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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. This is the baseline update of a Cochrane Review first published in 2017, in preparation for this Cochrane Review becoming a living systematic review.

Objectives

To compare the efficacy and safety of conventional systemic agents, small molecules, and biologics for people with moderate-to-severe psoriasis, and to provide a ranking of these treatments according to their efficacy and safety.

Search methods

We updated our research using the following databases to January 2019: the Cochrane Skin Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, LILACS and the conference proceedings of a number of dermatology meetings. We also searched five trials registers and the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) reports (until June 2019). We checked the reference lists of included and excluded studies for further references to relevant RCTs.

Selection criteria

Randomised controlled trials (RCTs) of systemic 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. The primary outcomes of this review were: the proportion of participants who achieved clear or almost clear skin, that is, at least Psoriasis Area and Severity Index (PASI) 90 at induction phase (from 8 to 24 weeks after the randomisation), and the proportion of participants with serious adverse effects (SAEs) at induction phase. We did not evaluate differences in specific adverse effects.

Data collection and analysis

Several 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 PASI 90 score) 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, as either very low, low, moderate, or high. We contacted study authors when data were unclear or missing.

Main results

We included 140 studies (31 new studies for the update) in our review (51,749 randomised participants, 68% men, mainly recruited from hospitals). The overall average age was 45 years; the overall mean PASI score at baseline was 20 (range: 9.5 to 39). Most of these studies were placebo-controlled (59%), 30% were head-to-head studies, and 11% were multi-armed studies with both an active comparator and a placebo. We have assessed a total of 19 treatments. In all, 117 trials were multicentric (two to 231 centres). All but two of the outcomes included in this review were limited to the induction phase (assessment from 8 to 24 weeks after randomisation). We assessed many studies (57/140) as being at high risk of bias; 42 were at an unclear risk, and 41 at low risk. Most studies (107/140) declared funding by a pharmaceutical company, and 22 studies did not report the source of funding.

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.

At class level, 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.

At drug level, in terms of reaching PASI 90, infliximab, all of the anti-IL17 drugs (ixekizumab, secukinumab, bimekizumab and brodalumab) and the anti-IL23 drugs (risankizumab and guselkumab, but not tildrakizumab) were significantly more effective in reaching PASI 90 than ustekinumab and 3 anti-TNF alpha agents: adalimumab, certolizumab and etanercept. Adalimumab and ustekinumab were significantly more effective in reaching PASI 90 than certolizumab and etanercept. There was no significant difference between tofacitinib or apremilast and between two conventional drugs: ciclosporin and methotrexate.

Network meta-analysis also showed that infliximab, ixekizumab, risankizumab, bimekizumab, guselkumab, secukinumab and brodalumab outperformed other drugs when compared to placebo in reaching PASI 90. The clinical effectiveness for these seven drugs was similar: infliximab (versus placebo): risk ratio (RR) 29.52, 95% confidence interval (CI) 19.94 to 43.70, Surface Under the Cumulative Ranking (SUCRA) = 88.5; moderate-certainty evidence; ixekizumab (versus placebo): RR 28.12, 95% CI 23.17 to 34.12, SUCRA = 88.3, moderate-certainty evidence; risankizumab (versus placebo): RR 27.67, 95% CI 22.86 to 33.49, SUCRA = 87.5, high-certainty evidence; bimekizumab (versus placebo): RR 58.64, 95% CI 3.72 to 923.86, SUCRA = 83.5, low-certainty evidence; guselkumab (versus placebo): RR 25.84, 95% CI 20.90 to 31.95; SUCRA = 81; moderate-certainty evidence; secukinumab (versus placebo): RR 23.97, 95% CI 20.03 to 28.70, SUCRA = 75.4; high-certainty evidence; and brodalumab (versus placebo): RR 21.96, 95% CI 18.17 to 26.53, SUCRA = 68.7; moderate-certainty evidence. Conservative interpretation is warranted for the results for bimekizumab (as well as tyrosine kinase 2 inhibitor, acitretin, ciclosporin, fumaric acid esters, and methotrexate), as these drugs, in the NMA, have been evaluated in few trials.

We found no significant difference between any of the interventions and the placebo for the risk of SAEs. Nevertheless, the SAE analyses were based on a very low number of events with low to very low certainty for just under half of the treatment estimates in total, and moderate for the others. Thus, the results have to be viewed with caution and we cannot be sure of the ranking.

For 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 several of the interventions.

Authors' conclusions

Our review shows that compared to placebo, the biologics infliximab, ixekizumab, risankizumab, bimekizumab, guselkumab, secukinumab and brodalumab were the best choices for achieving PASI 90 in people with moderate-to-severe psoriasis on the basis of moderate- to high-certainty evidence (low-certainty evidence for bimekizumab). This NMA evidence is limited to induction therapy (outcomes were measured from 8 to 24 weeks after randomisation) and is not sufficient for evaluation of longer-term outcomes in this chronic disease. Moreover, we

found low numbers of studies for some of the interventions, and the young age (mean age of 45 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, but the evidence for all the interventions was of very low to moderate quality. In order to provide long-term information on the safety of the treatments included in this review, it will also be necessary to evaluate non-randomised studies and postmarketing reports released from regulatory agencies.

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 participants, 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.

Editorial note: This is a living systematic review. Living systematic reviews offer a new approach to review updating, in which the review is continually updated, incorporating relevant new evidence as it becomes available. Please refer to the Cochrane Database of Systematic Reviews for the current status of this review.

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 moderate-to-severe 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 140 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 90% improvement in the Psoriasis Area and Severity Index (PASI). 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 on safety 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). 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 from 8 to 24 weeks after participants were allocated to their treatment group), and there was insufficient information to understand the relative benefits of treatments on longer-term outcomes for this 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 risks 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 negatively impacts 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 140 studies enrolled 51,749 people (mainly recruited from a hospital) with moderate-to-severe psoriasis: 34,624 men and 16,529 women (unknown for the remaining 596 participants); the overall average age was 45 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 = 82) compared the systemic medicine with a placebo treatment, 41 trials compared systemic treatments with other systemic treatments, and 17 trials compared systemic treatments with systemic treatments and placebo. Most studies were short-term; 117 trials were multicentric trials (2 to 231 centres). Most studies (107/140) declared pharmaceutical-company funding and 22 studies did not report the source of funding.

The outcomes presented here were measured from 8 to 24 weeks after the study participants were randomised (induction phase). The following results are based on network meta-analysis (a technique that synthesises direct and indirect comparisons of interventions).

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; and conventional systemic agents) were significantly 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 significantly better than the small molecules and the conventional systemic agents. IL is an abbreviation of interleukin; TNF is an abbreviation of tumour necrosis factor, and 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, infliximab, all of the anti-IL17 drugs (ixekizumab, secukinumab, bimekizumab, and brodalumab) and the anti-IL23 drugs (risankizumab and guselkumab, but not tildrakizumab) were significantly more effective than ustekinumab and three anti-TNF alpha agents: adalimumab, certolizumab and etanercept. Adalimumab and ustekinumab were superior to certolizumab and etanercept. We found no significant difference between tofacitinib or apremilast and two conventional drugs: ciclosporin and methotrexate.

Judged against placebo, seven biological medicines worked best at clearing psoriasis lesions (specifically, reaching PASI 90). These medicines were infliximab, ixekizumab (both based on moderate-certainty evidence), risankizumab (high-certainty evidence), bimekizumab (low-certainty evidence), guselkumab (moderate-certainty evidence), secukinumab (high-certainty evidence), and brodalumab (moderate-certainty evidence). There was little difference in how well these seven drugs worked.

For 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.

We must be cautious about the results for some biologics (bimekizumab), small molecules (tyrosine kinase 2 inhibitor), and conventional systemic treatments (acitretin, ciclosporin, fumaric acid esters, and methotrexate), as these drugs have been evaluated in few trials in the NMA.

For the risk of serious side effects, there were no significant differences between any of the systemic medicines compared with placebo treatment. However, the number of serious side effects was very low, and our rankings are based on low- to very low- (for just under half of the results) or moderate-certainty evidence, so they should be interpreted with caution.

For all studies, little information was recorded about quality of life; several 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 January 2019.

Editorial note: This is a living systematic review. Living systematic reviews offer a new approach to review updating, in which the review is continually updated, incorporating relevant new evidence as it becomes available. Please refer to the Cochrane Database of Systematic Reviews for the current status of this review.

Summary of findings 1. Any systemic treatment compared to placebo for chronic plaque psoriasis - PASI 90

Any systemic treatment compared to placebo for chronic plaque psoriasis - PASI 90[a]

Patient or population: people with chronic plaque psoriasis
Intervention: any systemic treatment
Comparison: placebo

Setting: Most trials recruited participants from hospital setting, but also in offices

Timescale: from 8 to 24 weeks after randomisation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	SUCRA[c]	№ of participants (studies)[d]	Certainty of the evidence (GRADE)	Comments
	Risk with placebo[b]	Risk with any systemic treatment					
Infliximab	Moderate		RR 29.52 (19.94 to 43.70)	88.5	1651 (5 RCTs)	⊕⊕⊕⊖ MODERATE	Downgraded by 1 level due to inconsistency: inconsistent loops of evidence
	15 per 1000	443 per 1000 (299 to 656)					
Ixekizumab	Moderate		RR 28.12 (23.17 to 34.12)	88.3	3268 (4 RCTs)	⊕⊕⊕⊖ MODERATE	Downgraded by 1 level due to inconsistency: inconsistent loops of evidence
	15 per 1000	422 per 1000 (348 to 512)					
Risankizumab	Moderate		RR 27.67 (22.86 to 33.49)	87.5	1476 (4 RCTs)	⊕⊕⊕⊕ HIGH	-
	15 per 1000	415 per 1000 (343 to 502)					
Bimekizumab	Moderate		RR 58.64 (3.72 to 923.86)	83.5	250 (1 RCT)	⊕⊕⊖⊖ LOW	Downgraded by 2 levels due to imprecision: wide CI
	15 per 1000	880 per 1000 (56 to 1000)					
Guselkumab	Moderate		RR 25.84 (20.90 to 31.95)	81	1767 (5 RCTs)	⊕⊕⊕⊖ MODERATE	Downgraded by 1 level due to risk of bias: 1 study contributing to this estimate at high risk of bias in selective reporting domain
	15 per 1000	388 per 1000					

		(313 to 479)					
Secukinumab	Moderate		RR 23.97 (20.03 to 28.70)	75.4	2895 (8 RCTs)	⊕⊕⊕⊕ HIGH	-
	15 per 1000	360 per 1000 (300 to 431)					
Brodalumab	Moderate		RR 21.96 (18.17 to 26.53)	68.7	4109 (5 RCTs)	⊕⊕⊕⊖ MODERATE	Downgraded by 1 level due to risk of bias: 3 studies contributing to this estimate at high risk of bias in selective reporting domain
	15 per 1000	329 per 1000 (273 to 398)					
Adalimumab	Moderate		RR 17.82 (14.62 to 21.72)	58.1	3421 (9 RCTs)	⊕⊕⊕⊖ MODERATE	Downgraded by 1 level due to inconsistency: inconsistent loops of evidence
	15 per 1000	267 per 1000 (219 to 326)					
Ustekinumab	Moderate		RR 17.17 (14.44 to 20.42)	55.6	4231 (9 RCTs)	⊕⊕⊕⊕ HIGH	-
	15 per 1000	258 per 1000 (217 to 306)					
Tildrakizumab	Moderate		RR 17.08 (12.93 to 22.56)	55.8	1903 (3 RCTs)	⊕⊕⊕⊕ HIGH	-
	15 per 1000	256 per 1000 (194 to 338)					
Oral tyrosine kinase 2 (TYK2) inhibitor	Moderate		RR 13.99 (1.99 to 98.10)	51.5	267 (1 RCT)	⊕⊕⊖⊖ LOW	Downgraded by 2 levels due to imprecision: wide CI
	15 per 1000	210 per 1000 (30 to 1000)					
Certolizumab	Moderate		RR 12.11 (8.78 to 16.71)	42.5	1026 (4 RCTs)	⊕⊕⊕⊖ MODERATE	Downgraded by 1 level due to risk of bias: 1 study at high risk of bias in blinding of participants and personnel (performance bias)
	15 per 1000	182 per 1000 (132 to 251)					
Ciclosporin	Moderate		RR 9.88 (5.45 to 17.91)	33.4	(0 RCTs)	⊕⊖⊖⊖ VERY LOW	Downgraded by 2 levels due to risk of bias/1 level due to imprecision: the studies contributing to this estimate are mostly at at high risk of bias, and wide CI
	15 per 1000	148 per 1000 (82 to 269)					
Etanercept	Moderate		RR 9.72 (8.12 to 11.63)	33	5650 (14 RCTs)	⊕⊕⊕⊖ MODERATE	Downgraded by 1 level due to risk of bias: 1 study contributing to this estimate is at high

	15 per 1000	146 per 1000 (122 to 174)					risk of bias in blinding domains (blinding of participants and personnel (performance bias))
Methotrexate	Moderate		RR 9.78 (7.15 to 13.37)	32.9	318 (3 RCTs)	⊕⊕⊖⊖ LOW	Downgraded by 1 level due to inconsistency (inconsistent loops of evidence) and 1 level due to risk of bias: 1 study at high risk of bias in selective reporting (reporting bias)
	15 per 1000	147 per 1000 (107 to 201)					
Tofacitinib	Moderate		RR 8.19 (6.53 to 10.29)	23.4	3092 (5 RCTs)	⊕⊕⊖⊖ LOW	Downgraded by 2 level due to risk of bias: 2 studies at high risk of bias in incomplete outcome data domain and 1 study at high risk of bias in incomplete outcome data (attrition bias) domain
	15 per 1000	123 per 1000 (98 to 154)					
Apremilast	Moderate		RR 7.30 (4.26 to 12.51)	21.9	2029 (5 RCTs)	⊕⊕⊕⊖ MODERATE	Downgraded by 1 level due to risk of bias: studies contributing to the estimates at high risk of bias in selective reporting domain
	15 per 1000	110 per 1000 (64 to 188)					
Fumaric acid	Moderate		RR 3.65 (2.49 to 5.36)	9.8	704 (1 RCT)	⊕⊖⊖⊖ VERY LOW	Downgraded by 2 levels due to risk of bias, and 1 level due to imprecision: the studies indirectly contributing to this estimate at high risk of bias in blinding domain, and only 1 study contributed to the direct estimation
	15 per 1000	55 per 1000 (37 to 80)					
Acitretin	Moderate		RR 2.13 (0.37 to 12.16)	8.1	(0 RCTs)	⊕⊖⊖⊖ VERY LOW	Downgraded by 2 levels due to imprecision (wide CI including 1) and 1 level due to risk of bias as the studies indirectly contributing to this estimate at high risk in blinding domain
	15 per 1000	32 per 1000 (6 to 182)					

*__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; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]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.
[b]'Risk with placebo' is the median placebo-group risk value in the included studies for the assumed risk with placebo.

[c]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).
[d]'Number of participants (studies)' is from the direct comparisons.

Summary of findings 2. Any systemic treatment compared to placebo for chronic plaque psoriasis - SAEs

Any systemic treatment compared to placebo for chronic plaque psoriasis - Serious adverse effects (SAEs)

Patient or population: people with chronic plaque psoriasis
Intervention: any systemic treatment
Comparison: placebo

Setting: Most trials recruited participants from hospital setting, but also in offices

Timescale: from 8 to 24 weeks after randomisation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	SUCRA[b]	№ of participants (studies)[c]	Certainty of the evidence (GRADE)	Comments
	Risk with placebo[a]	Risk with any systemic treatment					
Methotrexate	Moderate		RR 0.43 (0.20 to 0.95)	87.6	319 (3 RCTs)	⊕⊕⊕⊖ MODERATE	Downgraded by 1 level due to imprecision (wide CI)
	17 per 1000	7 per 1000 (3 to 16)					
Bimekizumab	Moderate		RR 0.20 (0.01 to 3.16)	84.3	250 (1 RCT)	⊕⊕⊖⊖ LOW	Downgraded by 2 levels due to imprecision (wide CI including 1)
	17 per 1000	3 per 1000 (0 to 54)					
Risankizumab	Moderate		RR 0.60 (0.37 to 0.96)	79.9	1476 (4 RCTs)	⊕⊕⊕⊖ MODERATE	Downgraded by 1 level due imprecision (wide CI)
	17 per 1000	10 per 1000 (6 to 16)					
Certolizumab	Moderate		RR 0.74 (0.31 to 1.75)	62.4	1026 (4 RCTs)	⊕⊕⊖⊖ LOW	Downgraded by 1 level due to risk of bias (1 study at high risk of bias in blinding of participants and personnel (performance bias)) and 1 level due to imprecision (wide CIs including 1)
	17 per 1000	13 per 1000 (5 to 30)					

Oral Tyrosine kinase 2 (TYK2) inhibitor	Moderate		RR 0.61 (0.06 to 5.71)	61.6	267 (1 RCT)	⊕⊕⊖⊖ LOW	Downgraded by 2 levels due to imprecision (wide CI including 1)
	17 per 1000	10 per 1000 (1 to 97)					
Tildrakizumab	Moderate		RR 0.84 (0.39 to 1.83)	54.6	1904 (3 RCTs)	⊕⊕⊕⊖ MODERATE	Downgraded by 1 level due to imprecision (wide CI including 1)
	17 per 1000	14 per 1000 (7 to 31)					
Apremilast	Moderate		RR 0.86 (0.48 to 1.51)	54.5	2290 (6 RCTs)	⊕⊕⊖⊖ LOW	Downgraded by 1 level due to risk of bias and 1 level due to imprecision due to wide CI including 1
	17 per 1000	15 per 1000 (8 to 26)					
Ustekinumab	Moderate		RR 0.89 (0.63 to 1.27)	52.7	4553 (10 RCTs)	⊕⊕⊕⊖ MODERATE	Downgraded by 1 level due to imprecision (wide CI including 1)
	17 per 1000	15 per 1000 (11 to 22)					
Etanercept	Moderate		RR 0.89 (0.61 to 1.31)	52.6	4265 (13 RCTs)	⊕⊕⊕⊖ MODERATE	Downgraded by 1 level due to imprecision (wide CIs including 1)
	17 per 1000	15 per 1000 (10 to 22)					
Fumaric acid esters	Moderate		RR 0.98 (0.50 to 1.94)	43.5	704 (1 RCT)	⊕⊖⊖⊖ VERY LOW	Reasons for downgrading by 2 level due to risk of bias and 1 level due to imprecision, and to wide CI including 1
	17 per 1000	17 per 1000 (9 to 33)					
Guselkumab	Moderate		RR 0.98 (0.54 to 1.79)	43.2	1767 (5 RCTs)	⊕⊕⊕⊖ MODERATE	Downgraded by 1 level due to imprecision (wide CI including 1)
	17 per 1000	17 per 1000 (9 to 30)					
Adalimumab	Moderate		RR 0.98 (0.65 to 1.49)	42.6	3485 (10 RCTs)	⊕⊕⊕⊖ MODERATE	Downgraded by 1 level due to imprecision (wide CI including 1)
	17 per 1000	17 per 1000 (11 to 25)					
Tofacitinib	Moderate		RR 1.01 (0.57 to 1.77)	41.2	3122 (7 RCTs)	⊕⊕⊕⊖ MODERATE	Downgraded by 1 level due to imprecision (wide CI including 1)
	17 per 1000	17 per 1000					

		(10 to 30)					
Brodalumab	Moderate		RR 1.04 (0.62 to 1.73)	38.4	4109 (5 RCTs)	⊕⊕⊕⊖ MODERATE	Downgraded by 1 level due to imprecision (wide CI including 1)
	17 per 1000	18 per 1000 (11 to 29)					
Infliximab	Moderate		RR 1.11 (0.59 to 2.07)	33.9	1678 (6 RCTs)	⊕⊕⊕⊖ MODERATE	Downgraded by 1 level due to imprecision (wide CI including 1)
	17 per 1000	19 per 1000 (10 to 35)					
Ixekizumab	Moderate		RR 1.09 (0.69 to 1.73)	33	3268 (4 RCTs)	⊕⊕⊕⊖ MODERATE	Downgraded by 1 level due to imprecision (wide CI including 1)
	17 per 1000	16 per 1000 (10 to 26)					
Ciclosporin	Moderate		RR 1.47 (0.19 to 11.22)	32	(0 RCTs)	⊕⊖⊖⊖ VERY LOW	Downgraded by 2 levels due to risk of bias/1 level due to imprecision (the studies contributing to this estimate are mostly at at high risk of bias), and wide CI including 1
	17 per 1000	25 per 1000 (3 to 191)					
Acitretin	Moderate		RR 1.53 (0.19 to 12.56)	31.2	(0 RCTs)	⊕⊖⊖⊖ VERY LOW	Downgraded by 2 levels due to imprecision (wide CI including 1) and 1 level due to risk of bias as the studies indirectly contributing to this estimate at high risk in blinding domain
	17 per 1000	26 per 1000 (3 to 214)					
Secukinumab	Moderate		RR 1.12 (0.74 to 1.70)	30.4	2904 (8 RCTs)	⊕⊕⊕⊖ MODERATE	Downgraded by 1 level due to imprecision (wide CI including 1)
	17 per 1000	19 per 1000 (13 to 29)					

*__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; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]'Risk with placebo' is the median placebo-group risk value in the included studies for the assumed risk with placebo.
[b]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).
[c]'Number of participants (studies)' is from the direct comparisons.

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 2.2% (USA) to 8.5% (Norway) (Boehncke 2015; Parisi 2013; Stern 2004). 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 (Capon 2017; 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 there are no lesions.

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 PASI 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 US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) used PASI 75, i.e. a 75% improvement in the PASI score, and more recently PASI 90, i.e. 90% improvement in the PASI score, as primary end points. PASI score has substantial limitations, such as low-response distribution, no consensus on interpretability, and low responsiveness in mild disease (Spuls 2010). However, PASI 90 is a stringent outcome, as patients reaching PASI 90 are almost clear.

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 is 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 people 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 period of time of the initial therapy intended to induce remission of the disease, and a maintenance therapy, e.g. to maintain the remission of the disease.

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 proposed methotrexate as the first choice of systemic agent. 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 new small molecules (apremilast) are more recent systemic therapies (Boehncke 2015). Many healthcare systems have developed elaborate psoriasis treatment algorithms to address the high cost of newer therapies. Indeed, in Europe and in Canada, there are mandatory reimbursement criteria that patients must meet before being considered for these treatments, due to their high costs (Nast 2015b), such as presenting a moderate-to-severe psoriasis after failure, intolerance or contraindication to at least two conventional systemic agents (French criteria).

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

Oral treatments

Conventional systemic agents

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

The existing oral pharmacological treatments licensed 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; Flytström 2008; Koo 1998; Heydendael 2003; Ho 1999; Mahrle 1995; Meffert 1997; Mrowietz 1995; Shupack 1997). In 2008, Saurat and colleagues conducted the only randomised trial comparing the efficacy of methotrexate versus 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 people with psoriasis not responding to conventional treatments. These small molecule drugs include apremilast (Papp 2012c), tofacitinib (Bachelez 2015), and BMS-986165 (Papp TYK2 2018). Tofacitinib and BMS-986165 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 20th 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 except mirikizumab (phase II still ongoing NCT02899988 Reich 2017): etanercept (Leonardi 2003), infliximab (Chaudhari 2001), adalimumab (Menter REVEAL 2008), certolizumab (Reich 2012a), ustekinumab (Lebwohl 2010), secukinumab (Reich 2015), ixekizumab (Leonardi 2012), brodalumab (Papp 2012a), bimekizumab (Papp BE ABLE 2018), guselkumab (Gordon X-PLORE 2015), tildrakizumab (Papp 2015), and risankizumab (NCT02672852 IMMhance). Bimekizumab and mirikizumab 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 an 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)-c, TNF alpha (by Th1 and Tc1 cells), IL-17A, and IL-23R (by Th17 and Tc17 cells) (Boehncke 2015).

Oral 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 a day.

Small molecules

Small molecule drugs modulate pro-inflammatory 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 IFNγ in people with psoriasis. Apremilast has recently been approved for psoriasis; its efficacy seems to be higher than conventional systemic therapy, but 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 target the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway, which is pivotal for the downstream signalling of inflammatory cytokines involved in psoriasis. Tofacitinib had not been approved for psoriasis at the time our analyses were done (Torres 2015).

BMS-986165

BMS-986165 is a potent, oral tyrosine kinase 2 (TYK2) inhibitor that binds to the pseudokinase domain of the enzyme and is functionally more selective than other tyrosine kinase inhibitors. Tyrosine kinase 2 (TYK2) is an intracellular signalling enzyme which activates signal transducer and activator of transcription (STAT)–dependent gene expression and functional responses of interleukin-12, interleukin-23, and type I and III interferon receptors. These cytokine pathways are involved in the pathologic processes associated with psoriasis, and are distinct from responses driven by Janus kinase (JAK) 1 (JAK1), JAK1 and JAK3 in combination, JAK2, as previously described. BMS-986165 had not been approved for psoriasis at the time our analyses were done.

Biological therapies

Biological therapies have been developed in recent years and first target and prevent T cell proliferation and then target cytokines involved in psoriasis physiopathology (e.g. anti-TNF alpha, anti-IL12/23, anti-IL23, anti-IL17).

Anti-TNF alpha

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

- Etanercept is a recombinant TNF-α 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 (Gisondi 2004).
- Infliximab is a chimeric antibody that neutralises the action of TNF-α. 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 (Gisondi 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-α 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. Certolizumab therefore does not display Fc-mediated effects (improving solubility, increasing drug stability, and decreasing immunogenicity) (Campanati 2017). Treatment starts with a 400-mg dose given as two injections, followed by a further 400-mg dose two and four weeks later. After this, depending on the condition being treated, patients should continue with 200 mg or 400 mg, given as one or two injections every two or four weeks.

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), risankizumab (high-affinity humanised IgG1 monoclonal antibody), and mirikizumab (Dong 2017). In July 2017, the FDA approved guselkumab for psoriasis. Guselkumab is given as a 100 mg subcutaneous injection every eight weeks, following two starter doses at week 0 and week 4. More recently both tildrakizumab and risankizumab were approved. The recommended dose for tildrakizumab is one 100 mg injection, followed by a further dose after 4 weeks and then an injection every 12 weeks. The dose

may be increased to 200 mg in certain patients, for example those badly affected by the disease or with bodyweight over 90 kg. The recommended dose for risankizumab is 150 mg, administered by two subcutaneous injections every 12 weeks following two initiation doses at week 0 and 4. Mirikizumab had not been approved for psoriasis at the time our analyses were done.

- Interleukin-17 inhibitors include secukinumab (a recombinant fully human anti-IL17A IgG1k monoclonal antibody), ixekizumab (a humanised anti-IL17 immunoglobulin G4 monoclonal antibody), brodalumab (a human IgG2 monoclonal antibody that decreases the downstream effect of IL-17 by antagonising the IL-17RA receptor), and bimekizumab (a humanised monoclonal IgG1 antibody that potently and selectively neutralises the biological function of both human IL-17A and IL-17F) (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 four weeks thereafter (Dong 2017). The recommended dose for brodalumab is 210 mg given once a week for the first three weeks and then every two weeks. Bimekizumab had not been approved for psoriasis at the time our analyses were done.

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 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; Gómez-García 2017; Gospodarevskaya 2009; Lin 2012; Loveman 2009; Nast 2015a; Nelson 2008; Reich 2008; Reich 2012b; Schmitt 2008; Signorovitch 2010; Signorovitch 2015; Spuls 1997; Strober 2006; Tan 2011; Turner 2009; Woolacott 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 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.

Following the publication of the 2019 update of this review, we are maintaining it as a living systematic review. This means we are continually running the searches and rapidly incorporating any newly-identified evidence into the review. We believe a living systematic review approach is appropriate for this review, for three reasons. Firstly, the review addresses an important health issue. The high prevalence of psoriasis (1% to 3% of the world population); the major impact on quality of life for many individuals; the cardiovascular comorbidities associated with significant mortality; the many therapeutic options; and the high costs of these new systemic treatments are reasons, among others, to help physicians in determining which treatment is best suited to a patient. Secondly, an important level of uncertainty remains in the existing evidence in the field of psoriasis, despite searches including the current update (up to 31 January 2019) identifying a total of 140 studies for inclusion in the review. Few head-to-head trials have compared systemic treatments against each other. Once the benefit of a treatment has been established against placebo using high quality of evidence, head-to-head trials would be helpful to provide physicians with efficacy estimates between the different biological treatments based on stronger evidence than indirect comparisons. Further head-to-head trials are needed to accurately rank drugs according to their risk/benefit ratio. Thirdly, we are aware of ongoing trials in this area of research that will be important to incorporate, and we expect that future research will have an impact on the conclusions. For instance, new molecules have emerged constantly (e.g. in 2017, four new biological treatments for psoriasis emerged).

The plans for this review were published as a protocol 'Systemic pharmacological treatments for chronic plaque psoriasis' (Sbidian 2015). This review is an update of 'Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis' (Sbidian 2017).

OBJECTIVES

To compare the efficacy and safety of conventional systemic agents (acitretin, ciclosporin, fumaric acid esters, methotrexate), small molecules (apremilast, tofacitinib, BMS-986165), anti-TNF alpha (etanercept, infliximab, adalimumab, certolizumab), anti-IL12/23 (ustekinumab), anti-IL17 (secukinumab, ixekizumab, brodalumab, bimekizumab), and anti-IL23 (guselkumab, tildrakizumab, risankizumab, mirikizumab) for people 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 treatments, irrespective of the dose and duration of treatment, compared with placebo or with an active comparator.

Systemic treatments included the following:

- Systemic conventional treatments
  - FAEs
  - Acitretin
  - Ciclosporin
  - Methotrexate
- Small molecules
  - Apremilast
  - Tofacitinib
  - BMS-986165
- Anti-TNF alpha
  - Infliximab
  - Etanercept
  - Adalimumab
  - Certolizumab
- Anti-IL12/23
  - Ustekinumab
- Anti-IL17
  - Secukinumab
  - Brodalumab
  - Ixekizumab
  - Bimekizumab
- Anti-IL23
  - Tildrakizumab
  - Guselkumab
  - Risankizumab
  - Mirikizumab

We were interested to compare both the different drugs (n = 20) and the different classes of drugs (n = 6).

Active comparators include the following:

- any of the aforementioned systemic 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).

Adaptive criteria for considering studies for this review

As a living systematic review, we are continually identifying new evidence for interventions already in the network of trials but **also for novel interventions**. Indeed, for the 2019 review update, we identified several new interventions in the 'Ongoing trials' section that were not part of the initial network (e.g. risankizumab). To provide an update and a useful network of interventions for physicians, we need first to identify new interventions but also, to **drop old interventions**, which are no longer of interest.

To achieve these goals, we have created a research community in psoriasis, including international experts in the field who will help to provide information of new 'eligible' drugs.

Once a year, a list of all systemic drugs used for psoriasis will be proposed by the scientific steering committee to the international experts' group, including:

- Drugs already involved in the network

- Marketed drugs, identified using the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) websites (www.accessdata.fda.gov/scripts/cder/drugsatfda and www.ema.europa.eu/ema, respectively).

- Drugs under development, identified using the World Health Organization International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) and ISRCTN registry (www.isrctn.com)

The international experts' group will select from this list all the systemic drugs needed for the future network. They will also add relevant new interventions not proposed in the list. **They will provide a rationale for all proposed network changes (adding or removing interventions)**. The international experts' group is necessary also to determine which drugs have to be deleted from the network, with clinical practice and market authorisation being different in each country.

It is sufficient to update the interventions network once a year, as we are including phase II and III RCTs. Indeed, the timing between the phase I and the phase II/III for a promising intervention is over one year.

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 (i.e. psoriasis flare clearing phase).

Primary outcomes

- The proportion of participants who achieved clear or almost clear skin, that is, at least PASI 90 at induction phase.
- The proportion of participants with serious adverse effects (SAEs) at induction phase. 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

- Proportion of participants who achieve PASI 75 at induction phase.

- Proportion of participants who achieve a Physician Global Assessment (PGA) value of 0 or 1 at induction phase.
- 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) at induction phase.
- The proportions of participants with adverse effects (AEs) at induction phase ("AE outcome" did not include SAE).
- Proportion of participants who achieve PASI 75 at 52 weeks.
- Proportion of participants who achieve PASI 90 at 52 weeks.

We defined the induction phase as an evaluation from 8 to 24 weeks after the randomisation. In case of multiple time points, we chose the longest one.

To avoid selection of good responders of participants entering into long-term extension, we selected participants who have been randomised since the induction phase.

We did not include studies that had timings outside of the time ranges stated in our outcomes in our review or analyses. We did not evaluate specific adverse effects, just the proportion of participants with at least one adverse effect and at least one serious adverse effect at induction 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 31 January 2019:

- the Cochrane Skin Specialised Register using the search strategy in Appendix 1;
- the Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 1) 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
- Latin American and Caribbean Health Science Information (LILACS) database (from 1982) using the strategy in Appendix 5.

Trials registers

We searched the following trials registers up to 03 June 2019 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/);
- ISRCTN registry (www.isrctn.com);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov);
- Australian New Zealand Clinical Trials Registry (www.anzctr.org.au); and
- EU Clinical Trials Register (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 US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for drug registration (using www.accessdata.fda.gov/scripts/cder/drugsatfda and www.ema.europa.eu/ema).

Conference proceedings

During the previous Cochrane Review, 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.

For the update, these conferences are included in the Cochrane skin specialised register.

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.

Adaptive search for treatments and trials

As this is a living systematic review, we will search the different data sources described for the initial NMA with the latest updated search strategy. The electronic searches are being performed by the Cochrane Skin Group.

Every month, the search is being re-run from the date of the last iteration to the following one (covering a one-month interval), on an automated basis, for electronic searches, trial registries and conference proceedings. We are using a script file (html extraction by automated http requests) to automatically and simultaneously search multiple sources every month. We are manually screening the reference list of any newly-included studies and systematic reviews.

Every year, we will manually check other sources (regulatory agencies and industry trial registries). We will also update the search strategy by adding or removing interventions. We will also review search methods and strategies approximately yearly, to

ensure that they reflect any terminology changes in the topic area, or in the databases.

As additional steps to inform the living systematic review, we are contacting corresponding authors of ongoing studies as we identify them, and asking them to advise when results are available, or to share early or unpublished data.

Data collection and analysis

Selection of studies

We conducted the selection process through Covidence (Covidence 2019), a web tool allowing a double selection on title, abstract and then full text by independent review authors. Thus, two review authors (from LLC, IGD, CD, CP, CM, SA, ES) 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.

As this is a living systematic review, we will immediately screen any new citations retrieved by the monthly searches.

Data extraction and management

Two review authors (from LLC, IGD, CD, CP, CM, SA, ES) 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 Review Manager 5 (RevMan) (Revman 2014).

We extracted the data from the reports of the US FDA when available, and if not from the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (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;
- reached PASI 90, PASI 75 during the maintenance phase (at week 52); 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.

For 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, including missing data for outcomes (see Table 2).

Assessment of risk of bias in included studies

We used Cochrane's 'Risk of bias' (RoB) tool to assess the risks of bias. Two review authors (from LLC, IGD, CD, CP, CM, SA, 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 2017), we graded the following 'Risk of bias' domains as 'low', 'high', or 'unclear'.

- Selection bias (random sequence generation and allocation concealment items)
  - 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 being at low risk of bias even if the paper did not describe the method of allocation concealment.
- Performance and detection bias (blinding of participants,and blinding of outcome assessor items)
  - 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.
- Attrition bias (incomplete outcome data item)
  - 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.
- Reporting bias (selective outcome reporting item)
  - 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 the protocols was lacking in the main report.
- 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 fewer 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 fewer domains as unclear risk, or no domains as high risk of bias, but three or fewer were rated as unclear risk.

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

Measures of treatment effect

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

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). The advantage of SUCRA compared to other ranking measures is that it takes into account the entire distribution of the relative effects. (For more information on SUCRA, see Chaimani 2017b; Chaimani 2017c; Veroniki 2018). It should be noted, though, that ranking measures might be of limited value in the presence of large uncertainty in the results and therefore they should always be reported along with the relative effects.

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. In this analysis, different comparisons were analysed separately and therefore no study participants were double-counted. 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 (for efficacy outcomes) or did not experience AEs (for safety outcomes), 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*) (Deeks 2017). 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.

In the classical meta-analyses, we assessed statistical heterogeneity by visual inspection of the forest plots and using the Q-test and the I^2 statistic. We interpreted the I^2 statistic according to the following thresholds (section 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions*; Deeks 2017): 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 (τ) estimated from the network meta-analysis models (Jackson 2014). We inferred the presence or absence of important heterogeneity by comparing the magnitude of τ with the empirical distributions provided in Rhodes 2015 and Turner 2012. We also estimated the prediction intervals to assess how much the estimated heterogeneity affects the relative effects with respect to the additional uncertainly 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 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

Classical meta-analysis

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.

Network meta-analysis

We then employed network meta-analysis for all outcomes and comparisons, 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 2017a). 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 fitted 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 2014), and we performed all other analyses in Stata 14 using the 'network' (www.stata-journal.com/article.html?article=st0410) and 'network graphs' packages (www.stata-journal.com/article.html?article=st0411).

As this is a living systematic review, whenever we find new evidence (i.e. studies, data or information) meeting the review inclusion criteria, we will extract the data and assess risk of bias. For trials identified as completed in clinical trial registries but without posted results or those identified only by a conference proceeding, and for missing outcome data, trained review authors will contact trialists to request complete results. Every three months, each newly-identified trial will be incorporated in the network. We will perform one network for each outcome (PASI-90, SAEs, PASI-75, PGA, QoL and AEs). We will re-analyse the data every three months using the standard approaches outlined in this Data synthesis section as well as the GRADE process. We will check the assumptions of the NMA each time we update it.

Subgroup analysis and investigation of heterogeneity

We had planned 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) during the induction phase, 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; (4) analysing only the observed participants and assuming that missing participants are missing at random; (5) analysing only the studies with a short-term assessment from 12 to 16 weeks (to better reassure the plausibility of the transitivity assumption); (6) excluding trials including systemic-treatment-naïve participants to better reassure the plausibility of the transitivity assumption too. Indeed, response to biologics is different depending on treatment status (systemic-naïve or not).

Summary of findings and assessment of the certainty of the evidence

We include two 'Summary of findings' tables in our review for each primary outcome. We downgraded evidence based on the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) (Schünemann 2011). We assessed the confidence of the evidence estimates from network meta-analysis, based on the CINeMA 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 risks 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.

We assessed indirectness by evaluating the distribution of the potential effect modifiers (baseline demographic and clinical characteristics of participants), and the relevance of each study to the research question.

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.gradepro.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.

We also performed full evaluation of the confidence in the results using the web application CINeMA (CINeMA 2017). CINeMA (Confidence in Network Meta-Analysis) is a web application that simplifies the evaluation of confidence in the findings from network

meta-analysis. It is based on six domains: within-study bias (referring to the impact of risk of bias in the included studies), across-studies bias (publication or reporting bias), indirectness (relevance to the research question and transitivity), imprecision (comparing the range of treatment effects included in the 95% confidence interval with the range of equivalence), heterogeneity (predictive intervals), and incoherence (if estimates from direct and indirect evidence disagree) (Salanti 2014). Judgements across the six domains are then summarised to obtain four levels of confidence for each relative treatment effect, corresponding to the usual GRADE approach: very low, low, moderate or high

RESULTS

Description of studies

Results of the search

The updated Electronic searches for this review identified an additional 1833 citations of potentially eligible studies through database searching, conferences and International Clinical Trials Registry Platform. We had a total of 1751 records after removal of duplicates.

After reviewing the titles and abstracts, we discarded 1408 citations. We examined the full text of the remaining 343 references: 183 references did not meet the inclusion criteria and were excluded with reasons (see Characteristics of excluded studies), we excluded seven studies (in 17 references) from the previous Cochrane Review, as the interventions were not eligible anymore (see Characteristics of excluded studies). We identified 11 trials as studies awaiting classification (reported in 18 references) (see Characteristics of studies awaiting classification). We identified 42 studies (reported in 44 references) as ongoing (see Characteristics of ongoing studies). Lastly, we identified 38 new studies (reported in 81 references) for this update.

In total, we included 140 studies (reported in 291 references). For a further description of our screening process, see the study flow diagram (Figure 1).

Figure 1. Study flow diagram

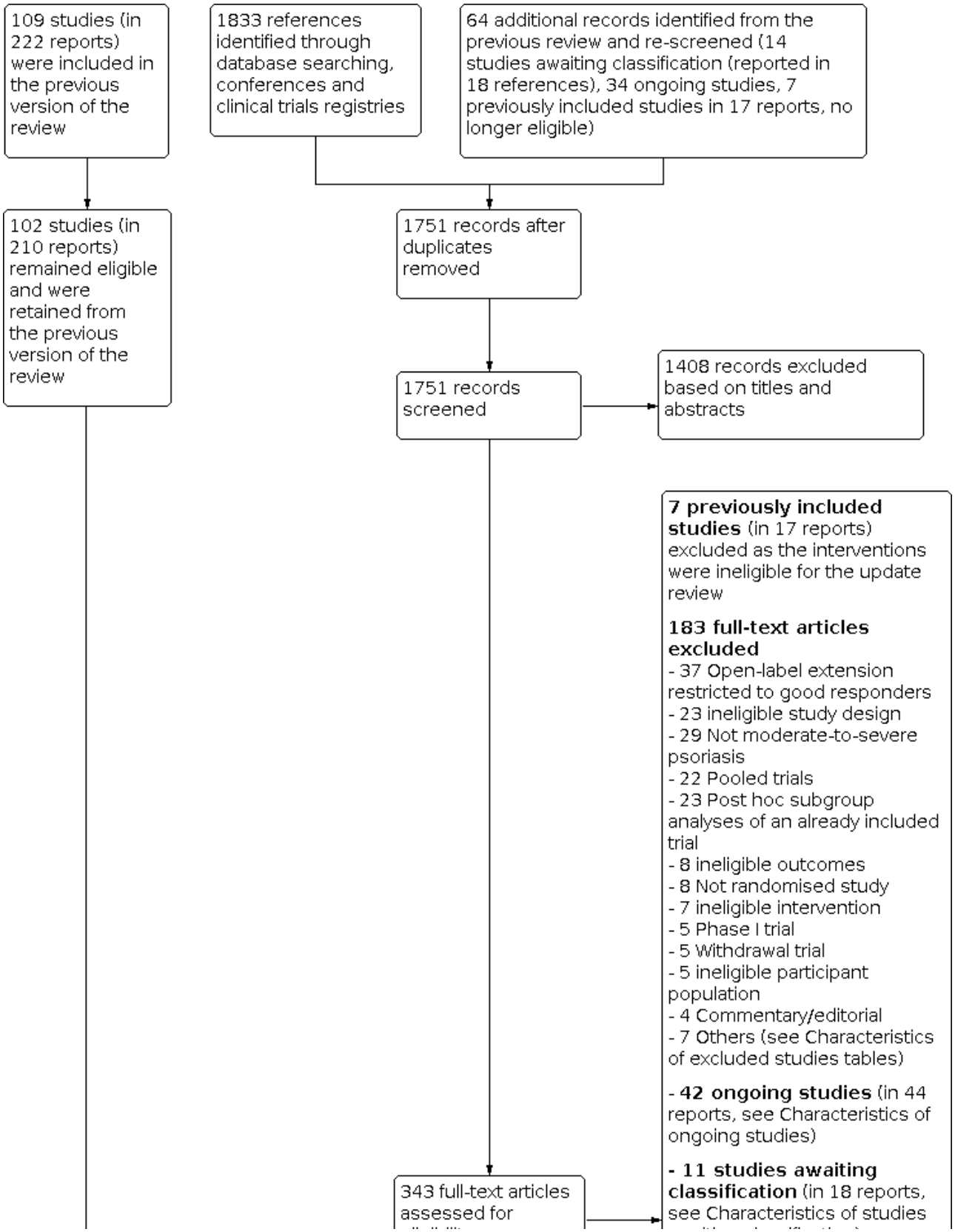
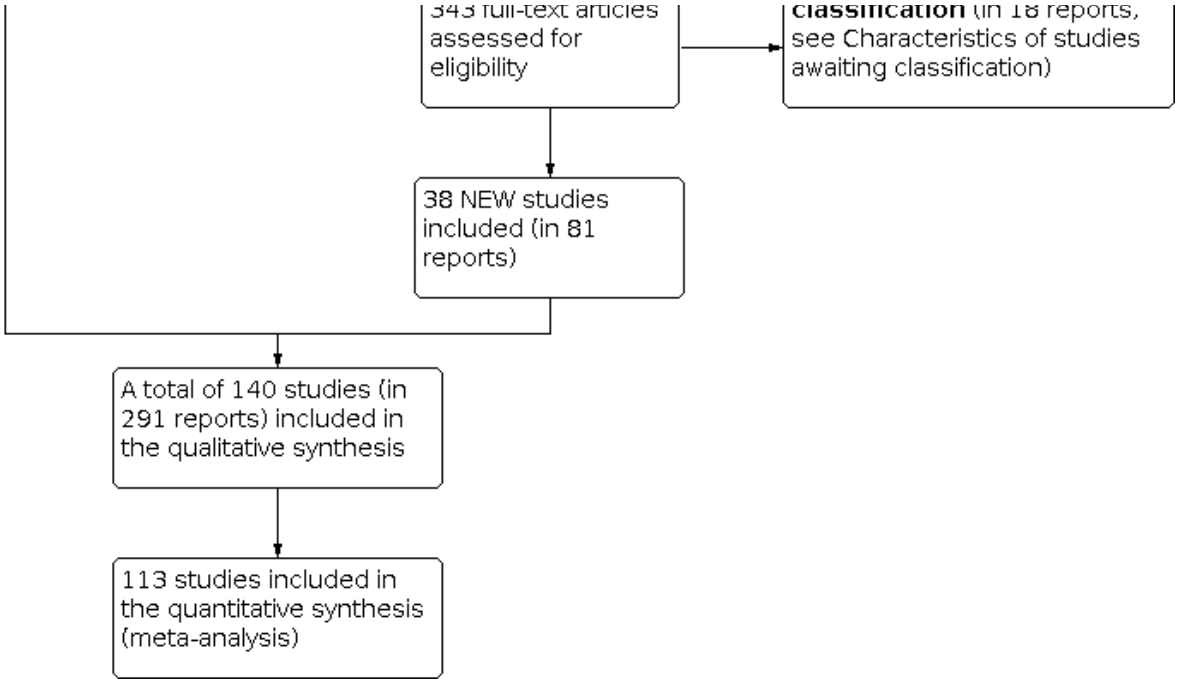


Figure 1. (Continued)



Included studies

Trial design

All trials used a parallel-group design. The mean sample size was 369 (range: 10 to 1881). In all, 117 trials were multicentric trials (2 to 231 centres) and 17 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; Ikonomidis 2017; Khatri 2016; Mahajan 2010; Shehzad 2004; Van Bezooijen 2016); for six trials, single-centre or multicentric status was not clear (Caproni 2009; Engst 1994; Goldfarb 1988; Jin 2017; Olsen 1989; Yilmaz 2002). Most of the trials recruited participants from a hospital setting, but some also from physicians' offices. The trials took place world-wide (n = 59, 42%), in Europe (n = 32, 23%), in North America (n = 23, 16%), in Asia (n = 21, 15%), or in the Middle East (n = 1, 0.7%). The location was not stated for four trials (Caproni 2009; Engst 1994; Goldfarb 1988; Olsen 1989).

In total, 73 trials out of 140 were multi-arm; 48 multi-arm trials assessed the same experimental drug at multiple dose levels; 14 assessed at least two different drugs; 11 assessed both the same experimental drug at multiple dose levels and different drugs. In total, seven trials assessed biosimilars versus original drugs for adalimumab (Blauvelt ADACCESS 2018; NCT02581345; NCT02660580 AURIEL-PsO; NCT02850965; Papp ABP 501 2017) and etanercept (Griffiths EGALITY 2017; NCT02134210 CHS-0214).

In total, 14 trials (Al-Hamamy 2014; Asawanonda 2006; Bissonnette 2013; Gottlieb 2012; Gurel 2015; 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 140 trials (31 new trials for the updated review), with a total of 51,749 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 45; there were more men (34,624) than women (16,529). Age and gender were unreported for, respectively, 743 and 596 participants (13 and 9 studies). The overall mean weight was 85.3 kg (range: 64 to 95 kg), 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: 82 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; Gottlieb 2012; Hunter 1963; Mahajan 2010; Shehzad 2004; Warren METOP, 2017)
- Twelve trials compared small molecule treatments versus placebo

- Apremilast (n = 5) (Ohtsuki 2017; Papp 2012c; Papp 2013b; Papp ESTEEM-1 2015; Paul ESTEEM-2 2015)
- Tofacitinib (n = 6) (Jin 2017; Krueger 2016a; Papp 2012b; Papp OPT Pivotal-1 2015; Papp OPT Pivotal-2 2015; Zhang 2017)
- Oral tyrosine kinase 2 (TYK2) inhibitor (BMS-986165) (n = 1) (Papp TYK2 2018)

- Forty-nine trials compared biological treatments versus placebo
  - Anti-TNF alpha
    - Etanercept (n = 8) (Bagel 2012; Gottlieb 2003a; Gottlieb 2011; Leonardi 2003; Papp 2005; Strober 2011; Tyring 2006; Van de Kerkhof 2008)
    - Adalimumab (n = 7) (Asahina 2010; Bissonnette 2013; Cai 2016; Elewski 2016; Gordon 2006; Menter REVEAL 2008; NCT01553058 VIP trial)
    - Infliximab (n = 6) (Chaudhari 2001; Gottlieb 2004a; Menter EXPRESS-II 2007; Reich EXPRESS 2005; Torii 2010; Yang 2012)
    - Certolizumab (n = 3) (Gottlieb CIMPASI-1 2018; Gottlieb CIMPASI-2 2018; Reich 2012a)

Intervention versus active comparators: 41 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 infliximab (n = 1) (Barker RESTORE-1 2011)
- Acitretin versus etanercept (n = 3) (Caproni 2009; Gisondi 2008; Lee 2016)
- FAEs versus secukinumab (n = 1) (Sticherling PRIME 2017)
- FAEs versus guselkumab (n = 1) (NCT02951533 POLARIS)
- Etanercept versus etanercept (n = 5) (Griffiths EGALITY 2017; NCT02134210 CHS-0214; 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)
- Adalimumab versus adalimumab (n = 5) (Blauvelt ADACCESS 2018; NCT02581345; NCT02660580 AURIEL-PsO; NCT02850965; Papp ABP 501 2017)
- Tofacitinib versus tofacitinib (n = 2) (Asahina 2016; Bissonnette 2015)
- Secukinumab versus secukinumab (n = 2) (Mrowietz SCULPTURE 2015; NCT01961609 SIGNATURE)
- Secukinumab versus ustekinumab (n = 2) (Thaçi CLEAR 2015; Bagel CLARITY 2018)
- Ixekizumab versus ixekizumab (n = 2) (Khatri 2016; Langley IXORA-P 2018)
- Ixekizumab versus ustekinumab (n = 1) (Reich IXORA-S 2017)
- Risankizumab versus adalimumab (n = 1) (EUCTR2015-003623-65-DE)
- Risankizumab versus ustekinumab (n = 1) (Papp NCT02054481 2017)

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

A total of 17 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)
- Certolizumab versus etanercept versus placebo (n = 1) (Lebwohl CIMPACT 2018)
- Ustekinumab versus etanercept versus ciclosporin (n = 1) (Ikonomidis 2017)
- Tildrakizumab versus etanercept versus placebo (n = 1) (Reich ReSURFACE-2 2017)
- Risankizumab versus ustekinumab versus placebo (n = 2) (Gordon UltIMMa-1 2018; Gordon UltIMMa-2 2018)
- Ixekizumab versus Methotrexate versus FAEs (n = 1) (NCT02634801)

In total, the dataset consisted of 140 studies, which provide information on 271, 149, and 141 comparisons between 36 different drug dosages, 19 different drugs (trials on mirikizumab were still ongoing), six different drug classes, and placebo. For the sensitivity analyses, the different drug doses were divided into the following:

- methotrexate, taken orally, ≥ 15 or < 15 mg a week;
- ciclosporin, taken orally, ≥ 3 or < 3 mg/Kg a day;
- acitretin, taken orally, ≥ 35 or < 35 mg a day;
- apremilast, taken orally, 30 mg twice a day or other dosages;
- tofacitinib, taken orally, 20 mg a day or other dosages;
- 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;
- certolizumab, S/C, 400 mg at week 0, 2, 4 then 400 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, 160 mg at week 0 then 80 mg every other week until week 12 then 80 mg monthly, or other dosages;
- brodalumab, S/C, 210 mg at week 0, 1, 2, then every other week, or other dosages;

- guselkumab, S/C, 100 mg at week 0 and 4 then every 8 weeks, or other dosages;
- tildrakizumab, S/C, 100 mg at week 0 and 4 then every 12 weeks, or other dosages;
- risankizumab, S/C, 150 mg (2 x 75 mg injections) at week 0, week 4 and every 12 weeks thereafter, or other dosages.

FAEs (taken orally), BMS-986165 (taken orally), ustekinumab (S/C 45 mg or 90 mg according to the weight), bimekizumab (S/C) and mirikizumab (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

For the efficacy outcomes during induction therapy (8 to 24 weeks), out of the 140 trials, 109 reported PASI 90, 102 reported on Physician Global Assessment (PGA) 0/1, 122 reported PASI 75, and 57 trials reported assessment of change in quality of life. Fifty-four studies used the dermatology-specific instrument Dermatology Life Quality Index (DLQI); five studies used other specific skin instruments (Skindex and PSS). For all of these studies, the investigators provided citations to reports indicating that the tools had been previously validated. For efficacy outcomes during maintenance phase (52 weeks), eight trials reported PASI 90 at one year (Blauvelt VOYAGE-1 2016; Gordon UltIMMa-1 2018; Gordon UltIMMa-2 2018; Langley IXORA-P 2018; Ohtsuki 2017; Ohtsuki 2018; Paul JUNCTURE 2015; Thaçi CLEAR 2015) and nine PASI 75 at one year (Blauvelt VOYAGE-1 2016; Gordon UltIMMa-1 2018; Gordon UltIMMa-2 2018; Langley IXORA-P 2018; Ohtsuki 2017; Ohtsuki 2018; Paul JUNCTURE 2015; Thaçi CLEAR 2015; Zhang 2017).

Out of 140 trials, 101 reported the number of participants with adverse effects (different from the number of adverse effects), and 116 reported the number of serious adverse effects.

These outcomes were evaluated between 8 and 24 weeks: eight weeks (five studies), 10 weeks (seven studies), 12 weeks (63 studies), 13 weeks (two studies), 15 weeks (one study), 16 weeks (44 studies), 24 weeks (11 studies) and 26 weeks (two studies). Timing of assessment was unknown or not clearly defined for four studies (Engst 1994; Hunter 1963; Saurat 1988; Shehzad 2004); one study had only a timing of assessment at 52 weeks (Langley IXORA-P 2018).

Funding

In all, 114 studies declared a source of funding: 107 studies declared a pharmaceutical company funding, seven studies declared a unique institutional funding (Chladek 2005; De Vries PIECE 2016; Flytström 2008; Heydendael 2003; Ikonomidis 2017; NCT01553058 VIP trial; NCT02634801), four studies had no funding source (Akcali 2014; Asawanonda 2006; Fallah Arani 2011; Gurel 2015), and 22 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; Jin 2017; 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 a total of 610 reports.

- We had excluded 410 full-text reports from the previous review. 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 have not presented characteristics of excluded studies for this group. We excluded 99 reports because they assessed another intervention, 45 were not a trial, three did not include plaque-type psoriasis, and we excluded 60 for other reasons.

- We excluded seven previously included studies (total of 17 references) from the previous review because the interventions did not belong to the update anymore (ponesimod (Vaclavkova 2014 - development of the drug for psoriasis stopped), alefacept (Ellis 2001 Jacobe 2008; Krueger 2002a; Lebwohl 2003; Yan 2011 - not used anymore for psoriasis), itolizumab (Krupashankar 2014 - not approved)).

- We excluded 183 full-text articles (in 185 references) from the updated review. The main reasons for exclusion were that there were open-label extensions restricted to good responders (n = 37) and the participants did not present with moderate-to-severe psoriasis (n = 29). We detail the reason for exclusion in Characteristics of excluded studies.

For seven 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).
- NCT01553058 VIP trial: adalimumab versus narrowband ultraviolet B phototherapy versus placebo (arm with narrowband ultraviolet B phototherapy was not included)
- Lee 2016; etanercept versus acitretin versus etanercept plus acitretin (arm with etanercept plus acitretin 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 ≥ 3 mg/kg/day group nor in the ciclosporin < 3 mg/day group for the subgroup meta-analysis.

Studies awaiting classification

We classified 11 trials reported in 18 references as studies awaiting classification. More details about the studies awaiting classification are available in Studies awaiting classification and Table 2.

Ongoing studies

We classified 42 trials (reported in 44 references) as ongoing studies. More details are available in Characteristics of ongoing studies and Table 2. Most of the ongoing studies compare a biological treatment versus another biological treatment or versus placebo (n = 36). Two ongoing studies assessed apremilast or oral tyrosine kinase 2 (TYK2) inhibitor, and four assessed conventional systemic treatments.

