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## Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis (Review)

Sbidian E, Chaimani A, Garcia-Doval I, Do G, Hua C, Mazaud C, Droitcourt C, Hughes C, Ingram JR, Naldi L, Chosidow O, Le Cleach L

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[Intervention Review]

# Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

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## ABSTRACT

### Background

Psoriasis is an immune-mediated disease for which some people have a genetic predisposition. The condition manifests in inflammatory effects on either the skin or joints, or both, and it has a major impact on quality of life. Although there is currently no cure for psoriasis, various treatment strategies allow sustained control of disease signs and symptoms. Several randomised controlled trials (RCTs) have compared the efficacy of the different systemic treatments in psoriasis against placebo. However, the relative benefit of these treatments remains unclear due to the limited number of trials comparing them directly head to head, which is why we chose to conduct a network meta-analysis.

### Objectives

To compare the efficacy and safety of conventional systemic agents (acitretin, ciclosporin, fumaric acid esters, methotrexate), small molecules (apremilast, tofacitinib, ponesimod), anti-TNF alpha (etanercept, infliximab, adalimumab, certolizumab), anti-IL12/23 (ustekinumab), anti-IL17 (secukinumab, ixekizumab, brodalumab), anti-IL23 (guselkumab, tildrakizumab), and other biologics (alefacept, itolizumab) for patients with moderate to severe psoriasis and to provide a ranking of these treatments according to their efficacy and safety.

### Search methods

We searched the following databases to December 2016: the Cochrane Skin Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, and LILACS. We also searched five trials registers and the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) reports. We checked the reference lists of included and excluded

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studies for further references to relevant RCTs. We searched the trial results databases of a number of pharmaceutical companies and handsearched the conference proceedings of a number of dermatology meetings.

### **Selection criteria**

Randomised controlled trials (RCTs) of systemic and biological treatments in adults (over 18 years of age) with moderate to severe plaque psoriasis or psoriatic arthritis whose skin had been clinically diagnosed with moderate to severe psoriasis, at any stage of treatment, in comparison to placebo or another active agent.

### **Data collection and analysis**

Three groups of two review authors independently undertook study selection, data extraction, 'Risk of bias' assessment, and analyses. We synthesised the data using pair-wise and network meta-analysis (NMA) to compare the treatments of interest and rank them according to their effectiveness (as measured by the Psoriasis Area and Severity Index score (PASI) 90) and acceptability (the inverse of serious adverse effects). We assessed the certainty of the body of evidence from the NMA for the two primary outcomes, according to GRADE; we evaluated evidence as either very low, low, moderate, or high. We contacted study authors when data were unclear or missing.

### **Main results**

We included 109 studies in our review (39,882 randomised participants, 68% men, all recruited from a hospital). The overall average age was 44 years; the overall mean PASI score at baseline was 20 (range: 9.5 to 39). Most of these studies were placebo controlled (67%), 23% were head-to-head studies, and 10% were multi-armed studies with both an active comparator and placebo. We have assessed all treatments listed in the objectives (19 in total). In all, 86 trials were multicentric trials (two to 231 centres). All of the trials included in this review were limited to the induction phase (assessment at less than 24 weeks after randomisation); in fact, all trials included in the network meta-analysis were measured between 12 and 16 weeks after randomisation. We assessed the majority of studies (48/109) as being at high risk of bias; 38 were assessed as at an unclear risk, and 23, low risk.

Network meta-analysis at class level showed that all of the interventions (conventional systemic agents, small molecules, and biological treatments) were significantly more effective than placebo in terms of reaching PASI 90.

In terms of reaching PASI 90, the biologic treatments anti-IL17, anti-IL12/23, anti-IL23, and anti-TNF alpha were significantly more effective than the small molecules and the conventional systemic agents. Small molecules were associated with a higher chance of reaching PASI 90 compared to conventional systemic agents.

At drug level, in terms of reaching PASI 90, all of the anti-IL17 agents and guselkumab (an anti-IL23 drug) were significantly more effective than the anti-TNF alpha agents infliximab, adalimumab, and etanercept, but not certolizumab. Ustekinumab was superior to etanercept. No clear difference was shown between infliximab, adalimumab, and etanercept. Only one trial assessed the efficacy of infliximab in this network; thus, these results have to be interpreted with caution. Tofacitinib was significantly superior to methotrexate, and no clear difference was shown between any of the other small molecules versus conventional treatments.

Network meta-analysis also showed that ixekizumab, secukinumab, brodalumab, guselkumab, certolizumab, and ustekinumab outperformed other drugs when compared to placebo in terms of reaching PASI 90: the most effective drug was ixekizumab (risk ratio (RR) 32.45, 95% confidence interval (CI) 23.61 to 44.60; Surface Under the Cumulative Ranking (SUCRA) = 94.3; high-certainty evidence), followed by secukinumab (RR 26.55, 95% CI 20.32 to 34.69; SUCRA = 86.5; high-certainty evidence), brodalumab (RR 25.45, 95% CI 18.74 to 34.57; SUCRA = 84.3; moderate-certainty evidence), guselkumab (RR 21.03, 95% CI 14.56 to 30.38; SUCRA = 77; moderate-certainty evidence), certolizumab (RR 24.58, 95% CI 3.46 to 174.73; SUCRA = 75.7; moderate-certainty evidence), and ustekinumab (RR 19.91, 95% CI 15.11 to 26.23; SUCRA = 72.6; high-certainty evidence).

We found no significant difference between all of the interventions and the placebo regarding the risk of serious adverse effects (SAEs): the relative ranking strongly suggested that methotrexate was associated with the best safety profile regarding all of the SAEs (RR 0.23, 95% CI 0.05 to 0.99; SUCRA = 90.7; moderate-certainty evidence), followed by ciclosporin (RR 0.23, 95% CI 0.01 to 5.10; SUCRA = 78.2; very low-certainty evidence), certolizumab (RR 0.49, 95% CI 0.10 to 2.36; SUCRA = 70.9; moderate-certainty evidence), infliximab (RR 0.56, 95% CI 0.10 to 3.00; SUCRA = 64.4; very low-certainty evidence), alefacept (RR 0.72, 95% CI 0.34 to 1.55; SUCRA = 62.6; low-certainty evidence), and fumaric acid esters (RR 0.77, 95% CI 0.30 to 1.99; SUCRA = 57.7; very low-certainty evidence). Major adverse cardiac events, serious infections, or malignancies were reported in both the placebo and intervention groups. Nevertheless, the SAEs analyses were based on a very low number of events with low to very low certainty for just over half of the treatment estimates in total, moderate for the others. Thus, the results have to be considered with caution.

Considering both efficacy (PASI 90 outcome) and acceptability (SAEs outcome), highly effective treatments also had more SAEs compared to the other treatments, and ustekinumab, infliximab, and certolizumab appeared to have the better trade-off between efficacy and acceptability.

Regarding the other efficacy outcomes, PASI 75 and Physician Global Assessment (PGA) 0/1, the results were very similar to the results for PASI 90.

Information on quality of life was often poorly reported and was absent for a third of the interventions.

### **Authors' conclusions**

Our review shows that compared to placebo, the biologics ixekizumab, secukinumab, brodalumab, guselkumab, certolizumab, and ustekinumab are the best choices for achieving PASI 90 in people with moderate to severe psoriasis on the basis of moderate- to high-certainty evidence. At class level, the biologic treatments anti-IL17, anti-IL12/23, anti-IL23, and anti-TNF alpha were significantly more effective than the small molecules and the conventional systemic agents, too. This NMA evidence is limited to induction therapy (outcomes were measured between 12 to 16 weeks after randomisation) and is not sufficiently relevant for a chronic disease. Moreover, low numbers of studies were found for some of the interventions, and the young age (mean age of 44 years) and high level of disease severity (PASI 20 at baseline) may not be typical of patients seen in daily clinical practice.

Another major concern is that short-term trials provide scanty and sometimes poorly reported safety data and thus do not provide useful evidence to create a reliable risk profile of treatments. Indeed, we found no significant difference in the assessed interventions and placebo in terms of SAEs. Methotrexate appeared to have the best safety profile, but as the evidence was of very low to moderate quality, we cannot be sure of the ranking. In order to provide long-term information on the safety of the treatments included in this review, it will be necessary to evaluate non-randomised studies and postmarketing reports released from regulatory agencies as well.

In terms of future research, randomised trials comparing directly active agents are necessary once high-quality evidence of benefit against placebo is established, including head-to-head trials amongst and between conventional systemic and small molecules, and between biological agents (anti-IL17 versus anti-IL23, anti-IL23 versus anti-IL12/23, anti-TNF alpha versus anti-IL12/23). Future trials should also undertake systematic subgroup analyses (e.g. assessing biological-naïve patients, baseline psoriasis severity, presence of psoriatic arthritis, etc.). Finally, outcome measure harmonisation is needed in psoriasis trials, and researchers should look at the medium- and long-term benefit and safety of the interventions and the comparative safety of different agents.

## **PLAIN LANGUAGE SUMMARY**

### **Systemic (oral or injected) medicines for psoriasis**

#### **What is the aim of this review?**

The aim of this review was to compare different systemic medicines (oral or injected medicines that work throughout the entire body) used to treat chronic plaque psoriasis in adults (over 18 years of age), to find out which are the safest and most effective at clearing psoriasis. We wanted to rank the medicines in order of their safety and how well they work, to help the development of a treatment pathway for people with chronic plaque psoriasis. We collected and analysed all relevant studies to answer this question and found 109 studies.

#### **Key messages**

The results showed that a selection of treatments from the class of biological medicines appear to be the most effective systemic medicines for achieving a chronic plaque psoriasis score of PASI (Psoriasis Area and Severity Index) 90, which translates into a 90% improvement in psoriasis from the beginning of the study. We found no significant difference in serious adverse effects (SAEs) (i.e. serious side effects) when comparing any of the assessed treatments with placebo. However, as the evidence was of very low to moderate quality, we cannot be sure of these results.

For some of the interventions, we found low numbers of studies, so more research needs to be conducted to directly compare the systemic medicines with each other, rather than comparing them with placebo (an inactive substance) (once effect against placebo has been established by high-quality evidence). In addition, longer-term studies are needed to provide more evidence about the benefit and safety of systemic medicines and to compare their safety profiles. Indeed, the results of this review are limited to the induction treatment (i.e. outcomes were measured up to 24 weeks after participants were allocated to their treatment group), which is not an appropriate treatment option for a chronic disease.

We rated the certainty of the evidence as ranging from very low (mainly conventional medicines) to high (mainly biological medicines). We downgraded the certainty of the evidence due to risk of bias (concerns with the study methods) and then for either inconsistent results or imprecision (inaccuracy).

### **What was studied in the review?**

Psoriasis is characterised by patches of red, flaky skin covered with scales (known as plaques) or other inflammatory effects that are seen on the skin or joints, or both. Psoriasis is caused by an abnormal response within the immune system in people who may have a genetic predisposition towards the condition.

Approximately 2% of the population have psoriasis, and 90% of those people have plaque psoriasis. Around 10% to 20% of people with chronic plaque psoriasis will need to have systemic treatments. Psoriasis impacts on quality of life, including a person's psychosocial life.

We compared 19 systemic medicines by identifying studies that compared one or more of these medicines with either placebo or with another medicine to treat moderate to severe forms of plaque psoriasis in adults who were at any stage of treatment. The medicines we assessed were conventional systemic treatments (a varied group of treatments that are the oldest treatments given to clear psoriasis), biologics (treatments that use substances made from living organisms, or synthetic versions, to target the immune system), and small molecules (which affect molecules inside immune cells). We included studies whose participants may also have had psoriatic arthritis. The main outcomes we were interested in were achievement of PASI 90 and any serious side effects that were thought to be associated with the medicines.

We combined all of the studies to allow indirect analysis of the treatments, so we could compare them with each other (network meta-analysis).

### **What are the main results of the review?**

The 109 studies enrolled 39,882 people (all recruited from a hospital) with moderate to severe psoriasis: 26,902 men and 12,384 women; the overall average age was 44 years, the overall mean PASI score at the start of the study was 20 (range: 9.5 to 39), indicating a high level of disease severity. Most studies ( $n = 73$ ) compared the systemic medicine with a placebo treatment, a total of 25 trials compared systemic treatments with other systemic treatments, and 11 trials compared systemic treatments with systemic treatments and placebo. Most studies were short-term, and in all, 86 trials were multicentric trials (two to 231 centres).

The outcomes presented here were measured 12 to 16 weeks after the study participants were randomised.

The results showed that compared with placebo, all treatments (assessed in the following groupings: anti-IL17, anti-IL12/23, anti-IL23, and anti-TNF alpha (i.e. the treatments known as the biologics); small molecule treatments; other biologics; and conventional systemic agents) were more effective in treating psoriasis when assessed using an index that required 90% improvement (PASI 90).

In relation to the same outcome (PASI 90), the biologic treatments anti-IL17, anti-IL12/23, anti-IL23, and anti-TNF alpha appeared to work better than the small molecules and the conventional systemic agents; and small molecules were associated with a better outcome compared to conventional systemic agents. (IL is an abbreviation of interleukin; TNF is an abbreviation of tumour necrosis factor - both are types of cytokine. A cytokine affects the behaviour of a cell.)

In terms of individual drugs, again when assessing the ability to reach PASI 90, all of the anti-IL17 drugs and guselkumab (an anti-IL23 drug) were more effective than the anti-TNF alpha drugs infliximab, adalimumab, and etanercept, but not certolizumab. Ustekinumab (an IL-12/-23 drug) was better than etanercept. No clear difference was shown between infliximab, adalimumab, and etanercept. Tofacitinib (a small molecule) was superior to methotrexate (a conventional systemic agent), and no difference was shown between the other small molecules and the conventional drugs.

Judged against placebo, six biological medicines worked best at clearing psoriasis lesions. These medicines were ranked as follows (most effective first): ixekizumab, secukinumab (both based on high-certainty evidence), brodalumab, guselkumab, certolizumab (all based on moderate-certainty evidence), and ustekinumab (high-certainty evidence). Regarding the outcomes PASI 75 and Physician Global Assessment (PGA) 0/1 (i.e. achieving 75% improvement and achieving a PGA score of 0 or 1), the results were very similar to the results for PASI 90.

For the risk of serious side effects, there were no clear differences between all of the systemic medicines compared with placebo treatment. Methotrexate had the best safety profile (based on moderate-certainty evidence), followed by ciclosporin (very low-certainty evidence), certolizumab (moderate-certainty evidence), infliximab (very low-certainty evidence), alefacept (low-certainty evidence), and fumaric

acid esters (very low-certainty evidence) (all of these are conventional treatments except for certolizumab, infliximab (anti-TNF alpha drugs), and alefacept (classed under 'other biologics'). Major adverse cardiac events, serious infections, or malignancies were reported in both placebo and intervention groups. However, the number of serious side effects was very low, and our conclusions are based on low to very low- (for just over half of the results) or moderate-certainty evidence, so they should be interpreted with caution. The most effective treatments (in terms of reaching PASI 90) had the highest numbers of reported side effects; ustekinumab, infliximab, and certolizumab appeared to have the best compromise between effectiveness and side effects.

For all studies, little information was recorded about quality of life; one third of the medicines studied had no quality of life data.

**How up-to-date is this review?**

We searched for studies that had been published up to December 2016.

## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Any systemic treatment compared to placebo for chronic plaque psoriasis (network meta-analysis)							
<b>Patient or population:</b> people with chronic plaque psoriasis <b>Intervention:</b> any systemic treatment <b>Comparison:</b> placebo <b>Setting:</b> all the participants were recruited from a hospital setting <b>Timescale:</b> 12 to 16 weeks after randomisation							
Intervention	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	SUCRA	No. of participants (studies) <sup>b</sup>	Certainty of the evidence (GRADE)	Comments
	Risk with placebo <sup>a</sup>	Risk with any systemic treatment					
<b>PASI 90</b>							
Ixekizumab	Moderate		RR 32.45 (23.61 to 44.60)	94.3	3268 (4 RCTs)	⊕⊕⊕⊕ High	-
	15 per 1000	487 per 1000 (354 to 669)					
Secukinumab	Moderate		RR 26.55 (20.32 to 34.69)	86.5	2707 (7 RCTs)	⊕⊕⊕⊕ High	-
	15 per 1000	398 per 1000 (305 to 520)					
Brodalumab	Moderate		RR 25.45 (18.74 to 34.57)	84.3	4109 (5 RCTs)	⊕⊕⊕○ Moderate	Reasons for downgrading by one level: three studies contributing to this estimate at high risk of bias in selective reporting domain
	15 per 1000	382 per 1000 (281 to 520)					

Guselkumab	Moderate	RR 21.03 (14.56 to 30.38)	77	1502 (3 RCTs)	⊕⊕⊕○ Moderate	Reasons for downgrading by one level: one study contributing to this estimate at high risk of bias in selective reporting domain
	15 per 1000	315 per 1000 (218 to 456)				
Certolizumab	Moderate	RR 24.58 (3.46 to 174.73)	75.7	176 (1 RCT)	⊕⊕⊕○ Moderate	Downgraded one level due to imprecision: wide CIs
	15 per 1000	369 per 1000 (52 to 1000)				
Ustekinumab	Moderate	RR 19.91 (15.11 to 26.23)	72.6	3832 (7 RCTs)	⊕⊕⊕⊕ High	-
	15 per 1000	299 per 1000 (227 to 393)				
Tildrakizumab	Moderate	RR 15.63 (2.22 to 110.07)	63.6	355 (1 RCT)	⊕⊕○○ Low	Downgraded one level due to risk of bias and one level due to imprecision. The single study contributing to this estimate at unclear risk of bias in both blinding domains; wide CIs
	15 per 1000	234 per 1000 (33 to 1000)				
Adalimumab	Moderate	RR 14.87 (10.45 to 21.14)	63.1	3199 (8 RCTs)	⊕⊕⊕○ Moderate	Downgraded one level due to inconsistency - inconsistent loops of evidence
	15 per 1000	223 per 1000 (157 to 317)				
Itolizumab	Moderate	RR 12.26 (0.76 to 198.53)	56	225 (1 RCT)	⊕⊕○○ Low	Downgraded one level due to imprecision (wide CIs) and one level due to risk of bias (moderate risk using credibility of evidence)
	15 per 1000					

	15 per 1000	184 per 1000 (12 to 1000)					
Infliximab	Moderate		RR 11.18 (5.67 to 22.04)	53.2	(0 RCTs)	⊕○○○ Very low	Downgraded one level due to risk of bias (credibility of risk), one level due to imprecision (wide CIs) and one level due to inconsistency (inconsistent loop of evidence)
		15 per 1000	168 per 1000 (85 to 331)				
Etanercept	Moderate		RR 10.79 (8.47 to 13.73)	52.6	4954 (12 RCTs)	⊕⊕⊕○ Moderate	Downgraded one level due to inconsistency (global inconsistency - side-splitting approach)
		15 per 1000	162 per 1000 (127 to 206)				
Tofacitinib	Moderate		RR 8.50 (6.23 to 11.60)	42.5	2826 (4 RCTs)	⊕⊕○○ Low	Downgraded one level due to risk of bias: two studies at high risk of bias in incomplete outcome data domain; and downgraded one level due to inconsistency (global approach)
		15 per 1000	128 per 1 000 (93 to 174)				
Apremilast	Moderate		RR 7.66 (4.30 to 13.66)	39.7	1775 (4 RCTs)	⊕⊕⊕○ Moderate	Downgraded one level due to risk of bias: one study had a slight risk of bias in selective reporting domain
		15 per 1000	115 per 1000 (65 to 205)				
Ponesimod	Moderate		RR 6.60 (1.63 to 26.67)	37.3	326 (1 RCT)	⊕⊕⊕○ Moderate	Downgraded one level due to imprecision: wide CIs
		15 per 1000	99 per 1000 (24 to 400)				



Alefaccept	Moderate	RR 4.39 (1.38 to 13.94)	25.3	(0 RCTs)	⊕○○○ Very low	Downgraded two levels due to risk of bias and a further one level due to imprecision - study indirectly contributing to the estimates at high risk of bias in selective reporting domain; wide CIs
	15 per 1000	66 per 1000 (21 to 209)				
Fumaric acid esters (FAEs)	Moderate	RR 4.09 (1.88 to 8.88)	21.9	704 (1 RCT)	⊕○○○ Very low	Downgraded two levels due to risk of bias, and one level due to imprecision - the studies indirectly contributing to this estimate at high risk of bias in blinding domain; wide CIs
	15 per 1000	61 per 1000 (28 to 133)				
Ciclosporin	Moderate	RR 3.99 (1.81 to 8.78)	21.3	(0 RCTs)	⊕○○○ Very low	Downgraded two levels due to risk of bias, and a further one level due to imprecision - the single study indirectly contributing to this estimate at high risk of bias in blinding; wide CIs
	15 per 1000	60 per 1000 (27 to 132)				
Methotrexate	Moderate	RR 3.61 (2.01 to 6.48)	20.2	282 (2 RCTs)	⊕⊕⊕○ Moderate	Downgraded one level due to inconsistency (inconsistent loop of evidence)
	15 per 1000	59 per 1000 (32 to 106)				
Acitretin	Moderate	RR 0.98 (0.06 to 17.24)	9.9	(0 RCTs)	⊕○○○ Very low	Downgraded two levels due to risk of bias and a further one level due to imprecision. The single study contributing to this estimate at high risk of

								bias in incomplete outcome data and blinding domains; wide CIs
	15 per 1000	15 per 1000 (1 to 259)						
<b>Serious adverse events</b>								
Methotrexate	Moderate		RR 0.23 (0.05 to 0.99)	90.7	282 (2 RCTs)	⊕⊕⊕○ Moderate		Downgraded one level due to imprecision (wide CIs)
		17 per 1000	4 per 1000 (1 to 17)					
Ciclosporin	Moderate		RR 0.23 (0.01 to 5.10)	78.2	(0 RCTs)	⊕○○○ Very low		Downgraded two levels due to risk of bias (credibility of evidence), and one level due to imprecision (wide CIs)
		17 per 1000	4 per 1000 (0 to 87)					
Certolizumab	Moderate		RR 0.49 (0.10 to 2.36)	70.9	176 (1 RCT)	⊕⊕⊕○ Moderate		Downgraded one level due to imprecision (wide CIs)
		17 per 1000	8 per 1000 (2 to 40)					
Infliximab	Moderate		RR 0.56 (0.10 to 3.00)	64.4	(0 RCTs)	⊕○○○ Very low		Downgraded two levels due to risk of bias, and one level due to imprecision: credibility of evidence; wide CIs
		17 per 1000	10 per 1000 (2 to 51)					
Alefacept	Moderate		RR 0.72 (0.34 to 1.55)	62.6	736 (2 RCTs)	⊕⊕○○ Low		Downgraded one level due to risk of bias (credibility of evidence), and one level due to imprecision (wide CIs)
		17 per 1000	12 per 1000 (6 to 26)					

Fumaric acid esters (FAEs)	Moderate	RR 0.77 (0.30 to 2.00)	57.7	704 (1 RCT)	⊕○○○ Very low	Downgraded by one level due to risk of bias and one level due to imprecision: credibility of evidence; wide CIs
	17 per 1000	13 per 1000 (5 to 34)				
Apremilast	Moderate	RR 0.84 (0.47 to 1.51)	54.7	2036 (5 RCTs)	⊕⊕○○ Low	Downgraded one level due to risk of bias and one level due to imprecision: credibility of evidence and wide CIs
	17 per 1000	14 per 1000 (8 to 26)				
Ustekinumab	Moderate	RR 0.89 (0.57 to 1.39)	52	4154 (8 RCTs)	⊕⊕○○ Low	Downgraded one level due to risk of bias and one level due to imprecision - credibility of evidence; wide CIs
	17 per 1000	15 per 1000 (10 to 24)				
Acitretin	Moderate	RR 0.99 (0.02 to 49.37)	46.9	(0 RCTs)	⊕○○○ Very low	Downgraded by two levels due to risk of bias and one level due to imprecision: credibility of evidence; wide CIs
	17 per 1000	17 per 1000 (0 to 839)				
Tofacitinib	Moderate	RR 0.98 (0.55 to 1.76)	44	2838 (5 RCTs)	⊕⊕⊕○ Moderate	Downgraded one level due to imprecision (wide CIs)
	17 per 1000	17 per 1000 (9 to 30)				
Etanercept	Moderate	RR 0.99 (0.65 to 1.51)	43.6	3783 (11 RCTs)	⊕⊕⊕○ Moderate	Downgraded one level due to imprecision (CIs including one)
	17 per 1000	17 per 1000 (11 to 26)				

Guselkumab	Moderate		RR 1.00 (0.49 to 2.04)	42.6	1502 (3 RCTs)	⊕⊕○○ Low	Downgraded one level due to risk of bias (credibility of evidence), and one level due to imprecision (CIs including one)
	15 per 1000	15 per 1000 (7 to 31)					
Adalimumab	Moderate		RR 1.02 (0.61 to 1.73)	40.4	3199 (8 RCTs)	⊕⊕⊕○ Moderate	Downgraded one level due to imprecision (CIs including one)
	18 per 1000	19 per 1000 (11 to 31)					
Brodalumab	Moderate		RR 1.04 (0.62 to 1.73)	39.8	4109 (5 RCTs)	⊕⊕○○ Low	Downgraded one level due to risk of bias (credibility of evidence) and one level due to imprecision (CIs including 1)
	17 per 1000	18 per 1000 (11 to 30)					
Tildrakizumab	Moderate		RR 1.36 (0.07 to 24.94)	37.8	355 (1 RCT)	⊕⊕○○ Low	Downgraded one level due to risk of bias (credibility of evidence) and one level due to imprecision (CIs including 1)
	0 per 1000	0 per 1000 (0 to 0)					
Ixekizumab	Moderate		RR 1.12 (0.66 to 1.90)	33.7	3268 (4 RCTs)	⊕⊕⊕○ Moderate	Downgraded one level due to imprecision (CIs including one)
	15 per 1000	16 per 1000 (10 to 28)					
Secukinumab	Moderate		RR 1.19 (0.69 to 2.03)	29.9	2707 (7 RCTs)	⊕⊕⊕○ Moderate	Downgraded one level due to imprecision (CIs including one)
	10 per 1000	12 per 1000 (7 to 20)					
Ponesimod	Moderate		RR 2.59 (0.34 to 19.85)	18.1	326 (1 RCT)	⊕⊕⊕○ Moderate	Downgraded one level due to imprecision (CIs including one)

15 per 1000	39 per 1000 (5 to 296)
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\* **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** confidence interval; **PASI<sup>c</sup>:** Psoriasis Area and Severity Index; **RR:** risk ratio; **SUCRA<sup>d</sup>:** Surface Under the Cumulative Ranking

**GRADE Working Group grades of evidence**

**High certainty/quality:** We are very confident that the true effect lies close to that of the estimate of the effect

**Moderate certainty/quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low certainty/quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

**Very low certainty/quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

<sup>a</sup> 'Risk with placebo' is the median placebo-group risk value in the included studies for the assumed risk with placebo.

<sup>b</sup> 'Number of studies (participants)' is from the direct comparisons.

<sup>c</sup> The Psoriasis Area and Severity Index combines the assessment of the severity of lesions and the area affected into a single score in the range of 0 (no disease) to 72 (maximal disease); PASI 90: 90% improvement in the PASI.

<sup>d</sup> SUCRA was expressed as a percentage between 0 (when a treatment is certain to be the worst) to 100% (when a treatment is certain to be the best).

## BACKGROUND

Please refer to our glossary (see [Table 1](#)).

### Description of the condition

Psoriasis is an immune-mediated disease for which a person can have genetic susceptibility, manifesting in chronic inflammatory effects on either the skin or joints, or both, with a prevalence ranging from 0.91% (United States) to 8.5% (Norway) ([Boehncke 2015](#); [Parisi 2013](#)). The causes of psoriasis are not fully understood. There appears to be interaction between environmental factors and genetic susceptibility. Genome-wide (or whole genome) association trials found several candidate genes relating to psoriasis ([Elder 2010](#)). Various environmental factors, including stress, injury, and infections, are suspected to trigger or aggravate the evolution of psoriasis. An inflammatory immune response involving dendritic cells, T cells, keratinocytes, neutrophils, and the cytokines released from immune cells initiates the pathophysiological process ([Jariwala 2007](#); [Lowes 2008](#); [Wilson 2007](#); [Zheng 2007](#)).

Diagnosis is made based on clinical findings; skin biopsy is rarely used to diagnose the disease ([Boehncke 2015](#)). Several clinical types of psoriasis exist: plaque, pustular, inverse, and erythrodermic. Plaque psoriasis is the most common form, affecting 90% of people with psoriasis ([Griffiths 2007](#)). Plaque psoriasis typically appears as raised erythematous and well-demarcated areas of inflamed skin covered with silvery white, scaly skin ([Griffiths 2007](#)). The location of the plaques is usually symmetrical on the elbows, knees, scalp, lower back, and the periumbilical region. For 5% to 25% of people with psoriatic rheumatic disease, their skin is also involved ([Helliwell 2005](#); [Zachariae 2003](#)).

### Severity

Chronicity characterises the natural history of plaque psoriasis; this means that severity varies over time, from minor localised patches to complete body coverage. The severity of the disease usually fluctuates around the same level for a particular person ([Nijsten 2007](#)), but for each person with this disease, the evolution and duration of remission is unpredictable. The psoriasis is declared clear when remission is complete.

More than a dozen outcome instruments are used to assess the severity of psoriasis and the efficacy of different treatments for psoriasis ([Naldi 2010](#); [Spuls 2010](#)); the Psoriasis Area and Severity Index (PASI) score is one of these instruments ([Schmitt 2005](#)). The Psoriasis Area and Severity Index combines the assessment of the severity of lesions and the area affected into a single score in the range of 0 (no disease) to 72 (maximal disease). Recent clinical trials evaluating biological therapies that have received secondary marketing authorisation by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) used PASI 75, i.e. 75% improvement in the PASI score, as the primary

end point. However, the PASI has substantial limitations, such as low-response distribution, no consensus on interpretability, and low responsiveness in mild disease ([Spuls 2010](#)).

### Impact and quality of life

Disease severity alone does not determine the burden of psoriasis. Multiple studies have described an impairment of the quality of life (QoL); others have focused on an evaluation of the stigma people experience; and others have studied the impact on psychosocial life ([Kimball 2005](#)).

Impairment of QoL in people with psoriasis, when measured with the 36-item Short Form Health Survey (SF-36) questionnaire has been found to be higher than that of people with hypertension, diabetes, or depression ([Rapp 1999](#)).

Many tools exist to measure the QoL of people with psoriasis and other skin disorders. These measures may be categorised as psoriasis-specific (Psoriasis Index of Quality of Life (PSORIQoL), Psoriasis Disability Index (PDI)); skin-specific (Dermatology Life Quality Index (DLQI), Skindex (a quality-of-life measure for patients with skin disease)); and generic QoL measures (SF-36). However, methodological weaknesses exist in the use of QoL questionnaires, and there is poor reporting of QoL outcomes in randomised clinical trials ([Le Cleach 2008](#)). Several case-control studies reported a higher risk of metabolic syndrome and cardiovascular comorbidities ([Kremers 2007](#); [Naldi 2005](#)).

### Description of the intervention

There is currently no cure for psoriasis, but various treatments can help to control the symptoms; thus, long-term treatment is usually needed. In daily practice, a treatment strategy needs to be defined, and this usually involves an induction therapy, e.g. the remission of the psoriasis flare, and a maintenance therapy, e.g. increasing the period of remission.

The therapeutic approach to psoriasis includes topical treatments as a single strategy and a first-line therapy in the management of minor forms ([Mason 2013](#)). Nevertheless, about 20% to 30% of people with psoriasis have a moderate to severe form requiring a second-line therapy including phototherapy and conventional systemic agents, such as ciclosporin, methotrexate, or acitretin. Among the systemic agents, the choice of drug is not clear. The [NICE 2012](#) clinical guidelines in the UK had proposed methotrexate as the first choice of systemic agent. Other countries, such as France, do not have any available guidelines. Systemic biological agents, such as the tumour necrosis factor (TNF) antagonists (infliximab, etanercept, adalimumab), the monoclonal antibody ustekinumab that targets interleukin-12 and -23 (IL-12/-23), anti-IL17 drugs (secukinumab or ixekizumab), and more recently new small molecules (apremilast) are “third-line” therapies ([Boehncke 2015](#)). Indeed, there are mandatory reimbursement criteria that patients must meet before being considered for these

treatments due to their high costs: moderate to severe psoriasis after failure, intolerance or contraindication to at least two conventional systemic agents (Nast 2015b).

We used the European S3 guidelines terminology to categorise the treatments (Nast 2015b).

## Oral systemic treatments

### Conventional systemic agents

Conventional systemic agents are a heterogeneous group of treatments that are the oldest interventions given to clear psoriasis.

The existing oral systemic pharmacological treatments available for psoriasis are ciclosporin, methotrexate, acitretin (which is the retinoid of choice for psoriasis), and fumaric acid esters (FAEs) which are licensed for psoriasis in Germany and used off-licence in other countries (Atwan 2015).

Randomised controlled trials against placebo for both induction and maintenance therapies have demonstrated the efficacy of ciclosporin for psoriasis (Bigby 2004; Christophers 1992; Ellis 1991; Flystrom 2008; Koo 1998; Heydendael 2003; Ho 1999; Mahrle 1995; Meffert 1997; Mrowietz 1995; Shupack 1997). In 2008, Saurat et al conducted the only randomised trial comparing the efficacy of methotrexate with placebo (Saurat CHAMPION, 2008). Randomised trials against placebo have demonstrated the efficacy of derivatives of vitamin A, the retinoids, in the treatment of plaque psoriasis (Pettit 1979). Fumaric acid esters are an alternative therapy for people with psoriasis, even though the mechanisms of action are not completely understood (Ormerod 2004). A Cochrane Review on FAEs for psoriasis was published in 2015 (Atwan 2015).

### Small molecules

Small molecules affect molecules inside immune cells. Recently, small molecule drugs have been developed and show potential to treat psoriasis patients not responding to conventional treatments. These small molecule drugs include apremilast (Papp 2012b), tofacitinib (Bachelez 2015), and ponesimod (Vaclavkova 2014). Tofacitinib and ponesimod had not been approved for psoriasis at the time our analyses were done.

### Biological therapies

Biological therapies use substances made from living organisms, or synthetic versions, to target the immune system. In the twentieth century, the development of biological treatments expanded the therapeutic spectrum of systemic treatments for psoriasis. All of the biologics have to be given by infusion or subcutaneous injection, and all have had at least one evaluation of their effectiveness against placebo: alefacept (Krueger 2002; Lebwohl 2003), etanercept (Leonardi 2003), infliximab (Chaudhari 2001), adalimumab (Menter REVEAL, 2008), certolizumab (Reich 2012),

ustekinumab (Lebwohl 2010), secukinumab (Reich 2015), ixekizumab (Leonardi 2012), brodalumab (Papp 2012), guselkumab (Gordon X-PLORE, 2015), tildrakizumab (Papp 2015a), and itolizumab (Krupashankar 2014). Certolizumab, tildrakizumab, and itolizumab had not been approved for psoriasis at the time our analyses were done.

## How the intervention might work

Dysregulation of the immune system is a critical event in psoriasis, and the evolving knowledge of the role of the immune system in the disease has had a significant impact on treatment development. Indeed, psoriatic plaque shows marked infiltration by activated T cells, especially CD4+ cells in the dermis. The activated T cells produce several important cytokines, namely, interferon (IFN)- $\gamma$ , TNF alpha (by Th1 and Tc1 cells), IL-17A, and IL-23R (by Th17 and Tc17 cells) (Boehncke 2015).

## Oral systemic treatments

### Conventional systemic agents

#### Ciclosporin

Ciclosporin is an immunosuppressive agent (a drug that reduces the efficacy of the immune system); it acts by inhibiting the initial phase of the activation of CD4+ T cells, which leads to a block on the synthesis of interleukin 2 by the complex cyclophilin-ciclosporin, thus, preventing T cell proliferation that is key to the pathogenesis of psoriasis (see above) (Ho 1996). This immunosuppression is rapid and reversible. Ciclosporin rapidly reduces the severity of the lesions (over one to three months), but the continuation of treatment is difficult after two years because of the development of adverse effects, such as elevated creatinine levels (Maza 2011). A dose of 5.0 mg/kg/day ciclosporin was significantly more effective than 2.5 mg/kg/day ciclosporin for induction of the remission of psoriasis; however, elevated creatinine was significantly more likely with 5.0 mg/kg/day ciclosporin than with 2.5 mg/kg/day ciclosporin (Christophers 1992).

#### Methotrexate

Methotrexate is an antimetabolite (an inhibitor of a chemical that is part of normal metabolism), which acts as an antagonist of folic acid (Montaudie 2011). Low doses of methotrexate exert anti-inflammatory and immunomodulatory activities (Montaudie 2011). The efficacy of methotrexate cannot be assessed earlier than three months; its long-term safety profile is good. In clinical practice, methotrexate is administered orally at 15 to 25 mg/week (Montaudie 2011).

## Retinoids

Retinoids, including acitretin, are involved in the growth and differentiation of skin tissue; they bind to nuclear receptors that belong to the large family of steroid hormone receptors (Sbidian 2011). Retinoids modulate many types of proteins, including epidermal structural proteins, metalloproteinases, and cytokines (Sbidian 2011). The efficacy of retinoids is evaluated after two to three months of treatment, but skin side effects (e.g. xerosis, cheilitis) may limit the ability to increase the dose. Treatment with retinoids is best avoided in women of childbearing age because of risks to a developing foetus and the necessity of using contraception two years after discontinuation of treatment (Sbidian 2011). People receiving 50 mg/day to 75 mg/day acitretin have significantly improved psoriasis compared with those receiving 10 mg/day to 25 mg/day acitretin (Goldfarb 1988).

## FAEs

FAEs are chemical compounds derived from the unsaturated dicarboxylic acid (Atwan 2015). Oral preparations of FAEs in psoriasis were developed containing dimethyl fumarate (DMF) and salts of monoethyl fumarate (MEF) as main compounds (Atwan 2015). FAEs produce anti-inflammatory effects by preventing the proliferation of T cells (Atwan 2015).

FAEs are an effective therapy in people with psoriasis (50% to 70% achieve PASI 75 improvement within four months of treatment). Tolerance is limited by gastrointestinal side effects and flushing of the skin (Atwan 2015). Several case-series described rare adverse events, such as progressive multifocal leukoencephalopathy (Balak 2016). In clinical practice, FAEs are administered orally. People receive this after a gradual dose incrementation the equivalent of 720 mg of DMF per day.

## Small molecules

Small molecule drugs modulate proinflammatory cytokines and selectively inhibit signalling pathways: phosphodiesterase 4 inhibitors (apremilast), Janus kinase (JAK) inhibitors (tofacitinib), or sphingosine 1-phosphate receptor agonists (ponesimod) (Torres 2015).

## Apremilast

Apremilast belongs to the phosphodiesterase 4 (PDE4) inhibitors family (Torres 2015). By increasing cyclic adenosine monophosphate (cAMP) levels, PDE4 inhibitors reduce production of pro-inflammatory TNF alpha and IFN $\gamma$  in patients with psoriasis. Apremilast has recently been approved for psoriasis; its efficacy seems to be higher than conventional systemic therapy; however, no randomised controlled trials (RCTs) have assessed apremilast versus methotrexate or ciclosporin. The safety of the drug should be detailed in the near future with phase 4 studies. In clinical practice, apremilast is administered orally at 30 mg twice a day (Torres 2015).

## Tofacitinib

Tofacitinib is a Janus kinase (JAK) inhibitor (Torres 2015). JAK inhibitors targets the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway, which is pivotal for the downstream signaling of inflammatory cytokines involved in psoriasis. Tofacitinib had not been approved for psoriasis at the time our analyses were done (Torres 2015).

## Ponesimod

Ponesimod is a sphingosine 1-phosphate receptor agonist that causes dose-dependent sequestration of lymphocytes in lymphoid organs, thus, preventing T cell proliferation, which is key to the pathogenesis of psoriasis. Ponesimod had not been approved for psoriasis at the time our analyses were done (Torres 2015).

## Biological therapies

Biological therapies have been developed in recent years and target and prevent T cell proliferation (e.g. alefacept and itolizumab, a humanised IgG1 (immunoglobulin G1) monoclonal antibody, which selectively targets CD6) or target cytokines involved in psoriasis pathophysiology (e.g. anti-TNF alpha, anti-IL12/23, anti-IL23, anti-IL17).

## Alefacept

Alefacept is an immunosuppressive agent (a fusion protein that blocks the growth of some types of T cells). Alefacept (either 7.5 mg intravenously (IV) or 15 mg intramuscularly (IM) once a week) is used to control inflammation in moderate to severe psoriasis with plaque formation, where it interferes with lymphocyte activation. This drug was never approved for the European drug market. It was sold in North America, Switzerland, Israel, and Australia. In 2011, the manufacturers made a decision to cease sales of alefacept. This decision was not related to any specific safety concern nor the result of any FDA-mandated or voluntary product recall (Heffernan 2010).

## Anti-TNF alpha

Two monoclonal antibodies against tumour necrosis factor alpha (TNF- $\alpha$ ) (infliximab, adalimumab) and one recombinant TNF- $\alpha$  receptor (etanercept) have been developed to inhibit TNF- $\alpha$  signalling, thus, preventing its inflammatory effects and are approved in psoriasis (Gisoni 2004). A third, certolizumab, is being assessed for psoriasis in phase 3 trials.

- Etanercept is a recombinant TNF- $\alpha$  receptor and weakly immunogenic (provokes only a mild immune response). Its efficacy is assessed at three months. A 50 mg dose of etanercept is administered subcutaneously twice weekly for three months during the induction phase (remission of the psoriasis flare) with 50 mg administered weekly as maintenance therapy (Gisoni 2004).



- Infliximab is a chimeric antibody that neutralises the action of TNF- $\alpha$ . Its efficacy is evaluated after six to eight weeks of treatment. A dose of 5.0 mg/kg infliximab is given as an intravenous (IV) induction regimen at 0, 2, and 6 weeks followed by a maintenance regimen of 5.0 mg/kg every 8 weeks. The presence of a murine sequence at recognition sites can lead to the development of anti-infliximab antibodies that may impair the therapeutic effect (Gisoni 2004).

- Adalimumab is a fully humanised antibody with very low immunogenicity. Its efficacy is estimated after eight and 12 weeks of treatment. One dose of 80 mg is administered subcutaneously, followed one week later by a 40 mg subcutaneous dose, which is administered every two weeks (Mossner 2009). Those receiving TNF- $\alpha$  blockers are potentially exposed to a greater risk of infection and require regular monitoring (Tubach 2009).

- Certolizumab is an anti-TNF alpha with a unique structure that does not contain an Fc (fragment crystallisable) portion as adalimumab or infliximab does based on the human immunoglobulin G1 Fc. Therefore, certolizumab does not display Fc-mediated effects (improving solubility, increasing drug stability, and decreasing immunogenicity). Certolizumab had not been approved for psoriasis at the time our analyses were done (Campanati 2017).

#### Anti-IL12/23, Anti-IL23, Anti-IL17

Additional monoclonal antibodies have been developed against pro-inflammatory cytokines: IL-12, IL-23, and IL-17 inhibit the inflammatory pathway at a different point to the anti-TNF alpha antibodies (Dong 2017).

- Interleukin-12 and IL-23 share a common domain, p40, which is the target of ustekinumab (which the FDA has recently approved) (Savage 2015). A 45 mg subcutaneous dose is administered initially (90 mg if body weight is over 100 kg), then 45 mg (or 90 mg) subcutaneously four weeks later, and thereafter 45 mg (or 90 mg) subcutaneously every 12 weeks (Savage 2015). Interleukin-23 plays an essential role in skin inflammation in psoriasis leading to the development of agents that selectively target the IL-23p19 subunit (Dong 2017). Drugs targeting the p19 subunit of IL-23 are guselkumab (a fully human IgG1k monoclonal IL-23 antagonist), tildrakizumab (a humanised IgG1k monoclonal antibody), and risankizumab (high affinity humanised IgG1 monoclonal antibody) (Dong 2017). In July 2017, the FDA approved guselkumab for psoriasis. Guselkumab is given as a 100 mg subcutaneous injection every 8 weeks, following two starter doses at week 0 and week 4. Risankizumab was assessed after we began the systematic review and will be added in the next update.

- Interleukin-17 inhibitors include secukinumab (a recombinant fully human anti-IL17A IgG1k monoclonal antibody), ixekizumab (a humanised anti-IL17 immunoglobulin G4 monoclonal antibody), and brodalumab (a human IgG2 monoclonal antibody that decreases the downstream effect of IL-

17 by antagonising the IL-17RA receptor) (Dong 2017). The recommended dosage for secukinumab is 300 mg administered subcutaneously at weeks 0, 1, 2, 3, and 4, and then every 4 weeks thereafter. Ixekizumab is administered at 160 mg (2 x 80 mg injections) at weeks 0, 2, 4, 6, 8, 10, and 12, and then every 4 weeks thereafter (Dong 2017).

#### Why it is important to do this review

To determine the treatment pathway in psoriasis, the efficacy and safety of each systemic treatment must be determined relative to other therapies. Several randomised controlled trials (RCTs) have compared against placebo the efficacy of the different systemic treatments for psoriasis. However, there are few trials comparing conventional systemic therapies head-to-head, systemic therapies against biological therapies, or biological therapies head-to-head. Several previous meta-analyses or indirect comparison meta-analyses have been published (Bansback 2009; Brimhall 2008; Gomez-Garcia 2017; Gospodarevskaya 2009; Lin 2012; Loveman 2009; Nast 2015; Nelson 2008; Reich 2008; Reich 2012a; Schmitt 2008; Signorovitch 2010; Signorovitch 2015; Spuls 1997; Strober 2006; Tan 2011; Turner 2009; Woolcott 2006). However, the number of studies included in these publications was low, the searches were not exhaustive, and several trials have been published since their search dates. Also, the publications did not evaluate some systemic and biological treatments.

A network meta-analysis enables the best use of the direct and indirect information available to determine the relative efficacy of treatments. In other words, a network meta-analysis will help to highlight the missing key comparisons that are needed to inform clinical practice.

The plans for this review were published as a protocol 'Systemic pharmacological treatments for chronic plaque psoriasis' (Sbidian 2015).

#### OBJECTIVES

To compare the efficacy and safety of conventional systemic agents (acitretin, ciclosporin, fumaric acid esters, methotrexate), small molecules (apremilast, tofacitinib, ponesimod), anti-TNF alpha (etanercept, infliximab, adalimumab, certolizumab), anti-IL12/23 (ustekinumab), anti-IL17 (secukinumab, ixekizumab, brodalumab), anti-IL23 (guselkumab, tildrakizumab), and other biologics (alefacept, itolizumab) for patients with moderate to severe psoriasis and to provide a ranking of these treatments according to their efficacy and safety.

#### METHODS

## Criteria for considering studies for this review

### Types of studies

We included randomised controlled trials (RCTs).

Phase I trials were not eligible because participants, outcomes, dosages, and schema of administration of interventions are too different from phase II, III, and IV studies. Cross-over trials were not eligible (because of the unpredictable evolution of psoriasis and risk of carry-over bias). Non-randomised studies, including follow-up studies, were not eligible.

### Types of participants

We considered trials that included adults (over 18 years of age) with moderate to severe plaque psoriasis (i.e. needed systemic treatment) or psoriatic arthritis whose skin had been clinically diagnosed with moderate to severe psoriasis and who were at any stage of treatment.

### Types of interventions

We considered trials that assessed systemic and biological treatments, irrespective of the dose and duration of treatment, compared with placebo or with each other.

Systemic and biological treatments included the following:

- Systemic conventional treatments
  - FAEs
  - Acitretin
  - Ciclosporin
  - Methotrexate
- Small molecules
  - Apremilast
  - Tofacitinib
  - Ponesimod
- Anti-TNF alpha
  - Infliximab
  - Etanercept
  - Adalimumab
  - Certolizumab
- Anti-IL12/23
  - Ustekinumab
- Anti-IL17
  - Secukinumab
  - Brodalumab
  - Ixekizumab
- Anti-IL23
  - Tildrakizumab
  - Guselkumab
- Other biologic treatments

- Itolizumab
- Alefacept

We were interested to compare both the different drugs (n = 19) and the different classes of drugs (n = 7).

A new anti-IL23 molecule (BI 655066, risankizumab) appeared after we began this review and was not included in this systematic review. However, the ongoing studies of risankizumab have been reported in this review.

Active comparators included the following:

- any of the aforementioned systemic and biological treatments; or
- additional treatment not of primary interest but used for the network synthesis, such as topical treatment or phototherapy.

In multi-arm trials, study groups assessing drugs other than those mentioned above were not eligible. In cases of multi-dose trials, we grouped together all of the different dose groups as a single arm and performed sensitivity analysis at dose level.

In our [Background](#) section, we have referred to ongoing Cochrane Reviews that address some of the systemic treatments administered to adults with plaque psoriasis. We considered these treatments in our review, and we have liaised with each of these teams to harmonise our protocols. However, the Cochrane Review on FAEs, published in 2015, included people with all types of psoriasis and not only plaque-type psoriasis ([Atwan 2015](#)).

### Types of outcome measures

Psoriasis is a chronic disease; treatments are symptomatic often with a return to baseline after discontinuation. In the absence of an existing defined core outcome set ([Spuls 2016](#)), we chose the most relevant outcomes for patients (COMET). The Psoriasis Area and Severity Index score (PASI) 75 is the most common outcome measure used. However, confronted with a debilitating and a socially and psychologically highly visible disease, a completely “clear or almost clear” skin is a more stringent test in the induction phase (remission of the psoriasis flare).

### Primary outcomes

1. The proportion of participants who achieved clear or almost clear skin, that is, at least PASI 90.
2. The proportion of participants with serious adverse effects (SAE). We used the definition of severe adverse effects from the International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, which includes death, life-threatening events, initial or prolonged hospitalisation, and adverse events requiring intervention to prevent permanent impairment or damage.

## Secondary outcomes

1. Proportion of participants who achieve PASI 75 at induction phase.
2. Proportion of participants who achieve a Physician Global Assessment (PGA) value of 0 or 1.
3. Quality of life measured by a specific scale. Available validated scales are the Dermatology Life Quality Index (DLQI), Skindex, Psoriasis Disability Index (PDI), or Psoriasis Symptom Inventory (PSI).
4. The proportions of participants with adverse effects (AE).
5. Proportion of participants with at least one relapse in the maintenance phase (between 52 to 104 weeks).

## Timings

Where possible, we evaluated the outcomes at two different timings:

- induction therapy (short-term remission) (evaluation less than 24 weeks after the randomisation); and
- maintenance therapy (long-term remission) (evaluation between 52 and 104 weeks after the randomisation).

We did not include studies that had timings outside of these time ranges in our review. All of the outcomes except the proportion of participants with at least one relapse in the maintenance phase were recorded during the randomisation phase.

## Search methods for identification of studies

We aimed to identify all relevant RCTs regardless of language or publication status (published, unpublished, in press, or in progress).

## Electronic searches

We searched the following databases up to 15 December 2016:

- the Cochrane Skin Specialised Register using the search strategy in [Appendix 1](#);
- the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 11) in the Cochrane Library using the strategy in [Appendix 2](#);
- MEDLINE Ovid (from 1946) using the strategy in [Appendix 3](#);
- Embase Ovid (from 1974) using the strategy in [Appendix 4](#); and
- LILACS (Latin American and Caribbean Health Science Information database, from 1982) using the strategy in [Appendix 5](#).

## Trials registers

We searched the following trials registers up to 22 December 2016 with the following search terms: psoriasis AND one by one each drug name listed in [Types of interventions](#):

- World Health Organization International Clinical Trials Registry Platform (ICTRP) ([apps.who.int/trialsearch/](http://apps.who.int/trialsearch/));
- ISRCTN registry ([www.isrctn.com](http://www.isrctn.com));
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov ([www.clinicaltrials.gov](http://www.clinicaltrials.gov));
- Australian New Zealand Clinical Trials Registry ([www.anzctr.org.au](http://www.anzctr.org.au)); and
- EU Clinical Trials Register ([www.clinicaltrialsregister.eu](http://www.clinicaltrialsregister.eu)).

## Searching other resources

### Previous meta-analyses and systematic reviews

We looked at the search strategies of previous meta-analyses to improve our search strategies.

### References from other studies

We checked the bibliographies of included and excluded studies for further references to relevant trials.

### Unpublished literature

We searched the trial results databases of various pharmaceutical companies to identify ongoing and unpublished trials. We made attempts to locate unpublished and ongoing trials through correspondence with authors and pharmaceutical companies (see [Table 2](#)).

We searched reviews submitted to the U.S. Food and Drug Administration and the European Medicines Agency (EMA) for drug registration (using [www.accessdata.fda.gov/scripts/cder/drugsatfda](http://www.accessdata.fda.gov/scripts/cder/drugsatfda) and [www.ema.europa.eu/ema](http://www.ema.europa.eu/ema)).

### Conference proceedings

We handsearched the proceedings of the following conferences during the periods not included in the Cochrane Skin Specialised Register:

- The American Academy of Dermatology (AAD) from 2008 to 2009 and from 2012 to 2013;
- The Society for Investigative Dermatology (SID) from 2008 to 2009 and from 2012 to 2013; and
- The European Academy of Dermatology and Venereology (EADV) from 2008 to 2013.

### Adverse effects

We did not perform a separate search for rare or delayed adverse effects of the target interventions. However, we examined data on adverse effects from the included studies we identified.

## Data collection and analysis

### Selection of studies

Two groups of two review authors (LLC/ES or IGD/GD) independently examined each title and abstract to exclude irrelevant reports. These authors independently examined full-text articles to determine eligibility. We contacted study authors for clarification when necessary and discussed disagreements to reach consensus. We list excluded studies and document the primary reason for exclusion.

### Data extraction and management

Three groups of two review authors (LLC, GD, CH, IGD, CM, or ES) each extracted the data from published and unpublished reports independently using a standardised form. We pilot-tested this form (Data Extraction Form) on a set of included trials. We extracted the data to populate the 'Characteristics of included studies' tables in RevMan Manager 5.3 (Revman 2014).

We extracted the data from the reports of the U.S. Food and Drug Administration (FDA) when available, if not from the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)), and finally from the published reports.

### Outcome data

We extracted (arm-level data) from each included trial; hence, the total number of participants randomised to each intervention. For binary outcomes, we also extracted the number of participants (if available) who:

- reached PASI 90, PASI 75, or PGA 0/1 during the induction phase;
- had at least one relapse in the maintenance phase; and
- had at least one SAE/one AE during the induction phase.

For quality of life, we extracted from each included trial the mean change score of the study specific scale from baseline to follow-up. When PASI 90 and PASI 75 outcomes were not reported and when the information was available, we extracted the PASI score at baseline and at the evaluation point (or the percentage reduction in PASI from baseline to follow up) to calculate the number of participants who reached PASI 75 and 90.

Regarding the assessment of quality of life, we recorded all specific quality of life (QoL) scales (Dermatology Life Quality Index (DLQI), Skindex, Psoriasis Disability Index (PDI), and Psoriasis Symptom Inventory (PSI)).

### Data on potential effect modifiers

We extracted baseline demographic and clinical characteristics of participants that may have acted as effect modifiers (age, sex, body weight, duration of psoriasis, severity of psoriasis at baseline, previous psoriasis treatment). One review author (ES) checked and entered the data into the RevMan computer software. We contacted the authors of the trials to request missing data (see [Table 2](#)).

### Assessment of risk of bias in included studies

We used Cochrane's 'Risk of bias' (RoB) tool to assess the risk of bias. Three groups of two review authors each (LLC, GD, CH, IGD, CM, or ES) independently assessed the risk of bias, and one author (LLC) resolved any disagreements. For each of the following domains and according to the general principles in section 8.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), we graded the following 'Risk of bias' domains as 'low', 'high', or 'unclear'.

#### 1. Selection bias

◦ Was the allocation sequence adequately generated? We considered randomisation adequate (low risk of bias) if the allocation sequence was generated from a table of random numbers or was computer-generated. We considered randomisation inadequate (high risk of bias) if sequences could be related to prognosis. We considered randomisation unclear if the paper stated that the trial was randomised, but did not describe the method.

◦ Was allocation adequately concealed? We deemed allocation concealment as adequate if the report stated that it was undertaken by means of sequentially pre-numbered sealed opaque envelopes or by a centralised system. We considered a double-blind double-dummy process as at low risk of bias even if the paper did not describe the method of allocation concealment.

#### 2. Performance and detection bias

◦ Was knowledge of the allocated intervention adequately prevented during the study? We evaluated the risk of bias separately for personnel and participants, outcomes assessors, and each outcome.

#### 3. Attrition bias

◦ Were incomplete outcome data adequately addressed? We examined if there was imbalance across intervention groups in numbers or reasons for missing data, type of measure undertaken to handle missing data, and whether the analysis was carried out on an intention-to-treat (ITT) basis. We assessed the use of strategies to handle missing data.

#### 4. Reporting bias

◦ Were reports of the study free of suggestion of selective outcome reporting? We evaluated if each outcome was measured, analysed, and reported. We compared outcomes specified in protocols (if available on the [FDA website](#) or [ClinicalTrials.gov](#)) and in material and methods with outcomes presented in the

results section. We considered reporting bias inadequate if one specified outcome in protocols was lacking in the main report.

#### 5. Other risk of bias

○ We did not fulfil the 'other risk of bias' item as we did not highlight particular circumstances leading to other risk of bias from particular trial designs, contamination between the experimental and control groups, and particular clinical settings.

### Overall risk of bias

To summarise the quality of evidence and to interpret the network results, we used these six RoB criteria (random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessor, incomplete outcome data, and selective outcome reporting) in order to classify each trial.

We would classify the trial as having low risk of bias if we rated none of the domains above as high risk of bias and two or less as unclear risk.

We would classify the trial as having moderate risk of bias if we rated one domain as high risk of bias, one or less domains as unclear risk, or no domains as high risk of bias but three or less were rated as unclear risk.

All other cases were assumed to pertain to high risk of bias.

### Measures of treatment effect

#### Relative treatment effects

For each pair-wise comparison and each dichotomous outcome at each time point, we used risk ratios (RR) with 95% confidence intervals (CI) as a measure of treatment effect. For continuous variables (e.g. quality of life scale), we used the standardised mean difference (SMD) with 95% CI.

#### Relative treatment ranking - network meta-analysis

For every treatment, we estimated the ranking probabilities of being at each possible rank for all outcomes. We inferred on treatment hierarchy using the surface under the cumulative ranking curve (SUCRA) (Salanti 2011). SUCRA was expressed as a percentage between 0 (when it is certain a treatment is the worst) to 100% (when it is certain a treatment is the best).

#### Unit of analysis issues

The primary unit of analysis was the participant. We did not consider studies with non-standard design features that would lead to clustering (e.g. cross-over trials).

We treated comparisons from trials with multiple intervention groups as independent two-arm studies in the pair-wise meta-analyses. At the network meta-analysis stage, we properly accounted for the within-trial correlation.

### Dealing with missing data

We extracted, when possible, both the number of randomised and analysed participants in each study arm. We contacted trial authors or sponsors by email to request missing outcome data (numbers of events and numbers of participants for important dichotomous clinical outcomes) when these were not available in study reports that were less than 10 years old (See Table 2). For the main analysis, we assumed that any participant with missing outcome data did not experience clearance, whatever the group. In a sensitivity analysis, we also synthesised the data ignoring the missing participants (complete case analysis) assuming that they were missing at random (Mavridis 2014).

### Assessment of heterogeneity

We undertook meta-analyses only if we judged participants, interventions, comparisons, and outcomes to be sufficiently similar (section 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions*) (Higgins 2011). Potential sources of heterogeneity included participants' baseline characteristics (weight, the duration of previous treatment, treatment doses, co-interventions, and duration of treatment). When enough data were available, we investigated the distributions of these characteristics across studies and treatment comparisons. The latter allows assessing transitivity, i.e. whether there were important differences between the trials evaluating different comparisons other than the treatments being compared (Salanti 2014). To further reassure the plausibility of the transitivity assumption, we only included in our analyses trials not involving co-interventions and with a timing of outcome assessment from 12 to 16 weeks.

In the classical meta-analyses, we assessed statistical heterogeneity by visual inspection of the forest plots and using the Q-test and the I<sup>2</sup> statistic. We interpreted the I<sup>2</sup> statistic according to the following thresholds (section 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions*; Higgins 2011): 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; 75% to 100% represents considerable heterogeneity.

In the network meta-analysis, the assessment of statistical heterogeneity in the entire network was based on the estimated heterogeneity standard deviation parameter ( $\tau$ ) estimated from the network meta-analysis models (Jackson 2014). We inferred on the presence or absence of important heterogeneity by comparing the magnitude of  $\tau$  with the empirical distributions provided in Turner et al and Rhodes et al (Rhodes 2015; Turner 2012). We also estimated the prediction intervals to assess how much the estimated heterogeneity affects the relative effects with respect to the additional uncertainty anticipated in future studies (Riley 2011). Where feasible, we would have investigated the possible sources of heterogeneity in subgroup analyses and meta-regression.

Although we restricted the risk of important heterogeneity in our data by considering eligible only studies with a follow-up period



between 12 and 16 weeks and without co-interventions, we investigated differences in heterogeneity across the different analyses. Specifically, we observed whether splitting the nodes of the network and analysing each drug separately reduced the heterogeneity estimate. We also ran a series of sensitivity analyses (see [Sensitivity analysis](#)), and we monitored whether heterogeneity became smaller or larger compared to the primary analysis.

### Assessment of reporting biases

To assess reporting biases, we used an adaptation of the funnel plot by subtracting from each study-specific effect size the mean of meta-analysis of the study-specific comparison, which we plotted against the study standard error ([Chaimani 2013](#)). We employed this 'comparison-adjusted funnel plot' for all comparisons of an active treatment against placebo. When we detected funnel plot asymmetry for the two primary outcomes, we investigated the presence of small-study effects in the network meta-regression ([Chaimani 2012](#)).

### Data synthesis

We conducted pair-wise meta-analyses to synthesise trials comparing one of the treatments against placebo or two treatments against each other. We performed pair-wise meta-analyses for all outcomes and comparisons, provided that at least two studies were available, using a random-effects model.

We then employed network meta-analysis to estimate the relative effects for all possible comparisons between any pair of treatments. We provided a graphical depiction of the evidence network for all outcomes to illustrate the network geometry ([Chaimani 2017](#)). We ran network meta-analysis using the approach of multivariate meta-analysis, which treats the different comparisons that appear in studies as different outcomes ([White 2012](#)).

We interpreted a statistically non-significant P value (e.g. larger than 0.05) as a finding of uncertainty unless confidence intervals were sufficiently narrow to rule out an important magnitude of effect.

We assessed inconsistency (i.e. the possible disagreement between the different pieces of evidence) locally and globally. Specifically, we used the loop-specific approach ([Bucher 1997](#)) and the side-splitting method ([Dias 2010](#)). We also fit the design by treatment interaction model to evaluate the presence of inconsistency in the entire network ([Higgins 2012](#)).

We conducted pair-wise meta-analyses using Review Manager 5 (RevMan 5) ([Revman 2014](#)), and we performed all other analyses in Stata 14 using the 'network' ([www.stata-journal.com/article.html?article=st0410](http://www.stata-journal.com/article.html?article=st0410)) and 'network graphs' packages ([www.stata-journal.com/article.html?article=st0411](http://www.stata-journal.com/article.html?article=st0411)).

### Subgroup analysis and investigation of heterogeneity

We considered running subgroup analyses and meta-regressions to investigate potential sources of heterogeneity or inconsistency

(such as weight of participants, duration of psoriasis, baseline severity, previous systemic treatments), but no sufficient data on these characteristics were available to perform these additional analyses.

### Sensitivity analysis

To assess the robustness of our results, we performed the following sensitivity analyses for the two primary outcomes: (1) running the analysis at dose-level considering that each different drug dose is a different intervention; (2) excluding trials at high risk of bias; (3) excluding trials with a total sample size smaller than 50 randomised participants; and (4) analysing only the observed participants assuming that missing participants are missing at random.

### 'Summary of findings' table

We included a 'Summary of findings' table in our review. We downgraded evidence based on the five Grading of Recommendations, Assessment, Development and Evaluation (GRADE) considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) ([Schunemann 2011](#)). We assessed the confidence of the evidence estimates from network meta-analysis, based on an extension of the standard GRADE approach which is based on the contributions of the direct comparisons to the estimation in the network meta-analysis ([Salanti 2014](#)).

We included an overall grading of the evidence for the two main outcomes:

- PASI 90 during the induction phase
- Serious adverse effects during the induction phase

We assessed the study limitations by first evaluating the risk of bias of each direct estimate and then integrating these judgements with the contribution of each direct estimate to the network estimates. We assessed inconsistency by considering the networks' heterogeneity (network meta-analysis estimate of between-study variance and prediction intervals) and using both local and global inconsistency in the networks.

We assessed imprecision by focusing on the CIs of the network meta-analysis treatment effect estimates and by examining ranking probabilities (rankograms).

We assessed indirectness by evaluating the distribution of the potential effect modifiers (baseline demographic and clinical characteristics of participants).

We assessed publication bias by considering the comprehensive search strategy that we performed and the risk of publication bias in the specific field. The comparison-adjusted funnel plots that test the presence of small-study effects in the network assisted our judgement.

For each outcome, we chose the median placebo-group risk value in the included studies for the assumed risk with placebo. According to the software GRADEpro 2008 ([www.grade.pro.org](http://www.grade.pro.org)), we assigned four levels of certainty of evidence: high, moderate, low, or

very low. We used this assessment, which two authors (LLC and ES) conducted, to inform the main text of the discussion section.

## RESULTS

### Description of studies

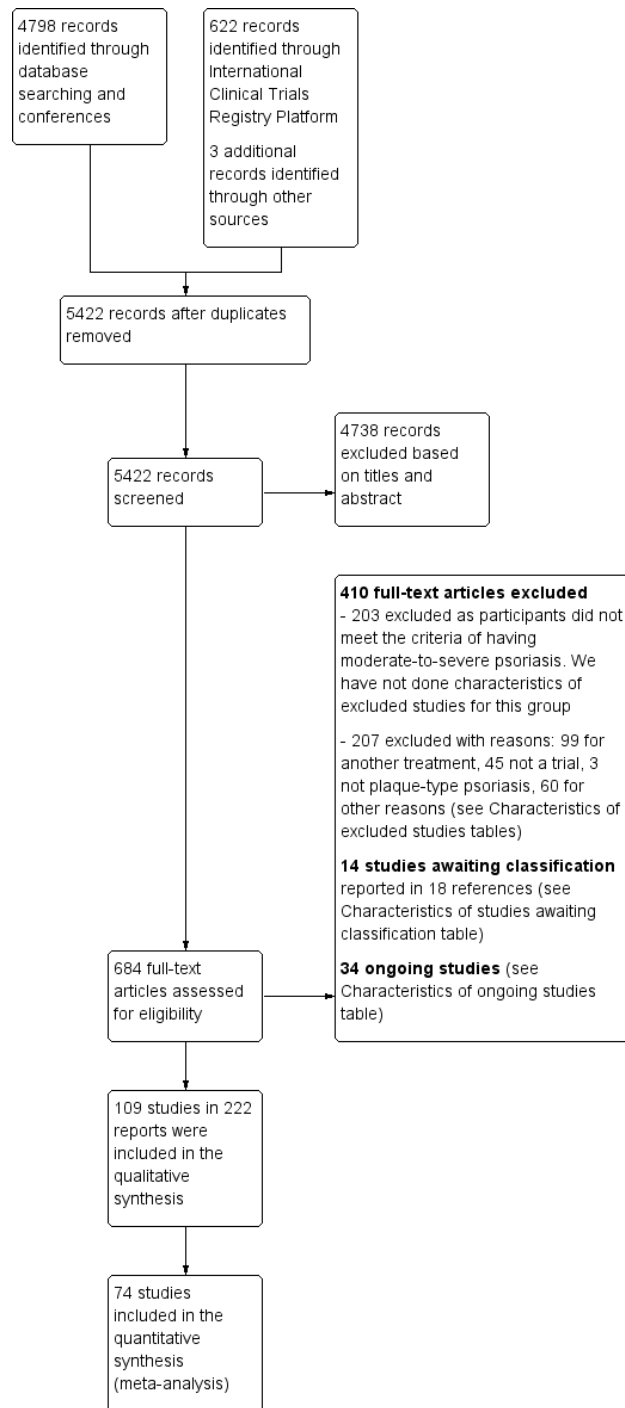
#### Results of the search

The [Electronic searches](#) retrieved 4798 records after deduplication. The searches of other sources identified 622 records from trials registers and three further records from other sources. We had a total of 5422 records after removal of duplicates.

After reviewing the titles and abstracts, we discarded 4738 citations. We examined the full text of the remaining 684 citations: 410 did not meet the inclusion criteria. Within this group, 203 did not include participants with moderate to severe psoriasis and so did not meet our inclusion criteria. We have not created 'Characteristics of excluded studies' tables for this group. We had a further 207 excluded studies (see [Characteristics of excluded studies](#)). We identified 14 trials as studies awaiting classification (reported in 18 references) (see [Characteristics of studies awaiting classification](#)). We identified 34 studies as ongoing (see [Characteristics of ongoing studies](#)).

We included 109 studies, reported in 222 references. For a further description of our screening process, see the study flow diagram ([Figure 1](#)).

**Figure 1. Study flow diagram**





## Included studies

### Trial design

All trials used a parallel-group design. The mean sample size was 366 (range: 10 to 1881). In all, 88 trials were multicentric trials (2 to 231 centres) and 15 were single-centre trials (Akcali 2014; Al-Hamamy 2014; Asawanonda 2006; Chaudhari 2001; Chladek 2005; Dogra 2013; Dogra 2012; Dubertret 1989; Ellis 1991; Gisondi 2008; Gurel 2015; Hunter 1963; Mahajan 2010; Shehzad 2004; Van Bezooijen 2016); for six trials, single-centre or multicentric status was not clear (Caproni 2009; Engst 1994; Goldfarb 1988; Jacobe 2008; Olsen 1989; Yilmaz 2002). All of the trials recruited participants from a hospital setting. The trials took place worldwide (n = 37, 33.9%), in Europe (n = 28, 25.7%), in North America (n = 21, 19.3%), in Asia (n = 17, 15.6%), or in the Middle East (n = 1, 0.9%). The location was not stated for five trials (Caproni 2009; Engst 1994; Goldfarb 1988; Jacobe 2008; Olsen 1989).

In total, 55 trials out of 109 were multiarm; 40 multiarm trials assessed the same experimental drug at multiple dose levels; seven assessed at least two different drugs; eight assessed both the same experimental drug at multiple dose levels and different drugs.

In total, 15 trials (Al-Hamamy 2014; Asawanonda 2006; Bissonnette 2013; Gottlieb 2012; Gurel 2015; Jacobe 2008; Lowe 1991; Mahajan 2010; Ruzicka 1990; Saurat 1988; Shehzad 2004; Sommerburg 1993; Tanew 1991; Van Bezooijen 2016; Yilmaz 2002) had a co-intervention mainly with phototherapy. Only 14 studies were carried out before the year 2000 (Dubertret 1989; Ellis 1991; Engst 1994; Goldfarb 1988; Hunter 1963; Laburte 1994; Lowe 1991; Meffert 1997; Nugteren-Huying 1990; Olsen 1989; Ruzicka 1990; Saurat 1988; Sommerburg 1993; Tanew 1991).

### Characteristics of the participants

This review included 109 trials, with a total of 39,882 randomised participants. We summarise the characteristics of the participants in the [Characteristics of included studies](#). The participants were reported to be between 27 and 56.5 years old, with an overall mean age of 44; there were more men (26,902) than women (12,384). Age and gender were unreported for, respectively, 743 and 596 participants (eight and nine studies). The overall mean weight was 85.6 (range: 64 to 97), and the overall mean Psoriasis Area and Severity Index (PASI) score at baseline was 20 (range: 9.5 to 39).

### Characteristics of the comparisons

## Trials with two parallel arms (the different dose groups were grouped together in one “arm”)

### *Intervention versus placebo: 73 trials compared systemic treatments with placebo*

- Twenty-one trials compared systemic conventional treatments versus placebo
  - Acitretin (n = 9) (Goldfarb 1988; Gurel 2015; Lowe 1991; Olsen 1989; Ruzicka 1990; Saurat 1988; Sommerburg 1993; Tanew 1991; Yilmaz 2002)
  - Fumaric acid esters (FAEs) (n = 3) (Nugteren-Huying 1990; Mrowietz BRIDGE, 2016; Van Bezooijen 2016)
  - Ciclosporin (n = 2) (Ellis 1991; Meffert 1997)
  - Methotrexate (n = 7) (Al-Hamamy 2014; Asawanonda 2006; Hunter 1963; Gottlieb 2012; Mahajan 2010; Shehzad 2004; Warren METOP, 2017)
- Nine trials compared small molecule treatments versus placebo
  - Apremilast (n = 4) (Papp 2012b; Papp 2013b; Papp ESTEEM-1, 2015; Paul ESTEEM-2, 2015)
  - Tofacitinib (n = 4) (Krueger 2016; Papp 2012a; Papp OPT Pivotal-1, 2015; Papp OPT Pivotal-2, 2015)
  - Ponesimod (n = 1) (Vaclavkova 2014)
- Forty-three trials compared biological treatments versus placebo
  - Anti-TNF alpha
    - ◊ Etanercept (n = 8) (Bagel 2012; Gottlieb 2003; Gottlieb 2011; Leonardi 2003; Papp 2005; Strober 2011; Tying 2006; Van de Kerkhof 2008)
    - ◊ Adalimumab (n = 5) (Asahina 2010; Bissonnette 2013; Gordon 2006; Menter REVEAL, 2008; Cai 2016)
    - ◊ Infliximab (n = 6) (Chaudhari 2001; Gottlieb 2004; Reich EXPRESS, 2005; Torii 2010; Yang 2012; Menter EXPRESS-II, 2007)
    - ◊ Certolizumab (n = 1) (Reich 2012)
  - Anti-IL12/23
    - ◊ Ustekinumab (n = 6) (Igarashi 2012; Krueger 2007; Leonardi PHOENIX-1, 2008; Papp PHOENIX-2, 2008; Tsai PEARL, 2011; Zhu LOTUS, 2013)
  - Anti-IL17
    - ◊ Secukinumab (n = 6) (Blauvelt FEATURE, 2015; Langley ERASURE, 2014; Papp 2013a; Paul JUNCTURE, 2015; Reich 2015; Rich 2013)

- ◊ Ixekizumab (n = 2) (Gordon UNCOVER-1, 2016; Leonardi 2012)
- ◊ Brodalumab (n = 3) (Papp AMAGINE-1, 2016; Papp 2012; Nakagawa 2016)
- Anti-IL23
  - ◊ Guselkumab (n = 0)
  - ◊ Tildrakizumab (n = 1) (Papp 2015a)
- Other biologics
  - ◊ itolizumab (n = 1) (Krupashankar 2014)
  - ◊ Alefacept (n = 4) (Ellis 2001; Jacobe 2008; Krueger 2002; Lebwohl 2003)

***Intervention versus active comparators: 25 trials compared systemic treatments with systemic treatments***

- Acitretin versus acitretin (n = 1) (Dogra 2013)
- Acitretin versus ciclosporin (n = 1) (Akcali 2014)
- Ciclosporin versus methotrexate (n = 4) (Flytström 2008; Heydendael 2003; Piskin 2003, Sandhu 2003)
- Ciclosporin versus ciclosporin (n = 3) (Dubertret 1989; Engst 1994; Laburte 1994)
- Methotrexate versus methotrexate (n = 2) (Chladek 2005; Dogra 2012)
- Methotrexate versus FAEs (n = 1) (Fallah Arani 2011)
- Methotrexate versus alefacept (n = 1) (Yan 2011)
- Methotrexate versus infliximab (n = 1) (Barker RESTORE-1, 2011)
- Acitretine versus etanercept (n = 2) (Caproni 2009; Gisondi 2008)
- Etanercept versus etanercept (n = 3) (Ortonne 2013; Sterry PRESTA, 2010; Strohal PRISTINE, 2013)
- Etanercept versus infliximab (n = 1) (de Vries PIECE, 2016)
- Etanercept versus ustekinumab (n = 1) (Griffiths ACCEPT, 2010)
- Tofacitinib versus tofacitinib (n = 2) (Asahina 2016; Bissonnette 2015)
- Secukinumab versus secukinumab (n = 1) (Mrowietz SCULPTURE, 2015)
- Secukinumab versus ustekinumab (n = 1) (Thaci CLEAR, 2015)

***Trials with three parallel arms (the different dose groups were grouped together in one “arm”)***

***A total of 11 trials compared systemic treatments with systemic treatments and placebo.***

- Methotrexate versus adalimumab versus placebo (n = 1) (Saurat CHAMPION, 2008)

- Etanercept versus ixekizumab versus placebo (n = 2) (Griffiths UNCOVER-2, 2015; Griffiths UNCOVER-3, 2015)
- Etanercept versus secukinumab versus placebo (n = 1) (Langley FIXTURE, 2014)
- Etanercept versus apremilast versus placebo (n = 1) (Reich LIBERATE, 2017)
- Guselkumab versus adalimumab versus placebo (n = 3) (Blauvelt VOYAGE-1, 2016; Gordon X-PLORE, 2015; Reich VOYAGE-2, 2017)
- Brodalumab versus ustekinumab versus placebo (n = 2) (Lebwohl AMAGINE-2, 2015; Lebwohl AMAGINE-3, 2015)
- Tofacitinib versus etanercept versus placebo (n = 1) (Bachelez 2015)

In total, the dataset consisted of 109 studies, which provide information on 204, 159, and 152 comparisons between 35 different drug doses, 20 different drugs, and 8 different drug classes, respectively (both including placebo). For the sensitivity analyses, the different drug doses were divided into the following:

- methotrexate, taken orally,  $\geq 15$  or  $< 15$  mg per week;
- ciclosporin, taken orally,  $\geq 3$  or  $< 3$  mg/Kg per day;
- acitretin, taken orally,  $\geq 35$  or  $< 35$  mg per day;
- apremilast, taken orally, 30 mg twice a day or other dosages per day;
- ponesimod, taken orally, 40 mg per day or other dosages per day;
- tofacitinib, taken orally, 20 mg per day or other dosages per day;
- etanercept, subcutaneous (S/C), 25 mg twice a week or etanercept 50 mg twice a week;
- infliximab, intravenous, 5 mg/kg at week 0, 2, and 4 then every 6 weeks or other dosages;
- adalimumab, S/C, 80 mg at week 0, 40 mg at week 1 then 40 mg every other week or other dosages;
- secukinumab, S/C, 300 mg at week 0, 1, 2, 3, and 4 then every 4 weeks or other dosages;
- ixekizumab, S/C, 80 mg every two weeks or other dosages;
- brodalumab, S/C, 210 mg every two weeks or other dosages;
- guselkumab, S/C, 100 mg at week 0 and 4 then every 16 weeks or other dosages.

Alefacept (S/C or intravenous (IV)), FAEs (taken orally), certolizumab (S/C), itolizumab (IV), ustekinumab (S/C 45 mg or 90 mg according to the weight) and tildrakizumab (S/C) were grouped in one dosage whatever the dosages.

For each study, we provide details of the dosage in [Characteristics of included studies](#).

**Characteristics of the outcomes**

Regarding the efficacy outcomes during induction therapy (eight to 24 weeks), out of 109 trials, 82 reported PASI 90, 76 reported on Physician Global Assessment (PGA) 0/1, 93 reported PASI 75,

and 54 trials reported assessment of change in quality of life. Fifty-two studies used the dermatology-specific instrument Dermatology Life Quality Index (DLQI); two studies used other specific skin instruments (Skindex). For all of these studies, the investigators provided citations to reports indicating that the tools had been previously validated.

Out of 109 trials, 73 reported the number of participants with adverse effects (different from the number of adverse effects), and 85 reported the number of serious adverse effects.

These outcomes were evaluated between eight and 24 weeks: eight weeks (five studies), 10 weeks (seven studies), 12 weeks (56 studies), 13 weeks (two studies), 14 weeks (two studies), 15 weeks (one study), 16 weeks (22 studies), and 24 weeks (10 studies). Timing of assessment was unknown or not clearly defined for four studies (Engst 1994; Hunter 1963; Saurat 1988; Shehzad 2004).

No trial assessed the outcome 'Proportion of participants with at least one relapse in the maintenance phase (between 52 to 104 weeks)'.

## Funding

In all, 82 studies declared a source of funding, 79 studies declared a pharmaceutical company funding, four studies declared a unique institutional funding (Chladek 2005; de Vries PIECE, 2016; Flytström 2008; Heydendael 2003), five studies had no funding source (Akcali 2014; Asawanonda 2006; Fallah Arani 2011; Gurel 2015; Yan 2011), and 21 studies did not report the source of funding (Al-Hamamy 2014; Caproni 2009; Dogra 2012; Dogra 2013; Dubertret 1989; Engst 1994; Gisondi 2008; Hunter 1963; Laburte 1994; Mahajan 2010; Meffert 1997; Nugteren-Huying 1990; Piskin 2003; Ruzicka 1990; Sandhu 2003; Saurat 1988; Shehzad 2004; Sommerburg 1993; Torii 2010; Yang 2012; Yilmaz 2002).

## Excluded studies

We excluded 410 full-text reports. The main reason for exclusion was that the participants did not present with moderate to severe psoriasis (n = 203): these psoriasis participants were included in trials assessing the efficacy of our treatments of interest for psoriatic arthritis or had cutaneous lesions of psoriasis but not moderate to severe psoriasis. We detail the reason for exclusion of the 207 full-text reports in [Characteristics of excluded studies](#): we excluded 99 because they assessed another intervention, 45 were not a trial, three did not include plaque-type psoriasis, and we excluded 60 for other reasons.

For six studies with three arms, one arm was not included as the intervention was not included in our search:

- Saurat 1988: acitretin versus placebo versus etretinate (etretinate arm was not included);
- Shehzad 2004: PUVA (psoralen and ultraviolet A) therapy versus methotrexate (methotrexate only was included);

- Gottlieb 2011; Strober 2011: briakinumab versus etanercept versus placebo (briakinumab arm was not included);
- Gisondi 2008: etanercept versus acitretin versus etanercept plus acitretin (etanercept plus acitretin arm was not included);
- Al-Hamamy 2014: narrowband ultraviolet B phototherapy plus methotrexate versus narrowband ultraviolet B alone and methotrexate alone (arm with methotrexate alone was not included).

Thaçi 2002 compared two different dosages of ciclosporin (a fixed dosage of 200 mg/day and a dosage corresponding to 2.5 mg/kg/day), and we were unable to classify the fixed dosage group either in the ciclosporin  $\geq 3$  mg/kg/day group nor in the ciclosporin  $< 3$  mg/day group for the subgroup meta-analysis.

## Studies awaiting classification

We classified 14 trials reported in 18 references as studies awaiting classification. More details regarding the studies awaiting classification are available in [Studies awaiting classification](#) and [Table 2](#).

## Ongoing studies

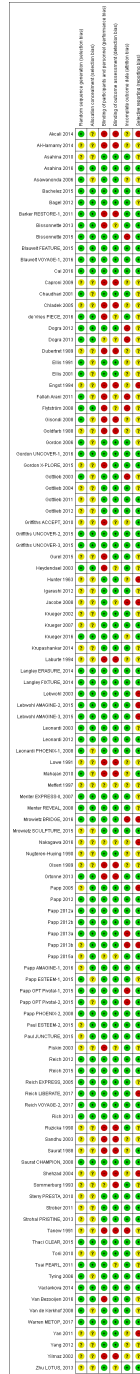
We classified 34 trials as ongoing studies. More details are available in [Characteristics of ongoing studies](#) and [Table 2](#). Most of the ongoing studies compare a biological treatments versus another biological treatment or versus placebo (n = 13 and n = 14, respectively). Three ongoing studies assess apremilast versus placebo, and four assess conventional systemic treatments versus conventional systemic treatments (n = 2) or placebo (n = 2).

## Risk of bias in included studies

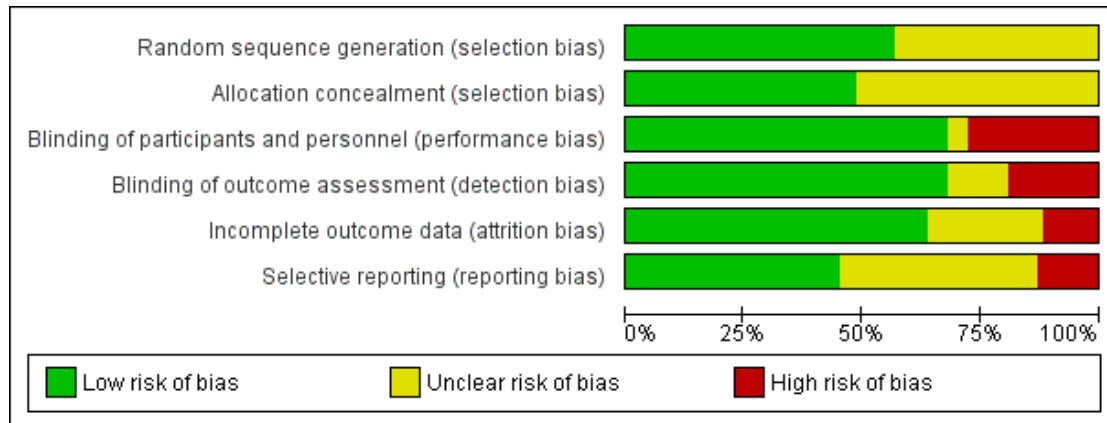
[Figure 2](#) and [Figure 3](#) summarise 'Risk of bias' assessments. Regarding the overall risk of bias across studies, 23 trials were at low risk of bias (Asahina 2016; Bachelez 2015; Blauvelt FEATURE, 2015; Blauvelt VOYAGE-1, 2016; Cai 2016; Gordon UNCOVER-1, 2016; Griffiths UNCOVER-2, 2015; Griffiths UNCOVER-3, 2015; Langley ERASURE, 2014; Langley FIXTURE, 2014; Leonardi 2012; Papp PHOENIX-2, 2008; Papp 2012; Papp 2012a; Papp 2012b; Reich 2015; Reich 2012; Reich VOYAGE-2, 2017; Rich 2013; Saurat CHAMPION, 2008; Thaci CLEAR, 2015; Vaclavkova 2014; Warren METOP, 2017). We categorised almost half of the studies (48/109) as at high risk of bias. Among the high-risk group, five studies had only one high risk of bias domain with all the other dimensions at low risk (Bissonnette 2015; Lebwohl 2003; Papp 2013a; Papp OPT Pivotal-1, 2015; Reich LIBERATE, 2017). We categorised the remaining 38 studies as unclear risk of bias because we assessed one or more criteria as unclear. Among the unclear 'Risk of bias' group, 11 studies had only one unclear risk of bias with all the other dimensions at low risk (Bagel 2012; Krueger 2016; Leonardi 2003; Leonardi PHOENIX-1, 2008; Menter EXPRESS-II, 2007; Menter REVEAL, 2008; Papp

AMAGINE-1, 2016; Paul JUNCTURE, 2015; Paul ESTEEM-2, 2015; Reich EXPRESS, 2005; Tyring 2006). Further details of these assessments are available in the 'Risk of bias' table corresponding to each trial in the [Characteristics of included studies](#).

**Figure 2. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study**



**Figure 3. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies**



### Allocation

The method of sequence generation was not described at all, or was at best unclear, in 48 trials. The remaining studies (n = 61) described the method used to generate the allocation sequence in sufficient detail; therefore, we judged this domain as low risk of bias for these studies. For allocation concealment, the majority of studies (n = 56) received a judgement of unclear risk of bias for this domain because of the absence of reporting the method used to guarantee concealment. We considered the risk low for the 53 remaining trials.

### Blinding

Blinding of participants and personnel was achieved in 74 studies, whereas 30 studies were at high risk of performance bias. The remaining five studies were at unclear risk of performance bias. Blinding of outcome assessment was reported clearly in only 74 of the 109 included studies, whereas 21 studies were at high risk of detection bias. The risk of detection bias was unclear in the remaining 14 studies.

### Incomplete outcome data

In more than half of the trials (69/109), incomplete outcome data appeared to have been adequately addressed, and any missing outcome data were reasonably well balanced across intervention groups, with similar reasons for missing data across the groups. However, in 13 studies the reporting of missing outcome data was

largely inadequate because of one or more of the following reasons: the high number of withdrawn participants, an imbalance between groups in the number of withdrawn participants, an imbalance in reasons for missing outcomes, or no intention-to-treat (ITT) analysis provided. In 27 studies, this domain was as at unclear risk of bias due to one or more of the following reasons: the numbers of participants, reasons, or missing data methods were not reported.

### Selective reporting

We considered 14 trials at high risk of selective outcome reporting because results for outcomes detailed in the methods section were not reported in the results section (Akcali 2014; Engst 1994; Hunter 1963; Jacobe 2008; Lebowhl 2003; Lebowhl AMAGINE-2, 2015; Lebowhl AMAGINE-3, 2015; Mrowietz BRIDGE, 2016; Nakagawa 2016; Papp 2013b; Papp 2005; Reich LIBERATE, 2017; Shehzad 2004; Yan 2011). In all, we considered 49 studies to be at low risk of bias for this domain as outcome details in the trial register and in the methods section were reported in the results section. For other trials (n = 46), we considered the risk of bias as unclear because we did not find these trials in any register.

### Other potential sources of bias

As detailed in the [Methods](#) section, we did not fulfil the 'other risk of bias' item as we did not highlight particular circumstances

leading to other risk of bias from particular trial designs, contamination between the experimental and control groups, and particular clinical settings.

## Effects of interventions

See: [Summary of findings for the main comparison](#) Any systemic treatment compared to placebo for chronic plaque psoriasis

See: [Summary of findings for the main comparison](#) The summary of findings for the main comparison provides overall estimates of treatment effects compared with placebo and the certainty of the available evidence for the two primary outcomes (PASI 90 and serious adverse effects during the induction phase), obtained through network meta-analysis.

Seven trials provided no usable or retrievable data and did not contribute further to the results of this review (Akcali 2014; Chladek 2005; Engst 1994; Lowe 1991; Piskin 2003; Olsen 1989; Shehzad 2004; see [Table 2](#)). The main reason we could not use their data was that these studies addressed none of our outcomes. Fifteen studies, involving 1113 participants (2.8% of the participants in this review), had a co-intervention and did not contribute further to the results of this review as we could not assess the specific intervention effect (Al-Hamamy 2014; Asawanonda 2006; Bissonnette 2013; Gottlieb 2012; Gurel 2015; Jacobe 2008; Lowe 1991; Mahajan 2010; Ruzicka 1990; Saurat 1988; Shehzad 2004; Sommerburg 1993; Tanew 1991; Van Bezooijen 2016; Yilmaz 2002). Twenty-six studies had an outcome assessment before 12 weeks (Akcali 2014; Chaudhari 2001; Goldfarb

1988; Gottlieb 2004; Hunter 1963; Menter EXPRESS-II, 2007; Meffert 1997; Olsen 1989; Reich EXPRESS, 2005; Ruzicka 1990; Sommerburg 1993; Saurat 1988; Torii 2010; Yang 2012), or later than 16 weeks (Al-Hamamy 2014; Asahina 2016; Asawanonda 2006; Bissonnette 2013; Bissonnette 2015; de Vries PIECE, 2016; Engst 1994; Gisondi 2008; Gottlieb 2012; Ortonne 2013; Strohal PRISTINE, 2013; Van Bezooijen 2016).

In total, 35 studies, involving 4433 participants, were not included in the classical or network meta-analysis. The interventions of the 35 studies particularly concerned the following:

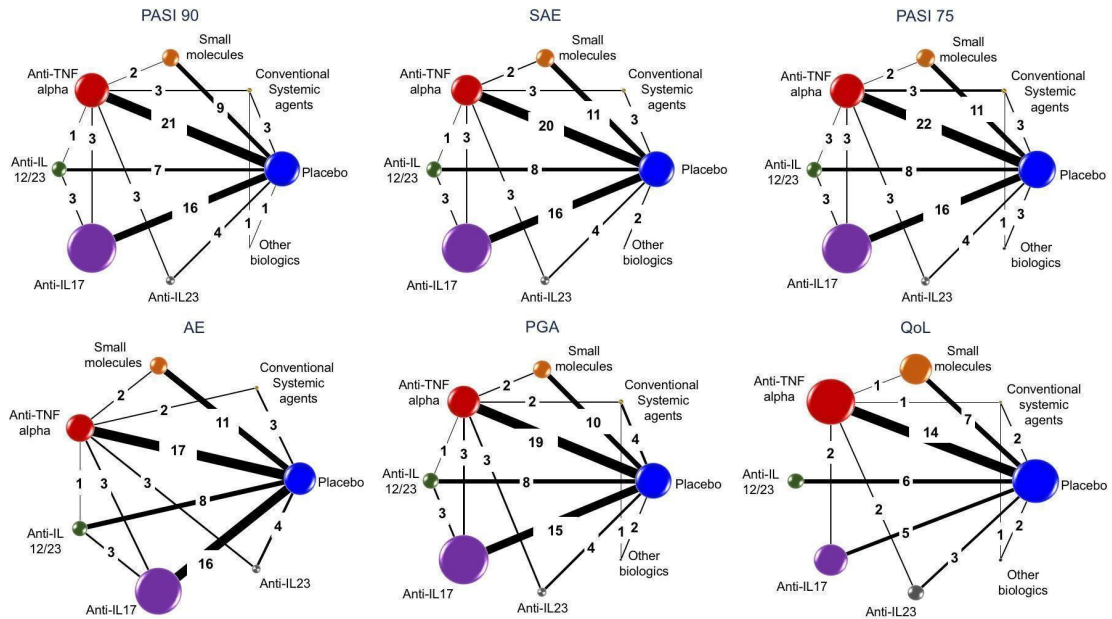
- infliximab (n = 7) (Chaudhari 2001; de Vries PIECE, 2016; Gottlieb 2004; Menter EXPRESS-II, 2007; Reich EXPRESS, 2005; Torii 2010; Yang 2012)
- acitretin (n = 8) (Akcali 2014; Goldfarb 1988; Gisondi 2008; Gurel 2015; Lowe 1991; Ruzicka 1990; Saurat 1988; Sommerburg 1993)
- methotrexate (n = 5) (Asawanonda 2006; Al-Hamamy 2014; Gottlieb 2012; Mahajan 2010; Shehzad 2004)
- ciclosporin (n = 1) (Meffert 1997)

We included a total of 74 studies, involving 35,454 participants (88.9% participants of this review), in the network meta-analysis for at least one of the outcomes.

[Figure 4](#) and [Figure 5](#) show the network diagrams for all of the outcomes included in the review. The size of the nodes is proportional to the total number of participants allocated to each class level ([Figure 4](#))/drug level ([Figure 5](#)) intervention, and the thickness of the lines is proportional to the number of trials evaluating each direct comparison.



**Figure 4. Network plot for all the outcomes at class-level**The size of the nodes is proportional to the total number of participants allocated to each intervention and the thickness of the lines proportional to the number of studies evaluating each direct comparison. **AE:** adverse events; **PASI:** Psoriasis Area and Severity Index; **PGA:** Physician Global Assessment; **QoL:** quality of life; **SAE:** serious adverse events





**Figure 5. Network plot for all the outcomes at drug-level**The size of the nodes is proportional to the total number of participants allocated to each intervention and the thickness of the lines proportional to the number of studies evaluating each direct comparison.**ACI: acitretin; ADA: adalimumab; APRE: apremilast; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; ITO: itolizumab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; PONE: ponesimod; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; USK: ustekinumab****AE: adverse events; PASI: Psoriasis Area and Severity Index; PGA: Physician Global Assessment; QoL: quality of life; SAE: serious adverse events**

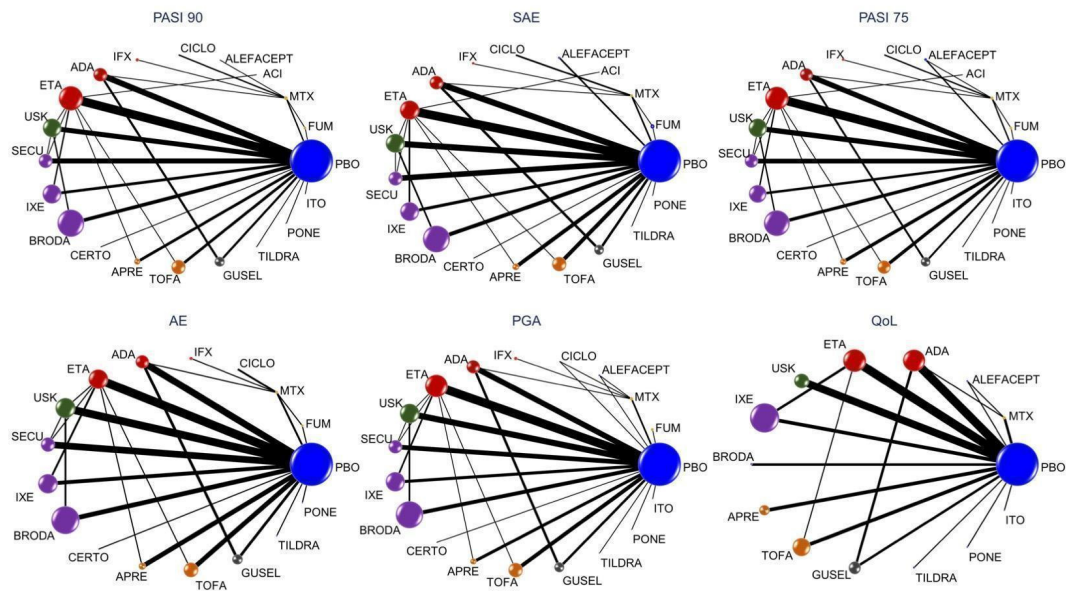


Figure 6 shows the network meta-analysis estimates of all of the outcomes for each comparisons at class level.

**Figure 6. Relative effects of the class-level intervention as estimated from the network meta-analysis model** Drugs are reported in order of primary benefit ranking. Each cell contains the risk ratio (RR) (for dichotomous outcomes: PASI 90, serious adverse events, PASI 75, PGA 0/I, adverse events) or the standardised mean difference (SMD) (for the quality-of-life outcome), plus the 95% confidence interval, of the class level in the respective column versus the class level in the respective row. RRs larger than 1 for the lower triangle and smaller than 1 (or SMDs smaller than zero) for the upper triangle favour the treatment on the left. Significant results are bolded and underscored. AE: adverse events; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment; QoL: quality of life; SAE: serious adverse events

SAE, $\tau = 0$							
Anti-IL17	1.25 (0.80,1.96)	1.12 (0.56,2.22)	1.12 (0.78,1.62)	1.17 (0.71,1.94)	1.54 (0.68,3.52)	<b>2.31</b> <u>(1.20,4.48)</u>	1.12 (0.82,1.52)
<b>1.33</b> <u>(1.19,1.49)</u>	Anti-IL12/23	0.89 (0.42,1.89)	0.90 (0.55,1.46)	0.94 (0.52,1.69)	1.23 (0.51,2.97)	1.85 (0.89,3.83)	0.89 (0.58,1.37)
1.86 <u>(1.54,2.26)</u>	1.40 <u>(1.14,1.72)</u>	Anti-IL23	1.01 (0.54,1.87)	1.05 (0.50,2.21)	1.38 (0.51,3.75)	2.07 (0.89,4.82)	1.00 (0.53,1.89)
2.66 <u>(2.34,3.03)</u>	2.00 <u>(1.72,2.33)</u>	1.43 <u>(1.24,1.65)</u>	Anti-TNF alpha	1.05 (0.66,1.67)	1.38 (0.60,3.13)	<b>2.06</b> <u>(1.13,3.75)</u>	0.99 (0.73,1.35)
3.52 <u>(2.65,4.66)</u>	2.64 <u>(1.99,3.52)</u>	1.89 <u>(1.43,2.49)</u>	1.32 <u>(1.02,1.71)</u>	Small molecules	1.32 (0.55,3.12)	1.97 (0.96,4.03)	0.95 (0.63,1.42)
6.44 <u>(2.44,17.04)</u>	4.84 <u>(1.83,12.84)</u>	3.46 <u>(1.30,9.16)</u>	2.42 (0.92,6.35)	1.83 (0.68,4.93)	Other biologics	1.50 (0.57,3.97)	0.72 (0.34,1.55)
8.15 <u>(6.07,10.93)</u>	6.12 <u>(4.53,8.28)</u>	4.37 <u>(3.24,5.89)</u>	3.06 <u>(2.34,3.99)</u>	<b>2.31</b> <u>(1.63,3.28)</u>	1.26 (0.50,3.22)	Conventional systemic agents	0.48 (0.26,0.88)
30.81 <u>(25.10,37.82)</u>	23.16 <u>(18.70,28.68)</u>	16.53 <u>(13.16,20.75)</u>	11.58 <u>(9.55,14.03)</u>	8.76 <u>(6.75,11.35)</u>	4.78 <u>(1.81,12.66)</u>	3.78 <u>(2.78,5.14)</u>	Placebo
PASI 90, $\tau = 0.09$							
AE, $\tau = 0.05$							
Anti-IL17	1.07 <u>(1.00,1.14)</u>	1.12 <u>(1.00,1.25)</u>	1.06 <u>(1.00,1.12)</u>	0.98 (0.91,1.07)	-	1.06 (0.97,1.17)	1.15 <u>(1.09,1.20)</u>
1.17 <u>(1.00,1.38)</u>	Anti-IL12/23	1.04 (0.93,1.17)	0.99 (0.92,1.05)	0.92 <u>(0.84,1.00)</u>	-	0.99 (0.90,1.10)	1.07 <u>(1.01,1.14)</u>
1.42 <u>(1.12,1.81)</u>	1.21 (0.94,1.57)	Anti-IL23	0.94 (0.86,1.04)	0.88 <u>(0.78,0.99)</u>	-	0.95 (0.84,1.08)	1.03 (0.93,1.13)
1.74 <u>(1.50,2.02)</u>	1.48 <u>(1.24,1.77)</u>	1.22 <u>(1.01,1.48)</u>	Anti-TNF alpha	0.93 <u>(0.86,1.00)</u>	-	1.01 (0.92,1.09)	1.09 <u>(1.04,1.14)</u>
2.59 <u>(2.01,3.35)</u>	2.21 <u>(1.70,2.88)</u>	1.82 <u>(1.36,2.44)</u>	1.49 <u>(1.20,1.86)</u>	Small molecules	-	1.08 (0.97,1.20)	1.17 <u>(1.09,1.25)</u>
4.74 <u>(3.07,7.31)</u>	4.04 <u>(2.59,6.28)</u>	3.33 <u>(2.10,5.27)</u>	2.72 <u>(1.79,4.14)</u>	1.83 <u>(1.16,2.88)</u>	Other biologics	-	-
3.90 <u>(2.99,5.09)</u>	3.32 <u>(2.51,4.39)</u>	2.74 <u>(2.03,3.69)</u>	2.24 <u>(1.79,2.81)</u>	1.50 <u>(1.13,2.01)</u>	0.82 (0.54,1.25)	Conventional systemic agents	1.08 (0.99,1.17)
14.32 <u>(12.20,16.81)</u>	12.21 <u>(10.23,14.57)</u>	10.07 <u>(8.03,12.63)</u>	8.23 <u>(7.20,9.42)</u>	5.53 <u>(4.52,6.76)</u>	3.02 <u>(2.00,4.57)</u>	3.67 <u>(2.90,4.65)</u>	Placebo
PASI 75, $\tau = 0.16$							
QoL, $\tau = 0.27$							
Anti-IL17	-0.23 (-0.58,0.12)	-0.14 (-0.53,0.24)	-0.41 <u>(-0.68,-0.14)</u>	-0.62 <u>(-0.94,-0.30)</u>	-1.08 <u>(-1.52,-0.63)</u>	-0.79 <u>(-1.22,-0.36)</u>	-1.44 <u>(-1.68,-1.19)</u>
1.34 <u>(1.10,1.64)</u>	Anti-IL12/23	0.09 (-0.30,0.48)	-0.18 <u>(-0.47,0.11)</u>	-0.39 <u>(-0.72,-0.07)</u>	-0.85 <u>(-1.29,-0.40)</u>	-0.56 <u>(-1.00,-0.12)</u>	-1.21 <u>(-1.45,-0.96)</u>
1.60 <u>(1.19,2.14)</u>	1.19 (0.87,1.62)	Anti-IL23	-0.27 (-0.58,0.04)	-0.48 <u>(-0.85,-0.11)</u>	-0.93 <u>(-1.41,-0.45)</u>	-0.65 <u>(-1.12,-0.18)</u>	-1.30 <u>(-1.60,-0.99)</u>
2.03 <u>(1.68,2.44)</u>	1.51 <u>(1.22,1.87)</u>	1.27 <u>(1.00,1.61)</u>	Anti-TNF alpha	-0.21 (-0.46,0.04)	-0.67 <u>(-1.06,-0.27)</u>	-0.38 (-0.76,-0.01)	-1.03 <u>(-1.18,-0.88)</u>
3.28 <u>(2.44,4.40)</u>	2.44 <u>(1.82,3.27)</u>	2.06 <u>(1.46,2.90)</u>	1.62 <u>(1.25,2.09)</u>	Small molecules	-0.45 (-0.88,-0.02)	-0.17 (-0.58,0.25)	-0.81 <u>(-1.02,-0.60)</u>
6.09 <u>(3.47,10.70)</u>	4.53 <u>(2.57,8.01)</u>	3.82 <u>(2.11,6.90)</u>	3.00 <u>(1.74,5.19)</u>	1.86 <u>(1.04,3.32)</u>	Other biologics	0.29 (-0.14,0.71)	-0.36 <u>(-0.74,0.01)</u>
4.53 <u>(3.28,6.26)</u>	3.37 <u>(2.42,4.71)</u>	2.84 <u>(1.98,4.08)</u>	2.23 <u>(1.69,2.95)</u>	1.38 (0.97,1.98)	0.74 (0.43,1.28)	Conventional systemic agents	-0.65 <u>(-1.01,-0.29)</u>
15.85 <u>(13.08,19.20)</u>	11.80 <u>(9.67,14.39)</u>	9.93 <u>(7.58,13.02)</u>	7.82 <u>(6.66,9.17)</u>	4.83 <u>(3.85,6.06)</u>	2.60 <u>(1.52,4.46)</u>	3.50 <u>(2.61,4.68)</u>	Placebo
PGA, $\tau = 0.21$							

Figure 7, Figure 8, and Figure 9 show the network meta-analysis estimates of all the outcomes for each comparison at drug level.

**Figure 7. Relative effects of the intervention as estimated from the network meta-analysis model for Psoriasis Area and Severity Index (PASI) 90 and serious adverse events (SAEs) Drugs are reported in order of primary benefit ranking. Each cell contains the risk ratio (RR) and 95% confidence interval for the two primary outcomes (PASI 90 and SAEs) of the intervention in the respective column versus the class level in the respective row. RRs larger than 1 for the lower triangle and smaller than 1 for the upper triangle favour the treatment on the left. Significant results are highlighted in grey. ACI: acitretin; ADA: adalimumab; APRE: apremilast; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; ITO: itolizumab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; PONE: ponesimod; SECU: secukinumab;  $\tau$  (Tau): estimated heterogeneity standard deviation parameter; TILDRA: tildrakizumab; TOFA: tofacitinib; USK: ustekinumab**

	SAE, $\tau = 0$																			
IXE	0.95 (0.46,1.94)	1.08 (0.52,2.25)	1.12 (0.46,2.71)	2.28 (0.44,11.96)	1.26 (0.65,2.45)	0.82 (0.04,15.77)	1.10 (0.52,2.31)	-	2.01 (0.35,11.72)	1.14 (0.66,1.94)	1.14 (0.54,2.42)	1.34 (0.61,2.92)	0.43 (0.05,3.56)	1.55 (0.61,3.93)	1.46 (0.49,4.35)	4.97 (0.21,117.41)	4.86 (1.03,22.88)	1.14 (0.02,57.54)	1.12 (0.66,1.90)	
1.22 (0.92,1.62)	SECU	1.15 (0.56,2.35)	1.18 (0.48,2.88)	2.42 (0.46,12.69)	1.33 (0.74,2.38)	0.87 (0.05,16.71)	1.16 (0.55,2.46)	-	2.13 (0.36,12.44)	1.20 (0.66,2.19)	1.21 (0.56,2.61)	1.41 (0.64,3.12)	0.46 (0.06,3.78)	1.64 (0.65,4.18)	1.55 (0.52,4.62)	5.26 (0.22,124.43)	5.14 (1.09,24.29)	1.20 (0.02,61.42)	1.19 (0.69,2.03)	
1.28 (0.95,1.71)	1.04 (0.82,1.33)	BRODA	1.03 (0.43,2.48)	2.11 (0.40,10.99)	1.16 (0.64,2.11)	0.76 (0.04,14.52)	1.01 (0.49,2.11)	-	1.86 (0.32,10.78)	1.05 (0.55,2.02)	1.05 (0.49,2.29)	1.23 (0.56,2.69)	0.40 (0.05,3.28)	1.43 (0.46,3.99)	1.35 (0.49,3.99)	4.59 (0.19,108.16)	4.48 (0.96,21.03)	1.05 (0.02,54.07)	1.04 (0.62,1.73)	
1.54 (0.94,2.54)	1.26 (0.80,2.00)	1.21 (0.74,1.98)	GUSEL	2.04 (0.37,11.44)	1.13 (0.49,2.61)	0.74 (0.04,14.66)	0.98 (0.51,1.88)	-	1.80 (0.30,10.87)	1.02 (0.44,2.33)	1.02 (0.41,2.57)	1.20 (0.47,3.01)	0.39 (0.04,3.36)	1.39 (0.49,3.95)	1.31 (0.40,4.29)	4.45 (0.18,107.22)	4.35 (0.89,21.33)	1.02 (0.02,54.16)	1.00 (0.49,2.04)	
1.32 (0.18,9.63)	1.08 (0.15,7.82)	1.04 (0.147,5.4)	CERTO	1.06 (0.12,6.30)	1.23 (0.17,8.95)	0.36 (0.01,9.79)	0.48 (0.09,2.51)	-	0.88 (0.09,8.79)	0.50 (0.10,2.53)	0.50 (0.09,2.67)	0.58 (0.11,3.13)	0.19 (0.01,2.49)	0.68 (0.12,3.90)	0.64 (0.10,4.01)	2.18 (0.07,71.39)	2.13 (0.35,18.10)	0.50 (0.01,39.65)	0.49 (0.10,2.96)	
1.63 (1.25,2.12)	1.33 (1.11,1.61)	1.28 (1.10,1.48)	1.06 (0.66,1.69)	1.23 (0.17,8.95)	USK	0.65 (0.03,3.36)	0.87 (0.18,9.14)	-	1.60 (0.28,10.1)	0.90 (0.52,1.57)	0.91 (0.44,1.86)	1.06 (0.51,2.21)	0.34 (0.04,2.78)	1.23 (0.51,2.99)	1.16 (0.19,192.12)	3.95 (0.84,17.71)	3.86 (0.23,152.37)	0.90 (0.01,180.41)	0.89 (0.02,45.84)	
2.08 (0.29,15.00)	1.70 (0.24,12.18)	1.63 (0.23,11.74)	1.35 (0.18,9.81)	1.57 (0.10,25.02)	1.27 (0.18,9.14)	TILDRA	1.33 (0.07,25.55)	-	2.45 (0.09,70.20)	1.38 (0.07,26.90)	1.39 (0.07,26.90)	1.62 (0.08,31.47)	0.53 (0.02,18.35)	1.89 (0.09,38.10)	1.78 (0.08,37.82)	6.04 (0.09,428.66)	5.91 (0.23,152.37)	1.38 (0.01,180.41)	1.36 (0.07,24.94)	
2.18 (1.37,3.48)	1.79 (1.15,2.77)	1.71 (1.08,2.71)	1.41 (1.21,1.65)	1.65 (0.23,12.13)	1.34 (0.86,2.08)	1.05 (0.14,7.64)	ADA	-	1.83 (0.33,10.21)	1.04 (0.53,2.03)	1.04 (0.47,2.28)	1.22 (0.55,2.68)	0.40 (0.05,3.24)	1.42 (0.56,3.58)	1.33 (0.45,3.94)	4.53 (0.20,104.39)	4.43 (0.99,19.81)	1.04 (0.02,53.58)	1.02 (0.61,1.73)	
2.65 (0.16,43.63)	2.08 (0.13,35.51)	2.08 (0.13,34.17)	1.72 (0.10,28.45)	2.00 (0.07,60.41)	1.62 (0.10,26.65)	1.27 (0.04,38.21)	1.21 (0.07,20.07)	-	1.10 (0.06,19.27)	1.33 (0.18,11.04)	1.33 (0.06,19.27)	0.56 (0.10,3.20)	0.57 (0.10,3.37)	0.66 (0.11,3.94)	0.22 (0.02,3.03)	0.77 (0.11,4.69)	2.47 (0.14,44.06)	2.41 (1.04,5.59)	0.56 (0.01,39.87)	0.56 (0.10,3.00)
2.90 (1.36,6.22)	2.38 (1.14,4.95)	2.28 (1.07,4.85)	1.88 (1.01,3.51)	2.20 (0.28,17.52)	1.78 (0.85,3.75)	1.40 (0.16,11.04)	1.33 (0.72,2.46)	-	1.14 (0.07,18.60)	1.04 (0.50,2.14)	1.04 (0.50,2.14)	1.01 (0.53,1.89)	0.38 (0.05,3.06)	1.37 (0.57,3.28)	1.29 (0.19,101.76)	4.38 (0.04,19.53)	4.28 (0.02,48.82)	1.00 (0.01,39.65)	0.99 (0.65,1.51)	
3.01 (2.46,3.68)	2.46 (0.01,3.02)	2.36 (1.83,3.04)	1.95 (1.25,3.04)	2.28 (0.32,16.44)	1.85 (1.50,2.27)	1.45 (0.20,10.36)	1.38 (0.90,2.11)	-	1.14 (0.07,18.60)	1.04 (0.50,2.14)	1.04 (0.50,2.14)	1.01 (0.53,1.89)	0.38 (0.05,3.06)	1.37 (0.57,3.28)	1.29 (0.19,101.76)	4.38 (0.04,19.53)	4.28 (0.02,48.82)	1.00 (0.01,39.65)	0.99 (0.65,1.51)	
3.83 (2.57,5.68)	3.12 (2.14,4.1)	2.99 (1.97,4.54)	2.47 (1.54,3.96)	2.89 (0.40,21.07)	2.34 (1.60,3.44)	1.84 (0.25,13.27)	1.75 (1.09,2.82)	-	1.44 (0.09,23.77)	1.33 (0.63,2.75)	1.37 (0.95,1.70)	1.17 (0.51,2.66)	0.38 (0.05,3.17)	1.36 (0.52,3.56)	1.28 (0.42,3.92)	4.35 (0.18,103.82)	4.25 (0.88,20.44)	0.99 (0.02,51.10)	0.98 (0.55,1.76)	
4.24 (2.32,7.75)	3.47 (1.91,6.28)	3.32 (1.80,6.14)	2.75 (1.38,5.46)	3.21 (0.42,24.80)	2.60 (1.43,4.72)	2.04 (0.27,15.63)	1.94 (0.99,3.82)	-	1.60 (0.09,27.51)	1.46 (0.60,3.57)	1.41 (0.80,2.49)	1.11 (0.59,2.07)	APRE	0.32 (0.04,2.71)	1.16 (0.44,3.05)	1.09 (0.36,3.36)	3.72 (0.16,88.89)	3.64 (0.76,17.52)	0.85 (0.02,44.25)	0.84 (0.47,1.52)
4.92 (1.17,20.61)	4.03 (0.97,16.69)	3.86 (0.92,16.13)	3.19 (0.75,13.52)	3.73 (0.34,41.40)	3.02 (0.73,12.54)	2.37 (0.21,26.13)	2.25 (0.53,9.52)	-	1.86 (0.08,41.90)	1.69 (0.36,8.01)	1.64 (0.40,6.75)	1.29 (0.31,5.39)	PONE	3.58 (0.41,31.56)	3.37 (0.35,31.96)	11.46 (0.28,474.97)	11.20 (0.91,157.11)	2.62 (0.03,215.48)	2.59 (0.34,19.85)	
7.40 (2.21,24.74)	6.06 (1.84,19.89)	5.80 (1.74,19.34)	4.80 (1.56,14.77)	5.60 (0.58,54.62)	4.54 (1.37,15.00)	3.56 (0.37,34.46)	3.39 (1.11,10.39)	-	2.80 (0.14,57.01)	2.55 (0.90,7.25)	2.46 (0.75,8.04)	1.94 (0.59,6.37)	1.75 (0.48,6.37)	1.50 (0.25,9.22)	ALEFACEPT	0.94 (0.28,3.19)	3.20 (0.13,79.25)	3.13 (0.60,16.20)	0.73 (0.01,39.33)	0.72 (0.34,1.55)
7.94 (3.42,18.42)	6.49 (2.86,14.76)	6.22 (2.69,14.38)	5.14 (2.21,11.96)	6.01 (0.73,49.53)	4.87 (2.13,11.13)	3.82 (0.47,31.22)	3.64 (1.57,8.41)	-	3.00 (0.17,53.98)	2.73 (1.01,7.37)	2.64 (1.17,5.95)	2.08 (0.90,4.78)	1.61 (0.71,4.93)	1.07 (0.33,7.97)	FUM	3.40 (0.14,85.24)	3.32 (0.63,17.61)	0.78 (0.01,43.56)	0.77 (0.30,1.99)	
8.14 (3.47,19.10)	6.66 (2.89,15.34)	6.38 (2.73,14.92)	5.38 (2.50,11.12)	6.17 (0.74,51.08)	4.99 (2.16,11.54)	3.82 (0.48,32.20)	3.73 (1.79,7.97)	-	3.08 (0.17,55.58)	2.80 (1.51,5.22)	2.71 (1.18,6.18)	2.13 (0.91,4.97)	1.92 (0.72,5.12)	1.03 (0.38,3.38)	CICLO	0.98 (0.35,3.00)	0.98 (0.06,15.38)	0.23 (0.00,33.96)	0.23 (0.15,1.10)	
8.30 (4.18,16.50)	6.79 (3.52,13.08)	6.51 (3.29,12.87)	5.38 (3.17,9.13)	6.29 (0.81,48.79)	5.09 (2.61,9.92)	4.00 (0.52,30.75)	3.80 (2.26,6.39)	-	3.14 (0.18,54.06)	2.86 (1.45,5.26)	2.76 (1.45,5.26)	1.17 (1.13,4.20)	1.96 (0.85,4.50)	1.12 (0.37,7.70)	1.05 (0.42,3.02)	1.02 (0.60,1.73)	MTX	0.23 (0.00,15.19)	0.23 (0.05,0.99)	
33.10 (1.89,580.22)	27.08 (1.54,474.83)	25.96 (1.47,456.98)	21.45 (3.19,236.47)	25.07 (0.78,808.57)	20.31 (1.16,356.13)	15.94 (0.50,511.51)	15.16 (0.84,272.32)	-	12.51 (0.23,680.52)	11.40 (0.60,217.26)	11.00 (0.63,191.47)	8.67 (0.49,153.16)	7.81 (0.42,143.83)	6.73 (0.20,98.53)	4.47 (0.20,98.53)	4.17 (0.21,79.56)	4.07 (0.21,74.61)	3.99 (0.21,74.61)	ACI	0.99 (0.02,49.37)
32.45 (23.61,44.60)	26.55 (20.32,34.69)	25.45 (18.74,34.57)	21.03 (3.46,174.73)	24.58 (1.45,30.38)	19.91 (15.11,26.23)	15.63 (2.22,110.07)	14.87 (10.45,21.14)	-	12.26 (0.76,198.53)	11.18 (5.67,22.04)	10.79 (8.47,13.73)	8.50 (6.23,11.60)	7.66 (4.30,13.66)	6.60 (1.63,26.67)	4.39 (1.38,13.94)	4.09 (1.88,8.88)	3.99 (1.81,8.78)	3.91 (2.16,7.08)	0.98 (0.06,17.24)	PBO

**Figure 8. Relative effects of the intervention as estimated from the network meta-analysis model for Psoriasis Area and Severity Index (PASI 75) and adverse events (AEs) Drugs are reported in order of primary benefit ranking. Each cell contains the Risk Ratio (RR) and 95% confidence interval for the two secondary outcomes (PASI 75 and adverse events) of the intervention in the respective column versus the comparator in the respective row. RRs larger than 1 for the lower triangle and smaller than 1 for the upper triangle favour the treatment on the left. Significant results are highlighted in grey. ACI: acitretin; ADA: adalimumab; APRE: apremilast; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; ITO: itolizumab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; PONE: ponesimod; SECU: secukinumab;  $\tau$  (Tau): estimated heterogeneity standard deviation parameter; TILDRA: tildrakizumab; TOFA: tofacitinib; USK: ustekinumab**

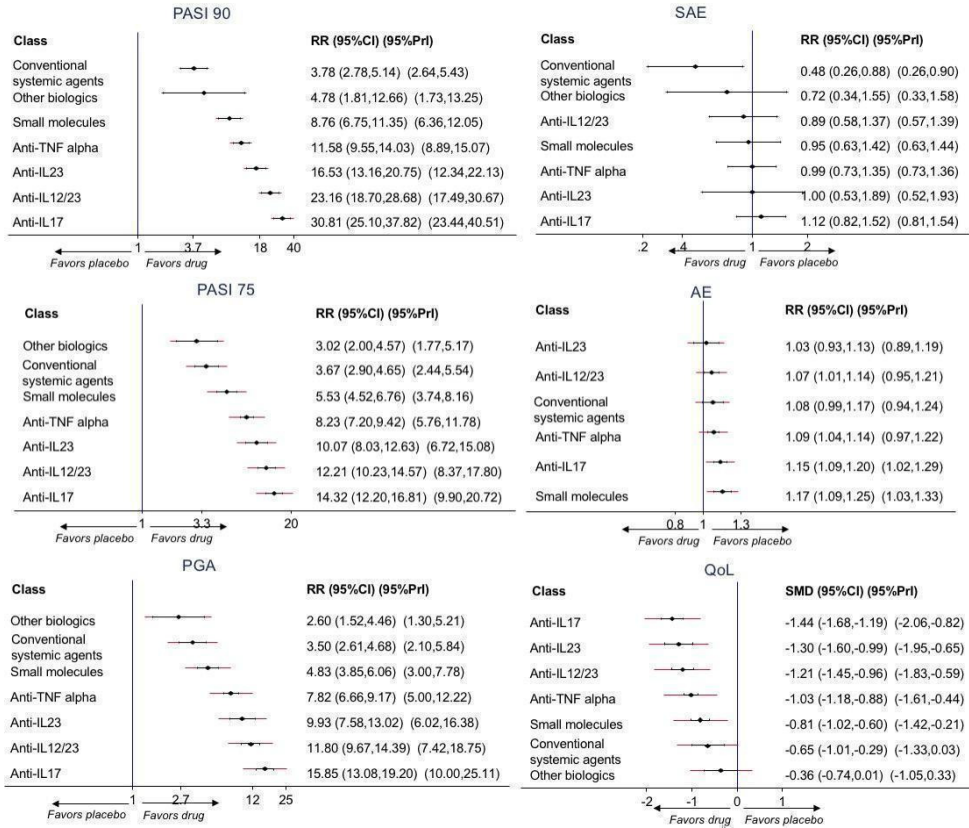
	AE, $\tau = 0.04$																		
1.06 (0.96,1.18)	1.09 (0.98,1.21)	1.27 (1.00,1.62)	1.13 (1.03,1.24)	1.22 (0.97,1.53)	1.19 (1.04,1.35)	-	1.15 (1.04,1.28)	1.09 (1.00,1.19)	1.06 (0.89,1.27)	1.09 (0.97,1.22)	1.05 (0.83,1.32)	0.98 (0.86,1.11)	-	1.15 (1.01,1.31)	0.99 (0.70,1.22)	-	0.99 (0.84,1.16)	1.21 (1.12,1.32)	
1.12 (0.82,1.51)	SECU (0.92,1.13)	1.03 (0.95,1.13)	1.20 (0.95,1.53)	1.07 (0.99,1.16)	1.15 (0.92,1.44)	1.12 (0.96,1.27)	-	1.09 (0.99,1.20)	1.02 (0.94,1.11)	1.00 (0.84,1.19)	1.03 (0.92,1.14)	0.99 (0.78,1.24)	0.92 (0.82,1.04)	-	1.08 (0.96,1.22)	0.87 (0.67,1.14)	-	0.93 (0.80,1.08)	1.14 (1.06,1.23)
1.21 (0.88,1.68)	1.09 (0.81,1.46)	BRODA (0.92,1.49)	1.17 (0.97,1.42)	1.04 (0.97,1.12)	1.12 (0.89,1.40)	1.09 (0.96,1.23)	-	1.06 (0.96,1.17)	1.00 (0.91,1.09)	0.98 (0.82,1.16)	1.00 (0.90,1.12)	0.96 (0.76,1.21)	0.90 (0.80,1.01)	-	1.05 (0.93,1.19)	0.85 (0.65,1.11)	-	0.91 (0.76,1.06)	1.11 (1.04,1.19)
1.09 (0.26,4.4)	0.98 (0.24,4.0)	0.90 (0.23,3.70)	TILDRA (0.70,1.12)	1.07 (0.70,1.31)	0.96 (0.72,1.20)	0.93 (0.72,1.20)	-	0.91 (0.71,1.15)	0.85 (0.67,1.08)	0.83 (0.63,1.10)	0.85 (0.67,1.09)	0.82 (0.60,1.13)	0.77 (0.60,0.98)	-	0.90 (0.70,1.16)	0.73 (0.51,1.03)	-	0.77 (0.59,1.01)	0.95 (0.76,1.19)
1.33 (1.01,1.75)	1.20 (0.95,1.50)	1.10 (0.89,1.36)	1.23 (0.90,1.60)	USK (0.86,1.34)	1.07 (0.93,1.18)	1.05 (0.93,1.18)	-	1.02 (0.92,1.11)	0.96 (0.90,1.03)	0.94 (0.79,1.11)	0.92 (0.87,1.06)	0.86 (0.74,1.16)	0.77 (0.72,0.96)	-	0.90 (0.90,1.13)	0.82 (0.63,1.07)	-	0.87 (0.75,1.01)	1.07 (1.01,1.13)
1.40 (0.50,3.92)	1.25 (0.45,3.50)	1.15 (0.41,3.23)	1.28 (0.23,7.13)	1.05 (0.38,2.90)	CERTO (0.77,1.24)	0.97 (0.77,1.24)	-	0.95 (0.76,1.19)	0.89 (0.71,1.11)	0.87 (0.67,1.14)	0.89 (0.71,1.13)	0.86 (0.63,1.17)	0.80 (0.64,1.02)	-	0.94 (0.74,1.19)	0.76 (0.54,1.07)	-	0.81 (0.63,1.04)	1.00 (0.80,1.23)
1.47 (1.02,2.13)	1.32 (0.91,1.90)	1.21 (0.84,1.76)	1.35 (0.93,1.90)	1.10 (0.79,1.54)	1.05 (0.77,1.34)	1.05 (0.77,1.34)	-	0.97 (0.86,1.08)	0.92 (0.81,1.03)	0.90 (0.74,1.08)	0.92 (0.80,1.05)	0.88 (0.65,1.12)	0.83 (0.72,0.95)	-	0.97 (0.84,1.11)	0.78 (0.59,1.03)	-	0.83 (0.70,0.98)	1.02 (0.92,1.13)
1.19 (0.16,8.7)	1.07 (0.15,7.82)	0.99 (0.13,7.20)	1.10 (0.10,12.29)	0.90 (0.12,6.50)	0.85 (0.09,7.81)	0.81 (0.11,5.97)	-	0.85 (0.09,7.81)	0.81 (0.11,5.97)	0.85 (0.09,7.81)	0.81 (0.11,5.97)	0.85 (0.09,7.81)	0.81 (0.11,5.97)	-	0.85 (0.09,7.81)	0.81 (0.11,5.97)	-	0.85 (0.09,7.81)	0.81 (0.11,5.97)
1.76 (1.25,2.4)	1.58 (1.13,2.21)	1.45 (1.03,2.05)	1.62 (0.99,2.65)	1.32 (0.98,1.79)	1.26 (0.45,3.52)	1.20 (0.99,1.45)	-	1.48 (0.20,10.78)	ADA (0.86,1.03)	0.94 (0.78,1.09)	0.92 (0.85,1.05)	0.94 (0.72,1.13)	0.91 (0.75,0.95)	-	1.00 (0.85,1.11)	0.80 (0.61,1.05)	-	0.86 (0.74,0.99)	1.05 (0.98,1.12)
1.87 (1.51,2.32)	1.67 (1.32,2.13)	1.54 (1.18,2.02)	1.72 (0.42,6.99)	1.40 (1.14,1.72)	1.34 (0.49,3.69)	1.27 (0.92,1.72)	-	1.57 (0.22,11.35)	1.06 (0.79,1.42)	ETA (0.82,1.16)	1.00 (0.91,1.10)	0.96 (0.77,1.21)	0.90 (0.81,1.01)	-	1.06 (0.94,1.19)	0.85 (0.65,1.11)	-	0.91 (0.78,1.05)	1.11 (1.05,1.18)
2.34 (1.32,4.12)	2.09 (1.19,3.69)	1.83 (1.09,3.40)	2.14 (0.49,9.44)	1.75 (1.01,3.02)	1.67 (0.55,5.12)	1.59 (0.94,2.69)	-	1.86 (0.25,14.99)	1.32 (0.81,2.18)	IFX (0.85,1.23)	1.03 (0.85,1.23)	0.98 (0.78,1.24)	0.92 (0.76,1.11)	-	1.08 (0.95,1.23)	0.87 (0.64,1.18)	-	0.93 (0.76,1.13)	1.14 (0.97,1.34)
2.37 (1.70,3.32)	2.12 (1.50,3.00)	1.96 (1.37,2.80)	2.18 (0.53,8.99)	1.78 (1.30,2.43)	1.70 (0.60,4.77)	1.61 (1.10,2.38)	-	1.99 (0.27,14.55)	1.34 (0.94,1.92)	1.27 (0.97,1.65)	1.02 (0.84,1.23)	TOFA (0.76,1.12)	0.90 (0.79,1.02)	-	1.05 (0.92,1.20)	0.85 (0.65,1.12)	-	0.91 (0.77,1.06)	1.11 (1.02,1.21)
3.30 (1.85,5.88)	2.95 (1.66,5.26)	2.72 (1.52,4.85)	3.03 (0.68,13.41)	2.47 (1.41,4.31)	2.36 (0.76,7.29)	2.24 (1.30,3.86)	-	2.76 (0.36,21.26)	1.87 (1.12,3.13)	1.76 (1.02,3.06)	1.41 (0.84,2.38)	1.39 (0.77,2.50)	CICLO (0.74,1.19)	0.94 (0.90,1.34)	1.10 (0.89,1.34)	0.89 (0.63,1.25)	-	0.94 (0.74,1.21)	1.16 (0.93,1.44)
3.26 (2.24,4.76)	2.92 (1.99,4.29)	2.69 (1.82,3.97)	2.99 (0.72,12.44)	2.44 (1.38,6.41)	2.33 (0.81,9.97)	2.22 (1.21,6.07)	-	2.73 (0.40,27.56)	1.85 (1.26,2.71)	1.74 (1.01,4.45)	1.40 (0.68,4.23)	1.38 (0.76,3.67)	APRE (0.54,1.80)	0.99 (0.55,2.72)	1.17 (1.02,1.35)	0.95 (0.72,1.25)	-	1.01 (0.85,1.19)	1.24 (1.12,1.36)
3.97 (2.78,6.78)	3.56 (2.49,6.07)	3.28 (2.29,5.60)	3.65 (0.94,16.82)	2.98 (2.14,4.94)	2.84 (1.07,8.99)	2.70 (1.59,4.38)	-	3.33 (0.49,27.03)	2.25 (1.73,3.50)	2.13 (1.55,3.47)	1.70 (1.31,2.64)	1.68 (1.17,2.86)	ACI (0.48,3.03)	1.22 (0.84,2.11)	1.09 (0.47,2.53)	0.81 (0.61,1.07)	-	0.86 (0.74,1.00)	1.06 (0.96,1.17)
4.51 (2.16,9.42)	4.04 (1.94,8.42)	3.72 (1.78,7.77)	4.34 (0.87,19.63)	3.38 (1.64,6.94)	3.22 (0.95,10.89)	3.07 (1.45,6.49)	-	3.77 (0.47,30.58)	2.56 (1.23,5.32)	2.41 (1.18,4.93)	1.93 (0.82,4.55)	1.90 (0.90,4.00)	1.37 (0.57,3.26)	1.38 (0.65,2.94)	1.13 (0.41,3.17)	1.04 (0.47,2.27)	-	1.07 (0.79,1.43)	1.31 (1.01,1.70)
5.59 (3.37,9.27)	5.00 (3.02,8.29)	4.61 (2.78,7.65)	5.13 (1.19,22.11)	4.19 (2.59,6.78)	4.00 (1.34,11.91)	3.80 (2.32,6.23)	-	4.68 (1.99,5.05)	3.17 (1.87,7.79)	2.99 (1.36,4.21)	2.39 (1.41,3.93)	2.36 (0.95,3.04)	1.69 (0.59,3.38)	1.71 (1.01,2.90)	1.41 (0.83,2.20)	1.29 (0.55,2.82)	-	1.29 (0.83,2.00)	1.41 (1.04,1.79)
5.99 (3.50,10.25)	5.36 (3.14,9.18)	4.94 (2.89,8.46)	5.50 (1.26,23.98)	4.49 (2.69,7.50)	4.28 (1.42,12.97)	4.08 (2.37,7.02)	-	5.01 (0.66,38.19)	3.40 (2.02,5.72)	3.20 (1.93,5.31)	2.56 (1.46,4.36)	2.53 (0.93,3.57)	1.84 (1.05,3.22)	1.51 (0.82,2.69)	1.38 (0.79,2.42)	1.33 (0.57,3.09)	-	1.07 (0.57,2.01)	1.23 (1.07,1.41)
15.81 (12.35,20.23)	14.16 (11.12,18.03)	13.04 (10.17,16.71)	14.51 (3.60,58.45)	11.84 (9.79,14.33)	11.31 (4.16,30.72)	10.76 (8.13,14.23)	-	8.96 (1.84,95.23)	8.96 (7.07,11.37)	8.45 (7.14,10.00)	6.77 (4.09,11.21)	6.66 (5.11,8.69)	4.79 (2.84,8.09)	4.85 (3.60,6.52)	3.98 (1.86,8.49)	3.64 (2.53,5.24)	-	3.51 (1.75,7.02)	2.64 (1.64,4.25)

PASI 75,  $\tau = 0.16$





**Figure 10. Interval plot. Network meta-analysis estimates of class-level versus placebo for all the outcomes** AE: adverse events; CI: confidence interval; PGA: Physician Global Assessment; PrI: predictive interval; QoL: Specific quality of life scale; RR: risk ratio; SAE: serious adverse events; SMD: standardised mean difference



**Figure 11. Interval plot. Network meta-analysis estimates of the interventions versus placebo for all the outcomes**AE: adverse events; CI: confidence interval; PGA: Physician Global Assessment; PrI: predictive interval; QoL: Specific quality of life scale; RR: risk ratio; SAE: serious adverse events; SMD: standardised mean differenceACI: acitretin; ADA: adalimumab; APRE: apremilast; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; ITO: itolizumab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; PONE: ponesimod; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; USK: ustekinumab

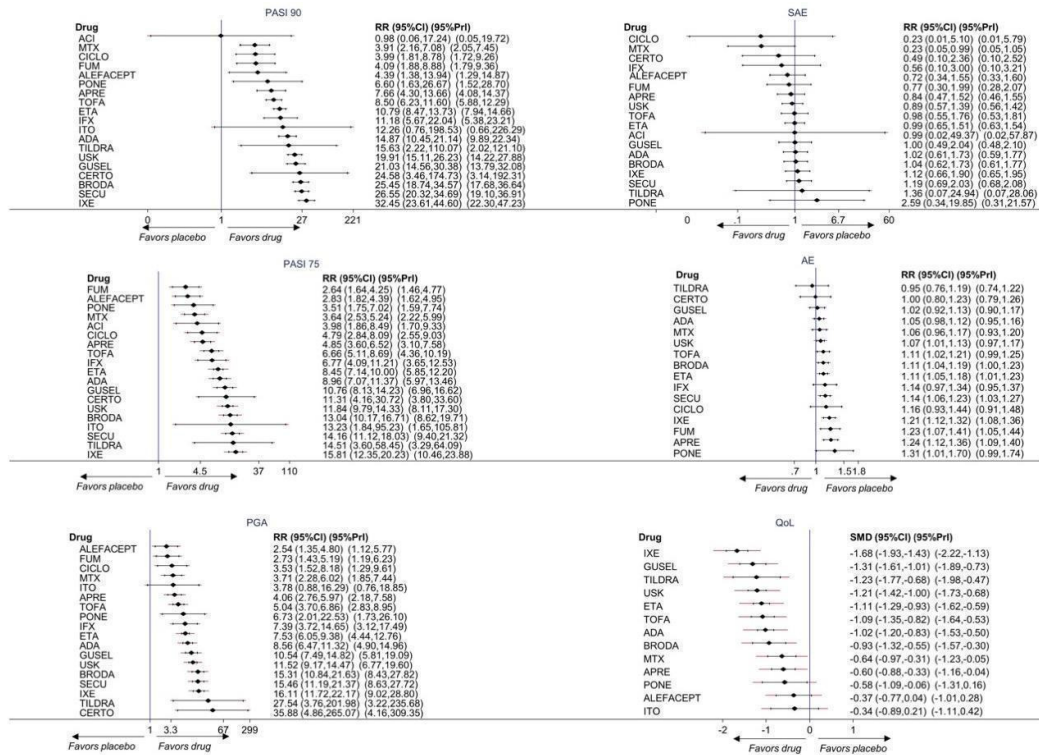


Figure 12 shows a two-dimensional ranking plot based on surface under the cumulative ranking curve (SUCRA) values for benefit (PASI 90) and acceptability (serious adverse events) at class and drug level. The different colours represent different groups of interventions considering their performance on both outcomes simultaneously. Interventions belonging to the same group were assumed to have a similar performance when the two primary outcomes were considered jointly (Chaimani 2013).

