Bilaga 1.till rapport

Ljusbehandling och systemisk behandling av psoriasis, rapport nr 278 (2018)

Bilaga 1 Tabell över inkluderade studier/ **Appendix 1** Description of included studies

Description of included studies

Table of content

Table 5.1. PUVA vs narrowband-UVB

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Yones et al 2006 [52] Single centre study performed in Great Britain RCT	**Population** *Inclusion criteria* Adult patients (18–70 years) with chronic plaque psoriasis involving ≥8% body surface area and PASI ≥8. No phototherapy in the previous 3 months BMI: not given Sex: 73% male, 27% female **Study period** April 2002–March 2005 **Follow-up** *For effects:* 8 sessions *For relapse:* 12 months	**Intervention** PUVA: 25 mg 8-methoxypsoralen/m^2 per os given 3 hours before phototherapy with UVA twice weekly in incremental doses to a final dose of 15 J/cm^2 *Duration of the intervention* Until complete clearance, minimal residual activity, no improvement after 16 sessions or once a total of 30 sessions was reached n=43 (37/43 with skin types I–IV) *Drop-out rate* <u>At 8 sessions:</u> 3 of the 46 initially randomised <u>After completed therapy → 12 months</u>: The 34/43 treated patients who were	**Comparison** **NB-UVB: twice weekly in incremental doses to a final dose of 5 J/cm^2. PBO per os 3 hours before phototherapy** n=45 (34/45 with skin types I–IV) *Drop-out rate* 3 of the 47 initially randomised <u>After completed therapy follow-up 12 months</u> The 23/47 treated patients who were "clear" from psoriasis after treatment were followed for 12 months	**Analysis model** Per protocol ("on-treatment-analysis"), of patients with skin types I–IV only **Results after 8 sessions** *PASI* <u>Change from baseline score</u> PUVA: –6.8 NB-UVB: –3.9 PUVA vs NB-UVB: p=0.001 *PGA* <u>Proportion clear</u> PUVA: 31/37 (84%) NB-UVB: 22/34 (65%) PUVA vs NB-UVB: p<0.001 *DLQI* <u>Change from baseline score</u> PUVA vs NB-UVB: p=0.02, favouring PUVA **Results at 6 months**	**Adverse events** As reported, in all patients (skin types I-VI) **During treatment** *Erythema* PUVA: 49% NB-UVB: 22% *Nausea* PUVA: 2/43 patients switched from 8-methoxy-psoralen to 5-methoxypsoralen due to nausea	**Risk of bias** Acceptable **Comment** *Conflict of interest* None reported

		”clear” from psoriasis after treatment were followed for 12 months		*No relapse (still clear among those clear after 8 sessions)* PUVA: 23/34 (68%) NB-UVB: 8/23 (35%) PUVA vs NB-UVB: p=0.02		

BMI – body mass index; DLQI – dermatology life quality index; NB-UVB – narrowband ultraviolet phototherapy; PASI – psoriasis area and severity index; PGA –physician’s’ global assessment; PUVA – psoralen and ultraviolet A phototherapy; UVA – ultraviolet A phototherapy

Table 6.1. Acitretin versus Etanercept

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Caproni et al 2009 [54] Single centre study performed in Italy RCT	**Population** *Inclusion criteria* Patients with moderate-to-severe plaque-type psoriasis, with PASI ≥10 and BSA (body surface area) ≥10% <u>Baseline characteristics</u> *Sex* I: 43.3% men, 56.7% women C: 36.7% men, 63.3 women Age I: 31-65 years C: 28-67 years BMI: No information **Study period** No information **Follow-up** Treatment for 12 weeks. No further follow-up	**Intervention** Acitretin (Neotigason) 0.4 mg/kg per day, for 12 weeks n=30 *Drop-out rate during treatment* 0/30 (0.0%)	**Comparison** Etanercept (Enbrel) 50 mg twice weekly for 12 weeks n=30 *Drop-out rate during treatment* 0/30 (0.0%)	**Analysis Model** ITT **Results** *Patients reaching PASI ≥75* I: 8/30 (26.7%) C: 17/30 (56.7%) I vs C: p<0.05 *Patients reaching PASI ≥50* I: 20/30 (66.7%) C: 26/30 (86.7%) I vs C: p<0.05	**Adverse events** No information	**Risk of bias** Acceptable **Comment** *Conflict of interest* No information

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
Gisondi et al 2008 [53] Single centre study performed in Italy RCT	**Population** *Inclusion criteria* Patients ≥18 years, with chronic, moderate to severe, plaque psoriasis <u>Baseline characteristics</u> *Sex* I: 60% men and 40% women C1: 54.5% men and 46.5% women C2: 50% men and 50% women *Mean BMI (kg/m^2)* I: 27.2 (SD 3,1) C1: 27.3 (SD 6.0) C2: 29.1 (SD 6.1) Age (mean yrs±SD) I: 55,0 ±11,3 C1: 55,3 ± 10,9 C2: 53,4 ± 12,3 **Study period** No information **Follow-up** Treatment for 24 weeks. No further follow-up	**Intervention** Acitretin, 0.4 mg/kg in a single oral dose per day, for 24 weeks n=20 *Drop-out rate during treatment* 4/20 (20.0%)	**Comparison** *Control 1 (C1):* Etanercept, 25 mg twice weekly subcutaneously, for 24 weeks *Control 2 (C2):* Etanercept, 25 mg once weekly subcutaneously, plus oral acitretin, 0.4 mg/kg per day, for 24 weeks C1: n=22 C2: n=18 *Drop-out rate during treatment* C1: 0/22 (0.0%) C2: 0/18 (0.0%)	**Analysis Model** ITT **Results at week 24** *PASI ≥50* I: 10/20 (50.0%) C1: 15/22 (68.2%) C2: 12/18 (66.7%) *PASI ≥75 (primary endpoint)* I: 6/20 (30.0%) C1: 10/22 (45.5%) C2: 8/18 (44.4%)	**Adverse events** Reported treatment emergent adverse events *Mild mucosal dryness:* I: 2/20 (10.0%) C1: 0/22 (0.0%) C2: 1/18 (5.6%)	**Risk of bias** Acceptable **Comment** *Conflict of interest* The authors have received consultation and lecture fees from Merck-Serono, Schering-Plough, Wyeth, Abbott, Janssen-Cilag

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Lee et al 2016 [55] Multicentre study performed in Korea RCT (open-label trial)	**Population** *Inclusion criteria* Patients ≥18 years, with active clinically stable moderate to severe plaque psoriasis, with BSA (body surface area) ≥10% or PASI ≥10 <u>Baseline characteristics</u> *Sex* I: 83.3% men, 16,7% women C1: 76.2% men, 23.8% women C2: 89.5% men, 10.5% women Mean body weight (kg) I: 74.2 (SD 9.8) C1: 74.1 (SD 16.0) C2: 74.0 (SD 11.6) Age (mean yrs±SD) I: 42,4 ±12,0 C1: 38,6 ±19,5 C2: 35,5 ± 8,8 **Study period** No information	**Intervention** Acitretin, 10 mg twice daily, for 24 weeks n=19 *Drop-out rate* 7/19 (36.8%)	**Comparison** *Control 1 (C1):* Etanercept, 50 mg twice weekly, for 12 weeks, followed by etanercept 25 mg twice weekly for a further 12 weeks *Control 2 (C2):* Etanercept, 25 mg twice weekly, plus acitretin, 10 mg twice daily, for 24 weeks C1: n=21 C2: n=20 *Drop-out rate* C1: 4/21 (19.0%) C2: 4/20 (20.0%)	**Analysis Model** Both ITT and per protocol is used **Results at week 24** *PASI ≥50* A greater proportion of patients in the control groups achieved PASI 50 than did the intervention group *PASI ≥75 (primary endpoint)* Reported results are approximations based on Fig 3. In Lee et al I: 4/19 (22.2%) C1: 11/21 (52.4%) C2: 12/20 (57.9%) I vs C1: p<0.0978 I vs C2: p<0.0448	**Adverse events** Patients experiencing treatment related adverse events: I: 8/18 (44.4%) C1: 9/21 (42.9%) C2: 10/20 (50.0%) (Analysed per protocol) No treatment related serious AEs reported *TEAEs (≥10% of patients in any group)* *Pruritus, n (%)* I: 1/18 (5.6%) C1: 3/21 (14.3%) C2: 2/20 (10.0%) *Alopecia, n (%)* I: 1/18 (5.6%) C1: - C2: 4/20 (20.0%) *Skin exfoliation, n (%)* I: 1/18 (5.6%) C1: - C2; 2/20 (10.0%) *Dry lip, n (%)* I: 2/18 (11.1%) C1: - C2: 3/20 (15.0%)	**Risk of bias** Acceptable **Comment** *Conflict of interest* Main author is an employee of Pfizer Funded by Pfizer Pharmaceuticals, who also supported the medical writing Etanercept is a product of Pfizer

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	Follow-up Treatment for 24 weeks. No further follow-up				*Chelitis, n (%)* I: 2/18 (11.1%) C1: - C2: 2/20 (10.0%) *Chapped lips, n (%)* I: 2/18 (11.1%) C1: - C2: 1/20 (5.0%) Myalgia, n (%) I: 2/18 (11.1%) C1: - C2: - Hypertension, n (%) I: - C1: - C2: 2/20 (10.0%)	

BMI – body mass index; BSA – body surface area; CI – confidence interval; ITT – intention-to-treat; PASI – psoriasis area and severity index; RCT – randomised controlled trial; PGA – physician´s global assessment; TNF – Tumour necrosis factor

Table 6.2. Apremilast versus placebo

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Papp et al 2012 [58] Multicentre study, 35 sites in USA and Canada RCT	**Population** *Inclusion criteria* ≥18 years of age Plaque psoriasis PASI ≥12, BSA ≥10%, for ≥6 months, eligible for phototherapy or systemic therapy *Baseline characteristics* *Female/Male, (%)* I: 43.2%/56.8% C: 39.8%/60.2% *Ethnicity – Caucasian* I: 90.9% C: 94.3% *Body mass index (kg/m²), mean±SD* I: 31.1±7.7 C: 30.8±6.7 **Study period** September 2008 - October 2009 **Follow-up** 16 weeks placebo-controlled phase (presented here). Followed by 8 weeks active phase dose	**Intervention (I)** Apremilast for 24 weeks, orally 30 mg twice daily (60 mg/day). Dose titrated for 5 days *Allocation – placebo controlled phase, n* I: 88 The study also included intervention groups treated with 20 mg and 40 mg per day *Drop-out rate – placebo controlled phase* I: n=18 (20.5%)	**Comparsion (C)** Placebo for 16 weeks, orally, twice daily (C) *Allocation – placebo controlled phase, n* C: 88 *Drop-out rate – placebo controlled phase, n (%)* C: 16 (18.2%)	**Analysis model** ITT *Missing data* LOCF **Results – 16 weeks** *PASI ≥50, n (%)* I: 53/88 (60.2%) C: 22/88 (25.0%) I vs C: p<0.001 *Primary endpoint* *PASI ≥75, n (%)* I: 36/88 (40.9%) C: 5/88 (5.7%) I vs C: OR 11.5 (95% CI, 4.24 to 31.16), p<0.0001 *PASI ≥90, n (%)* I: 10/88 (11.4%) I3 vs C: p=0.005 C: 1/88 (1.1%) *DLQI improvement* I: mean improvement 10.6–6.0; mean difference -4.4; SD: 5.1 C: mean improvement 10.7–8.6; mean difference -1.9; SD: 5.2.	**Adverse events – during 16 weeks placebo controlled phase** *Patients w ≥1 AE, n (%)* I: 72/88 (82%) C: 57/88 (65%) *Serious AE, n (%)* I: 2/88 (2%), (1 myocardial infarction, 1 prostate cancer) C: 2/88 (1 drug eruption, 1 death) *Patients with AE leading to drug withdrawal, n (%)* I: 10/88 (11.4%) C: 5/88 (5.7%) Treatment-emergent adverse events ≥5% of patients in any treatment groups *Nausea, n (%)* I: 16 (18%) C: 7 (8%)	**Risk of bias** Acceptable **Comment** *Conflict of interest study funded by Celgene. Study designed by sponsor. Data analysed by sponsor*

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	blinded OLE. Patients who discontinued or did not enrol in OLE were followed for 4 weeks post treatment			I vs C: p=0.0047 *SF-36, mean change ±SD* Physical component summary score I: 0.8 ±7.5 C: 0.7 ±8.5 I vs C: p=0.95 Mental component summary score I: 2.9 ±9.2 C: -0.8 ±10.0 I vs C: p=0.005	*URTI, n (%)* I: 14 (16%) C: 5 (6%) *Diarrhoea, n (%)* I: 12 (14%) C: 4 (5%) *Nasopharyngitis, n (%)* I: 5 (6%) C: 7 (8%) *Headache*, n (%)* I: 9 (10%) C: 5 (6%) *Tension headache, n (%)* I: 14 (16%) C: 6 (7%) *Viral URTI, n (%)* I: 7 (8%) C: 7 (8%) *Gastroenteritis, n (%)* I: 5 (6%) C: 3 (3%) *Dyspepsia, n (%)* I: 4 (5%) C: 2 (2%)	

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
					Arthralgia, n (%) I3: 2 (2%) C: 6 (7%) *Vomiting, n (%)* I: 4 (5%) C: 1 (1%) *migraine, sinus, and tension headaches were captured separately 0–16 weeks	
Papp *et al* 2015 [59] Study name Esteem 1 Multicentre study, performed at 72 sites RCT	**Population** *Inclusion criteria* Patients with plaque psoriasis of ≥18 years of age w. PASI score ≥12, BSA involvement ≥10%, sPGA ≥3 (moderate to severe), and eligible for phototherapy/systemic therapy *Baseline characteristics* *Female/Male* I: 32.6%/67.4% C: 31.2%/68.8% *Bodyweight, mean (kg) ±SD* I:93.2±21.4 C: 93.7±23.2	**Intervention (I)** 30 mg apremilast twice daily, 1 week titration period *Randomisation* n=562 *Drop-out rate, n (%)* 59/562 (10.5%)	**Comparison (C)** Placebo to match active treatment *Randomisation* C: n=282 *Drop-out rate, n (%)* 33/282 (11.7%)	**Analysis model** **Efficacy** *Efficacy outcomes* ITT *Safety outcomes* mITT (all randomised patients who received ≥1 dose of study medication) *Missing data* LOCF and NRI **Results – 16 weeks** PASI ≥75 (LOCF)* – primary endpoint I: 186 (33.1%) C: 15 (5.3%) Difference (LOCF)	**Adverse Events** *AEs reported during placebo controlled trial (week 0–16)* I: n=560 C: n282 *Patients w. AE ≥1 AE, n (%)* I: 388 (69.3%) C: 157 (55.7%) *Patients with ≥1 Severe AE, n (%)* I: 20 (3.6%) C: 9 (3.2%) *Patients with ≥1 Serious AE, n (%)* I: 12 (2.1%)	**Risk of bias** Acceptable **Comment** *Conflict of interest,* study sponsored and supported by Celgene

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	BMI, mean±SD I: 31.2±6.7 C: 31.3±7.4 *Ethnicity (Caucasian)* I: 90.2% C: 88.7% **Study period** September 2010–December 2012 **Follow-up** Placebo controlled phase 0–16 weeks (presented here). Followed by maintenance phase (week 16–32), and treatment withdrawal phase (week 32–52)			I vs C: 27.8% (95% CI, 23.1 to 32.5), p<0.0001 PASI ≥75 (NRI)* I: 183 (32.6%) C: 14 (5.0%) Difference (NRI) I vs C: p<0.0001 *PASI ≥50, n (%)* I: 330, (58.7%) C: 48 (17.0%) I vs C: p<0.0001 *DLQI change, mean ±SD (also presented in #4)* I: -6.6±6.66 C: -2.1±5.69 I vs C: p<0.0001 *Descriptive endpoints w.o. statistical analysis* *PASI ≥90, n (%)* C: 1 (0.4%) I: 55 (9.8%)	C: 8 (2.8%) *Patients with ≥1 AE leading to drug withdrawal, n (%)* I: 29 (5.2%) C: 9 (3.2%) *Patients with ≥1 AE leading to death, n (%)* I: 1 (0.2%) C: 1 (0.4%) *<u>AE reported by ≥5% of patients in any treatment group</u>* *Diarrhoea, n (%)* I: 105 (18.8%) C: 20 (7.1%) *URTI, n (%)* I: 57 (10.2%) C: 21 (7.4%) *Nausea, n (%)* I: 88 (15.7%) C: 19 (6.7%) *Nasopharyngitis, n (%)* I: 41 (7.3%) C: 23 (8.2%) Tension headache, n (%) I: 41 (7.3%)	

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
					C: 12 (4.3%) *Headache, n (%)* I: 31 (5.5%) C: 13 (4.6%)	
Paul et al 2015 [56] Study name ESTEEM 2 Multicentre study carried out at 40 sites in Austria, Canada, Denmark, France, Germany, Italy, Spain, Switzerland, and USA RCT	**Population** *Inclusion criteria:* Patients ≥18 years of age, with plaque psoriasis ≥12 months PASI score ≥12, BSA ≥10%, sPGA ≥3 (moderate to severe), and were eligible for phototherapy/systemic therapy. Patients previously treated with phototherapy or systemic therapy (conventional or biologic), including treatment failures, were permitted to enrol **Study period** November 2010-December 2012 **Baseline variables:** *Female (%)/Male (%)* I: 35.8%/64.2% C: 27.0%/73.0%	**Intervention (I)** 30 mg apremilast twice daily, 1 week titration period *Randomised pop* n=274 *Drop-out rate at 16 weeks* 35/274 (12.8%)	**Comparison (C)** Placebo to match active treatment *Randomised pop.* n=137 Drop-out rate at 16 weeks: 25/137 (18.2%)	**Analysis model** *Modified intention to treat (mITT):* excluding patients randomized in error and did not receive test substance *Safety population*: randomised patients who received ≥1 dose test substance Missing data: LOCF, NRI **Results – 16 weeks** *Primary endpoint* PASI ≥75 LOCF: I: 28.8% C: 5.8% I vs C: p<0.001 NRI: C: 5.1% I: 28.1% I vs C: p<0.001 <u>Other endpoints</u> PASI ≥50 LOCF I: 55.5%	**Adverse events** *Adverse events – 0–16 weeks* I: n=272 C: n=136 *Patients with ≥1 AE, n (%)* I: 185 (68.0%) C: 82 (60.3%) *Patients with ≥1 severe AE, n (%)* I: 12 (4.4%) C: 6 (4.4%) *Patients with ≥1 serious AE, n (%)* I: 5 (1.8%) C: 3 (2.2%) *AEs leading to drug withdrawal, n (%)* I: 15 (5.5%) C: 7 (5.1%)	**Risk of bias** Acceptable **Comment** *Conflict of interest,* study sponsored and supported by the Celgene corporation

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	Bodyweight (kg), mean±SD I: 91.4±23.0 C: 90.5±22.5 *BMI (kg/m^2), mean±SD* I: 30.9±6.7 C: 30.7±7.1 *Ethnicity (Caucasian)* I: 91.2% C: 93.4% **Follow-up** Treatment periods A: 0-16 weeks, placebo-controlled phase (presented here) B. 16-32 weeks, maintenance phase C: 32-52 weeks, treatment withdrawal phase			C: 19.7% I vs C: p<0.001 NRI I: 53.6% C:17.5% I vs C: p<0.001 PASI ≥90 LOCF I: 8.8% C: 1.5% I vs C: p=0.0042	*AE leading to death, n (%)* I: 0 (0.0%) C: 0 (0.0%) *AEs reported by ≥5% of patients in any treatment group – placebo controlled period (0–16 weeks)* *Nausea, n (%)* I: 50 (18.4%) C: 9 (6.6%) *Diarrhoea, n (%)* I: 43 (15.8%) C: 8 (5.9%) *Nasopharyngitis, n (%)* I: 20 (7.4%) C: 6 (4.4%) *URTI, n (%)* I: 13 (4.8%) C: 6 (4.4%) *Tension headache, n (%)* I: 20 (7.4%) C: 2 (1.5%)	

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
					Vomitting, n (%) I: 14 (5.1%) C: 5 (3.7%) *Headache, n (%)* I: 17 (6.3%) C: 1 (0.7%) *Back pain, n (%)* I: 6 (2.2%) C: 2 (1.5%) *Psoriasis, n (%)* I: 4 (1.5%) C: 7 (5.1%)	
Thaçi et al 2016 [62] Study names ESTEEM 1 [59] and ESTEEM 2 [56] This article presents patient-reported outcomes (PRO) of Health-related quality of life (HRQOL) from the ESTEEM 1 and ESTEEM 2 trials	**Population** Reported in [59] and [56] **Follow-up** Placebo-controlled phase 0–16 weeks (presented here) Maintenance phase 16–32 weeks	**Intervention (I)** ESTEEM 1 I1: n=562 For the DLQI outcome n=459 ESTEEM 2 I2: n=274 For the DLQI outcome: n=226	**Comparison (C)** *For 0–16 weeks* ESTEEM 1 C1: n=282 For the DLQI outcome n=236 ESTEEM 2 C2: n=137 For the DLQI outcome n=119	**Analysis model** Full analysis set (FAS): all patients randomised as specified in the protocols. *Missing data* LOCF **Results – week 16** *Secondary endpoints (for primary outcomes see main publications)* *DLQI change (results from ESTEEM 1 are also presented in #2, mean ±SD*	**Adverse events** Reported in [59] and [56]	**Risk of bias** Acceptable **Comment** Study sponsored and supported by the Celgene corporation

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
				I1: -6.6±6.66 C1: -2.1±5.69 I1 vs C1: p<0.0001 I2: -6.7±6.95 C2: -2.8±7.22 I2 vs C2: p<0.0001 *SF-36v2 MCS score* I1: 2,4±9.50 C1: -1.0±9.16 I1 vs C1: p<0.0001 I2: 2.6±10.13 C2: 0.0±10.50 I2 vs C2: p<0.0095 *SF-36v2 PCS, mean change±SD* I1: 1.15±7.20 C1: 0.17±6.22 I1 vs C1: ns I2: 1.60±7.24 C2: 0.28 (7.29) I2 vs C2: ns Exploratory endpoints *EQ-5D change, mean±SD* I1: 0.038±0.166 C1: -0.014±0.171 I1 vs C1: p<0.0001 I2: 0.051±0.178 C2: -0.0005±0.184 I2 vs C2: p≤0.0095		

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Crowley et al 2017 [63] This article is an open lable extension (OLE) from the ESTEEM 1 and ESTEEM 2 trials OLE to [56,59,62]	**Population** Reported in [56] and [59] Inclusion criteria to OLE phase: Participants in the ESTEEM 1 and 2 studies who, after completion of 52 weeks agreed to continue on Apremilast treatment for up to 4 additional years. **Follow-up** Placebo-controlled phase 0–16 weeks (presented in [56,59,62] Maintenance phase up to 52 weeks, followed by OLE for up to 156 weeks	**Intervention** 30 mg apremilast twice daily **N in safety analysis** *Whole period:* 0 to ≤ 156 weeks: n=1184 *Stratified in periods:* *1:* 0 to ≤ 52 weeks: n=1184 *2:* >52 to ≤ 104 weeks: n=654 *3:* >104 to ≤ 156 weeks: n=401		*Effects from OLE-studies are not reported*	**Adverse events** *Patients with ≥1 AE, n (%)* *Total:* 985 (83.2) Period 1: 939 (79.3) Period 2: 380 (58.1) Period 3: 230 (57.4) *Patients with ≥1 severe AE, n (%)* *Total:* 126 (10.6) Period 1: 86 (7.3) Period 2: 33 (5.0) Period 3: 17 (4.2) *Patients with ≥1 serious AE, n (%)* *Total:* 106 (9.0) Period 1: 58 (4.9) Period 2: 36 (5.5) Period 3: 18 (4.5) *AEs leading to drug withdrawal, n (%)* *Total:* 132 (11.1) Period 1: 93 (7.9) Period 2: 20 (3.1) Period 3: 14 (3.5) ***AE leading to death, n (%)* *Total:* 3 (0.3) Period 1: 1 (0.1)	**Risk of bias** Not assessed **Comment** Study sponsored and supported by the Celgene corporation **Patients with multiple diseases. Two died from heart failure and one from fatal cerebrovascular accident

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
					Period 2: 1 (0.2) Period 3: 1 (0.2) *AEs reported by ≥5% of patients* *Diarrhea, n (%)* *Total: 221* (18.7) Period 1: 205 (17.3) Period 2: 15 (2.3) Period 3: 7 (1.7) *Nausea, n (%)* *Total:* 195 (16.5) Period 1: 186 (15.7) Period 2: 5 (0.8) Period 3: 6 (1.5) *URTI, n (%)* *Total:* 227 (19.2) Period 1: 184 (15.5) Period 2: 58 (8.9) Period 3: 27 (6.7) *Nasopharyngitis, n (%)* *Total:* 196 (16.6) Period 1: 167 (14.1) Period 2: 43 (6.6) Period 3: 24 (6.0) *Tension headache, n (%)* *Total:* 115 (9.7) Period 1: 106 (9.0)	

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
					Period 2: 8 (1.2) Period 3: 5 (1.2) *Headache, n (%)* *Total:* 86 (7.3) Period 1: 75 (6.3) Period 2: 6 (0.9) Period 3: 7 (1.7)	
Ohtsuki et al 2017 [61] Multicentre study in Japan RCT	**Population** *Inclusion criteria* ≥20 years of age Plaque psoriasis PASI ≥12, BSA ≥10%, for ≥6 months, eligible for phototherapy or systemic therapy *Baseline characteristics* *Female/Male, (%)* I: 16.5%/83.5% C: 26.2%/73.8% *Ethnicity: Asian (Japan)* *Body mass index (kg/m^2), mean±SD* I: 24.9±3.7 C: 24.7±4.7 **Study period** July 2013 – December 2015	**Intervention (I)** Apremilast for 16 weeks, orally 30 mg twice daily (60 mg/day). Dose titrated (10-mg daily increments) for 6 days *Allocation – placebo controlled phase, n* I: 85 The study also included intervention groups treated with 20 mg per day *Drop-out rate – placebo controlled phase* I: n=9 (10.6%)	**Comparsion (C)** Placebo for 16 weeks (C) *Allocation – placebo controlled phase, n* C: 84 *Drop-out rate – placebo controlled phase, n (%)* C: 12 (14.3%)	**Analysis model** mITT and safety population *Missing data* LOCF **Results – 16 weeks** *PASI ≥50, n (%)* I: 43/85 (50.6%) C: 18/84 (21.4%) I vs C: p<0.0001 *Primary endpoint PASI ≥75, n (%)* I: 24/85 (28.2%) C: 6/84 (7.1%) I vs C: p<0.0003 *PASI ≥90, n (%)* I: 12/85 (14.1%) C: 1/84 (1.2%) I vs C: p<0.006 *DLQI improvement, mean (SD)*	**Adverse events – during 16 weeks placebo controlled phase** *Patients w ≥1 AE, n (%)* I: 44/85 (51.8%) C: 35/84 (41.7%) *Severe AE, n (%)* I: 0/85 (0%), C: 1/84 (1.2%) *Patients with AE leading to drug withdrawal, n (%)* I: 6/85 (7.1%) C: 4/84 (4.8%) Adverse events reported by ≥5% of patients in any treatment groups *Diarrhoea, n (%)* I: 8 (9.4%)	**Risk of bias** Acceptable **Comment** *Conflict of interest: study funded by Celgene*

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	Follow-up 16 weeks placebo-controlled phase (presented here). Followed by 52 weeks active phase dose OLE, and a four-week post-treatment observational follow-up			I: -2.2 (SD: 5.0) C: +1.3 (SD: 5.7) I vs C: p<0.0001	C:1 (1.2%) *Nasopharyngitis, n (%)* I: 10 (11.8%) C: 7 (8.3%) *Abdominal discomfort, n (%)* I: 6 (7.1%) C: 1 (1.2%)	
Reich et al 2017 [57] Multicentre study carried out at 82 sites in the USA, Australia, Canada and Europe. RCT	**Population** *Inclusion criteria* ≥18 years of age, Plaque psoriasis PASI ≥12, sPGA ≥3, BSA ≥10%, for ≥12 months, eligible for phototherapy or systemic therapy, inadequate response to one or two conventional systemic agents, and biologic naïve. *Baseline characteristics Female/Male, (%)* I: 41%/59% C: 29.8%/70.2% *Ethnicity – Caucasian* I: 95.2% C: 95.2%	**Intervention (I)** Apremilast for 16 weeks, orally 30 mg twice daily (60 mg/day). Dose titrated for the first week. *Allocation – placebo controlled phase, n* I: 83 *Drop-out rate – placebo controlled phase* I: n=6 (7.2%) The study also included intervention groups treated with etanercept	**Comparsion (C)** Placebo for 16 weeks, orally, twice daily *Allocation – placebo controlled phase, n* C: 84 *Drop-out rate – placebo controlled phase, n (%)* C: 9 (10.7%)	**Analysis model** mITT *Missing data* LOCF **Results – 16 weeks** *Primary endpoint PASI ≥75, n (%)* I: 33/83 (39.8%) C: 10/84 (11.9%) I vs C: p<0.0001 *PASI ≥90, n (%)* I: 12/83 (14.5%) C: 3/84 (3.6%) I vs C: p=0.0169 *DLQI improvement, mean (SD)* I: -8.3 (SD: 7.7) C: -3.8 (SD: 5.6) I vs C: p<0.0001	**Adverse events – during 16 weeks placebo controlled phase** *Patients w ≥1 AE, n (%)* I: 59/83 (71.1%) C: 45/84 (53.6%) *Patients w ≥1 serious AE, n (%)* I: 3/83 (3.6%) C: 0/84 (0%) *Patients with AE leading to drug withdrawal, n (%)* I: 3/83 (3.6%) C: 2/84 (2.4%) Treatment-emergent adverse events ≥5% of patients in any treatment groups	**Risk of bias** Acceptable **Comment** *Conflict of interest: study funded by Celgene. Editorial support by sponsor* The study was not powered for apremilast vs etanercept comparisons. A post hoc comparison yielded a calculated power of 19% for detecting the observed difference. *Information about study period found at https://clinicaltrials.gov/ct2/show/NCT01690299*

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	Body mass index (kg/m^2), mean±SD I: 29.2±5.8 C: 29.5±6.6 **Study period** October 2012 - July 2014 **Follow-up** 16 weeks placebo-controlled phase (presented here). At week 16 placebo patients were switched to apremilast. The OLE phase was maintained until week 104. Results for up to 52 weeks presented in the publication. Patients who did not achieve PASI 50 at week 32 could add complementary therapies to their treatments			*DLQI patients receiving a DLQI score of 0 or 1, n (%)* I: 22/83 (26.5%) C: 13/84 (15.5%)	*Nausea, n (%)* I: 9/83 (10.8%) C: 1/84 (1.2%) *URTI, n (%)* I: 6/83 (7.2%) C: 2/84 (2.4%) *Diarrhoea, n (%)* I: 9/83 (10.8%) C: 3/84 (3.6%) *Nasopharyngitis, n (%)* I: 4/83 (4.8%) C: 8/84 (9.5%) *Headache*, n (%)* I: 11/83 (13.3%) C: 3/84 (3.6%) *Tension headache, n (%)* I: 5/83 (6.0%) C: 4/84 (4.8%)	

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Strober et al 2017 [60] Multicentre study, conducted at 25 study sites in USA RCT	**Population** *Inclusion criteria* ≥18 years of age Moderate cronic plaque psoriasis, BSA 5-10%, and sPGA=3, for ≥6 months, no prior exposure to conventional systemics, biologic naïve *Baseline characteristics* *Female/Male, (%)* I: 50%/50% C: 43.8%/56.2% *Ethnicity – Caucasian* No information *Body mass index (kg/m^2), mean±SD* I: 30.5±7.4 C: 30.8±6.5 **Study period** April 2015 - February 2016 **Follow-up** 16 weeks placebo-controlled phase (presented here). At week 16 placebo patients were switched to apremilast. The OLE	**Intervention (I)** Apremilast, orally 30 mg twice daily (60 mg/day). Dose titrated for the first week. *Allocation – placebo controlled phase, n* I: 148 *Drop-out rate – placebo controlled phase* I: n=27 (18.2%)	**Comparsion (C)** Placebo orally, twice daily (C) *Allocation – placebo controlled phase, n* C: 73 *Drop-out rate – placebo controlled phase, n (%)* C: 9 (12.3%)	**Analysis model** ITT *Missing data* LOCF **Results – 16 weeks** *PASI ≥50, n (%)* I: 79/148 (53.4%) C: 18/73 (24.7%) I vs C: p<0.0001 *PASI ≥75, n (%)* I: 32/148 (21.6%) C: 6/73 (8.2%) I vs C: p=0.0136 *DLQI improvement, mean (SD)* I: -4.8 (SD: 5.80) C: -2.4 (SD: 6.62) I vs C: p=0.0008	**Adverse events – during 16 weeks placebo controlled phase** *Patients w ≥1 AE, n (%)* I: 92/148 (62.6%) C: 35/73 (47.9%) *Patients w ≥1 serious AE, n (%)* I: 3/148 (2.0%), C: 0/73 (0.0%) *Patients with AE leading to drug withdrawal, n (%)* I: 5/148 (3.4%) C: 3/73 (4.1%) Treatment-emergent adverse events ≥5% of patients in any treatment groups *Nausea, n (%)* I: 26 (17.7%) C: 7 (9.6%) *URTI, n (%)* I: 10 (6.8%) C: 3 (4.1%) *Diarrhoea, n (%)* I: 43 (29.3%)	**Risk of bias** Acceptable **Comment** *Conflict of interest: study funded by Celgene.* *Study information found mainly at https://clinicaltrials.gov/ct2/show/record/NCT02425826*

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	phase was maintained until week 52.				C: 12 (16.4%) *Headache, n (%)* I: 30 (20.4%) C: 8 (11.0%) *Decreased appetite, n (%)* I: 6 (4.1%) C: 4 (5.5%) *Vomiting, n (%)* I: 9 (6.1%) C: 2 (2.7%)	

AE – adverse events; BMI – body mass index; BSA – body surface area; DLQI – dermatology quality of life index; HRQOL – health-related quality of life; ITT – intention-to-treat; LOCF – last observation carried forward; MCS – mental component summary score; mITT – modified-ITT; NRI – non-responder imputation; PASI – psoriasis area and severity index; PCS – physical component summary score; PGA – physician's global assessment; PRO – patient reported outcome; SD – standard deviation; URTI – upper respiratory tract infection

