
1	2	2	3	3	1
2	0	1	3	0	1
3	0	1	1	0	0

Diabetes level	**Liver biopsy classification (n)**				
	1	**2**	**3**	**4**	**5**
0	6	11	8	2	4
+	1	0	1	1	1
1+	0	0	2	0	0

Obesity	**Liver biopsy classification (%)**				
	1	**2**	**3**	**4**	**5**
No	26.3	36.8	21.1	0.0	15.8
Yes	11.1	22.2	38.9	16.7	11.1

Diabetes	**Liver biopsy classification (%)**				
	1	**2**	**3**	**4**	**5**
No	19.4	35.5	25.8	6.5	12.9
Yes	16.7	0.0	50.0	16.7	16.7

ALCOHOL: poor correlation between the severity of abnormality on liver biopsy and level of alcohol consumption

Alcohol intake	Liver biopsy classification (n)				
	1	2	3	4	5
0	5	3	2	2	2
1+	2	3	6	0	2
2+	1	5	1	1	1
3+	0	1	0	0	0
4+	0	1	2	0	1

Alcohol intake	Liver biopsy classification (%)				
	1	2	3	4	5
0,1+ (minimal-to-non drinkers)	25.9	22.2	29.6	7.4	14.8
2+-4+ (moderate-to-heavy drinkers)	7.1	50.0	21.4	7.1	14.3

- 21% of moderate-to-heavy drinkers developed cirrhosis vs 9% of minimal-to-non-drinkers (plus 9% with early fibrosis)
- Correlation between level of alcohol consumption and liver biopsy results:

Category	Liver biopsy	
	Abnormal	Normal
Minimal to non drinkers	17 (73.9%)	6 (26.1%)
Moderate to heavy drinkers	13 (92.9%)	1 (7.1%)

- Poor correlation between liver function tests and liver biopsy grade
- No close correlation between total MTX dose and severity of liver damage
- 6 post-MTX patients developed cirrhosis:

Case	Risk factors					
	Excessive	Obesity	Diabetes	Age	MTX cumulative	Other

	alcohol			(years)	dose (mg)	
1	Yes	No	No	50	5000	
5	No	No	No	34	875	
24	Yes	No	No	16	600	Heroin and other addictive drug use; infectious hepatitis
27	Yes	Yes	Yes	56	5000	
31	No	Yes		50	260	
34	Yes	Yes	Yes	47	2520	

Cumulative methotrexate dose is not a risk factor for hepatotoxicity

- No close correlation between the cumulative methotrexate dose and the severity of liver damage.
- Mean cumulative dose at time of biopsies showing fibrosis or cirrhosis (n= 8): 2056 mg vs 2037 mg at time of biopsies graded as no fibrosis (n=33)

Author's conclusion

- Increased alcohol consumption may not necessarily be an additive risk in possible hepatotoxicity from MTX
- The obese, diabetic patient with psoriasis who receives MTX seems to acquire severe hepatic damage

H.12.1.12 STUDY 15

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
U. Wollina, K. Stander, and U. Barta. Toxicity of methotrexate treatment in psoriasis and psoriatic arthritis--short- and long-term toxicity in 104 patients. Clin.Rheumatol. 20 (6):406-410, 2001. Ref ID: WOLLINA 2001	**Observational:** Retrospective case series Data from patient files (department of dermatology and allergology) in a single hospital in Germany	N: 104	**Inclusion criteria:** patients (from Oct 1968 to Oct 1998) with psoriasis or psoriatic arthritis and had MTX treatment. **Exclusion criteria:** Not stated **Parameter** / **Total (N=104)** Mean age – years: 27.7 years (SD 15.1) Gender, male (%): 60 (58) Psoriatic arthritis, N (%): 81 (77.9) Extensive and /or recalcitrant psoriasis vulgaris, N (%): 15 (14.4) Pustular psoriasis, N (%): 6 (5.8) erythrodermic form, N: 2 (1.9)	**Methotrexate**: MTX was given once a week in an individualised dosage (7.5 to 40 mg iv or po) followed by 15 mg folate po the next day 2 groups: - ≤2000 mg (N=23) - >2000 mg (N=81) This cut-off dose was chosen because from literature hepatic ADRs seem to be more common above 1500-2500 mg MTX. **Prognostic factors:** cumulative dose	N/A	Serum enzymes increase: ASAT, ALAT, γ-GT Short-term toxicity: any side-effect within 90 days of starting MTX therapy Long-term toxicity; any side-effect after this time. Severity of ADRs were classified according to the CTC (common toxicity criteria): ranges from 0 (absent) to 4 (very severe, with the need for additional	Not stated

			(%)	**Confounders**: not controlled for		interventions)	

Effect Size

Outcomes

- within 90 days of initiating MTX Tx, 4 patients stopped Tx because of grade 2 side-effects or Tx failure.

Outcome measure	**MTX ≤2000 mg (N=23)**	**MTX >2000 mg (N=81)**	**Difference, p-value**
Serum enzyme increase: Total ASAT ALAT γ-GT	7 (35%) 6 (30%) 6 (30%) 1 (5%)	42 (52%) 40 (49%) 42 (52%) 9 (11%)	0.216 - - -
Serum enzyme increase >2.5 x ULN: Total ASAT ALAT γ-GT	6 (30%) 5 (22%) 5 (22%) 1 (5%)	19 (23%) 17 (21%) 19 (23%) 5 (6%)	
Serum enzyme increase >5 x ULN:	1 (5%)	5 (6%)	0.888

Total			
Liver changes	3 (15%)	27 (33%)	0.102
Total	3 (15%)	26 (32%)	-
Steatosis hepatis (by sonography)	0 (0%)	1 (1.2%)	-
Liver cirrhosis (by biopsy)			

Note: biopsy only performed in 12 patients with sonographically confirmed steatosis hepatis (not even all those with this diagnosis)

Author's conclusion

- Liver changes and serum enzyme level increases were not significantly more frequent in the higher cumulative dose group

H.12.1.13 STUDY 16

Reference	Study type	Number of patients	Patient characteristics	Intervention/Prognostic factors	Length of follow-up	Outcome measures	Source of funding
R. J. van Dooren-Greebe, A. L. Kuijpers, J. Mulder, T. de Boo, and P. C. van de Kerkhof. Methotrexate revisited: effects of long-term treatment in psoriasis. Br.J.Dermatol. 130 (2):204-210, 1994. Ref ID: VAN DOOREN-GREEBE 1994	**Observational:** Retrospective case series Patient records from a single hospital in The Netherlands (Aug 1970 to July 1992)	N=113 (N=25 still taking MTX at end of the study) Tx discontinued in 71 cases and 17 patients were lost to follow-up. N=2 patients died during MTX therapy (carcinoma and MI)	**Inclusion criteria:** Patients with psoriasis treated with MTX. The indication for MTX therapy was severe psoriasis unresponsive to local therapy, photo(chemo)therapy or oral retinoids. **Exclusion criteria:** Contraindications to therapy; people with cytopenia, abnormal liver function tests, infectious diseases, receiving concomitant medication which might interact with MTX, pregnant women or those wishing to become pregnant (and male partners of those wishing to become pregnant) **Parameter** / **Mean** / **Range** Age, years / 45.5 / 17–81 Gender, male N / 66 / - Recalcitrant / 95 / -	**Methotrexate**: Mean cumulative dose: 4803 mg (range 90 mg to 16580 mg). Weekly dosage did not exceed 15 mg in any patient. Oral MTX: Tx started 3 x 5 mg/week or 3 x 2.5 mg/week (from 1986 onwards), and thereafter gradual dose adjustments were made until a satisfactory minimum maintenance level was reached. Maximum dosage was 15 mg/week. **Techniques:** • From 1983 onwards policy to perform liver biopsies before Tx or during the first 3 months of Tx, and after	Mean duration of therapy: 8 years, 11 months (range 8 weeks to 20 years)	liver biopsy features, liver function tests, adverse events	None stated

			psoriasis vulgaris, N	(84%)		every 1.5 g of MTX. In N=108 of the patients, concomitant Tx was intermittently given in limited amounts **Histological techniques:** Biopsy method unclear Biopsy graded according to Roenigk classification **Prognostic factors:** cumulative dose **Confounders**: not controlled for			
			erythrodermic psoriasis, N	1 (9%)	-				
			generalised pustular psoriasis, N	2 (2%)	-				
			annular pustular psoriasis, N	1 (1%)	-				
			Concomitant Tx (N)						
			Topical CS	105	-				
			Short contact dithranol (home Tx)	15	-				
			coal tar products	10	-				

Effect Size

Outcome measure	N (%)
Abnormal liver function tests	37 (33)

Liver biopsy classification	
0 (not evaluable)	2 (4)
I (normal histology / minimal disturbances)	35 (62)
II (moderate to severe fatty infiltration)	9 (17)
IIIA (mild portal fibrosis)	6 (11)
IIIB (moderate to severe portal fibrosis)	1 (2)
IV (cirrhosis)	2 (4)
Total	55 (100)

- Analysis showed that there was no clear relation between liver biopsy classification and cumulative dose of MTX or duration of therapy (data shown on a graph)

Cumulative dose (mg)	**Biopsy grade**				
	I N=30	**II N=9**	**IIIA N=6**	**IIIB N=1**	**IV N=2**
0-2000	7 (23.3%)	1 (11.1%)	0	0	1 (50%)
2001-4000	5 (16.7%)	4 (44.4%)	3 (50%)	1 (100%)	0
4001-6000	7 (23.3%)	2 (22.2%)	2 (33.3%)	0	0
6001-8000	5 (16.7%)	1 (11.1%)	1 (16.7%)	0	0
8001-10000	6 (20.0%)	1 (11.1%)	0	0	0

10,001-12,000	0	0	0	0	1 (50%)

However, in the high dose group (>1.5g): 32/40 (80%) had grades I-II and 8/40 (20%) had grades IIIA-IV while in the low dose group (≤1.5g): 7/8 (87.5%) had grades I-II and 1/8 (12.5%) had grades IIIA-IV

Authors' conclusion

- Low dose MTX (≤ 15 mg/week) is a relatively safe therapy for severe psoriasis, if patients are carefully selected beforehand and regular monitoring of side-effects and drug interactions are performed during therapy
- A liver biopsy during the first 3 months of Tx, and subsequently after each 1.5 mg of MTX, should be part of the Tx protocol, until equally reliable non-invasive screening methods for liver damage are developed.

H.12.1.14 STUDY 17

Reference	Study type	Number of patients	Patient characteristics	Intervention/Prognostic factors	Length of follow-up	Outcome measures	Source of funding
S. Khan, D. Subedi, and M. M. Chowdhury. Use of amino terminal type III procollagen peptide (P3NP) assay in methotrexate therapy for psoriasis. Postgrad.Med.J. 82 (967):353-354, 2006. Ref ID; KHAN 2006	**Observational:** Retrospective case series Patient records from a single hospital in Cardiff, Wales (1999 to 2003)	N=65	**Inclusion criteria:** Patients with moderate to severe psoriasis treated with MTX. **Exclusion criteria:** Not stated **Baseline details:** not given	**Methotrexate**: Mean cumulative dose: 2000 mg (SD 1838 mg). **Histological techniques:** Biopsy by Tru-Cut needle; graded according to Roenigk classification **Prognostic factors:** cumulative dose **Confounders:** not controlled for	Mean duration of therapy: total of 278.9 years with a follow-up period of 1-14 years and mean duration of 4.3 (SD 3.9) years.	Liver biopsy histology, P3NP assays, liver function tests	Stated as: none.

Effect Size

- Patients with high mean P3NP levels (>4.2 µg/l) had received significantly higher cumulative dose (>1.5 g) MTX (p=0.002)
- The cumulative dose of MTX had significant correlation with the maximum P3NP levels (p=0.03)
- Long duration (>3 years) of MTX treatment, irrespective of the cumulative dose, was consistent with high (>4.2 ug/l) mean and maximum P3NP values but did not reach significance (p=0.217, p=0.112 respectively).
- 28% of P3NP estimations >4.2 ug/l correlated at some stage with an abnormal liver biopsy
- The median P3NP of those with abnormal liver histology was higher than other patients (>5.8 ug/l)
- Those with fibrosis or cirrhosis (n=4) had received a higher cumulative dose of MTX (median = 4260 mg; mean = 4247.5 mg) than those without fibrosis or cirrhosis (median = 3585 mg; mean = 3811.3 mg).

H.12.2 Cohort Studies – treated and untreated groups or different population groups

H.12.2.1 STUDY 1

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
J. Almeyda, D. Barnardo, H. Baker, G. M. Levene, and J. W. Landells. Structural and functional abnormalities of the liver in psoriasis before and during methotrexate therapy. Br.J.Dermatol. 87 (6):623-631, 1972. Ref ID: ALMEYDA1972	**Observational:** Retrospective cohort	N: 67 (42 treated)	**Inclusion criteria:** Not stated **Exclusion criteria:** Not stated **Parameter** / **Treated (n=42)** / **Untreated (n=25)** Mean age – years: 55 / 48 Cumulative MTX dose (mg), mean (range): N/A / N/A Duration of psoriasis (years), 17 (8-47) / 18 (1-35)	**Methotrexate**: 3 dosing schedules - 2.5 mg orally 4 or 5 days a week (or daily on alternate weeks) n=11 - 12.5-25 mg orally once a week (n=18) - 20-40 mg intramuscular or intravenous at weekly or greater intervals **Histological techniques:** Biopsy by Menghini or Vim Silverman needles; staining with H&E, iron, reticulin and van Giesen stains	N/A	Hepatotoxicity by biopsy: fibrosis or cirrhosis Liver function tests: bilirubin, aminotransferase, alkaline phosphatase Fibrosis grading: 0: none; 1: sparse intralobular; 2: just bridging portal tracts; 3: bridging portal tracts	One author in receipt of a MRC grant

mean (range)					

Parameter	All (n=67)
Gender M/F (%)	58/42
Severe disease - Widespread discoid - Erythrodermic - Generalised pustular	61.9% 21.4% 16.7%
History of liver disease - Jaundice (due to hepatitis) - Cholelithiasis	1/67 3/67

Definitions

Alcohol intake

Light or nil:

Moderate:

Heavy: regular average daily intake >3.5 litres beer or equivalent

Prognostic factors: alcohol, cumulative dose

Confounders

Those who developed fibrosis or cirrhosis had significantly greater mean cumulative dose of MTX than those with normal biopsies (p=0.05);

no SS differences in duration of treatment between those with and without abnormal biopsies;

the 3 patients with cirrhosis received MTX for a mean of

				52 months vs 33 months for those with normal biopsies; the 3 patients with cirrhosis had all received MTX by the daily oral regime, but fibrosis was found with approximately equal frequency in all 3 regimes Note: most patients had previously been exposed to tar, dithranol or corticosteroids			

Effect Size

Outcomes

Summary

- **Alcohol consumption may be a risk factor for cirrhosis**
  - 3/3 (100%) with cirrhosis had heavy alcohol intake
  - 0/12 (0%) with fibrosis had heavy alcohol intake
  - 2/10 (20%) with minor liver abnormalities had heavy alcohol intake
  - 2/17 (12%) with normal histology had heavy alcohol intake

- Of 25 untreated patients none had cirrhosis but 4 had fibrosis (16%) – this is compared with 31.6% fibrosis and 7.9% cirrhosis in the treated group
- Of the 4 untreated patients who developed fibrosis 1 (25%) had heavy alcohol intake

- Liver function test results did not correlate with histologically determined liver abnormalities

Cumulative methotrexate dose is a risk factor for fibrosis and cirrhosis

The mean cumulative dose of methotrexate was significantly higher in those with fibrosis and cirrhosis compared with those with normal liver biopsy, p=0.05.

Histology	Mean cumulative dose ±SE (g)
Normal	0.96±0.24
Non-specific changes	1.06±0.21
Fibrosis	1.54±0.34
Cirrhosis	2.73±1.19

The patient with the highest cumulative dose of 5.35g had a normal biopsy, although most of those with a normal biopsy had received less than 1.0g.