**Figure 12. Ranking plot.** Ranking plot representing simultaneously the efficacy (x axis, PASI 90) and the acceptability (y axis, serious adverse events) of all the interventions (class and drug levels) for patients with moderate-to-severe psoriasis. Optimal treatment should be characterised by both high efficacy and acceptability and should be in the right upper corner of this graph. The different colours represent different groups of interventions considering their performance on both outcomes simultaneously. Interventions belonging to the same group are assumed having a similar performance when the two primary outcomes are considered jointly. ACI: acitretin; ADA: adalimumab; APRE: apremilast; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; ITO: itolizumab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; PONE: ponesimod; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; USK: ustekinumab. PASI: Psoriasis Area and Severity Index; SAE: serious adverse events; SUCRA: surface under the cumulative ranking curve

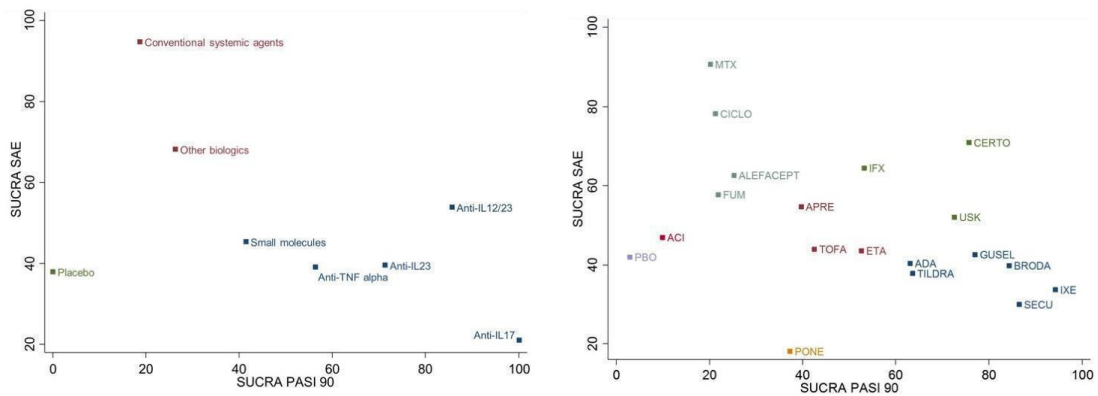
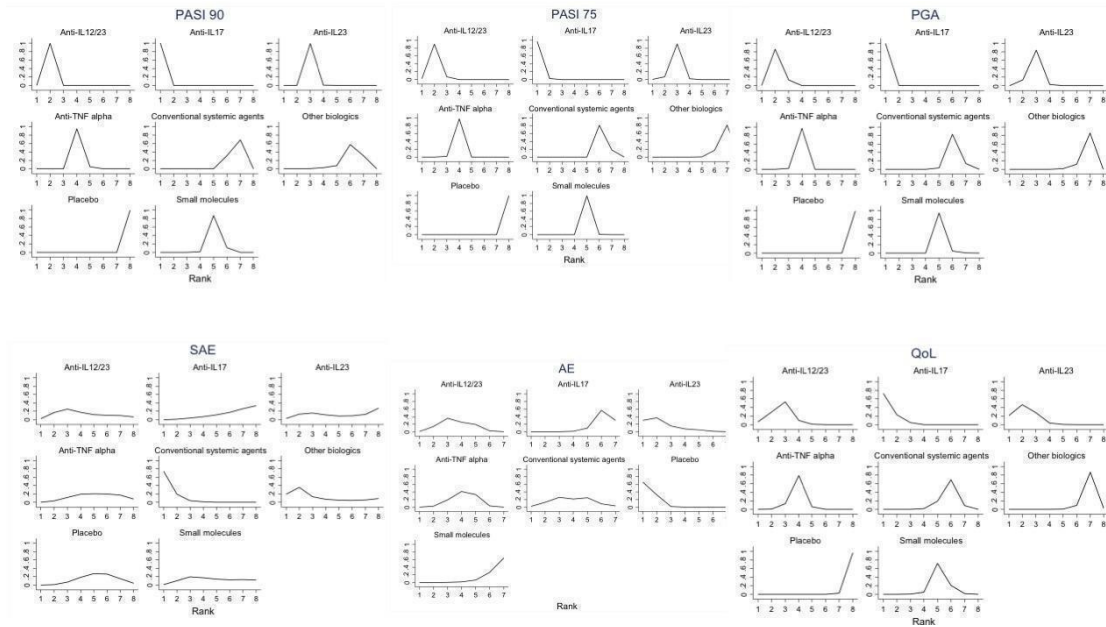


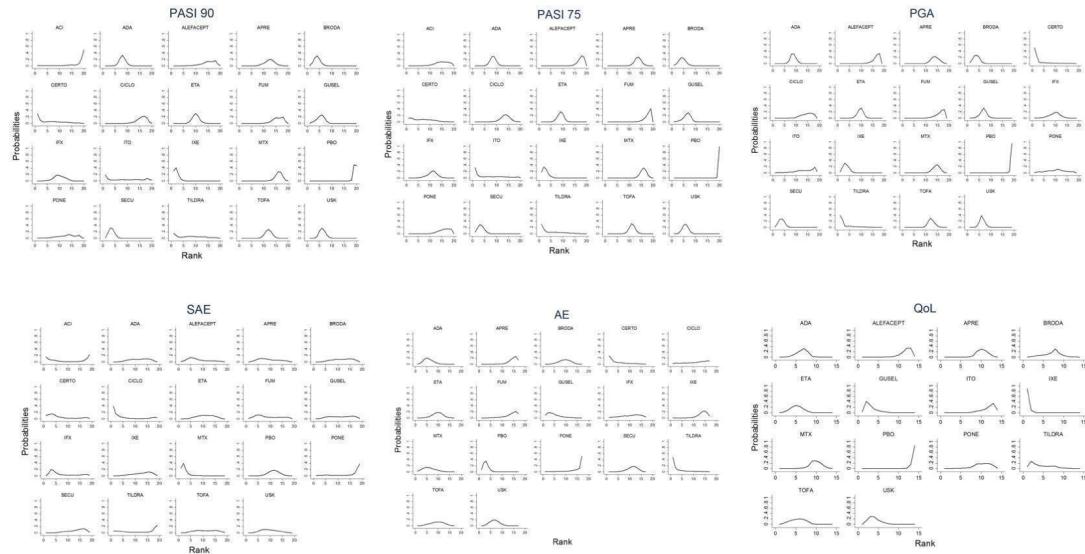
Figure 13 and Figure 14 show the ranking for all the outcomes at class and drug level, respectively.



**Figure 13. Ranking for all the outcomes at class level**AE: adverse events; PASI: Psoriasis Area and Severity Index; PGA: Physician Global Assessment; QoL: quality of life; SAE: serious adverse events



**Figure 14. Ranking for all the outcomes at drug level**ACI: acitretin; ADA: adalimumab; APRE: apremilast; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; ITO: itolizumab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; PONE: ponesimod; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; USK: ustekinumab  
AE: adverse events; PASI: Psoriasis Area and Severity Index; PGA: Physician Global Assessment; QoL: quality of life; SAE: serious adverse events



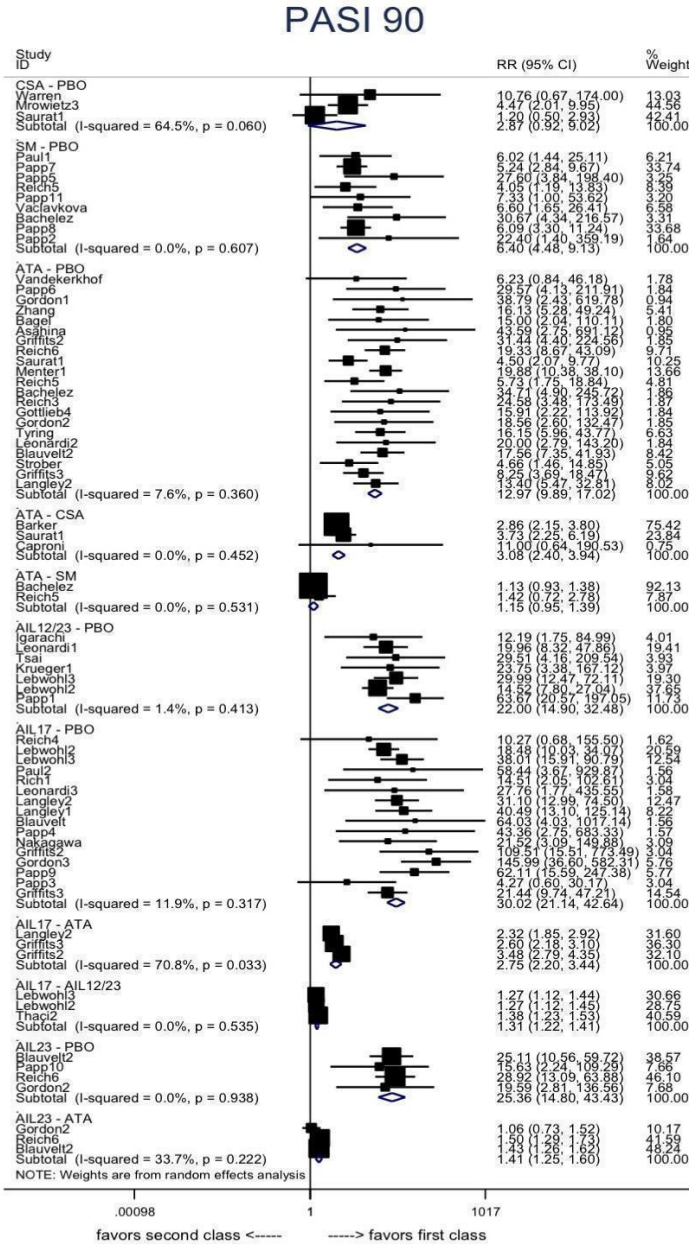
## I. Primary outcomes

### 1.1 The proportion of participants who achieved clear or almost clear skin, e.g. PASI 90

#### *DIRECT EVIDENCE*

We report treatment estimates for pair-wise meta-analyses at class (see Figure 15) and drug level in [Analysis 1.1](#); [Analysis 1.2](#); [Analysis 1.3](#); [Analysis 1.4](#); [Analysis 1.5](#); [Analysis 1.6](#); [Analysis 1.7](#); [Analysis 1.8](#); [Analysis 1.9](#); [Analysis 1.10](#); and [Analysis 1.11](#), respectively.

**Figure 15. PASI 90: direct summary effects for comparisons including at least two studies at class level AIL12/23: anti-IL12/23; AIL17: anti-IL17; AIL23: anti-IL23, ATA: anti-TNF alpha; CSA: conventional systemic agents; OB: other biologics; PBO: placebo; SM: small molecules CI: confidence interval; PASI: Psoriasis Area and Severity Index; RR: risk ratio**



In terms of reaching PASI 90, anti-IL17 treatments (secukinumab, ixekizumab, and brodalumab) were more effective than placebo (risk ratio at class level (RR) 30.02, 95% confidence interval (CI) 21.14 to 42.64). These findings were also confirmed for anti-IL23 (guselkumab and tildrakizumab) (class-level RR 25.36, 95% CI 14.80 to 43.43); ustekinumab (RR 22.00, 95% CI 14.90 to 32.48); anti-TNF alpha (etanercept, adalimumab, and certolizumab) (class-level RR 12.97, 95% CI 9.89 to 17.02); and small molecules (apremilast, tofacitinib, and ponesimod) (class-level RR 6.40, 95% CI 4.48 to 9.13). Both infliximab and adalimumab were more effective than methotrexate (respectively: RR 2.86, 95% CI 2.15 to 3.80; and RR 3.73, 95% CI 2.25 to 6.19). Ustekinumab, secukinumab, and ixekizumab were more effective than etanercept; secukinumab and brodalumab were more effective than ustekinumab; and guselkumab was more effective than adalimumab. No significant difference was observed between etanercept and tofacitinib or apremilast in terms of this outcome (reaching PASI 90).

### NETWORK META-ANALYSES

The PASI 90 outcome was available in 58 trials, involving 31,176 participants (87.9% of the participants in the meta-analysis). This outcome was reported in two other trials (Nugteren-Huying 1990; Sandhu 2003); however, the number of randomised participants was not available. These trials were added in the complete case analyses. This outcome was also reported in three other trials (Dogra 2012; Dogra 2013; Mrowietz SCULPTURE, 2015), comparing different dosages of the same drug in each case. These trials were added to the sensitivity analysis at dose level. PASI 90 was not reported for the remaining nine trials, and we were not able to obtain missing information from the trial authors (Table 2). Thirty-nine trials, involving 16,888 participants, were placebo-controlled trials; seven studies, involving 2048 participants, were head-to-head comparisons; and 12 studies, involving 12,240 participants, had both a placebo and at least two active treatments arms.

See Figure 4; Figure 5; Figure 6; Figure 7; Figure 10; Figure 11; Figure 13; and Figure 14.

Table 3 summarises the main results of both the direct and indirect evidence and the network meta-analysis for PASI 90 at 12 to 16 weeks. The summary relative effects from the network meta-analysis are presented in league tables for both class-level (Figure 6) and drug-level (Figure 7) analyses.

All of the interventions appeared superior to placebo in terms of reaching PASI 90. Anti-IL17 treatment was associated with a higher chance of reaching PASI 90 compared to all of the interventions: versus anti-IL12/23 (risk ratio (RR) 1.33, 95% confidence interval (CI) 1.19 to 1.49); versus anti-IL23 (RR 1.86, 95% CI 1.54 to 2.26); versus anti-TNF alpha (RR 2.66, 95% CI 2.34 to 3.03); versus small molecules (RR 3.52, 95% CI 2.65 to 4.66);

versus other biologics (RR 6.44, 95% CI 2.44 to 17.04); versus conventional systemic agents (RR 8.15, 95% CI 6.07 to 10.93) (Figure 6). In terms of reaching PASI 90, all of the biologic interventions (anti-IL17, anti-IL12/23, anti-IL23, anti-TNF alpha) appeared significantly superior to the small molecule class of treatments and the conventional systemic class of treatments. Small molecules were associated with a higher chance of reaching PASI 90 compared to conventional systemic agents (RR 2.31, 95% CI 1.63 to 3.28).

Results of comparisons between each of the drugs are available in Figure 7. There was no significant difference between the three anti-IL17 (brodalumab, ixekizumab, and secukinumab) and the two anti-IL23 (tildrakizumab and guselkumab) monoclonal antibodies in terms of reaching PASI 90. All of the anti-IL17 drugs (brodalumab, ixekizumab, and secukinumab) and guselkumab (an anti-IL23) were significantly more effective than three anti-TNF alpha agents: infliximab, adalimumab, and etanercept. The direct comparison regarding certolizumab and tildrakizumab only included one trial each, so the interpretation of the results regarding certolizumab and tildrakizumab was difficult (related to wide CIs). Ustekinumab was superior to etanercept (RR 1.85, 95% CI 1.50 to 2.27). No significant difference was shown between the anti-TNF alpha drugs. Tofacitinib was significantly superior to methotrexate (RR 2.17, 95% CI 1.13 to 4.20), and no significant difference was shown between apremilast and the conventional drugs (versus acitretin: RR 7.81, 95% CI 0.42 to 143.83; versus fumaric acid: RR 1.87, 95% CI 0.71 to 4.93; versus ciclosporin: RR 1.92, 95% CI 0.72 to 5.12; versus methotrexate: RR 1.96, 95% CI 0.85 to 4.50).

#### Ranking class-level analysis (Figure 10; Figure 13; Table 4)

Ranking analysis for PASI 90 performed with SUCRA strongly suggested that anti-IL17 was the best treatment at class level (versus placebo: RR 30.81, 95% confidence interval (CI) 25.10 to 37.82; SUCRA = 100; high-certainty evidence), followed by anti-IL12/23 (versus placebo: RR 23.16, 95% CI 18.70 to 28.68; SUCRA = 85.7; high-certainty of evidence), anti-IL23 (versus placebo: RR 16.53, 95% CI 13.16 to 20.75; SUCRA = 71.3; moderate-certainty evidence), then anti-TNF alpha (versus placebo: RR 11.58, 95% CI 9.55 to 14.03; SUCRA = 56.4; moderate-certainty evidence). The heterogeneity  $\tau$  for this network overall was 0.09, which we considered low heterogeneity.

#### Ranking drug-level analysis (Figure 11; Figure 14; Table 5)

Ranking analysis for PASI 90 performed with SUCRA strongly suggested that ixekizumab was the best treatment at drug level (versus placebo: RR 32.45, 95% CI 23.61 to 44.60; SUCRA = 94.3; high-certainty evidence), followed by secukinumab (versus placebo: RR 26.55, 95% CI 20.32 to 34.69; SUCRA = 86.5; high certainty of evidence), brodalumab (versus placebo: RR 25.45, 95% CI 18.74 to 34.57; SUCRA = 84.3; moderate-certainty evi-

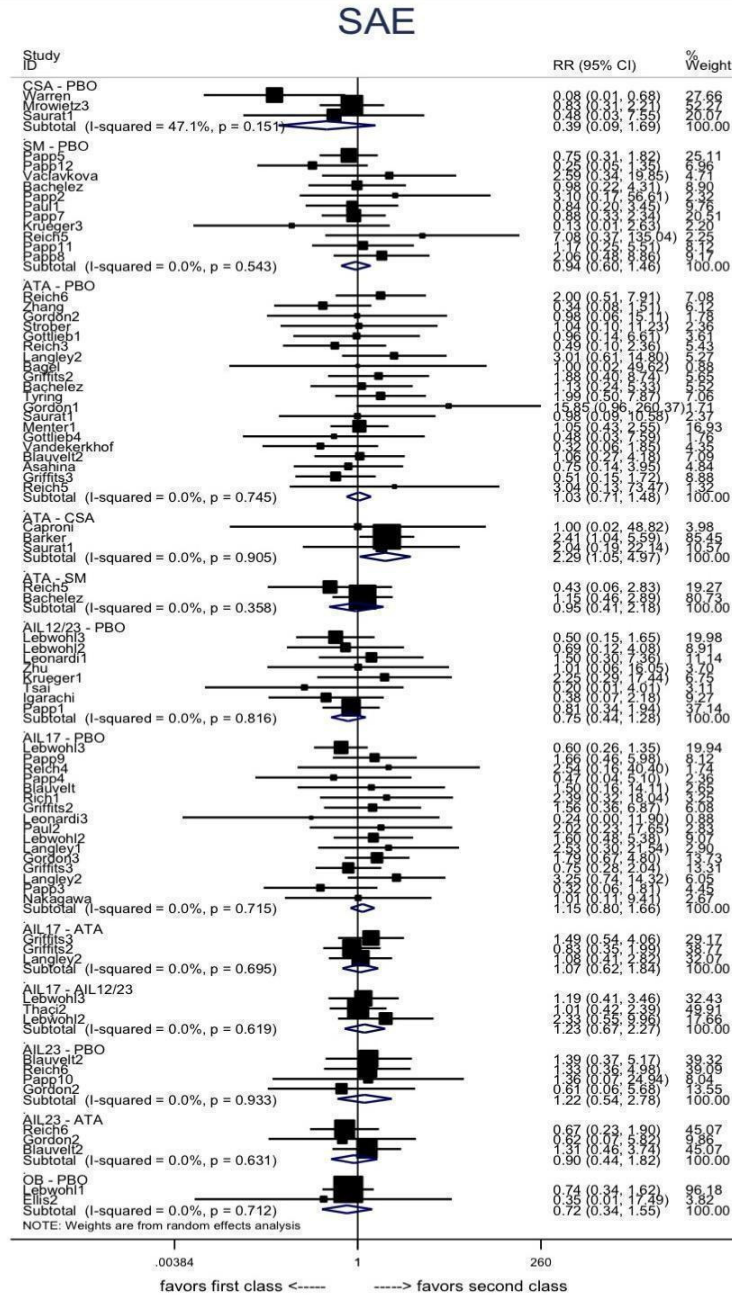
dence), guselkumab (versus placebo: RR 21.03, 95% CI 14.56 to 30.38; SUCRA = 77; moderate-certainty evidence), certolizumab (versus placebo: RR 24.58, 95% CI 3.46 to 174.73; SUCRA = 75.7; moderate-certainty evidence), then ustekinumab (versus placebo: RR 19.91, 95% CI 15.11 to 26.23; SUCRA = 72.6; high-certainty evidence). The heterogeneity  $\tau$  for this network overall was 0.09, which we considered low heterogeneity.

## 1.2 The proportion of participants with serious adverse effects

### *DIRECT EVIDENCE*

We report treatment estimates for pair-wise meta-analyses at class (Figure 16) and drug level in Analysis 2.1; Analysis 2.2; Analysis 2.3; Analysis 2.4; Analysis 2.5; Analysis 2.6; Analysis 2.7; Analysis 2.8; Analysis 2.9; and Analysis 2.10, respectively. We provide details of the serious adverse effects in Table 6 (number of serious infections, number of malignancies, number of major adverse cardiac events per arm at class level).

**Figure 16. Serious adverse effects: direct summary effects for comparisons including at least two studies at class level** AIL12/23: anti-IL12/23; AIL17: anti-IL17; AIL23: anti-IL23, ATA: anti-TNF alpha; CSA: conventional systemic agents; OB: other biologics; PBO: placebo; SM: small molecules CI: confidence interval; RR: risk ratio; SAE: serious adverse events





No significant differences were observed between methotrexate, FAEs, etanercept, adalimumab, certolizumab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab, alefacept, apremilast, tofacitinib, ponesimod, and placebo in terms of the number of participants with serious adverse effects (SAEs). The risk of SAEs was significantly higher for participants on infliximab compared to methotrexate (RR 2.41, 95% CI 1.04 to 5.59).

There were zero SAEs in the following trials: [Fallah Arani 2011](#) (comparing methotrexate with FAEs); [Flytström 2008](#) (comparing ciclosporin with methotrexate); and [Heydendael 2003](#) (comparing ciclosporin with methotrexate).

## NETWORK META-ANALYSES

The SAE outcome was available in 60 trials, involving 30,898 participants (87.1% of the participants in the meta-analysis). This outcome was reported in one other trial ([Sterry PRESTA, 2010](#)); however, the number of randomised participants was not available. This trial was added to the complete-cases analyses. This outcome was also reported in two other trials ([Laburte 1994](#); [Mrowietz SCULPTURE, 2015](#)), comparing different dosages of the same drug in each case. These studies were added to the sensitivity analysis at dose level. SAEs were not reported for the 11 remaining trials, and we were not able to obtain missing information from the trial authors ([Table 2](#)). Forty-two trials, involving 16,822 participants, were placebo-controlled trials; six, involving 1836 participants, were head-to-head comparisons, and 12, involving 12,240 participants, had both a placebo and at least two active treatments arms.

See [Figure 4](#); [Figure 5](#); [Figure 6](#); [Figure 7](#); [Figure 10](#); [Figure 11](#); [Figure 13](#); and [Figure 14](#).

[Table 7](#) summarised the main results of both direct and indirect evidences and the network meta-analysis for SAEs at 12 to 16 weeks. We present the summary relative effects from the network meta-analysis in league tables for both class-level ([Figure 6](#)) and drug-level ([Figure 7](#)) analyses. No significant difference was found between all of the interventions and the placebo regarding the risk of SAE. Two significant associations were found: anti-IL17 agents and anti-TNF alpha agents had a higher risk of SAE compared with conventional systemic agents (RR 2.31, 95%CI 1.20 to 4.48; RR 2.06, 95% CI 1.13 to 3.75, respectively). The results are available in [Figure 7](#) for comparison between each drug. Ixekizumab, secukinumab, and infliximab were at higher risk of SAE than methotrexate (RR 4.86, 95%CI 1.03 to 22.88; RR 5.14, 95% CI 1.09 to 24.29; RR 2.41, 95% CI 1.04 to 5.59, respectively).

### Ranking class-level analysis ([Figure 10](#); [Figure 13](#); [Table 4](#))

Ranking analysis for SAE performed with SUCRA strongly suggested that conventional systemic treatment was associated with

the best safety profile at class level in terms of serious adverse events (versus placebo: RR 0.48, 95% CI 0.26 to 0.88; SUCRA = 94.8), followed by other biologics (versus placebo: RR 0.72, 95% CI 0.34 to 1.55; SUCRA = 68.2), anti-IL12/23 (versus placebo: RR 0.89, 95% CI 0.58 to 1.37; SUCRA = 53.9), and then small molecules (versus placebo: RR 0.95, 95% CI 0.63 to 1.42; SUCRA = 45.4). The heterogeneity  $\tau$  for this network overall was 0, which we considered low heterogeneity.

### Ranking drug-level analysis ([Figure 11](#); [Figure 14](#); [Table 5](#))

Ranking analysis for SAE performed with SUCRA strongly suggested that methotrexate was associated with the best safety profile at drug level in terms of serious adverse events (versus placebo: RR 0.23, 95% CI 0.05 to 0.99; SUCRA = 90.7; moderate-certainty evidence), followed by ciclosporin (versus placebo: RR 0.23, 95% CI 0.01 to 5.10; SUCRA = 78.2; very low-certainty evidence), certolizumab (versus placebo: RR 0.49, 95% CI 0.10 to 2.36; SUCRA = 70.9; moderate-certainty evidence), infliximab (versus placebo: RR 0.56, 95% CI 0.10 to 3.00; SUCRA = 64.4; very low-certainty evidence), alefacept (versus placebo: RR 0.72, 95% CI 0.34 to 1.55; SUCRA = 62.6; low-certainty evidence), and then the FAEs (versus placebo: RR 0.77, 95% CI 0.30 to 1.99; SUCRA = 57.7; very low-certainty evidence). The heterogeneity  $\tau$  for this network overall was 0, which we considered low heterogeneity.

Placebo had a worse ranking for SAE than conventional systemic agents, other biologics, anti-IL12/23, and small molecules (see [Table 5](#)). Nevertheless, analyses on serious adverse events were based on a very low number of events and were reduced to the short time frame of the trials. [Table 6](#) gives details of the types of SAE; major adverse cardiac events, serious infections, or malignancies were reported in both placebo and intervention groups.

## 1.3 Relationship between PASI 90 and serious adverse events

See [Figure 12](#).

These findings for both efficacy (PASI 90) and acceptability (serious adverse events) were combined together in a bivariate ranking plot, where serious adverse events was transformed into acceptability by using the inverse values of the corresponding RRs so that higher values indicate higher acceptability (due to lower SAE): accordingly, the ideal treatment (highest performance = best efficacy + best acceptability) should appear in the upper right corner of the plot.

At class level, the highly effective treatments had serious adverse events. However, the anti-IL12/23 treatment group was the class with the better compromise between efficacy and acceptability.

At drug level, ustekinumab, certolizumab, and infliximab might be the overall best treatments considering both outcomes jointly. This result has to be considered with caution for certolizumab and infliximab as only one trial was available for this drug.

## 2. Secondary outcomes

### 2.1 Mean difference of quality of life measured by a specific scale

#### *DIRECT EVIDENCE*

We report treatment estimates for pair-wise meta-analyses at class (Figure 17) and drug level in [Analysis 3.1](#); [Analysis 3.2](#); [Analysis 3.3](#); [Analysis 3.4](#); [Analysis 3.5](#); [Analysis 3.6](#); [Analysis 3.7](#); [Analysis 3.8](#); [Analysis 3.9](#); [Analysis 3.10](#); and [Analysis 3.11](#) respectively.





## NETWORK META-ANALYSES

The quality of life outcome was available in 39 trials, involving 21,745 participants (61.3% of the participants in this review). This outcome was reported in one other trial (Krueger 2002); however, the number of randomised participants was not available. This trial were added to the complete case analyses. This outcome was also reported in another trial (Mrowietz SCULPTURE, 2015), comparing different dosages of the same drug. This trial, Mrowietz SCULPTURE, 2015, was added in the sensitivity analyses at dose level. The quality of life outcome was not reported for the 35 remaining trials, and we were not able to obtain missing information from the trial authors (Table 2). Twenty-eight trials, involving 13,040 participants, were placebo-controlled trials; two, involving 1080 participants, were head-to-head comparisons; and nine, involving 7625 participants, had both a placebo and at least two active treatments arms.

See Figure 4; Figure 5; Figure 6; Figure 9; Figure 10; Figure 11; Figure 13; and Figure 14.

We present the summary relative effects from the network meta-analysis in league tables for both class-level (Figure 6) and drug-level (Figure 9) analyses. All of the interventions appeared superior to placebo in terms of showing significant improvement on a quality of life scale. Anti-IL17, anti-IL23, and anti-IL12/23 were associated with a higher chance of improving quality of life compared to small molecules and conventional systemic agents (Figure 6). These differences were statistically significant for all of the classes. No significant difference was shown between the different biological agents except for anti-IL17 and anti-TNF alpha (anti-IL17 was more favourable than anti-TNF alpha). No significant differences were shown between the small molecules and the conventional agents. Results of comparisons between each of the drugs are available in Figure 9.

### Ranking class-level analysis (Figure 10; Figure 13; Table 4)

Ranking analysis for quality of life performed with SUCRA strongly suggested that anti-IL17 was the best treatment at class level (versus placebo: standardised mean difference (SMD) -1.44,

95% confidence interval (CI) -1.68 to -1.19; SUCRA = 95.4), followed by anti-IL23 (versus placebo: SMD -1.30 95% CI -1.60 to -0.99; SUCRA = 83.4), anti-IL12/23 (versus placebo: SMD -1.21 95% CI -1.45 to -0.96; SUCRA = 75.7), then anti-TNF alpha (versus placebo: SMD -1.03 95% CI -1.18 to -0.88 SUCRA = 58.4). The heterogeneity  $\tau$  for this network overall was 0.27, which we considered moderate heterogeneity.

### Ranking drug-level analysis (Figure 11; Figure 14 Table 5)

Ranking analysis for quality of life performed with SUCRA strongly suggested that ixekizumab was the best treatment at drug level (versus placebo: SMD -1.68 95% CI -1.93 to -1.43; SUCRA = 99.2), followed by guselkumab (versus placebo: SMD -1.31 95% CI -1.61 to -1.01; SUCRA = 84.3), ustekinumab (versus placebo: SMD -1.21 95% CI -1.42 to -1.00; SUCRA = 77.4), tildrakizumab (versus placebo: SMD -1.23 95% CI -1.77 to -0.68; SUCRA = 74.9), then etanercept (versus placebo: SMD -1.11 95% CI -1.29 to -0.93; SUCRA = 67.6). The heterogeneity  $\tau$  for this network overall was 0.22, which we considered low to moderate heterogeneity. Moreover, six interventions (acitretin, certolizumab, ciclosporin, fumaric acid, infliximab, secukinumab) were not included in the ranking at drug level, due to no available data.

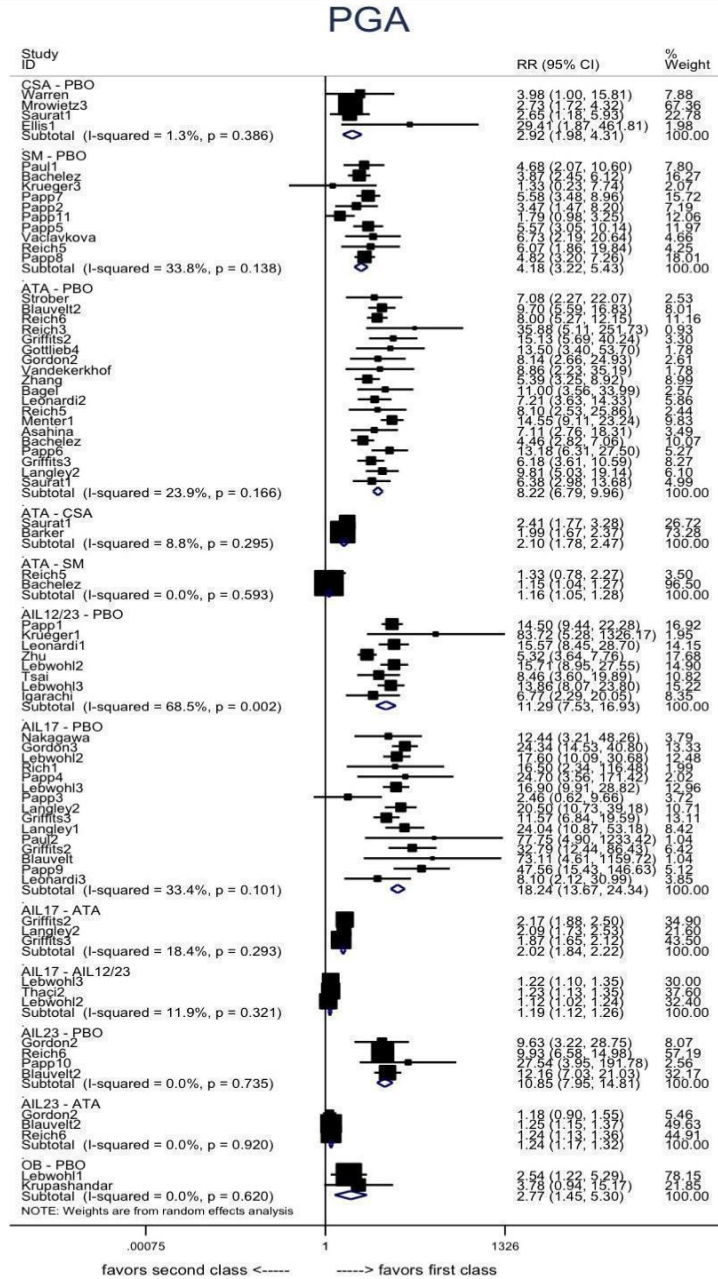
In total, available information on quality of life was poorly reported and lacking for a third of the interventions, so has to be considered with cautious.

## 2.2 Proportion of participants who achieve a Physician Global Assessment (PGA) value at 0 or 1

### DIRECT EVIDENCE

We report treatment estimates for pair-wise meta-analyses at class (Figure 18) and drug level in Analysis 4.1; Analysis 4.2; Analysis 4.3; Analysis 4.4; Analysis 4.5; Analysis 4.6; Analysis 4.7; Analysis 4.8; Analysis 4.9; Analysis 4.10; and Analysis 4.11, respectively.

**Figure 18. Physician Global Assessment 0/1: direct summary effects for comparisons including at least two studies at class-level** AIL12/23: anti-IL12/23; AIL17: anti-IL17; AIL23: anti-IL23, ATA: anti-TNF alpha; CSA: conventional systemic agents; OB: other biologics; PBO: placebo; SM: small molecules AE: adverse events; CI: confidence interval; PGA: Physician Global Assessment; RR: risk ratio



## NETWORK META-ANALYSES

The PGA 0/1 outcome was available in 56 trials, involving 31,030 participants (87.5% of the participants in this review). This outcome was reported in four other studies (Krueger 2002; Nugteren-Huying 1990; Sandhu 2003; Sterry PRESTA, 2010); however, the number of randomised participants was not available. These trials were added to the complete case analyses. This outcome was also reported in another trial (Mrowietz SCULPTURE, 2015), comparing different dosages of the same drug. These trials were added in the sensitivity analysis at dose level. PGA 0/1 was not reported for the 13 remaining trials, and we were not able to obtain missing information from the trial authors (Table 2). Forty trials, involving 16,946 participants, were placebo-controlled trials; four, involving 1844 participants, were head-to-head comparisons; and 12, involving 12,240 participants, had both a placebo and at least two active treatments arms.

See Figure 4; Figure 5; Figure 6; Figure 9 Figure 10; Figure 11; Figure 13; and Figure 14.

We presented the summary relative effects as estimated from the network meta-analysis in league tables at class level (Figure 6) and drug level (Figure 9). All of the interventions appeared superior to placebo in terms of reaching PGA 0/1, and anti-IL17 monoclonal antibodies were associated with a better chance in terms of this outcome compared to the other drug classes (Figure 6). These differences were statistically significant. All of the interventions (anti-IL17, anti-IL23, anti-IL12/23, anti-TNF alpha) appeared significantly superior to the small molecule class of treatments and the conventional systemic class of treatments. No significant difference was found between small molecule and conventional systemic agents. Results of comparisons between each of the drugs are available in Figure 9.

**Ranking class-level analysis** (Figure 10; Figure 13; Table 4)

Ranking analysis for PGA 0/1 performed with SUCRA strongly suggested that anti-IL17 was the best treatment at class level (versus placebo: RR 15.85, 95% confidence interval (CI) 13.08 to 19.20; SUCRA = 99.9), followed by anti-IL12/23 (versus placebo: RR 11.80, 95% CI 9.67 to 14.39; SUCRA = 83.8), anti-IL23 (versus placebo: RR 9.93, 95% CI 7.58 to 13.02; SUCRA = 73.1), then anti-TNF alpha (versus placebo: RR 7.82, 95% CI 6.66 to 9.17; SUCRA = 57.5). The heterogeneity  $\tau$  for this network overall was 0.21, which we considered low to moderate heterogeneity.

**Ranking drug-level analysis** (Figure 11; Figure 14; Table 5)

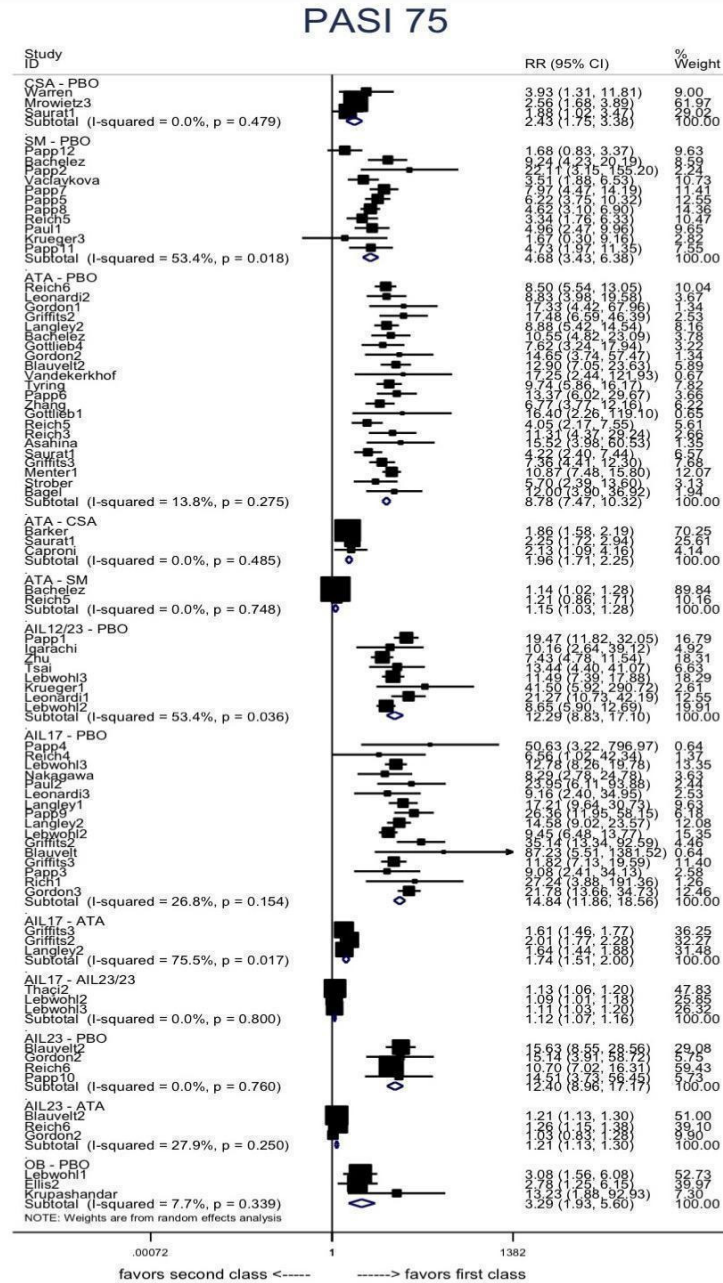
Ranking analysis for PGA 0/1 performed with SUCRA strongly suggested that certolizumab was the best treatment at drug level (versus placebo: RR 35.88, 95% CI 4.86 to 265.07; SUCRA = 90.1), followed by tildrakizumab (versus placebo: RR 27.54, 95% CI 3.76 to 201.98; SUCRA = 86.3), ixekizumab (versus placebo: RR 16.11, 95% CI 11.72 to 22.17; SUCRA = 85.9), secukinumab (versus placebo: RR 15.46, 95% CI 11.19 to 21.37; SUCRA = 84.4), brodalumab (versus placebo: RR 15.31, 95% CI 10.84 to 21.63; SUCRA = 84), then ustekinumab (versus placebo: RR 11.52, 95% CI 9.17 to 14.4; SUCRA = 70.4). The heterogeneity  $\tau$  for this network overall was 0.23, which we considered low to moderate heterogeneity.

## 2.3 Proportion of participants who achieve PASI 75

### DIRECT EVIDENCE

We report treatment estimates for pair-wise meta-analyses at class (Figure 19) and drug level in Analysis 3.1; Analysis 3.2; Analysis 3.3; Analysis 3.4; Analysis 3.5; Analysis 3.6; Analysis 3.7; Analysis 3.8; Analysis 3.9; Analysis 3.10; and Analysis 3.11, respectively.

**Figure 19. PASI 75: direct summary effects for comparisons including at least two studies at class level** AIL12/23: anti-IL12/23; AIL17: anti-IL17; AIL23: anti-IL23, ATA: anti-TNF alpha; CSA: conventional systemic agents; OB: other biologics; PBO: placebo; SM: small molecules CI: confidence interval; PASI: Psoriasis Area and Severity Index; RR: risk ratio





## NETWORK META-ANALYSES

PASI 75 outcome was available in 64 trials, involving 32,518 participants (91.7% of the participants in this review). This outcome was reported in two other trials ([Krueger 2002](#); [Sterry PRESTA, 2010](#)); however, the number of randomised participants was not available. These trials were added to the complete case analyses. This outcome was also reported in five other trials ([Dogra 2012](#); [Dogra 2013](#); [Dubertret 1989](#); [Laburte 1994](#); [Mrowietz SCULPTURE, 2015](#)), comparing different dosages of the same drug in each case. These trials were added in the sensitivity analysis at dose level. PASI 75 was not reported for the three remaining trials, and we were not able to obtain missing information from the trial authors ([Table 2](#)). Forty-five trials, involving 18,330 participants, were placebo-controlled trials; seven, involving 1948 participants, were head-to-head comparisons; and 12, involving 12,240 participants, had both a placebo and at least two active treatments arms.

See [Figure 4](#); [Figure 5](#); [Figure 6](#); [Figure 8](#); [Figure 10](#); [Figure 11](#); [Figure 13](#); and [Figure 14](#).

We present the summary relative effects from the network meta-analysis in league tables for both class-level ([Figure 6](#)) and drug-level ([Figure 8](#)) analyses. All of the interventions appeared superior to placebo in terms of reaching PASI 75. The anti-IL17 class of drugs was associated with a higher chance of reaching PASI 75 compared to the other classes ([Figure 6](#)). These differences were statistically significant for all of the classes. All of the interventions (anti-IL17, anti-IL23, anti-IL12/23, anti-TNF alpha) appeared significantly superior to the small molecule class and the conventional systemic class, and the small molecules appeared significantly superior to the conventional systemic agents. Results of comparisons between each of the drugs are available in [Figure 8](#).

**Ranking class-level analysis** ([Figure 10](#); [Figure 13](#); [Table 4](#))

Ranking analysis for PASI 75 performed with SUCRA strongly suggested that anti-IL17 was the best treatment at class level (versus placebo: RR 14.32, 95% CI 12.20 to 16.81; SUCRA = 99.6), followed by anti-IL12/23 (versus placebo: RR 12.21, 95% CI 10.23 to 14.57; SUCRA = 85.0), anti-IL23 (versus placebo: RR 10.07, 95% CI 8.03 to 12.63; SUCRA = 72.2), then anti-TNF alpha (versus placebo: RR 8.23 95% CI 7.20 to 9.42; SUCRA = 57.4). The heterogeneity  $\tau$  for this network overall was 0.16, which we considered low heterogeneity.

**Ranking drug-level analysis** ([Figure 11](#); [Figure 14](#); [Table 5](#))

Ranking analysis for PASI 75 performed with SUCRA strongly suggested that ixekizumab was the best treatment at drug level (versus placebo: RR 15.81, 95% CI 12.35 to 20.23; SUCRA = 91.8), followed by secukinumab (versus placebo: RR 14.16, 95% CI 11.12 to 18.03; SUCRA = 86.7), brodalumab (versus placebo: RR 13.04 95% CI 10.17 to 16.71; SUCRA = 82.1), tildrakizumab (versus placebo: RR 14.51, 95% CI 3.60 to 58.45; SUCRA = 78.3), then ustekinumab (versus placebo: RR 11.84, 95% CI 9.79 to 14.33; SUCRA = 75.2). The heterogeneity  $\tau$  for this network overall was 0.16, which we considered low heterogeneity.

Focusing on efficacy outcomes (PASI 90, PASI 75, and PGA 0/1), the results were identical at class level ([Figure 10](#)) and very close at drug level ([Figure 11](#)).

## 2.4 The proportions of participants with adverse effects

### DIRECT EVIDENCE

We report treatment estimates for pair-wise meta-analyses at class ([Figure 20](#)) and drug level in [Analysis 6.1](#); [Analysis 6.2](#); [Analysis 6.3](#); [Analysis 6.4](#); [Analysis 6.5](#); [Analysis 6.6](#); [Analysis 6.7](#); [Analysis 6.8](#); [Analysis 6.9](#); and [Analysis 6.10](#), respectively.



## NETWORK META-ANALYSES

Adverse events (AEs) outcome was available in 54 trials, involving 29,699 participants (83.8% of the participants in this review). AEs were not reported for the 36 remaining trials, and we were not able to obtain missing information from the trial authors (Table 2). This outcome was also reported in another trial (Mrowietz SCULPTURE, 2015), comparing different dosages of the same drug. Mrowietz SCULPTURE, 2015 was added to the sensitivity analyse at dose level. Thirty-seven trials, involving 15,683 participants, were placebo-controlled trials; five, involving 1,776 participants, were head-to-head comparisons; and 12, involving 12,240 participants, had both a placebo and at least two active treatments arms.

See Figure 4; Figure 5; Figure 6; Figure 8; Figure 10; Figure 11; Figure 13; and Figure 14.

We present the summary relative effects from the network meta-analysis in league tables for both class-level (Figure 6) and drug-level (Figure 8) analyses. All of the interventions had a more significant risk of AEs compared to placebo. Significant associations were found: anti-IL17 had a higher risk of AE compared with all the other interventions. Results of comparisons between each of the drugs are available in Figure 8.

**Ranking class-level analysis** (Figure 10; Figure 13; Table 4)

Ranking analysis for AEs performed with SUCRA strongly suggested that placebo was associated with the best safety profile regarding all the adverse events (SUCRA 94.0). Anti-IL23 was the best treatment at class level (versus placebo: RR 1.03, 95% CI 0.93 to 1.13; SUCRA = 78.7), followed by anti-IL12/23 (versus placebo: RR 1.07, 95% CI 1.01 to 1.14; SUCRA = 57.0), then conventional systemic treatment (versus placebo: RR 1.08, 95% CI 0.99 to 1.17; SUCRA = 50.8). The heterogeneity  $\tau$  for this

network overall was 0.05, which we considered low heterogeneity.

**Ranking drug-level analysis** (Figure 11; Figure 14; Table 5)

Ranking analysis for AE performed with SUCRA strongly suggested that placebo was associated with the best safety profile regarding all the adverse events (SUCRA = 88), then tildrakizumab (versus placebo: RR 0.95, 95% CI 0.76 to 1.19; SUCRA = 86.1), followed by guselkumab (versus placebo: RR 1.02, 95% CI 0.80 to 1.13; SUCRA = 78.2) and certolizumab (versus placebo: RR 1.00 95% CI 0.80 to 1.23; SUCRA = 78). The heterogeneity  $\tau$  for this network overall was 0.04, which we considered low heterogeneity.

### 2.5. Participants with at least 1 relapse in the maintenance phase (between 52 to 104 weeks)

There were no data available for the maintenance phase.

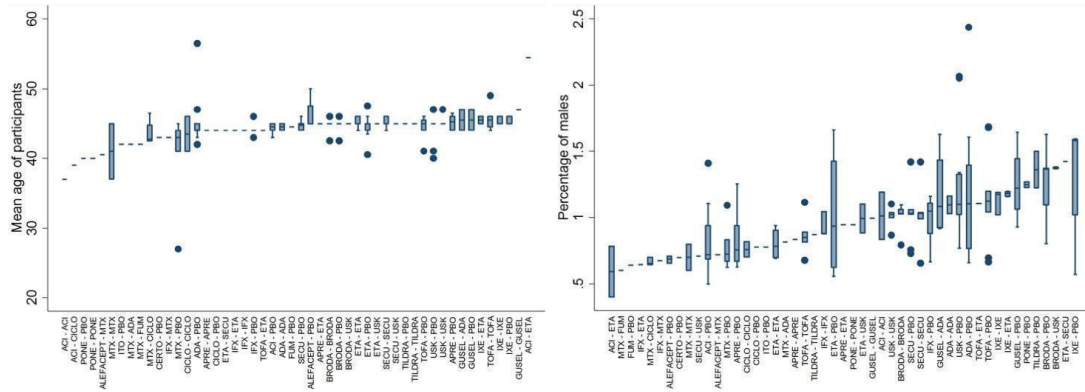
### 3. Assessment of heterogeneity and inconsistency

We did not identify important heterogeneity neither in direct meta-analyses nor in network meta-analysis. The common outcome-specified network heterogeneity and the prediction intervals suggested the presence of low heterogeneity for all outcomes except for quality of life, which appeared to have moderate heterogeneity. We investigated differences in heterogeneity between class- and drug-level analysis, and we also investigated differences in heterogeneity between primary and sensitivity analyses for the primary outcomes (see 4. subgroup and sensitivity analyses). The results were very closed.

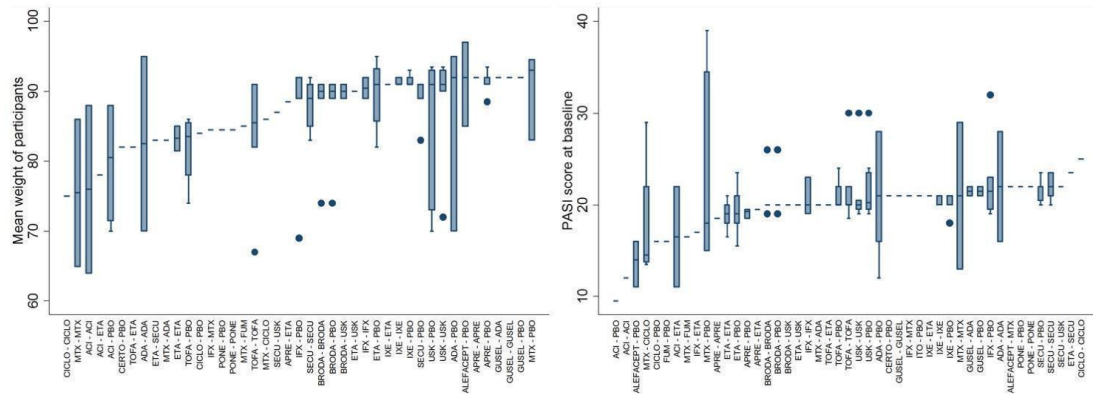
The distribution of some participant characteristics (age, sex ratio, weight, severity of psoriasis) did not give an indication of important differences in these characteristics across comparisons (see Figure 21; Figure 22).



**Figure 21. Distributions of age and sex ratio of participants across comparisons** ACI: acitretin; ADA: adalimumab; APRE: apremilast; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; ITO: itolizumab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; PONE: ponesimod; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; USK: ustekinumab



**Figure 22. Distributions of weight of participants and PASI score at baseline across comparisons**ACI: acitretin; ADA: adalimumab; APRE: apremilast; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; ITO: itolizumab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; PONE: ponesimod; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; USK: ustekinumab



At class-level analysis, the global test for inconsistency was not significant for all of the outcomes except for PASI 75 (data not shown). At drug-level analysis, the global test for inconsistency was not significant for all of the outcomes but only marginally non-significant for PASI 90. Results of a global test for inconsistency, at drug level, are detailed in [Figure 23](#) and [Figure 24](#) for PASI 90 and SAEs, respectively. The loop-specific and side-splitting approaches indicated a handful of loops and comparisons with statistically significant inconsistency ([Figure 25](#); [Figure 26](#)). This apparent inconsistency does not generally exceed however the expected level of inconsistency that has been suggested by empirical evidence ([Veroniki 2013](#)), which is about 10% of the total number of loops.

**Figure 23. Side-splitting approach and design-by-treatment interaction model for inconsistency for Psoriasis Area and Severity Index (PASI) 90** Treatment codes: A = PBO, B = FUM, C = MTX, D = ACI, E = ALEFACEPT, F = CICLO, G = IFX, H = ADA, I = ETA, J = USK, K = SECU, L = IXE, M = BRODA, N = CERTO, O = APRE, P = TOFA, Q = GUSEL, R = TILDRA, S = PONE, T = ITOACI: acitretin; ADA: adalimumab; APRE: apremilast; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; ITO: itolizumab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; PONE: ponesimod; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; USK: ustekinumab

**PASI 90**

Side	Direct		Indirect		Difference		
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P> z
A B	1.497381	.4179291	.6197685	1.240918	.877612	1.309405	0.503
A C	.4223373	.427813	2.842524	.5632235	-2.420187	.7946425	0.002
A I	2.363178	.176411	2.416913	.2220003	-.0537342	.3013986	0.859
A J	3.122477	.196001	2.885283	.1751146	.2371944	.2621884	0.366
A K	3.200051	.2535304	3.341023	.1996634	-.1409716	.3357972	0.675
B C	.6931279	1.200521	-.1844313	.5227856	.8775592	1.30941	0.503
C H	1.209756	.2586416	2.580326	.6926969	-1.37057	.703746	0.051
I J	.5889423	.1779841	.6674495	.1797493	-.0785072	.2529589	0.756
I K	.8461107	.1740841	.9619512	.1865655	-.1158406	.2557781	0.651
I L	1.07579	.0944686	1.745899	.5188704	-.6701083	.5293989	0.206
I O	-.326943	.355074	-.3735041	.4939757	.0465611	.6024607	0.938
I P	-.1221804	.1004496	-.707951	.2542509	.5857705	.273443	0.032
J K	.3191715	.1474431	.1767123	.2121463	.1424592	.2583515	0.581
J M	.2372011	.0729871	.4965464	.439592	-.2593453	.4472005	0.562

*p-value of the design-by-treatment interaction model=0.06*

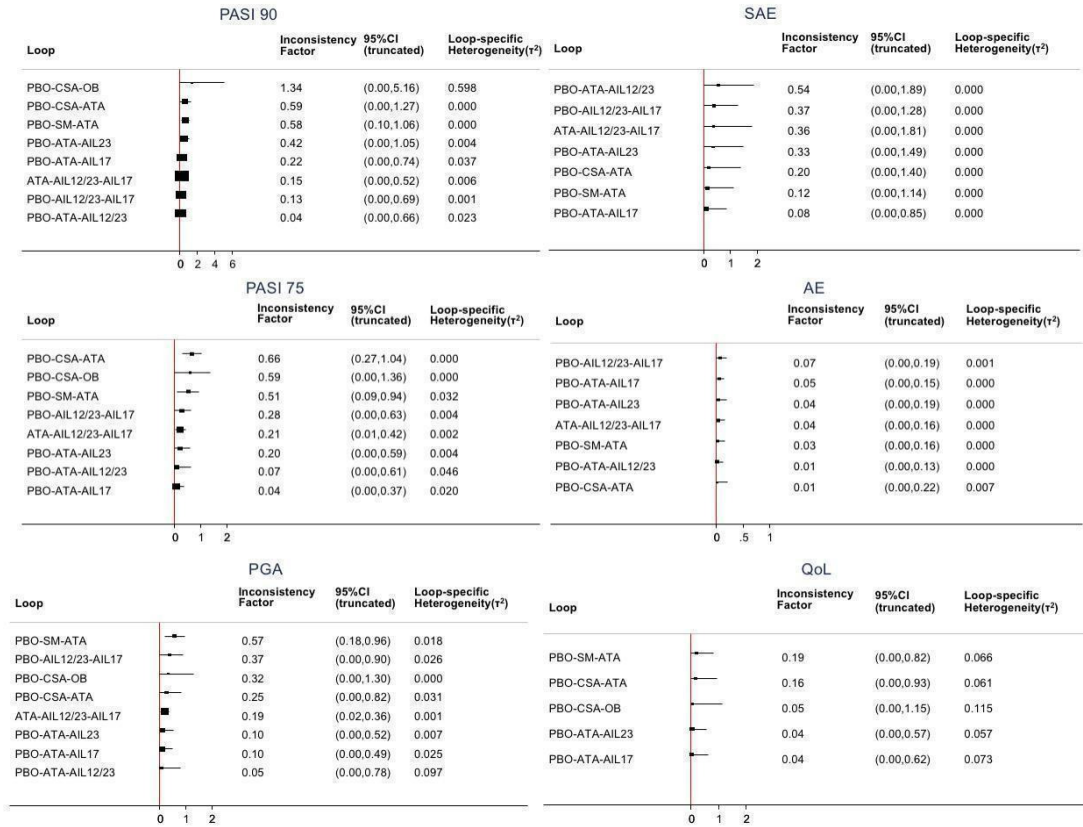
**Figure 24. Side-splitting approach and design-by-treatment interaction model for inconsistency for serious adverse events (SAEs)**Treatment codes: **A = PBO, B = FUM, C = MTX, D = ACI, E = ALEFACEPT, F = CICLO, G = IFX, H = ADA, I = ETA, J = USK, K = SECU, L = IXE, M = BRODA, N = CERTO, O = APRE, P = TOFA, Q = GUSEL, R = TILDRA, S = PONE, T = ITOACI**; acitretin; ADA: adalimumab; APRE: apremilast; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; ITO: itolizumab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; PONE: ponesimod; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; USK: ustekinumab

**SAE**

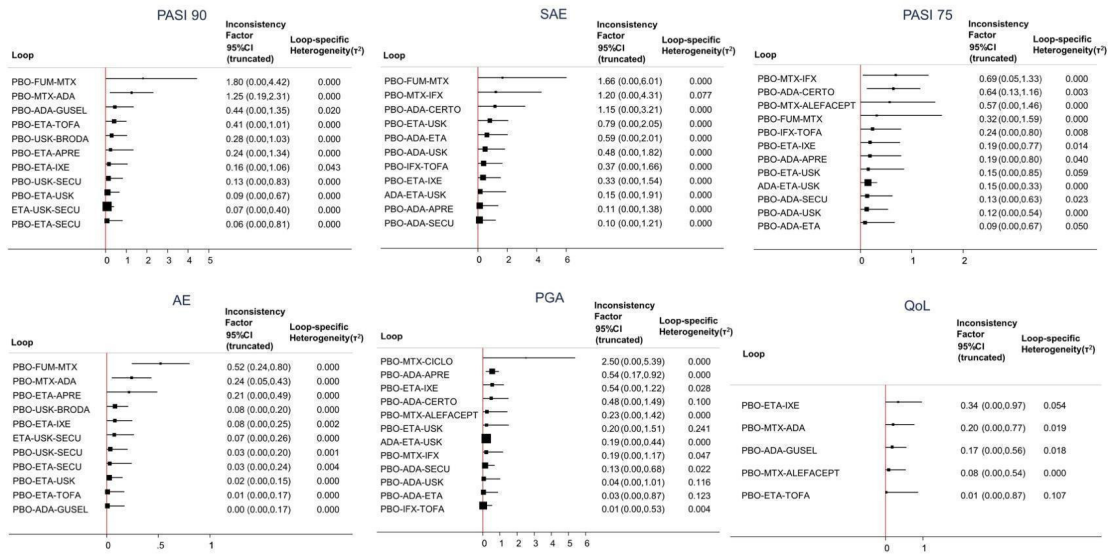
Side	Direct		Indirect		Difference		
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P> z
A B	-.187565	.4998103	-1.659383	2.138213	1.471818	2.195852	0.503
A C	-1.847262	.8647426	-.3872716	1.451164	-1.45999	1.688187	0.387
A I	.0880993	.2675187	-.2747869	.4646469	.3628862	.5672346	0.522
A J	-.2982012	.2707057	.3040432	.4044072	-.6022444	.4815077	0.211
A K	.4763566	.3703517	-.2879974	.4649878	.7643541	.6235231	0.220
B C	1.63e-10	1.983805	-1.471886	.9414853	1.471886	2.195878	0.503
C H	.8052525	1.201112	1.899652	.9468833	-1.094399	1.485049	0.461
I J	.2217037	.6085389	-.1918273	.3197499	.413531	.6874297	0.547
I K	.1605056	.4855422	.1993876	.3954003	-.0388821	.6294222	0.951
I L	.0176041	.3320897	.3868078	.5211956	-.3692037	.6311219	0.559
I O	.989995	.9552515	-.3548708	.3889303	1.344866	1.03354	0.193
I P	-.1372301	.469354	.1150165	.4487963	-.2522466	.6528653	0.699
J K	.0059172	.4405483	.5177843	.4004488	-.5118672	.5953503	0.390
J M	.2791589	.4149897	-.0518914	.5346442	.3310503	.7200053	0.646

*p-value of the design-by-treatment interaction model=0.87*

**Figure 25. Inconsistency plots for all the outcomes at class-level Inconsistency factor (IF) is calculated as the risk ratio (RR)/standardised mean difference (SMD) for direct evidence over the RR/SMD for indirect evidence in the loop with its 95% confidence interval (CI). IF value close to 0 indicates the absence of evidence for disagreement between direct and indirect evidence. AIL12/23: anti-IL12/23; AIL17: anti-IL17; AIL23: anti-IL23, ATA: anti-TNF alpha; CSA: conventional systemic agents; OB: other biologics; PBO: placebo; SM: small molecules**



**Figure 26. Inconsistency plots for all the outcomes at drug level.** Inconsistency factor (IF) is calculated as the risk ratio (RR)/standardised mean difference (SMD) for direct evidence over the RR/SMD for indirect evidence in the loop with its 95% confidence interval (CI). IF value close to 0 indicates the absence of evidence for disagreement between direct and indirect evidence. **ACI:** acitretin; **ADA:** adalimumab; **APRE:** apremilast; **BRODA:** brodalumab; **CERTO:** certolizumab; **CICLO:** ciclosporin; **ETA:** etanercept; **FUM:** fumaric acid; **IFX:** infliximab; **ITO:** itolizumab; **IXE:** ixekizumab; **GUSEL:** guselkumab; **MTX:** methotrexate; **PBO:** placebo; **PONE:** ponesimod; **SECU:** secukinumab; **TILDRA:** tildrakizumab; **TOFA:** tofacitinib; **USK:** ustekinumab



Possible explanation of this apparent inconsistency could be the differences between the previous treatment allowed across these trials: for example, participants enrolled in the [Saurat CHAMPION, 2008](#) trial (adalimumab versus methotrexate versus placebo) were naïve to methotrexate and TNF alpha antagonists whereas participants enrolled in the [Menter REVEAL, 2008](#) trial (adalimumab versus placebo) could have received previous systemic treatment including methotrexate.

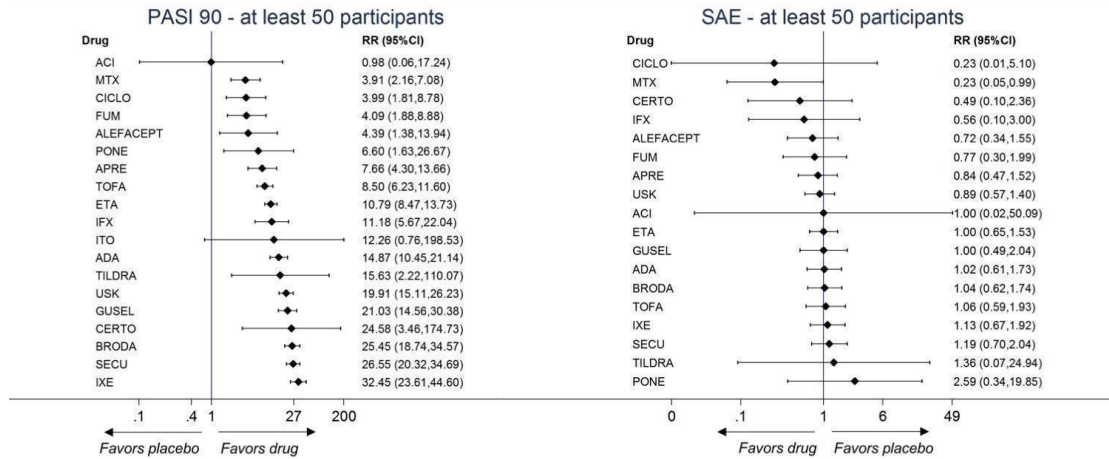
#### 4. Subgroup and sensitivity analyses

We had enough data for none of the aforementioned characteristics that may act as effect modifiers and therefore we were not able to run subgroup analyses and meta-regressions to investigate their potential effect on the results.

Results of the sensitivity analyses involving the following were similar to those of the main analysis for the two primary outcomes:

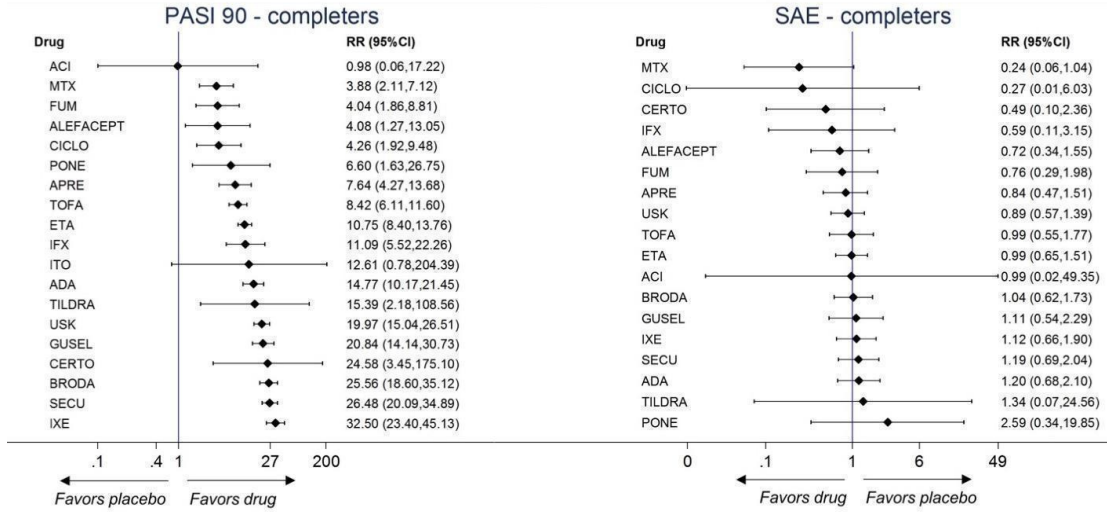
- excluding studies with less than 50 participants ([Figure 27](#)) (the heterogeneity  $\tau$  for this subgroup network was 0.08 for PASI 90 and 0 for SAEs, which we considered low heterogeneity);

**Figure 27. Sensitivity analyses - Interval plot. Network meta-analysis results for primary outcomes (PASI 90 and serious adverse events) for trials with at least 50 participants.** ACI: acitretin; ADA: adalimumab; APRE: apremilast; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; ITO: itolizumab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; PONE: ponesimod; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; USK: ustekinumab CI: confidence interval; PASI: Psoriasis Area and Severity Index; RR: risk ratio; SAE: serious adverse events



- completers (Figure 28) (the heterogeneity  $\tau$  for this subgroup network was 0.09 for PASI 90 and 0 for SAEs, which we considered low heterogeneity);

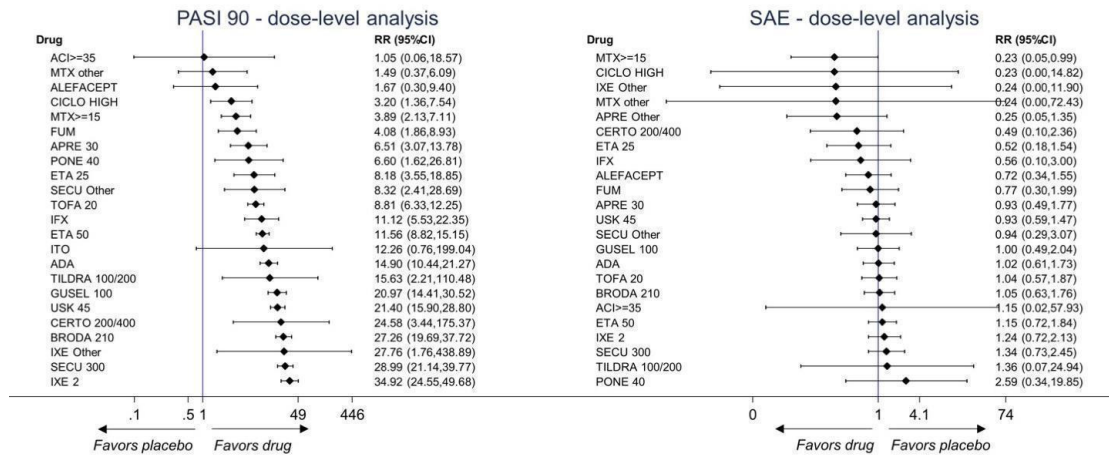
**Figure 28. Sensitivity analyses - Interval plot. Network meta-analysis results for primary outcomes (PASI 90 and serious adverse events) for the completers.** ACI: acitretin; ADA: adalimumab; APRE: apremilast; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; ITO: itolizumab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; PONE: ponesimod; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; USK: ustekinumab CI: confidence interval; PASI: Psoriasis Area and Severity Index; RR: risk ratio; SAE: serious adverse events



- analyses at dose level (Figure 29) (the heterogeneity  $\tau$  for this subgroup network was 0.10 for PASI 90 and 0 for SAEs, which we considered low heterogeneity); and

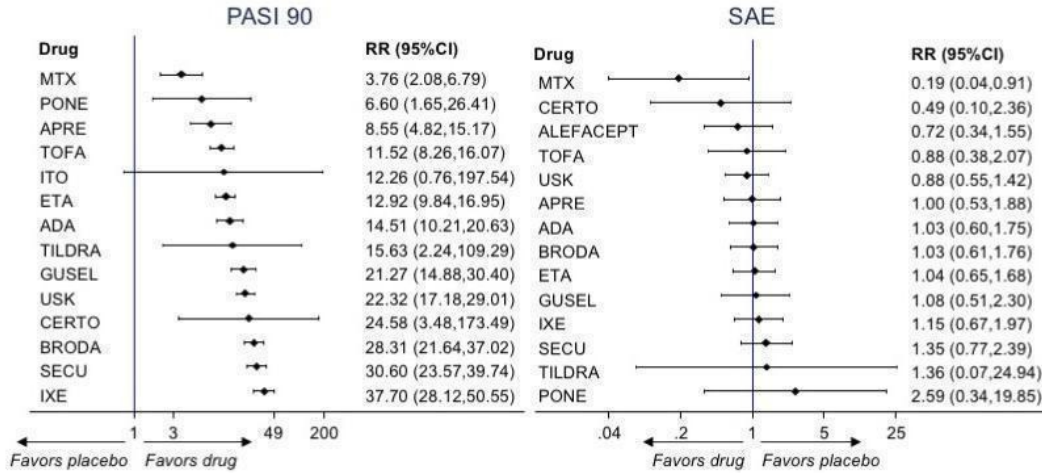


**Figure 29. Sensitivity analyses - Interval plot. Network meta-analysis results for primary outcomes (PASI 90 and serious adverse events) for all the interventions depending on the doses MTX  $\geq$  15/MTX other: methotrexate  $\geq$  15 mg per week/methotrexate  $<$  15 mg per week; ALEFACEPT: alefacept all dosages; CICLO High: ciclosporin  $\geq$  3 mg/kg/day; ACI  $\geq$  35: acitretin  $\geq$  35 mg per day; FUM: fumaric acid esters all dosages; APRE 30: apremilast 30 mg twice daily; PONE 40: ponesimod 40 mg per day; TOFA 20: tofacitinib 20 mg per day; ETA 25/ETA 50: etanercept 25 mg twice a week/etanercept 50 mg twice a week; IFX: infliximab 5 mg/kg week 0, 2, 4 every 6 weeks; ADA: adalimumab 80 mg Week 0, 40 mg Week 1 then 40 mg every other week; CERTO 200/400: certolizumab all dosages; USK 45: ustekinumab 45 mg; SECU 300/SECU other: secukinumab 300 mg every injection/secukinumab other dosages; IXE 200/IXE other: ixekizumab 200 mg per injection/ixekizumab other dosages; TILDRA 100/200: tildrakizumab all dosages; GUSEL 100: guselkumab 100 mg per injection; BRODA 210: brodalumab 210 mg per injection CI: confidence interval; PASI: Psoriasis Area and Severity Index; RR: risk ratio; SAE: serious adverse events**



- excluding studies at high risk of bias (Figure 30) (the heterogeneity  $\tau$  for this subgroup network was 0.12 for PASI 90 and 0 for SAEs, which we considered low heterogeneity).

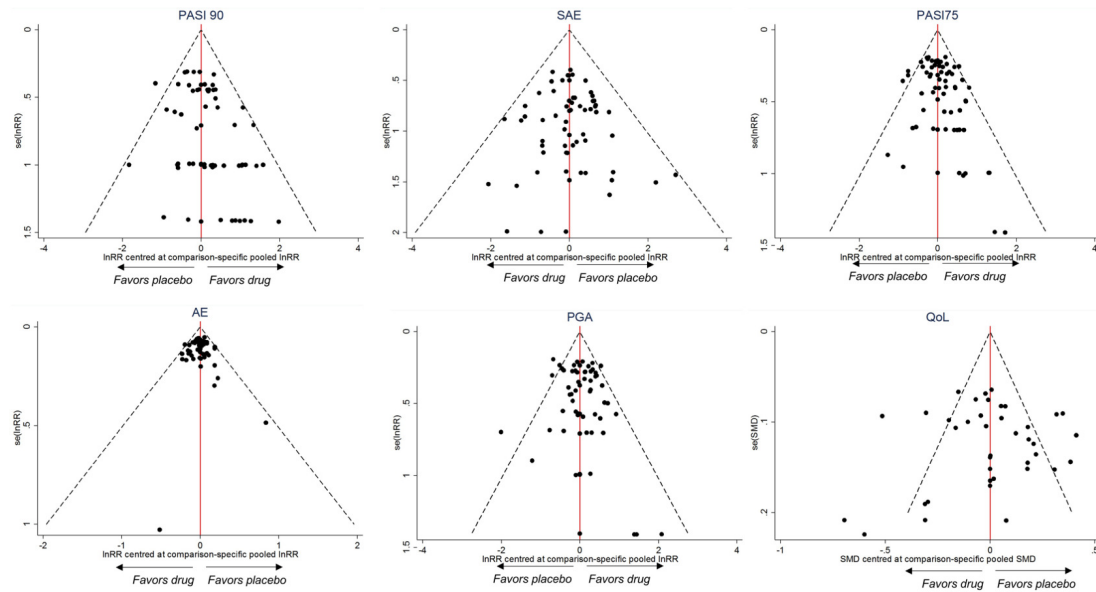
**Figure 30. Sensitivity analyses - Interval plot. Network meta-analysis results for primary outcomes (PASI 90 and serious adverse events) for all the interventions excluding studies at high risk of bias.** ACI: acitretin; ADA: adalimumab; APRE: apremilast; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; ITO: itolizumab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; PONE: ponesimod; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; USK: ustekinumab CI: confidence interval; PASI: Psoriasis Area and Severity Index; RR: risk ratio; SAE: serious adverse events



**5. Reporting bias**

The comparison-adjusted funnel plots generally appeared symmetrical, and only the graph for quality of life presented some evidence of small-study effects which might be caused by selective outcome reporting (Figure 31).

**Figure 31. Funnel plot for network meta-analysis of all the outcomes**AE: adverse event; InRR: Mean effect size; PASI: Psoriasis Area and Severity Index; QoL: Specific quality of life scale; RR: Risk ratio; SAE: serious adverse events; SMD: standardised mean difference

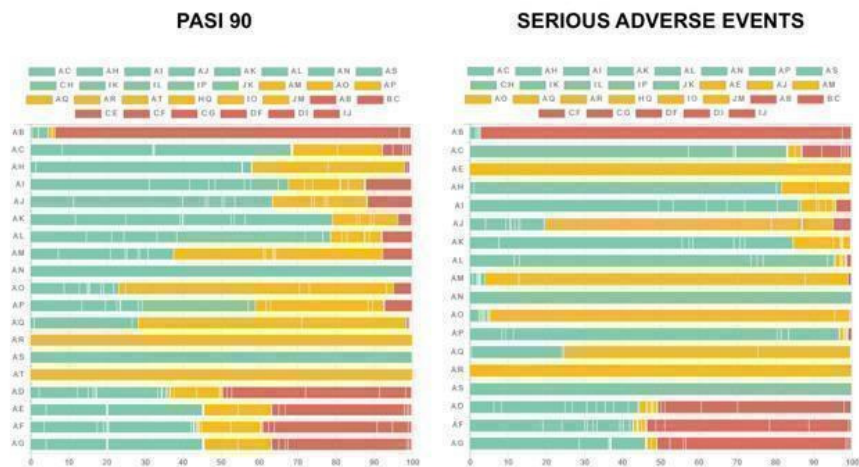


## 6. Grading of the evidence

We graded the evidence for the two primary outcomes, PASI 90 and serious adverse events, for all of the network intervention estimates according to the approach proposed by [Salanti 2014](#). We considered five domains: study limitations (by first evaluating the risk of bias of each direct estimate ([Figure 2](#)) and then by integrating these judgements with the contribution of each direct estimate to the network estimates ([Figure 32](#))), consistency of effect, imprecision, indirectness, and publication bias.

**Figure 32. Study bias distribution for each primary outcome (PASI 90 and serious adverse events)**The following graphs show how much information (i.e. the percentage contribution of each direct comparison in the network estimates) comes from low (green), unclear/moderate (yellow) and high (red) risk of bias studies.

Here we have all drugs versus placebo as it is difficult to have all comparisons due to space limitations. To evaluate the direct comparisons we used the mean level of bias of the included studies in each comparison. We used the web application CINeMA (CINeMA 2017). The codes of the treatments are A = Placebo, B = Fumaric acid esters, C = Methotrexate, D = Acitretin, E = Alefacept, F = Ciclosporin, G = Infliximab, H = Adalimumab, I = Etanercept, J = Ustekinumab, K = Secukinumab, L = Ixekizumab, M = Brodalumab, N = Certolizumab, O = Apremilast, P = Tofacitinib, Q = Guselkumab, R = Tildrakizumab, S = Ponesimod, T = Itolizumab



For PASI 90, we judged the confidence in the treatment estimate to be high for ixekizumab, secukinumab, and ustekinumab; moderate for brodalumab, guselkumab (reasons for downgrading: studies limitations), certolizumab (imprecision), adalimumab (inconsistency), etanercept (inconsistency), apremilast (study limitations), ponesimod (imprecision), and methotrexate (inconsistency); and low or very low for all of the other treatments (tildrakizumab, itolizumab, tofacitinib, infliximab, acitretin, ciclosporin, fumaric acid esters, alefacept). More detail on the reasons for downgrading are available in [Summary of findings for the main comparison](#).

For serious adverse events, we judged the confidence in the treatment estimate to be low to very low for almost all of the treatment, except methotrexate, certolizumab, tofacitinib, etanercept, adalimumab, ixekizumab, secukinumab, and ponesimod, which we assessed as moderate certainty (downgrading linked to imprecision for all “moderate certainty” drugs). More detail on the reasons for downgrading are available in [Summary of findings for the main comparison](#).

## DISCUSSION

### Summary of main results

Our systematic review and meta-analysis compared all drugs and drugs undergoing phase II/III trials used for moderate to severe psoriasis in 2017 except a new anti-IL23 molecule (BI 655066, risankizumab).

In total, this review included 109 studies, involving 39,882 randomised adult participants, which assessed outcomes during the induction phase (less than 24 weeks after randomisation). In total, 55 trials were multiarm. Seventy-three trials compared systematic treatment against placebo, 25 were head to head trials, and 11 had both active comparator and placebo. Fifteen trials had a co-intervention mainly phototherapy. Finally, 79 studies declared pharmaceutical company funding, and 21 studies did not report the source of funding.

We included 74 studies (without co-intervention and with a timing of outcome assessment from 12 to 16 weeks after randomisation (classified as induction therapy)), involving 35,454 participants

(88.9% participants of this review), in the network meta-analysis. Conventional systemic treatments, the oldest class-level treatment (acitretin, ciclosporin, fumaric acid esters, methotrexate); anti-TNF alpha treatments (etanercept, infliximab, adalimumab, certolizumab); an anti-IL12/23 treatment (ustekinumab); and anti-IL17 treatments (secukinumab, ixekizumab, brodalumab) have all been approved for psoriasis except certolizumab. And except for apremilast and alefacept, small molecule drugs (tofacitinib, ponesimod), anti-IL23 treatments (guselkumab and tildrakizumab), and other biologics (itolizumab) had not been approved for psoriasis at the time we conducted our analyses.

All of the assessed interventions appeared superior to placebo in terms of reaching Psoriasis Area and Severity Index (PASI) 90.

At class level, network meta-analysis showed that the biologics anti-IL17, followed by anti-IL12/23, anti-IL23, and anti-TNF alpha outperformed the small molecules and the conventional systemic agents in terms of reaching PASI 90 measured at the twelfth to the sixteenth week of treatment after randomisation, with small molecules producing a better outcome than conventional systemic agents.

The most effective drug for reaching PASI 90 when compared to placebo was ixekizumab (high-certainty evidence), followed by secukinumab (high-certainty evidence), brodalumab (moderate-certainty evidence), guselkumab (moderate-certainty evidence), certolizumab (moderate-certainty evidence), then ustekinumab (high-certainty evidence) (see [Summary of findings for the main comparison](#)).

At drug-level, all of the anti-IL17 agents and guselkumab (an anti-IL23 drug) were significantly more effective in reaching PASI 90 than three anti-TNF alpha agents (infliximab, adalimumab, and etanercept, but not certolizumab), and ustekinumab was superior to etanercept. No statistically significant difference was shown between infliximab, adalimumab, and etanercept. Only one trial assessed the efficacy of infliximab in this network; thus, the results involving infliximab have to be interpreted with caution. Tofacitinib was significantly superior to methotrexate, and no clear difference was shown between any of the other small molecules versus conventional treatments. The results were almost the same for the other efficacy outcome PASI 75.

No significant difference was found between all of the interventions and the placebo regarding the risk of serious adverse effects (SAEs). The relative ranking for SAEs strongly suggested that methotrexate was associated with the best safety profile regarding all the SAEs (moderate-certainty evidence), followed by ciclosporin (very low-certainty evidence), certolizumab (moderate-certainty evidence), infliximab (very low-certainty evidence), alefacept (low-certainty evidence), then fumaric acid esters (FAEs) (very low-certainty evidence). Major adverse cardiac events, serious infections, or malignancies (see [Table 6](#)) were reported in both placebo and intervention groups.

Information on quality of life was often poorly reported and was absent for a third of the interventions.

Finally, considering both efficacy (PASI 90 outcome) and acceptability (SAE outcome), highly effective treatments had also more SAE than the other treatments, and ustekinumab, infliximab, and certolizumab appeared to be the better compromise between efficacy and acceptability (bearing in mind the limitations that affect interpretation of the SAE results, such as the very low number of events on which the results were based, with just over half of the treatment estimates being based on low to very low certainty evidence (the rest moderate)).

## Overall completeness and applicability of evidence

We were able to draw some conclusions on the effectiveness (and ranking) of the systemic treatment options for moderate to severe chronic plaque psoriasis during the induction phase. Long-term efficacy and safety data are lacking. Specific details are listed below.

### Participants

Participants in the included studies had a mean age of 44 years and had moderate to severe psoriasis with an overall mean PASI score at baseline of 20 (range: 9.5 to 39). This young age and the high level of disease severity may not be typical of patients seen in daily clinical practice especially for patients who need a first-line systemic treatment. In addition, patients selected for randomised controlled trials (RCTs) generally have few major comorbidities. Almost all studies including one biological arm excluded patients with history of infectious diseases or malignancies and signs of severe renal, cardiac, hepatic, demyelinating, or other disorders. This may impact the generalisability of these results for clinical practice. However, some participants characteristics (such as being overweight, imbalanced sex ratio in favour of males, presence of metabolic syndrome) were reflective of a moderate to severe psoriasis population, comparable to literature data ([Wolkenstein 2009](#)).

### Interventions

Evidence on 19 treatments included in this review was derived from 74 trials (searched for up to December 2016). We included all interventions irrespective of the dose. Thus, we increased the number of available RCTs per intervention and had more power to assess SAEs and adverse events (AEs). The number of studies was still low for the following interventions: certolizumab, tildrakizumab, itolizumab, infliximab, ponesimod, acitretin, ciclosporin, alefacept, fumaric acid, and methotrexate, meaning we must be cautious of the conclusions drawn for these drugs. In terms of efficacy, the results from the subgroup analysis using a standard dose for each intervention was similar for PASI 90 (and SAE) compared to the main analyses, making us confident with the results of the main analysis.

For drugs just approved or not yet approved for psoriasis, ongoing studies are still investigating guselkumab, tildrakizumab, a

third anti-IL23 (risankizumab, which will be included in the next update of this review), certolizumab, tofacitinib, and itolizumab ([Characteristics of ongoing studies](#)). Ponesimod development in psoriasis is most uncertain and should be excluded from the next update of this review.

## Comparisons

The majority of the studies included in the review were placebo-controlled (around 70%) as were the identified ongoing studies. Once the benefit of a treatment has been established against placebo using high-quality evidence, only head-to-head trials would be helpful to provide physicians with efficacy estimates between the different biologics based on stronger evidence than indirect comparisons.

## Outcomes

Many of the trials included in this review provided evidence for the proportion of participants who reached PASI 90, PASI 75, or Physician Global Assessment (PGA) 0/1 or who experienced SAE or AE. On the other hand, patient-reported outcome (PRO) data were scanty and poorly reported. Moreover, the heterogeneity of the scales used for PRO in psoriasis trials required using the standardised mean difference in the network. So, from a clinical point of view, the interpretation of the results was difficult: a significant result for PRO between two drugs did not mean that the result was clinically useful for the patients.

## Timing

All of the included trials assessed the efficacy of the different treatments during the induction treatment phase (less than 24 weeks, with evidence in the network meta-analysis (NMA) assessed 12 to 16 weeks after randomisation). This is an unwelcome finding for a chronic disease. The trials were designed to detect differences in the severity of psoriasis in response to therapy over short periods of treatment and are often underpowered and of insufficient duration to detect rare or long-term adverse events. Therefore, it is of interest to conduct studies taking into account the induction of remission but also the long-term management (long-term remission) and the long-term safety of the drug. In order to provide long-term information on the safety of the treatments included in this review, it will be necessary to also evaluate non-randomised studies and postmarketing reports released from regulatory agencies.

## Quality of the evidence

Overall, we judged the confidence in the treatment estimate for PASI 90 to be high or moderate for anti-IL17 agents, anti-IL12/

23 agents, anti-IL23 agents, anti-TNF alpha agents (except infliximab), methotrexate, and apremilast. We judged the confidence in treatment estimate for PASI 90 as low or very low certainty for most of the comparisons involving conventional systemic agents (except for methotrexate), infliximab, other biologics, and tofacitinib; we downgraded the certainty of the evidence due to risk of bias and then either for inconsistency or imprecision. We judged the confidence in the treatment estimate for SAEs to be low to very low certainty for half of the treatment estimates, moderate for the others; we downgraded the certainty of the evidence due to imprecision and risk of bias.

## Risk of bias

The risk of bias in included studies appeared to be globally moderate to low ([Figure 2](#); [Figure 3](#)). However, some limitations should be discussed.

1. There was variation in how well the studies took measures to blind investigators and participants: a third of trials in this systematic review were considered at high or unclear risk of performance bias (35 out of 109). This is an important point to highlight as the outcomes used for assessing efficacy were subjective. However, the proportion of trials at high risk of blinding used in the network meta-analyses decreased to 15% (13 out of 74).

2. The reporting of missing outcome data was largely inadequate in a few studies. Since we chose a likely scenario that any participant with missing outcome data did not experience clearance for the overall analyses, the risk of overestimating efficacy due to how we reported missing data was minimised.

3. Finally, a few trials were considered at high risk of selective outcome reporting. However, we chose a stringent definition of studies at high risk of selective outcome reporting: we considered reporting bias inadequate if one specified outcome in protocols was lacking in the main report. A large proportion of included trials did not report the PRO outcomes in the main report but only in slicing publications (see [Included studies](#)). We extracted outcomes of interest both in main and slicing publications, but this disadvantaged trials that did not report all of the specified outcomes in the main report.

Indirect comparison and network meta-analyses as standard pairwise meta-analyses provide “observational” evidence since the treatments being compared have not been randomised across studies. However, we considered carefully the assumption underpinning the validity of indirect comparisons to reassure a sufficiently coherent evidence base ([Cipriani 2013](#)). The limitations of this review are reflected by the GRADE evaluations.

## Heterogeneity (i.e. variation in effect modifiers within comparisons) and inconsistency (imbalance in effect modifiers between comparisons)



No evidence of the presence of heterogeneity either in direct comparisons or in the entire networks was found except in relation to the quality of life outcome (poorly reported, few studies per comparisons). There was no global inconsistency for the two primary outcomes, and the global test for inconsistency was significant only for PASI 75 at the class-level analysis. According to the local tests, for each outcome, a handful of loops and comparisons, which does not exceed the expected level of inconsistency from empirical evidence (Veroniki 2013), appeared to have important inconsistency. Thus, we downgraded the strength of evidence for inconsistency for methotrexate, adalimumab, etanercept, infliximab, and tofacitinib.

### Imprecision

The number of studies was low for the following interventions (one to two studies per interventions): certolizumab, tildrakizumab, itolizumab, infliximab, ponesimod, acitretin, ciclosporin, alefacept, fumaric acid, and methotrexate. We downgraded the strength of evidence for imprecision for all of these interventions for the two primary outcomes.

### Indirectness or transitivity assumption

We did not find any evidence that important variables, such as age, sex, weight, and duration and severity of psoriasis, varied across comparisons (see [Characteristics of included studies](#) and [Figure 31](#) and [Figure 32](#)). However, several comparisons had only one or two studies, and the lack of data did not allow us to check the distributions of previous treatments across comparisons; thus, transitivity cannot be assessed statistically properly. Several participant characteristics have changed in newer trials, such as participants' exclusion criteria. However, most of the included trials were conducted after 2000, minimising the variability across trial participant characteristics. The location of the trial could also create some differences between participants as the response of treatment could be related to genetic background (Chiu 2014). To further reassure the plausibility of the transitivity assumption, we only included in our analyses trials not involving co-interventions. Moreover, the trials were also fairly similar in terms of outcome assessment (less than 24 weeks). As a consequence, we excluded from the meta-analyses most of the trials assessing infliximab efficacy. Indeed, timing of efficacy outcome assessments was from 8 to 10 weeks for infliximab trials. However, as differences in response rates of biologics for the treatment of psoriasis have been reported in several meta-analyses published to date mainly related to the primary endpoint times, we assumed the importance of a similar timing of outcome assessment between trials (Puig 2014). Thus, the possibility of intransitivity seems to be unlikely even if it could not be totally excluded.

### Publication bias

We assessed publication bias considering the comprehensive search strategy we performed and the risk for publication bias in the specific field. The comparison-adjusted funnel plot for all placebo-controlled trials for all the outcomes did not indicate any evident risk of publication bias for the two primary outcomes.

### Potential biases in the review process

We performed a wide search for trials, including five trials registers and databases of each company when available, and we searched the U.S. Food and Drug Administration and the European Medicines Agency (EMA) databases and abstract proceedings of seven congresses up to a maximum of 10 years. We did not approach pharmaceutical companies for additional data when their databases were not open access, and it is possible that additional data from this source could contribute to this review. The probability that we missed a trial is low considering our wide search and is supported by the absence of small-study effects (testing by the comparison-adjusted funnel plots). However, the fact that 14 studies have not yet been incorporated may be a source of potential bias.

Study selection, data extraction, and 'Risk of bias' assessments were done in duplicate and independently, and we reached consensus by discussing any discrepancies. Some published trial reports did not provide enough details to extract outcomes and adequately assess risk of bias, especially studies performed before 2000 (e.g. before the International Committee of Medical Journal Editors issued the requirement of trial registration for publication). However, we contacted the authors of the trials to request missing data, but we cannot avoid some biased assessment in the review process due to incomplete reporting of trial details, results, or both.

We had some departures from the protocol plans (see [Differences between protocol and review](#)). After protocol publication, we added five biological drugs either approved for psoriasis or for which there were ongoing phase 3 trials. We chose to keep only PASI 90 as the primary efficacy outcome and not a composite outcome including PASI and Physician Global Assessment (PGA). Indeed, PASI 90 and PGA do not reflect the same measures (see [Agreements and disagreements with other studies or reviews](#)). To minimise inconsistency, we assessed the primary outcome between the twelfth and the sixteenth week rather than less than 24 weeks.

### Agreements and disagreements with other studies or reviews

We searched in MEDLINE Ovid (from 1946) using the strategy "Psoriasis" AND "Meta-analysis" for already published network meta-analyses. Seven network meta-analyses were systematically reviewed and have compared the short-term efficacy of treatments for moderate to severe psoriasis (Gomez-Garcia 2017;

Gupta 2014; Jabbar-Lopez 2017; Lin 2012; Reich 2012a; Schmitt 2014; Signorovitch 2015).

We compared our findings with the four most recent network meta-analyses (Gomez-Garcia 2017; Jabbar-Lopez 2017; Schmitt 2014; Signorovitch 2015). Schmitt 2014 included 48 trials, involving 16,696 participants, assessing both conventional systemic (cyclosporin, methotrexate, acitretin, FAEs) and biologic treatments (infliximab, adalimumab, etanercept, alefacept, and ustekinumab). Signorovitch 2015 included 15 trials, involving 7388 participants, assessing only anti-TNF alpha agents (infliximab, adalimumab, etanercept) and anti-IL12/23 drugs (ustekinumab). Gomez-Garcia 2017 included 27 trials, involving 10,629 participants, assessing three anti-TNF alpha agents (infliximab, etanercept, and adalimumab), one anti-IL12/23 agent (ustekinumab), and one anti-IL17 agent (secukinumab). Jabbar-Lopez 2017 included 41 trials, involving 20,561 participants, assessing the same drugs as Gomez-Garcia 2017, plus ixekizumab (another anti-IL17 agent) and methotrexate.

Thus, compared to previous reviews, we included more interventions and consequently more trials ( $n = 109$ ) and participants ( $n = 39,882$ ). Regarding the overlapping period, we also included more trials than the other meta-analyses. Indeed, we performed a larger search in terms of the number of databases used, including trials registers and other resources (unpublished literature), irrespective of the date or language limitations.

Schmitt 2014 and Signorovitch 2015 chose PASI 75 as primary outcome during the induction phase (less than 16 weeks); however, data on PASI 90 were also available. Gomez-Garcia 2017 presented both PASI 75 and PASI 90 results. Finally, Jabbar-Lopez 2017 chose a composite outcome: PASI 90 or Physician Global Assessment (PGA) 1. We chose PASI 90 as our primary efficacy outcome because complete clearance seems the less subjective outcome and the most relevant regarding patient expectation in short-term assessment (induction phase). The composite outcome used by Jabbar-Lopez 2017 did not reflect complete or almost complete clearance. Indeed, PGA 1 is highly correlated to PASI 75 and not PASI 90, which could lead to a classification bias (Robinson 2012).

Jabbar-Lopez 2017 presented their results using number needed to treat (NNT). Although NNT is an easily understandable and very useful measure for patients and clinicians, it can be misleading in a network meta-analysis since it requires the assumption of a common average control group risk applying to all studies. This is a rather strong assumption particularly in networks involving also head-to-head studies without a control group as here.

Infliximab was the best drug in terms of reaching PASI 75 in the network meta-analyses of Schmitt 2014 and Signorovitch 2015. Adalimumab and ustekinumab were more likely to reach PASI 75 than etanercept. These last results are partly confirmed by our review: ustekinumab was more effective at reaching both PASI 75 and 90 than etanercept; however, no significant difference was shown between adalimumab and etanercept, as in the most recent

network meta-analyses from Gomez-Garcia et al (Gomez-Garcia 2017) and Jabbar-Lopez et al (Jabbar-Lopez 2017). Infliximab was also the most effective drug in Gomez-Garcia 2017, without significant difference between infliximab and secukinumab. Infliximab was ranked in third place after ixekizumab and secukinumab in Jabbar-Lopez 2017, without significant difference between infliximab and secukinumab. Our findings did not find such efficacy for infliximab. To prevent inconsistency in our network meta-analysis, we chose to include trials assessing outcomes between 12 to 16 weeks. Thus, only one trial, Barker RESTORE-1, 2011, which compared infliximab versus methotrexate, was taken into account for this intervention. Regarding the four previous network meta-analyses, two did not assess inconsistency (Schmitt 2014; Signorovitch 2015), and two reported significant global and local inconsistency for PASI 75, which preclude interpretation of their results (Gomez-Garcia 2017; Jabbar-Lopez 2017).

## AUTHORS' CONCLUSIONS

### Implications for practice

In terms of achieving PASI 90 with induction therapy (evaluation between 12 to 16 weeks after the randomisation), we found the following results.

- At class level, all of the assessed interventions (conventional systemic agents, small molecules, and biological treatments) showed significant superiority compared with placebo.
- The biologic treatments anti-IL17, anti-IL12/23, anti-IL23, and anti-TNF alpha showed significant superiority compared with small molecules and the conventional systemic agents, with small molecules achieving better results than conventional systemic agents.
- All of the anti-IL17 agents and the anti-IL23 guselkumab were significantly more effective than all of the anti-TNF alpha agents except for certolizumab (i.e. infliximab, adalimumab, and etanercept), and the anti-IL12/23 ustekinumab was superior to the anti-TNF alpha etanercept.
- When compared with placebo, in order of highest efficacy, the following biological agents are the best choices: ixekizumab (high-certainty evidence), secukinumab (high-certainty evidence), brodalumab (moderate-certainty evidence), guselkumab (moderate-certainty evidence), certolizumab (moderate-certainty evidence), and ustekinumab (high-certainty evidence).
- Tofacitinib was superior to methotrexate, and no difference was shown between the other small molecules and the conventional drugs.



Regarding the other efficacy outcome (PASI 75), the results were very similar to the results for PASI 90.

In terms of serious adverse events, there was no significant difference between all of the assessed interventions and placebo. The surface under the cumulative ranking curve (SUCRA) strongly suggested that methotrexate had the best safety profile regarding the serious adverse events (SAEs) (moderate-certainty evidence), followed by ciclosporin (very low-certainty evidence), certolizumab (moderate-certainty evidence), infliximab (very low-certainty evidence), alefacept (low-certainty evidence), and FAEs (very low-certainty evidence). Major adverse cardiac events, serious infections, or malignancies were reported in both placebo and intervention groups. Nevertheless, analyses on SAE events were based on a very low number of events with a low to very low certainty for just over half of the treatment estimates in total, moderate for the others. Thus, the results have to be considered with caution.

Considering both efficacy (PASI 90 outcome) and acceptability (SAE outcome), highly effective treatments also had more SAEs than the other treatments: ustekinumab, infliximab, and certolizumab appeared to be the better compromise between efficacy and acceptability.

Information on quality of life was often poorly reported and was absent for a third of the interventions.

Conservative interpretation is warranted with regard to the results for conventional systemic agents, as well as ponesimod, tildrakizumab, infliximab, certolizumab, alefacept, and itolizumab as these drugs have been evaluated in few trials. The evidence is limited to a selected trial population (participants were young (mean age of 44 years) and had a high level of disease severity (with an overall mean score of PASI 20 at baseline)) and to the induction treatment phase (for the NMA results, measurement was done 12 to 16 weeks after randomisation, but all results were measured less than 24 weeks after randomisation), which is not relevant enough for a chronic disease, which would require long-term treatment.

Our main results (i.e. superiority of efficacy of the biologic treatments anti-IL17, anti-IL12/23, anti-IL23, and anti-TNF alpha compared with small molecules and the conventional systemic agents, with small molecules achieving better results than conventional systemic agents) do not reflect the way patients are managed in “real-life”. Currently, biological treatments have been positioned as third-line therapies by regulatory bodies, with mandatory reimbursement criteria that patients must meet before being considered for these treatments (moderate to severe disease after failure, intolerance or contraindication to conventional systemic agents). Recently, the same restrictions were applied to apremilast. Such decisions were based on the lack of long-term safety knowledge but also taking into account economic consideration. In this review, we found insufficient evidence to evaluate long-term safety, and we did not address economic considerations; thus, the

question of the choice of the first-line treatment for moderate to severe psoriasis is still debated.

The first choice in conventional systemic agents is still in question as the limited number of trials assessing conventional systemic agents did not allow us to draw robust conclusions; this is also true for some small molecule treatments and biological treatments.

## Implications for research

From a clinical point of view, we need drugs that can be administered long term to provide continuous effective control, because continued remission after successful treatment is as important as successful induction of remission. Moreover, treatment should be easy to use, well accepted by patients, have minimal drug to drug interactions, and should have minimal monitoring requirements because convenience is also an important issue when dealing with chronic diseases that require prolonged treatments. Finally, the cost of the drug should be affordable by most patients and by any national health service.

Specific questions and issues in the management of psoriasis still remain unmet:

- Which conventional systemic agents have the best benefit/risk balance?
- Which patients are candidates for small molecule treatment?
- Which treatments work for subgroups of patients (age, psoriasis severity, previous treatment, psoriatic arthritis)?
- Adjustment of therapy for patients with stable low disease activity.
- Add-on therapy or switching for patients who failed with a systemic treatment.
- Long-term safety data for all the treatments.

### 1. Future trials need to ensure the following.

- **Participants:** enough information about participants is needed to enable systematic subgroup analyses for biological-naïve patients (or conventional systemic agent-naïve); future trials also need to provide an adequate description of data regarding other important potential effect modifiers such as previous systemic treatments, whether participants are overweight/obese, the duration of a participant's psoriasis, baseline psoriasis severity (efficacy differences could be expected for patients with PASI at 10 and patients with PASI at 40); and presence of psoriatic arthritis.
- **Interventions:** high-quality trials assessing the efficacy of conventional systemic agents are needed.
- **Comparators:** once the benefit of a treatment has been established against placebo, only head-to-head trials would be

helpful to provide physicians efficacy estimates between the different biologics with a stronger evidence than indirect comparisons. Thus, head-to-head comparisons are lacking between the conventional systemic agents and small molecules and against themselves. More head-to-head comparisons between biological agents are also needed (anti-IL17 versus anti-IL23, anti-IL23 versus anti-IL12/23, anti-TNF alpha versus anti-IL12/23).

- **Outcomes:** outcome measure harmonisation is needed for psoriasis as it has been done for eczema by the COMET (Core Outcome Measures in Effectiveness Trials) Initiative.

- **Timing assessment strategy:** all of the trials included in this review were limited to the induction phase (less than 24 weeks). Long-term efficacy data is critical for chronic diseases. Placebo-controlled long-term trials would not be ethical due to the suffering it would entail for the people in the placebo group. However, long-term studies comparing different drugs would be ethical and informative. Such long-term trials could also assess the adjustment of therapy for patients with stable cleared psoriasis.

**2. New trial designs** are needed such as pragmatic trials that permitted dose adjustment once in remission, switching, and additional treatments (i.e. adding two or more systemic treatments) as per normal clinical practice. All of this unmet medical need evidence would improve the management of the condition.

**3. Finally, evidence-based decision making and management of chronic plaque psoriasis request both efficacy AND safety data.** As we already know, the limitations of network meta-analysis and in the same way the limitations of randomised clinical trials (included in these meta-analyses) means we cannot reliably interpret the significance of rare events given their current design. Actually, these studies are designed to detect differences in the

severity of psoriasis in response to therapy over short periods of treatment and are often underpowered and of insufficient duration to detect rare or long-term adverse events. One way to counter this is to include observational cohort studies/registries in a network observational meta-analysis.

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## Department of Health Disclaimer

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, the Complex Reviews Support Unit, NIHR, NHS, or the Department of Health.

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\* Indicates the major publication for the study]

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Akcali 2014

Methods	RCT, active-controlled, open-label trial Date of study: January 2008-January 2009 Location: Gaziantep, Turkey (1 centre)	
Participants	<p><b>Randomised:</b> 55 participants (mean age 39 years, 33 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 10)</li> </ul> <p><b>Exclusion criteria</b></p> <p>None</p> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 9/55(16.4%)</li> <li>• AEs: 5</li> <li>• Other reason: 4</li> </ul>	
Interventions	<p><b>Intervention</b></p> <p>A. Acitretin (n = 25), orally, 0.3-0.5 mg/kg/d</p> <p><b>Control intervention</b></p> <p>B. Cyclosporin (n = 21), orally, 3 mg/kg/d</p>	
Outcomes	<p>Assessment at 8 weeks</p> <p><b>Primary outcome of the trial</b></p> <ul style="list-style-type: none"> <li>• Not stated</li> </ul> <p><b>Outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI score</li> <li>• Adverse effects</li> </ul>	
Notes	<p>Funding source: Quote (p 1121): "No specific grant"</p> <p>Declarations of interest: Quote (p 1121): "The authors declare that there are no conflicts of interest."</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p1119): "Patients were stratified into one of two groups via a computer-generated randomisation schedule" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Comment: no description of the method used to guarantee allocation concealment

**Akcali 2014** (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: not stated that it was a blinded trial. Acitretin has visible side effects (mucocutaneous dryness)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: no independent assessor. Not stated that it was a blind trial. Acitretin has visible side effects
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Randomly assigned 55, analysed 46 Management of missing data: not stated
Selective reporting (reporting bias)	High risk	Comment: no primary or secondary outcomes stated. No protocol available

**Al-Hamamy 2014**

Methods	RCT, active-placebo controlled, open-label trial Date of study: February 2010-October 2011 Location: Baghdad, Iraq (1 centre)
Participants	<b>Randomised:</b> 120 participants (mean age 41 years, 41 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (BSA &gt; 10%)</li> <li>• Age ≥ 18 and ≤ 60 years</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Pregnancy, kidney insufficiency, liver insufficiency, past history of malignant tumours</li> <li>• Had received conventional systemic treatments in the 4 past weeks</li> <li>• Had received biologics (anti-TNFα)</li> <li>• Had uncontrolled diabetes</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• 7 (6%)</li> </ul> No more statements regarding time and reasons of follow-up
Interventions	<b>Intervention</b> A. Methotrexate + NBUVB (n = 38), 20 mg/week + 45 mJ/cm <sup>2</sup> , 3 times/week <b>Control intervention</b> B. NBUVB (n = 38), 45 mJ/cm <sup>2</sup> , 3 times/week C. Methotrexate (n = 37), 20 mg/week
Outcomes	Assessment at 6 months <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• PASI 90</li> </ul> <b>Secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• Number of weeks for achieving clearance</li> <li>• Total cumulative dose of UVB</li> <li>• Relapses (PASI returning at 50% of original score for 1 year)</li> </ul>

Al-Hamamy 2014 (Continued)

Notes	Funding: not stated Declarations of interest: none	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote (page 1531): "three groups randomly..." Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: No description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: not stated that it was a blind trial, probably not blind
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: no independent assessor. Not stated that it was a blind trial, probably not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Randomly assigned 120, analysed 113 Management of missing data: not stated
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available. The outcomes mentioned in the methods section appeared to have been reported

Asahina 2010

Methods	RCT, active, placebo-controlled, double blind Date of study: September 2005-December 2006 Location: 42 centres in Japan
Participants	<p><b>Randomised:</b> 169 participants (mean age 45 years, 143 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12, BSA &gt; 10)</li> <li>• Age &gt; 20 years</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Pregnancy, immunosuppression, kidney insufficiency, liver insufficiency, past history of malignancy</li> <li>• Had received biologics</li> <li>• Had an active infection</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 22 (13%) (A/B/C/D)</li> </ul>

	<ul style="list-style-type: none"> <li>• 10 AEs (2/3/2/3)</li> <li>• 10 withdrawals of consent (2/4/2/2)</li> <li>• 1 worsening disease (D)</li> <li>• 1 prohibited medication (C)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Adalimumab (n = 38), 40 mg, SC, eow</p> <p>B. Adalimumab (n = 43), 40 mg, SC, 2 injections, week 0, 1 injection eow (week 2)</p> <p>C. Adalimumab (n = 41), 80 mg, SC, eow</p> <p><b>Control</b></p> <p>D. Placebo (n = 46), 0.8 mL, SC, eow</p>
Outcomes	<p>Assessment at 16 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• -PASI 50</li> <li>• -PASI 90</li> <li>• -PGA clear or minimal</li> <li>• -DLQI</li> <li>• -SF36</li> </ul>
Notes	<p>Funding: support by Abbott (Quote p309)</p> <p>Declarations of interest: not stated</p>

*Risk of bias*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p301): "Patients were randomised. .." Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p301): "Adalimumab 40mg/0.8mL and Placebo 0.8 mL were supplied two-vial cartons (Adalimumab+Adalimumab, Adalimumab+placebo, Placebo+Placebo)" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: no specific description of the method used to guarantee blinding of outcome assessment however considering that this was a placebo-controlled trial with no known systematic AEs we considered the

Asahina 2010 (Continued)

		risk as low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 169, analysed 169 Management of missing data: quote (p302) : "Patients without evaluation at week 16 were considered non-responders for the primary analysis" Comment: the report provided sufficient detail about the management of missing data to permit a clear judgment
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available. The outcomes mentioned in the methods section appeared to have been reported

Asahina 2016

Methods	RCT, active-controlled, double blind Date of study: March 2012-January 2014 Location: 16 centres in Japan
Participants	<p><b>Randomised:</b> 95 participants, 94 treated (mean age 49 years, 78 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12, PGA 3-4 or BSA <math>\geq</math> 10), age <math>\geq</math> 20 years,</li> <li>• Patients were to be considered candidates for systemic therapy or phototherapy for psoriasis (either treatment-naive or -experienced)</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Not plaque-type psoriasis</li> <li>• Inability to discontinue systemic, topical or phototherapies, concomitant oral or injectable corticosteroids</li> <li>• Active infection, history of disseminated herpes zoster or disseminated herpes simplex or recurrent localized dermatomal herpes zoster, a history of infection requiring hospitalization or parenteral microbial therapy</li> <li>• Any uncontrolled significant medical condition</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 6/95 (6.3%); tofacitinib 5 mg twice/d group (0), tofacitinib 10 mg twice-daily group (6)</li> <li>• Not received study medication; tofacitinib 10 mg twice-daily group (1)</li> <li>• AEs: tofacitinib 10 mg twice-daily group (1)</li> <li>• Lack of efficacy: tofacitinib 10 mg twice-daily group (1)</li> <li>• Withdrawal consent: tofacitinib 10 mg twice-daily group (1)</li> <li>• Other reason: tofacitinib 10 mg twice-daily group (2)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Tofacitinib (n = 43), orally, 5 mg twice daily</p> <p><b>Control intervention</b></p> <p>B. Tofacitinib (n = 44), orally, 10 mg twice daily</p>

Outcomes	Assessment at 16 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>● PASI 75 and PGA rating of clear or almost clear</li> </ul> <b>Secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>● PASI 50</li> <li>● PASI 90</li> <li>● Itch severity item score</li> <li>● Mean DLQI score</li> <li>● AEs</li> </ul>	
Notes	Funding source: Quote (p878): "This study was sponsored by Pfizer Inc. Medical writing support under the guidance of the authors was provided by Kate Silverthorne, Ph.D., at Complete Medical Communications and was funded by Pfizer Inc" Declarations of interest: Quote (p878): "A. A., A. I., S. I., H. S. and M. O. have received consultancy fees from Pfizer Inc. Y. S., Y. T., S. T. and M. N. are employees of Pfizer Japan Inc. T. E. has nothing to disclose."	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p870): "Patients were randomized 1:1 to tofacitinib 5 or 10 mg b.i.d. using a computer-generated randomization schedule" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p870): "patients were registered by the investigator in a central randomized management system" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p870): "Tofacitinib was supplied as 5 mg tablets with a corresponding matching placebo. Patients and study staff were unable to determine from the packaging which treatment group the patient was assigned to. Patients, investigators, study teams, the contract research organization and the sponsor remained blinded throughout the study period" Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement



Asahina 2016 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p870): “Tofacitinib was supplied as 5 mg tablets with a corresponding matching placebo. Patients and study staff were unable to determine from the packaging which treatment group the patient was assigned to. Patients, investigators, study teams, the contract research organization and the sponsor remained blinded throughout the study period ” Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned n = 95, 94 received at least 1 dose of study drug, 87 had moderate-severe psoriasis (study population) and 12 had psoriatic arthritis Management of missing data: Quote (page 871): “The full analysis set included all randomized patients who received one or more dose of study drug...Missing values were treated as non-responders (non-responder imputation).” Table 2: 87 analysed participants Comment: done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01519089) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

Asawanonda 2006

Methods	RCT, active placebo-controlled, double blind Date of study: not reported Location: Bangkok, Thailand, Asia
Participants	<b>Randomised:</b> 24 participants (mean age 40 years (methotrexate) 48 years (placebo), 15 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe plaque type psoriasis (BSA <math>\geq</math> 20)</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Pregnancy, immunosuppression, alcohol abuse</li> </ul> <b>Dropouts and withdrawals</b>

	<ul style="list-style-type: none"> <li>• 4 (17%)</li> <li>• Time and reasons: conflicts in schedule (1 methotrexate group, 3 placebo group)</li> </ul>	
Interventions	<p><b>Intervention</b> A. Methotrexate (n = 11), 15 mg/week, orally</p> <p><b>Control</b> B. Placebo (n = 13), orally Co-intervention: phototherapy UVB</p>	
Outcomes	<p>Assessment at 24 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 90</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• Time to relapse after clearance</li> </ul>	
Notes	<p>Funding: (quote 1013) no funding source Declarations of interest: (quote 1013) "None identified"</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p 1014): "randomized by way of randomization cards" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 1014): "to receive either MTX or placebo, which were identical in appearance" Comment: probably done, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 1015): "PASI scores were given by a investigator blinded to the treatment assignment" Comment: probably done, placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Randomly assigned 24, analyzed 24 Management of missing data: Comment: no more precision regarding methods for dealing with missing data
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available. The outcomes mentioned in the methods section appeared to have been reported

Methods	<p>RCT, active placebo-controlled, double blind  Date of study: 29 November 2010-13 September 2012  Location: 122 worldwide excluding the USA and Canada</p>
Participants	<p><b>Randomised:</b> 1106 participants (mean age 46 years, 458 male)  <b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12, PGA 3-4 or BSA <math>\geq</math> 10), age <math>\geq</math> 18 years, failed to respond to, had a contraindication to, or were intolerant to at least one conventional systemic treatment</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Not plaque-type psoriasis</li> <li>• Active infection, and any uncontrolled significant medical condition</li> <li>• Had previously been treated or had a contraindication to etanercept, had previously not responded to treatment with any tumor necrosis factor inhibitors, had previously participated in studies involving tofacitinib</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 86/1106 (7.8%); tofacitinib 5 mg group (24), tofacitinib 10 mg twice-daily group (26), etanercept group (23), placebo group (13)</li> <li>• Not received study medication; tofacitinib 5 mg twice-daily group (1), tofacitinib 10 mg twice-daily group (2), etanercept group (1), placebo group (1)</li> <li>• AEs: tofacitinib 5 mg twice-daily group (3), tofacitinib 10 mg twice-daily group (11), etanercept group (12), placebo group (4)</li> <li>• Lack of efficacy: tofacitinib 5 mg twice-daily group (5), tofacitinib 10 mg twice-daily group (2), etanercept group (2), placebo group (3)</li> <li>• Lost to follow-up: tofacitinib 5 mg twice-daily group (1), tofacitinib 10 mg twice-daily group (2), etanercept group (2), placebo group (2)</li> <li>• Withdrawal consent: tofacitinib 5 mg twice-daily group (6), tofacitinib 10 mg twice-daily group (4), etanercept group (2), placebo group (2)</li> <li>• Other reason: tofacitinib 5 mg twice-daily group (8), tofacitinib 10 mg twice-daily group (5), etanercept group (4), placebo group (1)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Tofacitinib (n = 330), orally, 5 mg twice daily</p> <p><b>Control intervention</b></p> <p>B. Tofacitinib (n = 332) orally, 10 mg twice daily  C. Etanercept (n = 336) SC, 50 mg twice weekly  D. Placebo (n = 108)</p>
Outcomes	<p>Assessment at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75 and PGA rating of clear or almost clear</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 50</li> <li>• PASI 90</li> <li>• Itch severity item score</li> <li>• Mean DLQI score</li> <li>• AEs</li> </ul>

Notes	<p>Funding source:          Quote (p 555): “This study was designed and funded by Pfizer Inc. Study investigators gathered the data, which were maintained in a database by Pfizer.”          Declarations of interest:          Quote (p 560): “HB has provided consultancy services for AbbVie, Amgen, Boehringer, Celgene, Janssen, Leo Pharma, Lilly, Novartis, MSD, Pfizer, and Sandoz. He has also acted as an adviser for AbbVie, Amgen, Boehringer, Celgene, Janssen, Leo Pharma, Lilly, Novartis, Pfizer, and Sandoz; has served on speaker’s bureaus for AbbVie, Amgen, Celgene, Janssen, Leo Pharma, Lilly, Novartis, and Pfizer; and has received a research grant from Pfizer. PCMvdK has provided consultancy services for Celgene, Centocor, Almirall, Amgen, Pfizer, Philips, Abbott, Ely Lilly, Galderma, Novartis, JanssenCilag, Leo Pharma, Sandoz, and Mitsubishi. He has also done clinical trials for Basilea, Pfizer, Ely Lilly, Amgen, AbbVie, Philips Lighting, JanssenCilag, and Leo Pharma. RS has served on speaker’s bureaus for Pfizer, Schu ¨ lke and Mayr, Lohmann &amp; Rauscher, Meda Pharmaceuticals, Menarini Pharmaceuticals, Stockhausen, and Smith &amp; Nephew; has had consulting agreements with Pfizer, Novartis, Lohmann &amp; Rauscher, Urgo, Chemomedica, Schu ¨ lke &amp; Mayr, and Pantec Biotechnologies; and has received research and educational grants from Stockhausen, 3M-Woundcare, Smith &amp; Nephew, Lohmann &amp; Rauscher, Enjo Commercial, Urgo, Chemomedica, and Schu ¨ lke &amp; Mayr. FV has been a principal investigator, member of a scientific advisory board, or speaker for AbbVie, Janssen, Eli Lilly, Merck, Novartis, and Pfizer. SC has been a consultant and/or speaker for Pfizer, AbbVie, Novartis, Merck, and Janssen-Cilag. JPa, JPr, PG, HT, MT, HV, and RW are employees of Pfizer Inc. AK, J-HL, and VY declare no competing interests.”</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	<p>Quote (page 553): “A computer-generated randomization schedule was used to assign patients to the treatment groups”          Comment: probably done</p>
Allocation concealment (selection bias)	Low risk	<p>Quote (page 553-4): “The study site contacted an interactive voice response system or web-based interactive response system..”          Comment: probably done</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote (p 553): “For this randomised, double-blind, double-dummy, placebo-controlled, parallel-group phase 3 study”          Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement</p>

**Bachelez 2015** (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 553): “Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Patients and study personnel were masked to treatment assignment: the study drug packaging was labelled....” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 1106, 1101 received at least 1 dose of study drug Management of missing data: Quote (page 554): “The primary analysis population for efficacy was the full analysis set, which was defined as all patients who received at least one dose of study drug... We judged patients with missing values for all binary endpoints to be non-responders in efficacy assessments” Table 2: 1101 analysed participants Comment: done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01241591) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

**Bagel 2012**

Methods	RCT, placebo-controlled, double blind Date of study: not stated Location: North America
Participants	<b>Randomised:</b> 124 participants (median age 39 years (etanercept) and 42 years (placebo), 69 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>Participants with moderate-severe psoriasis: <math>\geq 30\%</math> of scalp surface area affected (PASI &gt; 10, BSA &gt; 10)</li> <li>Age &gt; 18 years</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>Had past history of malignant tumours in the past 5 years, had an active infection, had a significant medical problem</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>26/124 (21%)</li> <li>Not received study treatment: etanercept (3), placebo (0)</li> <li>AEs: etanercept (5), placebo (0)</li> <li>Withdrawal of consent: etanercept (1), placebo (5)</li> </ul>

Interventions	<p><b>Intervention</b> A. Etanercept (n = 62), SC, 50 mg, twice a week</p> <p><b>Control intervention</b> B. Placebo (n = 62), SC, twice a week</p>	
Outcomes	<p>Assessment at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• % change in PSSI score</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• % change in PSSI score at 24 weeks for group B</li> <li>• Proportion PSSI at 12 weeks</li> <li>• Participant satisfaction</li> <li>• AEs</li> <li>• PASI 50/75/90 improvement through 24 weeks</li> <li>• Proportion PGA 0 or 1</li> <li>• Mean PASI improvement from baseline</li> </ul>	
Notes	<p>Funding: Amgen Inc</p> <p>Declarations of interest (quote p86): “Dr Bagel receives a salary as founder of the Psoriasis Treatment Center of Central New Jersey. He has received speaker honoraria from Leo Pharma, Galderma, Centocor, Abbott, and Amgen. He has also been compensated as a consultant for Galderma and has served as an investigator for Centocor, Abbott, and Amgen. Dr Lynde has received research grants and honoraria from Amgen, Abbott, Merck, Ortho Biotech, Leo Pharma, and Galderma, for whom he has served as an advisory board member, consultant, and speaker. He has also served as an investigator for Amgen, Abbott, Merck, Ortho Biotech, and Leo Pharma. Dr Tyring has received a research grant and honoraria from Amgen, for whom he has served as a consultant, investigator, and speaker. He has also served as an investigator and/or speaker for Abbott, Leo Pharma, Galderma, GSK, Novartis, Merck, Epiphany, Inhibitex, AiCuris, and Pfizer. Dr Kricorian, Yifei Shi, and Dr Klekotka are employees of Amgen Inc. and have received Amgen stock/stock options.”</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p87): “Each patient provided written informed consent and received a unique identification number and randomised assignment from an Interactive Web Response System” Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p87): “Each patient provided written informed consent and received a unique identification number and randomised assignment from an Interactive Web Response System”

Bagel 2012 (Continued)

		Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p87): “patients and clinicians were blinded throughout the study as to treatment assignments.” Comment: probably done, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “patients and clinicians were blinded throughout the study as to treatment assignments.” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 124, analysed 124 <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• 26/124 (21%)</li> <li>• Not received study treatment; etanercept (3), placebo (0)</li> <li>• AEs; etanercept (5), placebo (0)</li> <li>• Withdrawal of consent; etanercept (1), placebo (5)</li> </ul> Quote (p89): “included in ITT efficacy analysis” Management of missing data: Quote (p88): “Last observation carried forward imputation was used for missing values” Comment: probably done
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available. The outcomes mentioned in the methods section appeared to have been reported except for QoL

Barker RESTORE-1, 2011

Methods	RCT, active-controlled, open-label trial Date of study: September 2005-June 2008 Location: 106 centres in Europe
Participants	<b>Randomised:</b> 868 participants (mean age 43 years, 586 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12, BSA &gt; 10)</li> <li>• Age <math>\geq</math> 18 years and <math>\leq</math> 75</li> <li>• Non-response to topical treatment</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Immunosuppression, kidney insufficiency, liver insufficiency</li> <li>• Had received conventional systemic treatments (methotrexate)</li> </ul>

	<ul style="list-style-type: none"> <li>• Had received biologics</li> <li>• Had an active infection</li> <li>• Had uncontrolled cardiovascular disorder</li> <li>• Had past history of malignant tumours</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 71/868 (8%)</li> <li>• Infliximab (58), methotrexate (13)</li> </ul> <p>Reasons not stated at week 16</p>	
Interventions	<p><b>Intervention</b></p> <p>A. Infliximab (n = 653), IV, 5 mg/kg, weeks 0, 2, 6, 14, 22</p> <p><b>Control intervention</b></p> <p>B. Methotrexate (n = 215), orally, 15 mg/week for 22 weeks</p>	
Outcomes	<p>Assessment at 16 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 90</li> <li>• PGA 0/1 (Physician Global Assessment)</li> <li>• PASI 50</li> <li>• DLQI</li> <li>• SF36</li> </ul>	
Notes	<p>Funding: financial support for this study was provided by Schering-Plough Research Institute, now Merck, Sharp &amp; Dohme Corporation, Whitehouse Station, NJ, U.S.A</p> <p>Declarations of interest: (Quote Appendix 1): “J.B. has served as a consultant and/or paid speaker for, and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis including Abbott, Celgene, Centocor, Janssen-Cilag, Johnson and Johnson, Merck, Novartis, Pfizer, Schering-Plough and Wyeth. M.H. has served as a consultant and/or paid speaker for, and/or has participated in clinical trials sponsored by Abbott, Amgen, Essex, Janssen, Leo, Medac, Novartis, Pfizer, Schering-Plough and Wyeth. G.W. has no conflicts of interest to disclose. J.-P.O. has been a consultant for Schering-Plough, Abbott, Merck-Serono, Centocor, Wyeth, Janssen-Cilag, Meda-Pharma, Pierre-Fabre and Galderma. H.Z. is an employee of Merck, Sharp &amp; Dohme. H.v.H. was an employee of Merck, Sharp &amp; Dohme at the time of the RESTORE1 study and during the preparation of this manuscript. K.R. has served as a consultant and/or paid speaker for, and/or participated in clinical trials sponsored by Abbott, Celgene, Centocor, Janssen-Cilag, Leo, Medac and Merck.”</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p1110): “At each eligible subject’s baseline visit, study centres telephoned the Interactive Voice REsponse Syste .... for randomisation“ Comment: probably done



**Barker RESTORE-1, 2011** (Continued)

Allocation concealment (selection bias)	Low risk	Quote (p1110): “At each eligible subject’s baseline visit, study centres telephoned the Interactive Voice REsponse Syste .... for randomisation” Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (p1110): “open-label trial” Comment: no blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (p1110): “open-label trial” Comment: no blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 868, analysed 868 Quote (p1110-11): “Primary and secondary efficacy analyses were based on the ITT population, the ITT population included all randomised patients. At week 16, patients who dropped out early or had missing data for PASI 75 ... were considered nonresponders” Comment: probably done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00251641) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

**Bissonnette 2013**

Methods	RCT, placebo-controlled, single blind Date of study: May 2009-June 2011 Location: Montréal, Quebec, Canada (5 centres)
Participants	<b>Randomised:</b> 30 participants (median age 56 years (adalimumab) and 57 years (placebo), 23 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (BSA&gt;5)</li> <li>• Age ≥ 18 years and ≤ 80</li> <li>• Non-response to topical treatment</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Immunosuppression, kidney insufficiency</li> <li>• Had an active infection, had uncontrolled cardiovascular disorder, had uncontrolled diabetes, had uncontrolled hypertension, had past history of malignant tumours</li> </ul>

	<p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 2/30 (7%)</li> <li>• Discontinued intervention (1, placebo group)</li> <li>• Death myocardial infarction (1, adalimumab group)</li> </ul>
Interventions	<p><b>Intervention</b> A. Adalimumab (n = 20), SC, 80/40 mg, eow</p> <p><b>Control intervention</b> B. Topical treatment, phototherapy or no treatment (n = 10)</p>
Outcomes	<p>Assessment at 16 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• The change in the average of max TBR values of carotid arteries</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75 at week 16</li> <li>• Change in average of max TBR of vessels</li> <li>• Change in the most diseased segment T</li> </ul>
Notes	<p>Funding: Abbott laboratories</p> <p>Declarations of interest: (quote p 89) “Dr Bissonnette and Dr Bolduc have been investigators, advisors and/ or consultants and received grants and/or honoraria from Abbott, Amgen, Astellas, Novartis, Janssen Ortho, Pfizer, Celgene, and Tribute. Drs Tardif, Harel, Pressacco, and Guertin have no conflicts of interest to declare.”</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p84): “were randomised a concealed computer generated code created by the sponsor” Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p84): “were randomised a concealed computer generated code created by the sponsor” Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (83-4): “single-blind (cardiologist and all staff involved in vascular imaging and analysis were blinded to treatment assignment)” Comment: no blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (83-4): “single-blind (cardiologist and all staff involved in vascular imaging and analysis were blinded to treatment assignment)” Comment: probably done; however, no

**Bissonnette 2013** (Continued)

		statement regarding secondary outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 30, analysed 30 Quote (p84): “For all end points, the analysis was conducted on the ITT population, ... for the PASI 75 end point,... a non-responder imputation method was used” Comment: probably done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00940862) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

**Bissonnette 2015**

Methods	RCT, placebo-controlled, double blind Date of study: 20 August 2010-14 May 2014 Location: 65 centres in Europe, North and South America, and Australia
Participants	<p><b>Randomised:</b> 674 participants (mean age 46 years, 458 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12, PGA 3-4 or BSA <math>\geq</math> 10), age <math>\geq</math> 18 years</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Past history of malignant tumours and active infection</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 72/674(10.7%): tofacitinib 5 mg twice-daily group (39), tofacitinib 10 mg twice-daily group (41)</li> <li>• Not received study medication: tofacitinib 5 mg twice-daily group (5), tofacitinib 10 mg twice-daily group (3)</li> <li>• Death: tofacitinib 5 mg twice-daily group (1), tofacitinib 10 mg twice-daily group (0)</li> <li>• AEs: tofacitinib 5 mg twice-daily group (7), tofacitinib 10 mg twice-daily group (9)</li> <li>• Lack of efficacy: tofacitinib 5 mg twice-daily group (6), tofacitinib 10 mg twice-daily group (7)</li> <li>• Lost to follow-up: tofacitinib 5 mg twice-daily group (6), tofacitinib 10 mg twice-daily group (7)</li> <li>• Withdrawal consent: tofacitinib 5 mg twice-daily group (12), tofacitinib 10 mg twice-daily group (0)</li> <li>• Other reason: tofacitinib 5 mg twice-daily group (2), tofacitinib 10 mg twice-daily group (8)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Tofacitinib (n = 338), orally, 10 mg twice daily</p>