Table 6.3. Cyclosporine versus Methotrexate

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Control**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Flytström et al 2008 [65] The study was carried out at 5 study sites in Sweden. RCT	**Population** Adult patients (≥18 years of age) with chronic plaque psoriasis of moderate to severe severity according to the patient's and physician's common judgement. Topical treatment was allowed during the treatment period, reflecting normal clinical practice. <u>*Baseline characteristics*</u> *Female/male* MTX: 24.3%/75.7% Cyclosporine: 12.9%/87.1% *Age, mean (range)* MTX: 48 (23–78) Cyclosporine: 45 (18–70) *Weight (kg), mean (range)* MTX: 85 (56–132) Cyclosporine: 87 (61–130) *PASI at baseline, mean (SD):* MTX: 14.1 (±7.0)	**Cyclosporine** Initially 3 mg/kg daily. If inadequate response (<50% reduction of PASI) and no considerable adverse effects were recorded, the dose was increased to a maximum of 5 mg/kg daily n=43 n after dropouts: 31 *Drop-out rate* 12/43 (27,9%). All drop outs were withdrawn from the study before the first treatment dose.	**Methotrexate** Initially 7.5 mg weekly. If inadequate response (<50% reduction of PASI) and no considerable adverse effects were recorded, the dose was increased to a maximum of 15 mg weekly. Folic acid 5 mg was given daily except on the methotrexate days. n=41 n after drop outs: 37 *Drop-out rate* 4/41 (9.8%) All drop outs were withdrawn from the study before the first treatment dose.	**Analysis model** mITT, (all patients who received ≥ 1 dose of test substance). **Results** *PASI ≥50* MTX: 24/37 (65%) Cyclosporin:27/31 (87%) MTX vs Cyclosporine: n.s. *PASI≥75* MTX: 9/37 (24%) Cyclosporine: 18/31 (58%) MTX vs Cyclosporine: p 0.0094 *PASI≥90* MTX: 4/37 (11%) Cyclosporine: 9/31 (29%) MTX vs Cyclosporine n.s. *PASI, mean change* MTX: 58% Cyclosporine: 72% MTX vs Cyclosporine p 0.0028	**Adverse events (AE:s)** *Any reported AE:* MTX: 78% Cyclosporine: 97% (p=0.03) *Dose reduction due to side-effects:* MTX: approx. 33% Ciclosporin: approx. 33% <u>*AE:s reported by ≥5 patients*</u> *Fatigue* MTX: 16% Cyclosporine: 48% (p=0.008) *Gastrointestinal* MTX: 35% Cyclosporine: 39% (p=0.8) *Infection* MTX: 30% Cyclosporine: 35% (p=0.8) *Headache* MTX: 14% Cyclosporine: 29%	**Risk of bias** Acceptable **Comment** *Conflict of interest* None stated

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Control	Analysis model Results	Adverse events	Risk of bias Comment
	Cyclosporine: 15.5 (±6.3) **Study period** February 2002–February 2005. Inclusion restricted to September thru February each yr. **Follow up** 12 weeks			*DLQI, mean change* MTX: circa -8 Cyclosporine: circa -6 MTX vs Cyclosporine n.s.	(p=0.14) *Paresthesia* MTX: 0 Cyclosporine: 35% (p=<0.0001) *Arthralgia:* MTX: 11% Cyclosporine: 16% (p=0.72) *Urgency* MTX: 3% Cyclosporine: 13% (p=0.17) *Elevated liver enzymes* MTX: 19% Cyclosporine: 0 (p=0.01) *Elevated creatinine* MTX: 0 Cyclosporine: 19% (p=0.007)	

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Control	Analysis model Results	Adverse events	Risk of bias Comment
Heydendael et al 2003 [66] The study was carried out at local dermatological centers in Amsterdam, the Netherlands RCT	**Population** Adult patients (≥18 years of age), with chronic plaque psoriasis of moderate to severe severity defined as a PASI score of ≥8 and insufficient response to topical or UVB therapy. Naive to methotrexate or cyclosporine treatment. <u>*Baseline characteristics*</u> *Female/male* MTX: 35%/65% Cyclosporine: 31%/69% *Age, mean (SE)* MTX: 41.6 (±13.0 Cyclosporine: 38.3 (±12.4) *Weight* Not given *PASI at baseline, mean (SE):* MTX: 13.4 (±3.6) Cyclosporine: 14.0 (±6.6) *Psoriatic arthritis:* MTX: n=3 Cyclosporine: n=1 **Study period**	**Methotrexate** Initially 15 mg weekly. If inadequate response after 4 weeks (<25% reduction of PASI) the dose was increased to a maximum of 22.5 mg weekly. If side effects occurred the does was decreased according to regular clinical guidelines. n=44 randomised (43 included in analyses) *Drop-out rate* 13/44 (29.5%)	**Cyclosporine** Initially 3 mg/kg daily. If inadequate response after 4 weeks (<25% reduction of PASI) the dose was increased to a maximum of 5 mg weekly. If side effects occurred the does was decreased according to regular clinical guidelines. n=44 randomised (42 included in analyses) *Drop-out rate* 3/44 (6.9%)	**Analysis model** mITT (all who received at least 1 dose of test substance). **Results after 16 weeks** *PASI 75* MTX: 26/43 (60.4%) Cyclosporine: 30/42 (70%) MTX vs cyclosporine: *PASI 90* MTX: 17/43 (39.5%) Cyclosporine: 14/42 (32.5%) MTX vs cyclosporine: *Mean relative reduction in PASI:* MTX: 64% Cyclosporine: 72% MTX vs cyclosporine: p=0.14 *SF-36, physical component score – mean difference between groups after adjustment for baseline values (95% CI):* MTX vs cyclosporine: -0.8 (-4.6 to 3.0)	**Adverse events over 52 weeks** *Discontinuation of treatment due to side effects* MTX: 12/43, 27.9% (due to elevated liver enxymes) Cyclosporine: 1/42, 2.3% (due to elevated bilirubin) *Total number of reported side effects during treatment:* MTX: 113 events reported by 29 of 43 patients Cyclosporine: 166 events reported by 35 of 42 patients <u>*Specific events (reported by n patients)*</u> *Nausea:* MTX: 19/43 (44.2%) Cyclosporine: 4/42 (9.3%) MTX vs Cyc: p<0.001 *Headaches* MTX: 7/43 (16.3%) Cyclosporine: 18/42 (41.9%)	**Risk of bias** Acceptable **Comment** *Conflict of interest* None stated

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Control	Analysis model Results	Adverse events	Risk of bias Comment
	October 1998–June 2000 **Follow up** 16 weeks treatment phase and in total 52 weeks follow-up.			*SF-36, mental component score – mean difference between groups after adjustment for baseline values (95% CI):* MTX vs cyclosporine: -0.5 (-3.9 to 2.9)	MTX vs Cyc: p=0.009 *Muscle ache* MTX: 3/43 (7%) Cyclosporine: 12/42 (27.9%) MTX vs Cyc: p=0.007 *Paresthesia* MTX: 1/43 (2.3%) Cyclosporine: 14/42 (32.6%) MTX vs Cyc: p<0.001 No serious or irreversible side effects were reported in either group	

Table 6.4. Fumarates versus placebo

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Mrowietz et al 2016 [68] *Name of study* BRIDGE Main study Multicentre study performed in Austria, Germany, the Netherlands and Poland RCT	**Population** *Inclusion criteria* Patients, 18 years or older with moderate to severe chronic (≥12 months) plaque psoriasis, with BSA >10%, PGA ≥3 and PASI >10 Baseline characteristics Female/Male, I: 37,6%/62.4% C: 32,1%/67.9% **Study period** Start of patient recruitment: January 2013 **Follow-up** Primary analyses at week 16. Treatment week 0–16, treat-ment free follow-up for 12 month	**Intervention** Fumarates (DMF). I1: LAS41008 I2: Fumaderm Treatment was up-titrated over the first 9 weeks, up to a maximum daily dose of 720 mg, as per clinical practice I1: n=286 12: n=280 *Drop-out rate at 16* I1: 104/280 (37.1%) I2: 110/286 (38.5%) *Patients entering the follow-up period* n=150	**Comparison** Placebo n=138 *Drop-out rate at 16 weeks* 40/138 (28.9%) *Patients entering the follow-up period* n=66	**Analysis Model** FAS (Full analysis set) I1: 267 I2: 273 C: 131 *Missing data* LOCF **Results** *PASI ≥50 at week 16* I1: 53.6% I2: 61.9% C: 29.0% *PASI ≥75 at week 16 (primary endpoint)* I1: 37.5% I2: 40.3% C: 15.3% *PASI ≥90 at week 16* I1: 18.4% I2: 22.3% C: 4.6% *PGA clear or almost clear at week 16 (primary endpoint)* I1: 33.0% I2: 37.4% C: 13.0%	**Adverse events** 4 serious TEAE all in I2 One or more treatment-emergent adverse events (only events reported by ≥5% of the patients in the safety population are included) was reported by: I1: 234/279 (83.9%) I2: 238/283 (84.1%) C: 82/137 (59.9%) (Reported events: diarrhoea, upper abdominal pain, abdominal pain, nausea, flatulence, vomiting, pruritus, erythema, skin burning sensation, nasopharyngitis, flushing, lymphopenia, eosinophilia, headache)	**Risk of bias** Acceptable **Comment** *Conflict of interest* Sponsored by the manufacturer of the test substance, Almirall S.A.

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
				BSA at week 16 Mean change from baseline I1: -13,2 I2: -11,3 C: -4,9		

BSA – body surface area; ITT – intention-to-treat; LOCF – last observation carried forward; PASI – psoriasis area and severity index; PGA – physician's global assessment; SD – standard deviation; TEAE – treatment emergent adverse events.

Table 6.5. Fumarates versus Methotrexate

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Fallah Arani et al 2011 [69] Single centre study performed in the Netherlands RCT	**Population** *Inclusion criteria* Patients, 18 years or older with chronic plaque-type psoriasis and PASI ≥10 *Baseline characte-ristics for patients receiving treatment* Intervention Female: 26% Male: 74% Mean bodyweight 87 kg (SD ±21) Comparison Female: 41% Male: 59% Mean bodyweight 83 kg (SD ±17) **Study period** Recruitment between October 2006 – February 2009 **Follow up** Primary analyses at week 12. Treatment	**Intervention** Fumarates (per os), 30 mg, followed by 120 mg according to a standard progressive dosage regimen (maximum dose 720 mg after week 9) n=30 *Drop-out rate at 12 weeks* 4/30 (13.3%) *Drop-out rate at 20 weeks* 18 finished the follow-up period	**Comparison** Methotrexate (per os); 15 mg per week n=30 *Drop-out rate* at 12 weeks 5/30 (16.7%) *Drop-out rate at 20 weeks* 19 finished the follow-up period	**Analysis Model** ITT **Results** *Decrease in PASI (primary endpoint, mean ±SD)* I: Base line: 18.1±7.0 Week 12: 10.5±6.7 C: Base line: 14.5±3.0 Week 12: 6.7±4.5 I vs C (week 12): Adjusted absolute mean difference 1.4; 95% CI: –2.0 to 4.7; p=0.417 *PASI ≥50 at week 12* I: 11/26 (42.3%) C: 15/25 (60.0%) I vs C: p=0.325 *PASI ≥75 at week 12* I: 5/26 (19.2%) C: 6/25 (24.0%) I vs C: p=0.941	**Adverse events** Patient reported total number of adverse events were 60 in the intervention group (reported by 24 patients) and 78 in the control group (reported by 27 patients) p=0.236 for I vs C) *Flushing* I: 13/26 (50.0%) C: 2/25 (8.0%) I vs C: p=0.002 *Influenza-like syndrome* I: 1/26 (3.8%) C: 7/25 (28.0%) I vs C: p=0.050 *Other adverse events* I: 2/26 (7.7%) (Diarrhoea, worsening of psoriasis, itch) C: 4/25 (16.0%) (Elevations in liver enzymes, recurrent angina)	**Risk of bias** Acceptable **Comment** *Conflict of interest* None declared

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	week 0–16, follow-up until week 20			*PASI ≥90 at week 12* I: 1/26 (3.8%) C: 2/25 (8.0%) I vs C: p=0.610 *PASI ≥50 at week 20* I: 13/18 (72.2%) C: 10/19 (52.6%) I vs C: p=0.374 *PASI ≥75 at week 20* I: 7/18 (38.9%) C: 6/19 (31.6%) I vs C: p=0.642 *PASI ≥90 at week 20* I: 1/18 (5.6%) C: 2/19 (10.5%) I vs C: p=1.00		

BSA – body surface area; ITT – intention-to-treat; LOCF – last observation carried forward; PASI – psoriasis area and severity index; PGA – physician's global assessment; SD – standard deviation; TEAE – treatment emergent adverse events.

Table 6.6. Methotrexate versus placebo

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Ho et al 2010 [71] China RCT	**Population** Patients (≥18 years of age) with a history of chronic plaque psoriasis (≥12 months) with BSA involvement ≥20% *Baseline characteristics* Female/Male, % I: 10.0%/90.0% C: 10.0%/90.0% Ethnicity No information Bodyweight No information **Study period** No information **Follow-up** 6 months study period	**Intervention** Methotrexate, initial dose 2.5-5 mg. If tolerated the dose increased to 10 mg/week after 1 week. The dose was increased with 2.5 mg/week until a good clinical response was seen or to a maximum of 30 mg/week. In addition patients were given 5 mg folic acid daily Randomised patients n=20 Drop-out rate, n (%) 1/20=5% Included in analysis n=19	**Comparison** Placebo Randomised patients n=20 Drop-out rate, n (%) 3/20=15% Included in analysis n=17	**Analysis model** Outcomes analysed for those who completed the study **Results** **6 months** *PASI ≥50, achieved by % of patients* I: 79% C: 24% *PASI ≥75, achieved by % of patients* I: 63% C: 18% *PDI, change from baseline (mean±SD)* I: 18.3±31,6 C: 10.3±31.2 I vs C:ns	**Adverse Events** AEs, % of patients I: 65% C: 30% Nausea, vomiting, and increased liver enzyme levels were common in the methotrexate group. The placebo group reported infections and increased liver enzymes	**Risk of bias** Acceptable **Comment** Metotrexat arm was unblinded Blinding not described for placebo arm Method of randomisation not clearly described

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Saurat et al 2008 [72] Multicentre study carried out at 28 sites in Europe and Canada Study name CHAMPION RCT	**Population** Patients (≥18 years of age), with moderate to severe psoriasis, with PASI score≥10, BSA involvement ≥10%, diagnosed with plaque psoriasis (≥1 year), which was stable (≥2 months). All patients had to be naïve to TNF-antagonist therapy and methotrexate *Baseline characteristics* Female/Male, % I: 33.6%/66.4% C: 35.2%/64.8% Ethnicity, Caucasian, % I: 95.5% C: 95.4% *Bodyweight (kg), mean±SD* I: 83.1±17.5 C: 81.7±20.0 **Study period** Not reported **Follow-up**	**Intervention** Methotrexate (orally, once a week). Titrated from 7.5 mg/week, increased to 10 mg week 2, and 15 mg week 4. If PASI ≥50 was reached by or after week 8 the dosage was maintained. Week 8, patients who did not achieve PASI ≥50 had their dosage increased to 20 mg/week. By week 12, only patients who did not achieve PASI ≥50 and had PASI<50 at week 8 had dosage increased to 25 mg Subcutaneous injections with placebo to match control Background treatment with 5 mg of oral folate weekly *Randomised patients* n=110	**Comparison** C: placebo, administered to match active treatments Background treatment with 5 mg of oral folate weekly for both groups *Randomised patients* C: n=53 *Drop-out rate* C: 5/53 (9.4%)	**Method of analysis** ITT for efficacy outcomes *Missing data* NRI for efficacy analysis LOCF for mean PASI improvement **Results** **Week 12** *PASI ≥50* I: 54.5% C: 26.4% *PASI ≥75* I: 24.5% C: 15.1% *PASI ≥90* I: 9.1% C: 7.5% *PASI 100* I: 0.9% C: 0.0% **Results** **Week 16** *PASI ≥50* I: 61.8%	**Adverse events** AEs during placebo-controlled phase and follow-up period *Total adverse events, n (%)* I: 90/110 (81.8%) C: 42/53 (79.2%) *Serious AEs, n (%)* I: 1/110 (0.9%) C: 1/53 (1.9%) *Serious infections* None reported Adverse events leading to discontinuation, n (%) I: 6/110 (5.5%) C: 1/53 (1.9%) *Adverse events, (≥5% of patients in any treatment group)* *Infections (nonserious), n (%)* I: 46/110 (41.8%) C: 23/53 (43.4%) *Nasopharyngitis, n (%)* I: 46/110 (41.8%) C: 11/53 (20.8%)	**Risk of bias** Acceptable **Comment** Study funded by Abbot Laboratories, who also participated in designing, data collection/management/analysis and preparation of the manuscript. Several of the authors were affiliated with Abbott (employed/consultants) as well as other pharmaceutical companies.

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	Placebo-controlled phase (16 weeks), 70 days follow-up period	*Drop-out rate* 6/110 (5.5%) The study also included an intervention group treated with adalimumab		C: 30.2% *PASI ≥75 – primary endpoint* I: 35.5% C: 18.9% *PASI ≥90* I: 13.6% C: 11.3% *PASI 100* I: 7.3% C: 1.9% I vs C: p=0.04	*Headache, n (%)* I: 12/110 (10.9%) C: 5/53 (9.4%) *Pruritus, n (%)* I: 2/110 (1.8%) C: 6/53 (11.3%) *Rhinitis, n (%)* I: 4/110 (3.6%) C: 4/53 (7.5%) *Nausea, n (%)* I: 8/110 (7.3%) C: 4/53 (7.5%) *Rhinorrhea, n (%)* I: 0/110 (0) C: 3/53 (5.7%) *Viral infection, n (%)* I: 6/110 (5.5%) C: 1/53 (1.9%) *Arthralgia, n (%)* I: 5/110 (4.5%) C: 1/53 (1.9%)	

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Warren et al 2017 [73] Multicenter study performed at 16 sites in Germany, France, the Netherlands, and the UK RCT	**Population** Patients (≥18 years of age) with a history of chronic plaque psoriasis (≥6 months) currently moderate to severe disease based on the definition by *Finlay *Baseline characteristics* Female/Male, % I: 29%/71% C: 14%/86% Ethnicity White % I: 98% C: 100% Bodyweight, Mean kg (SD) I: 92.4 (18.6) C: 95.9 (20.9) BMI, kg/m2 (SD) I: 30.1 (6.3) C: 30.1 (6.1) Age, Mean (SD) I: 45.9 (12.9) C: 44.4 (10.8)	**Intervention** Methotrexate as self-administered subcutaneous injections, initial dose 17.5 mg/ week. Dose escalation to 22·5 mg/week allowed after 8 weeks if patients had not achieved PASI 50**.** Treatment was combined with folic acid, 5 mg/week, 24 hours after each injection Randomised patients n=91 Drop-out rate, n (%) 14/91=15.4%	**Comparison** Self-administered subcutaneous injections of placebo once a week. Treatment was combined with folic acid, 5 mg/week, 24 hours after each injection Randomised patients n=29 Drop-out rate, n (%) 7/29=24.1%	**Analysis model** Modified ITT (analysis of all patients who had received at least one injection of study drug) Missing data: NRI **Results** **16 weeks** *PASI 50, achieved by % of patients* I: 60/91 (66%) C: 9/29 (31%) *PASI 75,* I: 37/91 (41%) C: 3/29 (10%) *PASI 90,* I: 16/91 (18%) C: 0/29 (0%) *PASI 100,* I: 4/91 (4%) C: 0/29 (0%) *DLQI, absolute change, mean (SD)* I: -9.4 (6.58) C: -2.6 (5.83)	**Adverse Events** AE data given here for the placebo-controlled phase (16 weeks) for the control (placebo group, n=29) and for the whole follow-up period (week 0-52) for the intervention group (n=91) *Any AE, n (%)* I: 86/91 (95%) C: 27/29 (93%) *Any drug-related (as per judgement of investigator) AE, n (%)* I: 66/91 (73%) C: 14/29 (48%) *Serious AEs, n (%)* I: 3/91 (3%) C: 4/29 (14%) *Serious infections* None reported *Adverse events, (≥5% of patients in any treatment group)* *Any infection, n (%)* I: 58/91 (64%)	**Risk of bias** Acceptable **Comment** Study founded by Medac Germany. Medac also supplied study medication. Study design by consultant experts in psoriasis in conjunction with SCIderm GmbH, Germany, which served as clinical research organisation for study management, data collection, and statistical analysis. ** Reference: Finlay AY. Current severe psoriasis and the rule of tens. Br J Dermatol 2005;* ***152:*** *861–67*

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	Study period Feb 22, 2013 – May 13, 2015 **Follow-up** 16 weeks placebo controlled period, followed by 52 weeks OLE, where both groups received active reatment				C: 13/29 (45%) *White blood cell count decrease, n (%)* I: 5/91 (5%) C: 1/29 (3%) *Hepatic enzyme increased, n (%)* I: 21/91 (23%) C: 2/29 (7%) *Gastrointestinal disorders, n (%)* I: 30/91 (33%) C: 3/29 (10%) *Nausea or vomiting, n (%)* I: 20/91 (22%) C: 1/29 (3%) *Diarrhoea, n (%)* I: 6/91 (7%) C: 1/29 (3%)	

AE – adverse event; BSA – body surface area; ITT – intention-to-treat; LOCF – last observation carried forward; mITT – modified intention-to-treat; NRI – non-responder imputation; PASI – psoriasis area and severity index; PDI – psoriasis disability index (Health Related Quality of Life outcome); PGA – physician's global assessment; SD – standard deviation

Table 7.1. Adalimumab versus placebo

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Asahina et al 2010 [75] Multicentre study carried out at 42 sites in Japan	**Population** Patients (≥20 years of age) with plaque psoriasis for ≥6 months, with PASI score ≥12, and BSA involvement ≥10% *Baseline characteristics, (%)* Female/Male, (%) I: 18.6%/81.4% C: 10.9%/89.1% Bodyweight (kg), mean±SD I: 67.4±9.9 C: 71.3±15.3 All patients were Japanese **Study period** September 2005 – December 2006 **Follow-up** 16 weeks placebo controlled period, after which non-responders	**Intervention** Subcutaneous injection of 40 mg adalimumab every two weeks, initial dose 80 mg Randomised patients n=43 Drop-out, n (%) 8/43 (18.6%)	**Comparison** Placebo Randomised patients n=46 Drop-out, n (%) 6/46 (13.0%)	**Analysis model** mITT (i.e. all randomised patients who received at least one dose of study drug, and had at least one assessment) *Missing value* LOCF **Results** **Week 12** *PASI ≥90, n (%)* I: 13/43 (30.2%) C: 0/46 (0.0%) I vs C: p<0.01 **Week 16** *PASI ≥50, n (%)* I: 35/43 (81.4%) C: 9/46 (19.6%) I vs C: p<0.001 *PASI ≥75, n (%) – primary endpoint* I: 27/43 (62.8%) C: 2/46 (4.3%) I vs C: p<0.001	**Adverse events** **AEs – week 0–24** *Patients with any AE, n (%)* I: 39/43 (90.7%) C: 41/46 (89.1%) *Patients with serious AE, n (%)* I: 3/43 (7.0%) C: 2/46 (4.3%) *Patients with severe AEs, n (%)* I: 1/43 (2.3%) C: 1/46 (2.2%) Patients with AEs leading to discontinuation, n (%) I: 5/43 (11.6%) C: 5/46 (10.9%) *Patients with any infectious AEs, n (%)* I: 18/43 (41.9%) C: 23/46 (50.0%)	**Risk of bias** Acceptable **Comments** Funded by Abbott Japan, writing support funded by Abbott Laboratories, USA

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	had option of rescue therapy (topical steroids) until week 24. Thereafter 28 weeks extension period			*PASI ≥90, n (%)* I: 17/43 (39.5%) C: 0/46 (0%) I vs C: p<0.001 DLQI change from baseline, mean±SD I: -5.1±5.73 C: 1.0±6.69 I vs C: p<0.001 SF-36 (PCS) change from baseline, mean±SD I: 4.6±7.62 C: -0.4±7.34 I vs C: p<0.01 SF-36 (MCS) change from baseline, mean±SD I: 2.4±10.24 C: -2.6±10.56 I vs C: p<0.05	*Patients with injection site reactions, n (%)* I: 8/43 (18.6%) C: 3/46 (6.5%)	
Gordon et al 2006 [77] Multicentre study at 18 sites in the US and Canada	**Population** Patients (≥18-years of age), with plaque psoriasis (≥1 year), BSA involvement ≥5%. All patients were naïve to	**Intervention** 80 mg of adalimumab at week 0, followed by 40 mg every other week starting week 1. Subcutaneous injection	**Comparison** Placebo to match intervention n=52	**Analysis model** mITT: all patients who received ≥1 dose of test substance *Safety analysis*: all patients who received ≥1 dose of medication	**Adverse events** **AEs – week 0–12** *Patients reporting any AE, n (%)* I: 28/45 (62.2%	**Risk of bias** Acceptable **Comments** Study supported by Abbott Laboratories. Several authors were

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
RCT	anti-TNF treatment. Patients were stratified according to bodyweight (<70, 70–100, and >100 kg) *Baseline characteristics* *Female/Male. (%)* I: 29%/71% C: 35%/65% *Bodyweight (kg), mean (range)* I: 93 (63–159) C: 94 (50–147) *Ethnicity (Caucasian), %* I: 89% C: 92% **Study period** March 2003 – June 2004 **Follow-up period** Double-blind placebo-controlled phase (12 weeks), followed by double-blind active treatment phase (week 12–24), open-label phase (24–60 weeks)	n=46 mITT: n =45 One patient did not receive study medication after randomisation *Drop-out rate, n (%)* 3/46 (6.5%)	*Drop-out rate, n (%)* 2/52 (3.8%)	*Missing data:* NRI for binary outcomes **Results (12 weeks)** PASI ≥75 – percent of patients, (%) I: 24/45 (53.3%) C: 2/52 (3.8%) I vs C: p<0.001 PASI 100 – percent of patients, (%) I: 5/45 (11.1%) C: 0/52 (0%) I vs C: p<0.001	C: 35/52 (67.3%) *Any serious AE, n (%)* I: 1/45 (2.2%) C: 0/52 (0%) *Any infectious SAE* *I and C*: 0 Any AE leading to discontinuation, n (%) I: 2/45 (4.4%) C: 1/52 (1.9%) *AEs occurring ≥5% of patients in any group and more frequent in I than C, n (%)* *Nausea, n (%)* I: 3/45 (6.7%) C: 3/52 (5.8%) *Injection site pain, n (%)* I: 3/45 (6.7%) C: 3/52 (5.8%) *Increasing blood triglycerides, n (%)* I: 4/45 (8.9%) C: 2/52 (3.8%)	affiliated or employed by Abbott

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Shikiar et al 2007 [80] HRQOL outcomes**.** Efficacy results reported in Gordon K et al 2006 [77] Multicenter study at 18 sites in the US and Canada RCT	**Population** Patients (≥18-years of age), with plaque psoriasis (≥1 year), BSA involvement ≥5%. All patients were naïve to anti-TNF treatment. Patients were stratified according to bodyweight (<70, 70–100, and >100 kg) *Baseline characteristics* *Female/Male, (%)* I: 29%/71% C: 35%/65% *Ethnicity (Caucasian), (%* I: 89% C: 92% Bodyweight (kg), mean (range) I: 93 (63–159) C: 94 (50–147) **Study period** March 2003 – June 2004 **Follow-up period** HRQOL outcomes were reported at the end of	**Intervention** 80 mg of adalimumab at week 0, followed by 40 mg every other week starting week 1. Subcutaneous injection n=46 mITT: n=45 One patient did not receive study medication after randomisation *Drop-out rate, n (%)* 3/46 (6.5%)	**Comparison** Placebo to match intervention n=52 *Drop-out rate, n (%)* 2/52 (3.8%)	**Analysis model** mITT: all patients randomized who received ≥1 dose of study medication **Results (12 weeks)** *DLQI – total score change, mean (95% CI)* I: -10.8 (-13.1 to 8.5) C: -1.3 (-3.3 to 0.7) I vs C: p<0.001 *EQ-5D index score change, mean (95% CI)* I: 0.21 (0.11 to 0.31) C: 0.01 (-0.07 to 0.10) I vs c: p<0.001 *EQ-5D VAS change, mean (95% CI)* I: 17.9 (10.5 to 25.2) C: 0.5 (-5.7 to 6.8) I vs C: p<0.001 *SF-36 PCS score change, mean (95% CI)* I: 3.6 (0.2 to 7.0) C: 0.5 (-2.4 to 3.5) I vs C: p=0.118	**Adverse events** Presented in Gordon et al 2006, [2]	**Risk of bias** Acceptable **Comment** Study funded by Abbott/Abbott Laboratories, carried out by United BioSource Corporation. Abbott/Abbott Laboratories involved in the analysis of data and preparation of the manuscript. Several authors had been or were employed by Abbott/Abbott Laboratories or United BioSource

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
	the double-blind placebo-controlled phase (12 weeks). Study continued with a double-blind active treatment phase (week 12–24), open-label phase (24–60 weeks)			*SF-36 MCS score, mean (95% CI)* I: 7.8 (3.9 to 11.8) C: -0.1 (-3.5 to 3.3) I vs C: p<0.001		
Menter A et al 2008 [78] Multicenter study conducted in 67 centers in the US and 14 centers in Canada RCT	**Population** *Inclusion criteria* Patients (≥18 years of age) with clinical diagnosis of psoriasis (≥6 months) and stable plaque psoriasis (≥2 months). Patients had moderate to severe plaque psoriasis with BSA involvement of ≥10%, a PASI score ≥12, and a PGA of at least moderate severity at baseline Randomisation stratified by center Baseline characteristics Female/Male, (%) I: 32.9%/67.1%	**Intervention** 80 mg of adalimumab week 0, 40 mg of adalimumab every other week starting from week 1 and continued through week 15 Adalimumab administered subcutaneously n=814 *Drop-out rate (week 16), n (%)* 31/814 (3.8%)	**Comparison** Placebo to match intervention n=398 *Drop-out rate (week 16), n (%)* 43/398 (10.8%)	**Analysis model** ITT during first 12 weeks *Missing data:* NRI for PASI/PGA LOCF for continuous variables (PASI score improvement) **Results** **Week 12** PASI ≥75 (week 12), n (%) I: 554/814 (68.1%) C: 20/398 (5.0%) I vs C: p<0.001 PASI ≥90 (week 12), (%) I: 37% C: 2% I vs C: p<0.001	**Adverse events** <u>AEs (week 0–12)</u> *Patients with any AE, n (%)* I: 506/814 (62.2%) C: 221/398 (55.5%) *Patients with Serious AEs, n (%)* I: 15/814 (1.8%) C: 7/398 (1.8%) *Patients with serious infectious AEs, n (%)* I: 235/814 (28.9%) C: 89/398 (22.4%) I vs C: p<0.019 (Fisher's exact test)	**Risk of bias** Acceptable **Comments** Abbott Laboratories funded the agency, participated in the study design, data collection, data management, data analysis, and preparation of the manuscript. Authors affiliated with Abbott.

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
	C: 35.4%/64.6% *Ethnicity (Caucasian), %* I: 91.2% C: 90.2% Bodyweight (kg), mean±SD I: 92.3±23.0 C: 94.1±23,0 **Study period** Not stated **Follow-up** Placebo-controlled phase 0–15 weeks. Week 16–32 open-label active treatment phase. Week 33–52 withdrawal phase			PASI 100 (week 12), (%) I: 14% C: <1% I vs C: p<0.001 **Week 16** PASI ≥75 (week 16) – primary endpoint, n (%) I: 578/814 (71.0%) C: 26/398 (6.5%) I vs C: p<0.001 PASI ≥90 (week 16), (%) I: 45% C: 2% I vs C: p<0.001	*Patients with AEs leading to withdrawals, n (%)* I: 14/814 (1.7%) C: 8/398 (2.0%) *AEs reported by ≥5% in treatment group* *Nasopharyngitis, n (%)* I: 43/814 (5.3%) C: 26/398 (6.5%) *URTI, n (%)* I: 59/814 (7.2%) C: 14/398 (3.5%)	
Gordon et al. 2012 [84] Multicenter study conducted in 67 centers in the US and 14 centers in Canada OLE to [78] *REVEAL-study*.	**Population** *Inclusion criteria in the initial RCT:* Stable moderate to severe plaque psoriasis (PASI ≥12) *<u>Inclusion criteria to OLE phase:</u>* *Group A:* Entered the OLE w PASI ≤75 at week 16	**Intervention** 80 mg of adalimumab week 0, 40 mg of adalimumab every other week thereafter *Maximum possible exposure to Adalimumab* 165 weeks *N in safety analysis*		*Effects from OLE-studies are not reported*	**Adverse events** *N events and rates (events per 100 patient years of exposure to adalimumab)* *Adverse event leading to discontinuation* Year 1: 61 (6.0) Year 2: 14 (2.8) Year 3: 21 (4.0)	Gordon et al. 2012 [84] Multicenter study conducted in 67 centers in the US and 14 centers in Canada OLE to [78] *REVEAL-study*.