Author's conclusion

- Alcohol may be an important additive factor in the production of liver damage

STUDY 2

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>L. T. Reese, J. W. Grisham, R. D. Aach, and A. Z. Eisen. Effects of methotrexate on the liver in psoriasis. J.Invest.Dermatol. 62 (6):597-602, 1974.

Ref ID: REESE1974</td>
<td>Observational: Prospective cohort

Washington University Medical Centre</td>
<td>N: 70 (35 treated)</td>
<td>Inclusion criteria: psoriasis considered severe enough to require MTX

Exclusion criteria: Not stated

<table>
<tr><th>Parameter</th><th>Treated (n=35)</th><th>Untreated (n=35)</th></tr>
<tr><td>Mean age – years</td><td>43.4</td><td>42.9</td></tr>
</table>
</td>
<td>Methotrexate:

Post-biopsy dosing: single intermittent (IM or oral) but moderately high doses (25-50 mg); some cases used the divided dose, intermittent oral schedule over a 36-h period.

Histological techniques:

Biopsy with Menghini 1-sec technique; staining with H&E, Masson’s trichrome

Definitions

Alcohol intake
1. No to minimal intake (1-2 ox hard liquor or equivalent)</td>
<td>Studied at periods of 6-12 months</td>
<td>Hepatotoxicity by biopsy: non-diagnostic changes, fibrosis or cirrhosis

Grading: 0-4 scale including the following parameters: hyperploid nuclei, fat, inflammation, fibrosis (similar to Scheuer), necrosis degeneration

Liver function tests: bilirubin, alkaline phosphatase, SGOT, SGPT, BSP</td>
<td>US Public Health Service Research Grants AM 05611 and RR 00036</td>
</tr>
</table>

				2. Moderate-to-excessive intake (regular daily intake or sporadic heavy use) Alcohol abstinence encouraged following biopsy **Prognostic factors:** alcohol, cumulative dose **Confounders** Multivariate analysis: alcohol, MTX dose, MTX duration			

Effect Size

Outcomes

Summary

- **No clear association between alcohol consumption and hepatotoxicity in treated patients**

	No to low alcohol intake (n=16)	**Moderate-to-high alcohol intake (n=19)**
BSP abnormal	5/13 (38.6%)	6/14 (42.9%)

Normal biopsy	6 (37.5%)	1 (5.3%)
Non-diagnostic changes (excl. mild fibrosis)	5 (31.2%)	11 (57.9%)
Mild fibrosis	3 (18.8%)	6 (31.6%)
Fibrosis	1 (6.3%)	1 (5.3%)
Cirrhosis	1 (6.3%) Comorbid diabetes	0

- **Potential association between alcohol consumption and hepatotoxicity in untreated patients**

	No to low alcohol intake (n=17)	**Moderate-to-high alcohol intake (n=18)**
BSP abnormal	7/16 (43.8%)	8/16 (50.0%)
Normal biopsy	5 (29.5%)	1 (5.6%)
Non-diagnostic changes (excl. mild fibrosis)	11 (64.7%)	9 (50%)
Mild fibrosis	1 (5.9%)	7 (38.9%)
Fibrosis	0	1 (5.6%)
Cirrhosis	0	0

- BSP level showed a modest association with histological changes in those in whom it was performed

- Multivariate analysis:

- No significant effect of MTX (treated vs untreated); p=0.4
- Statistically significant effect of alcohol intake on biopsy histology ($p < 0.001$), mostly due to fat score and to a lesser extent the fibrosis score
- But, moderate-to-excess alcohol plus MTX showed no greater tendency to fat or fibrosis than other groupings
- Continuous therapy (any dose or duration) may result in more hyperploid nuclei and fibrosis ($p = 0.02$); c.f. intermittent regimen shows no evidence of significant hepatic damage.

Cumulative dose effect (in subset of 21 patients with repeat biopsies)

- No progression of fibrosis was found in those with follow up biopsies (average dose of methotrexate between biopsies was 823mg).

Author's conclusion

- MTX can cause cirrhosis in the absence of alcohol ingestion
- The adverse effect of alcohol on the liver may be synergistic with the potential hepatotoxic action of MTX, but more data are needed

H.12.2.2 STUDY 3

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
H. Amital, Y. Arnson, G. Chodick, and V. Shalev. Hepatotoxicity rates do not differ in patients with rheumatoid arthritis and psoriasis treated with methotrexate. Rheumatology 48 (9):1107-1110, 2009. Ref ID: AMITAL 2009	**Observational:** Retrospective cohort Database of patients in Israel	N: 809 (n=690 psoriasis, n=119 RA)	**Inclusion criteria:** Cases of psoriasis and RA diagnosed between Jan 1998 and July 2007. Patients diagnosed with Psoriasis, RA or PsA. **Exclusion criteria:** Not stated **Parameter** / **Psoriasis (n=690)** / **RA (n=119)** Mean age – years: 52.6 / 59.9 Gender, male (%): 333 (48.3) / 41 (34.5) Cumulative MTX dose (mg), median (range): 1000 / 3625 Weekly dose (mg): 19.0 / 20.0	**Methotrexate**: **Median dose:** • Psoriasis group: 1000 mg cumulative dose (dispensed at average amount of 182 mg) • RA group: 3625 mg cumulative dose (dispensed at average amount of 195 mg per prescription) **Prognostic factors:** cumulative dose **Definitions**	Mean follow-up: 883 days (psoriasis group) and 843 days (RA group).	Liver function tests: GGT, ALKP, AST and albumin	Not stated

			median	Elevated liver enzymes: anything above ULN **Confounders**: controlled for age, gender, cumulative dose as a time-dependent variable			

Effect Size

Outcomes

- RA patients did not differ from patients with either psoriasis or PsA in the rates of elevated liver function tests (or for each test separately).
- Analysis of risk showed that an elevation in liver enzymes was found to be related to the cumulative dose of MTX
  - Combined results for GGT/ALKP/AST: HR 1.07, 95%CI 1.01 – 1.12, p=0.01
  - AST: HR 1.07, 95% CI 1.02 – 1.12, p<0.001
- However there was no relationship for the following liver enzymes:
  - ALKP: HR 1.01, 95% CI 0.95 – 1.08, p=0.69
  - GGT: HR 0.86, 95% CI 0.70 – 1.04, p<0.12
  - Albumin: HR 0.97, 95% CI 0.70 – 1.34, p=0.85

H.12.3 Case-Control Study

H.12.3.1 STUDY 1

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
H. Zachariae, E. Grunnet, and H. Sogaard. Liver biopsy in methotrexate-treated psoriatics-a re-evalution. Acta Derm.Venereol. 55 (4):291-296, 1975. Ref ID: ZACHARIAE1975	**Observational:** Case-control	N: 139	**Cases** **Inclusion criteria:** severe psoriasis **Exclusion criteria:** Not stated No baseline data presented **Controls** 18 patients with Parkinson's considered for L-DOPA treatment; 42 biopsies from 6-58 hours after sudden death due to cardiac failure or traffic accidents	**Methotrexate**: Initially IM weekly 10-50 mg (occasionally shorter or longer intervals) Post-1971: divided-dose intermittent oral dose schedule over 36-h period **Histological techniques:** Biopsy by Menghini technique; staining with H&E and van Gieson **Prognostic factors:** alcohol **Definitions**	Unclear	Hepatotoxicity: Steatosis, nuclear variability, periportal inflammation, focal necrosis, fibrosis, cirrhosis Liver function tests: alkaline phosphatase, SGPT, BSP **Grading of 1-4 for each of**: Fatty infiltration, periportal inflammation, nuclear variability, focal necrosis, cholestasis and fibrosis (1: not present; 2: slight; 3: moderate; 4:severe); plus presence or	None stated

				High alcohol intake: >4 drinks per day **Confounders**: not controlled for		absence of cirrhosis	

Effect Size

Outcomes

Summary

- **In pre-MTX biopsies, fibrosis was significantly increased in patients with the highest alcohol intake (p<0.05); following MTX this difference disappeared:**
- **No significant association between alcohol consumption and hepatotoxicity in MTX-treated patients**
  - 6/76 (7.9%) with low alcohol consumption developed cirrhosis; 0/20 with moderate or high alcohol consumption developed cirrhosis
  - No significant difference in average biopsy grading between high and low alcohol consumers for fibrosis

Drinks per day prior to MTX	**N**	**Average grading**					**Cirrhosis**
		Steatosis	**Nuclear variability**	**Periportal inflammation**	**Focal necrosis**	**Fibrosis**	
<1	76	2.00±0.10	1.97±0.09	1.37±0.07	1.57±0.06	1.28±0.06	6
1-3	10	1.90±0.28	1.70±0.30	1.20±0.13	1.10±0.10	1.00±0.00	0
≥4	10	2.70±0.26	2.40±0.34	1.60±0.22	1.70±0.21	1.20±0.13	0

- Non-significant trend towards increased fibrosis and cirrhosis in treated vs untreated patients (only fatty infiltration found to be significantly increased; $p<0.05$)
- Significantly more liver abnormalities in people with psoriasis than in controls (with Parkinson's disease or death due to sudden cardiac failure or traffic accidents; $p<0.05$)
- Cirrhosis can occur with no or very small abnormalities in laboratory liver function tests

Author's conclusion

- A history of alcohol consumption correlated significantly with liver fibrosis in *pre*-MTX biopsies but not in *post*-MTX biopsies, where other factors seems to influence the data (e.g., dosing schedule)

H.13 Biological therapy

H.13.1 Stratified Case Series/Within-Group Comparisons

H.13.1.1 STUDY 1

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
A. Mazzotta, M. Esposito, A. Costanzo, and S. Chimenti. Efficacy and safety of etanercept in psoriasis after switching from other treatments: an observational study. Am.J.Clin.Dermatol. 10 (5):319-324, 2009.	**Observational:** Prospective case series **Washout period:** 4 weeks **Representative population sample:** Recruited from academic dermatology out-patient clinic **Confounders adjusted for:**	N: 234	**Inclusion criteria:** Aged 18-80; moderate-to-severe plaque-type psoriasis; unsatisfactory clinical response/loss of efficacy (<PASI50) or resistance (AEs that could compromise treatment continuation or poor compliance) to traditional or biologic systemic agents **Exclusion criteria:** Co-morbid conditions that were contraindications to anti-TNF-α treatment **Parameter** / **Psoriasis only (n=124)** / **Concomitant PsA (n-110)**	**Etanercept** (self-administered subcutaneously): 50 mg twice weekly for first 12 weeks reduced to 25 mg twice weekly for remaining 12 weeks	Treatment duration: 24 weeks	Change in PASI PASI75 PASI50 AEs	None

Ref ID: MAZZOTTA 2009	not assessed **Minimal attrition bias:** unclear **Outcomes adequately measured:** Yes **Appropriate statistical analysis:** yes		Mean age – years (±SD)	44.0±13.5	50.4±12.3				
			Male (%)	65.3%	60.9%				
			Previous treatment						
			CSA	104	66				
			PUVA	49	17				
			Retinoids	35	20				
			Corticosteroids	33	54				
			MTX	32	66				
			Biologics	**27**	**30**				
			Infliximab	23	30				
			Efalizumab	4	0				
			Fumaric acid esters	7	4				

Effect Size

Outcomes

Efficacy

Psoriasis only cohort

Parameter	Patients (%)	p-value

			(between groups)
	Previous biologic (n=26)	No previous biologic (n=98)	
Baseline PASI	14.5±5.2	16.1±7.1	NS
Week 12			
PASI score	5.4±3.8	4.9±4.0	NS
PASI50	18 (69.2%)	79 (80.2%)	NS
PASI75	8 (30.8%)	43 (43.7%)	NS
Week 24			
PASI score	4.0±4.5	2.8±3.4	NS
PASI50	18 (69.6%)	88 (89.9%)	0.013
PASI75	17 (65.2%)	74 (75.3%)	NS

Concomitant PsA cohort

Parameter	**Patients (%)**		**p-value (between groups)**
	Previous biologic (n=30)	**No previous biologic (n=80)**	
Baseline PASI	8.0±6.8	8.9±8.3	NS
Week 12			
PASI score	2.9±2.6	2.9±3.7	NS
PASI50	18 (59.3%)	53 (65.7%)	NS

PASI75	11 (37.0%)	36 (45.2%)	NS
Week 24			
PASI score	3.0±2.9	1.2±1.8	0.0010
PASI50	14 (45.8%)	74 (92.3%)	<0.0001
PASI75	9 (29.2%)	59 (73.8%)	<0.0001

Adverse events

- Not stratified by previous biologic exposure

Author's conclusion

- Etanercept may represent a valid, effective and well-tolerated therapeutic alternative treatment for patients with plaque-type psoriasis who have failed to respond to other biologic therapies
- However, etanercept had a lower efficacy in patients who have previously not responded to biologic therapy

H.13.1.2 STUDY 2

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
Van L, Modi SV, Yang DJ, Hsu S. Sustained Efficacy and Safety of Adalimumab in Psoriasis Treatment: A Retrospective Study of 49 Patients With and Without a History of TNF-Antagonist Treatment. Arch.Dermatol. 144 (6):804-806, 2008. Ref ID: VAN2008	**Observational:** Retrospective case series (medical chart review) **Washout period:** Patients switched from infliximab therapy had a washout period of at least 2 months, and those switched from etanercept or efalizumab had a washout period of at least 2 weeks. **Representative population sample:** Recruited from Baylor College of Medicine dermatology clinic; unclear how many (if any) had concomitant PsA **Confounders adjusted for:** not assessed	N: 49 Drop-outs: 9 (18.3%) discontinued before 12 months: 3 due to AEs 3 due to primary lack of efficacy 2 due to secondary lack of efficacy 1 lost to follow-up	**Inclusion criteria:** moderate-to-severe plaque psoriasis; started treatment with adalimumab injections at least 12 months previously **Note**: Patients who had undergone prior therapy with biological agents were switched to adalimumab therapy only after they had experienced lack or loss of efficacy with their prior treatment. **Exclusion criteria:** Not stated **Parameter** / **All (n=49)** **Biologics** / **39 (80%)** Anti-TNF-α / 37 (76%) Efalizumab / 6 (12%) Infliximab / 29 (59%)	**Adalimumab**, 40 mg weekly After 12 weeks patients whose disease was determined to be "clear" or "almost clear" by PGA had their doses decreased to once every 2 weeks, while the remainder continued weekly dosing for another 3 months. Patients were then reassessed at 3- to 6-month intervals, during which the dermatologist decreased the dosing frequency to once every 2 weeks or continued the weekly	**Treatment duration:** up to 12 months	Clear or nearly clear on PGA AEs	Not stated

	Minimal attrition bias: borderline – 18.3% **Outcomes adequately measured:** unclear **Appropriate statistical analysis:** unclear		Etanercept: 15 (31%)	schedule, depending on individual response.			

Effect Size

Outcomes

Efficacy (ITT analysis)

Initial response (not stratified)

Overall	**All (n=49)**
Clear or nearly clear	
3 months	43 (88%)
6 months	3

9 months	1
Continued weekly dosing (no response at 9 months)	2

Sustained response (stratified)

Parameter	**Patients (%)**		
	Previous biologic (n=39)	**Previous anti-TNF-α (n=37)**	**No previous biologic (n=10)**
12 months (sustained efficacy)			
Clear or nearly clear	31 (79%)	29 (78%)	7 (70%)

Adverse events

- Not stratified by previous biologic exposure
- No complications were observed during transitions from prior biological agents

Author's conclusion

- Patients with psoriasis who have received prior anti-TNF-a can expect a sustained clinical response to adalimumab.