Risk of bias in included studies

Figure 2 and Figure 3 summarise 'Risk of bias' assessments. For overall risk of bias across studies, 41 trials were at low risk of bias (Asahina 2016; Bachelez 2015; Blauvelt ADACCESS 2018; Blauvelt FEATURE 2015; Blauvelt VOYAGE-1 2016; Cai 2016; Elewski 2016; EUCTR2015-003623-65-DE; Griffiths EGALITY 2017; Gordon UNCOVER-1 2016; Gottlieb CIMPASI-1 2018; Gottlieb CIMPASI-2 2018; Griffiths UNCOVER-2 2015; Griffiths UNCOVER-3 2015; Langley ERASURE 2014; Langley FIXTURE 2014; Langley IXORA-P 2018; Leonardi 2012; NCT02581345; NCT02672852 IMMhance; NCT02850965; NCT02905331 ORION; Ohtsuki 2017; Papp 2012a; Papp 2012b; Papp 2012c; Papp ABP 501 2017; Papp BE ABLE 2018; Papp PHOENIX-2 2008; Papp TYK2 2018; Reich 2012a; Reich 2015; Reich IXORA-S 2017; Reich ReSURFACE-1 2017; Reich ReSURFACE-2 2017; Reich TRANSFIGURE 2016; Reich VOYAGE-2 2017; Rich 2013; Saurat CHAMPION 2008; Thaçi CLEAR 2015; Warren METOP, 2017). We categorised fewer than half of the studies (57/140) as being at high risk of bias. Among the high-risk group, seven studies had only one high 'Risk of bias' domain with all the other dimensions at low risk (Bissonnette 2015; Lebwohl CIMPACT 2018; Ohtsuki 2018; Papp 2013a; Papp OPT Pivotal-1 2015; Reich LIBERATE 2017; Zhang 2017). We categorised the remaining 42 studies as being at unclear risk of bias because we assessed one or more criteria as unclear. Among the unclear 'Risk of bias' group, 13 studies had only one unclear risk of bias with all the other dimensions at low risk (Bagel 2012; Gordon UltIMMa-2 2018; Krueger 2016a; Leonardi 2003; Leonardi PHOENIX-1 2008; Menter EXPRESS-II 2007; Menter REVEAL 2008; NCT03000075; Papp AMAGINE-1 2016; Paul ESTEEM-2 2015; Paul JUNCTURE 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

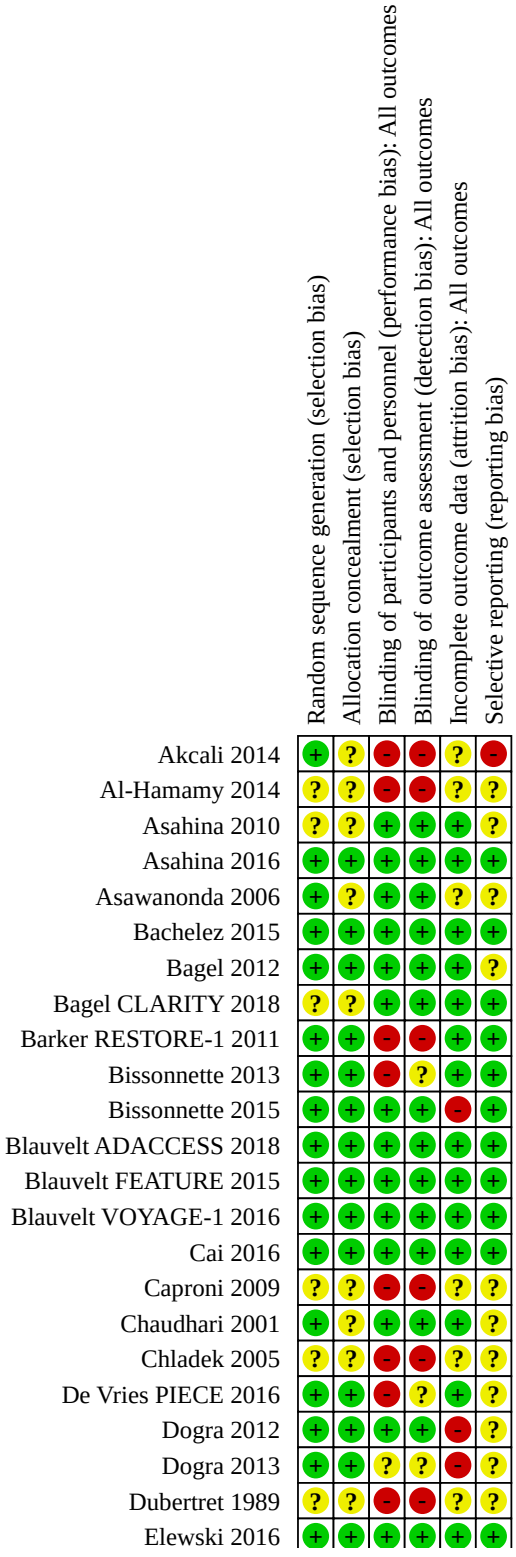
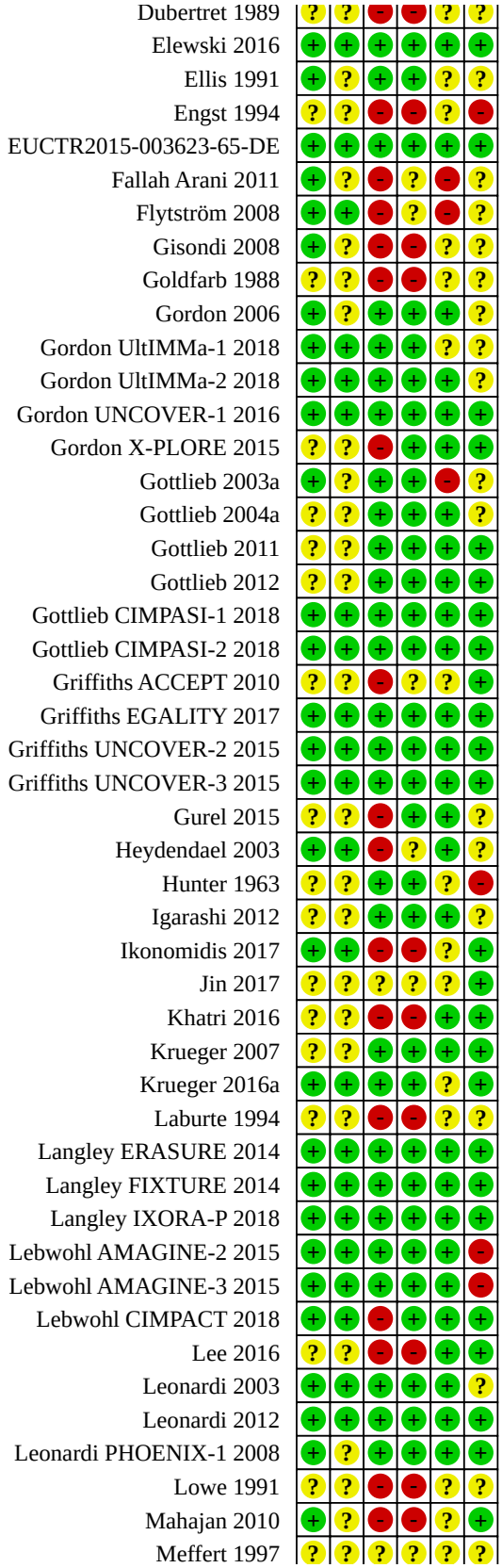


Figure 2. (Continued)



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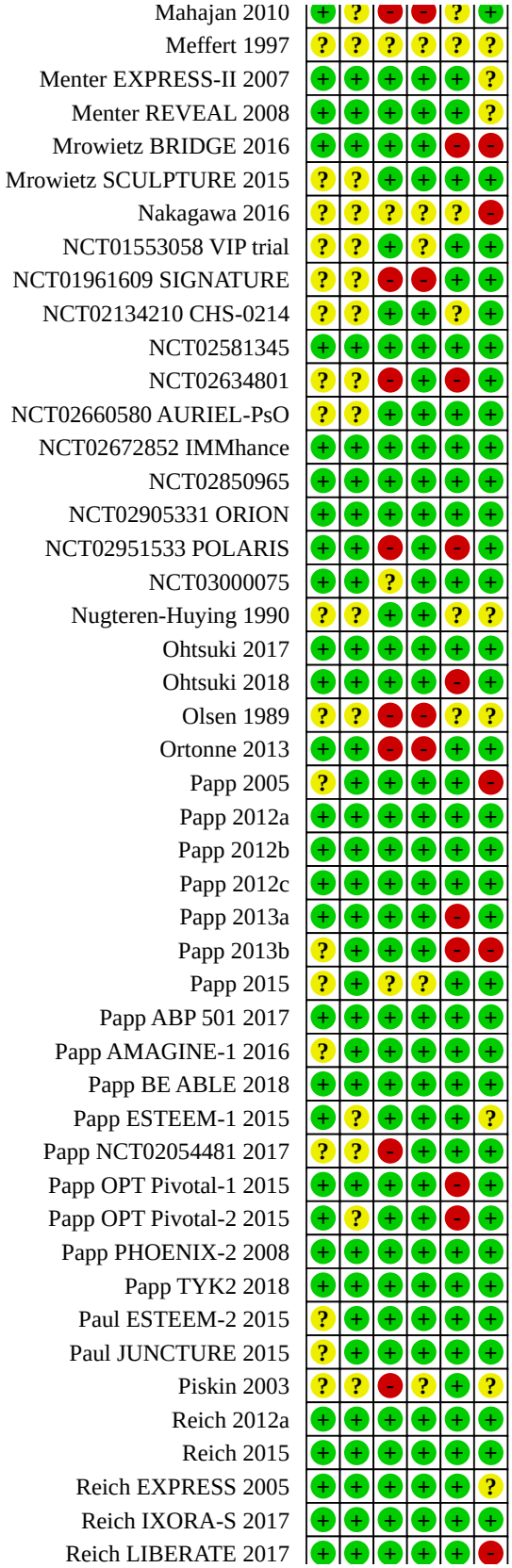

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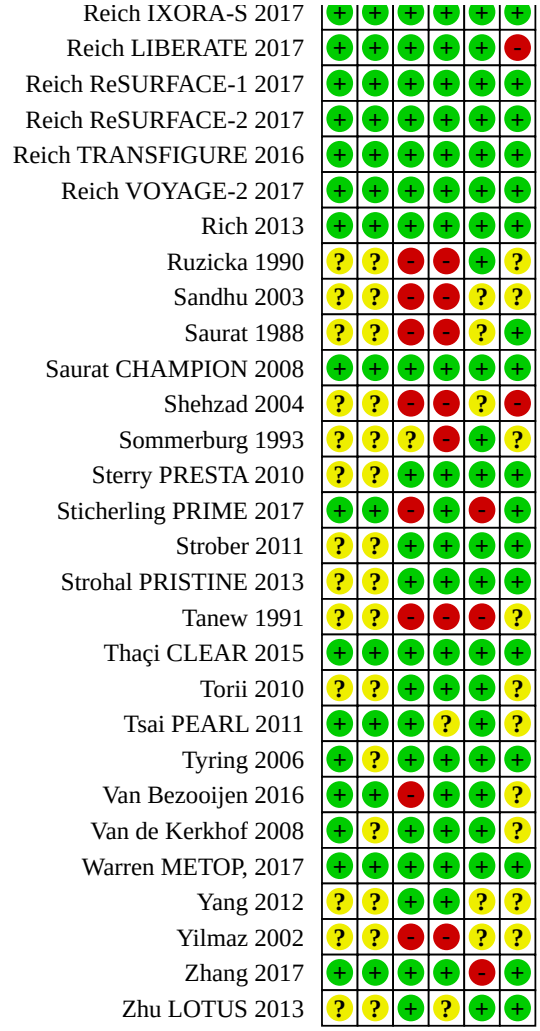
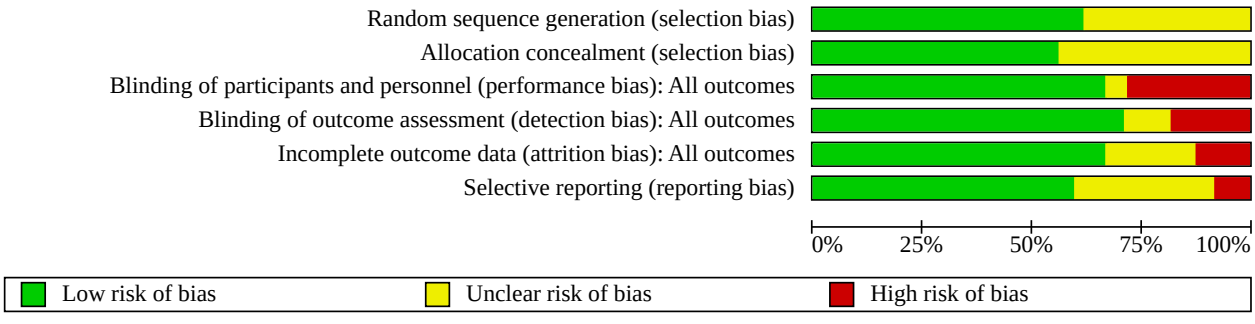


Figure 3. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies



Allocation

The method of sequence generation was not described at all, or was at best unclear, in 53 trials. The remaining studies (n = 87) described the method used to generate the allocation sequence in sufficient detail; we therefore judged this domain as low risk of bias for these studies. For allocation concealment, most studies (n = 77) received a judgement of low risk of bias. We considered the risk unclear

for the 61 remaining trials because of the absence of reporting the method used to guarantee concealment.

Blinding

Blinding of participants and personnel was achieved in 94 studies, whereas 39 studies were at high risk of performance bias. The remaining seven studies were at unclear risk of performance bias. Blinding of outcome assessment was reported clearly in only 100 of the 140 included studies, whereas 25 studies were at high risk of detection bias. The risk of detection bias was unclear in the remaining 15 studies.

Incomplete outcome data

In more than two-thirds of the trials (104/140) 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 17 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 29 studies, this domain was as at unclear risk of bias because the following were not reported: the number of participants, reasons for discontinuation, or missing data imputation.

Selective reporting

We considered 11 trials to be 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; Lebwohl AMAGINE-2 2015; Lebwohl AMAGINE-3 2015; Mrowietz BRIDGE 2016; Nakagawa 2016 Papp 2013b; Papp 2005; Reich LIBERATE 2017; Shehzad 2004). In all, we considered 84 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 = 45), 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 1** Any systemic treatment compared to placebo for chronic plaque psoriasis - PASI 90; **Summary of findings 2** Any systemic treatment compared to placebo for chronic plaque psoriasis - SAEs

See: Summary of findings 1; Summary of findings 2. 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.

Eight trials provided no usable or retrievable data and did not contribute further to the results of this review (Akcali 2014; Chladek 2005; Engst 1994; Ikonomidis 2017; Lowe 1991; Olsen 1989; Piskin 2003; Shehzad 2004, see Table 2). The main reason we could not use their data was that these studies addressed none of our outcomes.

Fourteen studies, involving 1171 participants (2.3% 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; Lowe 1991; Mahajan 2010; Ruzicka 1990; Saurat 1988; Shehzad 2004; Sommerburg 1993; Tanew 1991; Van Bezooijen 2016; Yilmaz 2002).

One study had only long-term outcome assessments (Langley IXORA-P 2018).

Seven trials assessed biosimilars versus original drugs for adalimumab (Blauvelt ADACCESS 2018; NCT02581345; NCT02660580 AURIEL-PsO; NCT02850965; Papp ABP 501 2017) and etanercept (Griffiths EGALITY 2017; NCT02134210 CHS-0214). These were non-inferiority trials, assessing same dosage and same administration schema of biosimilar and original drug.

In total, 27 studies, involving 4664 participants, were not included in the classical or network meta-analysis. The interventions of the 27 studies concerned the following:

- acitretin (n = 9) (Akcali 2014; Gurel 2015; Lowe 1991; Olsen 1989; Ruzicka 1990; Saurat 1988; Sommerburg 1993; Tanew 1991; Yilmaz 2002);
- methotrexate (n = 6) (Asawanonda 2006; Al-Hamamy 2014; Chladek 2005; Gottlieb 2012; Mahajan 2010; Shehzad 2004);
- ciclosporin (n = 2) (Engst 1994; Piskin 2003);
- adalimumab (n = 6) (Bissonnette 2013; Blauvelt ADACCESS 2018; NCT02581345; NCT02660580 AURIEL-PsO; NCT02850965; Papp ABP 501 2017);
- etanercept (n = 2) (Griffiths EGALITY 2017; NCT02134210 CHS-0214);
- others (n = 2) (Van Bezooijen 2016; Ikonomidis 2017).

We included a total of 113 studies, involving 47,085 participants (91% participants of this review), in the network classical or 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) and drug-level (Figure 5) intervention, with the thickness of the lines proportional to the number of trials evaluating each direct comparison.

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

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

Figure 10 and Figure 11 show all of the relative effects from the network meta-analyses against placebo with their 95% confidence and prediction intervals at class and drug level.

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

1. 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 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; and Analysis 1.10, respectively.

In terms of reaching PASI 90, anti-IL17 treatments (secukinumab, ixekizumab, and brodalumab) were more effective than placebo (risk ratio at class level (RR) 30.58, 95% confidence interval (CI) 21.73 to 43.03). These findings were also confirmed for anti-IL23 (guselkumab, tildrakizumab and risankizumab) (class-level RR 23.70, 95% CI 16.63 to 33.76); anti-IL12/23 (ustekinumab) (RR 20.02, 95% CI 13.01 to 30.81); anti-TNF alpha (infliximab, etanercept, adalimumab, and certolizumab) (class-level RR 13.59, 95% CI 10.63 to 17.38); and small molecules (apremilast, tofacitinib, and oral tyrosine kinase 2 (TYK2) inhibitor) (class-level RR 7.09, 95% CI 5.05 to 9.95). 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), and secukinumab was more effective than FAEs (RR 8.31, 95% CI 4.23 to 16.35). Ustekinumab, secukinumab, ixekizumab, and certolizumab were more effective than etanercept. Secukinumab, ixekizumab, brodalumab, and risankizumab were more effective than ustekinumab. Guselkumab and risankizumab were more effective than adalimumab. No significant difference was observed between etanercept and tofacitinib or apremilast for this outcome (reaching PASI 90).

NETWORK META-ANALYSES

The PASI 90 outcome was available in 95 trials, involving 43,512 participants (92.4% of the participants in the meta-analysis). This outcome was also reported in two 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 reported in eight trials out of 95 (Asahina 2016; Bissonnette 2015; Dogra 2012; Dogra 2013; Khatri 2016; Mrowietz SCULPTURE 2015; NCT01961609 SIGNATURE; Strohal PRISTINE 2013), 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 16 trials including Langley IXORA-P 2018 (only long-term assessment outcomes), and we were not able to obtain missing information from the trial authors (Table 2). Fifty-seven trials, involving 21,777 participants, were placebo-controlled trials; 18 studies, involving 5419 participants, were head-to-head comparisons; and 20 studies, involving 16,316 participants, had both a placebo and at least two active treatments arms.

See Figure 4; Figure 5; Figure 6; Figure 7; Figure 8; Figure 9; Figure 10; Figure 11.

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

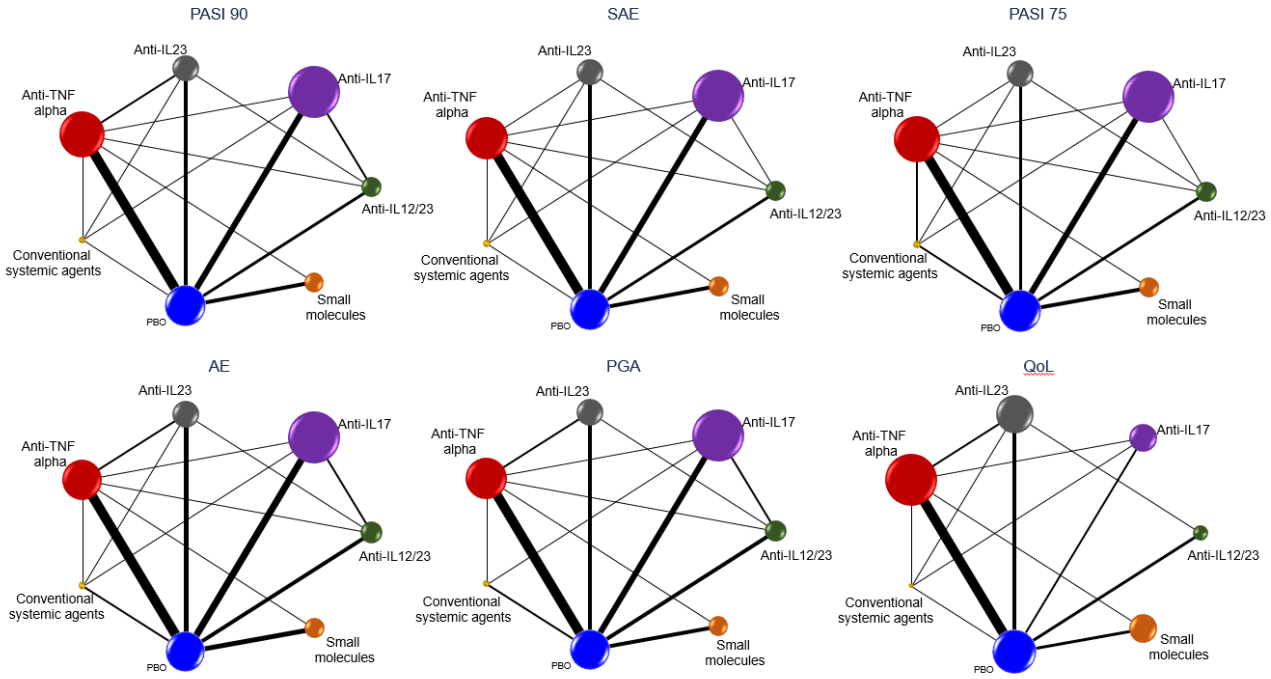


Figure 5. Network plot for all the outcomes at drug level The size of the nodes is proportional to the total number of participants allocated to each intervention and the thickness of the lines proportional to the number of studies evaluating each direct comparison. For PASI 90 and SEAs, interventions in bold and underlined are at high-certainty evidence; interventions in bold at moderate-certainty of evidence; very-low to low otherwise. ACI: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; TYK2: Oral Tyrosine kinase 2 inhibitor; USK: ustekinumab AE: adverse events; PASI: Psoriasis Area and Severity Index; PGA: Physician Global Assessment; QoL: quality of life; SAE: serious adverse events

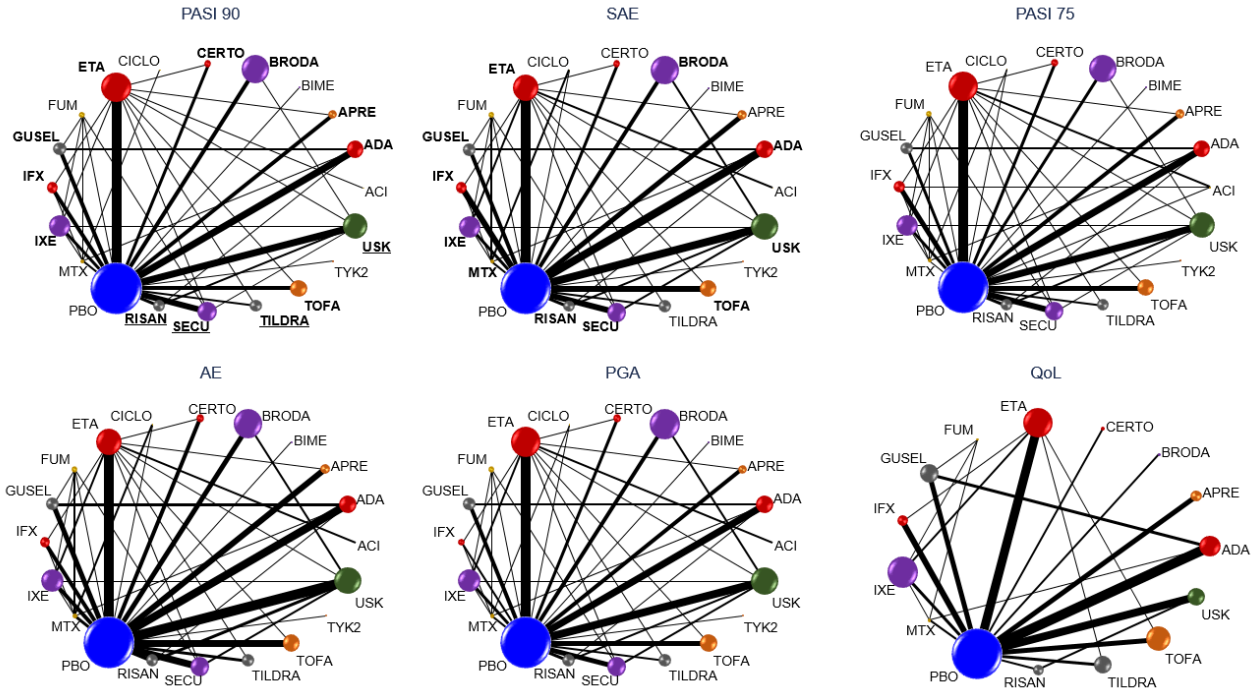


Figure 6. Relative effects of the class-level intervention as estimated from the network meta-analysis model Outcomes were all measured at the induction phase (assessment from 8 to 24 weeks after randomisation). Drugs are reported in order of primary benefit ranking. Each cell contains the risk ratio (RR) (for dichotomous outcomes: PASI 90, serious adverse events, PASI 75, PGA 0/1, 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 highlighted in grey. AE: adverse events; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment; QoL: quality of life; SAE: serious adverse events; AIL12/23: anti-IL12/23; AIL17: anti-IL17; AIL23: anti-IL23, ATA: anti-TNF alpha; CSA: conventional systemic agents; PBO: placebo; SM: small molecules

Serious adverse events

AIL17	1.47 (0.98,2.20)	1.17 (0.83,1.64)	1.15 (0.83,1.59)	1.16 (0.73,1.86)	1.66 (0.98,2.82)	1.08 (0.82,1.42)
1.25 (0.99,1.59)	AIL23	0.79 (0.52,1.20)	0.78 (0.55,1.11)	0.79 (0.48,1.31)	1.13 (0.64,1.99)	0.74 (0.52,1.03)
1.52 (1.26,1.83)	1.21 (0.96,1.51)	AIL12_23	0.98 (0.67,1.43)	1.00 (0.60,1.66)	1.42 (0.80,2.53)	0.93 (0.66,1.30)
2.20 (1.80,2.69)	1.75 (1.45,2.12)	1.45 (1.17,1.80)	ATA	1.02 (0.66,1.57)	1.45 (0.88,2.39)	0.94 (0.74,1.21)
3.26 (2.27,4.67)	2.60 (1.81,3.72)	2.15 (1.49,3.10)	1.48 (1.07,2.04)	SM	1.43 (0.77,2.66)	0.93 (0.63,1.38)
6.31 (4.64,8.59)	5.03 (3.64,6.96)	4.16 (3.00,5.78)	2.87 (2.13,3.85)	1.94 (1.28,2.94)	CSA	0.65 (0.40,1.07)
29.33 (23.38,36.79)	23.38 (18.49,29.56)	19.34 (15.28,24.48)	13.33 (10.95,16.21)	9.01 (6.58,12.33)	4.65 (3.38,6.39)	PBO

Adverse events

AIL17	1.19 (1.10,1.29)	1.07 (1.00,1.14)	1.05 (0.99,1.12)	0.94 (0.86,1.02)	0.98 (0.90,1.07)	1.13 (1.07,1.19)
1.16 (0.99,1.35)	AIL23	0.90 (0.83,0.97)	0.88 (0.82,0.95)	0.79 (0.71,0.87)	0.82 (0.75,0.91)	0.95 (0.89,1.01)
1.21 (1.07,1.37)	1.05 (0.91,1.21)	AIL12_23	0.99 (0.92,1.06)	0.88 (0.80,0.97)	0.92 (0.84,1.01)	1.06 (1.00,1.12)
1.57 (1.38,1.79)	1.36 (1.20,1.54)	1.29 (1.13,1.48)	ATA	0.89 (0.82,0.97)	0.93 (0.86,1.01)	1.07 (1.03,1.12)
2.36 (1.88,2.95)	2.04 (1.63,2.55)	1.94 (1.54,2.44)	1.50 (1.23,1.83)	SM	1.05 (0.94,1.16)	1.21 (1.12,1.30)
3.15 (2.62,3.79)	2.73 (2.25,3.31)	2.60 (2.13,3.16)	2.01 (1.70,2.37)	1.34 (1.05,1.71)	CSA	1.15 (1.06,1.25)
13.50 (11.76,15.50)	11.68 (10.12,13.49)	11.12 (9.64,12.83)	8.59 (7.66,9.64)	5.73 (4.76,6.90)	4.28 (3.58,5.12)	PBO

PASI 90

PASI 75

PGA 0/1

Quality of life scale

AIL23	-0.12 (-0.45,0.22)	-0.34 (-0.60,-0.09)	-0.68 (-1.02,-0.34)	-0.77 (-1.19,-0.34)	-0.12 (-0.49,0.26)	-1.41 (-1.64,-1.18)
1.07 (0.90,1.29)	AIL12_23	-0.23 (-0.54,0.09)	-0.56 (-0.95,-0.18)	-0.65 (-1.13,-0.16)	0.00 (-0.41,0.42)	-1.29 (-1.57,-1.01)
1.40 (1.20,1.64)	1.30 (1.10,1.54)	ATA	-0.34 (-0.63,-0.04)	-0.42 (-0.83,-0.01)	0.23 (-0.09,0.55)	-1.06 (-1.22,-0.91)
2.48 (1.92,3.21)	2.31 (1.78,2.99)	1.77 (1.40,2.23)	SM	-0.09 (-0.56,0.39)	0.56 (0.17,0.96)	-0.73 (-0.99,-0.47)
3.09 (2.35,4.06)	2.87 (2.19,3.76)	2.21 (1.73,2.81)	1.24 (0.91,1.70)	CSA	0.65 (0.20,1.10)	-0.64 (-1.04,-0.24)
0.76 (0.62,0.92)	0.70 (0.60,0.82)	0.54 (0.46,0.64)	0.31 (0.23,0.40)	0.25 (0.19,0.32)	AIL17	-1.29 (-1.60,-0.99)
11.45 (9.66,13.58)	10.65 (9.02,12.59)	8.18 (7.12,9.41)	4.62 (3.76,5.68)	3.71 (2.89,4.77)	15.13 (12.76,17.94)	PBO

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) Outcomes were all measured at the induction phase (assessment from 8 to 24 weeks after randomisation). 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; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; TYK2: Oral Tyrosine kinase 2 inhibitor; USK: ustekinumab

IFX	1.01 (0.47,2.18)	1.86 (0.85,4.08)	5.49 (0.33,92.34)	1.13 (0.48,2.66)	0.99 (0.47,2.08)	1.07 (0.48,2.40)	1.13 (0.54,2.37)	1.32 (0.49,3.56)	1.24 (0.61,2.53)	1.82 (0.18,18.67)	1.51 (0.52,4.39)	0.75 (0.10,5.91)	1.24 (0.60,2.56)	2.55 (1.26,5.18)	1.10 (0.48,2.55)	1.30 (0.56,3.02)	1.13 (0.46,2.76)	0.72 (0.08,6.46)	1.11 (0.59,2.07)
1.05 (0.72,1.53)	IXE	1.83 (0.96,3.49)	5.42 (0.33,88.21)	1.11 (0.53,2.35)	0.98 (0.54,1.75)	1.06 (0.54,2.07)	1.11 (0.60,2.05)	1.30 (0.54,3.11)	1.23 (0.73,2.06)	1.80 (0.18,17.71)	1.49 (0.56,3.95)	0.74 (0.09,5.93)	1.23 (0.75,2.01)	2.52 (1.03,6.15)	1.09 (0.54,2.19)	1.28 (0.62,2.63)	1.11 (0.50,2.46)	0.71 (0.09,5.97)	1.09 (0.69,1.73)
1.07 (0.72,1.58)	1.02 (0.85,1.22)	RISAN	2.95 (0.18,48.27)	0.61 (0.29,1.26)	0.53 (0.29,0.97)	0.58 (0.29,1.14)	0.61 (0.35,1.06)	0.71 (0.29,1.76)	0.67 (0.41,1.10)	0.98 (0.10,9.70)	0.81 (0.30,2.18)	0.40 (0.05,3.25)	0.67 (0.37,1.22)	1.37 (0.55,3.41)	0.59 (0.28,1.24)	0.70 (0.33,1.47)	0.61 (0.27,1.38)	0.39 (0.05,3.35)	0.60 (0.37,0.96)
0.50 (0.03,8.15)	0.48 (0.03,7.61)	0.47 (0.03,7.48)	BIME	0.21 (0.01,3.43)	0.18 (0.01,2.91)	0.19 (0.01,3.20)	0.21 (0.01,3.32)	0.24 (0.01,4.19)	0.23 (0.01,3.62)	0.33 (0.01,11.54)	0.27 (0.02,4.91)	0.14 (0.00,4.18)	0.23 (0.01,3.65)	0.46 (0.03,8.12)	0.20 (0.01,3.33)	0.24 (0.01,3.92)	0.21 (0.01,3.50)	0.13 (0.00,4.20)	0.20 (0.01,3.16)
1.14 (0.77,1.70)	1.09 (0.87,1.36)	1.07 (0.92,1.25)	2.27 (0.14,36.05)	GUSEL	0.88 (0.43,1.79)	0.95 (0.43,2.08)	1.00 (0.55,1.81)	1.17 (0.44,3.12)	1.10 (0.56,2.18)	1.62 (0.16,16.43)	1.34 (0.47,3.83)	0.67 (0.08,5.51)	1.10 (0.54,2.24)	2.26 (0.86,5.96)	0.98 (0.43,2.22)	1.15 (0.50,2.62)	1.00 (0.43,2.33)	0.64 (0.07,5.70)	0.98 (0.54,1.79)
1.23 (0.84,1.81)	1.17 (1.01,1.36)	1.15 (0.99,1.34)	2.45 (0.15,38.76)	1.08 (0.88,1.31)	SECU	1.08 (0.57,2.04)	1.14 (0.64,2.03)	1.33 (0.56,3.19)	1.26 (0.81,1.94)	1.84 (0.19,18.00)	1.52 (0.58,3.98)	0.76 (0.10,6.03)	1.26 (0.74,2.14)	2.58 (1.07,6.20)	1.11 (0.56,2.22)	1.31 (0.65,2.64)	1.14 (0.55,2.39)	0.73 (0.09,6.18)	1.12 (0.74,1.70)
1.34 (0.91,1.99)	1.28 (1.09,1.51)	1.26 (1.07,1.48)	2.67 (0.17,42.35)	1.18 (0.96,1.45)	1.09 (0.98,1.22)	BRODA	1.05 (0.55,2.02)	1.23 (0.49,3.12)	1.16 (0.66,2.04)	1.70 (0.17,16.96)	1.41 (0.51,3.85)	0.70 (0.09,5.70)	1.16 (0.62,2.18)	2.38 (0.94,6.06)	1.03 (0.48,2.20)	1.21 (0.56,2.60)	1.06 (0.45,2.45)	0.68 (0.08,5.86)	1.04 (0.62,1.73)
1.66 (1.12,2.45)	1.58 (1.29,1.94)	1.55 (1.37,1.76)	3.29 (0.21,52.21)	1.45 (1.32,1.59)	1.35 (1.12,1.61)	1.23 (1.02,1.49)	ADA	1.17 (0.48,2.83)	1.10 (0.65,1.86)	1.62 (0.17,15.80)	1.34 (0.51,3.50)	0.67 (0.08,5.28)	1.10 (0.63,1.94)	2.26 (0.95,5.39)	0.98 (0.49,1.97)	1.15 (0.57,2.33)	1.00 (0.46,2.18)	0.64 (0.08,5.47)	0.98 (0.65,1.49)
1.73 (1.11,2.69)	1.65 (1.28,2.12)	1.62 (1.22,2.15)	3.43 (0.21,54.85)	1.51 (1.11,2.05)	1.40 (1.08,1.82)	1.29 (0.98,1.68)	1.04 (0.78,1.40)	TILDRA	0.94 (0.41,2.19)	1.38 (0.13,14.83)	1.14 (0.36,3.65)	0.57 (0.06,5.02)	0.94 (0.43,2.06)	1.93 (0.64,5.82)	0.84 (0.33,2.13)	0.98 (0.38,2.56)	0.86 (0.31,2.40)	0.55 (0.06,5.00)	0.84 (0.39,1.83)
1.72 (1.17,2.52)	1.64 (1.43,1.88)	1.61 (1.41,1.85)	3.42 (0.22,54.10)	1.51 (1.25,1.82)	1.40 (1.31,1.49)	1.28 (1.17,1.40)	1.04 (0.88,1.23)	0.99 (0.77,1.28)	USK	1.47 (0.15,14.17)	1.21 (0.48,3.09)	0.61 (0.08,4.74)	1.00 (0.62,1.61)	2.05 (0.88,4.81)	0.89 (0.46,1.70)	1.04 (0.54,2.03)	0.91 (0.43,1.91)	0.58 (0.07,4.86)	0.89 (0.63,1.27)
2.11 (0.29,15.39)	2.01 (0.28,14.24)	1.98 (0.28,14.01)	4.19 (0.14,122.63)	1.85 (0.26,13.11)	1.71 (0.24,12.12)	1.57 (0.22,11.11)	1.27 (0.18,9.03)	1.22 (0.17,8.74)	1.23 (0.17,8.68)	TYK2	0.83 (0.07,9.13)	0.41 (0.02,8.48)	0.68 (0.07,6.62)	1.40 (0.13,15.01)	0.60 (0.06,6.09)	0.71 (0.07,7.17)	0.62 (0.06,6.44)	0.40 (0.02,8.56)	0.61 (0.06,5.71)
2.44 (1.52,3.90)	2.32 (1.72,3.13)	2.28 (1.65,3.16)	4.84 (0.30,77.70)	2.13 (1.51,3.01)	1.98 (1.46,2.68)	1.81 (1.32,2.48)	1.47 (1.05,2.06)	1.41 (0.99,2.01)	1.42 (1.05,1.92)	1.15 (0.16,8.31)	CERTO	0.50 (0.05,4.54)	0.83 (0.32,2.10)	1.69 (0.53,5.44)	0.73 (0.26,2.05)	0.86 (0.31,2.42)	0.75 (0.25,2.25)	0.48 (0.05,4.64)	0.74 (0.31,1.75)
2.99 (1.68,5.31)	2.85 (1.59,5.09)	2.80 (1.55,5.06)	5.94 (0.35,99.68)	2.62 (1.44,4.75)	2.43 (1.35,4.37)	2.22 (1.23,4.02)	1.80 (1.00,3.26)	1.73 (0.92,3.24)	1.74 (0.97,3.12)	1.42 (0.18,10.86)	1.23 (0.64,2.34)	CICLO	1.65 (0.21,13.02)	3.39 (0.45,25.65)	1.47 (0.18,12.04)	1.72 (0.21,14.18)	1.50 (0.18,12.56)	0.96 (0.05,17.84)	1.47 (0.19,11.22)
3.04 (2.07,4.45)	2.89 (2.57,3.26)	2.85 (2.39,3.39)	6.03 (0.38,95.59)	2.66 (2.15,3.29)	2.47 (2.16,2.81)	2.26 (1.94,2.63)	1.83 (1.51,2.23)	1.76 (1.40,2.20)	1.77 (1.56,2.00)	1.44 (0.20,10.17)	1.25 (0.94,1.64)	1.02 (0.57,1.83)	ETA	2.05 (0.87,4.85)	0.89 (0.48,1.63)	1.04 (0.54,2.02)	0.91 (0.42,1.96)	0.58 (0.07,4.59)	0.89 (0.61,1.31)
3.02 (2.30,3.96)	2.87 (2.16,3.82)	2.83 (2.08,3.84)	6.00 (0.37,96.14)	2.64 (1.92,3.63)	2.45 (1.82,3.31)	2.24 (1.65,3.05)	1.82 (1.34,2.47)	1.75 (1.21,2.53)	1.76 (1.31,2.36)	1.43 (0.20,10.28)	1.24 (0.83,1.85)	1.01 (0.61,1.68)	0.99 (0.74,1.34)	MTX	0.43 (0.17,1.13)	0.51 (0.19,1.34)	0.44 (0.17,1.17)	0.28 (0.03,2.66)	0.43 (0.20,0.95)
3.60 (2.37,5.47)	3.43 (2.78,4.24)	3.38 (2.66,4.29)	7.16 (0.45,113.81)	3.15 (2.41,4.12)	2.93 (2.36,3.63)	2.68 (2.14,3.36)	2.17 (1.69,2.81)	2.08 (1.57,2.78)	2.10 (1.70,2.59)	1.71 (0.24,12.13)	1.48 (1.06,2.05)	1.21 (0.66,2.22)	1.19 (0.99,1.42)	1.19 (0.85,1.68)	TOFA	1.18 (0.53,2.60)	1.02 (0.43,2.47)	0.66 (0.08,5.66)	1.01 (0.57,1.77)
4.04 (2.11,7.74)	3.85 (2.24,6.64)	3.79 (2.18,6.59)	8.03 (0.48,133.37)	3.54 (2.02,6.22)	3.29 (1.91,5.66)	3.01 (1.74,5.21)	2.44 (1.40,4.27)	2.34 (1.31,4.17)	2.35 (1.37,4.05)	1.92 (0.25,14.46)	1.66 (0.91,3.03)	1.35 (0.62,2.97)	1.33 (0.78,2.27)	1.34 (0.73,2.45)	1.12 (0.64,1.96)	APRE	0.87 (0.36,2.11)	0.56 (0.06,4.89)	0.86 (0.48,1.51)
8.08 (4.84,13.47)	7.69 (5.25,11.27)	7.57 (5.18,11.07)	16.05 (0.99,259.61)	7.07 (4.82,10.37)	6.56 (4.51,9.54)	6.01 (4.10,8.81)	4.88 (3.33,7.13)	4.67 (3.01,7.26)	4.70 (3.24,6.82)	3.83 (0.53,27.87)	3.31 (2.07,5.30)	2.70 (1.37,5.32)	2.66 (1.82,3.90)	2.68 (1.71,4.20)	2.24 (1.48,3.39)	2.00 (1.05,3.81)	FUM	0.64 (0.07,5.81)	0.98 (0.50,1.94)
13.85 (2.35,81.65)	13.20 (2.32,74.90)	12.98 (2.28,74.06)	27.52 (1.06,717.66)	12.13 (2.12,69.46)	11.25 (1.98,63.93)	10.30 (1.81,58.64)	8.36 (1.46,47.81)	8.02 (1.40,45.99)	8.06 (1.42,45.76)	6.56 (0.48,89.53)	5.69 (0.98,32.86)	4.63 (0.74,28.86)	4.56 (0.81,25.79)	4.59 (0.79,26.61)	3.85 (0.67,21.94)	3.42 (0.56,20.99)	1.72 (0.29,10.11)	ACI	1.53 (0.19,12.56)
29.52 (19.94,43.70)	28.12 (23.17,34.12)	27.67 (22.86,33.49)	58.64 (3.72,923.86)	25.84 (20.90,31.95)	23.97 (20.03,28.70)	21.96 (18.17,26.53)	17.82 (14.62,21.72)	17.08 (12.93,22.56)	17.17 (14.44,20.42)	13.99 (1.99,98.10)	12.11 (8.78,16.71)	9.88 (5.45,17.91)	9.72 (8.12,11.63)	9.78 (7.15,13.37)	8.19 (6.53,10.29)	7.30 (4.26,12.51)	3.65 (2.49,5.36)	2.13 (0.37,12.16)	PBO

Figure 8. Interval plot. Network meta-analysis estimates of class-level versus placebo for all the outcomes Outcomes were all measured at the induction phase (assessment from 8 to 24 weeks after randomisation). 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; AIL12/23: anti-IL12/23; AIL17: anti-IL17; AIL23: anti-IL23, ATA: anti-TNF alpha; CSA: conventional systemic agents; PBO: placebo; SM: small molecules

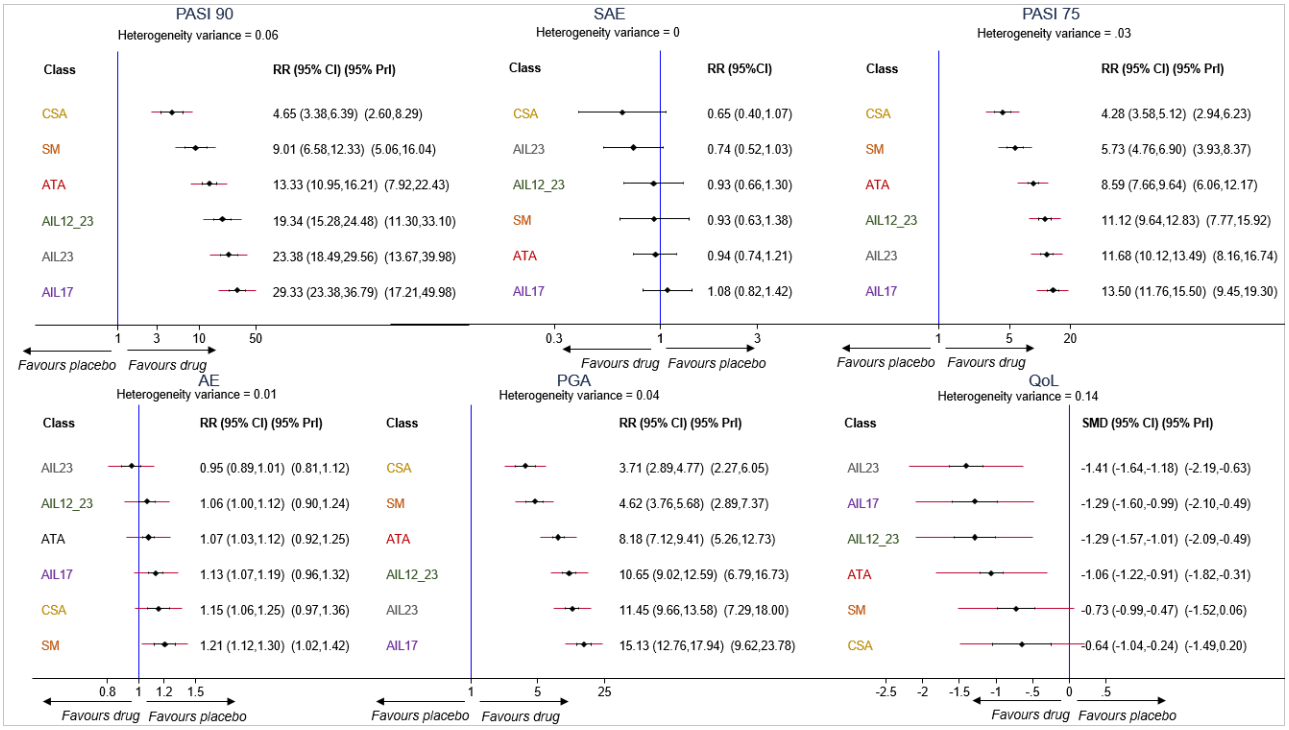


Figure 9. Interval plot. Network meta-analysis estimates of the interventions versus placebo for all the outcomes Outcomes were all measured at the induction phase (assessment from 8 to 24 weeks after randomisation). AE: adverse events; CI: confidence interval; PGA: Physician Global Assessment; PrI: predictive interval; QoL: Specific quality of life scale; RR: risk ratio; SAE: serious adverse events; SMD: standardised mean difference Interventions in bold and underligned are at high-certainty evidence; interventions in bold at moderate-certainty of evidence; very-low to low otherwise. ACI: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; TYK2: Oral Tyrosine kinase 2 inhibitor; USK: ustekinumab

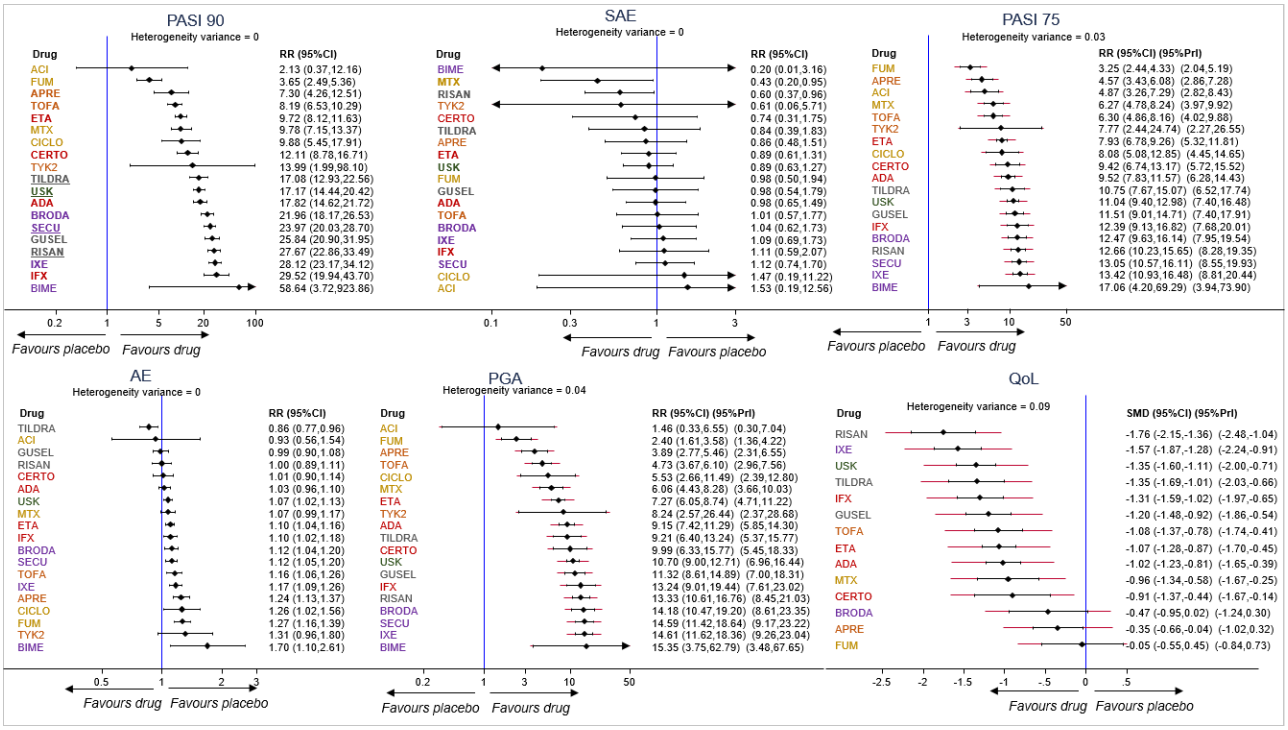


Figure 10. Ranking for all the outcomes at class level AIL12/23: anti-IL12/23; AIL17: anti-IL17; AIL23: anti-IL23, ATA: anti-TNF alpha; CSA: conventional systemic agents; PBO: placebo; SM: small molecules AE: adverse events; PASI: Psoriasis Area and Severity Index; PGA: Physician Global Assessment; QoL: quality of life; SAE: serious adverse events

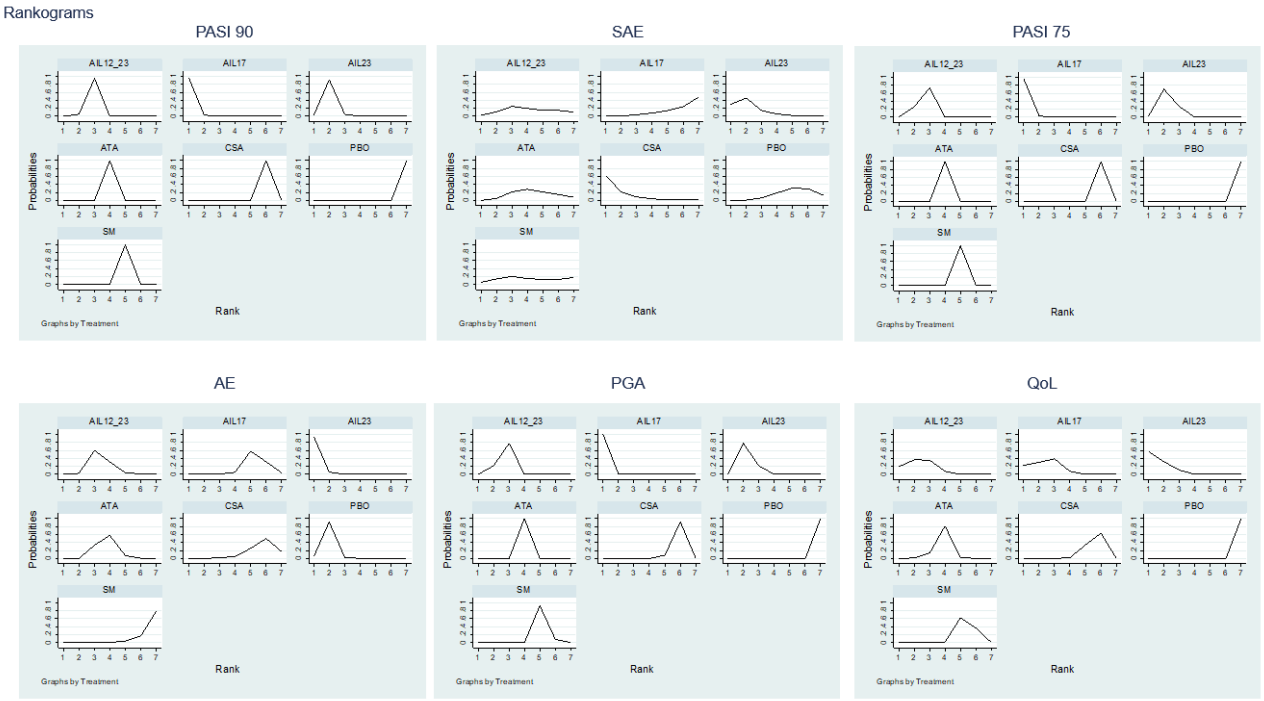


Figure 11. Ranking for all the outcomes at drug level ACI: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; TYK2: Oral Tyrosine kinase 2 inhibitor; USK: ustekinumab AE: adverse events; PASI: Psoriasis Area and Severity Index; PGA: Physician Global Assessment; QoL: quality of life; SAE: serious adverse events

Table 3 summarises the main results of both the direct and indirect evidence and the network meta-analysis for PASI 90. 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 except anti-IL23 (RR 1.25, 95% CI 0.99 to 1.99): versus anti-IL12/23 (RR 1.52, 95% CI 1.26 to 1.83); versus anti-TNF alpha (RR 2.20, 95% CI 1.80 to 2.69); versus small molecules (RR 3.26, 95% CI 2.27 to 4.67); versus conventional systemic agents (RR 6.31, 95% CI 4.64 to 8.59) (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 1.94, 95% CI 1.28 to 2.94).

Results of comparisons between each of the drugs are available in Figure 7. There was no significant difference between infliximab, ixekizumab, bimekizumab, risankizumab and guselkumab in terms of reaching PASI 90. The direct comparison regarding bimekizumab only included one trial each, so the interpretation of the results for this biological agent was difficult (related to wide CIs). All of the anti-IL17 drugs (ixekizumab, secukinumab and brodalumab) and all of the anti-IL23 drugs (risankizumab and guselkumab) except tildrakizumab were significantly more effective than ustekinumab and three anti-TNF alpha agents: adalimumab, certolizumab and etanercept. Adalimumab and ustekinumab were superior to certolizumab (RR 1.47, 95% CI 1.05 to 2.06 and RR 1.42, 95% CI 1.05 to 1.92, respectively) and etanercept (RR 1.83, 95% CI 1.51 to 2.23 and RR 1.77, 95% CI 1.56 to 2.00, respectively). No significant difference was shown between tofacitinib or apremilast and two conventional drugs: ciclosporin and methotrexate. The direct comparison for oral tyrosine kinase 2 inhibitor only included one trial each, so the interpretation of the results for this drug was difficult (related to wide CIs).

Ranking class-level analysis (Figure 8; Figure 10; 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 29.33, 95% CI 23.38 to 36.79; SUCRA = 99.5), followed by anti-IL23 (versus placebo: RR 23.38, 95% CI 18.49 to 29.56; SUCRA = 83), anti-IL12/23 (versus placebo: RR 19.34, 95% CI 15.28 to 24.48; SUCRA = 67.5), then anti-TNF alpha (versus placebo: RR 13.33, 95% CI 10.95 to 16.21; SUCRA = 49.9). The heterogeneity τ for this network overall was 0.06, which we considered low heterogeneity.

Ranking drug-level analysis (Figure 9; Figure 11; Table 5)

Ranking analysis for PASI 90 performed with SUCRA strongly suggested that infliximab was the best treatment at drug level (versus placebo: RR 29.52, 95% CI 19.94 to 43.70; SUCRA

= 88.5; moderate-certainty evidence), followed by ixekizumab (versus placebo: RR 28.12, 95% CI 23.17 to 34.12; SUCRA = 88.3; moderate-certainty evidence), risankizumab (versus placebo: RR 27.67, 95% CI 22.86 to 33.49; SUCRA = 87.5; high-certainty evidence), bimekizumab (versus placebo: RR 58.64, 95% CI 3.72 to 923.86; SUCRA = 83.5; low-certainty evidence), guselkumab (versus placebo: RR 25.84, 95% CI 20.90 to 31.95; SUCRA = 81; moderate-certainty evidence), secukinumab (versus placebo: RR 23.97, 95% CI 20.03 to 28.70; SUCRA = 75.4; high-certainty evidence), then brodalumab (versus placebo: RR 21.96, 95% CI 18.17 to 26.53; SUCRA = 68.7; moderate-certainty evidence). The heterogeneity τ for this network overall was 0, 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 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 found no significant differences between FAEs, etanercept, adalimumab, certolizumab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab, apremilast, tofacitinib, and placebo in the number of participants with serious adverse effects (SAEs). The risk of SAEs was significantly lower for participants on methotrexate compared to placebo (RR 0.16, 95% CI 0.03 to 0.88). 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); Heydendael 2003 (comparing ciclosporin with methotrexate); Gisondi 2008; (comparing etanercept with acitretin) and Hunter 1963 (comparing methotrexate with placebo).

NETWORK META-ANALYSES

The SAE outcome was available in 101 trials, involving 43,236 participants (91.8% 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 reported in seven trials out of 101 (Asahina 2016; Bissonnette 2015; Khatri 2016; Laburte 1994; Mrowietz SCULPTURE 2015; Ortonne 2013; Strohal PRISTINE 2013), 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). Sixty-one trials, involving 21,257 participants, were placebo-controlled trials; 18, involving 5447 participants, were head-to-head comparisons, and 22, involving 16,532 participants, had both a placebo and at least two active treatments arms.

It must be noted that at the end of the network meta-analysis process, we realised that we used the number of SAEs at 52 weeks for Zhang 2017. Thus, the network meta-analysis was done using six SAEs out of 178 for tofacitinib group instead of two SAEs out of 178. We have already corrected the number for the classical meta-analyses, and will do the same for the next update of the network meta-analysis.

See Figure 4; Figure 5; Figure 6; Figure 7; Figure 8; Figure 9; Figure 10; Figure 11.