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	Group B: Entered the OLE w PASI ≥50–≤75 at week 33 *Group C:* Re-randomised to ADA week 33, entered OLE week 52 *Group D:* Randomised to placebo in the initial RCT, started ADA week 16 *Baseline characteristics* See [78] **Study period** Not stated **Follow-up** 52 weeks RCT in three phases followed by 108 or 113 OLE	All exposure to adalimumab in all patients except one group who received placebo after week 33 Year 1: n=1159 (1009.5 yrs of exposure) Year 2: n=621 (504,8 yrs of exposure) Year ≥3: n=443 (529.5 yrs of exposure) *Drop-out rates in 4 groups during OLE phase (yr 2–3)* 17–37%			*Serious adverse events* Year 1: 60 (5.9) Year 2: 40 (7.9) Year 3: 49 (9.3) *Serious infection* Year 1: 18 (1.8) Year 2: 3 (0.6) Year 3: 9 (1.7) *Tuberculosis* Year 1: 2 (<1) Year 2: 0 Year 3: 1 (0.2) *Allergic reactions* Year 1: 8 (0.8) Year 2: 2 (0.4) Year 3: 2 (0.4) *Congestive heart failure* Year 1: 1 (<1) Year 2: 1 (0.2) Year 3: 4 (0.8) *Malignancies, excl non-melanoma skincancer and lymphoma* Year 1: 5 (0.5) Year 2: 5 (1.0) Year 3: 5 (0.9) *Lymphoma*	

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
					Year 1: 0 Year 2: 0 Year 3: 0	
Revicki et al 2007 [79] HRQOL outcomes**.** Efficacy results reported in Menter et al 2008 [78] Multicentre study conducted in 67 centres in the US and 14 centres in Canada RCT	**Population** *Inclusion criteria* Patients (≥18 years of age) with clinical diagnosis of psoriasis (≥6 months) and stable plaque psoriasis (≥2 months). Patients had moderate to severe plaque psoriasis with BSA involvement of ≥10%, a PASI score ≥12, and a PGA of at least moderate severity at baseline Randomisation stratified by center. Baseline characteristics Female/Male, (%) I: 32.9%/67.1% C: 35.4%/64.5% *Ethnicity (Caucasian), %* I: 91.3% C: 90.2% Bodyweight (kg), mean±SD I: 92.3±23.0	**Intervention** 80 mg of adalimumab week 0, 40 mg of adalimumab every other week starting from week 1 and continued through week 15 Adalimumab administered subcutaneously Efficacy outcomes (ITT) n=814 HRQOL outcomes (mITT) n=808 *ITT drop-out rate (week 16), n (%)* 31/814 (3.8%)	**Comparison** Placebo to match intervention Efficacy outcomes (ITT) n=398 HRQOL outcomes (mITT) n=397 *ITT drop-out rate (week 16), n (%)* 43/398 (10.8%)	**Analysis model** mITT: all patients randomized who completed baseline and one follow-up DLQI assement within 16 weeks **Results (change from baseline at week 16)** DLQI total, mean (95% CI) I: -8.4 (-8.8 to -7.9) C: -1.9 (-2.6 to -1.3) I vs C: p<0.001 SF-36 PCS, mean (95% CI) I: 3.7 (3.1 to 4.3) C: 0.4 (-0.5 to 1.2) I vs C: p<0.001 SF-36 MCS, mean (95% CI) I: 3.8 (3.1 to 4.5) C: 0.3 (-0.7 to 1.4) I vs C: p<0.001	**Adverse events** Reported by Menter et al 2008 [78]	**Risk of Bias** Acceptable **Comments** Abbott Laboratories funded the study, participated in the study design, data collection, data management, data analysis, and preparation of the manuscript. Authors affiliated with Abbott. Writing support provided by JK Associates Inc.

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
	C: 94.1±23,0 **Study-period** Not stated **Follow-up** Placebo-controlled phase 0–15 weeks. Week 16–32 active treatment phase. Week 33–52 withdrawal phase					
Saurat et al 2008 [72] Multicenter study carried out at 28 sites in Europe and Canada Study name CHAMPION RCT	**Population** Patients (≥18 years of age), with moderate to severe psoriasis, with PASI score≥10, BSA involvement ≥10%, diagnosed with plaque psoriasis (≥1 year), which was stable (≥2 months). All patients had to be naïve to TNF-antagonist therapy and methotrexate. Candidates for systemic or phototherapy *Baseline characterstics* Female/Male, % I: 35.2%/64.8%	**Intervention** Adalimumab 80 mg initial dose, 40 mg every two weeks, from week 1 through week 15. Subcutaneous injection of adalimumab, oral placebo to match control Background treatment with 5 mg of oral folate weekly. *Randomised patients* n =108 *Drop-out rate* 4/108 (3.7%)	**Comparison** C: placebo Placebo administered to match active treatments Subcutaneous injections with placebo to match control Background treatment with 5 mg of oral folate weekly *Randomised patients* C: n=53	**Method of analysis** ITT for efficacy outcomes *Missing data* NRI for efficacy analysis LOCF for mean PASI improvement **Results (week 12)** *PASI ≥50* I: 90.7% C: 26.4% I vs C: p<0.001 *PASI ≥75* I: 76.9% C: 15.1% I vs C: p<0.001	**Adverse events** AEs during placebo-controlled phase and follow-up period *Total adverse events, n (%)* I: 79/107 (73.8%) C: 42/53 (79.2%) *Serious AEs, n (%)* I: 2/107 (1.9%) C: 1/53 (1.9%) *Serious infections* None reported Adverse events leading to discontinuation,	**Risk of bias** Acceptable **Comment** Study funded by Abbot Laboratories, who also participated in designing, data collection / management / analysis and preparation of the manuscript. Several of the authors were affiliated with Abbott (employed/consultants) as well as other pharmaceutical companies.

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	C: 34.0%/66.0% Ethnicity, Caucasian, % I: 95.4% C: 92.5% *Bodyweight (kg), mean±SD* I: 81.7±20.0 C: 82.6±19.9 **Study period** Not reported **Follow-up** Placebo-controlled phase (16 weeks), 70 day follow-up period	The study also included an intervention group treated with methotrexat	*Drop-out rate* C: 5/53 (9.4%)	*PASI ≥90* I: 48.1% C: 7.5% I vs C: p<0.001 *PASI 100* I: 11.1% C: 0.0% I vs C: p=0.009 **Results (week 16)** *PASI ≥50* I: 88.0% C: 30.2% I vs C: p<0.001 *PASI ≥75 – primary endpoint* I: 79.6% C: 18.9% I vs C: p<0.001 *PASI ≥90* I: 51.9% C: 11.3% I vs C: p<0.001 *PASI 100* I: 16.7% C: 1.9%	n (%) I: 1/107 (0.9%) C: 1/53 (1.9%) *Adverse events, (≥5% of patients in any treatment group)* *Infections (nonserious), n (%)* I: 51/107 (47.7%) C: 23/53 (43.4%) *Nasopharyngitis, n (%)* I: 30/107 (28.0%) C: 11/53 (20.8%) *Headache, n (%)* I: 14/107 (13.1%) C: 5/53 (9.4%) *Pruritus, n (%)* I: 4/107 (3.7%) C: 6/53 (11.3%) *Rhinitis, n (%)* I: 3/107 (2.8%) C: 4/53 (7.5%) *Nausea, n (%)* I: 4/107 (3.7%) C: 4/53 (7.5%)	

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
				I vs C: p=0.004	*Rhinorrhea, n (%)* I: 3/107 (2.8%) C: 3/53 (5.7%) *Viral infection, n (%)* I: 0/107 (0%) C: 1/53 (1.9%) *Arthralgia, n (%)* I: 6/107 (5.6%) C: 1/53 (1.9%)	
Gordon et al 2015 [81] Multicenter study carried out at 43 sites in North America and in Europe *Study name* X-PLORE RCT	Adult patients (≥18 years) with chronique (≥6 months) moderate to severe plaque psoriasis defined as BSA ≥10%, ≥3 on PGA and a PASI score ≥12. Patients were to be treatment naïve to adalimumab. *Baseline characteristics* Female/Male, % I: 30%/70% C: 33%/67% Age, mean yrs I: 50 C: 46.5	Adalimumab 80 mg week 0, and 40 mg every other week thereafter in subcutaneous injections. n=43 *Drop-out* 4/43 (9.3%)	Placebo in subcutaneous injections. n=42 *Drop-out* 3/42 (7.1%)	**Analysis model** ITT with missing values assumed and imputated as non-responders. **Results** *PASI 75* I: 25/43 (58.1%) C: 2/42 (4.8%) I vs C: p<0.001 *PASI 90* I: 13/43 (30.2%) C: 1/42 (2,4%) I vs C: p<0.001 *PASI 100* I: 11/43 (25.6%) C: 0/42	**Adverse events** *Discontinued study drug due to AEs:* I: 3/43 (7%) C: 3/42 (7.1%) *More than 1 AE* I: 24/43 (55.8%) C: 22/42 (52.4%) *More than 1 serious AE* I: 1/43 (2.3%) C: 1/42 (2.4%) *Infections* I: 5/43 (11.6%) C: 6/42 (1.4%) *Serious infections*	**Risk of bias** Acceptable Administration of adalimumab was not blinded, but the evaluator of effect was blinded to study group assignment. **Comment** The main aim of the study was to investigate the effect of Guselkumab as compared to adalimumab or placebo. Only the comparison between adalimumab

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	Ethnicity. % (caucasian/non-caucasian) I: 91%/9% C: 93%/7% *Bodyweight (kg), mean±SD* I: 91.6 kg (±19.88) C: 93.6 kg (±22.6) *Psoriatic arthritis, %* I: 26% C: 29% **Study period** October 2011–August 2013 **Follow-up** 16 wees			I vs C: p<0.001 *DLQI, mean change in score post baseline (±SD)* I: -10.1 (±9.0) C: -2.3 (±6.8) I vs C: p<0.001	I: 0 C: 0 *Infections requiring treatment* I: 2/43 (4.6%) C: 3/42 (7.1%)	and placebo is reported here. *Conflict of interest* The study was sponsored by Janssen Research and Development.
Cai et al 2016 [76] Multicentre study performed at 16 sites in China. RCT	Adult patients (≥18 yrs) with chronique (≥6 months) moderate to severe plaque psoriasis and inadequate response or intolerance to prior systemic therapies. Patients were to be treatment naïve to prior biologic therapies. *<u>Baseline characteristics</u>* *<u>PASI, mean (±SD)</u>*	Adalimumab 80 mg week 0, and 40 mg every other week thereafter. n=338 *Drop-outs* 3/338 (0.9%)	Matching placebo n=87 *Drop-outs* 1/87 (1%)	**Analysis model** ITT – including all randomised and missing values assumed and imputated as non-responders. **Results week 12** *PASI 75* I: 77.8% C: 11.5% I vs C: p<0.001 *PASI 90*	**Adverse events** **At week 12** *Any adverse event* I: 158/338 (46.7%) C: 33/87 (37.9%) *AE leading to study discontinuation* I: 2/338 (0.6%) C: 0 *Any serious AE* I: 4/338 (1.2%)	**Risk of bias** Acceptable **Comment** *Conflict of interest* The study was sponsored by AbbVie. Authors received help with design, protocol development and data interpretation and medical writing from AbbVie.

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	22.7 (±11.83) *Female/Male, %* 33.3%/66.7% *Age, mean yrs (±SD)* 43.2 (±12.0) *BMI, mean (±SD)* 24.3 (±3.38) *Psoriatic arthritis, %* 12.5% **Study period** August 2012–December 2013 **Follow-up** 12 weeks placebo controlled phase, followed by 7 weeks open label period			I: 55.6% C: 3.4% I vs C: p<0.001 *PASI 100* I: 13.3% C: 1.1% I vs C: p=0.001 *DLQI, change in core from baseline* I: -9.07 C: -4.17 I vs C: p<0.05	C: 3/87 (3.4%) *Any infection* I: 59/338 (17.5%) C: 14/87 (16.1%) **At week 19 (all treated w adalimumab after week 12)** *Any infection* 128/423 (30.3%) *Serious infection* 5/423 (1.2%) Lung infection 2/423 (0.5%) Pneumonia 2/423 (0.5%) Tuberculosis 2/423 (0.5%)	
Blauvelt et al 2017 [82] The VOYAGE I study Multicentre study at 101 global sites RCT	**Population** Patients (≥18-years of age), with moderate to severe plaque psoriasis (≥6 months), BSA involvement ≥10%, IGA ≥3 and PASI ≥12. All patients were	**Intervention** 80 mg of adalimumab at week 0, followed by 40 mg every other week starting week 1, through week 47. Subcutaneous injection	**Comparison** Placebo injection at week 0, 4 and 12 n=174 *Drop-out rate, n (%)*	**Analysis model** ITT: all randomized patients included *Missing data:* NRI for binary outcomes, and LOCF for continuous endpoints.	**Adverse events** **AEs – week 0–16** *Patients reporting any AE, n (%)* I: 170/333 (51.1%) C: 86/174 (49.4%)	**Risk of bias** Acceptable **Comments** Supported by Janssen Research & Development LLC, Spring House, PA

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	candidates for systemic- or phototherapy, and had not had treatment with anti-TNF therapy within 3 months. They should never have been treated with guselkumab or adalimumab. *Baseline characteristics* *Female/Male. (%)* I: 25.4%/74.6% C: 31.6%/68.4% *BMI (kg/m2), mean (SD)* I: 29.8 (6.48) C: 28.9 (6.89) *Ethnicity (White), %* I: 277/334 (82.9%) C: 145/174 (83.3%) *Age* *mean (SD)* I: 42.9 (12.58) C: 44.9 (12.90) **Study period** December 2014-April 2016 **Follow-up period** Double-blind placebo-controlled phase (16 weeks), followed by	n=334 *Drop-out rate, n (%)* 10/334 (3%) The study also included intervention groups treated with guselkumab	7/174 (4%)	**Results (16 weeks)** PASI 75 – received by percent of patients, (%) I: 244/334 (73.1%) C: 10/174 (5.7%) PASI 90, (%) I: 166/334 (49.7%) C: 5/174 (2.9%) PASI 100, (%) I: 57/334 (17.1%) C: 1/174 (0.6 %) DLQI, change in score from baseline, mean (SD): I: -9.3 (7.8) C: -0.6 (6.36)	Any AE leading to discontinuation, n (%) I: 3/333 (0.9%) C: 2/174 (1.1%) *Serious Infections, n (%)* I: 2/333 (0.6%) C: 0/174 (0%) *AEs occurring ≥5% of patients in any treatment group, n (%)* *Nasopharyngitis, n (%)* I: 35/333 (10.5%) C: 17/174 (9.8%) *URTI, n (%)* I: 16/333 (4.8%) C: 9/174 (5.2%) *Infections, n (%)* I: 85/333 (25.5%) C: 44/174 (25.3%) *Pruritus, n (%)* I: 7/333 (2.1%) C: 10/174 (5.7%) *Injection site erythema, n (%)* I: 15/333 (4.5%) C: 1/174 (0.6%)	

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
	active treatment phase until week 48, (open-label)					
Reich et al 2017 [83] The VOYAGE II study Multicentre study at 115 global sites RCT	**Population** Patients (≥18-years of age), with moderate to severe plaque psoriasis (≥6 months), BSA involvement ≥10%, IGA ≥3 and PASI ≥12. All patients were candidates for systemic- or phototherapy, and had not had treatment with anti-TNF therapy within 3 months. They should never have been treated with guselkumab or adalimumab. *Baseline characteristics* *Female/Male. (%)* I: 31,5%/68.5% C: 30.2%/69.8% *BMI (kg/m2), mean (SD)* I: 29.6 (6.6) C: 29.6 (6.6) *Ethnicity (White), %* I: 200/248 (80.6%) C: 206/248 (83.1%)	**Intervention** 80 mg of adalimumab at week 0, followed by 40 mg every other week starting week 1, through week 23. Subcutaneous injection n =248 *Drop-out rate, n (%)* 11/248 (4.4%) The study also included intervention groups treated with guselkumab.	**Comparison** Placebo injection at week 0, 4 and 12 n=248 *Drop-out rate, n (%)* 15/248 (6%)	**Analysis model** ITT: all randomized patients included. *Missing data:* NRI. **Results (16 weeks)** PASI 75 – received by percent of patients, (%) I: 170/248 (68.5%) C: 20/248 (8.1%) PASI 90, (%) I: 116/248 (46.8%) C: 6/248 (2.4%) PASI 100, (%) I: 51/248 (20.6%) C: 2/248 (0.8%) DLQI, change in score from baseline, mean (SD): I: -9.7 (6.8) C: -2.6 (6.9)	**Adverse events** **AEs – week 0–16** *Patients reporting any AE, n (%)* I: 120/248 (48.4%) C: 111/248 (44.8%) Any AE leading to discontinuation, n (%) I: 4/248 (1.6%) C: 2/248 (0.8%) *Serious Infections, n (%)* I: 2/248 (0.8%) C: 1/248 (0.4%) *AEs occurring ≥5% of patients in any treatment group, n (%)* *Nasopharyngitis, n (%)* I: 20/248 (8.1%) C: 16/248 (6.5%) *Headache, n (%)* I: 5/248 (2.0%) C: 7/248 (2.8%)	**Risk of bias** Acceptable **Comments** Supported by Janssen Research & Development LLC, Spring House, PA

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	Age *mean (SD)* I: 43.2 (11.9) C: 43.3 (12.4) **Study period** November 2014-May 2016 **Follow-up period** Double-blind placebo-controlled phase (16 weeks), followed by active treatment phase until week 28, and a randomized withdrawal and retreatment period (weeks 28-72).				*URTI, n (%)* I: 4/248 (1.6%) C: 10/248 (4.0%) *Infections, n (%)* I: 58/248 (23.4%) C: 46/248 (18.5%)	

Table 7.2. Adalimumab versus Methotrexate

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Saurat et al 2008 [72] Multicenter study carried out at 28 sites in Europe and Canada Study name CHAMPION RCT	**Population** Patients (≥18 years of age), with moderate to severe psoriasis, with PASI score≥10, BSA involvement ≥10%, diagnosed with plaque psoriasis (≥1 year), which was stable (≥2 months). All patients had to be naïve to TNF-antagonist therapy and methotrexate. Candidates for systemic or phototherapy *Baseline characteristics* Female/Male, % I: 35.2%/64.8% C: 33.6%/66.4% Ethnicity, Caucasian, % I: 95.4% C: 95.5% *Bodyweight (kg), mean±SD* I: 81.7±20.0 C: 83.1±17.5 **Study period** Not reported	**Intervention** Adalimumab 80 mg initial dose, 40 mg every two weeks, from week 1 through week 15. Subcutaneous injection of adalimumab, oral placebo to match control Background treatment with 5 mg of oral folate weekly. *Randomised patients* n =108 *Drop-out rate* 4/108 (3.7%) The study also included a control group treated with placebo	**Comparison** C: methotrexate Metotrexate (orally) titrated from 7.5 mg/week, increased to 10 mg week 2, and 15 mg week 4. If PASI≥50 was reached by or after week 8 the dosage was maintained. Week 8, patients who did not achieve PASI-50 had their dosage increased to 20 mg/week. By week 12, only patients who did not achieve PASI-50 and had PASI<50 at week 8 had dosage increased to 25 mg Background treatment with 5 mg of oral folate weekly *Randomised patients* C: n=110	**Method of analysis** ITT for efficacy outcomes *Missing data* NRI for efficacy analysis LOCF for mean PASI improvement **Results (week 12)** *PASI ≥50* I: 90.7% C: 54.5% I vs C: p<0.001 *PASI ≥75* I: 76.9% C: 24.5% I vs C: p<0.001 *PASI ≥90* I: 48.1% C: 9.1% I vs C: p<0.001 *PASI 100* I: 11.1% C: 0.9% I vs C: p=0.001	**Adverse events** AEs during placebo-controlled phase and follow-up period *Total adverse events, n (%)* I: 79/107 (73.8%) C: 90/110 (81.8%) *Serious AEs, n (%)* I: 2/107 (1.9%) C: 1/110 (0.9%) *Serious infections* None reported Adverse events leading to discontinuation, n (%) I: 1/107 (0.9%) C: 6/110 (5.5%) *Adverse events, (≥5% of patients in any treatment group)* *Infections (nonserious), n (%)* I: 51/107 (47.7%) C: 46/110 (41.8%)	**Risk of bias** Acceptable **Comment** Study funded by Abbot Laboratories, who also participated in designing, data collection / management / analysis and preparation of the manuscript. Several of the authors were affiliated with Abbott (employed/consultants) as well as other pharmaceutical companies

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	Follow-up Placebo-controlled phase (16 weeks), 70 day follow-up period		*Drop-out rate* C: 6/110 (5.5%)	**Results (week 16)** *PASI ≥50* I: 88.0% C: 61.8% I vs C: p<0.001 *PASI ≥75 – primary endpoint* I: 79.6% C: 35.5% I vs C: p<0.001 *PASI ≥90* I: 51.9% C: 13.6% I vs C: p<0.001 *PASI 100* I: 16.7% C: 7.3% I vs C: p=0.04	*Nasopharyngitis, n (%)* I: 30/107 (28.0%) C: 26/110 (23.6%) *Headache, n (%)* I: 14/107 (13.1%) C: 12/110 (10.9%) *Pruritus, n (%)* I: 4/107 (3.7%) C: 2/110 (1.8%) *Rhinitis, n (%)* I: 3/107 (2.8%) C: 4/110 (3.6%) *Nausea, n (%)* I: 4/107 (3.7%) C: 8/110 (7.3%) *Rhinorrhea, n (%)* I: 3/107 (2.8%) C: 0/110 (0%) *Viral infection, n (%)* I: 0/107 (0%) C: 6/110 (5.5%) *Arthralgia, n (%)* I: 6/107 (5.6%) C: 5/110 (4.5%)	

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
Papp et al 2017 [85] Multicenter study carried out at 38 clinics in 13 countries. RCT	**Population** Patients (≥4 and <18 years of age) with a bodyweight of at least 13 kg, with severe plack psoriasis (PGA≥4, BSA≥20%, PASI ≥20, CDLQI≥10) for at least 6 months (stable for ≥2 months), and who had not responded to topical therapy or (if <12 years of age) heliotherapy or phototherapy. Randomisation was stratified by history of etanercept treatment. *Baseline characteristics* *Female/Male, %* I1: 55%/45% I2: 46%/54% C: 70%/30% *Ethnicity, White, %* I1: 35/38 (92%) I2: 34/39 (87%) C: 34/37 (92%) *Bodyweight (kg), mean (SD)* I1: 50.8 (19.90) I2: 50.2 (22.5) C: 53.1 (18.7)	**Intervention** Adalimumab (I1) 0.8 mg/kg (up to 40 mg total dose), or (I2), 0.4 mg/kg (up to 20 mg total dose) subcutaneously at week 0, and then every other week, starting at week 1. Folic acid supplementation was provided as recommended in guidelines. *Randomised patients* I1: n =38 I2: n =39 *Drop-out rate* I1: 1/38 (2.6%) I2: 3/39 (7.7%)	**Comparison** Metotrexat (orally) titrated from 0.1 mg/kg) (7.5 mg/week at base line, week 0), increased to 0.4 mg/kg (up to 25 mg/week total dose), once weekly. Folic acid supplementation was provided as recommended in guidelines. *Randomised patients* C: n=37 *Drop-out rate* C: 5/37 (13.5%)	**Method of analysis** ITT for efficacy outcomes *Missing data* NRI for categorical variables; LOCF for continuous variables. **Results (week 16)** *PASI 75* I1: 22/38 (57.9%) I2: 17/39 (43.6%) C: 12/37 (32.4%) I1 vs C, p=0.02679 *PASI 90* I1: 11/38 (29%) I2: 12/39 (31%) C: 8/37 (22%) I1 vs C, p=0.466 *PASI 100* I1: 7/38 (18%) I2: 4/39 (10%) C: 1/37 (3%) I1 vs C, p=0.056 *CDLQI, change from baseline, mean (SD)* I1: -6.6 (6.2) (n=38) I2: -4.9 (6.2) (n=38) C: -5.0 (7.1) (n=36) I1 vs C, p=0.304	**Adverse events** AEs during study periods 1 and 2 (16+26 weeks) *Total adverse events, n (%)* I1: 26/38 (68%) I2: 30/39 (77%) C: 28/37 (76%) *Severe AEs, n (%)* I1: 1/38 (3%) I2: 5/39 (13%) C: 2/37 (5%) *Serious AEs, n (%)* I1: 0/38 (0%) I2: 3/39 (8%) C: 0/37 (0%) *Serious infections, n (%)* I1: 0/38 (0%) I2: 1/39 (3%) C: 0/37 (0%) *Adverse events, (≥5% of patients in any treatment group)* *Infections (non-serious), n (%)* I1: 17/38 (45%)	**Risk of bias** Acceptable **Comment** Funded by AbbVie. Investigators gathered the data, the funder did the analysis, and the authors and the funder interpreted the data. AbbVie contributed to the study design and was involved in the collection, analysis, and interpretation of the data and in the writing, review, and approval of the publication

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	Age (years), mean (SD) I1: 13.0 (3.3) I2: 12.6 (4.4) C: 13.4 (3.5) *Previous etanercept treatment* I1: 4/38 (11%) I2: 4/39 (10%) C: 3/37 (8%) **Study period** Dec 14, 2010 – Feb 5, 2015 **Follow-up** The study included four periods: (1) Placebo-controlled phase (16 weeks); (2) up to 36-week withdrawal; (3) 16-week re-treatment; and (4) 52-week long-term follow-up.				I2: 22/39 (56%) C: 21/37 (57%) *Allergic reaction, n (%)* I1: 0/38 (0%) I2: 1/39 (3%) C: 2/37 (5%) *Injection site reaction, n (%)* I1: 4/38 (11%) I2: 3/39 (8%) C: 3/37 (8%)	

BSA – body surface area; DLQI – dermatology life quality index; HRQOL – health related quality of life; ITT – intention-to-treat; LOCF – last observation carried forward; MCS – mental component summary score; mITT – modified intention-to-treat; NRI – non-responder imputation; PASI – psoriasis area and severity index; PCS – physical component summary score; PGA – physician's global assessment; SD – standard deviation; VAS – visual analogue scale

Table 7.3. Etanercept versus placebo

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
van de Kerkhof et al 2008 [86] Multicentre study performed in nine European countries (Belgium, France, Germany, Hungary, Italy, the Netherlands, Poland, Romania and Spain) RCT	**Population** *Inclusion criteria* Adult patients with stable plaque psoriasis involving ≥10% of body surface area and PASI ≥10. Non-responders or intolerant to phototherapy or other systemic therapy BMI (inclusion criteria) <38 kg/m^2 Treatment naive to any TNF-inhibitor *Baseline characteristics* *Female/Male, (%)* I: 38.8%/61.5% C: 45.6%/54.4% *Ethnicity* No information *BMI (kg/m^2), mean±SD* I: 27.5±4.1 C: 26.8±5.9 **Study period** June 2006–May 2007	**Intervention (I)** Etanercept 50 mg per week for 24 weeks (sub-cutaneous injections, once weekly) n=96 *Drop-out rate at 12 weeks* 6/96 (6.3%)	**Comparison (C)** Placebo for 12 weeks, and etanercept 50 mg per week for 12 weeks thereafter (subcutan-eous injections, once weekly). n=46 *Drop-out rate at 12 weeks* 10/46 (21.7%)	**Analysis Model** Modified ITT (all who received ≥1 dose test substance) *Missing data* LOCF **Results** *PASI ≥50* I: 66/96 (68.8%) C: 4/46 (8.7%) I vs C: p<0.0001 *PASI ≥75 (primary endpoint)* I: 36/96 (37.5%) C: 1/46 (2.2%) I vs C: p<0.0001 *PASI ≥90* I: 13/96 (13,5%) C: 1/46 (2,2%) I vs C: p<0.05 *DLQI (mean improvement on DLQI-score)* I: 7,4 (54.5%) C: 1,2 (5.2%) I vs C: p<0.0001	**Adverse events** *AEs (week 0–12)* *Patients with serious AEs, n (%)* I: 2.1% C: 6.5% *AEs leading to discontinuation, n (%)* I: 3/96 (3.1%) C: 3/46 (6.5%) *Reported treatment emergent adverse events occurring in >5% of participants,* *Headache, n (%)* I: 13/96 (13.5%) C: 1/46 (2.2%) I vs C: p=0.04 *Injection-site reaction, n (%)* I: 16/96 (16.7%) C: 1/46 (2.2%) I vs C: p=0.01 *Influenza-like syndrome, n (%)*	**Risk of bias** Acceptable **Comment** Conflict of interest Sponsored by Wyeth Parmaceuticals, the manufacturer of the test substance. Several authors were employed by the study sponsor

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	Follow-up 12 weeks placebo controlled phase (plus 12 weeks OLE, not presented here)				I: 10/96 (10.4%) C: 0/46 (0%) I vs C: p=0.03 *Asthenia, n (%)* I: 5/96 (5.2%) C: 0/46 (0%) *Diarrhoea, n (%)* I: 5/96 (5.2%) C: 1/46 (2.2%) *Pruritus, n (%)* I: 14/96 (14.6%) C: 4/46 (8.7%) *Psoriasis, n (%)* I: 2/96 (2.1%) C: 3/46 (6.5%) *Pharyngitis/laryngitis, n (%)* I: 5/96 (5.2%) C: 1/46 (2.2%) *URTI, n (%)* I: 9/96 (9.4%) C: 5/46 (10.9%)	

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Tyring et al 2006 [92] Multicentre study performed at 39 sites in the USA and in Canada RCT	**Population** Inclusion criteria Adult patients (>18 years) with active, stable psoriasis involving ≥10% body surface area and PASI ≥10. Earlier photo-therapy or systemic treatment (or candidate for phototherapy) required *Baseline characteristics* *Female/Male, (%)* I: 34.7%/65.3% C: 29.6%/70.4% *Ethnicity (Caucasian), (%)** I: 90.4% C: 87.9% *Bodyweight (kg), mean** I: 92.6 C: 91.0 *Information from Tying et al 2008 Treatment naive to any TNF-inhibitor. **Study period** June 2003–January 2004	**Intervention (I)** Etanercept 100 mg/week (two injections of 25 mg per dose, twice weekly) n=311 *Drop-out rate* 6/311 (1.9%)	**Comparison (C)** Placebo (two injections, twice weekly) n=309 *Drop-out rate* 17/309 (5.5%)	**Analysis model** mITT (all who received ≥1 dose included) **Results – week 12** *PASI ≥50, n (%)* I: 229/311 (74%) C: 43/306 (14%) I vs C mean difference [95% CI]: 60% [53, 66], p<0.0001 *PASI ≥75 (primary outcome)* I: 147/311 (47%) C: 15/306 (5%) I vs C mean difference [95% CI]: 42% [36, 48], p<0.0001 *PASI ≥ 90* I: 65/311 (21%) C: 4/306 (1%) I vs C mean difference: 20% [15, 24], p<0.0001 *DLQI (mean improvement on DLQI-score)* I: 69.1% C: 22.1% I vs C mean difference [95% CI]: 47% [40,54]	**Adverse events** *At least one adverse event (headache, injections site bruising, fatigue or arthralgia)* I: 153/312 (49.0%) C: 137/306 (44.8%) *Withdrew due to adverse event* I: 4/312 (1.3%) C: 5/306 (1.6%) *At least 1 serious adverse event* I: 6/312 (1.9%) C: 3/306 (1.0%) *Reported treatment emergent adverse events occurring in >5% of participants* *At least one infection (nasopharyngitis, upper respiratory tract infection, sinusitis)* I: 87/312 (27.9%) C: 71/306 (23.2%) *At least one injections site reaction* I: 34/312 (10.9%) C: 2/306 (0.7%)	**Risk of bias** Acceptable **Comment** Conflict of interest Sponsored by the Immunex/Amgen the manufacturer of the test substance. Immunex was involved in the design of the study and Amgen in the analysis of data and the writing of the manuscript

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	Follow-up 12-week placebo-controlled trial, followed by an 84-week OLE					
Tyring et al 2007 [101] OLE after [92]	**Population** See [[92] **Study period** **Follow-up** 12+84 weeks	**Intervention** Etanercept 100 mg/week (two injections of 25 mg per dose, twice weekly) n=591 of 618 (95.6%) randomised patients from the original RCT (RN 1510) entered the OLE. I1 (randomised to etanercept in the initial 12 week RCT: n=304 I2 (randomised to etanercept in the initial 12 week RCT: n=287 *Total exposure in the cohort over 96 weeks (includes 12 weeks RCT)* 908.9 patient yrs *Drop-out rate* 127/591 (21.5%)		**Analysis model** All initially randomised patients included. All data treated as observational: no imputation of missing values. Calculations of exposure adjusted adverse event rates per 100 patient years.	**Adverse events** *Discontinued OLE due to adverse events, n (%)* I1: 15/287 (5.3%) I2: 16/304 (5.2%) *Events per 100 patient years under exposure to etanercept treatment.* *All non-infectious adverse events* 158.0 *All infections* 103.9 *Serious infections* 1.2 *Serious non-infectious adverse events* 7.7 *Death* 0.2	[101] OLE efter [92]

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
					All injection site reactions 12.2 *<u>Most common serious non-infections AE:s</u>* *Myocardial infarction* 0.4 *Basal cell carcinoma* 0.3 *Depression* 0.3 *<u>Most frequent AE:s</u>* *Headache* 9.2 *Injection site hemorrhage* 5.8 *Arthralgia* 4.8 *Back pain* 5.2 *<u>Most frequent infections</u>* *URTI* 20.2	

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Paller et al 2008 [91] Etanercept Psoriasis Study Group Multicentre study performed at 42 sites in the USA and in Canada RCT	**Population** Inclusion criteria Children aged 4–17, with stable plaque psoriasis for at least 6 months involving >10% body surface area, PGA score ≥3, and with PASI >12. Earlier or current phototherapy or systemic treatment, or poorly controlled disease with topical treatment BMI (median at baseline) was 18.1 in age group 4–11 (36% of patients) and 25.2 in age group 12–17 (64% of patients) *Baseline characteristics* *Female/Male, (%)* I: 48.1%/51.9% C: 49.5%/50.5% *Ethnicity (Caucasian), (%)* I: 78.3% C: 71.4% *Bodyweight (kg), median [range]* I: 59.6 [17.7, 168.3] C: 59.8 [17.2, 131.5]	**Intervention (I)** Etanercept, 0.8 mg/kg up to a maximum dose of 50 mg/week (subcutaneous injections, once weekly) n=106 (of which 38 aged 4–11 and 68 aged 12–17) *Drop-out rate at 12 weeks* 6/100 (6.0%)	**Comparison (C)** Placebo for 12 weeks, and thereafter etanercept, 0.8 mg/kg up to a maximum dose of 50 mg/week (subcutaneous injections) n=105 (of which 38 aged 4–11 and 67 aged 12–17) *Drop-out rate at 12 weeks* 27/105 (25.7%)	**Analysis model** ITT (all randomised patients) *Missing data* NRI **Results – week 12** *PASI ≥50* I: 79/106 (75%) C: 24/105 (23%) I vs C: p <0.001 *PASI ≥75 (primary endpoint)* I: 60/106 (57%) C: 12/105 (11%) I vs C: p <0.001 *PASI ≥90* I: 29/106 (27%) C: 7/105 (7%) I vs C: p <0.001 *CDLQI improvement* I: 55/106 (52%) C: 19/105 (18%) I vs C: p <0.001	**Adverse events** *Exposure adjusted adverse events through week 48 (occuring ≥10 times in the etanercept group/100 patient years*) *Total n of adverse events (infections)* I: 554.5/100 years C: 765.4/100 years Selected events through week 48 (n exposure adjusted events/100 years) after etanercept exposure *Adverse events leading to study* withdrawal I: 2.4/100 years C: 0/100 years *Adverse event excluding infection* I: 287.6/100 years C: 430.5/100 years *Infection* I: 229.3/100 years C: 308.3/100 years	**Risk of bias** Acceptable **Comment** Conflict of interest Sponsored by pharmaceutical company (Immunex/Amgen and by Wyeth Parmaceuticals) which contributed in data collection, analysis and interpretation of data, and in writing the report

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	Treatment naive to any TNF-inhibitor **Study period** September 2004–November 2005 **Follow-up** 12 weeks RCT plus 24 weeks OLE, plus 12 weeks withdrawal and retreatment RCT				*Severe adverse event, excluding infection* I: 1.8/100 years C:15.9/100 years *Severe infection* I: 2.4/100 years C: 0 *Injection site reaction* I: 37.6/100 years C: 26.6/100 years	
Langley et al 2011 [90] For main publication, see Paller et al. 2008 [91] RCT	**Population, study period and follow up** See [91]	**Intervention (I)** See [91]	**Comparison (C)** See [91]	**Analysis model** See [91] **Results – week 12** (not reported under [3]) *CDLQI, mean change on total score ±SD* I: 5.4±5.6 C: 3.1±5.1 I vs C: not given	**Adverse events** See [91]	**Risk of bias** Acceptable **Comment** Conflicts of interest See [91]
Paller et al 2016 [103] OLE efter [91]	**Population and study period** See [91] **Follow up** 5 yrs or until the patient reached adulthood at 18 yrs of age	**Intervention** Etanercept 0.8 mg/kg once weekly (to a maximum of 50 mg per week) in s.c. injections for up to 264 weeks n=182 (182/211, 86.3%, patients randomised in		**Analysis model** All patients who received ≥1 dose of study drug were included in the analyses. The subset of patients who were under 18 and still in study at week	**Adverse events** *Discontinued study* 112/182 (61.5%) *Discontinued due to adverse event* 5/182 (2.7%)	**Risk of bias** Not assessed **Comment** Risk of bias not assessed as only observational data on AE:s were collected.