H.13.1.3 STUDY 3

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
N. Cassano, A. Galluccio, Simone C. De, F. Loconsole, S. D. Massimino, A. Plumari, S. Dattola, Guerra A. Puglisi, L. Donato, F. Cantoresi, Pita O. De, G. Fenizi, V. Altamura, M. Congedo, R. Pellicano, and G. A. Vena. Influence of body mass index, comorbidities and prior systemic therapies on the response of psoriasis to adalimumab: an exploratory analysis from the APHRODITE data. *J.Biol.Regul.Homeost.Agents* 22 (4):233-237, 2008. Ref ID: CASSANO2008 Based on the original study: G. A. Vena, A. Galluccio, Simone C. De, V. Mastrandrea, R. Buquicchio, Greca S. La, S. Dattola, Guerra A. Puglisi, L. Donato, F. Cantoresi, Pita O. De, M. Pezza, D. Agostino, R.	**Observational:** Open label prospective case series (multicentre) **Washout period:** at least 2 weeks for topicals, 4 weeks for conventional systemics, and 12 weeks for biologics **Representative population sample:** No – 100 % with concomitant PsA) **Confounders adjusted for:** unclear **Minimal attrition bias:** yes **Outcomes adequately**	N: 147 **Drop-outs:** 3 (2.0%)	**Inclusion criteria:** adults with active PsA and chronic plaque psoriasis; moderate to severe disease (>10% BSA and PASI ≥10 or <10% BSA but lesions localised on visible difficult to treat sites e.g., hands and face) **Exclusion criteria:** Pregnancy and lactation, any active infection, latent or recurrent infectious diseases (including latent TB or seropositivity for hepatitis B and C); history of demyelinating diseases, heart failure, lupus erythematosus, immunodeficiencies, cancer or lymphoproliferative disease (other than successfully treated BCC) **Parameter** / **All (n=144)** % male / 51% Mean age – years / 48.6 (20-75) Psoriasis duration, mean / 15.2	**Adalimumab**, (subcutaneously) 40 mg every other week **Note:** concomitant therapies active in either PsA or psoriasis not permitted (except emollients and episodic administration of	**Treatment duration:** up to 12 weeks	PASI75 PASI50 PASI90 not stated as an outcome in methods but reported in results	Not stated

Vernaci, A. Miracapillo, G. Valenti, and N. Cassano. A multicentre open-label experience on the response of psoriasis to Adalimumab and effect of dose escalation in non-responders: the Aphrodite project. Int.J.Immunopathol.Pharmacol. 22 (1):227-233, 2009. REF ID VENA2009	**measured:** unclear (and PASI90 reported although explicitly said not to be an outcome in the methods due to lack of statistical power) **Appropriate statistical analysis:** unclear		years PsA duration, mean years: 7.6 Mean PASI: 18.8 Mean BSA: 22.1% Regular alcohol consumption: 29% Smokers: 32% Weight (kg): 74.8 (43-118) Concomitant treatment for comorbidities: 29% Previous use of biologics*: 56 (39%) ***Note:** the previous biologics were infliximab and/or etanercept in all but 2 cases (who used efalizumab)	NSAIDs) Patients requiring other concomitant strategies were considered non-responders and were withdrawn from the study analysis			
Effect Size Outcomes **<u>Efficacy (ACA); week 12</u>**							

Parameter	Patients (%)
	All (n=144)
PASI75	65 (45%)

Note: response rates at week 12 in non-stratified sample independent of gender, smoking, alcohol consumption, hypertension and/or metabolic comorbidities (p>0.05)

- Total response rate: PASI50 = 111 (77%); PASI75 = 65 (45%)
- There was no consistent or significant differences in the PASI50 response rates between patients previously treated with only traditional systemics and those treated with biologics (p>0.05)
- Among **responders** (at least PASI50) the likelihood of achieving PASI75 was higher in patients who were naïve to biologics (47.5%) compared to those who had been treated with biologics in the past (26%); p=0.03

Author's conclusion

- Previous use of biologics did not appear to affect the rate of responders per se, although it was associated with a lower PASI75 rate among responders

H.13.1.4 STUDY 4

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
K. Papp, V. Ho, H. D. Teixeira, K. Guerette, K. Chen, and C. Lynde. Efficacy and safety of adalimumab when added to inadequate therapy for the treatment of psoriasis: results of PRIDE, an open-label, multicentre, phase IIIb study [submitted]. J.Eur.Acad.Dermatol.Venereol., 2012. REF ID PAPP2012	**Observational:** Open label prospective case series (multicentre; 23 sites in Canada – routine care) **Washout period:** NA – concomitant therapies permitted **Representative population sample:** Yes **Confounders adjusted for:** unclear **Minimal attrition bias:** yes	N: 203 **Drop-outs:** 11.8% (4.4% due to adverse events)	**Inclusion criteria:** Adult patients (at least 18 years of age) with a clinical diagnosis of psoriasis for at least 6 months and stable plaque psoriasis for at least 2 months prior to entry; moderate to severely active plaque psoriasis (BSA> 10% and a PASI score ≥12; active psoriasis despite treatment with topical agents; failure to respond to, intolerant to, or unable to access phototherapy; failure to respond to, intolerant to or contraindicated for at least two of the following therapies: Ciclosporine A, methotrexate and/or oral retinoids. **Exclusion criteria:** Pregnancy, other active skin diseases or infections present, erythrodermic, pustular, medication-induced or -exacerbated psoriasis, or new onset guttate psoriasis as the primary morphology of psoriasis. **Parameter** | **All (n=203)**	**Adalimumab**, self- administered Loading dose of 80 mg adalimumab SC at baseline, followed by 40 mg SC every other week starting at week 1 **Note: concomitant therapies** Doses and regimens of concomitant medications	**Treatment duration:** min 24 weeks	PASI75	Abbott Laboratories

	Outcomes adequately measured: yes **Appropriate statistical analysis:** yes: Comparisons between patient subgroups used ANOVA with subgroup as a main effect for continuous scale variables and the Fisher's Exact test for categorical variables. The 95% confidence intervals for binomial proportion are provided by exact (Clopper-Pearson) method. ITT analysis: yes (non-responder imputation)		% male: 61.1% Mean age – years (SD): 45.5 (12.3) Psoriasis duration, mean years (SD): 22.2 (11.5) Mean PASI (SD): 20 (7.9) Mean BSA (SD): 27.3% (17.1%) PsA: 75 (36.9%) Mean DLQI (SD): 12.8 (6.98) Weight (kg), mean (SD): 94.8 (23.9) Prior and concomitant psoriasis therapy (n [%]) Phototherapy (any time before baseline): 169 (83.3) Topical treatments (within 12 months before baseline): 109 (53.7)		and therapies for the treatment of psoriasis that the patient was receiving at baseline (topical, systemic or phototherapy) could be tapered off, stopped or remain stable from baseline until week 16. BUT The initiation of new topical therapies (with the exception of topical therapies for the palms, soles of feet, axilla and groin), the initiation of new systemic therapies or an increase in the dosing regimen of existing			

			Systemic non-biologic (any time before baseline) - corticosteroids - tazarotene - acitretin - ciclosporine - methotrexate - other	149 (73.4) 3 (1.5) 4 (2.0) 57 (28.1) 51 (25.1) 101 (49.8) 27 (13.3)	therapies, and the initiation of or an increase in the existing regimen and frequency of UVB phototherapy could not occur before the week 16 visit.			
			Systemic Biologic (any time before baseline) - etanercept - infliximab - alefacept - efalizumab - ustekinumab - other	78 (38.4) 25 (12.3) 16 (7.9) 18 (8.9) 17 (8.4) 18 (8.9) 14 (6.4)				
			Note: for subgroup analysis 'failure' of previous therapy was defined as				

			either never achieving a satisfactory response or achieving a satisfactory response but losing it over time				

Effect Size

Outcomes

Note: Biologic therapies, which had been used by 38.4% of patients, were discontinued largely due to lack of efficacy or the termination of the clinical study/investigation in which the biologic had been administered.

A total of 137 patients (67.5%) received concomitant therapies for psoriasis; the most commonly used medications (≥5% of patients) were corticosteroids (40.4%), vitamin D and analogues (17.7%), and methotrexate (11.3%). Ten patients (4.9%) received phototherapy during this study. The most commonly used (occurring in ≥5% of patients) concomitant medications were paracetamol (18.2%); acetylsalicylic acid (13.8%), ibuprofen (12.3%), atorvastatin (10.3%), hydrochlorothiazide (8.4%), and ramipril (8.9%).

PASI75 (ITT)

PASI75	**Patients (%)**						
	All (n=203)	**No prior biologics (N=125)**	**Prior biologics (N=78)**	**Prior anti-TNF (N=37)**	**Failed prior biologic (N=40)**	**Failed prior anti-TNF (N=17)**	**Failed ≥2 biologics (N=25)**
Week 16	144 (70.9%)	93 (74.4%)	51 (65.4%)	27 (73.0%)	24 (60.0%)	12 (70.6%)	17 (68.0%)
Week 24	140 (69.0%)	92 (73.6%)	48 (61.5%)	28 (62.2%)	24 (60.0%)	10 (58.8%)	14 (56.0%)

Author's conclusion

- In patients who had failed previous biologic treatment, PASI 75 response rates at weeks 16 and 24 were good, including patients who had failed previous treatment with etanercept

H.13.1.5 STUDY 5

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
P.M. Laws , A.M. Downs, R. Parslew, B. Dever, C.H. Smith, J.N. Barker, B. Moriarty, R. Murphy, B. Kirby, A.D. Burden, S. McBride, A.V. Anstey, S. O'Shea, N. Ralph, C. Buckley, C.E.M. Griffiths, R.B. Warren. Practical experience of Ustekinumab in the treatment of psoriasis: experience from a multicentre, retrospective case cohort study across the U.K. and Ireland Not yet published RefID:	**Observational:** Open label retrospective case series; 10 centres in the UK and Ireland **Washout period:** NA – concomitant therapies permitted **Representative population sample:** Yes – included all who had completed 16 wk treatment (or stopped due to adverse events) between March 2009 and October 2010 outside clinical trials **Confounders adjusted for:** no	N: 129 **Drop-outs:** NA	**Inclusion criteria:** included all who had completed 16 wk treatment (or stopped due to adverse events) between March 2009 and October 2010 outside clinical trials **Exclusion criteria:** none stated **Parameter** / **All (N=129)** Age (years): 46.0 ± 11.4 Sex (male): 69 (53.5%) Weight (kg): 93.7 ± 25.0 BMI (kg/m^2): 32.4 ± 8.7 Obesity (%): 51/93 (54.8%) Smoking (yes): 51 (39.5%) PsA: 45 (34.9%) Depression: 35 (27.1%) Disease: 24.3 ± 10.2	**Ustekinumab**, induction therapy at weeks 0 and 4 and then every 12 weeks. Weight dependent dosing: ≤100kg given 45mg >100kg given 90mg **Overlap therapy:** medication co-prescribed during induction of ustekinumab therapy	**Treatment duration:** min 16 weeks	PASI75	None

LAWS2011	**Minimal attrition bias:** NA **Outcomes adequately measured:** yes **Appropriate statistical analysis:** yes **ITT analysis:** No: analysis performed on an available case basis throughout and therefore excludes 'drop outs' due to adverse events.		duration (years) PASI: 22.9 ± 10.1 Alcohol Nil: 60 (48.8%) Up to weekly limit: 48 (39.0%) Excess: 9 (7.3%) **Number of previous systemics*** 0: 1.6 (2/129) 1-2: 33.3 (43/129) 3-4: 52.7 (68/129) ≥5: 12.4 (16/129) * Includes methotrexate, ciclosporin, acitretin, fumaric acid esters, hydroxycarbamide, mycophenolate mofetil, azathioprine.		**Rescue therapy:** was defined as additional medication required following the induction phase.			
Effect Size Outcomes							

Note: 10/80 who achieved PASI75 at week 16 received overlap therapy during induction; 4 of these were still on an additional systemic therapy at 16 weeks. Additional therapies included: ciclosporin (n=5), methotrexate (n=4) and acitretin (n=1). Of these 10, 7 had had previous biologic exposure and 3 were biologic naïve

Also, of the 47 patients failed to achieve a PASI >75, 19 patients had additional systemic therapy (18 received treatment as overlap and 1 as rescue). Of the 19 patients 3 were biologic naïve. The patient who received rescue therapy was biologic naïve.

Efficacy at week 16 (ACA)

	Patients (%)			
	All (n=127)	**No prior biologics (N=21)**	**Prior biologics (N=106)**	**p-value (biologic vs naïve)**
PASI75	80 (63.0%)	16 (76.2%)	64 (60.4%)	0.14

	Patients (%)			
	All (n=127)	**None or 1 prior biologics (N=48)**	**2-4 prior biologics (N=79)**	**p-value (2-4 biologics vs 0-1 biologics)**
PASI75	80 (63.0%)	35 (72.9%)	45 (57.0%)	0.096

Efficacy at week 16 (ACA – excluding those who had overlap therapy)

	Patients (%)		
	All (n=98)	**No prior biologics (N=15)**	**Prior biologics (N=83)**
PASI75	70 (71.4%)	13 (86.7%)	57 (68.7%)

Author's conclusion

- Comparison of individuals who previously received 0 or 1 biologic agent with individuals who received 2-4 biologic agents prior to ustekinumab demonstrated a non-significant reduction in response (although the study may be underpowered to detect any differences)

H.13.2 Non-randomised comparison within RCT

H.13.2.1 STUDY 1

Reference	Study type	Number of patients	Patient characteristics	Intervention	Length of follow-up	Outcome measures	Source of funding
J. P. Ortonne, S. Chimenti, K. Reich, R. Gniadecki, P. Sprogel, K. Unnebrink, H. Kupper, O. Goldblum, and D. Thaci. Efficacy and safety of adalimumab in patients with	**Observational:** prospective case series/ subanalysis of RCT data **Note:** post-hoc analysis – not stated in initial study protocol **Blinding:** patients	N: 730 **Drop-outs (do not complete study)** 54: 15 (5.3%) with prior anti-TNF and 39 (8.7%) anti-TNF naïve	**Inclusion criteria:** Aged 18 or over; diagnosis of chronic plaque-type psoriasis for at least 6 months; previous failure, intolerance of or contraindication to at least 2 traditional or biologic systemic agents (at least one of which was CSA, MTX or oral PUVA); disease severity that meets at least two of the following criteria: PASI ≥10, BSA ≥10% and DLQI ≥10 **Exclusion criteria:** Previous exposure to adalimumab; topical calcipotriol + betamethasone therapy within 2 weeks; systemic or topical corticosteroids within 4 or 2 weeks respectively; etanercept <3wks; infliximab <8wks; efalizumab<6wks; abatacept<65 days	**Adalimumab** (subcutaneously): 80 mg at wk 0, then 40 mg every other week to week 15 **Note:** 50% of patients self-administered concomitant topical calcipotriol 52.2 µg/g plus betamethasone dipropionate 0.64 mg/g once daily (application not to	Treatment duration 16 weeks	Primary (at wk 16): PASI75 Primary (at wk 16): PASI90 PASI100 PGA – clear or minimal DLQI AEs (follow-up	Abbott Laboratories

<table>
<tr>
<td>psoriasis previously treated with anti-tumour necrosis factor agents: subanalysis of BELIEVE. J.Eur.Acad. Dermatol.Venereol., 2011.