	<p><b>Control intervention</b> B. Tofacitinib (n = 336), orally, 5 mg twice daily</p>	
<p>Outcomes</p>	<p>Assessment at 24 weeks  <b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>● PASI 75 and PGA rating of clear or almost clear</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>● Median time to PASI 75 response</li> <li>● Median time to PGA rating of clear or almost clear response</li> <li>● Percentage of participants achieving both a PASI 50-75 response and DLQI ≤ 5</li> <li>● Percentage of participants with PGA response of clear or almost clear</li> <li>● Mean change From baseline-A in PASI score</li> <li>● Percentage of participants achieving at least a 90% reduction in PASI relative to baseline-A (PASI 90)</li> <li>● Mean DLQI score</li> <li>● AEs</li> </ul>	
<p>Notes</p>	<p>Funding source:  Quote (p 1395 &amp; 1400): “This study was sponsored by Pfizer Inc. Pfizer conducted the data analysis and the authors interpreted the data and collaborated in the manuscript preparation. All authors have access to the study data.”  Declaration of interest: (quote: Appendix 1): “R.B. has received honoraria, grants or worked as a consultant for AbbVie, Amgen, Apopharma, Astellas, Celgene, Eli Lilly, Incyte, Janssen, LEO Pharma, Merck, Novartis, Pfizer and Tribute. L.I. has served as a consultant and/or paid speaker for, and/or participated in clinical trials sponsored by, AbbVie, Almirall, Amgen, Celgene, Centocor, Eli Lilly, Janssen-Cilag, LEO Pharma, MSD, Novartis, Pfizer and UCB. H.S. has served as a principal investigator and consultant for Pfizer, Celgene, Janssen, Amgen, Novartis, Eli Lilly and Merck. C.E.M.G has received grant/research support and/or received honoraria from AbbVie, Actelion, Biotest, Celgene, Eli Lilly, Incyte, Janssen, LEO Pharma, MSD, Novartis, Pfizer, Sandoz, Stiefel U.K., Trident, Zymogenetics and UCB. P.F. has served as a consultant for Galderma, LEO/Peplin, Ascent, Clinuvel, Aspen, Janssen-Cilag, Eli Lilly, Australian Ultraviolet Services, Novartis, Wyeth/Pfizer, Mayne Pharma, MedyTox and Roche. He has also served on advisory boards/speaker’s bureaus and/or as a clinical trial investigator for CSL, Galderma, 3M/iNova/Valeant, LEO/Peplin, Ascent, Clinuvel, GSK/Stiefel, Abbott/AbbVie, BiogenIdec, Janssen-Cilag, Merck Serono, ScheringPlough/MSD, Wyeth/Pfizer, Amgen, Novartis, Eli Lilly, Celgene, Roche, Aspen, Actelion, Sanofi Aventis, MedyTox, Shape and BMS. He has received travel grants from Galderma, LEO/Peplin, BiogenIdec, Merck Serono, Ascent, Abbott/AbbVie, Schering-Plough/MSD, Janssen-Cilag, Wyeth/Pfizer, Novartis and Roche. R.R. is a consultant, investigator and/or speaker for AbbVie, Eli Lilly, Galderma, Janssen-Cilag, LEO Pharma, Novartis and Pfizer. M.B., S.T.R., H. T., J.P., H.V., L.M., P.G. and R.W. are employees of Pfizer Inc.”</p>	
<p><i>Risk of bias</i></p>		
<p><b>Bias</b></p>	<p><b>Authors’ judgement</b></p>	<p><b>Support for judgement</b></p>

Random sequence generation (selection bias)	Low risk	Quote (page 1398): “A computer-generated central randomisation schema was implemented using an automated web/telephone system.” Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (page 1398): “A computer-generated central randomisation schema was implemented using an automated web/telephone system.” Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 1398, Clinical.gov, NCT01186744): “Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)” Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 1397): “Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	High risk	Randomly assigned 674, analysed 662 <b>Dropouts and withdrawals:</b> Tofacitinib 5 mg twice-daily group (39), tofacitinib 10 mg twice-daily group (41) Imbalanced numbers for withdrawal consent: tofacitinib 5 mg twice-daily group (12), tofacitinib 10 mg twice-daily group (0) Management of missing data: Quote (page 1398): “Efficacy analysis was performed on the full analysis set comprising patients who were randomised and received one or more doses of the study drug” (page 1400) “666 patients with moderate-severe psoriasis were randomised to the initial period and received study medication”. However only 662 patients were analysed for the outcomes Comment: we judged this as a high risk of bias
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT-NCT01186744) The pre-specified outcomes and those mentioned in the methods section ap-

peared to have been reported

## Blauvelt FEATURE, 2015

Methods	RCT, active/placebo-controlled, double blind Date of study: May 2012-January 2013 Location: 32 centres in the USA/Germany/France/Estonia/India/Switzerland
Participants	<p><b>Randomised:</b> 177 participants (mean age 45 years (secukinumab 300 mg), 46 years (secukinumab 150 mg), 47 years (placebo), 117 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12, Investigator's Global Assessment, IGA <math>\geq</math> 3, BSA <math>\geq</math> 10)</li> <li>• Age <math>\geq</math> 18 years</li> <li>• Non-response to topical treatment</li> <li>• Non-response to phototherapy</li> <li>• Non-response to systemic treatment</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Pregnancy, Immunosuppression, Kidney insufficiency, Liver insufficiency,</li> <li>• Had received biologics (IL17)</li> <li>• Had uncontrolled cardiovascular disorder</li> <li>• Had uncontrolled hypertension</li> <li>• Past history of malignant tumours</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 7/177(4%), secukinumab 300 group (3), secukinumab 150 group (1), placebo (3)</li> <li>• AEs: secukinumab 300 group (1), secukinumab 150 group (0), placebo (1)</li> <li>• Lost to follow-up: secukinumab 300 group (2), secukinumab 150 group (1), placebo (0)</li> <li>• Withdrew consent: secukinumab 300 group (0), secukinumab 150 group (0), placebo (2)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Secukinumab (n = 59), SC, 300 mg, weeks 1, 2, 3, 4, 8, 12</p> <p>B. Secukinumab (n = 59), SC, 150 mg, weeks 1, 2, 3, 4, 8, 12</p> <p><b>Control intervention</b></p> <p>C. Placebo (n = 59), SC, weeks 1, 2, 3, 4, 8, 12</p>
Outcomes	<p>Assessment at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75 and IGA 0-1</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• Usability of the pre-filled syringe as assessed by observer rating of successful, hazard-free self-injection and subject rating of acceptability by the SIAQ</li> <li>• PASI 90/100 over time</li> <li>• IGA 0/1 over time</li> </ul> <p>AEs</p>

Notes	<p>Funding: Novartis Pharmaceuticals, Basel, Switzerland.</p> <p>Declarations of interest (quote p 484): “A.B. has served as a scientific consultant and clinical study investigator for AbbVie, Amgen, Boehringer Ingelheim, Celgene, Janssen, Lilly, Merck, Novartis, Pfizer and Sandoz. J.C.P. has served as a consultant, investigator, speaker or advisory board member for Abbott, Biogen-Idec (formerly Biogen), Centocor, Essex Pharma, Galderma, Janssen-Cilag/Janssen-Ortho, Merck-Serono (formerly Serono), MSD, Novartis, Pfizer and Wyeth, and has received unrestricted research grants from Biogen-Idec and Wyeth. A.B.G. has served as scientific consultant and/or clinical study investigator for Abbott, Abbvie, Actelion, Akros Pharma, Amgen, Astellas Pharma, Beiersdorf, BMS, Canfite, Celgene, Coronado BioSciences, CSL Behring, GSK, Immune Control, Incyte, Janssen-Ortho, Lerner Medical Devices, Lilly ICOS, Merck, Novartis, Novo Nordisk, Pfizer, Teva, UCB, Vertex Pharmaceuticals and Xenoport. K.K. has served as a study investigator for Celgene, Hexal, Mitsubishi and Novartis. H.S. has served as a study investigator, consultant and speaker for Novartis. M.R.-M. has served as a study investigator for Novartis. V.S., R.P., C.P. and S.C. are full-time employees of Novartis. C.P. and S.C. own stock in Novartis”</p>
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**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 486): “were randomised via interactive response technology to one of the treatment arms...using a validate system that automated the random assignment of subject numbers to randomisation numbers” Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 486): “were randomised via interactive response technology to one of the treatment arms...using a validate system that automated the random assignment of subject numbers to randomisation numbers” Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p486): “Subjects, study management team, investigator staff, persons performing the assessments and data analysts were blinded...” Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p486): “Subjects, study management team, investigator staff, persons performing the assessments and data analysts were blinded...” Comment: probably done

**Blauvelt FEATURE, 2015** (Continued)

<p>Incomplete outcome data (attrition bias) All outcomes</p>	<p>Low risk</p>	<p>Randomly assigned 177, analysed 177 <b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>● 7/177(4%), secukinumab 300 group (3), secukinumab 150 group (1), placebo (3)</li> <li>● AEs: secukinumab 300 group (1), secukinumab 150 group (0), placebo (1)</li> <li>● Lost to follow-up: secukinumab 300 group (2), secukinumab 150 group (1), placebo (0)</li> <li>● Withdrew consent: secukinumab 300 group (0), secukinumab 150 group (0), placebo (2)</li> </ul> <p>Management of missing data: quote (supplemental appendix) “Missing values were imputed as non-response for all efficacy analyses regardless of the reason of missing data” Comment: probably done</p>
<p>Selective reporting (reporting bias)</p>	<p>Low risk</p>	<p>Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01555125) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported</p>

**Blauvelt VOYAGE-1, 2016**

<p>Methods</p>	<p>RCT, active placebo-controlled, double blind Date of study: December 2014-April 2016 Location: 101 centres worldwide</p>
<p>Participants</p>	<p><b>Randomised:</b> participants (mean age 44 years, 608 male) <b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>● Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12, IGA <math>\geq</math> 3, BSA <math>\geq</math> 10), age <math>\geq</math> 18 years</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>● Had a history or current signs of a severe, progressive, or uncontrolled medical condition</li> <li>● Had current or history of malignancy, except nonmelanoma skin cancer, within 5 years.</li> <li>● History or symptoms of active TB</li> <li>● Had previously received guselkumab or adalimumab</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>● 24/837 (2.9%): guselkumab (7), adalimumab (10), placebo group (7)</li> <li>● AEs: guselkumab (4), adalimumab (2), placebo group (2)</li> <li>● Lack of efficacy: guselkumab (0), adalimumab (1), placebo group (2)</li> </ul>



	<ul style="list-style-type: none"> <li>• Lost to follow-up: guselkumab (1), adalimumab (1), placebo group (1)</li> <li>• Withdrawal consent: guselkumab (0), adalimumab (4), placebo group (2)</li> <li>• Non compliance: guselkumab (2), adalimumab (1), placebo group (0)</li> <li>• Protocol violation: guselkumab (0), adalimumab (1), placebo group (0)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Guselkumab (n = 334), SC, 100 mg, weeks 0 and 4, then every 8 weeks</p> <p><b>Control intervention</b></p> <p>B. Adalimumab (n = 329), 80 mg week 0, then 40 mg week 1, and every 2 weeks</p> <p>C. Placebo (n = 174)</p>
Outcomes	<p>Assessment at 16 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 90 and IGA clear or almost clear</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 50/75</li> <li>• Mean Dermatology Life Quality Index (DLQI) Score</li> <li>• NAPSI (Nail Psoriasis Severity Index)</li> <li>• Scalp specific IGA</li> <li>• fingernail PGA</li> <li>• AEs</li> </ul>
Notes	<p>Funding source: Quote (p 405): “Supported by Janssen Research &amp; Development LLC, Spring House, PA.”</p> <p>DEclarations of interest Quote (p 405): “Dr Blauvelt has served as a scientific adviser and clinical study investigator for AbbVie, Amgen, Boehringer Ingelheim, Celgene, Dermira, Genentech, GSK, Janssen, Eli Lilly, Merck, Novartis, Pfizer, Regeneron, Sandoz, Sanofi-Genzyme, Sun, UCB, and Valeant, and as a paid speaker for Eli Lilly. Dr Papp has received honoraria or clinical research grants as a consultant, speaker, scientific officer, advisory board member, and/or steering committee member for AbbVie, Akesis, Akros, Allergan, Alza, Amgen, Anacor, Artax, Astellas, AstraZeneca, Baxalta, Baxter, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, CanFite, Celgene, Celtic, CIPHER, Dermira, Dow Pharmaceuticals, Eli Lilly, Ferring Pharmaceuticals, Formycon, Forward Pharma, Funxional Therapeutics, Fujisawa, Galderma, Genentech, Genexion, Genzyme, Gilead, GSK, Janssen, Kyowa Hakko Kirin, Leo, Lypanosys, Medimmune, Meiji Seika Pharma, Merck (MSD), Merck-Serono, Mitsubishi Pharma, Mylan, Novartis, NovImmune, Pan Genetics, Pfizer, Regeneron, Roche, Sanofi-Aventis, Stiefel, Takeda, UCB, Vertex, and Valeant. Dr Griffiths has received honoraria and/or grants as an investigator, speaker, and/or advisory board member for AbbVie, Eli Lilly, Janssen, Leo, Novartis, Pfizer, Sandoz, and Sun Pharma. Dr Kimball has received honoraria as a consultant for AbbVie, BMS, Dermira, Eli Lilly ICOS LLC, Merck, and Novartis; and received grants and/or funding for research or the residency/fellowship program as a principal investigator for AbbVie, Amgen, Boehringer Ingelheim, Dermira, Janssen, Merck, and Novartis. Drs Randazzo, Wasfi, Shen, and Li are all employees of Janssen Research &amp; Development LLC (subsidiary of Johnson &amp; Johnson) and own stock in Johnson &amp; Johnson.”</p>
<i>Risk of bias</i>	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p3): "Patients were randomised using a permuted block method Central randomisation was implemented using an interactive World Wide Web response system (Perceptive Informatics, East Windsor, NJ)." Comment: clearly defined
Allocation concealment (selection bias)	Low risk	Quote (p3): "Central randomisation was implemented using an interactive World Wide Web response system (Perceptive Informatics, East Windsor, NJ)." Comment: clearly defined
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 3): "To maintain the blind, matching placebos were used." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p3): "To maintain the blind, matching placebos were used." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 837, 837 analysed Management of missing data: quote (page 3): "Patients who discontinued study agent because of lack of efficacy or anAE of psoriasis worsening or who started a protocol-prohibited psoriasis treatment were considered nonresponders (binary end points) or had baseline values carried over (continuous end points). Other patients with missing data were considered nonresponders for binary end points (nonresponder imputation) and had last observation carried forward for continuous end points (and all PSSD end points)." Comment: done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02207231) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

Methods	RCT, placebo-controlled, double blind Date of study: 14 August 2012-21 December 2013 Location: China	
Participants	<p><b>Randomised:</b> 425 participants (mean age 43 years, 310 men)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• 18 years of age and older</li> <li>• Moderate-severe disease (PASI <math>\geq</math> 10, PGA <math>\geq</math> 3)</li> <li>• Had failed to respond to or were intolerant to previous systemic therapy</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Had previous exposure to a biologic treatment</li> <li>• Received other systemic therapies for psoriasis within 28 days of baseline</li> <li>• Severe uncontrolled or progressive medical conditions</li> <li>• Had a history of demyelinating disease or certain infections or cardiovascular events</li> <li>• Had certain malignancies or abnormal laboratory results</li> <li>• Had active TB, had immune deficiency or was immunocompromised</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 7/425 (1.6%)</li> <li>• AEs: adalimumab (2)</li> <li>• Withdrawal of consent adalimumab (1), placebo (1)</li> <li>• Others (3)</li> </ul>	
Interventions	<p><b>Intervention</b></p> <p>A. Adalimumab (n = 338), SC, 40 mg, week 0, 2 injections, eow 1 injection</p> <p><b>Control intervention</b></p> <p>B. Placebo (n = 87), SC</p>	
Outcomes	<p>Assessment at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PGA0/1, AE, PASI 50/90</li> </ul>	
Notes	<p>Funding source:</p> <p>Quote (p 2): “Abbvie Inc participated in the study design, study research, collection, analysis and interpretation of data”</p> <p>Declarations of interest:</p> <p>Quote (p 2): “L Cai, J Gu, J Zheng, M Zheng, G Wang, L-Y Xi, F Hao, X-M Liu, Q-N Sun, Y Wang, W Lai, H Fang, Y-T Tu, Q Sun, J Chen and X-H Gao were investigators for this study, and J-Z Zhang was the principal investigator for this study; all declare no financial, professional or personal relationships that might be perceived as a conflict of interest. Y Gu and HD Teixeira receive a salary as employees of AbbVie and may also receive stock, stock options and/or stock grants. MM Okun is a former AbbVie employee.”</p>	
<i>Risk of bias</i>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>

Random sequence generation (selection bias)	Low risk	Quote (p 2 & Appendix): “The randomisation schedule was prepared by the Statistics Department of AbbVie, US. Randomization was performed using an adequate block size.” Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 2 & Appendix): “An interactive voice/web response system determined patient randomisation. The randomisation schedule was prepared by the Statistics Department of AbbVie, US. Randomization was performed using an adequate block size.” Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 2 & Appendix): “Patients in Period A were randomised 4:1 to receive adalimumab 40 mg every-other-week (following a single 80 mg dose), or matching placebo...All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of the drug supply team), the investigator, study-site personnel and the patient remained blinded to each patient’s treatment throughout the 12 week blinded period of the study.” Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 2 & Appendix): “Patients in Period A were randomised 4 : 1 to receive adalimumab 40 mg every-other-week (following a single 80 mg dose), or matching placebo...All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of the drug supply team), the investigator, study-site personnel and the patient remained blinded to each patient’s treatment throughout the 12 week blinded period of the study.” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned: 425, analysed 425 (ITT) Quote (p 3): “Efficacy was analysed in Period A for all randomised patients [in-

**Cai 2016** (Continued)

		tent-to-treat (ITT_A Population)]... Missing data were handled using non-responder imputation (NRI) for categorical variables and last-observation-carried-forward (LOCF) for continuous variables.” Comment: ITT analyses
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01646073) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

**Caproni 2009**

Methods	RCT, active-controlled Date of study: not stated Location: not stated
Participants	<b>Randomised:</b> 60 participants (age range 28-67 years (etanercept), 32-65 years (acitretin), 24 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 10, BSA <math>\geq</math> 10)</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Pregnancy</li> <li>• Had an active infection</li> <li>• Past history of malignant tumours</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• Not stated</li> </ul>
Interventions	<b>Intervention</b> A. Etanercept (n = 30), SC, 50 mg, twice a week, 12 weeks <b>Control intervention</b> B. Acitretin (n = 30), orally, 0.4 mg/kg/day, 12 weeks
Outcomes	Assessment at 12 weeks <b>Primary and secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• Not stated</li> </ul> <b>Outcomes of the trial</b> <ul style="list-style-type: none"> <li>• Mean PASI at baseline and at 12 weeks</li> <li>• PASI 75, PASI 50</li> </ul>
Notes	Funding: not stated Declarations of interest: not stated
<b>Risk of bias</b>	

Caproni 2009 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p 211): "Patients were randomly assigned to one of the two groups" Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: probably open-label trial, term "blind" not used
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: probably open-label trial, term "blind" not used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no description of the method used to manage the missing data. No ITT analyses mentioned
Selective reporting (reporting bias)	Unclear risk	Comment: no primary or secondary outcomes stated

Chaudhari 2001

Methods	RCT, placebo-controlled, double blind Date of study: not stated Location: single centre, New Jersey, USA
Participants	<p><b>Randomised:</b> 33 participants (age mean 35 years (infliximab 10), 51 years (infliximab 5), 45 years (placebo), 23 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (BSA <math>\geq</math> 5)</li> <li>• Non-response to topical treatment</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Immunosuppression</li> <li>• Had received biologics</li> <li>• Had an active infection</li> <li>• Had past history of malignant tumours</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 3/33 (9%)</li> <li>• Time and reasons: worsening psoriasis (n = 1 from infliximab 10 mg/kg group), mild rash (n = 1 from infliximab 5mg/kg group), lack improvement disease (n = 1 from placebo group)</li> </ul>

Interventions	<b>Intervention</b> A. Infliximab (n = 11), IV, 5 mg/kg , weeks 0, 2, 6, 10 <b>Control intervention</b> B. Infliximab (n = 11), IV, 10 mg/kg , weeks 0, 2, 6, 10 C. Placebo (n = 11), IV, 20 mL, weeks 0, 2, 6, 10	
Outcomes	Assessment at 10 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• PGA good, excellent or clear</li> </ul> <b>Secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul>	
Notes	Funding : Y Johnson and Johnson, Centocor Inc Declarations of interest: not stated	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p 1843): "...were randomly assigned... by means of a lock-of-six randomisation scheme" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 1843): "Placebo was supplied in a identical manner except that it did not contain IFX...The infliximab infusion solution was given by investigators unaware of treatment assignment..." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 1843): "All assessments were done in a masked manner" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 33, analysed 33 <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• 3/33 (9%)</li> <li>• Time and reasons: worsening psoriasis (n = 1 from infliximab 10 mg/kg group), mild rash (n = 1 from infliximab 5mg/kg group), lack improvement disease (n = 1 from placebo group)</li> </ul> Management of missing data: quote (p 1844): "The primary analysis was done ac-

**Chaudhari 2001** (Continued)

		cording to ITT, all randomised patients were included Comment: probably done
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

**Chladek 2005**

Methods	RCT, active-controlled Date of study: not stated Location: Prague, Czech Republic
Participants	<b>Randomised:</b> 41 participants (mean age 50 years (A), 46 years (B), 44 years (C), 41 years (D), 24 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Not stated</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Not stated</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• Not stated</li> </ul>
Interventions	<b>Intervention</b> A. Methotrexate (n = 12), 7.5 mg/week, 2.5-2.5-2.5 at 12 h, for 13 weeks <b>Control intervention</b> B. Methotrexate (n = 12), 15 mg/week, 5-5-5 at 12 h, 13w C. Methotrexate (n = 7), 7.5 mg/week, once a week, for 13 weeks D. Methotrexate (n = 10), 15 mg/week, once a week, 13 weeks
Outcomes	Assessment at 13 weeks <b>Primary or secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• Not stated</li> </ul> <b>Outcomes of the trial</b> <ul style="list-style-type: none"> <li>• Red cell concentrations of methotrexate</li> <li>• PASI weeks 1, 5, 9, 13</li> </ul>
Notes	Funding: Czech Ministry of Education Declarations if interest: not stated

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p 247): "were randomly assigned" Comment: no description of the method used to guarantee random sequence gener-



Chladek 2005 (Continued)

		ation
Allocation concealment (selection bias)	Unclear risk	Quote (p 247): “were randomly assigned” Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: probably open-label trial, term “blind” not used
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: probably open-label trial, term “blind” not used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no description of the method used to manage the missing data. No ITT analyses mentioned
Selective reporting (reporting bias)	Unclear risk	Comment: no primary or secondary outcomes stated

de Vries PIECE, 2016

Methods	RCT, active-controlled, Date of study: April 2009 and June 2011 Location: 5 centres in The Netherlands
Participants	<p><b>Randomised:</b> 50 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• 18-75 years</li> <li>• Moderate to severe chronic plaque type psoriasis defined as PASI <math>\geq 10</math> and/or BSA <math>\geq 10</math> and/or PASI <math>\geq 8</math> plus a Skindex-29 score <math>\geq 35</math></li> <li>• Patients must have had unsuccessful treatment with or were contraindicated and/or intolerant to UV therapy, and methotrexate or cyclosporine</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Pregnant, breastfeeding</li> <li>• Malignancy in the previous 10 years</li> <li>• Active/chronic infections including TB</li> <li>• Demyelinating disease</li> <li>• Congestive heart failure</li> <li>• Severe liver function disorders <math>&gt;2</math> times and/or kidney function disorders <math>&gt;1.5</math> times upper limit of the parameters</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 15/50 (30%)</li> <li>• False inclusion: infliximab (0), etanercept (2)</li> <li>• AEs: infliximab (1), etanercept (3)</li> <li>• Injection fear: infliximab (0), etanercept (1)</li> <li>• Switch to etanercept: infliximab (3), etanercept (not applicable)</li> <li>• Switch to infliximab: infliximab (not applicable), etanercept (3)</li> </ul>

	<ul style="list-style-type: none"> <li>• No response: infliximab (0), etanercept (1)</li> <li>• Lost To follow-up: infliximab (1), etanercept (0)</li> </ul>	
Interventions	<p><b>Intervention (n = 48)</b> A. Infliximab (n = 25), IV, 5 mg/kg, weeks 0, 2, 6, 15, 22</p> <p><b>Control intervention</b> B. Etanercept (n = 23), SC, 50 mg twice weekly</p>	
Outcomes	<p>Assessment at 24 weeks</p> <p><b>Primary outcomes of the trial</b> PASI 75</p> <p><b>Secondary outcomes of the trial</b> QoL scale, Global assessment, treatment satisfaction</p>	
Notes	<p>Funding source quote (p 1): "study was funded by a program grant from the Netherlands Organization for Scientific Research-Medical Sciences (NWO-MW; project 152001006)</p> <p>“</p> <p>Declaration of interest: "A.C.Q. de Vries: none reported; H.B. Thio: has been a consultant and invited speaker for Biogen/Idex, Janssen, Abbvie, Pfizer, MSD, Leopharma, Teva and Novartis. He has received educational grants from Abbvie, Janssen, Pfizer and Biogen/Idex.; W.J.A. de Kort: medical advisor for Novartis; B.C. Opmeer: none reported; H.M. van der Stok: Involved in performing clinical trials with Abbvie, Pfizer, Novartis, Janssen, BioClinic, AMGEN and LeoPharma.; E.M.G.J. de Jong: received research grants for the independent research fund of the department of dermatology of University Medical Centre St Radboud Nijmegen, the Netherlands from AbbVie, Pfizer, and Janssen. Has acted as consultant and/or paid speaker for and/or participated in research sponsored by companies that manufacture drugs used for the treatment of psoriasis including AbbVie, Janssen, MSD, and Pfizer.; B. Horvath: Unrestricted Educational Grant from AbbVie, IIS Studies by Janssen, AbbVie, Performing clinical trial Novartis, Solenne B.V., Consultancies: Abbvie, Janssen, Philips, Galderma.; J.J.V.Busschbach: none reported; T.E.C. Nijsten: received research grants for the independent research fund of the department of dermatology of Erasmus MC, Rotterdam, the Netherlands from AbbVie, Leo Pharma, MSD, Pfizer, and Janssen. Has acted as consultant and/or paid speaker for and/or participated in research sponsored by companies that manufacture drugs used for the treatment of psoriasis including AbbVie, Leo Pharma, Galderma, Janssen, MSD, and Pfizer. ; Ph.I. Spuls: consultancies in the past for Leopharma, AbbVie and Novartis. In the past an independent research grant from Schering Plough and from Leopharma. Involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of psoriasis.“</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p 4 & 8): "...was a multi-centre, single-blind, investigator initiated, randomised controlled trial comparing infliximab and etanercept in the treatment of moderate to severe chronic plaque type psoriasis."

		<p>riasis... Adequate generation of an unpredictable allocation sequence and concealment of allocation was achieved by using a secure online internet facility (the TEN-ALEA Clinical Trial Data Management System, provided by the Trans European Network <a href="http://www.tenalea.com/">http://www.tenalea.com/</a>) performed in the coordinating centre by the main investigators. The sequence was generated in random block sizes of two and four to ensure it was unknown and not predictable by the investigators involved in randomising participants.”</p> <p>Comment: done</p>
Allocation concealment (selection bias)	Low risk	<p>Quote (p 4 &amp; 8): “...was a multi-centre, single-blind, investigator initiated, randomised controlled trial comparing infliximab and etanercept in the treatment of moderate to severe chronic plaque type psoriasis... Adequate generation of an unpredictable allocation sequence and concealment of allocation was achieved by using a secure online internet facility (the TEN-ALEA Clinical Trial Data Management System, provided by the Trans European Network <a href="http://www.tenalea.com/">http://www.tenalea.com/</a>) performed in the coordinating centre by the main investigators. The sequence was generated in random block sizes of two and four to ensure it was unknown and not predictable by the investigators involved in randomising participants.”</p> <p>Comment: done</p>
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Quote (p 4 &amp; 8): “...was a multi-centre, single-blind, investigator initiated, randomised controlled trial comparing infliximab and etanercept in the treatment of moderate to severe chronic plaque type psoriasis...”</p> <p>Comment: no blinding</p>
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	<p>Quote (p 8): “Efficacy outcomes were carried out by trained assessors who were blinded to treatment allocation.”</p> <p>Comment: no clear description of measures taken to guarantee the blinding of investigators</p>

Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 50, analysed 48 Quote (p 8 & 9): “Missing data on primary endpoint were imputed using last observation carried forward. Analyses were carried out according to intention-to-treat (ITT) principle, apart from the longer term data where a per protocol analysis (PPA) was performed” Comment: probably done
Selective reporting (reporting bias)	Unclear risk	The trial was prospectively registered on the Dutch Trial Register: <a href="http://www.trialregister.nl/trialreg/index.asp">www.trialregister.nl/trialreg/index.asp</a> ; NTR 1559 The pre-specified outcomes mentioned in the methods section appeared to have been reported

**Dogra 2012**

Methods	RCT, active-controlled, double blind Date of study: August 2008-September 2009 Location: Chandigarh, India
Participants	<b>Randomised:</b> 60 participants (mean age 37 years, 48 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (BSA <math>\geq</math> 10)</li> <li>• Age <math>\geq</math> 18 years <math>\leq</math> 65</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Pregnancy, kidney insufficiency, liver insufficiency</li> <li>• Had uncontrolled cardiovascular disorder</li> <li>• Had uncontrolled diabetes</li> <li>• had uncontrolled hypertension</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• 9/60 (15%): methotrexate 10 group (5), methotrexate 25 group (4)</li> <li>• 4 lost to follow-up: methotrexate 10 group (3), methotrexate 25 group (1)</li> <li>• 4 withdrawn due to side effects: methotrexate 10 group (1), methotrexate 25 group (3)</li> <li>• 1 refused to participate further in the study: methotrexate 10 group (1), methotrexate 25 group (0)</li> </ul>
Interventions	<b>Intervention</b> A. Methotrexate (n = 30), orally, 10 mg/week, for 12 weeks <b>Control intervention</b> B. Methotrexate (n = 30), orally, 25 mg/week, for 12 weeks
Outcomes	Assessment at 12 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• Change in PASI score</li> </ul>

	<b>Secondary outcomes of the trial</b>	
	<ul style="list-style-type: none"> <li>• PASI 75</li> <li>• AEs</li> </ul>	
Notes	Funding: none declared Declarations of interest: none declared	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p 730): "The randomisation list was generated using a random number table, and the code was kept by an investigator who was not directly involved in the study" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 730): "The randomisation list was generated using a random number table, and the code was kept by an investigator who was not directly involved in the study. All tablets were supplied in sealed envelopes bearing the code for any particular patient according to the randomisation list" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 730-31): "Double blind study, ..., the 10 mg group was also given an oral placebo tablet in addition to the MTX to give an equal number of tablets in both groups. The placebo tablets were identical in appearance to the MTX tablets in colour, texture, size, shape and markings. All tablets were supplied in sealed envelopes bearing the code for any particular patient according to the randomisation list" Comment: clearly described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 730-31): "Double blind study, ..., the 10 mg group was also given an oral placebo tablet in addition to the MTX to give an equal number of tablets in both groups. The placebo tablets were identical in appearance to the MTX tablets in colour, texture, size, shape and markings. All tablets were supplied in sealed envelopes bearing the code for any particular patient

**Dogra 2012** (Continued)

		according to the randomisation list” Comment: clearly described
Incomplete outcome data (attrition bias) All outcomes	High risk	Randomly assigned 60, analysed 51 <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>● 9/60 (15%): methotrexate 10 group (5), methotrexate 25 group (4)</li> <li>● 4 Lost to follow-up: methotrexate 10 group (3), methotrexate 25 group (1)</li> <li>● 4 withdrawn due to side effects: methotrexate 10 group (1), methotrexate 25 group (3)</li> <li>● 1 refused to participate further in the study: methotrexate 10 group (1), methotrexate 25 group (0)</li> </ul> Management of missing data: no ITT analyses
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

**Dogra 2013**

Methods	RCT, active-controlled, double blind Date of study: March 2008-March 2009 Location: Chandigarh, India
Participants	<b>Randomised:</b> 61 participants (mean age 37 years, 51 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>● Participants with moderate-severe psoriasis (BSA <math>\geq</math> 10)</li> <li>● Age <math>\geq</math> 18 years <math>\leq</math> 65</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>● Pregnancy, kidney insufficiency, liver insufficiency</li> <li>● Had uncontrolled cardiovascular disorder</li> <li>● Had uncontrolled diabetes</li> <li>● had uncontrolled hypertension</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>● 13/61 (21%): acitretin 25 group (5), acitretin 35 group (4), acitretin 50 group (4)</li> <li>● 10 lost to follow-up: acitretin 25 group (4), acitretin 35 group (2), acitretin 50 group (4)</li> <li>● 3 severe disease exacerbation: acitretin 25 group (1), acitretin 35 group (2)</li> </ul>
Interventions	<b>Intervention</b> A. Acitretin (n = 20), orally, 25 mg/day, for 12 weeks <b>Control intervention</b> B. Acitretin (n = 20), orally, 35 mg/day, for 12 weeks

	C. Acitretin (n = 21), orally, 50 mg/day, for 12 weeks	
Outcomes	<p>Assessment at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• Change in PASI score</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> <li>• % complete clearance</li> <li>• Time taken to achieve those parameters</li> <li>• AEs</li> </ul>	
Notes	<p>Funding (quote e305): none declared</p> <p>Declarations of interest (quote e305): none declared</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p e306): "Randomization list was generated using random number table and code was kept with a study coordinator who was not directly involved in assessment of endpoint" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p e306): "Randomization list was generated using random number table and code was kept with a study coordinator who was not directly involved in assessment of endpoint" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (p e306): "double blind" Comment: no description of the method used to guarantee blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (p e306): "double blind" "Randomization list was generated using random number table and code was kept with a study coordinator who was not directly involved in assessment of endpoint" Comment: no description of the method used to guarantee blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	Randomly assigned 61, analysed 48 Dropouts and withdrawals: <ul style="list-style-type: none"> <li>• 13/61(21%): acitretin 25 group (5), acitretin 35 group (4), acitretin 50 group</li> </ul>

Dogra 2013 (Continued)

		<p>(4)</p> <ul style="list-style-type: none"> <li>• 10 lost to follow-up: acitretin 25 group (4), acitretin 35 group (2), acitretin 50 group (4)</li> <li>• 3 severe disease exacerbation: acitretin 25 group (1), acitretin 35 group (2)</li> </ul> <p>Not ITT analyses</p>
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

Dubertret 1989

Methods	<p>RCT, active-controlled Date of study: July 1987-January 1988 Location: Paris</p>	
Participants	<p><b>Randomised:</b> 37 participants (mean age, sex ratio: not stated) <b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis: widespread psoriasis (PASI &gt; 18)</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Not stated</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• Not stated</li> </ul>	
Interventions	<p><b>Intervention</b> A. Cyclosporin (n = 18), orally, 2.5 mg/kg/d <b>Control intervention</b> B. Cyclosporin (n = 19), orally, 5 mg/kg/d</p>	
Outcomes	<p>Time to Assessment for the primary outcome: not stated <b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• Not stated</li> </ul>	
Notes	<p>Funding: not stated however one out of four authors was a staff member of Sandoz pharmaceutical company Declarations of interest: not stated</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>



Dubertret 1989 (Continued)

Random sequence generation (selection bias)	Unclear risk	Quote (p 136): “The patients were randomised...” Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (p 136): “The patients were randomised...” Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: not specified as blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: not specified as blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Randomly assigned 37, analysed 37 <b>Dropouts and withdrawals</b> Not stated Management of missing data: no description of the method used to guarantee management of missing data
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

Ellis 1991

Methods	RCT, active, controlled, double blind Date of study: not stated Location: single-centre (University of Michigan Medical Center, Ann Arbor)
Participants	<b>Randomised:</b> 85 participants (mean age 46 years (cyclosporine 3), 42 years (cyclosporine 5), 46 years (cyclosporine 7.5), 43 years (placebo), 66 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (BSA <math>\geq</math> 25)</li> <li>• Non-response to phototherapy</li> <li>• Non-response to conventional systemic treatment</li> <li>• Failure to at least 1 line</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Pregnancy</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• Not stated</li> </ul>

Interventions	<p><b>Intervention</b> A. Ciclosporin (Sandimmun) (n = 15), orally, 7.5 mg/kg, 8 weeks</p> <p><b>Control intervention</b> B. Ciclosporin (Sandimmun) (n = 20), orally, 5 mg/kg, 8 weeks C. Ciclosporin (Sandimmun) (n = 25), orally, 3 mg/kg, 8 weeks D. Vehicle (Sandimmun oral olive oil) (n = 25), orally, 8 weeks</p>	
Outcomes	<p>Assessment at 8 weeks</p> <p><b>Primary or secondary outcomes</b> not stated</p> <p><b>Outcomes</b></p> <ul style="list-style-type: none"> <li>• Target lesions</li> <li>• PASI</li> <li>• Urinary creatinine clearance</li> <li>• Blood count</li> <li>• Blood pressure</li> </ul>	
Notes	<p>Funding (p 277): Sandoz research Institute, the Babcock Dermatologic Endowment (Ann Arbor) and a Clinical research centre grant (M01-RR-00042) from the National Institutes of Health</p> <p>Declarations of interest: not stated (p 277) "Drs Ellis and Voorhees are consultants to Sandoz Pharmaceuticals corporation (the manufacturer of cyclosporine)</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p 278): "patients were assigned numbers in consecutive order; each number had been preassigned to one of four treatments groups by means of a computer generated random code in blocks 17" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 278): "The preparation of cyclosporine and vehicle were identical ... patients were blinded to their treatment" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 278): "Other physician who were blinded to group assignment and laboratory findings evaluated the patient" Comment: probably done

Ellis 1991 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Randomly assigned 85, analysed not stated <b>Dropouts and withdrawals</b> not stated Quote (p 279): “In the primary, intention-to-treat analysis” Management of missing data: no description of the method used to guarantee management of missing data
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

Ellis 2001

Methods	RCT, active placebo-controlled, double blind Date of study: 14 May 1998-22 February 1999 Location: 22 centres in USA
Participants	<b>Randomised:</b> 229 participants (mean age 45 years, 163 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (BSA <math>\geq</math> 10)</li> <li>• Age <math>\geq</math> 18 years <math>\leq</math> 70</li> <li>• Non-response to phototherapy</li> <li>• Non-response to conventional systemic treatment</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Pregnancy, kidney insufficiency, liver insufficiency,</li> <li>• Had an active infection</li> <li>• Had past history of malignant tumours</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• 32/229 (14%): alefacept 0.025 (6), alefacept 0.075 (7), alefacept (9), placebo (10)</li> <li>• 5 lost to follow-up: alefacept 0.025 (2), alefacept 0.075 (0), alefacept (2), placebo (1)</li> <li>• 9 withdrawals: alefacept 0.025 (0), alefacept 0.075 (1), alefacept (5), placebo (3)</li> <li>• 4 AEs: alefacept 0.025 (1), alefacept 0.075 (3), alefacept (0), placebo (0)</li> <li>• 2 lab abnormalities: alefacept 0.025 (1), alefacept 0.075 (3), alefacept (0), placebo (0)</li> <li>• 8 worsening: alefacept 0.025 (2), alefacept 0.075 (1), alefacept (0), placebo (5)</li> <li>• 4 other: alefacept 0.025 (1), alefacept 0.075 (1), alefacept (1), placebo (1)</li> </ul>
Interventions	<b>Intervention</b> A. Alefacept (n = 57), IV, 0.025 mg/kg, once a week, 12 weeks <b>Control intervention</b> B. Alefacept (n = 55), IV, 0.075 mg/kg, once a week, 12 weeks C. Alefacept (n = 58), IV, 0.150 mg/kg, once a week, 12 weeks D. Placebo (n = 59), IV, once a week, 12 weeks

Outcomes	Assessments at 14 weeks <b>Primary or secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• Not stated</li> </ul> <b>Outcomes of the trial</b> <ul style="list-style-type: none"> <li>• Mean change PASI</li> <li>• PGA clear/almost clear</li> <li>• PASI 75</li> <li>• PASI 50</li> </ul>	
Notes	Funding (p 254) : “supported by Biogen and a grant from the National Institutes of Health ... at the university of Utah” Declarations of interest (p 254): “A patent on the use of alefacept (LFA3TIP) for the treatment of psoriasis has been assigned to Biogen and the University of Michigan; neither Dr. Ellis nor Dr. Krueger has a financial interest in the patent. Dr. Ellis and Dr. Krueger are consultants to Biogen, as well as to other companies that manufacture treatments for psoriasis.”	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p 249): “Randomization scheme was generated before the study, with a block size of four at each center” Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Quote (p 249): “Randomization scheme was generated before the study, with a block size of four at each center” Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 249): “Double blind... all preparations were identical in appearance” Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: no specific description of the method used to guarantee blinding of outcome assessment however considering that this is a placebo-controlled trial with no known systematic AEs we considered the risk as low
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote (p 250): “were conducted according to the intention-to-treat principle” <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• 32/229 (14%); alefacept 0.025 (6), alefacept 0.075 (7), alefacept (9), placebo</li> </ul>

Ellis 2001 (Continued)

		(10) <ul style="list-style-type: none"> <li>no imbalance in reasons</li> </ul> Comment: no description of the method used to guarantee missing data management, number of participants analysed not stated
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

Engst 1994

Methods	RCT, active-controlled, open-label trial Date of study: not stated Location: not stated
Participants	<b>Randomised:</b> 22 participants (mean age 45.9 years, 18 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>Participants with moderate-severe psoriasis (PASI &gt; 16)</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>Pregnancy, kidney insufficiency, liver insufficiency,</li> <li>Had an active infection</li> <li>Had uncontrolled cardiovascular disorder</li> <li>Had past history of malignant tumours</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>Not stated</li> </ul>
Interventions	<b>Intervention</b> A. Ciclosporin A (n = 10), orally, 1.25 mg/kg/d (increase to 2.5 if PASI > 50% of initial PASI), 12 months <b>Control intervention</b> B. Ciclosporin A, (n = 12), orally, 2.5 mg/kg/d (increase to 5 if PASI > 50% of initial PASI), 12 months
Outcomes	Assessment period: not stated but longer than 16 weeks <b>Primary or secondary outcomes of the trial:</b> not stated <b>Outcomes of the trial</b> <ul style="list-style-type: none"> <li>PASI score</li> <li>Blood pressure</li> <li>Blood count</li> <li>Urine samples</li> </ul>
Notes	Funding: not stated Declarations of interest: not stated
<b>Risk of bias</b>	

Engst 1994 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p 189): "Patients enrolled in the study were randomised..." Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (p 189): "Patients enrolled in the study were randomised..." Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: not blinded (open-label)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: not blinded (open-label)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	<b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• Not stated</li> </ul> Management of missing data: no description of the method used to guarantee management of missing data, ITT analyses not mentioned
Selective reporting (reporting bias)	High risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section were not reported in results section

Fallah Arani 2011

Methods	RCT, active-controlled, open-label trial Date of study: October 2006-February 2009 Location: Rotterdam/Eindhoven
Participants	<b>Randomised:</b> 60 participants (mean age 41 years (methotrexate) and 43 years (fumarate), 36 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 10)</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Pregnancy, Immunosuppression, kidney insufficiency, liver insufficiency,</li> <li>• Had an active infection</li> <li>• Had uncontrolled cardiovascular disorder</li> <li>• Had uncontrolled diabetes</li> </ul> <b>Dropouts and withdrawals</b>

	<ul style="list-style-type: none"> <li>● 9/60 (15%): methotrexate group (5), fumarate group (4)</li> <li>● Time and reasons             <ul style="list-style-type: none"> <li>○ found ineligible: methotrexate group (2), fumarate group (3)</li> <li>○ withdrew consent: methotrexate group (1), fumarate group (0)</li> <li>○ non-appearance: methotrexate group (2), fumarate group (1)</li> </ul> </li> </ul>
Interventions	<p><b>Intervention</b> A. Methotrexate (n = 30), orally, 15 mg/week, Weinstein schema 15 mg weekly in 3 equal doses of 5 mg each 12 h apart, 16 weeks</p> <p><b>Control intervention</b> B. Fumarate (n = 30), orally, 720 mg, 30 mg followed by 120 mg and max 720 mg after week 9, 16 weeks</p>
Outcomes	<p>Assessments at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>● PASI decreased</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>● PASI decreased at 4, 16, 20 weeks</li> <li>● AEs</li> </ul>
Notes	<p>Funding source (p 855): none</p> <p>Declarations of interest (p 855): “none declared”</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 856): “patients were randomly assigned ... randomisation was performed centrally according to a computered-generated randomisation list” Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Quote (p 856): “Only the research nurse, who had no contact with the patients before randomisation had insight into the allocation schedule” Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (p 856): “could not be blinded because treatment intake differed in both groups” Comment: not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (p 857): “by the same trained assessors (one trained physician and a research nurse in consensus in each site)” Comment: not specified whether “trained

		assessors" were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Randomly assigned 60, analysed 51 Management of missing data: Quote (p 857): "Analysis was by Intention-to-treat.." Comment: ITT analysis not performed
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

**Flytström 2008**

Methods	RCT, active-controlled, open-label trial Date of study: Feb 2002-Feb 2005 Location: multicentre (n = 5), Sweden
Participants	<b>Randomised:</b> 84 participants (mean age: 48 years (methotrexate), 46 years (ciclosporin) ; 55 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis</li> <li>• Age ≥ 18</li> <li>• Non response to topical treatment</li> <li>• Non-response to phototherapy</li> <li>• One previous treatment line allowed</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Pregnancy, immunodepression, kidney insufficiency, liver insufficiency</li> <li>• Had uncontrolled hypertension</li> <li>• Had past history of malignant tumours</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• 16/84 (19%): methotrexate group (4), ciclosporin group (12)</li> <li>• 7 with exclusion criteria: methotrexate group (2), ciclosporin group (5)</li> <li>• 7 consent withdrawal: methotrexate group (2), ciclosporin group (5)</li> <li>• 2 ineligible: ciclosporin group</li> </ul>
Interventions	<b>Intervention</b> A. Methotrexate + folic acid (n = 41), orally, 7.5 mg/kg /week (5 mg folic acid except days of methotrexate), 12 weeks <b>Control intervention</b> B. Ciclosporin (n = 43), orally, 3 mg/kg, divided into 2 doses, 12 weeks
Outcomes	Assessments at 12 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• PASI</li> </ul> <b>Secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• DLQI</li> </ul>



	<ul style="list-style-type: none"> <li>• SF-36</li> <li>• VAS for patient assessment</li> </ul>	
Notes	<p>Funding (p121): “Financial support from the Swedish Psoriasis Association and the Welander foundation”</p> <p>Declarations of interest (p116): “none declared”</p>	
<b><i>Risk of bias</i></b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p 117): “Randomization was performed with the use of computer-generated random numbers, numbers by calling a central telephone number” Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 117): “Randomization was performed with the use of computer-generated random numbers, numbers by calling a central telephone number” Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (p 117): “Blinded assessors performed the PASI at baseline and monthly thereafter” Comment: no description of method used to guarantee no communication between care givers or participants and assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	Randomly assigned 84, analysed 68 Management of missing data: not ITT analysis
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

Gisondi 2008

Methods	<p>RCT, active-controlled, investigator-blinded pilot trial  Date of study: Feb 2002-Feb 2005  Location: Verona, Italy</p>	
Participants	<p><b>Randomised:</b> 60 participants (mean age 55 years (acitretin); 55 years (etanercept), 53 years (acitretin + etanercept), 33 male)  <b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis</li> <li>• Age <math>\geq</math> 18</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Fertile women, Kidney insufficiency (severe disorder), Liver insufficiency (severe disorder),</li> <li>• Had received biologics</li> <li>• Had an active infection (HIV, Hepatitis B &amp; C, latent TB)</li> <li>• Had demyelinating diseases</li> <li>• Has uncontrolled cardiovascular disorder (severe heart failure)</li> <li>• Had past history of malignant tumours</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 4/60 (6.6%): acitretin group (4), etanercept group (0), acitretin + etanercept group (0)</li> <li>• Inefficacy of the treatment: acitretin group (4)</li> </ul>	
Interventions	<p><b>Intervention</b>  A. Etanercept (25mg) and acitretin (0.4 mg/kg) (n = 18), SC (etanercept) and orally (acitretin), twice a week (etanercept) and once a day (acitretin), 24 weeks</p> <p><b>Control intervention</b>  B. Acitretin (n = 20), orally, 0.4 mg/kg, once a day, 24 weeks  C. Etanercept (n = 22), SC, 25 mg, twice a week, 24 weeks</p>	
Outcomes	<p>Assessments at 24 weeks  <b>Primary outcomes of the trial</b>  <math>\geq</math> PASI 75 improvement from baseline  <b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 50</li> <li>• BSA</li> <li>• Number of participants reporting significant changes (e.g. &gt; 3 times the normal value for AST and ALT and &gt; double the normal value for cholesterol and triglycerides)</li> </ul>	
Notes	<p>Funding: not stated  Declarations of interest (p 1345): "PG has received lecture fees from Merck-Serono, Schering-Plough, Wyeth. GG has received consultation and lecture fees from Abbott, Janssen-Cilag, Merck-Serono, Schering-Plough, Wyeth."</p>	
<i>Risk of bias</i>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>

**Gisondi 2008** (Continued)

Random sequence generation (selection bias)	Low risk	Quote (p 1346): “Randomization was performed with the use of computer-generated random numbers and block size of four patients” Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Quote (p 1346): “Randomization was performed with the use of computer-generated random numbers and block size of four patients” Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (p 1346): “The PASI assessor was blinded concerning the group allocation of the patient” Comment: acitretin provide visible AEs
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Randomly assigned 60, analysed 60 Management of missing data, quote (p 1346): “An ITT analysis was performed” Comment: no description of the method used to manage the missing data
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

**Goldfarb 1988**

Methods	RCT, placebo-controlled, double blind Date of study: not stated Location: not stated
Participants	<b>Randomised:</b> 38 participants (mean age 45-48 years, 31 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• BSA 10-70</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• No women of childbearing potential</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• 0/38 (0%)</li> </ul>

Interventions	<p><b>Intervention</b></p> <p>A. Acitretin (n = 10), orally, 10-25 mg/day, 8 weeks</p> <p>B. Acitretin (n = 16), orally, 50-75 mg/day, 8 weeks</p> <p><b>Control intervention</b></p> <p>C. Placebo (n = 12), orally, daily, 8 weeks</p>
Outcomes	<p>Assessments at 8 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• Not stated</li> </ul> <p><b>Outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• Percentage of skin involvement with psoriasis</li> <li>• Overall scaling, erythema, thickness, and global extent of the disease on a 0 through 6 scale</li> <li>• Improvement range from worse/unchanged/fair/good/excellent</li> <li>• AEs</li> </ul>
Notes	<p>Funding sources, quote (p 655): “Supported in part by Hoffman-La Roche Inc., Nutley, NJ, and the Babcock Dermatologic Endowment”</p> <p>Declarations of interest: not stated</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p 656): “21 patients were randomly and equally divided into 4 groups” Comment: no description of the method used to generate the sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (p 656): “21 patients were randomly and equally divided into 4 groups” Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (p 656): “we have studied 38 patients in a double-blind fashion” Comment: visible side effect of acitretin
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (p 656): “we have studied 38 patients in a double-blind fashion” Comment: visible side effect of acitretin
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Randomly assigned 38, analysed 38 No mention of how the missing data were managed
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been

## Gordon 2006

Methods	RCT, placebo-controlled, double-blind trial Date of study: March 2003-June 2004 Location: Multicentre (n = 18) in USA, Canada
Participants	<p><b>Randomised:</b> 148 participants (mean age 44 years, 99 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (BSA <math>\geq</math> 5)</li> <li>• Age <math>\geq</math> 18</li> <li>• Non-response to topical treatment</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Pregnancy</li> <li>• Had received biologics (anti-TNF)</li> <li>• Had an active infection</li> <li>• Had past history of malignant tumours</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 8/148 (5%)</li> <li>• Time and reasons: <ul style="list-style-type: none"> <li>◦ did not receive the treatment: adalimumab weekly (0), adalimumab eow (1), placebo (0)</li> <li>◦ AE: adalimumab weekly (2), adalimumab eow (2), placebo (1)</li> <li>◦ lack of efficacy: adalimumab weekly (0), adalimumab eow (0), placebo (1)</li> <li>◦ abnormal lab value: adalimumab weekly (1), adalimumab eow (0), placebo (0)</li> </ul> </li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Adalimumab (n = 46), SC, 40 mg, 12 weeks, week 0: 2 injections, 1 injection eow</p> <p>B. Adalimumab, (n = 50), SC, 40 mg, 12 weeks, week 0, week 1: 2 injections, 1 injection weekly</p> <p><b>Control intervention</b></p> <p>C. Placebo (n = 52), SC, 12 weeks</p>
Outcomes	<p>Assessments at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 50</li> <li>• PASI 100</li> <li>• PGA</li> <li>• DLQI</li> </ul>
Notes	<p>Funding, quote (p 598): "Supported by Abbott Laboratories"</p> <p>Declarations of interest (p 598): "Dr Gordon has received research support and honoraria and is a consultant for Abbott. Dr Langley is an investigator and has received research funding to conduct research studies with Abbott. Dr Leonardi is a consultant and speaker for Abbott. Dr Menter has received honoraria and is a consultant for Abbott. Dr Kang</p>

	is an ad-hoc consultant for Abbott. Dr Heffernan is a consultant for and has received research funding from Abbott. Drs Zhong, Hoffman, and Okun and Ms Lim are full-time employees of Abbott.”	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p 699): “Patients were centrally randomised...” Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Quote (p 699): “Patients were centrally randomised...” Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 599): “To maintain blinding, pre-filled syringes were identically labelled and all patients received the same number of injections at the same time points” Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 599): “To maintain blinding, pre-filled syringes were identically labelled and all patients received the same number of injections at the same time points” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 148, analysed 147 <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>● 8/148 (5%)</li> <li>● Time and reasons: <ul style="list-style-type: none"> <li>○ did not receive the treatment: adalimumab weekly (0), adalimumab eow (1), placebo (0)</li> <li>○ AE: adalimumab weekly (2), adalimumab eow (2), placebo (1)</li> <li>○ lack of efficacy: adalimumab weekly (0), adalimumab eow (0), placebo (1)</li> <li>○ abnormal lab value: adalimumab weekly (1), adalimumab eow (0), placebo (0)</li> </ul> </li> </ul> Management of missing data, quote (p 601): “modified intent-to-treat analysis... a patient with missing data was counted as a nonresponder at that visit”

**Gordon 2006** (Continued)

		Comment: few lost to follow-up, well-balanced number and reasons between groups
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

**Gordon UNCOVER-1, 2016**

Methods	RCT, placebo-controlled, double blind Date of study: November 2011-June 2014 Location: multicentre (104) in Europe, Australia, North America
Participants	<p><b>Randomised:</b> 1296 participants (mean age 45 years, 883 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12 or BSA <math>\geq</math> 10), age <math>\geq</math> 18 years</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>Pregnancy, immunosuppression, kidney insufficiency, liver insufficiency, past history of malignant tumours, active infection, uncontrolled cardiovascular disorder, uncontrolled diabetes, uncontrolled hypertension</li> <li>Had received anti IL17</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>66/1296 (5%);</li> <li>Ixekizumab 4-week group (24), ixekizumab 2-week group (18), placebo (24)</li> <li>AEs: ixekizumab 4-week group (10), ixekizumab 2-week group (10), placebo (6)</li> <li>Protocol violation: ixekizumab 4-week group (6), ixekizumab 2-week group (0), placebo (3)</li> <li>Participant decision: ixekizumab 4-week group (6), ixekizumab 2-week group (5), placebo (6)</li> <li>Lost to follow-up: ixekizumab 4-week group (0), ixekizumab 2-week group (2), placebo (1)</li> <li>Investigator decision: ixekizumab 4-week group (1), ixekizumab 2-week group (1), placebo (1)</li> <li>Lack of efficacy: ixekizumab 4-week group (1), ixekizumab 2-week group (0), placebo (7)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Ixekizumab (n = 432), SC, 80 mg, 2 injections week 0, 1 injection monthly</p> <p><b>Control intervention</b></p> <p>B. Ixekizumab (n = 433), SC, 80 mg, 2 injections week 0, 1 injection eow</p> <p>C. Placebo (n = 431), SC</p>
Outcomes	<p>Assessments at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>PGA 0-1</li> <li>PASI 75</li> </ul>

	<b>Secondary outcomes of the trial</b>	
	<ul style="list-style-type: none"> <li>● PASI 90</li> <li>● DLQI</li> <li>● NAPSI</li> <li>● AEs</li> </ul>	
Notes	<p>Funding source:            Quote (p 346): “The trials were sponsored by Eli Lilly and were designed by the scientific steering committee and Eli Lilly personnel. The site investigators collected the data, Eli Lilly personnel performed the data analyses, and all the authors had access to the data.”            Declarations of interest (p 355): ”<a href="#">Disclosure forms</a> provided by the authors are available with the full text of this article at NEJM.org.“ Gordon received grants and personal fees from Abbvie, Amgen, Celgene, Eli Lilly, Novartis; and personal fees from Pfizer and Medac</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (supplemental appendix): “Patients were assigned to treatment groups as determined by a computer-generated random sequence ..” Comment: clearly defined
Allocation concealment (selection bias)	Low risk	Quote (supplemental appendix): “Patients were assigned to treatment groups as determined by a computer-generated random sequence using an interactive voice response system (IVRS). Site personnel confirmed that they had located the correct assigned investigational product package by entering a confirmation number found on the package into the IVRS” Comment: clearly defined
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 346): “double-blind, placebo-controlled” Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 346): “double-blind, placebo-controlled” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 1296, analysed 1296 Management of missing data: Quote (p 348): “Unless otherwise specified, all analyses of efficacy during the induction period were performed according to the in-



Gordon UNCOVER-1, 2016 (Continued)

		tention-to-treat principle. Missing values for the PASI and the sPGA score were imputed conservatively as nonresponses, regardless of the reason for the missing data” Comment: probably done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01474512) The pre-specified outcomes mentioned in the protocol and in the methods section appeared to have been reported

Gordon X-PLORE, 2015

Methods	RCT, active placebo-controlled, double blind Date of study: October 2011-August 2013 Location: multicentre (n = 31), Europe & North America
Participants	<p><b>Randomised:</b> 293 participants (mean age 47 years, 207 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12 or BSA <math>\geq</math> 10), age <math>\geq</math> 18 years</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>Pregnancy, immunosuppression, kidney insufficiency, liver insufficiency, past history of malignant tumours, active infection, uncontrolled cardiovascular disorder, uncontrolled diabetes, uncontrolled hypertension</li> <li>Had received adalimumab or guselkumab</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>20/293 (6.8%);</li> <li>1 not treated (guselkumab 200)</li> <li>AEs: guselkumab 5 (0), guselkumab 15 (0), guselkumab 50 (1), guselkumab 100 (1), guselkumab 200 (4), adalimumab (3), placebo (2)</li> <li>Lack of efficacy: guselkumab 5 (0), guselkumab 15 (0), guselkumab 50 (0), guselkumab 100 (0), guselkumab 200 (0), adalimumab (0), placebo (1)</li> <li>Lost to follow-up: guselkumab 5 (1), guselkumab 15 (0), guselkumab 50 (1), guselkumab 100 (0), guselkumab 200 (0), adalimumab (1), placebo (0)</li> <li>Other: guselkumab 5 (2), guselkumab 15 (0), guselkumab 50 (1), guselkumab 100 (1), guselkumab 200 (0), adalimumab (0), placebo (0)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Guselkumab (n = 41), SC, 5 mg weeks 0, 4, 16</p> <p><b>Control intervention</b></p> <p>B. Guselkumab (n = 41), SC, 15 mg weeks 0, 4, 16</p> <p>C. Guselkumab(n = 42), SC, 50 mg weeks 0, 4, 16</p> <p>D. Guselkumab (n = 42), SC, 100 mg weeks 0, 4, 16</p> <p>E. Guselkumab (n = 42), SC, 200 mg weeks 0, 4, 16</p> <p>F. Adalimumab (n = 43), SC, 40 mg 2 injections week 0, 1 injection week 1, 1 injection</p>

	eow G Placebo (n = 42), SC (100 mg weeks 0, 4, 16)
Outcomes	Assessments at 16 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• PGA 0-1</li> </ul> <b>Secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• PASI 90</li> <li>• PASI 75</li> <li>• DLQI</li> </ul>
Notes	Funding source: Quote (p 137): “This study was sponsored by Janssen Research and Development. Janssen supplied the study agents and collected and analysed the data. All the authors had full access to the data” Declarations of interest (p 144): “ <a href="#">Disclosure forms</a> provided by the authors are available with the full text of this article at NEJM.org.” Gordon received grants and personal fees from Abbvie, Amgen, Celgene, Eli Lilly, Novartis; and personal fees from Pfizer and Medac. Reich received personal fees from Celgene, Centocor/Janssen, Forward Pharma, GSK, Janssen Cilag, LEO Pharma, Lilly Medoc, MSD, Novartis, Ocean Pharma, Pfizer, Regeneron, Takeda, Vertex

**Risk of bias**

Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p 137): “patients were randomised...” Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (p 137): “patients were randomised...” Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (p 137, p 143): “double-blind... Adalimumab was not administered in a blinded, placebo-controlled manner”, “Another potential issue was to use of a blinded efficacy evaluator at each site instead of the administration of ADA in a blinded manner” Quote (p 553-4): “Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor ), Patients and study personnel were masked to treatment assignment: the study drug packaging was labelled....” Comment: adalimumab group was not

		double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 137): “to ensure objectivity, all efficacy assessment were performed by an evaluator at each study site who was unaware of the study group” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 293, analysed 293 <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• 20/293 (6.8%);</li> <li>• 1 not treated (guselkumab 200)</li> <li>• AEs: guselkumab 5 (0), guselkumab 15 (0), guselkumab 50 (1), guselkumab 100 (1), guselkumab 200 (4), adalimumab(3), placebo (2) <ul style="list-style-type: none"> <li>• Lack of efficacy: guselkumab 5 (0), guselkumab 15 (0), guselkumab 50 (0), guselkumab 100 (0), guselkumab 200 (0), adalimumab (0), placebo (1)</li> <li>• Lost to follow-up: guselkumab 5 (1), guselkumab 15 (0), guselkumab 50 (1), guselkumab 100 (0), guselkumab 200 (0), adalimumab (1), placebo (0)</li> <li>• Other: guselkumab 5 (2), guselkumab 15 (0), guselkumab 50 (1), guselkumab 100 (1), guselkumab 200 (0), adalimumab (0), placebo (0)</li> </ul> </li> </ul> Management of missing data: Quote (p 138): “Patients with missing PGA or PASI score at week 16 were categorized as not having had a response” Comment: low number of withdrawals, balanced number and reasons between groups
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01483599) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

**Gottlieb 2003**

Methods	RCT, placebo-controlled, double blind Date of study: August 2000-January 2001 Location: multicentre (locations not specified)	
Participants	<p><b>Randomised:</b> 112 participants (mean age 47 years, 70 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (BSA <math>\geq</math> 10), age <math>\geq</math> 18 years</li> <li>• Had previously received phototherapy or systemic psoriasis therapy at least once</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Quote p 1628) "Patients were excluded if they had guttate, erythrodermic, or pustular psoriasis; other skin conditions; or other significant medical conditions that might interfere with evaluations of the effect of study medications on psoriasis"</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 19/112 (17%): etanercept 4/57 (7.0%), placebo 15/55 (27.3%)</li> <li>• Time and reasons: <ul style="list-style-type: none"> <li>◦ etanercept: AE (1), lack of efficacy (3)</li> <li>◦ placebo: AE (4), lack of efficacy (9), lost to follow-up (1), patient refusal (1)</li> </ul> </li> </ul>	
Interventions	<p><b>Intervention</b></p> <p>A. Etanercept (n = 57), SC, auto-administered, 25 mg twice a week, 24 weeks</p> <p><b>Control intervention</b></p> <p>B. Placebo (n = 55), SC, auto-administered, twice a week, 24 weeks</p>	
Outcomes	<p>Assessments at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <p>At 4, 8, 12, 24 weeks</p> <ul style="list-style-type: none"> <li>• PASI 50</li> <li>• PASI 75</li> <li>• PASI 90</li> <li>• DLQI</li> <li>• PGA</li> <li>• Safety</li> <li>• Participant global assessment of psoriasis</li> </ul>	
Notes	<p>Funding source, quote (p 1631): "This study was sponsored by Immunex Corp, a subsidiary of Amgen, Inc.)</p> <p>Declarations of interest not stated except "Dr Zitnik is an employee of Amgen" (p1627)</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p 1628): "Patients ... were to be randomised in block of 6 with equal allocation between the treatment group... Patients were assigned numbers based on randomisation tables verified by Immunex

		Pharmaceutical Planning” Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Quote (p 1628): “Patients ... were to be randomised in block of 6 with equal allocation between the treatment group... Patients were assigned numbers based on randomisation tables verified by Immunex Pharmaceutical Planning, after which the Immunex Clinical Distribution Department shaped blind-labelled vials of study drug to the pharmacies” Comment: we don't know whether the investigators were blinded or the numbers of participants per block. This probably was a centralized randomisation; however, it's not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 1628): “... performed blinded labelling and packaging of the study drug. . . . multicenter, randomised, double-blind” Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 1628): “... performed blinded labelling and packaging of the study drug. . . . multicenter, randomised, double-blind” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	High risk	Randomly assigned 112, 112 participants analysed for the primary endpoint <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• Etanercept 4/57 (7.0%), placebo 15/55 (27.3%)</li> <li>• Time and reasons: <ul style="list-style-type: none"> <li>○ etanercept: AE (1), lack of efficacy (3)</li> <li>○ placebo: AE (4), lack of efficacy (9), lost to follow-up (1), patient refusal (1)</li> </ul> </li> </ul> Management of missing data: Quote (1628): “Patients were analysed on an intent-to-treat basis... If a patient discontinued treatment before the end of the study, the last observation was carried forward for efficacy analyses” Comment: high rate of withdrawal in placebo group and imbalanced reasons for withdrawal

**Gottlieb 2003** (Continued)

Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported
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**Gottlieb 2004**

Methods	RCT, placebo-controlled, double blind Date of study: 2001-2003 Location: 24 centres in USA
Participants	<p><b>Randomised:</b> 249 participants (mean age 44 years, 174 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12 or BSA <math>\geq</math> 10), age <math>\geq</math> 18 years</li> <li>• Non-response to phototherapy</li> <li>• Non-response to conventional systemic treatment</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Pregnancy, past history of malignant tumours, active infection</li> </ul> <p><b>Dropouts and withdrawals after a 30-week study period</b></p> <ul style="list-style-type: none"> <li>• 85/249 (34%)</li> </ul> <p><b>Reasons</b></p> <ul style="list-style-type: none"> <li>• AE: infliximab 3 mg (7), infliximab 5 mg (3), placebo (1)</li> <li>• Lack of efficacy: infliximab 3 mg (11), infliximab 5 mg (5), placebo (26)</li> <li>• Other reasons: infliximab 3 mg (12), infliximab 5 mg (10), placebo (10)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Infliximab (n = 99), IV, 3 mg/kg, weeks 0, 2, 6, for 10 weeks</p> <p><b>Control intervention</b></p> <p>B. Infliximab (n = 99), IV, 5 mg/kg, weeks 0, 2, 6, for 10 weeks</p> <p>C. Placebo (n = 51), IV, equivalent, weeks 0, 2, 6, for 10 weeks</p>
Outcomes	<p>Assessments at 10 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI</li> <li>• PGA</li> <li>• DLQI</li> <li>• AEs</li> </ul>
Notes	<p>Funding source, quote (534): "Supported by Centocor Inc"</p> <p>Declarations of interest (p 534): "Drs Gottlieb and Menter have received research support from and served as consultants for Centocor Inc. Drs Baker, Bala, Dooley, Evans, Guzzo, and Marano, and Ms Li, are employees of Centocor Inc. "</p>

*Risk of bias*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p 535): "Randomisation was carried out using adaptive treatment allocation and was stratified by the investigational site" Comment: no description of the method used to generate random sequence
Allocation concealment (selection bias)	Unclear risk	Quote (p 535): "Randomisation was carried out using adaptive treatment allocation and was stratified by the investigational site" Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 535): "Patients and investigators were unaware of treatment assignments. Double blind was achieved and maintained by using an independent pharmacist or staff member to prepare all study infusion" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 535): "Patients and investigators were unaware of treatment assignments. Double blind was achieved and maintained by using an independent pharmacist or staff member to prepare all study infusion" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	249 randomised, 249 analysed Methods for dealing with missing data: Quote (p 536): "All randomised patients were included in the efficacy analysis at week 10... Patients who discontinued... were considered to have not achieved the dichotomous end points or were assigned the baseline value for continuous end points after the event occurrence" Comment: done
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

Methods	RCT, placebo-controlled, double blind Date of study: June 2008-March 2009 Location: 33 centres in the USA
Participants	<b>Randomised:</b> 209 participants (mean age 43.5 years, 145 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PGA <math>\geq</math> 3, PASI <math>\geq</math> 12, BSA <math>\geq</math> 10), age <math>\geq</math> 18 years</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Previous exposure to either etanercept or ABT-874</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• 12/209 (5.7%): etanercept 7, placebo 5</li> <li>• Time and reasons: <ul style="list-style-type: none"> <li>○ Etanercept: AE (4), lost to follow-up (1), protocol violation (1), Other (1)</li> <li>○ Placebo: AE (0), lost to follow-up (4), protocol violation (1)</li> </ul> </li> </ul>
Interventions	<b>Intervention</b> A. Etanercept (n = 141), SC, auto-administered, 50 mg twice a week, 11 weeks <b>Control intervention</b> B. Placebo (n = 68), SC, auto-administered, twice a week
Outcomes	Assessments at 12 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• PASI 75/PGA 0/1</li> </ul> <b>Secondary outcomes of the trial</b> At 4, 8, 12 weeks <ul style="list-style-type: none"> <li>• PASI 50</li> <li>• PASI 75</li> <li>• PASI 90</li> <li>• DLQI (Dermatology Life Quality Index)</li> <li>• PGA</li> <li>• Safety</li> <li>• Patient global assessment of psoriasis</li> </ul>
Notes	Funding source, quote (Appendix 1): “Abbott Laboratories funded this study and participated in the study design, data collection, data management, data analysis and preparation of the manuscript. All of the authors had full access to the data and were involved in the analysis of data, development and revision of the manuscript, and decision to submit the manuscript for publication. The corresponding author takes responsibility for the integrity of the data and the accuracy of the data analysis..)” Declarations of interest, quote (Appendix 1): “A.B.G. has been a consultant or served on an advisory board for Amgen, Centocor, Celgene, Bristol Myers Squibb, Beiersdorf, Abbott, TEVA, Actelion, UCB, Novo Nordisk, Immune Control, DermiPsor, Incyte, PureTech, Magen Biosciences, Cytokine Pharmasciences, Alnylam, Ono, Pfizer, Schering, Canfite, Schering, UCB, BIND Biosciences and Merck, and has received research/educational grants (paid to Tufts Medical Center) from Centocor, Amgen, Immune Control, Abbott, Novo Nordisk, UCB and Novartis. C.L. has been an investigator for Abbott, Allergan, Altana, Alza, Amgen, Astellas, Celgene, Centocor, Genentech, Bristol Myers, Eli Lilly, Galderma, Genzyme, Pfizer, Incyte, CombinatoRx, 3M Pharmaceuti-



	cals, Perrigo Israel Pharmaceutical, ScheringPlough, RTL, Novartis, Vitae and Wyeth; has served on an advisory board and has been a speaker for Abbott, Amgen and Centocor; and has been a consultant for Abbott, Amgen, Centocor and Pfizer. F.K. has been an investigator for Abbott, Centocor, Amgen, Wyeth, Novartis and Merck; and has served on an advisory board and has been a speaker for Abbott, Centocor, Amgen, Eisai, Astellas and Wyeth. S.M. has been an investigator for Abbott, Amgen, Celgene, Centocor, Graceway and Novo Nordisk; and has been a speaker for Abbott. M.O. and D.A.W. are employees of Abbott.”	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote (p 653): “Patients were randomised. ..” Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (p 653): “Patients were randomised” Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 653): “Patients enrolled in the placebo arm received SC injections matching active treatment to maintain the blind. To maintain the blind, all patients received two SC injections at weeks 0 and 4 and one SC injection at week 8, consisting of either briakinumab or matching placebo, depending on the treatment arm. In addition, each patient also received two SC injections biweekly, 3 days apart, week 0 through week 11, consisting of either etanercept or matching placebo, depending on the treatment arm.” Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 653): “Patients enrolled in the placebo arm received SC injections matching active treatment to maintain the blind. To maintain the blind, all patients received two SC injections at weeks 0 and 4 and one SC injection at week 8, consisting of either briakinumab or matching placebo, depending on the treatment arm. In addition, each patient also received two SC injections biweekly, 3 days apart, week 0 through week 11, consisting of either etan-

**Gottlieb 2011** (Continued)

		except or matching placebo, depending on the treatment arm.” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 209, analysed 209 Management of missing data: Quote (p 654): “The primary efficacy analysis consisted of four comparisons performed in the intent-to-treat population (i. e. all randomised patients), . . . , Nonresponder imputation was used to handle missing data.” Comment: done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00691964) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

**Gottlieb 2012**

Methods	RCT, placebo-controlled, double blind Date of study: November 2010-December 2011 Location: Multicentre in Boston/USA
Participants	<b>Randomised:</b> 478 participants (methotrexate: mean age 43 years & 153 male; placebo: mean age 45 years & 167 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (author assessment <math>\geq</math> 6 months or PASI <math>\geq</math> 10 or BSA <math>\geq</math> 10%), age <math>\geq</math> 18 years</li> <li>• Non-response to topical treatment</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Kidney insufficiency, liver insufficiency</li> <li>• Had received biologics</li> <li>• Had received conventional systemic treatments</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• 61/478 (12.8%)</li> <li>• Methotrexate 28/239 (11.7%); placebo 33/239 (13.8%)</li> <li>• Time and reasons : <ul style="list-style-type: none"> <li>○ Methotrexate: AE (10), lost to follow-up (5), ineligibility (4), noncompliance (4), full consent withdrawn (4)</li> <li>○ Placebo: AE (5), lost to follow-up (9) ineligibility (2), noncompliance (7), disease progression (3), full consent withdrawn (5), other (2)</li> </ul> </li> </ul>
Interventions	<b>Intervention</b> A. Methotrexate (n = 239), orally, 15 mg/week 7.5 mg-10 mg to a maximum of 15 mg, 24 weeks + etanercept, SC, 50 mg x 2/weeks, S1-S12 and 50 mg/week, S12-S24, 24

	weeks <b>Control intervention</b> B. Placebo (n = 239), orally, 24 weeks + etanercept, SC, 50 mg x 2/weeks, S1-S12 and 50 mg/week, S12-S24, 24 weeks	
Outcomes	Assessments at 24 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <b>Secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• PASI 75 at 12 weeks</li> <li>• PASI 50 at 12 weeks</li> <li>• PASI 50 at 24 weeks</li> <li>• PASI 90 at 12 weeks</li> <li>• PASI 90 at 24 weeks</li> <li>• PGA at 12 weeks and 24 weeks</li> <li>• BSA at 12 and 24 weeks</li> <li>• AEs</li> <li>• Change of laboratory assessment</li> </ul>	
Notes	Funding source, quote (p 649): “This study was funded by Immunex Corporation, a wholly owned subsidiary of Amgen Inc, and by Wyeth, which was acquired by Pfizer...” Declarations of interest (Appendix): “A.B.G. is a consultant and/or advisory board member for Abbott, Actelion, Amgen, Astellas, Beiersdorf, Bristol-Myers Squibb, Can-Fite, Celgene, Centocor (Janssen), Dermipor, Incyte, Lilly, Merck, Novartis, Novo Nordisk, Pfizer, TEVA, and UCB and is a recipient of research/educational grants paid to Tufts Medical Center by Abbott, Amgen, Celgene, Centocor (Janssen), Immune Control, Novartis, Novo Nordisk, Pfizer, and UCB. R.G.L. has served as an investigator, on the scientific advisory board, and speaker for Abbott, Amgen, Centocor, and Pfizer, and as an advisor and investigator for Celgene, Novartis, and Johnson & Johnson. B.E.S. has served as an advisor, consultant, investigator, and speaker for Abbott, Amgen, and Centocor, and as an advisor, consultant, and investigator for Celgene, Novartis, Maruho, and Pfizer. K.A.P. has been a consultant, advisory board member, and investigator for Abbott, Amgen, Celgene, Centocor, Janssen-Ortho, MedImmune, Merck, Pfizer, Schering-Plough, and Wyeth (Wyeth was acquired by Pfizer in October 2009); has consulted for Astellas and UCB; and has served as a speaker for Abbott, Amgen, Celgene, Janssen-Ortho, Pfizer, Schering-Plough, and Wyeth. P.K., K.C., E.H.Z.T., M.H., and G.K. are employees and stockholders of Amgen Inc.”	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote (p 650): “This was a randomised...” Comment: no description of the method used to guarantee random sequence generation

**Gottlieb 2012** (Continued)

Allocation concealment (selection bias)	Unclear risk	Quote (p 650): “This was a randomised... study” Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 650): “double-blinded placebo-controlled” Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 650): “double-blinded placebo-controlled” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 478, analysed 478 Management of missing data: Quote (p 651): “Efficacy analyses were performed using the ITT set (all randomised patients)... Missing postbaseline data were imputed using last observation carried forward for primary analyses of all efficacy endpoints...” Comment: done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01001208) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

**Griffiths ACCEPT, 2010**

Methods	RCT, active-controlled, open-label trial Date of study: 26 March 2007-15 January 2009 Location: 67 centres in Manchester/UK
Participants	<b>Randomised:</b> 903 participants (mean age 45 years, 613 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis</li> <li>• Authors’ assessment &gt; 6 months, PASI ≥ 12, PGA &gt; 3, BSA &gt; 10%</li> <li>• Age ≥ 18 years</li> <li>• Non-response to phototherapy</li> <li>• Non-response to conventional systemic treatment</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Had received biologics</li> <li>• Had an active infection</li> <li>• Had past history of malignant tumours</li> </ul> <b>Dropouts and withdrawals</b>

	<ul style="list-style-type: none"> <li>• 24/903 (2.7%)</li> <li>• Ustekinumab 45 mg (8): AE (2), lost to follow-up (2), other (4)</li> <li>• Ustekinumab 90 mg (5): AE (1), lost to follow-up (2), other (2)</li> <li>• Etanercept (11): AE (5), lost to follow-up (1), other (5)</li> </ul>	
Interventions	<p><b>Intervention</b></p> <p>A. Ustekinumab (n = 209), SC, 45 mg, weeks 0-4, 4 weeks</p> <p><b>Control intervention</b></p> <p>B. Ustekinumab (n = 347), SC, 90 mg, weeks 0-4, 4 weeks</p> <p>C. Etanercept (n = 347), SC, 50 mg x 2/weeks, 12 weeks</p>	
Outcomes	<p>Assessments at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• Number of participants PGA 0/1 at week 12</li> <li>• PASI 90 at weeks 8-12</li> <li>• Difference PASI at week 12 and 12 weeks after retreatment on recurrence of psoriasis</li> <li>• AEs</li> </ul>	
Notes	<p>Funding, quote (p 127): “Supported by Centocor Research and Development.”</p> <p>Declarations of interest (p 127) “Dr. Griffiths reports receiving consulting and lecture fees from Abbott, Janssen-Cilag, Merck Serono, Novartis, Schering-Plough, and Wyeth and grant support from Merck Serono; Dr. Strober, receiving consulting and lecture fees from Centocor, Johnson &amp; Johnson, Amgen, and Abbott Laboratories and grant support from Amgen and Abbott Laboratories; Dr. van de Kerkhof, receiving consulting fees from Schering-Plough, Celgene, Centocor, Almirall, UCB, Wyeth, Pfizer, Soffinova, Abbott, Actelion, Galderma, Novartis, Janssen-Cilag, and Leo Pharma; Dr. Ho, receiving advisory-board and lecture fees from Schering, Abbott, Janssen-Ortho, Pfizer, Amgen, and Wyeth and grant support from Centocor, Abbott, Amgen, and Wyeth; Dr. Menter, receiving advisory-board, consulting, and lecture fees from Abbott, Amgen, Astellas, Biogen Idec, Celgene, Centocor, Genentech, Warner Chilcott, and Wyeth; Drs. Yeilding, Guzzo, Xia, and Dooley and Ms. Li, being employees of Johnson &amp; Johnson and having equity and holding stock options in Johnson &amp; Johnson; Dr. Zhou, being an employee of Johnson &amp; Johnson, having equity and holding stock options in Johnson &amp; Johnson, and having equity in Wyeth; Dr. Fidelus-Gort, being a former employee of Johnson &amp; Johnson and having equity and holding stock options in Johnson &amp; Johnson; and Dr. Goldstein, receiving consulting fees from Centocor. No other potential conflict of interest relevant to this article was reported.”</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote (p 119): “We randomly assigned...” Comment: no description of the method used to guarantee random sequence generation

Allocation concealment (selection bias)	Unclear risk	Quote (p 119): “We randomly assigned...” Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (p 119): “Patients were aware of their treatment assignment”, ... “All study personnel, except those who dispensed or administered a study agent remained unaware of the treatment assignments” Comment: high risk for participants and unclear risk for personnel (no description of means used to avoid communication between participants and personnel and very difficult to avoid)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (p 119): “All study personnel, except those who dispensed or administered a study agent remained unaware of the treatment assignments” Comment: no description of the method used to assess the primary outcome
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	903 participants underwent randomisation, 903 were analysed Comment: methods for dealing with missing data not specified
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00454584) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

Griffiths UNCOVER-2, 2015

Methods	RCT, active, placebo-controlled, double blind Date of study: 10 May 2012-7 May 2015 Location: 118 centres in Europe, Australia, North America
Participants	<b>Randomised:</b> 1224 participants (mean age 45 years, 821 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12 or BSA <math>\geq</math> 10), age <math>\geq</math> 18 years</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Pregnancy, immunosuppression, kidney insufficiency, liver insufficiency, past history of malignant tumours, active infection, uncontrolled cardiovascular disorder, uncontrolled diabetes, uncontrolled hypertension</li> </ul>

	<ul style="list-style-type: none"> <li>• Had received etanercept and anti IL17</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 63/1224 (5%)</li> <li>• Ixekizumab 4-week group (19), ixekizumab 2-week group (9), etanercept group (25), placebo (10)</li> <li>• AEs: ixekizumab 4-week group (5), ixekizumab 2-week group (4), etanercept (5), placebo (1)</li> <li>• Protocol violation: ixekizumab 4-week group (5), ixekizumab 2-week group (2), etanercept (4), placebo (2)</li> <li>• Participant decision: ixekizumab 4-week group (6), ixekizumab 2-week group (2), etanercept (8), placebo (1)</li> <li>• Lost to follow-up: ixekizumab 4-week group (2), ixekizumab 2-week group (0), etanercept (5), placebo (1)</li> <li>• Investigator decision: ixekizumab 4-week group (0), ixekizumab 2-week group (1), etanercept (0), placebo (1)</li> <li>• Absence of efficacy: ixekizumab 4-week group (1), ixekizumab 2-week group (0), etanercept (3), placebo (3)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Ixekizumab (n = 347), SC, 80 mg, 2 injections week 0, 1 injection monthly</p> <p><b>Control intervention</b></p> <p>B. Ixekizumab (n = 351), SC, 80 mg, 2 injections week 0, 1 injection eow</p> <p>C. Etanercept (n = 358), SC, 50 mg 1 injection twice weekly</p> <p>D. Placebo (n = 168), SC</p>
Outcomes	<p>Assessments at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PGA 0-1</li> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 90</li> <li>• DLQI</li> <li>• AEs</li> </ul>
Notes	<p>Funding source:</p> <p>Quote (p 543): “The funder Eli Lilly. Data were collected by investigators, gathered by Parexel International, and analysed by the funder”. agents and collected and analysed the data. All the authors had full access to the data”</p> <p>Declarations of interest, Quote (p 550-551): ”CEMG has received grants and personal fees from Eli Lilly, Abbvie, Janssen, Novartis, Sandoz, Pfizer, and GlaxoSmithKline; personal fees from Actelion, Amgen, and UCB Pharma; grants from LEO Pharma and Merck Sharp &amp; Dohme; and is president of the International Psoriasis Council. KR has received personal fees from AbbVie, Amgen, Biogen, Celgene, Forward Pharma, Janssen-Cilag, LEO Pharma, Eli Lilly, Medac, Merck Sharp &amp; Dohme, Novartis, Pfizer, Regeneron, and Takeda. ML is an employee of the Mount Sinai Medical Center which receives research funds from AbGenomics, AbbVie, Amgen, Anacor, Aqua, Canfit Biopharma, Celgene, Clinuvel, Coronado Biosciences, Ferndale, Lilly, Janssen Biotech, LEO Pharmaceuticals, Merz, Novartis, Pfizer, Sandoz, and Valeant. PvdK has received grants from Celgene, Centocor, Allmiral, Pfizer, Philips, AbbVie, Eli Lilly, Galderma, Novar-</p>

tis, Janssen Cilag, and Leo Pharma; and has served as a speaker for Amgen, a consultant for Sandoz and Mitisibishu, and a speaker and consultant for Celgene, AbbVie, Eli Lilly, Galderma, Novartis, Janssen Cilag, and Leo Pharma. CP has received grants and personal fees from Amgen, Abbvie, Celgene, Eli Lilly, Novartis, Janssen, Pfizer, and Leo Pharma. KP has received honoraria as consultant and/or scientific officer and/or advisory board and/or steering committee member and/or acted as a paid speaker and/or participated in clinical trials and/or received clinical research grants sponsored by 3M, Abbott/AbbVie, Akesis, Akros, Allergan, Alza, Amgen, Anacor, Apotex, Astellas, Baxter, Berlex, Biogen, Boehringer Ingelheim, Celgene, Celtic, Centocor, Cipher, Dermira, Dow Pharma, Eli Lilly, Forward Pharma, Fujisawa, Funxional Therapeutics, Galderma, Genentech, Genexion, GlaxoSmithKline, Isotechnika, Janssen, Janssen Biotech, Johnson & Johnson, Kataka, Kirin, Kyowa, Leo Pharma, Lypanosys, Medical Minds, Medimmune, Merck, Mitsubishi, Novartis, NovImmune, Pan Genetics, Pfizer, Roche, Regneron, Merck-Serono, Stiefel, Takeda, UCB, Vertex, Wyeth/Pfizer, and Xoma. AM has served as an advisory board member and/or consultant and/or investigator and/or speaker and/or received compensation in the form of grants and/or honoraria from AbbVie, Allergan, Amgen, ApoPharma, Boehringer Ingelheim, Celgene, Convoy Therapeutics, Eli Lilly, Genentech, Janssen Biotech, LEO Pharma, Merck, Novartis, Pfizer, Symbio and Maruho, Syntrix, Wyeth, and XenoPort. GSC, JE, LZ, RJS, SB, DKB, OOO, MPH, and BJN were employees of and hold stock in Eli Lilly & Co during the conduct of this study. “

**Risk of bias**

<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p 542): “randomly assigned”, “An interactive voice response system” Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 542): “An interactive voice response system was used to assign double-blind investigational product to every patient. Site personnel confirmed that they had located the correct assigned investigational product package by entering a confirmation number found in the package into to IVRS” Comment: clearly defined
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 542): “Patients, investigators and study personnel were masked to the treatment allocation. A double-dummy design was used” Comment: clearly defined
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 542): “Patients, investigators and study personnel were masked to the treatment allocation. A double-dummy design



Griffiths UNCOVER-2, 2015 (Continued)

		was used” Comment: clearly defined
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 1224, analysed 1224 Management of missing data: Quote (p 543): “All missing data were imputed using non-responder imputation (NRI)” Comment: probably done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01597245) One pre-specified outcome in the protocol missing from the results section (assessment of efficacy at 60 weeks); however, as we assessed outcomes at induction phase (between 8-24 weeks), we judged that the risk of selective reporting was low

Griffiths UNCOVER-3, 2015

Methods	RCT, active, placebo-controlled, double blind Date of study: 18 July 2012-18 January 2016 Location: 101 in Europe, Asia, North and South America
Participants	<p><b>Randomised:</b> 1346 participants (mean age 46 years, 918 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12 or BSA <math>\geq</math> 10), age <math>\geq</math> 18 years</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Pregnancy, immunosuppression, kidney insufficiency, liver insufficiency, past history of malignant tumours, active infection, uncontrolled cardiovascular disorder, uncontrolled diabetes, uncontrolled hypertension</li> <li>• Had received etanercept and anti IL17</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 71/1346 (5%)</li> <li>• Ixekizumab 4-week group (10), ixekizumab 2-week group (13), etanercept group (26), placebo (22)</li> <li>• AEs: ixekizumab 4-week group (9), ixekizumab2-week group (8), etanercept (4), placebo (2)</li> <li>• Protocol violation: ixekizumab 4-week group (8), ixekizumab2-week group (7), etanercept (3), placebo (1)</li> <li>• Participant decision: ixekizumab 4-week group (4), ixekizumab2-week group (4), etanercept (2), placebo (3)</li> <li>• Lost to follow-up: ixekizumab 4-week group (2), ixekizumab2-week group (0), etanercept (2), placebo (3)</li> <li>• Investigator decision: ixekizumab 4-week group (1), ixekizumab2-week group (1),</li> </ul>

	<p>etanercept (2), placebo (1)</p> <ul style="list-style-type: none"> <li>● Absence of efficacy: ixekizumab 4-week group (2), ixekizumab2-week group (1), etanercept (0), placebo (0)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Ixekizumab (n = 386), SC, 80 mg, 2 injections week 0, 1 injection monthly</p> <p><b>Control intervention</b></p> <p>B. Ixekizumab (n = 385), SC, 80 mg, 2 injections week 0, 1 injection eow</p> <p>C. Etanercept (n = 382), SC, 50 mg 1 injection twice weekly</p> <p>D. Placebo (n = 193), SC</p>
Outcomes	<p>Assessments at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>● PGA 0-1</li> <li>● PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>● PASI 90</li> <li>● DLQI</li> <li>● AEs</li> </ul>
Notes	<p>Funding source: quote (p 543): “The funder Eli Lilly. Data were collected by investigators, gathered by Parexel International, and analysed by the funder”. agents and collected and analysed the data. All the authors had full access to the data”</p> <p>Declarations of interest: quote (p 550-551): ”CEMG has received grants and personal fees from Eli Lilly, Abbvie, Janssen, Novartis, Sandoz, Pfizer, and GlaxoSmithKline; personal fees from Actelion, Amgen, and UCB Pharma; grants from LEO Pharma and Merck Sharp &amp; Dohme; and is president of the International Psoriasis Council. KR has received personal fees from AbbVie, Amgen, Biogen, Celgene, Forward Pharma, Janssen-Cilag, LEO Pharma, Eli Lilly, Medac, Merck Sharp &amp; Dohme, Novartis, Pfizer, Regeneron, and Takeda. ML is an employee of the Mount Sinai Medical Center which receives research funds from AbGenomics, AbbVie, Amgen, Anacor, Aqua, Canfite Biopharma, Celgene, Clinuvel, Coronado Biosciences, Ferndale, Lilly, Janssen Biotech, LEO Pharmaceuticals, Merz, Novartis, Pfizer, Sandoz, and Valeant. PvdK has received grants from Celgene, Centocor, Allmiral, Pfizer, Philips, AbbVie, Eli Lilly, Galderma, Novartis, Janssen Cilag, and Leo Pharma; and has served as a speaker for Amgen, a consultant for Sandoz and Mitisibishu, and a speaker and consultant for Celgene, AbbVie, Eli Lilly, Galderma, Novartis, Janssen Cilag, and Leo Pharma. CP has received grants and personal fees from Amgen, Abbvie, Celgene, Eli Lilly, Novartis, Janssen, Pfizer, and Leo Pharma. KP has received honoraria as consultant and/or scientific officer and/or advisory board and/or steering committee member and/or acted as a paid speaker and/or participated in clinical trials and/or received clinical research grants sponsored by 3M, Abbott/AbbVie, Akesis, Akros, Allergan, Alza, Amgen, Anacor, Apotex, Astellas, Baxter, Berlex, Biogen, Boehringer Ingelheim, Celgene, Celtic, Centocor, Cipher, Dermira, Dow Pharma, Eli Lilly, Forward Pharma, Fujisawa, Funxional Therapeutics, Galderma, Genentech, Genexion, GlaxoSmithKline, Isotechnika, Janssen, Janssen Biotech, Johnson &amp; Johnson, Kataka, Kirin, Kyowa, Leo Pharma, Lypanosys, Medical Minds, Medimmune, Merck, Mitsubishi, Novartis, NovImmune, Pan Genetics, Pfizer, Roche, Regneron, Merck-Serono, Stiefel, Takeda, UCB, Vertex, Wyeth/Pfizer, and Xoma. AM has served as an advisory board member and/or consultant and/or investigator and/or</p>

	speaker and/or received compensation in the form of grants and/or honoraria from AbbVie, Allergan, Amgen, ApoPharma, Boehringer Ingelheim, Celgene, Convoy Therapeutics, Eli Lilly, Genentech, Janssen Biotech, LEO Pharma, Merck, Novartis, Pfizer, Symbio and Maruho, Syntrix, Wyeth, and XenoPort. GSC, JE, LZ, RJS, SB, DKB, OOO, MPH, and BJN were employees of and hold stock in Eli Lilly & Co during the conduct of this study. “	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p 542): “randomly assigned” “An interactive voice response system” Comment: probably done”
Allocation concealment (selection bias)	Low risk	Quote (p 542): “An interactive voice response system was used to assign double-blind investigational product to every patient. Site personnel confirmed that they had located the correct assigned investigational product package by entering a confirmation number found in the package into to IVRS” Comment: clearly defined
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 542): “Patients, investigators and study personnel were masked to the treatment allocation. A double-dummy design was used” Comment: clearly defined
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 542): “Patients, investigators and study personnel were masked to the treatment allocation. A double-dummy design was used” Comment: clearly defined
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 1346, analysed 1346 Management of missing data: Quote (p 543): “All missing data were imputed using non-responder imputation (NRI)” Comment: probably done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01646177) One pre-specified outcome in the protocol missing from the results section (assess-

		ment of efficacy at 60 weeks); however, as we assessed outcomes at induction phase (between 8-24 weeks), we judged that the risk of selective reporting was low
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**Gurel 2015**

Methods	RCT, placebo-controlled, single blind Date of study: not stated Location: one centre, Turkey	
Participants	<b>Randomised:</b> 50 participants (mean age 43 years, 25 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>Moderate-severe type plaque psoriasis BSA &gt; 10%</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>Pregnancy</li> <li>Had uncontrolled cardiovascular disorder</li> <li>Kidney or liver insufficiencies</li> <li>Had past history of malignant tumours</li> <li>Had received conventional systemic treatments</li> </ul> <b>Dropouts</b> No participants lost to follow-up	
Interventions	<b>Intervention</b> Acitretine (0.3-0.5 mg/kg/day, 25 mg) (n = 25) <b>Control intervention</b> Placebo (n = 25) Co-intervention NBUVB	
Outcomes	Assessment at 12 weeks <b>Primary outcome</b> <ul style="list-style-type: none"> <li>Not stated</li> </ul> <b>Outcomes:</b> <ul style="list-style-type: none"> <li>Change in PASI scores from baseline</li> <li>Change in self-PASI scores from baseline</li> <li>Skindex 30</li> </ul>	
Notes	Funding: none Declarations of interest: none	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description

**Gurel 2015** (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (p 3): “The physicians were not blinded” Comment: high risk of performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 3): “An independent assessor who is not from the team performed the outcome assessment.” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomized 50, analysed 50, no loss to follow-up during the 12 weeks Comment: probably done
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

**Heydendael 2003**

Methods	RCT, active-controlled, open-label trial Date of study: October 1998-June 2000 Location: multicentre (> 1) in Amsterdam/the Netherlands
Participants	<p><b>Randomised:</b> 88 participants, mean age 40 years, 57 male</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis, PASI&gt;8,</li> <li>• Age ≥18</li> <li>• Non-response to topical treatment</li> <li>• Non-response to phototherapy</li> <li>• Number of allowed previous treatment line: 2</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Pregnancy, kidney insufficiency, liver insufficiency, high-risk liver function abnormalities, hepatitis B</li> <li>• Had received methotrexate or ciclosporin</li> <li>• Had an active infection</li> <li>• Had uncontrolled diabetes (Insulino dependent)</li> <li>• Had uncontrolled cardiovascular disorder</li> <li>• Had uncontrolled hypertension</li> <li>• Had past history of malignant tumours</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 3/88 (3.4%)</li> <li>• Methotrexate group (1): withdrew consent (1)</li> <li>• Ciclosporin group (2): ineligible (2)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Methotrexate (n = 44), orally, 15 mg/week until 4 weeks then increase up to 22.5 mg if reduction from baseline PASI &lt; 25%, 3 divided doses with 12-h interval, 12 weeks</p>

	<b>Control intervention</b> B. Ciclosporin (n = 44), orally, 3 mg/kg until 4 weeks then increase up to 5 mg/kg if reduction from baseline PASI < 25%, 2 divided doses, 12 weeks	
Outcomes	Assessments at weeks 16 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"><li>• PASI</li></ul> <b>Secondary outcomes of the trial</b> <ul style="list-style-type: none"><li>• Side effects</li><li>• SF36</li></ul>	
Notes	Funding sources, quote (p 664): "Supported by a grant (OG 97-009) from the Dutch Health Authorities" Declarations of interest: not stated	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p 660): "Randomisation was performed centrally with the use of computer-generated random numbers and block size of eight patients" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 660): "Randomisation was performed centrally with the use of computer-generated random numbers and block size of eight patients" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (p 660): "The score of the PASI ... was determined... by trained assessors who were unaware of the treatment assignment" Comment: no description of method used to guarantee no communication between care givers or participants and assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	88 randomised, 85 analysed Quote (p 660-1): "If a patient missed a visit, we used the score from the previous visit" Comment: few lost to follow-up, well-balanced number and reasons between groups

Heydendael 2003 (Continued)

Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported
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Hunter 1963

Methods	RCT, placebo-controlled, double-blind trial Date of study: not stated Location: 1 centre in London	
Participants	<b>Randomised:</b> 41 participants (no description of the study population) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Not stated</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• included (41) analysed (36)</li> </ul>	
Interventions	<b>Intervention</b> A. Methotrexate (n = 19), orally, 2.5 mg every day for 1 week and 1 week after <b>Control intervention</b> B. Placebo (n = 17), orally, every day for 1 week and 1 week after	
Outcomes	Assessments not clearly stated (reported at 4 weeks) <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• Not stated</li> </ul> <b>Outcomes of the trial</b> <ul style="list-style-type: none"> <li>• Scale: <ul style="list-style-type: none"> <li>○ 0 = no improvement</li> <li>○ 1 = definite improvement</li> <li>○ 2 = marked improvement</li> <li>○ 3 = complete clearing</li> </ul> </li> </ul>	
Notes	Funding: not stated Declarations of interest: not stated	

*Risk of bias*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no description of the method used to guarantee random sequence generation

**Hunter 1963** (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 1 & 2): "Control tablet of identical appearance... thus neither physician, patient nor pharmacist was aware whether drug or control had been dispensed" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 1 & 2): "Control tablet of identical appearance... thus neither physician, patient nor pharmacist was aware whether drug or control had been dispensed" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	41 randomised participants and 38 analysed Comment: no description of the method used to manage missing data Not ITT analyses
Selective reporting (reporting bias)	High risk	No pre-specified outcomes mentioned in the methods section

**Igarashi 2012**

Methods	RCT, placebo-controlled, double-blind trial Date of study: March 2008-March 2010 Location: 35 centres in Japan
Participants	<p><b>Randomised:</b> 160 participants (age median 45 years, 126 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis</li> <li>• Authors' assessment &gt; 6 months, PASI <math>\geq</math> 12, BSA &gt; 10%</li> <li>• Age &gt; 20 years</li> <li>• Non-response to topical treatment</li> <li>• Non-response to phototherapy</li> <li>• Number of allowed previous treatment line: 2</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Pregnancy</li> <li>• Had an active infection</li> <li>• Had past history of malignant tumours</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 10/160 (6.2%)</li> <li>• Withdrawn before treatment (2)</li> <li>• Ustekinumab 45 mg group (64): discontinued (0)</li> <li>• Ustekinumab 90 mg group (62): discontinued (4)</li> <li>• Placebo (32): discontinued (4)</li> </ul>



Interventions	<b>Intervention</b> A. Ustekinumab (n = 64), SC, 45 mg, weeks 0-4, every 12 weeks, 64 weeks <b>Control intervention</b> B. Ustekinumab (n = 62), SC, 90 mg, weeks 0-4, every 12 weeks, 64 weeks C. Placebo (n = 32), SC, weeks 0-4, every 12 weeks, 64 weeks	
Outcomes	Assessments at 12 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <b>Secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• Proportion of participants with PGA 0/1 at week 12</li> <li>• Change in DLQI from baseline at 12 weeks</li> <li>• Improvement from baseline to week 12 through 64 in NAPS and joint pain, as measured by the change in VAS</li> </ul>	
Notes	Funding source, quote (p 242): "This study was supported by Janssen pharmaceutical KK, a part of the Johnson & Johnson family of companies Declarations of interest (p 242): "Igarashi has served as a consultant and speaker for Janssen Pharmaceutical K.K.; H. Nakagawa has served as a consultant for Abbott Japan and Tanabe Mitsubishi, and as a consultant and speaker for Janssen Pharmaceutical K. K.; M. Song is an employee of Centocor Research & Development, Inc., a division of Johnson & Johnson Pharmaceutical Research & Development, L.L.C., and owns stock in Johnson & Johnson; T. Kato and M. Kato are employees of Janssen Pharmaceutical K.K. and own stock in Johnson & Johnson."	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote (p 244): "randomised" Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (p 244): "randomised" Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 243): "double-blind placebo-control" Comment: used a placebo without visible side effect
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 243): "double-blind placebo-control" Comment: used a placebo without visible side effect

Igarashi 2012 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	160 randomised, 157 analysed (2 did not receive a dose of the drug and 1 was excluded in the placebo group due to lack of efficacy data after receiving a single dose) Methods for dealing with missing data Quote (p 244): "Efficacy analyses were based on all randomised patients with efficacy data after randomisation... Patients who discontinued the study... were considered as treatment failures" Comment: few lost of follow-up, well-balanced number and reasons between groups
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available The pre-specified outcomes mentioned in the methods section appeared to have been reported

Jacobe 2008

Methods	RCT, placebo-controlled, double blind Date of study: not stated Location: not stated
Participants	<b>Randomised:</b> 16 participants (mean age 50 years, 11 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (authors' assessment)</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Not stated</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• 1/16 (6%)</li> <li>• Non compliance before initiating treatment (1)</li> </ul>
Interventions	<b>Intervention</b> A. Alefacept (n = 8), IM, 15 mg, once a week, 12 weeks <b>Control intervention</b> B. Placebo (n = 8), IM, once a week, 12 weeks <b>Co-intervention:</b> UVB 3 times/week, 12 weeks
Outcomes	Assessments at 12 weeks <b>Primary or secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• Unclear</li> </ul> <b>Outcomes of the trial</b> <ul style="list-style-type: none"> <li>• -PASI</li> </ul>
Notes	Funding source (p 1068): "Biogen/IDEC provided alefacept and NB UVB for this study" Declarations of interest (p 1068): "none reported"

Jacobe 2008 (Continued)

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p 1067): "randomised... study" Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (p 1067): "randomised... study" Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 1067) 'double-blind study... placebo' Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no description of the method used to guarantee blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	Randomized (16), analysed (15) Comment: no description of the method used to manage the missing data, no ITT analyses
Selective reporting (reporting bias)	High risk	Comment: no pre-specified outcomes mentioned in the methods section except PASI score. In the results section, safety, biological data are reported

Krueger 2002

Methods	RCT, placebo-controlled, double blind Date of study: 21 November 1999-22 March 2001 Location: 51 centres in USA/Canada
Participants	<p><b>Randomised:</b> 553 participants analysed (mean age 45 years, 387 male) out of 569 patients randomised</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (BSA <math>\geq</math> 10)</li> <li>• Age <math>\geq</math> 16</li> <li>• Non-response to phototherapy</li> <li>• Non-response to conventional systemic treatment</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Pregnancy</li> <li>• Had an active infection</li> </ul> <p><b>Dropouts and withdrawals</b></p>

**Krueger 2002** (Continued)

	<ul style="list-style-type: none"> <li>• 79/569 (10%)</li> <li>• 16 excluded from analysis: 7 at 1 site because of poor compliance and 9 who were not dosed</li> <li>• 9 lost to follow-up: alefacept (3), placebo (6)</li> <li>• 13 disease worsening: alefacept (8), placebo (5)</li> <li>• 8 AEs: alefacept (7), placebo (1)</li> <li>• 29 by request: alefacept (10), placebo (19)</li> <li>• 4 other; alefacept (3), placebo (1)</li> </ul>
Interventions	<p><b>Intervention</b> A. Alefacept (n = 367), IV, 7.5 mg, once a week, 12 weeks</p> <p><b>Control intervention</b> B. Placebo (n = 186), IV, once a week, 12 weeks</p>
Outcomes	<p>Assessments at 14 weeks</p> <p><b>Primary or secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PGA clear or almost clear</li> <li>• PASI 50</li> <li>• AEs</li> </ul>
Notes	<p>Funding source, quote (p 821): “This study was funded by Biogen, Inc, Cambridge, Massachusetts”</p> <p>Declarations of interest p 821): “A patent on the use of alefacept for the treatment of psoriasis has been assigned to Biogen and the University of Michigan. None of the authors have a financial interest in the patent. Gerald G. Krueger, MD, Kim A. Papp, MD, and Charles N. Ellis, MD, are consultants to Biogen, as well as to other companies that have and are developing treatments for psoriasis.”</p>

***Risk of bias***

<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote (p 822): “ This was a randomised... ” Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (p 822): “ This was a randomised... ” Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 823): “... The active drug and placebo were visually indistinguishable from each other, and the injection volume was consistent. Physician who had no

**Krueger 2002** (Continued)

		contact with the patient, ... A pharmacist who had no contact with the patient... The physician and the pharmacist were instructed not to communicate any information to the examining physicians....” Comment: use of a placebo with no major side effects
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 823): “An examining physician administered the study drug” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	569 included/557 analysed (comment: 16 participants excluded, 7 because of poor compliance and 9 were not dosed) Quote (p 825): “Analyses of efficacy end points ... were based on the intent-to-treat population, which included patients who were randomised had a baseline assessment and had at least 1 injection” Methods for dealing with missing data: not stated Comment: not modified ITT (7 participants excluded because of poor compliance) however 7/557 low rate
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

**Krueger 2007**

Methods	RCT, placebo-controlled, double-blind trial Date of study: June 2003-March 2005 Location: 46 centres in Utah, USA
Participants	<b>Randomised:</b> 320 participants Ustekinumab 12/23 45 mg (64) (mean age 46 years; 38 male) Ustekinumab 12/23 90 mg (64) (mean age 46 years; 47 male) Ustekinumab 12/23 45 mg 4-weekly (64) (mean age 45 years; 39 male) Ustekinumab 12/23 90 mg 4-weekly (64) (mean age 44 years; 52 male) Placebo (64) (mean age 44 years; 46 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis</li> <li>• Authors’ assessment &gt; 6 months, PASI ≥ 12, BSA &gt; 10%</li> <li>• Age ≥ 18</li> </ul> <b>Exclusion criteria</b>

	<ul style="list-style-type: none"> <li>• Had received biologics (ustekinumab 12/23)</li> <li>• Had an active infection</li> <li>• Had past history of malignant tumours</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 32/320 (8.8%)</li> <li>• Ustekinumab 12/23 45 mg (7) (received no treatment (1) unsatisfactory therapeutic effect (2) AE (5))</li> <li>• Ustekinumab 12/23 90 mg (4) (received no treatment (1), other (3))</li> <li>• Ustekinumab 12/23 45 mg 4-weekly (3) (AE (2), withdrew consent (1))</li> <li>• Ustekinumab 12/23 90 mg 4-weekly (4) (unsatisfactory therapeutic effect (1), AE (1), withdrew consent (1), other (1))</li> <li>• Placebo (13) (unsatisfactory therapeutic effect (6), lost to follow-up (1), withdrew consent (2), other (4))</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Ustekinumab 12/23 (n = 64), SC, 45 mg, 45 mg 1 dose, 1 week</p> <p><b>Control intervention</b></p> <p>B. Ustekinumab 12/23 (n = 64), SC, 90 mg, 45 mg 1 dose, 1 week</p> <p>C. Ustekinumab 12/23 (n = 64), SC, 45 mg, 45 mg/week, 4 weeks</p> <p>D. Ustekinumab 12/23 (n = 64), SC, 90 mg, 45 mg/week, 4 weeks</p> <p>E. Placebo (n = 64), SC</p>
Outcomes	<p>Assessments at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• Proportion of participants achieving <math>\geq</math> PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• Safety</li> <li>• PGA</li> <li>• DLQI</li> </ul>
Notes	<p>Funding source (p 590): "Supported by Centocore, Malvern, PA"</p> <p>Declarations of interest (p 590-1): "Dr. Krueger reports receiving fees as a consultant or advisory board member for Abbott, Almirall, Alza, Amgen, Astellas, Boehringer Ingelheim, Barrier Therapeutics, Bristol-Myers Squibb, Centocor, Connetics, and Genentech; Dr. Langley, for Centocor, Abbott, and Amgen/Wyeth; Dr. Leonardi, for Abbott, Amgen, Centocor, and Genentech; and Dr. Lebwohl, for Abbott, Amgen, Astellas, Centocor, Connetics, Galderma, Genentech, Novartis, PharmaDerm, and Warner Chilcott. Dr. Krueger reports receiving lecture fees from Abbott, Amgen, Boehringer Ingelheim, Centocor, and Connetics; Dr. Langley, from Abbott and Amgen/ Wyeth; Dr. Leonardi, from Abbott, Amgen, Centocor, and Genentech; and Dr. Lebwohl, from Abbott, Astellas, Amgen, Centocor, Connetics, Galderma, Genentech, PharmaDerm, and Warner Chilcott. Dr. Krueger reports receiving stipends for a clinical research fellowship from Amgen and Centocor; Dr. Langley, grant support from Centocor, Abbott, and Amgen/ Wyeth; Dr. Leonardi, educational grants from Amgen and Genentech; and Dr. Lebwohl, grants from Abbott, Amgen, Astellas, Centocor, Connetics, Galderma, Genentech, PharmaDerm, and Warner Chilcott. Drs. Yeilding, Guzzo, Wang, and Dooley report being employees of Centocor. Dr. Krueger reports owning stock options from ZARS Pharma; Drs. Yeilding, Guzzo, and Dooley report holding stock and stock options in Johnson &amp; Johnson; and Dr. Wang reports being a stockholder in Johnson &amp; Johnson. No other</p>

potential conflict of interest relevant to this article was reported.”		
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote (p 581): “Patients ... were randomly assigned” Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (p 581): “Patients ... were randomly assigned” Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 581): “This placebo-controlled, double-blind...phase 2 study” Comment: placebo controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 581): “This placebo-controlled, double-blind...phase 2 study” Comment: no specific description of the method used to guarantee blinding of outcome assessment however considering that this is a placebo-controlled trial with no known systematic AEs we considered the risk as low
Incomplete outcome data (attrition bias) All outcomes	Low risk	320 included/320 analysed Quote (p 582): “Efficacy data from all patients who underwent randomisation were analysed... Missing values at week 12 were replaced with the most recently available values for all efficacy variables, missing data at other time points were not imputed” Comment: done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00320216) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

**Krueger 2016**

Methods	RCT, placebo-controlled, double blind Date of study: March 2013-November 2013 Location: 6 centres in the USA	
Participants	<p><b>Randomised:</b> 12 participants (mean age 45.5 years, 8 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12 or BSA <math>\geq</math> 10), age <math>\geq</math> 18 years</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Pregnancy, immunosuppression, kidney insufficiency, liver insufficiency, past history of malignant tumours, active infection, uncontrolled cardiovascular disorder, uncontrolled diabetes, uncontrolled hypertension</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 1/12 (1%);</li> <li>• Lost to follow-up: tofacitinib (1)</li> </ul>	
Interventions	<p><b>Intervention</b></p> <p>A. Tofacitinib (n = 9), orally, 10 mg twice daily</p> <p><b>Control intervention</b></p> <p>B. Placebo (n = 3)</p>	
Outcomes	<p>Assessments at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PGA 0-1</li> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• AEs</li> </ul>	
Notes	<p>Funding source:</p> <p>Quote (p 1079): “This study was sponsored by Pfizer Inc. Both Pfizer Inc and non-Pfizer Inc authors have participated in the study design, data collection, data analysis, and open scientific discussion of the data; its interpretation; and the development of the associated manuscript. The views and opinions expressed within the manuscript are those of all authors and do not necessarily represent those of the funding organization. Medical writing support was funded by Pfizer Inc.”</p> <p>Declarations of interest (p 1079) : “J. Krueger received research funding from Novartis, Pfizer Inc, Janssen, Lilly, Merck, Kadmon, Dermira, Boehringer, BMS, and Paraxel during the conduct of the study; grants paid to institutions from Amgen, Innovaderm and Kyowa; and personal fees from Serono, BiogenIdec, Delenex, AbbVie, Sanofi, Baxter, Xenoport, and Kineta. M. Suárez-Fariñas receives research funding and speakers’ fees from Pfizer. J. D. Clark, H. Tan, R. Wolk, S. T. Rottinghaus, M. Z. Whitley, H. Valdez, D. von Schack, S. P. O’Neil, P. S. Reddy, and S. Tatulich are employees of Pfizer Inc. The rest of the authors declare that they have no relevant conflicts of interest.”</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>



**Krueger 2016** (Continued)

Random sequence generation (selection bias)	Low risk	Quote (p 1079): “Patients were randomised 3:1 to receive 10 mg of oral tofacitinib or placebo twice daily for 12 weeks by using an automated Web or telephone randomization system” Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 1079): “Patients were randomised 3:1 to receive 10 mg of oral tofacitinib or placebo twice daily for 12 weeks by using an automated Web or telephone randomisation system” Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 1079): “This was a phase 2, randomised, placebo-controlled, double-blind study carried out in 6 centers” Comment: placebo-controlled, probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 1079): “This was a phase 2, randomised, placebo-controlled, double-blind study carried out in 6 centers” Comment: placebo controlled, probably done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Randomly assigned 12, analysed 11 Management of missing data: Quote: not mentioned
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01710046) The pre-specified outcomes in the protocol or those mentioned in the methods section have been reported in the results section

**Krupashankar 2014**

Methods	RCT, placebo-controlled, double blind Date of study: not stated Location: 20 centres in India
Participants	<b>Randomised:</b> 331 participants (mean age 37 years, 65 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>● Participants with moderate-severe psoriasis (PASI <math>\geq</math> 10, BSA <math>\geq</math> 10)</li> <li>● Age &gt; 18 years</li> <li>● Intolerance, contraindication, or inadequate response to systemic therapy; and</li> </ul>

	<p>requiring <math>\geq 15</math> mg/week of methotrexate</p> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Had an active infection (active tuberculosis)</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 26/225 (11.5%);</li> <li>• Lost to follow-up (10), withdrawn (7), disease worsening (7), AEs (5)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Itolizumab (n = 91), IV, 0.4 mg/kg for 4 weeks, then 1.6 mg/kg once a week for 4 weeks, then eow to 12 weeks</p> <p><b>Control intervention</b></p> <p>B. Itolizumab (n = 91), IV, 1.6 mg/kg for 4 weeks, then 1.6 mg/kg once a week for 4 weeks, then eow to 12 weeks</p> <p>C. Placebo (n = 43), IV</p>
Outcomes	<p>Assessments at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PGA</li> <li>• SF36</li> <li>• DLQI</li> <li>• Histopathology</li> <li>• Safety</li> </ul>
Notes	<p>Funding source (p 484): “Biocon limited funded this study and supplied the drug”</p> <p>Comment: Biocon Limited designed, performed, analysed and wrote the paper (medical writing)</p> <p>Declarations of interest (p 484): “Drs Krupashankar, Dogra, Kura, Saraswat, Leelavathy, Sumathy, Shah, Gopal, Narayana Rao, Srinivas, Bhat, Shetty, Manmohan, Sai Krishna, Padmaja, Pratap, Garg, Gupta, Pandey, and Khopkar were investigators who conducted the clinical trial described in this manuscript and collected the trial data; they received honoraria from the study sponsor. Dr Montero is a part-time employee of Biocon Research Limited. Drs Ramakrishnan, Nair, and Ganapathi are employees of Biocon Research Limited.”</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p 485): “This was a 52-week phase 3, double-blind, randomised, placebo-controlled...” Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (p 485): “This was a 52-week phase 3, double-blind, randomised, placebo-con-

**Krupashankar 2014** (Continued)

		trolled...” Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 485): “To maintain blind dummy infusion was given” Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 485): “To maintain blind dummy infusion was given” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	225 randomised, 220 analysed (not dosed (2), withdrawn the day after the first infusion (2), lost to follow-up (1)) Quote (p 486): “The full analysis set intent-to-treat population contained randomised patients who received at least 1 infusion and had at least 1 visit after enrollement, . . . , Missing values were imputed using last observation carried forward” Comment: few lost to follow-up, well-balanced number and reasons between groups
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

**Laburte 1994**

Methods	RCT, active-controlled, open-label trial Date of study: not stated Location: 27 centres worldwide
Participants	<b>Randomised:</b> 251 participants (mean age 41 years, 176 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 18)</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Kidney insufficiency</li> <li>• Had past history of malignant tumours</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• Not stated</li> </ul>
Interventions	<b>Intervention</b> A. Ciclosporin A (n = 119), orally, 2.5 mg/kg/d, 12 weeks <b>Control intervention</b> B. Ciclosporin A (n = 132), orally, 5 mg/kg/d, 12 weeks

Outcomes	Period assessments: 12 weeks <b>Primary or secondary outcomes of the trial:</b> <ul style="list-style-type: none"> <li>● PASI 75</li> <li>● PASI &lt; 8</li> </ul> <b>Outcomes of the trial</b> <ul style="list-style-type: none"> <li>● Overall assessment score</li> <li>● Nails, pruritus, severity, arthropathy</li> <li>● Safety</li> </ul>	
Notes	Funding and declarations of interest: not stated but the first author was employed by Sandoz Pharma Ltd	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote (p 367): "... was an open randomised study in parallel group" Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (p 367): "... was an open randomised study in parallel group" Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (p 367): "... was an open randomised study in parallel group" Comment: no blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (p 367): "... was an open randomised study in parallel group" Comment: no blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Management of missing data: no description of the method used to guarantee management of missing data
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

Methods	RCT, placebo-controlled, double-blind trial Date of study: June 2011-April 2013 Location: 88 centres worldwide (Erasure)
Participants	<p><b>Randomised:</b> 738 participants mean age 45 years, 509 male</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis</li> <li>• PASI <math>\geq</math> 12, IGA 3-4, BSA <math>\geq</math> 10%</li> <li>• Age <math>\geq</math> 18</li> <li>• Non response to topical treatment</li> <li>• Non-response to phototherapy</li> <li>• Non-response to conventional systemic treatment</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Immunosuppression,</li> <li>• Had an active infection</li> <li>• Had past history of malignant tumours</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 38/738 (5.1%)</li> <li>• AEs: secukinumab 300 (3), secukinumab 150 (5), placebo (4)</li> <li>• Lack of efficacy: secukinumab 300 (1), secukinumab 150 (1), placebo (0)</li> <li>• Withdrew consent: secukinumab 300 (1), secukinumab 150 (9), placebo (8)</li> <li>• Lost to follow-up: secukinumab 300 (0), secukinumab 150 (0), placebo (3)</li> <li>• Protocol deviation: secukinumab 300 (1), secukinumab 150 (0), placebo (1)</li> <li>• Became pregnant: secukinumab 300 (1), secukinumab 150 (0), placebo (0)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Secukinumab 300 (n = 245), SC, 300 mg, weeks 0, 1, 2, 3, 4 and every 4 weeks, 12 weeks</p> <p><b>Control intervention</b></p> <p>B. Secukinumab 150 (n = 245), SC, 150 mg, weeks 0, 1, 2, 3, 4 and every 4 weeks, 12 weeks</p> <p>C. Placebo (n = 248), SC, weeks 0, 1, 2, 3, 4 and every 4 weeks</p>
Outcomes	<p>Assessments at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> <li>• IGA score at 0 or 1</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 50, PASI 75, PASI 90, PASI 100</li> <li>• Response of 0 or 1 on the modified IGA at each study visit until week 52</li> <li>• Score of 0 or 1 on the DLQI at weeks 12 and 52</li> </ul>
Notes	<p>Funding source, quote (p 326): “funded by Novartis Pharmaceuticals”</p> <p>Declarations of interest (p 337): “Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.” Langley received personal fees from Eli Lilly, Leo, Novartis, Janssen, Amgen, AbbVie, Celgene, Merck, Pfizer</p>
<i>Risk of bias</i>	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (protocol and Appendix): "Randomization numbers were generated by the Interactive Response Technology (IRT) provider using a validated system, which automated the random assignment of subject numbers to randomisation numbers..." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (protocol and Appendix): "Randomization numbers were generated by the Interactive Response Technology (IRT) provider using a validated system, which automated the random assignment of subject numbers to randomisation numbers..." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (protocol and Appendix): "Subjects, investigator staff, persons performing the assessments, and data analysts were blinded to the identity of the treatment from the time of randomisation until primary objective analyses" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (protocol and Appendix): "Subjects, investigator staff, persons performing the assessments, and data analysts were blinded to the identity of the treatment from the time of randomisation until primary objective analyses" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	738 included/738 analysed Quote (p 329): "The analyses of the efficacy end points included all the patients who underwent randomisation according to the treatment assigned at randomisation. .. Missing values ... were conservatively imputed as nonresponses, regardless the reason of missing data" Comment: probably done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on

	ClinicalTrials.gov (NCT01365455) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported
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## Langley FIXTURE, 2014

Methods	RCT, active, placebo-controlled, double-blind trial Date of study: June 2011-June 2013 Location: 231 centres worldwide (Fixture)
Participants	<p><b>Randomised:</b> 1306 participants, mean age 44 years, 929 male</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis</li> <li>• PASI <math>\geq</math> 12, IGA 3-4, BSA <math>\geq</math> 10%</li> <li>• Age <math>\geq</math> 18</li> <li>• Non-response to topical treatment</li> <li>• Non-response to phototherapy</li> <li>• Non-response to conventional systemic treatment</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Immunosuppression</li> <li>• Had an active infection</li> <li>• Had past history of malignant tumours</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 73/1306 (5.6%)</li> <li>• AEs: sekunimab 300 (4), sekunimab 150 (2), etanercept (6), placebo (2)</li> <li>• Lack of efficacy: sekunimab 300 (0), sekunimab 150 (0), etanercept (2), placebo (9)</li> <li>• Withdrew consent: sekunimab 300 (5), sekunimab150 (5), etanercept (5), placebo (10)</li> <li>• Physician decision: sekunimab 300 (1), sekunimab 150 (2), etanercept (0), placebo (2)</li> <li>• Protocol deviation: sekunimab 300 (5), sekunimab 150 (3), etanercept (3), placebo (0)</li> <li>• Other: sekunimab 300 (0), sekunimab 150 (0), etanercept (5), placebo (2)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Sekunimab 300 (n = 327), SC, 300 mg, weeks 0, 1, 2, 3, 4 and every 4 weeks, 12 weeks</p> <p><b>Control intervention</b></p> <p>B. Sekunimab 150 (n = 327), SC, 150 mg, weeks 0, 1, 2, 3, 4 and every 4 weeks, 12 weeks</p> <p>C. Etanercept 50 (n = 326), SC, 50 mg/week twice a week, 12 weeks</p> <p>D. Placebo (n = 326), SC, weeks 0, 1, 2, 3, 4 and every 4 weeks, 12 weeks</p>
Outcomes	<p>Assessments at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul>

	<ul style="list-style-type: none"> <li>• and a IGA score at 0 or 1</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 50, PASI 75, PASI 90, PASI 100</li> <li>• Response of 0 or 1 on the modified IGA at each study visit until week 52</li> <li>• Score of 0 or 1 on the DLQI at weeks 12 and 52</li> </ul>	
Notes	Funding source, quote (p 326): “funded by Novartis Pharmaceuticals” Declarations of interest (p 337): “Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.” Langley received personal fees from Eli Lilly, Leo, Novartis, Janssen, Amgen, AbbVie, Celgene, Merck, Pfizer.“	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (protocol and Appendix): “Randomization numbers were generated by the Interactive Response Technology (IRT) provider using a validated system, which automated the random assignment of subject numbers to randomisation numbers...” “ Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (protocol and Appendix): “Subjects, investigator staff, persons performing the assessments, and data analysts were blinded to the identity of the treatment from the time of randomisation until primary objective analyses” “Randomization numbers were generated by the Interactive Response Technology (IRT) provider” Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (protocol and Appendix): “Subjects, investigator staff, persons performing the assessments, and data analysts were blinded to the identity of the treatment from the time of randomisation until primary objective analyses Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (protocol and Appendix): “Subjects, investigator staff, persons performing the assessments, and data analysts were blinded to the identity of the treatment from the time of randomisation until primary objective analyses Comment: probably done



Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote (p 329): “The analyses of the efficacy end points included all the patients who underwent randomisation according to the treatment assigned at randomisation. .. Missing values ... were conservatively imputed as nonresponses, regardless the reason of missing data” 1306 included/1306 analysed Comment: probably done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01358578) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

Lebwohl 2003

Methods	RCT, placebo-controlled, double blind Date of study: 23 March 2000-05 January 2001 Location: 64 centres in Europe, USA and Canada
Participants	<b>Randomised:</b> 507 participants (mean age 45 years, 333 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (BSA <math>\geq</math> 10)</li> <li>• Age <math>\geq</math> 18 years</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Pregnancy, immunosuppression</li> <li>• Had an active infection</li> <li>• had past history of malignant tumours</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• 62/507 (12.2%)</li> <li>• AE (10): alefacept 10 (4), alefacept 15 (2), placebo (4)</li> <li>• Worsening (13): alefacept 10 (5), alefacept 15 (2), placebo (6)</li> <li>• Request (25): alefacept 10 (8), alefacept 15 (6), placebo (11)</li> <li>• Laboratory (1): alefacept 10 (1), alefacept 15 (0), placebo (0)</li> <li>• Lost to follow-up (2): alefacept 10 (0), alefacept 15 (2), placebo (0)</li> <li>• Other (11): alefacept 10 (3), alefacept 15 (3), placebo (5)</li> </ul>
Interventions	<b>Intervention</b> A. Alefacept 10 (n = 173), IM, 10 mg once a week, 12 weeks <b>Control intervention</b> B. Alefacept 15 (n = 166), IM, 15 mg once a week, 12 weeks C. Placebo (n = 168), IM, 0.9 mL once a week, 12 weeks

Outcomes	Assessments at 12 weeks <b>Primary or secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• Not clearly identified</li> </ul> <b>Outcomes of the trial</b> <ul style="list-style-type: none"> <li>• PASI 50</li> <li>• PASI 75</li> <li>• PGA clear/almost clear</li> <li>• Side effects</li> </ul>	
Notes	Funding source, quote (p 725): "Support for this research and data monitoring and analysis were provided by Biogen Inc." Declarations of interest: not stated	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p 720): "The present multicenter, randomised...ICT Inc..., a contract research organization, was responsible for patient randomisation and tracking and study inventory" Comment: unlikely to introduce selection bias
Allocation concealment (selection bias)	Low risk	Quote: "a contract research organization, was responsible for patient randomisation and tracking and study inventory" "Unblinded pharmacist prepared, coded... and maintained drug accountability" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 720): "Unblinded pharmacist prepared, coded... and maintained drug accountability" Comment: placebo-controlled, probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 720): "All efficacy measures were assessed ... by a dermatologist blinded to treatment" Comment: placebo-controlled, probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	507 included/507 analysed Quote (p 721): "Statistical analyses for efficacy measures were based on the intent-to-treat population composed of those patients who were randomised, had at least 1

Lebwohl 2003 (Continued)

		injection and had a baseline assessment” Comment: no description of the method used to manage missing data however number and reasons for withdrawal well-balanced between groups
Selective reporting (reporting bias)	High risk	Comment: no protocol was available. No pre-specified primary outcome

Lebwohl AMAGINE-2, 2015

Methods	RCT, active/placebo-controlled, double blind Date of study: August 2012-September 2014 Location: 142 centres worldwide
Participants	<p><b>Randomised:</b> 1831 participants (mean age 45 years, 1258 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12, PGA 3-5, BSA <math>\geq</math> 10), age 18-75 years</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Pregnancy</li> <li>• Active infection, past history of malignant tumours, active infection, kidney or liver insufficiency, uncontrolled cardiovascular disorder, uncontrolled diabetes, uncontrolled hypertension</li> <li>• Had Crohn's disease</li> <li>• Had used ustekinumab and/or anti-IL17 biologic therapy</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 55/1831 (3%): brodalumab 140 group (22), brodalumab 210 group (15), ustekinumab 45/90 group (9), placebo group (9)</li> <li>• Ineligibility determined: brodalumab 140 group (3), brodalumab 210 group (0), ustekinumab 45/90 group (0), placebo group (0)</li> <li>• AEs: brodalumab 140 group (4), brodalumab 210 group (3), ustekinumab 45/90 group (2), placebo group (0)</li> <li>• Lost to follow-up: brodalumab 140 group (2), brodalumab 210 group (3), ustekinumab 45/90 group (2), placebo group (2)</li> <li>• Death; brodalumab 140 group (0), brodalumab 210 group (1), ustekinumab 45/90 group (0), placebo group (0)</li> <li>• Full consent withdrawal: brodalumab 140 group (11), brodalumab 210 group (2), ustekinumab 45/90 group (3), placebo group (5)</li> <li>• Other: brodalumab 140 group (2), brodalumab 210 group (6), ustekinumab 45/90 group (2), placebo group (3)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Brodalumab (n = 610), SC, 140 mg (2 injections week 0, 1 injection eow)</p> <p><b>Control intervention</b></p> <p>B. Brodalumab (n = 612), SC, 210 mg (2 injections week 0, 1 injection eow)</p> <p>C. Ustekinumab (n = 300), SC, 45/90 mg (week 0, week 4 and every 12 weeks)</p> <p>D. Placebo (n = 309), orally (same drug administration)</p>

Outcomes	Assessments at 12 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• PASI 75 &amp; PGA0/1 (brodalumab compared to placebo)</li> <li>• % of participants who had a 100% reduction in PASI score</li> </ul> <b>Secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• Improvement in PASI</li> <li>• PGA score</li> <li>• Participant-reported outcome</li> <li>• AEs</li> </ul>	
Notes	Funding source: Quote (p 1319) "Amgen funded both studies. ... and Amgen conducted the data analyses. All the authors interpreted the data" Declarations of interest (p 1327): "Disclosure forms provided by the authors are available with the full text of this article at NEJM.org." Dr. Lebwohl reports grant support from Amgen, AbbVie, Janssen Biotech, UCB Pharma, Pfizer, Celgene, Eli Lilly, and Novartis outside the submitted work	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (protocol): "The randomisation lists will be generated by Amgen using a permuted block design within each strata...via an interactive voice response system" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (protocol): "The randomisation lists will be generated by Amgen using a permuted block design within each strata...via an interactive voice response system" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (protocol, cf 6. Treatment procedure): "This is a double dummy procedure." .." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (protocol, cf 6. Treatment procedure): "This is a double dummy procedure." .." .."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 1831, analysed 1831 Dealing with missing data Quote (protocol & p 1321) "...with missing data imputed as indicating no response" Comment: well described

Lebwohl AMAGINE-2, 2015 (Continued)

Selective reporting (reporting bias)	High risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT0178603) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported except for participant-reported outcome
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Lebwohl AMAGINE-3, 2015

Methods	RCT, active/placebo-controlled, double blind Date of study: September 2012-August 2014 Location: 142 centres worldwide (no sites that were included in the AMAGINE-2 study)
Participants	<p><b>Randomised:</b> 1881 participants (mean age 45 years, 1288 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12, PGA 3-5, BSA <math>\geq</math> 10), age 18-75 years</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Pregnancy</li> <li>• Active infection, past history of malignant tumours, active infection, kidney or liver insufficiency, uncontrolled cardiovascular disorder, uncontrolled diabetes, uncontrolled hypertension</li> <li>• Had Crohn's disease</li> <li>• Had used ustekinumab and/or anti-IL17 biologic therapy</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 65/1881 (3.4%): brodalumab 140 group (25), brodalumab 210 group (16), ustekinumab 45/90 group (10), placebo group (14)</li> <li>• Ineligibility determined: brodalumab 140 group (3), brodalumab 210 group (0), ustekinumab 45/90 group (1), placebo group (2)</li> <li>• AEs: brodalumab 140 group (4), brodalumab 210 group (4), Usk 45/90 group (1), placebo group (0)</li> <li>• Lost to follow-up: brodalumab 140 group (5), brodalumab 210 group (5), ustekinumab 45/90 group (3), placebo group (1)</li> <li>• Full consent withdrawal: brodalumab 140 group (7), brodalumab 210 group (5), ustekinumab 45/90 group (3), placebo group (7)</li> <li>• Other: brodalumab 140 group (6), brodalumab 210 group (2), ustekinumab 45/90 group (2), placebo group (4)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Brodalumab (n = 629), SC, 140 mg (2 injections week 0, 1 injection eow)</p> <p><b>Control intervention</b></p> <p>B. Brodalumab (n = 624), SC, 210 mg (2 injections week 0, 1 injection eow)</p> <p>C. Ustekinumab (n = 313), SC, 45/90 mg (week 0, week 4 and every 12 weeks)</p> <p>D. Placebo (n = 315), orally (same drug administration)</p>