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
		the initial RCT also enrolled in the OLE) *Drop-out rate* 69/181 (37.9%) dropped out before week 264		264 were included in the analyses of growth.	**Adverse events expressed as incidence rates/100 patient yrs** *Serious adverse events* All occurred with an event rate of 0.2/100 patient yrs (or 1 event over the study): abortion induced, anxiety, cellulitis, infectious mononucleosis, osteonecrosis, post operative intestinal obstruction, thyroid cyst. *Common adverse events occurring at a rate of ≥5/100 patient yrs* *URTI* 23.2 *Nasopharyngitis* 15.0 *Streptococcal pharyngitis* 5.8 *Sinusitis* 5.0	

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Bachelez et al 2015 [97] Multicentre study performed at 122 centres all over the world (excluding the USA and Canada) RCT	**Population** *Inclusion criteria* Adult patients ≥18 yrs with chronic stable plaque psoriasis for at least 12 months, involving at least 10% body surface area, with PASI ≥12 and PGA (physician's) assessed as moderate to severe. Non-responder or intolerant to conventional systemic therapy. No previous exposure to etanercept *Baseline charactersitics* *Female/Male, %* I: 30%/70% C: 34%/66% *Ethnicity (Caucasian), %* I: 87% C: 84% *Bodyweight (kg), median [range]* I: 82.0 [48.0, 143.5] C: 80.2 [46.5, 130.0] **Study period** November 2010–September 2012	**Intervention (I)** Etanercept 100 mg/week (subcutaneous injections of 50 mg twice weekly) n=336 *Drop-out rate* 23/336 (6.8%) at 12 weeks	**Comparison (C)** Placebo injections twice weekly n=108 *Drop-out rate* 13/108 (12%) at 12 weeks	**Analysis model** ITT (all randomised who received at least 1 dose of study drug) *Missing data* NRI **Results – week 12** *PASI ≥50* I: 269/335 (80.3%) C: 22/107 (20.6%) I vs C: p<0.0001 *PASI ≥75 (co-primary outcome)* I: 197/335 (58.8%) C: 6/107 (5,6%) I vs C: p<0.0001 *PASI ≥90* I: 108/335 (32,2%) C: 1/107 (0,9%) I vs C: p<0.0001 *DLQI, ≥5 point reduction from baseline* I: 218/292 (74.7%)* C: 28/88 (31.8%)* I vs C: p<0.0001 *lower response rates	**Adverse events** **AEs at 12 weeks** *Treatment emergent adverse events (TEAE)** *Any TEAE* I: 192/335 (57%) C: 55/107 (51%) *Serious TEAEs* I: 7/335 (2%) C: 2/107 (2%) *Discontinuation due to TEAE* I: 11/335 (3%) C: 4/107 (4%) *Worsening of PASI score ≥25% during treatment* I: 6/335 (1.8%) C: 17/107 (15.9%) *Post treatment Worsening of PASI score ≥25% post treatment* I: 0/335 (0%) C: 1/107 (1%) *Most common TEAE was infection, in most cases respiratory infections	**Risk of bias** Acceptable **Comment** The study was designed primarily to investigate non-inferiority of tofacitinib vs etanercept or placebo. Conflict of interest Sponsored by pharmaceutical company (Pfizer Inc.) which contributed in data collection, analysis and interpretation of data, and in writing the report

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	Follow-up 12 weeks treatment plus 2–4 weeks post treatment					
Papp et al 2005 [87] Etanercept Psoriasis Study Group Multicenter study performed at 50 sites in the USA, Canada and Western Europe RCT	**Population** Adult patients (≥18 years), with stable psoriasis involving ≥10% body surface area and PASI ≥10. At least 1 previous phototherapeutic or systemic treatment. Treatment naive to TNF-inhibitors *Baseline characteristics* *Female/Male, %* I1: 35%/65% I2: 33%/67% C: 36%/64% *Ethnicity (Caucasian), (%)* I1: 92% I2: 89% C: 91% *Bodyweight* No information **Study period** May 2002–July 2003 **Follow-up**	**Intervention (I)** **Intervention 1** Etanercept 50 mg/week (in two 25 mg subcutaneous injections per week) for 24 weeks n=194 *Drop-out rate* 5/196 (2.5%) at 12 weeks 11/196 (5.6%) at 24 weeks **Intervention 2** Etanercept 100 mg/week for 12 weeks (in two 50 mg subcutaneous injections per week) and 50 mg/week, weeks 13–24 (in subcutaneous injections twice per week) n=196 *Drop-out rate*	**Comparison (C)** Placebo for 12 weeks and etanercept 50 mg/week, weeks 13–24 (in subcutaneous injections twice per week) n=193 *Drop-out rate* 15/193 (7.8%) at 12 weeks 25/193 (12.9%) at 24 weeks	**Analysis model** ITT (all randomised who received at least 1 dose of study drug) *Missing data* LOCF **Results – week 12** *PASI ≥50* I1: 126/196 (64%) I2: 150/194 (77%) C: 18/193 (9%) I1, I2 vs C: p<0.0001 *PASI ≥75 (primary endpoint)* I1: 67/196 (34%) I2: 96/194 (49%) C: 6/193 (3%) I1, I2 vs C: p<0.0001 *PASI ≥90* I1: 21/196 (11%) I2: 40/194 (21%) C: 1/193 (1%) I1, I2 vs C: p<0.0001	**Adverse events** Proportion afflicted by adverse events **At 0–12 weeks** *Withdrawal due to adverse events* I1: 3/196 (1.5%) I2: 2/194 (1%) C: 2/193 (1%) *Injection site reaction* I1: 26/196 (13%) I2: 35/194 (18%) C: 11/193 (6%) URTI I1: 26/196 (13%) I2: 25/194 (13%) C: 25/193 (13%) *Headache* I1: 23/196 (12%) I2: 21/194 (11%) C: 15/193 (8%) *Injection site ecchymosis* I1: 24/196 (12%) I2: 15/194 (8%)	**Risk of bias** Acceptable **Comment** Conflict of interest The study was sponsored by a pharmeceutical company: Immunex Corporation and Amgen

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	12 weeks RCT plus 12 weeks OLE (all patients received etanercept during the OLE)	4/194 (2%) at 12 weeks 9/194 (4,6%) at 24 weeks			C: 22/193 (11%) *Accidental injury* I1: 8/196 (4%) I2: 13/194 (7%) C: 12/193 (6%) *"Flu syndrome"* I1: 9/196 (5%) I2: 8/194 (4%) C: 3/193 (2%)	
Krueger et al. 2005 [89] For main publication, see [87] RCT	**Population, study period and follow-up** See [87] *<u>Baseline characteristics (DLQI only)</u>* *DLQI-score at baseline, mean (SD)* I1: 11.5 (7.2) 12: 11.4 (6.5) C: 12.2 (6.8)	**Interventions** See [87]	**Comparison** See [87]	**Analysis model** See [87] **Results at 12 weeks** *DLQI, mean percentage improvement:* I1: 65% I2: 70% C: 6% I1 vs C: p<0.0001 I2 vs C: p<0.0001 *Patients with ≥5 points improvement on the DLQI-score, n (%)* I1: 140/194 (72.2%) I2: 150/194 (77.3%) C: 50/193 (25.9%)	**Adverse events** See [87]	**Risk of bias and comment** See [87]

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
Leonardi et al 2003 [94] Etanercept Psoriasis Study Group Multicentre study performed at 47 sites in the USA RCT	**Population** Adult patients (≥18 yrs) with stable plaque psoriasis involving ≥10% body surface area and PASI ≥10. At least 1 previous phototherapeutic or systemic treatment. Treatment naive to TNF-inhibitors or other biologic therapies. *Baseline characteristics* *Female/Male, (%)* I1: 33%/67% I2: 35%/65% C: 37%/63% *Ethnicity (Caucasian), (%)* I1: 85% I2: 87% C: 90% *Bodyweight* No information **Study period** December 2001–October 2002 **Follow-up** 12 weeks (placebo-controlled phase) plus	**Intervention (I)** **Intervention 1** Etanercept 50 mg/week (in 25 mg subcutaneous injections twice weekly) for 24 weeks Allocation n=167 *Drop-out rate* n.g./group **Intervention 2** Etanercept 100 mg/week (in 50 mg subcutaneous injections twice weekly) for 24 weeks Allocation n=168 *Drop-out rate* Not given/group The trial also included a third intervention arm where patients received 25 mg etanercept per week	**Comparison (C)** Placebo for 12 weeks and etanercept 50 mg/week, weeks 13–24 (in subcutaneous injections twice weekly) n=168 *Drop-out rate* Not given/group	**Analysis model** ITT (all randomised who received at least 1 dose of study drug) *Missing data* LOCF **Results – week 12** *PASI ≥50* I1: 94/162 (58%) I2: 121/164 (74%) C: 24/166 (14%) I1, I2 vs C: p< 0.001 *PASI ≥75 (primary endpoint*) I1: 55/162 (34%) I2: 81/164 (49%) C: 6/166 (4%) I1, I2 vs C: p <0.001 *PASI ≥90* I1: 19/162 (12%) I2: 36/164 (22%) C: 1/166 (1%) I1, I2 vs C: p <0.001 *DLQI, mean relative improvement, %±SE* I1: 50.8±3.8 I2: 61.0±4.3 C: 10.9±4.8 I1, I2 vs C: p <0.001	**Adverse events** Proportion adverse events occurring in at least 5% of patients in any treatment group **AEs week 0–12** *Injection site reaction* I1: 17% I2: 13% C: 12% *Headache* I1: 12% I2: 7% C: 7% *URTI* I1: 9% I2: 5% C: 11% *Injection-site-ecchymosis* I1: 2% I2: 5% C: 4% *Asthenia* I1: 4% I2: 2% C: 3%	**Risk of bias** Acceptable **Comment** Drop-out rates per comparison groups not given Withdrawal rates due to adverse events per comparisn groups not given Conflict of interest The study was sponsored by a pharmeceutical company: Immunex Corporation and Amgen

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	12 weeks of active treatment all groups *Drop-out rate (overall)* 6% at 12 weeks with "similar" proportions of patients completing treatment in each group"				*Myalgia* I1: 4% I2: 2% C: 2% *Accidental injury* I1: 3% I2: 4% C: 4% *Sinusitis* I1: 0 I2: 0 C: 1% *Nausea* I1: 2% I2: 2% C: 1% *Rash* I1: 2% I2: 3% C: 2%	
Leonardi et al 2010 [102] CONSORT, USA and global OLE efter [94] och [87]	**Population** OLE after two original RCT-studies. For inclusion criteria, see RN 1334 (CONSORT, USA) and RN 476 (CONSORT, global). <u>*Baseline characteristics (OLE)*</u>	**Intervention** Etanercept 50 mg/week (in a subcutaneous injection once weekly) for 12 weeks from OLE-baseline. At week 12 eligible patients chose either to remain on 50 mg/week		**Analysis model** All patients who received ≥1 dose of study drug were included in the analyses of adverse events.	**Adverse events** Expressed as exposure adjusted incidence rates per 100 patient years. *All events* 235.7 *All non-infectious events* 135.7	**Risk of bias** Not assessed **Comment** Risk of bias not assessed as only observational data on AE:s were collected.

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	Female/male, % 32.3%/67.6% *Ethnicity (Caucasian), n (%)* 800/912 (87.7%) *Age, mean (SD)* 45.9 (11.9) *Weight in kg, mean (SD)* 91.2 (20.9) *PASI, mean (SD)* 18.9 (8.5) **Follow up** 60 weeks RCT+72 weeks OLE, for a combined follow up of 2.5 yrs	or escalate the dose to 100 mg/week (in 50 mg injections twice weekly) for the remainder of the study. n=912 enrolled in the OLE (439 from the US study and 473 from the global study) *Dose escalation from 50 to 100 mg/week at week 12* 591/912 (64.8%) *Drop-out rate* 485/912 (53.2%) completed 74 weeks before the study was closed 818/912 (89.7%) completed a minimum 48 weeks required *Total n patient years under exposure* 1056.2 *Patient yrs exposure to 50 mg/week only* 327.4			*All infections* 95.2 *Serious non-infectious adverse events* 5.6 (most common were 2 events of subdural hematoma and 2 of myocardial infarction) *Serious infections* 1.6 (most common were 3 events of pneumonia and 2 of cellulitis) *Injection site reactions* 4.8 *Malignancies* 1.5	

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
		Patient yrs exposure to first 50 and then 100 mg/week 728.8				
Gottlieb et al 2003 [93] Multicentre study performed in the USA RCT	**Population** Adult patients (≥18 years) with stable plaque psoriasis involving ≥10% body surface area. At least 1 previous systemic therapy or phototherapy *Baseline characteristics* *Female/Male, %* I: 42%/58% C: 33%/67% *Ethnicity (Caucasian), (%)* I: 89% C: 95% *Bodyweight (kg) mean* I: 91.8 C: 90.7 **Study period** August 2000–January 2001 **Follow-up** 24 weeks placebo controlled phase (primary endpoint after	**Intervention (I)** Etanercept 50 mg/week (in 25 mg subcutaneous injections twice weekly) for 24 weeks n=57 BMI: 30.9 *Drop-out rate, 12 weeks* 4/57 (7%) *Drop-out rate, 24 weeks* 9/57 (15.8%)	**Comparison (C)** Placebo (in subcutaneous injections twice weekly) for 24 weeks n=55 BMI: 29.8 *Drop-out rate* 15/55 (27.3%) at 12 weeks 43/55 (78.2%) at 24 weeks	**Analysis model** ITT (all randomised who received at least 1 dose of study drug). Missing values imputed by LOCF **Results – week 12** *PASI ≥50* I: 40/57 (70%) C: 6/55 (11%) I vs C: p <0.001 *PASI ≥75 (primary endpoint)* I: 17/57 (30%) C: 1/55 (2%) I vs C: p <0.001 *PASI ≥90* I: 7/57 (12%) C: 0/55 (0%) I vs C: p=0.03 **Results – week 12** *PASI ≥50* I: 44/57 (77%) C: 7/55 (13%) I vs C: p <0.001 *PASI ≥75*	**Adverse events** AEs occurring in more than 10% or more during 24 weeks *Withdrawals due to adverse events* I: 2/57 (3.5%) C: 6/55 (10.9%) *URTI* I: 35% C: 20% *Headache* I: 16% C: 13% *Bruise at injection site* I: 11% C: 9% *Sinusitis* I: 14% C: 4% *Pain* I: 7% C: 7%	**Risk of bias** Acceptable **Comment** Conflict of interest The study was sponsored by a pharmaceutical company: Immunex Corporation, a subsidiary of Amgen

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	12 weeks, but placebo controlled phase continued for an additional 12 weeks)			I: 32/57 (56%) C: 3/55 (5%) I vs C: p <0.001 *PASI ≥90* I: 12/57 (21%) C: 0/55 (0%) I vs C: p <0.001 *DLQI, % improvement mean±SE* I: 64±5 C: 7±8	*Peripheral edema* I: 2% C: 9% *Hypertension* I: 7% C: 4¤ *Accidental injury* I: 7% C: 4% 5 serious events occurred. None of them were considered as drug related	
Griffiths et al 2015 [88] (UNCOVER-2) Multicentre study performed at 126 study sites in north America, Europe and Australia RCT	**Population** Adult patients (≥18 years) with chronic plaque psoriasis (diagnosis ≥6 months) involving ≥10% body surface area, PGA (physician's) ≥3 and PASI ≥12. Treatment naive to etanercept *Baseline characteristics* *Female/Male, %* I: 34%/66% C: 29%/71% *Ethnicity (Caucasian), %* I: 94%	**Intervention (I)** Etanercept 100 mg/week (in 50 mg subcutaneous injections twice weekly) for 12 weeks n=358 *Drop-out rate* 25/358 (7%) The study also included an intervention group treated with ixekizumab	**Comparison (C)** Placebo (in subcutaneous injections twice weekly) for 12 weeks n=168 *Drop-out rate* 10/168 (5.9%)	**Analysis model** ITT. Continuous measures analysed using a mixed model for repeated measures *Missing data* NRI **Results – week 12** *PASI ≥75* I: 149/358 (41.6%) C: 4/168 (2.4%) I vs C: p <0.0001 *PASI ≥90* I: 67/358 (18.7%)	**Adverse events, as reported** *Any treatment emergent adverse event* I: 59.1% C: 53.3% *Death* I: 0 C: 0 *Non-fatal serious adverse event* I: 2.2% C: 1.2%	**Risk of bias** Acceptable **Comment** Study funded by Eli Lilly and Co. Study sponsor involved in the design of the study and carried out the data analysis The study was designed to compare ixekizumab with etanercept and placebo

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	C: 89% *BMI (kg/m^2), mean±SD* I: 31±7 C: 31±7 **Study period** May 2012–December 2013 **Follow-up** 12 weeks placebo-controlled trial			C: 1/168 (0.6%) I vs C: p <0.0001 *PASI-100* I: 19/358 (5.3%) C: 1/168 (0.6%) I vs C: p=0.0082 *DLQI, score change from baseline±SE* I: -7.7±0.3 C: -2.0±0.4 I vs C: p <0.0001	*Any infection* I: 27.5% C: 27.5% *Nasopharyngitis* I: 10.1% C: 10.2% *Injection site reaction* I: 10.9% C: 0.6% *Injection site erythema* I: 5.0% C: 1.2% *Injection-site pain* I: 1.1% C: 1.2% *Pruritus* I: 1.1% C: 2.4% *Headache* I: 5.6% C: 1.8% *Arthralgia* I: 2.8% C: 2.4%	

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Griffiths et al 2015 [88] (UNCOVER-3) Multicenter study performed at 126 study sites in north and south America, Europe and Russia RCT	**Population** Adult patients (≥18 years) with chronic plaque psoriasis (diagnosis ≥6 months) involving ≥10% body surface area, PGA (physician's) ≥3 and PASI ≥12. Treatment naive to etanercept *Baseline characteristics* *Female/Male, %* I: 30%/70% C: 29%/71% *Ethnicity (Caucasian), %* I: 92% C: 91% *BMI (kg/m^2), mean±SD* I: 31±8 C: 30±6 **Study period** August 2012–February 2014 **Follow-up** 12 weeks placebo-controlled phase	**Intervention (I)** Etanercept 100 mg/week (in 50 mg subcutaneous injections twice weekly) for 12 weeks n=382 *Drop-out rate* 13/382 (3.4%) The study also included an intervention group treated with ixekizumab	**Comparison (C)** Placebo (in subcutaneous injections twice weekly) for 12 weeks n=193 *Drop-out rate* 10/193 (5.2%)	**Analysis model** ITT. Continuous measures analysed using a mixed model for repeated measures *Missing data* NRI **Results – week 12** *PASI ≥75* I: 204/382 (53.4%) C: 14/193 (7.3%) I vs C: p<0.0001 *PASI ≥90* I: 98/382 (25.7%) C: 6/193 (3.1%) I vs C: p<0.0001 *PASI-100* I: 28/382 (7.3%) C: 0/193 I vs C: p<0.0001 *DLQI mean score change ±SE* I: -8.0±0.2 C: -1.7±0.3 I vs C: p<0.0001	**Adverse events, as reported** *Any treatment emergent adverse event* I: 49.0% C: 36.3% *Death* I: 0 C: 0 *Non-fatal serious adverse event* I: 1.3% C: 2.6% *Any infection* I: 15.4% C: 14.0% *Nasopharyngitis* I: 5.0% C: 5.7% *Injection site reaction* I: 10.7% C: 1.6% *Injection site erythema* I: 2.9% C: 0% *Injection-site pain* I: 1.3%	**Risk of bias** Acceptable **Comment** Conflict of interest Study was sponsored by a pharmaceutical company: Eli Lilly. Lilly also provided staff who helped analyse and interpret data

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
					C:1.6% *Pruritus* I: 1.0% C: 0.5% *Headache* I: 2.9% C: 2.6% *Arthralgia* I: 1.8% C: 2.1%	
Langley et al 2014 [98] (FIXTURE) RCT	**Population** Adult patients (≥18 years) with moderate to severe plaque diagnosed ≥6 months, involving ≥10% body surface area, with ≥3 on modified investigator's global assessment scale and PASI ≥12. Treatment naive to etanercept *Baseline characteristics* *Female/Male, %* I: 28.8%/71.2% C: 27.3%/72.7% *Ethnicity (Caucasian), %*	**Intervention (I)** Etanercept 100 mg/week (in 50 mg subcutaneous injections twice weekly) weeks 0–12 and 50 mg/week (once weekly injections) weeks 13–51 n=326 *Drop-out rate* 21/326 (6.4%) at 12 weeks The study also included an intervention group	**Comparison (C)** Placebo, (in subcutaneous injections twice weekly) for 12 weeks, n=326 *Drop-out rate* 25/326 (7.7%) at 12 weeks	**Analysis model** ITT, including all randomised patients. Missing values imputated as non-responders **Results – week 12** *PASI ≥75* I: 142/323 (44.0%) C: 16/324 (4.9%) I vs C: not given *PASI ≥90* I: 67/323 (20.7%) C: 5/324 (1.5%) I vs C: Not given *PASI 100*	**Adverse events** **At 0–12 weeks (%)** *Any AE* I: 57.5% C: 49.8% *Death* I: 0 C: 0 *Non-fatal serious event* I: 0.9% C: 1.8% *Discontinuation due to AE* I: 1.9% C: 0.9%	**Risk of bias** Acceptable **Comment** The main purpose of the study was to compare secukinumab with etanercept or placebo. Inferential statistics for comparison between etanercept and placebo were not calculated Conflicts of interest Study was sponsored by a pharmaceutical company: Novartis. Novartis also provided

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	I: 67.5% C: 66.9% *BMI (kg/m^2), mean±SD* I: 28.7±5.9 C:27.9±6.1 **Study period** June 2011–June 2013 **Follow-up** 12 weeks placebo-controlled trial (induction period). After 12 weeks patients in placebo group with PASI improvement less than 75 were rerandomised. Efficacy assesments were made at the end of induction period and of maintenance period (week 52)	treated with sekukinumab		I: 14/323 (4.3%) C: 0/324 I vs C: Not given *DLQI, mean absolute change* I: -7.9 C: -1.9 I vs C: Not given	*Infection or infestation* I: 24.5% C: 19.3%	staff who helped design the study
Gottlieb et al 2011 [95] Multicentre study performed at 33 sites in the USA RCT	**Population** Adult patients (≥18 years) with moderate to severe plaque diagnosed ≥6 months, involving ≥10% body surface area, with ≥3 on Physician's Global Assessment scale and PASI ≥12 at baseline. Treatment naive to IL-	**Intervention** Etanercept 100 mg/week (in 50 mg subcutaneous injections twice weekly) week 0–11. n=141 *Drop-out rate* 7/141 (5%)	**Comparison** Placebo in s.c. injections matching active treatment. n=68 *Drop-out rate* 5/68 (7.3%)	**Analysis model** ITT – all randomised included. Missing values imputated as non-responders. **Results at week 12** *PASI ≥75* I: 56.0% C: 7.4%	**Adverse events at week 12** *Any adverse event* I: 76/141 (53.9%) C: 31/68 (45.6%) *Any serious adverse event* I: 1/141 (0.7%) C: 1/68 (1.5%)	**Risk of bias** **Comment** The study was primarily designed to investigate the effect of briakinumab compared to etanercept and to placebo. Only the comparison between

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	12/23 inhibitor and to etanercept. <u>*Baseline characteristics*</u> *Female/male* I: 30.5%/69.5% C: 30.9%/69.1% *Age yrs, mean (SD)* I: 43.1 (12.5) C: 44.0 (13.6) *Body weight, mean (SD)* I: 94.5 kg (20.4) C: 96.5 kg (27.2) *Ethnicity (caucasian)* I: 95.6% C: 90.1% **Study period** June 2008–March 2009 **Follow-up** 12 weeks			*PASI ≥90* I: ca 10% C: ca 0% *PASI 100* I: ca 4% C: ca 0% *DLQI, patients with a score of 0 week 12* I: 30/141 (21.3%) C: 2/68 (2,9%)	*Any AE leading to discontinuation* I: 4/141 (2.8%) C: 0 *Any infection* I: 34/141 (24.1%) C: 13/68 (19.1%) *Any serious infection* I: 1/141 (0.7%) C: 0	etanercept and placebo is reported here. *Conflict of interest* The study was sponsored by Abbot Laboratories, the developer of briakinumab.
Strober et al 2011 [96] Multicentre study performed at 41 sites in the USA RCT	**Population** Adult patients (≥18 years) with moderate to severe plaque diagnosed ≥6 months, involving ≥10% body surface area, with ≥3 on Physician's Global Assessment scale and	**Intervention** Etanercept 100 mg/week (in 50 mg subcutaneous injections twice weekly) week 0–11. n=139	**Comparison** Placebo in s.c. injections matching active treatment. n=72 *Drop-out rate* 6/72 (8.3%)	**Analysis model** ITT – all randomised included. Missing values imputated as non-responders. **Results at week 12** *PASI ≥75* I: 39.6%	**Adverse events at week 12** *Any adverse event* I: 69/139 (49.6% C: 32/72 (44.4%) *Any serious adverse event* I: 1/139 (0.7%)	**Risk of bias** **Comment** The study was primarily designed to investigate the effect of briakinumab compared to etanercept and to placebo. Only the

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	PASI ≥12 at baseline. Treatment naive to IL-12/23 inhibitor and to etanercept. <u>*Baseline characteristics*</u> *Female/male* I: 38.9%/61.1% C: 36.1%/63.9% *Age yrs, mean (SD)* I: 45.2 (14.8) C: 45.0 (13.9) *Body weight, mean (SD)* I: 96.9 kg (24.9) C: 92.9 kg (25.2) *Ethnicity (caucasian)* I: 91.4% C: 93.1% **Study period** July 2008–April 2009 **Follow-up** 12 weeks	*Drop-out rate* 12/139 (8.6%)		C: 6.9% *PASI ≥90* I: 13.7% C: 4.2% *PASI 100* I: 5.8% C: 0 *DLQI, patients with a score of 0 week 12* I: 21/139 (15.1%) C: 2/72 (2.8%)	C: 2/72 (2.8%) *Any AE leading to discontinuation* I: 4/139 (2.9%) C: 2/72 (2.8%) *Any infection* I: 39/139 (28.1%) C: 10/72 (13.9%) *Any serious infection* I: 0 C: 0	comparison between etanercept and placebo is reported here. *Conflict of interest* The study was sponsored by Abbot Laboratories, the developer of briakinumab.

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
Reich et al 2017 [57] Global multicentre study RCT	**Population** *Inclusion criteria* ≥18 years of age, Plaque psoriasis PASI ≥12, sPGA ≥3, BSA ≥10%, for ≥12 months, eligible for phototherapy or systemic therapy, inadequate response to one or two conventional systemic agents, and biologic naïve. *Baseline characteristics* *Female/Male, (%)* I: 41%/59% C: 29.8%/70.2% *Ethnicity – Caucasian* I: 90.4% C: 95.2% *Body mass index (kg/m^2), mean±SD* I: 29.9±6.8 C: 29.5±6.6 **Study period** October 2012 - July 2014 **Follow-up**	**Intervention (I)** *Etanercept* for 16 weeks, two subcutaneous injections, 25 mg each, twice a week *Allocation placebo controlled phase, n* I: 83 *Drop-out rate placebo controlled phase* I: 2 (2.4%) The study also included intervention groups treated with Apremilast	**Comparsion (C)** Placebo: two subcutaneous injections, with saline placebo, twice a week *Allocation placebo controlled phase, n* C: 84 *Drop-out rate placebo controlled phase, n (%)* C: 9 (10.7%)	**Analysis model** mITT *Missing data* LOCF **Results – 16 weeks** *Primary endpoint* *PASI ≥75, n (%)* I: 40/83 (48.2%) C: 10/84 (11.9%) I vs C: p<0.0001 *PASI ≥90, n (%)* I: 17/83 (20.5%) C: 3/84 (3.6%) I vs C: p=0.0009 *DLQI improvement, mean (SD)* I: -7.8 (SD: 6.5) C: -3.8 (SD: 5.6) I vs C: p=0.0004 *DLQI patients receiving a DLQI score of 0 or 1, n (%)* I: 27/83 (32.5%) C: 13/84 (15.5%)	**Adverse events – during 16 weeks placebo controlled phase** *Patients w ≥1 AE, n (%)* I: 44/83 (53.0%) C: 45/84 (53.6%) *Patients w ≥1 serious AE, n (%)* I: 2/83 (2.4%) C: 0/84 (0%) *Patients with AE leading to drug withdrawal, n (%)* I: 2/83 (2.4%) C: 2/84 (2.4%) Treatment-emergent adverse events ≥5% of patients in any treatment groups *Nausea, n (%)* I: 4/83 (4.8%) C: 1/84 (1.2%) *URTI, n (%)* I: 2/83 (2.4%) C: 2/84 (2.4%) *Diarrhoea, n (%)* I: 1/83 (1.2%)	**Risk of bias** Acceptable **Comment** *Conflict of interest: study funded by Celgene. Editorial support by sponsor* The study was not powered for apremilast vs etanercept comparisons. A post hoc comparison yielded a calculated power of 19% for detecting the observed difference. Information about study period found at https://clinicaltrials.gov/ct2/show/NCT01690299

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	16 weeks placebo-controlled phase (presented here). At week 16 etanercept and placebo patients were switched to apremilast. The OLE phase was maintained until week 104. Results for up to 52 weeks presented in the publication. Patients who did not achieve PASI 50 at week 32 could add complementary therapies to their treatments				C: 3/84 (3.6%) *Nasopharyngitis, n (%)* I: 8/83 (9.5%) C: 8/84 (9.5%) *Headache*, n (%)* I: 5/83 (6.0%) C: 3/84 (3.6%) *Tension headache, n (%)* I: 3/83 (3.6%) C: 4/84 (4.8%)	
Reich et al 2017 [99] Multicentre study, reSURFACE 2 (at 132 sites in Europe, Canada, Israel and USA) RCT	**Population** Adult patients (age ≥18 years) with moderate to severe chronic plaque psoriasis, involving ≥10% of body surface area, PGA ≥3 and PASI ≥12. Candidates for phototherapy or other systemic therapy Randomisation was done by region and stratified for bodyweight (≤90 kg or >90 kg) and previous	**Intervention (I)** Etanercept 100 mg/week (in 50 mg subcutaneous injections twice weekly) for 12 weeks. n=313 *Drop-out rate at 12 weeks* 24/313 (7.7%) The study also included intervention groups	**Comparison (C)** Placebo in subcutaneous injections, matching active treatment. n=156 *Drop-out rate at 12 weeks* 14/156 (9.0%)	**Analysis Model** Modified ITT (all who received ≥1 dose test substance) *Missing data* NRI **Results (12 weeks)** *PASI 75* I: 151/313 (48%) C: 9/156 (6%) *PASI 90* I: 67/313 (21%) C: 2/156 (1%)	**Adverse events** *AEs (week 0–12)* *Any adverse event* I: 169/313 (54%) C: 86/156 (55%) *Serious AEs, n (%)* I: 7/313 (2%) C: 4/156 (3%) *AEs leading to discontinuation, n (%)* I: 6/313 (2%) C: 2/156 (1%)	**Risk of bias** Acceptable **Comment** Funded by Merck & Co. The study funder had roles in study design, data analysis, and data interpretation.