Ref ID: ORTONNE 2011</td>
<td>blinded to topical treatment

Washout period: see exclusion criteria

Representative population sample: yes

Confounders adjusted for: yes

Confounders accounted for: yes (see below)

Minimal attrition bias: yes

Outcomes adequately</td>
<td></td>
<td>
<table>
<tr><th></th><th>Prior TNF-antagonist (n=282)</th><th>No prior TNF-antagonist (n=448)</th><th>All patients (n=730)</th></tr>
<tr><td>Mean age – years (±SD)</td><td>45.6±12.1</td><td>44.8±12.4</td><td>45.1±12.3</td></tr>
<tr><td>Male (%)</td><td>64.9</td><td>71.0</td><td>68.6</td></tr>
<tr><td>BSA (%)</td><td>32.4±20.1</td><td>33.3±20.3</td><td>33.3±20.2</td></tr>
<tr><td>PASI</td><td>19.5±8.9</td><td>19.4±8.5</td><td>19.5±8.7</td></tr>
<tr><td>Mean duration of psoriasis – years (±SD)</td><td>22.4±11.8</td><td>20.3±11.5</td><td>21.1±11.7</td></tr>
<tr><td>History of PsA, n (%)</td><td>95 (33.7%)</td><td>110 (24.6%)</td><td>205 (28.1%)</td></tr>
<tr><td colspan="2">Previous treatment</td><td></td><td></td></tr>
<tr><td>Methotrexate</td><td>214 (75.9%)</td><td>297 (66.3%)</td><td>511 (70.0%)</td></tr>
<tr><td>CSA</td><td>171 (60.6%)</td><td>227 (50.7%)</td><td>398 (54.5%)</td></tr>
<tr><td>Oral PUVA</td><td>132 (46.8%)</td><td>181 (40.4%)</td><td>313 (42.9%)</td></tr>
</table>
</td>
<td>exceed 30% BSA or 100g per week); the other 50% received matching drug-free vehicle

(after wk 4 the dosing of topical switched from once daily to as needed – with the same restrictions on total dose)

Prior use of systemics within 12 months before study entry was recorded and reasons collected:
i. Never responded
ii. Lost response
iii. Discontinued for intolerance/side effects
iv. Other

Note: there is lack of information to support these subjective ratings</td>
<td></td>
<td>of up to 70 days post treatment)</td>
<td></td>
</tr>
</table>

	measured: Yes **Appropriate statistical analysis:** yes		**Biologics***			**47.7%**				
			Anti-TNF*			**38.6%**				
			Etanercept			29.9%				
			Infliximab			13.4%				
			Certolizumab			2.6%				
			*Includes 2.6% of the total population (5.5% of those previously using biologics) previously exposed to certolizumab							

Effect Size

Outcomes

Efficacy

PASI75 (ITT population – missing values imputed as non-response)	**Patients (%)**						**Odds ratio (95% CI)***	**p-value***
	ADA + vehicle		**ADA + topical**		**All ADA**			
	Prior TNF-antagonist (n=138)	**No prior TNF-antagonist (n=226)**	**Prior TNF-antagonist (n=144)**	**No prior TNF-antagonist (n=222)**	**Prior TNF-antagonist (n=282)**	**No prior TNF-antagonist (n=448)**		
Week 2	7 (5.1%)	14 (6.2%)	22	32	29 (10.3%)	46 (10.3%)	1.2 (0.7-2.0)	0.591
Week 4	41 (29.7%)	77 (34.1%)	53	96	94 (33.3%)	173 (38.6%)	0.8 (0.6-1.2)	0.252
Week 8	79 (57.2%)	139 (61.5%)	65	130	144 (51.1%)	269 (60.0%)	0.8 (0.6-1.1)	0.166
Week 12	99 (71.7%)	168 (74.3%)	71	141	170 (60.3%)	309 (69.0%)	0.8 (0.6-1.2)	0.339

Week 16	92 (66.7%)	166 (73.5%)	82	155	174 (61.7%)	321 (71.7%)	0.7 (0.5-1.1)	0.095

*Calculated by logistic regression adjusted for treatment group, number of prior systemics (>3, ≤3), age, duration of psoriasis, baseline PASI, baseline BSA affected, nail involvement, scalp involvement and presence of tender, swollen or stiff joints at baseline.

Note: no significant difference was revealed in this analysis between those using concomitant topical therapy and those using vehicle

Stratified efficacy rates at week 16

a) Prior anti-TNF treatment

ITT population – missing values imputed as non-response	**Patients (%)**			**p-value vs no prior TNF antagonist***
	No prior TNF-antagonist (n=448)	**Prior etanercept (n=170)**	**Prior infliximab (n=53)**	
PASI75	321 (71.7%)	111 (65.3%)	31 (58.5%)	ETA = 0.361 INF = 0.174
PASI90	222 (49.6%)	63 (37.1%)	18 (34.0%)	ETA = 0.051 INF = 0.118
PASI100	102 (22.8%)	25 (14.7%)	8 (15.1%)	ETA = 0.173 INF = 0.576
PGA clear or minimal	293 (65.4%)	97 (57.1%)	25 (47.2%)	ETA = 0.385 INF = 0.058

b) Number of prior anti-TNF treatments

ITT population – missing values imputed as non-response	**Patients (%)**			**p-value vs no prior TNF antagonist***
	No prior TNF-antagonist (n=448)	**1 prior TNF-antagonist (n=231)**	**≥2 TNF-antagonist (n=51)**	

PASI75	321 (71.7%)	149.0 (64.5%)	25.0 (49.0%)	1 = 0.234 ≥2 = 0.016
PASI90	94 (49.6%)	84.1 (36.4%)	19.0 (37.3%)	1 = 0.021 ≥2 = 0.276
PASI100	144 (22.8%)	34.0 (14.7%)	8.0 (15.7%)	1 = 0.166 ≥2 = 0.766
PGA clear or minimal	170 (65.4%)	128.0 (55.4%)	21.0 (41.2%)	1 = 0.176 ≥2 = 0.026

c) Reason for discontinuation of prior TNF-antagonist

ITT population – missing values imputed as non-response	**Patients (%)**				
	No prior TNF-antagonist (n=448)	**Prior TNF-antagonist (n=282)**	**Never responded (n=80)**	**Lost response (n=99)**	**Intolerance (n=16)**
PASI75	321 (71.7%)	174 (61.7%) p=0.095*	43 (53.8%) p=0.006*	65 (65.7%) p=0.673*	8 (50.0%) p=0.213*

*****All p-values calculated by logistic regression adjusted for treatment group, number of prior systemics (>3, ≤3), age, duration of psoriasis, baseline PASI, baseline BSA affected, nail involvement, scalp involvement and presence of tender, swollen or stiff joints at baseline.

d) ±PsA

ITT population – missing values imputed as non-response	**Patients (%)**			
	Prior TNF-antagonist (n=277)		**No prior TNF-antagonist (n=429)**	
	PsA (n=95)	**No PsA (n=187)**	**PsA (n=110)**	**No PsA (n=338)**
PASI75	51 (53.7%)	123 (65.8%)	77 (70.0%)	244 (72.2%)

PASI90	33 (34.7%)	70 (37.4%)	55 (50.0%)	167 (49.4%)
PASI100	14 (14.7%)	28 (15.0%)	23 (20.9%)	79 (23.4%)
PGA clear or minimal	49 (51.6%)	100 (53.5%)	72 (65.5%)	221 (65.4%)

DLQI

DLQI (ITT population – missing values imputed as non-response)	**Prior TNF-antagonist (n=281)**	**No prior TNF-antagonist (n=446)**	**p-value***
Baseline	13.8	14.0	0.165
Week 16	4.5	3.4	0.199
Change	-9.3	-10.6	

*Analysis performed using ANCOVA adjusted for treatment group, number of prior systemics (>3, ≤3), age, duration of psoriasis, baseline PASI, baseline BSA affected, nail involvement, scalp involvement and presence of tender, swollen or stiff joints at baseline.

Adverse events and withdrawals:

	Prior TNF-antagonist (n=282)	**No prior TNF-antagonist (n=448)**

Withdrawal due to lack of efficacy	3 (1.06%)	5 (1.1%)
Withdrawal due to AEs	5 (1.8%)	22 (4.9%)
Serious AEs	11 (3.9%)	20 (4.5%)

Author's conclusion

- Adalimumab was effective and well tolerated in patients previously treated with anti-TNF therapy
- There was no statistically significant difference in PASI75 between patients with and without prior TNF therapy (based on pooled ADA group)
- Switching to adalimumab therapy will result in improved clinical response in a large proportion of patients who have previously failed, lost response to or been intolerant to a prior TNF antagonist
- Rates of AEs were similar between patients with and without prior TNF therapy (based on pooled ADA group)

H.13.3 RCT (randomised and non-randomised data available)

H.13.3.1 STUDY 1

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
A. Menter, S. R. Feldman, G. D. Weinstein, K. Papp, R. Evans, C. Guzzo, S. Li, L. T. Dooley, C. Arnold, and A. B. Gottlieb. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment	**RCT** (plus observational data) Multicentre (63 sites in US, Canada and Europe) • Randomised (minimisation with biased coin assignment) • Double blind (adequate) • Allocation concealment (independent external	N: 835 **Drop-outs (do not complete study to week 10)** 62 (7.4%): Placebo: 24 (11.5%) INF 3 mg: 21 (6.7%) INF 5 mg: 17 (5.4%)	**Inclusion criteria:** Aged 18 or over; moderate to severe plaque-type psoriasis; candidates for phototherapy or systemic therapy; previous; no history of serious infection, lymphoproliferative disease, or active TB; PASI ≥12 and BSA ≥10% **Exclusion criteria:** Previous exposure to infliximab; concomitant topical therapy, phototherapy or systemic therapy for psoriasis (except low potency topical corticosteroids for face and groin after 10 weeks) or DMARDs (stable doses of NSAIDs permitted). **Placebo (n=208)** / **INF 3 mg (n=313)** / **INF 5 mg (n=314)**: Mean age – years (±SD): 44.4±12.5 / 43.4±12.6 / 44.5±13.0 Male: 69.2 / 65.8 / 65.0	**Infliximab** (intravenous infusion): 3 or 5 mg/kg at weeks 0, 2 and 6 N=627 **Note:** data from two dose groups pooled for our outcome	Placebo (n=208)	Treatment duration 10 weeks **Note:** this was the induction phase	Primary (at wk 10): PASI75	Centocor and Schering-Plough

of moderate-to-severe plaque psoriasis. J.Am.Acad. Dermatol. 56 (1):31, 2007. Ref ID: MENTER2007	centre) • Sample size calculation: yes • ITT analysis: yes • Washout period: **For observational data:** **Representative population sample:** yes **Confounders adjusted for:** no **Minimal attrition bias:** yes **Outcomes adequately measured:** Yes		(%)								
			BSA (%)	28.4±17.6	28.0±16.3	28.7±16.4					
			PASI	19.8±7.7	20.1±7.9	20.4±7.5					
			Mean duration of psoriasis – years (±SD)	17.8±10.8	18.1±11.8	19.1±11.7					
			PsA (%)	26	27.8	28.3					
			Caucasian (%)	90.9	93.0	93.3					
			Weight (kg)	91.1±22.6	92.0±22.5	92.2±23.3					
			Previous treatment (%)								
			Topicals	92.8	94.9	90.8					
			UVB	49.5	54.3	55.1					
			PUVA	29.8	28.4	27.4					
			MTX	33.7	32.6	34.7					
			Acitretin	14.4	15.0	15.6					
			CSA	13.5	13.4	11.1					
			Biologic	**13.0**	**15.7**	**14.3**					

	Appropriate statistical analysis: yes		**s**						

Effect Size

Outcomes

Efficacy

PASI75 (ITT population); week 10

Subset	**Placebo (n=208)**	**Infliximab (combined 3 and 5 mg/kg) (n=627)**	**% Difference (95% CI)**	**p-value**
Total responders	4 (1.9%)	457 (72.9%)		
Prior use of biologics	0/27 (0%)	68/94 (72.3%)	72.3 (60.9-83.8)	<0.001
No prior use of biologics	4/181 (2.2%)	389/533 (73.0%)	70.8 (66.1-75.5)	<0.001

Adverse events and withdrawals (not stratified by previous treatment):

	Placebo (n=208)	INF 3 mg (n=313)	INF 5 mg (n=314)
Withdrawal due to lack of efficacy	10 (4.8%)	1 (0.3%)	0 (0%)
Withdrawal due to AEs	4 (1.9%)	13 (4.2%)	12 (3.8%)

Author's conclusion

- Prior biologic therapy did not have an effect on PASI75 response to infliximab at 10 weeks

H.13.3.2 STUDY 2

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
C. E. Griffiths, B. E. Strober, P. C. van de Kerkhof, V. Ho, R. Fidelus-Gort, N. Yeilding, C. Guzzo, Y. Xia, B. Zhou, S. Li, L. T. Dooley, N. H. Goldstein, and A. Menter. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. New Engl.J.Med. 362	**RCT** Multicentre (67 international sites) • Randomised: 3:5:5 ratio (adequate: stratified by site and baseline weight <90 kg or ≥90kg) • Single blind (investigator) – patients also blinded to UST dose (not adequately	N: 903 **Drop-outs (do not complete study)** **Week 12** ETA: 11 (3.2%) UST 45 mg: 8 (3.8%) UST 90 mg: 5 (1.4%) **Week 12 to end of study** ETA: 8/295	**Inclusion criteria:** ≥18 years of age, diagnosis of plaque psoriasis for at least 6 months earlier, candidates for phototherapy or systemic treatment, PASI ≥12 or PGA ≥ 3 (range 0-5), and BSA ≥10%. Inadequate response, intolerance, or contraindication to at least one conventional systemic agent for psoriasis and no previous treatment with ustekinumab or etanercept **Exclusion criteria:** nonplaque (i.e., pustular, guttate, or erythrodermic) or drug-induced forms of psoriasis, recent serious infection or history of chronic or recurrent infectious disease, or a known malignant condition (except treated basal-cell or squamous-cell skin cancer or cervical cancer in situ with no evidence of recurrence for ≥5 years). Conventional systemic therapy or phototherapy within 4 weeks before enrolment, topical psoriasis agents within 2 weeks, investigational drugs within 4 weeks or five half-lives, or biologic agents within 3 months or five half-lives	**Ustekinumab 45 mg at weeks 0 and 4** (n=209) ---------- **Ustekinumab 90 mg at weeks 0 and 4** (n=347) **Both UST arms:** If no response (moderate, marked, or	**Etanercept** (n=347) 50 mg twice weekly ***Crossover***: If no response (moderate, marked, or severe psoriasis) at week 12 switched to 90 mg of ustekinumab at weeks 16 and 20 If had response	Treatment duration Up to 44 weeks	Primary outcome: PASI75 at week 12 Secondary: PGA clear or minimal; PASI90 and change in PASI all at week 12 Change in PASI from week 12 to 12 weeks after re-treatment due to recurrence AEs	Centocor R&D

(2):118-128, 2010. Ref ID: GRIFFITHS2010 AND Janssen Cilag. Clinical efficacy data from phase III study ACCEPT broken down into patients' medication history with biologic therapies [unpublished data]. Anonymous. Anonymous. 2011. 09-02-2011. Ref ID: JANSSENCILAG2011A	defined) • Allocation concealment (not stated) • Sample size calculation: yes • ITT analysis: yes for efficacy (assumptions not stated) • Washout period: see exclusion criteria	(2.7%) UST 45 mg: 2/174 (1.1%) UST 90 mg: 7/270 (2.6%)					severe psoriasis) to ustekinumab at week 12 received one additional dose of ustekinumab at week 16 **All arms:** Treatment interrupted at week 12 in all patients with cleared, minimal, or mild psoriasis; patients retreated with ustekinumab if moderate, marked, or severe	at wk 12 received 90 mg of ustekinumab at weeks 0 and 4 when psoriasis recurred			

	ETA (n=347)	**UST 45 mg (n=209)**	**UST 90 mg (n=347)**
Mean age – years (±SD)	45.7±13.4	45.1±12.6	44.8±12.3
Male (%)	70.9	63.6	67.4
BSA (%)	23.8±13.9	26.7±17.8	26.1±17.6
PASI	18.6±6.2	20.5±9.2	19.9±8.4
Mean duration of psoriasis – years (±SD)	18.8±12.2	18.9±11.8	18.7±11.8
PsA (%)	27.4	29.7	27.4
Caucasian (%)	91.1	92.3	89.0
Weight (kg)	90.8±20.9	90.4±21.1	91.0±22.8

			Previous treatment (%) Topicals: 96.8 / 96.7 / 96.8 Photo: 64.6 / 66.0 / 66.3 Conventional systemics: 57.3 / 61.7 / 52.4 **Biologics: 11.8 / 12.4 / 10.4** **Note:** for subgroup analysis, disease severity similar in biologic ever and never used groups, but longer duration (by 3.5 years) and 5% more males in those with prior biologic exposure.	psoriasis recurred				

Effect Size

Outcomes

Note: of those randomised to etanercept 336 completed 12-wk treatment and 41 did not cross over to 90 mg of ustekinumab after wk 12 (23 of whom completed treatment without requiring further intervention). Of the 295 who crossed over 50 did not have PGA response at wk 12 and received 90 mg of ustekinumab at wk 16 and 20, 245 had a PGA response at wk 12 and received 90 mg of ustekinumab at wk 0 and 4 when psoriasis recurred

Of those randomised to ustekinumab 45 mg 27 did not receive re-treatment with 45 mg of ustekinumab after wk 12 (17 of whom completed treatment without requiring additional treatment). Of the 174 who received additional ustekinumab treatment 20 did not have PGA response at wk 12 and received an additional dose at wk 16 and 154 had a PGA response at wk 12 and received two re-treatment doses when psoriasis recurred.