Outcomes	<p>Assessments at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>● PASI 75</li> <li>● PGA 0/1 (brodalumab compared to placebo)</li> <li>● % of participants who had a 100% reduction in PASI score</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>● Improvement in PASI</li> <li>● PGA score</li> <li>● Participant-reported outcome</li> <li>● AEs</li> </ul>	
Notes	<p>Funding source:                  Quote (p 1319) "Amgen funded both studies. ... and Amgen conducted the data analyses. All the authors interpreted the data"                  Declarations of interest (p 1327): "Disclosure forms provided by the authors are available with the full text of this article at NEJM.org." Dr. Lebwohl reports grant support from Amgen, AbbVie, Janssen Biotech, UCB Pharma, Pfizer, Celgene, Eli Lilly, and Novartis outside the submitted work</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (protocol): "The randomisation lists will be generated by Amgen using a permuted block design within each strata.. Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (protocol): "The randomisation lists will be generated by Amgen using a permuted block design within each strata...via an interactive voice response system" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (protocol, cf 6. Treatment procedure): "This is a double dummy procedure.." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (protocol, cf 6. Treatment procedure): "This is a double dummy procedure.."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 1881, analysed 1881 Dealing with missing data Quote (protocol & p 1321) "...with missing data imputed as indicating no response" Comment: well described

Selective reporting (reporting bias)	High risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01708629) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported except for participant-reported outcome
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Leonardi 2003

Methods	RCT, placebo-controlled, double-blind trial Date of study: December 2001-April 2002 Location: 47 centres in USA
Participants	<p><b>Randomised:</b> 672 participants (mean age 45 years, 672 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe stable plaque psoriasis, BSA &gt; 10%</li> <li>• Age ≥ 18</li> <li>• Quote (p 2015) “Had previously received phototherapy or systemic psoriasis therapy at least once or had been candidate to such therapy”</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Had received biologics treatments</li> <li>• Had an active infection</li> <li>• Had past history of malignant tumours</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 103/672 (15.3%)</li> <li>• Not received any treatment: etanercept LD (9), etanercept MD (5), etanercept HD (4), placebo (2)</li> <li>• AEs: etanercept LD (8), etanercept MD (7), etanercept HD (5), placebo (8)</li> <li>• Loss to follow-up: etanercept LD (4), etanercept MD (4), etanercept HD (3), placebo (3)</li> <li>• Lack of efficacy: etanercept LD (6), etanercept MD (2), etanercept HD (3), placebo (6)</li> <li>• Patient refusal: etanercept LD (3), etanercept MD (4), etanercept HD (1), placebo (4)</li> <li>• Protocol violation: etanercept LD (3), etanercept MD (4), etanercept HD (0), placebo (1)</li> <li>• Death: etanercept LD (1), etanercept MD (1), etanercept HD (0), placebo (0)</li> <li>• Unknown/other: etanercept LD (1), etanercept MD (0), etanercept HD (1), placebo (0)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Etanercept LD (n = 169), SC auto-administered, 25 mg, once/week, 12 weeks</p> <p><b>Control intervention</b></p> <p>B. Etanercept MD (n = 167), SC auto-administered, 25 mg, twice/week, 12 weeks</p> <p>C. Etanercept HD (n = 168), SC auto-administered, 50 mg, twice/week, 12 weeks</p> <p>D. Placebo (n = 168), SC, 12 weeks</p>

Outcomes	Assessments at 12 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>● PASI 75</li> </ul> <b>Secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>● PASI 50</li> <li>● PASI 90</li> <li>● DLQI</li> <li>● PGA</li> <li>● Safety</li> <li>● Patient global assessment of psoriasis</li> </ul>	
Notes	Funding source, quote (p 2021): “Supported by Immunex, Seattle, a wholly-owned subsidiary of Agen, Thousand Oaks, Calif” Declarations of interest (p 2021): “Drs. Leonardi, Powers, Goffe, and Gottlieb report having served as consultants for Amgen, and Drs. Leonardi, Goffe, and Gottlieb report having served as paid lecturers for Amgen. Dr. Gottlieb reports having served as a consultant and paid lecturer for Johnson & Johnson, Genentech, and Biogen; Dr. Leonardi reports having served as a consultant and paid lecturer for Johnson & Johnson and Genentech; Dr. Powers reports having served as a consultant for Genentech and Biogen; and Dr. Goffe reports having served as a consultant and paid lecturer for Biogen. Dr. Zitnik and Ms. Wang report owning equity in Amgen.”	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p 2016): “Patients underwent central randomisation with the use of a permuted block randomisation list, with equal allocation to each of the four treatment groups” Comment: probably done
Allocation concealment (selection bias)	Low risk	Comment: no description of the method used to guarantee the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 2015): “Double-blind... Etanercept ... was supplied to patients in syringes, each containing the contents of one reconstituted vial of etanercept or matching placebo...All patients received two injections per dose of study” Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 2015): “Double-blind... Etanercept ... was supplied to patients in syringes, each containing the contents of one



Leonardi 2003 (Continued)

		reconstituted vial of etanercept or matching placebo...All patients received two injections per dose of study” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	672 randomised participants, 652 analysed (20 participants did not receive the treatment and were excluded from the analyses) Comment: modified ITT but number of participants not receiving treatment and not included in the analysis low and comparable between groups
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

Leonardi 2012

Methods	RCT, placebo-controlled, double-blind trial Date of study: April 2010-May 2011 Location: 23 centres internationally
Participants	<p><b>Randomised:</b> 142 participants (mean age 46 years, 81 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis, PASI <math>\geq</math> 12, PGA 3-5, BSA <math>\geq</math> 10</li> <li>• Age <math>\geq</math> 18</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Pregnancy</li> <li>• Had an active infection</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 13/142 (9%) :</li> <li>• Placebo (4) (AE (4), withdrew (1) efficacy lack (2))</li> <li>• Ixekizumab 10 mg (6) (AE (2), protocol violations (2), lost to follow-up (1), efficacy lack (1))</li> <li>• Ixekizumab 25 mg (1) (AE (1))</li> <li>• Ixekizumab 75 mg (1) (withdrawal (1))</li> <li>• Ixekizumab 150 mg (1) (withdrawal (1))</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Placebo (n = 27), SC, 0, 2, 4, 8, 12, 16 weeks, 16 weeks</p> <p><b>Control intervention</b></p> <p>B. Ixekizumab (n = 28), SC, 10 mg, 0, 2, 4, 8, 12, 16 weeks, 16 weeks</p> <p>C. Ixekizumab (n = 30), SC, 25 mg, 0, 2, 4, 8, 12, 16 weeks, 16 weeks</p> <p>C. Ixekizumab (n = 29), SC, 75 mg, 0, 2, 4, 8, 12, 16 weeks, 16 weeks</p> <p>C. Ixekizumab (n = 28), SC, 150 mg, 0, 2, 4, 8, 12, 16 weeks, 16 weeks</p>

Outcomes	Assessments at 12 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>● PASI 75</li> </ul> <b>Secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>● % reduction of PASI</li> <li>● PASI 90/PASI 100</li> <li>● PGA</li> <li>● NAPSI</li> <li>● PSSI</li> </ul>	
Notes	Funding source, quote (p 1190): "Funded by Eli Lilly" Declarations of interest (p 1198): "Disclosure forms provided by the authors are available with the full text of this article at NEJM.org." Leonardi received personal fees from Abbott, Amgen, Certocor, Eli Lilly and Pfizer	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (protocol p 44): "... from the central randomisation center using an IVRS" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (protocol p 44): "... from the central randomisation center using an IVRS" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (protocol p 22): "The investigators and patients are blinded while the sponsor is unblinded to study assignment" Comment: placebo-controlled trial, no systematic AE for the drug, probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (protocol p 22): "The investigators and patients are blinded while the sponsor is unblinded to study assignment" Comment: placebo-controlled trial, no systematic AE for the drug, probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Included 142/141 analysed (1 in the placebo group who did not have any post-baseline assessment) Quote (protocol p 62 & p 1192): "All efficacy and health outcome analyses will be conducted on all patients who received any amount of study drug and have any post-baseline efficacy assessment....Missing data for the primary timepoint at week 12 will

Leonardi 2012 (Continued)

		be imputed by the last observation carried forward method” Comment: m-ITT and 1 participant out of 142 was not included in the analyses
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01107457) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

Leonardi PHOENIX-1, 2008

Methods	RCT, placebo-controlled, double-blind trial Date of study: December 2005-September 2007 Location: 48 centres in USA, Canada, Belgium
Participants	<b>Randomised:</b> 766 participants (mean age 45 years, 531 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis, authors’ assessment &gt; 6 months, PASI <math>\geq</math> 12, BSA &gt; 10%</li> <li>• Age <math>\geq</math> 18</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Had received conventional systemic treatments</li> <li>• Had received biologics (IL12/23)</li> <li>• Had an active infection</li> <li>• Had past history of malignant tumours</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• 23/766 (3%) :</li> <li>• Ustekinumab 45 (1) (other 1)</li> <li>• Ustekinumab 90 (10) (lack of efficacy (1), adverse event (2) other (7))</li> <li>• Placebo (12) (lack of efficacy (3), adverse event (6) other (3))</li> </ul>
Interventions	<b>Intervention</b> A. Ustekinumab (n = 255), SC, 45 mg, weeks 0-4 and every 12 weeks, 40 weeks <b>Control intervention</b> B. Ustekinumab (n = 256), SC, 90 mg, weeks 0-4 and every 12 weeks, 40 weeks C. Placebo (n = 255), SC, weeks 0-4, 40 weeks
Outcomes	Assessments at 12 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <b>Secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• PGA cleared or minimal at 12 weeks</li> <li>• Change of DLQI from baseline at 12 weeks</li> <li>• PASI 90 at week 12</li> <li>• Side effects</li> </ul>

Notes	<p>Funding source, quote (p 1665): Centocor Inc.</p> <p>Declarations of interest (p 1673): “CLL has served as a consultant for Abbott, Amgen, Centocor, and Genentech, as an investigator for Abbott, Allergan, Altana, Alza, Amgen, Astellas, Celgene, Centocor, Genentech, Bristol Myers, Eli Lilly, Fujisawa, Galderma, CombinatoRx, 3M Pharmaceuticals, Perrigo Isreal Pharamceutical, Schering-Plough, Serono, RTL, Novartis, Vitae, and Wyeth, and as a speaker for Abbott, Amgen, Centocor, Genentech, and Warner Chilcott. ABK has served as an investigator and consultant for Abbott, Amgen, and Centocor and has been a study steering committee member, speaker, and fellowship funding recipient from Centocor. KAP has served as a consultant and advisory board member for Abbott, Alza, Amgen, Celgene, Centocor, Johnson and Johnson, Isotechnika, Janssen Ortho Biotech, Medimmune, MerckSerono, and Wyeth. KBG has served as a consultant for Abbott, Amgen, Astellas, Centocor, and Genentech and has received grant support from Abbott, Astellas, and Centocor. NY, CG, YW, SL, and LTD are employees of Centocor and own stock in Johnson and Johnson.”</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	<p>Quote (p 1667-68): “...via a centralised interactive voice response system”</p> <p>Comment: probably done</p>
Allocation concealment (selection bias)	Unclear risk	<p>Quote (p 1667-68): “...via a centralised interactive voice response system”</p> <p>Comment: no description of the method used to guarantee allocation concealment</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote (p 1666-67): “This phase 3, double-blind, placebo-controlled... Patients received placebo injections as needed to preserve the blind. The study sponsor was unblinded to treatment... Site monitors, investigators, site personnel involved in the study conduct, and patients remained blinded until week 76”</p> <p>Comment: probably done</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Quote (p 1666-67): “This phase 3, double-blind, placebo-controlled... Patients received placebo injections as needed to preserve the blind. The study sponsor was unblinded to treatment... Site monitors, investigators, site personnel involved in the study conduct, and patients remained blinded until week 76”</p> <p>Comment: probably done</p>

Leonardi PHOENIX-1, 2008 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Included 255/256/255 Analysed 255/256/255 Quote (p 1668): "Efficacy data from all randomised patients were analysed according to the assigned treatment group.... Patients who discontinued study treatment... were deemed to be treatment failures" Comment: probably done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00267969) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

Lowe 1991

Methods	RCT, placebo-controlled, double-blind trial Date of study: not stated Location: 2 centres in Santa Monica and New York City, USA
Participants	<b>Randomised:</b> 34 participants, age range 20-75 years, 24 male <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis</li> <li>• BSA 20-80</li> <li>• <math>\geq 6</math> months duration</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Had received conventional systemic treatments or phototherapy for 4 weeks or topical therapy for 2 weeks</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• Not specified</li> </ul>
Interventions	<b>Intervention</b> A. Acitretin (n = 16), orally, 50 mg, daily, 12 weeks <b>Control intervention</b> B. Placebo (n = 18), orally, daily, 12 weeks Co-intervention: UVB (phototherapy)
Outcomes	Assessments at 12 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• PASI</li> </ul> <b>Secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• Side effects</li> </ul>

Notes	Funding source (p 591): “Supported by Roche dermatologics, Nutley, New Jersey and the Skin Research Foundation of California, Santa Monica, California” Declarations of interest; not stated	
<b>Risk of bias</b>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p 592): “Patients receiving UVB phototherapy were randomly assigned” Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (p 592): “Patients receiving UVB phototherapy were randomly assigned” Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (p 592): “were randomly assigned to either acitretin or placebo” Comment: no more precision however adverse effects of acitretin such as cheilitis are visible
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (p 592): “were randomly assigned to either acitretin or placebo... the same observer who was unaware of patient group examined the patients throughout the investigation” Comment: no more precision however adverse effects of acitretin such as cheilitis are visible
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	34 included / 34 analysed (Table 2) Comment: no description of the method used to manage the missing data or to perform the analyses
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

Methods	RCT, placebo-controlled, double-blind trial Date of study: January 2007-September 2007 Location: 1 centre in Chandigarh, India	
Participants	<p><b>Randomised:</b> 40 participants (mean age 37 years, 29 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis</li> <li>• BSA &gt; 10%</li> <li>• Age 18-60 years</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Pregnancy, immunosuppression, kidney insufficiency, liver insufficiency</li> <li>• Had uncontrolled diabetes</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 11/40 (28%)</li> <li>• 3 withdrawn (disease exacerbation)</li> <li>• 4 lost to follow-up (acitretin (3), placebo (1))</li> <li>• 4 alternative therapy</li> </ul>	
Interventions	<p><b>Intervention</b></p> <p>A. Methotrexate 0.5 mg/kg + folic acid, (n = 20), orally 5 mg/d Day-1; Day+1 + NBUVB 3/week max 1200 mJ/cm<sup>2</sup></p> <p><b>Control intervention</b></p> <p>B. Placebo + folic acid (n = 20), orally, 5 mg/d Day-1; Day+1 + NBUVB 3/week max 1200 mJ/cm<sup>2</sup></p>	
Outcomes	<p>Assessments at 6 months</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI at 4-12 weeks</li> <li>• Relapse (return of PASI at 50 weeks to baseline)</li> </ul>	
Notes	<p>Funding source: not stated</p> <p>Declarations of interest (p 595): "not declared"</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p 596): "... were randomised by way of random number table" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Quote (p 596): "... were randomised by way of random number table" Comment: no description of the method used to guarantee allocation concealment

**Mahajan 2010** (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (p 596): “patient-blinded study” Comment: not double blind
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (p 596): “patient-blinded study” Comment: not double blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	20/20 included; 20/20 analysed Quote (p 596): “Intention to treat principle was followed for the analysis of the observations” Comment: no description of the method used to manage the missing data
Selective reporting (reporting bias)	Low risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

**Meffert 1997**

Methods	RCT, placebo-controlled, double blind Date of study: not stated Location: 17 centres in Germany
Participants	<b>Randomised:</b> 128 participants <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI 8 to 25)</li> <li>• Age 18-70 years</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Pregnancy, leucopenia, kidney insufficiency, liver insufficiency</li> <li>• Had uncontrolled hypertension</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• 15/128 (12%) :</li> <li>• Protocol violation(6)</li> <li>• Lack efficacy(4)</li> <li>• AE (5)</li> </ul>
Interventions	<b>Intervention</b> A. Ciclosporin (n = 43), orally, 1.25 mg/kg/d, 10 weeks <b>Control intervention</b> B. Ciclosporin (n = 41), orally, 2.5 mg/kg/d, 10 weeks C. Placebo (n = 44), orally, 10 weeks
Outcomes	Assessments at 10 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• PASI</li> </ul>



	<b>Secondary outcomes of the trial</b>	
	<ul style="list-style-type: none"> <li>● PASI 25</li> <li>● PASI 50</li> <li>● PASI 75</li> </ul>	
Notes	Funding source not stated however 3 out of 4 authors from Sandoz pharmaceuticals Declarations of interest: not stated	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote (p 77): "patients were randomised" Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (p 77): "double blind study period" Comment: no description of the method used to guarantee blinding regarding the need of hypertension and renal function surveillance and modification in ciclosporin groups
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (p 77): "double blind study period" Comment: no description of the method used to guarantee blinding, regarding the need of hypertension and renal function surveillance and modification in ciclosporin groups
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	128 included/120 analysed Comment: methods for dealing with missing data not specified, not ITT analyses
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

Methods	RCT, placebo-controlled, double-blind trial Date of study: not stated Location: 63 centres in Europe, USA, Canada
Participants	<p><b>Randomised:</b> 835 participants (mean age 44 years, 551 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis</li> <li>• PASI <math>\geq</math> 12, BSA <math>\geq</math> 10</li> <li>• No history of serious infection, lymphoproliferative disease, or active TB</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Had received biologics</li> <li>• Had an active infection</li> <li>• Had past history of malignant tumours</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 62/835 (7.4%)</li> <li>• Infliximab 5 mg/kg (17) (AE (12), other (4), lost to follow-up (1))</li> <li>• Infliximab 3 mg/kg (21) (AE (13), other (7), low effect (1))</li> <li>• Placebo (24) (AE (4), other (9), lost to follow-up (1), low effect (10))</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Infliximab (n = 313), IV, 3 mg/kg, weeks 0, 2, 6; 10 weeks</p> <p><b>Control intervention</b></p> <p>B. Infliximab (n = 314), IV, 5 mg/kg, weeks 0, 2, 6; 10 weeks</p> <p>C. Placebo (n = 208), IV, weeks 0, 2, 6; 10 weeks</p>
Outcomes	<p>Assessments at 10 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 50/90</li> <li>• DLQIAE</li> <li>• PGA</li> </ul>
Notes	<p>Funding (p 31. e1) by Centocor, Inc, Malvern, Penn, and Schering-Plough, Kenilworth, NJ</p> <p>Declarations of interest (appendix): “Dr Menter has received consulting, research, and/or speaking support from Abbott Laboratories, Allergan Inc, Allered, Amgen Inc, Astralis Inc, Berlex Inc, Biogen Idec Inc, Centocor Inc, Cephalon, Collagenex Pharmaceuticals, CombinatoRx, Connetics Corp, Corixa Corporation, Dermik Laboratories, Doak Dermatologics, Dow, Ferndale Laboratories Inc, Fujisawa Healthcare Inc, Galderma, Genentech Inc, Genzyme, GlaxoSmithKline, Ligand Pharmaceuticals, Medicis, Med-Immune Inc, Novartis Pharmaceuticals, Otsuka Pharmaceutical Inc, Protein Design Labs, QLT USA, Regeneration Pharma AG, Roche Laboratories, Serono, Sinclair, Synta Pharma, Thermosurgery, 3M Pharmaceuticals, Vertex, XOMA, and Zars Inc. Dr Feldman has received consulting, research, and/or speaking support from Amgen, Centocor, and Biogen. Dr Papp’s support is as follows: Abbott: Investigator, Consultant; Amgen: Investigator, Consultant, Speaker, Advisory Boards; Centocor: Investigator, Consultant, Speaker, Senior Medical Officer for Canada (non-compensatory), Advisory Boards; Genentech: Investigator, Consultant, Speaker, Senior Medical Officer for Canada (non-compensatory);</p>

satory), Advisory Boards; Serono: Investigator, Consultant, Speaker, Advisory Boards; Schering: Investigator, Consultant, Speaker, Advisory Boards; and Wyeth: Speaker, Advisory Boards. Dr Weinstein has received consulting, research, and/or speaking support from Allergan, Amgen, Centocor, Biogen, Genentech, Valeant, Collagenex, Combina-toRx, Fujisawa, Abbott, and QLT. Dr Gottlieb has received research support from and/or is a consultant and/or speaker for Amgen, Inc, BiogenIdec, Inc, Centocor, Inc, Genentech, Inc, Abbott Labs, Ligand Pharmaceuticals, Inc, Beiersdorf, Inc, Fujisawa Health-care, Inc, Celgene Corp, Bristol Myers Squibb, Inc, Warner Chilcott, Paradigm, Wyeth Pharmaceuticals, Schering-Plough Corp, Eisai, Roche, Sankyo, Medarex, Kemia, Celera, TEVA, Actelion, and Amarill. At the time of the study, Dr Gottlieb was affiliated with the Clinical Research Center, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, New Brunswick, NJ. Dr Guzzo, Dr Dooley, Ms Li, and Ms Arnold are employees of Centocor, Inc. Mr Evans was an employee of Centocor, Inc at the time this study was conducted and is currently an employee of Scios, Inc.”

<i>Risk of bias</i>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p 31; e2): “Randomizations were performed by ClinPhone (Lawrenceville, NJ), allocating patients using a minimization algorithm with a biased coin assignment by means of an interactive voice response system” Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 31; e2): “Randomizations were performed by ClinPhone (Lawrenceville, NJ), allocating patients using a minimization algorithm with a biased coin assignment by means of an interactive voice response system” “Patients, investigators, and all study staff except pharmacists were blinded to treatment assignments” Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 31. e2): “Patients, investigators, and all study staff except pharmacists were blinded to treatment assignments... to receive IFX 3 mg/Kg or 5mg/Kg or placebo” Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 31. e2): “Patients, investigators, and all study staff except pharmacists were blinded to treatment assignments... to receive IFX 3 mg/Kg or 5mg/Kg or placebo” Comment: placebo-controlled, probably done

**Menter EXPRESS-II, 2007** (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	835 included / 835 analysed Quote (p 31.e3/4): "For patients who discontinued... these patients were considered as not meeting the respective end-points regardless of the observed data" Comment: ITT
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

**Menter REVEAL, 2008**

Methods	RCT, placebo-controlled, double-blind trial Date of study: December 2004-August 2007 Setting: 81 centres (67+14) in USA, Canada
Participants	<b>Randomised:</b> 1212 participants (mean age 44 years, 803 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>● Participants with moderate-severe psoriasis</li> <li>● PASI <math>\geq</math> 12, PGA moderate severity, BSA <math>\geq</math> 10</li> <li>● Age <math>\geq</math> 18 years</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>● Pregnancy</li> <li>● Had an active infection</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>● 74/1212 (6%)</li> <li>● 4/10 AEs</li> <li>● 9/6 withdrew consent</li> <li>● 8/6 lost to follow-up</li> <li>● 17/2 unsatisfactory effect</li> <li>● 5/1 others</li> </ul>
Interventions	<b>Intervention</b> A. Adalimumab (n = 814), SC, 40 mg, week 0: 2 injections, week 1: eow, 16 weeks <b>Control intervention</b> B. Placebo, SC (n = 398), week 0: 2 injections/week 1: eow, 16 weeks
Outcomes	Assessments at 16 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>● PASI 75</li> </ul> <b>Secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>● PGA</li> <li>● PASI 90</li> <li>● PASI 100</li> <li>● Safety</li> </ul>

Notes	<p>Funding source quote (p 106): “Supported by Abbott Laboratories</p> <p>Declarations of interest (p 106): ”Dr Menter has received research support and/or lecture honoraria from Abbott, Amgen, Astellas, Biogen, Centocor, Genentech, and Wyeth. Dr Tyring has received research support from, has consulted for, and is part of the speakers’ bureaus for Abbott. Dr Gordon has received research support and honoraria from Abbott, Amgen, and Centocor. Dr Kimball is an investigator, speaker, and consultant for Abbott, Amgen, Biogen, Centocor, and Genentech. Dr Leonard is a consultant for Abbott, Amgen, Centocor, and Genentech and is an investigator for Abbott, Allergan, Altana, Amgen, Astellas, Biogen, Bristol Myers, Centocor, Fujisawa, Galderma, Genentech, Serono, CombinatoRx, 3M Pharmaceuticals, Schering Plough, RTL, and Vitae; he also received an educational grant from Amgen and Genentech, and is part of the speakers’ bureaus for Abbott, Amgen, Centocor, Genentech, and Warner Chilcott. Dr Langley is a scientific advisory board member, investigator, and speaker for Abbott, Amgen, Astellas, Centocor, Novartis, and Wyeth. Dr Strober serves on the advisory boards of, has received honoraria from, and is an investigator for Abbott, Amgen, Astellas, Centocor, Genentech, and Wyeth, and is part of the speakers’ bureaus for Abbott, Amgen, Astellas, Genentech, and Wyeth. Dr Kaul, Ms Gu, and Dr Okun are employees of Abbott Laboratories. Dr Papp is a consultant for and has received honoraria and travel grants from Abbott, Alza, Amgen, Astellas, Celgene, Centocor, Genentech, Isoteknika, Johnson and Johnson, Serono, Schering-Plough, and UCB.”</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p 107): ”Randomization schedules were generated by one of our data management departments before study inception” Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 107): ”Patients were randomised by centre via an interactive voice response system”. “ADA and placebo-filled syringes were identically labelled and packaged, and self-administrated by patients” Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 107): “Double-blind, placebo-controlled... ADA and placebo-filled syringes were identically labelled and packaged, and self-administrated by patients” Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 107): “Double-blind, placebo-controlled... ADA and placebo-filled syringes were identically labelled and packaged, and self-administrated by patients” Comment: probably done

Menter REVEAL, 2008 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	1212 included/1212 analysed Quote (p 109): “The primary efficacy analyses were conducted on ITT population... a patient with missing data for a visit... had the last observation carried forward” Comment: probably done
Selective reporting (reporting bias)	Unclear risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT002377887) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported except for participant-reported outcome

Mrowietz BRIDGE, 2016

Methods	RCT, active-controlled, double blind Date of study: November 2012-November 2015 Setting: 57 centres in Austria, Germany, the Netherlands and Poland
Participants	<p><b>Randomised:</b> participants (mean age, male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12, BSA <math>\geq</math> 10), age <math>\geq</math> 18 years</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>Failed therapy with fumaric ester</li> <li>Baseline leucocyte counts <math>&lt;</math> <math>3 \times 10^9</math> cells/L and/or lymphocyte counts <math>&lt;</math> <math>1 \times 10^9</math> cells/L</li> <li>Pregnant or breastfeeding women</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>254/704 (36%);</li> <li>Not treated: Dimethyl Fumarate (DMF) (1), DMF + salt of monoethyl fumarate (MEF) (3), placebo (1)</li> <li>AEs: DMF (64), DMF + MEF (70), placebo (6)</li> <li>Lack of efficacy: DMF (12), DMF + MEF (9), placebo (20)</li> <li>Withdrew consent: DMF (13), DMF + MEF (11), placebo (7)</li> <li>Lost to follow-up: DMF (5), DMF + MEF (5), placebo (5)</li> <li>No compliance: DMF (3), DMF + MEF (7), placebo (1)</li> <li>Other: DMF (6), DMF + MEF (5), placebo (0)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Dimethyl fumarate (DMF) (n = 280), orally, maximum daily dose of 720 mg DMF</p> <p><b>Control intervention</b></p> <p>B. DMF + salt of monoethyl fumarate (n = 286), orally, maximum daily dose of 720 mg DMF</p> <p>C. Placebo (n = 138)</p>

Outcomes	Assessments at 16 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>● PASI 75</li> <li>● PGA 0/1</li> </ul> <b>Secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>● PASI 90</li> <li>● DLQI</li> <li>● AEs</li> </ul>	
Notes	Funding source: Quote (p 1) “This research was funded by Almirall S.A.” Declarations of interest (p 1): “U.M. has been an advisor and/or received speaker honoraria and/or received grants and/or participated in clinical trials for the following companies: Abbott/AbbVie, Almirall Hermal, Amgen, Biogen, Boehringer Ingelheim, Celgene, Centocor, Foamix, Forward Pharma, Galderma, Janssen, LEO Pharma, Lilly, Medac, Miltenyi Biotec, MSD, Novartis, Pfizer, Teva, UCB, VBL and XenoPort. J. C.S. receives advisory board/consulting fees from AbbVie, Biogen, Biogenetica International Laboratories, Egis Pharmaceuticals, Fresenius, LEO Pharma, Lilly, Novartis, Pierre Fabre, Polpharma, Sandoz and Toray Corporation; and receives speaker fees from AbbVie, Actavis, Adamed, Astellas, Berlin-Chemie Menarini, Fresenius, Janssen-Cilag, LEO Pharma, Mitsubishi Tanabe Pharma, Novartis, Pierre Fabre, Takeda and Vichy, and clinical trial funding from AbbVie, Actelion, Almirall, Amgen, GlaxoSmithKline, Janssen-Cilag, Merck, Mitsubishi Tanabe Pharma, Novartis, Regeneron and Takeda. P. V.K. declares consultancy fees for Celgene, Centocor, Almirall, Amgen, Pfizer, Philips, Abbott, Lilly, Galderma, Novartis, Janssen-Cilag, LEO Pharma, Sandoz and Mitsubishi Tanabe Pharma and carries out clinical trials for Basilea, Pfizer, Lilly, Amgen, AbbVie, Philips Lighting, Janssen-Cilag and LEO Pharma. R.L.”	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p 2): “Randomisation was performed by the investigators using an interactive web-based response system.” Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 2): “Randomisation was performed by the investigators using an interactive web-based response system. The randomisation sequence was kept concealed from the investigators during the trial.” Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 2): “Treatment was uptitrated over the first 9 weeks, with placebo or up to a maximum daily dose of 720 mg DMF in the LAS41008 or Fumaderm® groups” Comment: probably done

Mrowietz BRIDGE, 2016 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 2): "Treatment was uptitrated over the first 9 weeks, with placebo or up to a maximum daily dose of 720 mg DMF in the LAS41008 or Fumaderm® groups" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	High risk	Randomly assigned 704, analysed 671 Management of missing data: Quote (p 4): "All statistical analyses were based on the full analysis set (FAS) and the per protocol set (PPS). As the results of both were consistent, data are presented here only for the FAS. A last-observation-carried-forward approach was used to handle missing data for the PASI- and PGA-derived end points." DMF/DMF + MEF/placebo Randomized 280/286/138 Safety set analysis 279/283/137 (not treated patients excluded) Full set analysis 267/273/131 (not explained) Comment: not ITT analysis
Selective reporting (reporting bias)	High risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01726933) Some pre-specified outcomes and those mentioned in the methods section as DLQI had not been reported

Mrowietz SCULPTURE, 2015

Methods	RCT, active-controlled, double blind Date of study: August 2011-March 2013 Setting: 133 centres in North and South America, Europe and Asia
Participants	<b>Randomised:</b> 966 participants (mean age 46 years, 635 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12, BSA <math>\geq</math> 10), age <math>\geq</math> 18 years</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>Immunosuppression, active infection, uncontrolled cardiovascular disorder, uncontrolled diabetes, uncontrolled hypertension, had past history of malignant tumours</li> <li>Had received anti IL17 drug</li> </ul> <b>Dropouts and withdrawals</b>



	<ul style="list-style-type: none"> <li>• 38/966 (4%);</li> <li>• AEs: secukinumab 300 (9), secukinumab 150 (8)</li> <li>• Lack of efficacy: secukinumab 300 (0), secukinumab 150 (1)</li> <li>• Withdrew consent: secukinumab 300 (8), secukinumab 150 (6)</li> <li>• Lost to follow-up: secukinumab 300 (3), secukinumab 150 (2)</li> <li>• Protocol deviation: secukinumab 300 (0), secukinumab 150 (1)</li> </ul>
Interventions	<p><b>Intervention</b> A. Secukinumab (n = 482), SC, 150 mg weeks 0, 1, 2, 3 then monthly</p> <p><b>Control intervention</b> B. Secukinumab (n = 484), SC, 300 mg weeks 0, 1, 2, 3 then monthly</p>
Outcomes	<p>Assessments at 52 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 50/75/90 week 12</li> <li>• IGA 0/1</li> <li>• DLQI</li> <li>• AEs</li> </ul>
Notes	<p>Funding source: quote (p 27) “Study funded by Novartis Pharma...Novartis conducted data analyses, and all authors had access to data”</p> <p>Declarations of interest (p 27): “The authors received writing and editorial support from Barry Weichman and Jinling Wu in the preparation of the manuscript from BioScience Communications, New York, NY, supported by Novartis. Dr Mrowietz has served as advisor and/or received speaker honoraria and/or received grants and/or participated in clinical trials for Abbott/AbbVie, Almirall, Amgen, BASF, Biogen Idec, Celgene, Centocor, Eli Lilly, Forward Pharma, Galderma, Janssen, Leo Pharma, Medac, MSD, Miltenyi Biotech, Novartis, Pfizer, Teva, VBL, and Xenoport. Dr Leonardi has served as consultant and/or investigator and/or participated in a speaker’s bureau for AbbVie, Amgen, Celgene, Dermira, Eli Lilly, Galderma, Janssen, Leo Pharma, Merck, Novartis, Pfizer, Sandoz, Stiefel, and UCB. Dr Girolomoni has received advisory/speaker honoraria and/or research funding from AbbVie, Almirall, Boehringer Ingelheim, Celgene, Dompe, Eli Lilly, Galderma, Janssen, Leo Pharma, Merck Serono, Maruho, MSD, Novartis, and Pfizer. Dr Toth has served as investigator for Novartis, Amgen, Eli Lilly, Johnson &amp; Johnson, Abbott, Celgene, Merck, Galderma, and Leo Pharma. Dr Morita has served as consultant and/or paid speaker for and/or participated in psoriasis clinical trials sponsored by AbbVie, Mitsubishi Tanabe, Janssen, Novartis, Eli Lilly, Kyowa-Kirin, Leo Pharma, Maruho, and MSD. Dr Szepietowski has served as advisor and/or received speakers honoraria and/or participated in clinical trials for Abbott/AbbVie, Actavis, Amgen, BASF, Astellas, Berlin-Chemie/Menarini, Biogenetica International Laboratories, Centocor, Fresenius, Janssen, Leo Pharma, Mitsubishi Tanabe, Novartis, Pierre-Fabre, Takeda, Toray Corporation, and Vichy. Dr Regnault, Ms Thurston, and Dr Papavassilis are employees of and/or own stock in Novartis. Dr Balki has no conflicts of interest to declare.”</p>
<i>Risk of bias</i>	

Mrowietz SCULPTURE, 2015 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p 28): "were randomised" Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 28): "administered via 2 150-mg SC injections or one 150-mg SC and one placebo SC injection respectively" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 28): "administered via 2 150-mg SC injections or one 150-mg SC and one placebo SC injection respectively" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 966, analysed 966 Management of missing data: Quote (p 29): "Missing values for PASI or IGA 2011 modified version responses were imputed as non response regardless of the reason for missing data" Comment: probably done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01406938) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

Nakagawa 2016

Methods	RCT, active/placebo-controlled, double blind Date of study: October 2012- March 2013 Setting: multicentre (56) in Japan
Participants	<b>Randomised:</b> 151 participants (mean age 45 years, 120 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12, BSA <math>\geq</math> 10), age 20-70 years</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Past history of malignant tumours, active infection, uncontrolled cardiovascular disorder</li> </ul>

	<ul style="list-style-type: none"> <li>• Had received anti IL17 (RA) treatment</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 6/151 (4%); brodalumab 70 group (2), brodalumab 140 group (0), brodalumab 210 group (0), placebo group (4)</li> <li>• AEs: brodalumab 70 group (1)</li> <li>• Full consent withdrawal: brodalumab 70 group (1), placebo group (1)</li> <li>• Symptoms worsening: placebo group (1)</li> </ul>	
Interventions	<p><b>Intervention</b></p> <p>A. Brodalumab (n = 39), SC, 70 mg, 2 injections week 0, 1 injection eow</p> <p><b>Control intervention</b></p> <p>B. Brodalumab (n = 37), SC, 140 mg, 2 injections week 0, 1 injection eow</p> <p>C. Brodalumab (n = 37), SC, 210 mg, 2 injections week 0, 1 injection eow</p> <p>D. Placebo (n = 38), orally (same drug administration)</p>	
Outcomes	<p>Assessments at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• % improvement in PASI</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> <li>• PGA 0/1</li> <li>• PASI 90/100</li> <li>• AEs</li> </ul>	
Notes	<p>Funding source: Quote (p 51) “The study was supported by Kyowa Hakko Kirin Co., Ltd.”</p> <p>Declarations of interest (p 51): “H. Nakagawa is a consultant and/or received research grants and/or speaker honoraria from for Kyowa Hakko Kirin Co., Ltd., AbbVie, Mitsubishi-Tanabe Pharma, Janssen Pharmaceutical K.K., Novartis Pharma K.K., Eli Lilly Japan K.K., LEO Pharma Maruho Corporation Limited and MSD K.K.H. Niiro has no conflict of interest to declare. K. Ootaki is an employee of Kyowa Hakko Kirin Co., Ltd.”</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote (p 45): “were randomised to receive...” Comment: not stated
Allocation concealment (selection bias)	Unclear risk	Quote (p 45): “were randomised to receive...” Comment: not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (p 51): “double-blind...” Comment: not stated

**Nakagawa 2016** (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of the method used to guarantee blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Randomly assigned 151, analysed 151 Comment: no supplementary explanation regarding the management of missing data
Selective reporting (reporting bias)	High risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01748539) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported except for participant-reported outcome

**Nugteren-Huying 1990**

Methods	RCT, active/placebo-controlled, double blind Date of study: not stated Setting: multicentre in the Netherlands
Participants	<b>Randomised:</b> 39 participants (mean age 44 years, 27 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (BSA <math>\geq</math> 10)</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Pregnancy, kidney insufficiency, liver insufficiency</li> <li>• Had uncontrolled cardiovascular disorder</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• 5/39 (12.8%)</li> <li>• Time and reason: not stated</li> </ul>
Interventions	<b>Intervention</b> A. Dimethylfumarate (n = 12), orally, 120 mg, gradual increase 1-6 tablets, once a day, 16 weeks <b>Control intervention</b> B. Octyl hydrogen fumarate (n = 10), orally, 284 mg, gradual increase 1-6 tablets, once a day, 16 weeks C. Placebo (n = 12), orally, once a day, 16 weeks
Outcomes	Assessments at 16 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• BSA</li> </ul> <b>Secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• Score of infiltration and scaling</li> <li>• Side effects</li> </ul>

Notes	Funding source: not stated Declarations of interest: not stated	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote (p 331): "The patients were randomly assigned..." Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (p 331): "The patients were randomly assigned..." Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 331): "The double-blind treatment lasted 16 weeks for each patients... All tablets (provided by Fumapharm AG, Muri, Switzerland) had the same appearance, size and colour" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 331): "The double-blind treatment lasted 16 weeks for each patients... All tablets (provided by Fumapharm AG, Muri, Switzerland) had the same appearance, size and color" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Randomly assigned 39, analysed 34 Comment: no description of the method used to perform analyses of the primary outcome and to manage missing data
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

Olsen 1989

Methods	RCT, placebo-controlled, double-blind trial Date of study: not stated Setting: not stated
Participants	<b>Randomised:</b> 15 participants, age range 23-72 years, 11 male <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Moderate-severe psoriasis</li> <li>• BSA <math>\geq</math> 10</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Pregnancy, kidney insufficiency, liver insufficiency</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• 3/15 (20%)</li> <li>• Disease flare-up (n = 3)</li> </ul>
Interventions	<b>Intervention</b> A. Acitretin (n = 10), orally, 25/50 mg, daily, 8 weeks <b>Control intervention</b> B. Placebo (n = 5), orally, daily, 8 weeks
Outcomes	Assessments at 8 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• Not clearly defined</li> </ul> <b>Secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• Body surface area</li> <li>• Scale</li> <li>• Side effects</li> </ul>
Notes	Funding by Hoffman-La Roche Inc Declarations of interest: not stated

*Risk of bias*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p 681): "Patients were assigned to .. in a random, double-blind fashion" Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (p 681): "Patients were assigned to .. in a random, double-blind fashion" Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (p 681): "Patients were assigned to .. in a random, double-blind fashion" Comment: visible adverse effects of acitretin such as cheilitis were visible

**Olsen 1989** (Continued)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (p 681): "Patients were assigned to .. in a random, double-blind fashion" Comment: visible adverse effects of acitretin such as cheilitis were visible
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	15 included / Number of patients analysed not stated Comment: no description of the methods used to perform the efficacy analyses and to manage the missing data
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section were reported

**Ortonne 2013**

Methods	RCT, active-controlled, open-label study Date of study: 21 September 2007-August 2009 Setting: 17 centres in Austria, France, Greece and Italy
Participants	<p><b>Randomised:</b> 72 participants randomised, 69 analysed (mean age 46 years, 50 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis</li> <li>• PASI <math>\geq</math> 10, PGA moderate or severe, BSA &gt; 10, DLQI &gt; 10</li> <li>• Age 18-70 years</li> <li>• Overall NAPS1 &gt; 14</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• TB infection; recent serious infection within 1 month of etanercept administration or active infection at screening; or known history of HIV infection.</li> <li>• Prior exposure to any biologic treatment was prohibited</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 12/72 (17%), BIW/QW group (7), QW/QW group (5)</li> <li>• AEs: BIW/QW group (2), QW/QW group (1)</li> <li>• Participants' request or withdrawal request: BIW/QW group (1), QW/QW group (4)</li> <li>• Death: BIW/QW group (1)</li> <li>• Other: BIW/QW group (3)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Etanercept twice-a-week/once-a-week group (n = 38), 50 mg SC twice a week for 12 weeks then 50 mg once a week to week 24</p> <p><b>Control intervention</b></p> <p>B. Etanercept once-a-week/once-a-week group (n = 34), 50 mg SC injections once a week for the full 24-week treatment period</p>

Outcomes	Assessments at 24 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"><li>• NAPSI</li></ul> <b>Secondary outcomes of the trial</b> <ul style="list-style-type: none"><li>• NAPSI 50/75</li><li>• PASI 50/75</li><li>• PGA0/1</li><li>• DLQI</li><li>• AEs</li></ul>	
Notes	Funding source, quote (p 1080): “TWyeth Research, which was acquired by Pfizer in October 2009, sponsored this clinical trial and was responsible for the collection and analysis of data. Editorial medical writing assistance was funded by Pfizer Inc.” Declarations of interest (p 1080): “J.P.O. has been an investigator or consultant for Schering-Plough, Abbott, Merck-Serono, Centocor, Pfizer, Janssen-Cilag, Meda-Pharma, Pierre-Fabre, Galderma and Leo-Pharma. C.P. has been an investigator or consultant for Abbott, Amgen, Celgene, Janssen Cilag, Leo Pharma, Novartis and Pfizer Inc. E.B. has no conflicts of interest. V.M., G.G., Y.B. and J.M.G. are employees of Pfizer Inc.”	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p 1081): “Patients were randomised by the investigator or other authorized person using an automatic online enrolment system in a 1:1 ratio” Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 1081): “Patients were randomised by the investigator or other authorized person using an automatic online enrolment system in a 1:1 ratio” Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (p 1081): “This was a multicenter, multinational, randomised, open-label study” Comment: not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (p 1081): “This was a multicenter, multinational, randomised, open-label study” Comment: not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	72 included/69 analysed Quote (p 1082): “All efficacy analyses were based on the modified intent-to treat (mITT) population, which was defined



		as all patients who had received one or more doses of ETN and had baseline and post baseline data...The MMRM and GEE models have been developed for the analysis of longitudinal categorical data and to handle missing data without any imputation; this kind of model is preferred to the last-observation carried forward approach for analysis of longitudinal data” Comment: probably done
Selective reporting (reporting bias)	Low risk	Comment: The protocol for the study was available on ClinicalTrials.gov (NCT00581100) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

## Papp 2005

Methods	RCT, placebo-controlled, double blind Date of study: not stated Location: 50 centres in USA, Canada & Western Europe
Participants	<p><b>Randomised:</b> 611 participants (mean age 45 years, male 382 out of 583 participants who received 1 dose)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 10, BSA <math>\geq</math> 10%, age <math>\geq</math> 18 years)</li> <li>• Non-response to topical treatment</li> <li>• Only 1 previous systemic treatment allowed</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Kidney insufficiency, liver insufficiency</li> <li>• Had received biologics (antiTNF)</li> <li>• Had an active infection</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 52/611 (8.5%)</li> <li>• Placebo (26): refusal (7) eligibility (6) lost to follow-up (6) AE (2) lack efficacy (4) protocol requirement (1)</li> <li>• Etanercept 25 (13): refusal (5) eligibility (4) AE (3) lack efficacy (1)</li> <li>• Etanercept 50 (13): refusal (5) eligibility (2) lost to follow-up (3) AE (2) lack efficacy (1)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Etanercept (n = 204), SC, 25 mg twice a week, 12 weeks</p> <p><b>Control intervention</b></p> <p>B. Etanercept (n = 203), SC, 50 mg twice a week, 12 weeks</p> <p>C. Placebo (n = 204), SC, twice a week, 12 weeks</p>

Outcomes	Assessments at 12 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>● PASI 75</li> </ul> <b>Secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>● Proportion of participants with PGA score of 0 or 1 at Week 12</li> <li>● PASI 50 at Week 12</li> <li>● PASI 90 at Week 12</li> <li>● Percentage improvement from baseline at week 12 to PASI</li> <li>● AEs</li> <li>● QoL</li> </ul>	
Notes	Funding source, quote (p 1304): "This study was supported by Immunex Corporation (Seattle, WA, U.S.A)" Declarations of interest: (p 1304) S.T. has received research support from Amgen; C.E. M.G. has been a paid consultant for Wyeth and Amgen; A.M.N and R.Z. are both full-time employees of Amgen."	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote (p 1305): "Patients were randomly assigned (using an Interactive Voice Response system) to receive placebo or etanercept) Comment: not stated
Allocation concealment (selection bias)	Low risk	Quote (p 1305): "Patients were randomly assigned (using an Interactive Voice Response system) to receive placebo or etanercept) Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 1305): " the patients, study site personnel and all sponsor representatives remained blinded to the initial randomisation treatment groups..." Comment: placebo-controlled, probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 1305): " the patients, study site personnel and all sponsor representatives remained blinded to the initial randomisation treatment groups..." Comment: placebo-controlled, probably done

**Papp 2005** (Continued)

<p>Incomplete outcome data (attrition bias) All outcomes</p>	<p>Low risk</p>	<p>611 randomised participants, 583 analysed (28 participants did not receive the treatment and were excluded from the analyses). Sensitivity analysis (Table 2) were performed with the 611 randomised participants Management of missing data: quote "In the analyses, missing post baseline efficacy data were imputed using last observation carried forward. In addition, a sensitivity analysis was performed on the binary efficacy endpoints to evaluate the robustness of the primary analysis. This sensitivity analysis included all randomised patients. In addition, rather than using LOCF imputation patients with missing data at a given visit were assumed to have not met the response criteria for that endpoint" Comment: the main result (primary outcome) was not an ITT analysis</p>
<p>Selective reporting (reporting bias)</p>	<p>High risk</p>	<p>Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported except for the results of participant-reported endpoints summarized in a separate publication</p>

**Papp 2012**

<p>Methods</p>	<p>RCT, placebo-controlled, double-blind trial Date of study: December 2009-April 2010 Location: 23 centres worldwide</p>
<p>Participants</p>	<p><b>Randomised:</b> 198 participants (mean age 42 years, 107 male) <b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis</li> <li>• PASI <math>\geq</math> 12, BSA &gt; 10%</li> <li>• Age 18-70 years</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Pregnancy, immunosuppression</li> <li>• Had past history of malignant tumours</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 10/198 (5%)</li> <li>• Brodalumab 70: ineligible (1)</li> <li>• Brodalumab 140: decision (1)</li> <li>• Brodalumab 210: (3): deviation (1) consent withdrawn (1) decision (1)</li> <li>• Brodalumab 280: (2): ineligible (1), AE (1)</li> </ul>

	<ul style="list-style-type: none"> <li>• Placebo (3): ineligible (1), consent withdrawn (2)</li> </ul>	
Interventions	<p><b>Intervention</b></p> <p>A. Brodalumab 70 (n = 39), SC, 70 mg, day 1-weeks 1, 2, 4, 6, 8, 10, 10 weeks</p> <p><b>Control intervention</b></p> <p>B. Brodalumab 140 (n = 39), SC, 140 mg, day 1 and weeks 1, 2, 4, 6, 8, 10, 10 weeks</p> <p>C. Brodalumab 210 (n = 40), SC, 210 mg, day 1 and weeks 1, 2, 4, 6, 8, 10, 10 weeks</p> <p>D. Brodalumab 280 (n = 42), SC, 280 mg, day 1 and weeks 1, 2, 4, 6, 8, 10, 10 weeks</p> <p>E. Placebo (n = 38), SC, day 1 and weeks 1, 2, 4, 6, 8, 10, 10 weeks</p>	
Outcomes	<p>Assessments at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 50/90/100 at week 12</li> <li>• BSA</li> <li>• PGA</li> <li>• DLQI</li> <li>• AEs</li> </ul>	
Notes	<p>Funding source, quote (p 1182): “The study was funded by Amgen”</p> <p>Declarations of interest (p 1188-89): “Dr. Papp reports receiving consulting fees from Abbott, Amgen, Astellas, Celgene, Centocor, Eli Lilly, Galderma, Graceway Pharmaceuticals, Janssen, Johnson &amp; Johnson, Merck, Novartis, Pfizer, and UCB, lecture fees from Abbott, Amgen, Astellas, Celgene, Centocor, Galderma, Janssen, LEO Pharma, Merck, Novartis, Pfizer, and Stiefel, and grant support from Abbott, Amgen, Astellas, Celgene, Centocor, Eli Lilly, Galderma, Glaxo-SmithKline, Graceway Pharmaceuticals, Janssen, Johnson &amp; Johnson, Medimmune, Merck, Novartis, Pfizer, Stiefel, and UCB; Dr. Leonardi, receiving consulting fees from Abbott, Amgen, Centocor, Eli Lilly, and Pfizer, lecture fees from Abbott and Amgen, and investigator fees from Abbott, Amgen, Celgene, Centocor, Galderma, GlaxoSmithKline, Incyte, Maruho, Novartis, Novo Nordisk, Pfizer, Schering-Plough (now Merck), Sirtris, Stiefel, Vascular Biogenics, and Wyeth (now Pfizer); Dr. Menter, receiving consulting fees from Abbott, Amgen, Astellas, Centocor, Galderma, Genentech, and Wyeth, lecture fees from Abbott, Amgen, Centocor, Galderma, and Wyeth, and fees for expert testimony from Galderma; Dr. Krueger, receiving consulting fees from Centocor, Eli Lilly, and Pfizer and grant support from Amgen, Centocor, Eli Lilly, Merck, and Pfizer; and Drs. Krikorian, Aras, Li, Russell, Thompson, and Baumgartner being full-time employees of Amgen. No other potential conflict of interest was relevant to this article was reported.”</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (protocol p 30): “Randomization: IVRS will be used to randomise subjects into the study. The randomisation list will be generated by Amgen using a permuted block design within each of 4 strata based

**Papp 2012** (Continued)

		on BMI at baseline, and participation in the PK study” Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (protocol p 30): “Randomization: IVRS will be used to randomise subjects into the study Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (protocol p 24 & 50): “double-blind placebo controlled... Subjects randomised to active drug will receive additional placebo injections as necessary to maintain the blind” Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (protocol p 39): “PASI assessments will be performed by a blinded assessor. The blinded assessor will be a healthcare professional who has been certified as trained with the standard PASI” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	198 included/198 analysed Quote (p 1183): “The analyses of efficacy endpoints were performed on data from all patients who underwent randomisation (full set analysis), according to the intention-to-treat principle... Missing data were handled by means of the baseline-value-carried-forward method or the imputation of no response” Comment: probably done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00307437) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

**Papp 2012a**

Methods	RCT, placebo-controlled, double blind Date of study: July 2008-August 2009 Location: 42 centres in USA, Canada
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Participants	<p><b>Randomised:</b> 197 participants (tofacitinib 2 mg (49) mean age 46 years, 29 male; tofacitinib 5 (49) mean age 44 years, 29 male; tofacitinib 15 (49) mean age 44 years, 31 male; placebo (n = 50) mean age 44 years, 36 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 13, BSA <math>\geq</math> 15%), age <math>\geq</math> 18</li> <li>• Number of allowed previous biologic treatments: any</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Had an active infection</li> <li>• Had past history of malignant tumour (with the exception of adequately treated or excised basal cell or squamous cell carcinoma, or cervical carcinoma in situ)</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 48/197 (24%);</li> <li>• Tofacitinib 2 mg (11): AE (1), lack efficiency (2), lost to follow-up (4), decision (3), other (1)</li> <li>• Tofacitinib 5 mg (11): AE (2), lack efficiency (3), lost to follow-up (2), decision (4)</li> <li>• Tofacitinib 15 mg (6): AE (3), lack efficiency (1), other (1), decision (1)</li> <li>• Placebo (20): AE (3), lack efficiency (9), lost to follow-up (1), decision (7)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Tofacitinib (n = 49), orally, 2 mg, twice a day, 12 weeks</p> <p><b>Control intervention</b></p> <p>B. Tofacitinib, (n = 49), orally, 5 mg, twice a day, 12 weeks</p> <p>C. Tofacitinib (n = 49), orally, 15 mg, twice a day, 12 weeks</p> <p>D. Placebo (n = 50), orally, twice a day, 12 weeks</p>
Outcomes	<p>Assessments at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• Safety</li> <li>• Proportion of participants achieving a PASI 50 response (weeks 2, 4, 8, 12, 14 and 16)</li> <li>• Proportion of participants achieving a PASI 90 response week 12</li> <li>• Actual and change from baseline in PASI and PASI component scores baseline/day 1 and weeks 2, 4, 8, 12, 14 and 16</li> <li>• Proportion of participants with PGA of clear/almost clear, weeks 2, 4, 8, 12, 14 and 16</li> <li>• Proportion of participants achieving a PASI 75 response (weeks 2, 4, 8, 14 and 16)</li> </ul>
Notes	<p>Funding source, quote (p 668): "This study was funded by Pfizer Inc"</p> <p>Declarations of interest (appendix): "K.A.P. has been a principal investigator, an advisor or consultant, a Scientific Officer, member of a Scientific Advisory Board and a speaker for the following groups: Abbott, Amgen, Astellas, Celgene, Centocor-Ortho Biotech, Incyte, Isotechnika, Janssen, Lilly, Medimmune, Merck, Pfizer Inc. and Novartis. A. M. has been on the Advisory Board, been a consultant to, been an investigator for, been a speaker for, obtained a research grant from, or obtained honoraria from the following groups: Abbott, Allergan, Amgen, Astellas, Asubio, Celgene, Centocor, DUSA, Eli Lilly, Galderma, Genentech, Novartis, Novo Nordisk, Pfizer Inc., Promius, Stiefel,</p>

	Syntrix Biosystems, Warner Chilcott and Wyeth. B.S. has been a principal investigator, an advisor or consultant, or a speaker for the following groups: Abbot, Amgen, Celgene, Centocor-Ortho Biotech, Janssen, Pfizer Inc., Maruho and Novartis. R.G.L. has been an investigator, served as a principal investigator or on the Advisory Board, or been a speaker for the following groups: Abbott, Amgen, CentocorOrtho Biotech, Pfizer Inc., Novartis and Celgene. R.W., S.K., H.T., P.G. and M.B. are employees of Pfizer Inc. J.A. H. was a full-time employee of Pfizer Inc. during the conduct and reporting of the study and now works at Novartis Pharma AG, Basel, Switzerland. “	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p 669): “A computer-generated central randomisation schema was implemented in an automated web telephone system.” Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 669): “A computer-generated central randomisation schema was implemented in an automated Treatment identification was concealed by use of study drugs that were identical in labelling, packaging, appearance and odour“ web telephone system.” Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 669): “Patients, investigational site staff, the Pfizer study team and data analysts were blinded to treatment from the time of randomisation until database lock.. . Treatment identification was concealed by use of study drugs that were identical in labelling, packaging, appearance and odour” Comment: probably one
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 669): “Patients, investigational site staff, the Pfizer study team and data analysts were blinded to treatment from the time of randomisation until database lock.. . Treatment identification was concealed by use of study drugs that were identical in labelling, packaging, appearance and odour” Comment: probably one
Incomplete outcome data (attrition bias) All outcomes	Low risk	197 included / 195 analysed Quote (p 670): “The full analysis set included all randomised patients who re-

**Papp 2012a** (Continued)

		ceived one or more doses of investigational drug...This population ... represents a modified intent-to-treat analysis... Patients with missing values had the missing values imputed but last observation carried forward.... As a sensitivity analysis the patients [with missing values] were also considered nonresponders (NRI)” Comment: mITT and two patients out of 197 not analysed
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00678210) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

**Papp 2012b**

Methods	RCT, active/placebo-controlled, double blind Date of study: September 2008-October 2009 Location: 35 centres in Canada and USA
Participants	<b>Randomised:</b> 352 participants (mean age 44 years, 221 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12, BSA <math>\geq</math> 10%)</li> <li>• Age <math>\geq</math> 18 years</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Had a history of, or present, significant disease, including Mycobacterium TB or HIV infection</li> <li>• Had a positive screening test for hepatitis B or C</li> <li>• Pregnant or breastfeeding</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• 65/352 (11%) at 16w;</li> <li>• Apremilast 30 twice daily: (18): AE (10), lack efficacy (2), withdrew consent (4), lost to follow-up (1), Other (1)</li> <li>• Apremilast other (31): AE (9), lack efficacy (5), withdrew consent (8), protocol violation (7), other (2)</li> <li>• Placebo (16): AE (5), lack efficacy (4), withdrew consent (2), death (1), lost to follow up (2), protocol deviation (1), other (1)</li> </ul>
Interventions	<b>Intervention</b> A. Apremilast (n = 88), orally, 30 mg, twice a day, 16 weeks <b>Control intervention</b> B. Apremilast (n = 176), orally, 10-20 mg twice a day, 16 weeks C. Placebo (n = 88), orally, twice a day 16 weeks



Outcomes	<p>Assessments at 16 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PGA 0 or 1</li> <li>• PASI 50/90</li> <li>• DLQI</li> <li>• SF36</li> </ul>
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Notes	<p>Funding source quote (p 738): “Funding Celgene Corporation”</p> <p>Declarations of interest quote (p 745): “KP has served as an investigator for Abbott, Amgen, Celgene, Centocor, Galderma, Incyte, Isotechnika, Janssen, Lilly, Medimmune, Merck, Novartis, and Pfizer; an adviser for Abbott, Amgen, Astellas, BMS, Celgene, Centocor, Galderma, Incyte, Isotechnika, Janssen, Johnson &amp; Johnson, Lilly, Medimmune, Merck, Novartis, Pfizer, and UCB; and a speaker for Abbott, Amgen, Astellas, Celgene, Centocor, Isotechnika, Janssen, Novartis, and Pfizer. JCC has served as an investigator for Celgene, Centocor, Novartis, and Pfizer; as a speaker for Centocor and Abbott; and as an adviser for Pfizer, Abbott, and Novartis. LR has been a paid investigator for doing clinical trials for Amgen, Genentech, Abbott, Centocor, Basilea, Leo, Isotechnika, Stiefel, GSK, Galderma, 3-M, Serono, Novartis, Astellas, UCB, Celgene, Johnson &amp; Johnson, and Pfizer. HS has served as an investigator for Abbott, Centocor, Celgene, Amgen, and Pfizer; as a speaker for Abbott and Centocor; and as an adviser for Centocor. RGL has served as an investigator for Abbott, Centocor, Celgene, Amgen, Pfizer, Johnson &amp; Johnson/Ortho Biotech, and Novartis; as a speaker for Abbott, Centocor, Amgen, Pfizer, Johnson &amp; Johnson/Ortho Biotech, and Novartis; and as an adviser for Abbott, Centocor, Celgene, Amgen, Pfizer, Johnson &amp; Johnson/Ortho Biotech, and Novartis. RTM has served as an investigator for Abbott, Centocor, Celgene, Amgen, Novartis, Lilly, Pfizer, Allergan, and Galderma; as a speaker for Centocor and Amgen; and as an adviser for Centocor. CH and RMD are employees of Celgene Corporation.”</p>
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**Risk of bias**

Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 739): “Eligible patients were randomly assigned in a 1:1:1:1 ratio to oral apremilast 10 mg twice daily, apremilast 20 mg twice daily, apremilast 30 mg twice daily, or placebo, with a permuted-block randomisation list generated by an interactive voice response system (ClinPhone, East Windsor, NJ, USA).” Comment: clearly described
Allocation concealment (selection bias)	Low risk	Quote (p 739): “Eligible patients were randomly assigned in a 1:1:1:1 ratio to oral apremilast 10 mg twice daily, apremilast 20 mg twice daily, apremilast 30 mg twice daily, or placebo, with a permuted-block

**Papp 2012b** (Continued)

		randomisation list generated by an interactive voice response system (ClinPhone, East Windsor, NJ, USA). Comment: clearly described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 739): "Treatment was double-blind for the first 16 weeks of the 24-week treatment phase." Comment: probably done, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 739): "Treatment was double-blind for the first 16 weeks of the 24-week treatment phase." Comment: probably done, placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	352 included / 352 analysed Quote (p 740): "Efficacy data were assessed by intention to treat. Missing data were handled with the last-observation carried-forward method." Comment: number of lost to follow-up and reasons comparable across group
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00773734) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

**Papp 2013a**

Methods	RCT, placebo-controlled, double blind trial Date of study: March 2010-February 2011 Location: 19 international centres
Participants	<b>Randomised:</b> 125 participants (mean age 46 years, 91 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>● Participants with moderate-severe psoriasis</li> <li>● PASI <math>\geq</math> 12, IGA <math>\geq</math> 3, BSA <math>\geq</math> 10%</li> <li>● Age <math>\geq</math> 18 years</li> <li>● Non-response to topical treatment</li> <li>● Non-response to phototherapy</li> <li>● Non-response to conventional systemic treatment</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>● Pregnancy</li> </ul> <b>Dropouts and withdrawals</b>

	<ul style="list-style-type: none"> <li>• 47/125 (38%) at 36 weeks: secukinumab 25 (15); secukinumab 75 (10); secukinumab 225 (4); secukinumab 450 (7); placebo (11)</li> <li>• Unsatisfactory therapeutic effect: secukinumab 25 (4); secukinumab 75 (6); secukinumab 225 (2); secukinumab 450 (0); placebo (6)</li> <li>• Withdrew consent: secukinumab 25 (8); secukinumab 75 (2); secukinumab 225 (1); secukinumab 450 (2); placebo (3)</li> <li>• Administrative problems: secukinumab 25 (1); secukinumab 75 (1); secukinumab 225 (0); secukinumab 450 (2); placebo (1)</li> <li>• Lost to follow-up: secukinumab 25 (1); secukinumab 75 (0); secukinumab 225 (1); secukinumab 450 (2); placebo (0)</li> <li>• AEs: secukinumab 25 (1); secukinumab 75 (1); secukinumab 225 (0); secukinumab 450 (1); placebo (0)</li> <li>• Death: secukinumab 25 (0); secukinumab 75 (0); secukinumab 225 (0); secukinumab 450 (0); placebo (1)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Secukinumab (n = 29), SC, 25 mg, 0, 4, 8 weeks, 12 weeks</p> <p><b>Control intervention</b></p> <p>B. Secukinumab (n = 26), SC, 3 x 25 mg, 0, 4, 8 weeks, 12 weeks</p> <p>C. Secukinumab (n = 21), SC, 3 x 75 mg, 0, 4, 8 weeks, 12 weeks</p> <p>D. Secukinumab (n = 27), SC, 3 x 150 mg, 0, 4, 8 weeks, 12 weeks</p> <p>E. Placebo (n = 22), SC, 0, 4, 8 weeks, 12 weeks</p>
Outcomes	<p>Assessments at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• IGA 12 weeks</li> <li>• PASI 50/90 12 weeks</li> <li>• Time to relapse</li> <li>• Effect on PASI over time</li> <li>• ECG</li> <li>• AE</li> </ul>
Notes	<p>Funding source (p412): “Novartis Pharm AG, Basel, Switzerland”</p> <p>Declarations of interest (Appendix): “K.A.P. has received honoraria for lecturing at industry-sponsored meetings and has received industry funding for presentations and consultation at national and international meetings; he has also received research grants from and been a paid consultant to Novartis and other pharmaceutical companies; has served as a scientific officer for pharmaceutical and biotechnology corporations; and is a participant on clinical, scientific and corporate advisory boards. R.G.L. has been a member of scientific advisory boards and served as a clinical investigator for Abbott, Amgen, Celgene, Centocor/Johnson &amp; Johnson, Eli Lilly, Fujisawa, Novartis and Pfizer, and has served as a speaker for Abbott, Amgen, Centocor/Johnson &amp; Johnson, Fujisawa and Novartis. B.S. has consulted for Novartis and several other pharmaceutical companies; he has been a member of an advisory board for Novartis and several other pharmaceutical companies. S.H., H.J.T., C.P. and H.B.R. are full-time employees of and own stock in Novartis. M.A., D.R.B. and P.K. declare no conflicts of interest.”</p>

<i>Risk of bias</i>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p 414): "The randomisation numbers were generated by an interactive voice response provider using a validated automated system" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 414): "The randomisation numbers were generated by an interactive voice response provider using a validated automated system" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 413 & 414): "Double-blind, placebo controlled...Patients, investigator staff, persons performing the assessments and data analysts were blinded ... remained blind until final database lock" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 413 & 414): "Double-blind, placebo controlled...Patients, investigator staff, persons performing the assessments and data analysts were blinded ... remained blind until final database lock" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	High risk	125 included/125 analysed Quote (p 415): "The full analysis set consisted of all patients who were randomised. .. The missing score was imputed by carrying forward the last non missing post baseline PASI" Comment: very high number of withdrawals (38%)
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01071252) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

Methods	RCT, active/placebo-controlled, double blind Date of study: April 2006-May 2007 Location: multicentre (30) in Canada, the Czech Republic, and Germany
Participants	<p><b>Randomised:</b> 260 participants (mean age 46 years, 163 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12, BSA &gt; 10%)</li> <li>• Age <math>\geq</math> 18 years</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• History of clinically significant medical or psychiatric diseases</li> <li>• Pregnancy or lactation</li> <li>• History of active Mycobacterium TB infection</li> <li>• HIV, hepatitis B or C, history of malignancy within 5 years of screening or evidence of skin conditions</li> <li>• Current erythrodermic, guttate or pustular psoriasis</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 47/260 (18%) at 12w;</li> <li>• Apremilast (28): AE (8), lack efficiency (8), withdrew consent (4), lost to follow-up (3), protocol violation (3), other (2)</li> <li>• Placebo (19): AE (7), lack efficiency (5), withdrew consent (2), lost to follow-up (1), protocol violation (2), other(2)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Apremilast (n = 173), orally, 10-20 mg, twice a day, 12 weeks</p> <p><b>Control intervention</b></p> <p>B. Placebo (n = 87)</p>
Outcomes	<p>Assessments at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PGA</li> <li>• PASI 50/90</li> <li>• BSA</li> <li>• AEs</li> </ul>
Notes	<p>Funding source quote (p 27): “This study was sponsored by Celgene Corporation”</p> <p>Declarations of interest (p27): “Dr Papp is a consultant and investigator for Celgene Corporation, Abbott, Amgen, Centocor, Janssen-Ortho, Merck, Novartis and Pfizer and an investigator for Astellas, Leo Pharma and Galderma, receiving honoraria and grants. Dr Kaufmann is an investigator for Abbott, Centocor, Leo, Novartis, Wyeth and Celgene Corporation, but has not received financial compensation. The Department of Dermatology received investigator fees for performing the clinical trials. He served as a speaker for Basilea and Allmiral and received honoraria from each. Dr Thaci is on the advisory board of and is a consultant, investigator and speaker for Abbott, Leo, Novartis, Pfizer, Biogen-Idec, Janssen-Cilag and MSD, and received honoraria from each. He is also an investigator for Celgene Corporation. The Department of Dermatology received honoraria compensation for conducting studies; no direct compensation was received. Ms Hu receives a salary as an employee of Celgene Corporation. Ms Sutherland receives</p>

	a salary, stocks and stock options as an employee of Celgene Corporation. Dr Rohane received a salary and stock options as a former employee of Celgene Corporation. ”	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote (p 377): “ investigators randomised subjects 1 : 1 : 1 to double-blind treatments for 12 weeks with placebo, apremilast 20 mg QD or apremilast 20 mg twice daily” Comment: no description of the method to guarantee the random sequence generation
Allocation concealment (selection bias)	Low risk	Quote (p 377): “Using an interactive voice response system, investigators randomised subjects 1 : 1 : 1 to double-blind treatments” Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 377): “One capsule of placebo or apremilast was taken orally in the morning before meals, and one capsule of placebo or apremilast was taken in the evening” Comment: probably done, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 377): “One capsule of placebo or apremilast was taken orally in the morning before meals, and one capsule of placebo or apremilast was taken in the evening” Comment: probably done, placebo controlled
Incomplete outcome data (attrition bias) All outcomes	High risk	260 included / 260 analysed Management of missing data were not stated and substantial number lost to follow-up (18%)
Selective reporting (reporting bias)	High risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00606450) The pre-specified outcomes listed on ClinicalTrials.gov were not detailed, the choice of the primary outcome was not clearly defined. In the methods section, PASI 75 was defined as the primary outcome, no QoL outcomes were listed in the methods section although they were in the protocol on

## Papp 2015a

Methods	RCT, active/placebo-controlled, double blind Date of study: November 2010-June 2012 Location: 64 centres in Europe, Asia & North America
Participants	<p><b>Randomised:</b> 355 participants (mean age 45 years, 270 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12, BSA <math>\geq</math> 10, PGA moderate, marked or severe), age <math>\geq</math> 18 years</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>Active infection, past history of malignant tumours, active infection, kidney or liver insufficiency, uncontrolled cardiovascular disorder, uncontrolled diabetes, uncontrolled hypertension</li> <li>Had received <math>\geq</math> 2 TNF alpha antagonists with discontinuation owing to lack of efficacy</li> <li>Had received anti IL12/23</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>15/355 (4.5%)</li> <li>AEs: tildrakizumab 5 (1), tildrakizumab 25 (2), tildrakizumab 100 (1), tildrakizumab 200 (1), placebo (1)</li> <li>Withdrew consent: tildrakizumab 5 (0), tildrakizumab 25 (3), tildrakizumab 100 (0), tildrakizumab 200 (0), placebo (4)</li> <li>Protocol noncompliance: tildrakizumab 5 (0), tildrakizumab 25 (0), tildrakizumab 100 (0), tildrakizumab 200 (1), placebo (0)</li> <li>Did not meet protocol eligibility: tildrakizumab 5 (1), tildrakizumab 25 (0), tildrakizumab 100 (0), tildrakizumab 200 (0), placebo (1)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Tildrakizumab (n = 42), SC, 5 mg weeks 0, 4, every 12 weeks</p> <p><b>Control intervention</b></p> <p>B. Tildrakizumab (n = 92), SC, 15 mg weeks 0, 4, every 12 weeks C. Tildrakizumab (n = 89), SC, 50 mg weeks 0, 4, every 12 weeks D. Tildrakizumab (n = 86), SC, 100 mg weeks 0, 4, every 12 weeks E. Tildrakizumab (n = 46), SC, 200 mg weeks 0, 4, every 12 weeks</p>
Outcomes	<p>Assessments at 16 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>PASI 90</li> <li>PASI 75 at week 12</li> <li>PGA 0/1</li> <li>DLQI</li> </ul>

Notes	<p>Funding source:  Quote (p 930): “This study was funded by Merck &amp; Co, nc., Kenilworth, NJ, USA”  Declarations of interest (Appendix 1): ”E.P.B., A.M., Q.L., Y.Z. and R.S. are current or former employees of Merck &amp; Co., Inc. K.P. has served as a consultant, advisory board member and/or investigator for Abbott (AbbVie), Amgen, Biogen Idec, Boehringer Ingelheim, Celgene, Centocor, Foreward Pharma, Galderma, Genentech, Incyte, Isotechnika, Janssen, Kyowa Kirin, LEO Pharma, Lilly, Medimmune, Merck Sharp Dome, Merck Serono, Novartis, Regeneron, Stiefel, Takeda, Pfizer and USB. D.T. has served as a consultant, advisory board member and/or investigator for Abbott (AbbVie), Almiral, Amgen, Astellas, Biogen Idec, Boehringer Ingelheim, Celgene, Dignity, Forward Pharma, Galderma, GlaxoSmithKline, Isotechnika, Janssen-Cilag, LEO Pharma, Lilly, Maruho, Medac, Medimmune, Merck Sharp Dome, Merck Serono, Novartis, Regeneron, Sandoz, Sanofi-Aventis, Takeda and Pfizer. K.R. has served as a consultant and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Amgen, Biogen Idec, Celgene, Centocor, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Lilly, Medac, Merck, Novartis, Pfizer, Vertex and Takeda. E.R. has received travel support and nonfinancial support for histology study report preparation from Merck &amp; Co., Inc., and has received speaker’s fees and travel support, or served on advisory boards for Abb- Vie, Novartis, Pfizer, Janssen and Amgen. R.G.L. has served as a consultant and/or paid speaker for and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis, including AbbVie, Celgene, Centocor, Janssen-Cilag, LEO Pharma, Merck, MSD (formerly Essex, Schering-Plough), Novartis and Pfizer (formerly Wyeth). J.G.K. has received personal fees (consulting and/or speaking fees) and grants paid to his institution from Novartis, Pfizer, Janssen, Lilly, Merck, Kadmon, Dermira, Boehringer and BMS; Amgen, Innovaderm, Paraxel and Kyowa have paid grants to J.G.K.’s institution; J.G.K. has also received personal fees from Serono, Biogen Idec, Delenex, AbbVie, Sanofi, Baxter, Xenoport and Kineta. A.B.G. has current consulting/advisory board agreements with Amgen Inc., Astellas, Akros, Centocor (Janssen) Inc., Celgene Corp., Bristol Myers Squibb Co., Beiersdorf Inc., Abbott Labs (AbbVie), TEVA, Actelion, UCB, Novo Nordisk, Novartis, Dermipor Ltd, Incyte, Pfizer, Canfite, Lilly, Coronado, Vertex, Karyopharm, CSL Behring Biotherapies for Life, GlaxoSmithKline, Xenoport, Catabasis Meiji Seika Pharma Co., Ltd, Takeda, Mitsubishi Tanabe Pharma Development America, Inc, and has received research/educational grants (paid to Tufts Medical Center) from Centocor (Janssen), Amgen, Abbott (Abb- Vie), Novartis, Celgene, Pfizer, Lilly, Coronado, Levia, Merck and Xenoport. H.N. has received consultancy/speaker honoraria and/or grants from Novartis, Tanabe Mitsubishi, Maruho, Abbott/AbbVie, Eli Lilly, Merck Sharp &amp; Dohme, Janssen and LEO Pharma.”</p>	
<b><i>Risk of bias</i></b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote (p 931): “Randomisation of treatment and allocation was done centrally by means of an interactive web response system... Comment: no description of the method used to guarantee the random sequence



**Papp 2015a** (Continued)

		generation
Allocation concealment (selection bias)	Low risk	Quote (p 931): “Randomisation of treatment and allocation was done centrally by means of an interactive web response system...” Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (p 931): “double-blind” Comment: no description of the method used to guarantee blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (p 932): “double-blind” Comment: no description of the method used to guarantee blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 355, analysed 352 Management of missing data: Quote (p 932): “The primary analysis was performed on all randomised participants who received at least one or more doses of treatment. Participants who discontinued treatment prior to week 16... were considered to not have achieved PASI 75 at week 16” Comment: low number lost to follow-up
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01225731) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

**Papp AMAGINE-1, 2016**

Methods	RCT, placebo-controlled, double blind Date of study: 29 August 2012-12 March 2014 Location: 73 centres worldwide (Europe, USA & Canada)
Participants	<b>Randomised:</b> 661 participants (mean age 46 years, 484 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Aged 18-75</li> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12, PPGA <math>\geq</math> 3 and BSA <math>\geq</math> 10), failed to respond to, had a contraindication to, or were intolerant to at least one conventional systemic treatment</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Not plaque-type psoriasis</li> </ul>

	<ul style="list-style-type: none"> <li>• Active infection (TB, hepatitis B, C or HIV), had Crohn's disease and any uncontrolled significant medical condition</li> <li>• Had a myocardial infarction or unstable angina pectoris within 12 months before the first dose</li> <li>• Had active malignancy or a history of malignancy within 5 years</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 33/661(5%); brodalumab 210 (10), brodalumab 140 (11), placebo (12)</li> <li>• Ineligibility determined: brodalumab 210 (0), brodalumab 140 (0), placebo (2)</li> <li>• Not received study medication</li> <li>• AEs: brodalumab 210 (2), brodalumab 140 (3), placebo (3)</li> <li>• Death: brodalumab 210 (0), brodalumab 140 (0), placebo (0)</li> <li>• Lost to follow-up: brodalumab 210 (1), brodalumab 140 (1), placebo (1)</li> <li>• Withdrawal consent: brodalumab 210 (4), brodalumab 140 (3), placebo (3)</li> <li>• Other reason: brodalumab 210 (3), brodalumab 140 (4), placebo (3)</li> </ul>	
Interventions	<p><b>Intervention</b></p> <p>A. Brodalumab (n = 222), SC, 210 mg every 2 weeks</p> <p><b>Control intervention</b></p> <p>B. Brodalumab (n = 219), SC, 140 mg every 2 weeks</p> <p>C. Placebo (n = 220)</p>	
Outcomes	<p>Assessments at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> <li>• PGA success</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 100 &amp; PGA 0</li> <li>• Participant-reported outcomes)</li> <li>• AEs</li> </ul>	
Notes	<p>Funding source:</p> <p>Quote (p 1): "This study was funded by Amgen Inc. &amp; AstraZeneca/MedImmune."</p> <p>Declarations of interest (p 13-14): "K.A.P. has served as a consultant, investigator and/or speaker for AbbVie, Amgen Inc., Astellas Pharma, Bayer AG, Boehringer Ingelheim, Celgene, Eli Lilly and Company, Forward Pharma, Galderma, Janssen Biotech Inc., LEO Pharma, Merck, Novartis, Pfizer, Roche and UCB Pharma. K.R. has served as a consultant and/or paid speaker for and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis, including AbbVie, Amgen Inc., Biogen-Idec, Celgene, Centocor, Covagen, Forward Pharma, GSK, Janssen-Cilag, LEO Pharma, Lilly, Medac, MSD, Novartis, Pfizer, Takeda and Vertex. C.P. has served as a consultant and investigator for Amgen Inc., AbbVie, Boehringer, Janssen-Cilag, LEO Pharma, Lilly, Novartis and Pfizer. A.B. has served as a consultant and investigator for AbbVie, Amgen Inc., Anacor, Boehringer Ingelheim, Celgene, Eli Lilly and Company, Genentech, Janssen, Merck, Novartis, Pfizer, Regeneron and Sandoz."</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>

Random sequence generation (selection bias)	Unclear risk	Quote (p 2 & 3): “Patients were randomized... IP supply was controlled by interactive voice response system and box numbers were assigned at each visit” Comment: no description of the method used to guarantee the random sequence generation
Allocation concealment (selection bias)	Low risk	Quote (p 2 & 3): “Patients were randomized...IP supply was controlled by interactive voice response system and box numbers were assigned at each visit” Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 3): “Randomizations remained blinded to all patients and investigators.. . Throughout the study, patients received placebo as needed to maintain the blind until it was broken. ” Comment: probably done, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 3): “Randomizations remained blinded to all patients and investigators.. . Throughout the study, patients received placebo as needed to maintain the blind until it was broken. ” Comment: probably done, placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 661, 661 analysed Management of missing data: quote (p 4 & 5): “The full analysis set included all randomised patients... Mutiple imputations for missing data” Comment: probably done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01708590; AMAGINE-1). The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

Methods	RCT, placebo-controlled, double blind Date of study: September 2010-December 2012 Location: 72 centres in USA, Canada, Australia, Belgium, France, UK, Italy, Germany
Participants	<p><b>Randomised:</b> 844 participants (apremilast (562) mean age 46 years, 379 male; placebo (282) mean age 47 years, 194 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12, BSA <math>\geq</math> 10%, PGA <math>\geq</math> 3,</li> <li>• Age <math>\geq</math> 18 years</li> <li>• Number of allowed previous treatment line: any (candidate for systemic/phototherapy)</li> <li>• Number of allowed previous biologic treatments: any</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Pregnancy, immunodepression, clinically significant or major uncontrolled disease</li> <li>• Had an active infection</li> <li>• Clinically significant abnormality on 12-lead ECG at screening</li> <li>• Malignancy or history of malignancy (except for treated (ie, cured) basal cell or squamous cell in situ skin carcinomas and treated (ie, cured), CIN or carcinoma in situ of the cervix with no evidence of recurrence within the previous 5 years)</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 92/844 (11%) at 16w;</li> <li>• Apremilast (59): AE (23), lack efficiency (2), withdrew consent (12), lost to follow-up (7), deviation (7), noncompliance (7), other (1)</li> <li>• Placebo(33): AE (5), lack efficiency (7), withdrew consent (9), lost to follow-up (9), death (1), deviation (1), other (1)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Apremilast (n = 562), orally, 30 mg, twice a day, 16 weeks</p> <p><b>Control intervention</b></p> <p>B. Placebo (n = 282), orally, twice a day, 16 weeks</p>
Outcomes	<p>Assessments at 16 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• Static PGA 0 or 1</li> <li>• Number of participants with AEs (AE) in the placebo-controlled phase</li> <li>• Number of participants with a psoriasis flare or rebound during the placebo-controlled phase</li> <li>• Percent change from baseline in percent of affected BSA</li> <li>• Percent change from baseline in the PASI score</li> <li>• Percentage of participants who achieved a 50% improvement (response) in the PASI Score (PASI 50)</li> <li>• Change from baseline in pruritus VAS score</li> <li>• Change from baseline in the DLQI total score</li> <li>• Change from baseline in the Mental Component Summary score of the SF-36 Health Survey Version 2.0</li> <li>• Percentage of participants who achieved both a 75% improvement (response) in the PASI and static PGA score of clear (0) or almost clear (1) with at least 2 points'</li> </ul>

	reduction from baseline
Notes	Funding source quote (p 37): “This study was sponsored by Celgene Corporation” Declarations of interest (p 48): “Dr Papp has served as an investigator for Abbott (AbbVie), Amgen, Biogen Idec, Boehringer Ingelheim, Celgene, Centocor, Galderma, Genentech, Incyte, Isotechnika, Janssen, LEO Pharma, Lilly, MedImmune, Merck Sharp & Dohme, Merck-Serono, Novartis, Pfizer, Stiefel, and Wyeth; a consultant for Abbott, Amgen, Astellas, Biogen Idec, Boehringer Ingelheim, BMS, Celgene, Centocor, Forward Pharma, Galderma, Genentech, Incyte, Isotechnika, Janssen, Johnson & Johnson, Kyowa Kirin, LEO Pharma, Lilly, MedImmune, Merck Sharp & Dohme, Merck-Serono, Novartis, Pfizer, Takeda Pharmaceuticals, UCB, and Wyeth; and a speaker for Abbott, Amgen, Astellas, Celgene, Centocor, Isotechnika, Janssen, Novartis, and Pfizer. Dr Reich has served as a consultant and/or paid speaker for and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis including AbbVie, Amgen, Biogen Idec, Celgene, Centocor, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Lilly, Medac, Merck Sharp & Dohme, Novartis, Pfizer, Takeda, and Vertex. Dr Leonardi has served on the advisory board and as an investigator and/or speaker for Abbott, Amgen, Celgene, Centocor, Galderma, Genentech, GlaxoSmithKline, Lilly, Novartis, Novo Nordisk, Pfizer, Sirtris, Stiefel, Vascular Biogenics, and Wyeth.”

**Risk of bias**

Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 38): “ESTEEM 1 was.. multi-center, randomised, double-blind, placebo controlled study” Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Quote (p 38): “ESTEEM 1 was.. multi-center, randomised, double-blind, placebo controlled study” Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 38): “ESTEEM 1 was.. multi-center, randomised, double-blind, placebo controlled study... Blinding was maintained until all patients discontinued or completed the week 52 visit” Comment: probably done, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 38 & 39): “ESTEEM 1 was. . multicenter, randomised, double-blind, placebo controlled study... Blinding was maintained until all patients discontinued or completed the week 52 visit”

**Papp ESTEEM-1, 2015** (Continued)

		Comment: probably done, placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	844 included/844 analysed Quote (p 39): “Efficacy data were assessed for the full analysis set (all randomised patients)...Missing data were handled with the last-observation-carried-forward methodology” Comment: done
Selective reporting (reporting bias)	Unclear risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01194219) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported except the number of participants with a psoriasis flare or rebound during placebo-controlled phase

**Papp OPT Pivotal-1, 2015**

Methods	RCT, active/placebo-controlled, double blind Date of study: 12 January 2012-18 September 2014 Location: multicentre (74) in USA, Canada, Colombia, Germany, Japan, Hungary, Serbia, Taiwan, Ukraine
Participants	<p><b>Randomised:</b> 901 participants (mean age 46 years, 643 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12 or BSA <math>\geq</math> 10), age <math>\geq</math> 18 years</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Past history of malignant tumour, active infection, uncontrolled significant medical condition</li> <li>• Had received efalizumab treatment</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 136/901 (15%); tofacitinib 5 group (50), tofacitinib 10 group (40), placebo group (45) <ul style="list-style-type: none"> <li>• plus 1 participant not treated</li> <li>• AEs: tofacitinib 5 group (11), tofacitinib 10 group (8), placebo group (11)</li> <li>• Lack of efficacy: tofacitinib 5 group (20), tofacitinib 10 group (15), placebo group (25)</li> <li>• Withdrawal consent: tofacitinib 5 group (8), tofacitinib 10 group (5), placebo group (4)</li> <li>• Lost to follow-up: tofacitinib 5 group (3), tofacitinib 10 group (5), placebo group (3)</li> <li>• Participant died: tofacitinib 5 group (1), tofacitinib 10 group (0), placebo group</li> </ul> </li> </ul>

	(1) <ul style="list-style-type: none"> <li>• Other reason: tofacitinib 5 group (7), tofacitinib 10 group (7), placebo group (2)</li> </ul>	
Interventions	<p><b>Intervention</b> A. Tofacitinib (n = 363), orally, 5 mg twice daily</p> <p><b>Control intervention</b> B. Tofacitinib (n = 360), orally, 10 mg twice daily B. Placebo (n = 177), orally (same drug administration)</p>	
Outcomes	<p>Assessments at 16 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> <li>• PGA 0/1</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> <li>• PGA 0/1</li> <li>• PASI 90</li> <li>• DLQI</li> <li>• AEs</li> </ul>	
Notes	<p>Funding source: Quote (p 949): “Pfizer Inc”</p> <p>Declarations of interest (appendix): “K.A.P. has participated in advisory boards or panels for AbbVie, Amgen, Astellas, Baxter, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, LEO Pharma, Merck, Novartis, Pfizer Inc. and UCB. He has been an investigator for AbbVie, Allergan, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Genentech, Janssen, LEO Pharma, Merck, Novartis, Pfizer, Takeda and UCB. He has acted as a consultant for AbbVie, Amgen, Astellas, Baxter, Boehringer Ingelheim, Celgene, Eli Lilly, Forward Pharma, Janssen, Merck, Novartis, Pfizer Inc., Takeda and UCB. He has been a speaker for AbbVie, Allergan, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Genentech, Janssen, LEO Pharma, Merck, Novartis, Pfizer and UCB. M.A.M. has participated in advisory boards or panels for AbbVie, Allergan, Amgen, Boehringer Ingelheim, Genentech, Janssen Biotech, LEO Pharma and Pfizer Inc. He has served as a consultant for AbbVie, Allergan, Amgen, Convoy Therapeutics, Eli Lilly, Janssen Biotech, LEO Pharma, Novartis, Pfizer Inc., Syntrix, Wyeth and Xenoport. He has been an Investigator for AbbVie, Allergan, Amgen, ApoPharma, Boehringer Ingelheim, Celgene, Convoy Technologies, Eli Lilly, Genentech, Janssen Biotech, LEO Pharma, Merck, Novartis, Pfizer Inc., Symbio/Maruho, Syntrix and Wyeth. He has been a speaker for AbbVie, Amgen, Janssen Biotech, LEO Pharma and Wyeth. He has received grants from AbbVie, Allergan, Amgen, ApoPharma, Boehringer Ingelheim, Celgene, Convoy Technologies, Genentech, Janssen Biotech, LEO Pharma, Merck, Pfizer Inc., Symbio/Maruho and Syntrix. He has received honoraria from AbbVie, Allergan, Amgen, Boehringer Ingelheim, Convoy Technologies, Eli Lilly, Genentech, Janssen Biotech, LEO Pharma, Novartis, Pfizer Inc., Syntrix, Wyeth and Xenoport.”</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>

Random sequence generation (selection bias)	Low risk	Quote (p 951): “Randomization using an automated web/telephone randomization system at the study site ensured patient, investigator and sponsor blinding ” Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 951): “Randomization using an automated web/telephone randomization system at the study site ensured patient, investigator and sponsor blinding ” Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 951): “Investigator and sponsor blinding... with placebo tablets according to the treatment group, appropriately labelled to avoid treatment-group conflict. All patients took a total of two tablets for each dose” Comment: probably done, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 951): “Investigator and sponsor blinding... with placebo tablets according to the treatment group, appropriately labelled to avoid treatment-group conflict. All patients took a total of two tablets for each dose” Comment: probably done, placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	High risk	Randomly assigned 901, analysed 900 Management of missing data: Quote (p 951): “The full analysis set included all patients who were randomised and received at least one dose of the study drug...Non-responder imputation was used to manage missing values.” Comment: withdrawal for lack of efficacy: tofacitinib 5 group 5% (20/363), tofacitinib 10 group 4% (15/360), placebo group 14% (25/177)
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01276639) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported



Methods	RCT, active/placebo-controlled, double blind Date of study: 4 March 2011-18 September 2014 Location: multicentre (94) in Mexico, Poland, Puerto Rico, Serbia, Taiwan, Ukraine
Participants	<p><b>Randomised:</b> 960 participants (mean age 46 years, 648 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12 or BSA <math>\geq</math> 10), age <math>\geq</math> 18 years</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Past history of malignant tumour, active infection, uncontrolled significant medical condition</li> <li>• Had received efalizumab treatment</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 136/901 (15%); tofacitinib 5 group (51), tofacitinib 10 group (40), placebo group (44)</li> <li>• plus 1 participant not treated</li> <li>• AEs: tofacitinib 5 group (11), tofacitinib 10 group (10), placebo group (5)</li> <li>• Lack of efficacy: tofacitinib 5 group (15), tofacitinib 10 group (2), placebo group (24)</li> <li>• Withdrawal consent: tofacitinib 5 group (7), tofacitinib 10 group (6), placebo group (7)</li> <li>• Lost to follow-up: tofacitinib 5 group (7), tofacitinib 10 group (8), placebo group (3)</li> <li>• Participant died: tofacitinib 5 group (1), tofacitinib 10 group (0), placebo group (1)</li> <li>• Other reason: tofacitinib 5 group (10), tofacitinib 10 group (14), placebo group (4)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Tofacitinib (n = 382), orally, 5 mg twice daily</p> <p><b>Control intervention</b></p> <p>B. Tofacitinib (n = 381), orally, 10 mg twice daily</p> <p>C. Placebo (n = 196), orally (same drug administration)</p>
Outcomes	<p>Assessments at 16 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> <li>• PGA 0/1</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> <li>• PGA 0/1</li> <li>• PASI 90</li> <li>• DLQI</li> <li>• AEs</li> </ul>
Notes	<p>Funding source:</p> <p>Quote (p 949): "Pfizer Inc"</p> <p>Declarations of interest (appendix) : "K.A.P. has participated in advisory boards or panels for AbbVie, Amgen, Astellas, Baxter, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, LEO Pharma, Merck, Novartis, Pfizer Inc. and UCB. He has been an investigator for</p>

AbbVie, Allergan, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Genentech, Janssen, LEO Pharma, Merck, Novartis, Pfizer, Takeda and UCB. He has acted as a consultant for AbbVie, Amgen, Astellas, Baxter, Boehringer Ingelheim, Celgene, Eli Lilly, Forward Pharma, Janssen, Merck, Novartis, Pfizer Inc., Takeda and UCB. He has been a speaker for AbbVie, Allergan, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Genentech, Janssen, LEO Pharma, Merck, Novartis, Pfizer and UCB. M.A.M. has participated in advisory boards or panels for AbbVie, Allergan, Amgen, Boehringer Ingelheim, Genentech, Janssen Biotech, LEO Pharma and Pfizer Inc. He has served as a consultant for AbbVie, Allergan, Amgen, Convoy Therapeutics, Eli Lilly, Janssen Biotech, LEO Pharma, Novartis, Pfizer Inc., Syntrix, Wyeth and XenPort. He has been an Investigator for AbbVie, Allergan, Amgen, ApoPharma, Boehringer Ingelheim, Celgene, Convoy Technologies, Eli Lilly, Genentech, Janssen Biotech, LEO Pharma, Merck, Novartis, Pfizer Inc., Symbio/Maruho, Syntrix and Wyeth. He has been a speaker for AbbVie, Amgen, Janssen Biotech, LEO Pharma and Wyeth. He has received grants from AbbVie, Allergan, Amgen, ApoPharma, Boehringer Ingelheim, Celgene, Convoy Technologies, Genentech, Janssen Biotech, LEO Pharma, Merck, Pfizer Inc., Symbio/Maruho and Syntrix. He has received honoraria from AbbVie, Allergan, Amgen, Boehringer Ingelheim, Convoy Technologies, Eli Lilly, Genentech, Janssen Biotech, LEO Pharma, Novartis, Pfizer Inc., Syntrix, Wyeth and XenPort.”

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 951): "Randomization using an automated web/telephone randomization system at the study site ensured patient, investigator and sponsor blinding" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Quote (p 951): "Randomization using an automated web/telephone randomization system at the study site ensured patient, investigator and sponsor blinding" Comment: no description of the method to guarantee the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 951): "Investigator and sponsor blinding... with placebo tablets according to the treatment group, appropriately labelled to avoid treatment-group conflict. All patients took a total of two tablets for each dose" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 951): "Investigator and sponsor blinding... with placebo tablets according to the treatment group, appropriately labelled to avoid treatment-group conflict.

**Papp OPT Pivotal-2, 2015** (Continued)

		All patients took a total of two tablets for each dose” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	High risk	Randomly assigned 960, analysed 959 Management of missing data: Quote (p 951): “The full analysis set included all patients who were randomised and received at least one dose of the study drug...Non-responder imputation was used to manage missing values.” Comment: imbalance of withdrawal between groups: lack of efficacy: tofacitinib 5 group (15), tofacitinib 10 group (2), placebo group (24)
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01276639) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

**Papp PHOENIX-2, 2008**

Methods	RCT, placebo-controlled, double-blind trial Date of study: March 2006-September 2007 Location: 70 centres in Europe and North America
Participants	<b>Randomised:</b> 1230 participants (mean age 45 years, 840 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis</li> <li>• Authors’ assessment <math>\geq</math> 6 months, PASI <math>\geq</math> 12, BSA &gt; 10%</li> <li>• Age <math>\geq</math> 18 years</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Had received IL12/23 drug</li> <li>• Had an active infection</li> <li>• Had past history of malignant tumours</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• 33/1230 (2.7%)</li> <li>• Ustekinumab 45 (6): AE (2), other (4)</li> <li>• Ustekinumab 90 (9): AE (5), death (1), other (3)</li> <li>• Placebo (18): lack of efficacy (2), AE (8), other (8)</li> </ul>
Interventions	<b>Intervention</b> A. Ustekinumab (n = 409), SC, 45 mg, weeks 0-4 and every 12 weeks, 52 weeks <b>Control intervention</b> B. Ustekinumab (n = 411), SC, 90 mg, weeks 0-4 and every 12 weeks, 52 weeks

	C. Placebo (n = 410), SC, weeks 0-4, 4 weeks
Outcomes	<p>Assessments at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PGA cleared or minimal at 12 weeks</li> <li>• Change of QoL from baseline at week 12</li> <li>• PASI 90 at 12 weeks</li> </ul>
Notes	<p>Funding Centocor Inc (p1675)</p> <p>Declaration of interest (p1684): “KP has served as a consultant and advisory board member for Abbott, Alza, Amgen, Celgene, Centocor, Isotechnika, Janssen Ortho Biotech, Johnson &amp; Johnson, Medimmune, MerckSerono, and Wyeth. RGL has received research grants, served on scientific advisory boards, and has been a speaker for Amgen, Biogen-Idec, Centocor, Genentech, Novartis, Schering-Plough, and Serono. ML has received honoraria, served as a speaker and advisory board member for Abbott, Amgen, Centocor, Genentech, and Stiefel, and has served as an advisory board member for Astellas and a consultant for UCB. GK has received fees as a consultant or advisory board member for Abbott, Almirall, Alza, Amgen, Anacor, Astellas, Barrier Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Centocor, CombinatoRx, Exelixis, Genentech, Genzyme, Isis, L’Oreal, Lupin Limited, Magen Biosciences, MedaCorp, Medicis, Novartis, Nova Nordisc, Schering-Plough, Somagenics, theDerm.org, Synvista, Warner Chilcot, UCB, USANA Health Sciences, and ZARS, owns equities and stock in ZARS, and has received lecture fees from Abbott, Amgen, Astellas, Boehringer Ingelheim, Centocor, Connetics, National Psoriasis Foundation, The Foundation for Better Health Care, and Warner Chilcot, and has received partial stipend support for a clinical research fellowship from Abbott, Amgen, and Centocor. KR has received honoraria as a consultant and advisory board member and acted as a paid speaker for Abbot, Biogen-Idec, Centocor, Janssen-Cilag, Schering-Plough, MerckSerono, UCB, and Wyeth. PS, NY, CG, M-CH, YW, SL, and LTD are employees of Centocor. PS, NY, CG, YW, SL, and LTD own stock in Johnson and Johnson.”</p>

**Risk of bias**

Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote (p 1676): “Patients were randomly assigned... with bias coin assignment via a centralised interactive voice response system (ClinPhone, East Windsor, NJ, USA)”</p> <p>Comment: probably done</p>
Allocation concealment (selection bias)	Low risk	<p>Quote (p 1676): “Patients were randomly assigned... with bias coin assignment via a centralised interactive voice response system (ClinPhone, East Windsor, NJ, USA)”</p>

**Papp PHOENIX-2, 2008** (Continued)

		Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 1676 & 1977): “Double-blind, ..., placebo-controlled...Site monitors investigators personels involved in the study conduct,and patients remained blinded... until W52” Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 1676 & 1977): “Double-blind, ..., placebo-controlled...Site monitors investigators personels involved in the study conduct,and patients remained blinded... until W52” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	1230 included/ 1230 analysed Quote (p 1679): “Efficacy data were analysed by the assigned treatment group... Non-responder status was assigned for binary variables ... for those patients who discontinued study treatment ...” Comment: ITT analyses
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00307437) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

**Paul ESTEEM-2, 2015**

Methods	RCT, active/placebo-controlled, double blind Date of study: 29 October 2012-25 March 2016 Location: 40 centres in Europe & USA
Participants	<b>Randomised:</b> 413 participants (mean age 45 years, 276 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12 or BSA <math>\geq</math> 10), age <math>\geq</math> 18 years</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Pregnancy, immunosuppression, kidney insufficiency, liver insufficiency, past history of malignant tumours, active infection, uncontrolled cardiovascular disorder, uncontrolled diabetes, uncontrolled hypertension</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• 62/413 (15%); apremilast group (36), placebo group (26)</li> <li>• Error of randomization, did not receive study medication; apremilast group (1),</li> </ul>

	<p>placebo group (1)</p> <ul style="list-style-type: none"> <li>• AEs: apremilast group (12), placebo group (8)</li> <li>• Lack of efficacy: apremilast group (3), placebo group (2)</li> <li>• Withdrawal consent: apremilast group (9), placebo group (7)</li> <li>• Lost to follow-up: apremilast group (6), placebo group (6)</li> <li>• Protocol violation: apremilast group (2), placebo group (1)</li> <li>• Non compliance: apremilast group (1), placebo group (0)</li> <li>• Other reason: apremilast group (2), placebo group (1)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Apremilast (n = 275), orally, 30 mg twice a day until week 32</p> <p><b>Control intervention</b></p> <p>B. Placebo (n = 138), orally (same drug administration)</p>
Outcomes	<p>Assessments at 16 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 50</li> <li>• PASI 90</li> <li>• PASI 100</li> <li>• PGA 0/1</li> <li>• DLQI</li> <li>• Pruritus VAS</li> <li>• AEs</li> </ul>
Notes	<p>Funding source:</p> <p>Quote (p 1387): "This study was sponsored by Celgene Corporation"</p> <p>Declarations of interest (Appendix): C.P. has served as an investigator and consultant for AbbVie, Amgen, Celgene, Eli Lilly, Janssen, LEO Pharma, Novartis and Pfizer. J. Cather has been an investigator for Amgen, Celgene, Galderma, Merck, Novartis and Pfizer, and has served on advisory boards for AbbVie, Janssen, OrthoBiotech and Medac. M.G. has been an investigator for AbbVie, Allergan, Celgene, Dermira, Dr. Reddy's Laboratories, Eli Lilly, Galderma, Janssen Pharmaceutical, Kythera, Kyowa Hakko Kirin Pharma, LEO Pharma, Merck, Novartis, Pfizer, Regeneron and Takeda, and has served as a speaker for AbbVie, Actelion, Amgen, Astellas, Galderma, Janssen Pharmaceutical, LEO Pharma, Novartis and Pfizer. Y.P. has been an investigator for AbbVie, Amgen, Astellas, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Centocor/Janssen, Eli Lilly, Galderma, Isotechnika, LEO Pharma, Merck, Novartis, Pfizer, Pharmascience, Regeneron, Schering and Stiefel/GSK, and has served as a speaker for AbbVie, Amgen, Galderma, Janssen, LEO Pharma and Novartis. U.M. has been an advisor for and/or received speaker honoraria from and/or received grants from and/or participated in clinical trials for Abbott/AbbVie, Almirall-Hermal, Amgen, BASF, Biogen Idec, Celgene, Centocor, Eli Lilly, Forward Pharma, Galderma, Janssen, LEO Pharma, Medac, MSD, Miltenyi Biotech, Novartis, Pfizer, Teva, VBL and XenoPort. C.F. has served on the advisory board for and/or received speaker honoraria from Celgene, Novartis, Janssen and AbbVie. J. Crowley has been an investigator for AbbVie, Amgen, AstraZeneca, Celgene, Janssen, Maruho, Merck, Pfizer and Regeneron; has served on the advisory board for AbbVie, Amgen, Celgene and Lilly; and has been a speaker for AbbVie and Amgen."</p>

<i>Risk of bias</i>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote (p 1388): "Patient were randomised (2:1) via an interactive voice response system..." Comment: no description of the method used to guarantee the random sequence generation
Allocation concealment (selection bias)	Low risk	Quote (p 1388): "Patient were randomised (2:1) via an interactive voice response system..." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 1388) "identically matching placebo tablets twice daily during the placebo controlled phase" Comment: Probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 1388): "double-blind" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 413, analysed 411 Management of missing data: Quote (p 1389-90): "Efficacy assessments were conducted for the modified intention-to-treat population... The last-observation-carried-forward methodology was used..." Comment: we judged this as a low risk of bias
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00235820) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

Methods	RCT, active/placebo-controlled, double blind Date of study: 7 June 2012- 4 January 2013 Location: 38 centres worldwide
Participants	<p><b>Randomised:</b> 182 participants (mean age 45 years, 125 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12, IGA 3-4 or BSA <math>\geq</math> 10), age <math>\geq</math> 18 years</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Immunosuppression, active infection</li> <li>• Had received anti IL17 drug</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 5/182 (2.7%)</li> <li>• AEs: secukinumab 300 (0), secukinumab 150 (1), placebo (1)</li> <li>• Lack of efficacy: secukinumab 300 (0), secukinumab 150 (0), placebo (1)</li> <li>• Physician decision: secukinumab 300 (0), secukinumab 150 (1), placebo (0)</li> <li>• Participant/guardian decision: secukinumab 300 (0), secukinumab 150 (1), placebo (0)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Secukinumab (n = 61), SC, 150 mg weeks 0, 1, 2, 3 then monthly</p> <p><b>Control intervention</b></p> <p>B. Secukinumab (n = 60), SC, 300 mg weeks 0, 1, 2, 3 then monthly</p> <p>C. Placebo (n = 61), (same drug administration)</p>
Outcomes	<p>Assessments at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PGA0/1</li> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 50/75/90</li> <li>• DLQI</li> </ul>
Notes	<p>Funding source:</p> <p>Quote (supplemental file) “The study was sponsored by Novartis Pharma and designed by the scientific steering committee and Novartis personnel. Novartis conducted the data analysis, and all authors had access to the data”</p> <p>Declarations of interest (p 29): “Dr Paul has served as a consultant for AbbVie Pharmaceuticals, Amgen, Celgene Corporation, Eli Lilly and Company, Janssen Pharmaceuticals, LEO Pharma, Novartis Pharmaceuticals Corporation, Pfizer Inc and Pierre Fabre. Dr Lacour has participated in clinical trials sponsored by Novartis and has received honoraria as a coordinator of clinical trials sponsored by Novartis. Dr Kreutzer has received honoraria for giving speeches for, has received travel grants from, and conducts clinical trials for AbbVie Pharmaceuticals, Biogen, Novartis and Janssen-Cilag. Dr Jazayeri has served as investigator for and received grants from Novartis. Dr Adams has served as investigator for and received grants from Amgen, Eli Lilly and Company and Novartis. Ms Guindon and Dr Papavassilis are full-time employees of and own stock in Novartis. Mr You is a full-time employee of Novartis. Dr Tedremets has no conflicts of interest to declare.”</p>



<i>Risk of bias</i>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote (p 28 and supplemental file): “were randomly allocated”, “Randomization was conducted via Interactive Response Technology, which assigned a randomisation number that linked the subject to a treatment arm and specified unique medication pack number“ Comment: no description of the method used to guarantee the random sequence generation
Allocation concealment (selection bias)	Low risk	Quote: “Randomization was conducted via Interactive Response Technology, which assigned a randomisation number that linked the subject to a treatment arm and specified unique medication pack number” Comment: well described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 1083): “During the induction period, subjects...in the secu 150 mg group were administrated one 150 mg injection and one placebo,...,in the placebo group...2 placebo autoinjections” Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 1083): “During the induction period, subjects ... in the secu 150 mg group were administrated one 150 mg injection and one placebo, ..., in the placebo group ... 2 placebo autoinjections” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 182, analysed 181 Management of missing data: Quote (Supplemental file): “Missing values with respect to response variables based on PASI score or IGA mod 2011 score were imputed as nonresponse regardless of the reason for missing data” Comment: probably done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01636687)

		The pre-specified outcomes and those mentioned in the methods section appeared to have been reported
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**Piskin 2003**

Methods	<p>RCT, active-controlled, open-label trial          Date of study: not stated          Location: Amsterdam and throughout the Netherlands, number not stated</p>
Participants	<p><b>Randomised:</b> 10 participants (ciclosporin (5), mean age 41 years, 4 male; Methotrexate (5), mean age 45 years, 3 male)  <b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis, PASI <math>\geq</math> 8</li> <li>• Age <math>\geq</math> 18</li> <li>• Non-response to topical treatment</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Not stated</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• Not stated</li> <li>• All participants seemed to be evaluated at week 12</li> </ul>
Interventions	<p><b>Intervention</b>          A. Ciclosporin (n = 5), orally, 3 mg/kg/d, 16 weeks  <b>Control intervention</b>          B. Methotrexate (n = 5), orally, 15 mg/kg/week, 16 weeks</p>
Outcomes	<p>Assessments at 12 weeks  <b>Primary and secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• Not clearly defined</li> </ul> <p><b>Outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> <li>• Number of cutaneous T-cell 1-2</li> <li>• Creatine kinase balance</li> <li>• Psoriatic skin</li> </ul>
Notes	<p>Funding not declared          Declarations of interest: not stated</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote (p 559): "Patients were randomised. .."          Comment: no description of the method used to guarantee random sequence generation</p>

**Piskin 2003** (Continued)

Allocation concealment (selection bias)	Unclear risk	Quote (p 559): "Patients were randomised." .." Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (p 559): "Laboratory results were obtained in a blinded fashion before randomisation and at week 12 of therapy. The code was broken only after all definitive results were obtained from all participating patients." Comment: open-label trial, no double dummy used to guarantee blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no description of the method used to guarantee blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	10 included/10 analysed Comment: no statistical analyses section; however, the results were available for the 10 participants initially randomised. Methods for dealing with missing data: not applicable
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

**Reich 2012**

Methods	RCT, placebo-controlled, double blind Date of study: October 2005-November 2006 Location: 15 centres in France and Germany
Participants	<b>Randomised:</b> 176 participants, mean age 43 years, 213 male <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12, BSA <math>\geq</math> 10, age <math>\geq</math> 18 years)</li> <li>• Non-response to conventional systemic treatment</li> <li>• Non-response to biologics</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Pregnancy, kidney insufficiency, liver insufficiency</li> <li>• Had an active infection</li> <li>• Had uncontrolled cardiovascular disorder</li> <li>• Had uncontrolled diabetes</li> </ul>

	<ul style="list-style-type: none"> <li>• Had uncontrolled hypertension</li> <li>• Had past history of malignant tumours</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 28/176 (16%)</li> <li>• Placebo (19): lack efficacy (14), AE (3), lost to follow-up (2)</li> <li>• Certolizumab 200 (5): lack efficacy (3), AE (2)</li> <li>• Certolizumab 400 (4): lack efficacy (1), AE (2), pregnancy(1)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Certolizumab (n = 59), SC, 200 mg, Certolizumab pegol (CZP) 400 mg week 0 - certolizumab 200 mg weeks 1-10, 10 weeks</p> <p><b>Control intervention</b></p> <p>B. Certolizumab (n = 58), SC, 400 mg, certolizumab 400 mg week 0 - certolizumab 400 mg weeks 1-10, 10 weeks</p> <p>C. Placebo (n = 59), SC, certolizumab 400 mg week 0 - placebo weeks 1-10, 10 weeks</p>
Outcomes	<p>Assessments at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> <li>• PGA</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 50</li> <li>• PASI 90</li> <li>• Time to PASI 75 response</li> <li>• Time to relapse</li> <li>• Change from baseline BSA</li> <li>• DLQI Dermatology Life Quality Index)</li> <li>• PGA week 12</li> </ul>
Notes	<p>Funding source quote (p 180): “This study was funded by UCB Pharma, Brussels, Belgium”</p> <p>Declarations of interest (p 180): “K.R. has served as consultant and or paid speaker for and or has participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis, including Abbott, Biogen Idec, Celgene, Centocor, Janssen-Cilag, Leo, Medac, Merck, MSD (formerly Essex, Schering-Plough) , Novartis and Pfizer (formerly Wyeth). J.-P.O. is a consultant for Abbott, Centocor, Galderma, Janssen- Cilag, Leo, Meda Pharma, Merck Serono and UCB Pharma. A.B. G. has current consulting advisory board agreements with Amgen, Astellas, Centocor (Janssen), Celgene, Bristol-Myers Squibb, Beiersdorf, Abbott, TEVA, Actelion, UCB Pharma, Novo Nordisk, Novartis, Dermipso, Incyte, Pfizer, Canfite, Merck and Lilly. Research educational grants paid to Tufts Medical Center: Centocor (Janssen), Amgen, Immune Control, Abbott, Novo Nordisk, UCB Pharma, Novartis, Celgene and Pfizer. I.J.T. and G.C. are full-time employees of UCB Pharma. C.T. is a former employee of UCB Pharma. P.M. has served as consultant and or paid speaker for and has received grants, consulting and or speaker fees from Abott Amgen, Biogen Idec, Bristol-Myers Squibb, Celgene, Janssen, Novartis, Merck, Pfizer and UCB Pharma.”</p>
<i>Risk of bias</i>	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 181): "Eligible patients were randomised to receive... Randomization was centralized using a dynamic allocation procedure... Treatment was assigned using an interactive voice-response system" "Randomization was conducted via Interactive Response Technology, which assigned a randomisation number that linked the subject treatment arm and specified unique medication pack number Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 181): "Eligible patients were randomised to receive... Randomization was centralized using a dynamic allocation procedure... Treatment was assigned using an interactive voice-response system" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 181): "CZP.. or matching placebo in liquid formulation for subcutaneous injection... Study doses of CZP or placebo were prepared containing the same volume and labelled in the same manner by designed unblinded pharmacists" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 181): "CZP.. or matching placebo in liquid formulation for subcutaneous injection... Study doses of CZP or placebo were prepared containing the same volume and labelled in the same manner by designed unblinded pharmacists" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	176 included/176 analysed Quote (p 182): "Co-primary efficacy assessments were performed on the intention-to-treat population... Nonresponder imputations for missing values were used for the primary analysis" Comment: probably done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00245765)

Reich 2012 (Continued)

		The pre-specified outcomes and those mentioned in the methods section appeared to have been reported except for pharmacokinetic profile of CDP870
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Reich 2015

Methods	RCT, active/placebo-controlled, double blind Date of study: December 2008-July 2009 Location: 14 centres in the USA and Canada
Participants	<b>Randomised:</b> 100 participants (mean age 44 years, 100 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12, IGA <math>\geq</math> 3 or BSA <math>\geq</math> 10), age 18-65 years</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>Not stated</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>11/100 (11%); secukinumab 3 mg group (2), secukinumab 10 mg group (0), secukinumab 3 x 10 mg group (3), placebo group (6)</li> <li>AEs: secukinumab 3 mg group (0), secukinumab 10 mg group (0), secukinumab 3 x 10 mg group (1), placebo group (0)</li> </ul>
Interventions	<b>Intervention</b> A. Secukinumab (n = 30), SC, 3 mg/kg, 1 infusion (day 1) <b>Control intervention</b> B. Secukinumab (n = 29), SC, 10 mg/kg, 1 infusion (day 1) C. Secukinumab (n = 31), SC, 10 mg/kg, 3 infusions (days 1, 15, 29) D. Placebo (n = 10)
Outcomes	Assessments at 12 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>Change from baseline in PASI score at 12 weeks</li> <li>(Proportion of participants who did not relapse at any time through week 56)</li> </ul> <b>Secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>PASI 50</li> <li>PASI 75</li> <li>PASI 90</li> <li>Change in DLQI score</li> <li>AEs</li> </ul>
Notes	Funding source: Quote (p 534): "This trial and publication were funded by Novartis Pharma AG, Basel, Switzerland." Declarations of interest (p 534): "KR has served as a consultant or paid speaker for, or participated in clinical trials sponsored by, AbbVie, Amgen, Biogen-Idec, Celgene, Centocor, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, Leo, Lilly, Medac, MSD, Novartis, Pfizer, Takeda and Vertex. KAP has received grants and has consulted and served as an investigator for AbbVie, Amgen, Astellas, Biogen-Idec, Celgene, Cento-

cor, Eli Lilly, Forward Pharma, Fujisawa, GlaxoSmithKline, Janssen, Kyowa-Kirin, Leo, MSD, Novartis (outside the submitted work), Pfizer and Takeda. RTM has received grants/clinical trial stipends from Novartis. JHT served as a clinical investigator for Novartis during conduct of this study. RB received grants from Novartis during the conduct of this study and has received grants, personal fees and non-financial support from AbbVie, Amgen, Astellas, Celgene, Eli Lilly, Janssen, Pfizer and Tribute. MB has served as a clinical trial sponsor for Amgen, Eli Lilly and Novartis. DG has served as a clinical trial investigator for Novartis. RAK is a member of an advisory board for Novartis and several other pharmaceutical companies. YP has received grants from AbbVie, Amgen, Celgene, Eli Lilly, Janssen, Merck, Pfizer and Novartis (outside the submitted work). LAR, WMB, TMF and NAB-S declare no conflict of interests. GS has received grants/clinical trial payments from Janssen, MSD and Novartis (unrelated to secukinumab). JMS, US, TP, EK, GAW, FK and CCB are full-time employees of Novartis. WH and DML are full-time employees of and own stock in Novartis. MMS was a full-time employee of Novartis at the time the study was conducted and the manuscript”

<i>Risk of bias</i>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (supplemental appendix): “The randomisation scheme was generated by Novartis Drug Supply Management using a validated system. The randomisation scheme was reviewed and approved by the Biostatistics Quality Assurance group of Novartis and was locked after approval. Subjects were assigned randomisation numbers, according to the randomisation schedule. Each site, upon evaluation of a qualified subject for the trial, faxed the enrolment sheet to the clinical trial leader (CTL) at the fax number provided. The CTL then assigned the randomisation number in a sequential manner and faxed it back to the unblinded pharmacist or qualified site personnel at the site, who then prepared and provided the study medication for the clinic in a blinded fashion.” Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (supplemental appendix): “Each site, upon evaluation of a qualified subject for the trial, faxed the enrolment sheet to the clinical trial leader (CTL) at the fax number provided. The CTL then assigned the randomisation number in a sequential manner and faxed it back to the unblinded pharmacist or qualified site personnel at the

		<p>site, who then prepared and provided the study medication for the clinic in a blinded fashion..</p> <p>Treatment allocation and clinical assessment of the subjects were blinded. For preparation of the study medication from bulk supplies, treatment allocation cards were sent to the pharmacist or qualified site personnel at the investigator's site."</p> <p>Comment: probably done</p>
<p>Blinding of participants and personnel (performance bias) All outcomes</p>	<p>Low risk</p>	<p>Quote (supporting information): "To maintain the blind of the study, the appearance of placebo infusion bags, ready to administer to the subject, was identical to that of active drug infusion bags. Placebo and active medication were prepared by an unblinded pharmacist or qualified site personnel assigned at each site."</p> <p>Comment: probably done</p>
<p>Blinding of outcome assessment (detection bias) All outcomes</p>	<p>Low risk</p>	<p>Quote (supporting information): "To maintain data integrity, no subject-level data were circulated; therefore, blinding was maintained at the individual subject level"</p> <p>Comment probably done</p>
<p>Incomplete outcome data (attrition bias) All outcomes</p>	<p>Low risk</p>	<p>100 randomised participants, 94 analysed for PASI 75 or 90, 87 analysed for primary outcome (change in PASI)</p> <p>Quote (p 530): "Efficacy and pharmacodynamic parameters were evaluated in all subjects who received <math>\geq 1</math> dose of study medication and had a major protocol deviations... Subjects lost to follow-up were considered relapsed on the day of th first visit without available PASI data"</p> <p>Comment: low rate of loss to follow-up and reasons comparable between groups</p>
<p>Selective reporting (reporting bias)</p>	<p>Low risk</p>	<p>Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00805480) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported</p>



Methods	RCT, placebo-controlled, double blind Date of study: not stated Location: 32 centres in Europe and Canada	
Participants	<p><b>Randomised:</b> 378 participants (mean age 43 years, 268 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12, BSA <math>\geq</math> 10), age <math>\geq</math> 18 years</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Immunosuppression</li> <li>• Had received biologics</li> <li>• Had an active infection</li> <li>• Had past history of malignant tumours</li> </ul> <p><b>Dropouts and withdrawals</b> (week 24)</p> <ul style="list-style-type: none"> <li>• 41/378 (10.8%)</li> <li>• Discontinued study: infliximab (18), placebo (7)</li> <li>• No description of the reasons of withdrawals</li> </ul>	
Interventions	<p><b>Intervention</b></p> <p>A. Infliximab (n = 301), IV, 5 mg/kg weeks 0, 2, 6 and every 8 weeks, 10 weeks</p> <p><b>Control intervention</b></p> <p>B. Placebo (n = 77), IV, equivalent, weeks 0, 2, 6 and every 8 weeks, 10 weeks</p>	
Outcomes	<p>Assessments at 10 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI90/50</li> <li>• PGA</li> <li>• NAPSI</li> </ul>	
Notes	<p>Funding source (p 386): This study was funded by Centocor, and Schering-Plough, Kenilworth, NJ, USA“</p> <p>Declarations of interest (p 386): “Consultancies: Dr Reich (Abbott, Biogen Idec, Centocor, Schring-Plough, Essex, Serano, Wyeth), Dr Nestle (Biogen Idec, Centocor, Schring-Plough, Genentech, Galderma)...“</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p 1368): “A adaptative treatment allocation was used... The treatment assignment was stored electronically and the stored data were used to allocate future patients in such a way that the imbalance between treatment groups was kept to a minimum“ “Randomization was conducted via Interactive Response Technology, which as-

Reich EXPRESS, 2005 (Continued)

		signed a randomisation number that linked the subject to a treatment arm and specified unique medication pack number” Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 1368): “A adaptative treatment allocation was used... The treatment assignment was stored electronically and the stored data were used to allocate future patients in such a way that the imbalance between treatment groups was kept to a minimum” Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 1368): “The investigators, study site personnel, and patients remained blinded until the database lock at week 50. .. placebo group” Comment: probably done, placebo controlled trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 1368): “The investigators, study site personnel, and patients remained blinded until the database lock at week 50. .. placebo group” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	378 included / 378 analysed Quote (p 1368): “The primary endpoint .. as well as.. were analysed on an intention-to-treat basis... In patients who discontinued the study agent ... the patients were regarded as not achieving the endpoints for binary responses” Comment: probably done
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

Reich LIBERATE, 2017

Methods	RCT, active/placebo-controlled, double blind Date of study: October 2012-April 2016 Location: 82 centres worldwide (USA, Europe, Australia)
Participants	<b>Randomised:</b> 250 participants (mean age 45 years, 157 male) <b>Inclusion criteria</b>

	<ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12, PGA 3-4 or BSA <math>\geq</math> 10), a</li> <li>• Age <math>\geq</math> 18 years</li> <li>• Failed to respond to, had a contraindication to, or were intolerant to at least one conventional systemic treatment</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Failure of &gt; 3 systemic agents for psoriasis</li> <li>• Active infection</li> <li>• History of known demyelinating diseases</li> <li>• Congestive heart failure</li> <li>• Significant/major uncontrolled diseases</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 17/250 (6.8%); apremilast (6), etanercept (2), placebo group (9)</li> <li>• AEs: apremilast (2), etanercept (1), placebo group (2)</li> <li>• Lack of efficacy: apremilast (0), etanercept (0), placebo group (4)</li> <li>• Withdrawal consent: apremilast (3), etanercept (0), placebo group (1)</li> <li>• Other reason: apremilast (1), etanercept (1), placebo group (2)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Apremilast (n = 83), orally, 30 mg twice daily</p> <p><b>Control intervention</b></p> <p>B. Etanercept (n = 83), SC, 50 mg weekly</p> <p>D. Placebo (n = 84)</p>
Outcomes	<p>Assessments at 16 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 50</li> <li>• PASI 90</li> <li>• PGA rating of clear or almost clear</li> <li>• DLQI score</li> <li>• AEs</li> </ul>
Notes	<p>Funding source:</p> <p>Quote (p 2): "This study was sponsored by Celgene Corporation."</p> <p>Declarations of interest (p1): "K. Reich has received honoraria as a consultant and/or advisory board member and/or acted as a paid speaker and/or participated in clinical trials sponsored by AbbVie, Amgen, Biogen, Boehringer Ingelheim, Celgene Corporation, Centocor, Covagen, Eli Lilly, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Medac, Merck Sharp &amp; Dohme Corp., Novartis, Ocean Pharma, Pfizer, Regeneron, Takeda, UCB Pharma and Xenoport. M. Gooderham has received honoraria, grants and/or research funding as a speaker, investigator, advisory board member, data safety monitoring board member and/or consultant for AbbVie, Actelion, Amgen, Astellas Pharma US, Boehringer Ingelheim, Celgene Corporation, Dermira, Eli Lilly, Galderma, Janssen, Kyowa Hakko Kirin Pharma, LEO Pharma, MedImmune, Merck &amp; Co., Inc., Novartis, Pfizer, Regeneron, Roche"</p>
<p><i>Risk of bias</i></p>	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 3): "Eligible patients were randomised (1 : 1 : 1) via an interactive voice response system to placebo; apremilast oral tablet, 30 mg twice daily; or etanercept subcutaneous injection, 50 mg QW". "Randomization was conducted via Interactive Response Technology, which assigned a randomisation number that linked the subject to a treatment arm and specified unique medication pack number" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 3): "Eligible patients were randomised (1 : 1 : 1) via an interactive voice response system to placebo; apremilast oral tablet, 30 mg twice daily; or etanercept subcutaneous injection, 50 mg QW" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 3): "Per the double dummy design, patients received oral tablets (apremilast 30 mg or placebo) twice daily and two subcutaneous injections (etanercept 25 mg each dose or saline placebo) QW." Comment: clearly defined
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 3): "Per the double dummy design, patients received oral tablets (apremilast 30 mg or placebo) twice daily and two subcutaneous injections (etanercept 25 mg each dose or saline placebo) QW." Comment: clearly defined
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 250, 250 analysed Management of missing data: quote (p 3) : "Efficacy assessments were conducted for the modified intent-to treat (mITT) population (all randomised patients who received $\geq 1$ dose of study medication and had both baseline PASI and $\geq 1$ post-treatment PASI evaluations)... Last-observation-carried-forward (LOCF) methodology was used to impute missing efficacy measurements." Comment: done

Selective reporting (reporting bias)	High risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01241591) The pre-specified outcomes and those mentioned in the methods section have not been reported as DLQI
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Reich VOYAGE-2, 2017

Methods	RCT, active/placebo-controlled, double blind Date of study: November 2014-May 2016 Location: 115 centres worldwide
Participants	<p><b>Randomised:</b> 992 participants (mean age 44 years, 692 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12, IGA <math>\geq</math> 3 or BSA <math>\geq</math> 10), age <math>\geq</math> 18 years</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Had a history or current signs of a severe, progressive, or uncontrolled medical condition</li> <li>• Had current or history of malignancy, except nonmelanoma skin cancer, within 5 years</li> <li>• Patients with history or symptoms of active TB were excluded</li> <li>• Patients could not participate if they received guselkumab or adalimumab previously</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 44/992 (4.4%); guselkumab (18), adalimumab (11), placebo group (15)</li> <li>• AEs: guselkumab (9), adalimumab (4), placebo group (2)</li> <li>• Lack of efficacy: guselkumab (0), adalimumab (2), placebo group (4)</li> <li>• Lost to follow-up: guselkumab (3), adalimumab (2), placebo group (1)</li> <li>• Withdrawal consent: guselkumab (1), adalimumab (0), placebo group (7)</li> <li>• Non compliance: guselkumab (1), adalimumab (2), placebo group (0)</li> <li>• Protocol violation: guselkumab (3), adalimumab (1), placebo group (1)</li> <li>• Others: guselkumab (1), adalimumab (0), placebo group (0)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Guselkumab (n = 496), SC, 100 mg, weeks 0 and 4, then every 8 weeks</p> <p><b>Control intervention</b></p> <p>B. Adalimumab (n = 248), 80 mg week 0, then 40 mg week 1, and every 2 weeks</p> <p>C. Placebo (n = 248)</p>
Outcomes	<p>Assessments at 16 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 90</li> <li>• IGA clear or almost clear</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 50/75</li> <li>• Mean DLQI score</li> </ul>

	<ul style="list-style-type: none"> <li>• NAPSI</li> <li>• Scalp-specific IGA</li> <li>• Fingernail PGA</li> <li>• AEs</li> </ul>	
Notes	<p>Funding source:            Quote (p 1): “Supported by Janssen Research &amp; Development, LLC.”            Declarations of interest (p 1): “Dr Reich has served as advisor and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Amgen, Biogen, Boehringer Ingelheim Pharma, Celgene, Covagen, Eli Lilly, Forward Pharma, GlaxoSmithKline, Janssen, Leo, Medac, Merck Sharp &amp; Dohme, Novartis, Ocean Pharma, Pfizer, Regeneron, Takeda, UCB Pharma, and Xenoport. Dr Armstrong has served as investigator and/or advisor/consultant for AbbVie, Amgen, Celgene, Eli Lilly, Janssen, Merck, Novartis, and Pfizer. Dr Foley has served as a consultant, investigator, speaker, and/or advisor for and/or received travel grants from 3M/iNova/Valeant, Abbott/AbbVie, Amgen, Biogen Idec, BMS, Boehringer Ingelheim, Celtaxsys, Celgene, Cutanea, Eli Lilly, Galderma, GSK/Stiefel, Janssen, LEO/Peplin, Novartis, Regeneron, Schering-Plough/MSD, UCB, and Wyeth/Pfizer. Dr Gordon has received research support from AbbVie, Amgen, Boehringer Ingelheim, Eli Lilly, and Janssen, and consultant/ honoraria from AbbVie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, Novartis, and Pfizer. Drs Song, Wasfi, Randazzo, Li, and Shen are all employees of Janssen Research &amp; Development, LLC (subsidiary of Johnson &amp; Johnson) and own stock in Johnson &amp; Johnson.”</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p 3): “Patients were randomized 2:1:1 using a permuted block method at baseline to guselkumab 100 mg at weeks 0, 4, 12, and 20; placebo at weeks 0, 4, and 12, then guselkumab at weeks 16 and 20; or adalimumab 80 mg at week 0, 40 mg at week 1, and every 2 weeks thereafter through week 23 (Fig 1). Central randomization occurred using an interactive web based response system (Perceptive Informatics, East Windsor, NJ).” Comment: clearly defined
Allocation concealment (selection bias)	Low risk	Quote (p 3): “Patients were randomized using a permuted block method at baseline in a 2:1:2 ratio to guselkumab 100 mg at weeks 0, 4, 12, and every 8 weeks through week 44; placebo at weeks 0, 4, and 12 followed by guselkumab 100 mg at weeks 16 and 20, and every 8 weeks through week 44; or adalimumab 80 mg at week 0, 40 mg at week 1, and 40 mg ev-

Reich VOYAGE-2, 2017 (Continued)

		ery 2 weeks through week 47. Central randomization was implemented using an interactive World Wide Web response system (Perceptive Informatics, East Windsor, NJ). Comment: clearly defined
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 3): “double-blind, placebo- and adalimumab comparator controlled study” Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 3): “double-blind, placebo- and adalimumab comparator controlled study” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 992, 992 analyzed Management of missing data: quote (p 3): “All randomized patients were included in the primary analysis and some secondary efficacy analyses according to their assigned treatment group.... Patients who discontinued treatment due to lack of efficacy or an adverse event [AE] of worsening of psoriasis, or started a protocol-prohibited medication/therapy to improve psoriasis were considered treatment failures.” Comment: done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02207244) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

Rich 2013

Methods	RCT, placebo-controlled, double-blind trial Date of study: July 2009-December 2010 Location: 60 centres in Portland, USA
Participants	<b>Randomised:</b> 404 participants Secukinimab A (66) (mean age 43 years, 53 male) Secukinimab B (138) (mean age 44 years, 104 male) Secukinimab C (133) (mean age 45 years, 105 male) Placebo (67) (mean age 44 years, 44 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>Participants with moderate-severe psoriasis</li> </ul>

	<ul style="list-style-type: none"> <li>• PASI <math>\geq</math> 12, IGA <math>\geq</math> 3 or BSA <math>\geq</math> 10</li> <li>• Age <math>\geq</math> 18 years</li> <li>• Non-response to topical treatment</li> <li>• Non-response to phototherapy</li> <li>• Non-response to conventional systemic treatment</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Pregnancy</li> <li>• Immunosuppression</li> <li>• Had an active infection</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 24/404 (6%)</li> <li>• Secukinumab A (5): lack efficacy (2), withdrew consent (1), AE (1), other (1)</li> <li>• Secukinumab B (4): lack efficacy (1), withdrew consent (2), other (1)</li> <li>• Secukinumab C (6): withdrew consent (2), AE (3), other (1)</li> <li>• Placebo (9): lack efficacy (5), withdrew consent (2), AE (2)</li> </ul>	
Interventions	<p><b>Intervention</b></p> <p>A. Secukinumab (n = 66), SC, 150 mg, week 0, 12 weeks</p> <p><b>Control intervention</b></p> <p>B. Secukinumab (n = 138), SC, 150 mg, weeks 0, 4, 8, 12 weeks</p> <p>C. Secukinumab (n = 133), SC, 150 mg, weeks 0, 1, 2, 4, 12 weeks</p> <p>D. Placebo (n = 67), SC, weeks 0, 1, 2, 4, 8, 12 weeks</p>	
Outcomes	<p>Assessments at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75 20/28 weeks</li> <li>• IGA 12 weeks</li> <li>• PASI 90 12 weeks</li> </ul>	
Notes	<p>Funding support quote (p 402): “Novartis Pharma AG, Basel, Switzerland”</p> <p>Declarations of interest (appendix): “P.R. has received honoraria for lecturing in industry-sponsored meetings and has received research grants from pharmaceutical companies as an investigator. B.S. has consulted for Novartis and several other pharmaceutical companies; he has served on an advisory board for Novartis and several other pharmaceutical companies. D.T. has served as a speaker and served on advisory boards for Abbott, Biogen-Idex, Janssen-Cilag, Leo, MSD, Novartis and Pfizer. C. Paul has received honoraria from and has been a paid consultant to Abbott, Amgen, Celgene, Janssen-Cilag, Novartis and Pierre Fabre. K.R., E.H., A.G., M.M. and C. Papavassilis are full-time employees of, and own stock in Novartis. J.-P.O., A.M. and R.E.S. declare no conflicts of interest.”</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p 404): “Randomization numbers were generated by the interactive response technology provider using a validated sys-



**Rich 2013** (Continued)

		tem that automated the random assignment of patients numbers to randomisation numbers” Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 404): “Randomization numbers were generated by the interactive response technology provider using a validated system that automated the random assignment of patients numbers to randomisation numbers” Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 404): “Patients, investigator staff, persons performing the assessments and data analysts were blinded to the identity of treatment from the time of randomisation until primary outcome analysis” Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 404): “Patients, investigator staff, persons performing the assessment and data analysts were blinded to the identity of treatment from the time of randomisation until primary outcome analysis” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	404 included/404 analysed Quote (p 405): “Following the intent-to-treat principle, data were analysed... Missing values were replaced using the last-observation-carried-forward approach” Comment: ITT analyses
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00941031) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

**Ruzicka 1990**

Methods	RCT, placebo-controlled, double blind Date of study: December 1986-March 1988 Location: 7 centres in Germany
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Participants	<p><b>Randomised:</b> 82 participants (mean age 44 years, 55 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Aged 18-75</li> <li>• Generalized chronic plaque or exanthematic</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Pregnancy, kidney insufficiency, liver insufficiency</li> <li>• Had uncontrolled cardiovascular disorder</li> <li>• Had uncontrolled diabetes</li> <li>• Had uncontrolled hypertension</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 4/82 (5%)</li> <li>• Acitretin (2) overweight &amp; dyslipidaemia</li> <li>• Placebo (2) erythrodermia</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Acitretin, orally, 35 mg, daily, 8 weeks (n=42)</p> <p><b>Control intervention</b></p> <p>B. Placebo, orally, daily, 8 weeks (n=40)</p>
Outcomes	<p>Assessments at 8 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• Side effects</li> </ul>
Notes	<p>Funding sources: not stated</p> <p>Declarations of interest: not stated</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p 483): "The study was designed as a randomized, double-blind, placebo-controlled parallel group trial" Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (p 483): "The study was designed as a randomized, double-blind, placebo-controlled parallel group trial" Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (p 483): "The study was designed as a randomized, double-blind, placebo-controlled parallel group trial" Comment: no description of the method

Ruzicka 1990 (Continued)

		used to guarantee blinding as visible side effects are related to acitretin
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (p 483): “The study was designed as a randomized, double-blind, placebo-controlled parallel group trial... the investigators blinded to treatment assignment” Comment: no description of the method used to guarantee blinding of outcome assessment as visible side effects are related to acitretin
Incomplete outcome data (attrition bias) All outcomes	Low risk	82 included/78 analysed Quote (p 483): “... according to the intention-to-treat principle.. Dropout data were evaluated on the date of dropout” Comment: probably done
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

Sandhu 2003

Methods	RCT, active-controlled, open label Date of study: not stated Location: multicentric (number not stated) in North India
Participants	<b>Randomised:</b> 30 participants (methotrexate: mean age 39 years, 12 male; ciclosporin: mean age 46 years, 13 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (BSA &gt; 40%), age ≥ 18 years</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Pregnancy, kidney insufficiency, liver insufficiency</li> <li>• Had uncontrolled hypertension</li> <li>• Had past history of malignant tumours</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• Not stated</li> </ul>
Interventions	<b>Intervention</b> A. Methotrexate (n = 15), orally, 0.5 mg/kg dose tapered after PASI 75 obtained <b>Control intervention</b> B. Ciclosporin (n = 15), orally, 3 mg/kg increased to 4 if no change or rise of dose tapered after PASI 75 obtained
Outcomes	Assessments at 12 weeks <b>Primary or secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• Not clearly defined</li> </ul>

**Sandhu 2003** (Continued)

	<b>Outcomes of the trial</b>	
	<ul style="list-style-type: none"> <li>• PASI</li> </ul>	
Notes	Funding source: not stated Declarations of interest: not stated	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote (p 459): "Patients were randomly assigned to either..." Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (p 459): "Patients were randomly assigned to either..." Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: not blind
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	30 included/30 analysed Methods for dealing with missing data: not stated
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported.No primary outcome declared

**Saurat 1988**

Methods	RCT, active/placebo-controlled, double blind Date of study: not stated Location: 6 centres in France and Switzerland
Participants	<p><b>Randomised:</b> 42 participants (placebo (22) mean age 43 years, 16 male; acitretin (20), mean age 46 years, 16 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• BSA &gt; 20%</li> </ul> <p><b>Exclusion criteria</b></p>

	<ul style="list-style-type: none"> <li>• Kidney insufficiency, liver insufficiency, had uncontrolled cardiovascular disorder</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• 7/65 (11%)</li> </ul>	
Interventions	<b>Intervention</b> A. Acitretin (n = 20), orally, 2 x 25/d 2 weeks and 25/d + UVA 3/weeks, daily, 10 weeks <b>Control intervention</b> C. Placebo, orally (n = 22), daily, 10 weeks <b>Co-intervention:</b> UVA 3/week, 10 weeks	
Outcomes	Assessments not clearly stated (reported at 8 weeks) <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• Not clearly stated</li> </ul> <b>Outcomes of the trial</b> <ul style="list-style-type: none"> <li>• Change in PASI</li> <li>• Time to clear</li> <li>• AEs</li> </ul>	
Notes	Funding: not stated Declarations of interest: not stated	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote (p 219): "This multicenter study was performed in a double-blind, parallel fashion... The patients were randomly allocated to ..." Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (p 219): "This multicenter study was performed in a double-blind, parallel fashion... The patients were randomly allocated to ..." Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (p 219): "This multicenter study was performed in a double-blind, parallel fashion...All patients initially received 2 capsules of test medication (placebo, acitretin 2x25 mg, ..." Comment: no description of the method used to guarantee blinding of outcome assessment with visible AE in both acitretin and etretinate groups

Saurat 1988 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: no description of the method used to guarantee blinding of outcome assessment with visible AE in both acitretin and etretinate groups
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote (p 220): "Patients who left the study ... were not included in the evaluation of efficacy" Comment: not ITT analyses (number lost to follow-up unknown)
Selective reporting (reporting bias)	Low risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

Saurat CHAMPION, 2008

Methods	RCT, active/placebo-controlled, double blind Date of study: unreported Location: multicentre (n = 28) in Europe & Canada
Participants	<p><b>Randomised:</b> 271 participants (mean age 42, 178 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 10 or BSA <math>\geq</math> 10), age &gt; 18 years</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Pregnancy, immunosuppression, kidney insufficiency, liver insufficiency, past history of malignant tumours</li> <li>• Had received conventional systemic treatments for "Methotrexate" arm</li> <li>• Had received biologics</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 15/271 (5.5%): adalimumab group (4), methotrexate group (6), placebo group (5)</li> <li>• AEs: adalimumab group (1), methotrexate group (6), placebo group (1)</li> <li>• Lack of efficacy: adalimumab group (0), methotrexate group (0), placebo group (4)</li> <li>• Withdrawal consent: adalimumab group (2), methotrexate group (0), placebo group (0)</li> <li>• Other reason: adalimumab group (1), methotrexate group (0), placebo group (0)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Adalimumab (n = 108), SC, 80 mg at week 0, 40 mg at week 1 and 40 mg eow</p> <p><b>Control intervention</b></p> <p>B. Methotrexate (n = 110), orally, 7.5-25 mg weekly</p> <p>C. Placebo (n = 53), SC and orally (same drug administration)</p>

Outcomes	Assessments at 16 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>● PASI 75</li> </ul> <b>Secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>● PASI 50</li> <li>● PASI 90</li> <li>● PASI 100</li> <li>● PGA</li> <li>● DLQI</li> <li>● AEs</li> </ul>	
Notes	Funding source: Quote (p 561): “Abbott Laboratories funded this study and participated in the study design, data collection, data management, data analysis and preparation of the manuscript” Declarations of interest (p 558): “J.-H.S., G.S., L.D., K.P. and J.-P.O. have served as consultants for Abbott Laboratories. In addition, they have participated in continuing medical education events supported by unrestricted educational grants from Abbott. R. G.L. reports receiving fees as a consultant or advisory board member for Abbott, Amgen, Astellas, Boehringer- Ingelheim, Barrier Therapeutics and Genentech; he has received lecture fees from Abbott, Amgen/ Wyeth and Biogen-Idec, and has been the principal investigator and received grants from Abbott, Amgen, Astellas, Centocor, Galderma and Genentech. K.U., M.K. and A.C. are employees of Abbott. ”	
<b>Risk of bias</b>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 559): “Randomisation was completed through a central computer-generated scheme stratified by centre, with block sizes of four” Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 559): “Patient numbers were centrally assigned by an interactive voice-response system in consecutive order” Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 559): “Adalimumab (Humira; Abbott Laboratories) or matching placebo for SC injection was provided as sterile preservative-free solution in prefilled syringes. Oral methotrexate tablets were supplied by Wyeth Pharma (Münster, Germany), and placebo tablets were supplied by Abbott GmbH & Co. KG (Ludwigshafen, Germany). Both the methotrexate and placebo tablets were administered

		as capsules (encapsulated tablets) as a single weekly dose. The capsules for both methotrexate and placebo were supplied by Fisher Clinical Services (Basel, Switzerland).” Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 559): “Adalimumab (Humira; Abbott Laboratories) or matching placebo for SC injection was provided as sterile preservative-free solution in prefilled syringes. Oral methotrexate tablets were supplied by Wyeth Pharma (Münster, Germany), and placebo tablets were supplied by Abbott GmbH & Co. KG (Ludwigshafen, Germany). Both the methotrexate and placebo tablets were administered as capsules (encapsulated tablets) as a single weekly dose. The capsules for both methotrexate and placebo were supplied by Fisher Clinical Services (Basel, Switzerland).” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 271, analysed 271 Management of missing data: quote (p 562): “Data for 16 patients with missing week 16 assessments for PASI, including the 15 patients who discontinued and one additional patient in the methotrexate group, were imputed as nonresponse.” Comment: probably done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00235820) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported except for DLQI that was published in a second study

Shehzad 2004

Methods	RCT, active-controlled, open label Date of study: March 2001-November 2001 Location: 1 centre in Karachi, Pakistan
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Participants	<p><b>Randomised:</b> 40 participants (age from 18-50 years, 60 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI &gt; 10)</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Immunosuppression, kidney insufficiency, liver insufficiency</li> <li>• Had an active infection</li> <li>• Had uncontrolled cardiovascular disorder</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• Not stated</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. PUVA therapy (+ psoralen) (n = 20), 4 times/week</p> <p><b>Control intervention</b></p> <p>B. Methothrexate (n = 20), orally, 10 mg/week, 5 mg Saturday + Sunday</p>
Outcomes	<p>Time of assessments: not stated</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• Time to clearance</li> <li>• AEs</li> </ul>
Notes	<p>Funding source: Immunex Corporation</p> <p>Declarations of interest: not stated</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (in the method section): "The selected patients ... randomly allocated to..." Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (in the method section): "The selected patients ... randomly allocated to..." Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: not blinded

Shehzad 2004 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no description of the methods used to manage missing data, no description of the methods used to assess the primary outcome (ITT, PP...)
Selective reporting (reporting bias)	High risk	Comment: no protocol was available. The outcomes mentioned in the results section were not specified in the methods section

Sommerburg 1993

Methods	RCT, placebo-controlled, double blind Date of study: 1986-1988 Location: 7 centres in Germany
Participants	<b>Randomised:</b> 88 participants (mean age 45 years, 68 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Generalized chronic plaque psoriasis or exanthematic</li> <li>• Aged 19-75 years</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Pregnancy, kidney insufficiency, liver insufficiency</li> <li>• Had uncontrolled cardiovascular disorder</li> <li>• Had uncontrolled diabetes</li> <li>• Had uncontrolled hypertension</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• 5/88 (6%)</li> <li>• Acitretin (4), placebo (1)</li> <li>• Missing outcome (3) erythroderma (1)</li> </ul>
Interventions	<b>Intervention</b> A. Acitretin (n = 44), orally, 50 mg (15 days) then 25 mg, daily, 8 weeks <b>Control intervention</b> B. Placebo (n = 44), orally, daily, 8 weeks Co-intervention PUVA (8-methoxypsoralen), orally 0.6 mg/kg, 3-5/week, 8 weeks
Outcomes	Assessments at 8 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• PSI</li> </ul> <b>Secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• PSI 75</li> </ul>
Notes	Funding source: not stated Declarations of interest: not stated
<i>Risk of bias</i>	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p 310): "The study was designed as a randomised, double-blind, parallel groups trial... Both investigators and biostatisticians were blinded" Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (p 310): "The study was designed as a randomised, double-blind, parallel groups trial... Both investigators and biostatisticians were blinded" Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (p 310 & 311): "The study was designed as a randomised, double-blind, parallel group trial... Both investigators and biostatisticians were blinded... however due to well know side effect pattern of acitretin, ..., the possibility of an investigator bias cannot be excluded" Comment: visible AE in acitretin groups
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (p 310 & 311): " The study was designed as a randomised, double-blind, parallel group trial... Both investigators and biostatisticians were blinded... however due to well know side effect pattern of acitretin, ..., the possibility of an investigator bias cannot be excluded" Comment: visible AE in acitretin groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	88 included/83 analysed Quote (p 311): "Patients who discontinued the trial prematurely were evaluated on the date of discontinuation of therapy" Comment: not ITT, low number of drop-outs
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

Methods	RCT, active-controlled, double blind Date of study: December 2005-May 2008 Location: centres (n = 98) worldwide
Participants	<p><b>Randomised:</b> 754 participants (mean age 46 years, 473 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PGA moderate-severe, BSA &gt; 10)</li> <li>• Age ≥ 18</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Pregnancy</li> <li>• Had received biologics</li> <li>• Had an active infection</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 59/754 (8%)</li> <li>• No drug administered (2)</li> <li>• Etanercept twice a week (29): AE (14), lost to follow-up (2), deviation (4), decision (5), lack efficacy (4)</li> <li>• Etanercept once a week (28): AE (10), lost to follow-up (2)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Etanercept, SC, 50 mg, twice a week, 12 weeks</p> <p><b>Control intervention</b></p> <p>B. Etanercept, SC, 50 mg, once a week, 12 weeks</p>
Outcomes	<p>Assessments at 12 weeks</p> <p><b>Primary and secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• Clear or almost clear PGA (0/1)</li> </ul> <p><b>Outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PGA 24 weeks</li> <li>• PASI 75</li> <li>• PASI 90</li> <li>• Mean PASI</li> <li>• ACR (American College of Rheumatology) 20, 50 and 70 (weeks 12 and 24)</li> <li>• Participant-reported outcomes</li> </ul>
Notes	<p>Funding, quote (p 8): “Wyeth Research, which was acquired by Pfizer in October 2009, sponsored this clinical trial and was responsible for the collection and analysis of data...”</p> <p>Declarations of interest (p 8): “WS has received fees for speaking/consulting from Abbott, Schering-Plough, Wyeth, and Janssen-Cilag. J-PO has received fees for speaking/conferences/consulting from Schering-Plough, Abbott, Merck-Serono, Centocor, Wyeth, Janssen-Cilag, MedPharma, Laboratorios Pierre-Fabre, Galderma Laboratories, and Leo Pharma. BK has served on advisory boards for Schering-Plough and Roche; has received funds for research/travel/conferences from Wyeth, Centocor, Abbott, Schering-Plough, Roche, and Bristol-Myers Squibb; and has served on a speaker panel for Bristol-Myers Squibb. OB has received fees from Wyeth, Schering-Plough, Abbott, Roche, Chugai, and Bristol-Myers Squibb. DR, RDP, JE, CM, and BF are all employees of Pfizer.”</p>
<i>Risk of bias</i>	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p 3): "We randomly assigned participants to ..." Comment: no description of the method used to generate random sequences
Allocation concealment (selection bias)	Unclear risk	Quote (p 3): "We randomly assigned participants to ..." Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 3): "In the double blind period.." Comment: probably done, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 3): "In the double blind period.." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	754 included/752 analysed Quote (p 4): "The modified intention-to-treat (ITT) population included all randomised participants who took at least one dose of the test drug and at least one post baseline efficacy evaluation... Efficacy analyses used the last observation carried forward method for imputation of missing data" Comment: mITT and only 2 of 754 participants not included in the analysis of the primary outcome
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00245960) The pre-specified outcomes mentioned in the methods section appeared to have been reported except for the results of participant-reported endpoints summarized in a separate publication

Methods	RCT, placebo-controlled, double blind Date of study: July 2008-April 2009 Location: 41 centres in the USA
Participants	<b>Randomised:</b> 211 participants (mean age 45 years, 131 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>-Participants with moderate-severe psoriasis (PGA <math>\geq</math> 3, PASI <math>\geq</math> 12, BSA <math>\geq</math> 10), age <math>\geq</math> 18 years</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Previous exposure to either etanercept or ABT-874</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• 18/211 (8.5%): etanercept 12, placebo 6</li> <li>• Time and reasons: <ul style="list-style-type: none"> <li>◦ Etanercept: AE (3), lost to follow-up (1), withdrew consent (3), protocol violation (4), other (1)</li> <li>◦ Placebo: AE (2), lost to follow-up (1), protocol violation (2), other (1)</li> </ul> </li> </ul>
Interventions	<b>Intervention</b> A. Etanercept (n = 139), SC auto-administered, 50 mg twice a week, 11 weeks <b>Control intervention</b> B. Placebo (n = 72), SC auto-administered, twice a week
Outcomes	Assessments at 12 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• PASI 75</li> <li>• PGA 0/1</li> </ul> <b>Secondary outcomes of the trial</b> At 4, 8, 12 weeks <ul style="list-style-type: none"> <li>• PASI 50</li> <li>• PASI 75</li> <li>• PASI 90</li> <li>• DLQI</li> <li>• PGA</li> <li>• Safety</li> <li>• Patient global assessment of psoriasis</li> </ul>
Notes	Funding source, quote (Appendix 1): "Abbott Laboratories funded this study and participated in the study design, data collection, data management, data analysis and preparation of the manuscript. All of the authors had full access to the data and were involved in the analysis of data, development and revision of the manuscript, and decision to submit the manuscript for publication. The corresponding author takes responsibility for the integrity of the data and the accuracy of the data analysis." Declarations of interest (appendix 1): "B.E.S. has been an investigator, consultant, speaker, and served on an advisory board for Amgen, Abbott and Centocor; and has also been a speaker for Astellas. J.J.C. has received research support from Abbott, Amgen, Centocor, Celgene and Eli Lilly; has been a consultant for Abbott, Amgen and Centocor; and has been a speaker for Abbott. P.S.Y. has served as a consultant, principle investigator, speaker or advisory board member for Abbott, Amgen, Astellas and Centocor. M.O. and D.A.W. are employees of Abbott."