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	exposure to biologics therapy for psoriasis *Baseline characteristics* *Female/Male, (%)* I: 29%/71% C: 28%/72% *Ethnicity* *White* *(%)* I: 289/313 (92%) C: 144/156 (92%) *Weight (kg), mean (SD)* I: 87.97 (21.48) C: 88.74 (22.73) *Age (years), mean (SD)* I: 45.8 (14.0) C46.4 (12.2) **Study period** Feb 12, 2013–Sep 28, 2015 **Follow-up** 12 weeks placebo controlled phase (plus up to 52 weeks OLE, not presented here)	treated with tildrakizumab.		*PASI 100* I: 15/313 (5%) C: 0/156 (0%) *DLQI (% patients receiving a score of 0 or 1 after 12 weeks treatment)* I: 108/300 (36%) C: 12/150 (8%)	*adverse events occurring in >5% of participants,* *Injection-site erythema, n (%)* I: 27/313 (9%) C: 1/156 (1%) *Nasopharyngitis, n (%)* I: 36/313 (12%) C: 12/156 (8%)	

AE – adverse event; BMI – body mass index; CDLQI – children's DLQI; CI – confidence interval; DLQI – dermatology life quality index; ITT – intention-to-treat; LOCF – last observation carried forward; n.g. – not given; NRI – non-responder imputation; OLE – open-label extension; PASI – psoriasis area and severity index; PGA – physician's global assessment; RCT – randomised controlled trial; SD – standard deviation; SE – standard error; TNF – tumour necrosis factor; URTI – upper respiratory tract infection

Table 7.4. Infliximab versus placebo

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Reich et al 2005 [106] Study name: EXPRESS Multicenter at 32 locations in Europe and Canada RCT	**Population** *Inclusion criteria:* Moderate to severe plaque psoriasis ≥6 months, eligible for phototherapy or systemic therapy, PASI score of ≥12, BSA ≥10% *Permitted concomitant therapies after week* 10 2.5% hydrocortisone or equivalent, applied to groin and/or face after week 10 *Baseline characteristics* *Female/Male, (%)* I: 31.2%/68.8% C: 20.8%/79.2% *Ethnicity* No information *Bodyweight* No information Allocation stratified by investigation site	**Intervention (I)** Infliximab 5 mg/kg, intravenous infusion at week 0, 2 and 6 then every 8 weeks through to week 46 n=301 *Drop-out rate* 32/301=10.6%	**Comparison (C)** Placebo n=77 Placebo (week 0-24), infliximab 5mg/kg at weeks 24, 26 and 30 then every 8 weeks through to week 46 *Drop-out rate* 9/77=11.7%	**Analysis model** ITT *Missing data* NRI for ITT **Results – week 10** *PASI ≥50, n (%)* I: 274/301 (91.0%) C: 6/77 (7.8%) I vs C: p<0.0001 *Primary endpoint* *PASI ≥75, n (%)* I: 242/301 (80.4%) C: 2/77 (2.6%) I vs C: p<0.0001 *PASI ≥90, n (%)* I: 172/301 (57.1%) C. 1/77 (1.3%) I vs C: p<0.0001 **Results – week 24** *PASI ≥50, n (%)* I: 248/276 (89.9%) C: 6/77 (7.8%)	**Adverse events** I: n=298 C: n=76 *Serious AE (week 0–24)* I: 17/298 (5.7%), (1 death) C: 2/76 (2.6%) *AE (week 0–24)* I: 82% C: 71% *AE in ≥5% in any group (0–24 weeks)* *URTI, n (%)* I: 46/298 (15.4%) C: 12/76 (15.8%) *Headache, n (%)* I: 43/298 (14.4%) C: 9/76 (11.8%) *Fatigue, n (%)* I: 25/298 (8.4%) C: 3/76 (3.9%) *Hepatic enzymes Increased, n (%)*	**Risk of bias** Acceptable **Comment** Study supported and funded by Centocor, manufacturer of infliximab. The manufacturer was involved in study design, data acquisition, data analysis and preparation of the manuscript Randomisation of study population (without stratification for nail psoriasis)

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	Study period Not clear **Follow-up** 24 weeks placebo controlled trial (reported here), followed by 26 weeks OLE			I vs C: p<0.0001 *Secondary endpoints* *PASI ≥75, n (%)* I: 227/276 (82.2%) C 3/77 (3.9%) I vs C: p<0.0001 *PASI ≥90, n (%)* I: 161/276 (58.3%) C: 1/77 (1.3%) I vs C: p<0.0001	I: 26/298 (8.7%) C: 0/76 *Pruritus, n (%)* I: 22/298 (7.4%) C: 5/76 (6.6%) *Arthralgia, n (%)* I: 21/298 (7.0%) C: 3/76 (3.9%) *Rhinitis, n (%)* I: 18/298 (6.0%) C: 1/76 (1.3%) *Pain, n (%)* I: 17/298 (5.7%) C: 4/76 (5.3%) *Pharyngitis, n (%)* I: 17/298 (5.7%) C: 6/76 (7.9%) *Herpes simplex, n (%)* I: 10/298 (3.4%) C: 4/76 (5.3%) *Psoriasis, n (%)* I: 9/298 (3.0%) C: 10/76 (13.2%) *Sinusitis, n (%)* I: 4/298 (1.3%) C: 4/76 (5.3%)	

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
					AEs leading to withdrawals, n (%) I: 27/298 (9.1%) C: 5/77 (6.6%) *Infections, n (%)* I: 125/298 (41.9%) C: 30/76 (39.5%) *Neoplasms, n (%)* I: 3/298 (1.0%) C: 0/76 *Infusion reactions, number of infusions, n (%)* I: 38/1416 (3%) C: 7/347 (2%)	
Gottlieb et al 2004 [105] Study name: SPIRIT Multicenter at 24 centers in USA RCT	**Population** *Inclusion criteria:* Age ≥18 years, diagnosis of plaque psoriasis ≥6 months, previously treated with PUVA or other systemic antipsoriasis therapy, PASI score of ≥12, BSA ≥10% *Baseline characteristics Female/Male, (%)* I: 26.3%/73.7%	**Intervention (I)** I: Infliximab 5 mg/kg, intravenous infusion at week 0, 2 and 6 Patients with a PGA ≥3 at week 26 were eligible for a single additional infusion of their assigned treatment I: n=99	**Comparison (C)** Placebo, intravenous infusion n=51 *Drop-out rate* 37/51=72.5%	**Analysis model** ITT **Results – week 10** *Primary endpoint PASI ≥75, n (%)* I: 87/99 (87.9%) C: 3/51 (5.9%) I vs C: p<0.001 *Secondary endpoints*	**Adverse events (through week 30)** *Patients with ≥1 AE, n (%)* I: 78/99 (78.8%) C: 32/51 (62.7%) *Discontinued treatment as result of an AE* I: n=3 (3%) C: n=1 (2%) *Serious AE, n (%)* I: 8/99 (8.1%)	**Risk of bias** Acceptable **Comment** Study supported and funded by Centocor

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	C: 39.2%/60.8% *Ethnicity* No information *Bodyweight* No information *Randomisation stratified by investigational site* **Study period** 2001 to 2003 **Follow up** 26-week placebo controlled trial. (Treatment week 0, 2, 6 and additional treatment dose at week 26 if PGA≥3). Follow up until week 30	*Drop-out rate* I: 18/99=18.2% The trial also included a treatment arm where patients received infliximab 3 mg/kg		*PASI ≥50, n (%)* I: 96/99 (97.0%) C: 11/51 (21.6%) I vs C: p<0.001 *PASI ≥90, n (%)* I: 57/99 (57.6%) C: 1/51 (2.0%) I vs C: p<0.001 *DLQI, median change from baseline to week 10 (median score at week 10)* I: -10 (1) C: 0 (10) I vs C: p<0.001	C: 0/51 (0.0%) *Patients with infusion reactions, n (%)* I: 22/99 (22.2%) C: 1/51 (2.0%) *Patients newly positive for antinuclear antibodies, n (%)* I: 20/80 (25.0%) C: 1/44 (2.3%) *Patients newly positive for antibodies against double stranded DNA, n (%)* I: 4/94 (4.3%) C: 1/48 (2.1%) *Patients with antibodies to infliximab* I: 17/87 (19.5%) C: NA	
Feldman et al 2005 [104] Same as study population as in [105] Study name: SPIRIT	**Population** *Inclusion criteria:* Age ≥18 years, diagnosis of plaque psoriasis ≥6 months, previously treated with PUVA or other systemic antipsoriasis therapy,	**Intervention (I)** I: Infliximab 5 mg/kg, intravenous infusion at week 0, 2 and 6 Patients with a PGA ≥3 at week 26 were eligible for a single additional	**Comparison (C)** Placebo, intravenous infusion n=51 *Drop-out rate* 37/51=72.5%	**Analysis model** ITT Missing data: NRI before week 10 LOCF after week 10 **Results – week 10**	**Adverse events** See study Gottlieb 2004 [105]	**Risk of bias** Acceptable **Comment** Study supported and funded by Centocor

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Multicenter at 24 centers in USA RCT	PASI score of ≥12, BSA ≥10% *Baseline characteristics* *Female/Male (%)* I: 26.3%/73.7% C: 39.2%60.8% *Ethnicity* No information *Bodyweight* No information **Study period** 2001 to 2003 **Follow-up** 26 weeks placebo controlled trial. (Treatment week 0, 2, 6 and additional treatment dose at week 26 if PGA≥3). Follow up until week 30	infusion of their assigned treatment I: n=99 *Drop-out rate* I: 18/99=18.2% The trial also included a treatment arm where patients received infliximab 3 mg/kg		Baseline *DLQI, mean±SD* I: 13.2 ± 7.0 C: 13.8 ± 6.6 *Change from baseline, mean±SD* I: -10.3 ± 7.3 C: -2.6 ± 5.7 I vs C: p<0.001		
Menter et al 2007 [107] Study name: EXPRESS II	**Population** *Inclusion criteria:* Adult patients with moderate to severe plaque psoriasis, candidates for phototherapy or systemic therapy, PASI score of ≥12, BSA ≥10%	**Intervention (I)** I: Infliximab 5 mg/kg, intravenous infusion at week 0, 2 and 6. At week 14 patients were re-randomised to either every-8-week continuous	**Comparison (C)** Placebo, intravenous infusion Cross-over to infliximab 5 mg/kg at week 16, 18 and 22, and every 8 weeks thereafter	**Analysis model** ITT *Missing data* NRI **Results – week 10** *Primary endpoint* *PASI ≥75, n (%)*	**Adverse events (through week 14)** *Patients with ≥1 AE, n (%)* I: 216/314 (68.8%) C: 116/207 (56.0%) *Patients with ≥1 serious AE, n (%)*	**Risk of bias** Acceptable **Comment** Study supported and funded by Centocor

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
Multicenter study, at 63 sites in USA, Canada and Europe RCT	Baseline variables: *Female/Male, (%)* I: 35.0%/65.0% C: 30.8%/69.2% *Bodyweight (kg), mean ±SD* I: 92.2 ± 23.2 C: 91.1 ±22.6 *Ethnicity* - Caucasian I: 93.3% C: 90.9% **Study period** No information **Follow up** 16-week placebo controlled trial (reported here). (Treatment week 0, 2, 6 and thereafter additional dose per treatment schedule (see the "Intervention" and "Control" columns) OLE until week 50	maintenance therapy (week 14, 22, 30, 38 and 46) or intermittent as-needed maintenance therapy (infliximab at original dose if PASI ≤75%, otherwise placebo) I: n=314 *Drop-out rate, n (%)* I: 17/314=5.4% The trial also included a treatment arm where patients received infliximab 3 mg/kg	n=208 *Drop-out rate, n (%)* 24/208=11.5%	I: 237/314 (75.5%) C: 4/208 (1.9%) I vs C: p<0.001 *Secondary endpoints* *PASI ≥90, n (%)* I: 45.2% C: 0.5% I vs C: p<0.001 *DLQI, median change from baseline to week 10* I: -9.0 C: 0.0 I vs C: p<0.001	I: 9/314 (2.9%) C: 5/207 (2.4%) *Patients with ≥1 infection, n (%)* I: 97/314 (30.9%) C: 62/207 (30.0%) *Patients with ≥1 infusion reactions* I: 30/314 (9.6%) C: 12/207 (5.8%) *Common adverse events in ≥5% in any group* *URTI, n (%)* I: 42 (13.4%) C: 29 (14.0%) *Headache, n (%)* I: 38 (12.1%) C: 11 (5.3%) *Pharyngitis, n (%)* I: 16 (5.1%) C: 7 (3.4%) *Nausea, n (%)* I: 12 (3.8%) C: 8 (3.9%) *Sinusitis, n (%)* I: 20 (6.4%) C: 3 (1.4%)	

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Yang et al 2012 [108] Multicenter study, at 9 centers in China RCT	**Population** *Inclusion criteria:* Patients aged 18-65, diagnosis of plaque psoriasis ≥6 months, have failed to respond to conventional systemic anti-psoriasis therapy, PASI score of ≥12, BSA ≥10%, no history of serious infections, lymphoproliferative disease or active tuberculosis. **Baseline variables:** *Female/Male (%)* I: 28.6%/71.4% C: 22.2%/77.8% *Bodyweight (kg), mean ± SD* I: 68.2 ± 9.2 C: 67.4 ±9.9 *Ethnicity* No information, but study conducted in China to validate efficacy and safety in Chinese patients	**Intervention (I)** Infliximab 5 mg/kg, intravenous infusion at week 0, 2 and 6, and every 8 weeks thereafter (week 14, 22) n=84 Drop-out rate through week 10 (placebo-controlled phase) 1/84=1.2% (due to adverse event)	**Comparison (C)** Placebo, intravenous infusion, week 0, 2 and 6. Cross-over to infliximab 5mg/kg at week 10, 12 and 16 n=45 Drop-out rate through week 10 (placebo-controlled phase) 1/45=2.2% (Withdrawal of informed consent)	**Analysis model** ITT **Results – week 10** *Secondary endpoints* *PASI ≥50, n (%)* I: 79/84 (94.0%) C: 6/45 (13.3%) I vs C: p<0.001 *Primary endpoint* *PASI ≥75, n (%)* I: 68/84 (81.0%) C: 1/45 (2.2%) I vs C: p<0.001 *PASI ≥90, n (%)* I: 48/84 (57.1%) C: 0/45 (0.0%) I vs C: p<0.001 *DLQI change, mean ±SD* I: -8.0 ±7.1 C: -1.5 ±5.1 I vs C: p<0.001	**Adverse events** **10 weeks** *Patients with AE, n (%)* I: 36/84 (42.9%) C: 17/45 (37.8%) *Patients with serious AE, n (%)* I: 1/84 (1.2%) C: 0/45 (0.0%) *Tuberculosis, n (%)* I: 0/84 (0%) C: 0/45 (0%) *Infusion reactions, n (%)* I: 3/84 (3.6%) C: 0/45 (0%) *URTI, n (%)* I: 6/84 (7.1%) C: 4/45 (8.9%) *Asthenia, n (%)* I: 6/84 (7.1%) C: 2/45 (4.4%)	**Risk of bias** Acceptable **Comment**

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	Study period February 2009 – February 2010 **Follow up** 10 weeks placebo controlled trial. (Treatment week 0, 2 and 6) and thereafter a maintenance phase (week 10–26), where the control group were switched to active treatment as well.					

AE – adverse event; BSA – body surface area; CI – confidence interval; DLQI –dermatology life quality index; ITT –intention-to-treat; LOCF – last observation carried forward; NRI – non-responder imputation; OLE – open-label extension; PASI – psoriasis area and severity index; PGA – physician's global assessment; RCT – randomised controlled trial; SD – standard deviation; URTI – upper respiratory tract infection

Table 7.5. Infliximab versus Etanercept

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
de Vries et al 2017 [109] Multicenter study performed at 5 sites in the Netherlands RCT	**Population** Adult patients ≥18 yrs with moderate to severe plaque psoriasis (PASI ≥10, and/or BSA ≥10, and or PASI≥8 plus Skindex-29 ≥35). Contraindicated or intolerant for UV therapy, MTX or cyclosporine. No prior inadequate response to etanercept or infliximab. <u>*Baseline characteristics*</u> *Male/female* I: 72%/28% E: 66%/44% *Mean age (SD)* I: 45.9 (13.9) E: 42.4 (13.2) *PASI, mean (SD)* I: 17.8 (9.7) E: 15.9 (5.1) *Body weight or BMI* Not given **Study period** April 2009–June 2011 **Follow-up**	**Intervention (I)** Infliximab 5 mg/kg, intravenous infusion at week 0, 2 and 6, and every 8 weeks thereafter. In case of inadequate response or AE:s patients could switch to the other treatment arm (1/25 did switch to etanercept)). n=25 *Drop-out rate* 1/25 (4%)	**Comparison (E)** Etanercept 100 mg/week in self- administered s.c injections (50 mg twice weekly). In case of inadequate response or AE:s patients could switch to the other treatment arm. n=25 *Drop-out rate* 2/25 (8%)	**Analysis model** ITT – all who received ≥1 dose of test substance included. **Results week 12** *PASI ≥50* IFX: 24/25 (96%) ETA: 14/23 (60.9%) I vs E: p<0.05 *PASI ≥75* IFX: 19/25 (76%) ETA: 5/23 (21.7%) I vs E: p<0.05 *PASI ≥90* IFX: 5/25 (20%) ETA: 0/23 (0) I vs E: p=0.05 *PASI ≥100* IFX: 1/25 (4%) ETA: 0/23 (0) I vs E: p=1 *PASI, absolute mean reduction (SD)* IFX: 14.8 (9.6) ETA: 9.1 (6.0) I vs E: p=0.02	**Adverse events at 48 weeks** *Patients reporting any adverse event* IFX: 24/25 (96%) ETA: 23/23 (100%) *Patients reporting serious adverse events* IFX: 1 (stomach pain) ETA: 1 (angina pectoris) *Adverse events leading to discontinuation* IFX: 3 (1 reactive arthritis, 1 erythroderma, 1 liverdysfunction) ETA: 2 (1 neutropenia, 1 exacerbation of psoriasis) <u>*Adverse events w significant differences btw groups (in n patients)*</u> *Circulatory disorders* IFX: 8/25 (32%) ETA: 4 (17.4%) I vs E: p=0.01	**Risk of bias** Acceptable **Comment**

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	RCT for 12 weeks, with a total follow up for 48 weeks.			*PASI, relative mean reduction (SD)* IFX: 79.8% (17.8) ETA: 52.9% (24.0 I vs E: p<0.05 *SF-36 – physical component scale, mean improvement (SD)* IFX: 7.7 (9.7) ETA: 8.9 (10.6) I vs E: p=0.69 *SF-36 – mental component scale, mean improvement (SD)* IFX: 1.4 (11.7) ETA: 0.5 (7.8) I vs E: p=0.76	*Abnormalities in blood count* IFX: 12/25 (48%) ETA: 5/23 (21.7%)	

AE – adverse event; BSA – body surface area; CI – confidence interval; DLQI –dermatology life quality index; ITT –intention-to-treat; LOCF – last observation carried forward; NRI – non-responder imputation; OLE – open-label extension; PASI – psoriasis area and severity index; PGA – physician's global assessment; RCT – randomised controlled trial; SD – standard deviation; URTI – upper respiratory tract infection

Table 7.6. Brodalumab versus placebo

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Lebwohl et al 2015 [111] Data from the AMAGINE-2 (A) and AMAGINE 3 (B) studies are presented Multicentre trials AMAGINE-2 was conducted at 142 sites worldwide, AMAGINE-3 was conducted at 142 different sites worldwide RCT	**Population** *Inclusion criteria* Patients 18–75 years of age, candidates for biologic therapy, with plaque-psoriasis for ≥6 months with a PASI score ≥12, sPGA score ≥3 and BSA ≥10% *Baseline characteristics* *Female/Male, (%)* AMAGINE 2: 31%/69% AMAGINE 3: 32 %/68 % *BMI (kg/m^2), mean ±SD* AMAGINE 2: 30.6 ±7.2 AMAGINE 3: 30.1±6.9 *Ethnicity (Caucasian), %* AMAGINE 2: 90% AMAGINE 3: 91% **Study period** AMAGINE-2: August 2012-September 2014 AMAGINE-3: September 2012–August 2014	**Intervention (I)** I: Brodalumab 210 mg/injection Subcutaneous injection day 1 and week 1, 2, 4, 6, 8 and 10 Randomisation stratified by body weight (≤100 kg, >100 kg), geographic region, previous use of biologic agents AMAGINE-2 (n) I: 612 Drop-out rate (12 weeks) I: 15/612 (2.5%) AMAGINE-3 (n) I: 624 Drop-out rate (12 weeks) I: 16/624 (2.6%) At week 12 placebo controlled phase ended. Results from	**Comparison (C)** Subcutaneous injection with placebo on day 1 and weeks 1, 2, 4, 6, 8 and 10 At 12 weeks patients randomised to placebo switched to brodalumab AMAGINE-2 (n) C: 309 Drop-out rate (12 weeks) C: 9/309 (2.9%) AMAGINE-3 (n) C: 315 Drop-out rate (12 weeks) C: 14/315 (4.4%)	**Analysis Model** ITT Safety population: all patients who received ≥1 dose of the study product *Missing data* NRI **Results** <u>AMAGINE-2 week 12</u> PASI ≥75, % (95% CI), n – *primary endpoint* I: 86% (83, 89), 528 C: 8% (5,12), 25 I vs C: p<0.001 PASI 100, % (95% CI), n I: 44% (41, 49), 272 C: 1% (0, 2), 2 I vs C: p<0.001 <u>AMAGINE-3 week 12</u> PASI ≥75, % (95% CI), n – *primary endpoint* I: 85% (82, 88), 531 C: 6% (4,9), 19	**Adverse events** **AMAGINE-2, (week 12)** *Any AE, n (%)* I: 354/612 (57.8%) C: 165/309 (53.4%) *Serious AE, n (%)* I: 6/612 (1.0%) C: 8/309 (2.6%) *Fatal AE, n (%)* I: 1/612 (0.2%) C: 0/309 (0%) *AE leading to discontinuation of study, n (%)* I: 6/612 (1.0%) C: 0/309 (0%) *Leading to discontinuation of study drug, n (%)* I: 6/612 (1.0%) C: 1/309 (0.3%) *Common AE (≥5% of patients in any treatment group)* Nasopharyngitis, n (%)	**Risk of bias** Acceptable **Comment** Study funded and supported by Amgen. Weight-based analysis group was a prespecified subgroup that included patients with a body weight of 100 kg or less who were in the group that received 140 mg of brodalumab every 2 weeks and patients with a body weight greater that 100kg who were in the group that received 210 mg of brodalumab every 2 weeks.

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	Follow-up 12 weeks induction phase (placebo controlled), plus 40 weeks maintenance phase The study also included treatment group where patients received 140 mg brodalumab, same regime as for intervention, or ustekinumab (45 mg ≤100 kg bodyweight, 90 mg >100 kg) at day 1, week 4 and wevery 12 weeks thereafter	maintenance phase not included here		I vs C: p<0.001 PASI 100, % (95% CI), n I: 37% (33, 41), 229 C: 0.3% (0, 2), 1 I vs C: p<0.001	I: 45/612 (7.4%) C: 14/309 (4.5%) URTI, n (%) I: 30/612 (5.4%) C:23/309 (7.4%) Headache, n (%) I: 31/612 (5.1%) C: 9/309 (2.9%) Arthralgia, n (%) I: 28/612 (4.6%) C: 12/309 (3.9%) **AMAGINE-3, (week 12)** *Any AE, n (%)* I: 353/622 (56.8%) C: 152/313 (48.6%) *Serious AE, n (%)* I: 9/622 (1.4%) C: 3/313 (1.0%) *Fatal AE, n (%)* I: 0/622 (0%) C: 0/313 (0%) *AE leading to discontinuation of stuydy, n (%)* I: 5/622 (0.8%) C: 2/313 (0.6%)	

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
					Leading to discontinuation of study drug, n (%) I: 7/622 (1.1%) C: 3/313 (1.0%) *Common AE (≥5% of patients in any treatment group)* *Nasopharyngitis, n (%)* I: 31/622 (5.0%) C: 22/313 (7.0%) *URTI, n (%)* I: 33/622 (5.3%) C:17/313 (5.4%) *Headache, n (%)* I: 21/622 (3.4%) C: 14/313 (4.5%) *Arthralgia, n (%)* I: 36/622 (5.8%) C: 10/313 (3.2%)	
Nakagawa et al. 2016 [112] Study carried out at 56 sites in Japan RCT	**Population** Patients 20-70 years of age, stable plaque psoriasis for ≥6 months with a PASI score ≥12 and BSA ≥10%. Received or were candidates for photo	**Intervention (I)** Subcutaneous injection with Brodalumab 210 mg, on day 0 and week 1, 2, 4, 6, 8, and 10 *Dose & randomised population*	**Comparison (C)** Subcutaneous injection with Placebo on day 0 and week 1, 2, 4, 6, 8, and 10 *Dose & randomised population*	**Analysis model** ITT *Missing values* Baseline value carried-forward was used for the percentage improvement in PASI scores and BSA.	**Adverse Events** *All AE, n (%)* I: 27/37 (73.0%) C: 17/38 (44.7%) *Serious AE, n (%)* I: 1/37 (2.7%) C: 1/38 (2.6%)	**Risk of bias** Acceptable **Comment** Study supported by Kyowa Hakko Kirin Co., Ltd

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	therapy or systemic therapy *Baseline characteristics* Female/Male I: 21.6%/78.4% C: 28.9%/ 71.1% *BMI (kg/m²), mean±SD* I: 26.34±5.63 C: 26.02±4.68 All patients described as Japanese Randomisation stratified by psoriatic arthritis, additional pharmacokinetic blood sampling, prior biological therapy and study site **Study period** Not clear **Follow-up** 12-week placebo-controlled trial followed by a 1 year open-label extension	I: 210 mg, n=37 Drop-out rate, n (%) I: 0/37 The trial also included study groups that received injections with 70 mg or 140 mg brodalumab	C: n=38 Drop-out rate, n (%) 4/38 (10.5%)	NRI used for other efficacy endpoints **Results – week 12** *PAS I≥75, n (%)* I: 35/37 (94.6%) C: 3/38 (7.9%) I vs C: p<0.001 *PASI ≥90, n (%)* I: 34/37 (91.9%) C:1/38 (2.6%) I vs C: p<0.001 *PASI 100, n (%)* I: 22/37 (59.5%) C: 0/38 I vs C: p<0.001 DLQI change from baseline, mean ±SD I: -9.0±6.9 C: -2.0±6.7 I vs C: p<0.001 *SF-36 (change from baseline), mean ±SD* PCS I: 8.09±16.58 C: 0.16±10.66 I vs C: p<0.05 MCS I: 5.00±6.85	*Common adverse events (cut-off not specified)* *Nasopharygitis, n (%)* I: 4/37 (10.8%) C: 3/38 (7.9%) *Diarrhoea, n (%)* I: 3/37 (8.1%) C: 0/38 (0%) *Folliculitis, n (%)* I: 2/37 (5.4%) C: 0/38 (0%) *URTI, n (%)* I: 0/37 (0%) C: 0/38 (0%)	Randomisation of 151 patients, stratification based on 4 parameters, including 56 ”institutions” (study sites), may lead to selection bias

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
				C: -1.05±9.55 I vs C: p<0.05		
Umezawa et al 2016 [116] OLE (for main RCT, see [112])	**Population** For inclusion criteria to the initial RCT, see [112] **Follow-up** 52 weeks	**Intervention** Brodalumab 210 mg in s.c. injections every second week n=72 *Drop-out rate* Total: 3/72 (4.2%)		**Analysis model** ITT (all patients who received ≥1 dose of study drug included).	**Results** *<u>Adverse events at 52 weeks</u>* *Any AE:* 66/72 (91.7%) *AE:s resulting in discontinuation:* None *Patients electing to suspend study treatment due to AE:s:* 12/72 (16.7%) *Serious adverse events:* 4/72 (55.6%) *<u>Most common AE:s (% in both groups combined):</u>* *Nasopharyngitis:* 35.2% *URTI:* 10.3% *Contact dermatitis:* 9.7% *<u>AE:s of interest:</u>*	**Risk of bias** **Comment** Risk of bias for OLE:s not assessed (observational data collected only)

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
					Neutrophilia: 1/72 (1.4%) *Candidiasis:* 8/72 (11.1%) *Injection site reactions:* 2/72 (2.8%)	
Papp et al 2012 [113] Multicentre study at 23 international sites. Same study as described in Gordon et al. 2014 [110] RCT	**Population** Patients 18–70 years, stable plaque psoriasis ≥6 months, candidates for, or had received, phototherapy or systemic psoriasis therapy, BSA ≥10%, PASI score ≥12 *Baseline characteristics* Female/Male, (%) I: 38%/62% C: 42%/58% *BMI (kg/m^2), mean ±SD* I: 29.8±6.6 C:29.3±6.8 *Ethnicity (Caucasian), %* I: 85% C: 84% **Study period** Enrolment: December 2009-April 2010	**Intervention (I)** I: 210 mg brodalumab Randomised, n I: 40 Drop-out rate (week 12): n (%) I: 3/40 (7.5%) Subcutaneous injection day 1 and week 1, 2, 4, 6, 8, and 10	**Comparison (C)** C: placebo Randomised, n C:39, mITT: 38 Drop-out rate (week 12): n (%) C: 3/38 (7.9%) Subcutaneous injection day 1 and week 1, 2, 4, 6, 8, and 10	**Analysis model** Efficacy outcomes ITT Safety outcomes mITT (all randomized patients who received ≥1 dose of test substance). *Patient-reported outcomes* mITT (all randomized patients who completed ≥1 post baseline assessment). *Primary endpoint* analysed with baseline BMI and PASI score as covariates *Missing data* Baseline value carried forward **Results – week 12** PASI ≥50, n (%) I: 36 (90%)	**Adverse events** Safety population (n) I: 40 C: 37 **AEs – 12 weeks** *Any AE≥1, n (%)* I: 33 (82%) C: 23 (62%) *Serious AE, n (%)* I: 1 (2%) C: 1 (3%) *Leading to withdrawal from study, n (%)* I: 0 (0%) C: 0 (0%) *Leading to discontinuation of study drug, n (%)* I: 2 (5%) C: 1 (3%)	**Risk of bias** Acceptable **Comment** Funded and supported by Amgen

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	Follow-up Treatment (placebo controlled trial) week 0–10. Efficacy and safety assessment at week 12 and 16. The trial also included treatment arms where patients received 70, 140 or 280 mg brodalumab			I vs C: p<0.001 C: 6 (16%) PASI ≥75, n (%) I: 33 (82%) I vs C: p<0.001 C: 0 (0%) PASI ≥90, n (%) I: 30 (75%) I vs C: p<0.001 C: 0 (0%) PASI 100, n (%) I: 25 (62%) I vs C: p<0.001 C: 0 (0%) SF–36 PCS – baseline; w12; (change*), mean ±SD* I3: 48.1±8.9); (52.1±7.8); (4.0±8.4) C: (48.6±9.8); (50.1±10.5); (1.5±10.2) I vs C: ns *MCS – baseline; w12; (change), mean ±SD* I: 48.7±12.6; 53.8±7.5; (5.1±10.4) C: 45.2±14.5; 46.9±11.2; (1.7±13.0) I vs C: p<0.01	*Common AEs (≥4 patients in any treatment group, ~9.8%, 12 weeks)* *Nasopharyngitis, n (%)* I: 4 (10%) C: 3 (8%) *URTI, n (%)* I: 2 (5%) C: 2 (5%) *Arthraliga, n (%)* I: 0 (0%) C: 1 (3%) *Injection-site erythema, n (%)* I: 3 (8%) C: 1 (3%) *Pain in extremity, n (%)* I: 3 (8%) C: 0 (0%) *Nausea, n (%)* I: 1 (2%) C: 1 (3%)	

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Gordon et al 2014 [110] Same study as described in Papp et al 2012 [113]. In this publication additional DLQI data and psoriasis symptom inventory (PSI) score are reported Multicentre study at 23 international sites RCT	**Population** *Inclusion criteria* As described in Papp et al 2012 [113] Patients 18–70 years, stable plaque psoriasis ≥6 months, BSA ≥10%, PASI score ≥12 *Baseline characteristics* *Female/Male, (%)* I: 38%/62% C: 42%/52% *Bodyweight (kg), mean ±SD* I: 90.4±20.4 C: 86.9±20.6 *Ethnicity (Caucasian), %* I: 85% C: 84% **Study period** December 2009-April 2010 **Follow-up** Treatment (placebo controlled trial) week 0–10. Efficacy and safety assessment at week 12 and 16	**Intervention (I)** As described in Papp et al 2012 [113] I: 210 mg brodalumab Randomised, n I: 40 Drop-out rate (week 12), n (%) I: 3/40 (7.5%) Subcutaneous injection day 1 and week 1, 2, 4, 6, 8, and 10	**Comparison (C)** As described in Papp et al. 2012 [113]. C: placebo Randomised, n C:38 Drop-out rate (week 12): n (%) C: 3/38 (7.9%) **S**ubcutaneous injection day 1 and week 1, 2, 4, 6, 8, and 10	**Analysis Model** mITT all patients who received ≥1 dose of test substance *Missing data* LOCF P-value adjusted w, linear model for baseline BMI≤35, >35 **Results – week 12** *DLQI improvement: mean ±SD, n* I: 9.6±6.1, 40 I vs C: p<0.0001 C. 3.1±6.6, 37	**Adverse Events** Reported in Papp et al 2012 [113]	**Risk of bias** Acceptable **Comment** Funded and supported by Amgen

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
Papp et al 2016 [117] OLE (for main RCT, [113])	**Population** For inclusion criteria to the initial RCT, see [113] **Study period** **Follow-up** 120 weeks	**Intervention** Initially (from OLE baseline) Brodalumab 210 mg s.c. every other week. After protocol adjustment the dose was reduced to 140 mg in patients weighing ≤ 100 kg. If inadequate response the dose was increased back to 210 mg. n=181 (all patients, regardless of test dose in the RCT-phase were included). Of those patients who originally had 210 mg Brodalumab every other week, 35 remained, and of those who originally had placebo, 33 remained at the start of the OLE-study. *Drop-out rate (patients still on brodalumab therapy at week 120)* All: 33/181 (18.2%) Group ≤100 kg: 8/119 (6.7%)		**Analysis model** ITT (all patients who received at least 1 dose of test substance included). Missing values were not imputed.	**Adverse events** *Treatment emergent AE:s over 120 weeks, n (%)* *Any AE:* 171/181 (94.5%) *Serious AE:* 15 (8.3%) *AE:s leading to discontinuation of study drug:* 11 (6.1%) *Common AE:s (reported by ≥10 %):* *Nasopharyngitis:* 48 (26.5%) *URTI:* 36 (19.9%) *Arthralgia:* 29 (16%) *Back pain:* 20 (11%) *Events of interest* *Neutrophilia (transient):* 4 (2%)	**Risk of bias** Not assessed **Comment** Risk of bias for OLE-studies not assessed (observational data collected only)