Table 6 summarises the main results of both direct and indirect evidence and the network meta-analysis for SAEs. 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. We found no significant difference between any of the interventions and the placebo for the risk of SAE. Two trends close to significant associations were found: anti-IL17 agents had a higher risk of SAE compared with conventional systemic agents and compared with placebo (RR 1.66, 95% CI 0.98 to 2.82; RR 1.47, 95% CI 0.98 to 2.20, respectively). The results are available in Figure 7 for comparison between each drug. Infliximab, ixekizumab, and secukinumab were at higher risk of SAE than methotrexate (RR 2.55, 95% CI 1.26 to 5.18; RR 2.52, 95% CI 1.03 to 6.15; RR 2.58, 95% CI 1.07 to 6.20, respectively). A trend close to a significant association was found: brodalumab or adalimumab had a higher risk of SAE compared with methotrexate.

Ranking class-level analysis (Figure 8; Figure 10; 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 0.65, 95% CI 0.40 to 1.07; SUCRA = 87.9), followed by anti-IL23 (versus placebo: RR 0.74, 95% CI 0.52 to 1.03; SUCRA = 81.1), anti-IL12/23 (versus placebo: RR 0.93, 95% CI 0.66 to 1.30; SUCRA = 46.5), and then small molecules (versus placebo: RR 0.93, 95% CI 0.63 to 1.38; SUCRA = 45.1). The heterogeneity τ for this network overall was 0.03, which we considered low heterogeneity.

Ranking drug-level analysis (Figure 9; Figure 11; Table 5)

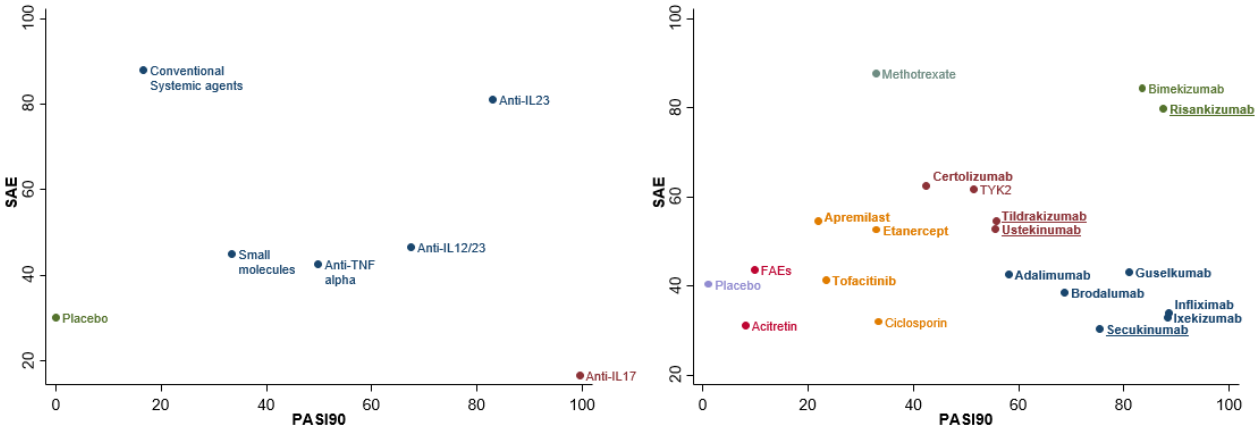
Ranking analysis for SAEs performed with SUCRA strongly suggested that methotrexate was associated with the best safety profile at drug level in terms of serious adverse events (versus placebo: RR 0.43, 95% CI 0.20 to 0.95; SUCRA = 87.6; moderate-certainty evidence), followed by bimekizumab (versus placebo: RR 0.20, 95% CI 0.01 to 3.16; SUCRA = 84.3; low-certainty evidence), risankizumab (versus placebo: RR 0.60, 95% CI 0.37 to 0.96; SUCRA = 79.9; moderate-certainty evidence), certolizumab (versus placebo: RR 0.74, 95% CI 0.31 to 1.75; SUCRA = 62.4; low-certainty evidence), oral tyrosine kinase 2 inhibitor (versus placebo: RR 0.61, 95% CI 0.06 to 5.71; SUCRA = 61.6; low-certainty evidence), and then tildrakizumab (versus placebo: RR 0.84, 95% CI 0.39 to 1.83; SUCRA = 54.6; moderate-certainty evidence). The heterogeneity τ for this network overall was 0, which we considered low heterogeneity.

Placebo had a worse ranking for SAE than conventional systemic agents, anti-IL23, anti-IL12/23, and small molecules (see Table 5). Nevertheless, analyses of serious adverse events were based on a very low number of events and were reduced to the short time frame of the trials. Studies evaluating the use of placebo as comparator in randomised controlled trials assessing systemic treatments in moderate-to-severe psoriasis, including the serious adverse events in the placebo group, are ongoing (Afach 2019).

1.3 Relationship between PASI 90 and serious adverse events

See Figure 12.

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. Outcomes were measured at the induction phase (assessment from 8 to 24 weeks after randomisation). 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 Interventions in bold and underlined are at high-certainty evidence; interventions in bold at moderate-certainty of evidence; very-low to low otherwise. ACI: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; TYK2: Oral Tyrosine kinase 2 inhibitor; USK: ustekinumab PASI: Psoriasis Area and Severity Index; SAE: serious adverse events; SUCRA: surface under the cumulative ranking curve



These findings for both efficacy (PASI 90) and acceptability (serious adverse events) were combined together in a bivariate ranking plot, where serious adverse events were 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 treatment (anti-IL17) had serious adverse events. However, the anti-IL23 treatment group was the class with the better compromise between efficacy and acceptability.

At drug level, risankizumab and bimekizumab might be the overall best treatments, considering both outcomes jointly. This result has to be considered with caution for bimekizumab, as only one trial was available for this drug (low-certainty evidence).

2. Secondary outcomes

2.1 Proportion of participants who achieve PASI 75

DIRECT EVIDENCE

We report treatment estimates for pair-wise meta-analyses at class 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; and Analysis 3.10, respectively.

NETWORK META-ANALYSES

PASI 75 outcome was available in 107 trials, involving 44,909 participants (95.4% of the participants in this review). This outcome was reported in one other trial (Sterry PRESTA 2010), but the number of randomised participants was not available. These trials were added to the complete case analyses. This outcome was reported in 11 trials out of 107 (Asahina 2016; Bissonnette 2015; Dogra 2012; Dogra 2013; Dubertret 1989; Khatri 2016; Laburte 1994; Mrowietz SCULPTURE 2015; NCT01961609 SIGNATURE; Ortonne 2013; Strohal PRISTINE 2013), 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 five remaining trials, and we were not able to obtain missing information from the trial authors (Table 2). Sixty-four trials, involving 22,598 participants, were placebo-controlled trials; 21, involving 5779 participants, were head-to-head comparisons; and 22, involving 16,532 participants, had both a placebo and at least two active treatments arms.

See Figure 4; Figure 5; Figure 6; Figure 13; Figure 8; Figure 9; Figure 10; Figure 11

Figure 13. 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) Outcomes were all measured at the induction phase (assessment from 8 to 24 weeks after randomisation). 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 are highlighted in grey. ACI: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; TYK2: Oral Tyrosine kinase 2 inhibitor; USK: ustekinumab

SECU	1.00 (0.91,1.10)	0.66 (0.43,1.02)	0.96 (0.87,1.05)	1.12 (0.99,1.27)	1.04 (0.97,1.12)	1.30 (1.15,1.48)	1.14 (1.02,1.27)	1.02 (0.92,1.12)	1.10 (0.97,1.26)	0.85 (0.62,1.17)	1.09 (0.99,1.19)	1.02 (0.94,1.10)	0.97 (0.87,1.08)	0.89 (0.71,1.11)	0.90 (0.80,1.01)	1.04 (0.94,1.16)	0.88 (0.80,0.98)	1.21 (0.72,2.01)	1.12 (1.05,1.20)
1.05 (0.78,1.41)	BRODA	0.66 (0.43,1.02)	0.95 (0.86,1.06)	1.12 (0.98,1.28)	1.04 (0.96,1.13)	1.30 (1.14,1.48)	1.13 (1.01,1.28)	1.01 (0.92,1.13)	1.10 (0.96,1.26)	0.85 (0.62,1.18)	1.09 (0.98,1.20)	1.02 (0.93,1.11)	0.97 (0.86,1.08)	0.89 (0.71,1.11)	0.90 (0.79,1.01)	1.04 (0.93,1.16)	0.88 (0.78,0.99)	1.20 (0.72,2.01)	1.12 (1.04,1.20)
0.76 (0.19,3.16)	0.73 (0.18,3.04)	BIME	1.45 (0.94,2.24)	1.70 (1.09,2.66)	1.58 (1.03,2.44)	1.97 (1.27,3.08)	1.72 (1.11,2.67)	1.54 (1.00,2.39)	1.67 (1.07,2.61)	1.29 (0.76,2.20)	1.65 (1.07,2.55)	1.54 (1.00,2.38)	1.47 (0.95,2.28)	1.35 (0.83,2.18)	1.36 (0.88,2.12)	1.58 (1.02,2.45)	1.34 (0.86,2.08)	1.83 (0.94,3.56)	1.70 (1.10,2.61)
0.97 (0.75,1.26)	0.93 (0.68,1.26)	1.27 (0.31,5.24)	IXE	1.18 (1.03,1.34)	1.09 (1.01,1.18)	1.36 (1.20,1.55)	1.19 (1.06,1.33)	1.06 (0.96,1.17)	1.15 (1.01,1.32)	0.89 (0.65,1.23)	1.14 (1.03,1.26)	1.06 (0.99,1.15)	1.01 (0.91,1.13)	0.93 (0.74,1.16)	0.94 (0.83,1.06)	1.09 (0.98,1.21)	0.92 (0.83,1.03)	1.26 (0.76,2.11)	1.17 (1.09,1.26)
1.03 (0.79,1.34)	0.98 (0.73,1.33)	1.35 (0.33,5.56)	1.06 (0.81,1.39)	RISAN	0.93 (0.83,1.04)	1.16 (0.99,1.35)	1.01 (0.88,1.16)	0.90 (0.79,1.03)	0.98 (0.84,1.15)	0.76 (0.54,1.06)	0.97 (0.86,1.10)	0.91 (0.80,1.02)	0.86 (0.75,0.99)	0.79 (0.62,1.01)	0.80 (0.69,0.93)	0.93 (0.81,1.06)	0.79 (0.68,0.90)	1.07 (0.64,1.81)	1.00 (0.89,1.11)
1.18 (0.97,1.44)	1.13 (0.89,1.43)	1.55 (0.38,6.33)	1.22 (0.98,1.51)	1.15 (0.94,1.40)	USK	1.25 (1.11,1.41)	1.09 (0.98,1.20)	0.97 (0.89,1.06)	1.06 (0.93,1.20)	0.82 (0.59,1.12)	1.04 (0.96,1.13)	0.97 (0.91,1.04)	0.93 (0.84,1.03)	0.85 (0.68,1.06)	0.86 (0.77,0.96)	1.00 (0.90,1.10)	0.84 (0.76,0.94)	1.15 (0.69,1.92)	1.07 (1.02,1.13)
1.21 (0.83,1.77)	1.16 (0.77,1.75)	1.59 (0.38,6.71)	1.25 (0.86,1.81)	1.18 (0.80,1.74)	1.03 (0.72,1.47)	TILDRA	0.87 (0.76,1.01)	0.78 (0.69,0.89)	0.85 (0.72,0.99)	0.65 (0.47,0.91)	0.84 (0.74,0.95)	0.78 (0.70,0.88)	0.74 (0.65,0.85)	0.68 (0.54,0.87)	0.69 (0.60,0.80)	0.80 (0.70,0.92)	0.68 (0.59,0.78)	0.93 (0.55,1.56)	0.86 (0.77,0.96)
1.13 (0.83,1.55)	1.08 (0.76,1.54)	1.48 (0.36,6.15)	1.17 (0.86,1.58)	1.10 (0.82,1.48)	0.96 (0.73,1.27)	0.93 (0.62,1.41)	GUSEL	0.90 (0.80,1.01)	0.97 (0.84,1.12)	0.75 (0.54,1.04)	0.96 (0.87,1.05)	0.90 (0.81,0.99)	0.85 (0.75,0.97)	0.78 (0.62,0.99)	0.79 (0.69,0.90)	0.92 (0.81,1.03)	0.78 (0.69,0.87)	1.06 (0.63,1.78)	0.99 (0.90,1.08)
1.05 (0.74,1.50)	1.01 (0.68,1.49)	1.38 (0.33,5.78)	1.08 (0.77,1.52)	1.02 (0.71,1.46)	0.89 (0.64,1.24)	0.87 (0.56,1.35)	0.93 (0.64,1.35)	IFX	1.08 (0.95,1.24)	0.84 (0.61,1.16)	1.07 (0.97,1.18)	1.00 (0.92,1.09)	0.95 (0.85,1.06)	0.87 (0.70,1.09)	0.88 (0.78,1.00)	1.02 (0.93,1.12)	0.87 (0.77,0.97)	1.19 (0.71,1.98)	1.10 (1.02,1.18)
1.39 (0.95,2.02)	1.32 (0.88,2.00)	1.81 (0.43,7.65)	1.42 (0.98,2.06)	1.34 (0.91,1.98)	1.17 (0.82,1.68)	1.14 (0.73,1.80)	1.22 (0.81,1.85)	1.32 (0.85,2.04)	CERTO	0.77 (0.55,1.08)	0.99 (0.86,1.13)	0.92 (0.82,1.04)	0.88 (0.76,1.01)	0.80 (0.63,1.03)	0.81 (0.70,0.95)	0.94 (0.82,1.09)	0.80 (0.69,0.93)	1.09 (0.65,1.84)	1.01 (0.90,1.14)
1.68 (0.52,5.45)	1.60 (0.49,5.26)	2.20 (0.36,13.53)	1.73 (0.53,5.60)	1.63 (0.50,5.29)	1.42 (0.44,4.58)	1.38 (0.41,4.62)	1.48 (0.45,4.84)	1.59 (0.48,5.28)	1.21 (0.36,4.05)	TYK2	1.28 (0.93,1.76)	1.19 (0.87,1.64)	1.14 (0.82,1.58)	1.04 (0.71,1.52)	1.05 (0.76,1.47)	1.22 (0.88,1.69)	1.04 (0.75,1.44)	1.42 (0.78,2.58)	1.31 (0.96,1.80)
1.37 (1.04,1.81)	1.31 (0.95,1.80)	1.79 (0.44,7.38)	1.41 (1.08,1.85)	1.33 (1.04,1.70)	1.16 (0.91,1.47)	1.13 (0.77,1.67)	1.21 (0.99,1.48)	1.30 (0.92,1.84)	0.99 (0.67,1.46)	0.82 (0.25,2.64)	ADA	0.93 (0.86,1.02)	0.89 (0.80,0.99)	0.82 (0.65,1.02)	0.82 (0.73,0.93)	0.96 (0.86,1.06)	0.81 (0.73,0.90)	1.11 (0.66,1.85)	1.03 (0.96,1.10)
1.65 (1.32,2.05)	1.57 (1.19,2.08)	2.15 (0.53,8.82)	1.69 (1.39,2.07)	1.60 (1.25,2.04)	1.39 (1.16,1.67)	1.36 (0.98,1.88)	1.45 (1.09,1.93)	1.56 (1.14,2.14)	1.19 (0.86,1.64)	0.98 (0.30,3.15)	1.20 (0.94,1.53)	ETA	0.95 (0.86,1.05)	0.87 (0.70,1.09)	0.88 (0.79,0.98)	1.02 (0.93,1.13)	0.87 (0.78,0.96)	1.19 (0.71,1.97)	1.10 (1.04,1.16)
2.07 (1.50,2.86)	1.98 (1.38,2.84)	2.71 (0.65,11.26)	2.13 (1.55,2.92)	2.01 (1.45,2.79)	1.75 (1.30,2.35)	1.71 (1.13,2.57)	1.83 (1.28,2.60)	1.97 (1.33,2.91)	1.50 (0.99,2.25)	1.23 (0.38,4.04)	1.51 (1.10,2.08)	1.26 (0.96,1.65)	TOFA	0.92 (0.73,1.15)	0.93 (0.82,1.06)	1.08 (0.95,1.21)	0.91 (0.80,1.04)	1.25 (0.74,2.09)	1.16 (1.06,1.26)
1.62 (0.98,2.67)	1.54 (0.91,2.62)	2.11 (0.48,9.25)	1.66 (1.03,2.68)	1.57 (0.95,2.58)	1.37 (0.84,2.22)	1.33 (0.75,2.35)	1.43 (0.86,2.36)	1.53 (0.94,2.52)	1.17 (0.66,2.06)	0.96 (0.28,3.35)	1.18 (0.73,1.90)	0.98 (0.61,1.58)	0.78 (0.46,1.32)	CICLO	1.01 (0.80,1.28)	1.17 (0.96,1.43)	0.99 (0.79,1.25)	1.36 (0.78,2.36)	1.26 (1.02,1.56)
2.86 (2.01,4.07)	2.73 (1.85,4.02)	3.74 (0.89,15.63)	2.94 (2.08,4.16)	2.77 (1.95,3.95)	2.42 (1.74,3.36)	2.36 (1.52,3.65)	2.52 (1.74,3.66)	2.71 (1.80,4.10)	2.06 (1.34,3.18)	1.70 (0.52,5.61)	2.08 (1.48,2.93)	1.74 (1.27,2.37)	1.38 (0.94,2.02)	1.77 (1.03,3.03)	APRE	1.16 (1.02,1.32)	0.98 (0.86,1.12)	1.34 (0.80,2.25)	1.24 (1.13,1.37)
2.08 (1.49,2.91)	1.99 (1.37,2.89)	2.72 (0.65,11.34)	2.14 (1.59,2.88)	2.02 (1.46,2.80)	1.76 (1.30,2.39)	1.71 (1.12,2.63)	1.84 (1.32,2.56)	1.98 (1.44,2.71)	1.50 (0.98,2.30)	1.24 (0.38,4.07)	1.52 (1.14,2.03)	1.26 (0.94,1.70)	1.00 (0.70,1.45)	1.29 (0.87,1.91)	0.73 (0.50,1.07)	MTX	0.85 (0.76,0.95)	1.16 (0.69,1.94)	1.07 (0.99,1.17)
4.01 (2.94,5.48)	3.83 (2.64,5.57)	5.24 (1.25,21.92)	4.12 (2.99,5.69)	3.89 (2.77,5.46)	3.39 (2.49,4.62)	3.30 (2.14,5.11)	3.54 (2.55,4.92)	3.81 (2.56,5.67)	2.90 (1.88,4.47)	2.39 (0.72,7.88)	2.93 (2.13,4.02)	2.44 (1.79,3.32)	1.94 (1.32,2.83)	2.48 (1.48,4.16)	1.40 (0.94,2.10)	1.93 (1.36,2.74)	FUM	1.37 (0.81,2.29)	1.27 (1.16,1.39)
2.68 (1.72,4.17)	2.56 (1.59,4.11)	3.50 (0.81,15.05)	2.75 (1.79,4.23)	2.60 (1.66,4.06)	2.27 (1.48,3.46)	2.21 (1.33,3.66)	2.36 (1.49,3.75)	2.54 (1.68,3.86)	1.93 (1.17,3.20)	1.59 (0.47,5.44)	1.95 (1.26,3.02)	1.63 (1.10,2.41)	1.29 (0.81,2.06)	1.66 (0.92,2.98)	0.94 (0.58,1.52)	1.29 (0.82,2.01)	0.67 (0.41,1.08)	ACI	0.93 (0.56,1.54)
13.05 (10.57,16.12)	12.47 (9.63,16.14)	17.06 (4.20,69.29)	13.42 (10.93,16.48)	12.66 (10.23,15.66)	11.04 (9.40,12.98)	10.75 (7.67,15.07)	11.51 (9.01,14.71)	12.39 (9.13,16.82)	9.42 (6.74,13.17)	7.77 (2.44,24.74)	9.52 (7.83,11.57)	7.93 (6.78,9.26)	6.30 (4.86,8.16)	8.08 (5.08,12.85)	4.57 (3.43,6.08)	6.27 (4.78,8.24)	3.25 (2.44,4.33)	4.87 (3.26,7.29)	PBO

We present the summary relative effects from the network meta-analysis in league tables for both class-level (Figure 6) and drug-level (Figure 13) 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 except for anti IL23 (close trend to association: RR 1.16, 95% CI 0.99 to 1.35). 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 13.

Ranking class-level analysis(Figure 8; Figure 10; 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 13.50, 95% CI 11.76 to 15.50; SUCRA = 99.4), followed by anti-IL23 (versus placebo: RR 11.68, 95% CI 10.12 to 13.49; SUCRA = 79.7), anti-IL12/23 (versus placebo: RR 11.12, 95% CI 9.64 to 12.83; SUCRA = 70.9), then anti-TNF alpha (versus placebo: RR 8.59 95% CI 7.66 to 9.64; SUCRA = 50). The heterogeneity τ for this network overall was 0.03, which we considered low heterogeneity.

Ranking drug-level analysis(Figure 9; Figure 11; Table 5)

Ranking analysis for PASI 75 performed with SUCRA strongly suggested that ixekizumab was the best treatment at drug level (versus placebo: RR 13.42, 95% CI 10.93 to 16.48; SUCRA = 86.4), followed by secukinumab (versus placebo: RR 13.05, 95% CI 10.57 to 16.11; SUCRA = 83.6), risankizumab (versus placebo: RR 12.66, 95% CI 10.23 to 15.65; SUCRA = 80.5), bimekizumab (versus placebo: RR 17.06, 95% CI 4.20 to 69.29; SUCRA = 80.3), then brodalumab (versus placebo: RR 12.47, 95% CI 9.63 to 16.14; SUCRA = 78.2). The heterogeneity τ for this network overall was 0.03, which we considered low heterogeneity.

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

DIRECT EVIDENCE

We report treatment estimates for pair-wise meta-analyses at class 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; and Analysis 4.10, respectively.

NETWORK META-ANALYSES

The PGA 0/1 outcome was available in 89 trials, involving 41,528 participants (88.2% of the participants in this review). This outcome was reported in three other studies (Nugteren-Huying 1990; Sandhu 2003; Sterry PRESTA 2010), but the number of randomised participants was not available. These trials were added to the complete-case analyses. This outcome was reported in six trials out of 89 (Asahina 2016; Bissonnette 2015; Khatri 2016; Mrowietz SCULPTURE 2015; Ortonne 2013; Strohal PRISTINE 2013), 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 21 remaining trials, and we were not able to obtain missing information from the trial authors (Table 2). Fifty-four trials, involving 20,123 participants, were placebo-controlled trials; 13, involving 4873 participants, were head-to-head comparisons; and 22, involving 16,532 participants, had both a placebo and at least two active treatments arms.

See Figure 4; Figure 5; Figure 6; Figure 14; Figure 8; Figure 9; Figure 10; Figure 11

Figure 14. Relative effects of the intervention as estimated from the network meta-analysis model for Physician's Global Assessment (PGA 0/1) and quality of life (QoL) Outcomes were all measured at the induction phase (assessment from 8 to 24 weeks after randomisation). Drugs are reported in order of primary benefit ranking. Each cell contains the risk ratio (RR) and 95% confidence interval (PGA 0/1) or standardized mean difference (quality of life) 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 (or SMDs smaller than zero) for the upper triangle favour the treatment on the left. Significant results are are highlighted in grey. ACI: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; TYK2: Oral Tyrosine kinase 2 inhibitor; USK: ustekinumab

IXE	-	-1.11 (-1.67,-0.54)	0.18 (-0.31,0.68)	-0.27 (-0.67,0.14)	-	-0.38 (-0.77,0.02)	-0.22 (-0.60,0.16)	-0.67 (-1.22,-0.12)	-0.23 (-0.67,0.21)	-	-0.55 (-0.91,-0.20)	-0.50 (-0.82,-0.18)	-0.61 (-1.04,-0.18)	-	-0.50 (-0.91,-0.09)	-1.23 (-1.65,-0.80)	-1.52 (-2.05,-1.00)	-	-1.57 (-1.87,-1.28)
1.00 (0.75,1.34)	SECU	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1.03 (0.73,1.45)	1.03 (0.73,1.44)	BRODA	1.29 (0.66,1.91)	0.84 (0.28,1.40)	-	0.73 (0.17,1.29)	0.89 (0.34,1.43)	0.44 (-0.24,1.11)	0.88 (0.29,1.47)	-	0.55 (0.02,1.08)	0.61 (0.08,1.13)	0.49 (-0.12,1.11)	-	0.61 (0.04,1.18)	-0.12 (-0.70,0.45)	-0.42 (-1.12,0.28)	-	-0.47 (-0.95,0.02)
1.10 (0.81,1.48)	1.09 (0.81,1.48)	1.06 (0.75,1.50)	RISAN	-0.45 (-0.94,0.04)	-	-0.56 (-1.04,-0.07)	-0.40 (-0.80,-0.01)	-0.85 (-1.46,-0.24)	-0.41 (-0.93,0.12)	-	-0.74 (-1.19,-0.28)	-0.68 (-1.13,-0.23)	-0.79 (-1.34,-0.25)	-	-0.68 (-1.17,-0.18)	-1.41 (-1.91,-0.90)	-1.70 (-2.35,-1.06)	-	-1.76 (-2.15,-1.36)
1.10 (0.73,1.66)	1.10 (0.71,1.71)	1.07 (0.67,1.72)	1.01 (0.65,1.56)	IFX	-	-0.11 (-0.51,0.29)	0.05 (-0.33,0.42)	-0.40 (-0.95,0.15)	0.04 (-0.40,0.48)	-	-0.29 (-0.64,0.07)	-0.23 (-0.57,0.10)	-0.35 (-0.82,0.13)	-	-0.23 (-0.63,0.18)	-0.96 (-1.38,-0.54)	-1.25 (-1.83,-0.68)	-	-1.31 (-1.59,-1.02)
0.95 (0.23,3.97)	0.95 (0.23,3.97)	0.92 (0.22,3.90)	0.87 (0.21,3.62)	0.86 (0.20,3.72)	BIME	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1.29 (0.91,1.83)	1.29 (0.90,1.85)	1.25 (0.83,1.89)	1.18 (0.85,1.63)	1.17 (0.74,1.85)	1.36 (0.32,5.69)	GUSEL	0.15 (-0.22,0.53)	-0.29 (-0.84,0.25)	0.15 (-0.29,0.59)	-	-0.18 (-0.48,0.12)	-0.12 (-0.47,0.22)	-0.24 (-0.68,0.21)	-	-0.12 (-0.53,0.29)	-0.85 (-1.27,-0.43)	-1.15 (-1.65,-0.65)	-	-1.20 (-1.48,-0.92)
1.37 (1.08,1.73)	1.36 (1.09,1.70)	1.33 (1.01,1.74)	1.25 (1.01,1.55)	1.24 (0.83,1.85)	1.43 (0.35,5.93)	1.06 (0.77,1.45)	USK	-0.45 (-0.97,0.08)	-0.01 (-0.42,0.41)	-	-0.33 (-0.66,-0.01)	-0.28 (-0.60,0.04)	-0.39 (-0.84,0.06)	-	-0.28 (-0.66,0.11)	-1.01 (-1.40,-0.61)	-1.30 (-1.86,-0.75)	-	-1.35 (-1.60,-1.11)
1.46 (0.91,2.34)	1.46 (0.90,2.37)	1.42 (0.86,2.35)	1.33 (0.81,2.21)	1.32 (0.75,2.34)	1.54 (0.35,6.75)	1.13 (0.66,1.94)	1.07 (0.67,1.70)	CERTO	0.44 (-0.14,1.02)	-	0.11 (-0.40,0.63)	0.17 (-0.34,0.68)	0.05 (-0.55,0.65)	-	0.17 (-0.38,0.72)	-0.56 (-1.12,0.00)	-0.86 (-1.54,-0.17)	-	-0.91 (-1.37,-0.44)
1.59 (1.07,2.36)	1.58 (1.05,2.39)	1.54 (0.98,2.41)	1.45 (0.95,2.21)	1.44 (0.86,2.39)	1.67 (0.39,7.14)	1.23 (0.78,1.94)	1.16 (0.79,1.70)	1.09 (0.64,1.85)	TILDRA	-	-0.33 (-0.73,0.07)	-0.27 (-0.65,0.10)	-0.39 (-0.89,0.12)	-	-0.27 (-0.72,0.18)	-1.00 (-1.46,-0.54)	-1.30 (-1.90,-0.69)	-	-1.35 (-1.69,-1.01)
1.77 (0.54,5.81)	1.77 (0.54,5.82)	1.72 (0.52,5.74)	1.62 (0.49,5.31)	1.61 (0.47,5.48)	1.86 (0.30,11.59)	1.37 (0.41,4.55)	1.30 (0.40,4.22)	1.21 (0.35,4.24)	1.12 (0.33,3.79)	TYK2	-	-	-	-	-	-	-	-	-
1.60 (1.18,2.16)	1.59 (1.16,2.19)	1.55 (1.07,2.24)	1.46 (1.12,1.89)	1.45 (0.95,2.20)	1.68 (0.40,6.97)	1.24 (0.99,1.55)	1.17 (0.90,1.51)	1.09 (0.66,1.82)	1.01 (0.66,1.53)	0.90 (0.28,2.94)	ADA	0.05 (-0.24,0.35)	-0.06 (-0.46,0.34)	-	0.06 (-0.30,0.42)	-0.67 (-1.05,-0.30)	-0.97 (-1.49,-0.45)	-	-1.02 (-1.23,-0.81)
2.01 (1.61,2.50)	2.01 (1.56,2.58)	1.95 (1.42,2.68)	1.83 (1.40,2.41)	1.82 (1.23,2.70)	2.11 (0.51,8.74)	1.56 (1.12,2.16)	1.47 (1.20,1.80)	1.37 (0.91,2.09)	1.27 (0.90,1.79)	1.13 (0.35,3.69)	1.26 (0.95,1.66)	ETA	-0.11 (-0.53,0.31)	-	0.00 (-0.33,0.34)	-0.73 (-1.10,-0.36)	-1.02 (-1.56,-0.49)	-	-1.07 (-1.28,-0.87)
2.41 (1.73,3.36)	2.41 (1.65,3.52)	2.34 (1.53,3.58)	2.20 (1.53,3.18)	2.19 (1.53,3.11)	2.53 (0.60,10.73)	1.87 (1.27,2.75)	1.77 (1.26,2.47)	1.65 (0.96,2.83)	1.52 (0.95,2.42)	1.36 (0.41,4.55)	1.51 (1.08,2.11)	1.20 (0.86,1.68)	MTX	-	0.12 (-0.36,0.59)	-0.61 (-1.10,-0.13)	-0.91 (-1.45,-0.37)	-	-0.96 (-1.34,-0.58)
2.64 (1.26,5.53)	2.64 (1.23,5.65)	2.57 (1.17,5.61)	2.41 (1.13,5.14)	2.39 (1.13,5.08)	2.78 (0.57,13.58)	2.05 (0.95,4.41)	1.93 (0.92,4.06)	1.81 (0.77,4.22)	1.67 (0.74,3.73)	1.49 (0.38,5.90)	1.66 (0.79,3.48)	1.31 (0.63,2.76)	1.10 (0.56,2.14)	CICLO	-	-	-	-	-
3.09 (2.21,4.31)	3.08 (2.18,4.37)	3.00 (2.00,4.49)	2.82 (2.02,3.93)	2.80 (1.77,4.42)	3.24 (0.78,13.58)	2.39 (1.66,3.45)	2.26 (1.67,3.06)	2.11 (1.25,3.56)	1.95 (1.26,3.01)	1.74 (0.53,5.74)	1.93 (1.40,2.66)	1.54 (1.15,2.05)	1.28 (0.86,1.90)	1.17 (0.54,2.53)	TOFA	-0.73 (-1.16,-0.30)	-1.03 (-1.61,-0.45)	-	-1.08 (-1.37,-0.78)
3.76 (2.52,5.59)	3.75 (2.49,5.66)	3.65 (2.33,5.71)	3.43 (2.29,5.15)	3.41 (2.05,5.65)	3.95 (0.93,16.82)	2.91 (1.89,4.50)	2.75 (1.89,4.00)	2.57 (1.48,4.48)	2.37 (1.46,3.85)	2.12 (0.63,7.14)	2.35 (1.58,3.51)	1.87 (1.30,2.69)	1.56 (0.99,2.46)	1.42 (0.64,3.18)	1.22 (0.80,1.85)	APRE	-0.30 (-0.89,0.29)	-	-0.35 (-0.66,-0.04)
6.08 (3.95,9.36)	6.08 (3.99,9.25)	5.91 (3.62,9.63)	5.55 (3.55,8.70)	5.51 (3.22,9.43)	6.39 (1.48,27.66)	4.72 (2.92,7.62)	4.46 (2.94,6.75)	4.16 (2.29,7.55)	3.83 (2.25,6.52)	3.43 (1.00,11.78)	3.81 (2.44,5.95)	3.03 (1.98,4.62)	2.52 (1.56,4.07)	2.30 (1.02,5.21)	1.97 (1.23,3.15)	1.62 (0.96,2.73)	FUM	-	-0.05 (-0.55,0.45)
9.99 (2.22,44.94)	9.98 (2.21,45.12)	9.70 (2.12,44.37)	9.12 (2.01,41.39)	9.05 (1.94,42.17)	10.50 (1.34,82.12)	7.74 (1.69,35.53)	7.31 (1.63,32.83)	6.83 (1.46,32.04)	6.30 (1.37,28.99)	5.64 (0.84,37.65)	6.26 (1.38,28.42)	4.97 (1.12,22.00)	4.14 (0.90,19.03)	3.78 (0.72,19.91)	3.24 (0.71,14.73)	2.66 (0.57,12.29)	1.64 (0.35,7.71)	ACI	-
14.61 (11.62,18.36)	14.59 (11.42,18.64)	14.18 (10.47,19.20)	13.33 (10.61,16.76)	13.24 (9.01,19.44)	15.35 (3.75,62.79)	11.32 (8.61,14.89)	10.70 (9.00,12.71)	9.99 (6.33,15.77)	9.21 (6.40,13.24)	8.24 (2.57,26.44)	9.15 (7.42,11.29)	7.27 (6.05,8.74)	6.06 (4.43,8.28)	5.53 (2.66,11.49)	4.73 (3.67,6.10)	3.89 (2.77,5.46)	2.40 (1.61,3.58)	1.46 (0.33,6.55)	PBO

We present the summary relative effects as estimated from the network meta-analysis in league tables at class level (Figure 6) and drug level (Figure 14). 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 for 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. We found no significant difference between small molecule and conventional systemic agents. Results of comparisons between each of the drugs are available in Figure 14.

Ranking class-level analysis(Figure 8; Figure 10; 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 15.13, 95% CI 12.76 to 17.94; SUCRA = 100), followed by anti-IL23 (versus placebo: RR 11.45, 95% CI 9.66 to 13.58; SUCRA = 79.8), anti-IL12/23 (versus placebo: RR 10.65, 95% CI 9.02 to 12.59; SUCRA = 70.3), then anti-TNF alpha (versus placebo:

RR 8.18, 95% CI 7.12 to 9.41; SUCRA = 50). The heterogeneity τ for this network overall was 0.04, which we considered low heterogeneity.

Ranking drug-level analysis(Figure 9; Figure 11; Table 5)

Ranking analysis for PGA 0/1 performed with SUCRA strongly suggested that ixekizumab was the best treatment at drug level (versus placebo: RR 14.61, 95% CI 11.62 to 18.36; SUCRA = 87.5), followed by secukinumab (versus placebo: RR 14.59, 95% CI 11.42 to 18.64; SUCRA = 87.2), brodalumab (versus placebo: RR 14.18, 95% CI 10.47 to 19.20; SUCRA = 84.7), risankizumab (versus placebo: RR 13.33, 95% CI 10.61 to 16.76; SUCRA = 80.4), infliximab (versus placebo: RR 13.24, 95% CI 9.01 to 19.44; SUCRA =79), then bimekizumab (versus placebo: RR 15.35, 95% CI 3.75 to 62.79; SUCRA = 76.9). The heterogeneity τ for this network overall was 0.04, 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 8) and very close at drug level (Figure 9).

2.3 Mean difference of quality of life measured by a specific scale

DIRECT EVIDENCE

We report treatment estimates for pair-wise meta-analyses at class and drug level in Analysis 5.1; Analysis 5.2; Analysis 5.3; Analysis 5.4; Analysis 5.5; Analysis 5.6; Analysis 5.7; Analysis 5.8; Analysis 5.9; and Analysis 5.10, respectively.

NETWORK META-ANALYSES

The quality-of-life outcome was available in 53 trials, involving 26,336 participants (55.9% of the participants in this review). This outcome was also reported in seven trials (out of 53) (Asahina 2016; Bissonnette 2015; Khatri 2016; Mrowietz SCULPTURE 2015; NCT01961609 SIGNATURE; Ortonne 2013; Strohal PRISTINE 2013), comparing different dosages of the same drug. These trials were added in the sensitivity analyses at dose level. The quality-of-life outcome was not reported for the 60 remaining trials, and we were not able to obtain missing information from the trial authors (Table 2). Thirty-one trials, involving 14,130 participants, were placebo-controlled trials; nine, involving 2486 participants, were head-to-head comparisons; and 13, involving 9720 participants, had both a placebo and at least two active treatments arms.

See Figure 4; Figure 5; Figure 6; Figure 14; Figure 8; Figure 9; Figure 10; Figure 11.

We present the summary relative effects from the network meta-analysis in league tables for both class-level (Figure 6) and drug-level (Figure 14) analyses. All of the interventions except fumaric acid esters appeared superior to placebo in terms of showing significant improvement on a quality-of-life scale. Anti-IL23, anti-IL12/23, anti-IL17 and anti-TNF agents 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-IL23 and anti-TNF alpha (anti-IL23 was more favourable than anti-TNF alpha). There were no significant differences between the small molecules and the conventional agents. Results of comparisons between each of the drugs are available in Figure 14.

Ranking class-level analysis(Figure 8; Figure 10; Table 4)

Ranking analysis for quality of life performed with SUCRA strongly suggested that anti-IL23 was the best treatment at class level (versus placebo: standardised mean difference (SMD) −1.41, 95% confidence interval (CI) −1.64 to −1.18; SUCRA = 91.3), followed by anti-IL17 (versus placebo: SMD −1.29, 95% CI −1.60 to −0.99; SUCRA = 78.1), anti-IL12/23 (versus placebo: SMD −1.29, 95% CI −1.57 to −1.01; SUCRA = 77.6), then anti-TNF alpha (versus placebo: SMD −1.06, 95% CI −1.22 to −0.91 SUCRA = 52.2). The heterogeneity τ for this network overall was 0.14, which we considered low heterogeneity.

Ranking drug-level analysis(Figure 9; Figure 11; Table 5)

Ranking analysis for quality of life performed with SUCRA strongly suggested that risankizumab was the best treatment at drug level (versus placebo: SMD −1.76, 95% CI −2.15 to −1.36; SUCRA = 97.3), followed by ixekizumab (versus placebo: SMD −1.57, 95% CI −1.87 to −1.28; SUCRA = 91.5), ustekinumab (versus placebo: SMD −1.35, 95% CI −1.60 to −1.11; SUCRA = 77.3), tildrakizumab (versus placebo: SMD −1.35, 95% CI −1.69 to −1.01; SUCRA = 76), then infliximab (versus placebo: SMD −1.31, 95% CI −1.59 to −1.02; SUCRA = 73.1). The heterogeneity τ for this network overall was 0.09, which we considered low heterogeneity. Moreover, five interventions (acitretin, ciclosporin, oral tyrosine kinase 2 inhibitor, bimekizumab and 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 almost half of the population included in the NMA, so has to be considered with cautious.

2.4 The proportions of participants with adverse effects

DIRECT EVIDENCE

We report treatment estimates for pair-wise meta-analyses at class 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 93 trials, involving 41,913 participants (89% of the participants in this review). AEs were not reported for the 20 remaining trials, and we were not able to obtain missing information from the trial authors (Table 2). This outcome was also reported in six trials out of 113 (Asahina 2016; Bissonnette 2015; Khatri 2016; Mrowietz SCULPTURE 2015; Ortonne 2013; Strohal PRISTINE 2013), comparing different dosages of the same drug, and were added to the sensitivity analyses at dose level. Fifty-five trials, involving 20,245 participants, were placebo-controlled trials; 16, involving 5136 participants, were head-to-head comparisons; and 22, involving 16,532 participants, had both a placebo and at least two active treatments arms.

See Figure 4; Figure 5; Figure 6; Figure 13; Figure 8; Figure 9; Figure 10; Figure 11

We present the summary relative effects from the network meta-analysis in league tables for both class-level (Figure 6) and drug-level (Figure 13) analyses. All of the interventions had a more significant risk of AEs compared to placebo, except anti IL23. Significant associations were found: anti-IL17 had a higher risk of

AE compared with anti-IL23 and anti-IL12/23; anti-IL23 also had a lower risk of AE compared with anti-IL12/23, anti-TNF, small molecules and conventional systemic agents (Figure 6). Results of comparisons between each of the drugs are available in Figure 13.

Ranking class-level analysis(Figure 8; Figure 10; Table 4)

Ranking analysis for AEs performed with SUCRA strongly suggested that anti-IL23 was associated with the best safety profile for all adverse events (versus placebo: RR 0.95, 95% CI 0.89 to 1.01; SUCRA = 98.9), followed by placebo (SUCRA 83.9), anti-IL12/23 (versus placebo: RR 1.06, 95% CI 1.00 to 1.12; SUCRA = 60.1), then anti-TNF agents (versus placebo: RR 1.07, 95% CI 1.03 to 1.12; SUCRA = 54.3). The heterogeneity τ for this network overall was 0.01, which we considered low heterogeneity.

Ranking drug-level analysis(Figure 9; Figure 11; Table 5)

Ranking analysis for AEs performed with SUCRA strongly suggested that tildrakizumab was associated with the best safety profile for all adverse events (versus placebo: RR 0.86, 95% CI 0.77 to 0.96; SUCRA = 97.5), followed by guselkumab (versus placebo: RR 0.99, 95% CI 0.90 to 1.08; SUCRA = 83.1), placebo (SUCRA = 81.5), then risankizumab (versus placebo: RR 1.00, 95% CI 0.89 to 1.11; SUCRA = 79.6). The heterogeneity τ for this network overall was 0, which we considered low heterogeneity.

2.5. Proportion of participants who achieve PASI 90 at 52 weeks

DIRECT EVIDENCE

We report treatment estimates for pair-wise meta-analyses at drug level in Analysis 7.1; and Analysis 7.2.

Six head-to-head comparisons compared two different biologics; one compared two different dosages of apremilast. One meta-analysis was done for the comparison risankizumab versus ustekinumab. For reaching PASI 90 at 52 weeks, risankizumab was more effective than ustekinumab (RR 1.73, 95% CI 1.46 to 2.05). Secukinumab was more effective than ustekinumab to reach PASI 90 at 52 weeks (RR 1.24, 95% CI 1.11 to 1.38; 1 study); guselkumab was more effective than adalimumab to reach PASI 90 at 52 weeks (RR 1.59, 95% CI 1.40 to 1.81; 1 study) and ixekizumab every other week was more effective than ixekizumab every four weeks to reach PASI 90 at 52 weeks (1RR 1.06, 95% CI 1.01 to 1.11; 1 study).

2.6. Proportion of participants who achieve PASI 75 at 52 weeks

DIRECT EVIDENCE

We report treatment estimates for pair-wise meta-analyses at drug level in Analysis 8.1; and Analysis 8.2

Six head-to-head comparisons compared two different biologics; two compared two different dosages of apremilast and tofacitinib respectively. One meta-analysis was done for the comparison risankizumab versus ustekinumab. For reaching PASI 75 at 52 weeks, risankizumab was more effective than ustekinumab (RR 1.26, 95% CI 1.12 to 1.41). Secukinumab was more effective than ustekinumab to reach PASI 75 at 52 weeks (RR 1.17, 95%CI 1.10 to 1.26; 1 study); guselkumab was more effective than adalimumab to reach PASI 75 at 52 weeks (RR 1.40, 95% CI 1.28 to 1.54; 1 study) and ixekizumab every other week was more effective than ixekizumab every four weeks to reach PASI 75 at 52 weeks (RR 1.14, 95% CI 1.07 to 1.22; 1 study).

We did not conduct network meta-analyses, given the low number of studies for this outcome.

3. Assessment of heterogeneity and inconsistency

We did not identify important heterogeneity either in direct meta-analyses or in network meta-analysis. The common outcome-specified network heterogeneity and the prediction intervals suggested the presence of low heterogeneity for all outcomes. 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 close.

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 15; Figure 16).

Figure 15. Distributions of age (on the left, mean age in years in the y axis) and sex (on the right, percentage of males in the y axis) ratio of participants across comparisons (x axis) ACI: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; TYK2: Oral Tyrosine kinase 2 inhibitor; USK: ustekinumab

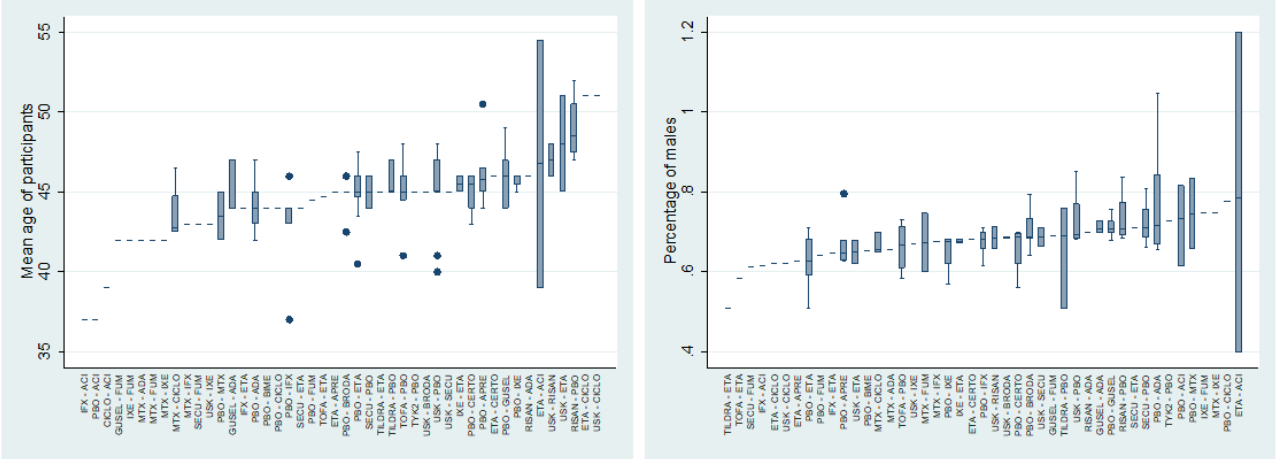
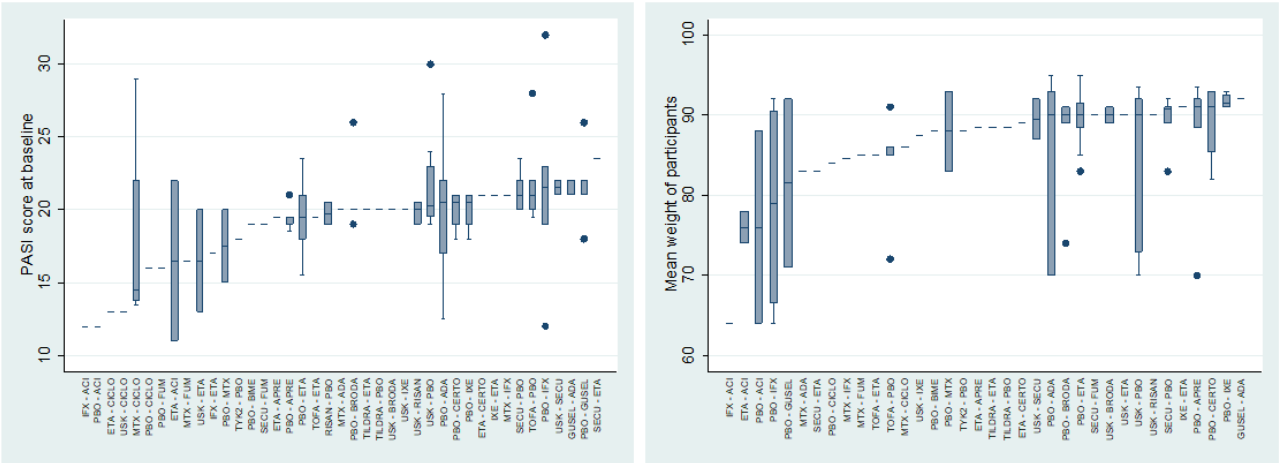


Figure 16. Distributions of PASI score at baseline (on the left, mean PASI in the y axis) and weight (on the right, mean weight in kilograms in the y axis) of participants across comparisons (x axis) ACI: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; TYK2: Oral Tyrosine kinase 2 inhibitor; USK: ustekinumab



At drug-level analysis, the global test for inconsistency was not significant for any of the outcomes, and only marginally significant for PASI 90. We detail results of a global test for inconsistency at drug level in Figure 17 and Figure 18 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 19; Figure 20). This apparent inconsistency does not however generally exceed 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 17. Side-splitting approach and design-by-treatment interaction model for inconsistency for Psoriasis Area and Severity Index (PASI) 90 ACI: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; TYK2: Oral Tyrosine kinase 2 inhibitor; USK: ustekinumab

PASI 90

Side	Direct		Indirect		Difference		
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P>|z|
PBO RISAN	3.376259	.1966839	3.292319	.1294273	.0839403	.2560835	0.743
PBO SECU	3.154642	.1991119	3.182079	.1001543	-.0274367	.2169311	0.899
PBO USK	2.922483	.151185	2.799309	.1113584	.1231735	.1904174	0.518
ADA PBO	-2.665699	.1545377	-3.051301	.1374233	.3856018	.2100233	0.066
ADA GUSEL	.3732129	.0469157	.3000086	.3346898	.0732043	.3389811	0.829
ADA MTX	-1.050948	.2513474	-.3359161	.1940472	-.7150317	.3123615	0.022
ADA RISAN	.4245993	.0701418	.5311186	.1711875	-.1065193	.1850001	0.565
APRE ETA	.3277468	.3430595	.219194	.4385798	.1085528	.5513739	0.844
BRODA USK	-.2375821	.0456174	-.7065097	.3957342	.4689276	.4002738	0.241
CERTO ETA	-.1831134	.1478518	-.6324912	.4969234	.4493779	.5189768	0.387
ETA PBO	-2.357324	.1386608	-2.185459	.1443359	-.1718651	.215583	0.425
ETA IFX	2.219212	1.008226	1.067485	.1988856	1.151728	1.027655	0.262
ETA IXE	1.068732	.0706785	1.042882	.1195703	.0258499	.1392204	0.853
ETA SECU	.8494574	.1157985	.9294124	.0821701	-.079955	.1420092	0.573
ETA TILDRA	.5708143	.1198175	.4725273	.4357813	.098287	.453671	0.828
ETA TOFA	-.1221352	.1004496	-.4196338	.2269361	.2974986	.2482517	0.231
ETA USK	.5889477	.1102207	.5585992	.0782817	.0303485	.135191	0.822
FUM PBO	-1.497381	.4083435	-1.235821	.2231036	-.2615599	.4653167	0.574
FUM GUSEL	1.795572	.3343536	2.038996	.2405286	-.2434231	.4118815	0.555
FUM IXE	1.541839	.358333	2.194015	.215859	-.6521757	.3932579	0.097
FUM MTX	1.696626	.3622712	.4775371	.3041461	1.219089	.4796976	0.011
FUM SECU	2.117976	.3450446	1.776644	.2290401	.341332	.4141439	0.410
GUSEL PBO	-3.368583	.2355262	-3.109483	.2774319	-.2590996	.4646451	0.577
IFX PBO	-3.752858	.4976311	-3.313989	.2186097	-.438869	.5435319	0.419
IFX MTX	-1.050419	.1449713	-1.685737	.4749783	.6353176	.4966096	0.201
IXE PBO	-3.480348	.1869103	-3.262029	.128287	-.2183183	.2406874	0.364
IXE MTX	-.7424199	.1822878	-1.575543	.2333096	.8331229	.2927942	0.004
IXE USK	-.5459573	.1049271	-.4499703	.0950505	-.095987	.1415778	0.498
MTX PBO	-.4686349	.3928452	-2.739014	.1837038	2.270379	.4497867	0.000
RISAN USK	-.4967916	.075995	-.3813978	.1687677	-.1153938	.1856281	0.534
SECU USK	-.3349898	.0352209	-.3195978	.1249839	-.015392	.1298518	0.906

P value of the design-by-treatment interaction model = 0.04

Figure 18. Side-splitting approach and design-by-treatment interaction model for inconsistency for serious adverse events (SAEs) ACI: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; TYK2: Oral Tyrosine kinase 2 inhibitor; USK: ustekinumab

SAE

Side	Direct		Indirect		Difference		
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P>|z|
PBO RISAN	-.7838557	.3452753	-.2028395	.3762536	-.5810162	.5286786	0.272
PBO SECU	.0991379	.2813605	.1358982	.323711	-.0367603	.4318368	0.932
PBO USK	-.0379048	.2428809	-.2034592	.2649986	.1655544	.3603988	0.646
ADA PBO	-.1686071	.2388568	.7615629	.488625	-.9301701	.5488668	0.090
ADA GUSEL	-.0910082	.3575384	.2424628	.5973536	-.333471	.7065003	0.637
ADA MTX	-.7214003	1.198857	-.8309632	.4728347	.1095628	1.2795	0.932
ADA RISAN	.1152776	.452216	-.8975744	.3630478	1.012852	.5799164	0.081
APRE ETA	-.3880408	.8126577	.130619	.3710999	-.5186598	.8942127	0.562
BRODA USK	-.2785358	.414084	.0230302	.4901786	-.301566	.6953316	0.665
CERTO ETA	.8644725	.96265	-.15633	.6439452	1.020802	1.268321	0.421
CICLO PBO	-1.739434	1.465376	.9603128	1.463886	-2.699746	2.071301	0.192
CICLO MTX	.0232739	1.406142	-2.676514	1.52089	2.699788	2.071324	0.192
ETA PBO	.2811794	.2329321	-.3343255	.3932763	.6155049	.4673228	0.188
ETA IFX	-.0833812	1.384382	.2414432	.3816079	-.3248244	1.436014	0.821
ETA IXE	.0283888	.3315718	.4526733	.3940003	-.4242845	.5217221	0.416
ETA SECU	.4315781	.6086117	.1784533	.3038429	.2531248	.6845701	0.712
ETA TILDRA	-.3565891	.487021	.5908308	.728923	-.94742	.8926144	0.289
ETA TOFA	-.1364121	.4693372	.3266025	.4184433	-.4630146	.6323015	0.464
ETA USK	.2217033	.6085386	-.0401834	.2643794	.2618866	.6634876	0.693
FUM PBO	.187565	.4998103	-.1379612	.4803056	.3255262	.6931839	0.639
FUM GUSEL	.3886572	.8942684	-.1146286	.4900371	.5032858	1.019732	0.622
FUM IXE	-1.035592	1.106149	.2934196	.4373224	-1.329012	1.195809	0.266
FUM MTX	-1.048171	.9648268	-.7322068	.5745872	-.3159644	1.119254	0.778
FUM SECU	-.0792492	.6929404	.2224552	.448719	-.3017044	.8255394	0.715
GUSEL PBO	-.0243328	.3838693	.1159576	.6412835	-.1402905	.7977957	0.860
IFX PBO	-.1656544	.3685871	.0817198	.6368488	-.2473742	.7358212	0.737
IFX MTX	-.881491	.4280319	-1.072366	.6740749	.1908746	.7984911	0.811
IXE PBO	-.0897302	.3049204	-.0913583	.4278232	.0016282	.5553048	0.998
IXE MTX	1.71e-09	1.401058	-1.03231	.4819991	1.03231	1.48165	0.486
IXE USK	-.6047977	.514199	-.0582819	.3097982	-.5465157	.6003129	0.363
MTX PBO	1.566716	.7920383	.5829949	.4621463	.9837207	.9168337	0.283
RISAN USK	.6115894	.3415955	.1388889	.3845089	.4727005	.5145102	0.358
SECU USK	-.2346298	.3051128	-.2216835	.3225208	-.0129463	.4439747	0.977

P value of the design-by-treatment interaction model = 0.38

Figure 19. 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; PBO: placebo; SM: small molecules

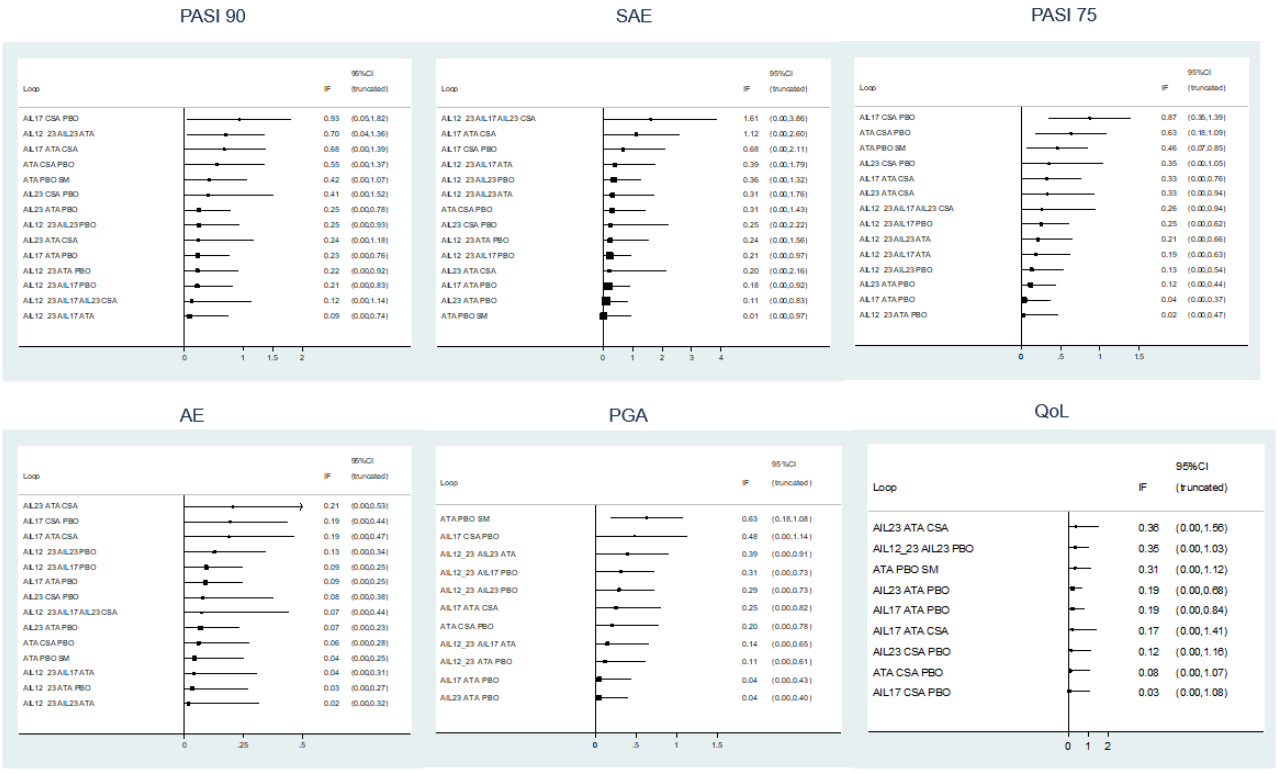
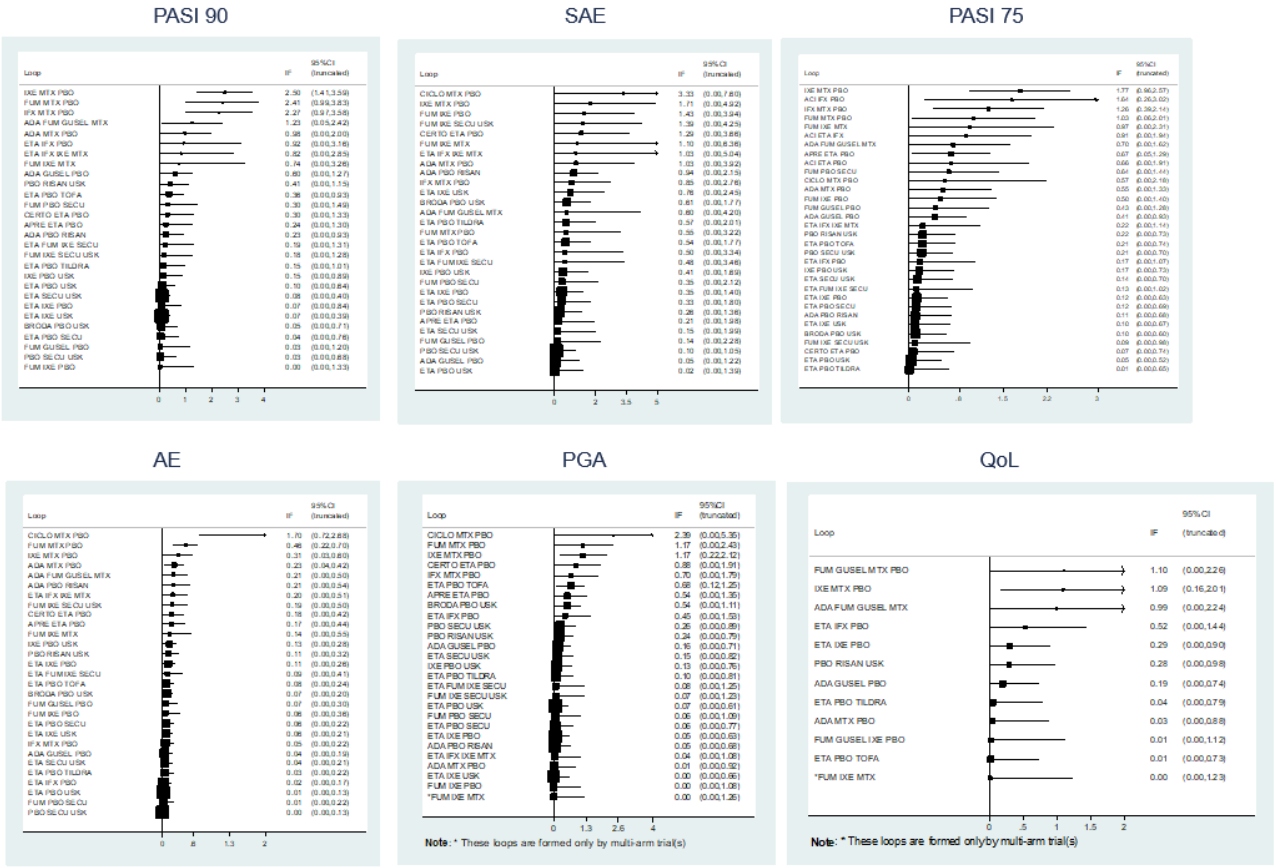


Figure 20. Inconsistency plots for all the outcomes at drug level Inconsistency factor (IF) is calculated as the risk ratio (RR)/standardised mean difference (SMD) for direct evidence over the RR/SMD for indirect evidence in the loop with its 95% confidence interval (CI). IF value close to 0 indicates the absence of evidence for disagreement between direct and indirect ACI: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; TYK2: Oral Tyrosine kinase 2 inhibitor; USK: ustekinumab



A possible explanation for this apparent inconsistency could be the differences between the previous treatment lines allowed across these trials: for example, participants enrolled in the Saurat CHAMPION 2008 or Barker RESTORE-1 2011 trials (adalimumab versus methotrexate versus placebo and infliximab versus methotrexate, respectively) were naïve to methotrexate and TNF-alpha antagonists, whereas participants enrolled in the Menter REVEAL 2008 or Menter EXPRESS-II 2007 trials (adalimumab versus placebo and infliximab versus placebo) could have received previous systemic treatment including methotrexate. These points were also verified for NCT02634801 and NCT02951533 POLARIS trials (participants were naïve to methotrexate and biological treatments).