<i>Risk of bias</i>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote (p 662): "Patients were randomised." .." Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (p 662): "Patients were randomised" Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 662): "Patients enrolled in the placebo arm received SC injections matching active treatment to maintain the blind. To maintain the blind, all patients received two SC injections at weeks 0 and 4 and one SC injection at week 8, consisting of either briakinumab or matching placebo, depending on the treatment arm. In addition, each patient also received two SC injections biweekly, 3 days apart, week 0 through week 11, consisting of either etanercept or matching placebo, depending on the treatment arm." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 662): "Patients enrolled in the placebo arm received SC injections matching active treatment to maintain the blind. To maintain the blind, all patients received two SC injections at weeks 0 and 4 and one SC injection at week 8, consisting of either briakinumab or matching placebo, depending on the treatment arm. In addition, each patient also received two SC injections biweekly, 3 days apart, week 0 through week 11, consisting of either etanercept or matching placebo, depending on the treatment arm." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 211, analysed 211 Management of missing data: Quote (p 663): "The primary efficacy analysis consisted of four comparisons per-

Strober 2011 (Continued)

		formed in the intent-to-treat population (i.e. all randomised patients), ..., Nonresponder imputation was used to handle missing data.” Comment: done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00710580) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

Strohal PRISTINE, 2013

Methods	RCT, active-controlled, double blind Date of study: April 2008-March 2012 Location: 32 centres in Europe, Latin America and Asia
Participants	<b>Randomised:</b> 273 participants (mean age 44 years, 190 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 10, BSA <math>\geq</math> 10), age <math>\geq</math> 18 years</li> <li>• Non-response to topical treatment</li> <li>• Non-response to phototherapy</li> <li>• Non-response to conventional systemic treatment</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Had received biologics</li> <li>• Had an active infection</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• 25/273 (9%)</li> <li>• Time and reasons: <ul style="list-style-type: none"> <li>○ No efficacy evaluations (3)</li> <li>○ Etanercept once a week (10): AE (3), lack of efficacy (1), decision (5), other (1)</li> <li>○ Etanercept twice a week (12): AE (6), lack of efficacy (1), decision (2), deviation (1), other (2)</li> </ul> </li> </ul>
Interventions	<b>Intervention</b> A. Etanercept (n = 137), SC, 50 mg, once a week, 24 weeks <b>Control intervention</b> B. Etanercept (n = 136), SC, 50 mg, twice a week, 24 weeks
Outcomes	Assessments at 24 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <b>Secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• PASI 50, 75, 90</li> <li>• Mean PASI</li> </ul>



	<ul style="list-style-type: none"> <li>• PGA (Physician Global Assessment) 0/1</li> <li>• DLQI</li> <li>• AE</li> </ul>	
Notes	<p>Funding source, quote (p 177): “The PRISTINE trial was sponsored by Pfizer Inc...”</p> <p>Declarations of interest (p 177-178): “Robert Strohal has been a paid consultant of and has received research grants from Pfizer Inc, which provided funding for the PRISTINE study. He is also a member of the Pfizer European Expert Board and of the Pfizer Speakers Bureau. Luis Puig has been a paid consultant of and has received research grants from Pfizer; he has served on Pfizer advisory boards and the Speakers Bureau. Edgardo Chouela is a paid consultant and speaker for Pfizer Inc and Galderma and has conducted clinical studies for Novartis, Jannssen, Pfizer and Roche. Tsen-Fang Tsai has been a paid consultant of Pfizer Inc; he has served as an investigator and received honoraria for serving as an advisor and speaker for Pfizer. Jeffrey Melin, Bruce Freundlich and Charles Molta were previous employees of Wyeth and Pfizer Inc. Joanne Fuiman, Ronald Pedersen and Deborah Robertson are current employees of Pfizer Inc.”</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote (p 170): “Subjects were randomly assigned to one of the 2 etanercept treatment groups... in 1:1 treatment allocation” Comment: not specified
Allocation concealment (selection bias)	Unclear risk	Quote (p 170): “Subjects were randomly assigned to one of the 2 etanercept treatment groups... in 1:1 treatment allocation” Comment: not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 170): “The study consisted of a 12-week double-blind treatment period” Comment: probably done, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 170): “The study consisted of a 12-week double-blind treatment period” Comment: probably done, placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	273 enrolled and randomised and 270 analysed Quote (p 171): “All efficacy analyses were performed using the modified intent-to-treat population which included all randomised subjects who received at least one dose of etanercept and had both baseline and on therapy PASI evaluations. The last

		observation-carried-forward method was used for the imputation of missing data...” Comment: mITT and only 3 of 273 participants not included in the analyses of the primary outcome
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00663052) The pre-specified outcomes mentioned in the methods section appeared to have been reported

Tanew 1991

Methods	RCT, placebo-controlled, double blind Date of study: not stated Location: 2 centres in Austria (Vienna, Innsbruck)
Participants	<b>Randomised:</b> 60 participants (mean age 40 years (acitretin), 49 years (placebo); 42 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (BSA <math>\geq</math> 20), age <math>\geq</math> 18 years</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Not stated</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• 12/60 (20%)</li> <li>• Time and reasons: <ul style="list-style-type: none"> <li>◦ acitretin group (7): severe muscle pain (1), serum triglycerides exceeding 400 mg/dL (2), irregular drug intake (4)</li> <li>◦ placebo group (5): unrelated to therapy</li> </ul> </li> </ul>
Interventions	<b>Intervention</b> A. Acitretin (n = 30), orally, 1 mg/kg, daily, 12 weeks or until complete clearing <b>Control intervention</b> B. Placebo (n = 30), orally, daily, 12 weeks <b>Co-intervention</b> PUVA, phototherapy, 4 times/week, 12 weeks
Outcomes	Assessments at 12 weeks <b>Primary and secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• Not defined</li> </ul> <b>Outcomes of the trial</b> <ul style="list-style-type: none"> <li>• Complete remission</li> <li>• Side effects</li> </ul>
Notes	Funding: supported by a grant from Hoffma La Roche & Co Ltd Declarations of interest: not stated

Tanew 1991 (Continued)

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p 682): "Only patients ... were included and assigned randomly..." Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (p 682): "Only patients ... were included and assigned randomly..." Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (p682): "Acitretin ... or placebo..." Comment: no description of the method used to guarantee blinding of participants and personnel as acitretin leads to visible adverse effects (cheilitis)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (p682): "Acitretin ... or placebo..." Comment: no description of the method used to guarantee blinding of participants and personnel as acitretin leads to visible adverse effects (cheilitis)
Incomplete outcome data (attrition bias) All outcomes	High risk	Randomly assigned 60, analysed 48 Quote (p 683): "Of the 60 patients, 48 completed the study and were included in the statistical analysis" Comment: not ITT
Selective reporting (reporting bias)	Unclear risk	No protocol available, no outcomes defined in the method section

Thaci CLEAR, 2015

Methods	RCT, active-controlled, double blind Date of study: 27 February 2014-11 May 2015 Location: 137 centres in Europe, Australia and Asia
Participants	<b>Randomised:</b> 676 participants (mean age 46 years, 481 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>-Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12, BSA <math>\geq</math> 10), age <math>\geq</math> 18 years</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Immunosuppression, active infection</li> </ul>

	<ul style="list-style-type: none"> <li>• Had received anti IL17 drug or ustekinumab</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 32/676 (4.7%)</li> <li>• Did not receive the treatment (4)</li> <li>• Information consent obtained the day after study-related procedure (1, excluded from the efficacy analysis)             <ul style="list-style-type: none"> <li>• AE (7)</li> <li>• Lost to follow-up (3)</li> <li>• Protocol deviation (5)</li> <li>• Participant/guardian decision (7)</li> <li>• Physician decision (1)</li> <li>• Non compliance with study treatment (1)</li> <li>• Technical problem (1)</li> </ul> </li> </ul>	
Interventions	<p><b>Intervention</b></p> <p>A. Secukinumab (n = 334), SC, 300 mg weeks 0, 1, 2, 3 then monthly</p> <p><b>Control intervention</b></p> <p>B. Ustekinumab (n = 335), SC, 45/90 mg weeks 0, 4 then every 12 weeks</p>	
Outcomes	<p>Assessments at 16 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 90</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> <li>• PASI 90 at week 54</li> <li>• DLQI</li> <li>• AEs</li> </ul>	
Notes	<p>Funding source:</p> <p>Quote (p 400): “Novartis Pharma supported this study”</p> <p>Declarations of interest (p 400): “Dr Thaci has served as a consultant, served as an advisory board member, and/or received honoraria for lecturing for AbbVie, Amgen, Biogen-Idec, Celgene, Eli Lilly, Janssen-Cilag, Leo Pharma, MSD, Novartis, Pfizer, Regeneron, and Sanofi. Dr Blauvelt has served as a scientific consultant and clinical study investigator for AbbVie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen Ortho Biotech, Merck, Novartis, Pfizer, and Sandoz. Dr Reich has served as a consultant and/or paid speaker for and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis including AbbVie, Amgen, Biogen-Idec, Celgene, Centocor, Covagen, Eli Lilly, Forward Pharma, GSK, Janssen-Cilag, Leo Pharma, Medac, MSD, Novartis, Pfizer, Vertex, Takeda, and Xenoport...”</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p 402): “were randomised via an interactive response technology system” Randomization was conducted via Interactive Response Technology, which assigned a

		randomisation number that linked the subject to a treatment arm and specified unique medication pack number Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p402): “were randomised via an interactive response technology system “ Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p402) : “To maintain blinding, placebo injections matching the secukinumab regimen were given in the ustekinumab group” Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p402) : “To maintain blinding, placebo injections matching the secukinumab regimen were given in the ustekinumab group” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 676, analysed 669 Management of missing data: Quote (p 403): “Missing values with respect to response variables based on PASI and IGA mod 2011 scores were imputed as nonresponse (nonresponder imputation).” Comment: however it was not an ITT analysis as 7 participants were not taken into account but low rate of dropout
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02074982) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

**Torii 2010**

Methods	RCT, placebo-controlled, double blind Date of study: not stated Location: 28 centres in Japan
Participants	<b>Randomised:</b> 54 participants (mean age 46 years, 36 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12, BSA <math>\geq</math> 10)</li> </ul> <b>Exclusion criteria</b>

	<ul style="list-style-type: none"> <li>• Active infection</li> <li>• Past history of malignant tumours</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 7/54 (13%) at W14;</li> <li>• Infliximab (3): therapeutic effect (2), adverse event (1)</li> <li>• Placebo (4): AE (1), withdrawal of consent (3)</li> </ul>	
Interventions	<p><b>Intervention</b> A. Infliximab (n = 35), IV, 5 mg/kg, weeks 0, 2, 6; 10 weeks</p> <p><b>Control intervention</b> B. Placebo (n = 19), IV, weeks 0, 2, 6; 10 weeks</p>	
Outcomes	<p>Assessments at 10 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI50</li> <li>• DLQI</li> <li>• PGA</li> <li>• AE</li> </ul>	
Notes	<p>Funding: not stated</p> <p>Declarations of interest: not stated</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote (p 41): "Eligible patients were randomised in a 2:1 ratio to either... using the dynamic allocation method" Comment: no description of the methods used to guarantee the random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (p41): "Eligible patients were randomised in a 2:1 ratio to either... using the dynamic allocation method" Comment: no description of the methods used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p41): "The induction phase of th treatment was .. double-blind placebo controlled trial... Infliximab or placebo was administered by IV drip infusion over a period of at least 2h .." Comment: probably done

Torii 2010 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p41): "The induction phase of th treatment was .. double-blind placebo controlled trial... Infliximab or placebo was administered by intravenous drip infusion over a period of at least 2h .. Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 54, analysed 54 Quote (p42): "This primary endpoint analysis was performed on an "intent-to-treat" basis...Patients who discontinued the study treatment ... were handled as "not improved" in the assessment" Comment: probably done
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

Tsai PEARL, 2011

Methods	RCT, placebo-controlled, double blind Date of study: December 2008-March 2010 Location: 13 centres in Taiwan and Korea
Participants	<b>Randomised:</b> 121 participants (mean age 41 years, 103 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12, BSA <math>\geq</math> 10), age &gt; 20 years</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Had an active infection</li> <li>• Past history of malignant tumours</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• 9/121 (7.4%): ustekinumab group (4), placebo group (5)</li> <li>• AEs: placebo group (3)</li> <li>• Unsatisfactory therapeutic effects: ustekinumab group (1), placebo group (2)</li> <li>• Invalid study entry criteria: ustekinumab group (2)</li> <li>• Withdrawal of consent: ustekinumab group (1)</li> </ul>
Interventions	<b>Intervention</b> A. Ustekinumab, SC, 45 mg, weeks 0, 4, 16 + placebo week 12, 16 weeks <b>Control intervention</b> B. Placebo, SC, weeks 0-4 + ustekinumab 45 mg weeks 12-16
Outcomes	Assessments at 12 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <b>Secondary outcomes of the trial</b>

	<ul style="list-style-type: none"> <li>• PGA cleared or minimal at 12 weeks</li> <li>• Change from baseline in the DLQI at 12 weeks</li> <li>• AEs</li> </ul>	
Notes	Funding source quote (p 162): "This study was supported by Centocore, Inc" Declarations of interest: not stated	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p 155): "Patients were enrolled in this multicenter..., double-blind, placebo-controlled study... Randomization was performed via an interactive voice response system based on minimization with bias-coin assignment..." "Randomization was conducted via Interactive Response Technology, which assigned a randomisation number that linked the subject to a treatment arm and specified unique medication pack number" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p155): "Patients were enrolled in this multicenter..., double-blind, placebo-controlled study... Randomization was performed via an interactive voice response system based on minimization with bias-coin assignment..." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p155): "Patients were enrolled in this multicenter..., double-blind, placebo-controlled study.. Comment: placebo trial, probably done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (p155): "Patients were enrolled in this multicenter..., double-blind, placebo-controlled study.. Comment: placebo trial, probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 121, analysed 121 Quote (p 156): "For all efficacy analyses, patients were analysed by assigned treatment groups...Data were analysed by intent-to-treat for the primary endpoint... Patients who discontinued study treatment.. were judged as non-responders for binary



		endpoints” Comment: ITT analyses
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been reported

## Tyring 2006

Methods	RCT, placebo-controlled, double blind Date of study: June 2003-January 2004 Location: 39 centres in Houston, USA and Canada
Participants	<b>Randomised:</b> 620 participants (mean age 46 years, 419 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 10, BSA <math>\geq</math> 10), age &gt; 18 years</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Kidney insufficiency, liver insufficiency, past history of malignant tumours</li> <li>• Had received conventional systemic treatments</li> <li>• Had received biologics (etanercept or anti-TNF)</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• 23/620 (3.7%); etanercept group (6), placebo group (15)</li> <li>• AEs: etanercept group (4), placebo group (3)</li> <li>• Disease progression: etanercept group (1), placebo group (4)</li> <li>• Withdrawal of consent: etanercept group (1), placebo group (5)</li> <li>• Lost to follow-up: placebo group (4)</li> <li>• Non-compliance: placebo group (1)</li> </ul>
Interventions	<b>Intervention</b> A. Etanercept (n = 311), 50 mg, SC, twice weekly, 12 weeks <b>Control intervention</b> B. Placebo (n = 309), SC, twice weekly, 12 weeks
Outcomes	Assessments at 12 weeks <b>Primary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <b>Secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• DLQI at 12w</li> <li>• PASI 50</li> <li>• PASI 90</li> <li>• the 17-item Hamilton rating scale for depression</li> <li>• Beck depression inventory</li> </ul>
Notes	Funding, quote (p 361): “The study was designed by Immunex, S Tyring, and other members of the Etanercept Psoriasis study group (The complete data set was held at the central data-processing facility at Amgen) Declarations of interest (p 367-368): ”S Tyring has received research support from Am-

gen. A Gottlieb is a consultant for several companies (Amgen, BiogenIdec, CellGate, Centocor, Genentech, Novartis AG, Wyeth Pharmaceuticals, Schering-Plough Corporation, Eisai, Celgene, Bristol Myers Squibb, Beiersdorf, Warner Chilcott, Abbott Labs, Allergan, Kemia, Roche, Sankyo, Medarex, Celera, TEVA, Actelion, and Advanced ImmuniT) and is on the speaker's bureau for Amgen, BiogenIdec, and Wyeth Pharmaceuticals. She has also received research funding from Amgen, BiogenIdec, Centocor, Genentech, Abbott Labs, Ligand Pharmaceuticals, Beiersdorf, Fujisawa Healthcare, Celgene Corp, Synta, Bristol Myers Squibb, Warner-Chilcott, and Paradigm. K Papp is a consultant, has received research funding, and has served as a speaker for Amgen, BiogenIdec, Centocor, Genentech, Novartis, Wyeth, Schering-Plough, Abbott, Allergan, Medimmune, Serono, Xoma, Isotechnica, and GlaxoSmithKline. He has also served as a medical or scientific officer for Amgen, Centocor, Genentech, and Serono. K Gordon has received research support and honoraria from Abbott, Amgen, Biogen-IDEc, Centocor, Genentech, and Synta. C Leonardi is: a consultant, investigator, and speaker for Amgen and Genentech and has received educational grants from these companies; a consultant, investigator, and speaker for Centocor; a consultant and investigator for Serono; and a consultant, investigator, and speaker for Abbott..."

<i>Risk of bias</i>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (p 30): "Randomisation code lists were generated in the Biostatistics Department at Amgen by a designed person with no other association with the study" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Quote (p 30): "Randomisation code lists were generated in the Biostatistics Department at Amgen by a designed person with no other association with the study" Comment: no precision
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 30): "All patients received 2 injections per dose of investigational product", Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 30): "To prevent study assessors from being influenced by the presence of an injection site reaction, patients applied dressings to the last three injection sites and to any erythematous injection sites before each psoriasis evaluation" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 620, analysed 617 for the primary outcome Management of missing data: quote (p 31)

**Tyning 2006** (Continued)

		<p>: “The primary analyses for all efficacy endpoints included all randomised patients who received at least one dose of investigational product. Missing values were imputed using last observation carried forward”</p> <p>Comment: only 2 participants did not receive at least one dose, 618 participants should be involved in the mITT, however 617 participants were analysed for the primary outcome</p>
Selective reporting (reporting bias)	Low risk	<p>Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00111449) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported</p>

**Vaclavkova 2014**

Methods	<p>RCT, active/placebo-controlled, double blind Date of study: 22 September 2010-24 October 2012 Location: 58 centres in Europe and Russia</p>
Participants	<p><b>Randomised:</b> 326 participants (mean age 40 years, 245 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 10, BSA <math>\geq</math> 10), age 18-60 years</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Immunosuppressive treatment for other diseases than psoriasis</li> <li>• Had an active infection</li> <li>• Had past history of malignant tumours</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 48/326 (14.7%); ponesimod 20 group (17), ponesimod 40 group (20), placebo group (11)</li> <li>• Patient decision: ponesimod 20 group (4), ponesimod 40 group (3), placebo group (7)</li> <li>• AE and patient decision: ponesimod 20 group (1), ponesimod 40 group (1), placebo group (1)</li> <li>• AEs: ponesimod 20 group (6), ponesimod 40 group (12), placebo group (0)</li> <li>• Withdrew consent: ponesimod 20 group (3), ponesimod 40 group (3), placebo group (0)</li> <li>• Lack of efficacy: ponesimod 20 group (1), ponesimod 40 group (0), placebo group (1)</li> <li>• Lack of efficacy and patient decision: ponesimod 20 group (0), ponesimod 40 group (0), placebo group (1)</li> <li>• Administrative : ponesimod 20 group (2), ponesimod 40 group (1), placebo</li> </ul>

	group (1)
Interventions	<p><b>Intervention</b></p> <p>A. Ponesimod (n = 126), orally, 10 mg for 7 days then 20 mg, 16 weeks</p> <p>B. Ponesimod (n = 133), orally, 10 mg for 7 days then 20 mg days 8 -15 then 40 mg, 16 weeks</p> <p><b>Control intervention</b></p> <p>C. Placebo (n = 67), orally, 16 weeks</p>
Outcomes	<p>Assessments at 16 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PGA 0 or 1</li> <li>• PASI 90</li> <li>• Change from baseline pain psoriatic arthritis</li> </ul>
Notes	<p>Funding (p 2044): “This study was sponsored by Actelions Pharmaceuticals”</p> <p>Declarations of interest (p 2044): “AV, MB, and DD’A were employees and stockholders of Actelion Pharmaceuticals when the study was done. SC has been lecturer, consultant, or both, for AbbVie, Janssen-Cilag, Leo-Pharma, Merck, Novartis, and Pfizer. MS has received personal fees for statistical consultancy from Actelion Pharmaceuticals and SDE Research. PA, PH, and P-GS declare that they have no competing interests.”</p>

**Risk of bias**

Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 2037): “A unique seven-digit randomisation number was assigned to each patient by an independent service provider (ICON Clinical Research, Dublin, Ireland) via an interactive voice or internet-based response system” Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 2037): “A unique seven-digit randomisation number was assigned to each patient by an independent service provider (ICON Clinical Research, Dublin, Ireland) via an interactive voice or internet-based response system” Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 2037): “The investigational drug and matching placebo were identical in appearance and packaging...The primary investigator, care providers, patients, and sponsor were unaware of study treatment

Vaclavkova 2014 (Continued)

		assignment and lymphocyte count. An independent physician monitored patients after the first dose was administered or increased until the end of the study.” Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 2037): “The investigational drug and matching placebo were identical in appearance and packaging...The primary investigator, care providers, patients, and sponsor were unaware of study treatment assignment and lymphocyte count. An independent physician monitored patients after the first dose was administered or increased until the end of the study.” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 326, analysed 326 Quote (p 2037): “All randomised patients were assessed by intention-to-treat for the primary, secondary, and all efficacy endpoints in the induction period... Missing or invalid values were handled with non-responder imputation” Comment: ITT analyses
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01208090) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

Van Bezoijen 2016

Methods	RCT, placebo-controlled, double blind Date of study: 2013 and June 2015 Location: single centre in the Netherlands
Participants	<b>Randomised:</b> 33 participants <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 10, BSA <math>\geq</math> 10), age &gt; 18 years</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Any other subtype of psoriasis</li> <li>• Previous treatment failure on etanercept or fumarates</li> <li>• Had a clinically significant adverse event with prior use of both drugs.</li> <li>• Pregnant or lactating women</li> </ul> <b>Dropouts and withdrawals</b>

	<ul style="list-style-type: none"> <li>• None at week 12</li> </ul>	
Interventions	<p><b>Intervention</b> A. Fumaric acid (n = 18), from 215 mg once daily up to a maximum of 215 mg 4 times a day, 24 weeks</p> <p><b>Control intervention</b> B. Placebo</p> <p><b>Co-intervention</b> Etanercept (n = 14) (50 mg SC twice weekly for 12 weeks followed by 50 mg once weekly for an additional 12 weeks)</p>	
Outcomes	<p>Assessments at 24 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PGA0/1</li> <li>• DLQI</li> <li>• AEs</li> </ul>	
Notes	<p>Funding, quote (supplemental appendix): "This investigator-initiated study was supported by a grant of Pfizer Pharmaceuticals. Pfizer was not involved in any study procedure, but Pfizer was granted the right to read, but not to edit, the manuscript prior to submission for publication."</p> <p>Declarations of interest (p 413): "Investigator-initiated project grant from Pfizer. E. Prens has acted as a consultant for AbbVie, Amgen, Astra-Zeneca, Baxter, Eli Lilly, Galderma, Janssen-Cilag, Novartis and Pfizer and has received investigator-initiated research grants (paid to Erasmus MC) from Pfizer, Janssen-Cilag and AbbVie. M.B.A. van Doorn has acted as a consultant for Abbott, Janssen, LEO Pharma, MSD and Pfizer, and has been an investigator for Eli Lilly, Idera Pharmaceuticals, Cutanea and Novartis. T. van Gelder has been on the speakers' bureau or worked as consultant for Sandoz, Novartis, Teva, Chiesi, Astellas and Roche"</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote (supplemental appendix): "Using a computer-generated randomisation list, patients were randomised at baseline to a 1:1 ratio to receive either etanercept combined with oral fumarates (combination group) or etanercept only (monotherapy group)." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (supplemental appendix): "Using a computer-generated randomisation list, patients were randomised at baseline to a 1:1 ratio to receive either etanercept com-

Van Bezoijen 2016 (Continued)

		bined with oral fumarates (combination group) or etanercept only (monotherapy group)." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (supplemental appendix): "Patients and the study physicians were not blinded for the allocated treatment group." Comment: not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (supplemental appendix): "The independent PASI assessor (E.P.P.) was blinded to treatment throughout the course of the study." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 33, analysed 33 for the primary outcome Management of missing data: quote (supplemental appendix): "Patients lost to follow-up were not included in the PASI 75 response and PGA score analyses." Comment: not ITT analyses however all randomised participants reached the primary outcome assessment
Selective reporting (reporting bias)	Unclear risk	Comment: the protocol for the study was available on European Clinical Trials Database (EudraCT) (EudraCT No. 2011-005685-38) (not found) The pre-specified results mentioned in the methods section appeared to have been reported

Van de Kerkhof 2008

Methods	RCT, placebo-controlled, double blind Date of study: Jun 2006-May 2007 Location: multicentre (numbers of centres not stated) in Belgium, France, Germany, Hungary, Italy, Netherlands, Poland, Romania, Spain
Participants	<b>Randomised:</b> 143 participants (mean age 45 years, 84 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 10, BSA <math>\geq</math> 10), age &gt; 18 years</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Had received biologics (etanercept, anti TNF)</li> <li>• Had an active infection</li> </ul> <b>Dropouts and withdrawals</b>

	<ul style="list-style-type: none"> <li>• 16/143 (11%): etanercept group (6), placebo group (10)</li> <li>• AEs: etanercept group (3), placebo group (3)</li> <li>• Lack of efficacy: etanercept group (2), placebo group (4)</li> <li>• Other reason: etanercept group (1), placebo group (3)</li> </ul>
Interventions	<p><b>Intervention</b> A. Etanercept, 50 mg, self-administered SC, once a week, 12 weeks (n=96)</p> <p><b>Control intervention</b> B. Placebo, self-administered SC, once a week, 12 weeks (n=46)</p>
Outcomes	<p>Assessments at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• Proportion of patients PASI 75 or greater</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75 at other time points</li> <li>• PASI 50 at 12, 24</li> <li>• PASI 90 at 12, 24</li> <li>• PASI 100 at 24</li> <li>• PASI improvement from baseline</li> <li>• PGA</li> <li>• DLQI</li> </ul>
Notes	<p>Funding source (p 1184): “This study was supported financially by Wyeth Pharmaceuticals, Collegeville, PA, USA”</p> <p>Comments: 3 authors were employed by Wyeth pharmaceuticals which supported this study financially</p> <p>Declarations of interest (p 1177): “C.Z., M.P.B., L.P. and J.W. are employed by Wyeth Pharmaceuticals, which supported this study financially. ”</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 1178): “Patients were randomly assigned (using the Clinical Operations Randomization Environment system) ... according to a 2:1 treatment allocation” Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Quote (p1178): “Patients were randomly assigned (using the Clinical Operations Randomization Environment system) ... according to a 2:1 treatment allocation” Comment: not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 1178): “In both the double blind controlled study..., etanercept was supplied as a sterile lyophilised powder. All study drugs were self-administrated QW by the



Van de Kerkhof 2008 (Continued)

		patient by subcutaneous injections” Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 1178): “In both the double blind controlled study..., etanercept was supplied as a sterile lyophilised powder. All study drugs were self-administrated QW by the patient by subcutaneous injections” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 142, analysed 142 Management of missing data, quote (p 1179): “The primary population for efficacy and safety analyses ... was the modified intent-to-treat population. The last observations were carried forward in cases of missing efficacy data” Comment: done
Selective reporting (reporting bias)	Unclear risk	Comment: the specified outcomes mentioned in the methods section appeared to have been reported however no protocol was available,

Warren METOP, 2017

Methods	RCT, placebo-controlled Date of study: 22 February 2013-13 May 2015 Location: 13 centres in Europe
Participants	<p><b>Randomised:</b> 120 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>● Definition moderate-severe psoriasis</li> <li>● Methotrexate treatment-naive</li> <li>● Aged <math>\geq 18</math> years</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>● Pregnancy, kidney insufficiency, liver insufficiency</li> <li>● Had an active infection</li> <li>● Had past history of malignant tumours</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>● 21/212 (17.5%), methotrexate n = 14, placebo, n = 7</li> <li>● AEs: methotrexate (10), placebo (4)</li> <li>● Lost to follow-up: methotrexate (2)</li> <li>● Participants’ choice: placebo (2)</li> <li>● Poor efficacy: methotrexate (1), placebo (1)</li> <li>● Other: methotrexate (1)</li> </ul>

Interventions	<p><b>Intervention</b> A. Methotrexate (n = 91), SC, IM, 17.5-22.5 mg/week, 12 weeks</p> <p><b>Control intervention</b> B. Placebo (n = 29)</p>	
Outcomes	<p>16 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>● PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>● PASI 90</li> <li>● PGA</li> <li>● NAPSI</li> <li>● DLQI</li> <li>● AEs</li> </ul>	
Notes	<p>Funding source: Quote (p 528) “Funding source: Medac. The funder of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and all authors had final responsibility for the decision to submit for publication”</p> <p>Declarations of interest (p 536): “RBW has received personal fees from AbbVie, Almirall, Amgen, Boehringer Ingelheim Pharma, Celgene, Janssen-Cilag, Leo, Lilly, Novartis, Pfizer, and Xenoport outside the submitted work. UM has been an advisor to, received speakers honoraria or grants from, or participated in clinical for Abbott/AbbVie, Almirall Hermal, Amgen, BASF, Biogen Idec, Boehringer Ingelheim, Celgene, Centocor, Eli Lilly, Foamix, Forward Pharma, Galderma, Janssen, Leo Pharma, Medac, MSD, Miltenyi Biotech, Novartis, Pfizer, Teva, VBL, and Xenoport. RvK has been an investigator, consultant, advisor, or speaker for Abbvie, Almirall, Amgen, Biogen Idec, Boehringer Ingelheim, Celgene, Eli Lilly, GSK, Leo, Janssen-Cilag, MSD, Novartis, Pfizer, UCB, and VBL Pharma. JN has received grants from Amgen, Novartis, Janssen-Cilag, LEO, Lilly, Medac, Regeneron, and Dermapharm, outside the submitted work. DW-T has been an advisor to, received speakers honoraria or grants from, or participated in clinical for Abbvie, Almirall, Amgen, Biogen, Boehringer Ingelheim Pharma, Celgene, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, Leo, Lilly, Medac, Merck Sharp &amp; Dohme, Novartis, Pfizer, UCB Pharma, and VBL. KG has been an advisor to, received speakers honoraria or grants from, or participated in clinical for Abbott/AbbVie, Almirall, Biogen, Boehringer Ingelheim, Celgene, Delenex, Eli Lilly, Galderma, Janssen, Medac, MSD, Novartis, and Pfizer. KR has received personal fees from AbbVie, Amgen, Biogen, Boehringer Ingelheim, Celgene, Centocor, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, Leo, Lilly, Medac, Merck Sharp &amp; Dohme, Novartis, Pfizer, Regeneron, Takeda, UCB Pharma, and Xenoport, outside the submitted work. IZ, TMF, and NB-S declare no competing interests.”</p>	
<i>Risk of bias</i>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>

Random sequence generation (selection bias)	Low risk	Quote (p 3): “Eligible patients were randomly assigned (3:1), via computer-generated random numbers (RandList 1.2) in an ascending order, to receive either methotrexate or placebo injections for the first 16 weeks of the study (phase 1).” Comments: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 3): “Eligible patients were randomly assigned (3:1), via computer-generated random numbers (RandList 1.2) in an ascending order, to receive either methotrexate or placebo injections for the first 16 weeks of the study (phase 1).” Comments: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 3): “Study phase 1 was done in a double-blind manner, with group allocation concealed from participants and investigators from the time of randomisation until an interim database lock at week 16. ..The syringes for placebo and active drug were not distinguishable and were fully coated to prevent identification of colour differences between injections” Comments: clearly defined
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 3): “Study phase 1 was done in a double-blind manner, with group allocation concealed from participants and investigators from the time of randomisation until an interim database lock at week 16. ..The syringes for placebo and active drug were not distinguishable and were fully coated to prevent identification of colour differences between injections” Comments: clearly defined
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of randomised participants, n = 120, 120 analysed Quote (p 4): “All outcomes were analysed in the modified intention to-treat population of patients who had received at least one injection of study drug, with missing data treated as indicating no response (non-responder imputation).” Comment: probably done

Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02902861) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported
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**Yan 2011**

Methods	RCT, active-controlled, Date of study: April 2007-January 2009 Setting: 7 centres in China	
Participants	<p><b>Randomised:</b> 212 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Definition moderate-severe psoriasis (PASI <math>\geq</math> 12, BSA <math>\geq</math> 10)</li> <li>• Age 18-65 years</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Pregnancy, kidney insufficiency, liver insufficiency</li> <li>• Had an active infection</li> <li>• Had past history of malignant tumours</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 20/212 (9%)</li> <li>• Alefacept (7): AE (1), lost to follow-up (6)</li> <li>• Methotrexate (13): AE (3), lost to follow-up (8), deviation (2)</li> </ul>	
Interventions	<p><b>Intervention</b></p> <p>A. Alefacept + placebo oral methotrexate (n = 107), IM, 15 mg/week, 12 weeks</p> <p><b>Control intervention</b></p> <p>B. Methotrexate + placebo (n = 105), IM, alefacept, orally, 7.5 mg/week, 12 weeks</p>	
Outcomes	<p>Time to evaluate assessment: not stated</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• Not clearly defined</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI</li> <li>• PGA</li> <li>• DLQI</li> <li>• VAS</li> </ul>	
Notes	<p>Funding source (p 742): none reported</p> <p>Declarations of interest (p 742): none reported</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>

Random sequence generation (selection bias)	Unclear risk	Quote (p 738): “Each patient was assigned a random number in a chronological order” Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 738): “ The present study,..., double-blind, double dummy... Patients in the experimental group were intramuscularly injected with... and orally administered with the bank dummy methotrexate. .. and the patients in the control group...” Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 738): “The present study,..., double-blind, double dummy... Patients in the experimental group were intramuscularly injected with... and orally administered with the bank dummy methotrexate... and the patients in the control group...” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote (p 739): “Full set analysis was assessed” Comment: no description of the methods used for dealing with missing data
Selective reporting (reporting bias)	High risk	Comment: no protocol available. No primary outcome clearly identified

Yang 2012

Methods	RCT, placebo-controlled, double blind Date of study: February 2009-February 2010 Location: 9 centres in China
Participants	<b>Randomised:</b> 129 participants (mean age 39 years (infliximab) and 40 years (placebo), 95 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI <math>\geq</math> 12, BSA <math>\geq</math> 10), age 18-65 years</li> <li>• Had a diagnosis of plaque psoriasis for at least 6 months</li> <li>• Had failed to respond to conventional systemic treatment of psoriasis including: ciclosporin, methotrexate, or acitretin as previous treatment</li> </ul> <b>Exclusion criteria</b>

	<ul style="list-style-type: none"> <li>• Non-plaque forms of psoriasis</li> <li>• A history of a chronic infectious disease or opportunistic infection</li> <li>• A serious infection within 2 months of enrolment</li> <li>• Active or latent TB</li> <li>• Pregnancy or planned pregnancy within 12 months of enrolment</li> <li>• A history of lymphoproliferative disease</li> <li>• An active malignancy or history of malignancy within 5 years</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 2/129 (1.55%): infliximab group (1), placebo group (1)</li> <li>• Withdrawal of informed consent: infliximab group (0), placebo group (1)</li> <li>• Adverse event: infliximab group (1), placebo group (0)</li> </ul>	
Interventions	<p><b>Intervention</b> A. Infliximab (n = 84), IV, 5 mg/kg, weeks 0, 2, 6, 14, 22; 22 weeks</p> <p><b>Control intervention</b> B. Placebo (n = 45), IV, weeks 0, 2, 6 then infliximab 5 mg/kg weeks 10, 12, 16</p>	
Outcomes	<p>Assessments at 10 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PGA</li> <li>• DLQI</li> </ul>	
Notes	<p>Funding source: not stated</p> <p>Declarations of interest: not stated</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote (p1846): "This randomised, double-blind, placebo controlled trial... Eligible patients were randomly assigned in a 1: 2 ratio to the placebo and infliximab" Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (p1846): "This randomised, double-blind, placebo controlled trial... Eligible patients were randomly assigned in a 1: 2 ratio to the placebo and infliximab" Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p1846): "This randomised, double-blind, placebo controlled trial... Eligible patients were randomly assigned in a 1:

Yang 2012 (Continued)

		2 ratio to the placebo and infliximab... In- fliximab 5 mg/kg or placebo was adminis- tered by intravenous drip infusion over a period of at least 2 hours on the starting day of treatment (week 0) and at weeks 2 and 6 (induction)” Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p1846): “This randomised, dou- ble-blind, placebo controlled trial... Eligi- ble patients were randomly assigned in a 1: 2 ratio to the placebo and infliximab... In- fliximab 5 mg/kg or placebo was adminis- tered by intravenous drip infusion over a period of at least 2 hours on the starting day of treatment (week 0) and at weeks 2 and 6 (induction)” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Randomly assigned 129, 129 Analysed Quote: “In the primary efficacy analysis, data from all randomised subjects were analysed according to their assigned treat- ment group...” Comment: no description of the method used to manage the missing data
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The pre-specified outcomes mentioned in the methods section appeared to have been re- ported

Yilmaz 2002

Methods	RCT, placebo-controlled, open-label trial Date of study: unreported Location: Turkey
Participants	<b>Randomised:</b> 50 participants (no description of the study population) <b>Inclusion/exclusion criteria</b> <ul style="list-style-type: none"> <li>• Not stated</li> </ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"> <li>• Not stated</li> </ul>
Interventions	<b>Intervention</b> A. Acitretin (n = 50), orally, 0.5-0.7 mg/kg, daily <b>Control intervention</b> B. Placebo (n = 50) <b>Co-intervention</b>

	PUVA, twice weekly, 8-MOP at a dosage of 0.4-0.6 g/kg, 2h before UVA exposure	
Outcomes	Time of assessments not stated <b>Primary or secondary outcomes of the trial</b> <ul style="list-style-type: none"> <li>• Not clearly defined</li> </ul> <b>Outcomes of the trial</b> <ul style="list-style-type: none"> <li>• Complete remission</li> </ul>	
Notes	Funding source: not stated Declarations of interest: not stated	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote (abstract): "The patients were equally allocated to treatment groups in the study" Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (abstract): "The patients were equally allocated to treatment groups in the study" Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (abstract): "We performed an open, controlled study..." Comment: not blinded, subjective outcome
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (abstract): "We performed an open, controlled study..." Comment: not blinded, subjective outcome
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Randomly assigned 50 Comment: no description of the number of participants analysed, no description of the method used to manage missing data
Selective reporting (reporting bias)	Unclear risk	Comment: only an abstract available



Methods	RCT, placebo-controlled, double blind (LOTUS) Date of study: 23 October 2009-07 July 2011 Location: 14 centres in China	
Participants	<p><b>Randomised:</b> 322 participants (mean age 40 years, 248 male)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Participants with moderate-severe psoriasis (PASI<math>\geq</math>12 and BSA <math>\geq</math> 10), age &gt;18 years</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Severe uncontrolled or progressive medical conditions</li> <li>• Known to be infected with HIV (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or syphilis</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>• 6/322 (1.86%): ustekinumab group (3), placebo group (3)</li> <li>• AEs: ustekinumab group (2), placebo group (1)</li> <li>• Other reasons: ustekinumab group (1), placebo group (2)</li> </ul>	
Interventions	<p><b>Intervention</b></p> <p>A. Ustekinumab (n = 160), SC, 45 mg, week 0, week 4, 4weeks</p> <p><b>Control intervention</b></p> <p>B. Placebo (n = 162), SC, week 0, week 4, 4weeks</p>	
Outcomes	<p>Assessments at 12 weeks</p> <p><b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>• - PGA 0 /1</li> <li>• - DLQI</li> </ul>	
Notes	<p>Funding source quote (p 173): "This study was supported by Janssen Research &amp; Development"</p> <p>Declarations of interest (p 173): "Drs Zhu, Zang and Wand served as investigators for this Janssen RD-sponsored study..."</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote (p 167): "The LOTUS study is a phase 3, multicenter, randomized, double blind, placebo-controlled.. Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (p 167): Comment: no description of the method used to guarantee allocation concealment

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 167): "The LOTUS study is a phase 3, multicenter, randomized, double blind, placebo-controlled.. Comment: placebo-controlled study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (p 167): "The LOTUS study is a phase 3, multicenter, randomized, double blind, placebo-controlled.. Comment: no description of the method used to guarantee blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 322, analyzed 322 Quote (p 167): "For efficacy analyses, all randomized patients were included... Patients who discontinued study treatment... were considered treatment failures" Comment: ITT analyses
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01008995) The pre-specified outcomes and those mentioned in the methods section appeared to have been reported

**AEs:** adverse events; **ACR:** American College of Rheumatology; **ALT:** alanine aminotransferase; **AST:** aspartate aminotransferase; **BSA:** Body Surface Area; **ew:** every other week; **CIN:** cervical intraepithelial neoplasia; **DLQI:** Dermatology Life Quality Index; **ECG:** electrocardiogram; **HD:** high dose; **IGA:** Investigator's Global Assessment; **IM:** intramuscular; **ITT:** intention-to-treat; **IV:** intravenous; **LD:** low dose; **m-ITT:** modified ITT; **MD:** medium dose; **NAPSI:** Nail psoriasis severity index; **NBUVB:** narrow-band UVB; **PASI:** Psoriasis Area and Severity Index; **PGA:** Physician Global Assessment; **PP:** per protocol; **PSI:** Psoriasis Severity Index; **PSSI:** Psoriasis Scalp Severity Index; **PUVA:** psoralen plus ultraviolet A; **QoL:** quality of life; **RCT:** randomised controlled trial; **SC:** subcutaneous; **SF36:** 36-item Short Form Health Survey; **SIAQ:** Self- Injection Assessment Questionnaire; **TB:** tuberculosis; **TBR:** target background ratio; **UVB:** ultraviolet B; **VAS:** visual analogue scale

### Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
<a href="#">Abufarag 2010</a>	Other treatment
<a href="#">Akhyani 2010</a>	Other treatment
<a href="#">Altmeyer 1994</a>	Not plaque-type psoriasis

(Continued)

Angsten 2007	Not a trial
Anonymous 2005	Not a trial
Anonymous 2008	Not a trial
Arifov 1998	Not a randomized trial
Armati 1972	Other treatment
Avgerinou 2011	Not randomized trial
Bagot 1994	Other treatment
Bartlett 2008	Not a trial
Barzegari 2004	Other treatment
Batchelor 2009	Not a trial
Bayerl 1992	Other treatment
Beissert 2009	Other treatment
Berbis 1989	Assessment < 8 weeks
Bhuiyan 2010	Other treatment
Bigby 2004	Not a trial
Bissonnette 2006	Other treatment
Bissonnette 2010	Other treatment
Bjerke 1989	Other treatment
Callis Duffin 2017	Comparison of the same drug with the same dosages
Cassano 2006	Identical dosing regimens
Cassano 2010	Not a trial
Cather 2006	Dose ranging after remission
Chládek 2002	Basic science (aim of study: to understand the physiopathology of the disease)
Chodorowska 1999a	Not a trial

(Continued)

Chodorowska 1999b	Not a trial
de Jong 2003	Other treatment
Dubiel 1972	Not a trial
Duffin 2016	Comparison of 2 different ways of drug injection for the same drug and the same dosage
Ecker-Schlipf 2009	Other treatment
Elewski 2007	Pooled trials
Ellis 1986	Assesment < 8 weeks
Ellis 2002	Medico-economic study
Ellis 2012	Other treatment
Engst 1989	Assessment < 8 weeks
Erkko 1997	Basic science (aim of study: to understand the physiopathology of the disease)
Ezquerria 2007	Other treatment
Fernandes 2013	Not a trial
Finzi 1993	Other treatment
Fleischer 2005	Other treatment
Fredriksson 1971	Other treatment
Fredriksson 1978	Other treatment
Friedrich 2001	Other treatment
Gambichler 2011	Other treatment
Ganguly 2004	Pooled trials
Gil 2003	Not a randomized trial
Goerz 1978	Not a trial
Gollnick 1988	Other treatment
Gollnick 1993	Other treatment
Gollnick 2002	Other treatment

(Continued)

Gottlieb 2002c	Other treatment
Gottlieb 2003a	Other Treatment
Gottlieb 2004b	Pooled trials
Gottlieb 2005a	Other treatment
Gottlieb 2010	Cross-over trial
Goupille 1995	Not a randomized trial
Griffiths 1998	Other treatment
Griffiths 2002a	Pooled trials
Griffiths 2002b	Pooled trials
Griffiths 2005	Pooled trials
Grim 2000	Basic science (aim of study: to understand the physiopathology of the disease)
Grossman 1994	Other treatment
Gulliver 1996	Not a trial
Gupta 2005	Other treatment
Gupta 2007	Other treatment
Gupta 2008	Other treatment
Han 2013	Other treatment
Hashizume 2007	Comparison of 2 methods of administration
Heule 1988	Assessment < 8 weeks
Ho 2010	Other treatment
Hunter 1972	Other treatment
Iest 1989	Not randomized trial
Kavanaugh 2009	Not a randomized trial
Kimball 2008	Drug withdrawn for safety reasons
Kimball 2011	Drug withdrawn for safety reasons

(Continued)

Koo 1998	Other treatment
Kopp 2015	Phase 1 trial
Kragballe 1989	Other treatment
Krishnan 2005	Pooled trials
Krueger 1980	Other treatment
Krueger 2002b	Not a trial
Krueger 2003	Not a trial
Krueger 2012	Phase 1 trial
Krueger 2015	Phase 1 trial
Kuijpers 1998	Other treatment
Lajevardi 2015	Other treatment
Langewouters 2005	Other treatment
Langley 2006	Other treatment
Langley 2010	Other treatment
Langner 2004	Not plaque-type psoriasis
Lauharanta 1989	Other treatment
Lawrence 1983	Other treatment
Leavell 1970	Other treatment
Lebwohl 2003a	Pooled trials
Lebwohl 2009	Pooled trials
Lebwohl 2012	Other treatment
Lebwohl 2013	Other treatment
Ledo 1988	Other treatment
Legat 2005	Other treatment

(Continued)

Leonardi 2010a	Pooled trials
Leonardi 2010b	Not a randomized trial
Leonardi 2010c	Pooled trials
Leonardi 2011a	Not plaque-type psoriasis
Levell 1995	Other treatment
Liang 1995	Assessment < 8 weeks
Lui 2011	Other treatment
Lui 2012	Other treatment
Lynde 2012	Other treatment
Macdonald 1972	Not a randomized trial
Mahrle 1995	Other treatment
Malik 2010	Other treatment
Marecki 2004	Other treatment
Marks 1986	Not a randomized trial
McInnes 2013	Pooled trials
Mease 2011	Drug withdrawn for safety reason
Meffert 1989	Other treatment
Menon 2012	Basic science (aim of study: to understand the physiopathology of the disease)
Menter 2007a	Pooled trials
Menter 2014	Drug withdrawn for safety reasons
Meyer 2011	Other treatment
Mittal 2009	Other treatment
Moller 2009	Other treatment
Monk 1986	Not a randomized trial
Montgomery 1993	Other treatment

(Continued)

Mrowietz 1991	The two study arms compared the same molecule with the same dosage
Mrowietz 2012	Pooled trials
Narang 2012	Other treatment
Nieboer 1990	Other treatment
Nijsten 2008	Not a trial
Noda 2011	Not a randomized trial
Novotny 1973	Not a trial
Nyfors 1978	Not a trial
Orfanos 1978	Other treatment
Orfanos 1979	Other treatment
Ortonne 2008	Comparison of 2 schemes of administration
Ortonne 2011	Other treatment
Osamu 2014	Phase 1 trial
Papp 2001	Other treatment
Papp 2006	Other treatment
Papp 2008a	Other treatment
Papp 2009	Pooled data
Papp 2011a	Pooled trials
Papp 2011b	Drug withdrawn for safety reasons
Papp 2011c	Drug withdrawn for safety reasons
Papp 2012c	Phase 1 trial
Papp 2012d	Pooled trials
Park 2013	Other treatment
Paul 2012	Other treatment



(Continued)

Paul 2014	Other treatment
Pettit 1979	Assessment < 8 weeks
Petzelbauer 1990	Not a randomized trial
Piasek 2003	Not a trial
Ports 2013	Other treatment
Punwani 2012	Other treatment
Rabasseda 2012	Not a trial
Radmanesh 2011	Comparison of 2 schemes of administration
Raman 1998	Other treatment
Reich 2011	Pooled trials
Reich 2014	Other treatment
Reitamo 1999	Other treatment
Reitamo 2001	Other treatment
Rim 2003	Other treatment
Rinsho Iyaku 1991	Other treatment
Ritchlin 2006a	Not a randomized trial
Ritchlin 2006b	Not a randomized trial
Ritchlin 2006c	Not a randomized trial
Salim 2006	Other treatment
Scholl 1981	Other treatment
Schopf 1998	Other treatment
Schulze 1991	Other treatment
Shintani 2011	Comparison of 2 schemes of administration
Shiohara 1992	Not a trial
Shupack 1997	Not a trial

(Continued)

<a href="#">Simonova 2005</a>	Other treatment
<a href="#">Sofen 2011</a>	Basic science (aim of study: to understand the physiopathology of the disease)
<a href="#">Sofen 2014</a>	Phase 1 trial
<a href="#">Spadaro 2008</a>	Not a trial
<a href="#">Spuls 2012</a>	Not a trial
<a href="#">Sticherling 1994</a>	Not a trial
<a href="#">Strober 2004</a>	Not a trial
<a href="#">Strober 2012</a>	Not a randomized trial
<a href="#">Sweetser 2006</a>	Cross over trial
<a href="#">Talwar 1992</a>	Not a randomized trial
<a href="#">Tejasvi 2012</a>	Other treatment
<a href="#">Thaçi 2002</a>	The two study arms compared the same molecule with the same dosage
<a href="#">Thaçi 2010</a>	Other treatment
<a href="#">Tong 2008</a>	Other treatment
<a href="#">Van Joost 1988</a>	Assessment shorter than 8 weeks
<a href="#">Vena 2005</a>	Comparison of 2 schemes of administration
<a href="#">Vena 2012</a>	Other treatment
<a href="#">Viglioglia 1978</a>	Not a trial
<a href="#">Witkamp 1995</a>	Other treatment
<a href="#">Wolf 2012</a>	Other treatment
<a href="#">Wright 1966</a>	Not a randomized trial
<a href="#">Wu 2015</a>	Other treatment
<a href="#">Yesudian 2013</a>	Other treatment
<a href="#">Yoon 2007</a>	Dose-escalation study

(Continued)

Zachariae 2008	Other treatment
Zhang 2007	Other treatment
Zhang 2009a	Other treatment
Zhang 2009b	Other treatment
Zhang 2012	Other treatment
Zhu 2009	Pooled trials
Zhuang 2016	Phase 1 trial
Zobel 1987	Not a trial

### Characteristics of studies awaiting assessment [ordered by study ID]

#### Chow 2015

Methods	RCT, active/placebo-controlled, double blind Date of study: not stated Location: Canada, Germany and Poland
Participants	<b>Randomised:</b> 455 participants (mean age 43, 313 male) <b>Inclusion criteria</b> <ul style="list-style-type: none"><li>• Aged <math>\geq 18</math> years at time of screening</li><li>• Diagnosed with plaque psoriasis <math>\geq 6</math> months prior to screening</li><li>• Diagnosis of stable, plaque psoriasis; i.e. psoriasis must not be spontaneously improving or worsening in the 4 weeks prior to the screening visit<ul style="list-style-type: none"><li>• Psoriasis failing <math>\geq 1</math> systemic treatment regimen or where other systemic therapies are contraindicated or where tolerability is an issue.</li><li>• Plaque psoriasis involving <math>\geq 10\%</math> of the body surface area and a SPGA score <math>\geq 3</math> at screening and prior to randomisation at the day 0 visit</li><li>• Not pregnant or nursing</li><li>• Sexually active women of childbearing potential or <math>&lt; 1</math> year post-menopausal and sexually active men who are not surgically sterile must use a reliable form of birth control during study treatment and for <math>\geq 3</math> months after the last dose of study drug. Surgically sterile women are not considered to be of childbearing potential. Reliable forms of birth control include oral or depot contraceptives, and double-barrier methods</li><li>• Written informed consent prior to washout and screening procedures</li><li>• Able to keep study appointments and co-operate with all study requirements, in the opinion of the Investigator</li></ul></li></ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"><li>• Has generalised erythrodermic, guttate, or pustular psoriasis</li><li>• Have other dermatoses that would interfere with the evaluation of psoriasis, at the discretion of the Investigator</li><li>• A current malignancy or history of malignancy within 5 years or a history of lymphoma at any time. Subjects can be enrolled with a history of squamous or basal cell carcinoma that has been surgically excised or removed with</li></ul>

	<p>curettage and electrodesiccation</p> <ul style="list-style-type: none"> <li>● Has a current, uncontrolled bacterial, viral, or fungal infection that requires IV antibiotics or antifungals or has had such infections within 60 days prior to screening</li> <li>● A known history of TB</li> <li>● Serologic evidence or known latent HIV, hepatitis B or C virus</li> <li>● Uncontrolled hypertension of systolic blood pressure <math>\geq 160</math> mmHg or diastolic blood pressure <math>\geq 90</math> mmHg</li> <li>● Modification of Diet in Renal Disease <math>&lt; 60</math> mL/min</li> <li>● Liver enzyme serum levels <math>\geq 2</math> x upper limit of normal (ULN)</li> <li>● White blood cell count <math>\leq 2.8 \times 10</math> to the ninth power/L</li> <li>● Requires the following prohibited medications or treatments during the washout or treatment period: drugs potentiating the nephrotoxicity of voclosporin, drugs interfering with its pharmacokinetics, drugs considered to contribute to psoriasis flare; or, systemic and topical psoriasis medication that may interfere with assessment of study drug efficacy             <ul style="list-style-type: none"> <li>● Has used any investigational drug or device within 30 days or 10 half lives (whichever is longer) prior to the screening visit</li> <li>● Current participation in another clinical trial of any drug or biological agent</li> <li>● Has taken biological agent(s), except flu shots, tetanus shots, or boosters, within 3 months of randomisation. Biological agents include any virus, live vaccine, therapeutic serum, toxin, antitoxin, monoclonal antibodies or analogous product applicable to the prevention, treatment, or cure of diseases or injuries of man</li> <li>● Previous exposure to voclosporin</li> <li>● A history of clinically defined allergy to ciclosporin, constituents of Neoral or any of the constituents of the ISA247 formulation</li> <li>● A history of alcoholism or drug addiction</li> <li>● Weighs <math>&lt; 45</math> kg (99 lbs)</li> <li>● A history of disease, including mental/emotional disorder that would interfere with the participant's participation in the study, in the evaluation of his/her response or that might cause the administration of voclosporin to pose a significant risk to the participant, in the opinion of the Investigator</li> <li>● White blood cell count <math>\leq 2.8 \times 10</math> to the ninth power/L.</li> </ul> </li> <li>● Requires the following prohibited medications or treatments during the washout or treatment period: drugs potentiating the nephrotoxicity of voclosporin, drugs interfering with its pharmacokinetics, drugs considered to contribute to psoriasis flare; or, systemic and topical psoriasis medication that may interfere with assessment of study drug efficacy             <ul style="list-style-type: none"> <li>● Has used any investigational drug or device within 30 days or 10 half lives (whichever is longer) prior to the screening visit</li> <li>● Current participation in another clinical trial of any drug or biological agent</li> <li>● Has taken biological agent(s), except flu shots, tetanus shots, or boosters, within 3 months of randomisation. Biological agents include any virus, live vaccine, therapeutic serum, toxin, antitoxin, monoclonal antibodies or analogous product applicable to the prevention, treatment, or cure of diseases or injuries of man</li> <li>● Previous exposure to voclosporin</li> <li>● A history of clinically defined allergy to ciclosporin, constituents of Neoral or any of the constituents of the ISA247 formulation</li> <li>● A history of alcoholism or drug addiction</li> <li>● Weighs <math>&lt; 45</math> kg (99 lbs)</li> <li>● A history of disease, including mental/emotional disorder that would interfere with the participant's participation in the study, in the evaluation of his/her response or that might cause the administration of voclosporin to pose a significant risk to the participant, in the opinion of the Investigator</li> </ul> </li> </ul>
Interventions	<p><b>Interventions</b> (n = 355)</p>

**Chow 2015** (Continued)

	<p>Drug: voclosporin 0.8 mg/kg/day          Drug: ciclosporin 3.0 mg/kg/day  <b>Control intervention</b>          (n = 89)          Drug: placebo</p>
Outcomes	<p><b>At week 24,</b>  <b>Primary outcome measures</b></p> <ul style="list-style-type: none"> <li>• Superiority in the proportion of participants achieving a score of clear or almost clear in the SPGA score</li> </ul> <p><b>Secondary outcome measures</b></p> <ul style="list-style-type: none"> <li>• To show non-inferiority of voclosporin compared to ciclosporin in the proportion of participants achieving a score of clear or almost clear in the SPGA score</li> <li>• Superiority in de novo hypertriglyceridemia, defined as proportion of participants developing fasting triglycerides <math>\geq 1.7</math> mmol/L</li> <li>• Superiority in de novo hypertension, defined as proportion of participants developing blood pressure <math>\geq 140</math> mmHg (systolic) or <math>\geq 90</math> mmHg (diastolic)</li> <li>• Superiority of renal function, defined as the proportion of participants experiencing a confirmed <math>\geq 30\%</math> rise in serum creatinine</li> <li>• Superiority in proportion of participants achieving a 75% reduction in the PASI score (PASI 75)</li> </ul>
Notes	<p>Randomised, placebo and ciclosporin controlled study of ISA247 in plaque psoriasis patients (ESSENCE), NCT00408187</p> <p>Participants in the voclosporin and ciclosporin arms (n = 355) were treated for 24 weeks; these participants were combined into a '24-week treatment group'. In the placebo group, 89 participants were included</p> <p>As the authors presented their results grouping ciclosporin and voclosporin together, we asked them to provide the results for the subgroup of participants with ciclosporin treatment arm</p> <p>Two emails were sent without response (8 November 2016, 16 December 2016)</p>

**CTRI/2015/05/005830**

Methods	<p>Randomised, parallel group, multiple arm trial          Date of study: 10/12/2013 (starting date)          Location: India</p>
Participants	<p><b>Total sample size:</b> 120  <b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• Be diagnosed to be suffering exclusively from Palmo-plantar psoriasis either by clinical examination or histopathology if required will be included in palmoplantar psoriasis group</li> <li>• Be diagnosed to be suffering from psoriasis vulgaris having more than 20% BSA will be included in psoriasis vulgaris group</li> <li>• Have completed 18 years of age</li> </ul> <p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• Hypersensitivity to drug or intolerance to the study medication</li> <li>• Pregnant and lactating</li> <li>• Clinically significant cardiovascular, haematological, pancreatic, metabolic neurological or any other laboratory anomaly, which in the judgement of investigator, would interfere in participation in study or proper evaluation</li> <li>• On any other systemic drugs therapy which in the judgement of investigator may interfere with interpretation of results</li> <li>• History of TB or chest X-ray showing evidence of any infective pathology</li> </ul>

Interventions	<p><b>Intervention 1:</b> acitretin: orally, 25-50 mg/day, daily single dose Total duration: 90 days</p> <p><b>Intervention 2:</b> ciclosporin: orally 2.5-5 mg/kg/day, daily in 2 divided doses Total duration: 90 days</p> <p><b>Intervention 3:</b> methotrexate: orally 7.5-15 mg/week in 3 divided doses Total duration: 90 days</p> <p><b>Control Intervention 1:</b> palmoplantar psoriasis: variant of psoriasis in which only palms and soles are affected</p> <p><b>Control Intervention 2:</b> psoriasis vulgaris: variant of psoriasis in which lesions appear on body skin</p>
Outcomes	<p><b>At 90 days</b></p> <ul style="list-style-type: none"> <li>• 75% reduction in PASI or modified PASI</li> <li>• 75% reduction in BSA</li> <li>• 75% reduction in psoriasis severity index. Timepoint: 90 days</li> <li>• DLQI</li> </ul>
Notes	<p>Starting date: 10-12-2013. Recruitment status: open to recruitment We sent an email to Prof. Shah (5 and 12 January 2017) without response</p>

## DRKS00000716

Methods	<p>Randomised, active-controlled, parallel-group, simple blind Date of study: 03/06/2008 (starting date) Location: Germany</p>
Participants	<p><b>Total sample size:</b> 50</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Aged 18-65 years</li> <li>• Clinical diagnosis of psoriasis for &gt; 6 months</li> <li>• Plaque-type psoriasis (PASI &gt; 10)</li> <li>• BSA &gt; 10%</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Contraindications for treatment with TNF-alpha inhibitors and FAEs</li> <li>• Women who are pregnant or who are breast-feeding. Women of childbearing potential must follow a medically recognised form of contraception</li> <li>• Currently receiving or have received within 4 weeks prior to first administration of study administration: systemic therapy for psoriasis; monoclonal antibody therapy for psoriasis; phototherapy</li> <li>• TB anamnesis, infections (Hepatitis B, C, HIV)</li> <li>• History of lymphoproliferative disorders, malignancies, demyelinating disease, severe heart failure</li> <li>• History of substance abuse (drugs or alcohol) or any factor (e.g. serious psychiatric condition) which limits the patient's ability to co-operate with the study procedures</li> <li>• Unco-operative, known to miss appointments (according to patient's records) and are unlikely to follow medical instructions or are not willing to attend regular visits</li> </ul>
Interventions	<p><b>Intervention 1:</b> adalimumab (Humira), SC, 80 mg initially and 40 mg eow for 24 weeks</p> <p><b>Intervention 2:</b> etanercept (Enbrel), SC, 50 mg twice a week for 12 weeks and 25 mg twice a week subsequently for another 12 weeks</p> <p><b>Intervention 3:</b> FAEs (Fumaderm), orally, up to 6 doses/day for 24 weeks</p>

Outcomes	<p><b>Week 8:</b></p> <ul style="list-style-type: none"> <li>• PASI: clinical score of skin lesions</li> <li>• DLQI</li> <li>• skin biopsy: immunohistology</li> <li>• T cells in peripheral blood</li> </ul> <p><b>Week 24:</b></p> <ul style="list-style-type: none"> <li>• PASI: clinical score of skin lesions</li> <li>• DLQI</li> <li>• skin biopsy: immunohistology</li> <li>• T cells in peripheral blood</li> </ul>
Notes	Starting date: 03/06/2008, Prof. Arnd Jacobi, Klinik für Dermatologie und Allergologie Philipps-Universität Marburg Recruitment status on ICTRP search portal: complete: follow-up complete We emailed Prof. Jacobi (5 January 2017) without response

**Elewski 2016**

Methods	Randomised, placebo-controlled, double-blind trial date: January 2014 to April 2016 Location: worldwide
Participants	<p><b>Total sample size:</b> 217</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Adults with clinical diagnosis of chronic plaque psoriasis (with a disease duration of <math>\geq 6</math> months) and <math>\geq 1</math> fingernail with nail psoriasis</li> <li>• BSA <math>\geq 10\%</math> and a target fingernail mNAPSI <math>\geq 8</math> at Week 0, OR BSA <math>\geq 5\%</math>, a target fingernail Nail Psoriasis Severity index (NAPSI) <math>\geq 8</math> and a total mNAPSI score of <math>\geq 20</math> at Week 0</li> <li>• Nail Psoriasis Physical Functioning Severity score of <math>&gt; 3</math>, OR a Nail Psoriasis Pain score of <math>&gt; 3</math></li> <li>• PGA of fingernail psoriasis and a PGA of skin psoriasis of <math>\geq</math> moderate</li> <li>• Must have discontinued use of all systemic therapies for the treatment of psoriasis, or systemic therapies known to improve psoriasis for <math>\geq 4</math> weeks prior to Week 0, ustekinumab must have been discontinued <math>\geq 12</math> weeks prior to Week 0</li> <li>• Target fingernail must have mNAPSI score of <math>\geq 8</math></li> </ul> <p><b>Exclusion Criteria</b></p> <ul style="list-style-type: none"> <li>• Prior adalimumab therapy</li> <li>• Diagnosis of other active skin diseases or skin infections (bacterial, fungal, or viral) that may interfere with evaluation of skin or fingernail psoriasis</li> <li>• Recent infection requiring treatment</li> <li>• Significant medical events or conditions that may put patients at risk for participation, including recent history of drug or alcohol abuse</li> <li>• Women who are pregnant or breast-feeding or considering becoming pregnant during the study</li> <li>• History of cancer, except successfully treated skin cancer</li> </ul>
Interventions	<p><b>Intervention</b> Adalimumab, SC, 40 mg, eow for 25 weeks starting 1 week after initial loading dose of 80 mg</p> <p><b>Control intervention</b> Placebo</p>

**Elewski 2016** (Continued)

Outcomes	<b>At week 12</b> mNAPSI 75, PGA of fingernails of clear or minimal PASI 75/90/100 for participants with baseline PASI at 5
Notes	NCT02016482 <ul style="list-style-type: none"> <li>• Enrollment: 217</li> <li>• Study start date: January 2014</li> <li>• Study completion date: April 2016</li> </ul> Abstract <ul style="list-style-type: none"> <li>• Journal of the European Academy of Dermatology and Venereology 2016, 30:65</li> </ul> No original paper published. We emailed the study authors (3 and 12 January 2017) for the protocol and results Abbvie response: "As this data has not been published in a manuscript at this time I am providing the link below for you to submit a request for this data. Please let me know if you have any further questions" Will be included when published

**Han 2007**

Methods	Randomised, double-blind, active-controlled trial Date: not stated Location: China
Participants	No statement except a total number of participants (n = 144)
Interventions	<b>Intervention</b> Recombinant human tumour necrosis factor receptor (50 mg/week) <b>Control intervention</b> Methotrexate (7.5 mg/week)
Outcomes	<b>At 12 weeks</b> Proportion of PASI 50, PASI 75, PASI 90
Notes	<b>Abstract in Journal of Clinical Dermatology 2007 (730-2)</b> HAN Ling, FANG Xu, HUANG Qiong, YANG Qin-ping, FU Wen-wen, ZHENG Zhi-zhong, GU Jun, SUN Jiao-fang, XU Ai-e (Department of Dermatology, Huashan Hospital, Fudan University, Shanghai 200040, China) <b>Objective:</b> To evaluate the effect of recombinant human tumour necrosis factor receptor (rhTNFR:Fc) in the treatment of moderate to severe plaque psoriasis on psoriasis area and severity index (PASI). <b>Methods:</b> Using randomised, double-blind and double-simulated, parallel-controlled with positive drug, multicenter, clinical trial was employed to investigate 144 cases of patients with moderate to severe plaque psoriasis, of which there were 72 cases in both trial group and the control group respectively, to evaluate the effect on PASI. <b>Results:</b> 124 cases of patients had accomplished the 12-week clinical trial. After 12 weeks the rate of PASI50, PASI75, PASI90 were significantly higher than those of the control group (P < 0.01). The therapeutic effects on trunk and limbs of the trial group were also much better. <b>Conclusion:</b> The effect of rhTNFR:Fc is more quick and significant, especially assessed by PASI sore Abstract not available at the BIUM and United States NLM libraries No email address for the authors available When we searched Google, we found another abstract of the same study "Chinese Journal of Dermatology 2007, 40(11) 655-658" <a href="http://manu41.magtech.com.cn/Jwk_cmazp/EN/abstract/abstract11844.shtml#">http://manu41.magtech.com.cn/Jwk_cmazp/EN/abstract/abstract11844.shtml#</a> ), which had no supplemental information to enable contacting the authors:



**Abstract**

“**Objective** To investigate the efficacy and tolerability of a recombinant human tumour necrosis factor:Fc fusion protein (rhTNFR:Fc, with a trade name of Yisaipu) in the treatment of moderate to severe psoriasis vulgaris. **Methods** A multicentre, randomised, double blind, and parallel-controlled trial was performed. One hundred and forty-four patients with moderate to severe psoriasis vulgaris from four centres were randomly assigned and treated with either once-weekly subcutaneous injection of rhTNFR:Fc (50 mg) or oral methotrexate (methotrexate) (7.5 mg) for 12 weeks. Patients were followed up at 2, 4, 8, 12 weeks after the treatment. **Results** One hundred and twenty-four patients finished the 12-week course of treatment. At 12 weeks after the treatment, a 50%, 75%, 90% improvement in psoriasis area and severity index (PASI) was achieved by 86.11%, 76.39%, 52.78% respectively of rhTNFR:Fc-treated patients, and by 63.89%, 44.44%, 22.22% respectively in methotrexate-treated patients, and all the three improvement rates were of significant difference between the two groups of patients (all  $P < 0.01$ ). Physician global assessment (PGA), dermatology life quality index (DLQI) and 10-cm visual analogue scale (VAS) all reduced more significantly, and more patients were cured or approximately cured in rhTNFR:Fc-treated patients than in MTX-treated patients (all  $P < 0.05$ ). Adverse reactions, mainly including decrease of leucocytes or neutrophils, infection, dysfunction of liver, edema and pruritus at the injection site, etc, occurred in 26.39% of rhTNFR:Fc-treated patients and 29.17% of MTX-treated patients ( $P > 0.05$ ). **Conclusion** Compared with MTX, rhTNFR:Fc acts more quickly with a higher cure rate and less toxic reactions in the treatment of psoriasis vulgaris.”

**No contact with the authors as Authors' emails were not found**

**Khatri 2016**

Methods	Randomised, double-blind, active-controlled trial Date: April 2015-August 2016 Location: USA
Participants	<p><b>Total sample size:</b> 12</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Present with chronic moderate-severe plaque psoriasis based on a confirmed (by a dermatologist) diagnosis of chronic plaque psoriasis for <math>\geq 6</math> months prior to baseline</li> <li>• Active psoriatic skin lesions of plaque psoriasis (Ps)</li> <li>• Are a candidate for phototherapy and/or systemic therapy</li> <li>• Men must agree to use a reliable method of birth control or remain abstinent during the study and for <math>\geq 12</math> weeks after stopping treatment</li> <li>• Women must agree to use reliable birth control or remain abstinent during the study and for <math>\geq 12</math> weeks after stopping treatment</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Are unable to commit to the photography schedule for the duration of the study</li> <li>• Have participated in any study with interleukin 17 (IL-17) or (IL-23) antagonists, including ixekizumab</li> <li>• Serious disorder or illness other than psoriasis</li> <li>• Serious infection within the last 3 months</li> <li>• Breastfeeding or nursing (lactating) women</li> </ul>
Interventions	<p><b>Intervention:</b> Ixezumab once every 2 weeks, SC, 160 mg 2 injections at week 0 followed by 80 mg ixekizumab given as a single SC injection once every 2 weeks through week 12. After week 12 participants will receive 80 mg ixekizumab every 4 weeks through week 44</p> <p><b>Control intervention:</b> Ixezumab once every 4 weeks, SC, 160 mg, 2 injections at week 0 followed by 80 mg ixekizumab given as a single SC injection once every 4 weeks through week 44</p>

**Khatri 2016** (Continued)

Outcomes	<p><b>At week 12,</b></p> <p><b>Primary outcome</b></p> <ul style="list-style-type: none"> <li>● Patient's Global Assessment of Disease Severity</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>● Itch Numeric Rating Scale</li> <li>● DLQI</li> <li>● PASI</li> <li>● BSA</li> <li>● AEs</li> </ul>
Notes	<p>NCT02387801</p> <p>Study start date: April 2015</p> <p>Study completion date: August 2016</p> <p>Published abstract entitled "Early onset of clinical improvement with ixekizumab in patients with moderate-severe plaque psoriasis" published in 2016 in Journal of the European Academy of Dermatology and Venereology, Vol 30</p> <p>No original paper published.</p> <p>We emailed the study authors (3 and 12 January 2017) for the protocol and results but have not had a response</p>

**Lee 2016**

Methods	<p>RCT, placebo-controlled, open-label trial</p> <p>Date of study: July 2009-April 2011</p> <p>Setting: Korea</p>
Participants	<p><b>Total sample size:</b> 60</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>● Active, moderate-severe psoriasis defined by the following criteria: clinically stable, plaque psoriasis involving more than 10% BSA or PASI 10</li> <li>● In the opinion of the investigator, failure, intolerance, contraindication or not a candidate for the following: methotrexate, ciclosporin, and psoralen plus ultraviolet A radiation (PUVA) therapy</li> <li>● Negative urine pregnancy test before the first dose of study drug in all female participants</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>● Evidence of skin conditions (e.g. eczema) other than psoriasis that would interfere with evaluations of the effect of study medication on psoriasis</li> <li>● Any rheumatologic disease such as rheumatoid arthritis, psoriatic arthritis, gout, systemic lupus erythematosus, systemic vasculitis, scleroderma and polymyositis, or associated syndromes</li> <li>● Prior exposure to TNF inhibitors including etanercept. Prior exposure to efalizumab (Raptiva®) and alefacept (Amevive®) is also prohibited.</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>Etanercept + acitretin (combination of etanercept, 25 mg twice a week and acitretin 10 mg twice a day for 24 weeks)</p> <p><b>Control intervention</b></p> <p>Etanercept, 50 mg twice a week for 12 weeks followed by 25 mg twice a week for 12 weeks</p> <p>Acitretin, 10 mg twice a day for 24 weeks</p>
Outcomes	<p><b>At week 24</b></p> <p><b>Primary outcome</b></p> <ul style="list-style-type: none"> <li>● PASI 75</li> </ul>

Lee 2016 (Continued)

	<p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>● PASI 50</li> <li>● PGA0/1</li> <li>● PSSQ (Psoriasis Subject Satisfaction Questionnaire)</li> </ul>
Notes	<p>NCT00936065 (Study evaluating the efficacy and safety of etanercept and acitretin in Korean patient with moderate to severe psoriasis)            Study start date: July 2009            Study completion date: April 2011            Abstracts:</p> <ul style="list-style-type: none"> <li>● BMC Dermatology 2016, 16:11</li> <li>● BMC dermatology 2016, 16 (no pagination)</li> </ul> <p>We emailed the study authors (3 and 12 January 2017) for the protocol and results as additional information request for risk of bias assessment but have not had a response</p>

Mrowietz 2005

Methods	<p>RCT, placebo-controlled, double-blind trial            Date of study: not stated            Setting: not stated</p>
Participants	<p><b>Randomised:</b> 175 participants (characteristics not stated)  <b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>● Not stated</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>● Not stated</li> </ul> <p><b>Dropouts and withdrawals</b></p> <ul style="list-style-type: none"> <li>● Not stated</li> </ul>
Interventions	<p><b>Intervention</b>            A. Dimethyl fumarate (n = 105), orally, 240 mg, 3 times/day; 16 weeks  <b>Control Intervention</b>            B. Placebo (n = 70), orally, 2 capsules , 3 times/day; 16 weeks</p>
Outcomes	<p>Assessments at 16 weeks  <b>Primary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>● PASI</li> </ul> <p><b>Secondary outcomes of the trial</b></p> <ul style="list-style-type: none"> <li>● PASI 50</li> <li>● PASI 75</li> <li>● SKINDEX-29</li> <li>● Side effects</li> </ul>
Notes	<p>Funding, quote (abstract) by Biogen Idec, Inc and Fumapharm            Abstracts:            “Results of a phase III study of a novel oral formulation of dimethyl fumarate in the treatment of moderate to severe plaque psoriasis: efficacy, safety, and quality of life effects” published in 2005 in the JEADV, Suppl. 2 (Poster P/06.97)            We asked the study authors to provide the protocol and results by email. Additional data to the publication not</p>

provided  
 Finally, as the 'Risk of bias' tool assessment was not possible and there were missing data for the results, Mrowietz 2005 was included in "awaiting classification"

## NCT01961609

Methods	RCT, active-controlled, double-blind trial (SIGNATURE) Date of study: October 2013-July 2016 Location: UK
Participants	<p><b>Randomised:</b> 230 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Chronic plaque-type psoriasis diagnosed for <math>\geq 6</math> months prior to screening, aged <math>\geq 18</math> years at screening</li> <li>• Moderate-severe disease severity: PASI <math>\geq 10</math> and DLQI <math>&gt; 10</math></li> <li>• Failed to respond to systemic therapies including ciclosporin and/or methotrexate and/or PUVA (or is intolerant and/or has a contraindication to these)</li> <li>• Previously treated with <math>\geq 1</math> anti-TNF<math>\alpha</math> for moderate or severe psoriasis but is a primary or secondary non-responder</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Forms of psoriasis other than chronic plaque-type (e.g. pustular, erythrodermic and guttate psoriasis)</li> <li>• Drug-induced psoriasis (i.e. new onset or current exacerbation from beta-blockers, calcium channel inhibitors or lithium)</li> <li>• Ongoing use of prohibited psoriasis treatments (e.g. topical or systemic corticosteroids (CS), UV therapy). Washout periods detailed in the protocol must be adhered to.</li> <li>• Ongoing use of other non-psoriasis prohibited treatments. Washout periods detailed in the protocol have to be adhered to. All other prior non-psoriasis concomitant treatments must be on a stable dose for <math>\geq 4</math> weeks before initiation of study drug.</li> <li>• Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or the IL-17 receptor</li> <li>• Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (<math>&gt; 5</math> mIU/mL)</li> <li>• Women of childbearing potential, defined as all women physiologically capable of becoming pregnant unless they use 2 effective forms of contraception during the study and for 16 weeks after stopping treatment</li> <li>• Men with a female partner of childbearing potential defined as all women physiologically capable of becoming pregnant unless they use 1 effective form of contraception during the study and for 16 weeks after stopping treatment</li> <li>• Active systemic infections during the last 2 weeks (exception: common cold) prior to initiation of study drug and any infections that recur on a regular basis; investigator discretion should be used regarding patients who have travelled or recently resided in areas of endemic mycoses, such as histoplasmosis, coccidioidomycosis or blastomycosis and for patients with underlying conditions that may predispose them to infection, such as advanced or poorly controlled diabetes</li> <li>• History of an ongoing, chronic or recurrent infectious disease, or evidence of TB infection as defined by a positive QuantiFERON TB-Gold test (QFT) at screening. Patients with a positive QFT test may participate in the study if further work up establishes conclusively that the patient has no evidence of active TB. If presence of latent TB is established, then treatment must have been initiated and maintained according to UK guidelines</li> <li>• Known infection with HIV, hepatitis B or hepatitis C at screening or at initiation of study drug</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>Biological: secukinumab 150 mg at day 0 (initiation of study drug) and at weeks 1, 2, 3 &amp; 4</p> <p><b>Control Intervention</b></p>

**NCT01961609** (Continued)

	Biological: secukinumab 300 mg at day 0 (initiation of study drug) and at weeks 1, 2, 3 & 4
Outcomes	<p><b>At 16 weeks</b></p> <p><b>Primary outcome</b></p> <ul style="list-style-type: none"> <li>● PASI 75</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>● PASI 90 and PASI 75 after 2, 4, 8, 12, 24, 48 and 72 weeks</li> <li>● Quality of life at 16 weeks</li> </ul>
Notes	<p>On <a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a></p> <p>Study completion date: July 2016</p> <p>Ongoing study</p>

**NCT01988103**

Methods	<p>RCT, placebo-controlled, double-blind trial, phase 2</p> <p>Date of study: July 2013-December 2015</p> <p>Location: Japan</p>
Participants	<p><b>Randomised:</b> 254 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>● Male or female Japanese people <math>\geq 20</math> years of age</li> <li>● Diagnosis of chronic, stable plaque psoriasis for <math>\geq 6</math> months prior to screening as defined by: PASI score <math>\geq 12</math> and BSA <math>\geq 10\%</math></li> <li>● Psoriasis considered inappropriate for topical therapy (based on severity of disease and extent of affected area) or has not been adequately controlled or treated by topical therapy in spite of <math>\geq 4</math> weeks of prior therapy with <math>\geq 1</math> topical medication for psoriasis or per label.</li> <li>● In otherwise good health based on medical history, physical examination, 12-lead ECG, serum chemistry, haematology, immunology, and urinalysis.</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>● Other than psoriasis, history of any clinically significant and uncontrolled systemic diseases; any condition, including the presence of laboratory abnormalities, which would place the subject at unacceptable risk or confound the ability to interpret the data in the study</li> <li>● Prior medical history of suicide attempt or major psychiatric illness requiring hospitalization within the last 3 years</li> <li>● Pregnant or breastfeeding</li> <li>● History of or ongoing chronic or recurrent infectious disease</li> <li>● Active TB or a history of incompletely treated TB</li> <li>● Clinically significant abnormality on 12-lead ECG or on chest radiograph at screening.</li> <li>● History of HIV infection or have congenital or acquired immunodeficiencies (e.g. Common Variable Immunodeficiency).</li> <li>● Hepatitis B surface antigen or hepatitis B core antibody positive at screening; positive for antibodies to hepatitis C at screening</li> <li>● Malignancy or history of malignancy, except for treated (i.e. cured) basal cell or squamous cell in situ skin carcinomas or treated (i.e. cured) cervical intraepithelial neoplasia (CIN) or carcinoma in situ of the cervix with no evidence of recurrence within previous 5 years</li> <li>● Psoriasis flare within 4 weeks of screening</li> <li>● Topical therapy within 2 weeks prior to randomisation or systemic therapy for psoriasis or psoriatic arthritis</li> </ul>

**NCT01988103** (Continued)

	<p>within 4 weeks prior to randomisation</p> <ul style="list-style-type: none"> <li>• Use of etretinate within 2 years prior to randomisation for women of childbearing potential or within 6 months for men, and within 4 weeks prior to randomisation for women not of childbearing potential</li> <li>• Use of phototherapy (i.e. UVB, PUVA) within 4 weeks prior to randomisation or prolonged sun exposure or use of tanning booths or other ultraviolet light sources.</li> <li>• Use of adalimumab, etanercept, certolizumab pegol, abatacept, tocilizumab, golimumab or infliximab within 12 weeks prior to randomisation; use of ustekinumab, alefacept or briakinumab within 24 weeks prior to randomisation</li> <li>• Any investigational drug within 4 weeks prior to randomisation</li> </ul>
Interventions	<p><b>Intervention:</b> A. Apremilast (30 mg tablet twice a day for 68 weeks)</p> <p><b>Control intervention:</b> B. Apremilast (20 mg tablet twice a day for 68 weeks) C. Placebo</p>
Outcomes	<p><b>At week 16</b> Primary outcome:</p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p>Secondary outcomes:</p> <ul style="list-style-type: none"> <li>• PGA 0/1</li> <li>• PASI 90</li> <li>• VAS</li> <li>• DLQI total score</li> <li>• Mental Component Summary (MCS) score of SF-36</li> <li>• AEs</li> </ul>
Notes	<p>Study completed, but not yet published Enrollment: 254 Study start date: July 2013 Study completion date: December 2015 Sent e-mail to Dr Nogarales, MD Celgene Corporation (12 January 2017) Will be included when published as the article has just been submitted</p>

**NCT02054481**

Methods	<p>RCT, placebo-controlled, double-blind trial, phase 2 Date of study: February 2014-July 2015 Location: world-wide</p>
Participants	<p><b>Randomised:</b> 166 participants <b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• BMI <math>\geq 18.5</math> and <math>&lt; 40</math> kg/m<sup>2</sup></li> <li>• Stable moderate-severe chronic plaque-type psoriasis with or without psoriatic arthritis involving <math>\geq 10\%</math> body surface area, with disease severity PASI <math>\geq 12</math> and sPGA score of moderate and above (score of <math>\geq 3</math>) at screening visit and visit 2 (randomisation), as assessed by the investigator</li> <li>• Psoriasis disease duration of <math>\geq 6</math> months prior to screening, as assessed by the investigator</li> <li>• Patients must be candidates for systemic psoriasis treatment or phototherapy, as assessed by the investigator</li> <li>• Patients must be suitable candidates for ustekinumab (Stelara®) therapy as given in the local labelling</li> </ul>

	<ul style="list-style-type: none"> <li>• Patient must give informed consent and sign an approved consent form prior to any study procedures in accordance with GCP and local legislation</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Patients with guttate, erythrodermic, or pustular psoriasis and patients with drug-induced psoriasis, as diagnosed by the investigator</li> <li>• Evidence of current or previous clinically significant disease, medical condition other than psoriasis, or finding of the medical examination (including vital signs and ECG), that in the opinion of the investigator, would compromise the safety of the patient or the quality of the data. This criterion provides an opportunity for the investigator to exclude patients based on clinical judgment, even if other eligibility criteria are satisfied. (Psoriatic arthritis is not considered an exclusion criterion)</li> <li>• Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders, diseases of the central nervous system (such as epilepsy) or psychiatric disorders or neurological disorders, or history of orthostatic hypotension, fainting spells or blackouts, that in the investigator's judgement, could jeopardize the safe conduct of the study.</li> <li>• Clinically important acute or chronic infections including hepatitis and HIV.</li> </ul> <p>With regards to TB the following applies:</p> <ul style="list-style-type: none"> <li>• Have signs or symptoms suggestive of current active or latent TB upon medical history, physical examination and/or a chest radiograph (both posterior-anterior and lateral views, taken within 3 months prior to the first administration of study drug and read by a qualified radiologist)</li> <li>• Have history of latent or active TB prior to screening, except for patients who have documentation of having completed an adequate treatment regimen <math>\geq 6</math> months prior to the first administration of study agent</li> <li>• Have positive IGRA testing (QuantIFERON-TB Gold) within 2 months prior to or during screening, in which active TB has not been ruled out, except for patients with history of latent TB and documentation of having completed an adequate treatment regimen <math>\geq 6</math> months prior to the first administration of study agent</li> <li>• Have had a live vaccination <math>\leq 12</math> weeks prior to randomisation (visit 2). Patients must agree not to receive a live vaccination during the study. No BCG vaccines should be given for one year prior to randomisation (visit 2), during the study and for one year after last administration of study drug (according to the Stelara® SPC).</li> <li>• History of clinically significant hypersensitivity to a systemically administered biologic agent or its excipient</li> <li>• History of malignancy in the past 5 years or suspicion of active malignant disease except treated cutaneous squamous cell or basal cell carcinoma</li> <li>• Has received any therapeutic agent directly targeted to IL-12, IL-23 (including ustekinumab (Stelara®))</li> <li>• Use of biologic agents within 12 weeks (infliximab, etanercept, adalimumab, other biologics) prior to treatment, systemic anti-psoriatic medications or phototherapy within 4 weeks prior to treatment, or topical anti-psoriasis medications within 2 weeks prior to treatment</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Drug: BI 655066 (low dose) (18 mg BI 655066 administered by SC injection plus 2 placebo-matching BI 655066 injections at week 0, followed by 2 placebo-matching BI 655066 injections each at weeks 4 and 16.)</p> <p><b>Control intervention</b></p> <p>B. Drug: BI 655066 (median dose) (90 mg BI 655066 administered by SC injection plus 2 placebo-matching BI 655066 injections at week 0, followed 90 mg BI 655066 plus 1 placebo-matching BI 655066 injection at weeks 4 and 16.)</p> <p>C. Drug: BI 655066 (high dose) (180 mg BI 655066 administered by SC injection as 2 injections plus a placebo-matching BI 655066 injection at week 0, followed 180 mg BI 655066 administered as 2 injections at weeks 4 and 16.)</p> <p>D. Drug: ustekinumab (Stelara administered by SC injection plus 2 saline injections at week 0, Stelara injection plus 1 saline injection at weeks 4 and 16. Stelara dose was 45 mg for participants with body weight <math>\leq 100</math> kg at randomisation or 90 mg for participants with body weight <math>&gt; 100</math> kg at randomisation.)</p>

**NCT02054481** (Continued)

Outcomes	<p><b>At week 12</b></p> <p><b>Primary outcome</b></p> <ul style="list-style-type: none"> <li>● PASI 90</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>● PASI 50, 75, 100 (weeks 12 &amp; 24)</li> <li>● PGA</li> </ul>
Notes	<p>Study completed July 2015 and the results are available on ClinicalTrials.gov</p> <p>BI 655066 is a new anti-IL23, not included in the initial search. It will be in the Cochrane Review update, so the trial will be included too</p>

**NCT02248792**

Methods	<p>RCT, active-controlled, double-blind trial, phase 3</p> <p>Date of study: November 2013-January 2015</p> <p>Location: India</p>
Participants	<p><b>Randomised:</b> 50 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>● Age range 18-65 years</li> <li>● Both sexes</li> <li>● Severe plaque-type psoriasis (BSA &gt; 10% or PASI &gt; 12)</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>● Pregnancy</li> <li>● Lactation</li> <li>● Malignancy or immunosuppression including HIV</li> <li>● Liver disease</li> <li>● Renal disease</li> <li>● Non compliant</li> <li>● Psychiatric illness</li> <li>● Hypersensitivity to methotrexate in the past</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>Methotrexate 10 mg/week</p> <p><b>Control intervention</b></p> <p>Methotrexate 25 mg/week</p>
Outcomes	<p><b>At week 12</b></p> <p><b>Primary outcome</b></p> <ul style="list-style-type: none"> <li>● Improvement in health related quality of life</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>● Comparison of improvement in health related quality of life between Group A and Group B</li> </ul>
Notes	<p>On ClinicalTrials.gov,</p> <p>Estimated Enrollment: 50</p> <p>Study start date: November 2013</p> <p>Estimated primary completion date: January 2015 (final data collection date for primary outcome measure)</p> <p>Emails sent to Prof. Krishna (5 and 12 January 2017)</p>



## Reich 2004

Methods	RCT, placebo-controlled, double blind Date of study: not stated Setting: multicenter (locations not stated)
Participants	<b>Randomised:</b> 195 participants (no description of the study population) <b>Inclusion criteria</b> <ul style="list-style-type: none"><li>• Participants with moderate-severe psoriasis (BSA <math>\geq</math> 10)</li><li>• Age <math>\geq</math> 16 years</li><li>• Non-response to phototherapy</li><li>• Non-response to conventional systemic treatment</li><li>• Number of allowed previous treatments: 3</li></ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"><li>• Previous treatments <math>&gt;</math> 3</li></ul> <b>Dropouts and withdrawals</b> <ul style="list-style-type: none"><li>• Not stated</li></ul>
Interventions	<b>Intervention</b> A. Alefacept (n = 130), IM, 15 mg, once a week, 12 weeks <b>Control Intervention</b> B. Placebo (n = 65), IM, once a week, 12 weeks
Outcomes	Assessments at 14 weeks <b>Primary or secondary outcomes of the trial</b> <ul style="list-style-type: none"><li>• PASI50</li></ul> <b>Outcomes of the trial</b> <ul style="list-style-type: none"><li>• AEs</li></ul>
Notes	Funding: not stated Abstracts: "Alefacept in the treatment of psoriasis for whom conventional therapies are ineffective or inappropriate" published in 2004 in the Journal of the European Academy of Dermatology and Venereology, Poster P105 We asked the study authors to provide the protocol and results by email. The had no acces to the data ("I do not have access to the data you require") Finally, as the 'Risk of bias' tool assessment was not possible and there were missing data for the results, Reich 2004 was included in "awaiting classification"

## Reich 2016

Methods	RCT, active-controlled, double-blind trial, phase 3 Date of study: November 2013-January 2015 Location: India
Participants	<b>Randomised:</b> 198 participants <b>Inclusion criteria</b> <ul style="list-style-type: none"><li>• Chronic moderate-severe plaque type psoriasis for <math>\geq</math> 6 months prior to randomisation, including significant nail involvement, defined as NAPSII score <math>\geq</math> 16 and number of fingernails involved <math>\geq</math> 4 and PASI score <math>\geq</math> 12 and BSA score <math>\geq</math> 10%</li><li>• Candidates for systemic therapy, i.e. psoriasis inadequately controlled by topical treatment (including super potent topical corticosteroids) and/or phototherapy and/or previous systemic therapy</li></ul>

	<p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Forms of psoriasis other than chronic plaque type psoriasis (e.g. pustular psoriasis, palmoplantar pustulosis, acrodermatitis of Hallopeau, erythrodermic and guttate psoriasis)</li> <li>• Drug-induced psoriasis (e.g. new onset or current exacerbation from <math>\beta</math>-blockers, calcium channel inhibitors or lithium)</li> <li>• Ongoing inflammatory skin diseases other than psoriasis or any other disease affecting the fingernails that may potentially confound the evaluation of study treatment effects</li> <li>• Ongoing use of prohibited treatments (e.g. topical or systemic corticosteroids (CS), UV therapy). Washout periods do apply</li> <li>• Prior exposure to secukinumab (AIN457) or any other biological drug directly targeting IL-17 or the IL-17 receptor</li> <li>• Exposure to any investigational drugs within 4 weeks prior to study treatment initiation or within a period of 5 half-lives of the investigational treatment, whichever is longer</li> <li>• History of hypersensitivity to constituents of the study treatment</li> <li>• Other protocol-defined inclusion/exclusion criteria do apply</li> </ul>
Interventions	<p><b>Intervention</b> Biological: secukinumab 150 mg weekly for 5 weeks, then once every 4 weeks up to and including Week 128</p> <p><b>Control Intervention</b> Biological: secukinumab 300 mg weekly for 5 weeks, then once every 4 weeks up to and including Week 128 Biological: Placebo</p>
Outcomes	<p><b>At week 16</b></p> <p><b>Primary outcome</b></p> <ul style="list-style-type: none"> <li>• NAPSI</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• NAPSI at 132 weeks</li> <li>• PASI 75 at weeks 16 and 132</li> <li>• IGA 0/1 at weeks 16 and 132</li> <li>• AEs</li> </ul>
Notes	<p>NCT01807520 Enrollment: 198 Study start date: June 2013 Estimated study completion date: January 2017</p> <p>Abstracts</p> <ul style="list-style-type: none"> <li>• Annals of the Rheumatic Diseases 2016, 75:603-4</li> <li>• Australasian Journal of Dermatology 2016, 57:77</li> </ul> <p>We asked the study authors to provide the protocol and results by email (3 January 2017) As there is no original publication available, the authors and the firm could not send us such details Will be included when published.</p>

**AEs:** adverse effects; **BMI:** body mass index; **BSA:** body surface area; **DLQI:** Dermatology Life Quality Index; **ECG:** electrocardiogram; **ew:** every other week; **FAEs:** fumaric acid esters; **IGA:** Investigator's Global Assessment; **IM:** intramuscular; **IV:** intravenous; **NAPSI:** Nail Psoriasis Severity Index; **PASI:** Psoriasis Area and Severity Index; **PGA:** Physician's Global Assessment; **PUVA:** psoralen plus ultraviolet A; **RCT:** randomised controlled trial; **SC:** subcutaneous; **SF36:** short-form 36; **SPGA:** static physician global assessment; **TB:** tuberculosis; **UVB:** ultraviolet B; **VAS:** visual analogue scale

## Characteristics of ongoing studies [ordered by study ID]

### ChiCTR-INR-16009710

Trial name or title	Acitretin plus methotrexate in the treatment of moderate to severe psoriasis vulgaris
Methods	Phase 4 RCT, active/placebo-controlled, double-blind trial Date of study: January 2016-December 2016 Location: China
Participants	<b>Randomised:</b> 350 participants <b>Inclusion criteria</b> <ul style="list-style-type: none"><li>• Men and women aged 18-75 years</li><li>• Mild psoriasis vulgaris defined by the following criteria: BSA &gt; 10% at screening and baseline and PASI &gt; 7 at screening and baseline</li><li>• Provide written informed consent and willing and able to comply with all aspects of the protocol</li></ul> <b>Main exclusion criteria</b> <ul style="list-style-type: none"><li>• Other types of psoriasis than mild psoriasis vulgaris e.g. guttate, pustular, erythrodermic, etc</li><li>• Active infectious disease, which was hard to control</li><li>• History of hepatitis B or hepatitis C, and advanced HIV infection</li><li>• Laboratory data such as alanine aminotransferase (ALT), aspartate aminotransferase (AST) and blood lipid profile was 1.5 times higher than the normal limits</li><li>• History of severe systemic disease or cancer</li><li>• Pregnant or lactating women or planning to get pregnant in 2 years</li><li>• Allergic to methotrexate and acitretin - any ingredient</li></ul>
Interventions	<b>Intervention group</b> A. Acitretin plus methotrexate group (n = 100) <b>Control intervention group</b> B. Acitretin Capsules (n = 100), 1 pill, twice a day C. Methotrexate (n = 100), 7.5 mg/week, and then 25 mg/week D. Blank group (n = 50), none
Outcomes	<b>Time point outcome measured:</b> not stated <b>Primary outcome</b> <ul style="list-style-type: none"><li>• PASI</li></ul> <b>Secondary outcome</b> <ul style="list-style-type: none"><li>• DLQI</li></ul>
Starting date	January 2016
Contact information	Prof. Xia Yumin; xiayumin1202@163.com
Notes	Ongoing study

Trial name or title	A randomised, double-blind, placebo-controlled, comparative, prospective, multicentre trial to assess efficacy and safety of apremilast tablets in subjects with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy
Methods	Phase 3 RCT, placebo-controlled, double-blind trial Date of study: October 2016 - Location: India
Participants	<p><b>Randomised:</b> 231 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Men and women, aged 18-65 years</li> <li>• Moderate-severe plaque psoriasis for <math>\geq 6</math> months who are candidates for phototherapy or systemic therapy</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Pregnant or lactating women</li> <li>• Known hypersensitivity to the study drug or any of the excipient</li> <li>• History of current erythrodermic, guttate or pustular psoriasis</li> <li>• Psoriasis flare or rebound within 4 weeks prior to screening</li> <li>• Used topical therapy within 2 weeks of randomisation or systemic therapy or phototherapy (i.e. UVB, PUVA) for psoriasis within 28 days of randomisation <ul style="list-style-type: none"> <li>• Used biological therapy for psoriasis within 6 months of randomisation</li> </ul> </li> <li>• History of malignancy (except for treated (i.e. cured) basal cell or squamous cell in situ skin carcinomas and treated (i.e. cured) cervical intraepithelial neoplasia (CIN) or carcinoma in situ of the cervix with no evidence of recurrence) within 5 years of screening <ul style="list-style-type: none"> <li>• Evidence of skin conditions that would interfere with clinical assessments in the opinion of the investigator <ul style="list-style-type: none"> <li>• Active substance abuse or a history of substance abuse within 6 months prior to Screening</li> <li>• Bacterial infections requiring treatment with oral or injectable antibiotics, or significant viral or fungal infections <ul style="list-style-type: none"> <li>• Used any investigational drug or device within 30 days of randomisation preceding informed consent or scheduled to participate in another clinical study involving an investigational product or investigational drug during the course of this study</li> </ul> </li> </ul> </li> </ul> </li> </ul>
Interventions	<p><b>Intervention</b></p> <p>Apremilast 30 mg tablets: administered 1 tablet twice daily for 16 weeks</p> <p><b>Control intervention</b></p> <p>Placebo tablets: administered 1 tablet twice daily for 16 weeks</p>
Outcomes	<p><b>At week 16</b></p> <p><b>Primary outcome</b></p> <ul style="list-style-type: none"> <li>• Proportion of participants achieving PASI 75 responses</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• Proportion of participants achieving PGA score of clear (0) or almost clear (1) at 16 weeks</li> <li>• Proportion of participants achieving PASI 50 at 16 weeks</li> <li>• Proportion of participants achieving PASI 90 at 16 weeks</li> <li>• Proportion of participants who have taken rescue medication during the treatment period at 16 weeks</li> </ul>
Starting date	20 October 016

Contact information	Dr Piyush Agarwal, DrPiyush.Agarwal@glenmarkpharma.com
Notes	Ongoing study

## EUCTR2013-004918-18-NL

Trial name or title	Optimising adalimumab treatment in psoriasis with concomitant methotrexate - OPTIMAP
Methods	Phase 4 RCT, placebo-controlled, open-label trial Date of study: February 2014 - Location: the Netherlands
Participants	<b>Randomised:</b> number of participants not stated <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Diagnosis of moderate-severe plaque psoriasis (PASI = 8 at time of screening)</li> <li>• Candidate for the treatment with biologic drugs according to the pertaining guidelines</li> <li>• Willing and able to use an adequate contraceptive during the study (all men and pre-menopausal women)</li> <li>• Adalimumab therapy will be started for the treatment of psoriasis</li> <li>• Signed informed consent</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• History of significant methotrexate or adalimumab toxicity, intolerance or contraindication</li> <li>• Prior treatment with adalimumab</li> <li>• Age &lt; 18 years</li> <li>• Pregnant and nursing women</li> <li>• Other immunosuppressive medication (prednisone, mycophenolate mofetil (e.g. Cellcept), ciclosporin (e.g. Neoral), sirolimus (Rapamune), systemic tacrolimus (e.g. Prograf)</li> </ul>
Interventions	<b>Intervention</b> Adalimumab with methotrexate <b>Control intervention</b> Adalimumab monotherapy Dosage and frequency of adalimumab and methotrexate: not stated
Outcomes	<b>Primary end point(s)</b> <ul style="list-style-type: none"> <li>• Drug survival at 1 year</li> <li>• Drug survival by efficacy</li> <li>• Drug survival by adverse events</li> </ul> <b>Timepoint(s) of evaluation of this end point: week 49</b> <b>Secondary end point(s)</b> <ul style="list-style-type: none"> <li>• Efficacy expressed as the proportion of participants achieving PASI 75 and 90 at weeks 13, 25, 37 and 49 and reduction of absolute PASI at these time points</li> <li>• Change in patient global assessment and IGA</li> <li>• Average adalimumab serum trough concentrations and titers</li> <li>• Change in impact on QoL (Skinex 29 and DLQI)</li> <li>• Treatment satisfaction (measured by Treatment Satisfaction Questionnaire for Medication)</li> <li>• Occurrence of (serious) AEs;</li> </ul>

**EUCTR2013-004918-18-NL** (Continued)

	<ul style="list-style-type: none"> <li>• Patient characteristics (age, gender, ethnicity, BMI, psoriatic arthritis, smoking, alcohol use, disease duration, disease severity by PASI, concomitant medication, naïve for biologics versus non-naïve (perhaps specified per biologic), trial medication and potential other co-variates (e.g. genetic polymorphisms)</li> </ul> <p>Timepoint(s) of evaluation of this end point: week 13, 25, 37 and 49</p>
Starting date	12 December 2013
Contact information	Pr Phyllis Spuls Department of Dermatology Academic Medical Center Meibergdreef 9 1105AZ Amsterdam Netherlands
Notes	Recruitment status (ICTRP search portal): authorised-recruitment may be ongoing or finished Target sample: not specified We emailed Prof. Phyllis Spuls (5 January 2017) Email response “The study is currently ongoing and has not yet been analysed. Therefore, we are not able to provide data on efficacy or safety. We can provide you with the study protocol. Will this be helpful? Kind regards, Phyllis Spuls and Celine Busard ” Will be included when published

**EUCTR2015-002423-26-FI**

Trial name or title	A randomised, multicenter Study to evaluate the Effect of secukinumab 300 mg s.c. administered during 52 weeks to patients suffering from new-onset moderate to severe plaque Psoriasis as early Intervention compared to standard treatment with narrow band UVB (STEPin study) - STEPin
Methods	RCT, placebo-controlled, open-label trial Date of study: November 2016 - Location: Europe Phase 4
Participants	<p><b>Randomised:</b> 196 participants</p> <p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• Aged 18-40 years inclusive</li> <li>• Moderate-severe plaque psoriasis with either new onset or lasting for <math>\geq 5</math> years</li> </ul> <p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• Forms of psoriasis other than plaque-type (e.g. pustular, erythrodermic, guttate, light sensitive, drug induced)</li> <li>• Ongoing use of prohibited treatments</li> <li>• Pregnant or nursing (lactating) women</li> <li>• Women of childbearing potential not willing to use contraception</li> <li>• Active ongoing inflammatory diseases other than psoriasis or psoriatic arthritis that might confound the evaluation of the benefit of secukinumab therapy</li> </ul>
Interventions	Secukinumab 300 mg SC. versus narrowband-UVB Dosage and frequency not stated
Outcomes	<b>At 52 weeks,</b> <b>Primary outcome</b>

**EUCTR2015-002423-26-FI** (Continued)

	<ul style="list-style-type: none"> <li>● PASI 90</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>● PASI 90 at week 104</li> <li>● IGA 0/1 at weeks 52 and 104</li> </ul>
Starting date	8 November 2016
Contact information	Novartis medical information service, novartis.laakeinformaatio@novartis.com
Notes	Ongoing study

**EUCTR2015-003623-65-DE**

Trial name or title	BI 655066 (risankizumab) versus adalimumab in a randomised, double blind, parallel group trial in moderate to severe plaque psoriasis to assess safety and efficacy after 16 weeks of treatment and after inadequate adalimumab treatment response (IMMvent) - BI 655066 (risankizumab) versus adalimumab
Methods	RCT, active/placebo-controlled, double-blind trial Date of study: February 2016 - Location: worldwide Phase 3
Participants	<p><b>Randomised:</b> 600 participants planned</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>● Men and women. Women of childbearing potential must be ready and able to use highly effective methods of birth control per ICH M3(R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information.</li> <li>● Age <math>\geq</math> 18 years at screening</li> <li>● Diagnosis of chronic plaque psoriasis (with or without psoriatic arthritis) for <math>\geq</math> 6 months before the first administration of study drug. Duration of diagnosis may be reported by the participant</li> <li>● Stable moderate-severe chronic plaque psoriasis with or without psoriatic arthritis at both screening and baseline (randomization)</li> <li>● BSA <math>\geq</math> 10%</li> <li>● PASI score <math>\geq</math> 12</li> <li>● sPGA score of <math>\geq</math> 3</li> <li>● Must be candidates for systemic therapy or phototherapy for psoriasis treatment, as assessed by the investigator</li> <li>● Must be candidates for treatment with adalimumab (Humira®) according to local label as confirmed by the investigator</li> </ul> <p><b>Exclusion criteria</b></p> <p>Patients with</p> <ul style="list-style-type: none"> <li>● Non-plaque forms of psoriasis (including guttate, erythrodermic, or pustular)</li> <li>● Current drug-induced psoriasis (including an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium)</li> <li>● Active ongoing inflammatory diseases other than psoriasis that might confound trial evaluations according to investigator's judgment</li> <li>● Previous exposure to BI 655066</li> </ul>

	<ul style="list-style-type: none"> <li>• Previous exposure to adalimumab (Humira®).</li> <li>• Major surgery performed within 12 weeks prior to randomisation or planned within 12 months after screening (e.g. hip replacement, removal aneurysm, stomach ligation).</li> <li>• Known chronic or relevant acute infections, such as active TB, HIV or viral hepatitis; confirmation of these diseases testing is required at screening. QuantiFERON® TB test or PPD skin test will be performed according to local labelling for Humira®. If the result is positive, patients may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active TB. If presence of latent TB is established, then treatment should have been initiated and maintained according to local country guidelines.</li> <li>• Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix.</li> <li>• Evidence of a current or previous disease, medical condition (including chronic alcohol or drug abuse) other than psoriasis, surgical procedure (i.e. organ transplant), medical examination finding (including vital signs and ECG), or laboratory value at the Screening Visit outside the reference range that in the opinion of the investigator is clinically significant and would make the study participant unreliable to adhere to the protocol or to complete the trial, compromise the safety of the patient, or compromise the quality of the data</li> </ul>
Interventions	<p><b>Intervention</b>            Product Name: BI 655066            Product Code: BI 655066 90 mg/mL            Pharmaceutical Form: solution for injection in pre-filled syringe            INN or proposed INN: risankizumab</p> <p><b>Control intervention</b>            Humira® (adalimumab) solution for Injection 40 mg/0.8 mL in a single-use, pre-filled syringe</p>
Outcomes	<p><b>At week 16</b></p> <p><b>Primary outcome</b></p> <ul style="list-style-type: none"> <li>• PASI 90</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• PGA 0/1</li> <li>• PASI 75 PASI 100</li> </ul>
Starting date	17 May 17 2016
Contact information	Boehringer Ingelheim Pharma GmbH & Co. KG
Notes	Ongoing study BI 655066 (a new anti-IL23) will be included

**NCT01553058**

Trial name or title	Vascular inflammation in psoriasis trial (The VIP Trial) (VIP)
Methods	RCT, active/placebo-controlled, double blind trial Date of study: February 2012 - Location: USA Phase 4



Participants	<p><b>Randomised:</b> 96 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>● Men and women <math>\geq 18</math> years</li> <li>● Clinical diagnosis of psoriasis for <math>\geq 6</math> months as determined by subject interview of his/her medical history and confirmation of diagnosis through physical examination by Investigator</li> <li>● Stable plaque psoriasis for <math>\geq 2</math> months before screening and at baseline (week 0) as determined by subject interview of his/her medical history</li> <li>● Moderate-severe psoriasis defined by <math>\geq 10</math> percent BSA involvement at the baseline (week 0) visit</li> <li>● PASI score of <math>\geq 12</math> at the baseline (week 0) visit</li> <li>● Subject is a candidate for systemic therapy or phototherapy and has active psoriasis despite prior treatment with topical agents</li> <li>● Women are eligible to participate in the study if they meet one of the following criteria: women of childbearing potential who are willing to undergo regular pregnancy testing and agree to use one method of contraception throughout the study are eligible to participate; women who are postmenopausal (for <math>\geq 1</math> year), sterile, or hysterectomised are eligible to participate; women who have undergone tubal ligation are eligible to participate; women who agree to be sexually abstinent, defined as total abstinence from sexual intercourse, as a form of contraception are eligible to participate in the study.</li> <li>● Judged to be in good general health as determined by the Principal Investigator based upon the results of medical history, laboratory profile, physical examination, and 12-lead ECG performed at screening</li> <li>● Able and willing to give written informed consent and to comply with requirements of this study protocol</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>● Previous AE following exposure to a TNF-alpha antagonist and/or UV phototherapy that led to discontinuation of either of these therapies and contraindicates future treatment</li> <li>● Previous lack of response to a TNF-alpha antagonist and/or UV phototherapy that led to discontinuation of either of these therapies</li> <li>● Diagnosis of erythrodermic psoriasis, generalised or localised pustular psoriasis, medication-induced or medication-exacerbated psoriasis, or new onset guttate psoriasis</li> <li>● Diagnosis of other active skin diseases or skin infections (bacterial, fungal, or viral) that may interfere with evaluation of psoriasis</li> <li>● Cannot avoid UVB phototherapy for <math>\geq 14</math> days prior to the baseline (week 0) visit</li> <li>● Cannot avoid psoralen-UVA phototherapy for <math>\geq 30</math> days prior to the baseline (week 0) visit and during the study</li> <li>● Cannot discontinue systemic therapies for the treatment of psoriasis, or systemic therapies known to improve psoriasis, during the study: systemic (investigational or marketed) therapies must be discontinued <math>\geq 30</math> days prior to the baseline (week 0) visit except for biologics. All biologics, except ustekinumab, must be discontinued for <math>\geq 90</math> days prior to baseline (week 0). The IL-12/IL-23 antagonist ustekinumab (half-life of <math>45.6 \pm 80.2</math> days) must be discontinued for <math>\geq 180</math> days prior to baseline (week 0). Investigational agents must be discontinued <math>\geq 30</math> days or 5 half-lives (whichever is longer) prior to the baseline (week 0) visit</li> <li>● Taking or requires oral or injectable corticosteroids during the study. Inhaled corticosteroids for stable medical conditions are allowed</li> <li>● Poorly controlled medical condition, such as unstable ischaemic heart disease, congestive heart failure, recent cerebrovascular accidents, psychiatric disease requiring frequent hospitalisation, and any other condition, which, in the opinion of the Investigator, would put the participant at risk by participation in the study</li> <li>● History of diabetes mellitus, type 1 or type 2</li> <li>● Uncontrolled hypertension, with measured systolic blood pressure <math>&gt; 180</math> mmHg or diastolic blood</li> </ul>
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	<p>pressure &gt; 90 mmHg</p> <ul style="list-style-type: none"> <li>● History of demyelinating diseases or lupus</li> <li>● Infection or risk factors for severe infections, for example: positive serology or known history of HIV, hepatitis B or C, or other severe, recurrent, or persistent infections; excessive immunosuppression or other factors associated with it, including HIV infection; active TB disease; evidence of latent TB infection demonstrated by Purified Protein Derivative (PPD) <math>\geq 5</math> mm of induration or positive Quantiferon-GOLD results; except if prophylactic treatment for TB, as recommended by local guidelines, is initiated prior to administration of study drug or if there is documentation that the subject has received prophylactic treatment for TB previously. Any other significant infection requiring hospitalisation or IV antibiotics in the month prior to baseline; infection requiring treatment with oral or parenteral antibiotics within 14 days prior to baseline; received vaccination with Bacille Calmette-Guerin (BCG) within 365 days prior to screening; received vaccination with a live viral agent 30 days prior to screening or will require a live vaccination during study participation including up to 30 days after the last dose of study drug</li> <li>● History of haematological or solid malignancy other than successfully treated basal cell carcinoma, non-metastatic cutaneous squamous cell carcinoma or cervical carcinoma in situ</li> <li>● Pregnant or breast-feeding or considering becoming pregnant during the study</li> <li>● Screening clinical laboratory analyses showing any of the following abnormal results: haemoglobin (Hgb) &lt; 10 g/dL in women or &lt; 12 g/dL in men; white blood cell (WBC) count &lt; <math>2.5 \times 10^9/L</math> or can be included if WBC count is &lt; <math>2.5 \times 10^9/L</math> and absolute neutrophil count (ANC) is &gt; 1000 cells/mm<sup>3</sup>. WBC count &gt; <math>15 \times 10^9/L</math>; platelet count &lt; <math>100 \times 10^9/L</math>; serum aspartate transaminase (AST) or alanine transaminase (ALT) &gt; 2.5 upper limits of normal (ULN); serum total bilirubin <math>\geq 2</math> mg/dL (<math>\geq 26 \mu\text{mol/L}</math>); or serum creatinine &gt; 1.6 mg/dL (<math>&gt; 141 \mu\text{mol/L}</math>)</li> <li>● Recent history of substance abuse or psychiatric illness that could preclude compliance with the protocol</li> <li>● History of any substance abuse within 365 days of screening visit</li> <li>● Alcohol use &gt; 14 drinks per week at the screening visit or within 30 days of the screening period</li> <li>● If on cholesterol-lowering medication (e.g. statin), dose and form of medication must be stable for 90 days prior to week 0 and remain stable throughout the duration of the study</li> <li>● History of photosensitivity of medical condition that may be exacerbated by UV exposures such as lupus or dermatomyositis</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Adalimumab (Humira). Humira will be given at an initial dose of 80 mg followed by 40 mg the 2nd week, subsequent doses will be given at 40 mg and follow FDA dosing schedule</p> <p><b>Control intervention</b></p> <p>B. NB-UVB phototherapy. Phototherapy will be given 3 times per week according to the Fitzpatrick scale for skin types</p> <p>C. Placebo injection will be given according to the same dose and schedule as the active comparator</p>
Outcomes	<p><b>At weeks 4 and 12</b></p> <p><b>Primary outcome measures</b></p> <ul style="list-style-type: none"> <li>● Vascular inflammation and biomarkers</li> <li>● Change in total vascular inflammation of 5 aortic segments as assessed on FDG-PET/CT between baseline and week 12</li> <li>● Change in metabolic, lipid, and inflammatory biomarker levels between baseline, week 4 and 12</li> </ul> <p><b>Secondary outcome measures:</b></p> <ul style="list-style-type: none"> <li>● Change in psoriasis activity (PASI 50, PASI 75, PASI 90, and PGA &lt; 1)</li> <li>● Number of participants with AEs</li> <li>● Change in participant-reported outcomes (e.g. EuroQoL-5D, DLQI, and International Physical</li> </ul>

**NCT01553058** (Continued)

	Activity Questionnaire (IPAQ))
Starting date	14 February 2012
Contact information	Joel Gelfand, MD MSCE (Principal investigator)
Notes	On ClinicalTrials.gov, Estimated Primary Completion Date: July 2017 Ongoing study

**NCT01558310**

Trial name or title	A study to evaluate the effectiveness of Stelara™ (ustekinumab) in the treatment of scalp psoriasis
Methods	RCT, placebo-controlled, double-blind trial Date of study: March 2012 - Location: USA Phase 4
Participants	<p><b>Randomised:</b> 30 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Capable of giving informed consent and the consent must be obtained prior to any study related procedures <ul style="list-style-type: none"> <li>• ≥ 18 years at the time of consent; may be male or female</li> <li>• Diagnosis of plaque psoriasis ≥ 6 months prior to administration of study agent</li> <li>• Presence of moderate or severe psoriasis on the body other than the scalp</li> <li>• ≥ 30% of scalp affected with erythema, induration and desquamation and s-PGA score ≥ 4</li> <li>• Candidates for phototherapy or systemic treatment of psoriasis</li> <li>• Women of childbearing potential and all men must be using adequate birth control measures (e.g. abstinence, oral contraceptives, intrauterine device, barrier method with spermicide, or surgical sterilization) and must agree to continue use of such measures and not become pregnant or plan a pregnancy until 12 months after receiving the last injection of study agent <ul style="list-style-type: none"> <li>• Be able to adhere to protocol requirements and study visit schedule</li> <li>• Must agree not to receive a live virus or live bacterial vaccination during the trial and 12 months after last study injection</li> <li>• Must agree not to receive a BCG vaccination during the trial and up to 12 months after the last injection</li> <li>• Must avoid prolonged sun exposure and avoid use of tanning booths or other ultraviolet light sources during the study</li> <li>• Considered eligible according to the following TB screening criteria. <ul style="list-style-type: none"> <li>○ Have no history of latent or active TB prior to screening. An exception is made for participants currently receiving treatment for latent TB with no evidence of active TB, or who have a history of latent TB and documentation of having completed appropriate treatment for latent TB within 3 years prior to the first administration of study agent. It is the responsibility of the investigator to verify the adequacy of previous antituberculous treatment and provide appropriate documentation.</li> <li>○ Have no signs or symptoms suggestive of active TB upon medical history or physical examination, or both.</li> <li>○ Within 6 weeks prior to the first administration of study agent, have a negative QuantiFERON-</li> </ul> </li> </ul> </li> </ul> </li> </ul>

TB Gold test result.