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
		Group >100 kg: 25/62 (40.3%)			*Candidiasis:* 5 (3%) *Injection site reactions:* 15 (8%) *Infections leading to withdrawal:* 4 (2%)	
Papp et al 2016 [114] Multicentre study performed carried out at 73 sites in Europe, Canada and USA. Study name AMAGINE-1 RCT	**Population** *Inclusion criteria* Patients aged 18–75 years with stable plaque psoriasis for ≥6 months, BSA ≥10%, PASI ≥12 and sPGA ≥3 *Baseline characteristics* Female/Male (%) I: 27%/73% C: 27%/73% *BMI (kg/m^2), mean ±SD* I: 31.0±7.7 C: 30.3±6.6 *Ethnicity (Caucasian), %* I: 91% C: 92% **Study period** August 2012 – March 2014 **Follow-up**	**Intervention (I)** I: 210 mg/injection Brodalumab injections every two weeks, route of administration not stated *Allocation* I: n=222 *Drop-out rate – week 12* I: 10/222 (4.5%)	**Comparison (C)** Placebo injections every two weeks, route of administration not stated *Allocation* n=220 *Drop-out rate – week 12* C: 11/220 (5.0%)	**Analysis model** *Efficacy endpoints* ITT *Safety population* All randomised patients who received ≥1 dose of test substance **Results – week 12** PASI ≥75, n (%) (95% CI) I: 185 (83.3%) (77.8, 88.0) C: 6 (2.7%) (1.0, 5.8) I vs C: p<0.001 PASI ≥90, n (%) (95% CI) I: 156 (70.3%) (63.8, 76.2) C: 2 (0.9%) (0.1, 3.2) I vs C: p<0.001 PASI 100, n (%) (95% CI) I: 93 (41.9%) (35.3, 48.7)	**Adverse Events** **AEs – week 12** *Any AE, n (%)* I: 131/222 (59.0%) C: 112/220 (50.9%) *Serious AE, n (%)* I: 4/222 (1.8%) C: 3/220 (1.4%) *Fatal AE, n (%)* I and C both 0 Leading to discontinuation from study*, n (%)* I: 2/222 (0.9%) C: 3/220 (1.4%) Leading to discontinuation of study drug*, n (%)* I: 2/222 (0.9%)	**Risk of bias** Acceptable **Comment** Study funded and supported by Amgen and AstraZeneca/MedImmune

First Author Year Reference Country Study design	Population Setting Study period Follow-up	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	12 weeks placebo-controlled phase (reported here), followed by 40 weeks of withdrawal and retreatment phase *Induction phase* Randomisation at baseline stratified by bodyweigh (≤100 kg, >100 kg), prior biological use (capped at 50%), and geographical region. Randomisation to brodamulab 140 mg, 210 mg or placebo The trial also included a treatment arm in which patients received 140 mg brodalumab			C: 1 (0.5%) (0.0, 2.5) I vs C: p<0.001	C: 3/220 (1.4%) *Common AE (≥5% of patients in any treatment group)* *Nasopharyngitis, n (%)* I: 21 (9.5%) C: 22 (10.0%) *URTI, n (%)* I: 18 (8.1%) C: 14 (6.4%) *Headache, n (%)* I: 11 (5.0%) C: 7 (3.2%)	

AE – adverse events; BMI – body mass index; BSA – body surface area; DLQI – dermatology life quality index; ITT – intention-to-treat; LOCF – last observation carried forward; MCS – mental component summary score; mITT – modified ITT; PASI – psoriasis area and severity index; PCS – physical component summary score; PGA – physician's global assessment; pp – palmoplantar psoriasis; SD – standard deviation; SE – standard error; sPGA – static physician's global assessment; URTI – upper respiratory tract infection

Table 7.7. Ixekizumab versus placebo

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Gordon *et al.* 2016 [119] Study name UNCOVER-1 Multicentre study perfomed at over 100 sites worldwide RCT	**Population** Adult patients (≥18 yrs) with chronic plaque psoriasis (diagnosis ≥6 months), involving ≥10% body surface area, sPGA ≥3 and PASI ≥12. Candidates for phototherapy and/or systemic therapy. **Study period** No information **Follow-up** Induction period: 12 weeks. Week 12-60 withdrawal period.	**Intervention** 80 mg of ixekizumab every 2 weeks after a starting dose of 160 mg at week 0. Subcutaneous injection. Injection with placebo to match active treatments Patients were stratified by geographic region (North America vs. other), weight (<100 kg or ≥100 kg), and previous non-biologic systemic therapy (inadequate response, intolerance, or contraindication to <3 or ≥3 conventional systemic therapies). **UNCOVER-1** n=433 *Drop-out rate (12 weeks), n (%)*	**Comparison** Placebo to match active treatments. n: 431 *Drop-out rate (12 weeks), n (%)* 24/431 (5.6%) *Baseline characteristics* Female/Male, (%) n: 29.7%/70.3% Ethnicity (Caucasian), % n:93.0% Bodyweight (kg), mean±SD 92±25	**Analysis model** ITT Safety population included all patients who received ≥1 dose of test substance or placebo *Missing values* For PASI and sPGA NRI **Results UNCOVER-1** **Week 12** *PASI ≥75, n (%) - primary endpoint* I: 386/433 (89.1%) C: 17/431 (3.9%) I vs C: p<0.0001 *PASI ≥90, n (%)* I: 307/433 (70.9%) C: 2/431 (0.5%) I vs C: p<0.0001 *PASI 100, n (%)* I: 153/433 (35.3%) C: 0/431 (0%) I vs C: p<0.0001	**Adverse events** Pooled for UNCOVER-1, UNCOVER-2 and UNCOVER-3 [88,119] Safety population, n I: 1167 C: 791 **Week 0-12** *Any AE, (%)* I: 58.4 C: 46.8 *Serious AE, (%)* I: 1.7 C: 1.5 *Discontinuation due to an AE, (%)* I:2.1 C: 1.1 *Common AEs* *Nasopharyngitis, (%)* I: 9.5 C: 8.7	**Risk of bias** Acceptable **Comment** Conflict of interest study sponsored, designed, data analysed and publication written by Eli Lilly,

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
		18/433 (4.2%) *Baseline characteristics* Female/Male, (%) n: 32.8%/67.2% Ethnicity (Caucasian), % n: 92.6% Bodyweight (kg), mean ±SD n: 92±23			URTI, (%) I: 4.4 C: 3.5 *Injection site reaction(%)* I:10.0 C: 1.1 *Arthralgia, (%)* I: 2.5 C: 2.1 *Headache, (%)* I: 4.4 C: 2.9	
Griffiths et al. 2015 [88] Multicentre studies carried out at sites in USA, Canada, Mexico, Argentina, Chile, the UK, Germany, Poland, Austria, France, the Netherlands, Spain, Bulgaria, Czech Republic, Hungary, Romania, Russia, and Australia. Study name UNCOVER-2 and UNCOVER-3	**Population** Adult patients (≥18 years) with chronic plaque psoriasis (diagnosis ≥6 months), involving ≥10% body surface area, sPGA ≥3 and PASI ≥12. Candidates for phototherapy and/or systemic therapy. **Study period** UNCOVER-2: May 2012 – December 2013 UNCOVER-3:	**Intervention** 80 mg of ixekizumab every 2 weeks after a starting dose of 160 mg at week 0. Subcutaneous injection. Injection with placebo to match active treatments **UNCOVER-2** n: 351 *Drop-out rate (12 weeks), n (%)*	**Comparison** C: Placebo Injection with placebo to match active treatments **UNCOVER-2** n: 168 *Drop-out rate (12 weeks), n (%)* 10/168 (6.0%) *Baseline characteristics* Female/Male, (%)	**Analysis model** ITT Safety population included all patients who received ≥1 dose of test substance or placebo *Missing values* For categorical variables: NRI **Results UNCOVER-2** **Week 12**	**Adverse events** Pooled data for UNCOVER-1, UNCOVER-2 and UNCOVER-3 (except AEs for etanercept treated patients) reported in [119] **AE:s for etanercept treated patients** **Week 0-12** *Any AE* 54% *Serious AE* 2%	**Risk of bias** Acceptable **Comment** Study funded, designed and carried out with the involvement of Eli Lilly

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
RCT	August 2012-February 2014 **Follow-up** Induction period: 12 weeks, placebo-controlled. Week 12-60 withdrawal period in UNCOVER-2, long-term extension period in UNCOVER-3	n: 9/351 (2.6%) *Baseline characteristics* Female/Male, (%) n: 27.0%/63.0% Ethnicity (Caucasian), % n: 94.3% BMI, kg/m^2±SD n: 30±7 **UNCOVER-3** n: 385 *Drop-out rate (12 weeks), n (%)* n: 22/385 (5.7%) *Baseline characteristics* Female/Male, (%) n: 34.0%/66.0% Ethnicity (Caucasian), % n: 93.8% BMI (kg/m^2), mean±SD n: 30±7 The studies also included intervention groups treated with etanercept	28.6%/71.4% Ethnicity (Caucasian), % 88.7 BMI (kg/m^2), mean±SD 31±7 **UNCOVER-3** n: 193 *Drop-out rate (12 weeks), n (%)* 10/193 (5.2%) *Baseline characteristics* Female/Male, (%) 29.0%/71.0% Ethnicity (Caucasian), % 91.2% BMI (kg/m^2), mean±SD 30±6	*PASI ≥75, n (%) - primary endpoint* I: 315/351 (89.7%) C: 4/168 (2.4%) *PASI ≥90, n (%)* I: 248/351 (70.7%) C: 1/168 (0.6%) *PASI 100, n (%)* I: 142/351 (40.5%) C: 1/168 (0.6%) DLQI change from baseline, mean±SE I: -10.4±0.3, 351 C: -2.0±0.4, 168 **Results UNCOVER-3 Week 12** *PASI ≥75, n (%) - primary endpoint* I: 336/385 (87.3%) C: 14/193 (7.3%) *PASI ≥90, n (%)* I: 262/385 (68.1%) C: 6/193 (3.1%)	*Common AEs* *Nasopharyngitis* *7 %* URTI 5% *Injection site reaction* *11%* *Arthralgia* 2% *Headache* 4%	

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
				PASI 100, n (%) I: 145/385 (37.7%) C: 0/193 (0%) DLQI change from baseline, mean±SE I: -10.2±0.2, 385 C: --1.7±0.3, 193		
Blauvelt et al. 2017 [120] This article is an open lable extension (OLE) from the UNCOVER-3 trial**,** [88] Some pooled AEs from The UNCOVER-3 trial is also reported in [119]	**Population** Reported in [88] **Follow-up** Placebo-controlled phase 0–12 weeks (presented in RN1253, OLE for up to 108 weeks.	**Intervention** 80 mg of ixekizumab every 2 weeks after a starting dose of 160 mg at week 0 Subcutaneous injection. Injection with placebo to match active treatments **N in safety analysis** 1274		*Effects from OLE-studies are not reported*	**Adverse events** *Patients with ≥1 AE, n (%)* 1077/1274 (84.5%) *Patients with severe AE, n (%)* 167/1274 (13.1%) *Patients with serious AE, n (%)* 148/1274 (11.6%) *Death, n (%)* 5/1274 (0.4%) *Common AEs reported by ≥5% of patients* *Nasopharyngitis, (%)* 300/1274 (23.5%) URTI, (%) 96/1274 (7.5%)	**Risk of bias** Not assessed **Comment** Study funded, designed and carried out with the involvement of Eli Lilly

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
					Injection site reaction(%) 96/1274 (7.5%) *Arthralgia, (%)* 80/1274 (6.3%) *Bronchitis, (%)* 72/1274 (5.7%) *Headache, (%)* 71/1274 (5.7%) Neutropenia, Grade 1, (%) 107/1274 (8.4%)	

BSA - body-surface area; DLQI - dermatology life quality index; EQ-5D – EuroQoL 5-Dimension health status; IGA – investigator's global assessment; ITT – intention to treat; NRI – non-responder imputation; PASI – psoriasis area and severity index; pp – palmoplantar psoriasis; SD – standard deviation; SE – standard error; sPGA – static physician's global assessment; URTI – upper respiratory tract infection

Table 7.8. Ixekizumab versus Etanercept

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Griffiths et al. 2015 [88] Multicentre studies carried out at sites in USA, Canada, Mexico, Argentina, Chile, the UK, Germany, Poland, Austria, France, the Netherlands, Spain, Bulgaria, Czech Republic, Hungary, Romania, Russia, and Australia. Study name UNCOVER-2 and UNCOVER-3 RCT	**Population** Adult patients (≥18 years) with chronic plaque psoriasis (diagnosis ≥6 months), involving ≥10% body surface area, sPGA ≥3 and PASI ≥12. Candidates for phototherapy and/or systemic therapy. **Study period** UNCOVER-2: May 2012 – December 2013 UNCOVER-3: August 2012-February 2014 **Follow-up** Induction period: 12 weeks, placebo-controlled. Week 12-60 withdrawal period in UNCOVER-2, long-term extension period in UNCOVER-3	**Intervention** 80 mg of ixekizumab every 2 weeks after a starting dose of 160 mg at week 0. Subcutaneous injection. Injection with placebo to match active treatments **UNCOVER-2** n: 351 *Drop-out rate (12 weeks), n (%)* n: 9/351 (2.6%) *Baseline characteristics* Female/Male, (%) n: 27.0%/63.0% Ethnicity (Caucasian), % n: 94.3% BMI, kg/m^2±SD n: 30±7 **UNCOVER-3** n: 385	**Comparison** C: 50 mg etanercept twice weekly, subcutaneous injection **UNCOVER-2** n: 358 *Drop-out rate (12 weeks), n (%)* : 25/358 (7.0%) *Baseline characteristics* Female/Male, (%) 34.1%/65.9% Ethnicity (Caucasian), % 93.5% BMI (kg/m^2), mean±SD 31±7, (n=2 missing) **UNCOVER-3** n: 382 *Drop-out rate (12 weeks), n (%)* 13/382 (3.4%) *Baseline characteristics* Female/Male, (%)	**Analysis model** ITT Safety population included all patients who received ≥1 dose of test substance or placebo *Missing values* For categorical variables: NRI **Results UNCOVER-2** **Week 12** *PASI ≥75, n (%) - primary endpoint* I: 315/351 (89.7%) C: 149/358 (41.6%) *PASI ≥90, n (%)* I: 248/351 (70.7%) C: 67/358 (18.7%) *PASI 100, n (%)* I: 142/351 (40.5%) C: 19/358 (5.3%) DLQI change from baseline, mean±SE	**Adverse events** Pooled data for UNCOVER-1, UNCOVER-2 and UNCOVER-3 (except AEs for etanercept treated patients) reported in [2] **AE:s for etanercept treated patients** **Week 0-12** *Any AE* 54% *Serious AE* 2% *Common AEs* *Nasopharyngitis* *7 %* URTI 5% *Injection site reaction* *11%* *Arthralgia* 2% *Headache* 4%	**Risk of bias** Acceptable **Comment** Study funded, designed and carried out with the involvement of Eli Lilly

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
		Drop-out rate (12 weeks), n (%) n: 22/385 (5.7%) *Baseline characteristics* Female/Male, (%) n: 34.0%/66.0% Ethnicity (Caucasian), % n: 93.8% BMI (kg/m^2), mean±SD n: 30±7 The studies also included control groups treated with placebo	29.6%/70.4% Ethnicity (Caucasian), % 91.9% BMI (kg/m^2), mean±SD 31±8	I: -10.4±0.3, 351 C: -7.7±0.3, 358 **Results UNCOVER-3** **Week 12** *PASI ≥75, n (%) - primary endpoint* I: 336/385 (87.3%) C: 204/382 (53.4%) *PASI ≥90, n (%)* I: 262/385 (68.1%) C: 98/382 (25.7%) *PASI 100, n (%)* I: 145/385 (37.7%) C: 28/382 (7.3%) DLQI change from baseline, mean±SE I: -10.2±0.2, 385 C: --8.0±0.2, 382		

BSA - body-surface area; DLQI - dermatology life quality index; EQ-5D – EuroQoL 5-Dimension health status; IGA – investigator's global assessment; ITT – intention to treat; NRI – non-responder imputation; PASI – psoriasis area and severity index; pp – palmoplantar psoriasis; SD – standard deviation; SE – standard error; sPGA – static physician's global assessment; URTI – upper respiratory tract infection

Table 7.9. Ixekizumab versus Ustekinumab

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Reich et al 2017 [121] Multicentre studies carried out at 51 sites in 13 countries. Study name IXORA-S RCT	**Population** Adult patients (≥18 years) with chronic plaque psoriasis (diagnosis ≥6 months), and PASI ≥10. Had previously failed phototherapy and/or systemic therapy. *Baseline characteristics* *Female/Male*, (%) I: 33.8%/66.2% C: 32.5%/67.5% *Ethnicity (Caucasian),* n, % I:125/136 (93.3%) C: 157/166 (95.7%) *Age* *mean (SD)* I: 42.7 (12.7) C: 44.0 (13.3) *Weight (kg),* mean (SD) I: 85.8 (20.3) C: 89.4 (24.8) *Weight>100 kg, n (%)* I: 31/136 (23.0%) C: 45/166 (27.1%) *BMI, (kg/m²),* mean (SD) I: 28.8 (5.6)	**Intervention** 80 mg of ixekizumab, subcutaneous injection, every 2 weeks, through week 12, after a starting dose of 160 mg at week 0. Thereafter 80 mg every 4 week until week 52. Injection with placebo to match active comparison treatment n: 136 *Drop-out rate (12 weeks), n (%)* n: 4/136 (2.9%)	**Comparison** Ustekinumab, subcutaneous injections, at weeks 0, 4, 16, 28 and 40, per label. Patients ≤ 100 kg receiving 45 mg and patients > 100 kg receiving 90 mg. Injection with placebo to match intervention treatment n: 166 *Drop-out rate (12 weeks), n (%)* n: 2/166 (1.2%)	**Analysis model** ITT Safety population included all patients who received ≥1 dose of test substance (I: n=135; C: n=166) *Missing values* NRI **Results (Week 12)** *PASI 75, n (%)* - I: 120/136 (88.2%) C: 114/166 (68.7%) P<0.001 *PASI 90, n (%)* - I: 99/136 (72.8%) C: 70/166 (42.2%) P<0.001 *PASI 100, n (%)* - I: 49/136 (36.0%) C: 24/166 (14.5%) P=0.009	**Adverse events** **AE:s through week 24** *Any AE* I: 94/135 (69.6%) C: 125/166 (75.3%) P=0.299 *Severe AE* I: 6/135 (4.4%) C: 10/166 (6.0%) P=0.613 *Infections* I: 57/135 (42.2%) C: 87/166 (52.4%) P=0.083 *Common AEs reported by ≥5% of patients in any treatment group* *Nasopharyngitis* I: 33/135 (24.4%) C: 45/166 (21.7%) *Headache* I: 10/135 (7.4%) C: 13/166 (7.8%)	**Risk of bias** Acceptable **Comment** Study fully funded by Eli Lilly

	C: 29.7 (7.0) **Study period** Oct 21, 2015 – Aug 3, 2016 **Follow-up** Induction period: 12 weeks, thereafter extension period up to 52 weeks.			*DLQI (% patients receiving a score of 0 or 1)* I: 83/136 (61.0%) C: 74/166 (44.6%) P=0.012 **Results (Week 24)** *PASI 75, n (%)* - I: 124/136 (91.2%) C: 136/166 (81.9%) P=0.015 *PASI 90, n (%)* - I: 113/136 (83.1%) C: 98/166 (59.0%) P<0.001 *PASI 100, n (%)* - I: 67/136 (49.3%) C: 39/166 (23.5%) P=0.001 *DLQI (% patients receiving a score of 0 or 1)* I: 90/136 (66.2%) C: 88/166 (53.0%) P=0.030	*Arthralgia* I: 6/135 (4.4%) C: 10/166 (6.0%)	

AE – adverse event; BMI – body mass index; CDLQI – children's DLQI; CI – confidence interval; DLQI – dermatology life quality index; ITT – intention-to-treat; LOCF – last observation carried forward; n.g. – not given; NRI – non-responder imputation; OLE – open-label extension; PASI – psoriasis area and severity index; PGA – physician's global assessment; RCT – randomised controlled trial; SD – standard deviation; SE – standard error; TNF – tumour necrosis factor; URTI – upper respiratory tract infection

Table 7.10. Secukinumab versus placebo

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Langley et al 2014 [98] Study name: ERASURE Multicentre study carried out at 88 sites worldwide	**Population** Patients ≥18 years of age with plaque psoriasis diagnosis (≥6 months). PASI score ≥12, modified IGA score of ≥3, BSA ≥10% **Study period** June 2011–April 2013 **Follow-up** 12-weeks induction period, 40 weeks maintenance period, and 8 week follow-up period	**Intervention** 300 mg secukinumab Subcuntaneous injections at baseline, week 1, 2, 3, 4 then every 4 weeks until week 48. Placebo injections to match active treatments as required n=245 *Drop-out rate (week 12), n (%)* 7/245 (2.9%) *Baseline characteristics* Male: 69.0% Ethnicity (Caucasian): 69.8% BMI kg/m^2 ±SD: 30.3±7.2 Age (yr) mean±SD: 44.9±13.5	**Comparison** Placebo Placebo injections to match active treatments as required n=248 *Drop-out rate (week 12), n (%)* 16/248 (6.5%) *Baseline characteristics* Male: 69.4% Ethnicity (Caucasian): 71.0% BMI kg/m^2 ±SD: 30.3±7.8 Age (yr) mean±SD: 45.4±12.6	**Analysis method** ITT for efficacy outcomes Per protocol: PASI score *Missing data* NRI Safety endpoints were evaluated for all patients who received ≥1 treatment dose **Results – week 12** *PASI ≥75, n (%) – primary endpoint* I: 200/245 (81.6%) C: 11/246 (4.5%) I vs C: p<0.001 *PASI ≥90, n (%)t* I: 145/245 (59.2%) C: 3/246 (1.2%) I vs C: p<0.001 *PASI 100, n (%)* I: 70/245 (28.6%) C: 2/246 (0.8%) I vs C: p<0.001	**Adverse events** ***Induction period – week 0–12*** *Any AE, n (%)* I: 135/245 (55.1%) C: 116/247 (47.0%) *Death, n (%)* I, C: 0 *Serious AE, n (%)* I: 6/245 (2.4%) C: 4/247 (1.6%) *Discontinuation due to AE, n (%)* I: 3/245 (1.2%) C: 4/247 (1.6%) *Infection or infestation, n (%)* I: 72/245 (29.4%) C: 40/247 (16.2%) *Common adverse events (affected more than 2%)* *Nasopharyngitis, n (%)* I: 22/245 (9.0%)	**Risk of Bias** Acceptable **Comment** Novartis Pharmaceuticals funded, designed and were involved in carrying out the study and writing the manuscript. Co-primary end points were analysed with stratification by geographic region and body weight

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
				DLQI change (week 0 vs 12) I: -11.4 C: -1.1	C: 19/247 (7.7%) *Headache, n (%)* I: 12/245 (4.9%) C: 7/247(2.8%) *Pruritus, n (%)* I: 9/245 (3.7%) C: 5/247 (2.0%) *URTI, n (%)* I: 9/245 (3.7%) C: 0/247 (0%) *Fatigue, n (%)* I: 2/245 (0.8%) C: 2/247 (0.8%) *Influenza-like illness, n (%)* I: 5/245 (2.0%) C: 3/247 (1.2%) *Hypertension, n (%)* I: 0/245 (0%) C: 3/247 (1.2%) Oropharyngeal pain, n (%) I: 4/245 (1.6%) C: 3/247 (1.2%)	

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Langley et al 2014 [98] Study name: FIXTURE Multicentre study carried out at 231 sites worldwide.	**Population** Patients ≥18 years of age with plaque psoriasis diagnosis (≥6 months). PASI score ≥12, modified IGA score of ≥3, BSA ≥10%. Treatment naïve to etanercept **Study period** June 2011–June 2013 **Follow-up** 12-weeks induction period, 40 weeks maintenance period, and 8 week follow-up period	**Interventon** 300 mg secukinumab Subcuntaneous injections at baseline, week 1, 2, 3, 4 then every 4 weeks until week 48. Placebo injections to match active treatments as required n=327 *Drop-out rate (week 12), n (%)* 15/327= 4.6% *Baseline characteristics* Female/Male, % 31.5%/68.5% Ethnicity (Caucasian): 68.5% BMI (kg/m^2), mean±SD: 28.4±6.4 Age (yr) mean±SD: 44.5±13.2 The study also included an intervention group treated with etanercept	**Comparison** C: placebo . Placebo injections to match active treatments as required n=326 *Drop-out rate (week 12), n (%)* 25/326=7.7% Baseline characteristics Female/Male, % 27.3%/72.7% Ethnicity (Caucasian) 66.9% BMI (kg/m^2), mean ±SD 27.9±6.1 Age (yr) mean±SD: 44.1±12.6	**Analysis method** ITT for efficacy outcomes Per protocol: PASI score *Missing data* NRI Safety endpoints were evaluated for all patients who received ≥1 treatment dose **Results – week 12** *PASI ≥75, n (%) – primary endpoint* I: 249/323 (77.1%) C: 16/324 (4.9%) I vs C: p<0.001 *PASI ≥90, n (%)* I: 175/323 (54.2%) C: 5/324 (1.5%) I vs C: p<0.001 *PASI 100, n (%)* I: 78/323 (24.1%) C: 0/324 (0%) No comparison done with C, since there were no patients with a	**Adverse events** ***Induction period – week 0-12*** *Any AE, n (%)* I: 181/326 (55.5%) C: 163/327 (49.8%) *Death, n (%)* I, C: 0 *Serious AE, n (%)* I: 4/326 (1.2%) C: 6/327 (1.8%) *Discontinuation due to AE, n (%)* I: 4/326 (1.2%) C: 3/327 (0.9%) *Infection or infestation, n (%)* I: 87/326 (26.7%) C: 63/327 (19.3%) *Common adverse events (affected more than 2%)* *Nasopharyngitis, n (%)* I: 35/326 (10.7%) C: 26/327 (8.0%)	**Risk of Bias** Acceptable **Comment** Novartis Pharmaceuticals funded, designed and were involved in carrying out the study and writing the manuscript. Co-primary end points were analysed with stratification by geographic region and body weight.

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
				response in the placebo group *DLQI change (week 0 vs 12)* I: -10.4 C: -1.9	*Headache, n (%)* I: 30/326 (9.2%) C: 23/327 (7.0%) *Diarrhoea, n (%(* I: 17/326 (5.2%) C: 6/327 (1.8%) *Pruritus, n (%)* I: 8/326 (2.5%) C: 11/327 (3.4%) *Arthralgia, n (%)* I: 5/326 (1.5%) C: 10/327 (3.1%) *URTI, n (%)* I: 7/326 (2.1%) C: 3/327 (0.9%) *Back pain, n (%)* I: 8/326 (2.5%) C: 6/327 (1.8%) *Cough, n (%)* I: 11/326 (3.4%) C: 4/327 (1.2%) *Hypertension, n (%)* I: 5/326 (1.5%) C: 4/327 (1.2%) Nausea, n (%) I: 8/326 (2.5%)	

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
					C: 7/327 (2.1%) Oropharyngeal pain, n (%) I: 9/326 (2.8%) C: 7/327 (2.1%)	
Blauvelt *et al* 2015 [122] Multicentre study carried out at 32 centres in North America and Europe. Study name FEATURE RCT	**Population** *Inclusion criteria* Patients ≥18 years of age with plaque psoriasis (diagnosis ≥6 months), PASI score ≥12, 2011 modified investigators global assessment (IGA mod 2011) score ≥3, BSA involvement ≥10% Randomisation was stratified by body weight (≥90 kg or >90kg) *Baseline characteristics* *Female/Male, %* I: 35.6%/64.4% C: 33.9%/66.1% *Ethnicity (Caucasian), %* I: 91.5% C: 96.6% *Body weight (kg), mean±SD* I: 92.6±25.94	**Intervention** 300 mg secukinumab Subcutaneous injections at baseline, week 1, 2, 3 and every 4th week from week 4 n =59 Drop-out rate 3/59= 5.1%	**Comparison** Placebo Subcutaneous injections at baseline, week 1, 2, 3 and every 4th week from week 4 n=59 Drop-out rate 3/59= 5.1%	**Analysis method** No information **Results (12 weeks)** PASI ≥75 (week 12), n (%) – primary endpoint I: 75.9% C: 0% I vs C: p<0.0001 PASI ≥90, (%) I: 60.3% C: 0% I vs C: p<0.0001 PASI 100, (%) I: 43.1% C: 0% I vs C: p<0.0001	**Adverse events** *AE, n (%)* I: 30/59 (50.8%) C: 28/59 (47.5%) *Death, n (%)* I: 0/59 (0%) C: 0/59 (0%) *Serious AE, n (%)* I: 3/59 (5.1%) C: 1/59 (1.7%) *Discontinuation due to AE, n (%)* I: 1/59 (1.7%) C: 1/59 (1.7%) *Injection site reactions, n (%)* I: 1/59 (1.7%) C: 1/59 (1.7%) Candidiasis, n (%) I: 2/59 (3.4%) C: 0/59 (0%)	**Risk of bias** Acceptable **Comments** Study funded by Novartis Pharmaceuticals Patients injected substance themselves, but during week 0-12 weeks all injections were monitored at a study site.

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	C: 88.4±21.55 Age (yr) mean±SD: I: 45.1±12.57 C: 46.5±14.14 **Study period** May 2012 – January 2013 **Follow-up** 12-week placebo-controlled treatment phase. Maintenance (12–52 weeks), optional treatment extension (week 52–208), and 8-week treatment follow-up. Efficacy data here reported for the placebo-controlled phase				*Common AEs* *Diarrhoea, n (%)* I: 5/59 (8.5%) C: 1/59 (1.7%) *Nasopharyngitis, n (%)* I: 3/59 (5.1%) C: 5/59 (8.5%) *Headache, n (%)* I: 0/59 (0%) C: 3/59 (5.1%) *Pyrexia, n (%)* I:2/59 (3.4%) C: 2/59 (3.4%) *Back pain, n (%)* I: 3/59 (5.1%) C: 0/59 (0%) *Bursitis, n (%)* I: 2/59 (3.4%) C: 0/59 (0%) *Cough, n (%)* I: 1/59 (1.7%) C: 0/59 (0%) *Depression, n (%)* I:1/59 (1.7%) C: 0/59 (0%)	

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
					Nausea, n (%) I: 3/59 (5.1%) C: 1/59 (1.7%) *Oropharyngeal pain, n (%)* I: 1/59 (1.7%) C: 0/59 (0%) *Rhinitis, n (%)* I: 1/59 (1.7%) C: 0/59 (0%)	
Gottlieb et al 2016 [124] This article is an open lable extension (OLE) from the FEATURE trial, [122]	**Population** Reported in [122] **Follow-up** Placebo-controlled phase 0–12 weeks (presented in [122]), OLE for up to 52 weeks presented here	**Intervention** 300 mg secukinumab Subcutaneous injections at baseline, week 1, 2, 3 and every 4th week from week 4 *Number of patients in safety population for intervention at week 52:* n=86		*Effects from OLE-studies are not reported*	**Adverse events** *AE, n (%)* 64/86 (74.4%) *Serious AE, n (%)* 5/86 (5.8%) Death, n (%) 1/86 (1.2%) *Discontinuation due to AE, n (%)* 3/86 (3.5%) *Common AEs reported by ≥5% of patients in any treatment group* *Nasopharyngitis, n (%)* 10/86 (11.6%)	**Risk of bias** Not assessed **Comment** Study funded by Novartis Pharmaceuticals

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
					Headache, n (%) 2/86 (2.3%) *Cough, n (%)* 6/86 (7.0%) URTI, n (%) 7/86 (8.1%) *Diarrhea, n (%)* 6/86 (7.0%) Neutropenia, ≥ grade 2, n (%) 1/86 (1.2%) Candidiasis, n (%) 3/86 (3.5%) Severe infections, n (%) 4/86 (4.7%)	
Paul *et al* 2015 [123] Multicentre study carried out at 38 worldwide. Study name JUNCTURE RCT	**Population** Patients ≥18 years of age with plaque psoriasis (diagnosis ≥6 months), PASI score ≥12, 2011 modified investigators global assessment (IGA mod 2011) score ≥3, BSA involvement ≥10% Randomisation was stratified by body	**Intervention** 300 mg secukinumab Subcutaneous injections at baseline, week 1, 2, 3 and every 4th week from week 4 n =60 Drop-out rate, week 0-12: 0/60= 0%	**Comparison** Placebo Subcutaneous injections at baseline, week 1, 2, 3 and every 4th week from week 4 n=61 Drop-out rate, week 0-12: 2/61= 3.3%	**Analysis method** ITT *Missing data* NRI **Results (12 weeks)** PASI 75, n (%) I: 86.7% C: 3.3% I vs C: p<0.0001	**Adverse events** *AE, n (%)* I: 42/60 (70.0%) C: 33/61 (54.1%) *Serious AE, n (%)* I: 1/60 (1.7%) C: 1/61 (1.7%) *Discontinuation due to AE, n (%)* I: 0/60 (0%) C: 1/61 (1.6%)	**Risk of bias** Acceptable **Comments** Study funded by Novartis Pharmaceuticals and designed by the scientific steering committee and Novartis personnel. Novartis conducted the data analyses.

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	weight (≥90 kg or >90kg) *Baseline characteristics* *Female/Male, %* I: 23.3%/76.7% C: 37.7%/62.3% *Ethnicity (Caucasian)n,(%)* I: 56/60 (93.3%) C: 59/61 (96.7%) *Body weight (kg), mean (SD)* I: 91.0 (23.13) C: 90.2 (21.16) *BMI (kg/m2), mean (SD)* I: 30.0 (6.9) C: 30.0 (6.82) *Age (yr)* *mean (SD)*: I: 46.6 (14.23) C: 43.7 (12.74) **Study period** October 2012 – April 2013 **Follow-up** 12-week placebo-controlled treatment phase. Maintenance (12–52 weeks), optional treatment extension (week 52–208), and 8-			PASI 90, (%) I: 55.0% C: 0% I vs C: p<0.0001 PASI 100, (%) I: 26.7% C: 0% I vs C: p<0.0001	*Common AEs reported by ≥5% of patients in any treatment group* *Nasopharyngitis, n (%)* I: 19/60 (31.7%) C: 10/61 (16.4%) *Headache, n (%)* I: 3/60 (5.0%) C: 3/61 (4.9%) *Pruritus, n (%)* I: 5/60 (8.3%) C: 2/61 (3.3%) *Sinusitis, n (%)* I: 3/60 (5.0%) C: 0/61 (0.0%) *Cough, n (%)* I: 3/60 (5.0%) C: 2/61 (3.3%) *Hypertension, n (%)* I: 1/60 (1.7%) C: 4/61 (6.6%)	Patients injected substance themselves, by autoinjector

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	week treatment follow-up. Efficacy data here reported for the placebo-controlled phase					
Lacour et al 2017 [125] This article is an open lable extension (OLE) from the JUNCTURE trial, [123]	**Population** Reported in [123] **Follow-up** Placebo-controlled phase 0–12 weeks (presented in [123]), OLE for up to 52 weeks presented here	**Intervention** 300 mg secukinumab Subcutaneous injections at baseline, week 1, 2, 3 and every 4th week from week 4 *Number of patients in safety population for intervention at week 52:* n=88		*Effects from OLE-studies are not reported*	**Adverse events** *AE, n (%)* 78/88 (88.6%) *Serious AE, n (%)* 7/88 (8.0%) *Discontinuation due to AE, n (%)* 0/88 (0.0%) *Common AEs reported by ≥5% of patients in any treatment group* *Nasopharyngitis, n (%)* 35/88 (39.8%) *Headache, n (%)* 10/88 (11.4%) *Pruritus, n (%)* 8/88 (9.1%) *Sinusitis, n (%)* 5/88 (5.7%)	**Risk of bias** Not assessed **Comment** Study funded by Novartis Pharmaceuticals.