We confirmed our hypothesis by performing a sensitivity analysis excluding trials with systemic-treatment-naïve participants (see: 4. subgroup and sensitivity analyses).

4. Subgroup and sensitivity analyses

We did not have enough data for any of the aforementioned characteristics that may act as effect modifiers, and were therefore unable to run subgroup analyses and meta-regressions to investigate their potential effects 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 fewer than 50 participants (Figure 21) (the heterogeneity τ for this subgroup network was 0 for PASI 90 and SAEs, which we considered low heterogeneity);
- completers (Figure 22) (the heterogeneity τ for this subgroup network was 0 for PASI 90 and SAEs, which we considered low heterogeneity);
- analyses at dose level (Figure 23) (the heterogeneity τ for this subgroup network was 0 for PASI 90 and SAEs, which we considered low heterogeneity);
- excluding studies at high risk of bias (Figure 24) (the heterogeneity τ for this subgroup network was 0 for PASI 90 and 0.01 for SAEs, which we considered low heterogeneity);
- analysing only the studies with a short-term assessment from 12 to 16 weeks (Figure 25): the heterogeneity τ for this subgroup network was 0 for PASI 90 and 0.01 for SAEs, which we

considered low heterogeneity. The global test for inconsistency for the subset analysis was not significant for PASI 90 (P value of the design-by-treatment interaction model = 0.28 versus 0.04 for the main analysis), but the loop-specific approach still indicated a loop with statistically significant inconsistency: Adalimumab-methotrexate-placebo related to Saurat CHAMPION 2008 trial (see: 3. assessment of heterogeneity and inconsistency);

- analysing excluding trials with systemic-treatment-naïve participants (Figure 26): the heterogeneity τ for this subgroup network was 0 for PASI 90 and SAEs, which we considered low heterogeneity. The global test for inconsistency for the subset analysis was not significant for PASI 90 (P value of the design-by-treatment interaction model = 0.77 versus 0.04 for the main analysis) and no loop with statistically significant inconsistency. Thus, we identified the source of the apparent inconsistency. When we took into account this point (i.e. when we excluded the naïve participants), the results did not change.

Figure 21. 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; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; TYK2: Oral Tyrosine kinase 2 inhibitor; USK: ustekinumab CI: confidence interval; PASI: Psoriasis Area and Severity Index; RR: risk ratio; SAE: serious adverse events

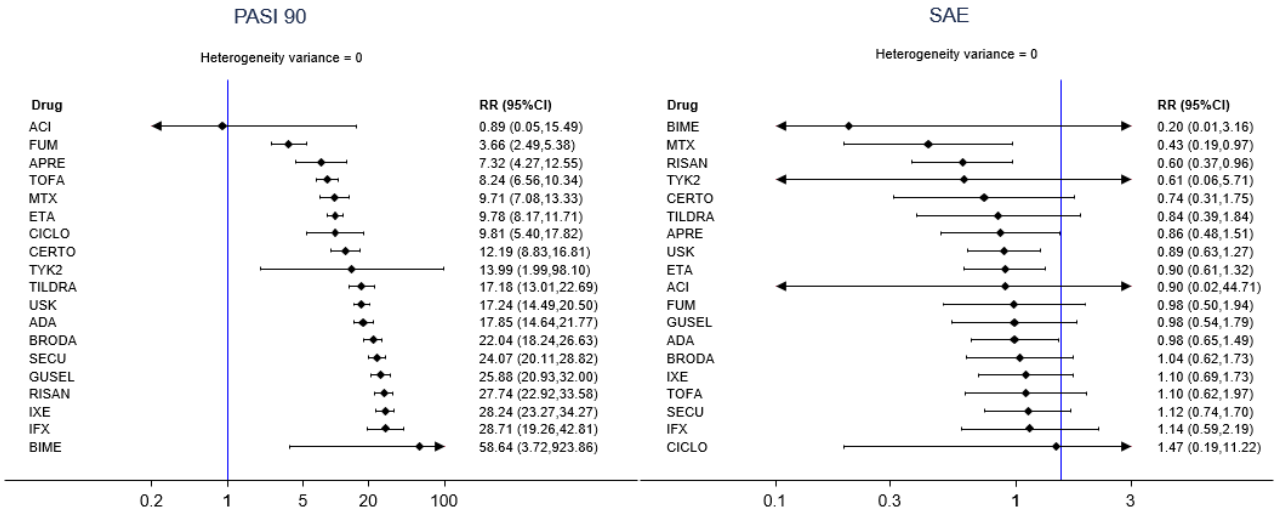


Figure 22. Sensitivity analyses - Interval plot. Network meta-analysis results for primary outcomes (PASI 90 and serious adverse events) for the completers. Outcomes were measured at the induction phase (assessment from 8 to 24 weeks after randomisation). ACI: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; TYK2: Oral Tyrosine kinase 2 inhibitor; USK: ustekinumab CI: confidence interval; PASI: Psoriasis Area and Severity Index; RR: risk ratio; SAE: serious adverse events

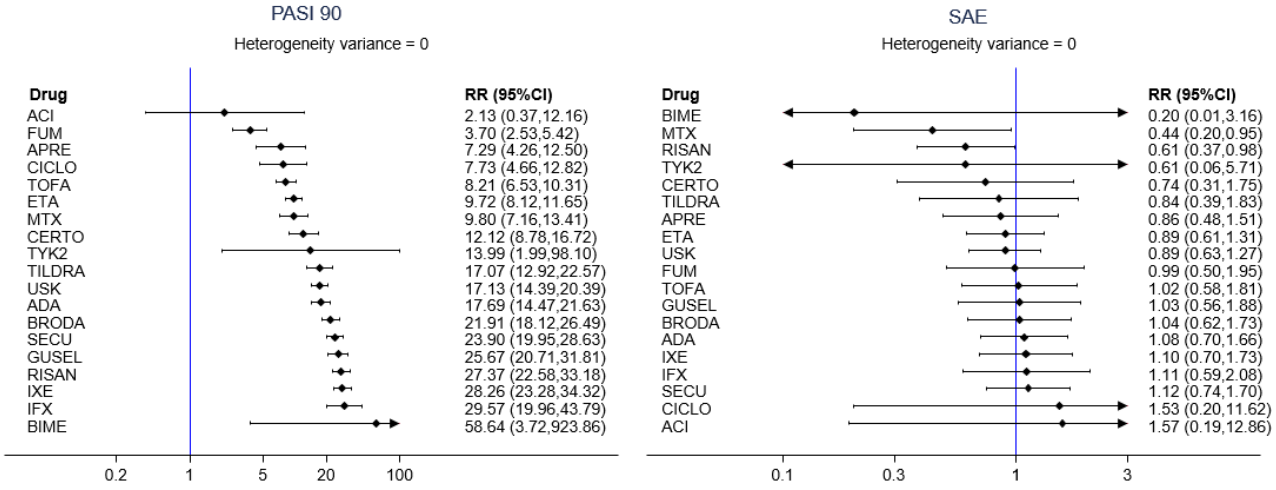


Figure 23. Sensitivity analyses - Interval plot. Network meta-analysis results for primary outcomes (PASI 90 and serious adverse events) for all the interventions depending on the doses Outcomes were measured at the induction phase (assessment from 8 to 24 weeks after randomisation). MTX_AMM/Other: methotrexate ≥ 15 mg per week/ < 15 mg per week; CICLO_AMM/Other: ciclosporin ≥ 3 mg/kg/day/<3 mg/kg/day; ACI_AMM/Other: acitretin ≥ 35 mg per day/<35 mg per day; FUM: fumaric acid esters all dosages; APRE_AMM/Other: apremilast 30 mg twice daily/ other dosages; TOFA_AMM/Other: tofacitinib 20 mg per day/Other dosages; ETA_AMM/Other: etanercept 50 mg twice a week/Other dosage; IFX_AMM/Other: infliximab 5 mg/kg week 0, 2, 4 every 6 weeks/Other dosages; ADA_AMM/ Other: adalimumab 80 mg Week 0, 40 mg Week 1 then 40 mg every other week/Other dosages; CERTO_AMM/Other: certolizumab 400 mg at week 0,2,4 then 400 mg every other week or other dosages/Other dosages; USK 45/90: ustekinumab 45/90 mg; SECU_AMM/Other: secukinumab 300 mg at week 0, 1, 2, 3, and 4 then every 4 weeks or other dosages/other dosages; IXE_AMM/Other: ixekizumab 160 mg at Week then 80 mg every other weeks until week 12 then 80 mg monthly or other dosages; TILDRA_AMM/Other: tildrakizumab 100 mg at week 0 and 4 then every 12 weeks/Other dosages; GUSEL 100: guselkumab 100 mg per injection; BRODA_AMM/Other: brodalumab 210 mg at week 0, 1, 2 then every other weeks/other dosages; RISAN_AMM/Other: risankizumab, S/C, 150 mg (two 75 mg injections) at Week 0, Week 4 and every 12 weeks thereafter/other dosages; TYK2 (Oral Tyrosine kinase 2 inhibitor) and BIME (bimekizumab) (S/C) were grouped in one dosage whatever the dosages. CI: confidence interval; PASI: Psoriasis Area and Severity Index; RR: risk ratio; SAE: serious adverse events

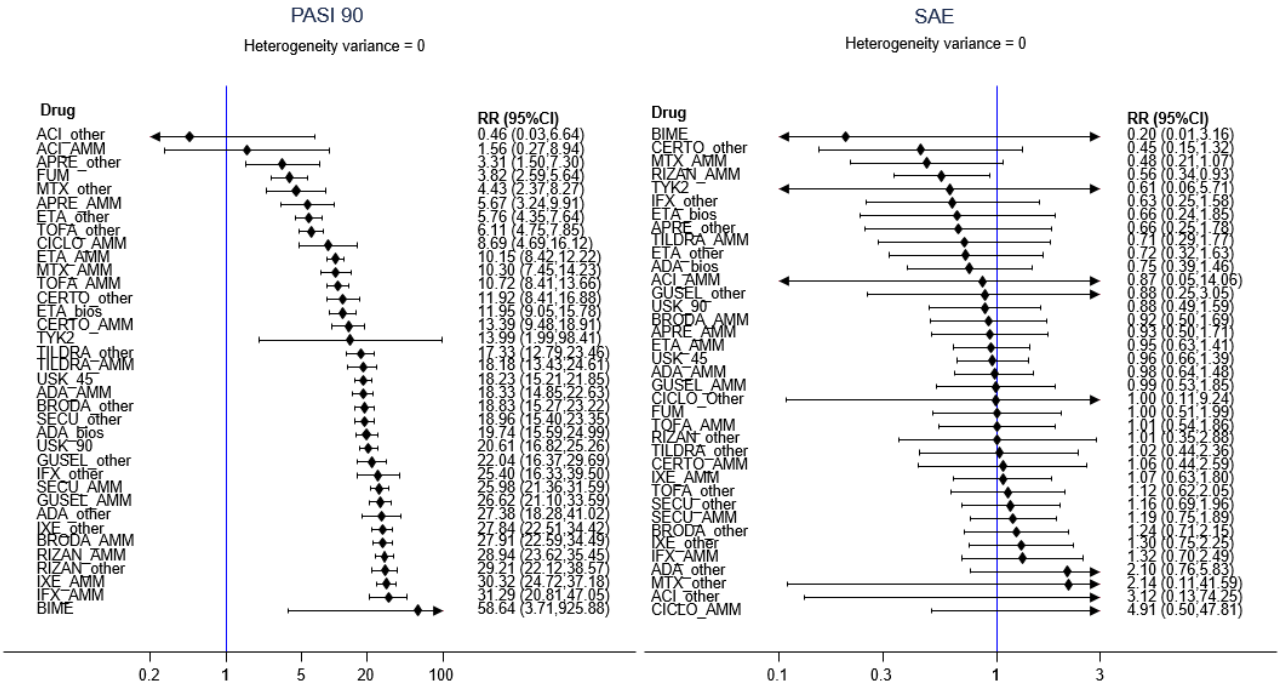


Figure 24. Sensitivity analyses - Interval plot. Network meta-analysis results for primary outcomes (PASI 90 and serious adverse events) for all the interventions excluding studies at high risk of bias. Outcomes were measured at the induction phase (assessment from 8 to 24 weeks after randomisation). ACI: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; TYK2: Oral Tyrosine kinase 2 inhibitor; USK: ustekinumab CI: confidence interval; PASI: Psoriasis Area and Severity Index; RR: risk ratio; SAE: serious adverse events

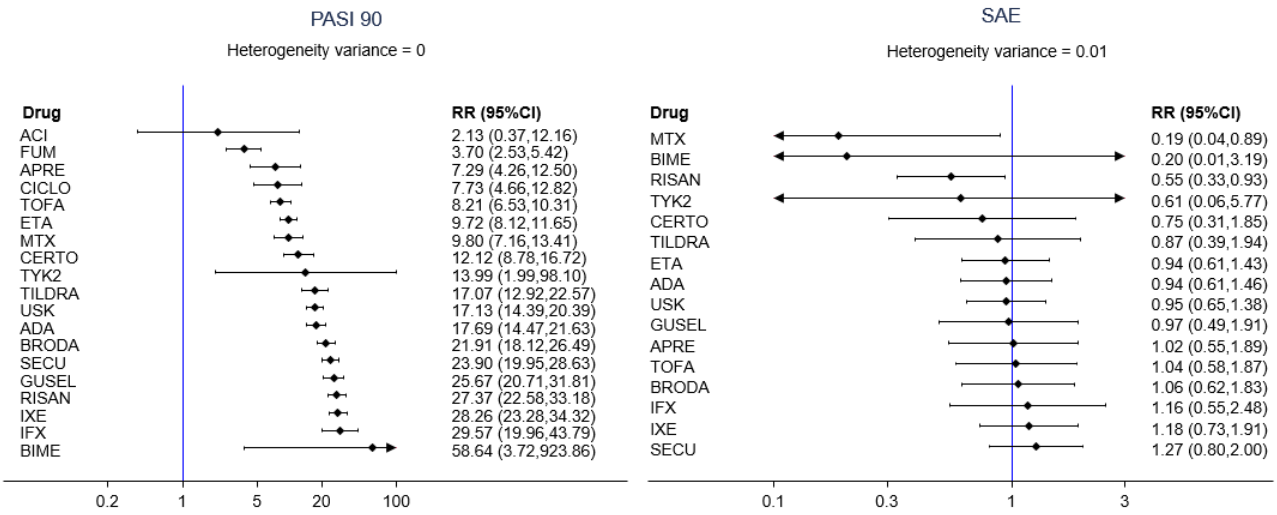


Figure 25. Sensitivity analyses - Interval plot. Network meta-analysis results for primary outcomes (PASI 90 and serious adverse events) for all the interventions including studies with a short-term assessment from 12 to 16 weeks. ACI: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; TYK2: Oral Tyrosine kinase 2 inhibitor; USK: ustekinumab CI: confidence interval; PASI: Psoriasis Area and Severity Index; RR: risk ratio; SAE: serious adverse events

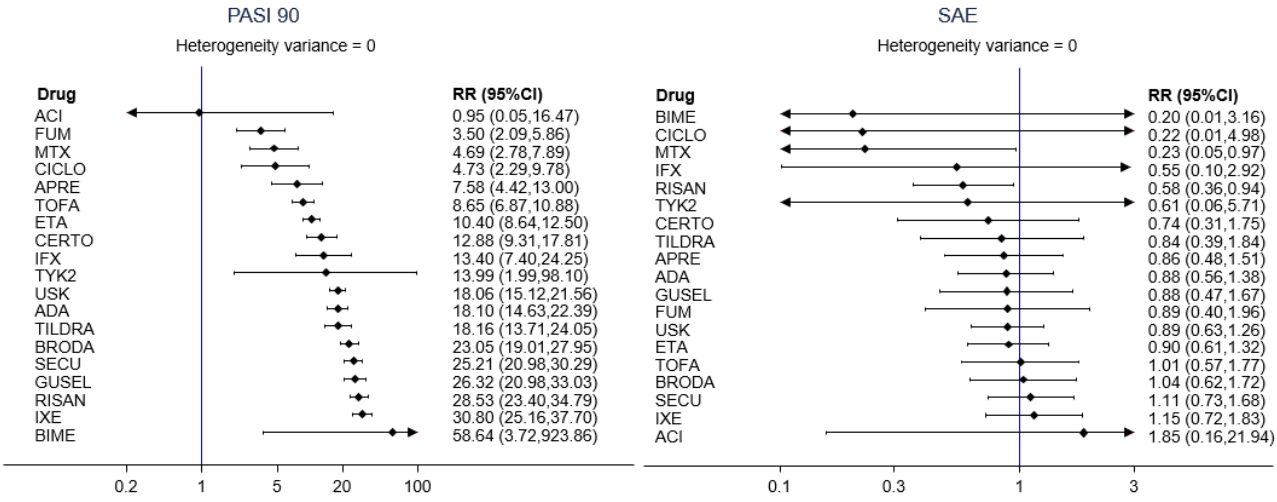
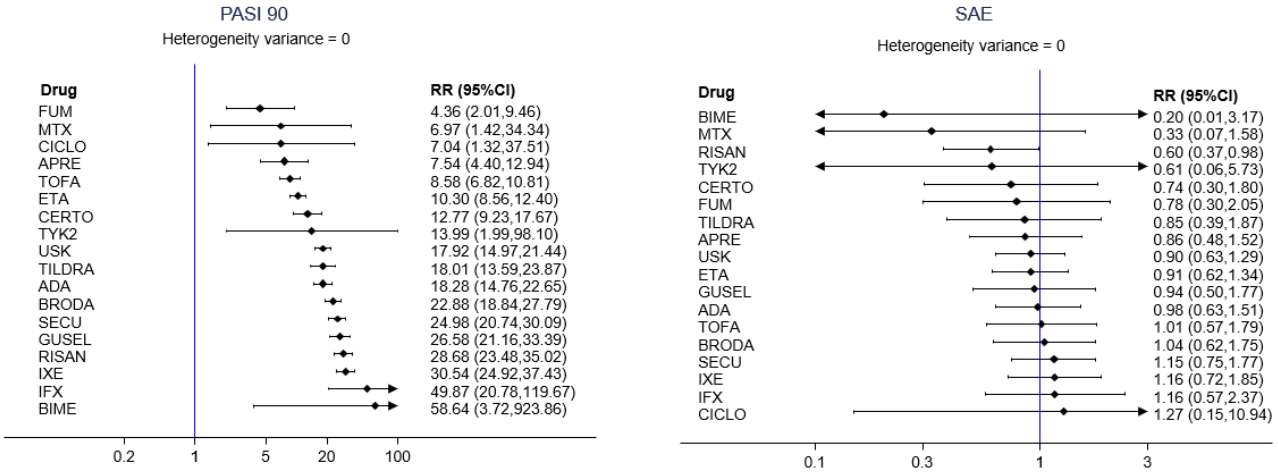


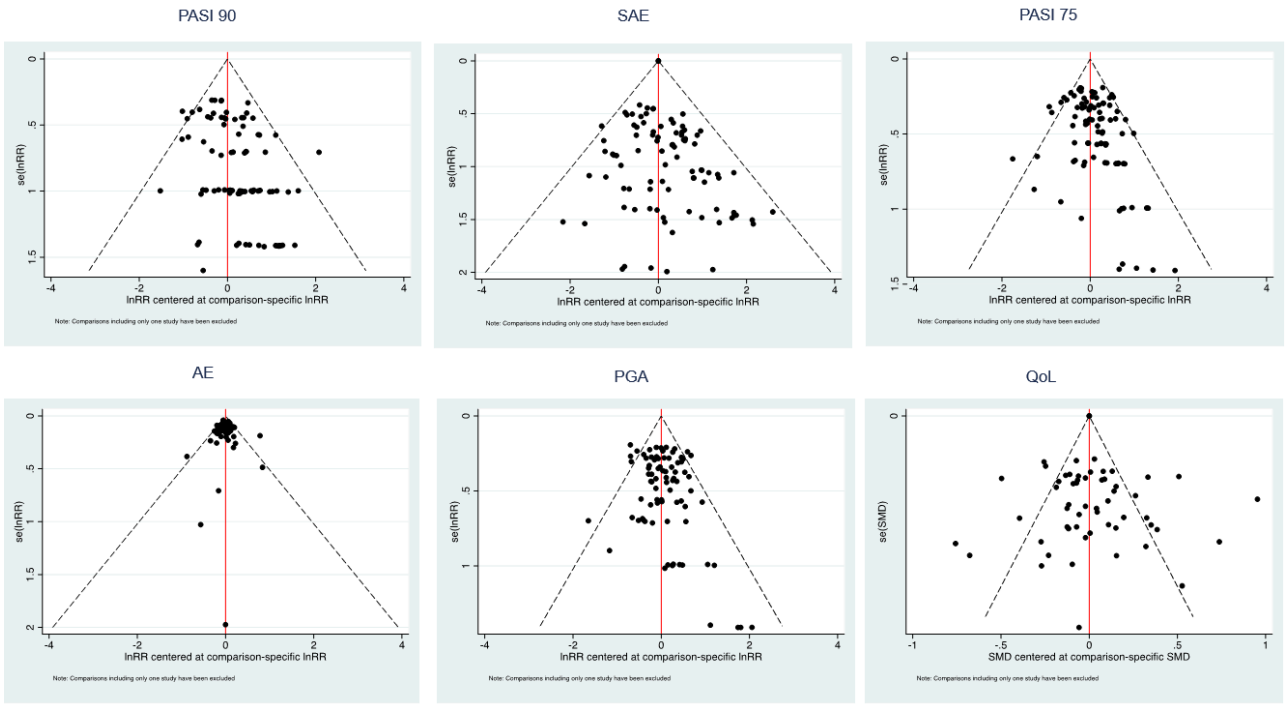
Figure 26. Sensitivity analyses - Interval plot. Network meta-analysis results for primary outcomes (PASI 90 and serious adverse events) for all the interventions excluding studies with systemic treatment-naive participants. Outcomes were measured at the induction phase (assessment from 8 to 24 weeks after randomisation). ACI: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; TYK2: Oral Tyrosine kinase 2 inhibitor; USK: ustekinumab CI: confidence interval; PASI: Psoriasis Area and Severity Index; RR: risk ratio; SAE: serious adverse



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 27). As the funnel plots were symmetrical, we did not consider meta-regression.

Figure 27. Funnel plot for network meta-analysis of all the outcomes AE: adverse event; lnRR: 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

1. Using GRADE

For PASI 90, we judged confidence in the treatment estimate to be high for risankizumab, secukinumab, ustekinumab and tildrakizumab; moderate for brodalumab, guselkumab (reasons for downgrading: study limitations), adalimumab (inconsistency), etanercept (study limitations), apremilast (study limitations), brodalumab (study limitations), certolizumab (study limitations), infliximab (inconsistency) and ixekizumab (inconsistency); and low or very low for all of the other treatments (bimekizumab, oral tyrosine kinase 2 inhibitor, methotrexate, tofacitinib, acitretin, ciclosporin, fumaric acid esters). More detail on the reasons for downgrading are available in Summary of findings 1.

For serious adverse events, we judged the confidence in the treatment estimate to be moderate certainty for almost all of the treatment (downgrading linked to imprecision for all 'moderate certainty' drugs): methotrexate, risankizumab, tildrakizumab, etanercept, ustekinumab, guselkumab, adalimumab, tofacitinib, brodalumab, ixekizumab, infliximab, secukinumab. No treatment was estimate to be at high level of certainty. More detail on the reasons for downgrading are available in Summary of findings 2.

2. Using CiNEMA

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 six domains: within-study bias (referring to the impact of risk of bias in the included studies), across-studies bias (publication or reporting bias), indirectness (relevance to the research question and transitivity), imprecision (comparing the range of treatment effects included in the 95% confidence interval with the range of equivalence), heterogeneity (predictive intervals) and incoherence (if estimates from direct and indirect evidence disagree). We present the results in Table 7; Table 8. They were consistent with the GRADE approach.

DISCUSSION

Summary of main results

Our review and meta-analysis compares all systemic pharmacological drugs and drugs undergoing phase II/III trials used for moderate-to-severe psoriasis in 2019.

This updated review included 140 studies, involving 51,749 randomised adult participants, which assessed outcomes during the induction phase (from 8 to 24 weeks after randomisation). Participants in the included studies were young, with a mean age of 45 years, and had moderate-to-severe psoriasis with an overall mean PASI score at baseline of 20. Eighty-two trials compared systemic treatment against placebo, 41 were head-to-head trials, and 17 had both an active comparator and a placebo. Fourteen trials had a co-intervention, mainly phototherapy. Seven trials assessed biosimilars versus original drugs for adalimumab or etanercept. Finally, 107 studies declared pharmaceutical company funding, and 22 studies did not report the source of funding.

We included 113 studies (without co-intervention and without trials in biosimilar development), involving 47,085 participants (91% of the participants in this review), in the network meta-analysis (NMA). 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); anti-IL17 treatments (secukinumab, ixekizumab, brodalumab); and anti-IL23 (guselkumab, tildrakizumab, risankizumab) have all been approved for psoriasis, except for bimekizumab and mirikizumab (but mirikizumab was not assessed by any included trial). Apart from apremilast, small molecule drugs (tofacitinib, tyrosine kinase 2 inhibitor (BMS-986165)), had not been approved for psoriasis at the time we conducted our analyses.

The following results are based on network meta-analysis.

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-IL23, anti-IL12/23, and anti-TNF alpha outperformed the small molecules and the conventional systemic agents to reach PASI 90.

For reaching PASI 90, the most effective drugs when compared to placebo were infliximab (moderate-certainty evidence), ixekizumab (moderate-certainty evidence), risankizumab (high-certainty evidence), bimekizumab (low-certainty evidence), guselkumab (moderate-certainty evidence), secukinumab (high-certainty evidence), and brodalumab (moderate-certainty evidence); see Summary of findings 1. The clinical effectiveness for these drugs was similar.

At drug level, all of the anti-IL17 drugs (ixekizumab, secukinumab, bimekizumab, and brodalumab) and the anti-IL23 drugs (risankizumab and guselkumab) except for tildrakizumab were significantly more effective in reaching PASI 90 than ustekinumab and three anti-TNF alpha agents: adalimumab, certolizumab, and etanercept.

Only one trial assessed the efficacy of bimekizumab in this network, so the results for bimekizumab have to be interpreted with caution. Adalimumab and ustekinumab were significantly more effective in reaching PASI 90 than certolizumab and etanercept. There was no significant difference between tofacitinib or apremilast and two conventional drugs: ciclosporin and methotrexate. The results were almost the same for the other efficacy outcomes (PASI 75 and PGA 0/1), but we found fewer differences between biologics: there was no statistically significant difference between anti-IL17 (ixekizumab, bimekizumab, secukinumab and brodalumab), anti-IL23 (risankizumab, guselkumab and tildrakizumab), infliximab and ustekinumab.

We found no significant difference between any of the interventions and the placebo for the risk of serious adverse effects (SAEs). Methotrexate (moderate-certainty evidence), bimekizumab (low-certainty evidence), risankizumab (moderate-certainty evidence), certolizumab (low-certainty evidence), oral tyrosine kinase 2 inhibitor (low-certainty evidence), and tildrakizumab (moderate-certainty evidence) were associated with the best safety profile for all the SAEs (see Summary of findings 2).

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

Finally, considering both efficacy (PASI 90 outcome) and acceptability (SAE outcome), highly-effective treatments also had

more SAEs than the other treatments, and risankizumab and bimekizumab 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 under 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 45 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 those who need a first-line systemic treatment. In addition, participants selected for randomised controlled trials (RCTs) generally have few major comorbidities. Almost all studies including one biological arm excluded patients with a 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 participant characteristics (such as being overweight, imbalanced sex ratio in favour of men, presence of metabolic syndrome) were reflective of a moderate-to-severe psoriasis population, comparable to literature data (Wolkenstein 2009).

Interventions

Evidence on 19 active treatments included in this review was derived from 113 trials (searched for up to January 2019). We included all interventions, irrespective of the dose. Thus, we increased the number of available RCTs for each intervention and had more power to assess SAEs and adverse events (AEs). The number of studies included in the NMA was still low for the following interventions: bimekizumab, tyrosine kinase 2 inhibitor, acitretin, ciclosporin, fumaric acid esters, and methotrexate, meaning we must be cautious about the conclusions drawn for these drugs. The results from the subgroup analysis using a standard dose for each intervention was similar for PASI 90 (and SAEs) compared to the main analyses, making us confident in the results of the main analysis.

For drugs just approved or not yet approved for psoriasis, ongoing studies are still investigating bimekizumab, a fourth and new anti-IL23 (mirikizumab, which we will include in the living review), risankizumab, brodalumab, ixekizumab, and BMS-986165 (Characteristics of ongoing studies).

Comparisons

Most studies included in the review were only placebo-controlled (around 60%). 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 provide evidence for the proportion of participants who reached PASI 90, PASI 75, or Physician Global Assessment (PGA) 0/1 or who experienced SAEs or AEs. We chose PASI 90 as the main efficacy outcome. The differences in PASI 90 rates must be balanced against the differences in quality-of-life improvements that are observed. Results for both outcomes cannot be correlated. On the other hand, patient-reported outcome (PRO) data were scanty and poorly reported in our review. Moreover, the heterogeneity of the scales used for PRO in psoriasis trials required use of the standardised mean difference in the NMA. 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. Results for SAEs have to be interpreted cautiously, because RCTs do not last long enough and are not powered to be able to detect rare and severe adverse events. We did not summarise individual SAE types or classes of SAE in this review, in part because classification differed across different data sources. This is the subject of a separate detailed assessment of types of SAE, adverse events leading to discontinuation of trial medication, and system-organ class adverse events (Afach 2019).

Timing

All of the trials included in the NMAs assessed the efficacy of the different treatments during the induction treatment phase (from 8 to 24 weeks). Assement of longer-term outcomes may also be relevant for this 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. It is therefore 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 also to evaluate non-randomised studies and postmarketing reports released from regulatory agencies.

Quality of the evidence

Overall, our confidence in the treatment estimates for PASI 90 is high or moderate for anti-IL17 agents (except bimekizumab), anti-IL12/23 agents, anti-IL23 agents, anti-TNF alpha agents, and small molecules (except tyrosine kinase 2 inhibitor and tofacitinib). We judged our confidence in treatment estimates for PASI 90 as low or very low certainty for the comparisons involving conventional systemic agents; we downgraded the certainty of the evidence for risk of bias and then either for inconsistency or imprecision. We judged our confidence in the treatment estimates for SAEs to be low to very low certainty for almost half of the treatment estimates, and moderate for the others; we downgraded the certainty of the evidence for imprecision and risk of bias.

Overall, we rate our confidence in the treatment estimates 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 judge our confidence in treatment estimates 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 for risk

of bias and then either for inconsistency or imprecision. We judge our confidence in the treatment estimates for SAEs to be low to very low certainty for half of the treatment estimates, and moderate for the others; we downgraded the certainty of the evidence for imprecision and risk of bias.

Risk of bias

The risks of bias in the included studies appear to be globally low (Figure 2; Figure 3). However, some limitations should be discussed.

- There was variation in how well the studies took measures to blind investigators and participants: a third of trials in this review were rated at high or unclear risk of performance bias (39 out of 140). 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 22% (25 out of 113).
- 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, we minimised the risk of overestimating efficacy due to how we reported missing data.
- Finally, we rated a few trials 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 pair-wise 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 assure a sufficiently coherent evidence base (Cipriani 2013). The limitations of this review are reflected by the GRADE and CINeMA evaluations.

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

We found no evidence of heterogeneity either in direct comparisons or in the entire networks. At drug-level analysis, the global test for inconsistency was not significant for any of the outcomes, and only marginally significant for PASI 90. According to the local tests for PASI 90, a handful of loops and comparisons which do not exceed the expected level of inconsistency from empirical evidence (Veroniki 2013), appeared to have important inconsistency. We therefore downgraded the strength of evidence for inconsistency for methotrexate, adalimumab, infliximab, and ixekizumab. We hypothesised that inconsistency could be related to the previous treatment lines allowed (or not) across some trials. For RCTs comparing biologics and conventional systemic agents, participants were naïve to systemic treatments, whereas they could have received previous lines of systemic therapies for the other RCTs. We confirmed our hypothesis by performing a sensitivity analysis excluding trials of systemic-treatment-naïve participants. The results for PASI 90 and SAEs did not change from the main analysis, but without any inconsistency (P value of the design-by-treatment interaction model = 0.77).

Imprecision

The number of studies included in the NMA was low for the following interventions (one or two studies for each interventions): bimekizumab, tyrosine kinase 2 inhibitor, acitretin, ciclosporin, fumaric acid esters, 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 15; Figure 16). However, the lack of data did not allow us to check the distributions of previous treatments across comparisons, so transitivity cannot properly be assessed statistically.

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 to treatment could be related to genetic background (Chiu 2014). To further confirm the plausibility of the transitivity assumption, we only included in our analyses trials not involving co-interventions, and performed several sensitivity analyses (see Quality of the evidence: Heterogeneity).

Publication bias

We assessed publication bias, considering the comprehensive search strategy we performed and the risk of 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 (Figure 27).

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 US Food and Drug Administration and the European Medicines Agency 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 10 studies have not yet been incorporated may be a potential source of bias.

We conducted study selection, data extraction, and 'Risk of bias' assessments 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 risks of bias, especially those 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 or results, or both.

We had some departures from the protocol plans (see Differences between protocol and review):

- we included new interventions and excluded others as they are no longer used as systemic treatments for psoriasis. We will add new interventions to the search strategy for the living searches;
- we added two new outcomes to assess efficacy during the maintenance phase;
- we kept all the trials with a short-term outcome assessment from 8 to 24 weeks (induction phase) for the NMA and did not systematically exclude trials with an assessment shorter than 12 or over 16 weeks, as we had done in the previous review.

Thus, to assess the transitivity assumption, we added two new sensitivity analyses: (1) including only trials with an assessment from 12 to 16 weeks, and (2) excluding trials of systemic-treatment-naïve participants.

We used two different methods to assess our confidence in the results by comparisons (GRADE and CINeMa), and found no major discrepancies.

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. Ten network meta-analyses were systematically reviewed and have compared the short-term efficacy of treatments for moderate-to-severe psoriasis (Geng 2018; Gómez-García 2017; Gupta 2014; Jabbar-Lopez 2017; Lin 2012; Loos 2018; Reich 2012b; Schmitt 2014; Signorovitch 2015; Xu 2019).

We compared our findings with the five most recent network meta-analyses (Geng 2018; Gómez-García 2017; Jabbar-Lopez 2017; Loos 2018; Xu 2019). Gómez-García 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 Gómez-García 2017, plus ixekizumab (another anti-IL17 agent) and methotrexate. Loos 2018 included 34 trials, involving 22,892 participants, assessing biologic treatments (infliximab, adalimumab, etanercept, ustekinumab, secukinumab, ixekizumab and brodalumab) and apremilast. As Geng 2018 and Xu 2019 included systemic treatments withdrawn from the market (briakinumab and efalizumab), we did not investigate these two reviews in detail.

Compared to previous reviews, we included more interventions and consequently more trials (n = 140) and participants (n = 51,749). Regarding the overlapping period between the different NMAs, 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.

Gómez-García 2017 presented both PASI 75 and PASI 90 results. 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 for patient expectations 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 with PASI 75 and not with PASI 90, which could lead to a classification bias (Robinson 2012). Loos 2018 presented PASI 50, 75, and 90 results.

Jabbar-Lopez 2017 presented their results using the number needed to treat for an additional beneficial outcome (NNTB). Although NNTB 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 head-to-head studies without a control group, as here.

Infliximab was also the most effective drug in Gómez-García 2017, without significant difference between infliximab and secukinumab. Infliximab was ranked in third place after ixekizumab and secukinumab in Jabbar-Lopez 2017, without a significant difference between infliximab and secukinumab. Infliximab was ranked in third place after ixekizumab and brodalumab in Loos 2018, without a significant difference between these three drugs and secukinumab (4th rank). Our findings were close to these results, but also included anti-IL23 agents (risankizumab and guselkumab were among the six biological medicines working best at clearing psoriasis lesions).

Among the previous network meta-analyses, Loos 2018 did not assess inconsistency, and two reported significant global and local inconsistency for PASI 75 (Gómez-García 2017; Jabbar-Lopez 2017).

AUTHORS' CONCLUSIONS

Implications for practice

In terms of achieving PASI 90 with induction therapy (evaluation from 8 to 24 weeks after the randomisation), we found the following results, based on network meta-analysis.

- At class level, all of the assessed interventions (conventional systemic agents, small molecules, and biological treatments) showed significant superiority compared with placebo;
- At class level, the biologic treatments anti-IL17, anti-IL12/23, anti-IL23, and anti-TNF alpha showed significant superiority compared with small molecules and conventional systemic agents, with small molecules achieving better results than conventional systemic agents;
- All of the anti-IL17 agents (ixekizumab, secukinumab, bimekizumab, and brodalumab) and the anti-IL23 agents (risankizumab and guselkumab) except for tildrakizumab were significantly more effective than all of the anti-TNF alpha agents, except for infliximab (i.e. certolizumab, adalimumab, and etanercept), and the anti-IL12/23 ustekinumab. Adalimumab and ustekinumab were significantly more effective in reaching PASI 90 than certolizumab and etanercept;
- When compared with placebo, the following biological agents are the best choices for reaching PASI 90: infliximab (moderate-certainty evidence), ixekizumab (moderate-certainty evidence), risankizumab (high-certainty evidence), bimekizumab (low-certainty evidence), guselkumab

(moderate-certainty evidence), secukinumab (high-certainty evidence) and brodalumab (moderate-certainty evidence). The clinical effectiveness of these seven drugs was similar.
- There was no significant difference between tofacitinib or apremilast and two conventional drugs: ciclosporin and methotrexate.

Regarding the other efficacy outcomes (PASI 75 and PGA0/1), the results were very similar to the results for PASI 90.

For serious adverse events, there was no significant difference between any of the assessed interventions and placebo.

The surface under the cumulative ranking curve (SUCRA) suggested that methotrexate (moderate-certainty evidence), bimekizumab (low-certainty evidence), risankizumab (moderate-certainty evidence), certolizumab (low-certainty evidence), oral tyrosine kinase 2 inhibitor (low-certainty evidence), and tildrakizumab (moderate-certainty evidence) may be associated with the best safety profile, based on all the SAEs.

Nonetheless, analyses of SAE events were based on a very low number of events with a low to very low certainty for just under half of the treatment estimates, and moderate for the others. The findings therefore have to be viewed with caution. Considering both efficacy (PASI 90 outcome) and acceptability (SAE outcome), highly effective treatments also had more SAEs than the other treatments: risankizumab and bimekizumab appeared to be the better compromise between efficacy and acceptability.

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

Conservative interpretation is warranted for the results for bimekizumab, tyrosine kinase 2 inhibitor, acitretin, ciclosporin, fumaric acid esters, and methotrexate, as these drugs in the NMA have been evaluated in few trials.

The evidence is limited to a selected trial population (participants were young (mean age of 45 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 (all results were measured from 8 to 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) do not reflect the 'real life' management of patients in Europe or Canada, as an example. Currently, biological treatments may be 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, so the question of the choice of 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 on 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 still needed.
- **Comparators**: once the benefit of a treatment has been established against placebo, only head-to-head trials would be helpful to provide physicians with efficacy estimates between the different biologics, with stronger evidence than indirect comparisons. Head-to-head comparisons are lacking between the conventional systemic agents and small molecules and against each other. 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 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 (from 8 to 24

weeks). Long-term efficacy data are 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 permit dose adjustment once in remission, switching, and additional treatments (i.e. adding two or more systemic treatments) as in 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 require both efficacy AND safety data. As we already know, the limitations of network meta-analysis and of randomised clinical trials (included in these meta-analyses) mean we cannot reliably interpret the significance of rare events, given their current design. 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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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Akcali 2014

Study characteristics	
Methods	RCT, active-controlled, open-label trial Date of study: January 2008 - January 2009 Location: Gaziantep, Turkey (1 centre)
Participants	**Randomised**: 55 participants (mean age 39 years, 33 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 10) **Exclusion criteria** None **Dropouts and withdrawals** • 9/55 (16.4%) • AEs: 5 • Other reason: 4
Interventions	**Intervention** A. Acitretin (n = 25), orally, 0.3 - 0.5 mg/kg/d **Control intervention** B. Cyclosporin (n = 21), orally, 3 mg/kg/d
Outcomes	Assessment at 8 weeks **Primary outcome of the trial** • Not stated **Outcomes of the trial**

Akcali 2014 *(Continued)*

- PASI score
- Adverse effects

Notes	Funding source: Quote (p 1121): "No specific grant" Declarations of interest: Quote (p 1121): "The authors declare that there are no conflicts of interest."

Risk of bias

Bias	Authors' judgement	Support for judgement
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
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 (muco cutaneous 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

Study characteristics

Methods	RCT, active-placebo controlled, open-label trial Date of study: February 2010 - October 2011 Location: Baghdad, Iraq (1 centre)
Participants	**Randomised**: 120 participants (mean age 41 years, 41 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (BSA > 10%) • Age ≥ 18 and ≤ 60 years **Exclusion criteria** • Pregnancy, kidney insufficiency, liver insufficiency, past history of malignant tumours

Al-Hamamy 2014 *(Continued)*

- Had received conventional systemic treatments in the 4 past weeks
- Had received biologics (anti-TNFα)
- Had uncontrolled diabetes

Dropouts and withdrawals

- 7 (6%)

No more statements regarding time and reasons of follow-up

Interventions	**Intervention** A. Methotrexate + NBUVB (n = 38), 20 mg/week + 45 mJ/cm^2, 3 times/week **Control intervention** B. NBUVB (n = 38), 45 mJ/cm^2, 3 times/week C. Methotrexate (n = 37), 20 mg/week
Outcomes	Assessment at 6 months **Primary outcomes of the trial** • PASI 90 **Secondary outcomes of the trial** • Number of weeks for achieving clearance • Total cumulative dose of UVB • Relapses (PASI returning at 50% of original score for 1 year)
Notes	Funding: not stated Declarations of interest: none

Risk of bias

Bias	Authors' judgement	Support for judgement
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

Al-Hamamy 2014 *(Continued)*

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

Asahina 2010

Study characteristics	
Methods	RCT, active, placebo-controlled, double-blind Date of study: September 2005 - December 2006 Location: 42 centres in Japan
Participants	**Randomised**: 169 participants (mean age 45 years, 143 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12, BSA > 10) • Age > 20 years **Exclusion criteria** • Pregnancy, immunosuppression, kidney insufficiency, liver insufficiency, past history of malignancy • Had received biologics • Had an active infection **Dropouts and withdrawals** • 22 (13%) (A/B/C/D) • 10 AEs (2/3/2/3) • 10 withdrawals of consent (2/4/2/2) • 1 worsening disease (D) • 1 prohibited medication (C)
Interventions	**Intervention** A. Adalimumab (n = 38), 40 mg, SC, eow B. Adalimumab (n = 43), 40 mg, SC, 2 injections, week 0, 1 injection eow (week 2) C. Adalimumab (n = 41), 80 mg, SC, eow **Control** D. Placebo (n = 46), 0.8 mL, SC, eow
Outcomes	Assessment at 16 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • PASI 50 • PASI 90 • PGA clear or minimal • DLQI

Asahina 2010 *(Continued)*

	• SF36
Notes	Funding: support by Abbott (Quote p 309) Declarations of interest: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p 301): "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 (p 301): "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 but considering that this was a placebo-controlled trial with no known systematic AEs we considered the risk as low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 169, analysed 169 Management of missing data: Quote (p 302): "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 judgement
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available. The outcomes mentioned in the Methods section appeared to have been reported

Asahina 2016

Study characteristics

Methods	RCT, active-controlled, double-blind Date of study: March 2012 - January 2014 Location: 16 centres in Japan
Participants	**Randomised**: 95 participants, 94 treated (mean age 49 years, 78 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12, PGA 3 - 4 or BSA ≥ 10), age ≥ 20 years) • Patients were to be considered candidates for systemic therapy or phototherapy for psoriasis (either treatment-naïve or -experienced) **Exclusion criteria**

Asahina 2016 *(Continued)*

- Not plaque-type psoriasis
- Inability to discontinue systemic, topical or phototherapies, concomitant oral or injectable corticosteroids
- Active infection, history of disseminated herpes zoster or disseminated herpes simplex or recurrent localised dermatomal herpes zoster, a history of infection requiring hospitalisation or parenteral microbial therapy
- Any uncontrolled significant medical condition

Dropouts and withdrawals

- 6/95 (6.3%); tofacitinib 5 mg twice/d group (0), tofacitinib 10 mg twice-daily group (6)
- Not received study medication; tofacitinib 10 mg twice-daily group (1)
- AEs: tofacitinib 10 mg twice-daily group (1)
- Lack of efficacy: tofacitinib 10 mg twice-daily group (1)
- Withdrawal of consent: tofacitinib 10 mg twice-daily group (1)
- Other reason:**t**ofacitinib 10 mg twice-daily group (2)

Interventions	**Intervention** A. Tofacitinib (n = 43), orally, 5 mg twice daily **Control intervention** B. Tofacitinib (n = 44), orally, 10 mg twice daily
Outcomes	Assessment at 16 weeks **Primary outcomes of the trial** • PASI 75 and PGA rating of clear or almost clear **Secondary outcomes of the trial** • PASI 50 • PASI 90 • Itch severity item score • Mean DLQI score • AEs
Notes	Funding source: Quote (p 878): "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 (p 878): "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."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 870): "Patients were randomized 1:1 to tofacitinib 5 or 10 mg b.i.d. using a computer-generated randomization schedule". Comment: probably done

Asahina 2016 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote (p 870): "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 (p 870): "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
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 870): "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 (p 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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Asawanonda 2006

Study characteristics	
Methods	RCT, active placebo-controlled, double-blind Date of study: not reported Location: Bangkok, Thailand, Asia
Participants	**Randomised**: 24 participants (mean age 40 years (methotrexate) 48 years (placebo), 15 male) **Inclusion criteria** • Participants with moderate-severe plaque type psoriasis (BSA ≥ 20) **Exclusion criteria**

Asawanonda 2006 *(Continued)*

	• Pregnancy, immunosuppression, alcohol abuse **Dropouts and withdrawals** • 4 (17%) • Time and reasons: conflicts in schedule (1 methotrexate group, 3 placebo group)
Interventions	**Intervention** A. Methotrexate (n = 11), 15 mg/week, orally **Control** B. Placebo (n = 13), orally Co-intervention: phototherapy UVB
Outcomes	Assessment at 24 weeks **Primary outcomes of the trial** • PASI 90 **Secondary outcomes of the trial** • Time to relapse after clearance
Notes	Funding: (quote p 1013) no funding source Declarations of interest: (quote p 1013) "None identified"

Risk of bias

Bias	Authors' judgement	Support for judgement
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, analysed 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.

Bachelez 2015

Study characteristics	
Methods	RCT, active placebo-controlled, double-blind Date of study: 29 November 2010 - 13 September 2012 Location: 122 worldwide excluding the USA and Canada
Participants	**Randomised**: 1106 participants (mean age 46 years, 458 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12, PGA 3 - 4 or BSA ≥ 10), age ≥ 18 years, failed to respond to, had a contraindication to, or were intolerant to at least 1 conventional systemic treatment **Exclusion criteria** • Not plaque-type psoriasis • Active infection, and any uncontrolled significant medical condition • Had previously been treated or had a contraindication to etanercept, had previously not responded to treatment with any tumour necrosis factor inhibitors, had previously participated in studies involving tofacitinib **Dropouts and withdrawals** • 86/1106 (7.8%); tofacitinib 5 mg group (24), tofacitinib 10 mg twice-daily group (26), etanercept group (23), placebo group (13) • Not received study medication; tofacitinib 5 mg twice-daily group (1), tofacitinib 10 mg twice-daily group (2), etanercept group (1), placebo group (1) • AEs: tofacitinib 5 mg twice-daily group (3), tofacitinib 10 mg twice-daily group (11), etanercept group (12), placebo group (4) • Lack of efficacy: tofacitinib 5 mg twice-daily group (5), tofacitinib 10 mg twice-daily group (2), etanercept group (2), placebo group (3) • Lost to follow-up: tofacitinib 5 mg twice-daily group (1), tofacitinib 10 mg twice-daily group (2), etanercept group (2), placebo group (2) • Withdrawal of consent: tofacitinib 5 mg twice-daily group (6), tofacitinib 10 mg twice-daily group (4), etanercept group (2), placebo group (2) • Other reason:**t**ofacitinib 5 mg twice-daily group (8), tofacitinib 10 mg twice-daily group (5), etanercept group (4), placebo group (1)
Interventions	**Intervention** A. Tofacitinib (n = 330), orally, 5 mg twice daily **Control intervention** B. Tofacitinib (n = 332) orally, 10 mg twice daily C. Etanercept (n = 336) SC, 50 mg twice weekly D. Placebo (n = 108)
Outcomes	Assessment at 12 weeks **Primary outcomes of the trial** • PASI 75 and PGA rating of clear or almost clear **Secondary outcomes of the trial**

Bachelez 2015 *(Continued)*

- PASI 50
- PASI 90
- Itch severity item score
- Mean DLQI score
- AEs

Notes	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, Schülke and Mayr, Lohmann & Rauscher, Meda Pharmaceuticals, Menarini Pharmaceuticals, Stockhausen, and Smith & Nephew; has had consulting agreements with Pfizer, Novartis, Lohmann & Rauscher, Urgo, Chemomedica, Schülke & Mayr, and Pantec Biotechnologies; and has received research and educational grants from Stockhausen, 3M-Woundcare, Smith & Nephew, Lohmann & Rauscher, Enjo Commercials, Urgo, Chemomedica, and Schülke & 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."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 553): "A computer-generated randomization schedule was used to assign patients to the treatment groups". Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (pp 553-4): "The study site contacted an interactive voice response system or web-based interactive response system..." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	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
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 (p 554): "The primary analysis population for efficacy was the full analysis set, which was defined as all patients who re-

Bachelez 2015 *(Continued)*

		ceived 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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported.