- Have a chest radiograph (both posterior-anterior and lateral views), taken within 3 months prior to the first administration of study agent and read by a qualified radiologist, with no evidence of current, active TB or old, inactive TB.

- Have screening laboratory test results within the following parameters:

- Hemoglobin > 10g/dL

- White Blood Cells > 3.5 x 10<sup>9</sup>/L

- Neutrophils > 1.5 x 10<sup>9</sup>/L

- Platelets > 100 X10<sup>9</sup>/L

- Serum Creatinine < 1.5 mg/dL (or 133 micromol/L)

- AST, ALT, and alkaline phosphatase levels must be within 1.5 times the upper limit of normal range for the laboratory conducting the test

**Exclusion criteria**

- Currently have non-plaque forms of psoriasis (erythrodermic, guttate, or pustular)

- Have current drug-induced psoriasis

- Presence of any skin conditions (including scalp) other than psoriasis that would interfere with evaluations of the effect of study agents

- Are pregnant, nursing, or planning pregnancy (both men and women) while enrolled in the study

- Have used any therapeutic agent targeted at reducing IL-12 and/or IL-23, including but not limited to ustekinumab and ABT -874

- Have used any investigational drug within the previous 4 weeks or 5 times the half-life of the investigational agent, whichever is longer

- Have used any investigational drug within the previous 3 months or 5 times the half-life of the biological, whichever is longer

- Have ever received natalizumab or other agents that target alpha-4-integrin

- Have received phototherapy or any systemic medications/treatments that could affect psoriasis or s-PGA/PASI evaluations (including but not limited to, oral or injectable corticosteroids, retinoids, 1, 25 dihydroxy vitamin D<sub>3</sub> and analogues, psoralens, sulfasalazine, hydroxyurea, or fumaric acid derivatives) within 4 weeks of administration of study agent

- Have used topical medications/treatments that could affect psoriasis or s-PGA/PASI evaluation (e.g. corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethyl psoralens) within 2 weeks of the first administration of study agent

- Have used any systemic immunosuppressants (e.g. methotrexate, azathioprine, ciclosporin, 6-thioguanine, mercaptopurine, mycophenolate, mofetil, hydroxyurea, and tacrolimus) within 4 weeks of the first administration of study agent

- Are currently receiving lithium, anti-malarials, or intramuscular gold, or have received lithium, anti-malarials, or intramuscular gold, or have received lithium, anti-malarials, or intramuscular gold within 4 weeks of the first administration of study agent

- Have received within 3 months prior to the first injection a live virus or bacterial vaccination.

Participants must agree not to receive a live virus or bacterial vaccination during the trial or up to 12 months after the last study agent injection

- Have had a BCG vaccination within 12 months of screening. Participants must agree not to receive a BCG vaccination during the trial or up to 12 months after the last study agent injection

- Have a history of chronic or recurrent infectious disease, including but not limited to chronic renal infection, chronic chest infections (e.g. bronchiectasis), recurrent urinary tract infections (recurrent pyelonephritis or chronic non-remitting cystitis), or open, draining, or infected skin wounds or ulcers

- Have or have had a serious infection (e.g. sepsis, pneumonia, or pyelonephritis) or have been hospitalised or received IV antibiotics for an infection during the 2 months prior to screening

	<ul style="list-style-type: none"> <li>• Have a history of latent or active granulomatous infection, including histoplasmosis or coccidioidomycosis, prior to screening</li> <li>• Have persistently indeterminate (indeterminate on repeat sampling) QuantiFERON-TB Gold test results</li> <li>• Have had a Bacille Calmette-Guérin (BCG) vaccination within 12 months of screening</li> <li>• Have a chest radiograph within 3 months prior to the first administration of study agent that shows an abnormality suggestive of a malignancy or current active infection, including TB</li> <li>• Have had a non-tuberculous mycobacterial infection or opportunistic infection (e.g. cytomegalovirus, pneumocystosis, aspergillosis) within 6 months prior to screening</li> <li>• Known to be infected with HIV, hepatitis B, or hepatitis C</li> <li>• Have current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, haematological, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease</li> <li>• Have a transplanted organ</li> <li>• Have a known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and /or splenomegaly</li> <li>• Have a known malignancy or have a history of malignancy (with the exception of basal cell carcinoma, squamous cell carcinoma in situ of the skin or cervix that has been treated with no evidence of recurrence, or squamous cell carcinoma of the skin that has been treated with no evidence of recurrence within 5 years prior to the first administration of study agent)</li> <li>• Have been hospitalised in the past 3 years for asthma, ever required intubation for treatment of asthma, currently require oral corticosteroids for the treatment of asthma, or required more than one short-term (&lt; 2 weeks) course of oral corticosteroids for asthma within the previous year</li> <li>• Have undergone allergy immunotherapy previously for prevention of anaphylactic reactions</li> <li>• Have shown a previous immediate hypersensitivity response, including anaphylaxis, to an immunoglobulin product (e.g. plasma-derived or recombinant monoclonal antibody).</li> <li>• Be known to have had a substance abuse (drug or alcohol) problem within the previous 12 months</li> <li>• Be participating in another trial using an investigational agent or procedure during participation in the trial</li> <li>• Use of tar shampoos within 14 days of first dose of study drug</li> <li>• Use of over-the-counter shampoos for scalp psoriasis will not be allowed during study</li> <li>• Use of topical corticosteroids or other topical agents for the treatment of psoriasis on the scalp will not be allowed during the study</li> </ul>
Interventions	<p><b>Intervention</b> Ustekinumab (at weeks 0, 4, 16, 28, and week 40 and placebo at weeks 12 and 52. The participants when assigned to ustekinumab, depending on body weight, will receive either 45 mg or 9 mg ustekinumab doses)</p> <p><b>Control intervention</b> Placebo</p>
Outcomes	<p><b>At week 12,</b></p> <p><b>Primary outcome</b></p> <ul style="list-style-type: none"> <li>• Scalp specific PGA</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• Not stated</li> </ul>
Starting date	August 2012
Contact information	Paul Steven Yamauchi, MD, PhD

**NCT01558310** (Continued)

Notes	<p>On ClinicalTrials.gov            Estimated enrolment: 30            Study start date: August 2012            Estimated study completion date: December 2013            We emailed Dr Yamauchi (5 and 12 January 2017)            Email response: Dear Dr Sbidian, Thank you for your kind email, forwarded to me by Dr Paul Yamauchi, MD, PhD. Our "Study to Evaluate the Effectiveness of STELARA™ (USTEKINUMAB) in the Treatment of Scalp Psoriasis (NCT 01558310)" completed enrolment in December 2016 and the last subject will complete in December 2017, as such we do not have the final data analysis. What is your absolute cut-off for publication data? Would an interim analysis report be acceptable? Best regards, Rickie Patnaik Director, Clinical Science Institute            Will be included when published</p>
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**NCT01722331**

Trial name or title	A study to evaluate the efficacy and safety of subcutaneous MK-3222, followed by an optional long-term safety extension study, in participants with moderate-severe chronic plaque psoriasis (MK-3222-010)
Methods	<p>RCT, placebo-controlled, double-blind trial            Date of study: December 2012 -            Location: not stated            Phase 3</p>
Participants	<p><b>Randomised:</b> 772 participants  <b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Clinical diagnosis of moderate-severe plaque psoriasis for <math>\geq 6</math> months prior to study enrolment</li> <li>• A candidate for phototherapy or systemic therapy</li> <li>• For the extension study: must have completed Part 3 of the base study</li> <li>• For the extension study: must have achieved <math>\geq</math> PASI 50 response by the end of Part 3 of the base study</li> <li>• For the extension study: must have received active MK-3222 treatment within 12 weeks prior to the end of Part 3 of the base study               <ul style="list-style-type: none"> <li>• Premenopausal female participants must agree to abstain from heterosexual activity or use a medically accepted method of contraception or use appropriate effective contraception as per local regulations or guidelines</li> <li>• If enrolled at a Japanese site, participants with psoriatic arthritis using non-steroidal anti-inflammatory drugs (NSAIDs) must be on a stable dose for <math>\geq 4</math> weeks prior to the first dose of study drug and must not be expected to require an increase in dose over the course of the study</li> </ul> </li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Has erythrodermic psoriasis, predominantly pustular psoriasis, medication-induced or medication-exacerbated psoriasis, or new onset guttate psoriasis               <ul style="list-style-type: none"> <li>• Current or history of severe psoriatic arthritis and is well-controlled on current treatment</li> <li>• Women of childbearing potential that are pregnant, intend to become pregnant within 6 months of completing the trial, or that are breastfeeding                   <ul style="list-style-type: none"> <li>• Expected to require topical treatment, phototherapy, or systemic treatment during the trial</li> <li>• Presence of any infection</li> <li>• History of recurrent infection requiring treatment with systemic antibiotics within 2 weeks of screening</li> <li>• Previous use of MK-3222 or other IL-23/Th-17 pathway inhibitors including P40, p19, and IL-17 antagonists</li> </ul> </li> </ul> </li> </ul>

**NCT01722331** (Continued)

	<ul style="list-style-type: none"> <li>• Evidence of active or untreated latent TB (TB)</li> <li>• Positive test for HIV (HIV), hepatitis B surface antigen (HBs Ag) or hepatitis C virus (HCV)</li> <li>• At Japanese sites, positive test for HBs antibody and hepatitis B virus (HBV) deoxyribonucleic acid (DNA)</li> <li>• At Japanese sites, positive test for the Hepatitis B core (HBc) antibody and HBV DNA</li> <li>• For the extension study: women of child-bearing potential that are pregnant, intend to become pregnant within 6 months of completing the trial, or that are breastfeeding</li> <li>• For the extension study: active or uncontrolled significant organ dysfunction or clinically significant laboratory abnormalities</li> <li>• For the extension study: expected to require topical treatment, phototherapy, or systemic treatment during the extension study</li> <li>• At Japanese sites, abnormal for Beta D Glucan and/or KL-6 test result(s) at the screening visit.</li> </ul>
Interventions	<p><b>Intervention</b> Drug: MK-3222 200 mg (SC, 200 mg at week 0 and week 4, and then every 12 weeks until study end or participant discontinuation.)</p> <p><b>Control intervention</b> Drug: MK-3222 100 mg (SC at a dose of 100 mg at week 0 and week 4, and then every 12 weeks until study end or participant discontinuation.) Drug: matching placebo (SC at week 0 and week 4)</p>
Outcomes	<p><b>At week 12</b></p> <p><b>Primary outcome</b> (composite outcome)</p> <ul style="list-style-type: none"> <li>• PASI 75</li> <li>• PGA 0/1</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• PASI 90</li> <li>• PASI 100</li> <li>• DLQI</li> <li>• AEs</li> </ul>
Starting date	December 2012
Contact information	Medical Director: Merck Sharp & Dohme Corp.
Notes	On ClinicalTrials.gov Estimated study completion date: October 2019 Still ongoing

**NCT01729754**

Trial name or title	A study to evaluate the efficacy and safety/tolerability of subcutaneous tildrakizumab (SCH 900222/MK-3222) in participants with moderate-to-severe chronic plaque psoriasis followed by a long-term extension study (MK-3222-011)
Methods	RCT, active/placebo-controlled, double-blind trial Date of study: February 2013 - Location: not stated

	Phase 3
Participants	<p><b>Randomised:</b> 1090 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Clinical diagnosis of moderate-severe plaque psoriasis for <math>\geq 6</math> months prior to enrolment</li> <li>• Candidate for phototherapy or systemic therapy</li> <li>• Premenopausal female participants must agree to abstain from heterosexual activity or use a medically approved method of contraception or use appropriate effective contraception as per local regulations or guidelines</li> <li>• For the extension study: must have completed Part 3 of the base study</li> <li>• For the extension study: must have achieved <math>\geq</math> PASI 50 response by the end of Part 3 of the base study</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Non-plaque forms of psoriasis</li> <li>• Presence or history of severe psoriatic arthritis and is well-controlled on current treatment regimen</li> <li>• Women of childbearing potential who are pregnant, intend to become pregnant, or are lactating</li> <li>• Participant is expected to require topical therapy, phototherapy, or systemic therapy during the trial</li> <li>• Presence of any infection or history of recurrent infection requiring treatment with systemic antibiotics</li> <li>• Previous use of etanercept, tildrakizumab (MK-3222), or other interleukin-23 (IL-23)/T- helper cell 17 (Th-17) pathway inhibitors including p40, p19, and IL-17 antagonists</li> <li>• Latex allergy or sensitivity</li> <li>• Active or untreated latent TB</li> </ul>
Interventions	<p><b>Intervention</b> Tildrakizumab 200 mg (SC on weeks 0, 4, 16, 28, 40 and 52)</p> <p><b>Control interventions</b> Tildrakizumab 100 mg (SC on weeks 0, 4, 16, 28, 40 and 52) Etanercept 50 mg (twice weekly until week 12 and once weekly from week 12 to week 28) Placebo</p>
Outcomes	<p><b>At week 12</b></p> <p><b>Primary outcome (composite outcome)</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> <li>• PGA 0/1</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• PASI 75 and PGA 0/1 (at weeks 28, 40, and 52)</li> <li>• PASI 90 (at weeks 12, 28, 40, and 52)</li> <li>• PASI 100 (at weeks 12, 28, 40, and 52)</li> <li>• DLQI (at weeks 12, 28, 40, and 52)</li> <li>• AEs</li> </ul>
Starting date	February 2013
Contact information	Medical director: Merck Sharp & Dohme Corp
Notes	On ClinicalTrials.gov Estimated Study Completion Date: June 2019 Ongoing study



Trial name or title	A study of guselkumab in participants with moderate to severe plaque-type psoriasis and an inadequate response to ustekinumab (NAVIGATE)
Methods	RCT, active/placebo-controlled, double-blind trial Date of study: October 2014 - Location: world-wide Phase 3
Participants	<p><b>Randomised:</b> 872 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Have a diagnosis of plaque-type psoriasis (with or without psoriatic arthritis for <math>\geq 6</math> months before the first administration of study drug)</li> <li>• PASI <math>\geq 12</math> at screening and at baseline</li> <li>• IGA <math>\geq 3</math> at screening and at baseline</li> <li>• BSA <math>\geq 10\%</math> at screening and at baseline</li> <li>• Be a candidate for phototherapy or systemic treatment for psoriasis (either naïve or history of previous treatment)</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• History or current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, haematologic, rheumatologic, psychiatric, or metabolic disturbances</li> <li>• Unstable cardiovascular disease, defined as a recent clinical deterioration (e.g. unstable angina, rapid atrial fibrillation) in the last 3 months or a cardiac hospitalization within the last 3 months</li> <li>• Currently has a malignancy or has a history of malignancy within 5 years before screening (with the exception of a nonmelanoma skin cancer that has been adequately treated with no evidence of recurrence for <math>\geq 3</math> months before the first study drug administration, or cervical carcinoma in situ that has been treated with no evidence of recurrence for <math>\geq 3</math> months before the first study drug administration)</li> <li>• Has previously received guselkumab or ustekinumab</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>Ustekinumab (45 mg or 90 mg given by SC injection at weeks 0 and 4 for all participants, Participants with an IGA score of 0 or 1 at week 16 will also receive ustekinumab every 12 weeks from week 16 to week 40)</p> <p><b>Control intervention</b></p> <p>Guselkumab (100 mg given by SC injection at weeks 16 and 20 and every 8 weeks) Placebo</p>
Outcomes	<p><b>At week 12</b></p> <p><b>Primary outcome (composite outcome)</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> <li>• PGA 0/1</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• PASI 75 and PGA 0/1 (at weeks 28, 40, and 52)</li> <li>• PASI 90 (at weeks 12, 28, 40, and 52)</li> <li>• PASI 100 (at weeks 12, 28, 40, and 52)</li> <li>• DLQI (at week 12, 28, 40, and 52)</li> <li>• AEs</li> </ul>
Starting date	October 2014 Final completion date: May 2016

**NCT02203032** (Continued)

Contact information	Janssen Research & Development, LLC Clinical Trial
Notes	Ongoing study

**NCT02258282**

Trial name or title	Safety and efficacy of etanercept in patients with psoriasis
Methods	RCT, placebo-controlled, double-blind trial Date of study: October 2014 - Location: China Phase 4
Participants	<p><b>Randomised:</b> 80 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>● Has plaque psoriasis and has shown an unsatisfactory response to traditional disease-modifying antirheumatic drugs (DMARDs) <ul style="list-style-type: none"> <li>● 18-75 years old</li> <li>● PGA <math>\geq</math> 3 at Day 0</li> <li>● BSA <math>\geq</math> 3% at Day 0</li> </ul> </li> <li>● Has psoriasis severe enough to be eligible for systemic therapy</li> <li>● Willing to use an effective method of contraception for <math>\geq</math> 30 days before day 0 and until <math>\geq</math> 1 month after the last drug administration <ul style="list-style-type: none"> <li>● Capable of giving informed consent</li> <li>● Normal or non clinically significant chest X-ray within 6 months prior to day 0</li> <li>● Negative Purified Protein Derivative (PPD) or Quantiferon TB Gold test within 90 days prior to day 0</li> <li>● Women of childbearing potential have a negative serum pregnancy test</li> </ul> </li> <li>● Able to start etanercept per the approved product monograph</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>● Used topical steroids, topical tar preparations, or other anti-psoriatic preparations within the two weeks prior to Day 0 or during the study period <ul style="list-style-type: none"> <li>● Presence of erythrodermic, pustular or guttate psoriasis</li> <li>● Significant infections within the 30 days prior to day 0</li> <li>● Received investigational drugs within the 4 weeks prior to screening or during the study period</li> <li>● Treated with systemic anti-psoriatic drugs such as steroids, retinoids, ciclosporin, PUVA therapy or methotrexate within the 4 weeks prior to day 0 or during the study period <ul style="list-style-type: none"> <li>● Received systemic antibiotics within the 4 weeks prior to day 0</li> </ul> </li> <li>● Treated with UV light therapy (UVB, nbUVB) within the 2 weeks prior to day 0 or during the study period <ul style="list-style-type: none"> <li>● Used infliximab within 14 days of day 0 or during the study period</li> <li>● Used other biologic agents for the treatment of psoriasis besides etanercept 8 weeks prior to day 0 or during the study period <ul style="list-style-type: none"> <li>● Had an allergic reaction to infliximab</li> </ul> </li> <li>● Unstable or serious medical condition as defined by the investigator or presence of any significant medical condition that might cause this study to be detrimental to the participant <ul style="list-style-type: none"> <li>● Uncontrolled or severe comorbidities such as poorly controlled diabetes mellitus, NYHA (New York Heart Association) class III or IV heart failure, history of myocardial infarction or cerebrovascular accident</li> </ul> </li> </ul> </li> </ul> </li></ul>

**NCT02258282** (Continued)

	<p>or transient ischaemic attack within three months of screening visit; unstable angina pectoris</p> <ul style="list-style-type: none"> <li>• Uncontrolled hypertension, oxygen-dependent severe pulmonary disease</li> <li>• Known sero-positivity for HIV virus or history of any other immunosuppressive disease</li> <li>• Active or chronic Hepatitis B or C</li> <li>• Any mycobacterial disease, patient with a chest X-ray suggestive of TB or taking anti-TB medication</li> <li>• Known hypersensitivity to etanercept or one of its components</li> <li>• Received a live attenuated vaccine within the 12 weeks prior to day 0 or plans to receive one during the study</li> <li>• Current pregnancy or lactation</li> </ul>
Interventions	<p><b>Intervention</b> Etanercept (participants under the treatment of 50 mg Etanercept)</p> <p><b>Control intervention</b> Placebo</p>
Outcomes	<p><b>At week 24</b></p> <p><b>Primary outcome</b></p> <ul style="list-style-type: none"> <li>• PGA</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• PASI</li> <li>• BSA</li> </ul>
Starting date	May 2014
Contact information	Yang Min, Ph.D, Chengdu PLA General Hospital
Notes	<p>On ClinicalTrials.gov</p> <p>Estimated Primary Completion Date: December 2016</p> <p>Ongoing study</p>

**NCT02313922**

Trial name or title	Optimizing psoriasis treatment of etanercept combined methotrexate
Methods	<p>RCT, placebo-controlled, double-blind trial</p> <p>Date of study: December 2014 -</p> <p>Location: China</p> <p>Phase 4</p>
Participants	<p><b>Randomised:</b> 488 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Adults of both sexes, <math>\geq 18</math> years of age</li> <li>• Stable plaque psoriasis for <math>\geq 6</math> months, psoriasis involving <math>\geq 10\%</math> BSA, minimal PASI of 10 at screening</li> <li>• Previously received phototherapy or systemic psoriasis therapy at least once or candidates for such therapy in the opinion of the investigator</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Patients with guttate, erythrodermic, or pustular psoriasis at the time of screening</li> <li>• Recent infection or opportunistic infections, active TB, hepatitis B and so on</li> </ul>

**NCT02313922** (Continued)

	<ul style="list-style-type: none"> <li>• Liver and kidney dysfunction</li> <li>• Other serious, progressive, uncontrolled disorders of vital organs and systems (including cardiovascular, liver, lung and kidney), other autoimmune diseases, cancer, HIV infection, which are not suitable for participation in the study of the disease</li> <li>• History of significant methotrexate toxicity or total cumulative methotrexate exposure &gt; 1000 mg (unless grade IIIb liver injury has not occurred)</li> <li>• Use of UVB therapy, topical ciclosporin or calcineurin inhibitors, class III through VII topical corticosteroids (permitted on the scalp, axillae, and/or groin), or topical vitamin A or D analogues within 14 days of screening</li> <li>• Psoralen or UVA therapy, systemic psoriasis therapy (including methotrexate), oral retinoids, class I or II topical corticosteroids, dithranol, cyclophosphamide, sulfasalazine, or intravenous or oral calcineurin inhibitors within 28 days of screening</li> <li>• Patients were excluded if they had received a tumour necrosis factor (TNF) blocking agent or other biologics within 3 months or interleukin (IL)-12 or IL-23 inhibitors within 6 months of study initiation</li> </ul>
Interventions	<p><b>Intervention</b> Methotrexate (dosage not stated)</p> <p><b>Control intervention</b> Co-intervention: etanercept (dosage not stated)</p>
Outcomes	<p><b>At week 24</b></p> <p><b>Primary outcome</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• PASI 90</li> <li>• DLQI</li> <li>• AEs</li> </ul>
Starting date	November 2014
Contact information	Min Zheng, director of dermatology, Zhejiang University
Notes	On ClinicalTrials.gov, Estimated Primary Completion Date: October 2016 (Final data collection date for primary outcome measure) Still ongoing

**NCT02325219**

Trial name or title	An efficacy and safety of CNTO 1959 (guselkumab) in participants with moderate to severe plaque-type psoriasis
Methods	RCT, active/placebo-controlled, double-blind trial Date of study: December 2014 - Location: Japan Phase 3
Participants	<b>Randomised:</b> 226 participants <b>Inclusion criteria</b>

	<ul style="list-style-type: none"> <li>• Have a diagnosis of plaque-type psoriasis with or without psoriatic arthritis for <math>\geq 6</math> months before screening</li> <li>• Have a PASI <math>\geq 12</math> at screening and at baseline</li> <li>• Have an IGA <math>\geq 3</math> at screening and at baseline</li> <li>• BSA <math>\geq 10\%</math> at screening and at baseline</li> <li>• Be a candidate for phototherapy or systemic treatment for psoriasis (either naive or history of previous treatment)</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• History of or current signs or symptoms of severe, progressive, or uncontrolled cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, psychiatric, or metabolic disturbances</li> <li>• Unstable cardiovascular disease, defined as a recent clinical deterioration (example, unstable angina, atrial fibrillation) in the last 3 months or a cardiac hospitalization within the last 3 months before screening</li> <li>• Currently has a malignancy or has a history of malignancy within 5 years before screening (with the exception of a nonmelanoma skin cancer that has been adequately treated with no evidence of recurrence for <math>\geq 3</math> months before the first study drug administration or cervical carcinoma in situ that has been treated with no evidence of recurrence for <math>\geq 3</math> months before screening)</li> <li>• History of lymphoproliferative disease, including lymphoma; a history of monoclonal gammopathy of undetermined significance (MGUS); or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly</li> <li>• History of chronic or recurrent infectious disease, including but not limited to chronic renal infection, chronic chest infection (e.g. bronchiectasis), recurrent urinary tract infection (recurrent pyelonephritis or chronic nonremitting cystitis), fungal infection (mucocutaneous candidiasis), or open, draining, or infected skin wounds or ulcers</li> </ul>
Interventions	<p><b>Intervention</b> CNTO 1959 50 mg (50 mg at weeks 0, 4 and then every 8 weeks thereafter)</p> <p><b>Control interventions</b> CTNO 1959 100 mg (100 mg at weeks 0, 4 and then every 8 weeks thereafter) Placebo</p>
Outcomes	<p><b>At week 16</b></p> <p><b>Primary composite outcome</b></p> <ul style="list-style-type: none"> <li>• IGA 0/1</li> <li>• PASI 90</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> <li>• DLQI</li> <li>• AEs</li> </ul>
Starting date	<p>Study start date: December 2014</p> <p>Final completion date: September 2018</p>
Contact information	Janssen Pharmaceutical K.K.
Notes	Ongoing study

Trial name or title	A study to evaluate the efficacy and safety of two dose levels of certolizumab pegol (CZP) in subjects with plaque psoriasis (PSO) (CIMPASI-2)
Methods	RCT, active/placebo-controlled, double-blind trial Date of study: December 2014 - Location: World-wide Phase 3
Participants	<p><b>Randomised:</b> 227 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Provided informed consent</li> <li>• Adult men or women <math>\geq 18</math> years</li> <li>• Chronic plaque psoriasis for <math>\geq 6</math> months</li> <li>• Baseline PASE <math>\geq 12</math> and BSA <math>\geq 10\%</math> and PGA score <math>\geq 3</math></li> <li>• Candidate for systemic psoriasis therapy and/or phototherapy and/or chemophototherapy</li> <li>• Other protocol-defined inclusion criteria may apply</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Erythrodermic, guttate, generalised pustular form of psoriasis</li> <li>• History of current, chronic, or recurrent infections of viral, bacterial, or fungal origin as described in the protocol</li> <li>• Congestive heart failure</li> <li>• History of a lymphoproliferative disorder including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease</li> <li>• History of other malignancy concurrent malignancy as described in the protocol</li> <li>• History of, or suspected, demyelinating disease of the central nervous system (e.g. multiple sclerosis or optic neuritis)</li> <li>• Breastfeeding, pregnant, or plan to become pregnant during the study or within 3 months following last dose of study drug. Men who are planning a partner pregnancy during the study or within 10 weeks following the last dose</li> <li>• Any other condition which, in the Investigator's judgment, would make the person unsuitable for participation in the study</li> <li>• Other protocol-defined exclusion criteria may apply</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>Certolizumab pegol (400 mg at weeks 0, 2, 4, followed by certolizumab pegol 200 mg every 2 weeks from week 6 to week 14)</p> <p><b>Control intervention</b></p> <p>Certolizumab pegol (certolizumab pegol 400 mg every 2 weeks through week 14) Placebo</p>
Outcomes	<p><b>At week 16</b></p> <p><b>Primary composite outcome</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> <li>• PGA 0/1</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• PASI 90</li> <li>• DLQI</li> </ul>
Starting date	Starting study date: 22 December 2014 Study completion date: September 2018

**NCT02326272** (Continued)

Contact information	UCB Biopharma S.P.R.L.
Notes	Ongoing study

**NCT02346240**

Trial name or title	Efficacy and safety study of certolizumab pegol (CZP) versus active comparator and placebo in subjects with plaque psoriasis (PSO) (CIMPACT)
Methods	RCT, active/placebo-controlled, double-blind trial Date of study: January 2015 - Location: worldwide Phase 3
Participants	<p><b>Randomised:</b> 559 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Provided informed consent</li> <li>• Adult men or women <math>\geq 18</math> years</li> <li>• Chronic plaque psoriasis for <math>\geq 6</math> months</li> <li>• Baseline PASI <math>\geq 12</math> and BSA <math>\geq 10\%</math> and PGA score <math>\geq 3</math></li> <li>• Candidate for systemic psoriasis therapy and/or phototherapy and/or chemophototherapy</li> <li>• Other protocol-defined inclusion criteria may apply</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Erythrodermic, guttate, generalised pustular form of psoriasis</li> <li>• History of current, chronic, or recurrent infections of viral, bacterial, or fungal origin as described in the protocol</li> <li>• Congestive heart failure</li> <li>• History of a lymphoproliferative disorder including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease</li> <li>• History of other malignancy, concurrent malignancy as described in the protocol</li> <li>• History of, or suspected, demyelinating disease of the central nervous system (e.g. multiple sclerosis or optic neuritis)</li> <li>• Breastfeeding, pregnant, or plan to become pregnant during the study or within 3 months following last dose of study drug. Men who are planning a partner pregnancy during the study or within 10 weeks following the last dose</li> <li>• Any other condition which, in the Investigator's judgment, would make the subject unsuitable for participation in the study</li> <li>• Other protocol-defined exclusion criteria may apply</li> <li>• Prior etanercept use</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>Certolizumab pegol (SC injection 400 mg at weeks 0, 2, 4, followed by certolizumab pegol 200 mg every 2 weeks from week 6 to week 14)</p> <p><b>Control intervention</b></p> <p>Certolizumab pegol (SC injection 400 mg every 2 weeks through week 14) Etanercept (SC injection 50 mg twice weekly through week 12) Placebo</p>

**NCT02346240** (Continued)

Outcomes	<p><b>At week 12</b></p> <p><b>Primary outcome</b></p> <ul style="list-style-type: none"> <li>● PASI (Psoriasis Activity and Severity Index) 75</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>● PGA 0/1 (at weeks 12 and 16)</li> <li>● PASI 75 (at week 16)</li> <li>● PASI 90 (at weeks 12 and 16)</li> </ul>
Starting date	<p>Start study date: 20 January 2015</p> <p>Study completion date: January 2019</p>
Contact information	UCB Biopharma S.P.R.L.
Notes	Ongoing study

**NCT02425826**

Trial name or title	A phase 4 study of efficacy and safety of apremilast in subjects with moderate plaque psoriasis (UNVEIL)
Methods	<p>RCT, placebo-controlled, double-blind trial</p> <p>Date of study: April 2015 -</p> <p>Location: USA</p> <p>Phase 4</p>
Participants	<p><b>Randomised:</b> 221 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>● Men or women, <math>\geq 18</math> years at the time of signing the informed consent document</li> <li>● Understand and voluntarily sign an informed consent document prior to any study-related assessments/procedures being conducted</li> <li>● Able to adhere to the study visit schedule and other protocol requirements</li> <li>● Diagnosis of chronic plaque psoriasis for <math>\geq 6</math> months prior to signing the informed consent</li> <li>● Have moderate plaque psoriasis at screening and baseline as defined by BSA 5%-10% and sPGA 3 (moderate) based on a 0-5-point scale</li> <li>● Must be in general good health (except for psoriasis) as judged by the investigator, based on medical history, physical examination, and clinical laboratories.</li> <li>● No prior exposure to systemic treatments or biologics for the treatment of psoriatic arthritis, psoriasis, or any other indication that could impact the assessment of psoriasis.</li> <li>● Women of childbearing potential must have a negative pregnancy test at screening and baseline. While on investigational product and for <math>\geq 28</math> days after taking the last dose of investigational product, women who engage in activity in which conception is possible must use one of the approved contraceptive options described below: <ul style="list-style-type: none"> <li>○ Option 1: any one of the following highly effective methods: hormonal contraception (oral, injection, implant, transdermal patch, vaginal ring); intrauterine device (IUD); tubal ligation; or partner's vasectomy; or</li> <li>○ Option 2: male or female condom (latex condom or nonlatex condom not made out of natural (animal) membrane (for example, polyurethane)) plus one additional barrier method: (a) diaphragm with spermicide; (b) cervical cap with spermicide; or (c) contraceptive sponge with spermicide.</li> </ul> </li> <li>● Men (including those who have had a vasectomy) who engage in activity in which conception is</li> </ul>



	<p>possible must use barrier contraception (male latex condom or nonlatex condom NOT made out of natural (animal) membrane (for example, polyurethane)) while on investigational product and for <math>\geq 28</math> days after the last dose of investigational product</p> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Other than psoriasis, any clinically significant (as determined by the Investigator) cardiac, endocrinologic, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, or other major disease that is currently uncontrolled</li> <li>• Any condition, including the presence of laboratory abnormalities, which would place the subject at unacceptable risk if he/she were to participate in the study</li> <li>• Any condition, including other inflammatory diseases or dermatologic conditions, which confounds the ability to interpret data from the study, including other types of psoriasis (i.e. erythrodermic, guttate, inverse, or pustular psoriasis), other than plaque psoriasis.</li> <li>• Prior history of suicide attempt at any time in the subject's life time prior to signing the informed consent and randomisation, or major psychiatric illness requiring hospitalization within the last 3 years prior to signing the informed consent</li> <li>• Pregnant or breast feeding</li> <li>• Active substance abuse or a history of substance abuse within 6 months prior to signing the informed consent</li> <li>• Malignancy or history of malignancy, except for: treated (i.e. cured) basal cell or squamous cell in situ skin carcinomas; treated (i.e. cured) cervical intraepithelial neoplasia (CIN) or carcinoma in situ of the cervix with no evidence of recurrence within 5 years of signing the informed consent</li> <li>• Topical therapy within 2 weeks of randomisation (including, but not limited to, topical corticosteroids, retinoids or vitamin D analogue preparations, tacrolimus, pimecrolimus, or anthralin/dithranol). Use of phototherapy within 4 weeks prior to randomisation</li> <li>• Use of any investigational drug within 4 weeks prior to randomisation, or 5 pharmacokinetic/ pharmacodynamic half-lives, if known (whichever is longer)</li> <li>• Prolonged sun exposure or use of tanning booths, which may confound the ability to interpret data from the study</li> <li>• Prior treatment with apremilast</li> </ul>
Interventions	<p><b>Intervention</b> Apremilast (30 mg tablets orally twice daily weeks 0-52)</p> <p><b>Control intervention</b> Drug: placebo</p>
Outcomes	<p><b>At week 16,</b></p> <p><b>Primary composite outcome</b></p> <ul style="list-style-type: none"> <li>• Change from baseline in the product of BSA (%) and PGA 0/1</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• PGA 0/1 at week 52</li> <li>• PASI 75</li> <li>• PASI 90</li> <li>• DLQI</li> </ul>
Starting date	<p>Study starting date: 3 April 2015</p> <p>Study completion date: November 2016</p>
Contact information	Joana Goncalves, MD Celgene Corporation

Notes	Ongoing study
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## NCT02474082

Trial name or title	Study of secukinumab compared to Fumaderm® in adults with moderate to severe psoriasis (PRIME)
Methods	RCT, active-controlled, open-label study Date of study: June 2015 - Location: USA Phase 3
Participants	<p><b>Randomised:</b> 202 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Men or women must be <math>\geq 18</math> years of age at the time of screening</li> <li>• Chronic plaque-type psoriasis diagnosed for <math>\geq 6</math> months before randomisation.</li> <li>• Patients with moderate-severe plaque psoriasis who are candidates for systemic therapy as defined at randomisation by: <ul style="list-style-type: none"> <li>○ PASI score of <math>&gt; 10</math></li> <li>○ BSA <math>&gt; 10\%</math></li> <li>○ DLQI <math>&gt; 10</math></li> </ul> </li> <li>• Inadequate response, intolerance or contraindication to topical psoriasis treatment as documented in the patient's medical history or reported by the patient or determined by the investigator at screening</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Previous systemic treatment of plaque psoriasis or known contraindication for systemic therapy at baseline</li> <li>• Ongoing use of other prohibited psoriasis and non-psoriasis treatment</li> <li>• Clinically important active infections or infestations, chronic, recurrent or latent infections or infestations</li> <li>• Severe liver diseases</li> <li>• Severe gastrointestinal diseases including but not limited to ventricular and duodenal ulcers</li> <li>• Severe kidney diseases or serum creatinine above <math>1 \times \text{ULN}</math></li> <li>• Known hematological disease or lab abnormalities</li> <li>• Pregnancy, breast feeding, or unwillingness/inability to use appropriate measures of contraception (if necessary)</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>Secukinumab (300 mg at weeks 0, 1, 2, 3, 4, 8, 12, 16 and 20)</p> <p><b>Control intervention</b></p> <p>Fumaderm® (week 0: 1 tablet of Fumaderm® INITIAL in the evening Week 1: 1 tablet Fumaderm® INITIAL, in the morning and evening Week 2: 1 tablet Fumaderm® INITIAL in the morning, at noon and in the evening until the last tablet of a 40-tablet-blister is consumed Week 2-3: At the day after the last tablet of the Fumaderm® INITIAL 40-tablet-blister is consumed and through week 3, 1 tablet of Fumaderm® in the evening Week 4: 1 tablet Fumaderm® in the morning and evening Week 5: 1 tablet Fumaderm® in the morning, at noon and in the evening Week 6: 1 tablet of Fumaderm® in the morning and at noon, 2 tablets of Fumaderm® in the evening Week 7: 2 tablets of Fumaderm® in the morning, 1 tablet of Fumaderm® at noon, 2 tablets of Fumaderm®</p>

**NCT02474082** (Continued)

	in the evening Weeks 8-24: 2 tablets of Fumaderm® in the morning, at noon and in the evening)
Outcomes	<b>At week 24</b> <b>Primary outcome</b> <ul style="list-style-type: none"> <li>● PASI 75</li> </ul> <b>Secondary outcomes</b> <ul style="list-style-type: none"> <li>● PASI 90</li> <li>● IGA 0/1</li> <li>● DLQI</li> </ul>
Starting date	Study starting date: April 2015 Study completion date: June 2016
Contact information	Novartis Pharmaceuticals
Notes	Ongoing study

**NCT02513550**

Trial name or title	A study comparing different dosing regimens of ixekizumab (LY2439821) in participants with moderate to severe plaque psoriasis (IXORA-P)
Methods	RCT, active/placebo-controlled, double-blind trial Date of study: July 2015 - Location: worldwide Phase 3
Participants	<b>Randomised:</b> 1227 participants <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>● Present with chronic plaque psoriasis for <math>\geq 6</math> months prior to enrolment</li> <li>● <math>\geq 10\%</math> BSA of psoriasis at screening and at enrolment</li> <li>● sPGA score of <math>\geq 3</math> and PASI score of <math>\geq 12</math> at screening and at enrolment</li> <li>● Candidates for phototherapy and/or systemic therapy</li> <li>● Participant must agree to use reliable method of birth control during the study; women must continue using birth control for <math>\geq 12</math> weeks after stopping treatment</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>● Predominant pattern of pustular, erythrodermic, or guttate forms of psoriasis</li> <li>● History of drug-induced psoriasis</li> <li>● Cannot avoid excessive sun exposure or use of tanning booths for <math>\geq 4</math> weeks prior to enrolment and during the study</li> <li>● Received systemic non-biologic psoriasis therapy or phototherapy within the previous 4 weeks; or had topical psoriasis treatment within the previous 2 weeks prior to enrolment</li> <li>● Concurrent or recent use of any biologic agent</li> <li>● Have participated in any study with ixekizumab</li> <li>● Received a live vaccination within 12 weeks prior to enrolment</li> <li>● Serious disorder or illness other than psoriasis</li> <li>● Ongoing or serious infection within the last 12 weeks or evidence of TB</li> </ul>

**NCT02513550** (Continued)

	<ul style="list-style-type: none"> <li>• Major surgery within 8 weeks of baseline, or will require surgery during the study</li> <li>• Breastfeeding or nursing (lactating) women</li> </ul>
Interventions	<p><b>Intervention</b> Ixekizumab (160 mg ixekizumab given as 2 SC injections at baseline and then 80 mg ixekizumab given as 1 SC injection every 2 weeks to week 52)</p> <p><b>Control interventions</b> Ixekizumab (160 mg ixekizumab given as 2 SC injections at baseline and then 80 mg ixekizumab given as 1 SC injection every 4 weeks to week 52) Placebo</p>
Outcomes	<p><b>At week 52</b></p> <p><b>Primary composite outcome</b></p> <ul style="list-style-type: none"> <li>• PGA 0/1</li> <li>• Achieving 75% improvement in PASI 75</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• PASI 90</li> <li>• PASI 75</li> <li>• NAPSI</li> <li>• Psoriasis Scalp Severity Index</li> <li>• Palmoplantar PASI</li> <li>• Itch Numeric Rating Scale</li> <li>• DLQI</li> </ul>
Starting date	<p>Study starting date: August 2015</p> <p>Study completion date: October 2017</p>
Contact information	<p>Call 1-877-CTLILLY (1-877-285-4559) or 1-317-615-4559 Mon - Fri 9 AM - 5 PM Eastern time (UTC/GMT - 5 hours, EST)</p>
Notes	<p>Ongoing study</p>

**NCT02555826**

Trial name or title	<p>Study of the efficacy and safety Of apremilast (CC-10004), in subjects with moderate plaque psoriasis</p>
Methods	<p>RCT, placebo-controlled, double-blind study</p> <p>Date of study: April 2015 -</p> <p>Location: USA</p> <p>Phase 4</p>
Participants	<p><b>Randomised:</b> 221 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Men or women, <math>\geq</math> 18 years of age</li> <li>• Able to adhere to the study visit schedule and other protocol requirements</li> <li>• Diagnosis of chronic plaque psoriasis for <math>\geq</math> 6 months prior to signing the informed consent</li> <li>• Have moderate plaque psoriasis at screening and baseline as defined by:             <ul style="list-style-type: none"> <li>◦ BSA (Body Surface Area) 5% to 10%, and</li> <li>◦ sPGA (Physician's Global Assessment) 3 (moderate) based on a 0 to 5 point scale</li> </ul> </li> </ul>

	<ul style="list-style-type: none"> <li>• Must be in general good health (except for psoriasis) as judged by the investigator</li> <li>• No prior systemic treatments or biologics for the treatment of psoriatic arthritis, psoriasis</li> <li>• Women must have a negative pregnancy test at screening and baseline. Participants must agree to use contraception during the course of the study</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Other than psoriasis, any clinically significant (as determined by the Investigator) major disease that is currently uncontrolled</li> <li>• Any condition, including the presence of laboratory abnormalities, which would place the subject at unacceptable risk if he/she were to participate in the study             <ul style="list-style-type: none"> <li>• Pregnant or breastfeeding</li> <li>• Active substance abuse or a history of substance abuse within 6 months prior to signing the informed consent</li> <li>• Malignancy or history of malignancy</li> <li>• Topical therapy within 2 weeks of starting trial</li> <li>• Use of phototherapy within 4 weeks prior to starting trial</li> <li>• Use of any investigational drug within 4 weeks prior to starting trial</li> <li>• Prolonged sun exposure or use of tanning booths, which may confound the ability to interpret data from the study</li> <li>• Prior treatment with apremilast</li> </ul> </li> </ul>
Interventions	<p><b>Intervention</b> Apremilast (30 mg tablets orally twice daily weeks 0-52)</p> <p><b>Control intervention</b> Placebo</p>
Outcomes	<p><b>At week 16,</b></p> <p><b>Primary composite outcome</b></p> <ul style="list-style-type: none"> <li>• Change from baseline in the product of BSA (%) and the sPGA which is considered as the Total Psoriasis Severity Index</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• Mean change from baseline in the DLQI</li> <li>• PGA 0/1</li> <li>• Treatment Satisfaction Questionnaire for Medication</li> <li>• PASI 75</li> </ul>
Starting date	<p>Study starting date: 18 September 2015</p> <p>Study completion date: November 2016</p>
Contact information	Joana Goncalves, MD Celgene Corporation
Notes	Ongoing study

Trial name or title	Evaluation of cardiovascular risk markers in psoriasis patients treated with secukinumab (CARIMA)
Methods	RCT, placebo-controlled, double-blind study Date of study: September 2015 - Location: Germany Phase 4
Participants	<b>Randomised:</b> 151 participants <b>Key inclusion criteria</b> <ul style="list-style-type: none"> <li>Chronic moderate-severe plaque type psoriasis for <math>\geq 6</math> months prior to randomisation with a PASI score <math>\geq 10</math> at randomisation</li> <li>Inadequate response, intolerance or contraindication to ciclosporin, methotrexate and psoralen plus ultraviolet A light treatment (PUVA) as documented in the patient's medical history or reported by the patient or determined by the investigator at screening. Relative contraindications such as interference of patient's lifestyle with the treatment are accepted</li> </ul> <b>Key exclusion criteria</b> <ul style="list-style-type: none"> <li>Forms of psoriasis other than chronic plaque-type (e.g. pustular, erythrodermic and guttata psoriasis) at screening or randomisation</li> <li>Ongoing use of prohibited psoriasis and non-psoriasis treatments. Washout periods have to be adhered to</li> </ul>
Interventions	<b>Intervention</b> Secukinumab 300 (300 mg every week for 4 weeks followed by 300 mg secukinumab every 4 weeks until week 48) <b>Control interventions</b> Secukinumab 150 (150 mg every week for 4 weeks followed by 300 mg secukinumab every 4 weeks until week 48) Placebo
Outcomes	<b>At week 12,</b> <b>Primary outcome</b> <ul style="list-style-type: none"> <li>Flow Mediated Dilation (FMD)</li> </ul> <b>Secondary outcomes</b> <ul style="list-style-type: none"> <li>Aortic Augmentation Index at heart rate of 75</li> <li>Pulse wave velocity</li> <li>Biomarkers</li> <li>PASI</li> <li>IGA</li> </ul>
Starting date	April 2014
Contact information	Novartis Pharmaceuticals
Notes	On ClinicalTrials.gov, Primary completion date: April 2016 (final data collection date for primary outcome measure) Still ongoing

Trial name or title	A study of ixekizumab (LY2439821) in participants with moderate-to-severe plaque psoriasis (IXORA-S)
Methods	<p>RCT, active-controlled, open-label study</p> <p>Date of study: September 2015 -</p> <p>Location: USA</p> <p>Phase 3</p>
Participants	<p><b>Randomised:</b> 300 participants</p> <p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>● Chronic plaque psoriasis for <math>\geq 6</math> months before baseline</li> <li>● Failure, contraindication, or intolerability to <math>\geq 1</math> systemic therapy (including ciclosporin, methotrexate, or phototherapy)</li> <li>● PASI score <math>\geq 10</math> at screening and at baseline</li> <li>● Participant must agree to use reliable method of birth control during the study; women must continue using birth control for <math>\geq 15</math> weeks after stopping treatment</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>● Predominant pattern of pustular, erythrodermic, and/or guttate forms of psoriasis</li> <li>● History of drug-induced psoriasis</li> <li>● Cannot avoid excessive sun exposure or use of tanning booths for <math>\geq 4</math> weeks before baseline and during the study</li> <li>● Have received systemic nonbiologic psoriasis therapy or phototherapy within 4 weeks of baseline, or have had topical psoriasis treatment within 2 weeks of baseline</li> <li>● Concurrent or recent use of any biologic agent within the following washout periods: etanercept &lt; 28 days; infliximab, adalimumab, or alefacept &lt; 60 days; golimumab &lt; 90 days; rituximab &lt; 12 months; or any other biologic agent &lt; 5 half-lives prior to baseline</li> <li>● Have prior use of ustekinumab, or have any condition or contraindication to ustekinumab that would preclude the participant from participating in this protocol</li> <li>● Have previously completed or withdrawn from this study, participated in any other study with ixekizumab, have participated in any study investigating other interleukin (IL)-17 or IL-12/23 antagonists, or have received treatment with other IL-17 or IL-12/23 antagonists</li> <li>● Have had a live vaccination within 12 weeks of baseline, or intend to have a live vaccination during the course of the study or within 15 weeks of completing treatment in this study</li> <li>● Have had a vaccination with Bacillus Calmette-Guérin (BCG) within 12 months of baseline or intend to have vaccination with BCG during the course of the study or within 12 months of completing treatment in this study</li> <li>● Have a known allergy or hypersensitivity to latex</li> <li>● Have had any major surgery within 8 weeks of baseline or will require such during the study</li> <li>● Have active or history of malignant disease within 5 years prior to baseline</li> <li>● Significant uncontrolled disorder</li> <li>● Ongoing infection or serious infection within 12 weeks of baseline; serious bone or joint infection within 24 weeks of baseline</li> <li>● Are women who are lactating or breastfeeding</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>Ixekizumab (160 mg ixekizumab given as 2 SC injections at baseline followed by 80 mg ixekizumab given as a single SC injection once every 2 weeks from week 2 through week 12. After week 12 participants will receive 80 mg ixekizumab every 4 weeks through week 52)</p> <p><b>Control intervention</b></p> <p>Ustekinumab (45 mg ustekinumab given as SC injection for participants <math>\leq 100</math> kg and 90 mg SC injection for participants &gt; 100 kg at weeks 0, 4, 16, 28, and 40)</p>

**NCT02561806** (Continued)

Outcomes	<p><b>At week 12,</b></p> <p><b>Primary outcome</b></p> <ul style="list-style-type: none"> <li>● PASI 90</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>● PASI 75</li> <li>● PGA</li> <li>● DLQI</li> </ul>
Starting date	<p>Start study date: October 2015</p> <p>Completion study date: May 2017</p>
Contact information	<p>Call 1-877-CTLILLY (1-877-285-4559) or 1-317-615-4559 Mon - Fri 9 AM - 5 PM Eastern time (UTC/GMT - 5 hours, EST)</p>
Notes	<p>Ongoing study</p>

**NCT02634801**

Trial name or title	<p>A study of ixekizumab (LY2439821) in participants with moderate-to-severe plaque psoriasis naive to systemic treatment</p>
Methods	<p>RCT, active-controlled, single-blind study</p> <p>Date of study: December 2015 -</p> <p>Location: Germany</p> <p>Phase 3</p>
Participants	<p><b>Randomised:</b> 162 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>● Present with moderate-to-severe chronic plaque psoriasis based on a diagnosis of chronic psoriasis for <math>\geq 6</math> months before baseline</li> <li>● Participants who are candidates for systemic therapy and who are naive to systemic treatment for psoriasis</li> <li>● Have PASI score <math>&gt; 10</math> or BSA <math>&gt; 10</math> and DLQI <math>&gt; 10</math> at screening and at baseline</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>● Have predominant pattern of pustular, erythrodermic, and/or guttate forms of psoriasis</li> <li>● Have received systemic nonbiologic psoriasis therapy</li> <li>● Have prior, concurrent, or recent use of ixekizumab or any other biological psoriasis therapy</li> <li>● Have any condition or contraindication as addressed in the local labelling for methotrexate or FAE</li> <li>● Presence of significant uncontrolled cerebro-cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neurologic, or neuropsychiatric disorders or abnormal laboratory values at screening</li> <li>● Have severe gastrointestinal disease, oral ulcer, or known, active gastrointestinal ulcer</li> <li>● Have had a serious infection or are immunocompromised</li> <li>● At screening, participants with significant, present, or early liver disease, e.g. explained by alcohol consumption or hepatic insufficiency</li> </ul>



**NCT02634801** (Continued)

Interventions	<p><b>Intervention</b> Ixekizumab (60 mg ixekizumab given as 2 SC injections followed by 80 mg ixekizumab given SC every 2 weeks until week 12 and then 80 mg ixekizumab given SC every 4 weeks until week 24)</p> <p><b>Control interventions</b> FAEs (105 mg FAE given orally followed by 215 mg FAE given orally 1-3 times/day until week 24) Methotrexate (7.5 mg starting dose up to 30 mg methotrexate given orally once a week until week 24)</p>
Outcomes	<p><b>At week 24</b></p> <p><b>Primary outcome</b></p> <ul style="list-style-type: none"> <li>● PASI 75</li> </ul> <p><b>Secondary outcome</b></p> <ul style="list-style-type: none"> <li>● PGA 0/1</li> <li>● PASI 90</li> <li>● DLQI</li> </ul>
Starting date	<p>Study start date: January 2016</p> <p>Study completion date: November 2017</p>
Contact information	Call 1-877-CTLILLY (1-877-285-4559) or 1-317-615-4559 Mon - Fri 9 AM - 5 PM Eastern time (UTC/GMT - 5 hours, EST)
Notes	Ongoing study

**NCT02655705**

Trial name or title	Comparison study of psoriasis severity assessment tools
Methods	<p>RCT, placebo-controlled, open-label study</p> <p>Date of study: September 2015 -</p> <p>Location: Korea</p> <p>Phase 4</p>
Participants	<p><b>Randomised:</b> 34 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>● Present with chronic plaque psoriasis based on a clinical diagnosis</li> <li>● Have &gt; 5% BSA involvement at screening</li> <li>● Are a candidate for systemic therapy</li> <li>● Are male or female patients ≥18 years</li> <li>● Have given written informed consent approved by the Institutional Review Board</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>● Have predominant pattern of pustular, erythrodermic, or guttate forms of psoriasis</li> <li>● Have had any of the systemic non-biologic psoriasis therapy (including neotigason, ciclosporin, and methotrexate) within 4 weeks prior to baseline</li> <li>● Have had etanercept within 4 weeks prior to baseline</li> <li>● Have had adalimumab and infliximab within 8 weeks prior to baseline</li> <li>● Have had ustekinumab within 16 weeks prior to baseline</li> <li>● Presence of significant hepatic or renal disorders</li> <li>● Have uncontrolled arterial hypertension</li> </ul>

**NCT02655705** (Continued)

	<ul style="list-style-type: none"> <li>• Are women who are lactating, breastfeeding or planning pregnancy</li> <li>• Have any other condition that precludes from following and completing the protocol</li> </ul>
Interventions	<p><b>Intervention</b> Ciclosporin A (men 200 mg/day, women 150 mg/day for 16 weeks)</p> <p><b>Control intervention</b> Methotrexate (initial dose 10 mg/week, increasing 2.5 mg every 2 weeks up to 15 mg/week)</p>
Outcomes	<p><b>At week 16</b></p> <p><b>Primary outcome</b></p> <ul style="list-style-type: none"> <li>• Change in PASI</li> </ul> <p><b>Secondary outcome</b></p> <ul style="list-style-type: none"> <li>• PASI 75, PASI 90</li> <li>• AEs</li> </ul>
Starting date	<p>Study start date: August 2014</p> <p>Study completion date: March 2016</p>
Contact information	Sang Woong Youn, Associate Professor, Seoul National University Hospital
Notes	Ongoing study

**NCT02672852**

Trial name or title	BI 655066/ABBV-066 (risankizumab) in moderate to severe plaque psoriasis with randomized withdrawal and re-treatment
Methods	<p>RCT, placebo-controlled, double-blind study</p> <p>Date of study: February 2016 -</p> <p>Location: worldwide</p> <p>Phase 3</p>
Participants	<p><b>Randomised:</b> 500 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Men or women</li> <li>• Women of childbearing potential must be ready and willing to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly</li> <li>• Age <math>\geq</math> 18 years at screening</li> <li>• Diagnosis of chronic plaque psoriasis (with or without psoriatic arthritis) <math>\geq</math> 6 months before the first administration of study drug. Duration of diagnosis may be reported by the patient.</li> <li>• Stable moderate-severe chronic plaque psoriasis with or without psoriatic arthritis at both screening and baseline (randomization);</li> <li>• Have an involved BSA <math>\geq</math> 10%, PASI <math>\geq</math> 12 a sPGA score of <math>\geq</math> 3</li> <li>• Must be a candidate for systemic therapy or phototherapy for psoriasis treatment, as assessed by the investigator</li> <li>• Signed and dated written informed consent prior to admission to the study and performance of any study procedures in accordance with GCP and local legislation</li> </ul>

	<p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• Non-plaque forms of psoriasis (including guttate, erythrodermic, or pustular); current drug-induced psoriasis (including a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium); active ongoing inflammatory diseases other than psoriasis and psoriatic arthritis that might confound trial evaluations according to the investigators judgment</li> <li>• Previous exposure to ABBV-066</li> <li>• Currently enrolled in another investigational study or &lt; 30 days (from screening) since completing another investigational study</li> <li>• Use of any restricted medication as noted or any drug considered likely to interfere with the safe conduct of the study</li> <li>• Major surgery performed within 12 weeks prior to randomisation or planned within 12 months after screening (e.g. hip replacement, removal aneurysm, stomach ligation)</li> <li>• Known chronic or relevant acute infections such as active TB, HIV, or viral hepatitis</li> <li>• Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix</li> <li>• Evidence of a current or previous disease (including chronic alcohol or drug abuse), medical condition other than psoriasis, surgical procedure (i.e. organ transplant), medical examination finding (including vital signs and ECG), or laboratory value at the screening visit outside the reference range that in the opinion of the -Investigator, is clinically significant and would make the study participant unable to adhere to the protocol or to complete the trial, compromise the safety of the patient, or compromise the quality of the data <ul style="list-style-type: none"> <li>• History of allergy/hypersensitivity to a systemically administered biologic agent or its excipients</li> <li>• Women who are pregnant, nursing, or who plan to become pregnant while in the trial</li> </ul> </li> </ul>
Interventions	<p><b>Intervention</b>  ABBV-066 (SC injection, dosage not stated)</p> <p><b>Control intervention</b>  Placebo</p>
Outcomes	<p><b>At week 16</b></p> <p><b>Primary composite outcome</b></p> <ul style="list-style-type: none"> <li>• PASI 90</li> <li>• PGA 0/1</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• PASI 75 at weeks 16 and 52</li> <li>• PASI 90 at weeks 52</li> <li>• PGA 0/1 at weeks 52</li> </ul>
Starting date	February 2016
Contact information	Boehringer Ingelheim
Notes	Ongoing study BI 655066 will be included

Trial name or title	BI 655066 compared to placebo & active comparator (ustekinumab) in patients with moderate to severe chronic plaque psoriasis
Methods	RCT, placebo/active-controlled, double-blind study Date of study: September 2017 - Location: worldwide Phase 3
Participants	<p><b>Randomised:</b> 500 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Male or female patients. Women of childbearing potential* must be ready and able to use highly effective methods of birth control per ICH M3(R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information. *Women of childbearing potential are defined as: having experienced menarche and are not postmenopausal (12 months with no menses without an alternative medical cause) and are not permanently sterilised (e.g. tubal occlusion, hysterectomy, bilateral oophorectomy or bilateral salpingectomy)</li> <li>• Age <math>\geq</math> 18 years at screening</li> <li>• Diagnosis of chronic plaque psoriasis (with or without psoriatic arthritis) for <math>\geq</math> 6 months before the first administration of study drug. Duration of diagnosis may be reported by the patient</li> <li>• Stable moderate-severe chronic plaque psoriasis with or without psoriatic arthritis at both screening and baseline (randomization)</li> <li>• Have an involved BSA <math>\geq</math> 10%, PASI score <math>\geq</math> 12 and sPGA score of <math>\geq</math> 3</li> <li>• Must be candidates for systemic therapy or phototherapy for psoriasis treatment, as assessed by the investigator</li> <li>• Must be a candidate for treatment with Stelara® (ustekinumab) according to local label</li> <li>• Signed and dated written informed consent prior to admission to the study in accordance with GCP and local legislation</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Non-plaque forms of psoriasis (including guttate, erythrodermic, or pustular), current drug-induced psoriasis (including an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium), active ongoing inflammatory diseases other than psoriasis and psoriatic arthritis that might confound trial evaluations according to investigator's judgment</li> <li>• Previous exposure to BI 655066</li> <li>• Currently enrolled in another investigational study or &lt; 30 days (from screening) since completing another investigational study (participation in observational studies is permitted)</li> <li>• Previous exposure to ustekinumab (Stelara®)</li> <li>• Use of any restricted medication, or any drug considered likely to interfere with the safe conduct of the study</li> <li>• Major surgery performed within 12 weeks prior to randomisation or planned within 12 months after screening (e.g. hip replacement, aneurysm removal, stomach ligation),</li> <li>• Known chronic or relevant acute infections including active TB, HIV or viral hepatitis; QuantiFERON® TB test or PPD skin test will be performed according to local labelling for comparator products. If the result is positive, patients may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that they have no evidence of active TB. If presence of latent TB is established, then treatment should have been initiated and maintained according to local country guidelines</li> <li>• Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal or squamous cell carcinoma of the skin or in situ carcinoma of</li> </ul>

**NCT02684357** (Continued)

	<p>uterine cervix</p> <ul style="list-style-type: none"> <li>• Evidence of a current or previous disease, medical condition (including chronic alcohol or drug abuse) other than psoriasis, surgical procedure (i.e. organ transplant), medical examination finding (including vital signs and ECG), or laboratory value at the screening visit outside the reference range that is in the opinion of the investigator, is clinically significant and would make the study participant unreliable to adhere to the protocol or to complete the trial, compromise the safety of the participant, or compromise the quality of the data</li> <li>• History of allergy/hypersensitivity to a systemically administered biologic agent or its excipients</li> <li>• Women who are pregnant, nursing, or who plan to become pregnant while in the trial</li> <li>• Previous enrolment in this trial</li> </ul>
Interventions	<p><b>Intervention</b> ABBV-066 (SC, dosage not stated)</p> <p><b>Control interventions</b> Ustekinumab (dosage not stated)) Placebo</p>
Outcomes	<p><b>At week 16</b></p> <p><b>Primary composite outcome</b></p> <ul style="list-style-type: none"> <li>• PASI 90</li> <li>• PGA 0/1</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• PASI 75 at weeks 16 and 52</li> <li>• PASI 90 at week 52</li> <li>• PGA 0/1 at week 52</li> </ul>
Starting date	February 2016
Contact information	Boehringer Ingelheim
Notes	Ongoing study BI 655066 will be included

**NCT02684370**

Trial name or title	BI 655066/ABBV-066 (risankizumab) versus ustekinumab and placebo comparators in a randomized double blind trial for maintenance use in moderate to severe plaque type psoriasis (UltIMMa-1)
Methods	RCT, active/placebo-controlled, double-blind study Date of study: February 2016 - Location: worldwide Phase 3
Participants	<p><b>Randomised:</b> 500 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Men or women aged <math>\geq 18</math> years at screening</li> <li>• Diagnosis of chronic plaque psoriasis (with or without psoriatic arthritis) for <math>\geq 6</math> months before the first administration of study drug</li> <li>• Stable moderate-severe chronic plaque psoriasis with or without psoriatic arthritis at both screening</li> </ul>

**NCT02684370** (Continued)

	<p>and baseline (randomisation)</p> <ul style="list-style-type: none"> <li>Involved BSA <math>\geq</math> 10%</li> <li>PASI score <math>\geq</math> 12</li> <li>sPGA score of <math>\geq</math> 3</li> <li>Must be candidates for systemic therapy or phototherapy for psoriasis treatment, as assessed by the investigator</li> <li>Must be a candidate for treatment with Stelara® (ustekinumab) according to local label</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>Non-plaque forms of psoriasis (including guttate, erythrodermic, or pustular) current drug-induced psoriasis (including an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium) active ongoing inflammatory diseases other than psoriasis and psoriatic arthritis that might confound trial evaluations according to investigator's judgment</li> <li>Previous exposure to BI 655066</li> <li>Previous exposure to ustekinumab (Stelara®)</li> </ul>
Interventions	<p><b>Intervention</b> ABBV-066 (SC, dosage not stated)</p> <p><b>Control interventions</b> Ustekinumab (dosage not stated) Placebo</p>
Outcomes	<p><b>At week 16</b></p> <p><b>Primary composite outcome</b></p> <ul style="list-style-type: none"> <li>PASI 90</li> <li>PGA 0/1</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>PASI 75 at weeks 16 and 52</li> <li>PASI 90 at week 52</li> <li>PGA 0/1 at week 52</li> </ul>
Starting date	February 2016
Contact information	Boehringer Ingelheim
Notes	Ongoing study BI 655066 will be included

**NCT02690701**

Trial name or title	Study to evaluate the effect of secukinumab compared to placebo on aortic vascular inflammation in subjects with moderate to severe plaque psoriasis (VIP-S)
Methods	RCT, placebo-controlled, double-blind study Date of study: February 2016 - Location: USA Phase 4

**NCT02690701** (Continued)

Participants	<p><b>Randomised:</b> 84 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Men and women <math>\geq</math> 18 years with moderate-severe plaque psoriasis</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Forms of psoriasis other than chronic plaque psoriasis</li> <li>• Previous exposure to IL-17A or IL-17 receptor targeting agents</li> <li>• Other active or ongoing disease that may interfere with evaluation of psoriasis or places the participant at unacceptable risk</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>Secukinumab 300 (300 mg once weekly at baseline, weeks 1, 2, 3 and 4 followed by monthly dosing starting at week 8 through week 48 inclusive)</p> <p><b>Control intervention</b></p> <p>Placebo</p>
Outcomes	<p><b>At week 12</b></p> <p><b>Primary outcome</b></p> <ul style="list-style-type: none"> <li>• Aortic vascular inflammation as measured by FDG-PET/CT</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> <li>• PASI 90</li> <li>• PASI 100</li> <li>• IGA 0/1</li> <li>• DLQI</li> </ul>
Starting date	<p>Study start date: February 2016</p> <p>Study completion date: March 2018</p>
Contact information	Novartis Pharmaceuticals, 1-888-669-6682
Notes	Ongoing study

**NCT02748863**

Trial name or title	Study of secukinumab with 2 mL pre-filled syringes (ALLURE)
Methods	<p>RCT, placebo-controlled, double-blind study</p> <p>Date of study: April 2016 -</p> <p>Location: worldwide</p> <p>Phase 4</p>
Participants	<p><b>Randomised:</b> 210 participants</p> <p><b>Inclusion criteria</b></p> <p>Subjects eligible for inclusion in this study must fulfil all of the following criteria:</p> <ul style="list-style-type: none"> <li>• Must be able to understand and communicate with the investigator and comply with the requirements of the study and must give a written, signed and dated informed consent before any study-related activity is performed. Where relevant, a legal representative will also sign the informed study consent according to local laws and regulations.</li> </ul>

	<ul style="list-style-type: none"> <li>• Men or women of <math>\geq 18</math> years of age at the time of screening</li> <li>• Chronic plaque-type psoriasis present for <math>\geq 6</math> months and diagnosed before randomization</li> <li>• Moderate-severe psoriasis as defined at randomization by: PASI score of <math>\geq 12</math>, IGA mod 2011 score of <math>\geq 3</math> (based on a scale of 0-4), and BSA affected by plaque-type psoriasis of <math>\geq 10\%</math></li> <li>• Candidate for systemic therapy. This is defined as having moderate-severe chronic plaque-type psoriasis that is inadequately controlled by topical treatment and/or phototherapy and/or previous systemic therapy</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Forms of psoriasis other than chronic plaque-type (e.g. pustular, erythrodermic and guttate psoriasis) at screening or randomization</li> <li>• Ongoing use of prohibited treatments. Washout periods detailed in the protocol have to be adhered to. Participants not willing to limit UV light exposure (e.g. sunbathing and/or the use of tanning devices) during the course of the study will be considered not eligible for this study since UV light exposure is prohibited. Note: administration of live vaccines 6 weeks prior to randomization or during the study period is also prohibited.</li> <li>• Previous exposure to secukinumab (AIN457) or any other biologic drug directly targeting IL-17 or the IL-17 receptor</li> <li>• Use of other investigational drugs at the time of enrolment, or within 5 half-lives of enrolment, or within 30 days until the expected pharmacodynamic effect has returned to baseline, whichever is longer; or longer if required by local regulations.</li> <li>• Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a woman after conception and until the termination of gestation, confirmed by a positive hCG laboratory test</li> <li>• History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system treated or untreated within the past 5 years, regardless of whether there is evidence of local recurrence or metastases (except for Bowen's disease, or basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 12 weeks; carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed)</li> <li>• History of hypersensitivity to any of study drug constituent</li> </ul>
Interventions	<p><b>Intervention</b> Secukinumab 2 mL form (secukinumab 300 mg/2 mL + 2 x 1 mL placebo SC. at randomization, weeks 1 , 3, 4, thereafter 4-weekly until week 48)</p> <p><b>Control interventions</b> Secukinumab 1 mL form (secukinumab 150 mg/1 mL x 2 + 2 mL placebo SC. at randomization, weeks 1 , 3, 4, thereafter 4-weekly until Week 48) Placebo (2 mL + 2 x 1 mL placebo SC at randomization, weeks 1, 3, and 4, thereafter 4-weekly until week 48)</p>
Outcomes	<p><b>At week 12</b></p> <p><b>Primary composite outcome</b></p> <ul style="list-style-type: none"> <li>• PASI 75 and IGA mod 2011 0 or 1 response</li> </ul> <p><b>Secondary outcome</b></p> <ul style="list-style-type: none"> <li>• PASI 90, 100 at weeks 12 and 52</li> <li>• PASI 75 at week 52</li> <li>• DLQI at weeks 12 and 52</li> </ul>
Starting date	Study start date: 8 March 2016 Study completion date: September 2018
Contact information	Novartis Pharmaceuticals, 1-888-669-6682, +41613241111



Notes	Ongoing study
<b>NCT02826603</b>	
Trial name or title	Study of secukinumab compared to ustekinumab in subjects with plaque psoriasis (CLARITY)
Methods	RCT, active-controlled, double-blind study Date of study: July 2016 - Location: worldwide Phase 3
Participants	<b>Randomised: 1100 participants</b> <b>Inclusion criteria</b> <ul style="list-style-type: none"> <li>• Must give a written, signed and dated informed consent</li> <li>• Chronic plaque-type psoriasis present for <math>\geq 6</math> months before randomisation</li> <li>• Moderate-severe plaque psoriasis as defined at randomisation by: PASI score of <math>\geq 12</math> and Body Surface Area (BSA) affected by plaque-type psoriasis <math>\geq 10\%</math> and IGA mod 2011 <math>\geq 3</math> (based on a scale of 0-4)</li> <li>• Candidate for systemic therapy, defined as having psoriasis inadequately controlled by: topical treatment (including topical corticosteroids) or phototherapy, or previous systemic therapy, or both</li> </ul> <b>Exclusion criteria</b> <ul style="list-style-type: none"> <li>• Forms of psoriasis other than plaque psoriasis</li> <li>• Drug-induced psoriasis</li> <li>• Ongoing use of prohibited treatments</li> <li>• Previous exposure to secukinumab or any other biologic drug directly targeting IL-17A or IL-17RA, or ustekinumab, or any therapies targeting IL-12 or IL-23</li> <li>• Use of any other investigational drugs within 5 half-lives of the investigational treatment before study drug initiation</li> <li>• Pregnant or nursing (lactating) women</li> </ul>
Interventions	<b>Intervention</b> Secukinumab 300 (300 mg, SC at randomization, weeks 1, 2 and 3 and thereafter 4-weekly till week 48) <b>Control intervention</b> Ustekinumab 45/90 (45 mg or 90 mg SC based on participant's weight (at randomization visit) to be administered at randomization, week 4, 16, 28 and 40)
Outcomes	<b>At week 12</b> <b>Primary composite outcome</b> <ul style="list-style-type: none"> <li>• IGA 0/1</li> <li>• PASI 90</li> </ul> <b>Secondary outcomes</b> <ul style="list-style-type: none"> <li>• PASI 75 at week 12 and 52</li> <li>• PASI 90 at week 52</li> <li>• AEs</li> </ul>
Starting date	Study start date: June 2016 Study completion date: August 2018
Contact information	Novartis Pharmaceuticals, 1-888-669-6682, +41613241111

Notes	Ongoing study
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## NCT02905331

Trial name or title	Efficacy and safety study of guselkumab in the treatment of participants with moderate to severe plaque-type psoriasis
Methods	RCT, placebo-controlled, double-blind study Date of study: September 2016 - Location: worldwide Phase 3
Participants	<p><b>Randomised: 78 participants</b></p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Women of childbearing potential must have a negative urine pregnancy test (beta-human chorionic gonadotropin) at screening and at week 0</li> <li>• Before randomisation, women must be either: <ul style="list-style-type: none"> <li>◦ not of childbearing potential: premenarchal; postmenopausal (&gt; 45 years of age with amenorrhea for <math>\geq 12</math> months or any age with amenorrhea for <math>\geq 6</math> months and a serum follicle-stimulating hormone level (FSH) &gt; 40 IU/L; permanently sterile (example, tubal occlusion, hysterectomy, bilateral salpingectomy); or otherwise be incapable of pregnancy</li> <li>◦ of childbearing potential and practicing a highly effective method of birth control, consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: example, established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device (IUD) or intrauterine system (IUS); barrier methods: condom or occlusive cap (diaphragm or cervical/vault caps) plus spermicidal foam/gel/film/cream/suppository (if available in their locale); male partner sterilization (the vasectomised partner should be the sole partner for that participant); true abstinence (when this is in line with the preferred and usual lifestyle of the participant)</li> </ul> </li> <li>• Agree not to receive a Bacillus Calmette Guerin (BCG) vaccination during the study, or within 12 months after the last administration of study drug</li> <li>• PASI <math>\geq 12</math> at screening and at baseline</li> <li>• Involved BSA <math>\geq 10\%</math> at screening and at baseline</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Unstable cardiovascular disease, defined as a recent clinical deterioration (e.g. unstable angina, rapid atrial fibrillation) in the last 3 months or a cardiac hospitalization within the last 3 months</li> <li>• History of lymphoproliferative disease, including lymphoma; a history of monoclonal gammopathy of undetermined significance (MGUS); or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy or splenomegaly</li> <li>• Transplanted organ (with exception of a corneal transplant &gt; 3 months before the first administration of study drug)</li> <li>• Non-plaque form of psoriasis (e.g. erythrodermic, guttate, or pustular)</li> <li>• Received any anti-tumour necrosis factor alpha (TNF-alpha) biologic therapy within 3 months before the first administration of study drug</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>Guselkumab (100 mg guselkumab administered as a 100 mg/mL solution in a single-use prefilled syringe (PFS) assembled in a self-dose device at weeks 0, 4, 12, 20, and 28)</p> <p><b>Control intervention</b></p>

**NCT02905331** (Continued)

	Placebo
Outcomes	<p><b>At week 16</b></p> <p><b>Primary outcome</b></p> <ul style="list-style-type: none"> <li>• IGA 0/1</li> <li>• PASI 90</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> <li>• PASI 100</li> </ul>
Starting date	<p>Study start date: 14 September 2016</p> <p>Study completion date: July 2018</p>
Contact information	Janssen Research & Development, LLC Clinical Trial
Notes	Ongoing study

**NCT02951533**

Trial name or title	A study to compare the efficacy of guselkumab to FAEs for the treatment of participants with moderate to severe plaque psoriasis (POLARIS)
Methods	<p>RCT, active-controlled, open-label study</p> <p>Date of study: November 2016 -</p> <p>Location: Germany</p> <p>Phase 3</p>
Participants	<p><b>Randomised:</b> 119 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Diagnosis of plaque-type psoriasis for <math>\geq 6</math> months before the first administration of study drug</li> <li>• PASI <math>\geq 10</math> or BSA <math>&gt;10</math> at screening and at baseline</li> <li>• DLQI <math>&gt;10</math> at screening and at baseline</li> <li>• Agree not to receive a live virus or live bacterial vaccination during the study, or within 3 months after the last administration of study drug; for information on Bacille Calmette-Guérin (BCG) vaccination, agree not to receive a BCG vaccination during the study, or within 12 months after the last administration of study drug</li> <li>• No dipstick detection of proteins or glucose in urine. If there are signs of proteins and/or glucose on urine test strip, the urine sample must be analysed centrally. Here, protein and glucose levels must not exceed trace levels, example, <math>\geq (+)</math>; one re-test (central urine analysis) is allowed</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• History or current signs or symptoms of severe, progressive, or uncontrolled liver or renal insufficiency, significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, haematologic, rheumatologic, psychiatric, or metabolic disturbances</li> <li>• Participants with non-plaque forms of psoriasis (for example, erythrodermic, guttate, or pustular) or with current drug-induced psoriasis (for example, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium)</li> <li>• Known allergies, hypersensitivity, or intolerance to guselkumab or its excipients</li> <li>• Pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study or within 12</li> </ul>

**NCT02951533** (Continued)

	<p>weeks after the last dose of study drug</p> <ul style="list-style-type: none"> <li>Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (for example, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments</li> </ul>
Interventions	<p><b>Intervention</b> Guselkumab (100 mg administered as 100 mg/mL solution SC by single-use prefilled syringe (PFS) at weeks 0, 4, 12 and 20)</p> <p><b>Control intervention</b> FAEs (to this aim, FAE doses will be slowly increased beginning with increasing doses of Fumaderm initial (containing 30 mg dimethylfumarate) over the first 3 weeks. Thereafter, participants will be switched to Fumaderm tablets (containing 120 mg dimethylfumarate) starting with 1 tablet per day. Fumaderm dose may be increased to a maximum of 3x2 tablets per day)</p>
Outcomes	<p><b>At week 24</b></p> <p><b>Primary outcome</b></p> <ul style="list-style-type: none"> <li>PASI 90</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>PASI 75</li> <li>DLQI</li> </ul>
Starting date	<p>Study start date: December 2016</p> <p>Study completion date: December 2017</p>
Contact information	Janssen-Cilag G.m.b.H, Germany Clinical Trial
Notes	Ongoing study

**NCT02982005**

Trial name or title	A Study of KHK4827 (brodalumab) in subjects with moderate to severe psoriasis in Korea
Methods	<p>RCT, placebo-controlled, double-blind study</p> <p>Date of study: December 2016 -</p> <p>Location: Korea</p> <p>Phase 3</p>
Participants	<p><b>Randomised:</b> 60 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>Stable moderate-severe plaque psoriasis for <math>\geq 6</math> months</li> <li>Involved BSA <math>\geq 10\%</math>, PASI <math>\geq 12</math>, and sPGA <math>\geq 3</math> at screening and at baseline</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>Diagnosed with erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, or a medication-induced psoriasis, or other skin conditions (e.g. eczema) at screening that would interfere with study evaluations</li> <li>Scheduled to undergo a surgical intervention during the study period</li> <li>Any active infection or history of infections as defined in the study protocol</li> <li>Known history of Crohn's disease</li> <li>Any other significant concurrent medical condition or laboratory abnormalities, as defined in the study</li> </ul>

	<p>protocol</p> <ul style="list-style-type: none"> <li>• Has not stopped using certain psoriasis therapies as defined in the study protocol</li> <li>• Previously used any anti-IL-17 biologic therapy</li> <li>• Pregnant or breastfeeding, or planning to become pregnant while enrolled in the study</li> <li>• Women of childbearing potential or fertile men who do not agree to use effective contraception from the day of providing consent through 12 weeks after the last dose of investigational product</li> <li>• Known history or evidence of suicidal ideation (severity of 4 or 5) or any suicidal behaviour based on an assessment with the Columbia-Suicide Severity Rating Scale (C-SSRS) at screening or at baseline</li> <li>• Severe depression based on a total score of <math>\geq 15</math> on the Patient Health Questionnaire-8 (PHQ-8) at screening or at baseline</li> <li>• Known history or evidence of a psychiatric disorder that, in the opinion of the investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion</li> <li>• Known history of alcohol and/or substance abuse within the last 12 months</li> </ul>
Interventions	<p><b>Intervention</b> KHK4827 (SC, dosage not stated)</p> <p><b>Control intervention</b> Placebo</p>
Outcomes	<p><b>At week 12</b></p> <p><b>Primary composite outcome</b></p> <ul style="list-style-type: none"> <li>• PPGA 0/1</li> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• PASI 90 at weeks 12 and 64</li> <li>• PASI 75 at week 64</li> <li>• NAPSI score at week 64</li> <li>• Psoriasis scalp severity index (PSSI) score at week 64</li> <li>• DLQI at week 64</li> <li>• AEs</li> </ul>
Starting date	<p>Study start date: 1 December 2016</p> <p>Study completion date: December 2018</p>
Contact information	Kyowa Hakko Kirin Korea Co., Ltd
Notes	Ongoing study

**RPCEC0000201**

Trial name or title	Randomized controlled double blind trial to study safety and efficacy of itolizumab (antiCD6) in moderate-to-severe psoriasis
Methods	<p>RCT, placebo-controlled, double-blind trial</p> <p>Date of study: February 2016 -</p> <p>Location: worldwide</p> <p>Phase 3</p>

<p>Participants</p>	<p><b>Randomised:</b> 144 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Able and willing to give written informed consent</li> <li>• Diagnosis of plaque psoriasis or vulgar</li> <li>• Time course of the disease in <math>\geq 1</math> year</li> <li>• Be tributary of systemic therapy</li> <li>• Willingness to complete a washout period prior to receiving the first dose of treatment (for participants in treatment only): interrupting or systemic therapy <math>\geq 4</math> weeks; interrupting or topical steroid treatment <math>\geq 2</math> weeks</li> <li>• Moderate-severe psoriasis activity, defined by: PASI <math>\geq 10</math>; BSA <math>\geq 10\%</math></li> <li>• Normal laboratory values, considering laboratory range of each institution: CBC: haemoglobin men <math>\geq 12.0</math> g/dL, women <math>\geq 11.0</math> g/dL, leukocytes <math>\geq 5 \times 10^9</math> L, platelets <math>\geq 150 \times 10^9</math>/L, neutrophils <math>\geq 1.8 \times 10^9</math>/L, lymphocytes <math>&gt; 1.2 \times 10^9</math> cells/mL; renal function: creatinine normal value; liver function: ALT, AST, GGT, up to 2.5 times the upper limit of normal</li> <li>• Aged 18-70 years (both included)</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Diagnosis of other types of psoriasis, psoriatic arthritis</li> <li>• Critical State of psoriasis (erythroderma)</li> <li>• Suffering from decompensated chronic diseases (heart disease, diabetes mellitus, hypertension, chronic kidney disease, bronchial asthma, etc) to the doctor involves an unreasonable risk to the participant's life</li> <li>• Malignancy</li> <li>• Immunocompromised patient</li> <li>• Received systemic retinoids or immunosuppressive therapy including steroids, within <math>&lt; 30</math> days prior to enrolment, except participants with psoriatic arthritis who are receiving stable treatment for <math>\geq 30</math> days prior to inclusion of oral steroids <math>\leq 10</math> mg/day</li> <li>• Significant acute or chronic systemic infection that to the doctor involves an unreasonable risk to the participant</li> <li>• Being treated with a monoclonal antibody, including itolizumab</li> <li>• Allergy to any component of the formulation</li> <li>• Pregnancy, postpartum and/or breastfeeding</li> <li>• Be reproductive age and refuse to use contraception (pills, IUDs, barrier methods, etc) during treatment and <math>\geq 8</math> weeks after the last dose of itolizumab</li> <li>• Suffering intellectual or sensory psychological dysfunction that may impede understanding and compliance with the requirements of the study at the discretion of the clinical investigator</li> </ul>
<p>Interventions</p>	<p><b>Intervention</b></p> <p>Itolizumab: itolizumab 1.6 mg/kg body weight bi-weekly administered IV by 12 weeks (weeks 0-8), and every 4 weeks by 24 weeks (Week 12-36)</p> <p><b>Control intervention</b></p> <p>Placebo 1.6 mg/kg body weight bi-weekly administered intravenously by 12 weeks (weeks 0-8), then 1.6 mg/kg body weight biweekly administered intravenously by 12 weeks (weeks 12-20), and every 4 weeks by 12 weeks (weeks 24-36)</p>
<p>Outcomes</p>	<p><b>At week 12</b></p> <p><b>Primary outcome</b></p> <ul style="list-style-type: none"> <li>• PASI 75</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• PASI 50, 75, 90, 100 at weeks 12, 24, 36, 48 and 60</li> <li>• IGA 0/1 at weeks 12, 24, 36, 48 and 60</li> </ul>

RPCEC00000201 (Continued)

	<ul style="list-style-type: none"> <li>• DLQI at weeks 12, 24, 36, 48 and 60</li> <li>• AEs</li> </ul>
Starting date	Start study date: 15/10/2015 Study completion date: not specified
Contact information	Dr Gray Lovio, <a href="mailto:ogray@infomed.sld.cu">ogray@infomed.sld.cu</a>
Notes	Ongoing study

TCTR20161028001

Trial name or title	A randomised, double-blind, placebo controlled, multicenter study of subcutaneous secukinumab, to demonstrate efficacy after twelve weeks of treatment and to assess safety, tolerability and long-term efficacy up to one year in subjects with moderate to severe chronic plaque-type psoriasis with or without psoriatic arthritis comorbidity
Methods	RCT, active/placebo-controlled, double-blind trial Date of study: February 2017 - Location: Thailand
Participants	<p><b>Randomised:</b> 40 participants</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Must be able to understand and communicate with the investigator and comply with the requirements of the study and must give a written, signed and dated informed consent before any study-related activity is performed. Where relevant, a legal representative will also sign the informed study consent according to local laws and regulations</li> <li>• Men and women <math>\geq</math> 18 years of age at the time of screening</li> <li>• Chronic plaque-type psoriasis present for <math>\geq</math> 6 months and diagnosed before baseline</li> <li>• Moderate-severe psoriasis</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Forms of psoriasis other than chronic plaque-type (e.g. pustular, erythrodermic and guttate psoriasis) at screening or baseline</li> <li>• Drug-induced psoriasis (i.e. new onset or current exacerbation from beta-blockers, calcium channel inhibitors or lithium) at baseline</li> <li>• Ongoing use of prohibited treatments. Washout periods detailed in the protocol have to be adhered to (Table 5-1). Participants not willing to limit UV light exposure (e.g. sunbathing and/or the use of tanning devices) during the course of the study will be considered not eligible for this study since UV light exposure is prohibited. Note: administration of live vaccines 6 weeks prior to Randomization or during the study period is also prohibited</li> <li>• Previous exposure to secukinumab (AIN457) or any other biologic drug directly targeting IL-17 or the IL-17 receptor</li> <li>• Use of other investigational drugs at the time of enrolment, or within 5 half-lives of enrolment, or within 30 days until the expected pharmacodynamic effect has returned to baseline, whichever is longer; or longer if required by local regulations</li> </ul>
Interventions	<p><b>Intervention</b></p> <p>A. Secukinumab 300 mg SC (administration not specified)</p> <p><b>Control intervention</b></p>

	B. Secukinumab 150 mg SC (administration not specified) C. Placebo
Outcomes	<p><b>At week 12</b></p> <p><b>Primary outcome (composite)</b></p> <ul style="list-style-type: none"> <li>● IGA 0/1</li> <li>● PASI 75</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>● ACR 20/50/70 (timeframe 12 weeks and 52 weeks)</li> <li>● PASI 50/75/90/100 (timeframe 12 weeks and 52 weeks PASI score)</li> <li>● Safety and tolerability</li> </ul>
Starting date	28 February 2017
Contact information	Kerstin Letzelter, kerstin.letzelter@novartis.com
Notes	Ongoing study

**BMI:** body mass index; **BSA:** Body Surface Area; **ECG:** electrocardiogram; **FAEs:** fumaric acid esters; **IV:** intravenous; **NAPSI:** Nail Psoriasis Severity Index; **PASI:** Psoriasis Area and Severity Index; **PGA:** Physician's Global Assessment; **QoL:** quality of life; **RCT:** randomised controlled trial; **SC:** subcutaneous; **sPGA:** static physician global assessment; **TB:** tuberculosis; **UVA/B:** ultraviolet A/B



## DATA AND ANALYSES

### Comparison 1. Primary outcome - PASI 90

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Conventional systemic agents versus placebo	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Methotrexate	2	282	Risk Ratio (M-H, Random, 95% CI)	2.60 [0.26, 25.90]
1.2 Fumaric acid esters	1	704	Risk Ratio (M-H, Random, 95% CI)	4.47 [2.01, 9.95]
2 Conventional systemic 1 versus conventional systemic 2	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Ciclosporin versus methotrexate	2	172	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.47, 2.98]
2.2 Methotrexate versus fumaric acid esters	1	60	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.19, 20.90]
3 Anti-TNF alpha versus placebo	21		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Etanercept versus placebo	12	4954	Risk Ratio (M-H, Random, 95% CI)	11.17 [7.66, 16.28]
3.2 Adalimumab versus placebo	8	3199	Risk Ratio (M-H, Random, 95% CI)	14.86 [8.93, 24.73]
3.3 Certolizumab versus placebo	1	176	Risk Ratio (M-H, Random, 95% CI)	24.58 [3.48, 173.49]
4 Ustekinumab versus placebo	7	3832	Risk Ratio (M-H, Random, 95% CI)	22.59 [14.74, 34.64]
5 Anti-IL17 versus placebo	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Secukinumab versus placebo	7	2707	Risk Ratio (M-H, Random, 95% CI)	26.52 [14.91, 47.17]
5.2 Ixekizumab versus placebo	4	3268	Risk Ratio (M-H, Random, 95% CI)	53.85 [15.34, 189.07]
5.3 Brodalumab versus placebo	5	4109	Risk Ratio (M-H, Random, 95% CI)	26.33 [16.77, 41.33]
6 Anti-IL23 versus placebo	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Guselkumab versus placebo	3	1502	Risk Ratio (M-H, Random, 95% CI)	24.87 [14.20, 43.55]
6.2 Tildrakizumab versus placebo	1	355	Risk Ratio (M-H, Random, 95% CI)	15.63 [2.24, 109.29]
7 Other biologics	1	225	Risk Ratio (M-H, Random, 95% CI)	12.26 [0.76, 197.54]
7.1 Itolizumab versus placebo	1	225	Risk Ratio (M-H, Random, 95% CI)	12.26 [0.76, 197.54]
8 Biologic versus conventional systemic treatments	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Etanercept versus acitretin	1	60	Risk Ratio (M-H, Random, 95% CI)	11.00 [0.64, 190.53]
8.2 Infliximab versus methotrexate	1	868	Risk Ratio (M-H, Random, 95% CI)	2.86 [2.15, 3.80]
8.3 Adalimumab versus methotrexate	1	218	Risk Ratio (M-H, Random, 95% CI)	3.73 [2.25, 6.19]
8.4 Alefacept versus methotrexate	1	212	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.42, 2.98]
9 Biologic 1 versus biologic 2	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

9.1 Ustekinumab versus Etanercept	1	903	Risk Ratio (M-H, Random, 95% CI)	1.80 [1.45, 2.24]
9.2 Secukinumab versus etanercept	1	980	Risk Ratio (M-H, Random, 95% CI)	2.32 [1.85, 2.92]
9.3 Ixekizumab versus etanercept	2	2209	Risk Ratio (M-H, Random, 95% CI)	2.98 [2.24, 3.98]
9.4 Secukinumab versus ustekinumab	1	676	Risk Ratio (M-H, Random, 95% CI)	1.38 [1.23, 1.53]
9.5 Brodalumab versus ustekinumab	2	3088	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.16, 1.39]
9.6 Guselkumab versus adalimumab	3	1658	Risk Ratio (M-H, Random, 95% CI)	1.41 [1.25, 1.60]
<b>10 Small molecules versus placebo</b>	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Apremilast versus placebo	4	1775	Risk Ratio (M-H, Random, 95% CI)	6.78 [3.03, 15.17]
10.2 Tofacitinib versus placebo	4	2826	Risk Ratio (M-H, Random, 95% CI)	6.80 [3.86, 11.99]
10.3 Ponesimod versus placebo	1	326	Risk Ratio (M-H, Random, 95% CI)	6.60 [1.65, 26.41]
<b>11 Biologic versus small molecules</b>	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Etanercept versus Tofacitinib	1	998	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.93, 1.38]
11.2 Etanercept versus apremilast	1	166	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.72, 2.78]

## Comparison 2. Primary outcome - serious adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<b>1 Conventional systemic agents versus placebo</b>	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Methotrexate	2	283	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.03, 0.88]
1.2 Fumaric acid esters	1	704	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.31, 2.21]
<b>2 Anti-TNF alpha versus placebo</b>	20		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Etanercept versus placebo	11	3783	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.61, 1.83]
2.2 Adalimumab versus placebo	8	3199	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.60, 1.73]
2.3 Certolizumab versus placebo	1	176	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.10, 2.36]
<b>3 Ustekinumab versus placebo</b>	8	4154	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.50, 1.58]
<b>4 Anti-IL17 versus placebo</b>	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Secukinumab versus placebo	7	2707	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.79, 3.53]
4.2 Ixekizumab versus placebo	4	3268	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.65, 2.32]
4.3 Brodalumab versus placebo	5	4109	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.52, 1.61]
<b>5 Anti-IL23 versus placebo</b>	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

5.1 Guselkumab versus placebo	3	1502	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.51, 2.85]
5.2 Tildrakizumab versus placebo	1	355	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.07, 24.94]
6 Other biologics	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Alefacept versus placebo	2	736	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.34, 1.62]
7 Biologic versus conventional systemic treatments	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Etanercept versus acitretin	1	60	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 Infliximab versus methotrexate	1	868	Risk Ratio (M-H, Random, 95% CI)	2.41 [1.04, 5.59]
7.3 Adalimumab versus methotrexate	1	218	Risk Ratio (M-H, Random, 95% CI)	2.04 [0.19, 22.14]
8 Biologic 1 versus biologic 2	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Ustekinumab versus etanercept	1	903	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.38, 4.11]
8.2 Secukinumab versus etanercept	1	980	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.41, 2.82]
8.3 Ixekizumab versus etanercept	2	2209	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.55, 2.06]
8.4 Secukinumab versus ustekinumab	1	676	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.42, 2.39]
8.5 Brodalumab versus ustekinumab	2	3088	Risk Ratio (M-H, Random, 95% CI)	1.51 [0.64, 3.56]
8.6 Guselkumab versus adalimumab	3	1658	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.44, 1.82]
9 Small molecules versus placebo	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Apremilast versus placebo	5	2036	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.41, 1.49]
9.2 Tofacitinib versus placebo	5	2838	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.53, 2.06]
9.3 Ponesimod versus placebo	1	326	Risk Ratio (M-H, Random, 95% CI)	2.59 [0.34, 19.85]
10 Biologic versus small molecules	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Etanercept versus tofacitinib	1	998	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.46, 2.89]
10.2 Etanercept versus apremilast	1	166	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.04, 3.14]

### Comparison 3. Secondary outcome - PASI 75

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Conventional systemic agents versus placebo	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Methotrexate	2	283	Risk Ratio (M-H, Random, 95% CI)	2.36 [1.19, 4.68]
1.2 Fumaric acid esters	1	704	Risk Ratio (M-H, Random, 95% CI)	2.56 [1.68, 3.89]
2 Conventional systemic 1 versus conventional systemic 2	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Ciclosporin versus methotrexate	2	172	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.84, 2.23]

2.2 Methotrexate versus fumaric acid esters	1	60	Risk Ratio (M-H, Random, 95% CI)	1.2 [0.41, 3.51]
<b>3 Anti-TNF alpha versus placebo</b>	22		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Etanercept versus placebo	13	5066	Risk Ratio (M-H, Random, 95% CI)	8.55 [6.94, 10.52]
3.2 Adalimumab versus placebo	8	3199	Risk Ratio (M-H, Random, 95% CI)	9.08 [6.52, 12.65]
3.3 Certolizumab versus placebo	1	176	Risk Ratio (M-H, Random, 95% CI)	11.31 [4.37, 29.24]
<b>4 Ustekinumab versus placebo</b>	8	4154	Risk Ratio (M-H, Random, 95% CI)	12.41 [8.69, 17.71]
<b>5 Anti-IL17 versus placebo</b>	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Secukinumab versus placebo	7	2707	Risk Ratio (M-H, Random, 95% CI)	15.70 [11.27, 21.87]
5.2 Ixekizumab versus placebo	4	3268	Risk Ratio (M-H, Random, 95% CI)	17.44 [10.45, 29.10]
5.3 Brodalumab versus placebo	5	4109	Risk Ratio (M-H, Random, 95% CI)	12.80 [8.46, 19.36]
<b>6 Anti-IL23 versus placebo</b>	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Guselkumab versus Placebo	3	1502	Risk Ratio (M-H, Random, 95% CI)	12.28 [8.79, 17.17]
6.2 Tildrakizumab versus placebo	1	355	Risk Ratio (M-H, Random, 95% CI)	14.51 [3.73, 56.45]
<b>7 Other biologics</b>	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Alefacept versus placebo	2	736	Risk Ratio (M-H, Random, 95% CI)	2.95 [1.76, 4.94]
7.2 Itolizumab versus placebo	1	225	Risk Ratio (M-H, Random, 95% CI)	13.23 [1.88, 92.93]
<b>8 Biologic versus conventional systemic treatments</b>	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Etanercept versus acitretin	1	60	Risk Ratio (M-H, Random, 95% CI)	2.13 [1.09, 4.16]
8.2 Alefacept versus methotrexate	1	212	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.46, 1.21]
8.3 Infliximab versus methotrexate	1	868	Risk Ratio (M-H, Random, 95% CI)	1.86 [1.58, 2.19]
8.4 Adalimumab versus methotrexate	1	218	Risk Ratio (M-H, Random, 95% CI)	2.25 [1.72, 2.94]
<b>9 Biologic 1 versus biologic 2</b>	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Ustekinumab versus etanercept	1	903	Risk Ratio (M-H, Random, 95% CI)	1.26 [1.13, 1.40]
9.2 Secukinumab versus etanercept	1	980	Risk Ratio (M-H, Random, 95% CI)	1.64 [1.44, 1.88]
9.3 Ixekizumab versus etanercept	2	2209	Risk Ratio (M-H, Random, 95% CI)	1.79 [1.43, 2.24]
9.4 Secukinumab versus ustekinumab	1	676	Risk Ratio (M-H, Random, 95% CI)	1.13 [1.06, 1.20]
9.5 Brodalumab versus ustekinumab	2	3088	Risk Ratio (M-H, Random, 95% CI)	1.10 [1.04, 1.17]
9.6 Guselkumab versus adalimumab	3	1658	Risk Ratio (M-H, Random, 95% CI)	1.21 [1.13, 1.30]
<b>10 Small molecules versus placebo</b>	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Apremilast versus placebo	5	2036	Risk Ratio (M-H, Random, 95% CI)	3.88 [2.42, 6.22]
10.2 Tofacitinib versus placebo	5	2838	Risk Ratio (M-H, Random, 95% CI)	6.41 [3.84, 10.71]

10.3 Ponesimod versus placebo	1	326	Risk Ratio (M-H, Random, 95% CI)	3.51 [1.88, 6.53]
<b>11 Biologic versus small molecules</b>	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Etanercept versus Tofacitinib	1	998	Risk Ratio (M-H, Random, 95% CI)	1.14 [1.02, 1.28]
11.2 Etanercept versus apremilast	1	166	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.86, 1.71]

#### Comparison 4. Secondary outcome - PGA 0/1

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<b>1 Conventional systemic agents versus placebo</b>	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Methotrexate	2	283	Risk Ratio (M-H, Random, 95% CI)	2.94 [1.47, 5.89]
1.2 Fumaric acid esters	1	704	Risk Ratio (M-H, Random, 95% CI)	2.73 [1.72, 4.32]
<b>2 Conventional systemic 1 versus conventional systemic 2</b>	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Ciclosporin versus methotrexate	1	88	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.47, 1.46]
<b>3 Anti-TNF alpha versus placebo</b>	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Etanercept versus placebo	11	4334	Risk Ratio (M-H, Random, 95% CI)	7.77 [5.98, 10.10]
3.2 Adalimumab versus placebo	7	3051	Risk Ratio (M-H, Random, 95% CI)	8.38 [6.28, 11.18]
3.3 Certolizumab versus placebo	1	176	Risk Ratio (M-H, Random, 95% CI)	35.88 [5.11, 251.73]
<b>4 Ustekinumab versus placebo</b>	8	4154	Risk Ratio (M-H, Random, 95% CI)	11.33 [7.38, 17.39]
<b>5 Anti-IL17 versus placebo</b>	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Secukinumab versus placebo	6	2607	Risk Ratio (M-H, Random, 95% CI)	17.16 [7.48, 39.36]
5.2 Ixekizumab versus placebo	4	3268	Risk Ratio (M-H, Random, 95% CI)	17.46 [9.87, 30.90]
5.3 Brodalumab versus placebo	5	4109	Risk Ratio (M-H, Random, 95% CI)	18.78 [13.29, 26.55]
<b>6 Anti-IL23 versus placebo</b>	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Guselkumab versus placebo	3	1502	Risk Ratio (M-H, Random, 95% CI)	10.59 [7.73, 14.51]
6.2 Tildrakizumab versus placebo	1	355	Risk Ratio (M-H, Random, 95% CI)	27.54 [3.95, 191.78]
<b>7 Other biologics</b>	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Alefacept versus placebo	1	507	Risk Ratio (M-H, Random, 95% CI)	2.54 [1.22, 5.29]
7.2 Itolizumab versus placebo	1	225	Risk Ratio (M-H, Random, 95% CI)	3.78 [0.94, 15.17]
<b>8 Biologic versus conventional systemic treatments</b>	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Alefacept versus methotrexate	1	212	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.37, 1.29]
8.2 Infliximab versus methotrexate	1	868	Risk Ratio (M-H, Random, 95% CI)	1.99 [1.67, 2.37]

8.3 Adalimumab versus methotrexate	1	218	Risk Ratio (M-H, Random, 95% CI)	2.44 [1.79, 3.32]
<b>9 Biologic 1 versus biologic 2</b>	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Ustekinumab versus etanercept	1	903	Risk Ratio (M-H, Random, 95% CI)	1.40 [1.24, 1.58]
9.2 Secukinumab versus etanercept	1	980	Risk Ratio (M-H, Random, 95% CI)	2.09 [1.73, 2.53]
9.3 Ixekizumab versus etanercept	2	2209	Risk Ratio (M-H, Random, 95% CI)	2.01 [1.74, 2.31]
9.4 Secukinumab versus ustekinumab	1	676	Risk Ratio (M-H, Random, 95% CI)	1.23 [1.13, 1.35]
9.5 Brodalumab versus ustekinumab	2	3088	Risk Ratio (M-H, Random, 95% CI)	1.17 [1.07, 1.27]
9.6 Guselkumab versus adalimumab	3	1658	Risk Ratio (M-H, Random, 95% CI)	1.24 [1.17, 1.32]
<b>10 Small molecules versus placebo</b>	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Apremilast versus placebo	4	1776	Risk Ratio (M-H, Random, 95% CI)	3.88 [2.04, 7.38]
10.2 Tofacitinib versus placebo	5	2838	Risk Ratio (M-H, Random, 95% CI)	4.48 [3.51, 5.71]
10.3 Ponesimod versus placebo	1	326	Risk Ratio (M-H, Random, 95% CI)	6.73 [2.19, 20.64]
<b>11 Biologic versus small molecules</b>	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Etanercept versus tofacitinib	1	998	Risk Ratio (M-H, Random, 95% CI)	1.15 [1.04, 1.27]
11.2 Etanercept versus apremilast	1	166	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.78, 2.27]

### Comparison 5. Secondary outcome - quality of life

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<b>1 Conventional systemic agents versus placebo</b>	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Methotrexate	2	283	Std. Mean Difference (IV, Random, 95% CI)	-0.67 [-1.40, 0.06]
<b>2 Anti-TNF alpha versus placebo</b>	14		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Etanercept versus placebo	7	2779	Std. Mean Difference (IV, Random, 95% CI)	-1.10 [-1.37, -0.83]
2.2 Adalimumab versus placebo	7	2774	Std. Mean Difference (IV, Random, 95% CI)	-1.02 [-1.16, -0.88]
<b>3 Ustekinumab versus placebo</b>	6	2917	Std. Mean Difference (IV, Random, 95% CI)	-1.21 [-1.39, -1.03]
<b>4 Anti-IL17 versus placebo</b>	5		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Ixekizumab versus placebo	3	3126	Std. Mean Difference (IV, Random, 95% CI)	-1.76 [-2.09, -1.43]
4.2 Brodalumab versus placebo	2	349	Std. Mean Difference (IV, Random, 95% CI)	-0.96 [-1.44, -0.47]
<b>5 Anti-IL23 versus placebo</b>	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Guselkumab versus placebo	2	1252	Std. Mean Difference (IV, Random, 95% CI)	-1.39 [-1.63, -1.14]

5.2 Tildrakizumab versus placebo	1	355	Std. Mean Difference (IV, Random, 95% CI)	-1.23 [-1.55, -0.91]
<b>6 Other biologics</b>	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Alefacept versus placebo	1	229	Std. Mean Difference (IV, Random, 95% CI)	-0.32 [-0.62, -0.02]
6.2 Itolizumab versus placebo	1	225	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-0.68, -0.01]
<b>7 Biologic versus conventional systemic treatments</b>	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Alefacept versus methotrexate	1	212	Mean Difference (IV, Fixed, 95% CI)	1.31 [-0.28, 2.90]
7.2 Adalimumab versus methotrexate	1	218	Mean Difference (IV, Fixed, 95% CI)	-3.40 [-5.75, -1.05]
<b>8 Biologic 1 versus biologic 2</b>	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Ixekizumab versus etanercept	2	2209	Mean Difference (IV, Fixed, 95% CI)	-1.99 [-2.39, -1.59]
8.2 Guselkumab versus adalimumab	2	1407	Mean Difference (IV, Fixed, 95% CI)	-1.73 [-2.50, -0.97]
<b>9 Small molecules versus placebo</b>	7		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 Apremilast versus placebo	3	1609	Std. Mean Difference (IV, Random, 95% CI)	-0.62 [-0.77, -0.47]
9.2 Tofacitinib versus placebo	3	2629	Std. Mean Difference (IV, Random, 95% CI)	-1.09 [-1.28, -0.89]
9.3 Ponesimod versus placebo	1	326	Std. Mean Difference (IV, Random, 95% CI)	-0.58 [-0.86, -0.31]
<b>10 Biologic versus small molecules</b>	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
10.1 Etanercept versus Tofacitinib	1	998	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.19, 0.07]

### Comparison 6. Secondary outcome - adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<b>1 Conventional systemic agents versus placebo</b>	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Methotrexate	2	283	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.81, 1.10]
1.2 Fumaric acid esters	1	704	Risk Ratio (M-H, Random, 95% CI)	1.40 [1.22, 1.62]
<b>2 Conventional systemic 1 versus conventional systemic 2</b>	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Ciclosporin versus methotrexate	2	172	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.90, 1.34]
2.2 Methotrexate versus fumaric acid esters	1	60	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.91, 1.39]
<b>3 Anti-TNF alpha versus placebo</b>	17		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Etanercept versus placebo	9	3529	Risk Ratio (M-H, Random, 95% CI)	1.12 [1.05, 1.20]
3.2 Adalimumab versus placebo	7	3051	Risk Ratio (M-H, Random, 95% CI)	1.06 [1.00, 1.13]
3.3 Certolizumab versus placebo	1	176	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.81, 1.22]
<b>4 Ustekinumab versus placebo</b>	8	4154	Risk Ratio (M-H, Random, 95% CI)	1.06 [1.00, 1.13]
<b>5 Anti-IL17 versus placebo</b>	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Secukinumab versus placebo	7	2707	Risk Ratio (M-H, Random, 95% CI)	1.15 [1.02, 1.29]

5.2 Ixekizumab versus placebo	4	3268	Risk Ratio (M-H, Random, 95% CI)	1.24 [1.07, 1.45]
5.3 Brodalumab versus placebo	5	4109	Risk Ratio (M-H, Random, 95% CI)	1.15 [1.00, 1.32]
<b>6 Anti-IL23 versus placebo</b>	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Guselkumab versus placebo	3	1502	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.92, 1.16]
6.2 Tildrakizumab versus placebo	1	355	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.76, 1.18]
<b>7 Biologic versus conventional systemic treatments</b>	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Infliximab versus methotrexate	1	868	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.97, 1.20]
7.2 Adalimumab versus methotrexate	1	218	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.78, 1.05]
<b>8 Biologic 1 versus biologic 2</b>	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Ustekinumab versus etanercept	1	903	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.89, 1.06]
8.2 Secukinumab versus etanercept	1	980	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.89, 1.12]
8.3 Ixekizumab versus etanercept	2	2209	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.97, 1.15]
8.4 Secukinumab versus ustekinumab	1	676	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.98, 1.25]
8.5 Brodalumab versus ustekinumab	2	3088	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.93, 1.09]
8.6 Guselkumab versus adalimumab	3	1658	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.88, 1.07]
<b>9 Small molecules versus placebo</b>	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Apremilast versus placebo	5	2036	Risk Ratio (M-H, Random, 95% CI)	1.22 [1.07, 1.38]
9.2 Tofacitinib versus placebo	4	2641	Risk Ratio (M-H, Random, 95% CI)	1.14 [1.03, 1.25]
9.3 Ponesimod versus placebo	1	326	Risk Ratio (M-H, Random, 95% CI)	1.31 [1.02, 1.68]
<b>10 Biologic versus small molecules</b>	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Etanercept versus tofacitinib	1	998	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.89, 1.12]
10.2 Etanercept versus apremilast	1	166	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.03, 1.69]

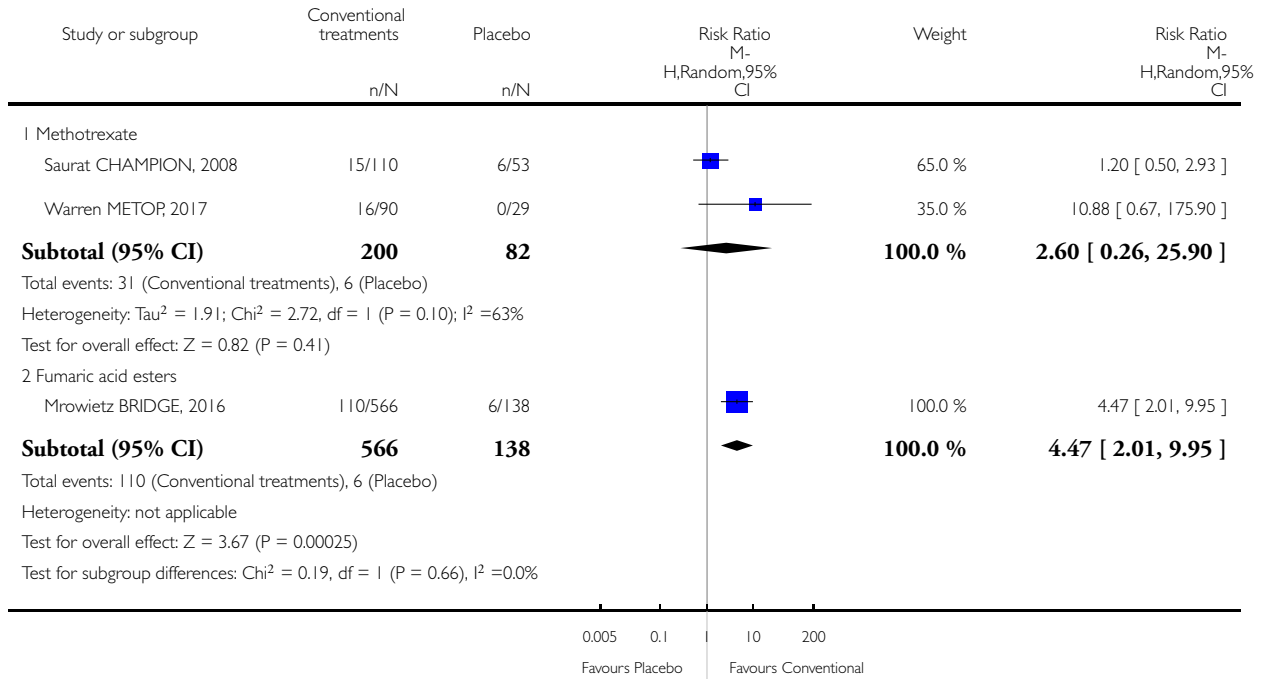


## Analysis I.1. Comparison I Primary outcome - PASI 90, Outcome I Conventional systemic agents versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: I Primary outcome - PASI 90

Outcome: I Conventional systemic agents versus placebo

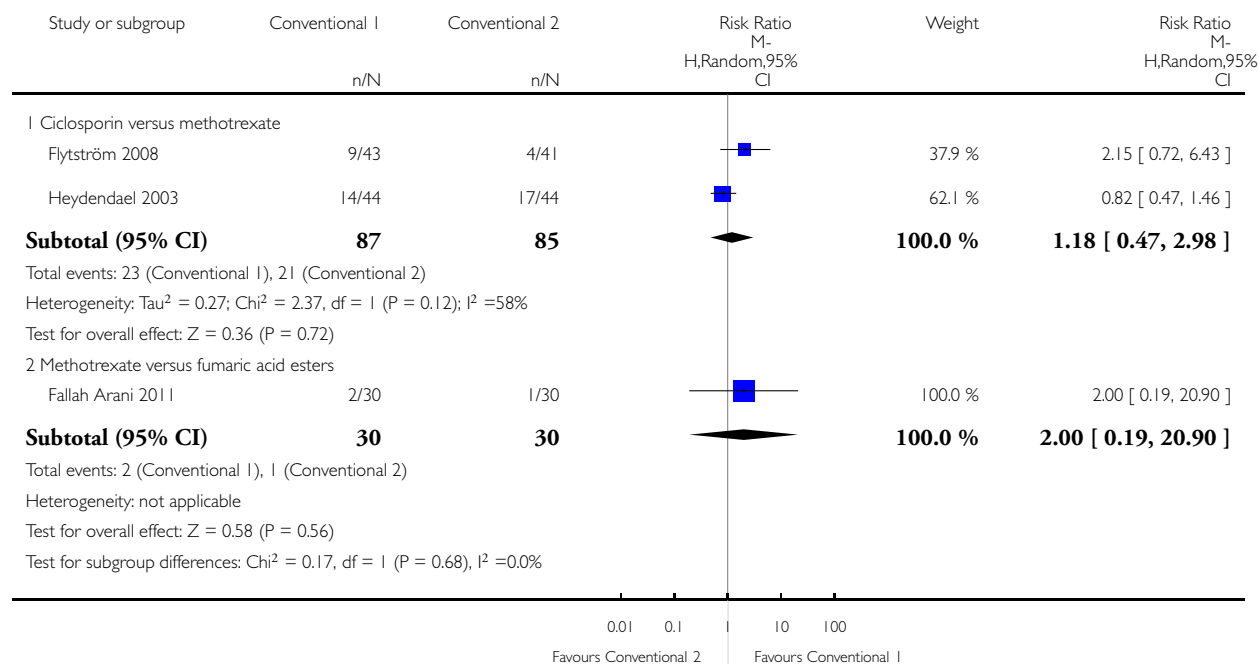


## Analysis 1.2. Comparison 1 Primary outcome - PASI 90, Outcome 2 Conventional systemic 1 versus conventional systemic 2.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 1 Primary outcome - PASI 90

Outcome: 2 Conventional systemic 1 versus conventional systemic 2

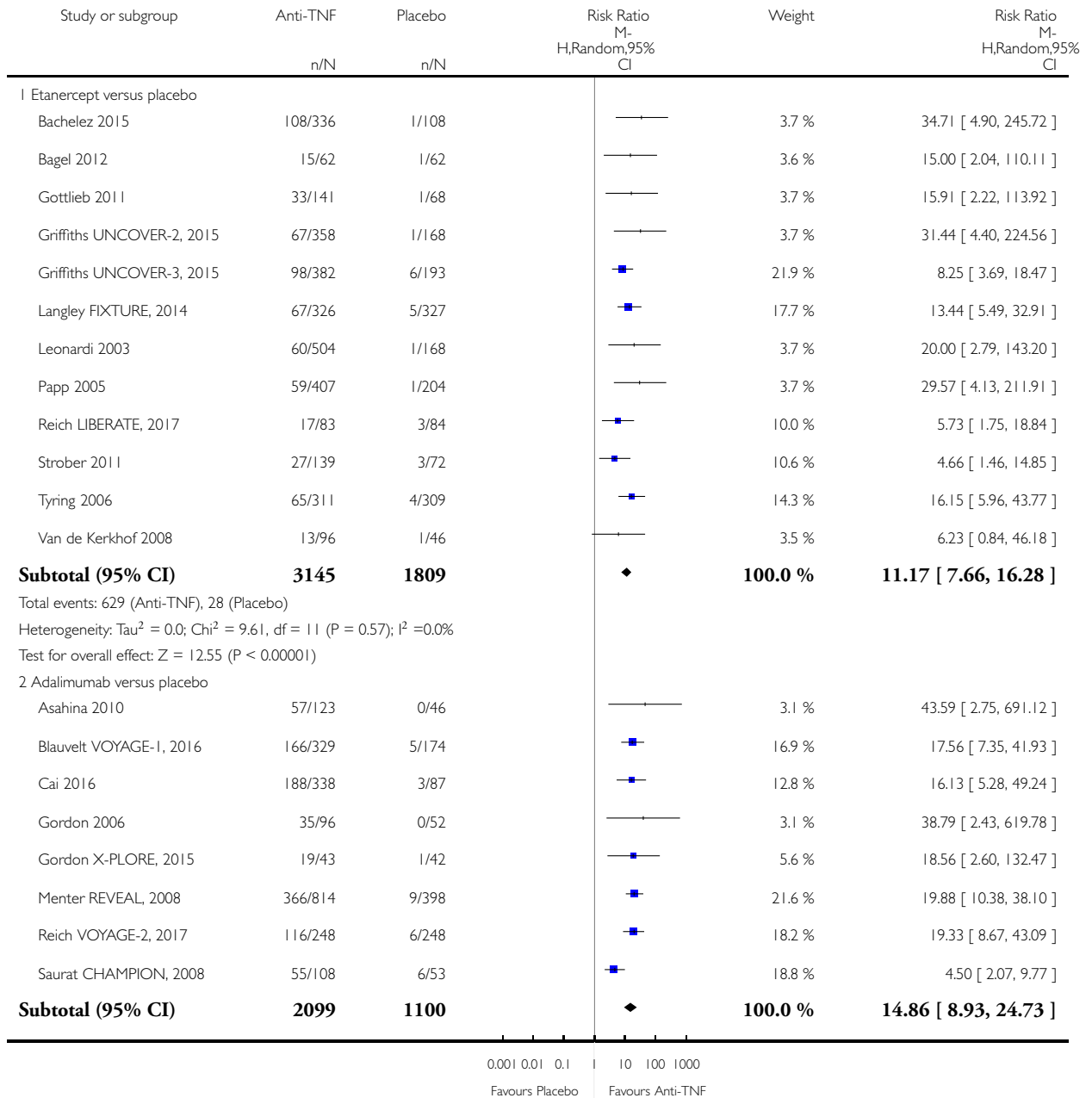


### Analysis I.3. Comparison I Primary outcome - PASI 90, Outcome 3 Anti-TNF alpha versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

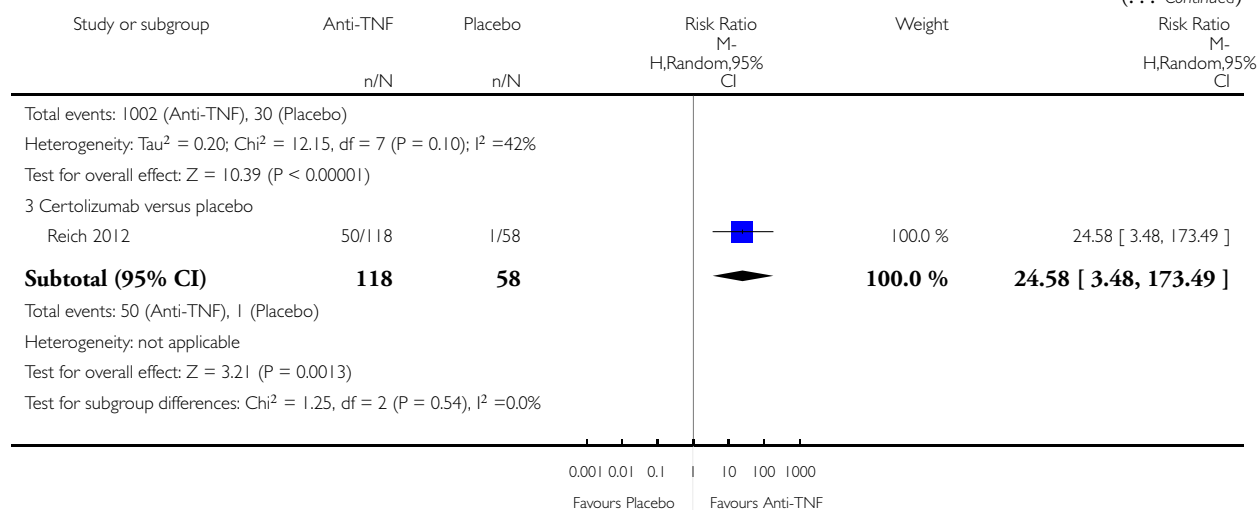
Comparison: I Primary outcome - PASI 90

Outcome: 3 Anti-TNF alpha versus placebo



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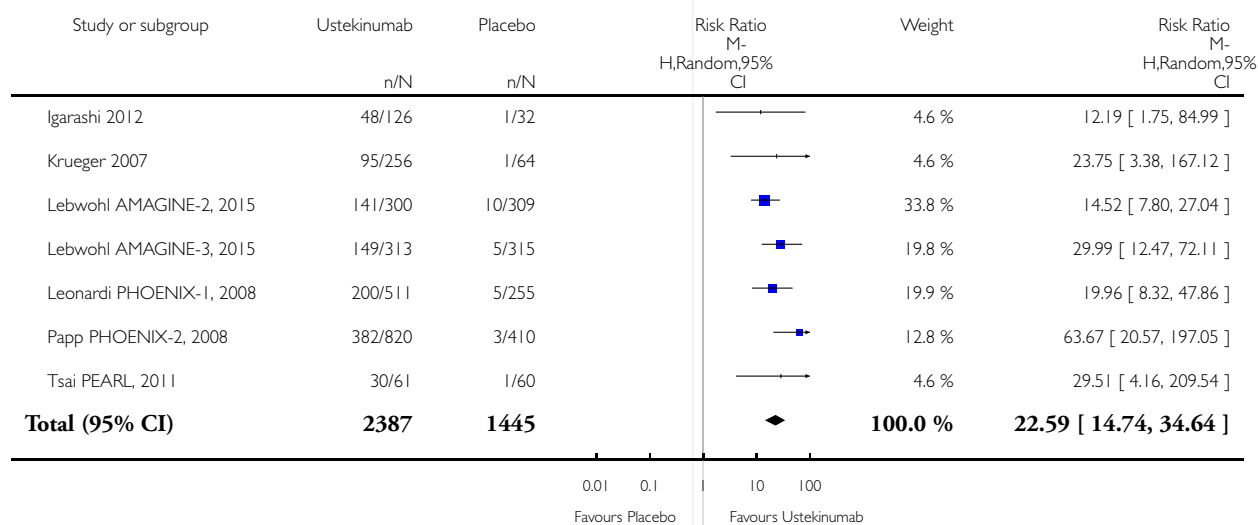


#### Analysis I.4. Comparison I Primary outcome - PASI 90, Outcome 4 Ustekinumab versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: I Primary outcome - PASI 90

Outcome: 4 Ustekinumab versus placebo



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Study or subgroup	Ustekinumab	Placebo	Risk Ratio M- H,Random,95% CI	Weight	Risk Ratio M- H,Random,95% CI
	n/N	n/N			

Total events: 1045 (Ustekinumab), 26 (Placebo)  
 Heterogeneity: Tau<sup>2</sup> = 0.04; Chi<sup>2</sup> = 6.79, df = 6 (P = 0.34); I<sup>2</sup> = 12%  
 Test for overall effect: Z = 14.30 (P < 0.00001)  
 Test for subgroup differences: Not applicable

0.01 0.1 10 100  
 Favours Placebo Favours Ustekinumab

### Analysis 1.5. Comparison 1 Primary outcome - PASI 90, Outcome 5 Anti-IL17 versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 1 Primary outcome - PASI 90

Outcome: 5 Anti-IL17 versus placebo

Study or subgroup	Anti IL17	Placebo	Risk Ratio M- H,Random,95% CI	Weight	Risk Ratio M- H,Random,95% CI
	n/N	n/N			

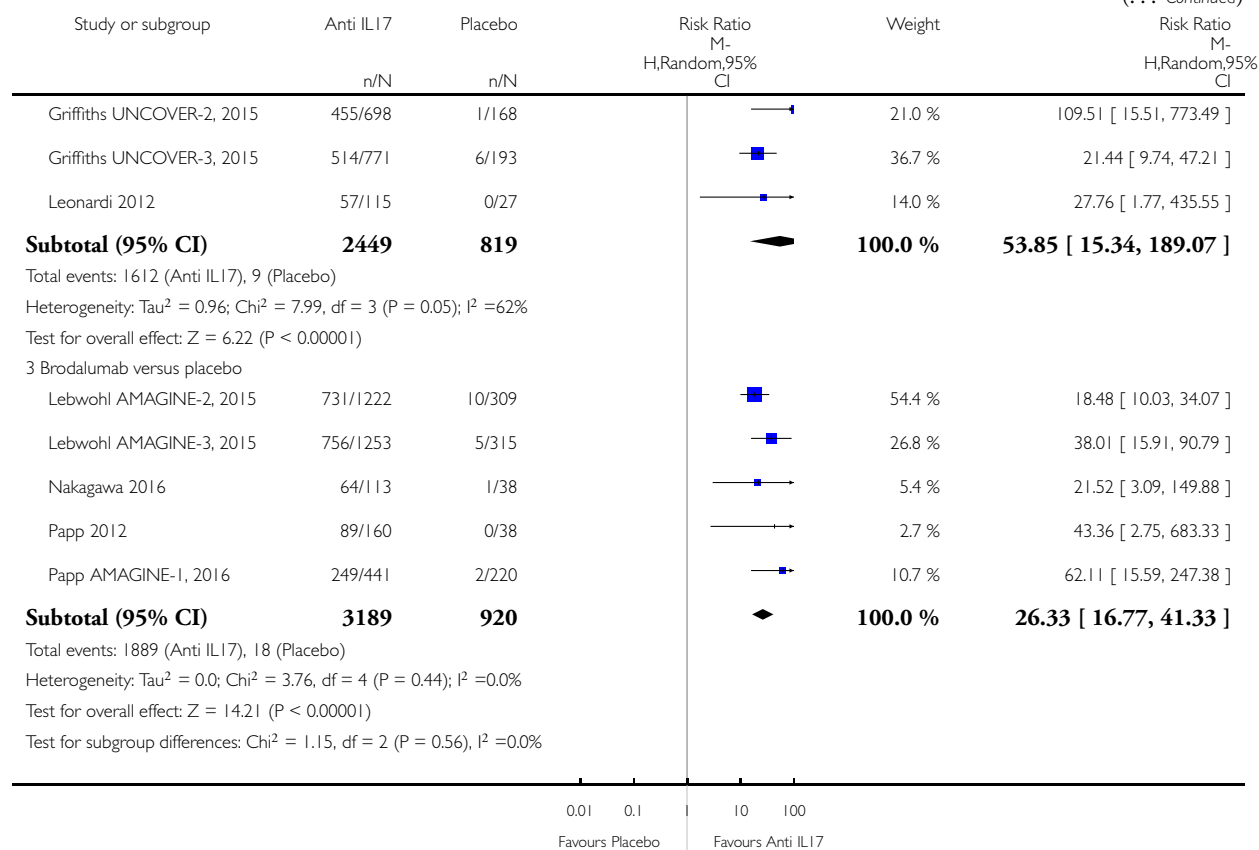
  

1 Secukinumab versus placebo					
Blauvelt FEATURE, 2015	63/118	0/59		4.3 %	64.03 [ 4.03, 1017.14 ]
Langley ERASURE, 2014	240/490	3/248		26.0 %	40.49 [ 13.10, 125.14 ]
Langley FIXTURE, 2014	312/654	5/327		43.5 %	31.20 [ 13.03, 74.73 ]
Papp 2013a	20/103	1/22		8.7 %	4.27 [ 0.60, 30.17 ]
Paul JUNCTURE, 2015	57/121	0/61		4.3 %	58.44 [ 3.67, 929.87 ]
Reich 2015	42/90	0/10		4.5 %	10.27 [ 0.68, 155.50 ]
Rich 2013	73/337	1/67		8.7 %	14.51 [ 2.05, 102.61 ]
<b>Subtotal (95% CI)</b>	<b>1913</b>	<b>794</b>		<b>100.0 %</b>	<b>26.52 [ 14.91, 47.17 ]</b>
Total events: 807 (Anti IL17), 10 (Placebo) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> = 5.77, df = 6 (P = 0.45); I <sup>2</sup> = 0.0% Test for overall effect: Z = 11.16 (P < 0.00001)					
2 Ixekizumab versus placebo					
Gordon UNCOVER-1, 2016	586/865	2/431		28.2 %	145.99 [ 36.60, 582.31 ]

0.01 0.1 10 100  
 Favours Placebo Favours Anti IL17

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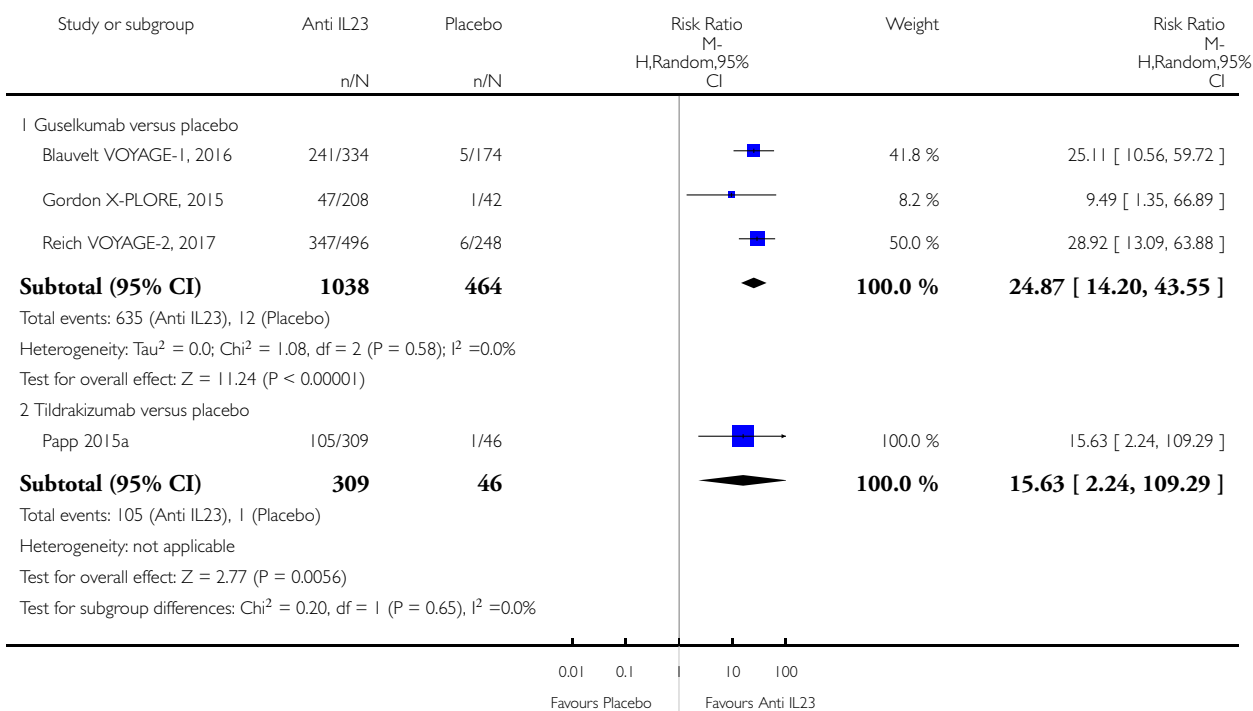


## Analysis 1.6. Comparison 1 Primary outcome - PASI 90, Outcome 6 Anti-IL23 versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 1 Primary outcome - PASI 90