Of those randomised to ustekinumab 90 mg 72 did not receive re-treatment with 90 mg of ustekinumab after wk 12 (47 of whom completed treatment without requiring further intervention). Of the 270 Received additional ustekinumab treatment 25 did not have PGA response at wk 12 and received an additional dose at wk 16; 245 had a PGA response at wk 12 and received two re-treatment doses when psoriasis recurred.

Efficacy

Week 12 – initial randomised phase (ITT population)

	ETA (n=347)	**UST 45 mg (n=209)**	**UST 90 mg (n=347)**	**% treatment difference between UST and ETA (95% CI)**	**p-value (between UST and ETA)**
PASI75	197 (56.8%)	141 (67.5%)	256 (73.8%)	45 mg: 10.7 (2.4-19.0) 90 mg: 17.0 (10.0-24.0)	45 mg: 0.01 90 mg: <0.001
PASI90	80 (23.1%)	76 (36.4%)	155 (44.7%)	45 mg: 13.3 (5.8-20.7) 90 mg: 21.6 (14.6-28.5)	45 mg: <0.001 90 mg:<0.001
PGA (clear or minimal)	170 (49.0%)	136 (65.1%)	245 (70.6%)	45 mg: 16.1 (7.6-24.4) 90 mg: 21.6 (14.4-28.6)	45 mg: <0.001 90 mg:<0.001

Week 16 to 28 – crossover (ITT population)

	ETA non responders who crossed over to UST 90 mg (n=50)
PASI75	24 (48.9%)
PASI90	12 (23.4%)
PGA (clear or minimal)	20 (40.4%)

Withdrawals:

	UST 90 mg 0-12 weeks (n=347)	**UST 90 mg 16-44 weeks (n=295)**
Serious adverse events	4 (1.1%)	10 (3.4%)
Withdrawal due to AEs	4 (1.2%)	2 (0.68%)

Additional unpublished data from call for evidence (data stratified for those who have ever of never used biologics before – adalimumab, etanercept and/or infliximab)

Week 12

Proportion of subjects achieving a PASI 50 response at week 12

	Etanercept			Ustekinumab						
	N	n	(%)	N	n	(%)	Diff	95% CI		p-value
All subjects	347	286	(82.4%)	556	501	(90.1%)	7.7%	3.0%	12.4%	<0.001
Never used	319	265	(83.1%)	519	473	(91.1%)	8.1%	3.3%	12.9%	<0.001
Ever used	27	20	(74.1%)	36	28	(77.8%)	3.7%	-17.7%	25.1%	0.735

Proportion of subjects achieving a PASI 75 response at week 12

	Etanercept			Ustekinumab						
	N	n	(%)	N	n	(%)	Diff	95% CI		p-value
All subjects	347	197	(56.8%)	556	397	(71.4%)	14.6%	8.2%	21.1%	<0.01
Never used	319	186	(58.3%)	519	377	(72.6%)	14.3%	7.7%	21.0%	<0.01
Ever used	27	10	(37.0%)	36	20	(55.6%)	18.5%	-5.9%	42.9%	0.149

Proportion of subjects achieving a PASI 90 response at week 12

	Etanercept			Ustekinumab						
	N	n	(%)	N	n	(%)	Diff	95% CI		p-value
All subjects	347	80	(23.1%)	556	231	(41.5%)	18.5%	12.5%	24.5%	<0.001
Never used	319	76	(23.8%)	519	221	(42.6%)	18.8%	12.4%	25.1%	<0.001
Ever used	27	4	(14.8%)	36	10	(27.8%)	13.0%	-6.9%	32.8%	0.224

Mean of percent improvement in PASI from baseline at week 12

	Etanercept		Ustekinumab					
	N	change	N	change	Diff	95% CI		p-value
All subjects	339	72.06 ± 25.947	544	81.10 ± 21.919	9.04	5.84	12.24	<0.001
Never used	311	72.59 ± 25.953	508	82.05 ± 20.799	9.46	6.22	12.70	<0.001
Ever used	27	65.55 ± 25.870	35	68.30 ± 31.676	2.75	-12.26	17.76	0.715

Proportion of subjects achieving PGA score of cleared (0) or minimal (1) at week 12

	Etanercept			Ustekinumab						
	N	n	(%)	N	n	(%)	Diff	95% CI		p-value
All subjects	347	170	(49.0%)	556	381	(68.5%)	19.5%	13.0%	26.1%	<0.001
Never used	319	159	(49.8%)	519	362	(69.7%)	19.9%	13.1%	26.7%	<0.001
Ever used	27	10	(37.0%)	36	19	(52.8%)	15.7%	-8.7%	40.2%	0.219

Author's conclusion

- Those who had failed to respond to etanercept could still respond to subsequent ustekinumab 90 mg, although at a lower rate than patients who had not previously failed a biologic

H.13.3.3 STUDY 3

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
C. L. Leonardi, A. B. Kimball, K. A. Papp, N. Yeilding, C. Guzzo, Y. Wang, S. Li, L. T. Dooley, K. B. Gordon, and Investigators Study. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a	**RCT:** multicentre – 48 sites in USA, Canada and Belgium (Dec 2005-Sept 2007) • Randomised: 1:1:1 ratio (adequate: minimisation) Baseline randomisation was stratified by investigational site, weight (≤90 kg or >90 kg), and the number of convention	N: 766 **Drop-outs (do not complete study)** **Up to week 12** Ust 45: 1 Ust 90: 11 (1 received no Tx; 1 lack of efficacy; 2 AEs; 7 other) Placebo: 12 (3 lack of efficacy; 6 AE; 3 other) **Week 12-40** Ust 45: 38 (19 lack of efficacy; 11 AE)	**Inclusion criteria:** Aged 18 or over; diagnosis of plaque-type psoriasis for at least 6 months; PASI ≥12; BSA ≥10%; candidates for phototherapy or systemic therapy **Exclusion criteria:** History or symptoms of active tuberculosis; non-plaque psoriasis; recent systemic or local infection; known malignancy (except treated BCC or SCC of at least 5 years duration); treatment with agents targeting IL-12 or -23, biological or investigational agents within 3 months (or 5 drug half lives), conventional systemics or phototherapy within 4 weeks, topicals for psoriasis within 2 weeks **Ustekinumab 45 mg (n=255)** / **Ustekinumab 90 mg (n=256)** / **Placebo (n=255)** Mean age – years: 44.8±12.5 / 46.2±11.3 / 44.8±11.3	**Ustekinumab** (subcutaneously): 45 or 90 mg at weeks 0 and 4 and then every 12 weeks At week 40 those who achieved long-term response (at least PASI 75 at weeks 28 and 40) were re-randomised to continue maintenance treatment with ustekinumab or were withdrawn from active treatment (placebo). Patients withdrawn from	**Placebo**, weeks 0 and 4 then crossover to ustekinumab (half to 90 and half to 45 mg) at weeks 12 and 16 then every 12 weeks Placebo controlled phase is 0-12 weeks	Treatment duration Placebo-controlled phase (0-12 weeks) Placebo crossover and active treatment phase (12-40 weeks) Randomised withdrawal phase (40-76 weeks)	PASI90 PASI75 PASI50 % change in PASI PGA (clear/minimal on 6-pt scale (0), minimal (1), mild (2), moderate (3), marked (4), or severe (5)) Change in DLQI	Centocor Inc

randomised, double-blind, placebo-controlled trial (PHOENIX 1).[Erratum appears in Lancet. 2008 May 31;371(9627):1838]. Lancet 371 (9625):1665-1674, 2008. Ref ID: LEONARDI2008 AND Janssen Cilag. Clinical efficacy data from phase III study PHOENIX 1, broken down into patients' medication history with biologic therapies [unpublish	al systemic therapies to which patients had an inadequate response, intolerance, or contraindication (<3 or ≥3). Week 40 randomisation was stratified by investigational site and baseline weight (≤90 kg or >90 kg). • Double blind (adequate) • Allocation concealment: adequate (centralised interactive voice response system)	Ust 90: 19 (6 lack of efficacy; 7 AEs;) Placebo-> Ust 45: 11/123 (7 lack of efficacy; 2 AE) Placebo-> Ust 90: 5/120 (2 lack of efficacy; 1 AE)	(±SD)				treatment at week 40 were retreated when they lost at least 50% of PASI improvement. Patients not achieving PASI 75 at week 28 or 40 were not re-randomised, and their dosing was discontinued or modified				
			Male (%)	68.6	67.6	71.8					
			Weight (kg)	93.7±23.8	93.8±23.9	94.2±23.5					
			PASI	20.5±8.6	19.7±7.6	20.4±8.6					
			PGA (marked or severe)	114 (44.7%)	109 (42.6%)	112 (43.9%)					
			DLQI	11.1±7.1	11.6±6.9	11.8±7.4					
			Mean duration of psoriasis – years (±SD)	19.7±11.7	19.6±11.1	20.4±11.7					
			PsA, n (%)	74 (29.0%)	94 (36.7%)	90 (35.3%)					
			Previous treatment								
			Topicals	245	239	242					
			Photo	173	169	150					
			Conventional	141	141	142					

ed data]. Anonymous. Anonymous. 2011. 09-02-2011. Ref ID: JANSSEN CILAG2011	• Sample size calculation: yes • ITT analysis: yes for efficacy (non-responder imputation for dichotomous data at week 12 [but for other efficacy analyses missing data were not imputed and were treated as missing] ACA for continuous); safety analyses based on actual treatment received		systemics **Biologics*** **134 (52.5%)** **130 (50.8%)** **128 (50.2%)** *Includes etanercept, alefacept, efalizumab, infliximab and adalimumab **Note**: for subgroup analysis, disease slightly more severe, (PASI [2 pt higher], PGA [3.6% more marker or severe], BSA [4% higher], DLQI [1 pt higher]) and longer duration (by 1 year) in those with prior biologic exposure. Also, slightly higher weight (by 3 kg but all means >90kg) and greater proportion male (7% higher) in those with prior exposure						

	• Washout period: see exclusion criteria							

Effect Size

Outcomes

Additional unpublished data from call for evidence (data stratified for those who have ever of never used biologics before – adalimumab, etanercept and/or infliximab)

Week 12

Proportion of subjects achieving a PASI 50 response at week 12

	Placebo			Ustekinumab						
	N	n	(%)	N	n	(%)	Diff	95% CI		p-value
All subjects	255	26	(10.2%)	511	433	(84.7%)	74.5%	69.7%	79.4%	<0.001
Never used	150	24	(16.0%)	299	262	(87.6%)	71.6%	64.7%	78.6%	<0.001
Ever used	105	2	(1.9%)	212	171	(80.7%)	78.8%	72.8%	84.7%	<0.001

Proportion of subjects achieving a PASI 75 response at week 12

	Placebo			Ustekinumab						
	N	n	(%)	N	n	(%)	Diff	95% CI		p-value
All subjects	255	8	(3.1%)	511	341	(66.7%)	63.6%	59.0%	68.2%	<0.001
Never used	150	8	(5.3%)	299	213	(71.2%)	65.9%	59.6%	72.2%	<0.001
Ever used	105	0	(0.0%)	212	128	(60.4%)	60.4%	53.8%	67.0%	<0.001

Proportion of subjects achieving a PASI 90 response at week 12

	Placebo			Ustekinumab						
	N	n	(%)	N	n	(%)	Diff	95% CI		p-value
All subjects	255	5	(2.0%)	511	200	(39.1%)	37.2%	32.6%	41.7%	<0.001
Never used	150	5	(3.3%)	299	125	(41.8%)	38.5%	32.2%	44.8%	<0.001
Ever used	105	0	(0.0%)	212	75	(35.4%)	35.4%	28.9%	41.8%	<0.001

Mean of percent improvement in PASI from baseline at week 12

	Placebo		Ustekinumab					
	N	change	N	change	Diff	95% CI		p-value
All subjects	253	6.98 ± 30.773	506	76.41 ± 25.414	69.43	65.30	73.56	<0.001

Never used	148		12.69 ± 32..248	298		78.69 ± 23.338	66.00	60.74	71.26	<0.001
Ever used	105		-1.07 ± 26.701	208		73.14 ± 27.856	74.21	67.74	80.68	<0.001

Proportion of subjects achieving PGA score of cleared (0) or minimal (1) at week 12

	Placebo			Ustekinumab						
	N	n	(%)	N	n	(%)	Diff	95% CI		p-value
All subjects	255	10	(3.9%)	511	312	(61.1%)	57.1%	52.3%	62.0%	<0.001
Never used	150	8	(5.3%)	299	190	(63.5%)	58.2%	51.7%	64.8%	<0.001
Ever used	105	2	(1.9%)	212	122	(57.5%)	55.6%	48.5%	62.8%	<0.001

Mean of improvement in DLQI from baseline at week 12

	Placebo		Ustekinumab					
	N	change	N	change	Diff	95% CI		p-value
All subjects	252	-0.6 ± 5.97	503	-8.3 ± 6.68	-7.70	-8.68	-6.72	<0.001
Never used	147	-1.07 ± 6.08	296	-8.0 ± 6.31	-6.93	-8.17	-5.69	<0.001
Ever used	105	0.14 ± 5.78	207	-8.9 ± 7.15	-9.04	-10.62	-7.46	<0.001

Week 24/28

Proportion of subjects achieving a PASI 50 response at week 24

	Ustekinumab		
	N	n	(%)
All subjects	497	461	(92.8%)
Never used	290	275	(94.8%)
Ever used	207	186	(89.9%)

Proportion of subjects achieving a PASI 75 response at week 24

	Ustekinumab		
	N	n	(%)
All subjects	497	400	(80.5%)
Never used	290	245	(84.5%)
Ever used	207	155	(74.9%)

Proportion of subjects achieving a PASI 90 response at week 24

	Ustekinumab		
	N	n	(%)
All subjects	497	296	(59.6%)
Never used	290	182	(62.8%)
Ever used	207	114	(55.1%)

Mean of percent improvement in PASI from baseline at week 24

	Ustekinumab	
	N	change (m±SD)
All subjects	497	85.14 ± 21.28
Never used	290	86.96 ± 19.36
Ever used	207	82.59 ± 23.52

Proportion of subjects achieving PGA score of cleared (0) or minimal (1) at week 24

	Ustekinumab		
	N	n	(%)
All subjects	497	350	(70.4%)
Biologics (etanercept, infliximab, or adalimumab)			
Never used	290	213	(73.4%)
Ever used	207	137	(66.2%)

Mean of improvement in DLQI from baseline at week 28

	Ustekinumab	
	N	change (m±SD)
All subjects	490	-8.8 ± 7.23
Never used	286	-8.7 ± 7.03
Ever used	204	-9.1 ± 7.52

Week 52

Proportion of subjects achieving a PASI 50 response at week 52

	Ustekinumab		
	N	n	(%)
All subjects	162	158	(97.5%)
Never used	103	101	(98.1%)
Ever used	59	57	(96.6%)

Proportion of subjects achieving a PASI 75 response at week 52

	Ustekinumab		
	N	n	(%)
All subjects	162	144	(88.9%)
Never used	103	93	(90.3%)
Ever used	59	51	(86.4%)

Proportion of subjects achieving a PASI 90 response at week 52

	Ustekinumab		
	N	n	(%)
All subjects	162	105	(64.8%)
Never used	103	66	(64.1%)
Ever used	59	39	(66.1%)

Mean of percent improvement in PASI from baseline at week 52

	Ustekinumab	
	N	change (m±SD)
All subjects	162	89.90 ± 14.62
Never used	103	90.15 ± 14.62
Ever used	59	89.45 ± 14.73

Proportion of subjects achieving PGA score of cleared (0) or minimal (1) at week 52

	Ustekinumab		
	N	n	(%)

All subjects	162	115	(71.0%)
Never used	103	72	(69.9%)
Ever used	59	43	(72.9%)

Mean of percent improvement in DLQI from baseline at week 52

	Ustekinumab	
	N	change (m±SD)
All subjects	162	-9.6 ± 6.83
Never used	103	-9.0 ± 6.84
Ever used	59	-10.6 ± 6.73