Bagel 2012

Study characteristics	
Methods	RCT, placebo-controlled, double-blind Date of study: not stated Location: North America
Participants	**Randomised**: 124 participants (median age 39 years (etanercept) and 42 years (placebo), 69 male) **Inclusion criteria** • Participants with moderate-severe psoriasis: ≥ 30% of scalp surface area affected (PASI > 10, BSA > 10) • Age > 18 years **Exclusion criteria** • Had past history of malignant tumours in the past 5 years, had an active infection, had a significant medical problem **Dropouts and withdrawals** • 26/124 (21%) • Not received study treatment: etanercept (3), placebo (0) • AEs: etanercept (5), placebo (0) • Withdrawal of consent: etanercept (1), placebo (5)
Interventions	**Intervention** A. Etanercept (n = 62), SC, 50 mg, twice a week **Control intervention** B. Placebo (n = 62), SC, twice a week
Outcomes	Assessment at 12 weeks **Primary outcomes of the trial** • % change in PSSI score **Secondary outcomes of the trial** • % change in PSSI score at 24 weeks for group B • Proportion PSSI at 12 weeks

Bagel 2012 *(Continued)*

- Participant satisfaction
- AEs
- PASI 50/75/90 improvement through 24 weeks
- Proportion PGA 0 or 1
- Mean PASI improvement from baseline

Notes	Funding: Amgen Inc Declarations of interest (Quote p 86): "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."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 87): "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 (p 87): "Each patient provided written informed consent and received a unique identification number and randomised assignment from an Interactive Web Response System" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 87): "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 **Dropouts and withdrawals** • 26/124 (21%) • Not received study treatment; etanercept (3), placebo (0) • AEs; etanercept (5), placebo (0) • Withdrawal of consent; etanercept (1), placebo (5) Quote (p 89): "included in ITT efficacy analysis" Management of missing data:

Bagel 2012 *(Continued)*

		Quote (p 88): "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

Bagel CLARITY 2018

Study characteristics	
Methods	RCT, active-controlled, double-blind study Date of study: July 2016 - July 2018 Location: worldwide Phase 3
Participants	**Randomised: 1102 participants** (mean age 46 years, 458 male) **Inclusion criteria** • Must give a written, signed and dated informed consent • Chronic plaque-type psoriasis present for ≥ 6 months before randomisation • Moderate-severe plaque psoriasis as defined at randomisation by: PASI score of ≥ 12 and Body Surface Area (BSA) affected by plaque-type psoriasis ≥ 10% and IGA mod 2011 ≥ 3 (based on a scale of 0 - 4) • Candidate for systemic therapy, defined as having psoriasis inadequately controlled by: topical treatment (including topical corticosteroids) or phototherapy, or previous systemic therapy, or both **Exclusion criteria** • Forms of psoriasis other than plaque psoriasis • Drug-induced psoriasis • Ongoing use of prohibited treatments • 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 • Use of any other investigational drugs within 5 half-lives of the investigational treatment before study drug initiation • Pregnant or nursing (lactating) women **Dropouts and withdrawals** • 35/1102 (7.8%); secukinumab group (18), ustekinumab group (17) • AEs: secukinumab group (6), ustekinumab group (4) • Other reason: secukinumab group (12), ustekinumab group (13)
Interventions	**Intervention** A. Secukinumab 300 (300 mg, SC at randomisation, weeks 1, 2 and 3 and thereafter 4-weekly till week 48), n = 550 **Control intervention** B. Ustekinumab 45/90 (45 mg or 90 mg SC based on participant's weight (at randomisation visit) to be administered at randomisation, week 4, 16, 28 and 40), n = 552

Bagel CLARITY 2018 *(Continued)*

Outcomes	**Assessment at week 12** **Primary composite outcome** • IGA 0/1 • PASI 90 **Secondary outcomes** • PASI 75 at week 12 and 52 • PASI 90 at week 52 • AEs
Notes	Funding source Quote (p 572): "Funding: Novartis Pharma AG, Basel, Switzerland." Declarations of interest: Quote (p 578): Disclosures. Jerry Bagel is an investigator and/or consultant and/or speaker for AbbVie, Amgen, Boehringer-Ingelheim, Janssen, Leo, Novartis, Celgene, Eli Lilly, Sun, and Valiant. Manmath Patekar is an employee of Novartis Pharma AG, Basel, Switzerland. Ana de Vera is an employee of Novartis Pharma AG, Basel, Switzerland. Sophie Hugot is an employee ofNovartis Pharma AG, Basel, Switzerland. Isabelle Gilloteau is an employee of Novartis Pharma AG, Basel, Switzerland. Elisa Muscianisi is an employee of Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA. Kuan Sheng is an employee of Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA. Summer Xia is an employee of Beijing Novartis Pharma Co. Ltd, Shanghai, China. Andrew Blauvelt has served as a scientific consultant and clinical study investigator for AbbVie, Aclaris, Akros, Allergan, Almirall, Amgen, Boehringer Ingelheim, Celgene, Dermavant, Dermira, Eli Lilly and Company, Galderma, Genentech/Roche, GlaxoSmithKline, Janssen, Leo, Meiji, Merck Sharp & Dohme, Novartis, Pfizer, Purdue Pharma, Regeneron, Revance, Sandoz, Sanofi Genzyme, Sienna Pharmaceuticals, Sun Pharma, UCB, Valeant, and Vidac and as a paid speaker for Janssen, Regeneron, and Sanofi Genzyme. Mark Lebwohl is an employee of Mount Sinai which receives research funds from AbbVie, Boehringer Ingelheim, Celgene, Eli Lilly, Incyte, Janssen/Johnson & Johnson, Leo Pharmaceuticals, Medimmune/Astra Zeneca, Novartis, Pfizer, Sciderm, UCB, Valeant, and Vidac. Mark Lebwohl is also a consultant for Allergan, Aqua, Boehringer-Ingelheim, LEO Pharma, Menlo, and Promius. John Nia and Peter W. Hashim have nothing to disclose.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p 572): "CLARITY (NCT02826603) is a multicenter, randomized, double-blinded, active-controlled, parallel-group, phase 3b trial. Eligible patients were randomized 1:1 to receive either..." 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 572): “CLARITY (NCT02826603) is a multicenter, randomized, double-blinded, active-controlled” Comment: probably done
Blinding of outcome assessment (detection bias)	Low risk	Quote (p 572): “CLARITY (NCT02826603) is a multicenter, randomized, double-blinded, active-controlled”

Bagel CLARITY 2018 *(Continued)*

All outcomes		Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 1102 Management of missing data: Quote (p 573): "Missing values were handled by multiple imputation except for DLQI 0/1, where missing values were handled using last observation carried forward." Table 2: 1101 analysed participants Comment: done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02826603). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Barker RESTORE-1 2011

Study characteristics	
Methods	RCT, active-controlled, open-label trial Date of study: September 2005 - June 2008 Location: 106 centres in Europe
Participants	**Randomised**: 868 participants (mean age 43 years, 586 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12, BSA > 10) • Age ≥ 18 years and ≤ 75 • Non-response to topical treatment **Exclusion criteria** • Immunosuppression, kidney insufficiency, liver insufficiency • Had received conventional systemic treatments (methotrexate) • Had received biologics • Had an active infection • Had uncontrolled cardiovascular disorder • Had past history of malignant tumours **Dropouts and withdrawals** • 71/868 (8%) • Infliximab (58), methotrexate (13) Reasons not stated at week 16
Interventions	**Intervention** A. Infliximab (n = 653), IV, 5 mg/kg, weeks 0, 2, 6, 14, 22 **Control intervention** B. Methotrexate (n = 215), orally, 15 mg/week for 22 weeks

Barker RESTORE-1 2011 *(Continued)*

Outcomes	Assessment at 16 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • PASI 90 • PGA 0/1 • PASI 50 • DLQI • SF36
Notes	Funding: financial support for this study was provided by Schering-Plough Research Institute, now Merck, Sharp & Dohme Corporation, Whitehouse Station, NJ, USA 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 & Dohme. H.v.H. was an employee of Merck, Sharp & 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."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 1110): “At each eligible subject's baseline visit, study centres telephoned the Interactive Voice REsponse Syste .... for randomisation" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 1110): “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 (p 1110): “open-label trial” Comment: no blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (p 1110): “open-label trial” Comment: no blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 868, analysed 868 Quote (p 1110-11): "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

Barker RESTORE-1 2011 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00251641). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Bissonnette 2013

Study characteristics	
Methods	RCT, placebo-controlled, single-blind Date of study: May 2009 - June 2011 Location: Montréal, Quebec, Canada (5 centres)
Participants	**Randomised**: 30 participants (median age 56 years (adalimumab) and 57 years (placebo), 23 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (BSA > 5) • Age ≥ 18 years and ≤ 80 • Non-response to topical treatment **Exclusion criteria** • Immunosuppression, kidney insufficiency • Had an active infection, had uncontrolled cardiovascular disorder, had uncontrolled diabetes, had uncontrolled hypertension, had past history of malignant tumours **Dropouts and withdrawals** • 2/30 (7%) • Discontinued intervention (1, placebo group) • Death myocardial infarction (1, adalimumab group)
Interventions	**Intervention** A. Adalimumab (n = 20), SC, 80/40 mg, eow **Control intervention** B. Topical treatment, phototherapy or no treatment (n = 10)
Outcomes	Assessment at 16 weeks **Primary outcomes of the trial** • The change in the average of max TBR values of carotid arteries **Secondary outcomes of the trial** • PASI 75 at week 16 • Change in average of max TBR of vessels • Change in the most diseased segment T
Notes	Funding: Abbott Laboratories

Bissonnette 2013 *(Continued)*

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."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 84): "were randomised a concealed computer generated code created by the sponsor" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 84): "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 (pp 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 (pp 83-4): "single-blind (cardiologist and all staff involved in vascular imaging and analysis were blinded to treatment assignment)" Comment: probably done, but no statement about secondary outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 30, analysed 30 Quote (p 84): "For all end points, the analysis was conducted on the ITT population, ... for the PASI 75 end point,... a nonresponder 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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Bissonnette 2015

Study characteristics

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	**Randomised**: 674 participants (mean age 46 years, 458 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12, PGA 3 - 4 or BSA ≥ 10), age ≥ 18 years

Bissonnette 2015 *(Continued)*

Exclusion criteria

- Past history of malignant tumours and active infection

Dropouts and withdrawals

- 72/674(10.7%): tofacitinib 5 mg twice-daily group (39), tofacitinib 10 mg twice-daily group (41)
- Not received study medication: tofacitinib 5 mg twice-daily group (5), tofacitinib 10 mg twice-daily group (3)
- Death: tofacitinib 5 mg twice-daily group (1), tofacitinib 10 mg twice-daily group (0)
- AEs: tofacitinib 5 mg twice-daily group (7), tofacitinib 10 mg twice-daily group (9)
- Lack of efficacy: tofacitinib 5 mg twice-daily group (6), tofacitinib 10 mg twice-daily group (7)
- Lost to follow-up: tofacitinib 5 mg twice-daily group (6), tofacitinib 10 mg twice-daily group (7)
- Withdrawal of consent: tofacitinib 5 mg twice-daily group (12), tofacitinib 10 mg twice-daily group (0)
- Other reason: tofacitinib 5 mg twice-daily group (2), tofacitinib 10 mg twice-daily group (8)

Interventions

Intervention

A. Tofacitinib (n = 338), orally, 10 mg twice daily

Control intervention

B. Tofacitinib (n = 336), orally, 5 mg twice daily

Outcomes

Assessment at 24 weeks

Primary outcomes of the trial

- PASI 75 and PGA rating of clear or almost clear

Secondary outcomes of the trial

- Median time to PASI 75 response
- Median time to PGA rating of clear or almost clear response
- Percentage of participants achieving both a PASI 50 - 75 response and DLQI ≤ 5
- Percentage of participants with PGA response of clear or almost clear
- Mean change from baseline-A in PASI score
- Percentage of participants achieving at least a 90% reduction in PASI relative to baseline-A (PASI 90)
- Mean DLQI score
- AEs

Notes

Funding source:

Quote (p 1395 & 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,

Bissonnette 2015 *(Continued)*

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."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 1398): "A computer-generated central randomisation schema was implemented using an automated web/telephone sytem." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 1398): "A computer-generated central randomisation schema was implemented using an automated web/telephone sytem." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 1398, ClinicalTrials.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 **Dropouts and withdrawals:** Tofacitinib 5 mg twice-daily group (39), tofacitinib 10 mg twice-daily group (41) Imbalanced numbers for withdrawal of consent: tofacitinib 5 mg twice-daily group (12), tofacitinib 10 mg twice-daily group (0) Management of missing data: Quote (p 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" (p 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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Blauvelt ADACCESS 2018

Study characteristics

Methods	RCT, active-controlled, double-blind study

Blauvelt ADACCESS 2018 *(Continued)*

	Date of study: December 2013 and March 2015 Location: 73 study centres in Bulgaria, France, Slovakia and the USA Phase 3
Participants	**Randomised:** 465 participants (mean age 46 years, 184 male) **Inclusion criteria** • Eligible patients were ≥ 18 years of age • Active, clinically stable, moderate-to-severe chronic plaque psoriasis for ≥ 6 months, defined as PASI ≥ 12, IGA score ≥ 3 and ≥ 10% body surface area affected by plaque psoriasis • Chronic plaque-type psoriasis patients who have previously received phototherapy or systemic psoriasis therapy at least once or who are candidates for such therapies in the opinion of the investigator **Exclusion criteria** • Forms of psoriasis other than plaque psoriasis • Drug-induced psoriasis • Ongoing use of prohibited psoriasis treatments • Previous exposure to adalimumab Active • Ongoing inflammatory diseases other than psoriasis that might confound the evaluation of the benefit of treatment with adalimumab **Dropouts and withdrawals** • 63/465 (13.5%); GP2017 group (30), ref-ADMB group (33) • Protocol violation: GP2017 group (2), ref-ADMB group (8) • Physician decision: GP2017 group (0), ref-ADMB group (2) • Lack of efficacy: GP2017 group (4), ref-ADMB group (2) • AEs: GP2017 group (3), ref-ADMB group (5) • Withdrawal by participant: GP2017 group (15), ref-ADMB group (11) • Lost to follow-up: GP2017 group (6), ref-ADMB group (4) • Pregnancy: GP2017 group (0), ref-ADMB group (1)
Interventions	**Intervention** A. GP2017, n = 231 **Control intervention** B. ref-ADMB (Humira; AbbVie Ltd, Maidenhead, UK; AbbVie Inc., North Chicago, IL, U.S.A), n = 234 sourced from Europe or the USA, an initial dose of 80 mg subcutaneous, then followed by 40 mg every other week, starting 1 week after the initial dose until week 15
Outcomes	**Assessment at week 16** **Primary outcome** • Proportion of participants who achieved PASI 75 **Secondary outcomes** • PASI 50, 75, 90 and 100 response rates • PASI over time • IGA of disease activity • Pharmacokinetics • Safety • Tolerability and immunogenicity

Blauvelt ADACCESS 2018 *(Continued)*

Notes	Funding source Quote (p 623): "The study was funded by Hexal AG, a Sandoz company. The funder had a role in the study design, data collection, data analysis and manuscript preparation" Confict of interest Quote (p 623): "A. Blauvelt has served as a scientific adviser and clinical study investigator for AbbVie, Allergan, Amgen, Boehringer Ingelheim, Celgene, Dermira Inc., Eli Lilly and Company, Janssen, Merck Sharp & Dohme, Novartis, Sandoz, UCB Pharma and Valeant; and as a paid speaker for Eli Lilly and Company and Janssen. J.P.L. has served as a clinical study investigator for Sandoz and has received a grant from University Hospital Nice. J.F.F. has served as a clinical study investigator for and has received research grants from Sandoz. J.M.W.served as a clinical study investigator for and has received research grants from Sandoz, and has received research grants and honoraria from Novartis. D.G. has served as a clinical study investigator for Sandoz. E.S., J.J.L. and A. Balfour are employees of Hexal AG (a Novartis Division). C.L.L. has served as a consultant or advisory board member for AbbVie, Amgen, Boehringer Ingelheim, Dermira, Eli Lilly and Company, Janssen, LEO Pharma, Pfizer, Sandoz, VCB and Vitae; as an investigator for Actavis, AbbVie, Amgen, Boehringer Ingelheim, Celgene, Coherus, Cellceutix, Corrona, Dermira, Eli Lilly and Company, Galderma, Glenmark, Janssen, LEO Pharma, Merck, Novartis, Novella, Pfizer, Sandoz, Sienna, Stiefel and Wyeth; and as a participant in speaker bureaus for AbbVie, Celgene, Eli Lilly and Company and Novartis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 624): "This was a randomized, multicentre phase III confirmatory study consisting of four periods...Randomization was stratified by prior systemic therapy, region and body weight, and was performed centrally" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 624): "This was a randomized, multicentre phase III confirmatory study consisting of four periods...Randomization was stratified by prior systemic therapy, region and body weight, and was performed centrally" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 624): “The study was double blinded; patients, investigator staff and the people performing the study assessments remained blinded to the identity of the given treatments until week 51.” Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 624): “The study was double blinded; patients, investigator staff and the people performing the study assessments remained blinded to the identity of the given treatments until week 51.” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 465 Management of missing data: Quote (supplemental appendix): "No imputation of missing values was performed." Non-inferiority trial: Quote (p 626): "In line with guidance from the U.S. Food and Drug Administration (FDA), efficacy analyses were conducted using the per protocol analysis set. The per protocol set is considered conservative, as protocol violators who could bias study results towards equivalence are excluded. Supportive analyses were performed using the full analysis set."

Blauvelt ADACCESS 2018 *(Continued)*

		Table 1: Both per protocol and full-set analyses Comment: done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02016105) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported Results posted on ClinicalTrials.gov

Blauvelt FEATURE 2015

Study characteristics	
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	**Randomised**: 177 participants (mean age 45 years (secukinumab 300 mg), 46 years (secukinumab 150 mg), 47 years (placebo), 117 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12, IGA ≥ 3, BSA ≥ 10) • Age ≥ 18 years • Non-response to topical treatment • Non-response to phototherapy • Non-response to systemic treatment **Exclusion criteria** • Pregnancy, Immunosuppresion, kidney insufficiency, liver insufficiency, • Had received biologics (IL17) • Had uncontrolled cardiovascular disorder • Had uncontrolled hypertension • Past history of malignant tumours **Dropouts and withdrawals** • 7/177(4%), secukinumab 300 group (3), secukinumab 150 group (1), placebo (3) • AEs: secukinumab 300 group (1), secukinumab 150 group (0), placebo (1) • Lost to follow-up: secukinumab 300 group (2), secukinumab 150 group (1), placebo (0) • Withdrew consent: secukinumab 300 group (0), secukinumab 150 group (0), placebo (2)
Interventions	**Intervention** A. Secukinumab (n = 59), SC, 300 mg, weeks 1, 2, 3, 4, 8, 12 B. Secukinumab (n = 59), SC, 150 mg, weeks 1, 2, 3, 4, 8, 12 **Control intervention** C. Placebo (n = 59), SC, weeks 1, 2, 3, 4, 8, 12
Outcomes	Assessment at 12 weeks

Blauvelt FEATURE 2015 *(Continued)*

Primary outcomes of the trial

- PASI 75 and IGA 0-1

Secondary outcomes of the trial

- Usability of the pre-filled syringe as assessed by observer rating of successful, hazard-free self-injection and participant rating of acceptability by the SIAQ
- PASI 90/100 over time
- IGA 0/1 over time

AEs

Notes	Funding: Novartis Pharmaceuticals, Basel, Switzerland 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"

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 (p 486): “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 (p 486): “Subjects, study management team, investigator staff, persons performing the assessments and data analysts were blinded...” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 177, analysed 177 **Dropouts and withdrawals** - 7/177(4%), secukinumab 300 group (3), secukinumab 150 group (1), placebo (3)

Blauvelt FEATURE 2015 *(Continued)*

		• AEs: secukinumab 300 group (1), secukinumab 150 group (0), placebo (1) • Lost to follow-up: secukinumab 300 group (2), secukinumab 150 group (1), placebo (0) • Withdrew consent: secukinumab 300 group (0), secukinumab 150 group (0), placebo (2) 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
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01555125) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Blauvelt VOYAGE-1 2016

Study characteristics	
Methods	RCT, active placebo-controlled, double-blind Date of study: December 2014 - April 2016 Location: 101 centres worldwide
Participants	**Randomised**: 837 participants (mean age 44 years, 608 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12, IGA ≥ 3, BSA ≥ 10), age ≥ 18 years • **Exclusion criteria** • Had a history or current signs of a severe, progressive, or uncontrolled medical condition • Had current or history of malignancy, except nonmelanoma skin cancer, within 5 years • History or symptoms of active TB • Had previously received guselkumab or adalimumab **Dropouts and withdrawals** • 24/837 (2.9%): guselkumab (7), adalimumab (10), placebo group (7) • AEs: guselkumab (4), adalimumab (2), placebo group (2) • Lack of efficacy: guselkumab (0), adalimumab (1), placebo group (2) • Lost to follow-up: guselkumab (1), adalimumab (1), placebo group (1) • Withdrawal of consent: guselkumab (0), adalimumab (4), placebo group (2) • Non-compliance: guselkumab (2), adalimumab (1), placebo group (0) • Protocol violation: guselkumab (0), adalimumab (1), placebo group (0)
Interventions	**Intervention** A. Guselkumab (n = 334), SC, 100 mg, weeks 0 and 4, then every 8 weeks **Control intervention** B. Adalimumab (n = 329), 80 mg week 0, then 40 mg week 1, and every 2 weeks

Blauvelt VOYAGE-1 2016 *(Continued)*

	C. Placebo (n = 174)
Outcomes	Assessment at 16 weeks **Primary outcomes of the trial** • PASI 90 and IGA clear or almost clear **Secondary outcomes of the trial** • PASI 50/75 • Mean DLQI score • NAPSI (Nail Psoriasis Severity Index) • Scalp-specific IGA • fingernail PGA • AEs
Notes	Funding source: Quote (p 405): "Supported by Janssen Research & Development LLC, Spring House, PA." 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 & Development LLC (subsidiary of Johnson & Johnson) and own stock in Johnson & Johnson."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 3): "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 (p 3): "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)	Low risk	Quote (p 3): "To maintain the blind, matching placebos were used." Comment: probably done

Blauvelt VOYAGE-1 2016 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 3): "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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Cai 2016

Study characteristics	
Methods	RCT, placebo-controlled, double-blind Date of study: 14 August 2012 - 21 December 2013 Location: China
Participants	**Randomised**: 425 participants (mean age 43 years, 310 men) **Inclusion criteria** • 18 years of age and older • Moderate-severe disease (PASI ≥ 10, PGA ≥ 3) • Had failed to respond to or were intolerant of previous systemic therapy **Exclusion criteria** • Had previous exposure to a biologic treatment • Received other systemic therapies for psoriasis within 28 days of baseline • Severe uncontrolled or progressive medical conditions • Had a history of demyelinating disease or certain infections or cardiovascular events • Had certain malignancies or abnormal laboratory results • Had active TB, had immune deficiency or was immunocompromised **Dropouts and withdrawals** • 7/425 (1.6%) • AEs: adalimumab (2) • Withdrawal of consent adalimumab (1), placebo (1) • Others (3)

Cai 2016 *(Continued)*

Interventions	**Intervention** A. Adalimumab (n = 338), SC, 40 mg, week 0, 2 injections, eow 1 injection **Control intervention** B. Placebo (n = 87), SC
Outcomes	Assessment at 12 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • PGA0/1, AE, PASI 50/90
Notes	Funding source: Quote (p 2): "Abbvie Inc participated in the study design, study research, collection, analysis and interpretation of data" Declarations of interest: 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."

Risk of bias

Bias	Authors' judgement	Support for judgement
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

Cai 2016 *(Continued)*

		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 [intent-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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Caproni 2009

Study characteristics	
Methods	RCT, active-controlled Date of study: not stated Location: not stated
Participants	**Randomised**: 60 participants (age range 28 - 67 years (etanercept), 32 - 65 years (acitretin), 24 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 10, BSA ≥ 10) **Exclusion criteria** • Pregnancy • Had an active infection • Past history of malignant tumours **Dropouts and withdrawals** • Not stated
Interventions	**Intervention** A. Etanercept (n = 30), SC, 50 mg, twice a week, 12 weeks **Control intervention** B. Acitretin (n = 30), orally, 0.4 mg/kg/day, 12 weeks
Outcomes	Assessment at 12 weeks **Primary and secondary outcomes of the trial** • Not stated **Outcomes of the trial**

Caproni 2009 *(Continued)*

	• Mean PASI at baseline and at 12 weeks • PASI 75, PASI 50
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	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

Study characteristics

Methods	RCT, placebo-controlled, double-blind Date of study: not stated Location: single centre, New Jersey, USA
Participants	**Randomised**: 33 participants (age mean 35 years (infliximab 10), 51 years (infliximab 5), 45 years (placebo), 23 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (BSA ≥ 5) • Non-response to topical treatment **Exclusion criteria** • Immunosuppression • Had received biologics • Had an active infection

Chaudhari 2001 *(Continued)*

	• Had past history of malignant tumours **Dropouts and withdrawals** • 3/33 (9%) • Time and reasons: worsening psoriasis (n = 1 from infliximab 10 mg/kg group), mild rash (n = 1 from infliximab 5 mg/kg group), lack improvement disease (n = 1 from placebo group)
Interventions	**Intervention** A. Infliximab (n = 11), IV, 5 mg/kg, weeks 0, 2, 6, 10 **Control intervention** 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 **Primary outcomes of the trial** • PGA good, excellent or clear **Secondary outcomes of the trial** • PASI 75
Notes	Funding: Y Johnson and Johnson, Centocor Inc Declarations of interest: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
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 **Dropouts and withdrawals** • 3/33 (9%) • Time and reasons: worsening psoriasis (n = 1 from infliximab 10 mg/kg group), mild rash (n = 1 from infliximab 5 mg/kg group), lack improvement disease (n = 1 from placebo group)

Chaudhari 2001 *(Continued)*

		Management of missing data: Quote (p 1844): "The primary analysis was done according to ITT, all randomised patients were included" Comment: probably done
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The prespecified outcomes mentioned in the Methods section appeared to have been reported

Chladek 2005

Study characteristics	
Methods	RCT, active-controlled Date of study: not stated Location: Prague, Czech Republic
Participants	**Randomised**: 41 participants (mean age 50 years (A), 46 years (B), 44 years (C), 41 years (D), 24 male) **Inclusion criteria** • Not stated **Exclusion criteria** • Not stated **Dropouts and withdrawals** • Not stated
Interventions	**Intervention** A. Methotrexate (n = 12), 7.5 mg/week, 2.5 - 2.5 - 2.5 at 12 hours, for 13 weeks **Control intervention** B. Methotrexate (n = 12), 15 mg/week, 5 - 5 - 5 at 12 hours, 13 weeks 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 **Primary or secondary outcomes of the trial** • Not stated **Outcomes of the trial** • Red cell concentrations of methotrexate • PASI weeks 1, 5, 9, 13
Notes	Funding: Czech Ministry of Education Declarations if interest: not stated
Risk of bias	

Chladek 2005 *(Continued)*

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 generation
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

Study characteristics	
Methods	RCT, active-controlled Date of study: April 2009 and June 2011 Location: 5 centres in The Netherlands
Participants	**Randomised**: 50 participants **Inclusion criteria** • 18 - 75 years • Moderate-to-severe chronic plaque type psoriasis defined as PASI ≥ 10 and/or BSA ≥ 10 and/or PASI ≥ 8 plus a Skindex-29 score ≥ 35 • Patients must have had unsuccessful treatment with or were contraindicated and/or intolerant of UV therapy, and methotrexate or cyclosporin **Exclusion criteria** • Pregnant, breastfeeding • Malignancy in the previous 10 years • Active/chronic infections including TB • Demyelinating disease • Congestive heart failure • Severe liver function disorders > 2 times and/or kidney function disorders > 1.5 times upper limit of the parameters

De Vries PIECE 2016 *(Continued)*

Dropouts and withdrawals

- 15/50 (30%)
- False inclusion: infliximab (0), etanercept (2)
- AEs: infliximab (1), etanercept (3)
- Injection fear: infliximab (0), etanercept (1)
- Switch to etanercept: infliximab (3), etanercept (not applicable)
- Switch to infliximab: infliximab (not applicable), etanercept (3)
- No response: infliximab (0), etanercept (1)
- Lost to follow-up: infliximab (1), etanercept (0)

Interventions	**Intervention** (n = 48) A. Infliximab (n = 25), IV, 5 mg/kg, weeks 0, 2, 6, 15, 22 **Control intervention** B. Etanercept (n = 23), SC, 50 mg twice weekly
Outcomes	Assessment at 24 weeks **Primary outcomes of the trial** PASI 75 **Secondary outcomes of the trial** QoL scale, Global assessment, treatment satisfaction
Notes	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)." Declaration of interest: "A.C.Q. de Vries: none reported; H.B. Thio: has been a consultant and invited speaker for Biogen/Idec, Janssen, Abbvie, Pfizer, MSD, Leopharma, Teva and Novartis. He has received educational grants from Abbvie, Janssen, Pfizer and Biogen/Idec.; 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."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (pp 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... Adequate generation of an unpredictable allocation sequence and concealment of allocation was achieved by using a secure online internet facility (the TEN-ALEA Clinical Tri-

De Vries PIECE 2016 *(Continued)*

		al Data Management System, provided by the Trans European Network http://www.tenalea.com/) 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." Comment: done
Allocation concealment (selection bias)	Low risk	Quote (pp 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... 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 http://www.tenalea.com/) 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." Comment: done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (pp 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..." Comment: no blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (p 8): "Efficacy outcomes were carried out by trained assessors who were blinded to treatment allocation." Comment: no clear description of measures taken to guarantee the blinding of investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 50, analysed 48 Quote (pp 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: www.trialregister.nl/trialreg/index.asp; NTR 1559 The prespecified outcomes mentioned in the Methods section appeared to have been reported

Dogra 2012

Study characteristics	
Methods	RCT, active-controlled, double-blind Date of study: August 2008 - September 2009 Location: Chandigarh, India
Participants	**Randomised**: 60 participants (mean age 37 years, 48 male)

Dogra 2012 *(Continued)*

	Inclusion criteria • Participants with moderate-severe psoriasis (BSA ≥ 10) • Age ≥ 18 years ≤ 65 **Exclusion criteria** • Pregnancy, kidney insufficiency, liver insufficiency • Had uncontrolled cardiovascular disorder • Had uncontrolled diabetes • had uncontrolled hypertension **Dropouts and withdrawals** • 9/60 (15%): methotrexate 10 group (5), methotrexate 25 group (4) • 4 lost to follow-up: methotrexate 10 group (3), methotrexate 25 group (1) • 4 withdrawn due to side effects: methotrexate 10 group (1), methotrexate 25 group (3) • 1 refused to participate further in the study: methotrexate 10 group (1), methotrexate 25 group (0)
Interventions	**Intervention** A. Methotrexate (n = 30), orally, 10 mg/week, for 12 weeks **Control intervention** B. Methotrexate (n = 30), orally, 25 mg/week, for 12 weeks
Outcomes	Assessment at 12 weeks **Primary outcomes of the trial** • Change in PASI score **Secondary outcomes of the trial** • PASI 75 • AEs
Notes	Funding: none declared Declarations of interest: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
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

Dogra 2012 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (pp 730-1): "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 (pp 730-1): "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
Incomplete outcome data (attrition bias) All outcomes	High risk	Randomly assigned 60, analysed 51 **Dropouts and withdrawals** • 9/60 (15%): methotrexate 10 group (5), methotrexate 25 group (4) • 4 Lost to follow-up: methotrexate 10 group (3), methotrexate 25 group (1) • 4 withdrawn due to side effects: methotrexate 10 group (1), methotrexate 25 group (3) • 1 refused to participate further in the study: methotrexate 10 group (1), methotrexate 25 group (0) Management of missing data: no ITT analyses
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The prespecified outcomes mentioned in the Methods section appeared to have been reported

Dogra 2013

Study characteristics	
Methods	RCT, active-controlled, double blind Date of study: March 2008 - March 2009 Location: Chandigarh, India
Participants	**Randomised**: 61 participants (mean age 37 years, 51 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (BSA ≥ 10) • Age ≥ 18 years ≤ 65 **Exclusion criteria** • Pregnancy, kidney insufficiency, liver insufficiency • Had uncontrolled cardiovascular disorder • Had uncontrolled diabetes • had uncontrolled hypertension

Dogra 2013 *(Continued)*

Dropouts and withdrawals

- 13/61 (21%): acitretin 25 group (5), acitretin 35 group (4), acitretin 50 group (4)
- 10 lost to follow-up: acitretin 25 group (4), acitretin 35 group (2), acitretin 50 group (4)
- 3 severe disease exacerbation: acitretin 25 group (1), acitretin 35 group (2)

Interventions	**Intervention** A. Acitretin (n = 20), orally, 25 mg/day, for 12 weeks **Control intervention** B. Acitretin (n = 20), orally, 35 mg/day, for 12 weeks C. Acitretin (n = 21), orally, 50 mg/day, for 12 weeks
Outcomes	Assessment at 12 weeks **Primary outcomes of the trial** • Change in PASI score **Secondary outcomes of the trial** • PASI 75 • % complete clearance • Time taken to achieve those parameters • AEs
Notes	Funding (quote e305): none declared Declarations of interest (quote e305): none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
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

Dogra 2013 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Randomly assigned 61, analysed 48 Dropouts and withdrawals: • 13/61(21%): acitretin 25 group (5), acitretin 35 group (4), acitretin 50 group (4) • 10 lost to follow-up: acitretin 25 group (4), acitretin 35 group (2), acitretin 50 group (4) • 3 severe disease exacerbation: acitretin 25 group (1), acitretin 35 group (2) Not ITT analyses
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The prespecified outcomes mentioned in the Methods section appeared to have been reported

Dubertret 1989

Study characteristics	
Methods	RCT, active-controlled Date of study: July 1987 - January 1988 Location: Paris, France
Participants	**Randomised**: 37 participants (mean age, sex ratio: not stated) **Inclusion criteria** • Participants with moderate-severe psoriasis: widespread psoriasis (PASI > 18) **Exclusion criteria** • Not stated **Dropouts and withdrawals** • Not stated
Interventions	**Intervention** A. Cyclosporin (n = 18), orally, 2.5 mg/kg/d **Control intervention** B. Cyclosporin (n = 19), orally, 5 mg/kg/d
Outcomes	Time to assessment for the primary outcome: not stated **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • Not stated
Notes	Funding: not stated, but 1 out of 4 authors was a staff member of Sandoz pharmaceutical company Declarations of interest: not stated

Dubertret 1989 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
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 **Dropouts and withdrawals** 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 prespecified outcomes mentioned in the Methods section appeared to have been reported

Elewski 2016

Study characteristics

Methods	Randomised, placebo-controlled, double-blind trial date: January 2014 to April 2016 Location: worldwide
Participants	**Total sample size**: 217 **Inclusion criteria** • Adults with clinical diagnosis of chronic plaque psoriasis (with a disease duration of ≥ 6 months) and ≥ 1 fingernail with nail psoriasis • BSA ≥ 10% and a target fingernail mNAPSI ≥ 8 at Week 0, OR BSA ≥ 5%, a target fingernail NAPSI ≥ 8 and a total mNAPSI score of ≥ 20 at Week 0 • Nail Psoriasis Physical Functioning Severity score of > 3, OR a Nail Psoriasis Pain score of > 3 • PGA of fingernail psoriasis and a PGA of skin psoriasis of ≥ moderate • Must have discontinued use of all systemic therapies for the treatment of psoriasis, or systemic therapies known to improve psoriasis for ≥ 4 weeks prior to Week 0, ustekinumab must have been discontinued ≥ 12 weeks prior to Week 0

Elewski 2016 *(Continued)*

- Target fingernail must have mNAPSI score of ≥ 8

Exclusion Criteria

- Prior adalimumab therapy
- Diagnosis of other active skin diseases or skin infections (bacterial, fungal, or viral) that may interfere with evaluation of skin or fingernail psoriasis
- Recent infection requiring treatment
- Significant medical events or conditions that may put patients at risk for participation, including recent history of drug or alcohol abuse
- Women who are pregnant or breast-feeding or considering becoming pregnant during the study
- History of cancer, except successfully treated skin cancer

Dropouts and withdrawals

- 29/217 (13.3%); Adalimumab group (15), placebo group (14)
- Protocol violation: Adalimumab group (0), placebo group (1)
- Lack of efficacy: Adalimumab group (1), placebo group (2)
- AEs: Adalimumab group (5), placebo group (3)
- Withdrawal by participant: Adalimumab group (4), placebo group (3)
- Lost to follow-up: Adalimumab group (3), placebo group (3)
- Others: Adalimumab group (3), placebo group (1)

Interventions	**Intervention** A. Adalimumab, SC, 40 mg, eow for 25 weeks starting 1 week after initial loading dose of 80 mg, n = 109 **Control intervention** B. Placebo, n = 108
Outcomes	**At week 12** mNAPSI 75, PGA of fingernails of clear or minimal PASI 75/90/100 for participants with baseline PASI at 5
Notes	Funding source: Quote (p 90): "AbbVie funded this study and participated in the study design; study research; collection, analysis and interpretation of data; and writing, review, and approval of this article. All authors had access to the data and participated in the development, review, and approval of this article and in the decision to submit it for publication." Conflict of interest Quote (p 90): "Dr Elewski has received research funding (paid to her institution) from AbbVie, Amgen, Boehinger Ingelheim, Celgene, Incyte, Lilly, Merck, Novan, Novartis, Pfizer, Valeant, and Viament and honoraria for serving as a consultant to Anacor, Celgene, Lilly, Novartis, Pfizer, and Valeant. Dr Okun has received honoraria for serving on an advisory board and/or as a speaker for AbbVie, Crescendo Biosciences, Gilead Science, and UCB, and he is a former AbbVie employee. Dr Papp has received honoraria for serving on an advisory board or panel, serving as a consultant and speaker for and has received grants (as an investigator) from Allergan, Amgen, Celgene, Centocor, Eli Lilly, Galderma, Genentech, Janssen, LEO Pharma, Merck, Merck-Serono, Novartis, Pfizer, Schering Plough, and Wyeth. In addition, Dr Papp has received honoraria (as a consultant) and grants (as an investigator) from Astellas, Apotex, Baxter, Boehringer Ingelheim, Kyowa Kirin, Regeneron, and UCB; received honoraria (for serving on an advisory board and panel) from AbbVie, Apotex, Baxter, Boehringer Ingelheim, and UCB; received honoraria (as a consultant) from AbbVie and Bristol-Myers Squibb; received honoraria (as a speaker) from AbbVie, Astellas, and Janssen-Cilag; and received grants (as an investigator) from Bristol-Myers Squibb and GlaxoSmithKline Beecham. Mr Baker has received honoraria (for serving on an advisory board and panel) from Abbvie, Pfizer, Novartis, and Celgene. Dr Crowley has received honoraria (as a consultant and speaker) from AbbVie, Amgen, Celgene, Lilly, and Novartis and has received

Elewski 2016 *(Continued)*

grants (as an investigator) from AbbVie, Amgen, Astra-Zeneca, Boehringer Ingelheim, Celgene, Janssen, Lilly, Maruho, Merck, Novartis, Pfizer, Regeneron, and Sandoz. Dr Guillet has received grants (as an investigator) from AbbVie. Dr Sudaram is a former AbbVie employee. Dr Poulin has received grants (as an investigator) and honoraria (as a speaker and for serving on advisory boards) from AbbVie, Amgen, and Centocor/Janssen-Ortho and has received grants (as an investigator) from Aquinox, Baxter, Boehringer Ingelheim,
Bristol-Myers-Squibb, Celgene, DS Biopharma, Eli Lilly, Galderma, Genentech, GlaxoSmithKline Beecham, LEO Pharma, Medimmune, Merck, Novartis, Pfizer, Regeneron, Schering Plough, Serono, Takeda, and UCB Pharma. Ms Gu, Dr Geng, and Dr Williams are salaried employees of AbbVie and they receive stocks and stock options. Dr Rich has received honoraria
(for serving on an advisory board) from AbbVie, Eli Lilly, Novartis, Sandoz, and Valeant; honoraria (as a consultant) from
AbbVie, Novartis, Polichem, and Valeant; and grants (as an investigator) from AbbVie, Allergan, Amgen, Anacor, Cassiopea,
Dusa, Eli Lilly, Galderma, Janssen, Leo, Meiji, Merck, Neothetics, Novartis, Pfizer, Psolar, Sandoz, Ranbaxy, and Viamet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (pp 91-2): "This was a phase 3, multicenter, double-blind, randomized, parallel-arm, placebo-controlled trial...Randomization was determined by an interactive voice/web response system." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (pp 91-2): "This was a phase 3, multicenter, double-blind, randomized, parallel-arm, placebo-controlled trial...Randomization was determined by an interactive voice/web response system." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (pp 91-2): "This was a phase 3, multicenter, double-blind, randomized, parallel-arm, placebo-controlled trial...The investigator, study site, and patients remained blinded to treatment." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (pp 91-2): "This was a phase 3, multicenter, double-blind, randomized, parallel-arm, placebo-controlled trial...The investigator, study site, and patients remained blinded to treatment." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 217 Management of missing data: Quote (p 90): "The primary efficacy analysis was performed for the period A intent-to-treat population. The primary analysis and ranked secondary end points were tested in ranked order to control multiplicity, and missing data were handled by multiple imputation for all end points." Table 2: 217 analysed participants Comment: done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02016482)

Elewski 2016 *(Continued)*

	The prespecified outcomes and those mentioned in the Methods section appeared to have been reported Results posted on ClinicalTrials.gov

Ellis 1991

Study characteristics	
Methods	RCT, active, controlled, double-blind Date of study: not stated Location: single-centre (University of Michigan Medical Center, Ann Arbor, USA)
Participants	**Randomised**: 85 participants (mean age 46 years (cyclosporin 3), 42 years (cyclosporin 5), 46 years (cyclosporin 7.5), 43 years (placebo), 66 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (BSA ≥ 25) • Non-response to phototherapy • Non-response to conventional systemic treatment • Failure to at least 1 line **Exclusion criteria** • Pregnancy **Dropouts and withdrawals** • Not stated
Interventions	**Intervention** A. Ciclosporin (Sandimmun) (n = 15), orally, 7.5 mg/kg, 8 weeks **Control intervention** 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
Outcomes	Assessment at 8 weeks **Primary or secondary outcomes** not stated **Outcomes** • Target lesions • PASI • Urinary creatinine clearance • Blood count • Blood pressure
Notes	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

Ellis 1991 *(Continued)*

	Declarations of interest: not stated (p 277) "Drs Ellis and Voorhees are consultants to Sandoz Pharmaceuticals corporation (the manufacturer of cyclosporine).

Risk of bias

Bias	Authors' judgement	Support for judgement
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
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Randomly assigned 85, analysed not stated **Dropouts and withdrawals** 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 prespecified outcomes mentioned in the Methods section appeared to have been reported

Engst 1994

Study characteristics

Methods	RCT, active-controlled, open-label trial Date of study: not stated Location: not stated
Participants	**Randomised**: 22 participants (mean age 45.9 years, 18 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI > 16) **Exclusion criteria** • Pregnancy, kidney insufficiency, liver insufficiency,

Engst 1994 *(Continued)*

	• Had an active infection • Had uncontrolled cardiovascular disorder • Had past history of malignant tumours **Dropouts and withdrawals** • Not stated
Interventions	**Intervention** A. Ciclosporin A (n = 10), orally, 1.25 mg/kg/d (increase to 2.5 if PASI > 50% of initial PASI), 12 months **Control intervention** 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 **Primary or secondary outcomes of the trial**: not stated **Outcomes of the trial** • PASI score • Blood pressure • Blood count • Urine samples
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	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	**Dropouts and withdrawals** • Not stated Management of missing data: no description of the method used to guarantee management of missing data, ITT analyses not mentioned

Engst 1994 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: no protocol was available. The prespecified outcomes mentioned in the Methods section were not reported in Results section

EUCTR2015-003623-65-DE

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind trial Date of study: February 2016 - August 2017 Location: worldwide Phase 3
Participants	**Randomised**: 605 participants planned **Inclusion criteria** • 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 < 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information • Age ≥ 18 years at screening • Diagnosis of chronic plaque psoriasis (with or without psoriatic arthritis) for ≥ 6 months before the first administration of study drug. Duration of diagnosis may be reported by the participant • Stable moderate-severe chronic plaque psoriasis with or without psoriatic arthritis at both screening and baseline (randomisation) • BSA ≥ 10% • PASI score ≥ 12 • sPGA score of ≥ 3 • Must be candidates for systemic therapy or phototherapy for psoriasis treatment, as assessed by the investigator • Must be candidates for treatment with adalimumab (Humira®) according to local label as confirmed by the investigator **Exclusion criteria** Patients with • 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 that might confound trial evaluations according to investigator's judgment • Previous exposure to BI 655066 • Previous exposure to adalimumab (Humira®). • Major surgery performed within 12 weeks prior to randomisation or planned within 12 months after screening (e.g. hip replacement, removal aneurysm, stomach ligation) • 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

EUCTR2015-003623-65-DE *(Continued)*

- 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
- 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

Dropouts and withdrawals

- 20/605 (3.3%); risankizumab group (7), adalimumab group (13)
- AEs: risankizumab group (3), adalimumab group (7)
- Protocol violation: risankizumab group (0), adalimumab group (1)
- Withdrawal: risankizumab group (1), adalimumab group (3)
- Lost to follow-up: risankizumab group (2), adalimumab group (1)
- Other reason: risankizumab group (1), adalimumab group (1)

Interventions	**Intervention** Risankizumab: 150 mg (2 syringes of 75 mg) at Weeks 0, 4 and every 12 weeks, n = 301 **Control intervention** Adalimumab: 80 mg at randomisation; then 40 mg at Weeks 1, 3, 5 and every other week, n = 304
Outcomes	**At week 16** **Primary outcome** • PASI 90 **Secondary outcomes** • PGA 0/1 • PASI 75 PASI 100
Notes	Funding: Abbvie, Boehringer Ingelheim Conflict of interest; not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (Protocol): "Active-controlled, double-blind, double dummy, randomized, parallel design comparison of BI 655066 and adalimumab over 44 weeks... An IRT will be used to allocate medication to patients through medication numbers. At randomization as well as subsequent medication dispense visit, IRT will assign medication numbers" Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (Protocol): "Active-controlled, double-blind, double dummy, randomized, parallel design comparison of BI 655066 and adalimumab over 44 weeks... An IRT will be used to allocate medication to patients through medication numbers. At randomization as well as subsequent medication dispense visit, IRT will assign medication numbers" Comment: Probably done

EUCTR2015-003623-65-DE *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (Protocol and statistical plan): "Active-controlled, double-blind, double dummy, randomized, parallel design comparison of BI 655066 and adalimumab over 44 weeks...Subjects will be blinded to treatment. Subjects in each dose group will receive the same injections at each designated time point, in order to maintain blinding." Comment: Probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (Protocol and statistical plan): "Active-controlled, double-blind, double dummy, randomized, parallel design comparison of BI 655066 and adalimumab over 44 weeks...Subjects will be blinded to treatment. Subjects in each dose group will receive the same injections at each designated time point, in order to maintain blinding." Comment: Probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (Protocol and statistical plan): "Efficacy variables will be summarized in all ITT populations... The NRI will be the primary approach in the analyses of categorical variables" Results posted on ClinicalTrials.gov: ITT results
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02694523) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Fallah Arani 2011

Study characteristics	
Methods	RCT, active-controlled, open-label trial Date of study: October 2006 - February 2009 Location: Rotterdam/Eindhoven, Netherlands
Participants	**Randomised**: 60 participants (mean age 41 years (methotrexate) and 43 years (fumarate), 36 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 10) **Exclusion criteria** • Pregnancy, Immunosuppression, kidney insufficiency, liver insufficiency, • Had an active infection • Had uncontrolled cardiovascular disorder • Had uncontrolled diabetes **Dropouts and withdrawals** • 9/60 (15%): methotrexate group (5), fumarate group (4)

Fallah Arani 2011 *(Continued)*

- Time and reasons
  - found ineligible: methotrexate group (2), fumarate group (3)
  - withdrew consent: methotrexate group (1), fumarate group (0)
  - non-appearance: methotrexate group (2), fumarate group (1)

Interventions	**Intervention** A. Methotrexate (n = 30), orally, 15 mg/week, Weinstein schema 15 mg weekly in 3 equal doses of 5 mg each 12 hours apart, 16 weeks **Control intervention** B. Fumarate (n = 30), orally, 720 mg, 30 mg followed by 120 mg and max 720 mg after week 9, 16 weeks
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PASI decreased **Secondary outcomes of the trial** • PASI decreased at 4, 16, 20 weeks • AEs
Notes	Funding source (p 855): none Declarations of interest (p 855): "none declared"

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

Fallah Arani 2011 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The prespecified outcomes mentioned in the Methods section appeared to have been reported

Flytström 2008

Study characteristics	
Methods	RCT, active-controlled, open-label trial Date of study: February 2002 - February 2005 Location: multicentre (n = 5), Sweden
Participants	**Randomised**: 84 participants (mean age: 48 years (methotrexate), 46 years (ciclosporin); 55 male) **Inclusion criteria** • Participants with moderate-severe psoriasis • Age ≥ 18 • Non response to topical treatment • Non-response to phototherapy • One previous treatment line allowed • **Exclusion criteria** • Pregnancy, immunodepression, kidney insufficiency, liver insufficiency • Had uncontrolled hypertension • Had past history of malignant tumours **Dropouts and withdrawals** • 16/84 (19%): methotrexate group (4), ciclosporin group (12) • 7 with exclusion criteria: methotrexate group (2), ciclosporin group (5) • 7 consent withdrawal: methotrexate group (2), ciclosporin group (5) • 2 ineligible: ciclosporin group
Interventions	**Intervention** A. Methotrexate + folic acid (n = 41), orally, 7.5 mg/kg /week (5 mg folic acid except days of methotrexate), 12 weeks **Control intervention** B. Ciclosporin (n = 43), orally, 3 mg/kg, divided into 2 doses, 12 weeks
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PASI **Secondary outcomes of the trial** • DLQI • SF-36 • VAS for patient assessment
Notes	Funding (p 121): "Financial support from the Swedish Psoriasis Association and the Welander foundation"

Flytström 2008 *(Continued)*

Declarations of interest (p 116): "none declared"

Risk of bias

Bias	Authors' judgement	Support for judgement
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 prespecified outcomes mentioned in the Methods section appeared to have been reported

Gisondi 2008

Study characteristics

Methods	RCT, active-controlled, investigator-blinded pilot trial Date of study: February 2002 - February 2005 Location: Verona, Italy
Participants	**Randomised**: 60 participants (mean age 55 years (acitretin); 55 years (etanercept), 53 years (acitretin + etanercept), 33 male) **Inclusion criteria** • Participants with moderate-severe psoriasis • Age ≥ 18 **Exclusion criteria** • Fertile women, kidney insufficiency (severe disorder), liver insufficiency (severe disorder) • Had received biologics • Had an active infection (HIV, Hepatitis B & C, latent TB) • Had demyelinating diseases

Gisondi 2008 *(Continued)*

- Has uncontrolled cardiovascular disorder (severe heart failure)
- Had past history of malignant tumours

Dropouts and withdrawals

- 4/60 (6.6%): acitretin group (4), etanercept group (0), acitretin + etanercept group (0)
- Inefficacy of the treatment: acitretin group (4)

Interventions	**Intervention** A. Etanercept (25 mg) and acitretin (0.4 mg/kg) (n = 18), SC (etanercept) and orally (acitretin), twice a week (etanercept) and once a day (acitretin), 24 weeks **Control intervention** 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
Outcomes	Assessments at 24 weeks **Primary outcomes of the trial** ≥ PASI 75 improvement from baseline **Secondary outcomes of the trial** • PASI 50 • BSA • Number of participants reporting significant changes (e.g. > 3 times the normal value for AST and ALT and > double the normal value for cholesterol and triglycerides)
Notes	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."

Risk of bias

Bias	Authors' judgement	Support for judgement
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"

Gisondi 2008 *(Continued)*

		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 prespecified outcomes mentioned in the Methods section appeared to have been reported

Goldfarb 1988

Study characteristics	
Methods	RCT, placebo-controlled, double-blind Date of study: not stated Location: not stated
Participants	**Randomised**: 38 participants (mean age 45 - 48 years, 31 male) **Inclusion criteria** • BSA 10 - 70 **Exclusion criteria** • No women of childbearing potential **Dropouts and withdrawals** • 0/38 (0%)
Interventions	**Intervention** A. Acitretin (n = 10), orally, 10 - 25 mg/day, 8 weeks B. Acitretin (n = 16), orally, 50 - 75 mg/day, 8 weeks **Control intervention** C. Placebo (n = 12), orally, daily, 8 weeks
Outcomes	Assessments at 8 weeks **Primary outcomes of the trial** • Not stated **Outcomes of the trial** • Percentage of skin involvement with psoriasis • Overall scaling, erythema, thickness, and global extent of the disease on a 0 through 6 scale • Improvement range from worse/unchanged/fair/good/excellent • AEs
Notes	Funding sources, quote (p 655): "Supported in part by Hoffman-La Roche Inc., Nutley, NJ, and the Babcock Dermatologic Endowment"

Goldfarb 1988 *(Continued)*

Declarations of interest: not stated

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 prespecified outcomes mentioned in the Methods section appeared to have been reported

Gordon 2006

Study characteristics

Methods	RCT, placebo-controlled, double-blind trial Date of study: March 2003 - June 2004 Location: Multicentre (n = 18) in USA, Canada
Participants	**Randomised**: 148 participants (mean age 44 years, 99 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (BSA ≥ 5) • Age ≥ 18 • Non-response to topical treatment **Exclusion criteria** • Pregnancy • Had received biologics (anti-TNF) • Had an active infection • Had past history of malignant tumours

Gordon 2006 *(Continued)*

Dropouts and withdrawals

- 8/148 (5%)
- Time and reasons:
  - did not receive the treatment: adalimumab weekly (0), adalimumab eow (1), placebo (0)
  - AE: adalimumab weekly (2), adalimumab eow (2), placebo (1)
  - lack of efficacy: adalimumab weekly (0), adalimumab eow (0), placebo (1)
  - abnormal lab value: adalimumab weekly (1), adalimumab eow (0), placebo (0)

Interventions	**Intervention** A. Adalimumab (n = 46), SC, 40 mg, 12 weeks, week 0: 2 injections, 1 injection eow **B.** Adalimumab, (n = 50), SC, 40 mg, 12 weeks, week 0, week 1: 2 injections, 1 injection weekly **Control intervention** C. Placebo (n = 52), SC, 12 weeks
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • PASI 50 • PASI 100 • PGA • DLQI
Notes	Funding, Quote (p 598): "Supported by Abbott Laboratories" 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 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."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 599): "Patients were centrally randomised..." Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Quote (p 599): "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, prefilled syringes were identically labelled and all patients received the same number of injections at the same time points" Comment: probably done

Gordon 2006 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 599): "To maintain blinding, prefilled 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
		
		Dropouts and withdrawals
		
		• 8/148 (5%)
		• Time and reasons:
		  * did not receive the treatment: adalimumab weekly (0), adalimumab eow (1), placebo (0)
		  * AE: adalimumab weekly (2), adalimumab eow (2), placebo (1)
		  * lack of efficacy: adalimumab weekly (0), adalimumab eow (0), placebo (1)
		  * abnormal lab value: adalimumab weekly (1), adalimumab eow (0), placebo (0)
		
		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"
		
		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 prespecified outcomes mentioned in the Methods section appeared to have been reported

Gordon UltIMMa-1 2018

Study characteristics	
Methods	RCT, placebo/active-controlled, double-blind study Date of study: 24 February 2016 to 31 August 2016 Location: worldwide Phase 3
Participants	**Randomised**: 506 participants **Inclusion criteria** • Men or 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 < 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) • Age ≥ 18 years at screening • Diagnosis of chronic plaque psoriasis (with or without psoriatic arthritis) for ≥ 6 months before the first administration of study drug. Duration of diagnosis may be reported by the patient • Stable moderate-severe chronic plaque psoriasis with or without psoriatic arthritis at both screening and baseline (randomisation) • Have an involved BSA ≥ 10%, PASI score ≥ 12 and sPGA score of ≥ 3

Gordon UltIMMa-1 2018 *(Continued)*

- Must be candidates for systemic therapy or phototherapy for psoriasis treatment, as assessed by the investigator
- Must be a candidate for treatment with Stelara® (ustekinumab) according to local label
- Signed and dated written informed consent prior to admission to the study in accordance with GCP and local legislation

Exclusion criteria

- 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 judgement
- Previous exposure to BI 655066
- Currently enrolled in another investigational study or < 30 days (from screening) since completing another investigational study (participation in observational studies is permitted)
- Previous exposure to ustekinumab (Stelara®)
- Use of any restricted medication, or any drug considered likely to interfere with the safe conduct of the study
- Major surgery performed within 12 weeks prior to randomisation or planned within 12 months after screening (e.g. hip replacement, aneurysm removal, stomach ligation)
- 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
- 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 uterine cervix
- 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
- History of allergy/hypersensitivity to a systemically administered biologic agent or its excipients
- Women who are pregnant, nursing, or who plan to become pregnant while in the trial
- Previous enrolment in this trial

Dropouts and withdrawals

- 10/506 (2%); rizankizumab group (5), ustekinumab group (1), placebo group (4)
- AEs: rizankizumab group (1), ustekinumab group (0), placebo group (0)
- Withdrawal: rizankizumab group (3), ustekinumab group (0), placebo group (1)
- Disease worsening: rizankizumab group (0), ustekinumab group (0), placebo group (2)
- Lost to follow-up: rizankizumab group (0), ustekinumab group (1), placebo group (1)
- Other reason: rizankizumab group (1), ustekinumab group (0), placebo group (0)

Interventions	**Intervention** A. Risankizumab, S/C, 150 mg, n = 304 **Control interventions** B. Ustekinumab, S/C, based on weight per label (45 mg for participants with body weight ≤ 100 kg or 90 mg for participants with body weight > 100 kg), n = 100 C. Placebo, n = 102

Gordon UltIMMa-1 2018 *(Continued)*

Outcomes	**At week 16** **Primary composite outcome** • PASI 90 • PGA 0/1 **Secondary outcomes** • PASI 75 at weeks 16 and 52 • PASI 90 at week 52 • PGA 0/1 at week 52
Notes	Funding source Quote (p 650): "AbbVie and Boehringer Ingelheim" Conflict of interest Quote (p 660): " KBG has received honoraria for serving as a consultant and/or grants as an investigator from AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermira, Eli Lilly, GlaxoSmithKline, Janssen, Leo Pharma, Novartis, Pfizer, Regeneron, Sanofi-Aventis, Sun, and UCB. BS has received honoraria as a consultant for AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermavant, Dermira, Eli Lilly, Galderma, GlaxoSmithKline, Janssen, Leo Pharma, Medac, Meiji Seika Pharma, Menlo Therapeutics, Merck, Novartis, Ortho Dermatologics/Valeant, Pfizer, Regeneron, Sanofi Genzyme, Sebela, Sienna, Sirtris, Sun Pharma, and UCB pharma, and as scientific director for the CORRONA-NPF Psoriasis Registry. He is an investigator for AbbVie, Boehringer Ingelheim, Celgene, Eli Lilly, Galderma, GlaxoSmithKline, Janssen, Merck, Pfizer, and Sienna. ML has received grants as an investigator from AbbVie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen Research & Development, Kadmon, Leo Pharma, Novartis, Pfizer, and ViDac and has received honoraria for serving as a consultant for Allergan, Aqua, Boehringer Ingelheim, Leo Pharma, Menlo, and Promius. MA has received honoraria or fees for serving on advisory boards, as a speaker, and as a consultant; and grants as an investigator from AbbVie, Amgen, Biogen, Boehringer Ingelheim, Celgene, Centocor, Hexal, Janssen, Leo Pharma, Eli Lilly, Medac, Mundipharma, MSD, Novartis, Pfizer, Sandoz, UCB, and Xenoport. AB has received honoraria or fees for serving on advisory boards, as a speaker, and as a consultant; and grants as an investigator from AbbVie, Aclaris, Akros, Allergan, Almirall, Amgen, Boehringer Ingelheim, Celgene, Dermavant, Dermira, Eli Lilly, Genentech/Roche, GlaxoSmithKline, Janssen, Leo Pharma, Meiji, Merck Sharp & Dohme, Novartis, Pfizer, Purdue Pharma, Regeneron, Sandoz, Sanofi Genzyme, Sienna pharmaceuticals, UCB, Valeant, and Vidac. YP has received honoraria or fees for serving on advisory boards, as a speaker, and as a consultant, and grants as an investigator from AbbVie, Amgen, Baxalta, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermira, Eli Lilly, Galderma, GlaxoSmithKline, Incyte, Janssen/Centocor, Leo Pharma, MedImmune, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi-Genzyme, Sun Pharma, Takeda, Valeant, and UCB. KAP has received honoraria or fees for serving on advisory boards, as a speaker, as a consultant, or as a steering committee member or grants as an investigator from AbbVie, Akros, Allergan, Amgen, Anacor, Arcutis, Astellas, AstraZeneca, Baxalta, Baxter, Boehringer Ingelheim, Bristol-Myers Squibb, CanFite, Celgene, Coherus, Dermira, Eli Lilly, Forward Pharma, Galderma, Genentech, GlaxoSmithKline, Janssen, Kyowa-Hakko Kirin, Leo Pharma, MedImmune, Meiji Seika Pharma, Merck (MSD), Merck-Serono, Mitsubishi Pharma, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, Takeda, UCB, and Valeant. HS has received honoraria or fees for serving on advisory boards, as a speaker, and as a consultant, and grants as an investigator from AbbVie, Amgen, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novartis, and Pfizer. LP has received honoraria or fees for serving on advisory boards, as a speaker, and as a consultant, and grants as an investigator from AbbVie, Amgen, Baxalta, Biogen, Boehringer Ingelheim, Eli Lilly, Janssen, Leo Pharma, Merck-Serono, MSD, Novartis, Pfizer, Regeneron, Roche; Sandoz, and Sanofi Genzyme. PF has received honoraria and/or research grants from and/or served as an investigator and/or advisory board member for AbbVie, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Celtaxsys, CSL, Cutanea, Dermira, Galderma, Genentech, GSK, iNova, Janssen, Leo Pharma, Lilly, Merck, Novartis, Pfizer,