Outcome: 6 Anti-IL23 versus placebo

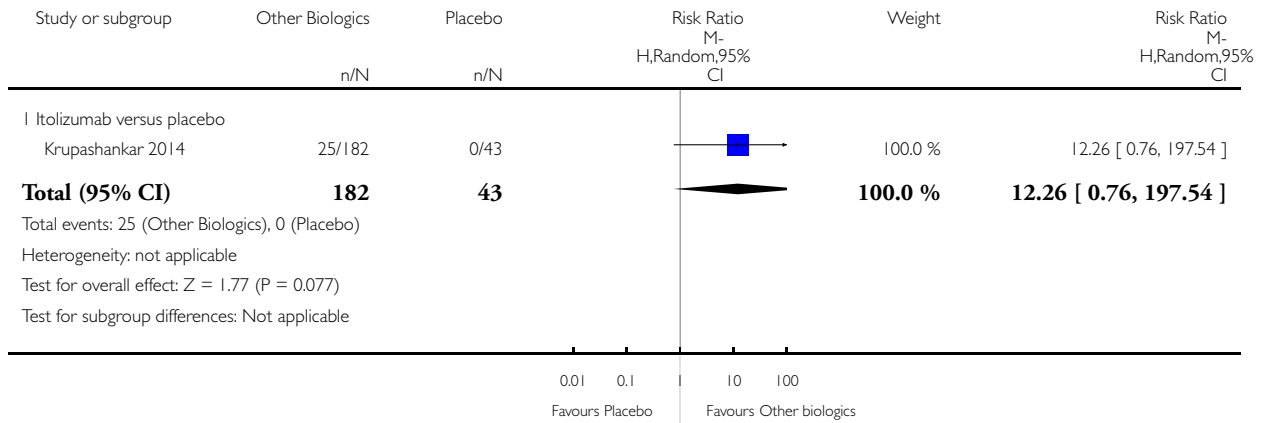


### Analysis 1.7. Comparison 1 Primary outcome - PASI 90, Outcome 7 Other biologics.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 1 Primary outcome - PASI 90

Outcome: 7 Other biologics



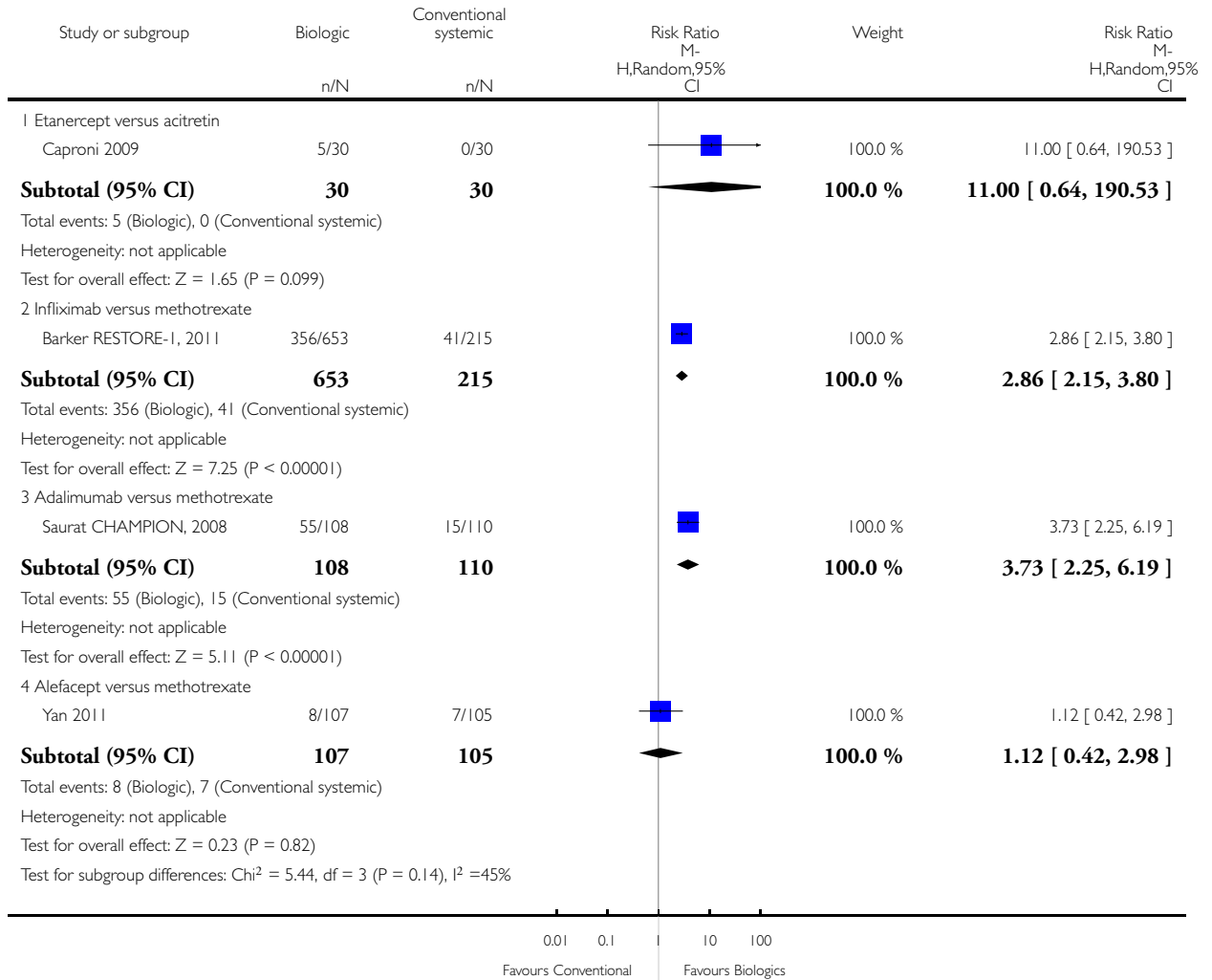


### Analysis 1.8. Comparison 1 Primary outcome - PASI 90, Outcome 8 Biologic versus conventional systemic treatments.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 1 Primary outcome - PASI 90

Outcome: 8 Biologic versus conventional systemic treatments

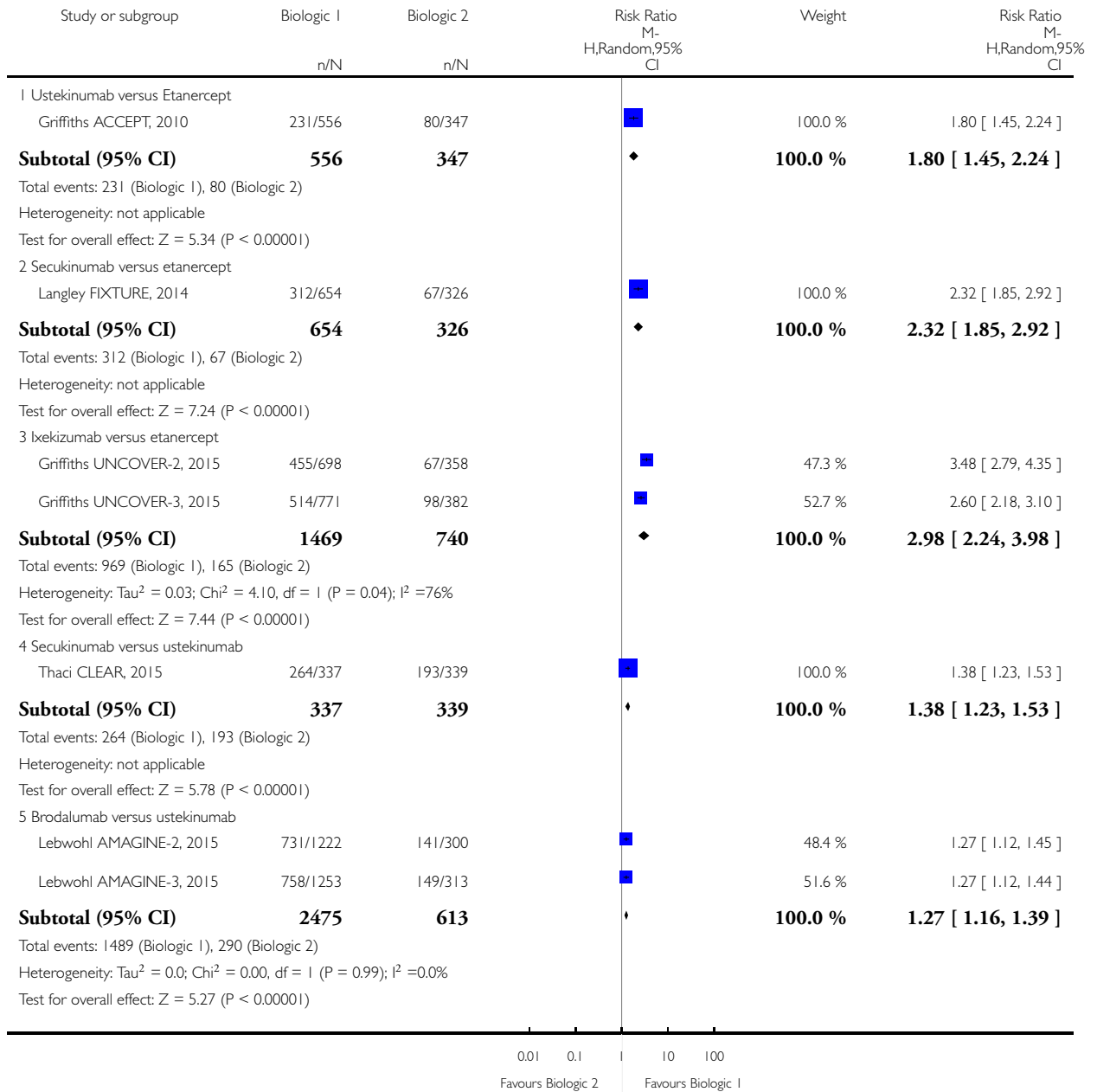


### Analysis 1.9. Comparison 1 Primary outcome - PASI 90, Outcome 9 Biologic 1 versus biologic 2.

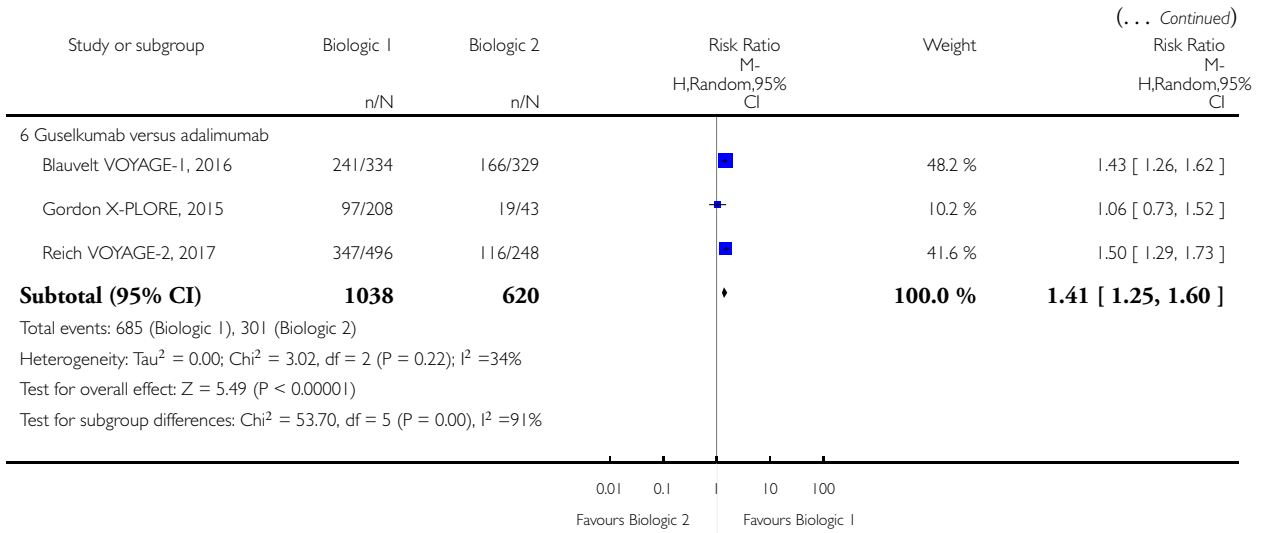
Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 1 Primary outcome - PASI 90

Outcome: 9 Biologic 1 versus biologic 2



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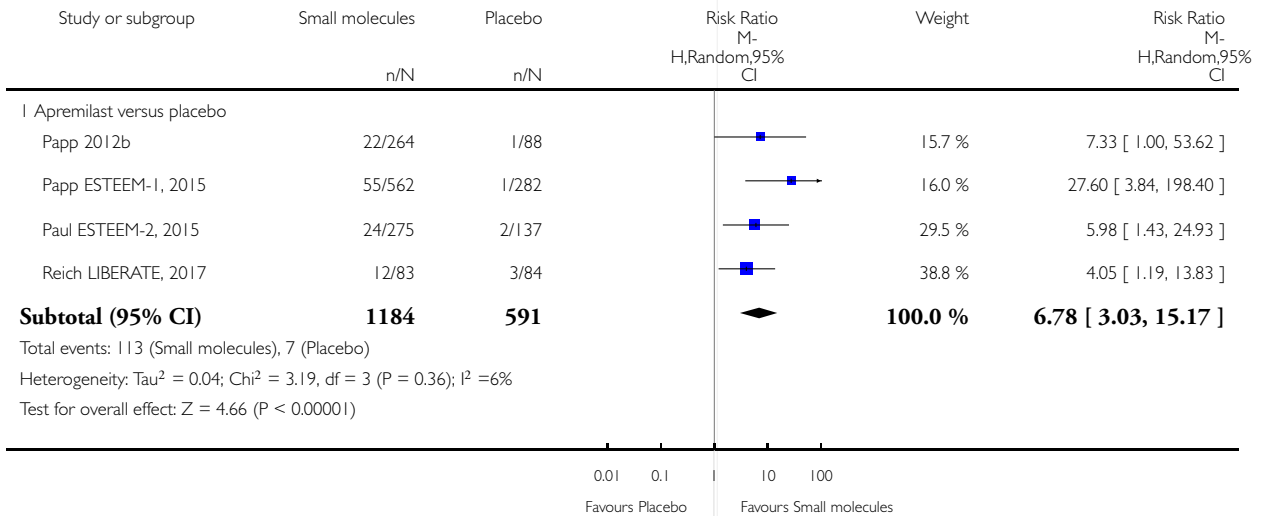


### Analysis 1.10. Comparison 1 Primary outcome - PASI 90, Outcome 10 Small molecules versus placebo.

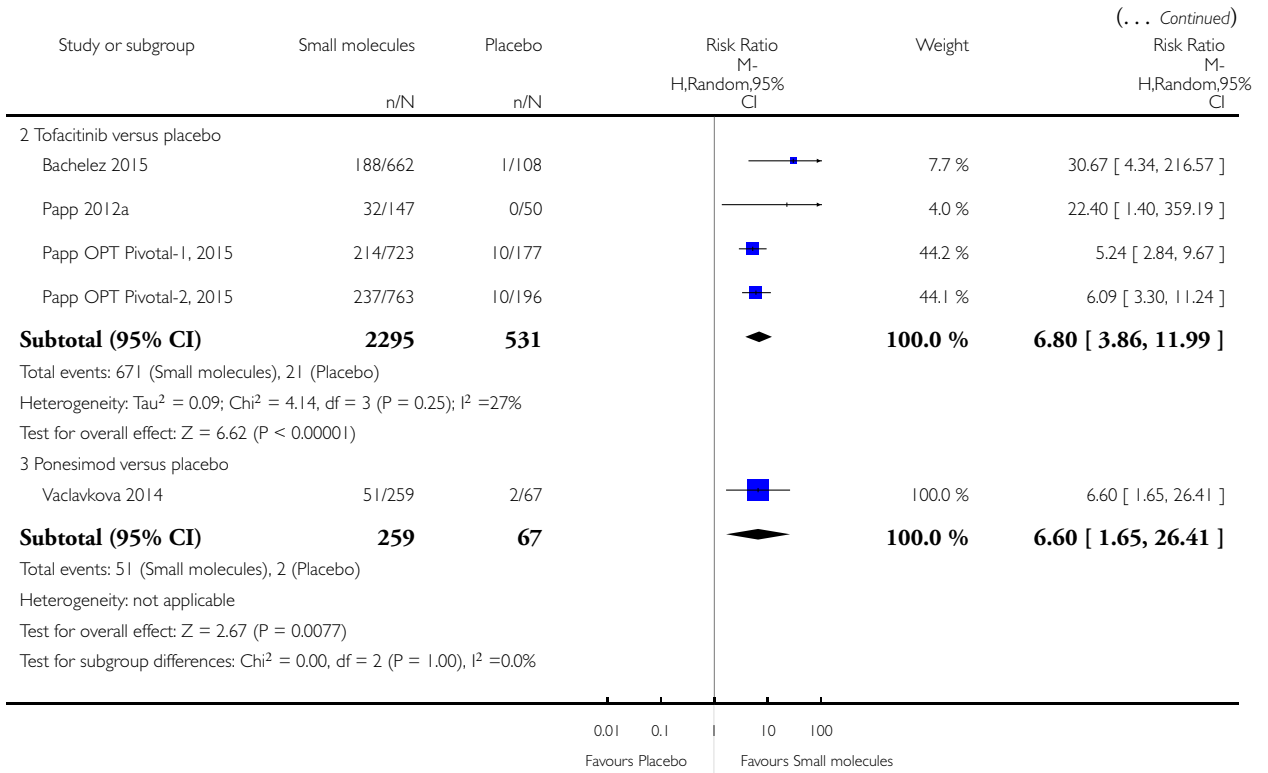
Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 1 Primary outcome - PASI 90

Outcome: 10 Small molecules versus placebo



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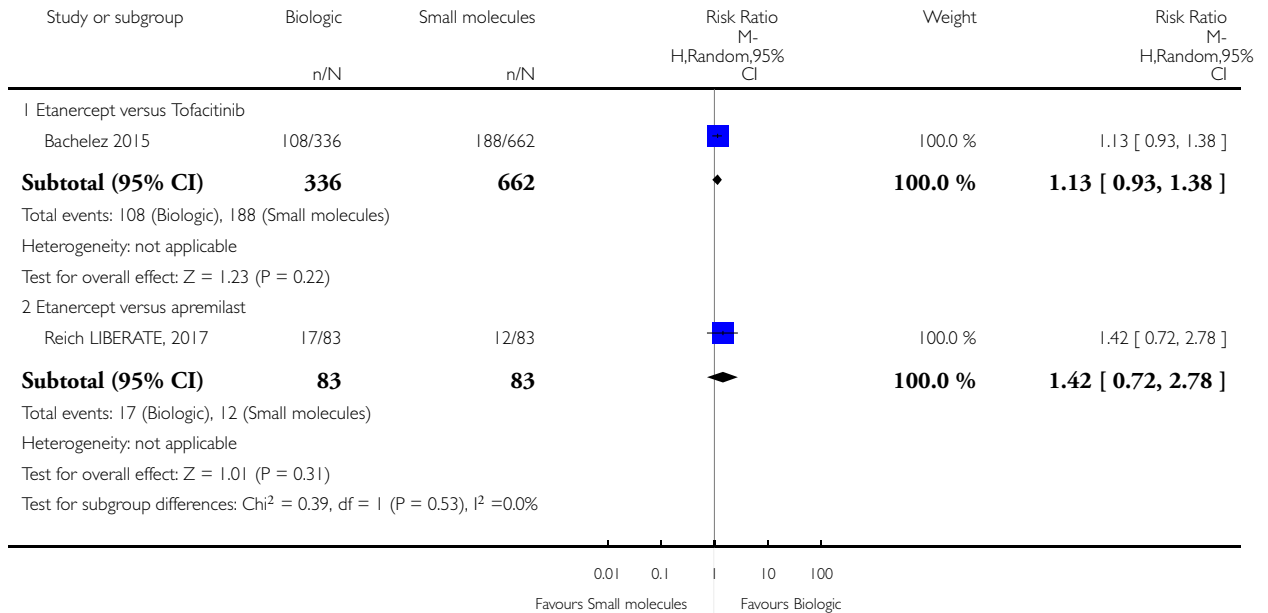


### Analysis 1.11. Comparison 1 Primary outcome - PASI 90, Outcome 11 Biologic versus small molecules.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 1 Primary outcome - PASI 90

Outcome: 11 Biologic versus small molecules

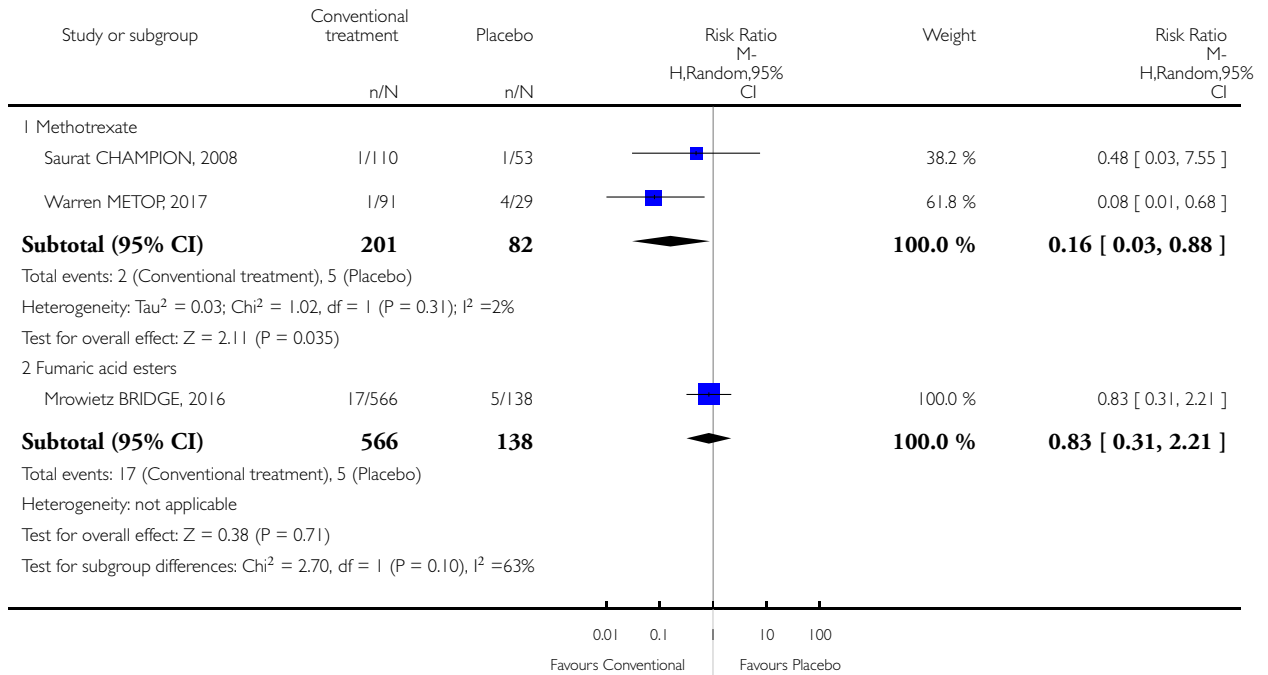


## Analysis 2.1. Comparison 2 Primary outcome - serious adverse events, Outcome 1 Conventional systemic agents versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 2 Primary outcome - serious adverse events

Outcome: 1 Conventional systemic agents versus placebo

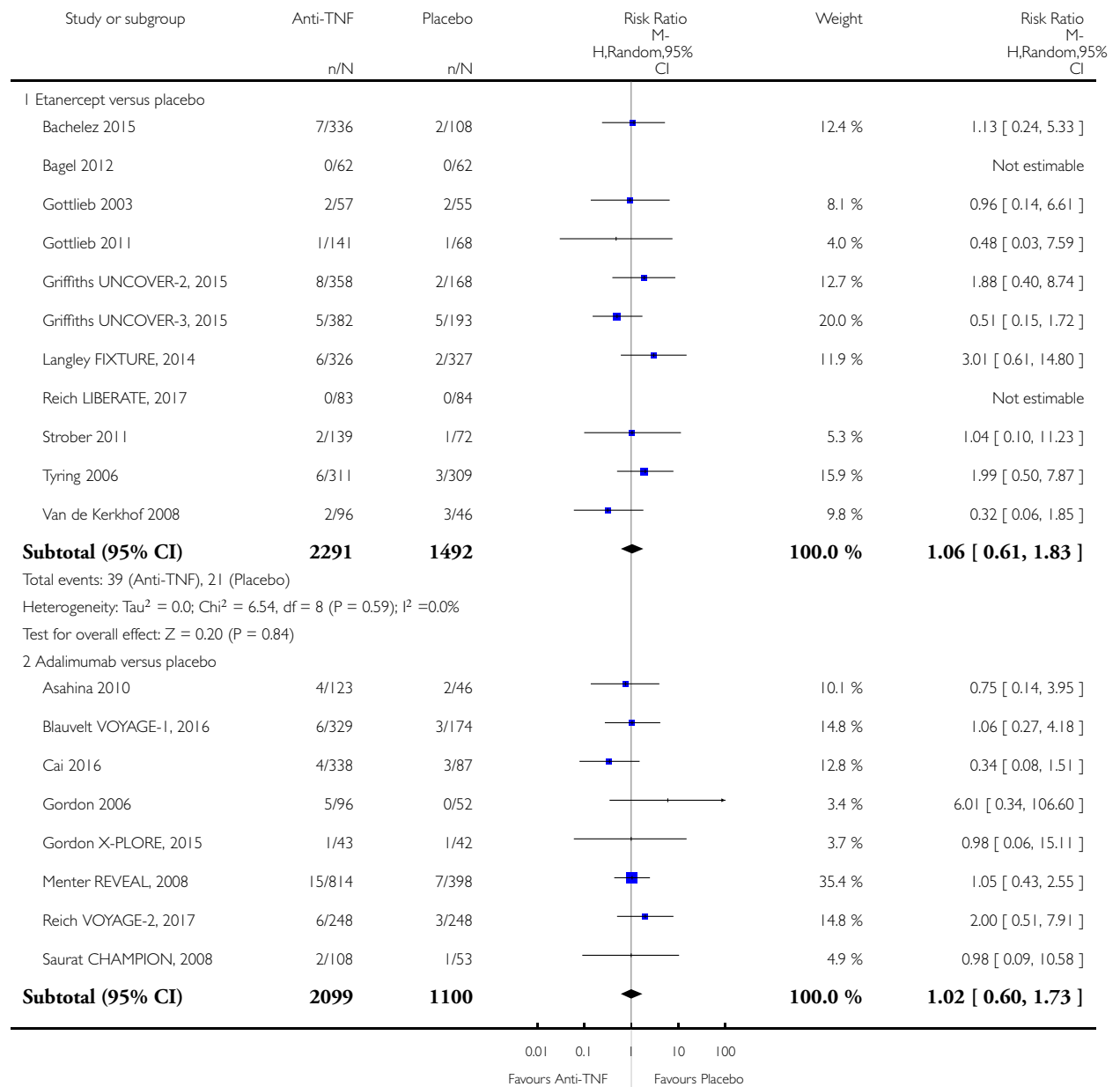


## Analysis 2.2. Comparison 2 Primary outcome - serious adverse events, Outcome 2 Anti-TNF alpha versus placebo.

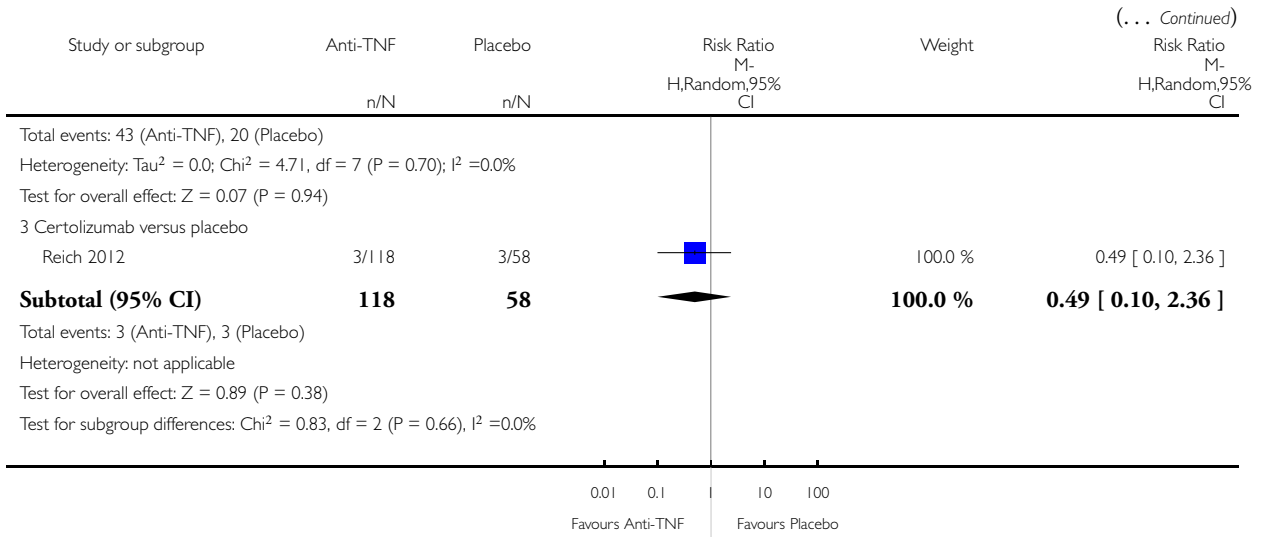
Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 2 Primary outcome - serious adverse events

Outcome: 2 Anti-TNF alpha versus placebo



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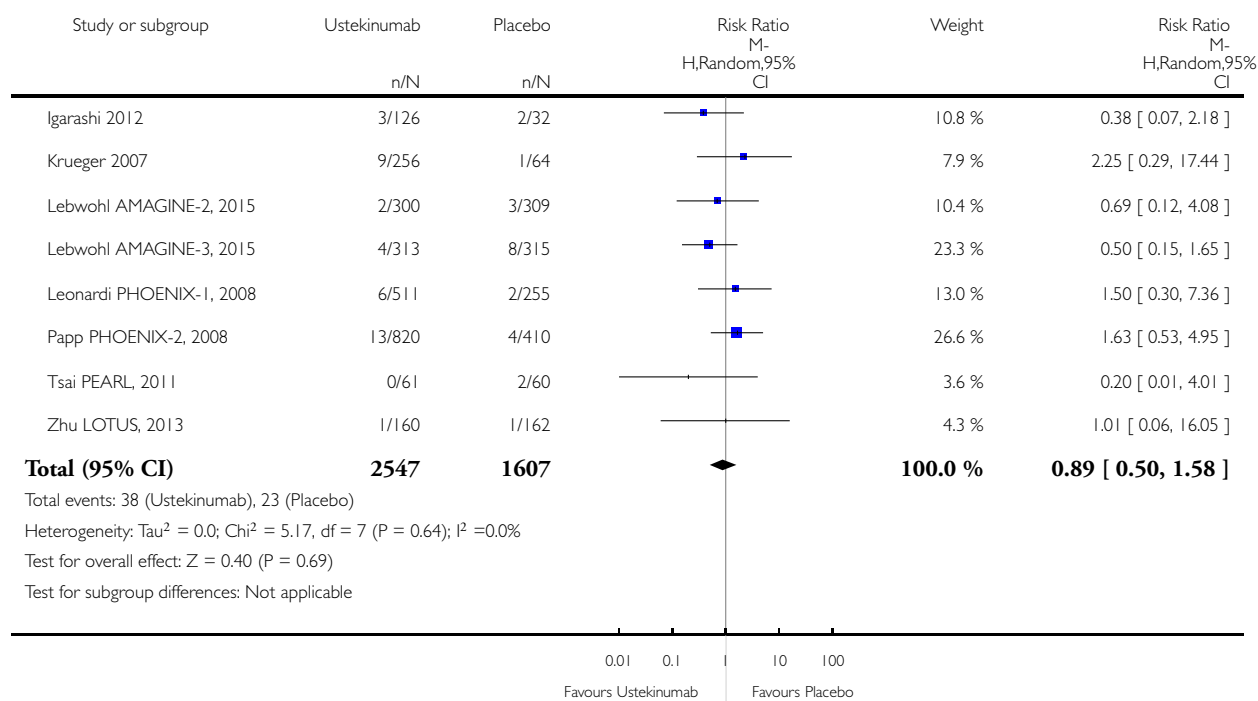


### Analysis 2.3. Comparison 2 Primary outcome - serious adverse events, Outcome 3 Ustekinumab versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 2 Primary outcome - serious adverse events

Outcome: 3 Ustekinumab versus placebo

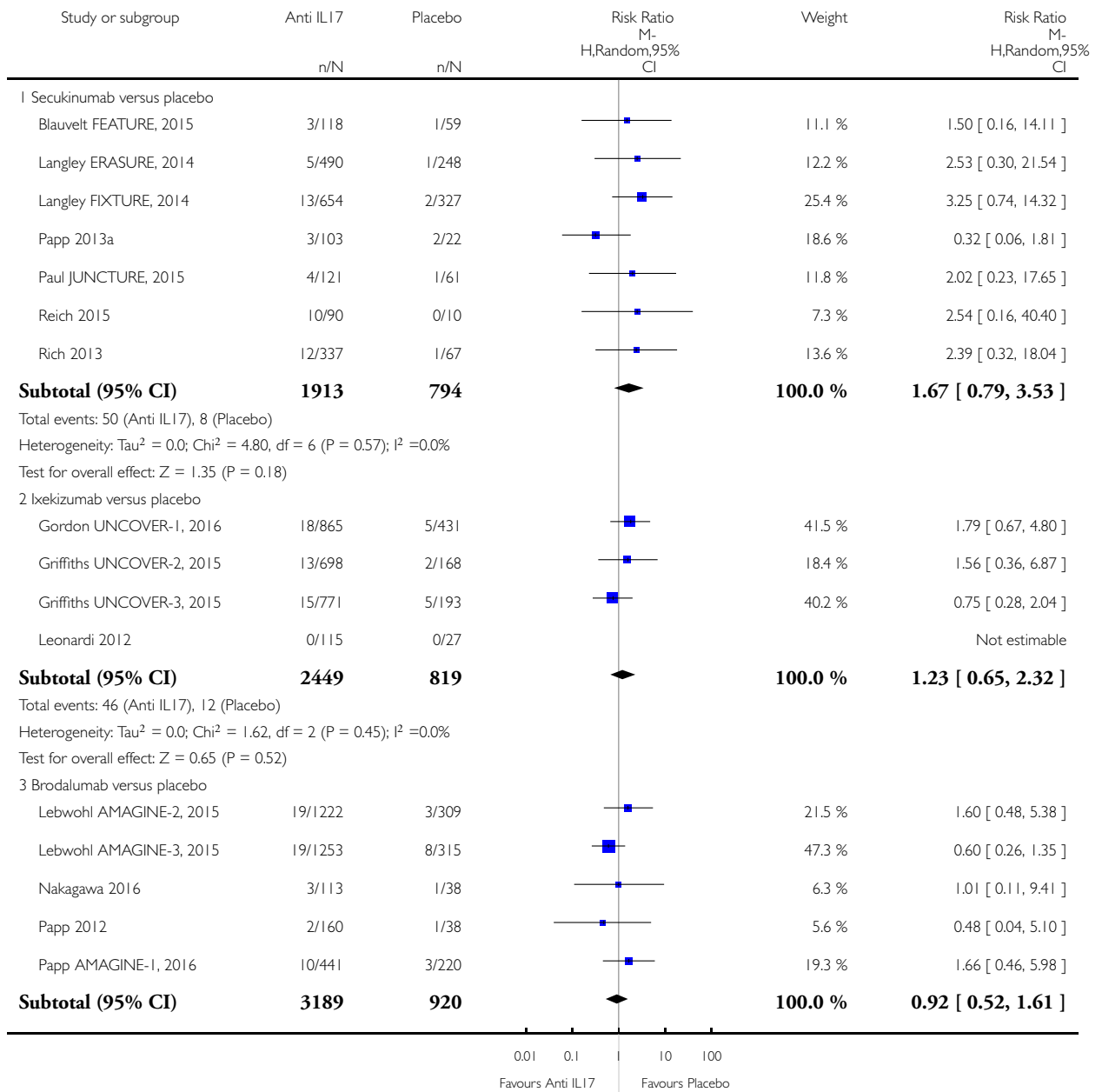


## Analysis 2.4. Comparison 2 Primary outcome - serious adverse events, Outcome 4 Anti-IL17 versus placebo.

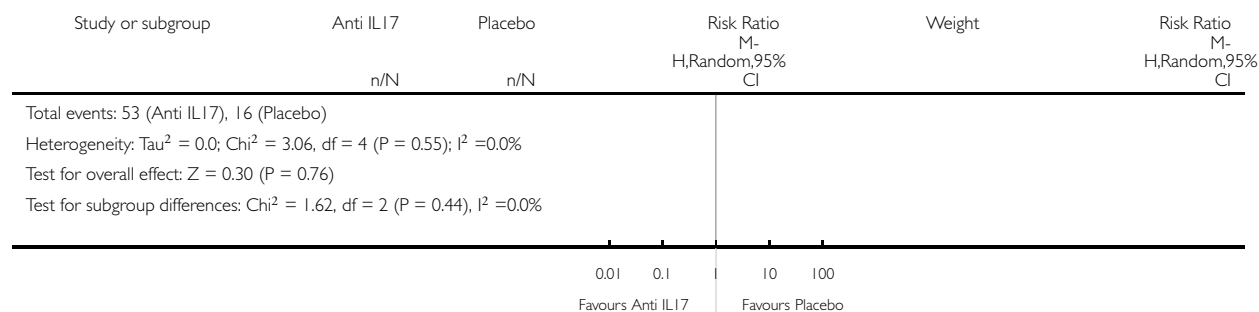
Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 2 Primary outcome - serious adverse events

Outcome: 4 Anti-IL17 versus placebo



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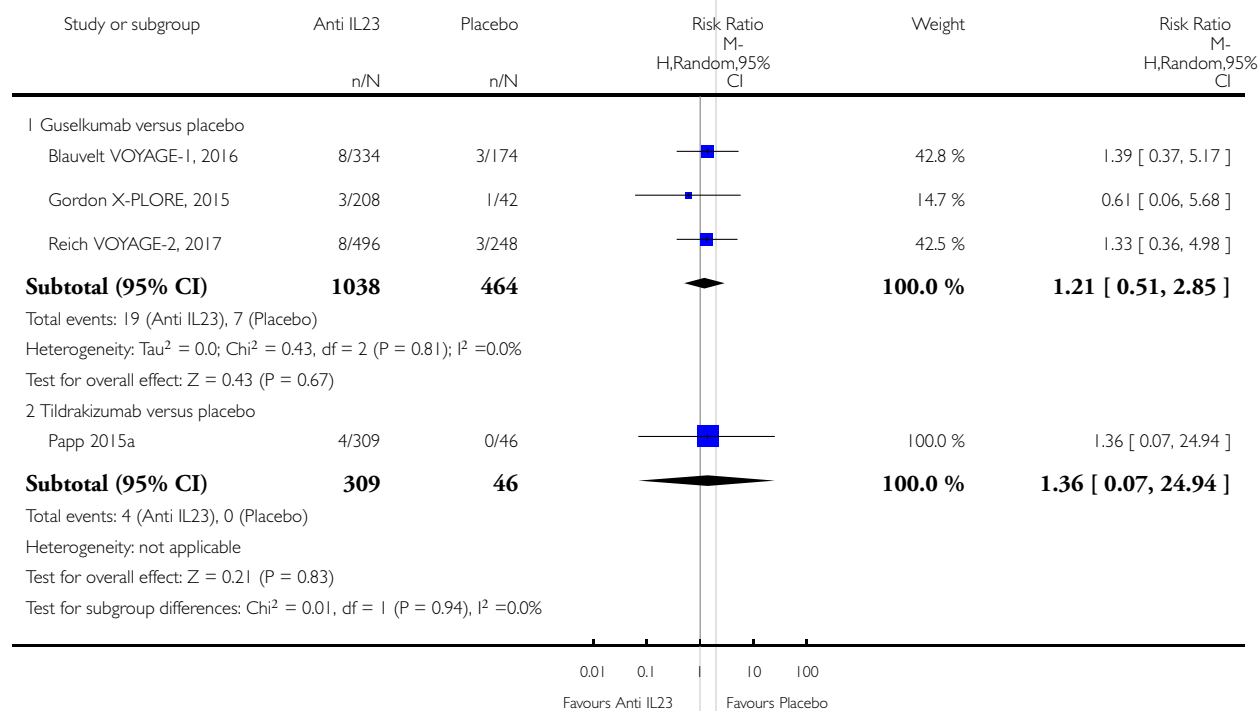


### Analysis 2.5. Comparison 2 Primary outcome - serious adverse events, Outcome 5 Anti-IL23 versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 2 Primary outcome - serious adverse events

Outcome: 5 Anti-IL23 versus placebo

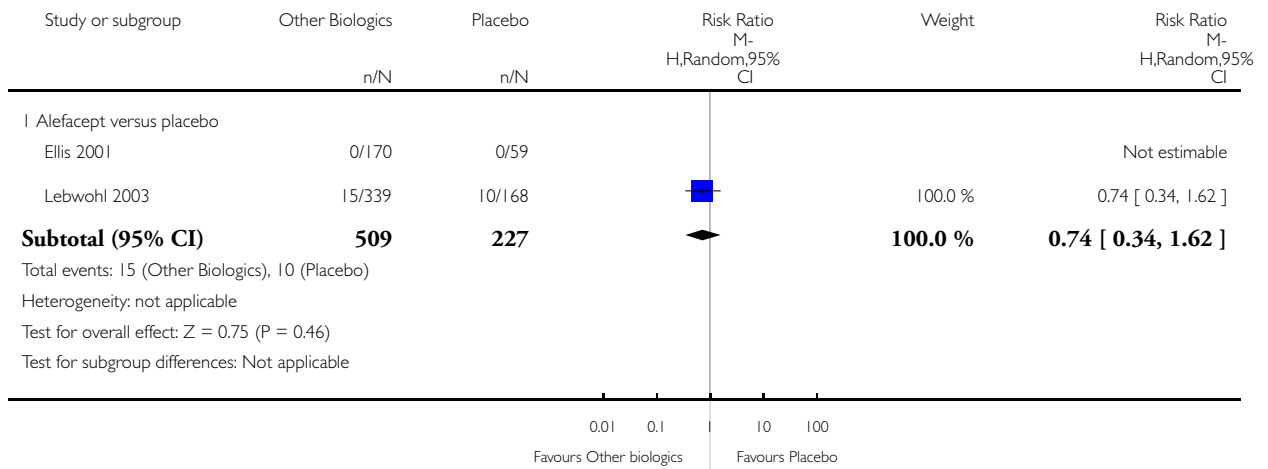


## Analysis 2.6. Comparison 2 Primary outcome - serious adverse events, Outcome 6 Other biologics.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 2 Primary outcome - serious adverse events

Outcome: 6 Other biologics

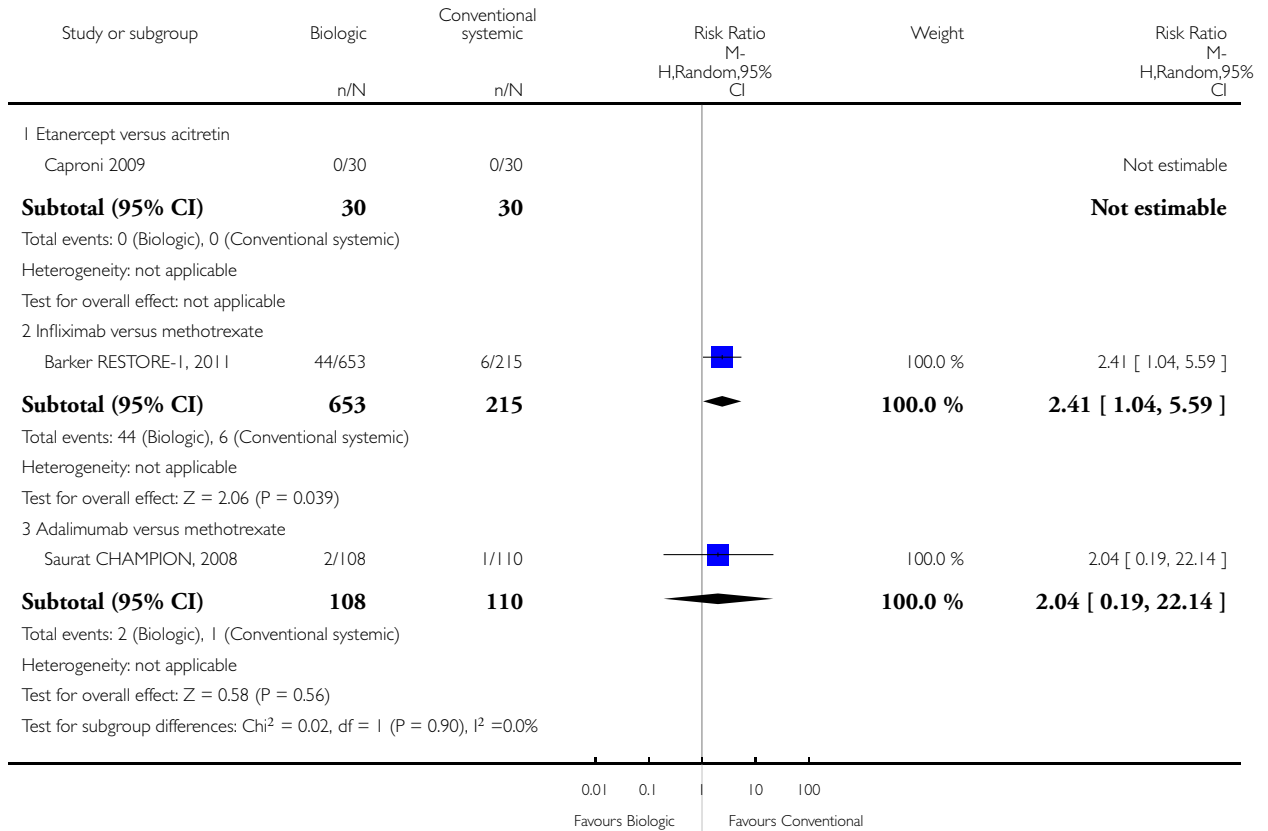


## Analysis 2.7. Comparison 2 Primary outcome - serious adverse events, Outcome 7 Biologic versus conventional systemic treatments.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 2 Primary outcome - serious adverse events

Outcome: 7 Biologic versus conventional systemic treatments

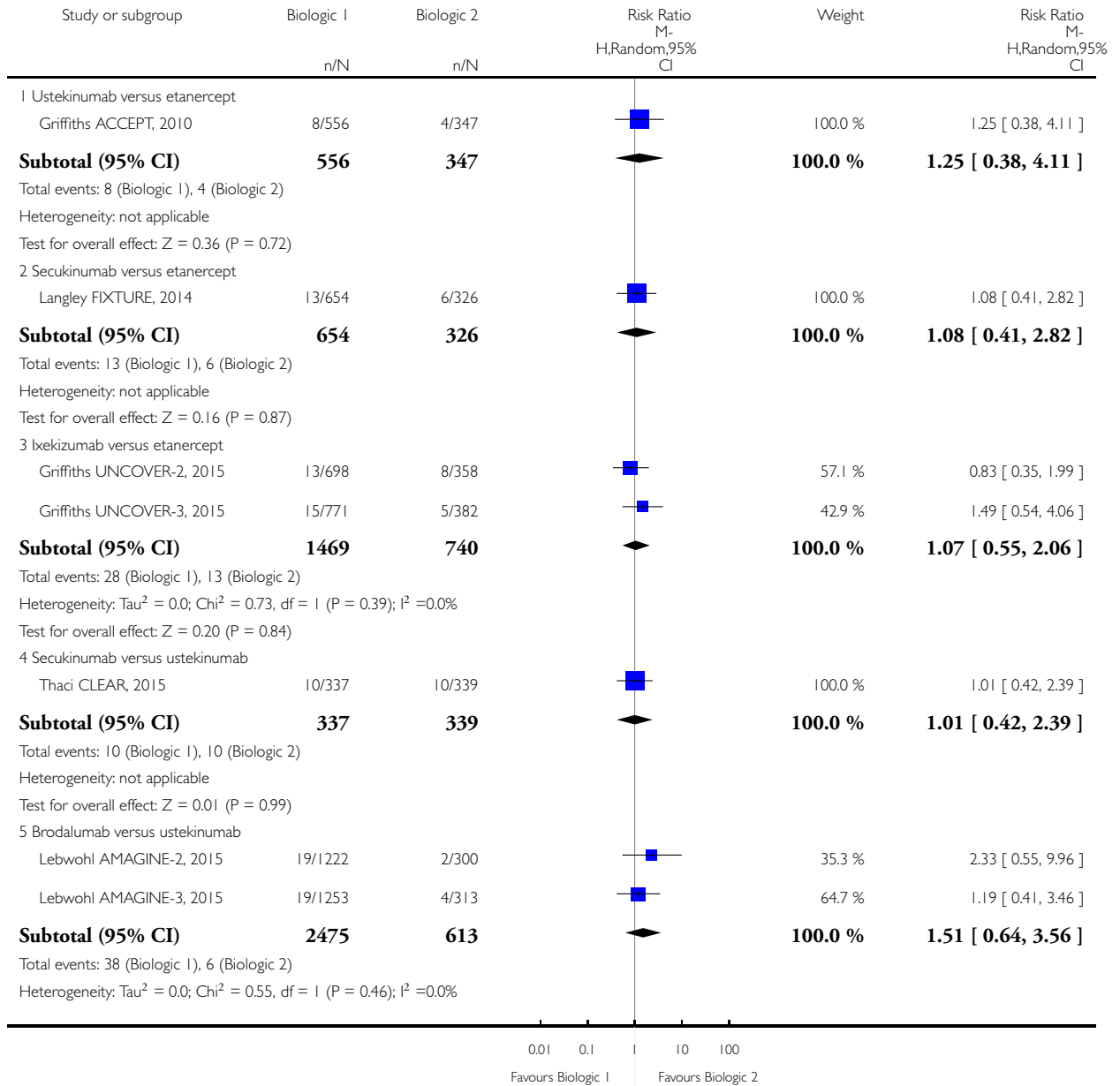


## Analysis 2.8. Comparison 2 Primary outcome - serious adverse events, Outcome 8 Biologic 1 versus biologic 2.

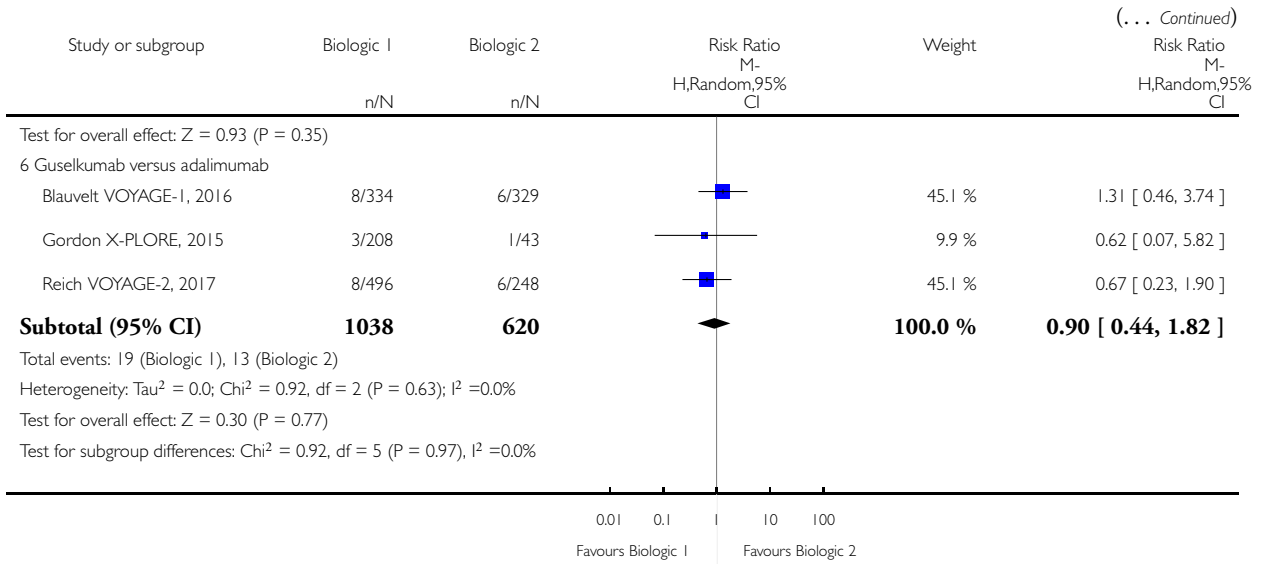
Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 2 Primary outcome - serious adverse events

Outcome: 8 Biologic 1 versus biologic 2



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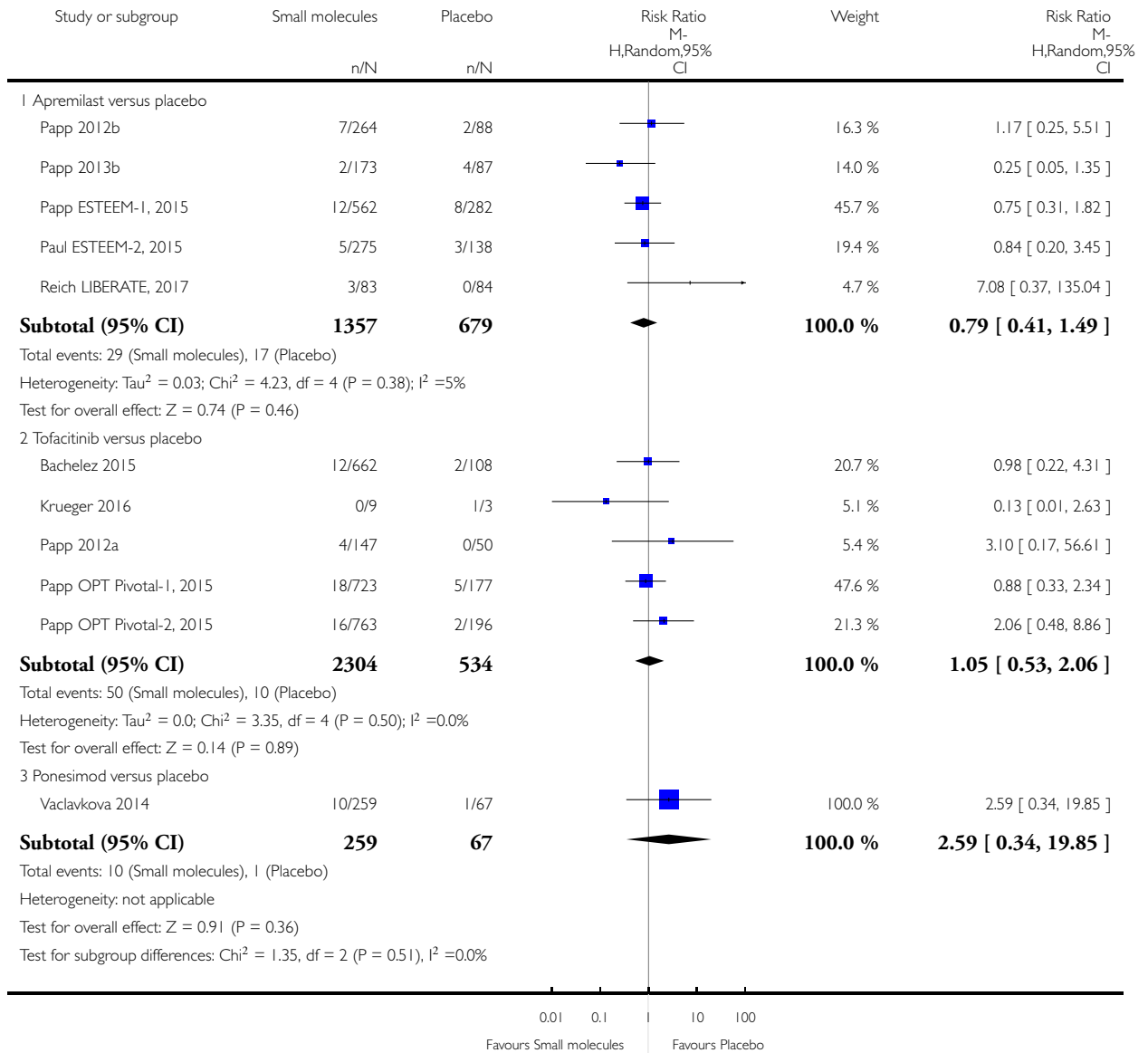


## Analysis 2.9. Comparison 2 Primary outcome - serious adverse events, Outcome 9 Small molecules versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 2 Primary outcome - serious adverse events

Outcome: 9 Small molecules versus placebo



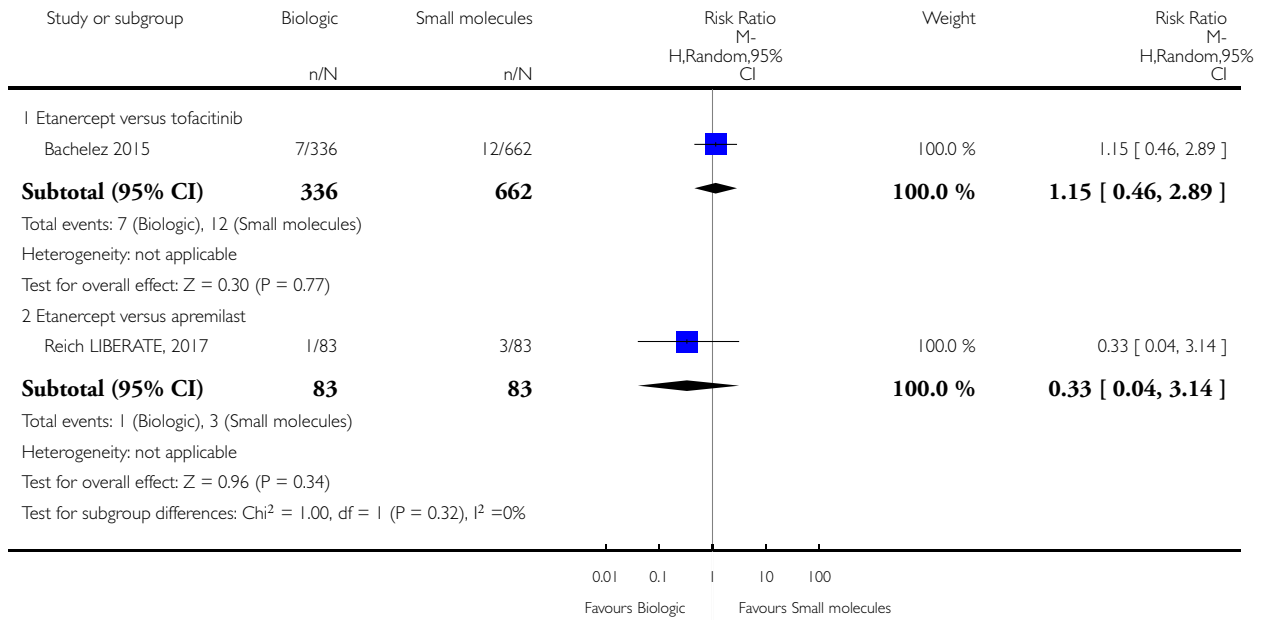


## Analysis 2.10. Comparison 2 Primary outcome - serious adverse events, Outcome 10 Biologic versus small molecules.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 2 Primary outcome - serious adverse events

Outcome: 10 Biologic versus small molecules

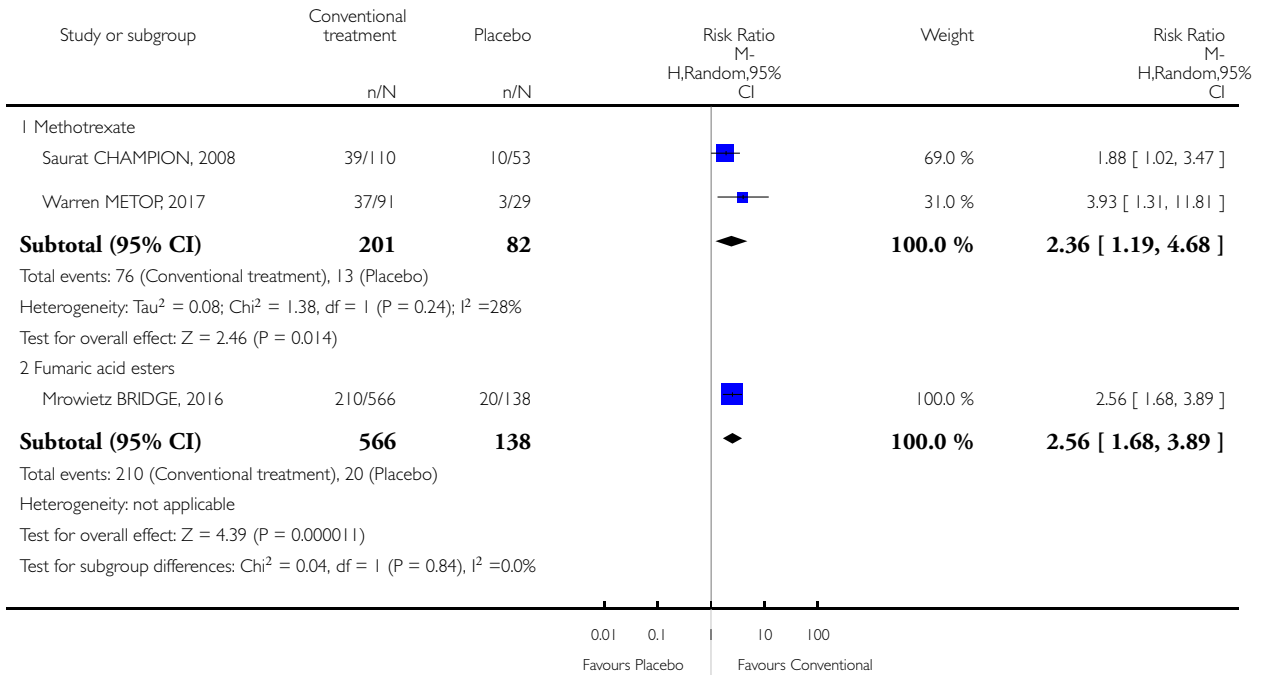


### Analysis 3.1. Comparison 3 Secondary outcome - PASI 75, Outcome 1 Conventional systemic agents versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 3 Secondary outcome - PASI 75

Outcome: 1 Conventional systemic agents versus placebo

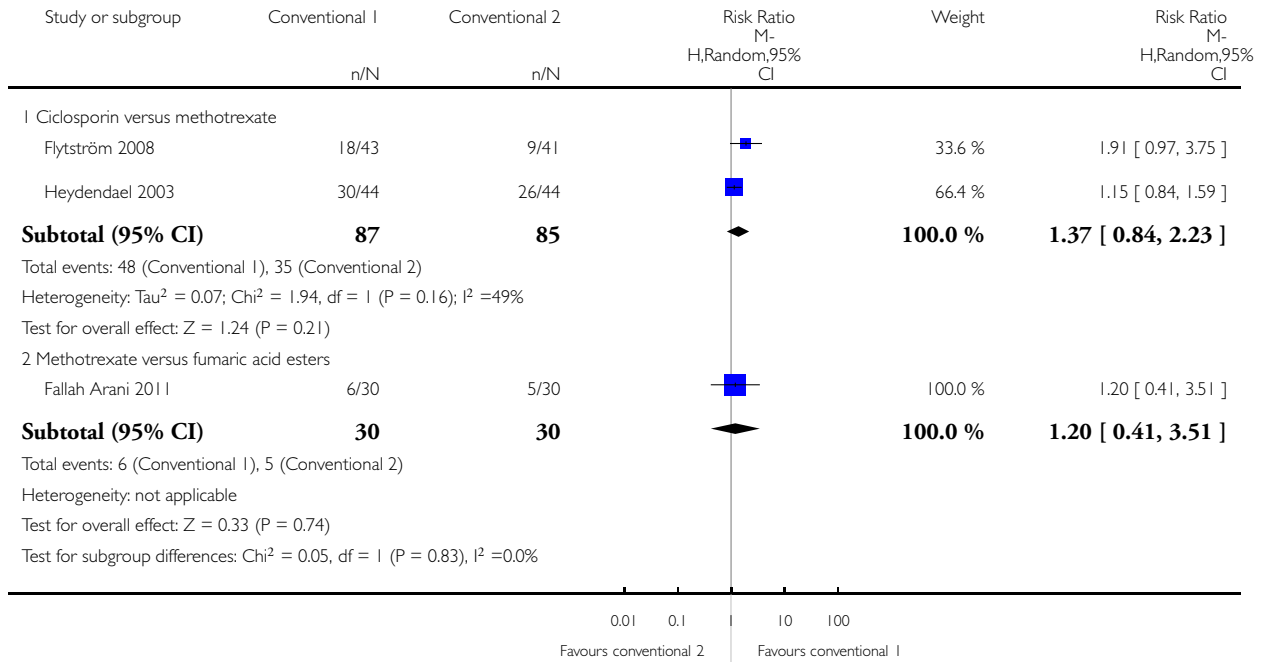


### Analysis 3.2. Comparison 3 Secondary outcome - PASI 75, Outcome 2 Conventional systemic 1 versus conventional systemic 2.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 3 Secondary outcome - PASI 75

Outcome: 2 Conventional systemic 1 versus conventional systemic 2

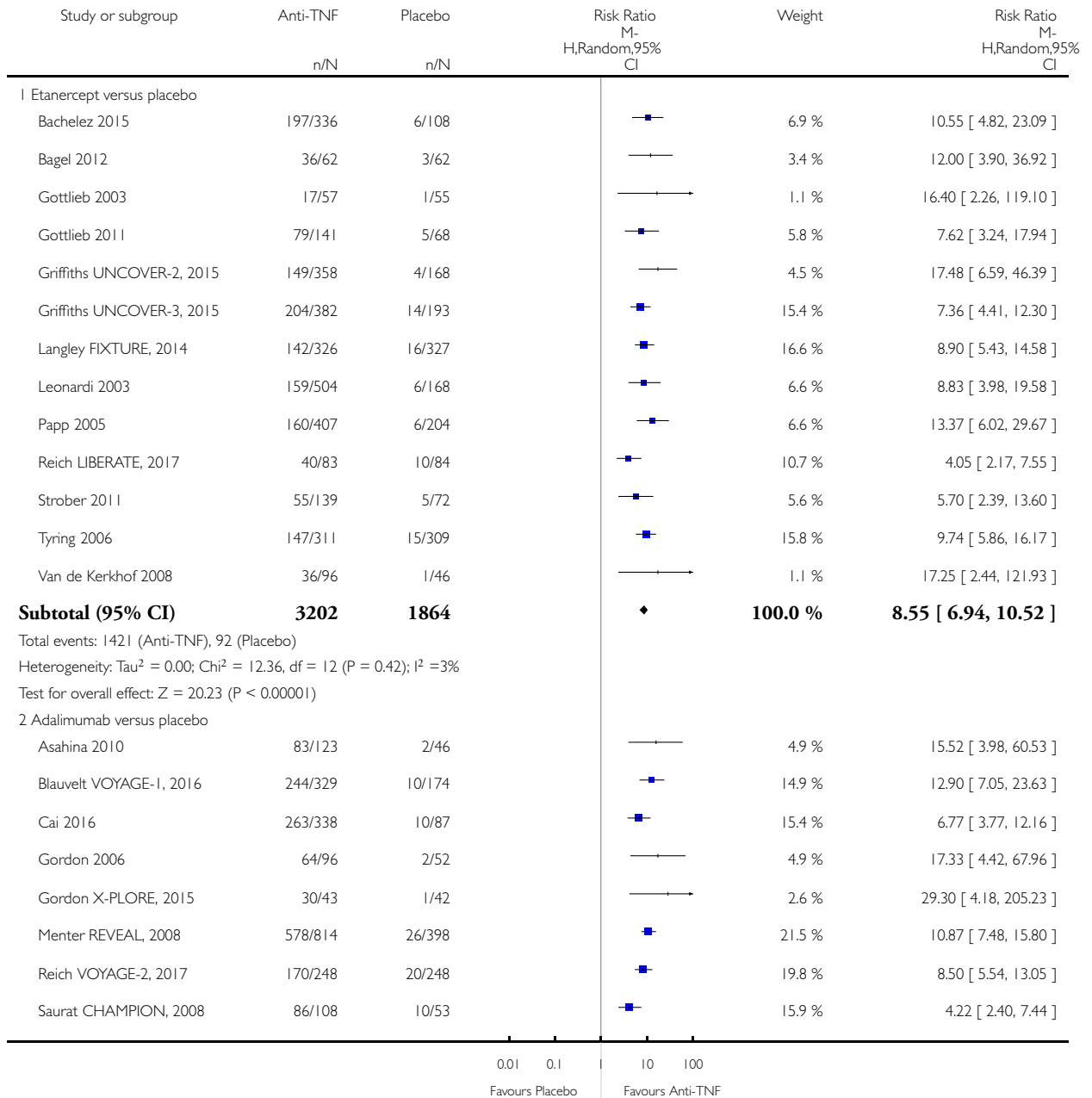


### Analysis 3.3. Comparison 3 Secondary outcome - PASI 75, Outcome 3 Anti-TNF alpha versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

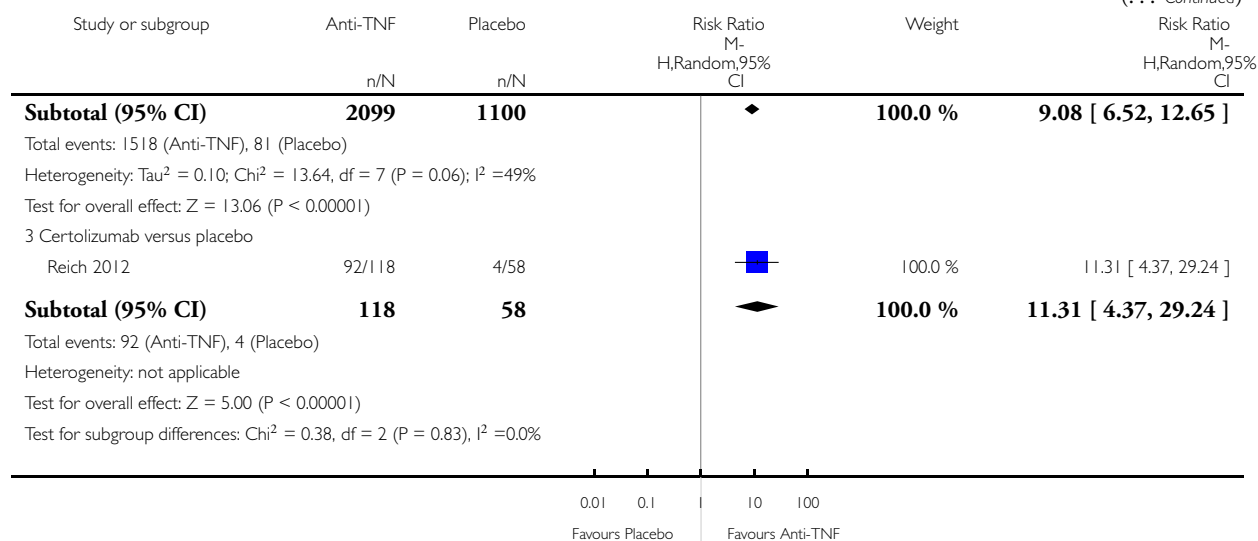
Comparison: 3 Secondary outcome - PASI 75

Outcome: 3 Anti-TNF alpha versus placebo



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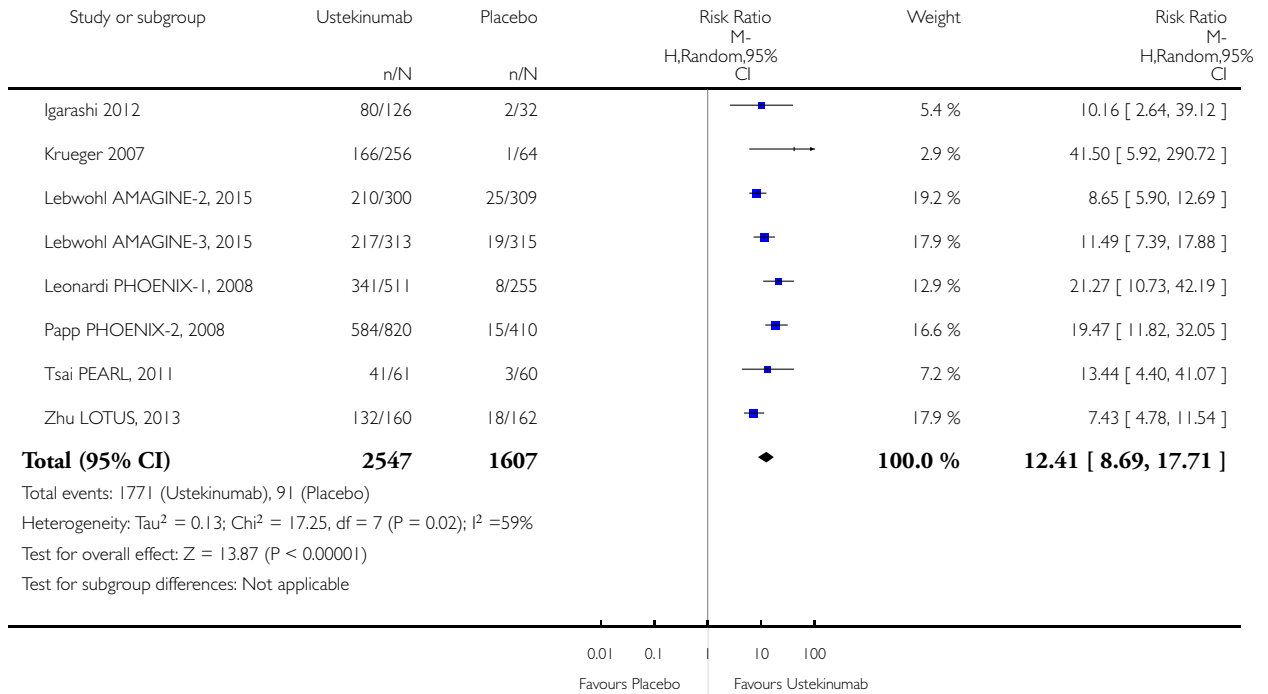


### Analysis 3.4. Comparison 3 Secondary outcome - PASI 75, Outcome 4 Ustekinumab versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 3 Secondary outcome - PASI 75

Outcome: 4 Ustekinumab versus placebo

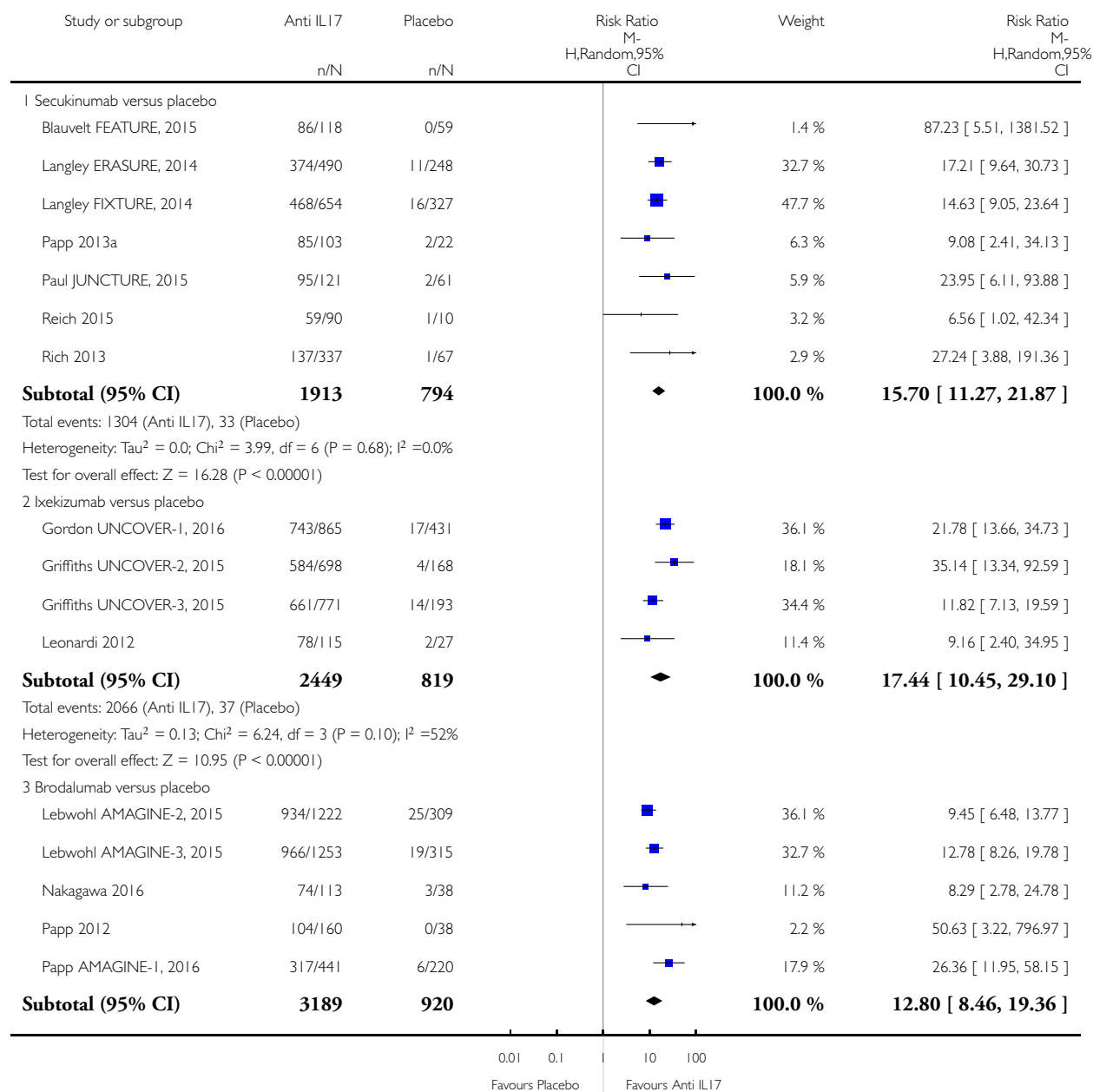


### Analysis 3.5. Comparison 3 Secondary outcome - PASI 75, Outcome 5 Anti-IL17 versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 3 Secondary outcome - PASI 75

Outcome: 5 Anti-IL17 versus placebo



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Study or subgroup	Anti IL17 n/N	Placebo n/N	Risk Ratio M- H,Random,95% CI	Weight	Risk Ratio M- H,Random,95% CI
Total events: 2395 (Anti IL17), 53 (Placebo) Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 7.13, df = 4 (P = 0.13); I <sup>2</sup> = 44% Test for overall effect: Z = 12.08 (P < 0.00001) Test for subgroup differences: Chi <sup>2</sup> = 0.97, df = 2 (P = 0.62), I <sup>2</sup> = 0.0%					
			0.01 0.1 10 100		
			Favours Placebo		Favours Anti IL17

### Analysis 3.6. Comparison 3 Secondary outcome - PASI 75, Outcome 6 Anti-IL23 versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 3 Secondary outcome - PASI 75

Outcome: 6 Anti-IL23 versus placebo

Study or subgroup	Anti IL23 n/N	Placebo n/N	Risk Ratio M- H,Random,95% CI	Weight	Risk Ratio M- H,Random,95% CI
1 Guselkumab versus Placebo					
Blauvelt VOYAGE-1, 2016	300/334	10/174		30.9 %	15.63 [ 8.55, 28.56 ]
Gordon X-PLORE, 2015	150/208	2/42		6.1 %	15.14 [ 3.91, 58.72 ]
Reich VOYAGE-2, 2017	428/496	20/248		63.0 %	10.70 [ 7.02, 16.31 ]
<b>Subtotal (95% CI)</b>	<b>1038</b>	<b>464</b>		<b>100.0 %</b>	<b>12.28 [ 8.79, 17.17 ]</b>
Total events: 878 (Anti IL23), 32 (Placebo) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> = 1.13, df = 2 (P = 0.57); I <sup>2</sup> = 0.0% Test for overall effect: Z = 14.68 (P < 0.00001)					
2 Tildrakizumab versus placebo					
Papp 2015a	195/309	2/46		100.0 %	14.51 [ 3.73, 56.45 ]
<b>Subtotal (95% CI)</b>	<b>309</b>	<b>46</b>		<b>100.0 %</b>	<b>14.51 [ 3.73, 56.45 ]</b>
Total events: 195 (Anti IL23), 2 (Placebo) Heterogeneity: not applicable Test for overall effect: Z = 3.86 (P = 0.00011) Test for subgroup differences: Chi <sup>2</sup> = 0.05, df = 1 (P = 0.82), I <sup>2</sup> = 0.0%					
			0.01 0.1 10 100		
			Favours Placebo		Favours Anti IL23

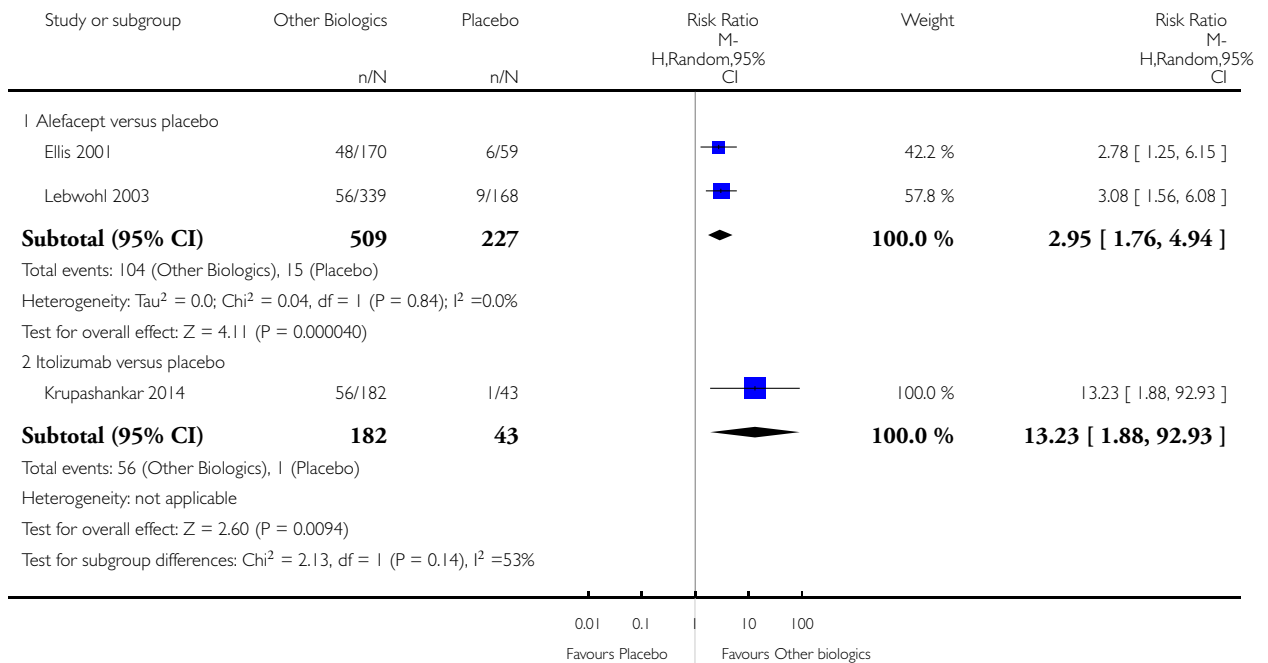


### Analysis 3.7. Comparison 3 Secondary outcome - PASI 75, Outcome 7 Other biologics.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 3 Secondary outcome - PASI 75

Outcome: 7 Other biologics

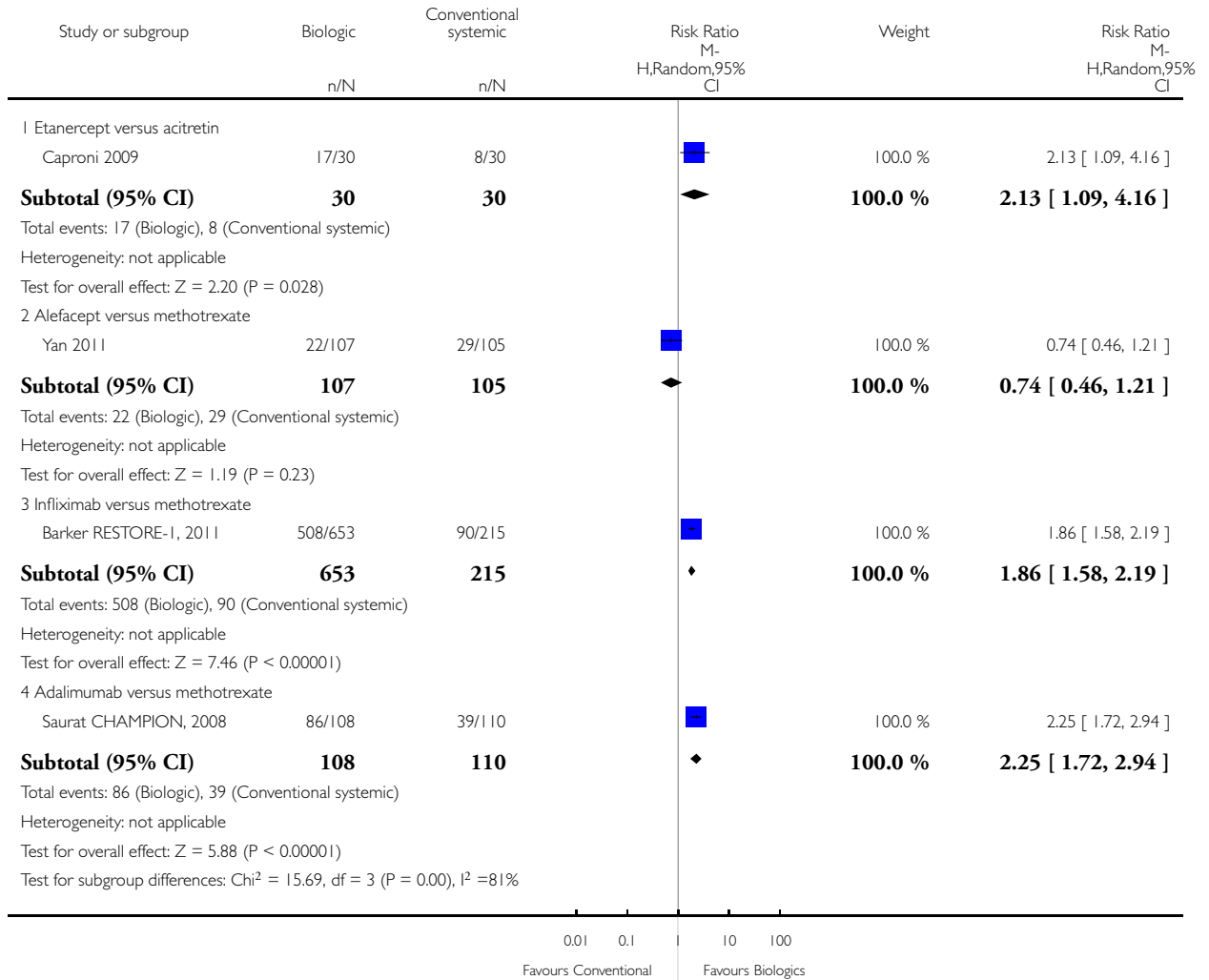


### Analysis 3.8. Comparison 3 Secondary outcome - PASI 75, Outcome 8 Biologic versus conventional systemic treatments.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 3 Secondary outcome - PASI 75

Outcome: 8 Biologic versus conventional systemic treatments

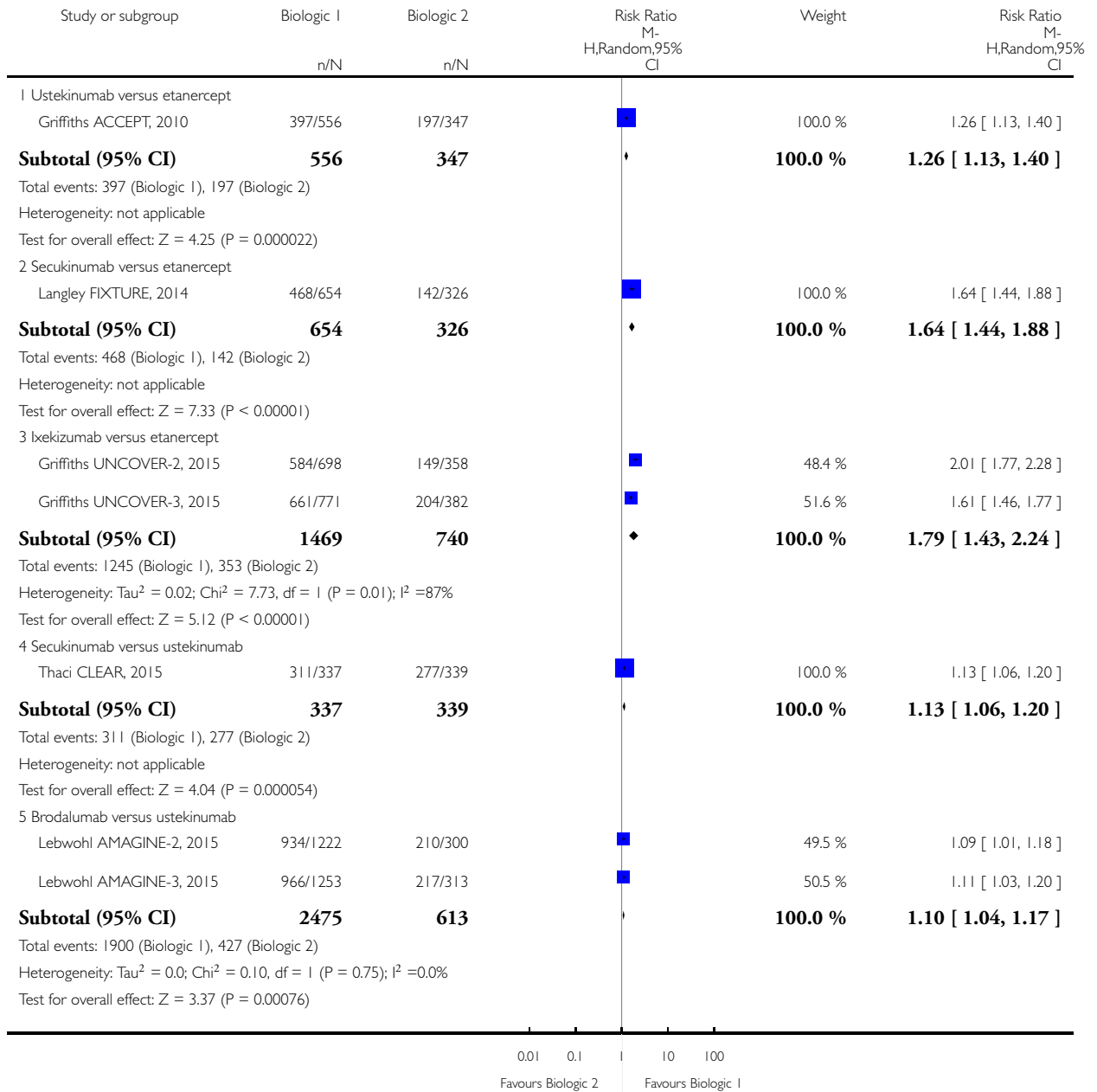


### Analysis 3.9. Comparison 3 Secondary outcome - PASI 75, Outcome 9 Biologic 1 versus biologic 2.

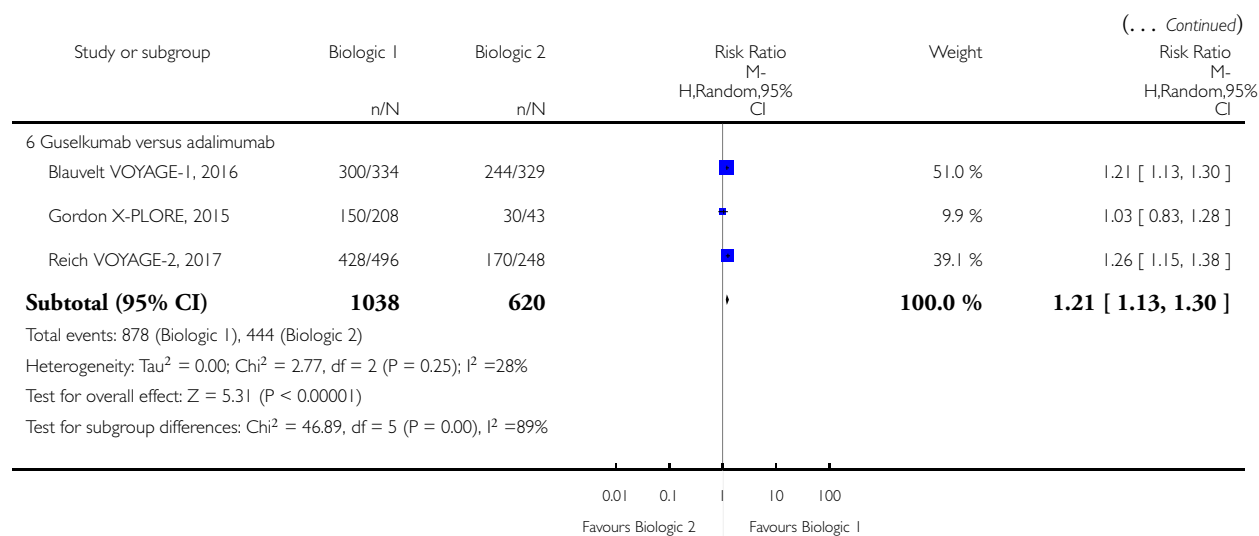
Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 3 Secondary outcome - PASI 75

Outcome: 9 Biologic 1 versus biologic 2



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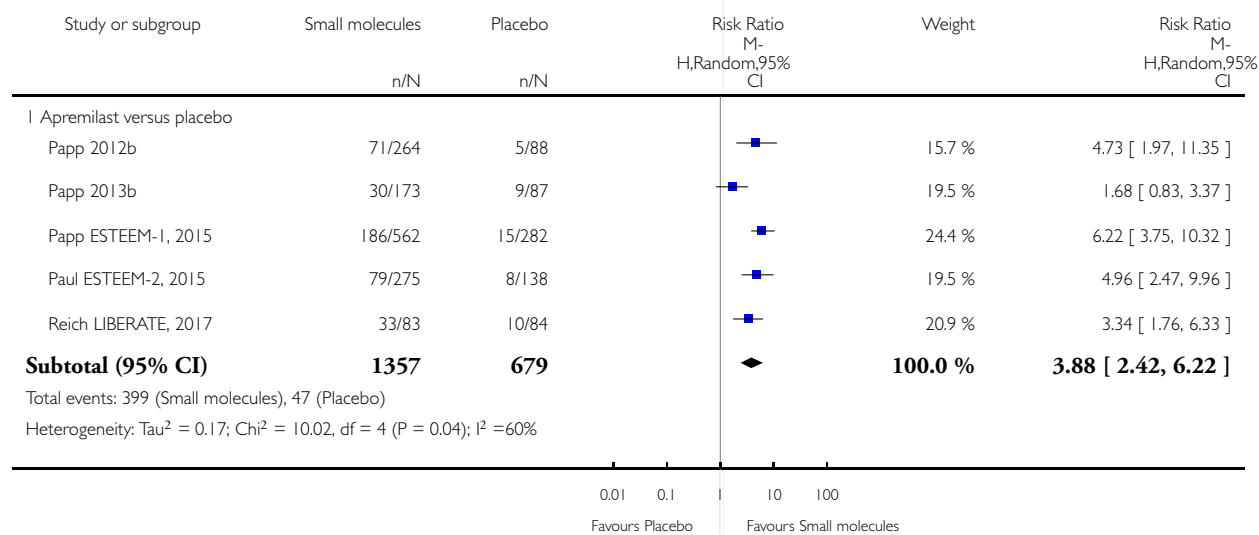


### Analysis 3.10. Comparison 3 Secondary outcome - PASI 75, Outcome 10 Small molecules versus placebo.

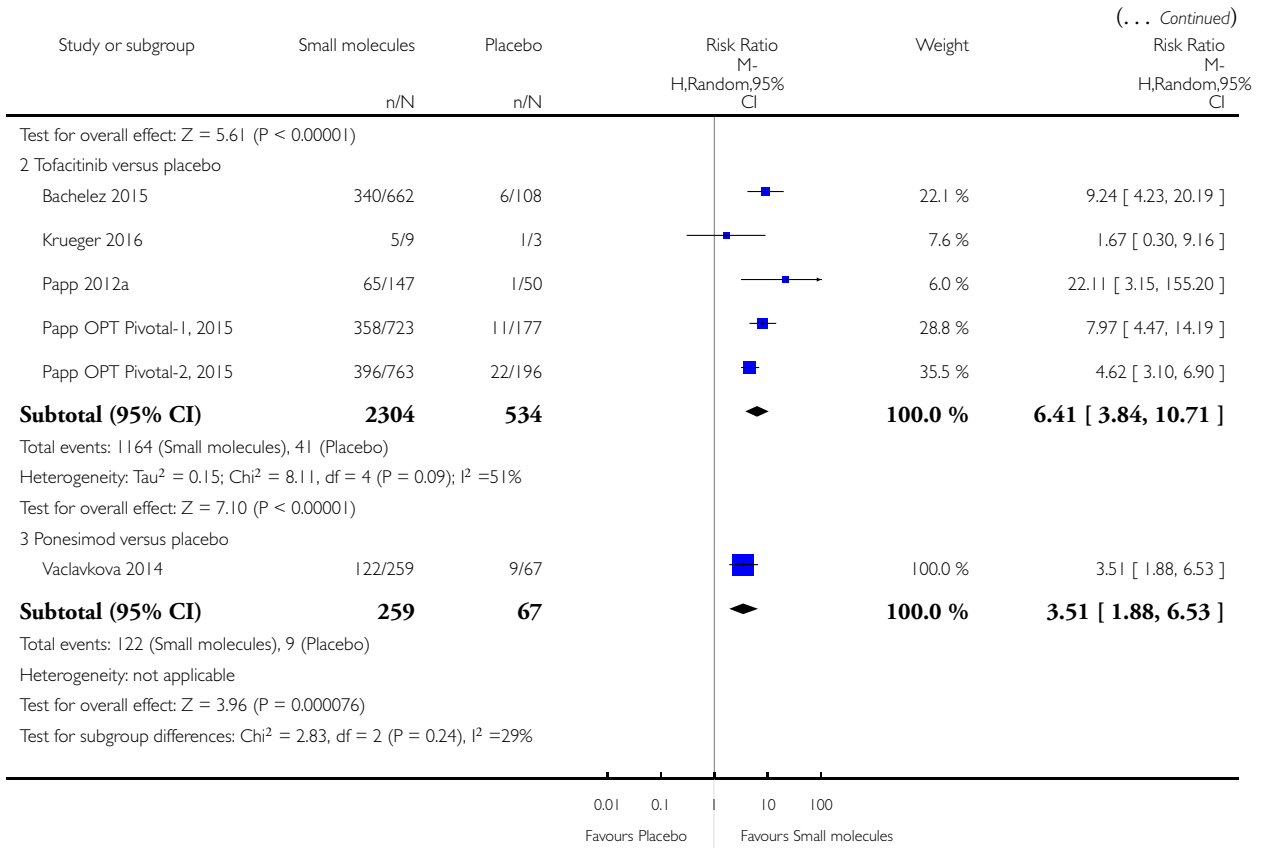
Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 3 Secondary outcome - PASI 75

Outcome: 10 Small molecules versus placebo



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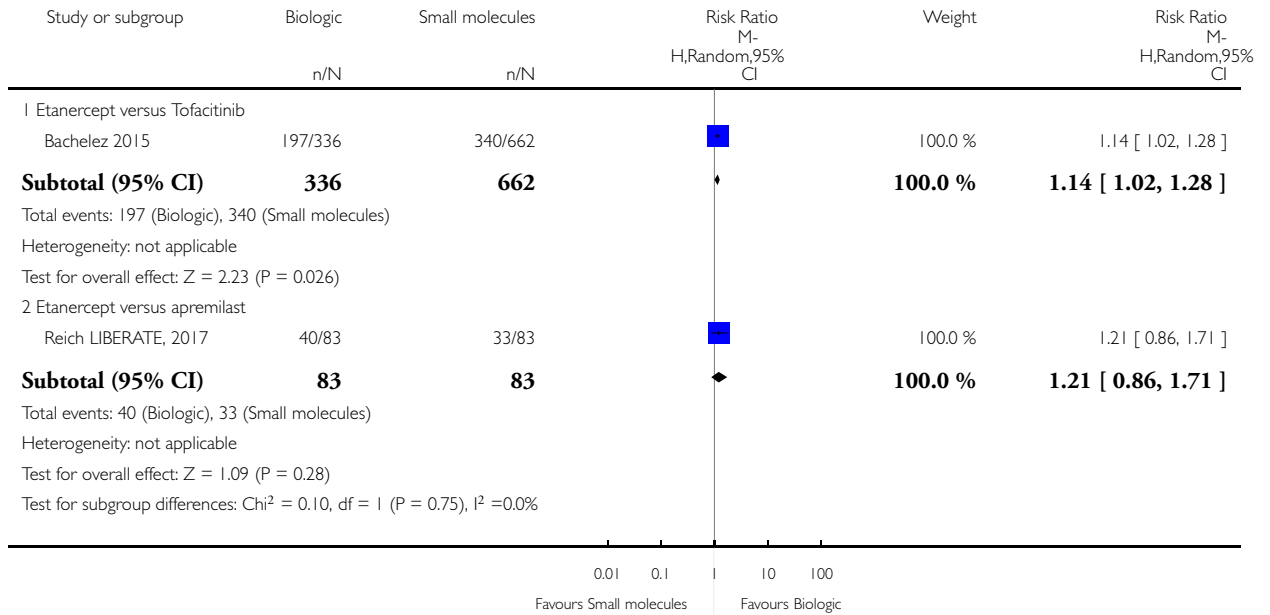


### Analysis 3.11. Comparison 3 Secondary outcome - PASI 75, Outcome 11 Biologic versus small molecules.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 3 Secondary outcome - PASI 75

Outcome: 11 Biologic versus small molecules

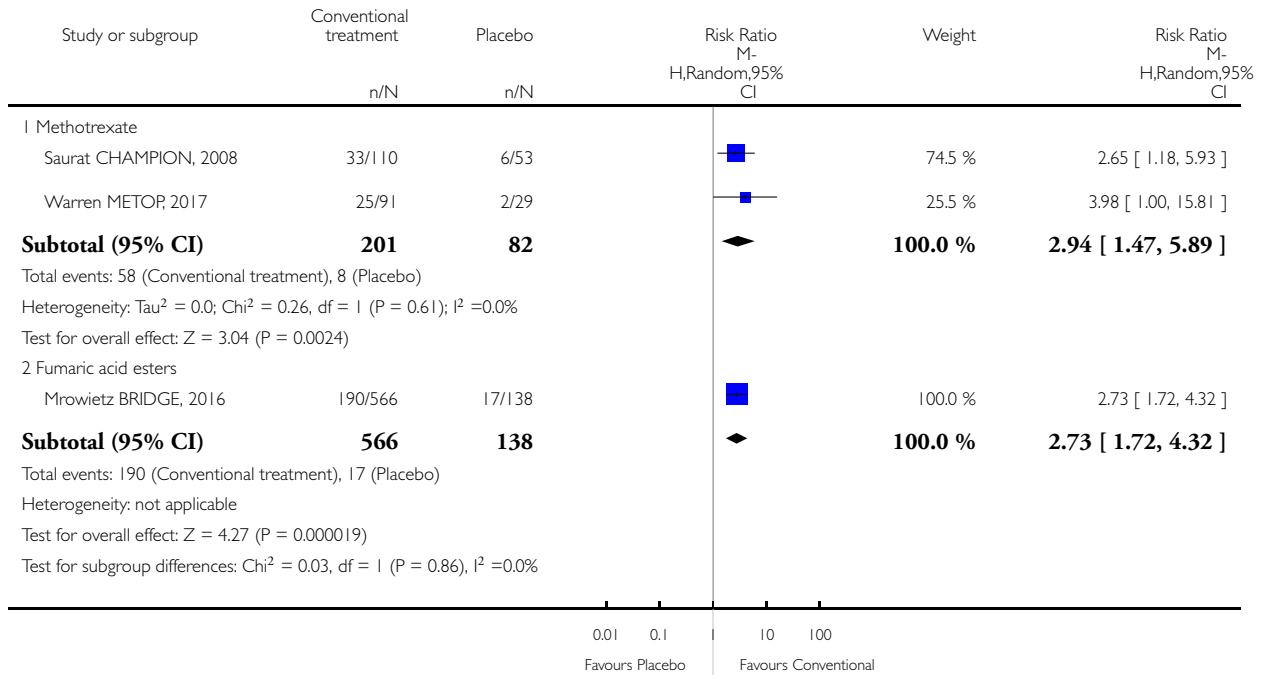


**Analysis 4.1. Comparison 4 Secondary outcome - PGA 0/1, Outcome 1 Conventional systemic agents versus placebo.**

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 4 Secondary outcome - PGA 0/1

Outcome: 1 Conventional systemic agents versus placebo

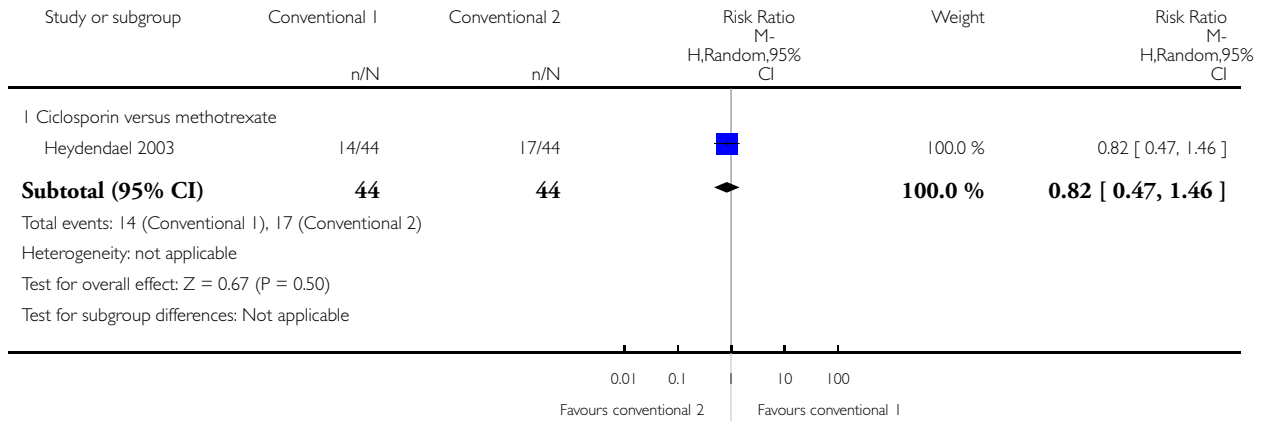


**Analysis 4.2. Comparison 4 Secondary outcome - PGA 0/1, Outcome 2 Conventional systemic 1 versus conventional systemic 2.**

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 4 Secondary outcome - PGA 0/1

Outcome: 2 Conventional systemic 1 versus conventional systemic 2



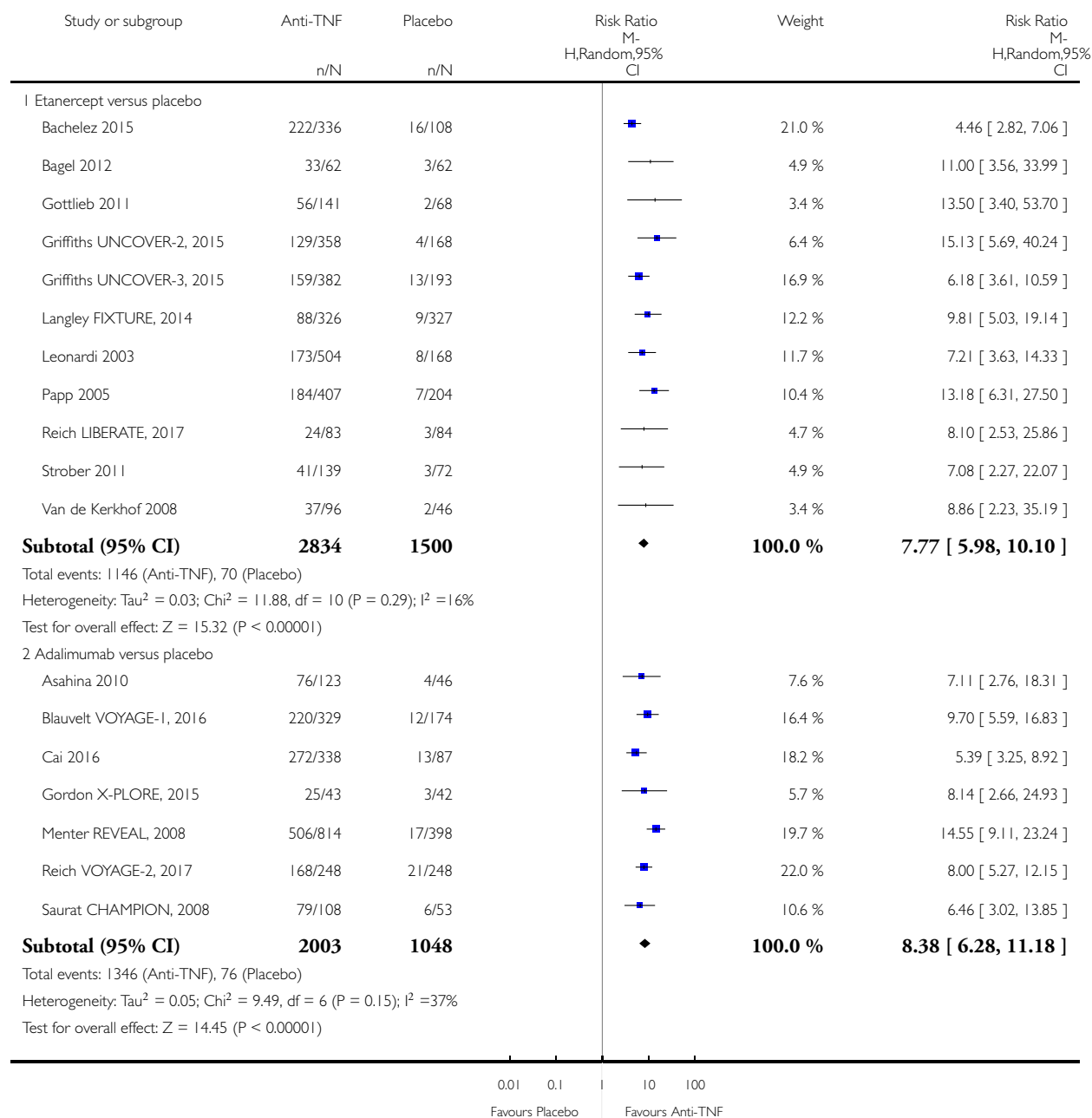


### Analysis 4.3. Comparison 4 Secondary outcome - PGA 0/1, Outcome 3 Anti-TNF alpha versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

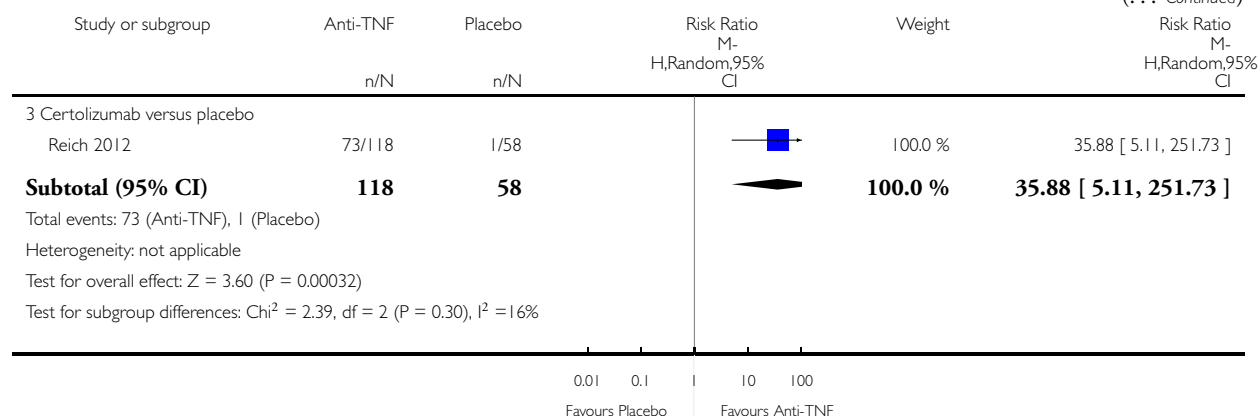
Comparison: 4 Secondary outcome - PGA 0/1

Outcome: 3 Anti-TNF alpha versus placebo



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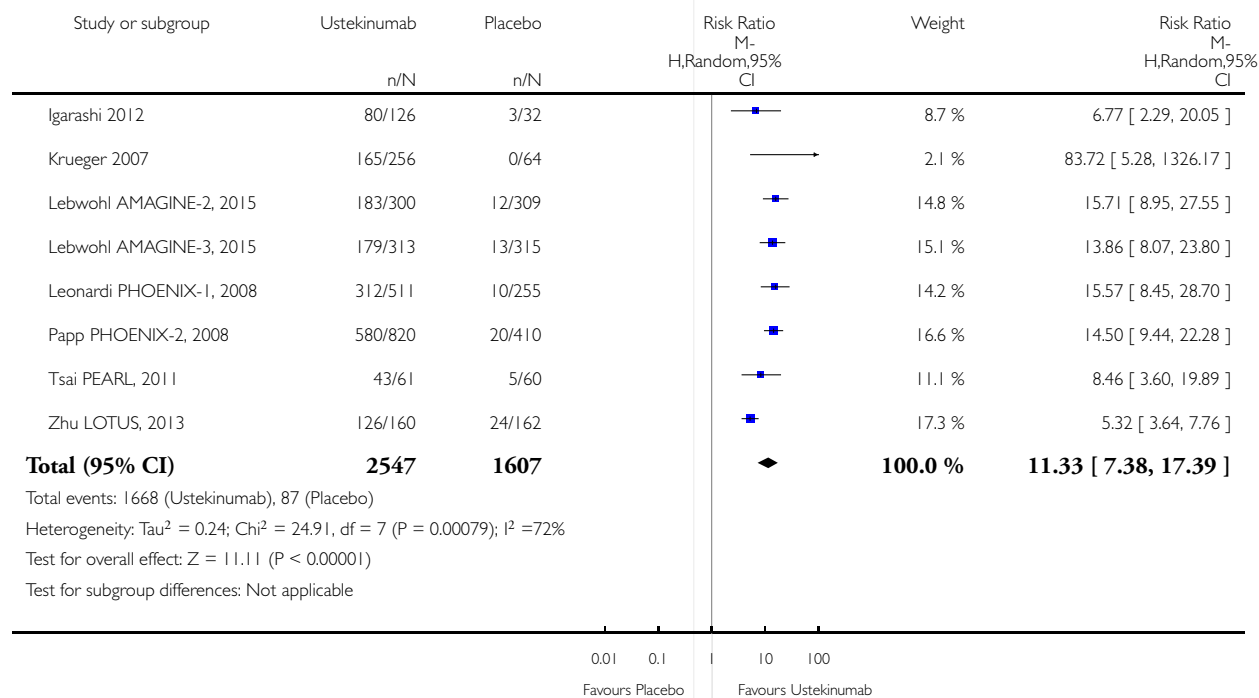


#### Analysis 4.4. Comparison 4 Secondary outcome - PGA 0/1, Outcome 4 Ustekinumab versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 4 Secondary outcome - PGA 0/1

Outcome: 4 Ustekinumab versus placebo

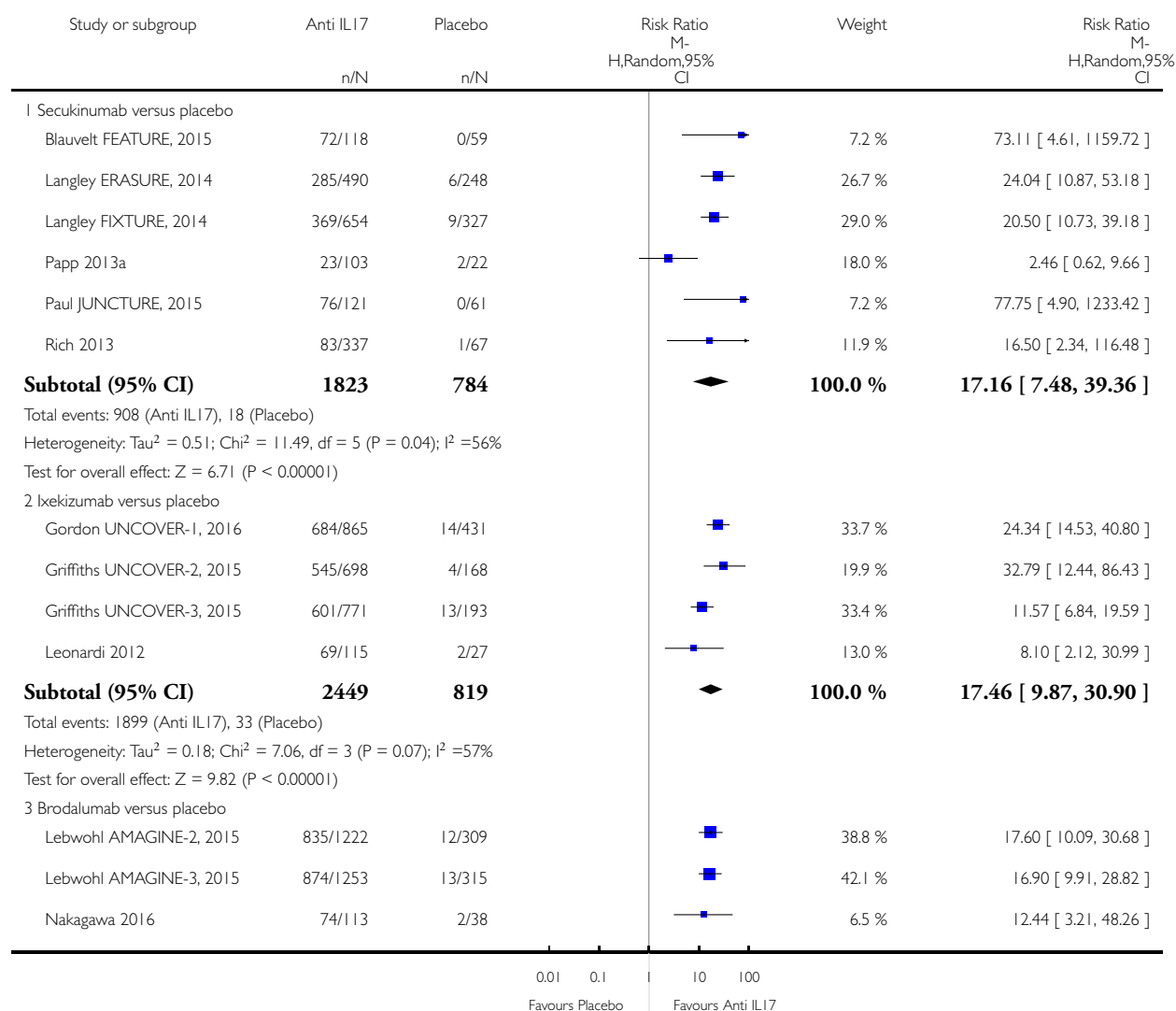


### Analysis 4.5. Comparison 4 Secondary outcome - PGA 0/1, Outcome 5 Anti-IL17 versus placebo.

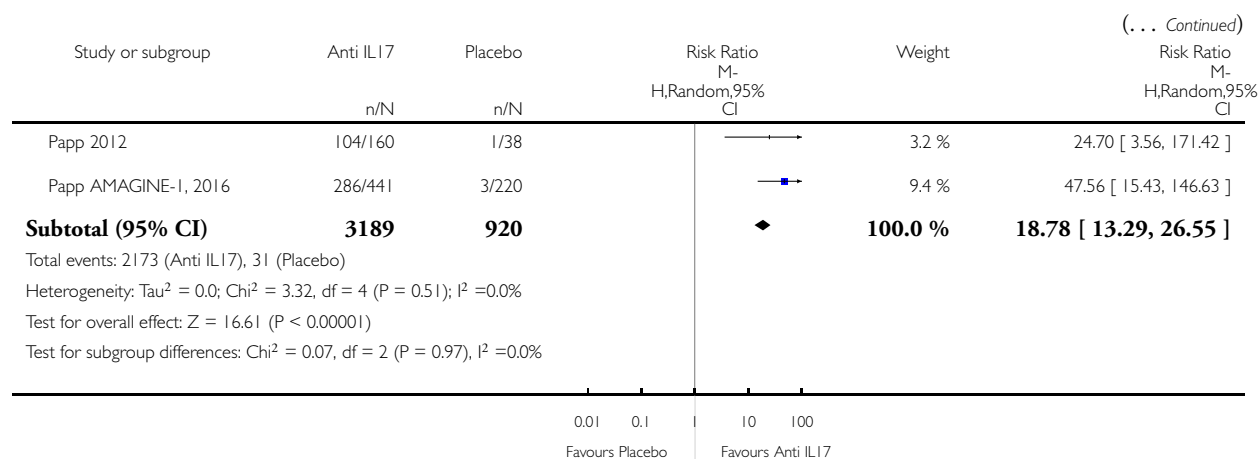
Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 4 Secondary outcome - PGA 0/1

Outcome: 5 Anti-IL17 versus placebo



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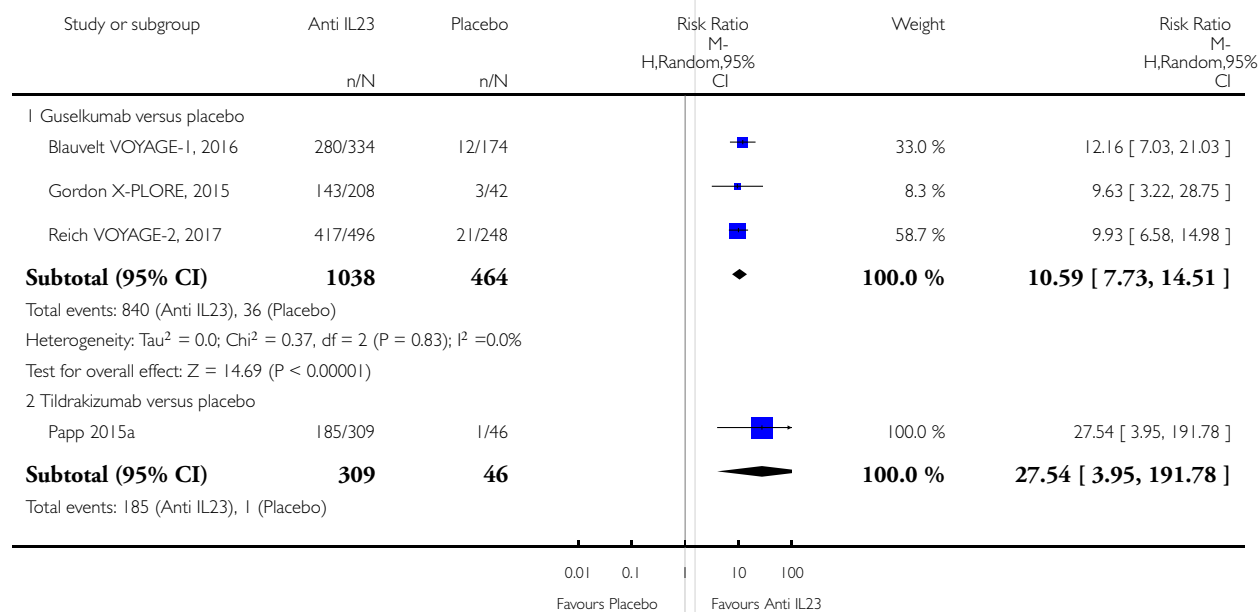


#### Analysis 4.6. Comparison 4 Secondary outcome - PGA 0/1, Outcome 6 Anti-IL23 versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 4 Secondary outcome - PGA 0/1

Outcome: 6 Anti-IL23 versus placebo



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Study or subgroup	Anti IL23 n/N	Placebo n/N	Risk Ratio M- H,Random,95% CI	Weight	Risk Ratio M- H,Random,95% CI
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Heterogeneity: not applicable  
 Test for overall effect:  $Z = 3.35$  ( $P = 0.00081$ )  
 Test for subgroup differences:  $\text{Chi}^2 = 0.91$ ,  $df = 1$  ( $P = 0.34$ ),  $I^2 = 0.0\%$

0.01 0.1 10 100  
 Favours Placebo Favours Anti IL23

#### Analysis 4.7. Comparison 4 Secondary outcome - PGA 0/1, Outcome 7 Other biologics.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 4 Secondary outcome - PGA 0/1

Outcome: 7 Other biologics

Study or subgroup	Other Biologics n/N	Placebo n/N	Risk Ratio M- H,Random,95% CI	Weight	Risk Ratio M- H,Random,95% CI
1 Alefacept versus placebo					
Lebwohl 2003	41/339	8/168		100.0 %	2.54 [ 1.22, 5.29 ]
<b>Subtotal (95% CI)</b>	<b>339</b>	<b>168</b>		<b>100.0 %</b>	<b>2.54 [ 1.22, 5.29 ]</b>
Total events: 41 (Other Biologics), 8 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: $Z = 2.49$ ( $P = 0.013$ )					
2 Itolizumab versus placebo					
Krupashankar 2014	32/182	2/43		100.0 %	3.78 [ 0.94, 15.17 ]
<b>Subtotal (95% CI)</b>	<b>182</b>	<b>43</b>		<b>100.0 %</b>	<b>3.78 [ 0.94, 15.17 ]</b>
Total events: 32 (Other Biologics), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: $Z = 1.88$ ( $P = 0.061$ )					
Test for subgroup differences: $\text{Chi}^2 = 0.25$ , $df = 1$ ( $P = 0.62$ ), $I^2 = 0.0\%$					

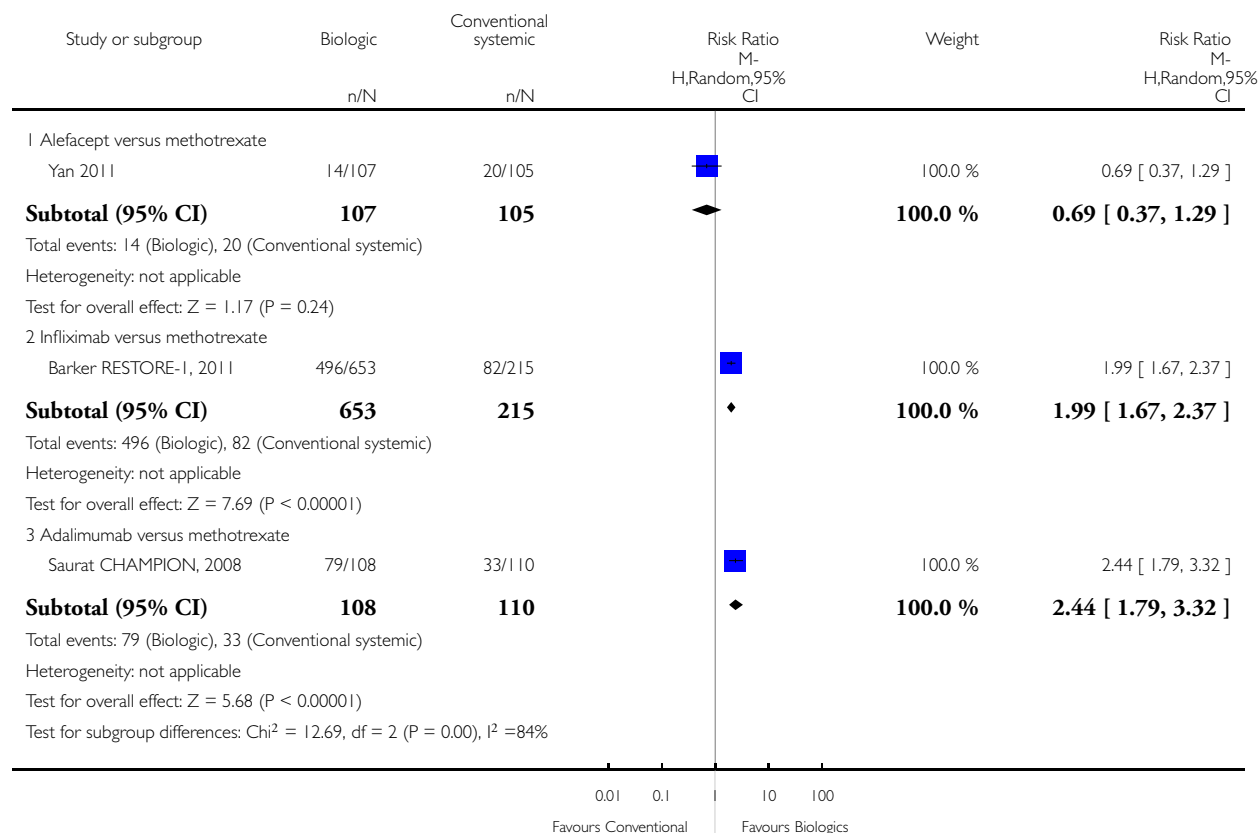
0.01 0.1 1 10 100  
 Favours Placebo Favours Other biologics

### Analysis 4.8. Comparison 4 Secondary outcome - PGA 0/I, Outcome 8 Biologic versus conventional systemic treatments.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 4 Secondary outcome - PGA 0/I

Outcome: 8 Biologic versus conventional systemic treatments

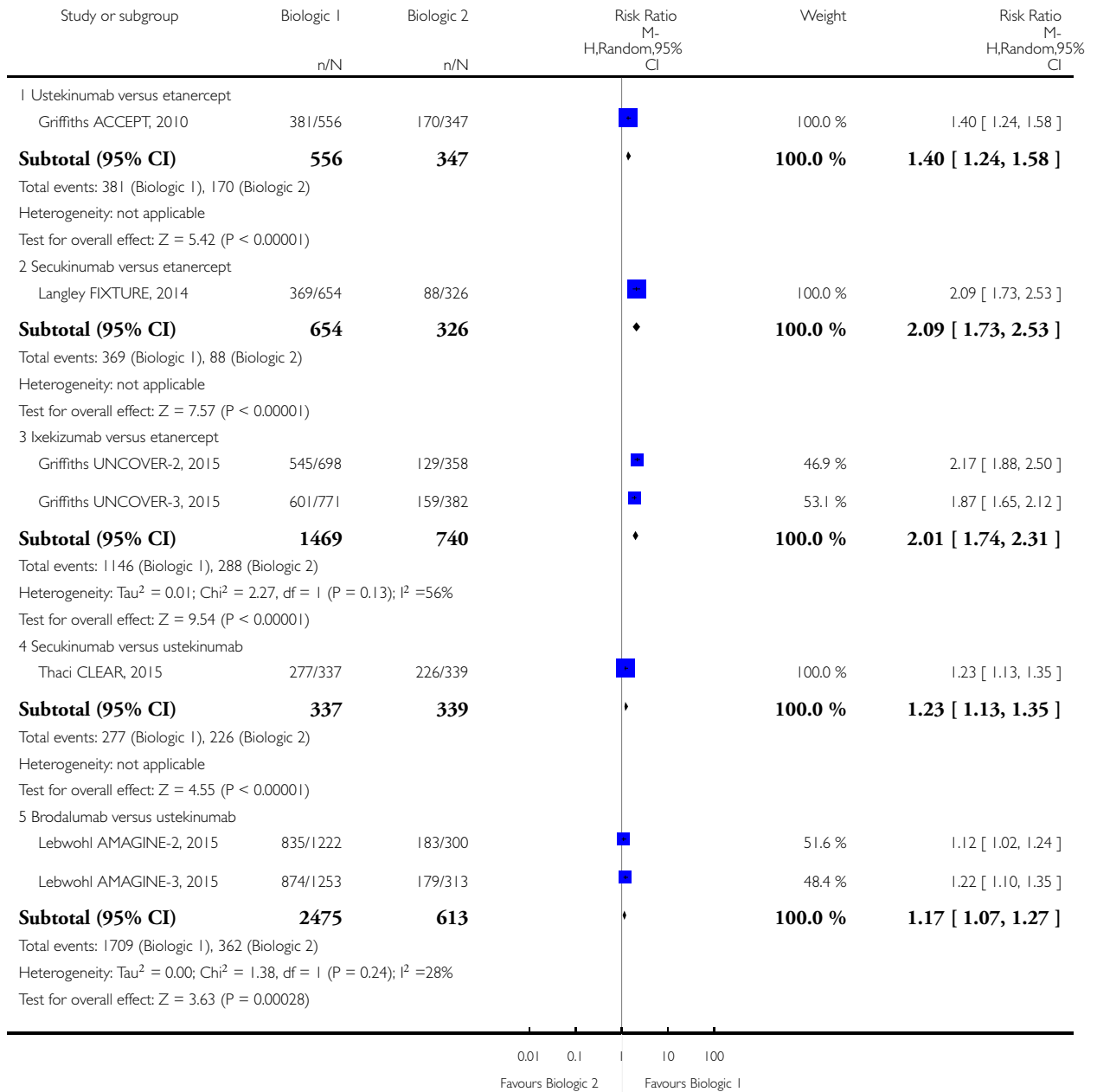


## Analysis 4.9. Comparison 4 Secondary outcome - PGA 0/I, Outcome 9 Biologic 1 versus biologic 2.

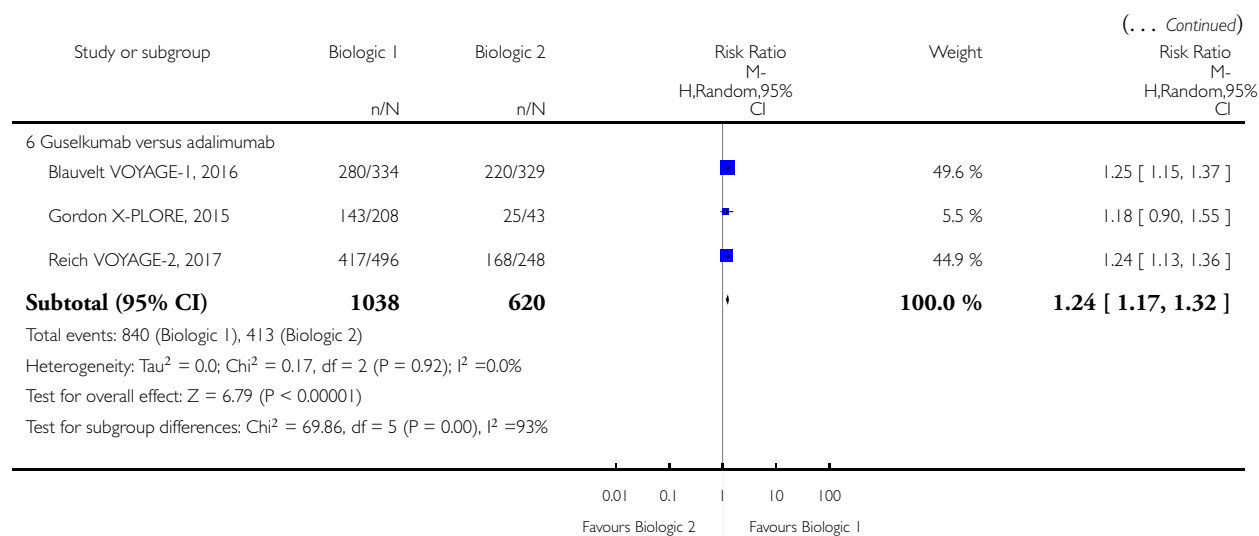
Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 4 Secondary outcome - PGA 0/I