H.13.3.4 STUDY 4

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
K. A. Papp, R. G. Langley, M. Lebwohl, G. G. Krueger, P. Szapary, N. Yeilding, C. Guzzo, M. C. Hsu, Y. Wang, S. Li, L. T. Dooley, K. Reich, and Investigators Study. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody,	**Observational:** prospective case series/prognostic study based on RCT data (70 sites in Europe and North America) **Note:** post-hoc analysis – not stated in study protocol **Washout period:** 4 weeks for conventional systemics; 2 weeks for	N: 1230 (N=820 for our cohort of which 84 (10.2%) dropped out) 40 due to lack of efficacy; 16 AEs; 28 'other' **Up to week 12** Ust 45: 6 (0 lack of efficacy; 2 AEs) Ust 90: 9 (0 lack of efficacy; 5 AEs) Placebo: 18 (2 lack of	**Inclusion criteria:** Aged 18 or over; diagnosis of plaque-type psoriasis for at least 6 months; PASI ≥12; BSA ≥10%; candidates for phototherapy or systemic therapy **Note:** data on switching biologics only available for those initially randomised to ustekinumab (and both doses are pooled together) **Exclusion criteria:** History or symptoms of active tuberculosis; non-plaque psoriasis; recent systemic or local infection; known malignancy (except treated BCC or SCC of at least 5 years duration); treatment with agents targeting IL-12 or -23, biological or investigational agents within 3 months (or 5 drug half lives), conventional systemics or phototherapy within 4 weeks, topicals for psoriasis within 2 weeks	**Ustekinumab** (subcutaneously): 40 or 90 mg at weeks 0 and 4 and then every 12 weeks	Placebo	Treatment duration Placebo-controlled phase (0-12 weeks) Placebo crossover and active treatment phase (12-28 weeks) Randomised dose intensification phase (28-52 weeks)	PASI90 PASI75 PASI50 % change in PASI PGA (clear/minimal on 6-pt scale (0), minimal (1), mild (2), moderate (3), marked (4), or severe (5)) Change in DLQI	Centocor Inc

in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet 371 (9625):1675-1684, 2008. Ref ID: PAPP2008 AND Janssen Cilag. Clinical efficacy data from phase III study PHOENIX 2 broken down into patients' medication history with biologic therapies	topicals; 3 months for biologics **Representative population sample:** yes **Confounders accounted for:** unclear (see below) **Minimal attrition bias:** yes **Outcomes adequately measured:** Yes **Appropriate statistical analysis:** yes (but post-hoc) **For**	efficacy; 8 AE) **Week 12-28** Ust 45: 37 (25 lack of efficacy; 2 AEs) Ust 90: 32 (15 lack of efficacy; 7 AEs) Placebo-> Ust 45: 22/197 (9 lack of efficacy; 4 AE) Placebo-> Ust 90: 17/195 (7lack of efficacy; 2 AE)		**Ustekinumab 45 mg (n=409)**	**Ustekinumab 90 mg (n=411)**	**Placebo (n=410)**			Note: data for switching biologics only available for those who had a constant dose of ustekinumab for 28 weeks		
			Mean age – years (±SD)	45.1±12.1	46.6±12.1	47.0±12.5					
			Male (%)	69.2	66.7	69.0					
			BSA (%)	25.9±15.5	27.1±17.4	26.1±17.4					
			PASI	19.4±6.8	20.1±7.5	19.4±7.5					
			Mean duration of psoriasis – years (±SD)	19.3±11.7	20.3±12.3	20.8±12.2					
			PsA, n (%)	107 (26.2%)	94 (22.9%)	105 (25.6%)					
			Previous treatment								
			Topicals	393	384	396					
			Photo	286	267	276					
			Convent	223	224	241					

[unpublished data]. Anonymous. Anonymous. 2011. 09-02-2011. REF ID JANSSENCILAG2011B	**randomised data** • Randomised: 1:1:1 ratio (adequate: minimisation) Baseline randomisation was stratified by investigational site, weight (≤90 kg or >90 kg), and the number of conventional systemic therapies to which patients had an inadequate response, intolerance, or contraindication (<3 or ≥3).		ional systemics **Biologics*** **157 (38.4%)** **450 (36.5%)** **159 (38.8%)** *Includes etanercept, alefacept, efalizumab, infliximab and adalimumab **Note**: for subgroup analysis, disease slightly more severe, (PASI [1 pt higher], PGA [9% more marker or severe], BSA [1.4% higher], DLQI [1 pt higher]) and longer duration (by 2 years) in those with prior biologic exposure. Also, slightly higher weight (by 5 kg but all means >90kg)							

	Second randomisation was stratified by investigational site and baseline weight (≤90 kg or >90 kg). • Double blind (not explained) • Allocation concealment: adequate (centralised interactive voice response system) • Sample size calculation: yes • ITT analysis: yes for efficacy (non-responder imputation for dichotomou							

	s data at week 12 and dose intensification phase [but for other efficacy analyses missing data were not imputed and were treated as missing]); safety analyses based on actual treatment received • Washout period: see exclusion criteria							

Effect Size

Outcomes

Efficacy – post hoc analysis of baseline factors predictive of week 28 response (PASI75) vs partial responders (PASI50, but not PASI75) **for those treated with**

either dose of ustekinumab

Predictive characteristic	**Patients, n (%)**	
	PASI 75 responders at week 28 (n=589)	**Partial responders at week 28 (n=158)**
Patients with PsA	131 (22.2%)	54 (34.8%)
Patients treated previously with biologic agents	209 (35.5%)	71 (44.9%)
Failed at least one previous biologic	71 (12.1%)	34 (21.5%)
Total sample	*590/797 (74%)*	*159/797 (19.9%)*

Parameter	**Patients (%)**	
	Previous biologic (n=307)	**No previous biologic (n=513)**
28 weeks		

PASI75	209 (68.1%)	380 (74.1%)

Note: Logistic regression analysis revealed that inadequate response to at least one biologic agent was an independent predictor of partial response (p=0.024), as was a history of psoriatic arthritis (p=0.047)

Potential predictive factors included in the model: age, sex, bodyweight, duration of psoriasis, BSA affected, PGA marked or severe, history of PsA, use of phototherapy, traditional systemics or biologics and inadequate response to at least one conventional systemic or one biologic agent, but it is unclear whether the results have been adjusted for these covariates.

Adverse events

- Not stratified by previous biologic exposure

Additional data for call for evidence (data stratified for those who have ever of never used biologics before – adalimumab, etanercept and/or infliximab)

Week 12

Proportion of subjects achieving a PASI 50 response at week 12

	Placebo			Ustekinumab						
	N	n	(%)	N	n	(%)	Diff	95% CI		p-value
All subjects	410	41	(10.0%)	820	709	(86.5%)	76.5%	72.7%	80.2%	<0.001

Never used	286	33	(11.5%)	570	496	(87.0%)	75.5%	70.9%	80.1%	<0.001
Ever used	124	8	(6.5%)	250	213	(85.2%)	78.7%	72.6%	84.9%	<0.001

Proportion of subjects achieving a PASI 75 response at week 12

	Placebo			Ustekinumab						
	N	n	(%)	N	n	(%)	Diff	95% CI		p-value
All subjects	410	15	(3.7%)	820	584	(71.2%)	67.6%	64.0%	71.2%	<0.001
Never used	286	11	(3.8%)	570	426	(74.7%)	70.9%	66.7%	75.1%	<0.001
Ever used	124	4	(3.2%)	250	158	(63.2%)	60.0%	53.2%	66.7%	<0.001

Proportion of subjects achieving a PASI 90 response at week 12

	Placebo			Ustekinumab						
	N	n	(%)	N	n	(%)	Diff	95% CI		p-value
All subjects	410	3	(0.7%)	820	382	(46.6%)	45.9%	42.3%	49.4%	<0.001

Never used	286	2	(0.7%)	570	288	(50.5%)	49.8%	45.6%	54.0%	<0.001
Ever used	124	1	(0.8%)	250	94	(37.6%)	36.8%	30.6%	43.0%	<0.001

Mean of percent improvement in PASI from baseline at week 12

	Placebo			Ustekinumab						
	N		change	N		change	Diff	95% CI		p-value
All subjects	404		4.91 ± 34.784	812		79.52 ± 24.342	74.61	71.24	77.98	<0.001
Never used	281		7.54 ± 35.168	564		80.80 ± 24.558	73.26	69.17	77.35	<0.001
Ever used	123		-1.10 ± 33.256	248		76.61 ± 23.638	77.71	71.81	83.61	<0.001

Proportion of subjects achieving PGA score of cleared (0) or minimal (1) at week 12

	Placebo			Ustekinumab						
	N	n	(%)	N	n	(%)	Diff	95% CI		p-value
All subjects	410	20	(4.9%)	820	580	(70.7%)	65.9%	62.1%	69.6%	<0.001

Never used	286	17	(5.9%)	570	418	(73.3%)	67.4%	62.8%	71.9%	<0.001
Ever used	124	3	(2.4%)	250	162	(64.8%)	62.4%	55.9%	68.9%	<0.001

Mean of improvement in DLQI from baseline at week 12

	Placebo		Ustekinumab					
	N	change	N	change	Diff	95% CI		p-value
All subjects	400	-0.5 ± 5.66	803	-9.6 ± 6.90	-9.10	-9.88	-8.32	<0.001
Never used	277	-0.9 ± 5.95	560	-9.3 ± 6.74	-8.40	-9.34	-7.46	<0.001
Ever used	123	0.3 ± 4.88	243	-10.3 ± 7.24	-10.60	-12.02	-9.18	<0.001

Week 24/28

Proportion of subjects achieving a PASI 50 response at week 24

	Ustekinumab		
	N	n	(%)
All subjects	800	742	(92.8%)

Never used	558	517	(92.7%)
Ever used	242	225	(93.0%)

Proportion of subjects achieving a PASI 75 response at week 24

	Ustekinumab		
	N	n	(%)
All subjects	800	627	(78.4%)
Never used	558	446	(79.9%)
Ever used	242	181	(74.8%)

Proportion of subjects achieving a PASI 90 response at week 24

	Ustekinumab		
	N	n	(%)
All subjects	800	442	(55.3%)
Never used	558	329	(59.0%)

Ever used	242	113	(46.7%)

Mean of percent improvement in PASI from baseline at week 24

	Ustekinumab	
	N	change (m±SD)
All subjects	406	84.25 ± 21.613
Never used	283	85.07 ± 21.640
Ever used	123	82.38 ± 21.478

Proportion of subjects achieving PGA score of cleared (0) or minimal (1) at week 24

	Ustekinumab		
	N	n	(%)
All subjects	800	578	(72.3%)
Never used	558	419	(75.1%)
Ever used	242	159	(65.7%)

Mean of improvement in DLQI from baseline at week 28

	Ustekinumab	
	N	change (m±SD)
All subjects	793	-9.9 ± 7.12
Biologics (etanercept, infliximab, or adalimumab)		
Never used	555	-9.7 ± 7.01
Ever used	238	-10.2 ± 7.36

Week 24/28

Proportion of subjects achieving a PASI 50 response at week 52

	Ustekinumab		
	N	n	(%)
All subjects	537	532	(99.1%)
Never used	389	386	(99.2%)
Ever used	148	146	(98.6%)

Proportion of subjects achieving a PASI 75 response at week 52

	Ustekinumab		
	N	n	(%)
All subjects	537	487	(90.7%)
Never used	389	360	(92.5%)
Ever used	148	127	(85.8%)

Proportion of subjects achieving a PASI 90 response at week 52

	Ustekinumab		
	N	n	(%)
All subjects	537	362	(67.4%)
Never used	389	276	(71.0%)
Ever used	148	86	(58.1%)

Mean of percent improvement in PASI from baseline at week 52

	Ustekinumab	
	N	change (m±SD)
All subjects	537	90.83 ± 13.280-
Never used	389	91.86 ± 12.670
Ever used	148	88.12 ± 14.464

Proportion of subjects achieving PGA score of cleared (0) or minimal (1) at week 52

	Ustekinumab		
	N	n	(%)
All subjects	537	389	(72.4%)
Never used	389	291	(74.8%)
Ever used	148	98	(66.2%)

Author's conclusion

- Partial responders to ustekinumab were more likely than responders to have failed a previous biologic
- The majority of patients who had received a previous biologic (but not necessarily failed to respond to it) achieved PASI75 on ustekinumab

H.13.4 Cohort Study

H.13.4.1 STUDY 1

Reference	Study type	Number of patients	Patient characteristics	Intervention	Cohorts – previous treatment	Length of follow-up	Outcome measures	Source of funding
B. E. Strober, Y. Poulin, F. A. Kerdel, R. G. Langley, Y. Gu, S. R. Gupta, M. M. Okun, and K. A. Papp. Switching to adalimumab for psoriasis patients with a suboptimal response to etanercept, methotrexate, or phototherapy: efficacy and safety results	**Prospective cohort study** Multicentre (24 in Canada and USA) • Nonrandomised • Blinding: open label • Sample size calculation: yes • ITT analysis: yes for efficacy (non-responder imputation for dichotomous and LOCF	N: 152 **Drop-outs (do not complete study): 16** E: 9 (11.0%) M: 2 (4.9%) P: 5 (17.2%)	**Inclusion criteria:** ≥18 years of age, diagnosis of chronic plaque psoriasis for at least 6 months earlier; contraception for women of childbearing age; suboptimal response* to prior psoriasis therapy ***Note:** Definition of **suboptimal response** Substudy E: PGA mild or worse following etanercept treatment for at least 6 months or at least 3 months of etanercept therapy with deterioration of efficacy (as determined by treating physician) Substudy M: PGA mild or worse following methotrexate treatment for at least 4 months Substudy P: PGA of moderate or worse after at least 2 months of NB-UVB phototherapy **PGA definitions** Mild=slight plaque elevation, fine scale covering lesions and erythema up to definite red colouration Moderate= moderate degree of plaque elevation, coarse scale covering lesions and erythema with definite red colouration **Exclusion criteria:** history of neurological	**Adalimumab** **(n=152)** 80 mg at week 0 and 40mg every other week beginning at week 1 through to week 15 Self-administered using pre-filled auto-injection device **All arms:**	**Etanercept (n=82)** (substudy E) 50 mg twice weekly or 25 mg twice weekly (data pooled) **Methotrexate (n=41)** (substudy M) Various regimens median maximum dose = 15 mg/wk (IQR: 10-20 mg/wk) **NB-UVB phototherapy (n=29)** (substudy P)	Treatment duration 16 weeks (safety data collected up to 70 days after last treatment)	Primary outcome: PGA clear or minimal at 16 weeks Secondary: PASI DLQI AEs	Abbott Laboratories

<table>
<tr>
<td>from an open-label study. J.Am.Acad. Dermatol. 64 (4):671-681, 2011.