Gordon UltIMMa-1 2018 *(Continued)*

Regeneron Pharmaceuticals, Roche, Sanofi, Sun Pharma, UCB Pharma, and Valeant. MO has received honoraria or fees for serving on advisory boards, as a speaker, and as a consultant, and grants as an investigator from AbbVie, Actelion, Astellas, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eisai, Eli Lilly, and Company, Galderma, Janssen, Kaken, Kyowa-Kirin, Leo Pharma, Maruho, Mochida, Nichi-Iko, Nippon Kayaku, Nippon Zoki, Novartis, Ono, Ohtsuka, Pola Pharma, Pfizer, Sanofi, Shionogi, Taiho, Tanabe-Mitsubishi, Teijin, and Torii. MF is a full-time employee of Boehringer Ingelheim. ZG, YG, and JMV are full-time employees of AbbVie and own stock or options. EHZT, a former employee of AbbVie, currently owns stock. HB has received honoraria or fees for serving on advisory boards, as a speaker, and as a consultant, and grants as an investigator from AbbVie, Almirall, Amgen, Bayer, Baxalta, Biocad, Boehringer Ingelheim, Celgene, Dermavant, Eli Lilly, Janssen, Leo Pharma, Menarini, MSD, Novartis, Pfizer, Pierre Fabre, Sandoz, Sun Pharmaceuticals, and UCB.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 651-2): "UltIMMa-1 and UltIMMa-2 were replicate phase 3,randomised, double-blind, placebo-controlled and active comparator-controlled...In each study, patients were randomly assigned (3:1:1) to receive risankizumab, ustekinumab, or matching placebo (appendix). Randomisation was stratified by weight (≤100 kg vs >100 kg) and previous exposure to tumour necrosis factor (TNF) inhibitor (yes vs no); there was no restriction on the number of patients with prior TNF inhibitor exposure. Interactive response technology was used for randomisation and allocation of double-blind treatment to each patient." Comment Probably done
Allocation concealment (selection bias)	Low risk	Quote (p 651-2): "UltIMMa-1 and UltIMMa-2 were replicate phase 3,randomised, double-blind, placebo-controlled and active comparator-controlled...In each study, patients were randomly assigned (3:1:1) to receive risankizumab, ustekinumab, or matching placebo (appendix). Randomisation was stratified by weight (≤100 kg vs >100 kg) and previous exposure to tumour necrosis factor (TNF) inhibitor (yes vs no); there was no restriction on the number of patients with prior TNF inhibitor exposure. Interactive response technology was used for randomisation and allocation of double-blind treatment to each patient." Comment Probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 651-2): "UltIMMa-1 and UltIMMa-2 were replicate phase 3,randomised, double-blind, placebo-controlled and active comparator-controlled...Patients, investigators, and study personnel involved in the trial conduct or analyses remained masked to treatment assignments until study completion. To maintain blinding, the studies utilised a double-dummy strategy where in risankizumab and its matching placebo or ustekinumab and its matching placebo were identical in appearance." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 651-2): "UltIMMa-1 and UltIMMa-2 were replicate phase 3,randomised, double-blind, placebo-controlled and active comparator-controlled...Patients, investigators, and study personnel involved in the trial conduct or analyses remained masked to treatment assignments until study completion. To maintain blinding, the studies utilised a double-dummy strategy where in risankizumab and its matching placebo or ustekinumab and its matching placebo were identical in appearance." Comment: probably done

Gordon UltIMMa-1 2018 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Randomly assigned 506 Management of missing data: Quote (p 652-3): "For both UltIMMa-1 and UltIMMa-2 studies, efficacy analyses were done in the intention-to-treat population (all randomised patients)... Missing efficacy data for categorical variables were handled with non-responder imputation and for continuous variables with last observation carried forward" Table 2: 506 analysed participants Comment: done
Selective reporting (reporting bias)	Unclear risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02684370) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Gordon UltIMMa-2 2018

Study characteristics	
Methods	RCT, placebo/active-controlled, double-blind study Date of study: 1 March 2016 and 30 August 2016 Location: worldwide Phase 3
Participants	**Randomised**: 491 participants **Inclusion criteria** • Men or 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 < 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) • Age ≥ 18 years at screening • Diagnosis of chronic plaque psoriasis (with or without psoriatic arthritis) for ≥ 6 months before the first administration of study drug. Duration of diagnosis may be reported by the patient • Stable moderate-severe chronic plaque psoriasis with or without psoriatic arthritis at both screening and baseline (randomisation) • Have an involved BSA ≥ 10%, PASI score ≥ 12 and sPGA score of ≥ 3 • Must be candidates for systemic therapy or phototherapy for psoriasis treatment, as assessed by the investigator • Must be a candidate for treatment with Stelara® (ustekinumab) according to local label • Signed and dated written informed consent prior to admission to the study in accordance with GCP and local legislation **Exclusion criteria** • 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 lithi-

Gordon UltIMMa-2 2018 *(Continued)*

um), active ongoing inflammatory diseases other than psoriasis and psoriatic arthritis that might confound trial evaluations according to investigator's judgement
- Previous exposure to BI 655066
- Currently enrolled in another investigational study or < 30 days (from screening) since completing another investigational study (participation in observational studies is permitted)
- Previous exposure to ustekinumab (Stelara®)
- Use of any restricted medication, or any drug considered likely to interfere with the safe conduct of the study
- Major surgery performed within 12 weeks prior to randomisation or planned within 12 months after screening (e.g. hip replacement, aneurysm removal, stomach ligation)
- 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
- 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 uterine cervix
- 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
- History of allergy/hypersensitivity to a systemically administered biologic agent or its excipients
- Women who are pregnant, nursing, or who plan to become pregnant while in the trial
- Previous enrolment in this trial

Dropouts and withdrawals

- 9/491 (1.8%); rizankizumab group (2), ustekinumab group (3), placebo group (4)
- Withdrawal: rizankizumab group (0), ustekinumab group (0), placebo group (3)
- Disease worsening: rizankizumab group (0), ustekinumab group (0), placebo group (1)
- Lost to follow-up: rizankizumab group (2), ustekinumab group (2), placebo group (1)
- Other reason: rizankizumab group (0), ustekinumab group (1), placebo group (0)

Interventions	**Intervention** A. Risankizumab, S/C, 150 mg, n = 294 **Control interventions** B. Ustekinumab, S/C, based on weight per label (45 mg for patients with body weight ≤100 kg or 90 mg for patients with body weight >100 kg), n = 99 C. Placebo, n = 98
Outcomes	**At week 16** **Primary composite outcome** • PASI 90 • PGA 0/1 **Secondary outcomes** • PASI 75 at weeks 16 and 52 • PASI 90 at week 52

Gordon UltIMMa-2 2018 *(Continued)*

- PGA 0/1 at week 52

Notes

Funding source

Quote (p 650): "AbbVie and Boehringer Ingelheim"

Conflict of interest

Quote (p 660): "KBG has received honoraria for serving as a consultant and/or grants as an investigator from AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermira, Eli Lilly, GlaxoSmithKline, Janssen, Leo Pharma, Novartis, Pfizer, Regeneron, Sanofi-Aventis, Sun, and UCB. BS has received honoraria as a consultant for AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermavant, Dermira, Eli Lilly, Galderma, GlaxoSmithKline, Janssen,

Leo Pharma, Medac, Meiji Seika Pharma, Menlo Therapeutics, Merck, Novartis, Ortho Dermatologics/Valeant, Pfizer, Regeneron, Sanofi Genzyme, Sebela, Sienna, Sirtris, Sun Pharma, and UCB pharma, and as scientific director for the CORRONA-NPF Psoriasis Registry. He is an investigator for AbbVie, Boehringer Ingelheim, Celgene, Eli Lilly,

Galderma, GlaxoSmithKline, Janssen, Merck, Pfizer, and Sienna. ML has received grants as an investigator from AbbVie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen Research & Development, Kadmon, Leo Pharma, Novartis, Pfizer, and ViDac and has received honoraria for serving as a consultant for Allergan, Aqua, Boehringer Ingelheim, Leo Pharma, Menlo, and Promius. MA has received honoraria or fees for serving on advisory boards, as a speaker, and as a consultant; and grants as an investigator from AbbVie, Amgen, Biogen, Boehringer Ingelheim, Celgene, Centocor, Hexal, Janssen, Leo Pharma, Eli Lilly, Medac, Mundipharma, MSD, Novartis, Pfizer, Sandoz, UCB, and Xenoport. AB has received honoraria or fees for serving on advisory boards, as a speaker, and as a consultant; and grants as an investigator from AbbVie, Aclaris, Akros, Allergan, Almirall, Amgen, Boehringer Ingelheim, Celgene, Dermavant, Dermira, Eli Lilly, Genentech/Roche, GlaxoSmithKline, Janssen, Leo Pharma, Meiji, Merck Sharp & Dohme, Novartis, Pfizer, Purdue Pharma, Regeneron, Sandoz, Sanofi Genzyme, Sienna pharmaceuticals, UCB, Valeant, and Vidac. YP has received honoraria or fees for serving on advisory boards, as a speaker, and as a consultant, and grants as an investigator from AbbVie, Amgen, Baxalta, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermira, Eli Lilly, Galderma, GlaxoSmithKline, Incyte, Janssen/Centocor, Leo Pharma, MedImmune, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi-Genzyme, Sun Pharma, Takeda, Valeant, and UCB. KAP has received honoraria or fees for serving on advisory boards, as a speaker, as a consultant, or as a steering committee member or grants as an investigator from AbbVie, Akros, Allergan, Amgen, Anacor, Arcutis, Astellas, AstraZeneca, Baxalta, Baxter, Boehringer Ingelheim, Bristol-Myers Squibb, CanFite, Celgene, Coherus, Dermira, Eli Lilly, Forward Pharma, Galderma, Genentech, GlaxoSmithKline, Janssen, Kyowa-Hakko Kirin, Leo Pharma, MedImmune, Meiji Seika Pharma, Merck (MSD), Merck-Serono, Mitsubishi Pharma, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, Takeda, UCB, and Valeant. HS has received honoraria or fees for serving on advisory boards, as a speaker, and as a consultant, and grants as an investigator from AbbVie, Amgen, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novartis, and Pfizer. LP has received honoraria or fees for serving on advisory boards, as a speaker, and as a consultant, and grants as an investigator from AbbVie, Amgen, Baxalta, Biogen, Boehringer Ingelheim, Eli Lilly, Janssen, Leo Pharma, Merck-Serono, MSD, Novartis, Pfizer, Regeneron, Roche; Sandoz, and Sanofi Genzyme. PF has received honoraria and/or research grants from and/or served as an investigator and/or advisory board member for AbbVie, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Celtaxsys, CSL, Cutanea, Dermira, Galderma, Genentech, GSK, iNova, Janssen, Leo Pharma, Lilly, Merck, Novartis, Pfizer, Regeneron Pharmaceuticals, Roche, Sanofi, Sun Pharma, UCB Pharma, and Valeant. MO has received honoraria or fees for serving on advisory boards, as a speaker, and as a consultant, and grants as an investigator from AbbVie, Actelion, Astellas, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eisai, Eli Lilly, and Company, Galderma, Janssen, Kaken, Kyowa-Kirin, Leo Pharma, Maruho, Mochida, Nichi-Iko, Nippon Kayaku, Nippon Zoki, Novartis, Ono, Ohtsuka, Pola Pharma, Pfizer, Sanofi, Shionogi, Taiho, Tanabe-Mitsubishi, Teijin, and Torii. MF is a full-time employee of Boehringer Ingelheim. ZG, YG, and JMV are full-time employees of AbbVie and own stock or options. EHZT, a former employee of AbbVie, currently owns stock. HB has received honoraria or fees for serving on advisory boards, as a speaker, and as a consultant, and grants as an investigator from AbbVie, Almirall, Amgen, Bayer, Baxalta, Biocad, Boehringer Ingelheim, Celgene, Dermavant, Eli Lilly, Janssen, Leo Pharma, Menarini, MSD, Novartis, Pfizer, Pierre Fabre, Sandoz, Sun Pharmaceuticals, and UCB.

Gordon UltIMMa-2 2018 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (pp 651-2): "UltIMMa-1 and UltIMMa-2 were replicate phase 3, randomised, double-blind, placebo-controlled and active comparator-controlled...In each study, patients were randomly assigned (3:1:1) to receive risankizumab, ustekinumab, or matching placebo (appendix). Randomisation was stratified by weight (≤100 kg vs >100 kg) and previous exposure to tumour necrosis factor (TNF) inhibitor (yes vs no); there was no restriction on the number of patients with prior TNF inhibitor exposure. Interactive response technology was used for randomisation and allocation of double-blind treatment to each patient." Comment Probably done
Allocation concealment (selection bias)	Low risk	Quote (pp 651-2): "UltIMMa-1 and UltIMMa-2 were replicate phase 3, randomised, double-blind, placebo-controlled and active comparator-controlled...In each study, patients were randomly assigned (3:1:1) to receive risankizumab, ustekinumab, or matching placebo (appendix). Randomisation was stratified by weight (≤100 kg vs >100 kg) and previous exposure to tumour necrosis factor (TNF) inhibitor (yes vs no); there was no restriction on the number of patients with prior TNF inhibitor exposure. Interactive response technology was used for randomisation and allocation of double-blind treatment to each patient." Comment Probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (pp 651-2): "UltIMMa-1 and UltIMMa-2 were replicate phase 3, randomised, double-blind, placebo-controlled and active comparator-controlled...Patients, investigators, and study personnel involved in the trial conduct or analyses remained masked to treatment assignments until study completion. To maintain blinding, the studies utilised a double-dummy strategy where in risankizumab and its matching placebo or ustekinumab and its matching placebo were identical in appearance." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (pp 651-2): "UltIMMa-1 and UltIMMa-2 were replicate phase 3, randomised, double-blind, placebo-controlled and active comparator-controlled...Patients, investigators, and study personnel involved in the trial conduct or analyses remained masked to treatment assignments until study completion. To maintain blinding, the studies utilised a double-dummy strategy where in risankizumab and its matching placebo or ustekinumab and its matching placebo were identical in appearance." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 491 Management of missing data: Quote (pp 652-3): "For both UltIMMa-1 and UltIMMa-2 studies, efficacy analyses were done in the intention-to-treat population (all randomised patients)... Missing efficacy data for categorical variables were handled with non-responder imputation and for continuous variables with last observation carried forward" Table 2: 491 analysed participants Comment: done

Gordon UltIMMa-2 2018 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT0268435). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Gordon UNCOVER-1 2016

Study characteristics	
Methods	RCT, placebo-controlled, double-blind Date of study: November 2011 to June 2014 Location: multicentre (104) in Europe, Australia, North America
Participants	**Randomised**: 1296 participants (mean age 45 years, 883 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12 or BSA ≥ 10), age ≥ 18 years **Exclusion criteria** • Pregnancy, immunosuppression, kidney insufficiency, liver insufficiency, past history of malignant tumours, active infection, uncontrolled cardiovascular disorder, uncontrolled diabetes, uncontrolled hypertension • Had received anti-IL17 **Dropouts and withdrawals** • 66/1296 (5%); • Ixekizumab 4-week group (24), ixekizumab 2-week group (18), placebo (24) • AEs: ixekizumab 4-week group (10), ixekizumab 2-week group (10), placebo (6) • Protocol violation: ixekizumab 4-week group (6), ixekizumab 2-week group (0), placebo (3) • Participant decision: ixekizumab 4-week group (6), ixekizumab 2-week group (5), placebo (6) • Lost to follow-up: ixekizumab 4-week group (0), ixekizumab 2-week group (2), placebo (1) • Investigator decision: ixekizumab 4-week group (1), ixekizumab 2-week group (1), placebo (1) • Lack of efficacy: ixekizumab 4-week group (1), ixekizumab 2-week group (0), placebo (7)
Interventions	**Intervention** A. Ixekizumab (n = 432), SC, 80 mg, 2 injections week 0, 1 injection monthly **Control intervention** B. Ixekizumab (n = 433), SC, 80 mg, 2 injections week 0, 1 injection eow C. Placebo (n = 431), SC
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PGA 0-1 • PASI 75 **Secondary outcomes of the trial**

Gordon UNCOVER-1 2016 *(Continued)*

- PASI 90
- DLQI
- NAPSI
- AEs

Notes	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): "Disclosure forms 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

Risk of bias

Bias	Authors' judgement	Support for judgement
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 intention-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 prespecified outcomes mentioned in the protocol and in the Methods section appeared to have been reported

Gordon X-PLORE 2015

Study characteristics	
Methods	RCT, active placebo-controlled, double-blind Date of study: October 2011 - August 2013 Location: multicentre (n = 31), Europe and North America
Participants	**Randomised**: 293 participants (mean age 47 years, 207 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12 or BSA ≥ 10), age ≥ 18 years **Exclusion criteria** • Pregnancy, immunosuppression, kidney insufficiency, liver insufficiency, past history of malignant tumours, active infection, uncontrolled cardiovascular disorder, uncontrolled diabetes, uncontrolled hypertension • Had received adalimumab or guselkumab **Dropouts and withdrawals** • 20/293 (6.8%); • 1 not treated (guselkumab 200) • AEs: guselkumab 5 (0), guselkumab 15 (0), guselkumab 50 (1), guselkumab 100 (1), guselkumab 200 (4), adalimumab (3), placebo (2) • Lack of efficacy: guselkumab 5 (0), guselkumab 15 (0), guselkumab 50 (0), guselkumab 100 (0), guselkumab 200 (0), adalimumab (0), placebo (1) • Lost to follow-up: guselkumab 5 (1), guselkumab 15 (0), guselkumab 50 (1), guselkumab 100 (0), guselkumab 200 (0), adalimumab (1), placebo (0) • Other: guselkumab 5 (2), guselkumab 15 (0), guselkumab 50 (1), guselkumab 100 (1), guselkumab 200 (0), adalimumab (0), placebo (0)
Interventions	**Intervention** A. Guselkumab (n = 41), SC, 5 mg weeks 0, 4, 16 **Control intervention** B. Guselkumab (n = 41), SC, 15 mg weeks 0, 4, 16 C. Guselkumab(n = 42), SC, 50 mg weeks 0, 4, 16 D. Guselkumab (n = 42), SC, 100 mg weeks 0, 4, 16 E. Guselkumab (n = 42), SC, 200 mg weeks 0, 4, 16 F. Adalimumab (n = 43), SC, 40 mg 2 injections week 0, 1 injection week 1, 1 injection eow G Placebo (n = 42), SC (100 mg weeks 0, 4, 16)
Outcomes	Assessments at 16 weeks **Primary outcomes of the trial** • PGA 0-1 **Secondary outcomes of the trial** • PASI 90 • PASI 75

Gordon X-PLORE 2015 *(Continued)*

- DLQI

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): "Disclosure forms 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 **Dropouts and withdrawals** • 20/293 (6.8%); • 1 not treated (guselkumab 200) • AEs: guselkumab 5 (0), guselkumab 15 (0), guselkumab 50 (1), guselkumab 100 (1), guselkumab 200 (4), adalimumab(3), placebo (2) • Lack of efficacy: guselkumab 5 (0), guselkumab 15 (0), guselkumab 50 (0), guselkumab 100 (0), guselkumab 200 (0), adalimumab (0), placebo (1) • Lost to follow-up: guselkumab 5 (1), guselkumab 15 (0), guselkumab 50 (1), guselkumab 100 (0), guselkumab 200 (0), adalimumab (1), placebo (0) • Other: guselkumab 5 (2), guselkumab 15 (0), guselkumab 50 (1), guselkumab 100 (1), guselkumab 200 (0), adalimumab (0), placebo (0) 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”

Gordon X-PLORE 2015 *(Continued)*

		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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Gottlieb 2003a

Study characteristics	
Methods	RCT, placebo-controlled, double-blind Date of study: August 2000 - January 2001 Location: multicentre (locations not specified)

Participants	**Randomised**: 112 participants (mean age 47 years, 70 male)
	
	Inclusion criteria
	
	• Participants with moderate-severe psoriasis (BSA ≥ 10), age ≥ 18 years
	• Had previously received phototherapy or systemic psoriasis therapy at least once
	
	Exclusion criteria
	
	• 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"
	
	Dropouts and withdrawals
	
	• 19/112 (17%): etanercept 4/57 (7.0%), placebo 15/55 (27.3%)
	• Time and reasons:
	  * etanercept: AE (1), lack of efficacy (3)
	  * placebo: AE (4), lack of efficacy (9), lost to follow-up (1), patient refusal (1)

Interventions	**Intervention** A. Etanercept (n = 57), SC, auto-administered, 25 mg twice a week, 24 weeks **Control intervention** B. Placebo (n = 55), SC, auto-administered, twice a week, 24 weeks
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** At 4, 8, 12, 24 weeks • PASI 50 • PASI 75 • PASI 90

Gottlieb 2003a *(Continued)*

- DLQI
- PGA
- Safety
- Participant global assessment of psoriasis

Notes	Funding source, quote (p 1631): "This study was sponsored by Immunex Corp, a subsidiary of Amgem, Inc.)" Declarations of interest not stated except "Dr Zitnik is an employee of Amgen" (p 1627)

Risk of bias

Bias	Authors' judgement	Support for judgement
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 do not know whether the investigators were blinded or the numbers of participants per block. This probably was a centralised randomisation but this is 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
		
		Dropouts and withdrawals
		
		• Etanercept 4/57 (7.0%), placebo 15/55 (27.3%)
		• Time and reasons:
		  * etanercept: AE (1), lack of efficacy (3)
		  * placebo: AE (4), lack of efficacy (9), lost to follow-up (1), participant refusal (1)
		
		Management of missing data:
		
		Quote (p 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 2003a *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The prespecified outcomes mentioned in the Methods section appeared to have been reported

Gottlieb 2004a

Study characteristics	
Methods	RCT, placebo-controlled, double-blind Date of study: 2001 - 2003 Location: 24 centres in USA
Participants	**Randomised**: 249 participants (mean age 44 years, 174 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12 or BSA ≥ 10), age ≥ 18 years • Non-response to phototherapy • Non-response to conventional systemic treatment **Exclusion criteria** • Pregnancy, past history of malignant tumours, active infection **Dropouts and withdrawals after a 30-week study period** • 85/249 (34%) **Reasons** • AE: infliximab 3 mg (7), infliximab 5 mg (3), placebo (1) • Lack of efficacy: infliximab 3 mg (11), infliximab 5 mg (5), placebo (26) • Other reasons: infliximab 3 mg (12), infliximab 5 mg (10), placebo (10)
Interventions	**Intervention** A. Infliximab (n = 99), IV, 3 mg/kg, weeks 0, 2, 6, for 10 weeks **Control intervention** B. Infliximab (n = 99), IV, 5 mg/kg, weeks 0, 2, 6, for 10 weeks C. Placebo (n = 51), IV, equivalent, weeks 0, 2, 6, for 10 weeks
Outcomes	Assessments at 10 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • PASI • PGA • DLQI • AEs
Notes	Funding source, Quote (p 534): "Supported by Centocor Inc"

Gottlieb 2004a *(Continued)*

	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. "

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): "Randomissation 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 prespecified outcomes mentioned in the Methods section appeared to have been reported

Gottlieb 2011

Study characteristics

Methods	RCT, placebo-controlled, double-blind Date of study: June 2008 - March 2009 Location: 33 centres in the USA
Participants	**Randomised**: 209 participants (mean age 43.5 years, 145 male) **Inclusion criteria**

Gottlieb 2011 *(Continued)*

- Participants with moderate-severe psoriasis (PGA ≥ 3, PASI ≥ 12, BSA ≥ 10), age ≥ 18 years

Exclusion criteria

- Previous exposure to either etanercept or ABT-874

Dropouts and withdrawals

- 12/209 (5.7%): etanercept 7, placebo 5
- Time and reasons:
  - Etanercept: AE (4), lost to follow-up (1), protocol violation (1), Other (1)
  - Placebo: AE (0), lost to follow-up (4), protocol violation (1)

Interventions	**Intervention** A. Etanercept (n = 141), SC, auto-administered, 50 mg twice a week, 11 weeks **Control intervention** B. Placebo (n = 68), SC, auto-administered, twice a week
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PASI 75/PGA 0/1 **Secondary outcomes of the trial** At 4, 8, 12 weeks • PASI 50 • PASI 75 • PASI 90 • DLQI • PGA • Safety • Patient global assessment of psoriasis
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 Pharmaceuticals, 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."

Risk of bias

Gottlieb 2011 *(Continued)*

Bias	Authors' judgement	Support for judgement
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 etanercept 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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Gottlieb 2012

Study characteristics	
Methods	RCT, placebo-controlled, double-blind Date of study: November 2010 – December 2011 Location: Multicentre in Boston, USA

Gottlieb 2012 *(Continued)*

Participants	**Randomised**: 478 participants (methotrexate: mean age 43 years and 153 male; placebo: mean age 45 years and 167 male)
	
	Inclusion criteria
	
	• Participants with moderate-severe psoriasis (author assessment ≥ 6 months or PASI ≥ 10 or BSA ≥ 10%), age ≥ 18 years
	• Non-response to topical treatment
	
	Exclusion criteria
	
	• Kidney insufficiency, liver insufficiency
	• Had received biologics
	• Had received conventional systemic treatments
	
	Dropouts and withdrawals
	
	• 61/478 (12.8%)
	• Methotrexate 28/239 (11.7%); placebo 33/239 (13.8%)
	• Time and reasons :
	  * Methotrexate: AE (10), lost to follow-up (5), ineligibility (4), noncompliance (4), full consent withdrawn (4)
	  * Placebo: AE (5), lost to follow-up (9) ineligibility (2), noncompliance (7), disease progression (3), full consent withdrawn (5), other (2)

Interventions	**Intervention** 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 **Control intervention** 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 **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • PASI 75 at 12 weeks • PASI 50 at 12 weeks • PASI 50 at 24 weeks • PASI 90 at 12 weeks • PASI 90 at 24 weeks • PGA at 12 weeks and 24 weeks • BSA at 12 and 24 weeks • AEs • Change of laboratory assessment
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), Dermipsor, 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),

Gottlieb 2012 *(Continued)*

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."

Risk of bias

Bias	Authors' judgement	Support for judgement
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
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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Gottlieb CIMPASI-1 2018

Study characteristics

Methods	RCT, active/placebo-controlled, double-blind trial Date of study: December 2014 - October 2016 Location: World-wide

Gottlieb CIMPASI-1 2018 *(Continued)*

	Phase 3
Participants	**Randomised**: 234 participants **Inclusion criteria** • Provided informed consent • Adult men or women ≥ 18 years • Chronic plaque psoriasis for ≥ 6 months • Baseline PASE ≥ 12 and BSA ≥ 10% and PGA score ≥ 3 • Candidate for systemic psoriasis therapy and/or phototherapy and/or chemophototherapy • Other protocol-defined inclusion criteria may apply **Exclusion criteria** • Erythrodermic, guttate, generalised pustular form of psoriasis • History of current, chronic, or recurrent infections of viral, bacterial, or fungal origin as described in the protocol • Congestive heart failure • History of a lymphoproliferative disorder including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease • History of other malignancy concurrent malignancy as described in the protocol • History of, or suspected, demyelinating disease of the central nervous system (e.g. multiple sclerosis or optic neuritis) • 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 • Any other condition which, in the Investigator's judgement, would make the person unsuitable for participation in the study • Other protocol-defined exclusion criteria may apply **Dropouts and withdrawals** • 9/234 (3.8%); Certolizumab 400 (1), Certolizumab 200 (3), placebo group (5) • Adverse events: Certolizumab 400 (1), Certolizumab 200 (0), placebo group (0) • Lack of efficacy: Certolizumab 400 (0), Certolizumab 200 (0), placebo group (1) • Withdrawal: Certolizumab 400 (0), Certolizumab 200 (2), placebo group (3) • Lost to follow-up: Certolizumab 400 (0), Certolizumab 200 (1), placebo group (1) • Other reason:Certolizumab 400 (2), Certolizumab 200 (0), placebo group (0)
Interventions	**Intervention** A. Certolizumab pegol (400 mg at weeks 0, 2, 4, followed by certolizumab pegol 200 mg every 2 weeks from week 6 to week 14) (n = 95) **Control intervention** B. Certolizumab pegol (certolizumab pegol 400 mg every 2 weeks through week 14) (n = 88) C. Placebo (n = 51)
Outcomes	**At week 16** **Primary composite outcome** • PASI 75 • PGA 0/1 **Secondary outcomes** • PASI 90

Gottlieb CIMPASI-1 2018 *(Continued)*

- DLQI

Notes	Funding source Quote (p 302): "Supported by Dermira Inc and UCB Inc." Conflicts of interest Quote (p 302): "Dr Gottlieb has consulted and/or received other fees from Janssen Inc, Celgene Corp, Bristol-Myers Squibb Co, Beiersdorf Inc, AbbVie, UCB, Novartis, Incyte, Eli Lilly, Reddy Labs, Valeant, Dermira Inc, Allergan, and Sun Pharmaceutical Industries; and has received research or educational grants (paid to TuftsMedical Center) from Janssen Incyte, Lilly, Novartis, Allergan, and LEO Pharma. Dr Blauvelt has received honoraria or fees for consulting, being a clinical investigator, and/or speaker for AbbVie, Aclaris, Allergan, Almirall, Amgen, Boehringer Ingelheim, Celgene, Dermavant, Dermira Inc, Eli Lilly, Genentech/Roche, GlaxoSmith-Kline, Janssen, LEO Pharma,Merck Sharp & Dohme, Novartis, Pfizer, Purdue Pharma, Regeneron, Sandoz, Sanofi Genzyme, Sienna Pharmaceuticals, Sun Pharma, UCB Pharma, Valeant, and Vidac. Dr Leonardi has received fees or honoraria for consulting, speaking, or serving on the advisory board for AbbVie, Actavis, Amgen, Boehringer Ingelheim Pharma, Celgene, Coherus, Corrona, Dermira Inc, Eli Lilly, Galderma, Glenmark, Janssen, LEO Pharma, Merck, Novartis, Pfizer, Sandoz, Stiefel, UCB Pharma, Vitae, and Wyeth. Dr Poulin has received research grants as an investigator for AbbVie, Baxter, Boehringer Ingelheim Pharma, Celgene, Centocor/Janssen, Eli Lilly, EMD Serono, GlaxoSmithKline, LEO Pharma, MedImmune, Merck, Novartis, Pfizer, Regeneron, Takeda, and UCB Pharma; and has received honoraria speaking for AbbVie, Celgene, Janssen, Eli Lilly, LEO Pharma, Novartis, Regeneron, and Sanofi Genzyme. Dr Reich has received speaker's fees or honoraria from and/or served on the advisory board for AbbVie, Amgen, Biogen, Boehringer Ingelheim Pharma, Celgene, Centocor, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Eli Lilly, Medac, Merck Sharp & Dohme, Novartis, Ocean Pharma, Pfizer, Regeneron, Takeda, UCB Pharma, and Xenoport. Dr Thaç has received research support from AbbVie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Celgene, Dignity, Eli Lilly, Forward-Pharma, GlaxoSmithKline, LEO Pharma, Janssen-Cilag, Maruho, Merck Sharp & Dohme, Mitsubishi Pharma, Novartis, Pfizer, Roche, Regeneron, and Sandoz; received honoraria from AbbVie, Biogen, Celgene, Janssen, LEO Pharma, Pfizer, Roche-Possay, Novartis, and Mundipharma; served as a consultant for AbbVie, Biogen, Celgene, Dignity, Galapagos, Maruho, Mitsubishi, Novartis, Pfizer, and Xenoport; and sat on the scientific advisory boards for AbbVie, Amgen, Biogen, Celgene, Eli Lilly, GlaxoSmithKline, LEO Pharma, Pfizer, Novartis, Janssen, Mundipharma, and Sandoz. Ms Drew and Dr Burge have received stock options fromDermira Inc. Mr Peterson owns stock in UCB Inc. Dr Arendt owns stock in and has received stock options from UCB Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (pp 303-4): " CIMPASI-1 (NCT02326298) and CIMPASI-2 (NCT02326272) are ongoing, replicate, phase 3, randomized, double-blinded, multicenter... At the baseline visit, an interactive voice web response system was used to assign patients to... according to the randomization schedule produced by an independent biostatistician (2:2:1, stratified by site)." Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (pp 303-4): " CIMPASI-1 (NCT02326298) and CIMPASI-2 (NCT02326272) are ongoing, replicate, phase 3, randomized, double-blinded, multicenter... At the baseline visit, an interactive voice web response system was used to assign patients to... according to the randomization schedule produced by an independent biostatistician (2:2:1, stratified by site)." Comment: Probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (pp 303-4): " CIMPASI-1 (NCT02326298) and CIMPASI-2 (NCT02326272) are ongoing, replicate, phase 3, randomized, double-blinded, multicenter... to assign patients to subcutaneous treatment with CZP 400 mg every 2 weeks,

Gottlieb CIMPASI-1 2018 *(Continued)*

		CZP 200 mg every 2 weeks (after loading dose of CZP 400 mg at weeks 0, 2, and 4), or placebo every 2 weeks until week 16 (initial treatment period)" Comment: Probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (pp 303-4): " CIMPASI-1 (NCT02326298) and CIMPASI-2 (NCT02326272) are ongoing, replicate, phase 3, randomized, double-blinded, multicenter... to assign patients to subcutaneous treatment with CZP 400 mg every 2 weeks, CZP 200 mg every 2 weeks (after loading dose of CZP 400 mg at weeks 0, 2, and 4), or placebo every 2 weeks until week 16 (initial treatment period)" Comment: Probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 234 Management of missing data: Quote (p 308): "Efficacy analyses were performed on the randomized set (all randomized patients)...The Markov chain Monte Carlo method for multiple imputation was used to account for missing data." Table 2: 234 analysed participants Comment: done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02326298) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported Results are posted on ClinicalTrials.gov

Gottlieb CIMPASI-2 2018

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind trial Date of study: December 2014 - December 2016 Location: World-wide Phase 3
Participants	**Randomised**: 227 participants **Inclusion criteria** • Provided informed consent • Adult men or women ≥ 18 years • Chronic plaque psoriasis for ≥ 6 months • Baseline PASE ≥ 12 and BSA ≥ 10% and PGA score ≥ 3 • Candidate for systemic psoriasis therapy and/or phototherapy and/or chemophototherapy • Other protocol-defined inclusion criteria may apply **Exclusion criteria** • Erythrodermic, guttate, generalised pustular form of psoriasis

Gottlieb CIMPASI-2 2018 *(Continued)*

- History of current, chronic, or recurrent infections of viral, bacterial, or fungal origin as described in the protocol
- Congestive heart failure
- History of a lymphoproliferative disorder including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease
- History of other malignancy concurrent malignancy as described in the protocol
- History of, or suspected, demyelinating disease of the central nervous system (e.g. multiple sclerosis or optic neuritis)
- 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
- Any other condition which, in the Investigator's judgment, would make the person unsuitable for participation in the study
- Other protocol-defined exclusion criteria may apply

Dropouts and withdrawals

- 15/227 (6.6%); Certolizumab 400 (4), Certolizumab 200 (7), placebo group (4)
- Adverse events: Certolizumab 400 (1), Certolizumab 200 (3), placebo group (0)
- Withdrawal: Certolizumab 400 (1), Certolizumab 200 (2), placebo group (3)
- Lost to follow-up: Certolizumab 400 (0), Certolizumab 200 (2), placebo group (1)
- Other reason:Certolizumab 400 (2), Certolizumab 200 (0), placebo group (0)

Interventions	**Intervention** A. Certolizumab pegol (400 mg at weeks 0, 2, 4, followed by certolizumab pegol 200 mg every 2 weeks from week 6 to week 14) (n = 91) **Control intervention** B. Certolizumab pegol (certolizumab pegol 400 mg every 2 weeks through week 14) (n = 87) C. Placebo (n = 49)
Outcomes	**At week 16** **Primary composite outcome** • PASI 75 • PGA 0/1 **Secondary outcomes** • PASI 90 • DLQI
Notes	Funding source Quote (p 302): "Supported by Dermira Inc and UCB Inc." Conflicts of interest Quote (p 302): "Dr Gottlieb has consulted and/or received other fees from Janssen Inc, Celgene Corp, Bristol-Myers Squibb Co, Beiersdorf Inc, AbbVie, UCB, Novartis, Incyte, Eli Lilly, Reddy Labs, Valeant, Dermira Inc, Allergan, and Sun Pharmaceutical Industries; and has received research or educational grants (paid to TuftsMedical Center) from Janssen Incyte, Lilly, Novartis, Allergan, and LEO Pharma. Dr Blauvelt has received honoraria or fees for consulting, being a clinical investigator, and/or speaker for AbbVie, Aclaris, Allergan, Almirall, Amgen, Boehringer Ingelheim, Celgene, Dermavant, Dermira Inc, Eli Lilly, Genentech/Roche, GlaxoSmith-Kline, Janssen, LEO Pharma,Merck Sharp & Dohme, Novartis, Pfizer, Purdue Pharma, Regeneron, Sandoz, Sanofi Genzyme, Sienna Pharmaceuticals, Sun Pharma, UCB Pharma, Valeant, and Vidac. Dr Leonardi has received fees or honoraria for consulting, speak-

Gottlieb CIMPASI-2 2018 *(Continued)*

ing, or serving on the advisory board for AbbVie, Actavis, Amgen, Boehringer Ingelheim Pharma, Celgene, Coherus, Corrona, Dermira Inc, Eli Lilly, Galderma, Glenmark, Janssen, LEO Pharma, Merck, Novartis, Pfizer, Sandoz, Stiefel, UCB Pharma, Vitae, and Wyeth. Dr Poulin has received research grants as an investigator for AbbVie, Baxter, Boehringer Ingelheim Pharma, Celgene, Centocor/Janssen, Eli Lilly, EMD Serono, GlaxoSmithKline, LEO Pharma, MedImmune, Merck, Novartis, Pfizer, Regeneron, Takeda, and UCB Pharma; and has received honoraria speaking for AbbVie, Celgene, Janssen, Eli Lilly, LEO Pharma, Novartis, Regeneron, and Sanofi Genzyme. Dr Reich has received speaker's fees or honoraria from and/or served on the advisory board for AbbVie, Amgen, Biogen, Boehringer Ingelheim Pharma, Celgene, Centocor, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Eli Lilly, Medac, Merck Sharp & Dohme, Novartis, Ocean Pharma, Pfizer, Regeneron, Takeda, UCB Pharma, and Xenoport. Dr Thaç has received research support from AbbVie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Celgene, Dignity, Eli Lilly, Forward-Pharma, GlaxoSmithKline, LEO Pharma, Janssen-Cilag, Maruho, Merck Sharp & Dohme, Mitsubishi Pharma, Novartis, Pfizer, Roche, Regeneron, and Sandoz; received honoraria from AbbVie, Biogen, Celgene, Janssen, LEO Pharma, Pfizer, Roche-Possay, Novartis, and Mundipharma; served as a consultant for AbbVie, Biogen, Celgene, Dignity, Galapagos, Maruho, Mitsubishi, Novartis, Pfizer, and Xenoport; and sat on the scientific advisory boards for AbbVie, Amgen, Biogen, Celgene, Eli Lilly, GlaxoSmithKline, LEO Pharma, Pfizer, Novartis, Janssen, Mundipharma, and Sandoz. Ms Drew and Dr Burge have received stock options fromDermira Inc. Mr Peterson owns stock in UCB Inc. Dr Arendt owns stock in and has received stock options from UCB Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (pp 303-4): "CIMPASI-1 (NCT02326298) and CIMPASI-2 (NCT02326272) are ongoing, replicate, phase 3, randomized, double-blinded, multicenter... At the baseline visit, an interactive voice web response system was used to assign patients to... according to the randomization schedule produced by an independent biostatistician (2:2:1, stratified by site)." Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (pp 303-4): "CIMPASI-1 (NCT02326298) and CIMPASI-2 (NCT02326272) are ongoing, replicate, phase 3, randomized, double-blinded, multicenter... At the baseline visit, an interactive voice web response system was used to assign patients to... according to the randomization schedule produced by an independent biostatistician (2:2:1, stratified by site)." Comment: Probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (pp 303-4): "CIMPASI-1 (NCT02326298) and CIMPASI-2 (NCT02326272) are ongoing, replicate, phase 3, randomized, double-blinded, multicenter... to assign patients to subcutaneous treatment with CZP 400 mg every 2 weeks, CZP 200 mg every 2 weeks (after loading dose of CZP 400 mg at weeks 0, 2, and 4), or placebo every 2 weeks until week 16 (initial treatment period)" Comment: Probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (pp 303-4): "CIMPASI-1 (NCT02326298) and CIMPASI-2 (NCT02326272) are ongoing, replicate, phase 3, randomized, double-blinded, multicenter... to assign patients to subcutaneous treatment with CZP 400 mg every 2 weeks, CZP 200 mg every 2 weeks (after loading dose of CZP 400 mg at weeks 0, 2, and 4), or placebo every 2 weeks until week 16 (initial treatment period)" Comment: Probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 227 Management of missing data: Quote (p 308): "Efficacy analyses were performed on the randomized set (all randomized patients)...The Markov chain

Gottlieb CIMPASI-2 2018 *(Continued)*

		Monte Carlo method for multiple imputation was used to account for missing data." Table 2: 227 analysed participants Comment: done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02326272). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported Results are posted on ClinicalTrials.gov

Griffiths ACCEPT 2010

Study characteristics	
Methods	RCT, active-controlled, open-label trial Date of study: 26 March 2007 - 15 January 2009 Location: 67 centres in Manchester, UK
Participants	**Randomised**: 903 participants (mean age 45 years, 613 male) **Inclusion criteria** • Participants with moderate-severe psoriasis • Authors' assessment > 6 months, PASI ≥ 12, PGA > 3, BSA > 10% • Age ≥ 18 years • Non-response to phototherapy • Non-response to conventional systemic treatment **Exclusion criteria** • Had received biologics • Had an active infection • Had past history of malignant tumours **Dropouts and withdrawals** • 24/903 (2.7%) • Ustekinumab 45 mg (8): AE (2), lost to follow-up (2), other (4) • Ustekinumab 90 mg (5): AE (1), lost to follow-up (2), other (2) • Etanercept (11): AE (5), lost to follow-up (1), other (5)
Interventions	**Intervention** A. Ustekinumab (n = 209), SC, 45 mg, weeks 0 - 4, 4 weeks **Control intervention** B. Ustekinumab (n = 347), SC, 90 mg, weeks 0 - 4, 4 weeks C. Etanercept (n = 347), SC, 50 mg x 2/weeks, 12 weeks
Outcomes	Assessments at 12 weeks

Griffiths ACCEPT 2010 *(Continued)*

Primary outcomes of the trial

- PASI 75

Secondary outcomes of the trial

- Number of participants PGA 0/1 at week 12
- PASI 90 at weeks 8 - 12
- Difference PASI at week 12 and 12 weeks after retreatment on recurrence of psoriasis
- AEs

Notes	Funding, Quote (p 127): "Supported by Centocor Research and Development." 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 & 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 & Johnson and having equity and holding stock options in Johnson & Johnson; Dr. Zhou, being an employee of Johnson & Johnson, having equity and holding stock options in Johnson & Johnson, and having equity in Wyeth; Dr. Fidelus-Gort, being a former employee of Johnson & Johnson and having equity and holding stock options in Johnson & Johnson; and Dr. Goldstein, receiving consulting fees from Centocor. No other potential conflict of interest relevant to this article was reported."

Risk of bias

Bias	Authors' judgement	Support for judgement
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

Griffiths ACCEPT 2010 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00454584). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Griffiths EGALITY 2017

Study characteristics	
Methods	Randomised, active-controlled, double-blind phase 3 trial date: 24 June 2013 to 30 March 2015 Location: 74 centres in 11 European countries and South Africa
Participants	**Total sample size**: 531 **Inclusion criteria** • Men or women at least 18 years of age at time of screening • Chronic plaque-type psoriasis diagnosed for at least 6 months before baseline • Moderate-to-severe psoriasis as defined at baseline by: PASI score of 10 or greater and, Investigator´s Global Assessment score of 3 or greater (based on a scale of 0 - 4) and, BSA affected by plaque-type psoriasis of 10% or greater • Chronic plaque-type psoriasis patients who have previously received phototherapy or systemic psoriasis therapy at least once or who are candidates for such therapies in the opinion of the investigator **Exclusion Criteria** • Forms of psoriasis other than chronic plaque-type • Drug-induced psoriasis • Ongoing use of prohibited treatments • Previous exposure to etanercept • Active ongoing inflammatory diseases other than psoriasis that might confound the evaluation of the benefit of treatment with etanercept **Dropouts and withdrawals** • 20/531 (3.8%); GP2015 group (8), etanercept group (12) • Protocol deviation: GP2015 group (1), etanercept group (1) • Participant's decision: GP2015 group (2), etanercept group (5) • AEs: GP2015 group (4), etanercept group (3) • Lost to follow-up: GP2015 group (1), etanercept group (0) • Death: GP2015 group (0), etanercept group (1) • Others: GP2015 group (0), etanercept group (2)
Interventions	**Intervention** A. GP2015, n = 264 **Control intervention** B. Etanercept ((Enbrel; Amgen Inc., Thousand Oaks, CA, USA; European Union authorised), n = 267 50 mg subcutaneous injection until week 12
Outcomes	**Assessment at week 12**

Griffiths EGALITY 2017 *(Continued)*

Primary outcome

- proportion of participants who achieved PASI 75

Secondary outcomes

- PASI 50, 75, 90 and 100 response rates
- IGA of disease activity
- Safety
- Tolerability and immunogenicity

Notes

Funding source:

Quote (p 928): "The study was funded by Hexal AG, a Sandoz company. The funder had a role in the study design, data collection, data analysis and manuscript preparation."

Conflict of interest

Quote (appendix): "Dr Gerdes has been an advisor and/or received speakers' honoraria and/or received grants and/or participated in clinical trials of the following companies: Abbott/AbbVie, Almirall-Hermal, Amgen, Bayer HealthCare, Biogen
Idec, Bioskin, Boehringer-Ingelheim, Celgene, Centocor, Dermira, Eli Lilly, Foamix, Forward Pharma, Galderma,
Hexal AG, Isotechnika, Janssen-Cilag, Leo Pharma, Medac, Merck Serono, Mitsubishi Tanabe, MSD, Novartis,
Pfizer, Sandoz Biopharmaceuticals, Schering-Plough, Takeda, Teva, UCB Pharma, VBL therapeutics and Wyeth
Pharma. Professor Thaci has received research support from Abbvie, Almiral, Amgen, Astellas, Biogen-Idec, Boehringer-
Ingelheim, Celgene, Dignity, Elli-Lilly, Forward-Pharma, GlaxoSmithKline, Leo, Janssen-Cilag, Maruho, MSD, Mitsubishi Pharma, Novartis, Pfizer, Roche and Sandoz and honoraria from AbbVie, Biogen-Idec, Celgene, Janssen, Leo, Mundipharma, Novartis, Pfizer and Roche-Possay. Professor Thaci has acted as a consultant for Abbvie, Biogen-Idec, Celgene, Dignity, Galapagos, Maruho, Mitsubishi, Novartis, Pfizer and Xenoport and been part of scientific advisory boards for AbbVie, Amgen, Biogen-Idec, Celgene, Eli-Lilly, GlaxoSmithKline, Janssen, Leo-Pharma, Mundipharma, Novartis, Pfizer and Sandoz. Professor Griffiths has received consultancy/honoraria and/or research funding from Abbvie, Galderma, Janssen, LEO-Pharma, Lilly, MSD, Novartis, Pfizer, Regeneron, Roche, Sandoz, Sun Pharmaceuticals and UCB Pharma. Professor Arenberger has received grants from Novartis. J Poetzl and H Woehling are employees of Hexal AG. G Wuerth and M Afonso were employees of Hexal AG at the time of the study.3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 929-Supplemental Appendix): "EGALITY was a multicentre, randomized, double-blind, confirmatory efficacy and safety study conducted..In treatment period 1, patients were randomized 1 : 1 to self-administer50 mg GP2015 or 50 mg ETN."; " During treatment period 1, patients were randomised via the Interactive Response Technology (IRT) that assigned a unique patient identification number in the IRT system with the treatment arm to which the patient had been assigned. Randomisation was stratified by body weight (<90 kg; ≥90 kg) and prior therapy (no prior systemic therapy, any prior systemic therapy including biologic immunomodulating agents, or prior treatment with a tumour necrosis factor [TNF antagonist])." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 929-Supplemental Appendix): "EGALITY was a multicentre, randomized, double-blind, confirmatory efficacy and safety study conducted..In treatment period 1, patients were randomized 1 : 1 to self-administer50 mg GP2015 or 50 mg ETN."; " During treatment period 1, patients were randomised via the

Griffiths EGALITY 2017 *(Continued)*

		Interactive Response Technology (IRT) that assigned a unique patient identification number in the IRT system with the treatment arm to which the patient had been assigned. Randomisation was stratified by body weight (<90 kg; ≥90 kg) and prior therapy (no prior systemic therapy, any prior systemic therapy including biologic immunomodulating agents, or prior treatment with a tumour necrosis factor [TNF antagonist])" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 929): "EGALITY was a multicentre, randomized, double-blind, confirmatory efficacy and safety study conducted..In treatment period 1, patients were randomized 1 : 1 to self-administer50 mg GP2015 or 50 mg ETN." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 929): "EGALITY was a multicentre, randomized, double-blind, confirmatory efficacy and safety study conducted..In treatment period 1, patients were randomized 1 : 1 to self-administer50 mg GP2015 or 50 mg ETN." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 531 Management of missing data: Quote (Supplemental appendix): "The FAS during treatment period 1 included all randomised patients to whom the study treatment was assigned. For the primary endpoint analysis based on the FAS missing values with respect to the PASI response at week 12 were included as non-responders regardless of the reason for missing data." Equivalence trial: Quote (p 931): "The primary efficacy analysis was based on the per protocol set (PPS), which consisted of all patients who completed the study until week 12 without major protocol deviations...The analysis was repeated on the full analysis set (FAS) following the intent-to-treat principle as a sensitivity analysis." Table 1: Both per protocol and full-set analyses Comment: done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01891864) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. Results posted on ClinicalTrials.gov

Griffiths UNCOVER-2 2015

Study characteristics	
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	**Randomised**: 1224 participants (mean age 45 years, 821 male) **Inclusion criteria**

Griffiths UNCOVER-2 2015 *(Continued)*

- Participants with moderate-severe psoriasis (PASI ≥ 12 or BSA ≥ 10), age ≥ 18 years

Exclusion criteria

- Pregnancy, immunosuppression, kidney insufficiency, liver insufficiency, past history of malignant tumours, active infection, uncontrolled cardiovascular disorder, uncontrolled diabetes, uncontrolled hypertension
- Had received etanercept and anti IL17

Dropouts and withdrawals

- 63/1224 (5%)
- Ixekizumab 4-week group (19), ixekizumab 2-week group (9), etanercept group (25), placebo (10)
- AEs: ixekizumab 4-week group (5), ixekizumab 2-week group (4), etanercept (5), placebo (1)
- Protocol violation: ixekizumab 4-week group (5), ixekizumab 2-week group (2), etanercept (4), placebo (2)
- Participant decision: ixekizumab 4-week group (6), ixekizumab 2-week group (2), etanercept (8), placebo (1)
- Lost to follow-up: ixekizumab 4-week group (2), ixekizumab 2-week group (0), etanercept (5), placebo (1)
- Investigator decision: ixekizumab 4-week group (0), ixekizumab 2-week group (1), etanercept (0), placebo (1)
- Absence of efficacy: ixekizumab 4-week group (1), ixekizumab 2-week group (0), etanercept (3), placebo (3)

Interventions	**Intervention** A. Ixekizumab (n = 347), SC, 80 mg, 2 injections week 0, 1 injection monthly **Control intervention** B. Ixekizumab (n = 351), SC, 80 mg, 2 injections week 0, 1 injection eow C. Etanercept (n = 358), SC, 50 mg 1 injection twice weekly D. Placebo (n = 168), SC
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PGA 0-1 • PASI 75 **Secondary outcomes of the trial** • PASI 90 • DLQI • AEs
Notes	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”. Declarations of interest, Quote (pp 550-1): "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 & 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 & Dohme, Novartis, Pfizer, Regen-

Griffiths UNCOVER-2 2015 *(Continued)*

eron, 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 & 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

Bias	Authors' judgement	Support for judgement
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 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 prespecified outcome in the protocol missing from the Results section (assessment of efficacy at 60 weeks), but as we assessed outcomes at induc-

Griffiths UNCOVER-2 2015 *(Continued)*

	tion phase (between 8 - 24 weeks), we judged that the risk of selective reporting was low

Griffiths UNCOVER-3 2015

Study characteristics	
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	**Randomised**: 1346 participants (mean age 46 years, 918 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12 or BSA ≥ 10), age ≥ 18 years **Exclusion criteria** • Pregnancy, immunosuppression, kidney insufficiency, liver insufficiency, past history of malignant tumours, active infection, uncontrolled cardiovascular disorder, uncontrolled diabetes, uncontrolled hypertension • Had received etanercept and anti IL17 **Dropouts and withdrawals** • 71/1346 (5%) • Ixekizumab 4-week group (10), ixekizumab 2-week group (13), etanercept group (26), placebo (22) • AEs: ixekizumab 4-week group (9), ixekizumab2-week group (8), etanercept (4), placebo (2) • Protocol violation: ixekizumab 4-week group (8), ixekizumab2-week group (7), etanercept (3), placebo (1) • Participant decision: ixekizumab 4-week group (4), ixekizumab2-week group (4), etanercept (2), placebo (3) • Lost to follow-up: ixekizumab 4-week group (2), ixekizumab2-week group (0), etanercept (2), placebo (3) • Investigator decision: ixekizumab 4-week group (1), ixekizumab2-week group (1), etanercept (2), placebo (1) • Absence of efficacy: ixekizumab 4-week group (2), ixekizumab2-week group (1), etanercept (0), placebo (0)
Interventions	**Intervention** A. Ixekizumab (n = 386), SC, 80 mg, 2 injections week 0, 1 injection monthly **Control intervention** B. Ixekizumab (n = 385), SC, 80 mg, 2 injections week 0, 1 injection eow C. Etanercept (n = 382), SC, 50 mg 1 injection twice weekly D. Placebo (n = 193), SC
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PGA 0-1

Griffiths UNCOVER-3 2015 *(Continued)*

- PASI 75

Secondary outcomes of the trial

- PASI 90
- DLQI
- AEs

Notes	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”. Declarations of interest: Quote (pp 550-1): "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 & 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 & 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 & 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

Bias	Authors' judgement	Support for judgement
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

Griffiths UNCOVER-3 2015 *(Continued)*

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 prespecified outcome in the protocol missing from the Results section (assessment of efficacy at 60 weeks), but as we assessed outcomes at induction phase (between 8 - 24 weeks), we judged that the risk of selective reporting was low

Gurel 2015

Study characteristics	
Methods	RCT, placebo-controlled, single-blind Date of study: not stated Location: one centre, Turkey
Participants	**Randomised**: 50 participants (mean age 43 years, 25 male) **Inclusion criteria** • Moderate-severe type plaque psoriasis BSA > 10% **Exclusion criteria** • Pregnancy • Had uncontrolled cardiovascular disorder • Kidney or liver insufficiencies • Had past history of malignant tumours • Had received conventional systemic treatments **Dropouts** No participants lost to follow-up
Interventions	**Intervention** Acitretine (0.3 - 0.5 mg/kg/day, 25 mg) (n = 25) **Control intervention** Placebo (n = 25) Co-invervention NBUVB

Gurel 2015 *(Continued)*

Outcomes	Assessment at 12 weeks **Primary outcome** • Not stated **Outcomes:** • Change in PASI scores from baseline • Change in self-PASI scores from baseline • Skindex 30
Notes	Funding: none Declarations of interest: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
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	Randomised 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 prespecified outcomes mentioned in the Methods section appeared to have been reported

Heydendael 2003

Study characteristics

Methods	RCT, active-controlled, open-label trial Date of study: October 1998-June 2000 Location: multicentre (> 1) in Amsterdam/the Netherlands
Participants	**Randomised**: 88 participants, mean age 40 years, 57 male **Inclusion criteria** • Participants with moderate-severe psoriasis, PASI>8,

Heydendael 2003 *(Continued)*

- Age ≥18
- Non-response to topical treatment
- Non-response to phototherapy
- Number of allowed previous treatment line: 2

Exclusion criteria

- Pregnancy, kidney insufficiency, liver insufficiency, high-risk liver function abnormalities, hepatitis B
- Had received methotrexate or ciclosporin
- Had an active infection
- Had uncontrolled diabetes (Insulin-dependent)
- Had uncontrolled cardiovascular disorder
- Had uncontrolled hypertension
- Had past history of malignant tumours

Dropouts and withdrawals

- 3/88 (3.4%)
- Methotrexate group (1): withdrew consent (1)
- Ciclosporin group (2): ineligible (2)