Outcome: 9 Biologic 1 versus biologic 2



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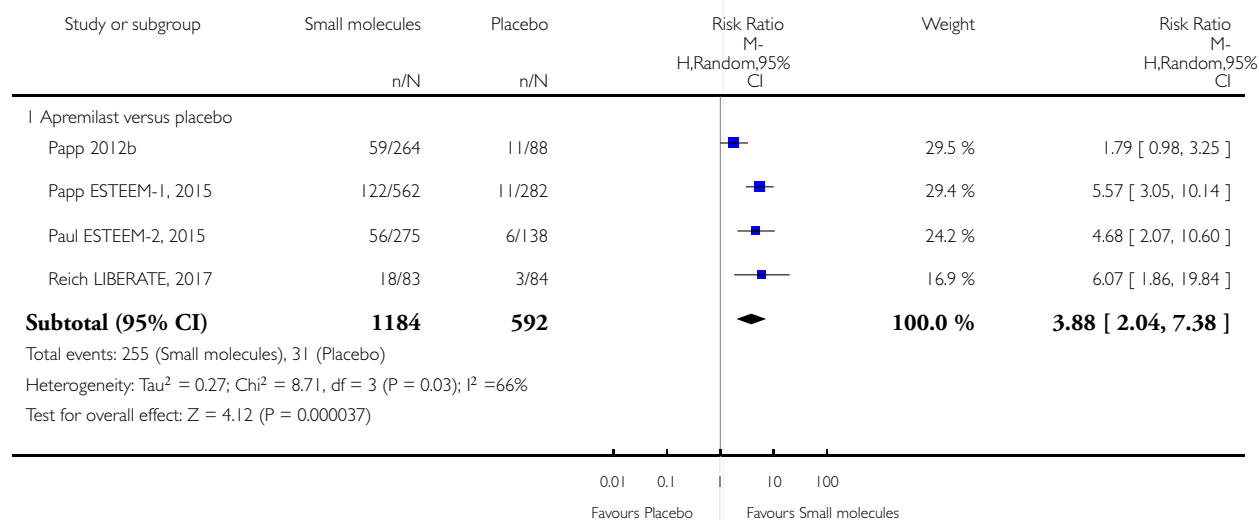


#### Analysis 4.10. Comparison 4 Secondary outcome - PGA 0/1, Outcome 10 Small molecules versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

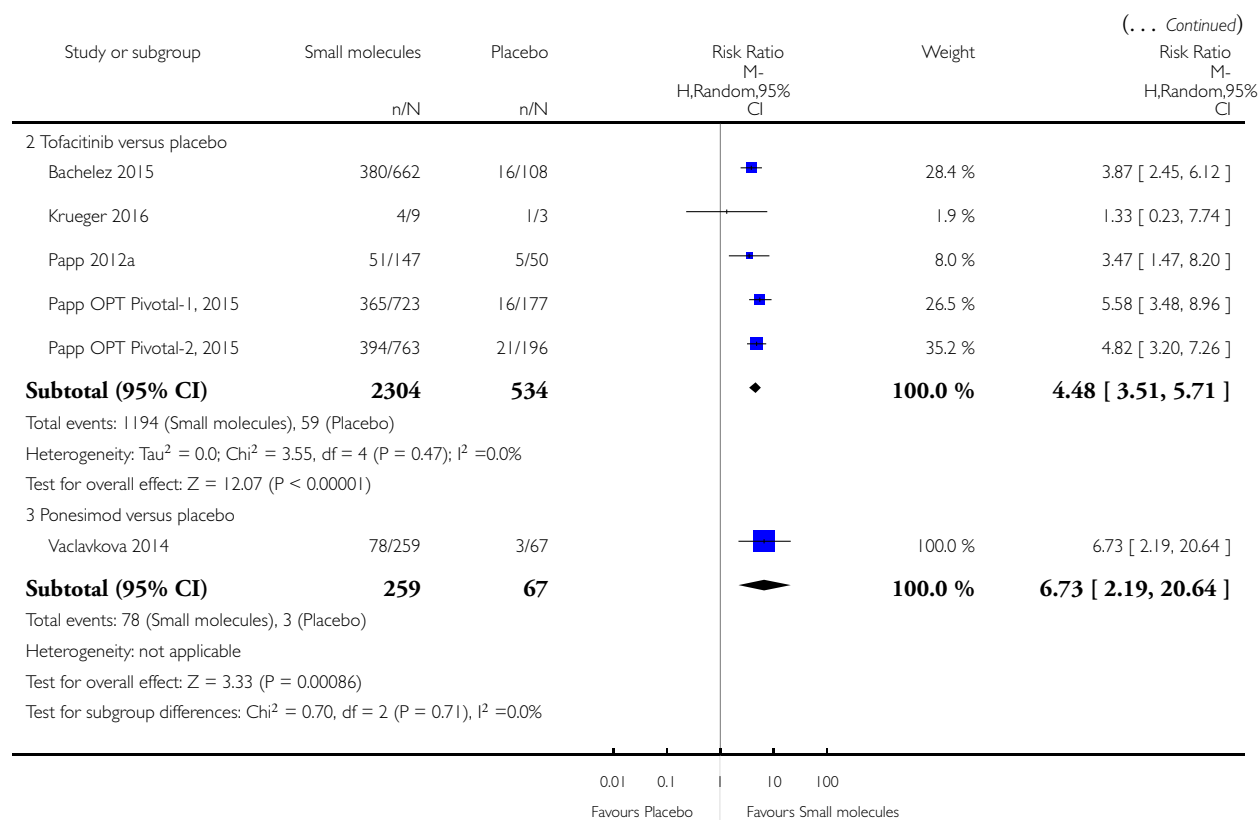
Comparison: 4 Secondary outcome - PGA 0/1

Outcome: 10 Small molecules versus placebo



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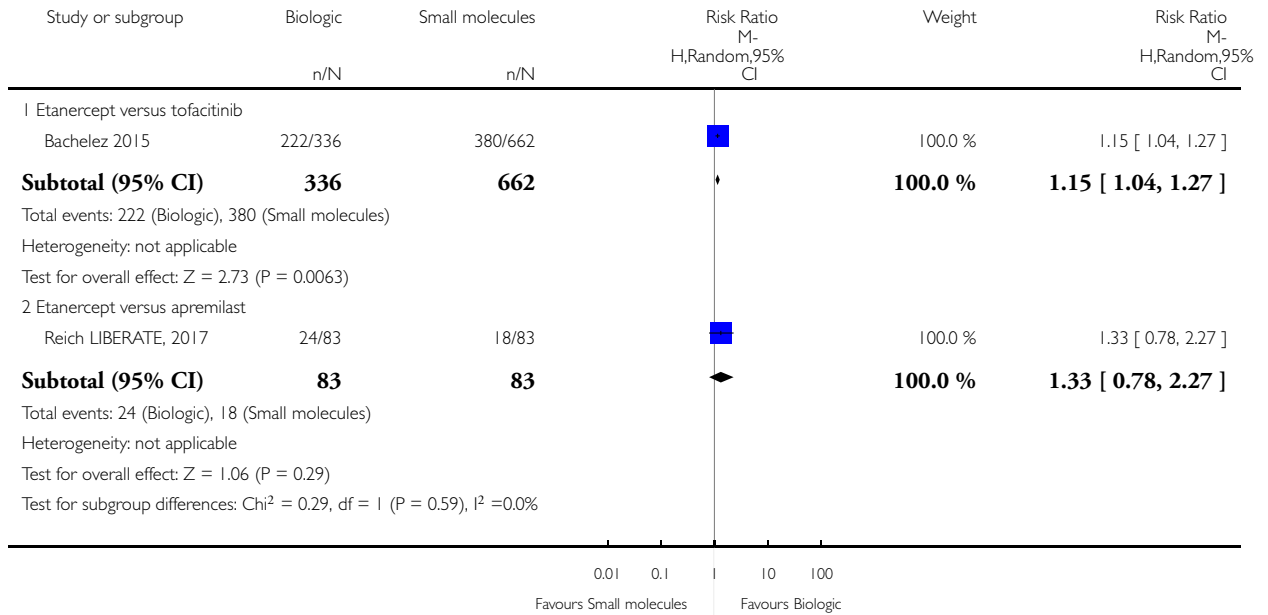


### Analysis 4.11. Comparison 4 Secondary outcome - PGA 0/I, Outcome 11 Biologic versus small molecules.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 4 Secondary outcome - PGA 0/I

Outcome: 11 Biologic versus small molecules

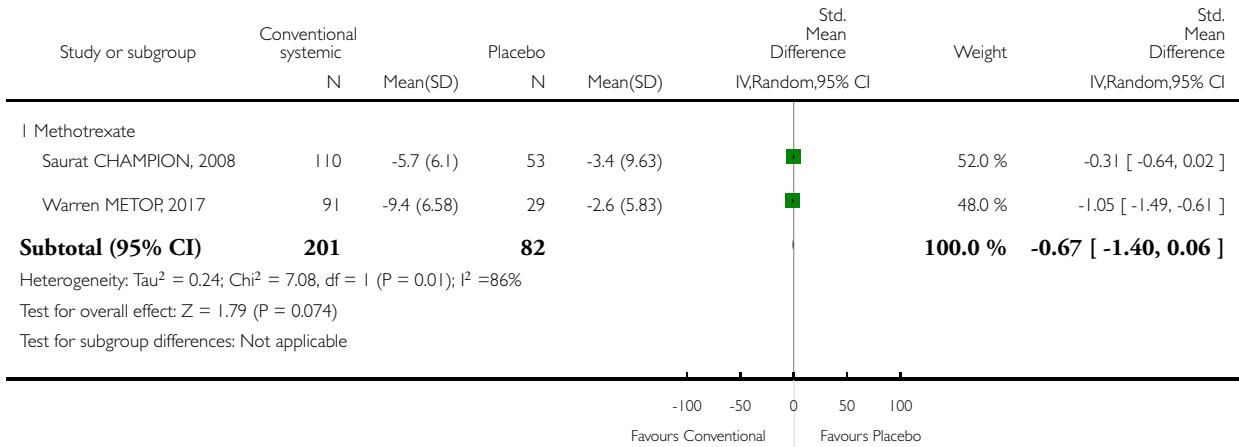


**Analysis 5.1. Comparison 5 Secondary outcome - quality of life, Outcome 1 Conventional systemic agents versus placebo.**

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 5 Secondary outcome - quality of life

Outcome: 1 Conventional systemic agents versus placebo

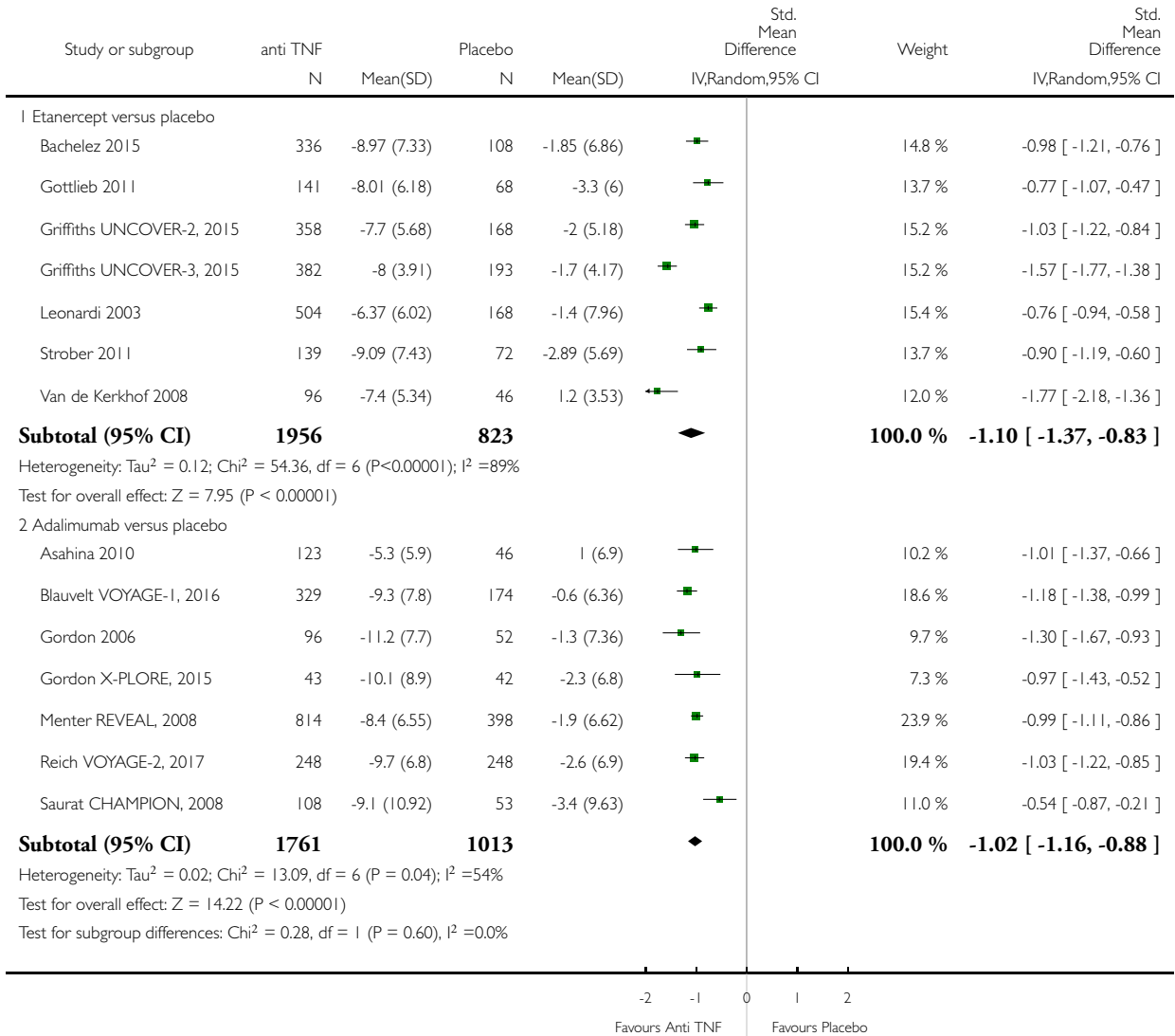


## Analysis 5.2. Comparison 5 Secondary outcome - quality of life, Outcome 2 Anti-TNF alpha versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 5 Secondary outcome - quality of life

Outcome: 2 Anti-TNF alpha versus placebo

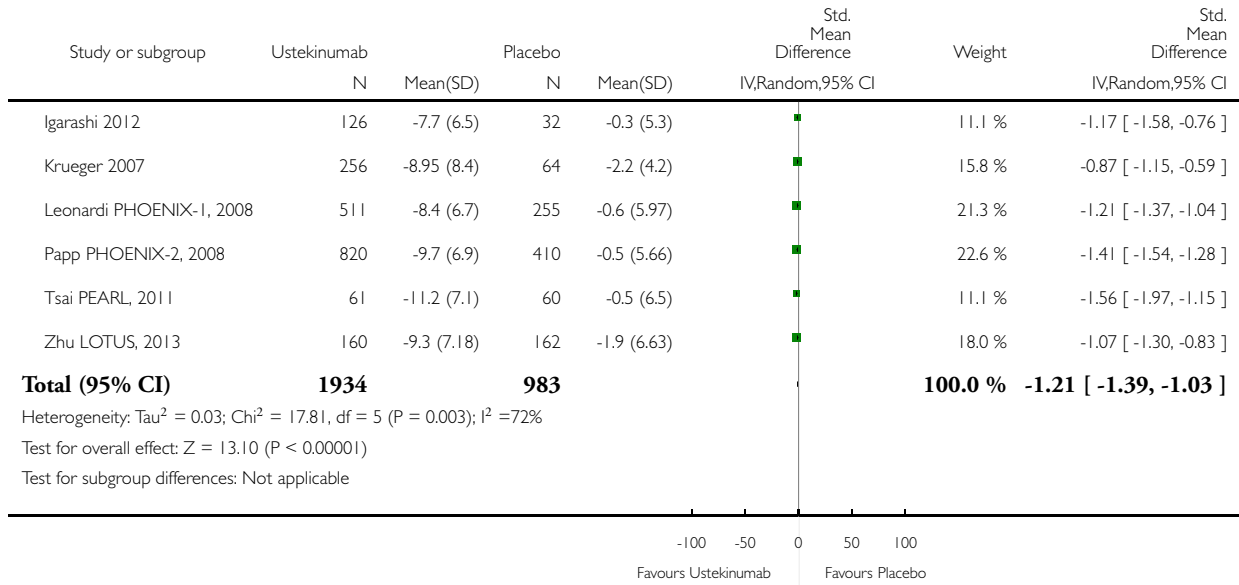


### Analysis 5.3. Comparison 5 Secondary outcome - quality of life, Outcome 3 Ustekinumab versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 5 Secondary outcome - quality of life

Outcome: 3 Ustekinumab versus placebo

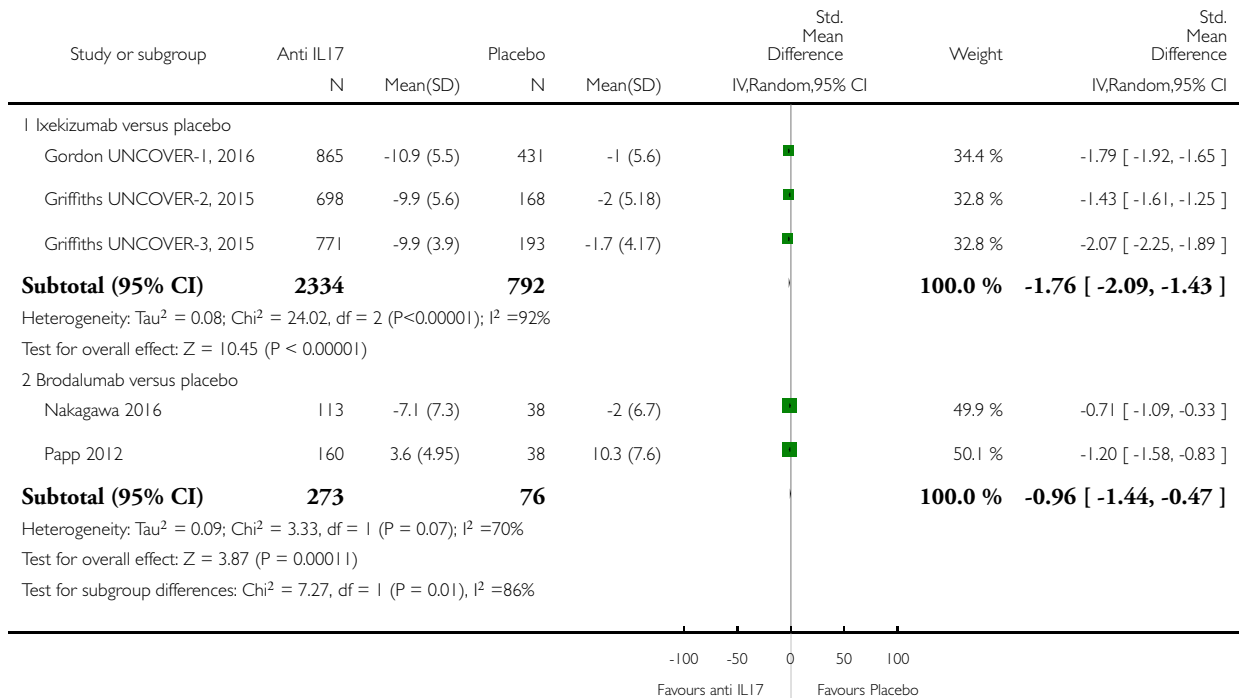


### Analysis 5.4. Comparison 5 Secondary outcome - quality of life, Outcome 4 Anti-IL17 versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 5 Secondary outcome - quality of life

Outcome: 4 Anti-IL17 versus placebo

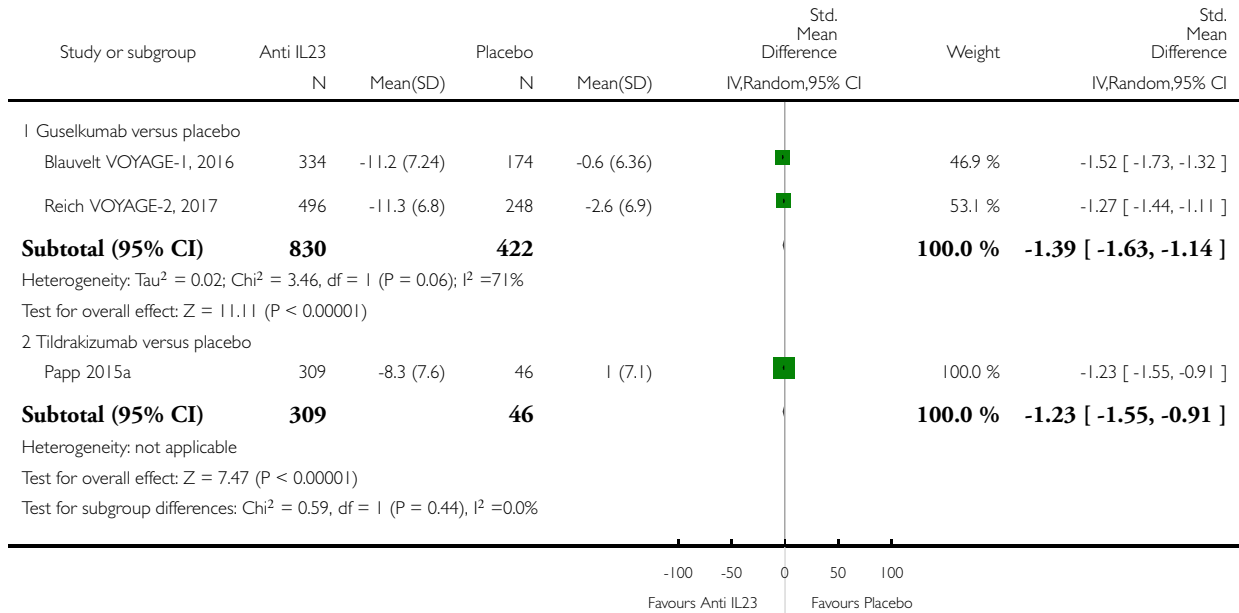


### Analysis 5.5. Comparison 5 Secondary outcome - quality of life, Outcome 5 Anti-IL23 versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 5 Secondary outcome - quality of life

Outcome: 5 Anti-IL23 versus placebo

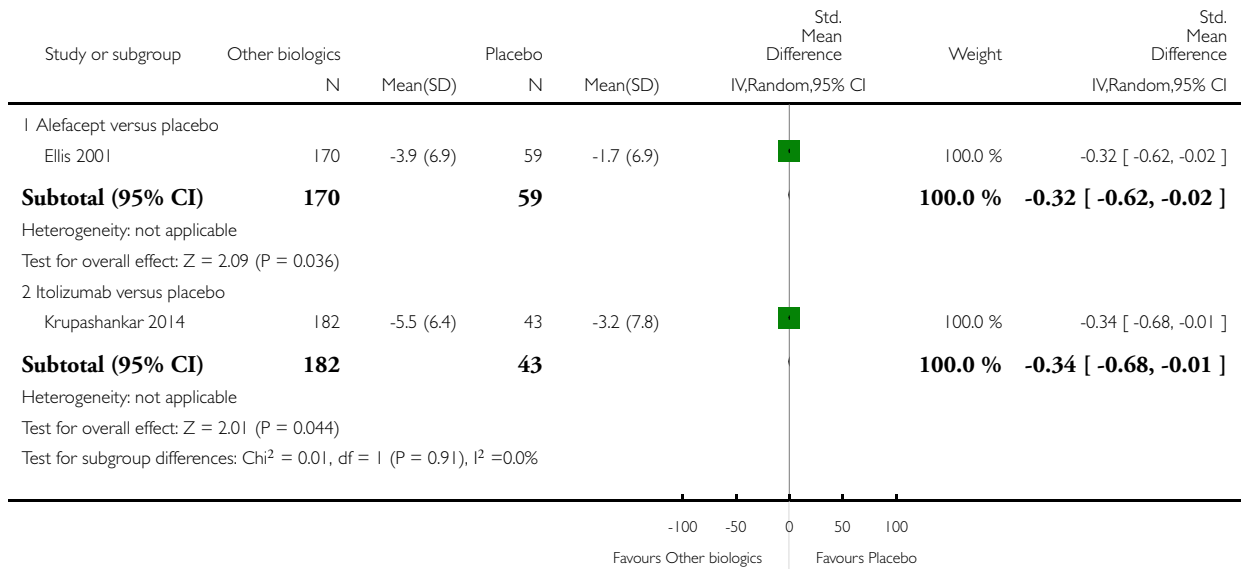


### Analysis 5.6. Comparison 5 Secondary outcome - quality of life, Outcome 6 Other biologics.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 5 Secondary outcome - quality of life

Outcome: 6 Other biologics



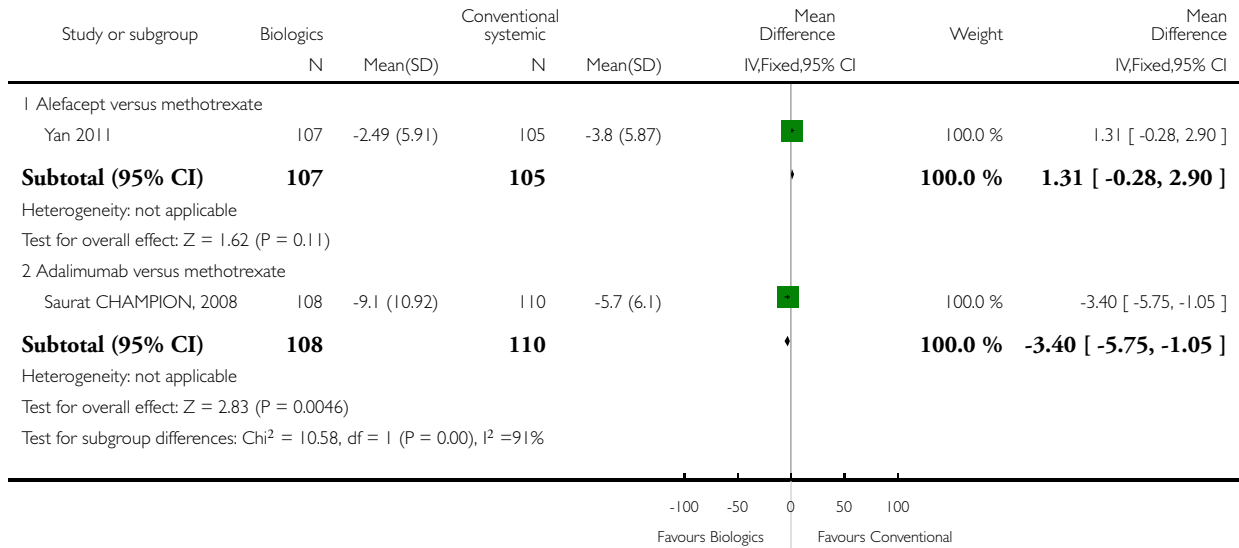


### Analysis 5.7. Comparison 5 Secondary outcome - quality of life, Outcome 7 Biologic versus conventional systemic treatments.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 5 Secondary outcome - quality of life

Outcome: 7 Biologic versus conventional systemic treatments

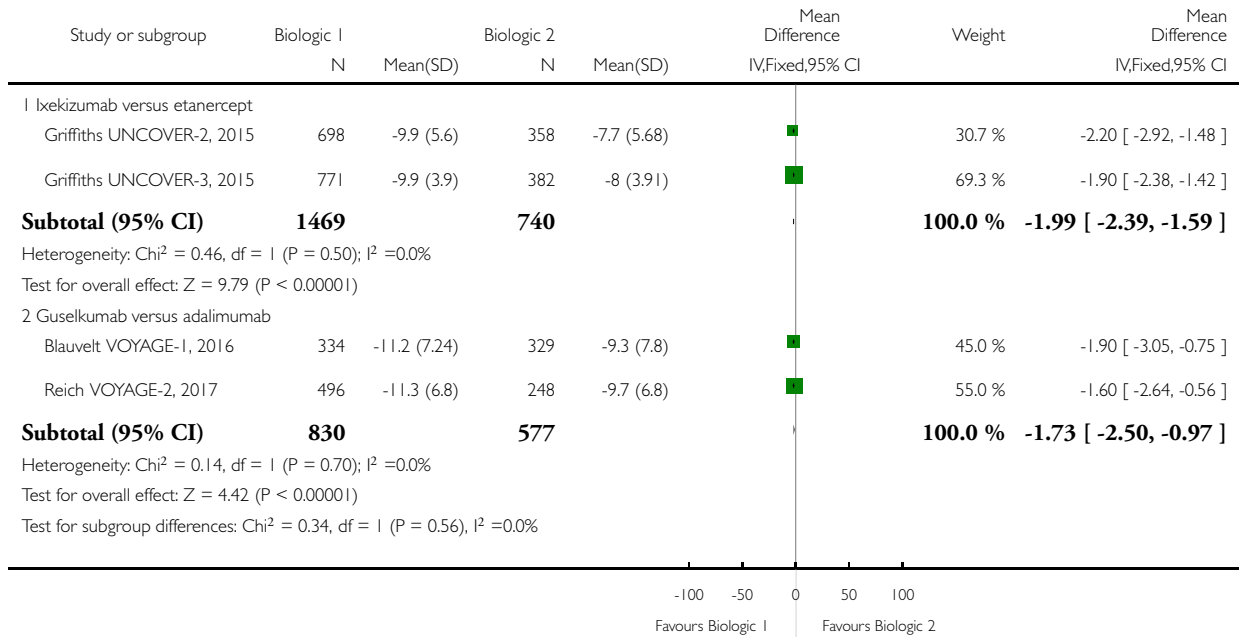


### Analysis 5.8. Comparison 5 Secondary outcome - quality of life, Outcome 8 Biologic 1 versus biologic 2.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 5 Secondary outcome - quality of life

Outcome: 8 Biologic 1 versus biologic 2

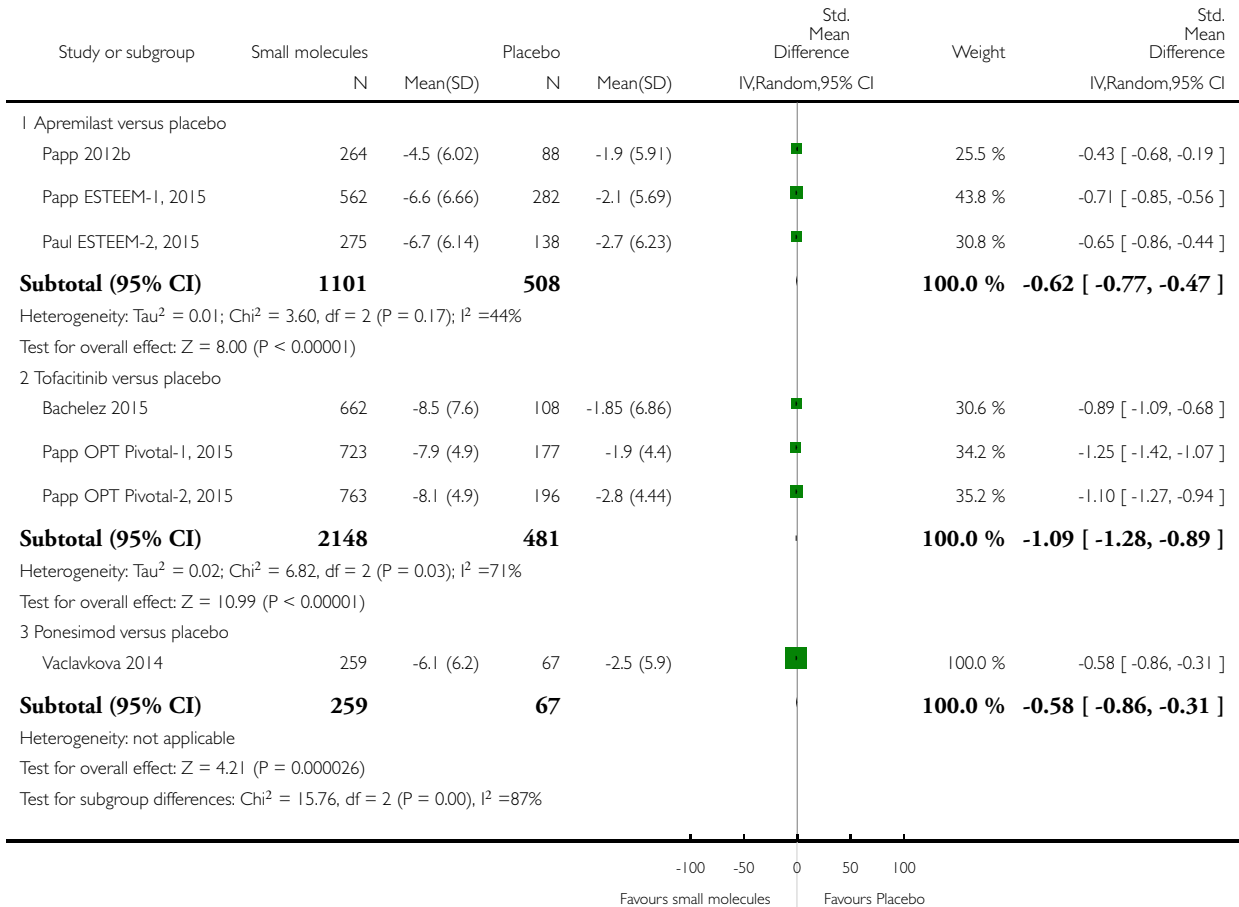


### Analysis 5.9. Comparison 5 Secondary outcome - quality of life, Outcome 9 Small molecules versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 5 Secondary outcome - quality of life

Outcome: 9 Small molecules versus placebo

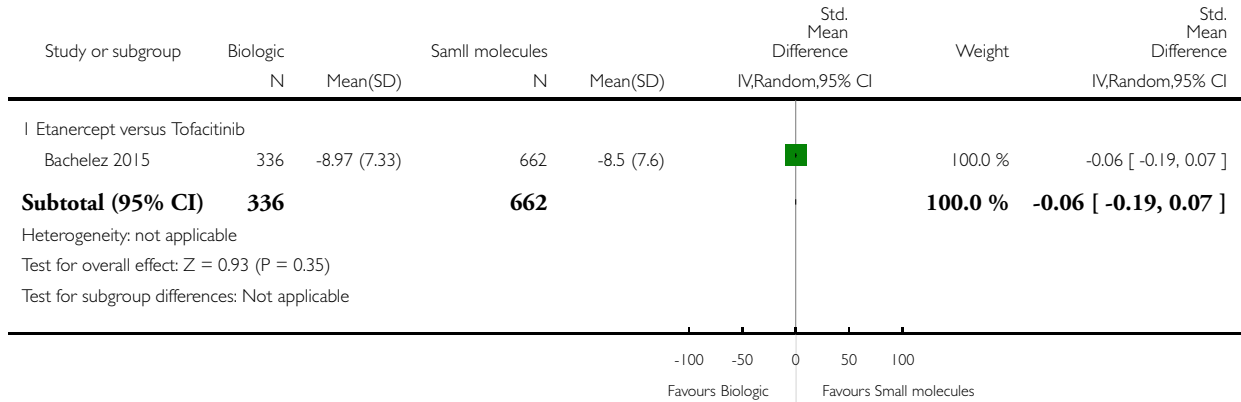


**Analysis 5.10. Comparison 5 Secondary outcome - quality of life, Outcome 10 Biologic versus small molecules.**

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 5 Secondary outcome - quality of life

Outcome: 10 Biologic versus small molecules

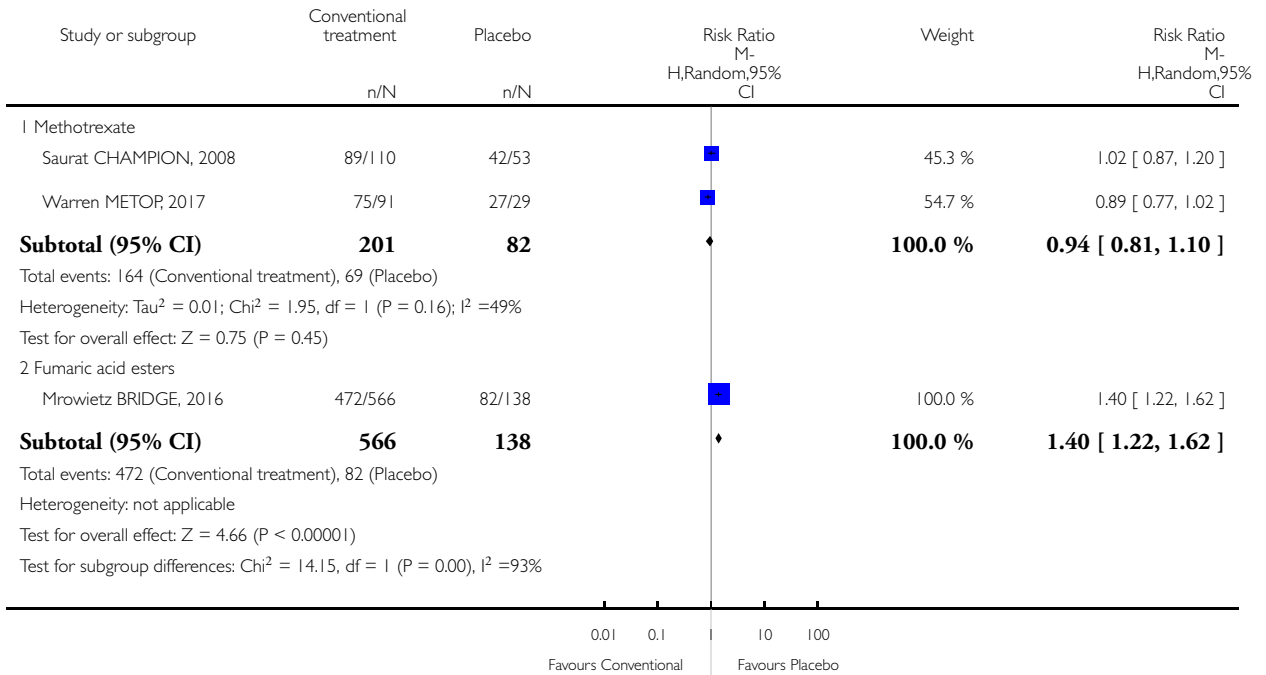


**Analysis 6.1. Comparison 6 Secondary outcome - adverse events, Outcome 1 Conventional systemic agents versus placebo.**

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 6 Secondary outcome - adverse events

Outcome: 1 Conventional systemic agents versus placebo

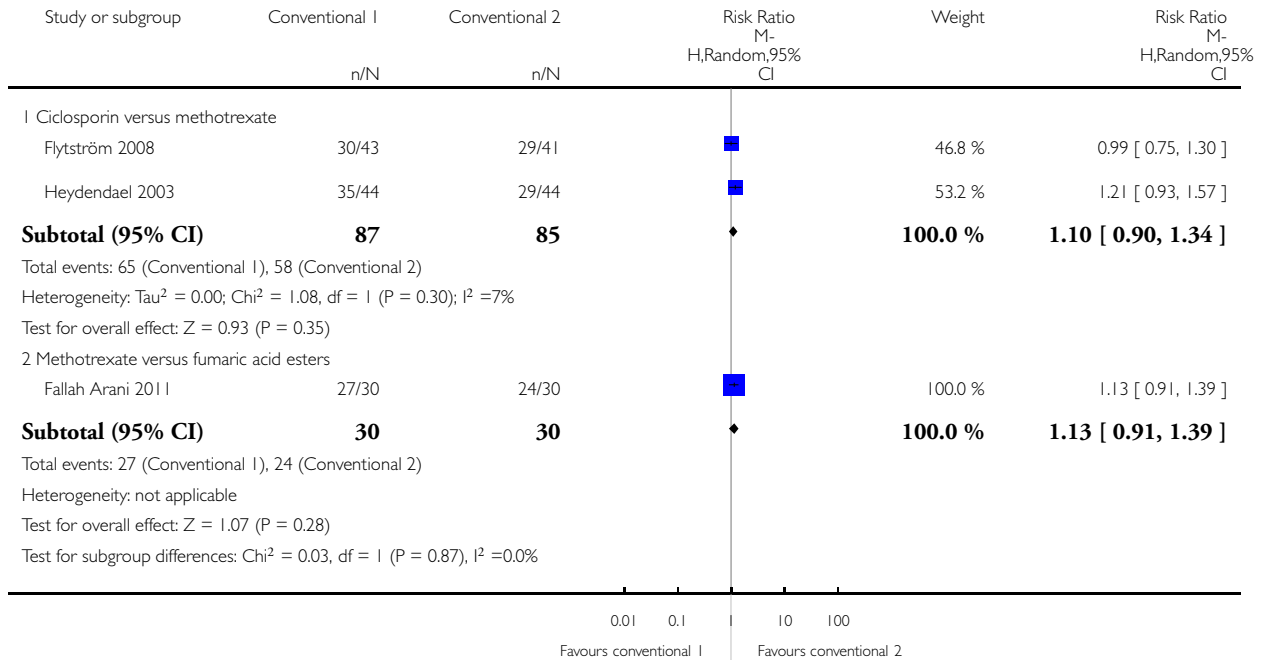


## Analysis 6.2. Comparison 6 Secondary outcome - adverse events, Outcome 2 Conventional systemic 1 versus conventional systemic 2.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 6 Secondary outcome - adverse events

Outcome: 2 Conventional systemic 1 versus conventional systemic 2

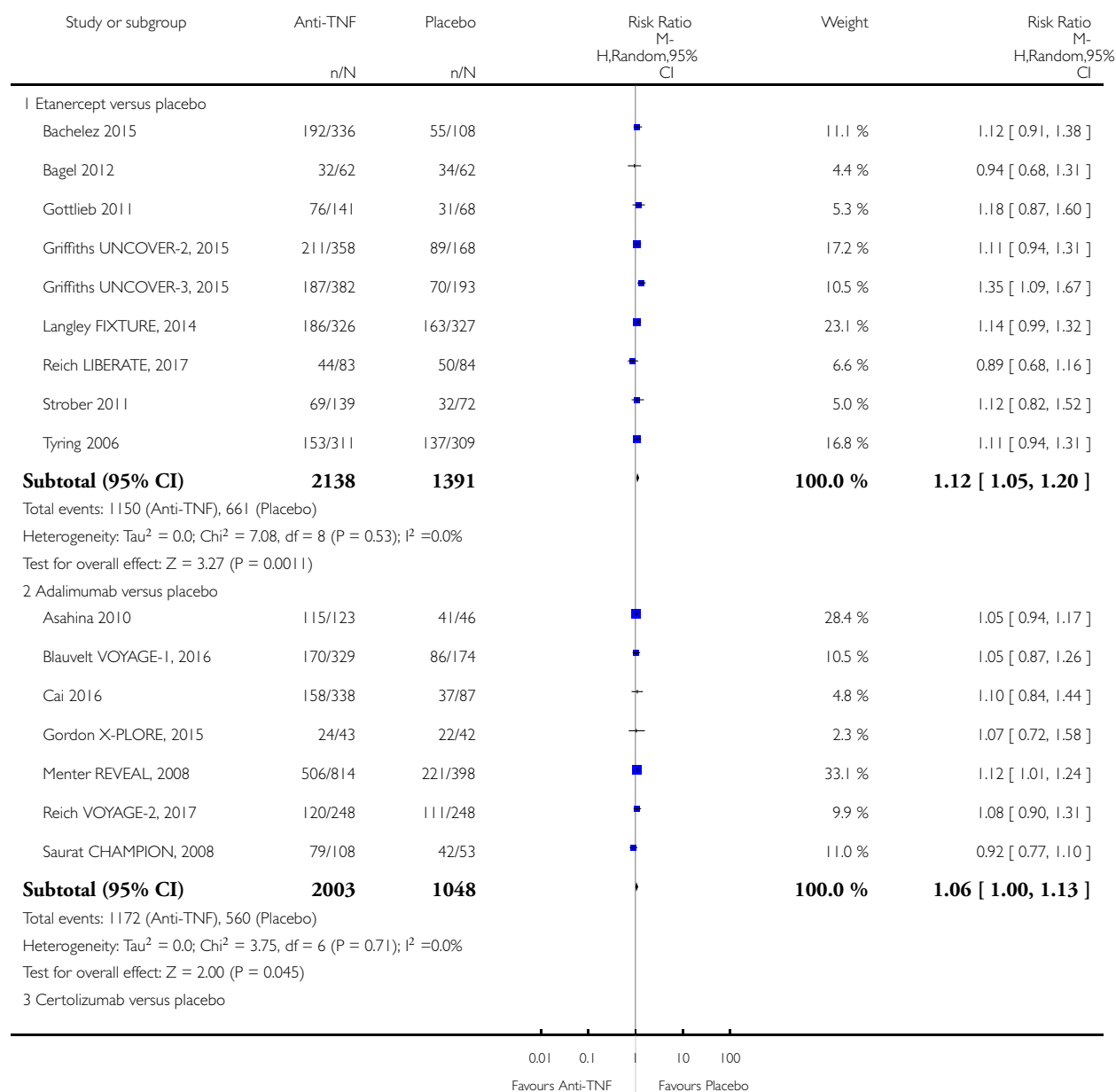


### Analysis 6.3. Comparison 6 Secondary outcome - adverse events, Outcome 3 Anti-TNF alpha versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

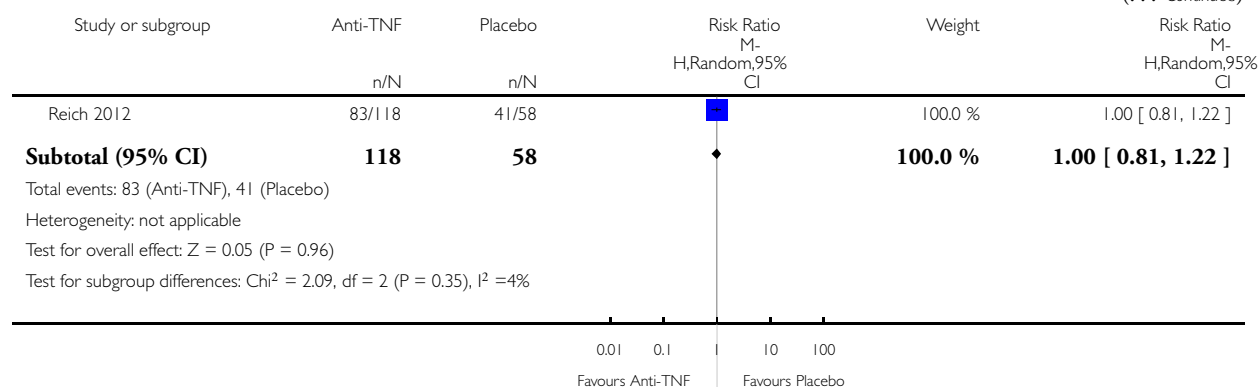
Comparison: 6 Secondary outcome - adverse events

Outcome: 3 Anti-TNF alpha versus placebo



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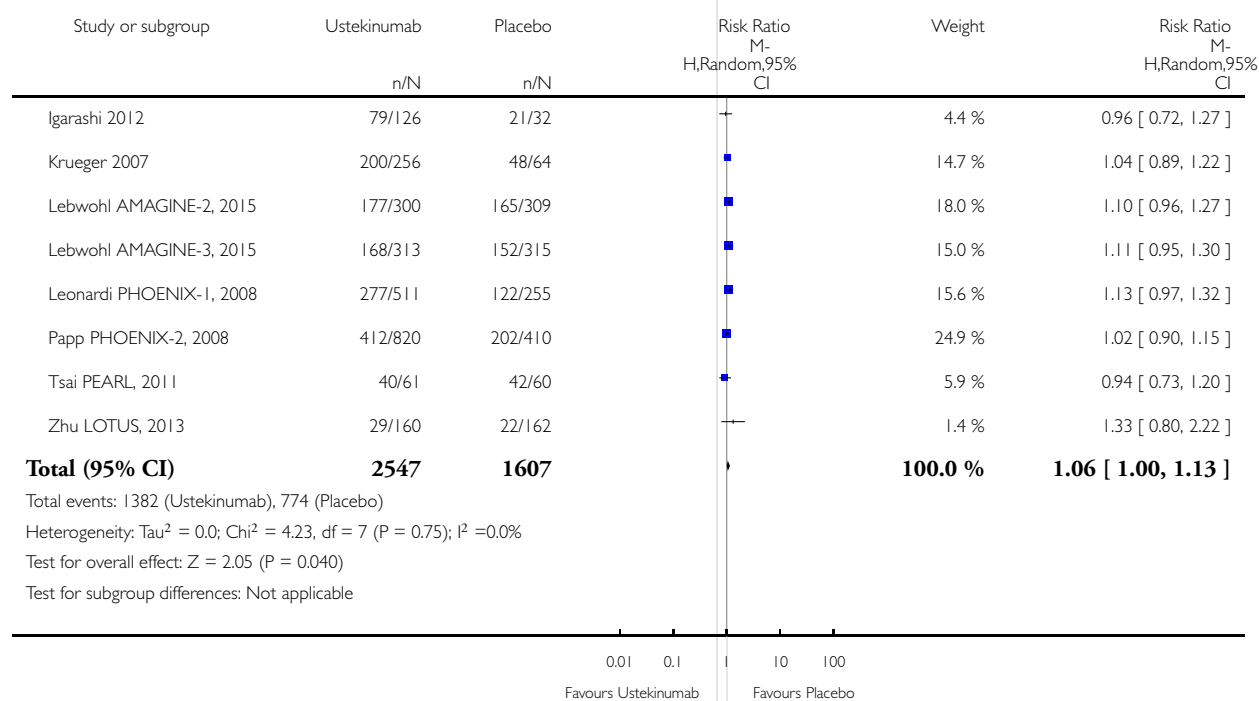


#### Analysis 6.4. Comparison 6 Secondary outcome - adverse events, Outcome 4 Ustekinumab versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 6 Secondary outcome - adverse events

Outcome: 4 Ustekinumab versus placebo



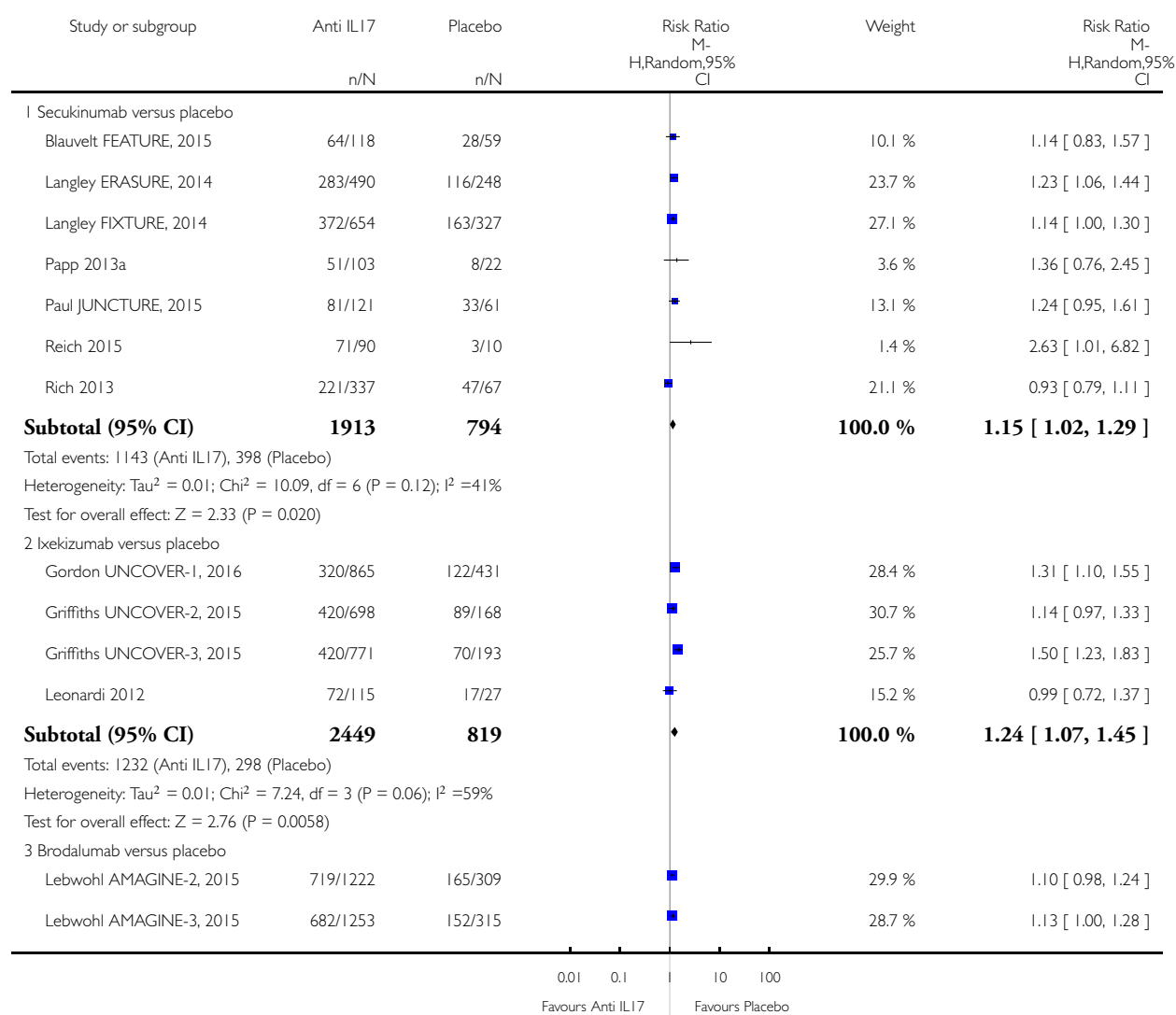


### Analysis 6.5. Comparison 6 Secondary outcome - adverse events, Outcome 5 Anti-IL17 versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

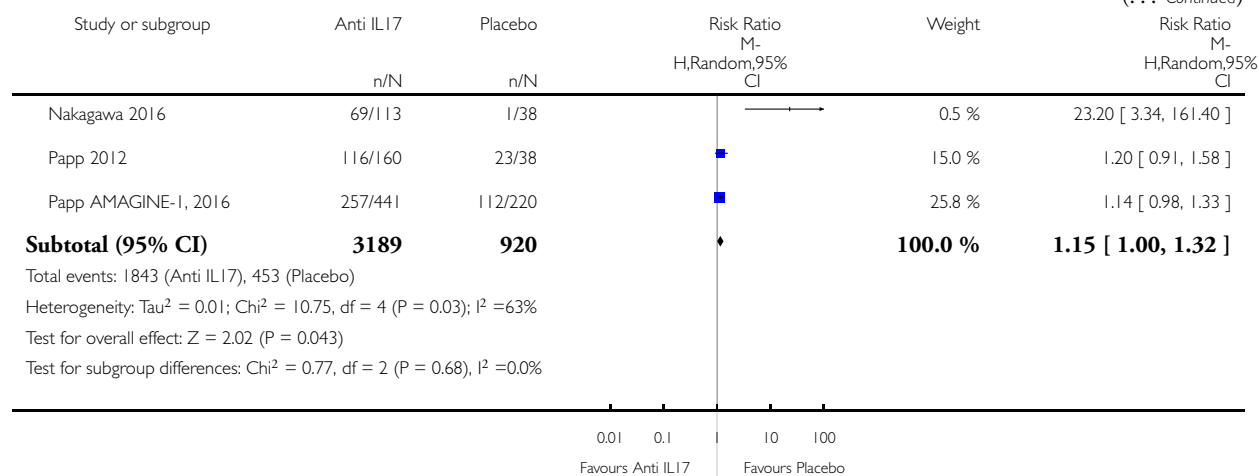
Comparison: 6 Secondary outcome - adverse events

Outcome: 5 Anti-IL17 versus placebo



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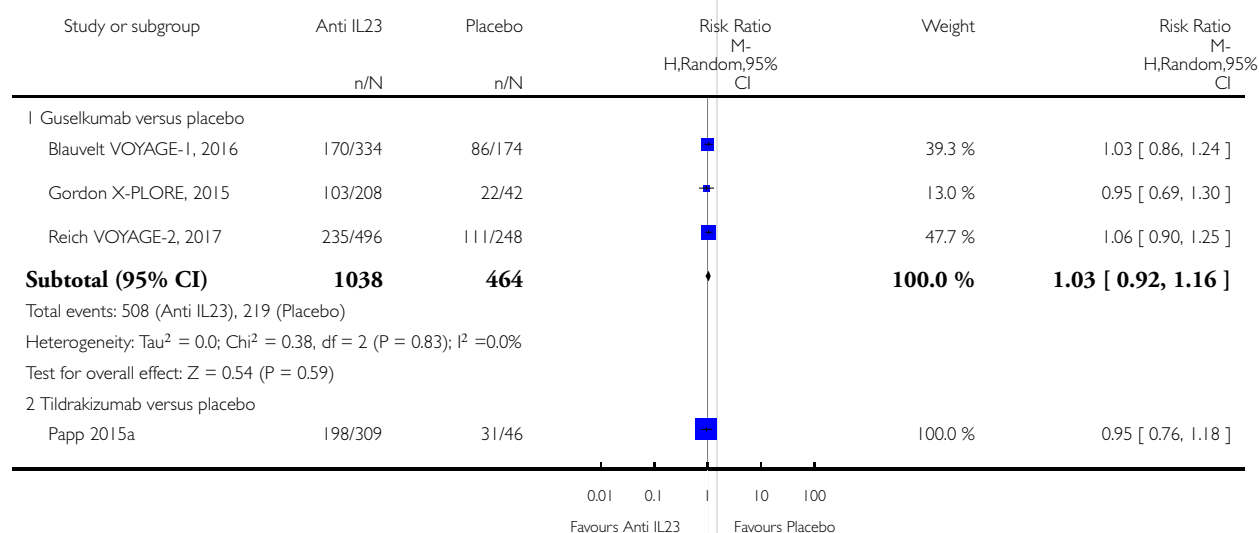


### Analysis 6.6. Comparison 6 Secondary outcome - adverse events, Outcome 6 Anti-IL23 versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

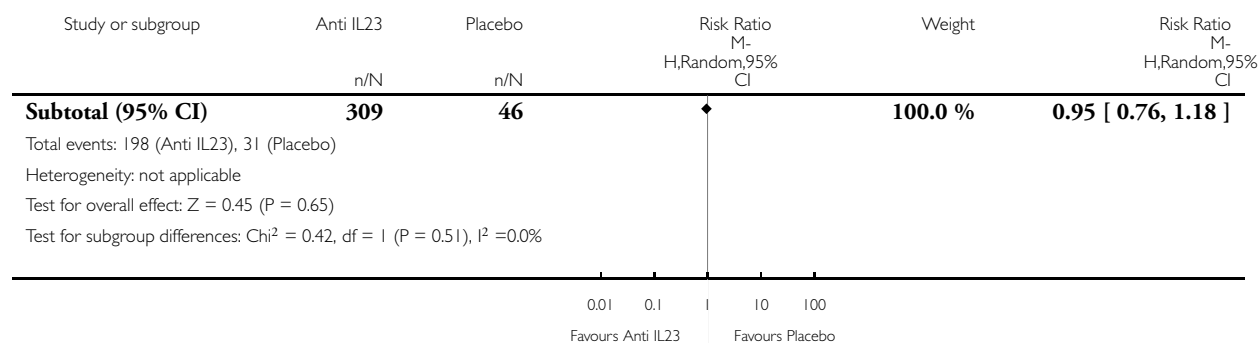
Comparison: 6 Secondary outcome - adverse events

Outcome: 6 Anti-IL23 versus placebo



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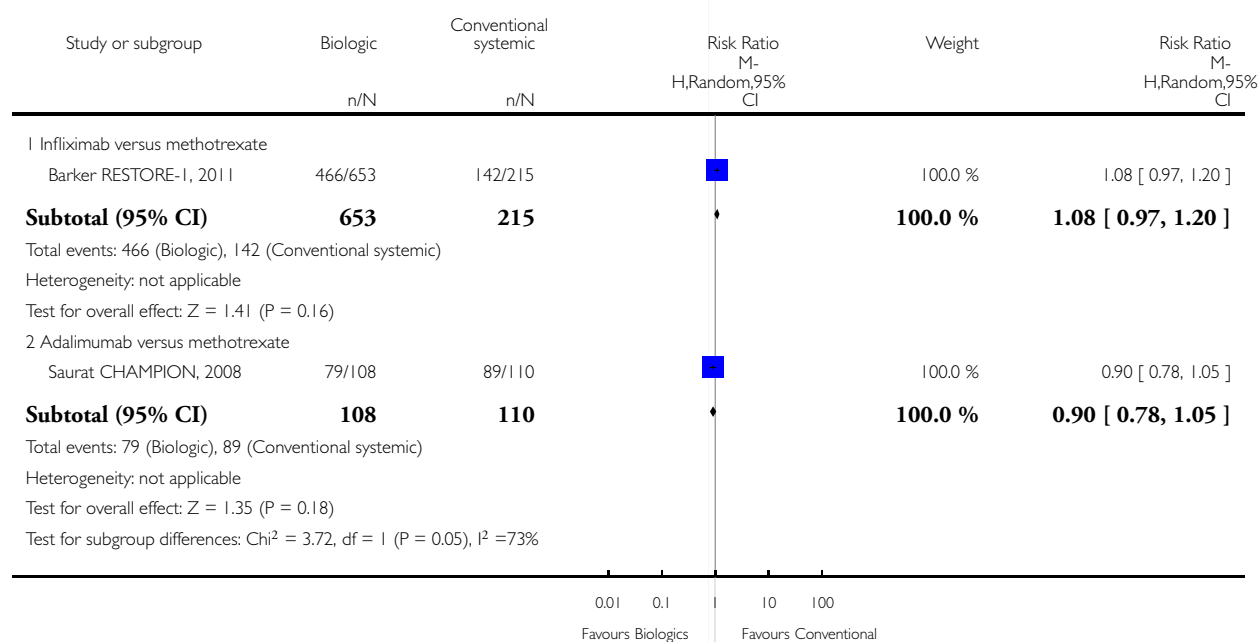


### Analysis 6.7. Comparison 6 Secondary outcome - adverse events, Outcome 7 Biologic versus conventional systemic treatments.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 6 Secondary outcome - adverse events

Outcome: 7 Biologic versus conventional systemic treatments

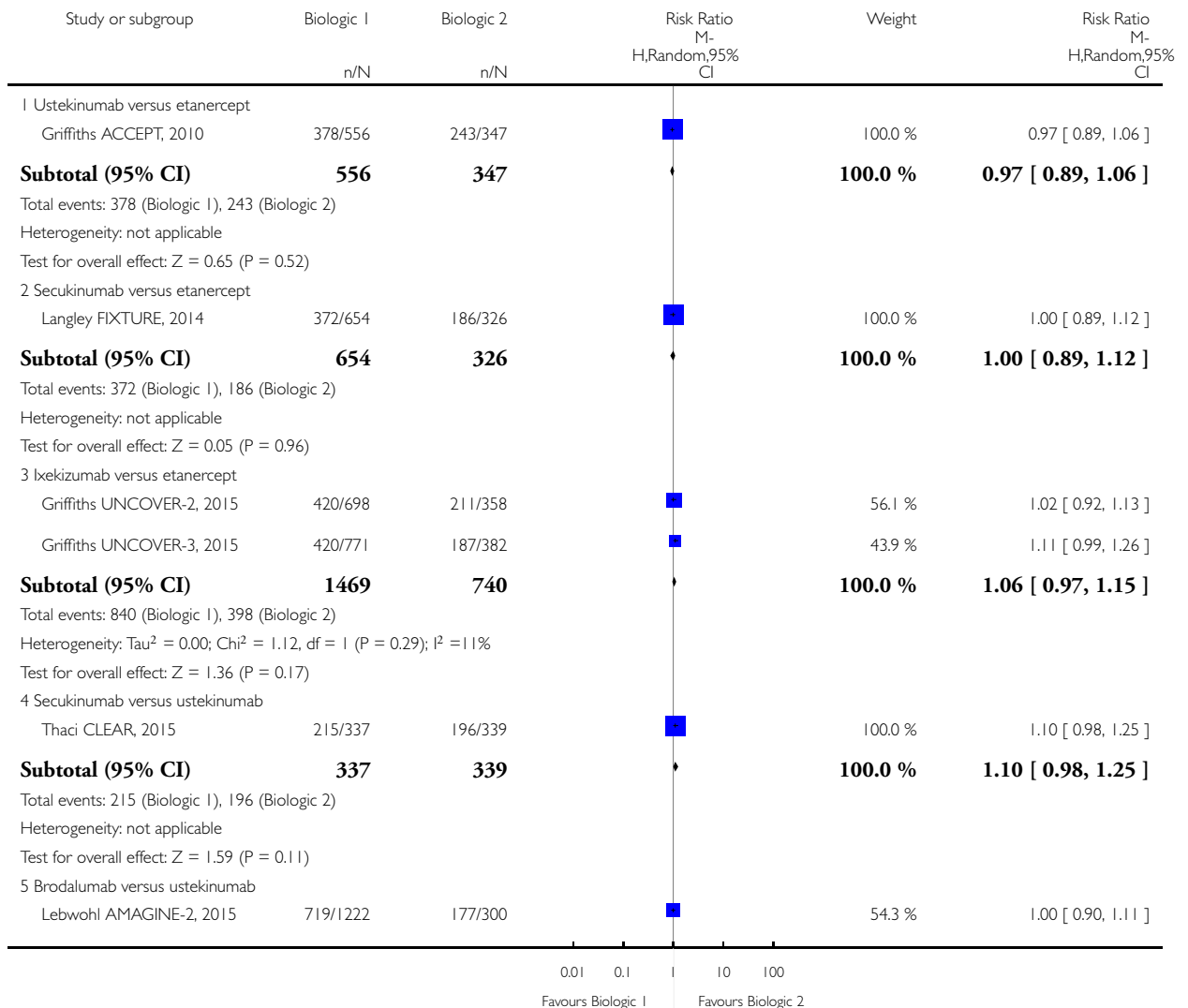


## Analysis 6.8. Comparison 6 Secondary outcome - adverse events, Outcome 8 Biologic 1 versus biologic 2.

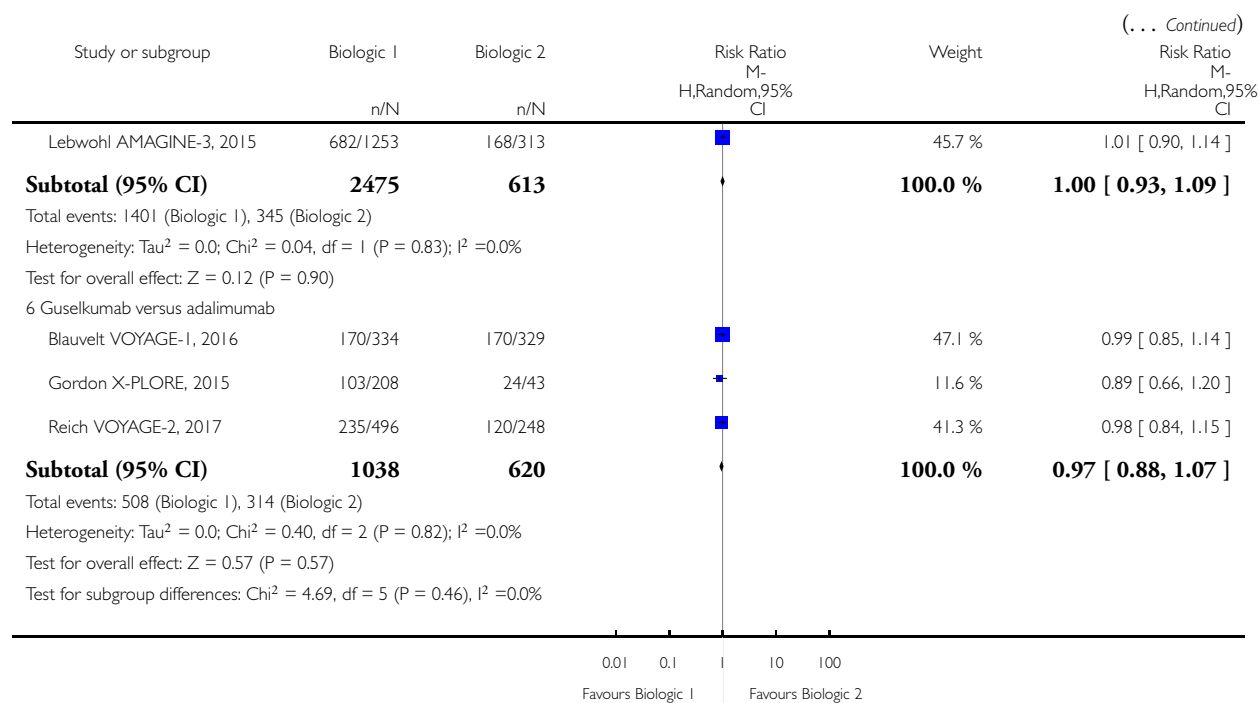
Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 6 Secondary outcome - adverse events

Outcome: 8 Biologic 1 versus biologic 2



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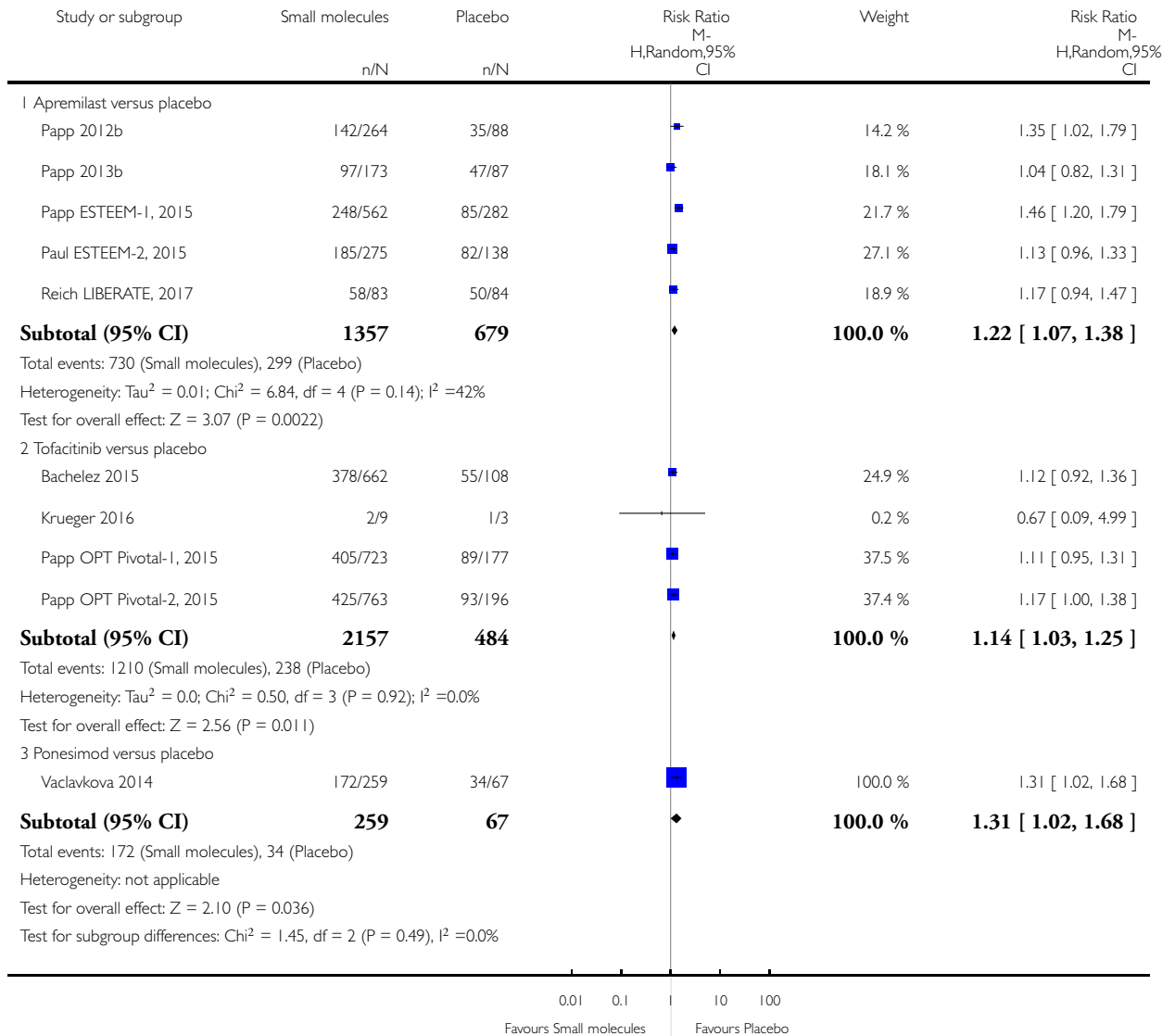


### Analysis 6.9. Comparison 6 Secondary outcome - adverse events, Outcome 9 Small molecules versus placebo.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 6 Secondary outcome - adverse events

Outcome: 9 Small molecules versus placebo

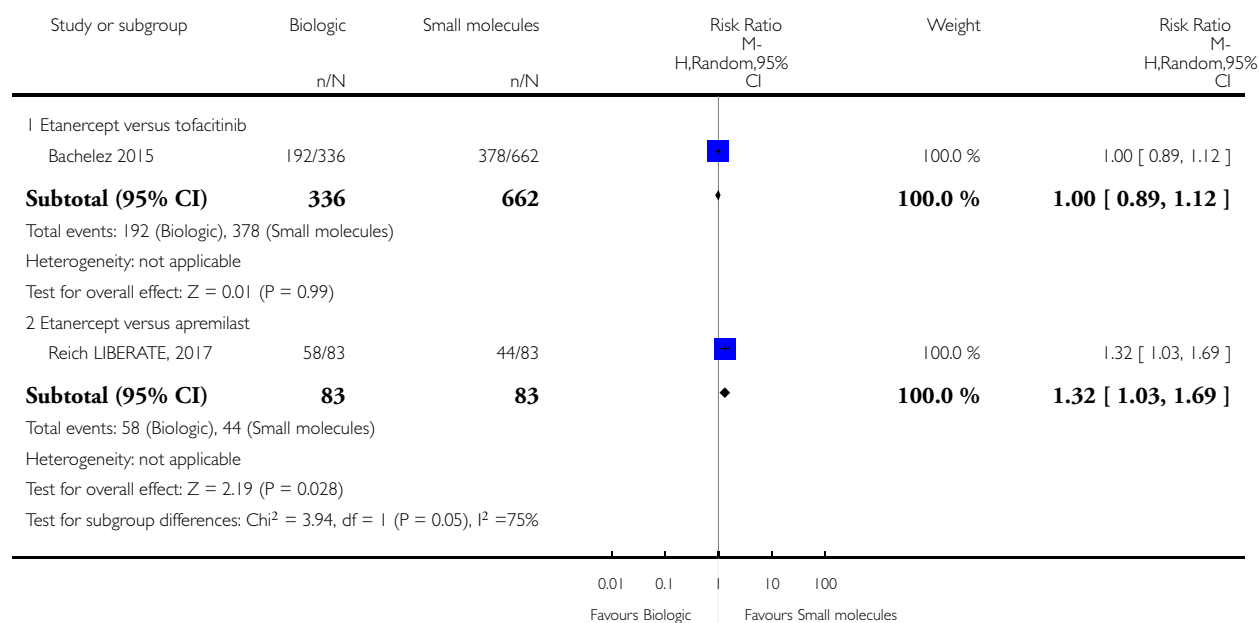


### Analysis 6.10. Comparison 6 Secondary outcome - adverse events, Outcome 10 Biologic versus small molecules.

Review: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Comparison: 6 Secondary outcome - adverse events

Outcome: 10 Biologic versus small molecules



## ADDITIONAL TABLES

Table 1. Glossary

Term	Definition
<b>Antagonist</b>	A substance that interferes with or inhibits the physiological action of another
<b>Antigen</b>	A molecule capable of inducing an immune response
<b>Anti-TNF alpha</b>	A pharmaceutical drug that suppresses the physiologic response to tumor necrosis factor (TNF)
<b>Biological agent</b>	Therapeutic agents consisting of immune molecules such as soluble receptors, recombinant cytokines, and monoclonal antibodies that target effector molecules or cells of the immune system

Table 1. Glossary (Continued)

<b>CD6</b>	Cluster of differentiation (CD) 6 is a protein encoded by the CD6 gene
<b>Cheilitis</b>	An inflammation of the lips
<b>Chimeric protein</b>	A chimeric protein can be made by combining two different genes
<b>Complex cyclophilin-ciclosporin</b>	Cyclophilins are a family of proteins that bind to ciclosporin, an immunosuppressant agent
<b>Creatinine</b>	A compound that is produced by metabolism of creatine and excreted in the urine
<b>Cyclic adenosine monophosphate</b>	It is a second messenger important in many biological processes
<b>Cytokines</b>	Small proteins produced by a broad range of cells that are important in cell signaling; they are immunomodulating agents
<b>Dendritic cells</b>	Antigen-presenting cells of the immune system
<b>Dermis</b>	It is a layer of the skin
<b>Epitope</b>	It is a part of an antigen
<b>Erythematous</b>	Redness of the skin
<b>Folic acid</b>	B vitamin
<b>Humanised antibody</b>	Antibodies from non-human species whose protein sequences have been modified to increase their similarity to antibody variants produced naturally in humans
<b>IL-17A</b>	A pro-inflammatory cytokine
<b>IL-23R</b>	A cytokine receptor
<b>Immune-mediated</b>	A group of diseases that are characterised by common inflammatory pathways leading to inflammation, and which may result from a dysregulation of the normal immune response
<b>Immunogenicity</b>	This is the ability of a particular substance, such as an antigen or epitope, to provoke an immune response in the body of a human or animal
<b>Immunoglobulin 1 Fc</b>	An antibody
<b>Interferon (IFN)-c</b>	A protein released by cells, usually in response to a pathogen
<b>Interleukin</b>	A kind of cytokine



Table 1. Glossary (Continued)

<b>Janus kinase (JAK) inhibitors</b>	A pharmaceutical drug that inhibits the activity of one or more of the Janus kinase family of enzymes
<b>Keratinocytes</b>	Epidermal cells that constitute 95% of the epidermis
<b>Lymphocyte</b>	A subtype of a white blood cell
<b>Lymphoid organ</b>	Part of the body that defends the body against invading pathogens that cause infections or the spread of tumours
<b>Metalloproteinases</b>	A protease enzyme
<b>Monoclonal antibodies</b>	Antibodies that are made by identical immune cells that are all clones of a unique parent cell
<b>Murine sequence</b>	Mouse genomic sequencing
<b>Neutrophils</b>	Type of white blood cell involved in the innate immune system
<b>p40</b>	Subunit beta of interleukin 12 and 23
<b>Periumbilical</b>	Around the navel
<b>Pharmacological treatments</b>	Drugs
<b>Phase I</b>	First-in-man studies
<b>Phase II</b>	Studies to assess how well the drug works, as well as to continue phase I safety assessments in a larger group of volunteers and participants
<b>Phase III</b>	Randomised controlled multicenter trials on large patient groups and are aimed at being the definitive assessment of how effective the drug is
<b>Phase IV</b>	Post-marketing trials involve the safety surveillance
<b>Phosphodiesterase 4 inhibitors</b>	A pharmaceutical drug used to block the degradative action of phosphodiesterase 4
<b>Progressive multifocal leukoencephalopathy</b>	A rare viral neurological disease characterised by progressive damage of the white matter of the brain at multiple locations
<b>Receptor</b>	A protein molecule that receives chemical signals from outside a cell
<b>Small molecules</b>	Chemically manufactured molecules (or SMOLs for short)
<b>Sphingosine 1-phosphate receptor agonists</b>	A class of protein-coupled receptors that are targets of the lipid signalling molecule Sphingosine-1-phosphate

**Table 1. Glossary** (Continued)

<b>T cells/CD4 T cells</b>	A type of white blood cell that is of key importance to the immune system
<b>Th1 and Tc1 cells</b>	A type of T cell
<b>Th17 and Tc17 cells</b>	A type of T cell
<b>TNF-alpha</b>	A protein that is part of the inflammatory response
<b>Tumour necrosis factor antagonists</b>	Class of biological agents
<b>Umbilic</b>	Navel
<b>Xerosis</b>	Dry skin

**Table 2. Investigators contacted**

	Contact	Requested Information	Contacted	Reply (last check 1/03/2017)
<b>Missing data</b>				
<a href="#">Akcali 2014</a>	Prof. Akcali	Outcomes: PASI 90, PASI 75, PGA 0/1, QoL scale, AEs & SAEs	8 and 21 November 2016	No response
<a href="#">Al-Hamamy 2014</a>	Prof. Al-Hamamy	Outcomes: PASI 75, PGA 0/1, QoL scale, AEs & SAEs	8 and 21 November 2016	No response
<a href="#">Asahina 2010</a>	Prof. Asahina	Outcome: PASI 90	8 November 2016	<a href="#">Asahina 2010</a> detailed report
<a href="#">Asahina 2016</a>	Prof. Asahina Pfizer	Outcomes: AEs & SAEs	3 and 12 January 2017	Additional data to the publication not provided
<a href="#">Asawanonda 2006</a>	Prof. Asawanonda	Outcomes: PASI 75, PGA 0/1, AEs & SAEs	21 November 2016 15 December 2016	<a href="#">Asawanonda 2006</a> sent detailed report for PASI 75 and AEs. PGA was not collected during this study
<a href="#">Bissonnette 2015</a>	Prof. Bissonnette Innova-derm Recherches Inc.	Outcomes: PASI 90, PGA 0/1, AEs	8 and 21 November 2016	Additional data to the publication not provided
<a href="#">Blauvelt FEATURE, 2015</a>	Dr Blauvelt Novartis	Outcome: QoL scale	8 and 21 November 2016	Additional data to the publication not provided

**Table 2. Investigators contacted** (Continued)

Caproni 2009	Prof. Fabri	Outcomes: PASI 90, PASI 75, PGA 0/1, QoL scale, AEs & SAEs	8 and 21 November 2016	Caproni 2009 sent detailed report for PASI 90 and SAEs. Other outcomes (PGA, QoL and AEs) not collected during this study
Dogra 2013	Prof. Dogra	Outcomes: PGA 0/1, QoL scale, AEs & SAEs	8 and 21 November 2016	No response
Dogra 2012	Prof. Dogra	Outcomes: PGA 0/1, QoL scale, AEs & SAEs	8 November 2016	PGA & QoL scale not collected during this study. AEs & SAEs not provided per arm
Fallah Arani 2011	Dr Fallah Arani	Outcomes: PASI 90, PGA 0/1 and QoL scale	8 and 21 November 2016	Outcomes not collected during this study
Flytström 2008	Prof. Flytstrom	Outcomes: PGA 0/1	12 and 19 January 2017	Additional data to the publication not provided
Gisoni 2008	Prof. Gisoni	Outcomes: PASI 90, PGA 0/1, QoL scale, AEs & SAEs	8 November 2016	Gisoni 2008 sent detailed report for the requested outcomes except for QoL (not assessed during the study)
Gordon 2006	Prof. Gordon	Outcomes: PGA0/1, AEs	3 and 12 January 2017	No response
Gottlieb 2012	Prof. Gottlieb Abbvie	Outcomes: PASI 90 & QoL scale	8 November 2016	Gottlieb 2012 sent detailed report for the requested outcomes
Gottlieb 2011	Prof. Gottlieb Amgen	Outcomes: PASI 90, PGA 0/1, QoL scale, AEs & SAEs	8 November 2016	Gottlieb 2011 sent detailed report for the requested outcomes
Griffiths 2010	ACCEPT, Prof. Griffiths Janssen	Outcome: QoL scale	16 December 2016	QoL was not collected during this study
Jacobe 2008	Prof. Jacobe	Outcomes: PASI 90, PGA 0/1, QoL scale, AEs & SAEs	8 and 20 November 2016	No response
Krueger 2016	Pfizer	Outcomes: PASI 90, QoL scale	3 and 12 January 2017	No response

**Table 2. Investigators contacted** (Continued)

<a href="#">Krupashankar 2014</a>	Prof. Ganapathi R&D, Biocon Research Limited	Outcomes: QoL scale, AEs & SAEs	8 and 21 November 2016	Krupashankar sent de- tailed report for the re- quested outcomes, how- ever AEs and SAEs were only available for the en- tire trial and not at the time of the major out- come assessment
<a href="#">Lebwohl AMAGINE-2, 2015</a>	Prof. Lebwohl Valeant Pharmaceuticals NA LLC	Outcomes: PASI 90 & QoL scale	8 and 21 November 2016	<a href="#">Lebwohl AMAGINE-2, 2015</a> sent detailed report for PASI 90, individual scores and median dif- ference from baseline of QoL were not available
<a href="#">Lebwohl AMAGINE-3, 2015</a>	Prof. Lebwohl Valeant Pharmaceuticals NA LLC	Outcomes: PASI 90 & QoL scale	8 and 21 November 2016	<a href="#">Lebwohl AMAGINE-3, 2015</a> sent detailed report for PASI 90, individual scores and median dif- ference from baseline of QoL were not available
<a href="#">Leonardi 2012</a>	Prof. Leonardi	Outcomes: QoL scale & AEs	8 and 21 November 2016	No response
<a href="#">Mahajan 2010</a>	Prof. Kaur	Outcomes: PASI 90, PGA 0/1, QoL scale, AEs & SAEs	8 and 21 November 2016	No response
<a href="#">Menter REVEAL, 2008</a>	Prof. Menter	Outcome: PGA 0/1	8 and 21 November 2016	No response
<a href="#">Menter EXPRESS-II, 2007</a>	Prof. Menter	Outcome: PGA 0/1	8 and 21 November 2016	No response
<a href="#">Mrowietz BRIDGE, 2016</a>	Prof. Mrowietz	Outcome: QoL scale	3 and 12 January 2017	Additional data to the publication not provided
<a href="#">Ortonne 2013</a>	Prof. Paul Novartis	Outcome: PASI 90	3 January 2017	Additional data to the publication not provided
<a href="#">Papp 2013a</a>	Prof. Papp	Outcome: QoL scale	22 November 2016 13 December 2016	Additional data to the publication not provided
<a href="#">Papp AMAGINE-1, 2016</a>	Prof. Papp	Outcome: QoL scale	22 November 2016 13 December 2016	Additional data to the publication not provided

**Table 2. Investigators contacted** (Continued)

Papp 2005	Prof. Papp	Outcome: QoL scale, AEs & SAEs	22 November 2016 13 December 2016	Additional data to the publication not provided
Papp 2012a	Prof. Papp	Outcome: QoL scale	22 November 2016 13 December 2016	Additional data to the publication not provided
Papp 2013b	Prof. Papp	Outcome: PASI 90, PGA0/1, QoL scale	3 January 2017	Additional data to the publication not provided
PaulJUNCTURE, 2015	Prof. Paul Novartis	Outcome: QoL scale	15 December 2016, 2 January 2017	Additional data to the publication not provided
Reich 2015	Prof. Reich Novartis	Outcomes: PGA 0/1 & QoL scale	8 November 2016, 16 December 2016	Additional data to the publication not provided
Reich LIBERATE, 2017	Prof. Reich PelotonAdvantage	Outcome: QoL scale	4 January 2017	Additional data to the publication not provided
Rich 2013	Prof. Rich	Outcome: QoL scale	22 November 2016, 13 December 2016	No response
Sterry PRESTA, 2010	Prof. Sterry	Outcomes: PASI 90 & QoL scale	8 and 21 November 2016	No response
Strober 2011	Prof. Strober Abbvie	Outcome: QoL scale	8 November 2016	Strober sent detailed report for the requested outcomes
Thaci CLEAR, 2015	Prof. Thaçi Novartis	Outcome: QoL scale	8 and 21 November 2016	Additional data to the publication not provided
Torii 2010	Prof. Torii	Outcomes: PASI 90 & PGA0/1	21 November 2016	Torii sent detailed report for the requested outcomes
Tyring 2006	Prof. Tyring	Outcomes: PGA 0/1 & QoL scale	8 and 21 November 2016	No response
Van Bezooijen 2016	Dr van Bezooijen	Outcomes: PASI 90, adverse effects	4 and 12 January 2017	Additional data to the publication not provided
Van de Kerkhof 2008	Prof. van der Kerkhof Pfizer	Outcome: AEs	8 and 21 November 2016	Additional data to the publication not provided
Yan 2011	No contact	Outcomes: AEs and SAEs	No	Authors' email not found

**Table 2. Investigators contacted** (Continued)

Zhu LOTUS, 2013	No contact	Outcome: PASI 90	No	Authors' email not found
<b>Awaiting classification studies</b>				
Elewski 2016	Prof. Elewski Abbvie	Study's protocol and outcomes: PASI 90, PASI 75, PGA 0/1, QoL scale, AEs & SAEs	3 and 12 January 2017	Will be included when published
Khatri 2016	Prof. Khattri	Study's protocol and outcomes: PASI 90, PASI 75, PGA 0/1, QoL scale, AEs & SAEs	3 and 12 January 2017	No response
Lee 2016	Prof. Lee	Study's protocol and outcomes: PASI 90, PASI 75, PGA 0/1, QoL scale, AEs & SAEs	3 and 12 January 2017	No response
Reich 2016	Prof. Reich	Study's protocol and outcomes: PASI 90, PASI 75, PGA 0/1, QoL scale, AEs & SAEs	3 January 2017	Will be included when published
Chow 2015	Prof. Chow	outcomes: PASI 90, PASI 75, PGA 0/1, QoL scale, AEs & SAEs	8 November 2016, 16 December 2016	No response
Gurel 2015	Prof. Gurel	Study's protocol and outcomes: PASI 90, PASI 75, PGA 0/1, QoL scale, AEs & SAEs	17 and 24 January 2017	Gurel 2015 sent detailed report for the requested outcomes. Finally Gurel study was classified in the included studies section
Han 2007	No contact	Outcomes: PASI 90, PASI 75, PGA 0/1, QoL scale, AEs & SAEs	No	Authors' email not found
NCT01988103	Dr Nogarales, MD Celgene Corporation	Asking for study protocol and efficacy/safety results	12 and 19 January 2017	Email response: "Thank you very much for your email and your interest in our study in Japanese subjects. May I please enquire as to the planned timing for publication for your meta-analysis as we have just recently submitted our primary

**Table 2. Investigators contacted** (Continued)

				manuscript? Will be included when published
<a href="#">NCT02248792</a>	Prof. Krishna	Asking for study protocol and efficacy/safety results	5 and 12 January 2017	No response
<a href="#">DRKS00000716</a>	Prof. Jacobi	Asking for study protocol and efficacy/safety results	12 and 19 January 2017	No response
<a href="#">CTRI/2015/05/005830</a>	Prof. Shah	Asking for study protocol and efficacy/safety results	12 and 19 January 2017	
<b>Abstracts</b>				
<a href="#">Yilmaz 2002</a>	Prof. Yilmaz	Outcomes: PASI 90, PASI 75, PGA 0/1, QoL scale, AEs & SAEs	16 December 2016	<a href="#">Yilmaz 2002</a> sent detailed report for the requested outcomes. Finally <a href="#">Yilmaz 2002</a> study was classified in the included studies section.
<a href="#">Mrowietz 2005</a>	Prof. Mrowietz	Study's protocol and outcomes: PASI 90, PASI 75, PGA 0/1, QoL scale, AEs & SAEs	16 December 2016, 3 January 2017	Additional data to the publication not provided. Finally Mrowietz study was classified in the awaiting classification section
<a href="#">Reich 2004</a>	Prof. Reich	Study's protocol and outcomes: PASI 90, PASI 75, PGA 0/1, QoL scale, AEs & SAEs	16 December 2016	Additional data to the publication not provided. Finally Reich 2004 study was classified in the awaiting classification section
<b>Ongoing studies</b>				
<a href="#">NCT01558310</a>	Dr Yamauchi Dr Patnaik, Director, Clinical Science Institute	Asking for study protocol and efficacy/safety results	5 January 2017	Email response: Dear Dr Sbidian, Thank you for your kind email, forwarded to me by Dr Paul Yamauchi, MD,PhD. Our " Study to Evaluate the Effectiveness of STELARA™ (USTEKINUMAB)

**Table 2. Investigators contacted** (Continued)

				in the Treatment of Scalp Psoriasis (NCT 01558310)” completed enrolment in December 2016 and the last subject will complete in December 2017, as such we do not have the final data analysis. What is your absolute cut-off for publication data? Would an interim analysis report be acceptable? Best regards, Rickie Patnaik Director, Clinical Science Institute Will be included when published
<a href="#">EUCTR2013-004918-18-NL</a>	Prof. Spuls	Asking for study protocol and efficacy/safety results	5 January 2017	Email response “The study is currently ongoing and has not yet been analysed. Therefore, we are not able to provide data on efficacy or safety. We can provide you with the study protocol. Will this be helpful? Kind regards, Phyllis Spuls and Celine Busard” Will be included when published

**AE:** adverse events; **PASI:** Psoriasis Area and Severity Index; **PGA:** Physician Global Assessment; **QoL:** quality of life; **SAE:** serious adverse events

**Table 3. Direct and indirect evidences and network meta-analysis results summary table for PASI 90 at 12 to 16 weeks**

Comparisons*	Network meta-analysis			Direct evidence			Indirect evidence		
	RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI
FAEs vs placebo	4.09	1.88	8.88	4.47	1.97	10.14	1.86	0.16	21.16



**Table 3. Direct and indirect evidences and network meta-analysis results summary table for PASI 90 at 12 to 16 weeks (Continued)**

Methotrexate vs placebo	3.91	2.16	7.08	1.53	0.66	3.53	17.16	5.69	51.75
Adalimumab vs placebo	14.87	10.45	21.14	14.42	10.08	20.64	108.8	2.24	5287.86
Etanercept vs placebo	10.79	8.47	13.73	10.62	7.52	15.01	11.21	7.26	17.32
Ustekinumab vs placebo	19.91	15.11	26.23	22.7	15.46	33.34	17.91	12.71	25.24
Secukinumab vs placebo	26.55	20.32	34.69	24.53	14.93	40.32	28.25	19.1	41.78
Ixekizumab vs placebo	32.45	23.61	44.60	39.46	20.64	75.44	24.51	10.05	59.77
Brodalumab vs placebo	25.45	18.74	34.57	26.58	16.65	42.41	23.74	10.09	55.86
Apremilast vs placebo	7.66	4.30	13.66	6.72	3.07	14.69	10.83	2.43	48.31
Tofacitinib vs placebo	8.50	6.23	11.60	6.3	4.14	9.56	17.91	8.3	38.62
Guselkumab vs placebo	21.03	14.56	30.38	26.1	14.71	46.3	12.7	4.28	37.69
Methotrexate vs FAEs	0.96	0.38	2.44	2	0.19	21.03	0.83	0.3	2.32
Alefacept vs methotrexate	1.12	0.42	3.02	1.12	0.42	3.02			

**Table 3. Direct and indirect evidences and network meta-analysis results summary table for PASI 90 at 12 to 16 weeks (Continued)**

Ci-closporin vs methotrexate	1.02	0.60	1.73	1.02	0.6	1.73			
Infliximab vs methotrexate	2.86	2.06	3.97	2.86	2.06	3.97			
Adalimumab vs methotrexate	3.80	2.26	6.39	3.35	2.02	5.57	13.2	3.4	51.32
Etanercept vs acitretin	11.00	0.63	191.47	11	0.63	191.47			
Guselkumab vs adalimumab	1.41	1.21	1.65	1.4	1.18	1.66	2.88	0.68	12.21
Ustekinumab vs etanercept	1.85	1.50	2.27	1.8	1.27	2.55	1.95	1.37	2.77
Secukinumab vs etanercept	2.46	2.01	3.02	2.33	1.66	3.28	2.62	1.82	3.77
Ixekizumab vs etanercept	3.01	2.46	3.68	2.93	2.44	3.53	5.73	2.07	15.85
Apremilast vs etanercept	0.71	0.40	1.25	0.72	0.36	1.45	0.69	0.26	1.81
Tofacitinib vs etanercept	0.79	0.59	1.06	0.88	0.73	1.08	0.49	0.3	0.81
Secukinumab vs ustekinumab	1.33	1.11	1.61	1.38	1.03	1.84	1.19	0.79	1.81

**Table 3. Direct and indirect evidences and network meta-analysis results summary table for PASI 90 at 12 to 16 weeks (Continued)**

Bro-dalumab vs ustekinumab	1.28	1.10	1.48	1.27	1.1	1.46	1.64	0.69	3.89
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**FAES:** fumaric acid esters; **LCI:** low confidence interval; **RR:** risk ratio; **UCI:** upper confidence interval; **vs:** versus,

\*The comparisons listed in this table were included in at least one direct-evidence analysis.

**Table 4. Ranking findings for all outcomes at class level**

Class-level interventions	SU-CRA PASI 90	Rank PASI 90	SU-CRA SAE	Rank SAE	SU-CRA PASI 75	Rank PASI 75	SU-CRA AE	Rank AE	SU-CRA PGA	Rank PGA	SU-CRA QoL	Rank QoL
Anti-IL12/23	85.7	2	53.9	3	85.0	2	57.0	3	83.8	2	75.7	3
Anti-IL17	100.0	1	21.0	8	99.6	1	14.1	6	99.9	1	95.4	1
Anti-IL23	71.3	3	39.6	5	72.2	3	78.7	2	73.1	3	83.4	2
Anti-TNF alpha	56.4	4	39.2	6	57.4	4	47.5	5	57.5	4	58.4	4
Other biologics	26.3	6	68.2	2	17.0	7	-	-	16.6	7	15.5	7
Small molecule:	41.5	5	45.4	4	42.7	5	7.9	7	42.0	5	40.4	5
Conventional systemic treatments	18.7	7	94.8	1	26.0	6	50.8	4	27.1	6	30.8	6
Placebo	0	8	38.0	7	0	8	94.0	1	0	8	0.4	8

AE: adverse events; FAEs: fumaric acid esters; PGA: Physician Global Assessment; QoL: Specific quality of life scale; SAE: serious adverse events

**Table 5. Ranking findings for all outcomes at drug level**

Drug	SU-CRA PASI 90	Rank PASI 90	SU-CRA SAE	Rank SAE	SU-CRA PASI 75	Rank PASI 75	SU-CRA AE	Rank AE	SU-CRA PGA	Rank PGA	SU-CRA QoL	Rank QoL
Acitretin	9.9	19	46.9	9	26.0	15	-	-	-	-	-	-
Adalimumab	63.1	8	40.4	14	60.2	9	70.1	5	56.9	8	57.6	7
Alefacept	25.3	15	62.6	5	12.6	18	-	-	13.1	18	15.9	13
Apremilast	39.7	13	54.7	7	33.2	14	14.3	16	27.9	14	28.6	10
Brodalumab	84.3	3	39.8	15	82.1	3	46.4	9	84.0	5	52.3	8
Certolizumab	75.7	5	70.9	3	71.6	6	78.0	4	90.1	1	-	-
Ciclosporin	21.3	17	78.2	2	33.2	13	36.8	12	24.0	16	-	-
Etanercept	52.6	11	43.6	11	57.7	10	45.9	10	51.7	10	67.6	5
FAEs	21.9	16	57.7	6	11.1	19	17.8	15	15.4	17	-	-
Guselkumab	77.0	4	42.6	12	71.6	7	78.2	3	67.5	7	84.3	2
Infliximab	53.2	10	64.4	4	48.0	11	40.1	11	52.4	9	-	-
Itolizumab	56.0	9	-	-	71.6	8	-	-	29.4	13	16.0	12
Ixekizumab	94.3	1	33.7	17	91.8	1	18.1	14	85.9	3	99.2	1

**Table 5. Ranking findings for all outcomes at drug level (Continued)**

Methotrate	20.2	18	90.7	1	21.3	16	68.4	6	24.9	15	31.5	9
Placebo	2.9	20	42.0	13	0.0	20	88.0	1	0.3	19	1.2	14
Ponesimod	37.3	14	18.1	19	21.3	17	14.0	17	48.7	11	28.1	11
Secukinumab	86.5	2	29.9	18	86.7	2	36.3	13	84.4	4	-	-
Tildrakizumab	63.6	7	37.8	16	78.3	4	86.1	2	86.3	2	74.9	4
Tofacitinib	42.5	12	44.0	10	46.2	12	47.3	8	36.6	12	65.1	6
Ustekinumab	72.6	6	52.0	8	75.2	5	64.3	7	70.4	6	77.4	3

**AE:** adverse events; **FAEs:** fumaric acid esters; **PASI:** Psoriasis Area and Severity Index; **PGA:** Physician Global Assessment; **QoL:** specific quality of life scale; **SAE:** serious adverse events; **SUCRA:** Surface Under the Cumulative Ranking

**Table 6. Total number of serious adverse events during the induction phase at class-level and most severe types**

	Number of randomised participants		Number of serious adverse events		Number of serious infections		Number of malignancies		Number of MACE	
	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo
Conventional systemic agents	767	220	19	10	0	0	0	0	0	0
Anti-TNF	4508	2640	85	44	21	9	20	7	6	2
Anti-IL12/23	2547	1607	38	23	7	5	4	1	4	3
Anti-IL17	7551	2533	149	36	47	7	21	2	19	3

**Table 6. Total number of serious adverse events during the induction phase at class-level and most severe types** (Continued)

Anti-IL23	1347	510	23	7	4	1	0	0	1	0
Other biologics	509	227	15	10	-	-	2	1	-	-
Small molecules	3920	1280	89	28	15	5	14	0	5	1

MACE: Major adverse cardiac events

**Table 7. Direct and indirect evidence and network meta-analysis results summary table for serious adverse events at 12 to 16 weeks**

Comparisons*	Network meta-analysis			Direct evidence			Indirect evidence		
	RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI
FAEs vs placebo	0.77	0.30	1.99	0.83	0.31	2.21	0.19	0	12.57
Methotrexate vs placebo	0.23	0.05	0.99	0.16	0.03	0.86	0.68	0.04	11.67
Adalimumab vs placebo	1.02	0.61	1.73	1.05	0.62	1.78	0.07	0	26.92
Etanercept vs placebo	0.99	0.65	1.51	1.09	0.65	1.84	0.76	0.31	1.89
Ustekinumab vs placebo	0.89	0.57	1.39	0.74	0.44	1.26	1.36	0.61	2.99
Secukinumab vs placebo	1.19	0.69	2.03	1.61	0.78	3.33	0.75	0.3	1.87
Ixekizumab vs placebo	1.12	0.66	1.90	1.16	0.62	2.16	0.97	0.18	5.12

**Table 7. Direct and indirect evidence and network meta-analysis results summary table for serious adverse events at 12 to 16 weeks** (Continued)

Bro-dalumab vs placebo	1.04	0.62	1.73	0.92	0.53	1.62	2.77	0.38	20.28
Apremilast vs placebo	0.84	0.47	1.52	0.78	0.42	1.44	4.33	0.09	201.27
Tofacitinib vs placebo	0.98	0.55	1.76	1.05	0.53	2.06	0.67	0.08	5.35
Guselkumab vs placebo	1.00	0.49	2.04	1.21	0.51	2.85	0.52	0.08	3.41
Methotrexate vs FAEs	0.30	0.06	1.59	1	0.02	48.83	0.23	0.04	1.45
Ciclosporin vs methotrexate	0.98	0.06	15.38	0.98	0.06	15.38	-	-	-
Infliximab vs methotrexate	2.41	1.04	5.59	2.41	1.04	5.59	-	-	-
Adalimumab vs methotrexate	4.43	0.99	19.81	2.24	0.21	23.56	6.68	1.04	42.76
Etanercept vs acitretin	1.00	0.02	48.82	1	0.02	48.83	-	-	-
Guselkumab vs adalimumab	0.98	0.51	1.88	0.89	0.44	1.79	2.07	0.26	16.45
Ustekinumab vs etanercept	0.90	0.52	1.57	1.25	0.38	4.11	0.83	0.44	1.54
Secukinumab vs etanercept	1.20	0.66	2.19	1.17	0.45	3.04	1.22	0.56	2.65

**Table 7. Direct and indirect evidence and network meta-analysis results summary table for serious adverse events at 12 to 16 weeks** (Continued)

Ixek-izumab vs etanercept	1.14	0.66	1.94	1.02	0.53	1.95	1.47	0.53	4.09
Apremi-last vs etanercept	0.85	0.42	1.72	2.69	0.41	17.5	0.7	0.33	1.5
To-facitinib vs etanercept	0.99	0.53	1.87	0.87	0.35	2.19	1.12	0.47	2.7
Secukinumab vs ustekinumab	1.33	0.74	2.38	1.01	0.42	2.39	1.68	0.77	3.68
Bro-dalumab vs ustekinumab	1.16	0.64	2.11	1.32	0.59	2.98	0.95	0.33	2.71

FAES: fumaric acid esters; LCI: low confidence interval; RR: risk ratio; UCI: upper confidence interval

\*The comparisons listed in this table were included in at least one direct-evidence analysis.

## APPENDICES

### Appendix I. CRS/Cochrane Skin Group Specialised Register search strategy

(Psoria\* or “palmoplantar\* pustulosis” or “pustulosis palmaris et plantaris” or (pustulosis and palms and soles)) and (methotrexate\* or amethopterin or mtx or mexate or fumar\* or dimethylfumarate or fae or dmf or fumaderm or acitretin or tegison or soriatane or neotigason or ((oral or orally or systemic) and retinoid\*)) or isotretinoin or accutane or etretin\* or ustekinumab or stelara or secukinumab or “CNTO 1275” or “cdp571” or etanercept\* or enbrel or adalimumab\* or d2e7 or humira or golimumab or simponi or briakinumab or “ABT-874” or “psoralen uva” or ciclosporin or cyclosporine or cyclosporine or alefacept or brodalumab or ixekizumab or phototherap\* or ultraviolet or PUVA or photochemotherap\* or photodynamic or “light therap\*” or photoradiation or “broad band uvb” or “broad band ultraviolet b” or “narrow band uvb” or “narrow band ultraviolet b” or BBUVB or NBUVB or BB-UVB or NB-UVB or infliximab\* or “monoclonal antibod\*” or remicade or interleukin\* or “anti tumour necrosis factor” or “anti tumor necrosis factor” or “tumour necrosis factor antibod\*” or “tumor necrosis factor antibod\*” or “tnf antibod\*” or “tnf alpha antibod\*” or “anti tnf” or “immunoglobulin fab fragment\*” or “p40 subunit” or “tumor necrosis factor\*” or tnf or “antitumor necrosis factor\*” or “antitumour necrosis factor\*” or ampremilast or ponesimod or guselkumab or tofacitinib or itolizumab or certolizumab or tildrakizumab)



## Appendix 2. Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library, search strategy

#1MeSH descriptor: [Psoriasis] this term only  
#2psoria\*:ti,ab,kw  
#3palmoplantar\* pustulosis:ti,ab,kw  
#4pustulosis palmaris et plantaris:ti,ab,kw  
#5pustulosis and palms and soles:ti,ab,kw  
#6#1 or #2 or #3 or #4 or #5  
#7MeSH descriptor: [Methotrexate] explode all trees  
#8MeSH descriptor: [Fumarates] explode all trees  
#9MeSH descriptor: [Etretinate] explode all trees  
#10MeSH descriptor: [Acitretin] explode all trees  
#11MeSH descriptor: [Isotretinoin] explode all trees  
#12MeSH descriptor: [Retinoids] explode all trees  
#13MeSH descriptor: [Antibodies, Monoclonal] explode all trees  
#14MeSH descriptor: [Interleukin-12] explode all trees  
#15MeSH descriptor: [Interleukin-23] explode all trees  
#16MeSH descriptor: [Interleukin-12 Subunit p40] explode all trees  
#17MeSH descriptor: [Tumor Necrosis Factors] explode all trees  
#18MeSH descriptor: [Tumor Necrosis Factor-alpha] explode all trees  
#19MeSH descriptor: [Receptors, Tumor Necrosis Factor, Type II] explode all trees  
#20MeSH descriptor: [Receptors, Tumor Necrosis Factor] explode all trees  
#21MeSH descriptor: [Receptors, Tumor Necrosis Factor, Type I] explode all trees  
#22MeSH descriptor: [TNF-Related Apoptosis-Inducing Ligand] explode all trees  
#23MeSH descriptor: [Antibodies, Monoclonal] explode all trees  
#24MeSH descriptor: [Immunoglobulin Fab Fragments] explode all trees  
#25MeSH descriptor: [Phototherapy] explode all trees  
#26MeSH descriptor: [Ultraviolet Therapy] explode all trees  
#27MeSH descriptor: [PUVA Therapy] explode all trees  
#28MeSH descriptor: [Photochemotherapy] explode all trees  
#29MeSH descriptor: [Cyclosporine] explode all trees  
#30(methotrexate\* or amethopterin or mtx or mexate or fumar\* or dimethylfumarate or fae or dmf or fumaderm or acitretin or tegison or soriatane or neotigason or ((oral or orally or systemic) and retinoid\*) or isotretinoin or accutane or etretin\* or ustekinumab or stelara or secukinumab or "CNTO 1275" or "cdp571" or etanercept\* or enbrel or adalimumab\* or "d2e7" or humira or golimumab or simponi or briakinumab or "ABT-874" or "psoralen uva" or ciclosporin or cyclosporine or cyclosporine or alefacept or brodalumab or ixekizumab or phototherap\* or ultraviolet or PUVA or photochemotherap\* or photodynamic or "light therap\*" or photoradiation or "broad band uvb" or "broad band ultraviolet b" or "narrow band uvb" or "narrow band ultraviolet b" or BBUVB or NBUVB or BB-UVB or NB-UVB or infliximab\* or "monoclonal antibod\*" or remicade or interleukin\* or "anti tumour necrosis factor" or "anti tumor necrosis factor" or "tumour necrosis factor antibod\*" or "tumor necrosis factor antibod\*" or "tnf antibod\*" or "tnf alpha antibod\*" or "anti tnf" or "immunoglobulin fab fragment\*" or "p40 subunit" or "tumor necrosis factor\*" or tnf or "antitumor necrosis factor\*" or "antitumour necrosis factor\*" or ampremilast or ponesimod or guselkumab or tofacitinib or itolizumab certolizumab or tildrakizumab):  
ti,ab,kw  
#31{or #7-#30}  
#32#6 and #31

### Appendix 3. MEDLINE (Ovid) search strategy

1. exp Psoriasis/ or psoria\$.ti,ab.
2. palmoplantar\$ pustulosis.ti,ab.
3. pustulosis palmaris et plantaris.ti,ab.
4. (pustulosis and palms and soles).ti,ab.
5. 1 or 2 or 3 or 4
6. exp Methotrexate/
7. methotrexate\$.mp.
8. amethopterin.mp.
9. mtx.ti,ab.
10. mexate.mp.
11. exp Fumarates/
12. (fumar\$ and esters).mp.
13. dimethylfumarate.mp.
14. fae.ti,ab.
15. dmf.ti,ab.
16. fumarate\$1.mp.
17. fumaderm.mp.
18. Etretinate/
19. Acitretin/
20. Tegison.mp.
21. (Soriatane or Neotigason).mp.
22. ((oral or orally or systemic) and retinoid\$.ti,ab.
23. Isotretinoin/
24. Accutane.mp.
25. isotretinoin.ti,ab.
26. etretin\$.mp.
27. acitretin.mp.
28. Retinoids/
29. Ustekinumab.mp.
30. stelara.mp.
31. secukinumab.mp.
32. apremilast.mp.
33. ponesimod.mp.
34. guselkumab.mp.
35. tofacitinib.mp.
36. itolizumab.mp.
37. CNTO 1275.mp.
38. exp antibodies, monoclonal/
39. monoclonal antibod\$.mp.
40. exp Interleukin-23/ or exp Interleukin-12/
41. exp Interleukin-12 Subunit p40/ or p40 subunit.mp.
42. exp Tumor Necrosis Factors/ or exp Tumor Necrosis Factor-alpha/ or exp Receptors, Tumor Necrosis Factor, Type II/ or exp Receptors, Tumor Necrosis Factor/ or exp Receptors, Tumor Necrosis Factor, Type I/ or exp TNF-Related Apoptosis-Inducing Ligand/
43. (anti tumour necrosis factor or anti tumor necrosis factor).mp.
44. (tumor necrosis factor-alpha or tumour necrosis factor-alpha).mp.
45. anti tnf.mp.
46. (tnf antibod\$ or tnf alpha antibod\$.mp.
47. (tumour necrosis factor antibod\$ or tumor necrosis factor antibod\$.mp.
48. (antitumor necrosis factor or antitumour necrosis factor).mp.
49. exp Immunoglobulin Fab Fragments/
50. (infliximab\$ or monoclonal antibody cA2 or remicade).mp.

51. cdp571.mp.
  52. (etanercept\$ or enbrel).mp.
  53. (adalimumab\$ or d2e7 or humira).mp.
  54. (golimumab or simponi).mp.
  55. (Briakinumab or ABT-874).mp.
  56. exp Phototherapy/
  57. exp Ultraviolet Therapy/
  58. exp PUVA Therapy/
  59. exp Photochemotherapy/
  60. photodynamic therap\$.mp.
  61. phototherap\$.mp.
  62. photochemotherap\$.mp.
  63. puva.mp.
  64. ultraviolet.mp.
  65. light therap\$.mp.
  66. photoradiation therap\$.mp.
  67. BBUVB.mp.
  68. NBUVB.mp.
  69. BB-UVB.mp.
  70. NB-UVB.mp.
  71. broad band uvb.mp.
  72. broad band ultraviolet b.mp.
  73. narrow band uvb.mp.
  74. narrow band ultraviolet b.mp.
  75. psoralen ultraviolet a.mp.
  76. psoralen uva.mp.
  77. Cyclosporine/
  78. (Ciclosporin or cyclosporine or cyclosporin).mp.
  79. alefacept.mp.
  80. brodalumab.mp.
  81. ixekizumab.mp.
  82. certolizumab.mp.
  83. tildrakizumab.mp.
  84. or/6-83
  85. randomized controlled trial.pt.
  86. controlled clinical trial.pt.
  87. randomized.ab.
  88. placebo.ab.
  89. clinical trials as topic.sh.
  90. randomly.ab.
  91. trial.ti.
  92. 85 or 86 or 87 or 88 or 89 or 90 or 91
  93. exp animals/ not humans.sh.
  94. 92 not 93
  95. 5 and 84 and 94
- [Lines 85-94: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)]

#### Appendix 4. Embase (Ovid) search strategy

1. exp PSORIASIS/
2. psoria\$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]
3. palmoplantar\$ pustulosis.mp.
4. pustulosis palmaris et plantaris.mp.
5. (pustulosis and palms and soles).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]
6. 1 or 2 or 3 or 4 or 5
7. methotrexate/
8. methotrexate\$.ti,ab.
9. amethopterin.ti,ab.
10. mtx.ti,ab.
11. mexate.ti,ab.
12. fumaric acid derivative/
13. (fumar\$ and esters).ti,ab.
14. dimethylfumarate.ti,ab.
15. fae.ti,ab.
16. dmf.ti,ab.
17. fumarate\$1.ti,ab.
18. fumaderm.ti,ab.
19. etretinate/
20. acitretin.ti,ab.
21. tegison.ti,ab.
22. (Soriatane or Neotigason).ti,ab.
23. ((oral or orally or systemic) and retinoid\$).ti,ab.
24. isotretinoin/
25. isotretinoin.ti,ab.
26. Accutane.ti,ab.
27. etretin\$.ti,ab.
28. retinoid/
29. ustekinumab.ti,ab.
30. ustekinumab/
31. stelara.ti,ab.
32. secukinumab/
33. secukinumab.ti,ab.
34. ampemilast.ti,ab.
35. ponesimod/
36. ponesimod.ti,ab.
37. guselkumab/
38. guselkumab.ti,ab.
39. tofacitinib/
40. tofacitinib.ti,ab.
41. itolizumab/
42. itolizumab.ti,ab.
43. "CNTO 1275".ti,ab.
44. monoclonal antibod\$.ti,ab.
45. exp monoclonal antibody/
46. interleukin 23/
47. interleukin 12/
48. interleukin 12p40/
49. p40 subunit.ti,ab.

50. exp tumor necrosis factor/
51. tumor necrosis factor alpha/
52. tumor necrosis factor receptor 2/
53. tumor necrosis factor receptor/
54. tumor necrosis factor related apoptosis inducing ligand/
55. (anti tumour necrosis factor or anti tumor necrosis factor).ti,ab.
56. (tumor necrosis factor-alpha or tumour necrosis factor-alpha).ti,ab.
57. anti tnf.ti,ab.
58. (tnf antibod\$ or tnf alpha antibod\$).ti,ab.
59. (tumour necrosis factor antibod\$ or tumor necrosis factor antibod\$).ti,ab.
60. (antitumor necrosis factor or antitumour necrosis factor).ti,ab.
61. "immunoglobulin F(ab) fragment"/
62. (infliximab\$ or monoclonal antibody cA2 or remicade).ti,ab.
63. cdp571.ti,ab.
64. (etanercept\$ or enbrel).ti,ab.
65. (adalimumab\$ or d2e7 or humira).ti,ab.
66. (golimumab or simponi).ti,ab.
67. (Briakinumab or ABT-874).ti,ab.
68. exp phototherapy/
69. PUVA/
70. photochemotherapy/
71. photodynamic therap\$.ti,ab.
72. phototherap\$.ti,ab.
73. photochemotherap\$.ti,ab.
74. puva.ti,ab.
75. ultraviolet.ti,ab.
76. light therap\$.ti,ab.
77. photoradiation therap\$.ti,ab.
78. BBUVB.ti,ab.
79. NBUVB.ti,ab.
80. BB-UVB.ti,ab.
81. NB-UVB.ti,ab.
82. broad band uvb.ti,ab.
83. broad band ultraviolet b.ti,ab.
84. narrow band uvb.ti,ab.
85. narrow band ultraviolet b.ti,ab.
86. psoralen ultraviolet a.ti,ab.
87. psoralen uva.ti,ab.
88. cyclosporin/
89. (Ciclosporin or cyclosporine or cyclosporin).ti,ab.
90. alefacept/
91. alefacept.ti,ab.
92. brodalumab.ti,ab.
93. ixekizumab.ti,ab.
94. ixekizumab/
95. brodalumab/
96. certolizumab.mp.
97. tildrakizumab.mp.
98. or/7-97
99. crossover procedure.sh.
100. double-blind procedure.sh.
101. single-blind procedure.sh.
102. (crossover\$ or cross over\$).tw.

103. placebo\$.tw.
104. (doubl\$ adj blind\$).tw.
105. allocat\$.tw.
106. trial.ti.
107. randomized controlled trial.sh.
108. random\$.tw.
109. or/99-108
110. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
111. human/ or normal human/
112. 110 and 111
113. 110 not 112
114. 109 not 113
115. 6 and 98 and 114

## **Appendix 5. LILACS search strategy**

psoria\$

We searched using the term above and the Controlled clinical trials topic-specific query filter.

## **CONTRIBUTIONS OF AUTHORS**

ES and LLC were the contacts with the editorial base.

ES co-ordinated contributions from the co-authors and wrote the final draft of the review.

LLC, GD, IGD, and ES screened papers against eligibility criteria.

ES obtained data on ongoing and unpublished studies.

LLC, GD, IGD, CH, CM, CD, and ES appraised the quality of papers.

LLC, GD, IGD, CH, CM, CD, and ES extracted data for the review and sought additional information about papers.

ES entered data into RevMan.

AC analysed and interpreted data.

AC, LLC, and ES worked on the methods sections.

ES and LLC drafted the clinical sections of the background and responded to the clinical comments of the referees.

AC responded to the methodology and statistical comments of the referees.

CH was the consumer co-author and checked the review for readability and clarity, as well as ensuring outcomes are relevant to consumers.

ES is the guarantor of the update.

## DECLARATIONS OF INTEREST

Emilie Sbidian: grant support came from the French Society of Dermatology and the French Ministry of Health, France, the Programme Hospitalier de Recherche Clinique (DGOS no.14-0322). The funding agencies have no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation and review of the manuscript.

Anna Chaimani: nothing to declare.

Ignacio Garcia-Doval: nothing to declare.

Giao Do: nothing to declare.

Camille Hua: nothing to declare.

Canelle Mazaud: nothing to declare.

Catherine Droitcourt: nothing to declare.

Carolyn Hughes: nothing to declare.

John R Ingram: Dr Ingram is Deputy Editor of the British Journal of Dermatology.

Luigi Naldi: I received compensation for consultancy or participating in advisory board meetings from the following pharmaceutical companies: AbbVie, Almirall, Janssen-Cilag, Novartis, Sanofi, L'Oreal. My institution also received an unrestricted grant from AbbVie. The money did not fund the review.

Olivier Chosidow: nothing to declare.

Laurence Le Cleach: two grants were obtained to support this review work, one from the French Ministry of Health, France (Programme Hospitalier de Recherche Clinique (DGOS no.14-0322), and one from the French Society of Dermatology (SFD).

Key Editor Gloria Sanclemente: "I have not been involved in any study included in this review, but in the last three years, I have received sponsoring for attending scientific meetings or congresses by Janssen-Cilag, Novartis, and AbbVie. I also declare that I am currently co-ordinating a Diploma in Evidence-Based Dermatology in which attendees have been sponsored by Pfizer, AbbVie and Novartis laboratories."

Clinical referee Steven Feldman: "I have received research, speaking and/or consulting support from a variety of companies including Galderma, GSK/Stiefel, Almirall, Leo Pharma, Baxter, Boeringer Ingelheim, Mylan, Celgene, Pfizer, Valeant, AbbVie, Cosmederm, Anacor, Astellas, Janssen, Lilly, Merck, Merz, Novartis, Qurient, National Biological Corporation, Caremark, Advance Medical, Suncare Research, Informa, UpToDate and National Psoriasis Foundation. I am founder and majority owner of [www.DrScore.com](http://www.DrScore.com). I am a founder and part owner of Causa Research, a company dedicated to enhancing patients' adherence to treatment."

## SOURCES OF SUPPORT

### Internal sources

- No sources of support supplied

## External sources

- The National Institute for Health Research (NIHR), UK.

The NIHR, UK, is the largest single funder of the Cochrane Skin Group.

- The French Society of Dermatology (SFD), France; French Ministry of Health, France.

Grant support was from the Programme Hospitalier de Recherche Clinique (DGOS n°14-0322). The funding agencies have no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation and review of the manuscript.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

### I. Between the first protocol submission (January 2014) and the first search (February 2015), we identified and added in the protocol new systemic therapeutics for psoriasis.

- Background > Description of the intervention
  - Oral systemic treatment
  - Biological therapies
- Background > How the intervention might work?
  - Oral systemic treatment
  - Biological therapies
- Objectives

We expanded our objectives to clarify the types of systemic treatments for psoriasis. We changed: “To assess the effects of systemic pharmacological treatments for chronic plaque psoriasis” to “To compare the efficacy and safety of conventional systemic agents (acitretin, ciclosporin, fumaric acid esters, methotrexate), small molecules (apremilast, tofacitinib, ponesimod), anti-TNF alpha (etanercept, infliximab, adalimumab, certolizumab), anti-IL12/23 (ustekinumab), anti-IL17 (secukinumab, ixekizumab, brodalumab), anti-IL23 (guselkumab, tildrakizumab), and other biologics (alefacept, itolizumab) for patients with moderate to severe psoriasis and to provide a ranking of these treatments according to their efficacy and safety.”

- Methods > Types of intervention

We changed: “Systemic and biological treatments include the following: fumaric acid esters, retinoids (acitretin), ciclosporin, methotrexate, infliximab, etanercept, adalimumab, ustekinumab, briakinumab, alefacept, brodalumab, ixekizumab” to the following:

“Systemic and biological treatments included the following:

- Systemic conventional treatments:
  - Fumaric acid esters
  - Acitretin
  - Ciclosporin
  - Methotrexate
- Small molecules
  - Apremilast
  - Tofacitinib
  - Ponesimod
- Anti-TNF alpha
  - Infliximab
  - Etanercept
  - Adalimumab
  - Certolizumab
- Anti-IL12/23



- Ustekinumab
- Anti-IL17
  - Secukinumab
  - Brodalumab
  - Ixekizumab
- Anti-IL23
  - Tildrakizumab
  - Guselkumab
- Other biologic treatment
  - Itolizumab
  - Alectable

A new anti-IL23 molecule (BI 655066, risankizumab) appeared after we began this review and was not included in this systematic review. However, the ongoing studies of risankizumab have been reported in this review.”

## 2. Background > Why it is important to do this review?

We updated the published literature regarding other systemic reviews and meta-analyses.

## 3. Methods > Criteria for considering studies for this review

### Selection of trials

We added: “Phase I trials were not eligible because participants, outcomes, dosages, and schema of administration of interventions are too different from phase II, III, and IV studies.”

### Outcomes

#### Primary outcome 1

In the Protocol, we wrote, “The proportion of participants who achieved clear or almost clear skin. (By clear or almost clear, we mean a Physician Global Assessment (PGA) value of 0 or 1 or a 90/100 PASI.)”

In the review, we changed this sentence to “The proportion of participants who achieved clear or almost clear skin, that is, at least PASI 90”.

As PASI and PGA are two different scales, we preferred to assess them separately and added as a secondary outcome “Proportion of participants who achieve a Physician Global Assessment (PGA) value of 0 or 1”.

#### Primary outcome 1

We also modified the sentence about serious adverse effects (SAEs) (in the protocol we said we would use the FDA’s definition): “The proportion of participants with serious adverse effects (SAE). We used the definition of severe adverse effects from the International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, which includes death, life-threatening events, initial or prolonged hospitalisation, and adverse events requiring intervention to prevent permanent impairment or damage.” The definition remains the same.

#### Secondary outcome 3

For ‘Quality of life measured by a specific scale’, we listed Dermatology Life Quality Index (DLQI), Skindex, Psoriasis Disability Index (PDI), or Psoriasis Symptom Inventory (PSI). It is not an exhaustive list. Moreover, we had PSI as a validated scale because it was used by some study authors.

## Timings

We modified the period of the induction therapy assessment to less than 24 weeks after randomisation instead of 12 to 24 weeks because Nast et al defined the induction period as being with a duration less than 24 weeks (Nast 2015b).

To avoid duplicating text, we removed the text discussing timing for remission, as published in the protocol, and edited the timings for induction and maintenance therapy to include the relevant short- or long-term remission classification. We also removed the timings given in the protocol for the quality of life outcome for the same reason (we felt the text was duplicative).

We clarified that our inclusion criteria was to only include studies that reported our timings of interest by editing as follows: “We did not include studies that had timings outside of these time ranges in our analyses” to “We did not include studies that had timings outside of these time ranges in our review.”

## 4. Methods > Search methods for identification of studies

We removed the following two sentences from the review:

“We contacted key investigators and experts in the field to identify further published or unpublished data.”

“We contacted pharmaceuticals companies producing fumaric acid esters, and retinoids (fumaric acid esters, retinoids (acitretin), ciclosporin, methotrexate, alefacept, infliximab, etanercept, adalimumab, certolizumab, ustekinumab, secukinumab, brodalumab, ixekizumab, tildrakizumab, guselkumab, Itolizumab, apremilast, tofacitinib, ponesimod.”

We replaced them with the following:

“We searched in the trial results databases of each company to identify ongoing and unpublished trials.”

## 5. Methods > Data extraction and management

We added some details regarding the data extraction (outcome data, other data) for greater clarity and added the sentence, “We extracted the data from the reports of the U.S. Food and Drug Administration (FDA) when available, if not from the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)), and finally from the published reports.”

## 6. Methods > Assessment of risk of bias in included studies

We added information regarding the network meta-analysis ‘Risk of bias’ assessment (under “overall risk of bias”).

### Network meta-analysis

“To summarise the quality of evidence and to interpret the network results, we used these six RoB criteria (random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessor, incomplete outcome data, and selective outcome reporting) in order to classify each trial.

We would classify the trial as having low risk of bias if we rated none of the domains above as high risk of bias and two or less as unclear risk.

We would classify the trial as having moderate risk of bias if we rated one domain as high risk of bias, one or less domains as unclear risk, or no domains as high risk of bias but three or less were rated as unclear risk.

All other cases were assumed to pertain to high risk of bias.”

## 7. Methods > Measure of treatment effect

We added an explanation related to relative treatment ranking.

## 8. Methods > Dealing with missing data

We clarified who the authors or sponsors we contacted were: “We contacted trial authors or sponsors by email to request missing outcome data (numbers of events and numbers of participants for important dichotomous clinical outcomes) when these were not available in study reports that were less than 10 years old.”

## 9. Methods > Assessment of reporting bias and Assessment of heterogeneity

We added an explanation regarding the network meta-analysis:

“We undertook meta-analyses only if we judged participants, interventions, comparisons, and outcomes to be sufficiently similar (section 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions*) (Higgins 2011). Potential sources of heterogeneity included participants’ baseline characteristics (weight, the duration of previous treatment, treatment doses, co-interventions, and duration of treatment). When enough data were available, we investigated the distributions of these characteristics across studies and treatment comparisons. The latter allows assessing transitivity, i.e. whether there were important differences between the trials evaluating different comparisons other than the treatments being compared (Salanti 2014). To further reassure the plausibility of the transitivity assumption, we only included in our analyses trials not involving co-interventions and with a timing of outcome assessment from 12 to 16 weeks. In the classical meta-analyses, we assessed statistical heterogeneity by visual inspection of the forest plots and using the Q-test and the I<sup>2</sup> statistic. We interpreted the I<sup>2</sup> statistic according to the following thresholds (section 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions*; Higgins 2011): 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; 75% to 100% represents considerable heterogeneity.

In the network meta-analysis, the assessment of statistical heterogeneity in the entire network was based on the estimated heterogeneity standard deviation parameter ( $\tau$ ) estimated from the network meta-analysis models (Jackson 2014). We inferred on the presence or absence of important heterogeneity by comparing the magnitude of  $\tau$  with the empirical distributions provided in Turner et al and Rhodes et al (Rhodes 2015; Turner 2012). We also estimated the prediction intervals to assess how much the estimated heterogeneity affects the relative effects with respect to the additional uncertainty anticipated in future studies (Riley 2011). Where feasible, we would have investigated the possible sources of heterogeneity in subgroup analyses and meta-regression.

Although we restricted the risk of important heterogeneity in our data by considering eligible only studies with a follow-up period between 12 and 16 weeks and without co-interventions, we investigated differences in heterogeneity across the different analyses. Specifically, we observed whether splitting the nodes of the network and analysing each drug separately reduced the heterogeneity estimate. We also ran a series of sensitivity analyses (see [Sensitivity analysis](#)), and we monitored whether heterogeneity became smaller or larger compared to the primary analysis.”

### Assessment of reporting biases

To assess reporting biases, we used an adaptation of the funnel plot by subtracting from each study-specific effect size the mean of meta-analysis of the study-specific comparison, which we plotted against the study standard error (Chaimani 2013). We employed this ‘comparison-adjusted funnel plot’ for all comparisons of an active treatment against placebo. When we detected funnel plot asymmetry for the two primary outcomes, we investigated the presence of small-study effects in the network meta-regression (Chaimani 2012).

## 10. Methods > Data synthesis

We added the software used for the review: “We conducted pair-wise meta-analyses using Review Manager 5 (RevMan 5) (Revman 2014), and we performed all other analyses in Stata 14 using the ‘network’ ([www.stata-journal.com/article.html?article=st0410](http://www.stata-journal.com/article.html?article=st0410)) and ‘network graphs’ packages ([www.stata-journal.com/article.html?article=st0411](http://www.stata-journal.com/article.html?article=st0411)).”

## 11. Methods > Sensitivity analysis

We added “To assess the robustness of our results, we performed the following sensitivity analyses for the two primary outcomes: (1) running the analysis at dose-level considering that each different drug dose is a different intervention; (2) excluding trials at high risk of bias; (3) excluding trials with a total sample size smaller than 50 randomised participants; and (4) analysing only the observed participants assuming that missing participants are missing at random.”

## 12. Methods > ‘Summary of findings’ table

We added a section detailing the methods used to create the ‘Summary of findings’ tables; we also explained how we used GRADE to assess the certainty (quality/confidence) of the evidence.

### **13. Contributions of authors**

We changed or added authors' contributions:

LLC, GD, IGD, and ES screened papers against eligibility criteria.

LLC, GD, IGD, CH, CM, CD, and ES appraised the quality of papers.

LLC, GD, IGD, CH, CM, CD, and ES extracted data for the review and sought additional information about papers.

AC responded to the methodological and statistical comments of the referees instead of LT (Ludovic Trinquard was no longer available and was replaced by Anna Chaimani).

AC, LLC, and ES worked on the methods sections instead of LT, ES, and LLC (Ludovic Trinquard was no longer available and was replaced by Anna Chaimani).

## **INDEX TERMS**

### **Medical Subject Headings (MeSH)**

\*Network Meta-Analysis; Antibodies, Monoclonal [adverse effects; \*therapeutic use]; Chronic Disease; Immunosuppressive Agents [adverse effects; \*therapeutic use]; Psoriasis [\*drug therapy; pathology]; Randomized Controlled Trials as Topic; Remission Induction; Tumor Necrosis Factor-alpha [antagonists & inhibitors]

### **MeSH check words**

Adult; Humans