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
					Cough, n (%) 9/88 (10.2%) URTI, n (%) 5/88 (5.7%) *Hypertension, n (%)* 6/88 (6.8%) Arthralgia, n (%) 5/88 (5.7%) Oropharyngeal pain, n (%) 5/88 (5.7%) Neutropenia, grade 2/3, n (%) 5/88 (5.7%) Candidiasis, n (%) 4/88 (4.5%) Severe infections, n (%) 2/88 (2.3%)	

AE – adverse event; BSA – body-surface area; BMI – body mass index; DLQI – dermatology life quality index; IGA – investigator's global assessment; ITT – intention-to-treat; NRI – non-responder imputation; PASI – psoriasis area and severity index; SD – standard deviation; SE – standard error; URTI – upper respiratory tract infection

Table 7.11. Secukinumab versus Etanercept

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Langley et al 2014 [98] Study name: FIXTURE Multicentre study carried out at 231 sites worldwide.	**Population** Patients ≥18 years of age with plaque psoriasis diagnosis (≥6 months). PASI score ≥12, modified IGA score of ≥3, BSA ≥10%. Treatment naïve to etanercept **Study period** June 2011–June 2013 **Follow-up** 12-weeks induction period, 40 weeks maintenance period, and 8 week follow-up period	**Interventon** 300 mg secukinumab Subcuntaneous injections at baseline, week 1, 2, 3, 4 then every 4 weeks until week 48. Placebo injections to match active treatments as required n=327 *Drop-out rate (week 12), n (%)* 15/327= 4.6% *Baseline characteristics* Female/Male, % 31.5%/68.5% Ethnicity (Caucasian): 68.5% BMI (kg/m^2), mean±SD: 28.4±6.4 Age (yr) mean±SD: 44.5±13.2	**Comparison** C: 50 mg etancercept Subcuntaneous injections of etancercept twice weekly from baseline to week 12 thereafter once weekly through week 51. Placebo injections to match active treatments as required n=326 *Drop-out rate (week 12), n (%)* 21/326=6.4% Baseline characteristics Female/Male, % 28.8%/71.2% Ethnicity (Caucasian) 67.2% BMI (kg/m^2), mean ±SD 28.7±5.9 Age (yr) mean±SD: 43.8±13.0	**Analysis method** ITT for efficacy outcomes Per protocol: PASI score *Missing data* NRI Safety endpoints were evaluated for all patients who received ≥1 treatment dose **Results – week 12** *PASI ≥75, n (%) – primary endpoint* I: 249/323 (77.1%) C:142/323(44.0%) I vs C: p<0.001 *PASI ≥90, n (%)* I: 175/323 (54.2%) C: 67/323 (20.7%) I vs C: p<0.001 *PASI 100, n (%)* I: 78/323 (24.1%) C: 14/323 (4.3%)	**Adverse events** ***Induction period – week 0-12*** *Any AE, n (%)* I: 181/326 (55.5%) C: 186/323 (57.6%) *Death, n (%)* I, C: 0 *Serious AE, n (%)* I: 4/326 (1.2%) C: 3/323 (0.9%) *Discontinuation due to AE, n (%)* I: 4/326 (1.2%) C: 6 /323 (1.9%) *Infection or infestation, n (%)* I: 87/326 (26.7%) C: 79/323 (24.5%) *Common adverse events (affected more than 2%)* *Nasopharyngitis, n (%)* I: 35/326 (10.7%)	**Risk of Bias** Acceptable **Comment** Novartis Pharmaceuticals funded, designed and were involved in carrying out the study and writing the manuscript. Co-primary end points were analysed with stratification by geographic region and body weight.

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
		The study also included a control group treated with placebo		I vs C: p<0.001 *DLQI change (week 0 vs 12)* I: -10.4 C: -7.9	C: 36/323 (11.1%) *Headache, n (%)* I: 30/326 (9.2%) C: 23/323 (7.1%) *Diarrhoea, n (%(* I: 17/326 (5.2%) C: 11/323 (3.4%) *Pruritus, n (%)* I: 8/326 (2.5%) C: 8/323 (2.5%) *Arthralgia, n (%)* I: 5/326 (1.5%) C: 12/323 (3.7%) *URTI, n (%)* I: 7/326 (2.1%) C: 7/323 (2.2%) *Back pain, n (%)* I: 8/326 (2.5%) C: 9/323 (2.8%) *Cough, n (%)* I: 11/326 (3.4%) C: 4/323 (1.2%) *Hypertension, n (%)* I: 5/326 (1.5%) C: 5/323 (1.5%)	

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
					Nausea, n (%) I: 8/326 (2.5%) C: 4/323 (1.2%) Oropharyngeal pain, n (%) I: 9/326 (2.8%) C: 4/323 (1.2%)	

AE – adverse event; BSA – body-surface area; BMI – body mass index; DLQI – dermatology life quality index; IGA – investigator's global assessment; ITT – intention-to-treat; NRI – non-responder imputation; PASI – psoriasis area and severity index; SD – standard deviation; SE – standard error; URTI – upper respiratory tract infection

Table 7.12. Secukinumab versus Ustekinumab

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Blauvelt A. et al. 2016 [126] Study name CLEAR RCT	**Population** *Inclusion criteria* Patients ≥18 years of age, diagnosed with plaque psoriasis (≥6 months), PASI score ≥12, Investigator's Global Assessment, 2011 modified version (IGA mod 2011) score 3 (moderate) or 4 (severe). BSA affected ≥10% Randomisation was stratified by body weight ≤100 kg or >100 kg <u>*Baseline characteristics*</u> Male (%) I: 68.0% C: 74.3% *Race - Caucasian (%)* I: 88.7% C: 85.0% *Weight (kg±SD)* I: 87.4±19.95 C: 87.2±22.11 *BMI (kg/m²±SD)*	**Intervention** Secukinumab 300 mg dose per injection. Injections at baseline, week 1, 2, 3, and every 4 weeks from week 4 onward. n=337 Drop-outs n (%) 25/337 (7.4%)	**Comparison** Ustekinumab Treatment dose stratified by body weight with a dose of 45 mg of ustekinumab per injection for patients ≤100 kg and 90 mg for patients >100 kg. Injections at baseline, week 4 and then every 12 weeks. Placebo injections to match secukinumab injection regime. n=339 Drop-outs n (%) 41/339 (12.1%)	**Analysis model** ITT (all randomized patients, except one in the intervention group due to problems with informed consent) Safety population: All patients that received at least one dose of study treatment. *Missing data* NRI for PASI and IGA mod 2011 **Results** **Week 16** <u>*PASI≥90, n (%)*</u> Subjects ≤100 kg. I: 214/256 (83.6%) C: 152/252 (60.3%) Subjects >100 kg. I: 50/78 (64.1%) C: 40/83 (48.2%) All subjects (both < and > 100 kg) I: 264/334 (79.0%)	**Adverse events** *C: pooled for 45 and 90 mg /dose regime* *IR: incidence rate per 100 years* *Any AE, n (IR) [95% CI]* I: 286/335 (280.9) [249.3-315.4] C: 278/336 (250.1) [221.6-281.3] *Serious AE, n (IR) [95% CI]* I: 30/335 (9.6) [6.5-13.7] C: 26/336 (8.5) [5.5-12.4] *Death, n (%)* I: 0/335 (0%) C: 1/336 (0.3%) *Discontinued treatment* due to AE, n (%) I: 10/335 (3.0%) C: 9/336 (2.7%)	**Risk of bias** Acceptable **Comment** Study funded by Novartis Pharma The stratification of treatment dose based on body weight means that most patients in the comparison group received 45 mg ustekinumab.

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	I: 29.1±5.87 C: 29.0±6.69 **Study period** **Follow-up** Head-to-head comparison between secukinumab och ustekinumab with 16 weeks as primary endpoint and 52 weeks as secondary.			C: 193/335 (57.6%) I vs C: p <0.001 *DLQI, proportion responders w 0 or 1, all subjects* I: ca 70% C: ca 60% I vs C: p<0.01 **Week 52** *PASI≥90, n (%)* Subjects ≤100 kg. I: 201/256 (78.5%) C: 157/252 (62.3%) Subjects >100 kg. I: 49/78 (62.8%) C: 46/83 (55.4%) All subjects (both < and > 100 kg) I: 247/334 (74.0%) C: 203/335 (60.6%) I vs C: p <0.001 *DLQI, proportion responders w 0 or 1, all subjects* I: 237/331 (71.6%) C: 197/333 (59.2%) I vs C: p=0.008	*Infections and infestations, n (IR)* [95% CI] I: 197/335 (98.4) [85.1-113.1] C: 194/336 (95.8) [82.8-110.3] *Most frequent AEs* *Nasopharygitis, n (IR) [95% CI]* I: 77/335 (27.1) [21.4-33.8] C: 83/336 (31.0) [24.7-38.5] *Headache, n (IR) [95% CI]* I: 40/335 (13.5) [9.7-18.4] C: 41/336 (14.2) [10.2-19.3] *URTI, n (IR) [95% CI]* I: 31/335 (10.1) [6.9-14.3] C: 30/336 (9.9) [6.7-14.2] *Arthralgia, n* (IR) [95% CI] I: 25/335 (8.1) [5.3-12.0]	

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
					C: 28/336 (9.2) [6.1-13.3] *Diarrhoea, n* (IR) [95% CI] I: 23/335 (7.5) [4.7-11.2] C: 24/336 (7.9) [5.1-11.8] *Back pain, n (*IR) [95% CI] I: 22/335 (7.1) [4.4-10.7] C: 26/336 (8.5) [5.6-12.5]	

AE – adverse event; BSA – body-surface area; BMI – body mass index; DLQI – dermatology life quality index; IGA – investigator's global assessment; ITT – intention-to-treat; NRI – non-responder imputation; PASI – psoriasis area and severity index; SD – standard deviation; SE – standard error; URTI – upper respiratory tract infection

Table 7.14. Ustekinumab versus placebo

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Landells *et al* 2015 [127] Multicentre trial carried out at 36 sites in Canada and Europe. RCT	**Population** Patients 12 to 17 years with moderate-to-severe plaque psoriasis (for ≥6 months) with PASI≥12, PGA≥3, and BSA≥10% *Baseline characteristics* Females/Males, % I: 55.6%/44.4% C: 45.9%/54.1% *Body-weight (kg), mean±SD* I: 62.0±17.1 C: 64.7±14.7 *Ethnicity (Caucasian), %* I: 94.4% C: 91.9% **Study period** March 2010 – January 2014 **Follow-up** 12 weeks placebo-controlled phase, through week 52 active treatment phase, follow-up phase	**Intervention** Ustekinumab 0.75 mg/kg for patients with a body weight of ≤60 kg, 45 mg for patients >60 to ≤100 kg, 90 mg dose for patients >100 kg Subcutaneous injections at week 0, 4, 12 week *Randomised pop* n=36 *Drop-out rate, n (%)* 1/36 (2.8%)	**Comparison** Placebo n=37 *drop-out rate, n (%)* 0/37 (0%)	**Model of analysis** ITT Per protocol for AEs *Missing data* NRI for PGA and PASI **Results – week 12** *PASI ≥75, n (%)* I: 29/36 (80.6%) C: 4/37 (10.8%) I vs C: p<0.001 *PASI ≥90, n (%)* I: 22/36 (61.1%) C: 2/37 (5.4%) I vs C: p<0.001 *CDLQI change from baseline, mean±SD, n* I: -6.7±5.6, 32 C: -1.5±3.2. 32 I vs C: p<0.001	**Adverse events** *Patients with ≥1 AE* I: 16/36 (44.4%) C: 21/37 (56.8%) *Discontinued due to AE, n* I: 0/36 (0%) C: 0/37 (0%) *Infections, n (%)* I: 8/36 (22.2%) C: 14/37 (37.8%) *Patients with ≥1 SAE* I: 0/36 (0%) C: 0/37 (0%)	**Risk of Bias** Acceptable **Comment** The study was funded by Janssen Research & Development, LLC Several authors affiliated with Janssen Research & Development, LCC

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	through week 60. Results from placebo-controlled phase reported here					
Lebwohl et al 2010 [128] Efficacy results reported in Leonardi et al 2008 [129] Study name PHOENIX I Multicentre trial carried out in the US, Canada and Belgium. RCT	**Population** Reported in Leonardi et al 2008 [129] **Baseline characteristics** Female/Male, % I1: 32.4%/67.6% I2: 31.4%/68.6% C: 28.2%/71.8% *Body weight (kg), mean±SD* I1: 93.8±23.9 I2: 93.7±23.8 C: 94.2±23.5 **Study period** December 2005 – September 2007 **Follow-up** 12 weeks placebo-controlled phase, followed by active treatment period (weeks 12-40) where placebo group received ustekinumab, followed by a withdrawal period (weeks 40–76). Results	**Intervention** I1: 90 mg ustekinumab I2: 45 mg of ustekiumab *Randomised, n* I1: n=256 I2: n=255 Subcutaneous injection were administered at weeks 0, 4 and every 12 weeks thereafter	**Comparison** C: placebo *Randomised, n* C: n=255 Subcutaneous injections of placebo to match active treatment	**Analysis model** Per protocol **Results** **Week 12** *DLQI change, mean±SD, n* I1: -8.7±6.47, 249 I2: -8.0±6.87, 254 C: -0.6±5.97, 252 I1, I2 vs C: p<0.001 *SF-36 PCS score change, mean±SD, n* I1: 3.2±7.6 I2: 2.0±7.4 C: -0.51±7.5 I1, I2, vs C: p<0.001 *SF-36 MCS score change, mean±SD, n* I1: 2.5±9.5 I2: 2.1±9.3 C: -1.3±7.5 I1, I2, vs C: p<0.001	**Adverse events** Reported in Leonardi et al 2008 [129]	**Risk of bias** Acceptable **Comments** Ustekinumab produced by Centocor, Inc. Study supported by Centocor, Inc. Several of the authors had financial ties/were employed by Centocor, Inc. as well as other pharmaceutical companies

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	from placebo-controlled phase reported here					
Leonardi et al 2008 [129] Quality of life related outcomes reported in Lebwohl et al. 2010 [128] Multicentre trial, conducted at 48 sites in the US, Canada and Belgium Study name PHOENIX I RCT	**Population** Patients ≥18 years of age, with a diagnosis of plaque psoriasis (≥6 months), baseline PASI score ≥12, BSA involvement ≥10%. No other form or psoriasis. Baseline randomisation stratified by investigational site, weight (≤90 kg or >90 kg) *Baseline characteristics* *Female/Male, %* I1: 32.4%/67.6% I2: 31.4%/68.6% C: 28.2%/71.8% *Bodyweight (kg), mean±SD* I1: 93.8±23.9 I2: 93.7±23.8 C: 94.2±23.5 **Study period** December 2005 – September 2007	**Intervention** I1: 90 mg ustekinumab I2: 45 mg of ustekiumab Subcutaneous injection were administered at weeks 0, 4 and every 12 weeks thereafter *Randomised, n* I1: 256 I2: 255 *Drop-out rate (week 12), n (%)* I1: 11/256 (4.3%) I2: 2/255 (0.8%)	**Comparison** C: placebo Subcutaneous injections of placebo to match active treatment Randomised, n C: 255 Drop-out rate (week 12), n (%) C: 12/255 (4.7%)	**Analysis model** ITT for efficacy outcomes Per protocol (≥1 dose of test substance) for safety analyses **Results – week 12** *PASI ≥50, n (%)* I1: 220/256 (85.9%) I2: 213/255 (83.5%) C: 26/255 (10.2%) I1, I2 vs C: p<0.0001 *PASI ≥75, n (%)* I1: 170/256 (66.4%) I2: 171/255 (67.1%) C: 8/255 (3.1%) I1, I2 vs C: p<0.0001 *PASI ≥90, n (%)* I1: 94/256 (36.7%) I2: 106/255 (41.6%) C: 5/255 (2.0%) I1, I2 vs C: p<0.0001 *PASI100, n (%)* I1: 28/256 (10.9%) I2: 32/255 (12.5%) C: 0/255 (0.0%) I1, I2 vs C: p<0.0001	**Adverse Events** AEs - week 0–12 *Patients with ≥1 AE, n (%)* I1: 131/255 (51.4%) I2: 147/255 (57.6%) C: 123/255 (48.2%) *AEs leading to withdrawal, n (%)* I1: 4/255 (1.6%) I2: 1/255 (0.4%) C: 6/255 (2.4%) *Serious AEs, n (%)* I1: 2/255 (0.8%) I2: 4/255 (1.6%) C: 2/255 (0.8%) *Common AEs* *URTI, n (%)* I1: 16/255 (6.3%) I2: 18/255 (7.1%) C: 16/255 (6.3%) *Nasopharyngitis, n (%)* I1: 21/255 (8.2%) I2: 26/255 (10.2%) C: 22/255 (8.6%)	**Risk of bias** Acceptable **Comment** Study funded by Centocor Inc. who was also involved in the design of the study, carried out the analysis. Several authors have been affiliated with or have financial ties to Centocor inc. or other pharmaceutical companies.

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	Follow-up 12 weeks placebo-controlled phase, followed by active treatment period (weeks 12–40), followed by a withdrawal period (weeks 40-76) and a long term extension period through week 264. Efficacy results from placebo-controlled phase reported here.				*Arthralgia, n (%)* I1: 6/255 (2.4%) I2: 7/255 (2.7%) C: 7/255 (2.7%) *Headache, n (%)* I1: 13/255 (5.1%) I2: 14/255 (5.5%) C: 6/255 (2.4%)	
Kimball et al 2013 [133] This article is an open lable extension (OLE) from the PHOENIX I trial, [129] and [128]	**Population** Reported in [129] and [128] 68.7% (n = 517) completed study agent through the last Year-5 dose at or before Week 244 **Follow-up** Placebo-controlled phase 0–12 weeks (presented in [129] and [128]), OLE for up to 5 years presented here	**Intervention** I1: 90 mg ustekinumab I2: 45 mg of ustekiumab Subcutaneous injection were administered at weeks 0, 4 and every 12 weeks thereafter. *Number of patients in safety population for intervention at week 244:* n=753		*Effects from OLE-studies are not reported*	**Adverse events** *Patients treated:* 753 *Patient years (follow-up):* 3104.2 *Key safety events per 100 patient-years of follow-up through year 5:* *AE*: 214.94 *Serious AE:* 5.35 *Discontinuation due to AE:* 2.13	**Risk of bias** Not assessed **Comment** Study funded by Janssen Research & Development, LLC, Spring House, PA, USA

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
					Infections: 82.66 Infections requiring treatment: 29.41 Serious infections: 1.03 Malignant neoplasms: 0.93 Non-melanoma skin cancer (NMSC): 0.45 Other malignancies (exklucding NMSC): 0.48 Major adverse cardiovascular event (MACE): 0.32	
T-F Tsai et al 2011 [131] Multicentre study carried out at 13 sites in Taiwan and Korea Study name PEARL RCT	**Population** Patients (≥20 year of age with Korean or Taiwanese ancestry), with moderate-to-severe plaque psoriasis and PASI score ≥12, BSA involvement ≥10% *Baseline characteristics* *Female/Male, %* I: 18.0%/82.0% C: 11.7%/88.3%	**Intervention** I: Ustekinumab 45 mg. Subcutaneous injections weeks 0, 4, 16 and placebo at week 12 n=61 *Drop-out rate (12 weeks), n (%)* 4/61 (6.6%)	**Comparison** C: placebo. Subcutaneous injections week 0 and 4, crossover to ustekinumab 45 mg at week 12 and 16 n=60 *Drop-out rate (12 weeks), n (%)* 5/60 (8.3%)	**Analysis model** ITT for efficacy outcomes through week 12. Per protocol analysis after week 12 **Results** **Week 12** *PASI ≥75 – primary endpoint, n (%)* I: 41/61 (67.2%) C: 3/60 (1.7%)	**Adverse effects** **AEs week 0–12** *Patients with ≥1 AE, n (%)* I: 40/61 (65.6%) C: 42/60 (70.0%) *AE leading to withdrawal, n (%)* I: 0/61 (0.0%) C: 3/60 (5.0%) *Patients with SAE, n (%)*	**Risk of bias** Acceptable **Comments** Study funded by Centocor Inc., who also provided statistical analysis and writing assistance

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	Ethnicity, n (%) *Taiwanese/Chinese* I: 49.2% C: 50.0% *Korean* I: 50.8% C: 50.0% *BMI (kg/m^2), n (%)* *Normal (BMI<25)* I: 29/61 (47.5%) C: 33/60 (55.0%) *Overweight (BMI ≥25, <30)* I: 27/61 (44.3%) C: 21/60 (35.0%) *Obese (BMI ≥30)* I: 5/61 (8.2%) C: 6/60 (10.0%) **Study period** December 2008 – March 2010 **Follow-up** Placebo-controlled phase 0–12 weeks. At 12 weeks placebo group received active treatment, both I and C 45 mg ustekinumab. Results from placebo-			I vs C: p<0.001 *PASI ≥50, n (%)* I: 51/61 (83.6%) C: 8/60 (13.3%) I vs C: p<0.001 *PASI ≥90, n (%)* I: 30/61 (49.2%) C: 1/60 (1.7%) I vs C: p<0.001 *PASI 100, n (%)* I: 5/61 (8.2%) C: 0/60 (0.0%) I vs C: 0.024 DLQI change from baseline mean±SD, n I: -11.2±7.1, 59 C: -0.5±6.5, 60 I vs C: p<0.001	I: 0/61 (0.0%) C: 2/60 (3.3%) *Common AEs* *URTI, n (%)* I: 7/61 (11.5%) C: 7/60 (11.7%) *Hyperglycemia, n (%)* I: 5/61 (8.2%) C: 5/60 (8.3%) *Nasopharyngitis, n (%)* I: 5/61 (8.2%) C: 3/60 (5.0%) *Pruritus, n (%)* I: 5/61 (8.2%) C: 16/60 (26.7%) *Cough, n (%)* I: 4/61 (6.6%) C: 3/60 (5.0%) *Eosinophilia, n (%)* I: 2/61 (3.3%) C: 2/60 (3.3%) *Psoriasis, n (%)* I: 2/61 (3.3%) C: 6/60 (10.0%) *Anaemia, n (%)* I: 1/61 (1.6%)	

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	controlled phase reported here				C: 1/60 (1.7%) *Injection site reactions, n (%)* I: 1/61 (1.6%) C: 3/60 (5.0%) *Eczema, n (%)* I: 0/61 (0.0%) C: 0/60 (0.0%) *Abnormal hepatic function, n (%)* I: 0/61 (0.0%) C: 2/60 (3.3%) *Psoriatic arthropathy, n (%)* I: 0/61 (0.0%) C: 3/60 (5.0%)	
Papp et al 2008 [130] Multicentre study carried out at 70 sites in Europe (Austria, France, Germany, Switzerland and UK) and North America (Canada and USA). Study name PHOENIX 2	**Population** Patients (≥18 years old) with a diagnosis of plaque psoriasis (≥6 months), with a PASI score of ≥12, BSA involvement ≥10% *Baseline characteristics* *Female/Male, %* I1: 30.8%/69.2% I2: 33.3%/66.7% C: 31.0%/69.0% *Ethnicity*	**Intervention** I1: 45 mg ustekinumab I2: 90 mg ustekinumab Subcutaneous injections of ustekinumab at week 0, 4 (placebo-controlled phase), and week 12, 16 and every 12 weeks thereafter. *Randomised population* I1: n=409 I2: n=411	**Comparison** C: placebo After 12 weeks patients were re-randomised to active treatment (45 mg or 90 mg ustekinumab every 12 weeks) *Randomised population* C: n=410 *Drop-out rate (week 0-12)*	**Analysis model** ITT Safety population: patients who received ≥1 dose of substance **Results** **Week 12** *PASI ≥50, n (%)* I1: 342/409 (83.6%) I2: 367/411 (89.3%) C: 41/410 (10.0%) I1, I2 vs C: p<0.0001	**Adverse events** **AEs week 0-12** *Patients with ≥1 AE, n (%)* I1: 217/409 (53.1%) I2: 197/411 (47.9%) C: 204/410 (49.8%) *AEs leading to withdrawal, n (%)* I1: 1/409 (0.2%) I2: 6/411 (1.5%)	**Risk of bias** Acceptable **Comments** Study funded by Centocor Inc., Centocor was involved in the design of the study and data analysis

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
RCT	No information *Bodyweight (kg), mean±SD* I1: 90.3±21.0 I2: 91.5±21.3 C: 91.1±21.6 Randomisation was stratified based by investigational site and bodyweight (≤90 kg, or >90 kg), and history of response, intolerance, or contraindication to more/less than three conventional therapies. **Study period** March 2007 – September 2007 **Follow-up** Placebo-controlled phase week 0–12, followed by a crossover phase were all groups received active treatment (week 12–28), and a randomised dose intensification phase (week 28–52). Results from placebo-controlled phase reported here	*Drop-out rate (week 0-12)* I1: 6/409=1.5% I2: 9/411=2.2%	C: 18/410=4.4%	*PASI ≥75, n (%) – primary endpoint* I1: 273/409 (66.7%) I2: 311/411 (75.7%) C: 15/410 (3.7%) I1, I2 vs C: p<0.0001 *PASI ≥90, n (%)* I1: 173/409 (42.3%) I2: 209/411 (50.9%) C: 3/410 (0.7%) I1, I2 vs C: p<0.0001 *PASI 100, n (%)* I1: 74/409 (18.1%) I2: 75/411 (18.2%) C: 0/410 (0.0%) I1, I2 vs C: p<0.0001 *DLQI change, mean±SD; median [IQR], n* I1: -9.3±7.12, -8.00 (-14.0, -4.0), 401 I2: -10.0±6.67, -9.00 (-14.0, -5.0), 402 C: -0.5±5.66; -0.50 (-4.0, 3.0), 400 I1, I2 vs C: p<0.0001	C: 8/410 (2.0%) *Serious AEs, n (%)* I1: 8/409 (2.0%) I2: 5/411 (1.2%) C: 8/410 (2.0%) Common adverse events, week 0-12 presented here *Arthralgia, n (%)* I1: 14/409 (3.4%) I2: 10/411 (2.4%) C: 12/204 (2.9%) *Cough, n (%)* I1: 3/409 (0.7%) I2: 4/411 (1.0%) C: 7/410 (1.7%) *Headache, n (%)* I1: 19/409 (4.6%) I2: 19/411 (4.6%) C: 17/410 (4.1%) *Injection site erythema, n (%)* I1: 6/409 (1.5%) I2: 6/411 (1.5%) C: 1/410 (0.2%) *Nasopharyngitis, n (%)* I1: 30/409 (7.3%) I2: 28/411 (6.8%)	

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
					C: 29/410 (7.1%) *URTI, n (%)* I1: 18/409 (4.4%) I2: 12/411 (2.9%) C: 14/410 (3.4%)	
Papp et al 2013 [132] OLE – after ACCEPT [134] and PHOENIX I and II [130]	**Population** For inclusion criteria, see [134] and [130] **Follow up** 5 yrs *Drop-out rate* 1482/3117 patients completed ≥4 yrs of treatment and follow up 838/3117 patients completed ≥5 yrs of treatment and follow up	**Intervention** I1: Ustekinumab 45 mg I2: Ustekinumab 90 mg S.c. injections every 12 weeks. I1: n=1319 I2: n=2001 *Total n patient yrs exposure to Ustekinumab:* I1: 3776 yrs I2: 5232 yrs		**Analysis model** All patients receiving ≥1 dose of study drug included	**Adverse events** *Expressed as event rates of n events/100 patient yrs of exposure to ustekinumab* *Adverse events* I1: 242.6 I2: 225.3 *Serious adverse events:* I1: 7.0 I2: 7.2 *AE:s leading to discontinuation:* I1: 2.4 I2: 2.5 *Infections, any* I1: 89.8 I2: 84.1 *<u>Serious AE:s occurring ≥1/100 patient yrs</u>* *Serious infections* I1: 0.9 I2: 1.2 *Cardiac disorders* I1: 1.1 I2: 1.1	**Risk of bias** Not assessed **Comment** Results from OLE:s were not assessed for bias as only observational data of AE:s were collected.

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
					Malignancies I1: 1.2 I2: 1.1 *<u>Common adverse events occurring ≥5/100 patient yrs</u>* *Nasopharyngitis* I1: 21.0 I2: 20.6 *URTI* I1: 17.4 I2: 15.4 *Headache* I1: 7.5 I2: 6.8 *Arthralgia* I1: 5.0 I2: 4.5	

AE – adverse events; BSA – body surface area; CDLQI – children's dermatology life quality index; DLQI – dermatology life quality index; ITT – intention-to-treat; IQR – Interquartile range; MCS; mental component summary score; NRI – non-responder imputation; PASI – psoriasis area and severity index; PCS – physical component summary score; PGA – physician's global assessment; SD – standard deviation; SE – standard error; URTI – upper respiratory tract infection

Table 7.14. Ustekinumab versus Etanercept

First Author **Year** **Reference** **Country** **Study design**	**Population** **Setting** **Study period** **Follow-up (FU)**	**Intervention**	**Comparison**	**Analysis model** **Results**	**Adverse events**	**Risk of bias** **Comment**
Griffiths et al 2010 [134] Multicentre study carried out at 67 sites worldwide RCT	**Population** Patients (≥18 year of age), with plaque psoriasis (diagnosis ≥6 months, no other form of psoriasis permitted), with PASI score ≥12, PGA score ≥3, BSA involvement ≥10% *Baseline characteristics* *Female/Male%* I1: 36.4%/63.6% I2: 32.6%/67.4% C: 29.1%/70.9% *Ethnicity (Caucasian), %* I1: 92.3% I2: 89.0% C: 91.1% *Bodyweight (kg), mean±SD* I1: 90.8±20.9 I2: 90.4±21.1 C: 91.0±22.8 Randomisation stratified according to site and bodyweight (<90 kg, ≥90 kg) **Study period**	**Intervention** I1: 45 mg ustekinumab I2: 90 mg ustekinumab Subcutaneous injections at 0 and 4 weeks I1: n=209 I2: n=347 *Drop-out rate (week 12), n (%)* I1: 8/209 (3.8%) I2: 5/347 (1.4%)	**Comparison** C: 50 mg etanercept, subcutaneous injections twice weekly for 12 weeks C: n=347 *Drop-out rate (week 12), n (%)* C: 11/347 (3.2%)	**Analysis model** ITT for efficacy outcomes Per protocol for safety outcomes **Results (week 12)** PASI ≥90, n (%) I1: 76/209 (36.4%) I2: 155/347 (44.7%) C: 80/347 (23.1%) I1 vs C: p<0.001 I2 vs C: p<0.001 PASI ≥75, n (%) – primary endpoint I1: 141/209 (67.5%) I2: 256/347 (73.8%) C: 197/347 (56.8%) I1 vs C: p=0.01 I2 vs C: p<0.001	**Adverse Events** **Results (week 0–12)** *Patients with ≥1 AE, n (%)* I1: 138/209 (66.0%) I2: 240/347 (69.2%) C: 243/347 (70.0) *Patients with ≥1 serious AEs, n (%)* I1: 4/209 (1.9%) I2: 4/347 (1.2%) C: 4/347 (1.2%) *AEs leading to withdrawal, n (%)* I1: 4/209 (1.9%) I2: 4/347 (1.2%) C: 8/347 (2.3%) *Common AEs* *Nasopharyngitis, n (%)* I1: 21/209 (10.0%) I2: 34/347 (9.8%) C: 30/347 (8.6%) *URTI, n (%)* I1: 13/209 (6.2%) I2: 22/347 (6.3%) C: 20/347 (5.8%)	**Risk of bias** Acceptable **Comment** Study sponsored by Centocor Research and Development. Centocor designed the study, conducted the data analyses, and participated in the writing of the manuscript

First Author Year Reference Country Study design	Population Setting Study period Follow-up (FU)	Intervention	Comparison	Analysis model Results	Adverse events	Risk of bias Comment
	March 2007 – January 2009 **Follow-up** Controlled phase for 12 weeks. Week 12-44 treatment of patients with poor response with ustekinumab (all groups), treatment with ustekinumab if response lost. Week 44–64 follow-up. Results from placebo-controlled phase reported here				*Headache, n (%)* I1: 31/209 (14.8%) I2: 42/347 (12.1%) C: 38/347 (11.0%) *Back pain, n (%)* I1: 14/209 (6.7%) I2: 15/347 (4.3%) C: 7/347 (2.0%) *Injection-site reaction, n (%)* I1: 9/209 (4.3%) I2: 13/347 (3.7%) C: 86/347 (24.8%)	

AE – adverse events; BSA – body surface area; CDLQI – children's dermatology life quality index; DLQI – dermatology life quality index; ITT – intention-to-treat; IQR – Interquartile range; MCS; mental component summary score; NRI – non-responder imputation; PASI – psoriasis area and severity index; PCS – physical component summary score; PGA – physician's global assessment; SD – standard deviation; SE – standard error; URTI – upper respiratory tract infection

Table 8. Methotrexate versus cyclosporine, economic evaluation

Author **Year** **Reference** **Country**	**Study design** **Population** **Setting** **Perspective**	**Intervention versus control**	**Incremental cost**	**Incremental effect**	**ICER**	**Study quality and transferability*** **Further information** **Comments**
Opmeer et al 2004 [137] Netherlands	RCT-based CUA/CEA Patients with moderate to severe psoriasis and no previous methotrexate or cyclosporine treatment Follow up period of 16 and 36 weeks. Societal perspective	Methotrexate versus cyclosporine	Week 16: $ -521 (185*) Week 36: $ -409 (-9*) Costs reported in USD ($) year 1999 *indirect costs	No significant effect difference	NA	*Quality* Moderate quality Moderate transferability *Comments* Did not control for active treatment with UV-B therapy during trail. Higher pharmaceutical costs then in Sweden and indirect costs not valued with the human capital method.