Interventions	**Intervention** A. Methotrexate (n = 44), orally, 15 mg/week until 4 weeks then increase up to 22.5 mg if reduction from baseline PASI < 25%, 3 divided doses with 12-h interval, 12 weeks **Control intervention** 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 **Primary outcomes of the trial** • PASI **Secondary outcomes of the trial** • Side effects • SF36
Notes	Funding sources, Quote (p 664): "Supported by a grant (OG 97-009) from the Dutch Health Authorities" Declarations of interest: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
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

Heydendael 2003 *(Continued)*

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 (pp 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
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The prespecified outcomes mentioned in the Methods section appeared to have been reported

Hunter 1963

Study characteristics	
Methods	RCT, placebo-controlled, double-blind trial Date of study: not stated Location: 1 centre in London, UK
Participants	**Randomised**: 41 participants (no description of the study population) **Inclusion criteria** • Participants with moderate-severe psoriasis **Exclusion criteria** • Not stated **Dropouts and withdrawals** • included (41) analysed (36)
Interventions	**Intervention** A. Methotrexate (n = 19), orally, 2.5 mg every day for 1 week and 1 week after **Control intervention** B. Placebo (n = 17), orally, every day for 1 week and 1 week after
Outcomes	Assessments not clearly stated (reported at 4 weeks) **Primary outcomes of the trial** • Not stated

Hunter 1963 *(Continued)*

	Outcomes of the trial
	• Scale:
	  * 0 = no improvement
	  * 1 = definite improvement
	  * 2 = marked improvement
	  * 3 = complete clearing

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
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (pp 1 and 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 (pp 1 and 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

Study characteristics

Methods	RCT, placebo-controlled, double-blind trial Date of study: March 2008 - March 2010 Location: 35 centres in Japan
Participants	**Randomised**: 160 participants (age median 45 years, 126 male) **Inclusion criteria** • Participants with moderate-severe psoriasis

Igarashi 2012 *(Continued)*

- Authors' assessment > 6 months, PASI ≥ 12, BSA > 10%
- Age > 20 years
- Non-response to topical treatment
- Non-response to phototherapy
- Number of allowed previous treatment line: 2

Exclusion criteria

- Pregnancy
- Had an active infection
- Had past history of malignant tumours

Dropouts and withdrawals

- 10/160 (6.2%)
- Withdrawn before treatment (2)
- Ustekinumab 45 mg group (64): discontinued (0)
- Ustekinumab 90 mg group (62): discontinued (4)
- Placebo (32): discontinued (4)

Interventions	**Intervention** A. Ustekinumab (n = 64), SC, 45 mg, weeks 0 - 4, every 12 weeks, 64 weeks **Control intervention** 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 **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • Proportion of participants with PGA 0/1 at week 12 • Change in DLQI from baseline at 12 weeks • Improvement from baseline to week 12 through 64 in NAPSI and joint pain, as measured by the change in VAS
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."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p 244): “randomised”

Igarashi 2012 *(Continued)*

		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
Incomplete outcome data (attrition bias) All outcomes	Low risk	160 randomised, 157 analysed (2 did not received 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 at follow-up, well-balanced number and reasons between groups.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available The prespecified outcomes mentioned in the Methods section appeared to have been reported

Ikonomidis 2017

Study characteristics	
Methods	RCT, active-controlled, single-blinded trial Date of study: January 2013 - still ongoing Location: 1 centre, Athens, Greece
Participants	**Randomised**: 150 participants (age median 51 years, 93 male) **Inclusion criteria** • Participants with plaque-type psoriasis • Moderate-to-severe psoriasis **Exclusion criteria** • Psoriatic arthritis or inflammatory bowel syndrome • Presence of wall motion abnormalities, and ejection fraction of ≤ 50%, history of acute coronary syndrome, familial hyperlipidaemia, diabetes mellitus, chronic obstructive pulmonary disease or asthma, moderate or severe valvular heart disease, primary cardiomyopathies, and malignant tumours

Ikonomidis 2017 *(Continued)*

- Coronary artery disease was excluded in psoriatic patients by absence of clinical history, angina, and reversible myocardial ischaemia, as assessed by treadmill test and stress echocardiography

Dropouts and withdrawals

- Not stated

Interventions	**Intervention** A. Ustekinumab 45 mg, SC, at baseline and at 4 and 16 weeks (n = 50) **Control intervention** B. Etanercept 50 mg SC, 2 days a week for 16 weeks (n = 50) C. Cyclosporine 2.5 to 3 mg/kg daily (n = 50) for 16 weeks
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • Comparison of effect (improvement or deterioration) of treatment with biological vs non biological agents on endothelial function in psoriasis • Comparison of effect (improvement or deterioration) of treatment with biological vs non biological agents on vascular function in psoriasis • Comparison of effect (improvement or deterioration) of treatment with biological vs non biological agents on cardiac function in psoriasis **Secondary outcomes of the trial** • Differences and similarities in endothelial function between psoriasis and control groups • Differences and similarities in vascular function between psoriasis and control groups • Differences and similarities in cardiac function between psoriasis and control groups
Notes	Funding source, Quote (p 12): "This study was supported by a grant from the Hellenic Cardiology Society and Hellenic Society of Lipidiology and Atherosclerosis. This study was not funded by any pharmaceutical company and that none of the coauthors received support from the manufacturers of the agents used for treatment" Declarations of interest (p 12): "none"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 5) "Patients were randomized to receive ... Randomization was performed by an attending dermatologist (E.P.) using a table of random numbers as reproduced from the online randomization software http://www.graphpad.com/quickcalcs/ index.cfm." Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (p 5) "Patients were randomized to receive ... Randomization was performed by an attending dermatologist (E.P.) using a table of random numbers as reproduced from the online randomization software http://www.graphpad.com/quickcalcs/ index.cfm." Comment: Probably done
Blinding of participants and personnel (performance bias)	High risk	Quote (p 5): "Studies were performed using a Vivid 7 (GE Medical Systems, Horten, Norway) ultrasound system. All studies were digitally stored in a com-

Ikonomidis 2017 *(Continued)*

All outcomes		puterized station (Echopac 201; GE Medical Systems, Horten, Norway) and were analyzed by 2 observers, blinded to clinical and laboratory data." Comment: participants not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (p 5): "Studies were performed using a Vivid 7 (GE Medical Systems, Horten, Norway) ultrasound system. All studies were digitally stored in a computerized station (Echopac 201; GE Medical Systems, Horten, Norway) and were analyzed by 2 observers, blinded to clinical and laboratory data." Comment: participants not blinded. Physicians were blinded for cardiac outcomes, but not for PASI evaluation, so rated high risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote (p 6): "All analyses were intention to treat." No statement on number of missing data and how authors dealt with it
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02144857) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Jin 2017

Study characteristics	
Methods	RCT, placebo-controlled trial Date of study: not stated Location: China (number of centres not specified
Participants	**Randomised**: 18 participants (age median 48 years, 11 male) **Inclusion criteria** • Participants with moderate-severe psoriasis • Authors' assessment > 6 months, PASI ≥ 12, BSA > 10% • Age > 18 years • Candidates for systemic therapy or phototherapy for psoriasis **Exclusion criteria** • Non-plaque or drug-induced psoriasis, or other skin conditions that would interfere with psoriasis evaluation • Inability to discontinue current systemic therapy (for at least 4 weeks), topical therapy,or phototherapy (for at least 2 weeks); concomitant oral or injection of corticosteroids; and previous treatment with efalizumab or having participated in studies involving oral tofacitinib • Patients were also excluded from the study if they were pregnant or had immune-deficient diseases or severe systemic disorders **Dropouts and withdrawals** • No statement
Interventions	**Intervention** A. Tofacitinib (n = 7), orally 10 mg, twice a day, 16 weeks

Jin 2017 *(Continued)*

	Control intervention B. Tofacitinib (n = 5), orally, 5 mg, twice a day, 16 weeks C. Placebo (n = 6)
Outcomes	Assessments at 16 weeks **Outcomes of the trial (not primary ou secondary outcomes)** • PASI 75 • Serum hBD-2 concentration
Notes	Funding source: Not stated Declarations of interest (p 169): "The authors have no conflict of interest to declare"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (supplemental appendix) "The patients were randomized to receive placebo or tofacitinib 5or 10mg twice daily (b.i.d.) for 16 weeks" 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 allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (supplemental appendix) "The patients were randomized to receive placebo or tofacitinib 5or 10mg twice daily (b.i.d.) for 16 weeks" Comment: no more description than using a placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (supplemental appendix) "The patients were randomized to receive placebo or tofacitinib 5or 10mg twice daily (b.i.d.) for 16 weeks" Comment: no more description than using a placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote (supplemental appendix): "All analyses were intention to treat." No statement on number of missing data and how authors dealt with it
Selective reporting (reporting bias)	Low risk	Comment: no protocol for the study available on ClinicalTrials.gov The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Khatri 2016

Study characteristics

Methods	Randomised, double-blind, active-controlled trial Date: April 2015 - August 2016 Location: USA (1 centre: Mont Sinai)

Khatri 2016 *(Continued)*

Participants	**Total sample size**: 12 **Inclusion criteria** • Present with chronic moderate-severe plaque psoriasis based on a confirmed (by a dermatologist) diagnosis of chronic plaque psoriasis for ≥ 6 months prior to baseline • Active psoriatic skin lesions of plaque psoriasis (Ps) • Are a candidate for phototherapy and/or systemic therapy • Men must agree to use a reliable method of birth control or remain abstinent during the study and for ≥ 12 weeks after stopping treatment • Women must agree to use reliable birth control or remain abstinent during the study and for ≥ 12 weeks after stopping treatment **Exclusion criteria** • Are unable to commit to the photography schedule for the duration of the study • Have participated in any study with interleukin 17 (IL-17) or (IL-23) antagonists, including ixekizumab • Serious disorder or illness other than psoriasis • Serious infection within the last 3 months • Breastfeeding or nursing (lactating) women **Dropouts and withdrawals** • No missing data at week 12 (ClinicalTrials.gov)
Interventions	**Intervention**: A. Ixekizumab 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, n = 6 **Control intervention**: B. Ixekizumab 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, n = 6
Outcomes	**At week 12,** **Primary outcome** • Patient's Global Assessment of Disease Severity **Secondary outcomes** • Itch Numeric Rating Scale • DLQI • PASI • BSA • AEs
Notes	FUNDING: Quote (p 33) "Funding provided by Eli Lilly and Company." Conflict of interest: Quote (p 33) "Dr. Khattri has received grant/research support from and is an investigator for Eli Lilly and Company. Dr. Lebwohl is an employee of Mount Sinai, which receives research funds from AbGenomics, Amgen, Anacor, Boehringer Ingelheim, Celgene, Ferndale, Janssen Biotech, Kadmon, LEO Pharma, Eli Lilly and Company, Medimmune, Novartis, Pfizer, Sun Pharma, and Valeant. Dr. Goldblum, Ms. Solotkin,

Khatri 2016 *(Continued)*

	Ms. Ridenour, and Dr. Yang own stock and are employees of Eli Lilly and Company. Dr. Amir and Dr. Min have no conflicts of interest relevant to the content of this article."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p 34): "For this 48-week, randomized, single-center, open-label study, patients were randomized at a ratio of 1:1 to receive 80mg of ixekizumab either every two (Q2W) or four (Q4W) weeks during the induction dosing period (0–12 weeks) following an initial 160mg dose of ixekizumab." 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 allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (p 34): "For this 48-week, randomized, single-center, open-label study, patients were randomized at a ratio of 1:1 to receive 80mg of ixekizumab either every two (Q2W) or four (Q4W) weeks during the induction dosing period (0–12 weeks) following an initial 160mg dose of ixekizumab." Comment: no blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (p 34): "For this 48-week, randomized, single-center, open-label study, patients were randomized at a ratio of 1:1 to receive 80mg of ixekizumab either every two (Q2W) or four (Q4W) weeks during the induction dosing period (0–12 weeks) following an initial 160mg dose of ixekizumab." Comment: no blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote (p 35 - ClinicalTrials.gov): "Response rates were summarized using non-responder imputation to account for missing data." No missing data at week 12 Comment: done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02387801) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Krueger 2007

Study characteristics

Methods	RCT, placebo-controlled, double-blind trial Date of study: June 2003 – March 2005 Location: 46 centres in Utah, USA
Participants	**Randomised**: 320 participants Ustekinumab 12/23 45 mg (64) (mean age 46 years; 38 male)

Krueger 2007 *(Continued)*

	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) **Inclusion criteria** • Participants with moderate-severe psoriasis • Authors' assessment > 6 months, PASI ≥ 12, BSA > 10% • Age ≥ 18 **Exclusion criteria** • Had received biologics (ustekinumab 12/23) • Had an active infection • Had past history of malignant tumours **Dropouts and withdrawals** • 32/320 (8.8%) • Ustekinumab 12/23 45 mg (7) (received no treatment (1) unsatisfactory therapeutic effect (2) AE (5)) • Ustekinumab 12/23 90 mg (4) (received no treatment (1), other (3)) • Ustekinumab 12/23 45 mg 4-weekly (3) (AE (2), withdrew consent (1)) • Ustekinumab 12/23 90 mg 4-weekly (4) (unsatisfactory therapeutic effect (1), AE (1), withdrew consent (1), other (1)) • Placebo (13) (unsatisfactory therapeutic effect (6), lost to follow-up (1), withdrew consent (2), other (4))
Interventions	**Intervention** A. Ustekinumab 12/23 (n = 64), SC, 45 mg, 45 mg 1 dose, 1 week **Control intervention** B. Ustekinumab 12/23 (n = 64), SC, 90 mg, 45 mg 1 dose, 1 week C. Ustekinumab 12/23 (n = 64), SC, 45 mg, 45 mg/week, 4 weeks D. Ustekinumab 12/23 (n = 64), SC, 90 mg, 45 mg/week, 4 weeks E. Placebo (n = 64), SC
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • Proportion of participants achieving ≥ PASI 75 **Secondary outcomes of the trial** • Safety • PGA • DLQI
Notes	Funding source (p 590): "Supported by Centocore, Malvern, PA" 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,

Krueger 2007 *(Continued)*

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 & Johnson; and Dr. Wang reports being a stockholder in Johnson & Johnson. No other potential conflict of interest relevant to this article was reported."

Risk of bias

Bias	Authors' judgement	Support for judgement
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, but 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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Krueger 2016a

Study characteristics

Methods	RCT, placebo-controlled, double-blind

Krueger 2016a *(Continued)*

	Date of study: March 2013 - November 2013 Location: 6 centres in the USA
Participants	**Randomised**: 12 participants (mean age 45.5 years, 8 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12 or BSA ≥ 10), age ≥ 18 years **Exclusion criteria** • Pregnancy, immunosuppression, kidney insufficiency, liver insufficiency, past history of malignant tumours, active infection, uncontrolled cardiovascular disorder, uncontrolled diabetes, uncontrolled hypertension **Dropouts and withdrawals** • 1/12 (1%); • Lost to follow-up: tofacitinib (1)
Interventions	**Intervention** A. Tofacitinib (n = 9), orally, 10 mg twice daily **Control intervention** B. Placebo (n = 3)
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PGA 0-1 • PASI 75 **Secondary outcomes of the trial** • AEs
Notes	Funding source: 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.”. 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. Tatulych are employees of Pfizer Inc. The rest of the authors declare that they have no relevant conflicts of interest."

Risk of bias

Bias	Authors' judgement	Support for judgement
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”

Krueger 2016a *(Continued)*

		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: not mentioned
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01710046) The prespecified outcomes in the protocol or those mentioned in the Methods section have been reported in the Results section

Laburte 1994

Study characteristics	
Methods	RCT, active-controlled, open-label trial Date of study: not stated Location: 27 centres worldwide
Participants	**Randomised**: 251 participants (mean age 41 years, 176 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 18) **Exclusion criteria** • Kidney insufficiency • Had past history of malignant tumours **Dropouts and withdrawals** • Not stated
Interventions	**Intervention** A. Ciclosporin A (n = 119), orally, 2.5 mg/kg/d, 12 weeks **Control intervention**

Laburte 1994 *(Continued)*

	B. Ciclosporin A (n = 132), orally, 5 mg/kg/d, 12 weeks
Outcomes	Period assessments: 12 weeks **Primary or secondary outcomes of the trial**: • PASI 75 • PASI < 8 **Outcmes of the trial** • Overall assessment score • Nails, pruritus, severity, arthropathy • Safety
Notes	Funding and declarations of interest: not stated, but the first author was employed by Sandoz Pharma Ltd

Risk of bias

Bias	Authors' judgement	Support for judgement
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 prespecified outcomes mentioned in the Methods section appeared to have been reported

Langley ERASURE 2014

Study characteristics

Methods	RCT, placebo-controlled, double-blind trial Date of study: June 2011 - April 2013 Location: 88 centres worldwide (Erasure)

Langley ERASURE 2014 *(Continued)*

Participants	**Randomised**: 738 participants mean age 45 years, 509 male **Inclusion criteria** • Participants with moderate-severe psoriasis • PASI ≥ 12, IGA 3 - 4, BSA ≥ 10% • Age ≥ 18 • Non-response to topical treatment • Non-response to phototherapy • Non-response to conventional systemic treatment **Exclusion criteria** • Immunosuppression, • Had an active infection • Had past history of malignant tumours **Dropouts and withdrawals** • 38/738 (5.1%) • AEs: secukinumab 300 (3), secukinumab 150 (5), placebo (4) • Lack of efficacy: secukinumab 300 (1), secukinumab 150 (1), placebo (0) • Withdrew consent: secukinumab 300 (1), secukinumab 150 (9), placebo (8) • Lost to follow-up: secukinumab 300 (0), secukinumab 150 (0), placebo (3) • Protocol deviation: secukinumab 300 (1), secukinumab 150 (0), placebo (1) • Became pregnant: secukinumab 300 (1), secukinumab 150 (0), placebo (0)
Interventions	**Intervention** A. Secukinumab 300 (n = 245), SC, 300 mg, weeks 0, 1, 2, 3, 4 and every 4 weeks, 12 weeks **Control intervention** B. Secukinumab 150 (n = 245), SC, 150 mg, weeks 0, 1, 2, 3, 4 and every 4 weeks, 12 weeks C. Placebo (n = 248), SC, weeks 0, 1, 2, 3, 4 and every 4 weeks
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PASI 75 • IGA score at 0 or 1 **Secondary outcomes of the trial** • PASI 50, PASI 75, PASI 90, PASI 100 • Response of 0 or 1 on the modified IGA at each study visit until week 52 • Score of 0 or 1 on the DLQI at weeks 12 and 52
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

Risk of bias

Bias	Authors' judgement	Support for judgement

Langley ERASURE 2014 *(Continued)*

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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Langley FIXTURE 2014

Study characteristics	
Methods	RCT, active, placebo-controlled, double-blind trial Date of study: June 2011 - June 2013 Location: 231 centres worldwide (Fixture)
Participants	**Randomised**: 1306 participants, mean age 44 years, 929 male **Inclusion criteria** • Participants with moderate-severe psoriasis • PASI ≥ 12, IGA 3 - 4, BSA ≥ 10% • Age ≥ 18 • Non-response to topical treatment

Langley FIXTURE 2014 *(Continued)*

- Non-response to phototherapy
- Non-response to conventional systemic treatment

Exclusion criteria

- Immunosuppression
- Had an active infection
- Had past history of malignant tumours

Dropouts and withdrawals

- 73/1306 (5.6%)
- AEs: sekunimab 300 (4), sekunimab 150 (2), etanercept (6), placebo (2)
- Lack of efficacy: sekunimab 300 (0), sekunimab 150 (0), etanercept (2), placebo (9)
- Withdrew consent: sekunimab 300 (5), sekunimab150 (5), etanercept (5), placebo (10)
- Physician decision: sekunimab 300 (1), sekunimab 150 (2), etanercept (0), placebo (2)
- Protocol deviation: sekunimab 300 (5), sekunimab 150 (3), etanercept (3), placebo (0)
- Other: sekunimab 300 (0), sekunimab 150 (0), etanercept (5), placebo (2)

Interventions	**Intervention** A. Sekunimab 300 (n = 327), SC, 300 mg, weeks 0, 1, 2, 3, 4 and every 4 weeks, 12 weeks **Control intervention** B. Sekunimab 150 (n = 327), SC, 150 mg, weeks 0, 1, 2, 3, 4 and every 4 weeks, 12 weeks C. Etanercept 50 (n = 326), SC, 50 mg/week twice a week, 12 weeks D. Placebo (n = 326), SC, weeks 0, 1, 2, 3, 4 and every 4 weeks, 12 weeks
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PASI 75 • and a IGA score at 0 or 1 **Secondary outcomes of the trial** • PASI 50, PASI 75, PASI 90, PASI 100 • Response of 0 or 1 on the modified IGA at each study visit until week 52 • Score of 0 or 1 on the DLQI at weeks 12 and 52
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."

Risk of bias

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

Langley FIXTURE 2014 *(Continued)*

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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Langley IXORA-P 2018

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind trial Date of study: August 2015 - August 2017 Location: worldwide Phase 3
Participants	**Randomised**: 1227 participants **Inclusion criteria** • Present with chronic plaque psoriasis for ≥ 6 months prior to enrolment • ≥ 10% BSA of psoriasis at screening and at enrolment • sPGA score of ≥ 3 and PASI score of ≥ 12 at screening and at enrolment • Candidates for phototherapy and/or systemic therapy • Participant must agree to use reliable method of birth control during the study; women must continue using birth control for ≥ 12 weeks after stopping treatment **Exclusion criteria** • Predominant pattern of pustular, erythrodermic, or guttate forms of psoriasis

Langley IXORA-P 2018 *(Continued)*

- History of drug-induced psoriasis
- Cannot avoid excessive sun exposure or use of tanning booths for ≥ 4 weeks prior to enrolment and during the study
- 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
- Concurrent or recent use of any biologic agent
- Have participated in any study with ixekizumab
- Received a live vaccination within 12 weeks prior to enrolment
- Serious disorder or illness other than psoriasis
- Ongoing or serious infection within the last 12 weeks or evidence of TB
- Major surgery within 8 weeks of baseline, or will require surgery during the study
- Breastfeeding or nursing (lactating) women

Dropouts and withdrawals

- 148/1227 (12.1%)
- Ixekizumab 4-week group (38), ixekizumab 2-week group (72), ixekizumab 2/4-week group (36)
- AEs: Ixekizumab 4-week group (5), ixekizumab 2-week group (17), ixekizumab 2/4-week group (13)
- Protocol violation: Ixekizumab 4-week group (1), ixekizumab 2-week group (4), ixekizumab 2/4-week group (1)
- Participant decision: ixekizumab 4-week group (11), ixekizumab2-week group (25) ixekizumab 2/4-week group (11)
- Lost to follow-up: Ixekizumab 4-week group (9), ixekizumab 2-week group (11), ixekizumab 2/4-week group (7)
- Investigator decision: ixekizumab 4-week group (2), ixekizumab2-week group (4) ixekizumab 2/4-week group (0)
- Absence of efficacy: Ixekizumab 4-week group (4), ixekizumab 2-week group (6), ixekizumab 2/4-week group (5)
- death: Ixekizumab 4-week group (2), ixekizumab 2-week group (2), ixekizumab 2/4-week group (2)
- Others: ixekizumab 4-week group (3), ixekizumab2-week group (5) ixekizumab 2/4-week group (1)

Interventions	**Intervention** A. 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), n = 611 **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), n = 310 C. 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, with a dose adjustment to Q2W until week 50 for patients meeting prespecified criteria to which investigators were blinded (Q4W/Q2W dose adjustment), n = 306
Outcomes	**At week 52** **Primary composite outcome** • PGA 0/1 • Achieving 75% improvement in PASI 75 **Secondary outcomes** • PASI 90 • PASI 75 • NAPSI • Psoriasis Scalp Severity Index • Palmoplantar PASI

Langley IXORA-P 2018 *(Continued)*

- Itch Numeric Rating Scale
- DLQI

Notes	Funding Quote (p 1315): "This study was funded in full by Eli Lilly and Company, Indianapolis, IN, U.S.A" Conflict of interest Quote (p 1323): "R.G.L. has been a consultant and/or scientific adviser and/or investigator and/or scientific officer and/or speaker for AbbVie, Amgen, Celgene, Pfizer, Eli Lilly and Company, Novartis and Boehringer Ingelheim. K.P. has been a consultant and/or scientific adviser and/or investigator and/or scientific officer and/or speaker for Amgen, Anacor, AbbVie, Akros, Allergan, Astellas, AstraZeneca, Baxalta, Baxter, Bristol-Myers Squibb, Boehringer Ingelheim, Can-Fite, Celgene, Coherus, Dermira, Dow Pharma, Eli Lilly and Company, Forward Pharma, Galderma, Genentech, GlaxoSmithKline, Janssen, Kyowa Hakko Kirin, LEO Pharma, Medimmune, Meiji Seika Pharma, Merck (MSD), Merck-Serono, Mitsubishi Pharma, Novartis, Pfizer, Regeneron, Roche, Sanofi/Genzyme, Takeda, UCB and Valeant. M.G. has been a consultant and/or scientific adviser and/or investigator and/or scientific officer and/or speaker for AbbVie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly and Company, Galderma, Janssen, LEOPharma, Novartis, Pfizer, Akros, Dermira, UCB and Coherus. A.B. has been a consultant and/or scientific adviser and/or investigator and/or scientific officer and/or speaker for AbbVie, Aclaris, Allergan, Almirall, Amgen, Boehringer Ingelheim, Celgene, Dermavant, Dermira, Genentech/Roche, GlaxoSmithKline, Janssen, Eli Lilly and Company, LEO Pharma, Merck Sharp& Dohme, Novartis, Pfizer, Purdue Pharma, Regeneron, Sandoz, Sanofi Genzyme, Sun Pharma, Sienna Pharmaceuticals, UCB, Valeant and Vidac. P.F. has been a consultant and/or scientific adviser and/or investigator and/or scientific officer and/or speaker for Abbot/AbbVie, Amgen, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Celtaxsys, Cutanea, Galderma, Genentech, GlaxoSmithKline/Stiefel, Janssen, LEO Pharma, Eli Lilly and Company, Novartis, Regeneron, Roche, Sanofi, Schering-Plough/Merck, 3M/iNova/Valeant, UCB and Wyeth/Pfizer. C.M., L.Z., N.A. and P.P. are employees of/and or own stock in Eli Lilly and Company.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 1316): "This multicentre, randomized, double-blinded, parallel group, phase III trial was conducted...Assignment to dosing regimens was determined by a computer-generated random sequence using an interactive web response system (IWRS). Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 1316): "This multicentre, randomized, double-blinded, parallel group, phase III trial was conducted...Assignment to dosing regimens was determined by a computer-generated random sequence using an interactive web response system (IWRS). Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 1316): "This multicentre, randomized, double-blinded, parallel group, phase III trial was conducted..... To maintain investigator blinding, site personnel entered an sPGA score into the IWRS every 4 weeks, beginning at week 0 through week 48." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 1316): "This multicentre, randomized, double-blinded, parallel group, phase III trial was conducted..... To maintain investigator blinding, site personnel entered an sPGA score into the IWRS every 4 weeks, beginning at week 0 through week 48."

Langley IXORA-P 2018 *(Continued)*

		Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote (p 1317): "Missing data were imputed as nonresponse (NRI). The multiple imputation (MI) method was also used to impute missing values as a sensitivity analysis..." Included population 1227, table 2 1227 Comment: done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02513550) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported Results are posted on ClinicalTrials.gov

Lebwohl AMAGINE-2 2015

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind Date of study: August 2012 - September 2014 Location: 142 centres worldwide
Participants	**Randomised**: 1831 participants (mean age 45 years, 1258 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12, PGA 3-5, BSA ≥ 10), age 18 - 75 years **Exclusion criteria** • Pregnancy • Active infection, past history of malignant tumours, active infection, kidney or liver insufficiency, uncontrolled cardiovascular disorder, uncontrolled diabetes, uncontrolled hypertension • Had Crohn's disease • Had used ustekinumab and/or anti-IL17 biologic therapy **Dropouts and withdrawals** • 55/1831 (3%): brodalumab 140 group (22), brodalumab 210 group (15), ustekinumab 45/90 group (9), placebo group (9) • Ineligibility determined: brodalumab 140 group (3), brodalumab 210 group (0), ustekinumab 45/90 group (0), placebo group (0) • AEs: brodalumab 140 group (4), brodalumab 210 group (3), ustekinumab 45/90 group (2), placebo group (0) • Lost to follow-up: brodalumab 140 group (2), brodalumab 210 group (3), ustekinumab 45/90 group (2), placebo group (2) • Death; brodalumab 140 group (0), brodalumab 210 group (1), ustekinumab 45/90 group (0), placebo group (0) • Full consent withdrawal: brodalumab 140 group (11), brodalumab 210 group (2), ustekinumab 45/90 group (3), placebo group (5) • Other: brodalumab 140 group (2), brodalumab 210 group (6), ustekinumab 45/90 group (2), placebo group (3)

Lebwohl AMAGINE-2 2015 *(Continued)*

Interventions	**Intervention** A. Brodalumab (n = 610), SC, 140 mg (2 injections week 0, 1 injection eow) **Control intervention** B. Brodalumab (n = 612), SC, 210 mg (2 injections week 0, 1 injection eow) C. Ustekinumab (n = 300), SC, 45/90 mg (week 0, week 4 and every 12 weeks) D. Placebo (n = 309), orally (same drug administration)
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PASI 75 and PGA0/1 (brodalumab compared to placebo) • % of participants who had a 100% reduction in PASI score **Secondary outcomes of the trial** • Improvement in PASI • PGA score • Participant-reported outcome • AEs
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.

Risk of bias

Bias	Authors' judgement	Support for judgement
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...”

Lebwohl AMAGINE-2 2015 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 1831, analysed 1831 Dealing with missing data Quote (protocol and 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 (NCT0178603) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported, except for participant-reported outcome

Lebwohl AMAGINE-3 2015

Study characteristics	
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	**Randomised**: 1881 participants (mean age 45 years, 1288 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12, PGA 3-5, BSA ≥ 10), age 18 - 75 years **Exclusion criteria** • Pregnancy • Active infection, past history of malignant tumours, active infection, kidney or liver insufficiency, uncontrolled cardiovascular disorder, uncontrolled diabetes, uncontrolled hypertension • Had Crohn's disease • Had used ustekinumab and/or anti-IL17 biologic therapy **Dropouts and withdrawals** • 65/1881 (3.4%): brodalumab 140 group (25), brodalumab 210 group (16), ustekinumab 45/90 group (10), placebo group (14) • Ineligibility determined: brodalumab 140 group (3), brodalumab 210 group (0), ustekinumab 45/90 group (1), placebo group (2) • AEs: brodalumab 140 group (4), brodalumab 210 group (4), Usk 45/90 group (1), placebo group (0) • Lost to follow-up: brodalumab 140 group (5), brodalumab 210 group (5), ustekinumab 45/90 group (3), placebo group (1) • Full consent withdrawal: brodalumab 140 group (7), brodalumab 210 group (5), ustekinumab 45/90 group (3), placebo group (7) • Other: brodalumab 140 group (6), brodalumab 210 group (2), ustekinumab 45/90 group (2), placebo group (4)
Interventions	**Intervention** A. Brodalumab (n = 629), SC, 140 mg (2 injections week 0, 1 injection eow) **Control intervention**

Lebwohl AMAGINE-3 2015 *(Continued)*

	B. Brodalumab (n = 624), SC, 210 mg (2 injections week 0, 1 injection eow) C. Ustekinumab (n = 313), SC, 45/90 mg (week 0, week 4 and every 12 weeks) D. Placebo (n = 315), orally (same drug administration)
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PASI 75 • PGA 0/1 (brodalumab compared to placebo) • % of participants who had a 100% reduction in PASI score **Secondary outcomes of the trial** • Improvement in PASI • PGA score • Participant-reported outcome • AEs
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.

Risk of bias

Bias	Authors' judgement	Support for judgement
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 and p 1321) "...with missing data imputed as indicating no response"

Lebwohl AMAGINE-3 2015 *(Continued)*

		Comment: well described
Selective reporting (reporting bias)	High risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01708629) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported, except for participant-reported outcome

Lebwohl CIMPACT 2018

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind trial Date of study: January 2015 - December 2016 Location: worldwide Phase 3
Participants	**Randomised**: 559 participants **Inclusion criteria** • Provided informed consent • Adult men or women ≥ 18 years • Chronic plaque psoriasis for ≥ 6 months • Baseline PASI ≥ 12 and BSA ≥ 10% and PGA score ≥ 3 • Candidate for systemic psoriasis therapy and/or phototherapy and/or chemophototherapy • Other protocol-defined inclusion criteria may apply **Exclusion criteria** • Erythrodermic, guttate, generalised pustular form of psoriasis • History of current, chronic, or recurrent infections of viral, bacterial, or fungal origin as described in the protocol • Congestive heart failure • History of a lymphoproliferative disorder including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease • History of other malignancy, concurrent malignancy as described in the protocol • History of, or suspected, demyelinating disease of the central nervous system (e.g. multiple sclerosis or optic neuritis) • 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 • Any other condition which, in the Investigator's judgement, would make the person unsuitable for participation in the study • Other protocol-defined exclusion criteria may apply • Prior etanercept use **Dropouts and withdrawals** • 24/559 (4.3%) • Placebo (2), Etanercept (11), Certo 200 (6), Certo 400 (5) • AEs: Placebo (0), Etanercept (4), Certo 200 (1), Certo 400 (1) • Protocol violation: Placebo (0), Etanercept (1), Certo 200 (0), Certo 400 (0) • Participant decision: Placebo (0), Etanercept (2), Certo 200 (3), Certo 400 (1)

Lebwohl CIMPACT 2018 *(Continued)*

- Lost to follow-up: Placebo (1), Etanercept (2), Certo 200 (1), Certo 400 (2)
- Absence of efficacy: Placebo (1), Etanercept (1), Certo 200 (0), Certo 400 (0)
- Others: Placebo (0), Etanercept (1), Certo 200 (1), Certo 400 (1)

Interventions	**Intervention** A. 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), n = 165 **Control intervention** B. Certolizumab pegol (SC injection 400 mg every 2 weeks through week 14), n = 167 C. Etanercept (SC injection 50 mg twice weekly through week 12), n = 170 D. Placebo, n = 57
Outcomes	**At week 12** **Primary outcome** • PASI (Psoriasis Activity and Severity Index) 75 **Secondary outcomes** • PGA 0/1 (at weeks 12 and 16) • PASI 75 (at week 16) • PASI 90 (at weeks 12 and 16)
Notes	Funding source : Quote (p 226): "Funding sources: Supported by Dermira Inc and UCB Inc. UCB is the regulatory sponsor of certolizumab pegol in psoriasis." Conflicts of interest: Quote (p 226): "Dr Lebwohl is an employee of Mount Sinai which receives research funds from AbbVie, Boehringer Ingelheim, Celgene, Eli Lilly, Incyte, Janssen/Johnson & Johnson, Leo Pharmaceutucals, Medimmune/Astra Zeneca, Novartis, Pfizer, Sciderm, UCB, Valeant, and ViDac; and is a consultant for Allergan, Aqua, Boehringer-Ingelheim, LEO Pharma, Menlo, and Promius. Dr Blauvelt has received honoraria or fees for consulting, serving as a clinical investigator, and/or speaking for AbbVie, Aclaris, Allergan, Almirall, Amgen, Boehringer Ingelheim, Celgene, Dermavant, Dermira Inc, Eli Lilly and Company, Genentech/Roche, GSK, Janssen, LEO Pharma, Merck Sharp & Dohme, Novartis, Pfizer, Purdue Pharma, Regeneron, Sandoz, Sanofi Genzyme, Sienna Pharmaceuticals, Sun Pharma, UCB, Valeant, and Vidac. Dr Paul is a consultant and investigator for AbbVie, Almirall, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly and Company, Janssen/Johnson & Johnson, LEO Pharma, Novartis, Pierre Fabre, Pfizer, and Sanofi/Regeneron. Dr Sofen has received honoraria or fees for consulting, serving as a clinical investigator, and/or speaking for AbbVie, Amgen, Boehringer Ingelheim, Celgene, Dermira Inc, Janssen, Eli Lilly, Merck, Novartis, Pfizer, Sun Pharma, UCB, and Valeant. Dr Węgłowska is an investigator and/or speaker for Amgen, Celgene, Coherus, Dermira Inc, Eli Lilly and Company, Galderma, Janssen, LEO Pharma, Merck, Pfizer, Regeneron, Sandoz, and UCB. Dr Piguet has received honoraria or fees for consulting and/or speaking for AbbVie, Almirall, Celgene, Janssen, Novartis, and Pfizer; and has received departmental support for Cardiff University from AbbVie, Almirall, Alliance, Beiersdorf UK Ltd, Biotest, Celgene, Dermal, Eli Lilly, Galderma, Genus Pharma, GlobeMicro, Janssen-Celag, LaRoche-Posay, L'Oreal, LEO Pharma, Meda, MSD, Novartis, Pfizer, Sinclair Pharma, Spirit, Stiefel, Samumed, Thornton Ross, TyPham, and UCB. Dr Augustin has received honoraria or fees for consulting and/or speaking for clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis, including AbbVie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Celgene, Centocor, Eli Lilly and Company, GSK, Hexal, Janssen-Cilag, LEO Pharma, Medac, Merck, MSD, Mundipharma, Novartis, Pfizer, Sandoz, UCB BioSciences Inc, and Xenoport. Ms Drew and Dr Burge have received stock options from Dermira Inc. Mr Peterson owns stock in UCB Inc. Dr Rolleri has received stock options from UCB Inc."

Risk of bias

Lebwohl CIMPACT 2018 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 286): "Study drug kits were distributed based on the subject's interactive voice web response system assigned randomization number; the randomization schedule was produced by an independent biostatistician." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 286): "Study drug kits were distributed based on the subject's interactive voice web response system assigned randomization number; the randomization schedule was produced by an independent biostatistician." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (p 268): "Double-blind CZP and placebo treatments were administered subcutaneously at the study site by study personnel not involved in any other study procedures; etanercept treatment was administered subcutaneously on-site by unblinded study staff or self-administered off-site by the patient after sufficient training. To maintain the single-blind for etanercept, efficacy assessments were performed by a designated blinded assessor not involved in any other study procedures during blinded study periods." Comment: participants not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 268): "Double-blind CZP and placebo treatments were administered subcutaneously at the study site by study personnel not involved in any other study procedures; etanercept treatment was administered subcutaneously on-site by unblinded study staff or self-administered off-site by the patient after sufficient training. To maintain the single-blind for etanercept, efficacy assessments were performed by a designated blinded assessor not involved in any other study procedures during blinded study periods." Comment: assessment by a blinded assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote (p 269): "Analyses were based on the randomized set (all randomized patients)...Imputation of missing data was performed using the Markov chain Monte Carlo method for multiple imputation during the initial period " Included population 559, Table 2 559 Comment: done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02346240) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported Results are posted on ClinicalTrials.gov

Lee 2016

Study characteristics	
Methods	RCT, placebo-controlled, open-label trial Date of study: July 2009 - April 2011

Lee 2016 *(Continued)*

	Setting: Korea (multicentric)
Participants	**Total sample size**: 60 **Inclusion criteria** • Active, moderate-severe psoriasis defined by the following criteria: clinically stable, plaque psoriasis involving more than 10% BSA or PASI 10 • 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 • Negative urine pregnancy test before the first dose of study drug in all female participants **Exclusion criteria** • Evidence of skin conditions (e.g. eczema) other than psoriasis that would interfere with evaluations of the effect of study medication on psoriasis • Any rheumatologic disease such as rheumatoid arthritis, psoriatic arthritis, gout, systemic lupus erythematous, systemic vasculitis, scleroderma and polymyositis, or associated syndromes • Prior exposure to TNF inhibitors including etanercept. Prior exposure to efalizumab (Raptiva®) and alefacept (Amevive®) is also prohibited. **Dropouts and withdrawals** • 16/60 (26.7%) • ETA (4), ETA+ACI (4), ACI (7) • AEs: ETA (1), ETA+ACI (0), ACI (1) • Protocol violation: ETA (1), ETA+ACI (2), ACI (1) • Participant decision: ETA (0), ETA+ACI (2), ACI (4) • Lost to follow-up: ETA (1), ETA+ACI (0), ACI (0) • Absence of efficacy: ETA (1), ETA+ACI (0), ACI (1)
Interventions	**Intervention** A. Etanercept + acitretin (combination of etanercept, 25 mg twice a week and acitretin 10 mg twice a day for 24 weeks), n = 20 **Control intervention** B. Etanercept, 50 mg twice a week for 12 weeks followed by 25 mg twice a week for 12 weeks, n = 21 C. Acitretin, 10 mg twice a day for 24 weeks, n = 19
Outcomes	**At week 24** **Primary outcome** • PASI 75 **Secondary outcomes** • PASI 50 • PGA0/1 • PSSQ (Psoriasis Subject Satisfaction Questionnaire)
Notes	Funding source Quote (p 8): "This study was funded by Pfizer Pharmaceuticals Korea Limited; etanercept is a product of Pfizer." Conflics of interest

Lee 2016 *(Continued)*

Quote (p 8): "Hyun-Jeong Yoo is an employee of Pfizer Pharmaceuticals Korea Limited; etanercept is a product of Pfizer. All other authors report no competing interests."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p 2): "In this multicenter, randomized, open-label trial, patients were randomly assigned to one of three treatment groups: (a) etanercept 50 mg twice weekly (BIW) for 12 weeks followed by etanercept 25 mg BIW for a further 12 weeks (ETN–ETN); (b) etanercept 25 mg BIW and acitretin 10 mg twice daily (BID) for 24 weeks (ETN-ACT); (c) acitretin 10 mg BID for 24 weeks (ACT;Fig. 1)" Comment: No description
Allocation concealment (selection bias)	Unclear risk	Quote (p 2): "In this multicenter, randomized, open-label trial, patients were randomly assigned to one of three treatment groups: (a) etanercept 50 mg twice weekly (BIW) for 12 weeks followed by etanercept 25 mg BIW for a further 12 weeks (ETN–ETN); (b) etanercept 25 mg BIW and acitretin 10 mg twice daily (BID) for 24 weeks (ETN-ACT); (c) acitretin 10 mg BID for 24 weeks (ACT;Fig. 1)" Comment: No description
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (p 2): "In this multicenter, randomized, open-label trial, patients were randomly assigned to one of three treatment groups: (a) etanercept 50 mg twice weekly (BIW) for 12 weeks followed by etanercept 25 mg BIW for a further 12 weeks (ETN–ETN); (b) etanercept 25 mg BIW and acitretin 10 mg twice daily (BID) for 24 weeks (ETN-ACT); (c) acitretin 10 mg BID for 24 weeks (ACT;Fig. 1)" Comment: Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (p 2): "In this multicenter, randomized, open-label trial, patients were randomly assigned to one of three treatment groups: (a) etanercept 50 mg twice weekly (BIW) for 12 weeks followed by etanercept 25 mg BIW for a further 12 weeks (ETN–ETN); (b) etanercept 25 mg BIW and acitretin 10 mg twice daily (BID) for 24 weeks (ETN-ACT); (c) acitretin 10 mg BID for 24 weeks (ACT;Fig. 1)" Comment: Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote (p 2): "Efficacy evaluation was performed on the modified intent-to-treat (mITT) and per protocol (PP) population sets. The mITT population included all randomly assigned patients who received at least one dose of test medication and had both baseline and on-therapy PASI evaluation...and the patients who did not experience the event were censored at the time of last observation" Included population 60, Table 59 Comment: done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00936065) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported Results are posted on ClinicalTrials.gov

Leonardi 2003

Study characteristics	
Methods	RCT, placebo-controlled, double-blind trial Date of study: December 2001 - April 2002 Location: 47 centres in USA
Participants	**Randomised**: 672 participants (mean age 45 years, 672 male) **Inclusion criteria** • Participants with moderate-severe stable plaque psoriasis, BSA > 10% • Age ≥ 18 • Quote (p 2015) “Had previously received phototherapy or systemic psoriasis therapy at least once or had been candidate to such therapy” **Exclusion criteria** • Had received biologics treatments • Had an active infection • Had past history of malignant tumours **Dropouts and withdrawals** • 103/672 (15.3%) • Not received any treatment: etanercept LD (9), etanercept MD (5), etanercept HD (4), placebo (2) • AEs: etanercept LD (8), etanercept MD (7), etanercept HD (5), placebo (8) • Loss to follow-up: etanercept LD (4), etanercept MD (4), etanercept HD (3), placebo (3) • Lack of efficacy: etanercept LD (6), etanercept MD (2), etanercept HD (3), placebo (6) • Patient refusal: etanercept LD (3), etanercept MD (4), etanercept HD (1), placebo (4) • Protocol violation: etanercept LD (3), etanercept MD (4), etanercept HD (0), placebo (1) • Death: etanercept LD (1), etanercept MD (1), etanercept HD (0), placebo (0) • Unknown/other: etanercept LD (1), etanercept MD (0), etanercept HD (1), placebo (0)
Interventions	**Intervention** A. Etanercept LD (n = 169), SC auto-administered, 25 mg, once/week, 12 weeks **Control intervention** B. Etanercept MD (n = 167), SC auto-administered, 25 mg, twice/week, 12 weeks C. Etanercept HD (n = 168), SC auto-administered, 50 mg, twice/week, 12 weeks D. Placebo (n = 168), SC, 12 weeks
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • PASI 50 • PASI 90 • DLQI

Leonardi 2003 *(Continued)*

- PGA
- Safety
- Patient global assessment of psoriasis

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."

Risk of bias

Bias	Authors' judgement	Support for judgement
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 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 prespecified outcomes mentioned in the Methods section appeared to have been reported

Leonardi 2012

Study characteristics

Methods	RCT, placebo-controlled, double-blind trial Date of study: April 2010 - May 2011

Leonardi 2012 *(Continued)*

	Location: 23 centres internationally
Participants	**Randomised**: 142 participants (mean age 46 years, 81 male) **Inclusion criteria** • Participants with moderate-severe psoriasis, PASI ≥ 12, PGA 3-5, BSA ≥ 10 • Age ≥ 18 **Exclusion criteria** • Pregnancy • Had an active infection **Dropouts and withdrawals** • 13/142 (9%) : • Placebo (4) (AE (4), withdrew (1) efficacy lack (2)) • Ixekizumab 10 mg (6) (AE (2), protocol violations (2), lost to follow-up (1), efficacy lack (1)) • Ixekizumab 25 mg (1) (AE (1)) • Ixekizumab 75 mg (1) (withdrawal (1)) • Ixekizumab 150 mg (1) (withdrawal (1))
Interventions	**Intervention** A. Placebo (n = 27), SC, 0, 2, 4, 8, 12, 16 weeks, 16 weeks **Control intervention** B. Ixekizumab (n = 28), SC, 10 mg, 0, 2, 4, 8, 12, 16 weeks, 16 weeks C. Ixekizumab (n = 30), SC, 25 mg, 0, 2, 4, 8, 12, 16 weeks, 16 weeks C. Ixekizumab (n = 29), SC, 75 mg, 0, 2, 4, 8, 12, 16 weeks, 16 weeks C. Ixekizumab (n = 28), SC, 150 mg, 0, 2, 4, 8, 12, 16 weeks, 16 weeks
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • % reduction of PASI • PASI 90/PASI 100 • PGA • NAPSI • PSSI
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.

Risk of bias

Bias	Authors' judgement	Support for judgement

Leonardi 2012 *(Continued)*

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 and 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 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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Leonardi PHOENIX-1 2008

Study characteristics	
Methods	RCT, placebo-controlled, double-blind trial Date of study: December 2005 – September 2007 Location: 48 centres in USA, Canada, Belgium
Participants	**Randomised**: 766 participants (mean age 45 years, 531 male) **Inclusion criteria** • Participants with moderate-severe psoriasis, authors' assessment > 6 months, PASI ≥ 12, BSA > 10% • Age ≥ 18 **Exclusion criteria** • Had received conventional systemic treatments

Leonardi PHOENIX-1 2008 *(Continued)*

- Had received biologics (IL12/23)
- Had an active infection
- Had past history of malignant tumours

Dropouts and withdrawals

- 23/766 (3%) :
- Ustekinumab 45 (1) (other 1)
- Ustekinumab 90 (10) (lack of efficacy (1), adverse event (2) other (7))
- Placebo (12) (lack of efficacy (3), adverse event (6) other (3))

Interventions	**Intervention** A. Ustekinumab (n = 255), SC, 45 mg, weeks 0 - 4 and every 12 weeks, 40 weeks **Control intervention** 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 **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • PGA cleared or minimal at 12 weeks • Change of DLQI from baseline at 12 weeks • PASI 90 at week 12 • Side effects
Notes	Funding source, Quote (p 1665): Centocor Inc. 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 Israel Pharamceutical, ScheringPlough, 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."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (pp 1667-68): "...via a centralised interactive voice response system" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Quote (pp 1667-68): "...via a centralised interactive voice response system" Comment: no description of the method used to guarantee allocation concealment

Leonardi PHOENIX-1 2008 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (pp 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” Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (pp 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” Comment: probably done
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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Lowe 1991

Study characteristics	
Methods	RCT, placebo-controlled, double-blind trial Date of study: not stated Location: 2 centres in Santa Monica and New York City, USA
Participants	**Randomised**: 34 participants, age range 20 - 75 years, 24 male **Inclusion criteria** • Participants with moderate-severe psoriasis • BSA 20 - 80 • ≥ 6 months duration **Exclusion criteria** • Had received conventional systemic treatments or phototherapy for 4 weeks or topical therapy for 2 weeks **Dropouts and withdrawals** • Not specified
Interventions	**Intervention** A. Acitretin (n = 16), orally, 50 mg, daily, 12 weeks

Lowe 1991 *(Continued)*

	Control intervention B. Placebo (n = 18), orally, daily, 12 weeks Co-intervention: UVB (phototherapy)
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PASI **Secondary outcomes of the trial** • Side effects
Notes	Funding source (p 591): Quote: "Supported by Roche dermatologics, Nutley, New Jersey and the Skin Research Foundation of California, Santa Monica, California" Declarations of interest; not stated

Risk of bias

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 but 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 prespecified outcomes mentioned in the Methods section appeared to have been reported

Mahajan 2010

Study characteristics	
Methods	RCT, placebo-controlled, double-blind trial Date of study: January 2007 – September 2007 Location: 1 centre in Chandighar, India
Participants	**Randomised**: 40 participants (mean age 37 years, 29 male) **Inclusion criteria** • Participants with moderate-severe psoriasis • BSA > 10% • Age 18 - 60 years **Exclusion criteria** • Pregnancy, immunosuppression, kidney insufficiency, liver insufficiency • Had uncontrolled diabetes **Dropouts and withdrawals** • 11/40 (28%) • 3 withdrawn (disease exacerbation) • 4 lost to follow-up (acitretin (3), placebo (1)) • 4 alternative therapy
Interventions	**Intervention** A. Methotrexate 0.5 mg/kg + folic acid, (n = 20), orally 5 mg/d Day-1; Day+1 + NBUVB 3/week max 1200 mJ/cm2 **Control intervention** B. Placebo + folic acid (n = 20), orally, 5 mg/d Day-1; Day+1 + NBUVB 3/week max 1200 mJ/cm2
Outcomes	Assessments at 6 months **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • PASI at 4 - 12 weeks • Relapse (return of PASI at 50 weeks to baseline)
Notes	Funding source: not stated Declarations of interest (p 595): "not declared"

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (p 596): "... were randomised by way of random number table" Comment: probably done

Mahajan 2010 *(Continued)*

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
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 prespecified outcomes mentioned in the Methods section appeared to have been reported

Meffert 1997

Study characteristics	
Methods	RCT, placebo-controlled, double-blind Date of study: not stated Location: 17 centres in Germany
Participants	**Randomised**: 128 participants **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI 8 to 25) • Age 18 - 70 years **Exclusion criteria** • Pregnancy, leucopenia, kidney insufficiency, liver insufficiency • Had uncontrolled hypertension **Dropouts and withdrawals** • 15/128 (12%) • Protocol violation (6) • Lack efficacy (4) • AE (5)
Interventions	**Intervention** A. Ciclosporin (n = 43), orally, 1.25 mg/kg/d, 10 weeks **Control intervention**

Meffert 1997 *(Continued)*

	B. Ciclosporin (n = 41), orally, 2.5 mg/kg/d, 10 weeks C. Placebo (n = 44), orally, 10 weeks
Outcomes	Assessments at 10 weeks **Primary outcomes of the trial** • PASI **Secondary outcomes of the trial** • PASI 25 • PASI 50 • PASi 75
Notes	Funding source not stated but 3 out of 4 authors from Sandoz pharmaceuticals Declarations of interest: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
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 prespecified outcomes mentioned in the Methods section appeared to have been reported

Menter EXPRESS-II 2007

Study characteristics

Methods	RCT, placebo-controlled, double-blind trial Date of study: not stated

Menter EXPRESS-II 2007 *(Continued)*

	Location: 63 centres in Europe, USA, Canada
Participants	**Randomised**: 835 participants (mean age 44 years, 551 male) **Inclusion criteria** • Participants with moderate-severe psoriasis • PASI ≥ 12, BSA ≥ 10 • No history of serious infection, lymphoproliferative disease, or active TB **Exclusion criteria** • Had received biologics • Had an active infection • Had past history of malignant tumours **Dropouts and withdrawals** • 62/835 (7.4%) • Inflximab 5 mg/kg (17) (AE (12), other (4), lost to follow-up (1)) • Infliximab 3 mg/kg (21) (AE (13), other (7), low effect (1)) • Placebo (24) (AE (4), other (9), lost to follow-up (1), low effect (10))
Interventions	**Intervention** A. Infliximab (n = 313), IV, 3 mg/kg, weeks 0, 2, 6; 10 weeks **Control intervention** B. Infliximab (n = 314), IV, 5 mg/kg, weeks 0, 2, 6; 10 weeks C. Placebo (n = 208), IV, weeks 0, 2, 6; 10 weeks
Outcomes	Assessments at 10 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • PASI 50/90 • DLQIAE • PGA
Notes	Funding (p 31. e1) by Centocor, Inc, Malvern, Penn, and Schering-Plough, Kenilworth, NJ. Declarations of interest (appendix): "Dr Menter has received consulting, research, and/or speaking support from Abbott Laboratories, Allergan Inc, Allermed, 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, MedImmune 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), Advisory Boards; Serono: Investigator, Consultant, Speaker, Advisory Boards; Schering: Investigatory, 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,

Menter EXPRESS-II 2007 *(Continued)*

Valeant, Collagenex, CombinatoRx, 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 Healthcare, 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."

Risk of bias

Bias	Authors' judgement	Support for judgement
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
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 prespecified outcomes mentioned in the Methods section appeared to have been reported

Menter REVEAL 2008

Study characteristics

Methods	RCT, placebo-controlled, double-blind trial Date of study: December 2004 - August 2007

Menter REVEAL 2008 *(Continued)*

	Setting: 81 centres (67+14) in USA, Canada
Participants	**Randomised**: 1212 participants (mean age 44 years, 803 male) **Inclusion criteria** • Participants with moderate-severe psoriasis • PASI ≥ 12, PGA moderate severity, BSA ≥ 10 • Age ≥ 18 years **Exclusion criteria** • Pregnancy • Had an active infection **Dropouts and withdrawals** • 74/1212 (6%) • 4/10 AEs • 9/6 withdrew consent • 8/6 lost to follow-up • 17/2 unsatisfactory effect • 5/1 others
Interventions	**Intervention** A. Adalimumab (n = 814), SC, 40 mg, week 0: 2 injections, week 1: eow, 16 weeks **Control intervention** B. Placebo, SC (n = 398), week 0: 2 injections/week 1: eow, 16 weeks
Outcomes	Assessments at 16 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • PGA • PASI 90 • PASI 100 • Safety
Notes	Funding source quote (p 106): "Supported by Abbott Laboratories" 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 Leonardi 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, Norvartis, 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

Menter REVEAL 2008 *(Continued)*

honoraria and travel grants from Abbott, Alza, Amgen, Astellas, Celgene, Centocor, Genentech, Isotechnika, Johnson and Johnson, Serono, Schering-Plough, and UCB."

Risk of bias

Bias	Authors' judgement	Support for judgement
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
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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported, except for participant-reported outcome

Mrowietz BRIDGE 2016

Study characteristics

Methods	RCT, active-controlled, double-blind Date of study: November 2012 - November 2015 Setting: 57 centres in Austria, Germany, the Netherlands and Poland
Participants	**Randomised**: 704 participants (mean age 44.5 years, 452 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12, BSA ≥ 10), age ≥ 18 years

Mrowietz BRIDGE 2016 *(Continued)*

Exclusion criteria

- Failed therapy with fumaric ester
- Baseline leucocyte counts < 3 x 10^9 cells L1 and/or lymphocyte counts < 1 x 10^9 cells L1
- Pregnant or breastfeeding women

Dropouts and withdrawals

- 254/704 (36%);
- Not treated: Dimethyl Fumarate (DMF) (1), DMF + salt of monoethyl fumarate (MEF) (3), placebo (1)
- AEs: DMF (64), DMF + MEF (70), placebo (6)
- Lack of efficacy: DMF (12), DMF + MEF (9), placebo (20)
- Withdrew consent: DMF (13), DMF + MEF (11), placebo (7)
- Lost to follow-up: DMF (5), DMF + MEF (5), placebo (5)
- No compliance: DMF (3), DMF + MEF (7), placebo (1)
- Other: DMF (6), DMF + MEF (5), placebo (0)

Interventions	**Intervention** A. Dimethyl fumarate (DMF) (n = 280), orally, maximum daily dose of 720 mg DMF **Control intervention** B. DMF + salt of monoethyl fumarate (n = 286), orally, maximum daily dose of 720 mg DMF C. Placebo (n = 138)
Outcomes	Assessments at 16 weeks **Primary outcomes of the trial** • PASI 75 • PGA 0/1 **Secondary outcomes of the trial** • PASI 90 • DLQI • AEs
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."