Ref ID: STROBER 2011

B. Strober, J. Weisman, Y. Gu, and M. Okun. Adalimumab is Effective for Psoriasis Patients Who Are Primary Nonresponders to Etanercept: Subanalysis of an Open-Label Clinical Trial [submitted]. American Academy of Dermatology.70th</td>
<td>for continuous)
• Washout period: Etanercept= 11-17 days; MTX or NB-UVB = 4-10 days (i.e. at least 4 half lives)
• Standard washout for other concomitant interventions

Representative population sample: yes

Confounders adjusted for: no

Minimal attrition bias: yes</td>
<td></td>
<td>symptoms suggestive of CNS demyelinating disease; history of cancer or lymphoproliferative disease (except successfully treated non-melanoma skin cancer or localised carcinoma in situ of the cervix)
<table>
<tr><th></th><th>Etanercept (n=82)</th><th>Methotrexate (n=41)</th><th>NB-UVB (n=29)</th></tr>
<tr><td>Mean age – years (±SD)</td><td>48.3±13.7</td><td>47.4±13.1</td><td>47.5±14.6</td></tr>
<tr><td>Male (%)</td><td>57.3</td><td>68.3</td><td>55.2</td></tr>
<tr><td>BSA (%)</td><td>11.6±10.3</td><td>10.9±7.3</td><td>14.5±12.6</td></tr>
<tr><td>PASI</td><td>10.0±6.3</td><td>10.2±5.5</td><td>12.8±5.7</td></tr>
<tr><td>Mean duration of psoriasis – years (±SD)</td><td>17.2±12.0</td><td>19.8±13.5</td><td>23.0±14.1</td></tr>
<tr><td>PsA (%)</td><td>57.3</td><td>41.5</td><td>24.1</td></tr>
</table></td>
<td>Concomitant therapy with previously prescribed topical therapies permitted (but no new prescriptions or changes in concentrations were permitted)</td>
<td>Median highest dose 725 mJ (IQR: 447-1000 mJ)

Median number of session = 33</td>
<td></td>
<td></td>
<td></td>
</tr>
</table>

Annual Meeting, 16-20th March, 2012. Ref ID: STROBER 2012	**Outcomes adequately measured:** Yes **Appropriate statistical analysis:** yes		Caucasian (%)	84.1	95.1	86.2					
			Weight (kg)	96.4±23.4	89.5±17.5	86.0±17.8					
			Median duration of suboptimal therapy, months	20.0	8.0	4.0					
			DLQI (0-30) (mean ±SD)	8.8±6.0	10.9±6.3	10.4±6.9					
			PGA (%)								
			Clear or minimal	1.2	2.4	0					
			Mild	20.7	19.5	3.4					
			Moderate	62.2	63.4	75.9					
			Severe	15.9	12.2	20.7					
			Very severe	0	2.4	0					
Effect Size											

Outcomes

Efficacy

Week 16 (ITT population)

Patients, n (%)	**All** **(n=152)**	**Etanercept (n=82)**	**Methotrexate (n=41)**	**NB-UVB (n=29)**
Week 16 PGA (clear or minimal)	79 52 (44-66)%	40 49 (38-60)% *Note: lower dose 47% and higher dose 50%*	25 61 (25-76)%	14 48 (29-67)%
Week 16 PGA (clear)	31 20 (14-28)%	10 (12%) *Note: lower dose 8% and higher dose 16%*	15 (37%)	6 (21%)
DLQI *Screening mean* Change to week 16	**N=149** *9.6* -5.2	**N=80** *8.9* -3.8	**N=40** *10.5* -7.0	**N=29** *10.4* -6.5

Additional information from conference abstract submitted by Abbott in call for evidence (STROBER2012): summary evidence for subgroups of primary nonresponders (never achieved satisfactory response to the prior therapy) and secondary nonresponders (achieved satisfactory response initially but lost it over time).

Note: Patients who reported both primary and secondary non-response were included in both subgroups; patients who discontinued their prior therapies due to reasons other than efficacy were not included in either subgroup

ITT analysis.

Patients, n (%)	**Etanercept (n=82)**		**Methotrexate (n=41)**		**NB-UVB (n=29)**	
N (%)	Primary N=26	Secondary N=58	Primary N=27	Secondary N=12	Primary N=18	Secondary N=11
Week 16 PGA (clear or minimal)	15	27	17	6	11	3

Note: the discrepancy in number of primary and secondary non-responders and total numbers is due to some people being included in both categories

Withdrawals and AEs:

	Etanercept (n=82)	**Methotrexate (n=41)**	**NB-UVB (n=29)**
Withdrawal due to AEs	0 (0%)	0 (0%)	1 (3.4%)
Withdrawal due to lack of efficacy	4 (4.9%)	1 (2.4%)	2 (6.9%)
Serious AEs	4 (4.9%)	0 (0%)	1 (3.4%)

Author's conclusion

- Patients who previously experienced suboptimal response to MTX treatment had the most robust response to adalimumab, but etanercept treated patients may also experience improvement in psoriasis symptoms upon switching to adalimumab
- Switching from etanercept to adalimumab was an effective therapeutic approach in approximately half of patients with prior suboptimal response to etanercept
- Adalimumab treatment led to clinical response in the majority of patients who had been suboptimally controlled on etanercept, methotrexate, or narrow-band ultraviolet B phototherapy. The majority of patients who had never achieved satisfactory response with etanercept were able to achieve clinical response after switching to adalimumab.

H.14 Cognitive behavioural therapy

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
D. G. Fortune, H. Richards, B. Kirby, S. Bowcock, C. J. Main, and C. E. Griffiths. A cognitive-behavioural symptom management programme as an adjunct in psoriasis therapy. Br.J.Dermatol. 146 (3):458-465, 2002. FORTUNE2002B	• Patient-preference randomization (non-randomised controlled study) • No allocation concealment	N=93 PSMP, n=40 Standard pharmacological treatment only, N=53 Analysed using ITT analysis. Assessed at 6 weeks: 30 PSMP and 42 standard; at 6 months 28 and 30 Attrition: PSMP 25% at 6	Patients with psoriasis attending speciality clinic in UK. See Table 1 Excluded people suffering from any other significant medical condition (e.g. heart disease) and were not diagnoses with any axis II disorder.	6 session CBT programme delivered by medical, clinical psychology, and nursing personnel (PSMP). Duration = 2.5hours The same psychology and nursing staff led each session. Consisted didactic teaching about medical and biological	Standard care - See table 2 for treatments	6 months	Changes in clinical severity of psoriasis as measured by PASI, anxiety as measured by HADS and psoriasis-related life stress scores as assessed by PLSI.	NHS executive research and development programme for physical and complex disabilities grant

		wk and 30% at 6 months Standard care: 21% at 6 weeks and 43% at 6 months		basis of psoriasis, stress-reduction techniques, cognitive techniques and homework in relation to individual perceptions.				

Table 1. Baseline characteristics of patients with psoriasis treated with Psoriasis Symptom Management Programme (PSMP) or standard care and those not interested in participating in the study at induction.

Variable	Psoriasis Symptom Management Programme (PSMP) (n=40)	Standard care (n=53)	Not interested (n=116)
Age (years), mean ± SD	42.7 ± 11.6	43.1 ± 12.0	42.8 ± 14.1
Duration of psoriasis (years), mean ± SD	20.6 ± 11.9	18.8 ± 11.1	18.9 ± 13.2
Age at onset of psoriasis (years), mean ± SD	22.7 ± 14.2	23.3 ± 12.3	23.0 ± 14.7
Clinical severity of psoriasis (PASI), mean ± SD	10.5 ± 2.7	9.2 ± 3.2	9.9 ± 4.7
Gender: M/F (%)	30/70	35/65	42/58
Family history of psoriasis, 1st or 2nd generation (%)	45%	58%	56%
Anxiety (HADS), mean ± SD	11.8 ± 3.8	11.7 ± 4.6	9.4 ± 4.8
Depression (HADS), mean ± SD	7.6 ± 3.5	8.5 ± 3.4	5.0 ± 3.7

Disability (PDI), mean ± SD	10.1 ± 6.6	15.4 ± 11.4	11.5 ± 8.2
Stress (PLSI), mean ± SD	21.7 ± 10.2	25.6 ± 11.0	23.1 ± 11.2

**P=0.02, as compared with PSMP and 'not interested'. All other values are not significantly different from each other. PASI, Psoriasis Area and Severity Index; HADS, Hospital Anxiety and Depression Scale; PDI, Psoriasis Disability Index; PLSI, Psoriasis Life Stress Inventory

Table 2. Psoriasis symptom management programme (PSMP) and the standard care patients prescribed topical, systemic or combination of treatments over the course of the study

		Psoriasis Symptom Management Programme (PSMP)		Standard care	
Time	Type of treatment	n	%	n	%
Baseline	Nothing	6	15	1	2
	Topical	24	60	21	40
	Systemic	6	15	21	39
	Combination	4	10	10	19
Total		40		53	
6 weeks	Topical	17	57	16	39
	Systemic	9	30	18	43
	Combination	4	13	8	18
Total		30		42	
6 months	Topical	12	41	12	40
	Systemic	10	38	8	27

	Combination	6	21	10	33
Total		28		30	

Table 3. Mean difference between Psoriasis Symptom Management Programme (PSMP) and standard care groups at 3 time points

	Baseline		6 weeks		6 months	
Variable	t-value	P-value	t-value	P-value	t-value	P-value
Clinical Severity (PASI)	1.96	NS	-2.2	0.03	-2	0.04
Disability (PDI)	-2.44	0.02	-3.33	0.001	-3.05	0.003
Anxiety (HADS)	0.2	NS	-2.8	0.007	-2.92	0.004
Depression (HADS)	-1.07	NS	-4.7	<0.001	-3.29	0.001
Stress (PLSI)	-1.5	NS	-3.9	<0.001	-3.06	0.003

Table 4. Clinical severity of psoriasis as assessed by Psoriasis Area and Severity Index (PASI) at baseline, 6 weeks and 6 months follow-up are presented graphically in paper:

PASI	Psoriasis Symptom Management Programme (mean ± SD clinical severity of psoriasis (PASI)	Standard treatment controls	Mean difference
Baseline	10.5 ± 2.7	9.2 ± 3.2	-1.3 (NS)
6 weeks	6.5 ± 4.1	8.4 ± 4.5	1.9 (p=0.03)
6 months	6.5 ± 4.1	8.0 ± 4.8	1.5 (p=0.04)
PASI75 at 6 months	64%	23%	SS

PASI: Psoriasis Area and Severity Index; PDI, Psoriasis Disability Index; HADS: Hospital Anxiety and Depression Scale; PLSI: Psoriasis Life Stress Inventory; NS: Not significant.

Table 5. Mean anxiety scores, as assessed by Hospital Anxiety and Depression Scale (HADS), for Psoriasis Symptom Management Programme patients and standard care patients (presented graphically in paper):

HADS (anxiety)	PSMP	Standard treatment	Mean difference
Baseline	12 (P=ns)	12	0 (P=ns)
6 weeks	8 (P=0.007)	11	-3 (P=0.007)
6 months	8 (P=0.004)	11	-3 (P=0.004)

Table 6. Mean psoriasis-related life stress scores as assessed by Psoriasis Life Stress Inventory (PLSI) for Psoriasis Symptom Management Programme patients and standard care patients (presented graphically in paper):

PLSI	PSMP	Standard treatment	Mean difference
Baseline	22	26	-4 (P=ns)
6 weeks	15	24	-9 (P<0.001)
6 months	15	23	-8 (P=0.003)

Table 2. Psoriasis symptom management programme (PSMP) and the standard care patients prescribed topical, systemic or combination of treatments over the course of the study

		Psoriasis Symptom Management Programme (PSMP)		Standard care	
Time	Type of treatment	n	%	n	%
Baseline	Nothing	6	15	1	2
	Topical	24	60	21	40
	Systemic	6	15	21	39
	Combination	4	10	10	19
Total		40		53	
6 weeks	Topical	17	57	16	39
	Systemic	9	30	18	43
	Combination	4	13	8	18
Total		30		42	
6 months	Topical	12	41	12	40
	Systemic	10	38	8	27
	Combination	6	21	10	33
Total		28		30	

Table 3. Mean difference between Psoriasis Symptom Management Programme (PSMP) and standard care groups at 3 time points

	Baseline		6 weeks		6 months	
Variable	t-value	P-value	t-value	P-value	t-value	P-value
Clinical Severity (PASI)	1.96	NS	-2.2	0.03	-2	0.04
Disability (PDI)	-2.44	0.02	-3.33	0.001	-3.05	0.003
Anxiety (HADS)	0.2	NS	-2.8	0.007	-2.92	0.004
Depression (HADS)	-1.07	NS	-4.7	<0.001	-3.29	0.001
Stress (PLSI)	-1.5	NS	-3.9	<0.001	-3.06	0.003

Table 4. Clinical severity of psoriasis as assessed by Psoriasis Area and Severity Index (PASI) at baseline, 6 weeks and 6 months follow-up are presented graphically in paper:

PASI	Psoriasis Symptom Management Programme (mean ± SD clinical severity of psoriasis (PASI)	Standard treatment controls	Mean difference

Baseline	10.5 ± 2.7	9.2 ± 3.2	-1.3 (NS)
6 weeks	6.5 ± 4.1	8.4 ± 4.5	1.9 (p=0.03)
6 months	6.5 ± 4.1	8.0 ± 4.8	1.5 (p=0.04)
PASI75 at 6 months	64%	23%	SS

PASI: Psoriasis Area and Severity Index; PDI, Psoriasis Disability Index; HADS: Hospital Anxiety and Depression Scale; PLSI: Psoriasis Life Stress Inventory; NS: Not significant.

Table 5. Mean anxiety scores, as assessed by Hospital Anxiety and Depression Scale (HADS), for Psoriasis Symptom Management Programme patients and standard care patients (presented graphically in paper):

HADS (anxiety)	PSMP	Standard treatment	Mean difference
Baseline	12 (P=ns)	12	0 (P=ns)
6 weeks	8 (P=0.007)	11	-3 (P=0.007)
6 months	8 (P=0.004)	11	-3 (P=0.004)

Table 6. Mean psoriasis-related life stress scores as assessed by Psoriasis Life Stress Inventory (PLSI) for Psoriasis Symptom Management Programme patients and standard care patients (presented graphically in paper):

PLSI	PSMP	Standard treatment	Mean difference
Baseline	22	26	-4 (P=ns)
6 weeks	15	24	-9 (P<0.001)

6 months	15	23	-8 (P=0.003)

H.15 Self-management

H.15.1 Randomised controlled trials

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
N. J. Mork, J. Austad, and L. Brolund. An open, parallel groups, study of the importance of thoroughness of application in the treatment of psoriasis with a dithranol cream (Micanol). Acta Derm.Venereol. Supplementum. 172:23-	RCT Single centre study, Norway • **Setting:** outpatient • **Randomised**: Unclear method. • **Washout period**: unclear • **Unblinded.** • **Allocation concealment**	N=29 **Drop-outs (don't complete the study):** N =2 1 in each group due to irritation – week 4 and week 2 (classified as treatment failures; all available data from these	**Inclusion criteria** Chronic, stable, plaque-type psoriasis; 4-14 plaques of ≥6cm^2; severity of erythema and induration ≥2 on 0-3 scale and desquamation ≤1(permitted to receive salicylic acid or urea ointment before the study to reach this score) **Exclusion criteria** None stated Parameter: Micanol (N=14); Micanol + info (n=15) **% male**: 42.9%; 46.7%	N=15 **Micanol plus additional education** (information about the importance of being thorough when rubbing the cream in to the lesions) – repeated at each follow-up visit At the first visit the investigator applied Micanol on one plaque to demonstrate correct application	N=14 **Micanol plus standard information**	**Treatment duration**: 6 weeks (or until complete clearance [TSS = 0])	**Primary outcome**: Total severity score (sum of desquamation , erythema and induration each on 0-3 scale divided by 3) – assessed at baseline weeks 2, 4 and 6	None stated

24, 1992. REF ID: MORK1992A	Not reported • **Sample size calculation** no. • **ITT analysis** unclear (may be ACA) **Drop-outs/withdrawals**. N=2	patients was included in analyses)	**Age (years)**	43.8±14.1 (28-78)	45.1±16.1 (25-79)	**Both arms:** Micanol 1% once daily, removed after 30 mins with water and mild soap Emollients were permitted during the study				
			Duration of disease and body surface area affected were not different							

Effect Size

Outcomes

TSS	**Micanol**	**Micanol + extra info**	**p-value**
Baseline score	1.98	1.91	
% reduction at week 2	23% (1.52)	34% (1.26)	
% reduction at week 4	31% (1.37)	47% (1.01)	
% reduction at week 6	39% (1.21)	67% (0.63)	<0.05

Author's conclusion

- Thoroughness of application is an important factor for rate of healing in short-contact dithranol treatment