CA = Cost analysis; CBA = Cost-benefit analysis; CEA = Cost-effectiveness analysis; CUA = Cost-utility analysis; ICER = Incremental cost-effectiveness ratio; USD = United States Dollar

References

Note: the reference list contains all references from the main report, not only of included studies. The list is given in the same order as in the main report.

1. SBU. Utvärdering av metoder i hälso- och sjukvården: en handbok. Stockholm: Statens beredning för medicinsk och social utvärdering (SBU). Available from: http://www.sbu.se/sv/var-metod/.
2. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol 2013;133:377-85.
3. Hagg D, Eriksson M, Sundstrom A, Schmitt-Egenolf M. The higher proportion of men with psoriasis treated with biologics may be explained by more severe disease in men. PLoS One 2013;8:e63619.
4. Christophers E. Psoriasis--epidemiology and clinical spectrum. Clin Exp Dermatol 2001;26:314-20.
5. Vachatova S, Andrys C, Krejsek J, Salavec M, Ettler K, Rehacek V, et al. Metabolic Syndrome and Selective Inflammatory Markers in Psoriatic Patients. J Immunol Res 2016;2016:5380792.
6. Noe MH, Shin DB, Wan MT, Gelfand JM. Objective Measures of Psoriasis Severity Predict Mortality: A Prospective Population-Based Cohort Study. J Invest Dermatol 2018;138:228-230.
7. World Health Organization. Global report on psoriasis. 2016; [cited 2018 May 29] Available from: World Health Organization http://www.who.int/iris/handle/10665/204417
8. Läkemedelsverket. Behandling av psoriasis – ny rekommendation. Information från Läkemedelsverket 2011;22(4):11-24.
9. Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. Dermatologica 1978;157:238-44.
10. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19:210-6.
11. Nast A, Gisondi P, Ormerod AD, Saiag P, Smith C, Spuls PI, et al. European Dermatology Forum. European S3-Gudielines on the systemic treatment of psorisas vulgaris. 2015;29:2277-2294.
12. Finlay AY. Current severe psoriasis and the rule of tens. Br J Dermatol 2005;152:861-7.
13. Svenska sällskapet för dermatologi och venereologi (SSDV). SSDV:s behandlingsrekommendationer för systemisk behandling av psoriasis (2017-09-22). 2017.
14. Lomholt G. Prevalence of skin diseases in a population; A census study from the Faroe islands. Dan Med Bull 1964;11:1-7.
15. Swanbeck G, Inerot A, Martinsson T, Enerback C, Enlund F, Samuelsson L, et al. Genetic counselling in psoriasis: empirical data on psoriasis among first-degree relatives of 3095 psoriatic probands. Br J Dermatol 1997;137:939-42.
16. Duvic M, Johnson TM, Rapini RP, Freese T, Brewton G, Rios A. Acquired immunodeficiency syndrome-associated psoriasis and Reiter's syndrome. Arch Dermatol 1987;123:1622-32.
17. Telfer NR, Chalmers RJ, Whale K, Colman G. The role of streptococcal infection in the initiation of guttate psoriasis. Arch Dermatol 1992;128:39-42.
18. Abel EA, DiCicco LM, Orenberg EK, Fraki JE, Farber EM. Drugs in exacerbation of psoriasis. J Am Acad Dermatol 1986;15:1007-22.

19. Naldi L, Peli L, Parazzini F. Association of early-stage psoriasis with smoking and male alcohol consumption: evidence from an Italian case-control study. Arch Dermatol 1999;135:1479-84.

20. Poikolainen K, Reunala T, Karvonen J, Lauharanta J, Karkkainen P. Alcohol intake: a risk factor for psoriasis in young and middle aged men? Bmj 1990;300:780-3.

21. Frankel HC, Han J, Li T, Qureshi AA. The association between physical activity and the risk of incident psoriasis. Arch Dermatol 2012;148:918-24.

22. de Korte J, Sprangers MA, Mombers FM, Bos JD. Quality of life in patients with psoriasis: a systematic literature review. J Investig Dermatol Symp Proc 2004;9:140-7.

23. Wong T, Hsu L, Liao W. Phototherapy in psoriasis: a review of mechanisms of action. J Cutan Med Surg 2013;17:6-12.

24. Läkemedelsverket. Otezla (apremilast). Information från Läkemedelsverket 2017;28(4). ISSN 1101-7104. 2017.

25. FASS. Produktresumé för Skilarence (dimetylfumarat); [citerad 2018-05-28]. Hämtad från: www.fass.se

26. Raaby L, Zachariae C, Ostensen M, Heickendorff L, Thielsen P, Gronbaek H, et al. Methotrexate Use and Monitoring in Patients with Psoriasis: A Consensus Report Based on a Danish Expert Meeting. Acta Derm Venereol 2017;97:426-432.

27. FASS. Produktresumé för Neotigason (acitretin); [citerad 2018-05-28]. Hämtad från: www.fass.se

28. Socialstyrelsen. Tandvårdriktlinjer: läkemedelsorsakad gingival överväxt (omfattande hyperplasi). [Citerad 2018-05-28]. Tillgänglig från: https://www.socialstyrelsen.se/tandvardsriktlinjer/sokiriktlinjerna/lakemedelsorsakadgingivaloverv1.

29. Folkehelseinstituttet och Statens legemiddelverk N. Dimetylfumarat (LAS-41008) til behandling av moderat til alvorlig plakkpsoriasis hos voksne pasienter som har behov for systemisk beahndling: Folkehelseinstituttet och Statens legemiddelverk, Norge; 2016.

30. FASS. Produktresumé för Tecfidera (dimetylfumarat); [citerad 2018-05-28]. Hämtad från: www.fass.se

31. Läkemedelsverket. Biologiska läkemedel; [citerad 2018-05-28]. Hämtad från: https://lakemedelsverket.se/malgrupp/Foretag/Lakemedel/Biologiska-lakemedel/.

32. Rane A, Hammarlund-Udenaes M. Kliniskt farmakologiska principer: terapifrekommendationer. In: Läkemedelsboken.

33. Roman M, Chiu MW. Spotlight on brodalumab in the treatment of moderate-to-severe plaque psoriasis: design, development, and potential place in therapy. Drug Des Devel Ther 2017;11:2065-2075.

34. Läkemedelsverket. Biosimilar. 2017; [citerad 2018-05-28]. Hämtad från: https://lakemedelsverket.se/malgrupp/Foretag/Lakemedel/Biologiska-lakemedel/Biosimilar/.

35. Spuls PI, Lecluse LL, Poulsen ML, Bos JD, Stern RS, Nijsten T. How good are clinical severity and outcome measures for psoriasis?: quantitative evaluation in a systematic review. J Invest Dermatol 2010;130:933-43.

36. Wallace AB. Burns; some experiences in local care. Br J Plast Surg 1951;4:224-9.

37. Aitken RC. Measurement of feelings using visual analogue scales. Proc R Soc Med 1969;62:989-93.

38. Bronsard V, Paul C, Prey S, Puzenat E, Gourraud PA, Aractingi S, et al. What are the best outcome measures for assessing quality of life in plaque type psoriasis? A systematic review of the literature. J Eur Acad Dermatol Venereol 2010;24 Suppl 2:17-22.

39. Shikiar R, Willian MK, Okun MM, Thompson CS, Revicki DA. 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 2006;4:71.

40. McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993;31:247-63.

41. Sullivan M, Karlsson J, Ware JE, Jr. The Swedish SF-36 Health Survey--I. Evaluation of data quality, scaling assumptions, reliability and construct validity across general populations in Sweden. Soc Sci Med 1995;41:1349-58.

42. Burstrom K, Sun S, Gerdtham UG, Henriksson M, Johannesson M, Levin LA, et al. Swedish experience-based value sets for EQ-5D health states. Qual Life Res 2014;23:431-42.

43. Socialstyrelsen. Nationella riktlinjer för vård vid psoriasis. Stöd för styrning och ledning. Remissversion. Artikelnummer: 2018-3-15 2018.

44. Norlin JM, Calara PS, Persson U, Schmitt-Egenolf M. Real-world outcomes in 2646 psoriasis patients: one in five has PASI >/=10 and/or DLQI >/=10 under ongoing systemic therapy. J Dermatolog Treat 2017;28:500-504.

45. Socialstyrelsen. Patientregistret; [citerad 2018-05-28]. Hämtad från http://www.socialstyrelsen.se/register/halsodataregister/patientregistret

46. Psoriasisförbundet. [Citerad 2018-05-28]. Hämtad från https://www.psoriasisforbundet.se/

47. PsoReg - Register för systembehandling av psoriasis. Årsrapport för 2017; [citerad 2018-05-28]. Hämtad från: http://www.psoreg.se/publikationer/.

48. Socialstyrelsen. PsoReg (Register för systembehandling av psoriasis); [citerad 2018-05-28]. Hämtad från: http://www.socialstyrelsen.se/register/registerservice/nationellakvalitetsregister/psoregregisterforsystembehandl.

49. Geale K, Henriksson M, Schmitt-Egenolf M. Evaluating equality in psoriasis healthcare: a cohort study of the impact of age on prescription of biologics. Br J Dermatol 2016;174:579-87.

50. Hagg D, Sundstrom A, Eriksson M, Schmitt-Egenolf M. Severity of Psoriasis Differs Between Men and Women: A Study of the Clinical Outcome Measure Psoriasis Area and Severity Index (PASI) in 5438 Swedish Register Patients. Am J Clin Dermatol 2017;18:583-590.

51. Calara PS, Althin R, Carlsson KS, Schmitt-Egenolf M. Regional Differences in the Prescription of Biologics for Psoriasis in Sweden: A Register-Based Study of 4168 Patients. BioDrugs 2017;31:75-82.

52. Yones SS, Palmer RA, Garibaldinos TT, Hawk JL. Randomized double-blind trial of the treatment of chronic plaque psoriasis: efficacy of psoralen-UV-A therapy vs narrowband UV-B therapy. Archives of Dermatology 2006;142:836-42.

53. Gisondi P, Del Giglio M, Cotena C, Girolomoni G. Combining etanercept and acitretin in the therapy of chronic plaque psoriasis: a 24-week, randomized, controlled, investigator-blinded pilot trial. British Journal of Dermatology 2008;158:1345-9.

54. Caproni M, Antiga E, Melani L, Volpi W, Del Bianco E, Fabbri P. Serum levels of IL-17 and IL-22 are reduced by etanercept, but not by acitretin, in patients with psoriasis: a randomized-controlled trial. Journal of Clinical Immunology 2009;29:210-4.

55. Lee JH, Youn JI, Kim TY, Choi JH, Park CJ, Choe YB, et al. A multicenter, randomized, open-label pilot trial assessing the efficacy and safety of etanercept 50 mg twice weekly followed by etanercept 25 mg twice weekly, the combination of etanercept 25 mg twice weekly and acitretin, and acitretin alone in patients with moderate to severe psoriasis. BMC Dermatology 2016;16:11.

56. Paul C, Cather J, Gooderham M, Poulin Y, Mrowietz U, Ferrandiz C, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2). British Journal of Dermatology 2015;173:1387-99.

57. Reich K, Gooderham M, Green L, Bewley A, Zhang Z, Khanskaya I, et al. The efficacy and safety of apremilast, etanercept and placebo in patients with moderate-to-severe plaque psoriasis: 52-week results from a phase IIIb, randomized, placebo-controlled trial (LIBERATE). Journal of the European Academy of Dermatology & Venereology 2017;31:507-517.

58. Papp K, Cather JC, Rosoph L, Sofen H, Langley RG, Matheson RT, et al. Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial. Lancet 2012;380:738-46.

59. Papp K, Reich K, Leonardi CL, Kircik L, Chimenti S, Langley RG, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). Journal of the American Academy of Dermatology 2015;73:37-49.

60. Strober B, Bagel J, Lebwohl M, Stein Gold L, Jackson JM, Chen R, et al. Efficacy and Safety of Apremilast in Patients With Moderate Plaque Psoriasis With Lower BSA: Week 16 Results from the UNVEIL Study. Journal of Drugs in Dermatology: JDD 2017;16:801-808.

61. Ohtsuki M, Okubo Y, Komine M, Imafuku S, Day RM, Chen P, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in the treatment of Japanese patients with moderate to severe plaque psoriasis: Efficacy, safety and tolerability results from a phase 2b randomized controlled trial. Journal of Dermatology 2017;44:873-884.

62. Thaci D, Kimball A, Foley P, Poulin Y, Levi E, Chen R, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, improves patient-reported outcomes in the treatment of moderate to severe psoriasis: Results of two phase III randomized, controlled trials. Journal of the European Academy of Dermatology & Venereology 2016;18:18.

63. Crowley J, Thaci D, Joly P, Peris K, Papp KA, Goncalves J, et al. Long-term safety and tolerability of apremilast in patients with psoriasis: Pooled safety analysis for >=156 weeks from 2 phase 3, randomized, controlled trials (ESTEEM 1 and 2). Journal of the American Academy of Dermatology 2017;77:310-317.e1.

64. Meddelande till hälso- och sjukvårdspersonal. Otezla (apremilast): Nya viktiga råd angående självmordsstankar och självmordsbeteende; [citerad 2018-05-28]. Hämtad från: https://lakemedelsverket.se/upload/halso-och-sjukvard/forskrivning/DHPC/Otezla-DHPC-2016-11-07.pdf.

65. Flytstrom I, Stenberg B, Svensson A, Bergbrant IM. Methotrexate vs. ciclosporin in psoriasis: effectiveness, quality of life and safety. A randomized controlled trial. British Journal of Dermatology 2008;158:116-21.

66. Heydendael VM, Spuls PI, Opmeer BC, de Borgie CA, Reitsma JB, Goldschmidt WF, et al. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. New England Journal of Medicine 2003;349:658-65.

67. Weinstein GD, Frost P. Methotrexate for psoriasis. A new therapeutic schedule. Arch Dermatol 1971;103:33-8.

68. Mrowietz U, Szepietowski JC, Loewe R, Van de Kerkhof P, Lamarca R, Ocker WG, et al. Efficacy and safety of LAS41008 (dimethyl fumarate) in adults with moderate-to-severe chronic plaque psoriasis: A randomised, double-blind, Fumaderm() and placebo-controlled trial (BRIDGE). British Journal of Dermatology 2016;12:12.

69. Fallah Arani S, Neumann H, Hop WC, Thio HB. Fumarates vs. methotrexate in moderate to severe chronic plaque psoriasis: a multicentre prospective randomized controlled clinical trial. British Journal of Dermatology 2011;164:855-61.

70. Pathirana D, Ormerod AD, Saiag P, Smith C, Spuls PI, Nast A, et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris. J Eur Acad Dermatol Venereol 2009;23 Suppl 2:1-70.

71. Ho SG, Yeung CK, Chan HH. Methotrexate versus traditional Chinese medicine in psoriasis: a randomized, placebo-controlled trial to determine efficacy, safety and quality of life. Clinical & Experimental Dermatology 2010;35:717-22.

72. Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). British Journal of Dermatology 2008;158:558-66.

73. Warren RB, Mrowietz U, von Kiedrowski R, Niesmann J, Wilsmann-Theis D, Ghoreschi K, et al. An intensified dosing schedule of subcutaneous methotrexate in patients with moderate to severe plaque-type psoriasis (METOP): a 52 week, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;389:528-537.

74. van Roon EN, van de Laar MAFJ. Methotrexate bioavailability. Clin Exp Rheumatol 2010;28:S27-S32.

75. Asahina A, Nakagawa H, Etoh T, Ohtsuki M, Author A, Department of Dermatology S, et al. Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: Efficacy and safety results from a Phase II/III randomized controlled study. Journal of Dermatology 2010;37:299-310.

76. Cai L, Gu J, Zheng J, Zheng M, Wang G, Xi LY, et al. Efficacy and safety of adalimumab in Chinese patients with moderate-to-severe plaque psoriasis: results from a phase 3, randomized, placebo-controlled, double-blind study. Journal of the European Academy of Dermatology & Venereology 2016;9:9.

77. Gordon KB, Langley RG, Leonardi C, Toth D, Menter MA, Kang S, et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. Journal of the American Academy of Dermatology 2006;55:598-606.

78. Menter A, Tyring SK, Gordon K, Kimball AB, Leonardi CL, Langley RG, et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. Journal of the American Academy of Dermatology 2008;58:106-15.

79. Revicki DA, Willian MK, Menter A, Gordon KB, Kimball AB, Leonardi CL, et al. Impact of adalimumab treatment on patient-reported outcomes: results from a Phase III clinical trial in patients with moderate to severe plaque psoriasis. Journal of Dermatological Treatment 2007;18:341-50.

80. Shikiar R, Heffernan M, Langley RG, Willian MK, Okun MM, Revicki DA. Adalimumab treatment is associated with improvement in health-related quality of life in psoriasis: patient-reported outcomes from a phase II randomized controlled trial. Journal of Dermatological Treatment 2007;18:25-31.

81. Gordon KB, Duffin KC, Bissonnette R, Prinz JC, Wasfi Y, Li S, et al. A Phase 2 Trial of Guselkumab versus Adalimumab for Plaque Psoriasis. New England Journal of Medicine 2015;373:136-44.

82. Blauvelt A, Papp K, Griffiths C, Randazzo B, Wasfi Y, Shen Y, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. Journal of the american academy of dermatology 2017;76:405-417.

83. Reich K, Armstrong AW, Foley P, Song M, Wasfi Y, Randazzo B, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. Journal of the American Academy of Dermatology 2017;76:418-431.

84. Gordon K, Papp K, Poulin Y, Gu Y, Rozzo S, Sasso EH. Long-term efficacy and safety of adalimumab in patients with moderate to severe psoriasis treated continuously over 3 years: results from an open-label extension study for patients from REVEAL. Journal of the American Academy of Dermatology 2012;66:241-51.

85. Papp K, Thaci D, Marcoux D, Weibel L, Philipp S, Ghislain PD, et al. Efficacy and safety of adalimumab every other week versus methotrexate once weekly in children and adolescents with severe chronic plaque psoriasis: a randomised, double-blind, phase 3 trial. Lancet 2017;390:40-49.

86. van de Kerkhof PC, Segaert S, Lahfa M, Luger TA, Karolyi Z, Kaszuba A, et al. Once weekly administration of etanercept 50 mg is efficacious and well tolerated in patients with moderate-to-severe plaque psoriasis: a randomized controlled trial with open-label extension. British Journal of Dermatology 2008;159:1177-85.

87. Papp KA, Tyring S, Lahfa M, Prinz J, Griffiths CE, Nakanishi AM, et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. The British journal of dermatology 2005;152:1304-12.

88. Griffiths CE, Reich K, Lebwohl M, van de Kerkhof P, Paul C, Menter A, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. Lancet 2015;386:541-51.

89. Krueger GG, Langley RG, Finlay AY, Griffiths CE, Woolley JM, Lalla D, et al. Patient-reported outcomes of psoriasis improvement with etanercept therapy: results of a randomized phase III trial. British Journal of Dermatology 2005;153:1192-9.

90. Langley RG, Paller AS, Hebert AA, Creamer K, Weng HH, Jahreis A, et al. Patient-reported outcomes in pediatric patients with psoriasis undergoing etanercept treatment: 12-week results from a phase III randomized controlled trial. Journal of the American Academy of Dermatology 2011;64:64-70.

91. Paller AS, Siegfried EC, Langley RG, Gottlieb AB, Pariser D, Landells I, et al. Etanercept treatment for children and adolescents with plaque psoriasis. New England Journal of Medicine 2008;358:241-51.

92. Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet 2006;367:29-35.

93. Gottlieb AB, Matheson RT, Lowe N, Krueger GG, Kang S, Goffe BS, et al. A randomized trial of etanercept as monotherapy for psoriasis. Archives of Dermatology 2003;139:1627-32; discussion 1632.

94. Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, et al. Etanercept as monotherapy in patients with psoriasis. New England Journal of Medicine 2003;349:2014-22.

95. Gottlieb AB, Leonardi C, Kerdel F, Mehlis S, Olds M, Williams DA, et al. Efficacy and safety of briakinumab vs. etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. British Journal of Dermatology 2011;165:652-660.

96. Strober BE, Crowley JJ, Yamauchi PS, Olds M, Williams DA, Author A, et al. Efficacy and safety results from a phase III, randomized controlled trial comparing the safety and efficacy of briakinumab with etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. British Journal of Dermatology 2011;165:661-668.

97. Bachelez H, Kerkhof PC, Strohal R, Kubanov A, Valenzuela F, Lee JH, et al. Tofacitinib versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial. Lancet (London, England) 2015;386:552-61.

98. Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. New England Journal of Medicine 2014;371:326-38.

99. Reich K, Papp KA, Blauvelt A, Tyring SK, Sinclair R, Thaci D, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials.[Erratum appears in Lancet. 2017 Jul 15;390(10091):230; PMID: 28721878]. Lancet 2017;390:276-288.

100. Klein A, Schiffner R, Schiffner-Rohe J, Einsele-Krämer B, Heinlin J, Stolz W, et al. A randomized clinical trial in psoriasis: synchronous balneophototherapy with bathing in Dead Sea salt solution plus narrowband UVB vs. narrowband UVB alone (TOMESA-study group). Journal of the European Academy of Dermatology and Venereology : JEADV 2011;25:570-8.

101. Tyring S, Gordon KB, Poulin Y, Langley RG, Gottlieb AB, Dunn M, et al. Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. Archives of Dermatology 2007;143:719-26.

102. Leonardi C, Strober B, Gottlieb AB, Elewski BE, Ortonne JP, van de Kerkhof P, et al. Long-term safety and efficacy of etanercept in patients with psoriasis: an open-label study. Journal of Drugs in Dermatology: JDD 2010;9:928-37.

103. Paller AS, Siegfried EC, Pariser DM, Rice KC, Trivedi M, Iles J, et al. Long-term safety and efficacy of etanercept in children and adolescents with plaque psoriasis. Journal of the American Academy of Dermatology 2016;74:280-7.e1-3.

104. Feldman SR, Gordon KB, Bala M, Evans R, Li S, Dooley LT, et al. Infliximab treatment results in significant improvement in the quality of life of patients with severe psoriasis: a double-blind placebo-controlled trial. British Journal of Dermatology 2005;152:954-60.

105. Gottlieb AB, Evans R, Li S, Dooley LT, Guzzo CA, Baker D, et al. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. Journal of the American Academy of Dermatology 2004;51:534-42.

106. Reich K, Nestle FO, Papp K, Ortonne JP, Evans R, Guzzo C, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. Lancet 2005;366:1367-74.

107. Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, Guzzo C, et al. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. Journal of the American Academy of Dermatology 2007;56:31.e1-15.

108. Yang HZ, Wang K, Jin HZ, Gao TW, Xiao SX, Xu JH, et al. Infliximab monotherapy for Chinese patients with moderate to severe plaque psoriasis: a randomized, double-blind, placebo-controlled multicenter trial. Chinese Medical Journal 2012;125:1845-51.

109. de Vries AC, Thio HB, de Kort WJ, Opmeer BC, van der Stok HM, de Jong EM, et al. A prospective randomised controlled trial comparing infliximab and etanercept in patients with moderate to severe chronic plaque type psoriasis Psoriasis Infliximab versus Etanercept Comparison Evaluation, the PIECE study. British Journal of Dermatology 2016;15:15.

110. Gordon KB, Kimball AB, Chau D, Viswanathan HN, Li J, Revicki DA, et al. Impact of brodalumab treatment on psoriasis symptoms and health-related quality of life: use of a novel patient-reported outcome measure, the Psoriasis Symptom Inventory. British Journal of Dermatology 2014;170:705-15.

111. Lebwohl M, Strober B, Menter A, Gordon K, Weglowska J, Puig L, et al. Phase 3 Studies Comparing Brodalumab with Ustekinumab in Psoriasis. New England Journal of Medicine 2015;373:1318-28.

112. Nakagawa H, Niiro H, Ootaki K. Brodalumab, a human anti-interleukin-17-receptor antibody in the treatment of Japanese patients with moderate-to-severe plaque psoriasis: Efficacy and safety results from a phase II randomized controlled study. Journal of dermatological science 2016;81:44-52.

113. Papp KA, Leonardi C, Menter A, Ortonne JP, Krueger JG, Kricorian G, et al. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. New England Journal of Medicine 2012;366:1181-9.

114. Papp KA, Reich K, Paul C, Blauvelt A, Baran W, Bolduc C, et al. A prospective phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. British Journal of Dermatology 2016;175:273-86.

115. Gottlieb A, Langley R, Philipp S, Martin R, Papavassilis C, Mpfofu S. Improvement in psoriasis symptoms and physical functioning with secukinumab compared with placebo and etanercept in subjects with moderate-to-severe plaque psoriasis and psoriatic arthritis: Results of a subanalysis from the phase 3 fixture study. Arthritis and rheumatism 2013;65:3322.

116. Umezawa Y, Nakagawa H, Niiro H, Ootaki K, Japanese Brodalumab Study G. Long-term clinical safety and efficacy of brodalumab in the treatment of Japanese patients with moderate-to-severe plaque psoriasis. Journal of the European Academy of Dermatology & Venereology 2016;29:29.

117. Papp K, Leonardi C, Menter A, Thompson EH, Milmont CE, Kricorian G, et al. Safety and efficacy of brodalumab for psoriasis after 120 weeks of treatment. Journal of the American Academy of Dermatology 2014;71:1183-1190.e3.

118. FASS. Produktresumé för Kyntheum (brodalumab); [citerad 2018-05-28]. Hämtad från: https://www.fass.se/LIF/product?userType=0&nplId=20151118000032&docType=6&scrollPosition=0.

119. Gordon KB, Blauvelt A, Papp KA, Langley RG, Luger T, Ohtsuki M, et al. Phase 3 Trials of Ixekizumab in Moderate-to-Severe Plaque Psoriasis. New England Journal of Medicine 2016;375:345-56.

120. Blauvelt A, Gooderham M, Iversen L, Ball S, Zhang L, Agada NO, et al. Efficacy and safety of ixekizumab for the treatment of moderate-to-severe plaque psoriasis: Results through 108 weeks of a randomized, controlled phase 3 clinical trial (UNCOVER-3). Journal of the American Academy of Dermatology 2017;77:855-862.

121. Reich K, Pinter A, Lacour JP, Ferrandiz C, Micali G, French LE, et al. Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24-week results from IXORA-S, a phase III study. British Journal of Dermatology 2017;177:1014-1023.

122. Blauvelt A, Prinz JC, Gottlieb AB, Kingo K, Sofen H, Ruer-Mulard M, et al. Secukinumab administration by pre-filled syringe: efficacy, safety and usability results from a randomized controlled trial in psoriasis (FEATURE). British Journal of Dermatology 2015;172:484-93.

123. Paul C, Lacour JP, Tedremets L, Kreutzer K, Jazayeri S, Adams S, et al. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). Journal of the European Academy of Dermatology & Venereology 2015;29:1082-90.

124. Gottlieb AB, Blauvelt A, Prinz JC, Papanastasiou P, Pathan R, Nyirady J, et al. Secukinumab Self-Administration by Prefilled Syringe Maintains Reduction of Plaque Psoriasis Severity Over 52 Weeks: Results of the FEATURE Trial. Journal of Drugs in Dermatology: JDD 2016;15:1226-1234.

125. Lacour JP, Paul C, Jazayeri S, Papanastasiou P, Xu C, Nyirady J, et al. Secukinumab administration by autoinjector maintains reduction of plaque psoriasis severity over 52 weeks: results of the randomized controlled JUNCTURE trial. Journal of the European Academy of Dermatology & Venereology 2017;31:847-856.

126. Blauvelt A, Reich K, Tsai TF, Tyring S, Vanaclocha F, Kingo K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: Results from the CLEAR study. Journal of the American Academy of Dermatology 2016;20:20.

127. Landells I, Marano C, Hsu MC, Li S, Zhu Y, Eichenfield LF, et al. Ustekinumab in adolescent patients age 12 to 17 years with moderate-to-severe plaque psoriasis: Results of the randomized phase 3 CADMUS study. Journal of the American Academy of Dermatology 2015;73:594-603.

128. Lebwohl M, Papp K, Han C, Schenkel B, Yeilding N, Wang Y, et al. Ustekinumab improves health-related quality of life in patients with moderate-to-severe psoriasis: results from the PHOENIX 1 trial. British Journal of Dermatology 2010;162:137-46.

129. Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1).[Erratum appears in Lancet. 2008 May 31;371(9627):1838]. Lancet 2008;371:1665-74.

130. Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet 2008;371:1675-84.

131. Tsai TF, Ho JC, Song M, Szapary P, Guzzo C, Shen YK, et al. Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: a phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL). Journal of Dermatological Science 2011;63:154-63.

132. Papp KA, Griffiths CE, Gordon K, Lebwohl M, Szapary PO, Wasfi Y, et al. Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. British Journal of Dermatology 2013;168:844-54.

133. Kimball AB, Papp KA, Wasfi Y, Chan D, Bissonnette R, Sofen H, et al. Long-term efficacy of ustekinumab in patients with moderate-to-severe psoriasis treated for up to 5 years in the PHOENIX 1 study. Journal of the European Academy of Dermatology & Venereology 2013;27:1535-45.

134. Griffiths CEM, Strober BE, Van PK, Ho V, Fidelus-Gort R, Yeilding N, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. New England Journal of Medicine 2010;362:118-128.

135. Langan SM, Heerey A, Barry M, Barnes L. Cost analysis of narrowband UVB phototherapy in psoriasis. Journal of the American Academy of Dermatology 2004;50:623-6.

136. Psoriasisförbundet. Behandling av psoriasis; [citerad 2018-05-28]. Hämtad från: https://www.psoriasisforbundet.se/fakta-o-rad/om-psoriasis/behandling-av-psoriasis/. 2018.

137. Opmeer BC, Heydendael VM, De Borgie CA, Spuls PI, Bossuyt PM, Bos JD, et al. Costs of treatment in patients with moderate to severe plaque psoriasis: economic analysis in a randomized controlled comparison of methotrexate and cyclosporine. Archives of Dermatology 2004;140:685-90.

138. Socialstyrelsen. Statistikdatabas för diagnoser i öppen vård; [citerad 2018-05-28]. Hämtad från: http://www.socialstyrelsen.se/statistik/statistikdatabas/diagnoserispecialiseradoppenvard. 2017.

139. Norrlandstingens regionförbund. Regional Prislista 2017 för Norra sjukvårdsregionen, länssjukvård och primärvård; [citerad 2018-05-28]. Hämtad från: http://www.norrlandstingen.se/halso-och-sjukvard/avtal-och-priser/prislistor-norra-sjukvardsregionen/.

140. Samverkansnämnden sydöstra sjukvårdsregionen. Priser och ersättningar för sydöstra sjukvårdsregionen 2017; [citerad 2018-05-28]. Hämtad från https://plus.rjl.se/infopage.jsf?nodeId=41089.

141. Södra regionvårdsnämnden. Regionala priser och ersättningar för södra sjukvårdsregionen 2017; [citerad 2018-05-28]. Hämtad från: http://sodrasjukvardsregionen.se/avtal-priser/regionala-priser-och-ersattningar-foregaende-ar/.

142. Västra sjukvårdsregionen. Utomlänspriser 2017. För vårdtjänster enligt samverkansavtal om hälso- och sjukvård inom Västra sjukvårdsregionen; [citerad 2018-05-28]. Hämtad från https://alfresco.vgregion.se/alfresco/service/vgr/storage/node/content/workspace/SpacesStore/56e76d52-2328-42b0-822d-a52919d0791a/Utoml%C3%A4nsprislista%202017-1.pdf?a=false&guest=true.

143. Samverkansnämnden Uppsala-Örebro sjukvårdsregion. Regional prislista 2017; [citerad 2018-05-28]. Hämtad från: http://svnuppsalaorebro.se/3-styrande/prislistor/2017/kommentarer_regionala_prislistan_2017.pdf

144. Tandvårds- och läkemedelsförmånsverket (TLV). Databas för läkemedel och beslut; [citerad 2018-05-28]. Hämtad från: https://www.tlv.se/beslut/sok-i-databasen.html.

145. Psoriasisföreningen i Stockholms län. ”Nya riktlinjer för provtagning vid systembehandling” Psoriasisföreningen i Stockholms län. 2011.

146. Tandvårds- och läkemedelsförmånsverket (TLV). Tandvårds- och läkemedelsförmånsverkets allmänna råd TLVAR 2017:1

147. SCB. Inkomst av tjänst: [citerad 2018-05-28]. Hämtad från: http://www.statistikdatabasen.scb.se/pxweb/sv/ssd/START__HE__HE0110__HE0110A/InkAvTjanst/?rxid=f3cf8b74-5b21-4288-bf2a-46599a21725b. 2017;2017.

148. ekonomifakta.se. Sociala avgifter; [citerad 2018-05-28]. Hämtad från: http://www.ekonomifakta.se/sv/Fakta/Arbetsmarknad/Arbetsgivaravgift/Sociala-avgifter. 2017.

149. National Institute for Health and Care Excellence (NICE). Psorisasis: assessment and management: National Institute for Health and Care Excellence (NICE). Clinical gudieline [CG153]. 2012, last updated 2017

150. FASS. Produktresumé för Stelara (ustekinumab); [citerad 2018-05-28]. Hämtad från: www.fass.se

151. Larsson PA, Liden S. Prevalence of skin diseases among adolescents 12--16 years of age. Acta Derm Venereol 1980;60:415-23.

152. Matusiewicz D, Koerber A, Schadendorf D, Wasem J, Neumann A. Childhood psoriasis--an analysis of German health insurance data. Pediatr Dermatol 2014;31:8-13.

153. Rose K, Happle R. The Effect of Regulation on Pediatric Psoriasis Drug Approvals: The Challenge of the European Union Pediatric Investigation Plans. Pediatr Dermatol 2017;34:e154-e159.

154. Fortina AB, Bardazzi F, Berti S, Carnevale C, Di Lernia V, El Hachem M, et al. Treatment of severe psoriasis in children: recommendations of an Italian expert group. Eur J Pediatr 2017;176:1339-1354.

155. Osmancevic A, Ståhle M. Behandling av psoriasis: från tjära till biologiska läkemedel. Läkartidningen 2017;114:1-6.

156. Chen X, Yang M, Cheng Y, Liu GJ, Zhang M. Narrow-band ultraviolet B phototherapy versus broad-band ultraviolet B or psoralen-ultraviolet A photochemotherapy for psoriasis. Cochrane Database Syst Rev 2013:Cd009481.