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
C. Gradwell, K. S. Thomas, J. S. English, and H. C. Williams. A randomized controlled trial of nurse follow-up clinics: do they help patients and do they free up consultants' time? Br.J.Dermatol. 147 (3):513-517, 2002. REF ID: GRADWELL2002	RCT Single centre study, UK Recruited over a 3-month period and enrolled for 6 weeks • **Setting:** outpatient • **Randomised**: Computer-generated list with block size of 8 (stratified by diagnosis). • **Washout period**: N/A • **Unblinded.**	N=66 **Note:** mixed population (psoriasis and eczema – 46% psoriasis) **Drop-outs (don't complete the study):** N =10 5 in each group did not return the final questionnaire (in the control	**Inclusion criteria** Newly referred patients aged ≥14 years with a diagnosis of psoriasis or eczema **Exclusion criteria** None stated **Parameter** / **Usual (N=32)** / **Usual + nurse (n=33)** **% male**: 47% / 39% **Age (years)**: 47.0± 19.0 / 31.8± 15.7 **Diagnosis**: Psoriasis: 47% / 45% Eczema: 53% / 49% Other: 0 / 3% **Disease**	N=33 **Normal care plus session with dermatology nurse specialist** 20-min interview with dermatology nurse specialist in addition to initial consultation with dermatologist An appropriate teaching aid was selected per patient (demo/leaflet, video, touch-screen computer or verbal Information was given regarding the skin condition, treatment application (including how much and where), where	N=33 **Normal care** Initial consultation and follow-up with a dermatologist	6 weeks	**Primary outcome**: Change in DLQI **Other outcomes:** Patient knowledge, number of consultations during follow-up	Crookes Healthcare

	• **Allocation concealment** sealed, numbered opaque envelopes • **Sample size calculation** no – pilot study (constrained by length of study) • **ITT analysis** yes for DLQI – following DLQI instructions for missing fields and LOCF for other missing values Participants with missing data at baseline were excluded from further analysis on that scale **Drop-outs/withdrawals**. N=10	arm 2 of the 5 also had no baseline data)	**severity** Mild Moderate Severe	 6% 59% 34%	 24% 30% 45%	to receive support and how to get repeat prescriptions Participants were also provided with an individualised booklet and treatment programme Instructions about the quantity were based on the finger-tip unit or corticosteroids and used a teaspoon estimate for emollients				
			Despite randomisation age and disease severity were notably different							
Effect Size Outcomes										

Quality of life

DLQI	Baseline	Change at 6 weeks	Mean difference in change	95% CI	p-value
Normal care (n=31)	10.7	-2.9	0.27	-2.3 to 2.8	0.83
Normal care + nurse (n=31)	10.1	-2.6			

Treatment concordance/knowledge

Numbers who adequately understood:	Normal care (n=28)	Normal care + nurse (n=28)	p-value
- **How much treatment to apply**	24/26 (92%)	28/28 (100%)	0.23
- **How long to apply for**	23/27 (85%)	28/28 (100%)	0.05
- **How to obtain a repeat prescription**	14/24 (58%)	25/28 (89%)	0.01
- **Where to get support**	14/26 (54%)	26/27 (96%)	<0.001

Note: numbers vary for individual questions because of missing values

Impact on service use

	Normal care (n=28)	Normal care + nurse (n=28)	p-value
% follow-up appointments with dermatologist cancelled because nurse could perform the assessment	0%	33%	
Visited GP during 6-wk follow-up	11 (39%)	3 (11%)	0.01

Author's conclusion

- Dermatology nurses can add to a dermatology consultation and provide effective patient education and support in managing a skin condition.
- With this added service nurses could help to free up dermatologists' time, thus allowing them to see more new patients.
- Cost-effectiveness studies are now needed

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
S. J. Ersser, F. C. Cowdell, P. G. Nicholls, S. M. Latter, and E. Healy. A pilot randomized controlled trial to examine the feasibility and efficacy of an educational nursing intervention to improve self-management practices in patients with mild-moderate psoriasis. J Eur Acad Dermatol Venereol, 2011. **REF ID:** ERSSER2011	RCT Multicentre study (8 centres), UK Conducted June and September 2009 • **Setting**: primary care • **Randomised**: Cluster randomisation by toss of a coin (inadequate) • **Washout period**: N/A • **Unblinded**.	N=64 **Drop-outs (don't complete the study):** N =5 2 (7.1%) in experimental and 3 (8.3%) in control group Note: of those invited to participate (n=340) 53.2% did not respond and another 22.1% declined to participate of the 24.7% positive responses 23.8% were unable to attend	**Inclusion criteria** Age ≥18 years, mild-moderate plaque psoriasis (currently using topical therapies only and having no contact with secondary care in 3 months before or after recruitment) **Exclusion criteria** None stated **Parameter** / **Usual (N=36)** / **Usual + nurse (n=28)** / **p-value** % male / 55% / 29% / 0.031 Age (years) / 59.03± 13.53 / 56.86± 12.67 / 0.515 Mean disease duration / 24.17± 18.63 / 22.68± 17.99 / 0.749 **Current topicals**	**N=28** **Normal care plus session with dermatology specialist nurse and education materials** The intervention has three components: (i) structured, nurse-led group learning experience; (ii) supporting written and audiovisual material to provide additional information and a relaxation resource and (iii) Follow-up telephone consultation.	**N=36** **Normal care** Initial visit and follow-up for data collection only	6 weeks	**Primary outcome**: Change in DLQI **Other outcomes**: Change in PASI	Psoriasis Association

	• **Allocation concealment** unclear (randomisation performed by an independent investigator) • **Sample size calculation** no – pilot study • **ITT analysis** no – available case **Drop-outs/withdrawals**. N=5		None Emollients only GP prescribed active therapies	2 2 32	2 6 20		A dermatology specialist nurse and the research nurse attended training on self-efficacy based education. The specialist nurse delivered each group session				

Effect Size

Outcomes

Full group	**Intervention (n=26)**			**Control (n=33)**			**95% CI**	**p-value**
	Baseline	**Final**	**Change**	**Baseline**	**Final**	**Change**		
Mean DLQI (SD)	4.86±5.14	4.58±5.05	0.28±2.16	4.18±3.91	3.70±3.71	0.48±3.02	-1.20 to 1.61	0.772
Mean PASI (SD)	2.34±2.66	1.78±1.62	0.56±1.42	3.22±2.26	2.82±2.20	0.40±1.06	-0.81 to 0.49	0.619

Post-hoc subgroup analysis for those with moderate disease severity/impact

Baseline DLQI or PASI >6	Intervention (n=9)			Control (n=13)			95% CI for change	p-value
	Baseline	Final	Change	Baseline	Final	Change		
Mean DLQI (SD)	9.56±5.96	9.22±5.14	0.33±2.50	7.15±4.34	5.62±4.11	1.54±3.93	-1.90 to 4.31	0.427
Mean PASI (SD)	4.61±3.33	3.17±1.67	1.44±2.06	4.75±2.68	4.14±2.60	0.62±1.30	-2.32 to 0.66	0.259

Usefulness of intervention (n=26)

Score	Group learning	DVD	Workbook	Telephone conversation
Not useful	3.8%	3.8%	3.8%	7.7%
Moderately useful	30.8%	26.9%	38.5%	30.8%
Very useful	65.4%	26.9%	57.7%	53.8%
No response	0%	42.3%	0%	7.7%

Author's conclusion

- This study highlights the feasibility of delivering a self-efficacy based educational intervention for people with mild-moderate psoriasis in primary care establishing the numbers and design required for an adequately powered multi-centred trial.
- People with moderate disease severity may be most likely to benefit from this intervention.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
D. Kernick, A. Cox, R. Powell, D. Reinhold, J. Sawkins, and A. Warin. A cost consequence study of the impact of a dermatology -trained practice nurse on the quality of life of primary care patients with eczema and psoriasis. Br.J.Gen.Pract. 50:555-558, 2000. REF ID: KERNICK2000	RCT Single centre study, UK • **Setting:** primary care • **Randomised**: Computer-generated random numbers • **Washout period**: N/A • **Unblinded.** • **Allocation**	N=109 **Note:** mixed population (psoriasis and eczema – 41% psoriasis) **Drop-outs (don't complete the study):** N =28 9 (16%) in intervention group refused the initial appointment 11 (24%) in the	**Inclusion criteria** Routine GP care for 4 months before seeing the nurse; minimum of 3 repeat prescriptions for topical medication in the last year; aged 18-65 years; diagnosis of psoriasis or eczema **Exclusion criteria** None **Parameter** / **Usual + nurse (n=46)** / **Usual (n=54)** **% male**: 39% / 48% **Age (years)**: 47.4±18.4 / 51.7±15.8 **Diagnosis**: Psoriasis: 35% / 37% Eczema: 57% / 61% Mixed: 9% / 2%	N=55 **Routine GP care + sessions with trained practice nurse** Practise nurses attended a structured training programme at a local hospital dermatology department over 87 hours This included tuition, ward and out-patient attendance and background reading around the treatment, education and	N=54 **Routine GP care** (delayed intervention – received routine GP care for 4 months before seeing a nurse)	4 months	**Primary outcome**: Change in DLQI **Other outcomes:** Visual analogue scale from Euroqol; Response to care; Disease severity (assessed by patient-assessment of 3 signs from scaling,	Leo Pharmaceuticals

	concealment unclear • **Sample size calculation** yes • **ITT analysis** yes – assumptions not stated Participants who did not attend the initial clinic visit were excluded from further analysis **Drop-outs/withdrawals**. N=28	intervention group and 8 (15%) in the control group were lost to follow-up (4-month questionnaire was not completed); there were no differences in initial DLQI between these groups	Previous consultant referral	48%	50%	psychological support of patients, carers and families The nurse was able to offer as many consultations over 4 months as she deemed necessary (GPs signed prescriptions as indicated by the nurse without seeing the patients)			redness, itchiness, pustules, swelling, dryness, extent of rash and thickness of rash. Each was scored as mild (1) to very severe (5). The sum was used as the clinical score and ranged from 3-15	
			DLQI (0-30)	6.1 ± 4.9	6.8 ± 5.0					
			Clinical score (3-15)	9.3 ± 2.9	8.4 ± 3.1					
			Euroqol (0-100)	69.2±20.8	62.5±23.1					
			Despite randomisation % male and disease severity were notably different							

Effect Size

Outcomes

Note that the median number of clinic attendances was 2 and during the trial 2 patients saw the GP for eczema or psoriasis in the intervention group compared with 14 in the control group (p<0.005)

Quality of life

Outcome	Intervention group (n=46)		Control group (n=54)		Change (p-value)
	Entry	Completion	Entry	Completion	
DLQI	6.1 ±4.9	4.6 ±4.7	6.8 ±5.0	6.2 ±5.2	-1.5 vs -0.6 (NS)
Clinical score (0-15)	9.3 ±2.9	7.6 ±3.3	8.4 ±3.1	8.1 ±3.3	-1.7 vs -0.3(<0.05)
Euroqol generic QoL (0-100)	62.9±20.8	68.4 ±20.8	62.5 ±23.1	65.1 ±23.8	+5.5 vs +2.6 (NS)

Authors conclusion

- The study was underpowered to detect the change in DLQI (power calculation based on 50% reduction in DLQI based on nurse intervention) but the intervention did achieve a 25% reduction in DLQI
- Nurse intervention significantly reduced clinical burden

H.15.1.1 Cohort study

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
C. Renzi, Pietro C. Di, P. Gisondi, L. M. Chinni, M. Fazio, A. Ianni, and S. Tabolli. Insufficient knowledge among psoriasis patients can represent a barrier to participation in decision-making. Acta Derm.Venereol. 86 (6):528-534, 2006. REF ID: RENZI2006	Cohort study (2 consecutive phases; initial control phase followed by later experimental phase) Single centre study, Italy (recruited n waiting rooms of out-patient clinic and at hospital admission) • **Setting:** outpatients and in-patients • **Representative population sample:** yes – consecutive (but high	N=402 **Drop-outs (don't complete the study):** N =0	**Inclusion criteria** Attending Istituto Dermopatico dell'Immacolata (IDI-IRCCS) for out-patient visit or in-patient admission for psoriasis **Exclusion criteria** age < 18 years; having visited the clinic during the last 3 months, (to exclude those attending for a follow-up visit) **Parameter** / **Routine (n=231)** / **Decision board (n=171)** **% male** / 68% / 62% **Age (years)** / 45±15 / 43±13 **Severity***: Mild / *Approximate values* 28%	N=171 (87 out-patients and 84 in-patients) **Decision board aid** (Sept 2003-Jan 2004) Decision board designed using information from literature review by a group including one dermatologist, one internist, one medical epidemiologist and one physician specialized in public health and preventive medicine. The draft was then discussed separately with five dermatologists and five patients and refined. The aim was	N=231 (116 out-patients and 115 in-patients) **Routine clinical practice** (Jan-April 2004)	Unclear	Satisfaction with decision making process Overall satisfaction with care (outcomes were assessed using a modified version of validated questionnaires, which was piloted before the study and included 25 questions)	Italian Ministry of Health

	proportion of in-patients) • **Confounders accounted for:** no • **Minimal attrition bias:** N/A – patients and		Moderate Severe	53% 18%		to present all the important information on different treatment options in a simple easily comprehensible and visually clear manner. The revised decision-board was piloted among 30 patients and minor			Note: 5 dermatologists visiting out-patients and 6 treating in-patients were included	
			Diagnosis: Diffuse CPP (>10% BSA) Localised CPP (<10% BSA) PsA	 47.3% 36% 6.8%	 42.9% 33.9% 10.7%					

	dermatologists completed questionnaire either at discharge or after the out-patient visit Response rate was 88% in control and 86% in intervention groups • **Outcomes adequately measured:** Yes • **Appropriate statistical analysis:** yes		*Based on a 5-point scale according to dermatologists answer to the following question "In your experience, among all patients you have seen with this condition, how severe is the patient's condition"? Patient characteristics were not significantly different between the groups However, in- and out-patients differed significantly in severity of disease: the majority of outpatients had mild (44.6%) and moderate (40.9%) disease, compared with the majority of inpatients having moderate (65.0%) and severe (22.3%) disease (p <0.001).	corrections were made The final version consisted of an A4-page printed on both sides separated in to topics, phototherapy and systemics. Possible side-effects of each treatment option were colour-coded, depending on whether they occur frequently, sometimes or rarely. Additional information that could influence treatment choices was also included				

Effect Size

Outcomes

Note that the proportion of patients in the control group wanting to be more involved in decision making was significantly higher among in-patients than out-patients (42.7% vs. 24.8%; p = 0.002).

However, satisfaction with all aspects of doctor-patient communication in the control group was always significantly higher (p < 0.001) for outpatients compared with

inpatients, except for overall satisfaction

There was no significant differences between in-patients and out-patients among the decision-board group regarding the preferred role in decision making and aspects of doctor-patient communication, except that fewer in-patients were completely satisfied with the opportunity the had to express an opinion about treatment (p=0.002)

Satisfaction

Outcome	Control group (n=231)	Decision-board group (n=171)	p-value
Satisfaction with decision-making			
Wanted to be more involved	76 (33.0%)	59 (34.7%)	
Satisfied	146 (63.2%)	107 (62.6%)	
Wanted to be less involved	9 (3.8 %)	5 (2.7%)	0.823
Opportunity to express opinion/doubts			
Completely satisfied	107 (46.5%)	83 (48.7%)	
Fairly satisfied	63 (27.2%)	46 (26.9%)	
Not satisfied	34 (14.8%)	19 (10.9%)	
Had no doubts	27 (11.5%)	23 (13.5%)	0.707
Information on treatment options			
Completely satisfied	126 (54.7%)	98 (57.1%)	
Fairly satisfied	82 (35.4%)	61 (35.9%)	
Not satisfied	23 (9.9%)	12 (7.1%)	0.626

Doctor considered patient's preferences			
Very much	130 (56.2%)	96 (55.9%)	
Somewhat	43 (18.6%)	34 (19.6%)	
Very little/not at all	58 (25.2%)	96 (24.5%)	0.967
Information on treatment side-effects			
Completely satisfied	118 (51.0%)	42 (56.1%)	
Fairly satisfied	77 (33.2%)	62 (36.5%)	
Not satisfied	37 (15.9%)	13 (7.4%)	0.059
Overall patient satisfaction with care			
Completely satisfied	144 (62.5%)	114 (66.7%)	
Not completely satisfied	87 (37.5%)	57 (33.3%)	0.408

Authors' conclusion

- Satisfaction with specific aspects of doctor-patient communication was not significantly different between the control and the decision-board.
- A higher proportion of patients were satisfied with information on treatment side-effects among the decision-board group compared with the control group (this reached borderline significance)