Risk of bias

Bias	Authors' judgement	Support for judgement

Mrowietz BRIDGE 2016 *(Continued)*

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
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 Randomised 280/286/138 Safety set analysis 279/283/137 (not-treated participants 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 prespecified outcomes and those mentioned in the Methods section as DLQI had not been reported

Mrowietz SCULPTURE 2015

Study characteristics	
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	**Randomised**: 966 participants (mean age 46 years, 635 male)

Mrowietz SCULPTURE 2015 *(Continued)*

	Inclusion criteria • Participants with moderate-severe psoriasis (PASI ≥ 12, BSA ≥ 10), age ≥ 18 years **Exclusion criteria** • Immunosuppression, active infection, uncontrolled cardiovascular disorder, uncontrolled diabetes, uncontrolled hypertension, had past history of malignant tumours • Had received anti IL17 drug **Dropouts and withdrawals** • 38/966 (4%); • AEs: secukinumab 300 (9), secukinumab 150 (8) • Lack of efficacy: secukinumab 300 (0), secukinumab 150 (1) • Withdrew consent: secukinumab 300 (8), secukinumab 150 (6) • Lost to follow-up: secukinumab 300 (3), secukinumab 150 (2) • Protocol deviation: secukinumab 300 (0), secukinumab 150 (1)
Interventions	**Intervention** A. Secukinumab (n = 482), SC, 150 mg weeks 0, 1, 2, 3 then monthly **Control intervention** B. Secukinumab (n = 484), SC, 300 mg weeks 0, 1, 2, 3 then monthly
Outcomes	Assessments at 52 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • PASI 50/75/90 week 12 • IGA 0/1 • DLQI • AEs
Notes	Funding source: Quote (p 27) “Study funded by Novartis Pharma...Novartis conducted data analyses, and all authors had access to data”. 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 & 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 Corpo-

Mrowietz SCULPTURE 2015 *(Continued)*

ration, 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."

Risk of bias

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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Nakagawa 2016

Study characteristics

Methods	RCT, active/placebo-controlled, double-blind Date of study: October 2012 – March 2013 Setting: multicentre (56) in Japan
Participants	**Randomised**: 151 participants (mean age 45 years, 120 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12, BSA ≥ 10), age 20 - 70 years **Exclusion criteria** • Past history of malignant tumours, active infection, uncontrolled cardiovascular disorder

Nakagawa 2016 *(Continued)*

- Had received anti IL17 (RA) treatment

Dropouts and withdrawals

- 6/151 (4%); brodalumab 70 group (2), brodalumab 140 group (0), brodalumab 210 group (0), placebo group (4)
- AEs: brodalumab 70 group (1)
- Full consent withdrawal: brodalumab 70 group (1), placebo group (1)
- Symptoms worsening: placebo group (1)

Interventions	**Intervention** A. Brodalumab (n = 39), SC, 70 mg, 2 injections week 0, 1 injection eow **Control intervention** B. Brodalumab (n = 37), SC, 140 mg, 2 injections week 0, 1 injection eow C. Brodalumab (n = 37), SC, 210 mg, 2 injections week 0, 1 injection eow D. Placebo (n = 38), orally (same drug administration)
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • % improvement in PASI **Secondary outcomes of the trial** • PASI 75 • PGA 0/1 • PASI 90/100 • AEs
Notes	Funding source: Quote (p 51) “The study was supported by Kyowa Hakko Kirin Co., Ltd.” 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."

Risk of bias

Bias	Authors' judgement	Support for judgement
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 about the management of missing data
Selective reporting (reporting bias)	High risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01748539) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported, except for participant-reported outcome

NCT01553058 VIP trial

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind trial Date of study: February 2012 - October 27, 2016 Location: 8 centres in the USA Phase 4
Participants	**Randomised**: 96 participants **Inclusion criteria** • Men and women ≥ 18 years • Clinical diagnosis of psoriasis for ≥ 6 months as determined by interview of his/her medical history and confirmation of diagnosis through physical examination by Investigator • Stable plaque psoriasis for ≥ 2 months before screening and at baseline (week 0) as determined by interview of his/her medical history • Moderate-severe psoriasis defined by ≥ 10 per cent BSA involvement at the baseline (week 0) visit • PASI score of ≥ 12 at the baseline (week 0) visit • Participant is a candidate for systemic therapy or phototherapy and has active psoriasis despite prior treatment with topical agents • 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 1 method of contraception throughout the study are eligible to participate; women who are postmenopausal (for ≥ 1 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. • 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 • Able and willing to give written informed consent and to comply with requirements of this study protocol **Exclusion criteria** • 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

NCT01553058 VIP trial *(Continued)*

- Previous lack of response to a TNF-alpha antagonist and/or UV phototherapy that led to discontinuation of either of these therapies
- Diagnosis of erythrodermic psoriasis, generalised or localised pustular psoriasis, medication-induced or medication-exacerbated psoriasis, or new onset guttate psoriasis
- Diagnosis of other active skin diseases or skin infections (bacterial, fungal, or viral) that may interfere with evaluation of psoriasis
- Cannot avoid UVB phototherapy for ≥ 14 days prior to the baseline (week 0) visit
- Cannot avoid psoralen-UVA phototherapy for ≥ 30 days prior to the baseline (week 0) visit and during the study
- 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 ≥ 30 days prior to the baseline (week 0) visit except for biologics. All biologics, except ustekinumab, must be discontinued for ≥ 90 days prior to baseline (week 0). The IL-12/IL-23 antagonist ustekinumab (half-life of 45.6 ± 80.2 days) must be discontinued for ≥ 180 days prior to baseline (week 0). Investigational agents must be discontinued ≥ 30 days or 5 half-lives (whichever is longer) prior to the baseline (week 0) visit
- Taking or requires oral or injectable corticosteroids during the study. Inhaled corticosteroids for stable medical conditions are allowed
- 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
- History of diabetes mellitus, type 1 or type 2
- Uncontrolled hypertension, with measured systolic blood pressure > 180 mmHg or diastolic blood pressure > 90 mmHg
- History of demyelinating diseases or lupus
- 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) ≥ 5 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
- History of haematological or solid malignancy other than successfully treated basal cell carcinoma, non-metastatic cutaneous squamous cell carcinoma or cervical carcinoma in situ
- Pregnant or breast-feeding or considering becoming pregnant during the study
- Screening clinical laboratory analyses showing any of the following abnormal results: haemoglobin (Hgb) < 10 g/dL in women or < 12 g/dL in men; white blood cell (WBC) count < 2.5 x 109/L or can be included if WBC count is < 2.5 x 109/L and absolute neutrophil count (ANC) is > 1000 cells/mm3. WBC count > 15 x 109/L; platelet count < 100 x 109/L; serum aspartate transaminase (AST) or alanine transaminase (ALT) > 2.5 upper limits of normal (ULN); serum total bilirubin ≥ 2 mg/dL (≥ 26 µmol/L); or serum creatinine > 1.6 mg/dL (> 141 µmol/L)
- Recent history of substance abuse or psychiatric illness that could preclude compliance with the protocol
- History of any substance abuse within 365 days of screening visit
- Alcohol use > 14 drinks per week at the screening visit or within 30 days of the screening period
- 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
- History of photosensitivity of medical condition that may be exacerbated by UV exposures such as lupus or dermatomyositis

Dropouts and withdrawals

NCT01553058 VIP trial *(Continued)*

- 5/96 (12.1%):

ADA group (1), UV group (3), Placebo group (1)

- Participant decision: ADA group (0), UV group (1), Placebo group (1)
- Lost to follow-up: ADA group (1), UV group (1), Placebo group (0)
- Investigator decision: ADA group (0), UV group (1), Placebo group (0)

Interventions	**Intervention** 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, n = 33 **Control intervention** B. NB-UVB phototherapy. Phototherapy will be given 3 times a week according to the Fitzpatrick scale for skin types, n = 33 C. Placebo injection will be given according to the same dose and schedule as the active comparator, n = 1
Outcomes	**At weeks 12** **Primary outcome measures** • Vascular inflammation and biomarkers • Change in total vascular inflammation of 5 aortic segments as assessed on FDG-PET/CT between baseline and week 12 • Change in metabolic, lipid, and inflammatory biomarker levels between baseline, week 4 and 12 **Secondary outcome measures**: • Change in psoriasis activity (PASI 50, PASI 75, PASI 90, and PGA < 1) • Number of participants with AEs • Change in participant-reported outcomes (e.g. EuroQoL-5D, DLQI, and International Physical Activity Questionnaire (IPAQ)
Notes	Funding Quote (p 10): "This study was supported by grants (National Heart, Lung, and Blood Institute R01-HL111293, K24-AR-064310) and by an unrestricted grant from AbbVie (to the Trustees of the University of Pennsylvania). Dr Mehta is supported by National Institutes of Health Intramural Research Program (Z01 HL-06193). The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the article; and decision to submit the article for publication." Conflict of interest Quote (p 10): Dr Mehta is a full-time US Government Employee and receives research grants to the National Heart, Lung, and Blood Institute (NHLBI) from AbbVie, Janssen, Celgene, and Novartis. Dr Gelfand in the past 12 months has served as a consultant for Coherus (DSMB), Dermira, Janssen Biologics, Merck (DSMB), Novartis Corp, Regeneron, Dr. Reddy's Laboratories, Sanofi and Pfizer Inc, receiving honoraria; and receives research grants (to the Trustees of the University of Pennsylvania) from Abbvie, Janssen, Novartis Corp, Regeneron, Sanofi, Celgene, and Pfizer Inc; and received payment for continuing medical education work related to psoriasis that was supported indirectly by Lilly and Abbvie. Dr Gelfand is a copatent holder of resiquimod for treatment of cutaneous T cell lymphoma. Dr Takeshita receives a research grant from Pfizer Inc (to the Trustees of the University of Pennsylvania) and has received payment for continuing medical education work related to psoriasis that was supported indirectly by Eli Lilly. A.B. Troxel is a co-patent holder of resiquimod for treatment of cutaneous T cell lymphoma. Dr Tyring conducts clinical studies sponsored by the following companies: Abbvie/ BI; Celgene; Coherus; Dermira; Eli Lilly; Janssen; Leo; Merck; Novartis; Pfizer; Regeneron/Sanofi; and Valeant. He is a speaker for Abbvie, Eli Lilly, Janssen, Leo, Novartis, Pfizer, Regeneron/Sanofi, and Valeant. Dr Armstrong has received

NCT01553058 VIP trial *(Continued)*

research grants and honorarium from AbbVie, Celgene, Janssen, Novartis, Eli Lilly, Regeneron, Sanofi, and Valeant and has participated in continuing medical education work related to psoriasis that was indirectly supported by Eli Lilly and
AbbVie. Dr Duffin has received grant/research/clinical trial support from Amgen, Abbvie, Celgene, Eli Lilly, Janssen, Bristol-Myers Squibb, Stiefel, Novartis, and Pfizer over the last 24 months. Additionally, Dr Duffin has served as a consultant/ on the advisory boards for Amgen, Abbvie, Celgene, Eli Lilly, Janssen, Bristol-Myers Squibb, Stiefel, Novartis, and Pfizer. Dr Chiesa Fuxench has no conflicts of interest. However, she was being funded, at the time, by a research grant from the National Psoriasis Foundation and a training grant from the National Institutes of Health. Dr Hubbard receives grant funding from the National Institutes of Health and Patient-Centered Outcomes Research Institute. Dr Rader is the co-founder of Vascular Strategies and holds equity in the company. Dr Kalb has received grants/research funding from AbbVie, Amgen, Boehringer Ingelheim, Janssen- Ortho Inc, Merck & Co, Inc, and Novartis Pharmaceuticals Corp over the last 24 months. During this time frame, he has also served as a consultant honoraria for Dermira, Janssen-Ortho Inc, Sun Pharmaceutical Industries Ltd, and a DSMB member honoraria for Eli Lilly and Co. Dr Simpson has served as a consultant for AbbVie, Anacor, Celgene, Dermira, Genentech, Leo, Glaxo Smith Kline, Pfizer, Regeneron, Sanofi-Genzyme, Menlo, and Eli Lilly in the last 24 months. During this time frame, he has also acted as the primary investigator for the following sponsored trials: Anacor, Celgene, Chugai, Dermira, Eli Lilly, Genentech, MedImmune, Merck, Novartis, Regeneron, Roivant, Tioga, and Vanda. Dr Torigian is the co-founder of Quantitative Radiology Solutions LLC. Dr Van Voorhees has served on the advisory board of Celgene, Dermira, Allergan, Merck, Pfizer, Aqua, Astra Zeneca, Jannsen, Amgen, Leo, Allergan, and Lilly. For Novartis and AbbVie, Dr Van Voorhees acts as a consultant as well as serves on the board. Dr Van Voorhees has received a portion of ex-spouse pension from Merck. Dr Menter in the last 24 months has served on the advisory board for AbbVie, Allergan, Amgen, Boehringer Ingelheim, Eli Lilly, Janssen Biotech, Inc, and LEO Pharma. He has also worked as a consultant for AbbVie, Allergan, Amgen, Eli Lilly, Galderma, Janssen Biotech, Inc, LEO Pharma, Novartis, Pfizer, Vitae, and Xenoport. Additionally, he has acted as an investigator for AbbVie, Allergan, Amgen, Anacor, Boehringer Ingelheim, Celgene, Dermira, Eli Lilly, Janssen Biotech, Inc, LEO Pharma, Merck, Neothetics, Novartis, Pfizer, Regeneron, Symbio/Maruho, and Xenoport. He also serves as a speaker for AbbVie, Amgen, Janssen Biotech, Inc, and LEO Pharma. He has received compensation in the form of grants from AbbVie, Allergan, Amgen, Anacor, Boehringer Ingelheim, Celgene, Dermira, Janssen Biotech, Inc, LEO Pharma, Merck, Neothetics, Novartis, Pfizer, Regeneron, Symbio/Maruho, and Xenoport. He has also received honoraria from AbbVie, Allergan, Amgen, Boehringer Ingelheim, Eli Lilly, Galderma, Janssen Biotech, Inc, LEO Pharma, Novartis, Pfizer, Vitae, and Xenoport. The other authors report no conflicts.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p 2): "The study was a multicenter randomized controlled trial designed to enroll 96 patients across 8 centers in the United States with 1:1:1 allocation to..." 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 3): "Adalimumab (or corresponding placebo) therapy was administered in a double-blind manner as a subcutaneous injection with an initial 80 mg dose at week 0, followed by maintenance doses of 40 mg every other week, starting from week 1 and then continued throughout the study" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (p 3): "Adalimumab (or corresponding placebo) therapy was administered in a double-blind manner as a subcutaneous injection with an initial 80 mg dose at week 0, followed by maintenance doses of 40 mg every other week, starting from week 1 and then continued throughout the study"

NCT01553058 VIP trial *(Continued)*

		Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomised: 96; analysed 92 Dealing with missing data: not stated but few withdrawal (1/3/0)
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01553058) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

NCT01961609 SIGNATURE

Study characteristics	
Methods	RCT, active-controlled, double-blind trial (SIGNATURE) Date of study: October 2013-July 2016 Location: UK-Ireland
Participants	**Randomised**: 235 participants **Inclusion criteria** • Chronic plaque-type psoriasis diagnosed for ≥ 6 months prior to screening, aged ≥ 18 years at screening • Moderate-severe disease severity: PASI ≥ 10 and DLQI > 10 • Failed to respond to systemic therapies including ciclosporin and/or methotrexate and/or PUVA (or is intolerant and/or has a contraindication to these) • Previously treated with ≥ 1 anti-TNFα for moderate or severe psoriasis but failed to respond to this (these) drug(s) **Exclusion criteria** • Forms of psoriasis other than chronic plaque-type (e.g. pustular, erythrodermic and guttate psoriasis) • Drug-induced psoriasis (i.e. new onset or current exacerbation from beta-blockers, calcium channel inhibitors or lithium) • 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. • 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 ≥ 4 weeks before initiation of study drug • Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or the IL-17 receptor • 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 (> 5 mIU/mL) • 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 • 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 • 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 for people

NCT01961609 SIGNATURE *(Continued)*

	who have travelled or recently resided in areas of endemic mycoses, such as histoplasmosis, coccidioidomycosis or blastomycosis and for people with underlying conditions that may predispose them to infection, such as advanced or poorly-controlled diabetes • 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. People with a positive QFT test may participate in the study if further work-up establishes conclusively that the person 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 • Known infection with HIV, hepatitis B or hepatitis C at screening or at initiation of study drug **Dropouts and withdrawals** • 25/235 (10.6%) Secu 150 group (13), Secu 300 group (12) • Death: Secu 150 group (1), Secu 300 group (0) • Lack of efficacy: Secu 150 group (1), Secu 300 group (2) • Participant decision: Secu 150 group (2), Secu 300 group (1) • Lost to follow-up: Secu 150 group (2), Secu 300 group (3) • Protocol deviation: Secu 150 group (0), Secu 300 group (1) • AEs: Secu 150 group (5), Secu 300 group (3) • Others: Secu 150 group (2), Secu 300 group (2)
Interventions	**Intervention** A. Biological: secukinumab 150 mg at day 0 (initiation of study drug) and at weeks 1, 2, 3 and 4, n = 116 **Control Intervention** B. Biological: secukinumab 300 mg at day 0 (initiation of study drug) and at weeks 1, 2, 3 & 4, n = 119
Outcomes	**At 16 weeks** **Primary outcome** • PASI 75 **Secondary outcomes** • PASI 90 and PASI 75 after 2, 4, 8, 12, 24, 48 and 72 weeks • Quality of life at 16 weeks
Notes	Funding: Quote (Clinical.Trials.gov): Novartis Conflict of interest: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (Clinical.Trials.gov): "Allocation: randomized" 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

NCT01961609 SIGNATURE *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (Clinical.Trials.gov): "Masking: None (Open Label)" Comment: not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (Clinical.Trials.gov): "Masking: None (Open Label)" Comment: not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: not stated but reasonable rate of withdrawal (10%) and number and reason comparable between groups Results posted on ClinicalTrials.gov: ITT analyses
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01961609) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

NCT02134210 CHS-0214

Study characteristics	
Methods	RCT, active-controlled, double-blind study Date of study: June 2014 - May 2016 Location: worldwide Phase 3
Participants	**Randomised**: 521 participants **Inclusion criteria** • Men or women • PsO diagnosis for 6 months • Active disease: PASI ≥ 12, Physician's Static Global Assessment (PSGA) score ≥ 3 (based on a scale or 0 - 5) • BSA involved with PsO ≥ 10% • DQLI ≥ 10 • Previously received phototherapy or systemic non-biologic therapy for PsO **Exclusion criteria** • Forms of psoriasis other than PsO • Drug-induced psoriasis • Positive QuantiFERON-tuberculosis (TB) Gold Test • Presence of significant comorbid conditions • Chemistry and haematology values outside protocol specified range • Major systemic infections **Dropouts and withdrawals** • 25/521 (1.4%) CHS-0214 group (6), Enbrel group (19)

NCT02134210 CHS-0214 *(Continued)*

	Reasons not stated
Interventions	**Intervention** A. CHS-0214 50 mg twice weekly times 12 weeks, n = 261 **Control intervention** B. Enbrel 50 mg twice weekly times 12 weeks, n = 260
Outcomes	**At week 12** **Primary composite outcome** • PASI 75 **Secondary outcomes** • PASI 90 • PGA 0/1 • EuroQol 5-dimension health status questionnaire
Notes	Funding: Quote (ClinicalTrials.gov) Coherus Biosciences, Inc. Conflict of interest: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (ClinicalTrials.gov): "A Double-Blind, Randomized, Parallel-Group, Active-Control Study to Compare the Efficacy and Safety of CHS-0214 Versus Enbrel...Allocation: randomized" 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 (ClinicalTrials.gov): "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (ClinicalTrials.gov): "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dealing with missing data: not stated Results posted on ClinicalTrials.gov: ITT analyses Reasons for treatment 's discontinuation not stated
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02634801) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

NCT02581345

Study characteristics	
Methods	RCT, active-controlled, triple-blind trial Date of study: September 2015 - April 2017 Location: world-wide
Participants	**Randomised**: 572 participants **Inclusion criteria** • Must be able to understand and communicate with the investigator and comply with the requirements of the study • Chronic plaque-type psoriasis diagnosed for at least 6 months before screening • Stable plaque psoriasis • History of receipt of or candidate for therapy. • Moderate-to-severe psoriasis at screening and baseline • Must be willing and able to self-administer SC injections or have a caregiver available to administer injections • Men of childbearing potential must employ a highly effective contraceptive measure • Women must have a negative pregnancy test; are not planning to become pregnant; and must not be lactating. They must also agree to employ a highly effective contraceptive measure **Exclusion criteria** • Forms of psoriasis other than chronic plaque-type • Drug-induced psoriasis • Other skin conditions which would interfere with assessment of psoriasis • Medical conditions other than psoriasis for which systemic corticosteroids were used in the last year prior to screening • Other inflammatory conditions other than psoriasis or psoriatic arthritis • Prior use of systemic tumour necrosis factor (TNF) inhibitors, or 2 or more non-TNF biologic therapies • Ongoing use of prohibited psoriasis treatments • Ongoing use of other non-psoriasis prohibited treatments • All other prior non-psoriasis concomitant treatments must be on a stable dose for at least 4 weeks • Laboratory abnormalities at screening deemed clinically significant by the investigator • Any condition or illness which in the opinion of the investigator or sponsor poses an unacceptable safety risk • History of latex allergy • History of or current signs or symptoms or diagnosis of a demyelinating disorder • History of or current Class III or IV New York Heart Association congestive heart failure • Signs, symptoms, or diagnosis of lymphoproliferative disorders, lymphoma, leukaemia, myeloproliferative disorders, or multiple myeloma • Current malignancy or history of any malignancy except adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ; no more than 3 lifetime basal cell and squamous cell carcinomas permitted • Chronic infections, recurrent infections; recent infection to be evaluated • History of or presence of HIV, or Hepatitis B (HBV) or C virus (HCV) • History of active tuberculosis (TB) or untreated or inadequately-treated latent TB • Exposure to an investigational product ≤ 30 days prior to enrolment or participation in another clinical study during the course of this study • Participant is a family member or employee of the investigator or site staff or study team

NCT02581345 *(Continued)*

	Dropouts and withdrawals • 38/572 (6.7%): Biosimilar group (15), Humira group (23) • Participant decision: Biosimilar group (4), Humira group (7) • Lost to follow-up: Biosimilar group (2), Humira group (0) • Physician decision: Biosimilar group (2), Humira group (4) • AEs: Biosimilar group (3), Humira group (8) • Others: Biosimilar group (4), Humira group (4)
Interventions	**Intervention** A. Biological: M923, S/C, Biosimilar adalimumab week 0: 80 mg, week 1: 40 mg, then 40 mg EOW, n = 286 **Control Intervention** B. Biological: M923, S/C, adalimumab (Humira) week 0: 80mg, week 1: 40 mg, then 40 mg EOW, n = 286
Outcomes	**At 16 weeks** **Primary outcome** • PASI 75 **Secondary outcomes** • PASI 90 and PASI 75 after 2, 4, 8, 12, 24, 48 and 72 weeks • Quality of life at 16 weeks
Notes	Funding: Quote (ClinicalTrials.gov): Novartis Conflict of interest: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (ClinicalTrials.gov and Statistical analysis plan): "Allocation: randomized... The blocking scheme will be specified in the randomization specifications. Randomization will occur via an Interactive Response Technology (IRT) System until..." Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (ClinicalTrials.gov and Statistical analysis plan): "Allocation: randomized... The blocking scheme will be specified in the randomization specifications. Randomization will occur via an Interactive Response Technology (IRT) System until..." Comment: Probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (ClinicalTrials.gov): "Masking: Triple (Participant, Care Provider, Investigator)" Comment:probably done
Blinding of outcome assessment (detection bias)	Low risk	Quote (ClinicalTrials.gov): "Masking: Triple (Participant, Care Provider, Investigator)"

NCT02581345 *(Continued)*

All outcomes		Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (Statistical analysis plan): "The primary analysis will be based on the non-responder imputation (NRI) method." Results posted on ClinicalTrials.gov: Per protocol analyses (non-inferiority trial)
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02581345) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

NCT02634801

Study characteristics	
Methods	RCT, active-controlled, single-blind study Date of study: December 2015 - November 2017 Location: Germany (multicentric) Phase 3
Participants	**Randomised**: 162 participants **Inclusion criteria** • Present with moderate-to-severe chronic plaque psoriasis based on a diagnosis of chronic psoriasis for ≥ 6 months before baseline • Participants who are candidates for systemic therapy and who are naïve to systemic treatment for psoriasis • Have PASI score > 10 or BSA > 10 and DLQI > 10 at screening and at baseline **Exclusion criteria** • Have predominant pattern of pustular, erythrodermic, and/or guttate forms of psoriasis • Have received systemic nonbiologic psoriasis therapy • Have prior, concurrent, or recent use of ixekizumab or any other biological psoriasis therapy • Have any condition or contraindication as addressed in the local labelling for methotrexate or FAE • Presence of significant uncontrolled cerebro-cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neurologic, or neuropsychiatric disorders or abnormal laboratory values at screening • Have severe gastrointestinal disease, oral ulcer, or known, active gastrointestinal ulcer • Have had a serious infection or are immunocompromised • At screening, participants with significant, present, or early liver disease, e.g. explained by alcohol consumption or hepatic insufficiency **Dropouts and withdrawals** • 38/162 (23.5%): Ixe group (4), FAEs group (31), Methotrexate group (5) • Participant decision: Ixe group (0), FAEs group (8), Methotrexate group (3)

NCT02634801 *(Continued)*

- Lost to follow-up: Ixe group (2), FAEs group (1), Methotrexate group (1)
- Lack of efficacy: Ixe group (0), FAEs group (2), Methotrexate group (0)
- AEs: Ixe group (2), FAEs group (20), Methotrexate group (0)
- Protocol violation: Ixe group (0), FAEs group (0), Methotrexate group (1)

Interventions	**Intervention** 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), n = 54 **Control interventions** FAEs (105 mg FAE given orally followed by 215 mg FAE given orally 1 - 3 times/day until week 24), n = 54 Methotrexate (7.5 mg starting dose up to 30 mg methotrexate given orally once a week until week 24), n = 54
Outcomes	**At week 24** **Primary outcome** • PASI 75 **Secondary outcome** • PGA 0/1 • PASI 90 • DLQI
Notes	Funding Quote (ClinicalTrials.gov): "Sponsor: Eli Lilly and Company" Conflict of interest Not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (ClinicalTrials.gov): "Allocation: randomized" 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	Quote (ClinicalTrials.gov): "Masking: Single (Outcomes Assessor)" Comment: no double-blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (ClinicalTrials.gov): "Masking: Single (Outcomes Assessor)" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	High risk	Dealing with missing data: not stated Results posted on clinical.Trials: ITT analyses

NCT02634801 *(Continued)*

		Unbalance discontinuation treatments: Ixe group (4), FAEs group (31), Methotrexate group (5)
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02634801) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

NCT02660580 AURIEL-PsO

Study characteristics	
Methods	RCT, active-controlled, double-blind trial Date of study: February 2016 - December 2017 Location: world-wide
Participants	**Randomised**: 443 participants **Inclusion criteria** • Men or women ≥ 18 years old with a clinical diagnosis of stable moderate-to-severe plaque psoriasis (defined by PASI score ≥ 12, PGA score ≥ 3, and ≥ 10% of body surface area affected at Screening and Baseline [Day 1 of Week 1]) who have a history of receipt of or are candidates for systemic therapy or phototherapy for active plaque-type psoriasis despite topical therapy • Participants must not have received more than 1 biologic therapy • Other protocol-defined inclusion criteria could apply **Exclusion criteria** • People were excluded if they have erythrodermic, pustular, guttate, or medication-induced forms of psoriasis or other active skin diseases/infections that may interfere with the evaluation of plaque psoriasis • Participants must not have received adalimumab or an investigational or licensed biosimilar of adalimumab; topical therapies for the treatment of psoriasis or ultraviolet B phototherapy within 2 weeks of investigational medicinal product (IMP) administration or plan to take such treatment during the trial; or psoralen combined with ultraviolet A phototherapy or nonbiological systemic therapies for psoriasis within 4 weeks prior to IMP administration • People was excluded if they have a history of an ongoing, chronic, or recurrent infectious disease (except for latent tuberculosis [TB]); history of active TB; or a history of hypersensitivity to any component of the IMP formulation, comparable drugs, or latex • Other protocol-defined exclusion criteria could apply **Dropouts and withdrawals** • 28/443 (6.3%): Biosimilar group (9), Humira group (19) • Not treated: Biosimilar group (1), Humira group (1) • Participant decision: Biosimilar group (1), Humira group (4) • Lost to follow-up: Biosimilar group (1), Humira group (2) • Lack of efficacy: Biosimilar group (0), Humira group (2) • Protocol violation: Biosimilar group (3), Humira group (1) • AEs: Biosimilar group (2), Humira group (9)

NCT02660580 AURIEL-PsO *(Continued)*

- Others: Biosimilar group (1), Humira group (0)

Interventions	**Intervention** A. Biological: MSB11022, S/C, Biosimilar adalimumab week 0: 80 mg, week 1: 40 mg, then 40 mg EOW, n = 222 **Control Intervention** B. Biological: adalimumab (Humira) week 0: 80mg, week 1: 40 mg, then 40 mg EOW, n = 221
Outcomes	**At 16 weeks** **Primary outcome** • PASI 75 **Secondary outcomes** • PASI 90 and PASI 75 after 2, 4, 8, 12, 24, 48 and 52 weeks • Quality of life at 16 weeks
Notes	Funding: Quote (ClinicalTrials.gov): EMD Serono Research and Development Institute, Inc. Conflict of interest: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (ClinicalTrials.gov): "Allocation: randomized" 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 (ClinicalTrials.gov): "Double (Participant, Investigator)" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (ClinicalTrials.gov): "Double (Participant, Investigator)" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: not stated Results posted on ClinicalTrials.gov: Per protocol analyses (non-inferiority trial)
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02660580) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

NCT02672852 IMMhance

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study Date of study: February 2016 - July 2018 Location: worldwide Phase 3
Participants	**Randomised**: 507 participants **Inclusion criteria** • Men or women • 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 • Age ≥ 18 years at screening • Diagnosis of chronic plaque psoriasis (with or without psoriatic arthritis) ≥ 6 months before the first administration of study drug. Duration of diagnosis may be reported by the patient • Stable moderate-severe chronic plaque psoriasis with or without psoriatic arthritis at both screening and baseline (randomisation); • Have an involved BSA ≥ 10%, PASI ≥ 12 a sPGA score of ≥ 3 • Must be a candidate for systemic therapy or phototherapy for psoriasis treatment, as assessed by the investigator • 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 **Exclusion criteria**: • 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 investigator's judgement • Previous exposure to ABBV-066 • Currently enrolled in another investigational study or < 30 days (from screening) since completing another investigational study • Use of any restricted medication as noted or any drug considered likely to interfere with the safe conduct of the study • Major surgery performed within 12 weeks prior to randomisation or planned within 12 months after screening (e.g. hip replacement, removal aneurysm, stomach ligation) • Known chronic or relevant acute infections such as active TB, HIV, or viral hepatitis • 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 • 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 • History of allergy/hypersensitivity to a systemically administered biologic agent or its excipients • Women who are pregnant, nursing, or who plan to become pregnant while in the trial • Previous enrolment in this trial **Dropouts and withdrawals** • 7/507 (1.4%)

NCT02672852 IMMhance *(Continued)*

	Risankizumab group (4), Placebo group (3) • Lost to follow-up: Risankizumab group (1), Placebo group (2) • Disease worsening: Risankizumab group (1), Placebo group (0) • Withdrawal by participant: Risankizumab group (1), Placebo group (1) • AEs: Risankizumab group (0), Placebo group (1)
Interventions	**Intervention** A. Risankizumab 150 mg by subcutaneous injection at Weeks 0 and 4, n = 407 **Control intervention** B. Placebo by subcutaneous injection at Weeks 0 and 4, n = 100
Outcomes	**At week 16** **Primary composite outcome** • PASI 90 • PGA 0/1 **Secondary outcomes** • PASI 75 at weeks 16 and 52 • PASI 90 at weeks 52 • PGA 0/1 at weeks 52
Notes	Funding: AbbVie, Boehringer Ingelheim Conflict of interest: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (ClinicalTrials.gov and study protocol/statistical analysis plan): "This is a confirmatory, multinational, multicenter, randomized, double-blind, placebo controlled, study... During Visit 2 and after the patient's eligibility has been confirmed, the treatment will be assigned via Interactive Response Technology (IRT). To facilitate the use of the IRT, the Investigator will receive all necessary instructions." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (ClinicalTrials.gov and study protocol/statistical analysis plan): "This is a confirmatory, multinational, multicenter, randomized, double-blind, placebo controlled, study... During Visit 2 and after the patient's eligibility has been confirmed, the treatment will be assigned via Interactive Response Technology (IRT). To facilitate the use of the IRT, the Investigator will receive all necessary instructions." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (ClinicalTrials.gov and study protocol/statistical analysis plan): "Injections should be at least 2 cm. apart and should not be close to a vein. The injection sites should avoid sites of psoriasis involvement as well as sites where the skin is tender, bruised, erythematous, or indurated, and should be alternated to other areas for subsequent doses. Injections will be given in a double blind fashion with each patient receiving 2 injections of BI 655066 or matching placebo administered within approximately 5 minutes at each dosing visit as indicated in the Flow Charts"

NCT02672852 IMMhance *(Continued)*

		Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (ClinicalTrials.gov and study protocol/statistical analysis plan): "Injections should be at least 2 cm. apart and should not be close to a vein. The injection sites should avoid sites of psoriasis involvement as well as sites where the skin is tender, bruised, erythematous, or indurated, and should be alternated to other areas for subsequent doses. Injections will be given in a double blind fashion with each patient receiving 2 injections of BI 655066 or matching placebo administered within approximately 5 minutes at each dosing visit as indicated in the Flow Charts" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (statistical analysis plan): "The NRI will be the primary approach in the analyses of categorical variables." ITT results on ClinicalTrials.gov
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02672852) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

NCT02850965

Study characteristics	
Methods	RCT, active-controlled, double-blind trial Date of study: August 2016 - January 2018 Location: world-wide
Participants	**Randomised**: 318 participants **Inclusion criteria** • Men and women aged ≥ 18 to 80 years who have a diagnosis of moderate-to-severe chronic plaque psoriasis (with or without psoriatic arthritis) for at least 6 months before the first administration of study drug (a self-reported diagnosis confirmed by the investigator is acceptable), and which has been stable for the last 2 months with no changes in morphology or significant flares at both Screening and Baseline (randomisation): involved BSA ≥ 10% and PASI score ≥ 12 and sPGA score of ≥ 3 • Participants of reproductive potential (childbearing potential) must be willing and able to use highly-effective methods of birth control per International Council for Harmonization (ICH) M3 (R2) that result in a low failure rate of < 1% a year when used consistently and correctly during the trial and for 6 months following completion or discontinuation from the trial medication • Signed and dated written informed consent in accordance with Good Clinical Practice (GCP) and local legislation prior to admission to the trial • Patients who are candidates for systemic therapy **Exclusion criteria** • Active ongoing inflammatory diseases other than psoriasis that might confound trial evaluations according to investigator`s judgement • Previous treatment with more than 1 biological agent, or adalimumab or adalimumab biosimilar • No prior biologic exposure within last 6 months of screening

NCT02850965 *(Continued)*

- Patients with a significant disease other than psoriasis and/or a significant uncontrolled disease (such as, but not limited to, nervous system, renal, hepatic, endocrine, haematological, autoimmune or gastrointestinal disorders)
- Major surgery performed within 12 weeks prior to randomisation or planned within 6 months after screening, e.g. total hip replacement
- Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin or in situ carcinoma of uterine cervix.
- Patients who must or wish to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial
- Currently enrolled in another investigational device or drug study, or < 30 days since ending another investigational device or drug study(s), or receiving other investigational treatment(s)
- Chronic alcohol or drug abuse
- Women who are pregnant, nursing, or who plan to become pregnant during the course of this study or within the period at least 6 months following completion or discontinuation from the trial
- Forms of psoriasis (e.g. pustular, erythrodermic and guttate) other than chronic plaque psoriasis
- Drug-induced psoriasis (i.e. new onset or current exacerbation from e.g. beta blockers or lithium)
- Primary or secondary immunodeficiency (history of, or currently active), including known history of HIV infection or a positive HIV test at screening (at the investigator's discretion and where mandated by local authorities)
- Known chronic or relevant acute tuberculosis; no evidence of active tuberculosis
- Known clinically significant coronary artery disease, significant cardiac arrhythmias, moderate to severe congestive heart failure (New York Heart Association Classes III or IV) or interstitial lung disease observed on chest X-ray
- History of a severe allergic reaction, anaphylactic reaction, or hypersensitivity to a previously used biological drug or its excipients
- Positive serology for hepatitis B virus (HBV) or hepatitis C virus (HCV)
- Receipt of a live/attenuated vaccine within 12 weeks prior to the Screening Visit; patients who are expecting to receive any live/attenuated virus or bacterial vaccinations during the trial or up to 3 months after the last dose of trial drug
- Any treatment (including biologic therapies) that, in the opinion of the investigator, may place the patient at unacceptable risk during the trial. Known active infection of any kind (excluding fungal infections of nail beds), any major episode of infection requiring hospitalisation or treatment with intravenous (i.v.) anti infectives within 4 weeks of the Screening Visit
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 times upper limit of normal (ULN) at Screening. Haemoglobin < 8.0 g/dL at Screening. Platelets < 100,000/µL at Screening. Leukocyte count < 4000/µL at Screening. Creatinine clearance < 60 mL/min/1.73 m2 at Screening
- Patients with a history of any clinically significant adverse reaction to murine or chimeric proteins, or natural rubber and latex, including serious allergic reactions

Dropouts and withdrawals

- 43/318 (13.5%):

Biosimilar group (18), Humira group (25)

- Not treated: Biosimilar group (0), Humira group (1)
- Participant decision: Biosimilar group (3), Humira group (4)
- Physician decision: Biosimilar group (0), Humira group (1)
- Lost to follow-up: Biosimilar group (5), Humira group (3)
- Lack of efficacy: Biosimilar group (4), Humira group (8)
- Protocol violation: Biosimilar group (0), Humira group (2)
- AEs: Biosimilar group (3), Humira group (2)
- Others: Biosimilar group (3), Humira group (4)

Interventions	**Intervention**

NCT02850965 *(Continued)*

	A. Biological: BI 695501, S/C, Biosimilar adalimumab week 0: 80 mg, week 1: 40 mg, then 40 mg EOW (n = 159) **Control Intervention** B. Biological: adalimumab (Humira) week 0: 80 mg, week 1: 40 mg, then 40 mg EOW (n = 159)
Outcomes	**At 16 weeks** **Primary outcome** • PASI 75 **Secondary outcomes** • PASI 90 and PASI 75 after 2, 4, 8, 12, 24, 48 and 52 weeks • Quality of life at 16 weeks
Notes	Funding: Quote (ClinicalTrials.gov): Boehringer Ingelheim Conflict of interest: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (ClinicalTrials.gov and clinical trial synopsis): "Allocation: randomized...Randomization will be performed in a blinded fashion via IRT. Patients will be randomized sequentially (the lowest sequentially available randomization number)." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (ClinicalTrials.gov and clinical trial synopsis): "Allocation: randomized...Randomization will be performed in a blinded fashion via IRT. Patients will be randomized sequentially (the lowest sequentially available randomization number)." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (ClinicalTrials.gov): "Double (Participant, Investigator)" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (ClinicalTrials.gov): "Double (Participant, Investigator)" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: not stated Results posted on ClinicalTrials.gov: Per protocol analyses (non-inferiority trial)
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02850965) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

NCT02905331 ORION

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study Date of study: March 2017 - 07 February 2018 Location: world-wide Phase 3

Participants	**Randomised:** 78 participants
	
	Inclusion criteria
	
	• Women of childbearing potential must have a negative urine pregnancy test (beta-human chorionic gonadotropin) at screening and at week 0
	• Before randomisation, women must be either:
	  * not of childbearing potential: premenarchal; postmenopausal (> 45 years of age with amenorrhoea for ≥ 12 months or any age with amenorrhoea for ≥ 6 months and a serum follicle-stimulating hormone level (FSH) > 40 IU/L; permanently sterile (example, tubal occlusion, hysterectomy, bilateral salpingectomy); or otherwise be incapable of pregnancy
	  * of childbearing potential and practicing a highly effective method of birth control, consistent with local regulations regarding the use of birth control methods for people 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)
	• Agree not to receive a Bacillus Calmette Guerin (BCG) vaccination during the study, or within 12 months after the last administration of study drug
	• PASI ≥ 12 at screening and at baseline
	• Involved BSA ≥ 10% at screening and at baseline
	
	Exclusion criteria
	
	• Unstable cardiovascular disease, defined as a recent clinical deterioration (e.g. unstable angina, rapid atrial fibrillation) in the last 3 months or a cardiac hospitalisation within the last 3 months
	• 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
	• Transplanted organ (with exception of a corneal transplant > 3 months before the first administration of study drug)
	• Non-plaque form of psoriasis (e.g. erythrodermic, guttate, or pustular)
	• Received any anti-tumour necrosis factor alpha (TNF-alpha) biologic therapy within 3 months before the first administration of study drug
	
	Dropouts and withdrawals
	
	• 4/78 (5.1%):
	
	Guselkumab group (3), Placebo group (1)
	
	• Lost to follow-up: Guselkumab group (1), Placebo group (0)
	• Lack of efficacy: Guselkumab group (0), Placebo group (2)
	• AEs: Guselkumab group (0), Placebo group (1)

Interventions	**Intervention**

NCT02905331 ORION *(Continued)*

	A. 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), n = 62 **Control intervention** Placebo, n = 16
Outcomes	**At week 16** **Primary outcome** • IGA 0/1 • PASI 90 **Secondary outcomes** • PASI 75 • PASI 100
Notes	Funding: Quote (p 7): "Janssen Research & Development, LLC funded this study. Authors employed by Janssen participated in designing the study; collecting, analyzing, and interpreting the data; and in preparing, reviewing, and approving the manuscript. A professional medical writer supported by Janssen provided editorial and submission support." Conflict of interest: Quote (p 7): "Laura K. Ferris has been an investigator and consultant for EliLilly, Janssen, and Pfizer; a consultant for UCB; and an investigator for AbbVie, Amgen, Galderma, Leo Pharma, and Regeneron. H. Chih-Ho Hong has been an investigator/consultant/or advisory board member for AbbVie, Amgen, Eli Lilly, Galderma, Janssen, Leo Pharma, Merck, Novartis, Pfizer, Regeneron, Sanofi, and UCB. Elyssa Ott, Jingzhi Jiang, Shu Li, and Chenglong Han are employed by Janssen Research & Development, LLC and own stock/stock options in its parent company. Wojciech Baran has been an investigator and consultant for AbbVie, Amgen, Eli Lilly, Janssen, Leo Pharma, Merck, Mylan, Novartis, Pfizer, and Regeneron."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (ClinicalTrials.gov and p 2): "Allocation: randomized"; "ORION (Clinicaltrials.gov identifier: NCT02905331) was a Phase 3, multicentre, double-blind, placebo-controlled study in which patients were centrally randomized (4:1) to receive...Randomization employed a computer-generated permuted block schedule with stratification by country. An interactive web response system assigned a unique treatment code dictating treatment assignment and matching study drug kit. Codes were not provided to investigators. Guselkumab and placebo were delivered by identical devices (see Interventions)." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (ClinicalTrials.gov and p 2): "Allocation: randomized"; "ORION (Clinicaltrials.gov identifier: NCT02905331) was a Phase 3, multicentre, double-blind, placebo-controlled study in which patients were centrally randomized (4:1) to receive...Randomization employed a computer-generated permuted block schedule with stratification by country. An interactive web response system assigned a unique treatment code dictating treatment assignment and matching study drug kit. Codes were not provided to investigators. Guselkumab and placebo were delivered by identical devices (see Interventions)." Comment: probably done

NCT02905331 ORION *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (ClinicalTrials.gov and p 2): "Double (Participant, Investigator)"; " Patients randomized to guselkumab received placebo at Week 16 to maintain the blind...Guselkumab and placebo were delivered by identical devices (see Interventions)." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (ClinicalTrials.gov and p 2): "Double (Participant, Investigator)"; " Patients randomized to guselkumab received placebo at Week 16 to maintain the blind...Guselkumab and placebo were delivered by identical devices (see Interventions)." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (p 3):"Efficacy analyses employed all randomized patients who received 1 injection of study agent, analyzed according to assigned treatment groups (full analysis set). The co-primary endpoints were the proportions of patients achieving IGA 0/1 and PASI90 responses at Week 16. Patients who met treatment failure criteria (discontinued study agent due to lack of efficacy/an AE of worsening psoriasis or started a protocol-prohibited treatment before Week 16) were considered nonresponders for the co-primary endpoints at Week 16, as were patients who did not return for evaluation at Week 16." Randomised 78; analysed 78
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02905331) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

NCT02951533 POLARIS

Study characteristics	
Methods	RCT, active-controlled, open-label study Date of study: November 2016 - September 2017 Location: Germany (multicentric) Phase 3
Participants	**Randomised**: 119 participants **Inclusion criteria** • Diagnosis of plaque-type psoriasis for ≥ 6 months before the first administration of study drug • PASI) ≥ 10 or BSA > 10 at screening and at baseline • DLQI > 10 at screening and at baseline • 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

NCT02951533 POLARIS *(Continued)*

- 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, ≥ (+); 1 re-test (central urine analysis) is allowed

Exclusion criteria

- 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
- 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)
- Known allergies, hypersensitivity, or intolerance to guselkumab or its excipients
- Pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study or within 12 weeks after the last dose of study drug
- 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

Dropouts and withdrawals

- 27/119 (22.7%):

Guselkumab group (4), FAEs group (23)

- Participant decision: Guselkumab group (2), FAEs group (4)
- Non-compliance: Guselkumab group (0), FAEs group (1)
- Lost to follow-up: Guselkumab group (2), FAEs group (2)
- AEs: Guselkumab group (0), FAEs group (16)

Interventions	**Intervention** A. Guselkumab (100 mg administered as 100 mg/mL solution SC by single-use prefilled syringe (PFS) at weeks 0, 4, 12 and 20), n = 60 **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 a day. Fumaderm dose may be increased to a maximum of 3 x 2 tablets a day), n = 59
Outcomes	**At week 24** **Primary outcome** • PASI 90 **Secondary outcomes** • PASI 75 • DLQI
Notes	Funding Quote (ClinicalTrials.gov): Janssen-Cilag G.m.b.H Conflict of interest: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement

NCT02951533 POLARIS *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote (ClinicalTrials.gov and statistical analysis plan): "Procedures for Randomization Central randomization is implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment groups (1:1 ratio) based on a computer generated randomization schedule prepared before the study by or under the supervision of the sponsor. Therandomization will be balanced by using randomly permuted blocks. The interactive web based eCRF will assign a unique treatment code, which will dictate the treatment assignment at baseline visit of the subject. The investigator will not be provided with randomization codes. The randomization codes will be stored invisible for the investigator in a separate, blind part of the EDC system." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (ClinicalTrials.gov and statistical analysis plan): "Procedures for Randomization Central randomization is implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment groups (1:1 ratio) based on a computer generated randomization schedule prepared before the study by or under the supervision of the sponsor. Therandomization will be balanced by using randomly permuted blocks. The interactive web based eCRF will assign a unique treatment code, which will dictate the treatment assignment at baseline visit of the subject. The investigator will not be provided with randomization codes. The randomization codes will be stored invisible for the investigator in a separate, blind part of the EDC system." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (ClinicalTrials.gov and statistical analysis plan): "Blinding: As this is an open study, blinding procedures for the treatment are not applicable. However, a blinded efficacy evaluator will assess effectiveness of treatment as described in Section 9.2.3 of the CSP)... An independent, blinded efficacy assessor, approved by the Sponsor, will be designated at each study site to perform all efficacy assessments (BSA%, IGA, ssIGA, and PASI) starting with baseline visit until end of treatment phase (ie, Week 56)" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (ClinicalTrials.gov and statistical analysis plan): "Blinding: As this is an open study, blinding procedures for the treatment are not applicable. However, a blinded efficacy evaluator will assess effectiveness of treatment as described in Section 9.2.3 of the CSP)... An independent, blinded efficacy assessor, approved by the Sponsor, will be designated at each study site to perform all efficacy assessments (BSA%, IGA, ssIGA, and PASI) starting with baseline visit until end of treatment phase (ie, Week 56)" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	High risk	Dealing with missing data: Quote (ClinicalTrials.gov and statistical analysis plan): "Nonresponder imputation will be applied for binary endpoints i.e., subjects with missing data at Week 4/16/24 will be considered non-responders at Week 4/16/24" Results posted on ClinicalTrials.gov: ITT Unbalance discontinuation proportion (< 1% for Guselkumab and 39% for FAEs)
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02951533)

NCT02951533 POLARIS *(Continued)*

	The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

NCT03000075

Study characteristics	
Methods	RCT, active-controlled, double-blind study Date of study: December 2016 - June 2018 Location: multicentre, Japan Phase 2/3
Participants	**Randomised**: 171 participants **Inclusion criteria** • Have a diagnosis of chronic plaque psoriasis (with or without psoriatic arthritis) for at least 6 months before the first administration of study drug. Duration of diagnosis may be reported by the participant • Have stable moderate-to-severe chronic plaque psoriasis with or without psoriatic arthritis at both Screening and Baseline (Randomisation): Have an involved body surface area (BSA) ≥ 10% and have a PASI score ≥ 12 and have a sPGA score of ≥ 3 **Exclusion criteria** • Patients with 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 judgement • Previous exposure to BI 655066 **Dropouts and withdrawals** • 4/171 (2.3%): Risan 150 group (0), Risan 75 group (0), Placebo group (4= AEs)
Interventions	**Intervention** A. Risankizumab 150 mg by SC injection at Weeks 0 and 4 (Part A), n = 55 **Control intervention** B. Risankizumab 75 mg by SC injection at Weeks 0 and 4, n = 58 C. Placebo, n = 55
Outcomes	**At week 16** **Primary outcome** • PASI 90 **Secondary outcomes** • PASI 75 • DLQI
Notes	Funding

NCT03000075 *(Continued)*

Quote (ClinicalTrials.gov): AbbVie Boehringer Ingelheim

Conflict of interest: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (ClinicalTrials.gov and statistical analysis plan): "This randomized, double-blind, double-dummy, placebo controlled, parallel design study compares two different dose regiments of risankizumab with placebo...After the eligibility criteria are confirmed, the investigator or designee will randomise the patient on Day 1 (Visit 2) through IRT call or website entry. At visits where study medication is to be administered, study sites will be required to complete the medication resupply module in the IRT. Details regarding the use of the IRT are described in the site-user manual available in the ISF." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (ClinicalTrials.gov and statistical analysis plan): "This randomized, double-blind, double-dummy, placebo controlled, parallel design study compares two different dose regiments of risankizumab with placebo...After the eligibility criteria are confirmed, the investigator or designee will randomise the patient on Day 1 (Visit 2) through IRT call or website entry. At visits where study medication is to be administered, study sites will be required to complete the medication resupply module in the IRT. Details regarding the use of the IRT are described in the site-user manual available in the ISF." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (ClinicalTrials.gov and statistical analysis plan): "Study drugs will be administered subcutaneously. Injections will be given in a double blind/double-dummy fashion with each patient receiving 2 injections at each dosing visit: 2 injections of BI 655066, one injection of BI 655066 and one injection of matching placebo or 2 injections of matching placebo depending on randomized dosing group. Syringes will be administered per Flow Chart schedule as assigned by IRT." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (ClinicalTrials.gov and statistical analysis plan): "Study drugs will be administered subcutaneously. Injections will be given in a double blind/double-dummy fashion with each patient receiving 2 injections at each dosing visit: 2 injections of BI 655066, one injection of BI 655066 and one injection of matching placebo or 2 injections of matching placebo depending on randomized dosing group. Syringes will be administered per Flow Chart schedule as assigned by IRT." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (ClinicalTrials.gov and statistical analysis plan): "The primary analysis will be carried out in the ITT Population and the PP Population. Non-responder imputation will be used as the primary approach for missing values. LOCF and MI will be performed as sensitivity analyses." Results posted on ClinicalTrials.gov: ITT
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT03000075)

NCT03000075 *(Continued)*

	The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Nugteren-Huying 1990

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind Date of study: not stated Setting: multicentre in the Netherlands
Participants	**Randomised**: 39 participants (mean age 44 years, 27 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (BSA ≥ 10) **Exclusion criteria** • Pregnancy, kidney insufficiency, liver insufficiency • Had uncontrolled cardiovascular disorder **Dropouts and withdrawals** • 5/39 (12.8%) • Time and reason: not stated
Interventions	**Intervention** A. Dimethylfumarate (n = 12), orally, 120 mg, gradual increase 1 - 6 tablets, once a day, 16 weeks **Control intervention** 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 **Primary outcomes of the trial** • BSA **Secondary outcomes of the trial** • Score of infiltration and scaling • Side effects
Notes	Funding source: not stated Declarations of interest: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p 331): "The patients were randomly assigned..."

Nugteren-Huying 1990 *(Continued)*

		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 prespecified outcomes mentioned in the Methods section appeared to have been reported

Ohtsuki 2017

Study characteristics	
Methods	RCT, placebo-controlled, double-blind trial, phase 2 Date of study: July 2013 - December 2015 Location: Japan
Participants	**Randomised**: 254 participants **Inclusion criteria** • Japanese men and women ≥ 20 years of age • Diagnosis of chronic, stable plaque psoriasis for ≥ 6 months prior to screening as defined by: PASI score ≥ 12 and BSA ≥ 10% • 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 ≥ 4 weeks of prior therapy with ≥ 1 topical medication for psoriasis or per label • In otherwise good health based on medical history, physical examination, 12-lead ECG, serum chemistry, haematology, immunology, and urinalysis **Exclusion criteria** • Other than psoriasis, history of any clinically significant and uncontrolled systemic diseases; any condition, including the presence of laboratory abnormalities, which would place the person at unacceptable risk or confound the ability to interpret the data in the study • Prior medical history of suicide attempt or major psychiatric illness requiring hospitalisation within the last 3 years

Ohtsuki 2017 *(Continued)*

- Pregnant or breastfeeding
- History of or ongoing chronic or recurrent infectious disease
- Active TB or a history of incompletely-treated TB
- Clinically significant abnormality on 12-lead ECG or on chest radiograph at screening
- History of HIV infection or have congenital or acquired immunodeficiencies (e.g. Common Variable Immunodeficiency)
- Hepatitis B surface antigen or hepatitis B core antibody positive at screening; positive for antibodies to hepatitis C at screening
- 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
- Psoriasis flare within 4 weeks of screening
- Topical therapy within 2 weeks prior to randomisation or systemic therapy for psoriasis or psoriatic arthritis within 4 weeks prior to randomisation
- 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
- 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
- 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
- Any investigational drug within 4 weeks prior to randomisation

Dropouts and withdrawals

- 37/254 (14.6%)

Apremilast 30 group (9), Apremilast 20 group (16), Placebo group (12)

- Participant decision: Apremilast 30 group (1), Apremilast 20 group (8), Placebo group (4)
- Lack of efficacy: Apremilast 30 group (2), Apremilast 20 group (2), Placebo group (1)
- AEs: Apremilast 30 group (6), Apremilast 20 group (10), Placebo group (3)

Interventions	**Intervention**: A. Apremilast (30 mg tablet twice a day for 68 weeks), n = 85 **Control intervention**: B. Apremilast (20 mg tablet twice a day for 68 weeks), n = 85 C. Placebo, n = 84
Outcomes	**At week 16** Primary outcome: • PASI 75 Secondary outcomes: • PGA 0/1 • PASI 90 • VAS • DLQI total score • Mental Component Summary (MCS) score of SF-36 • AEs
Notes	Funding

Ohtsuki 2017 *(Continued)*

Quote (p 883): "The authors received editorial support in the preparation of the manuscript from Kathy Covino, Ph.D., of Peloton Advantage, LLC, funded by Celgene Corporation. This study was funded by Celgene Corporation."

Conflict of interest

Quote (p 883): "Mamitaro Ohtsuki reports consultancy and speaker fees. Yukari Okubo reports consultancy fees. Shinichi Imafuku reports research funds, consultancy fees and speaker fees. Robert M. Day, Peng Chen, Rosemary Petric and Allan Maroli report stock or shares in Celgene Corporation and/or employment by Celgene Corporation. Osamu Nemoto has no relevant financial or personal relationships and no potential conflicts of interest to declare."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 874): "After the screening period, eligible patients began a 16-week placebo-controlled period and were randomized via a centralized interactive web response system or interactive voice response system (1:1:1) to placebo, apremilast 20 mg b.i.d. or apremilast 30 mg b.i.d." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 874): "After the screening period, eligible patients began a 16-week placebo-controlled period and were randomized via a centralized interactive web response system or interactive voice response system (1:1:1) to placebo, apremilast 20 mg b.i.d. or apremilast 30 mg b.i.d." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 874): "This phase 2b multicenter, randomized, double-blind, placebo-controlled study" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 874): "This phase 2b multicenter, randomized, double-blind, placebo-controlled study" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (p 874): "Efficacy and safety assessments were conducted for the modified intent-to-treat (mITT) population, which included all patients who were randomized and received at least one dose of study medication; patients not dispensed study medication were excluded from the mITT population... For the primary analysis of PASI-75, missing values were accounted for using the last observation carried forward methodology; multiple sensitivity analyses (including nonresponder imputation [NRI]) were conducted for the primary end-point" Randomised 254; analysed 254
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01988103) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported.

Ohtsuki 2018

Study characteristics	
Methods	RCT, phase 3, randomised, double-blind, placebo-controlled study Date of study: 15 January 2015 - 11 November 2016 Location: Japan (35 sites)
Participants	**Randomised**: 192 participants **Inclusion criteria** • Japanese men and women ≥ 20 years of age • Diagnosis of chronic, stable plaque psoriasis for ≥ 6 months prior to screening as defined by: PASI score ≥ 12 and BSA ≥ 10% **Exclusion criteria** • Patients were excluded if they had non-plaque-type psoriasis, drug-induced psoriasis, latent or active tuberculosis, chronic or recurrent infectious disease, malignancy within 5 years (except non-melanoma skin cancer or cervical carcinoma that had been treated, and with no evidence of recurrence within 3 months), anaphylactic reactions, or history or current signs or symptoms of any severe, progressive or uncontrolled medical disorders. • Patients who had received prior treatment with guselkumab, anti-TNF-a agents within 3 months or 5 half-lives, whichever was longer, biological therapy targeting IL-12, IL-17 or IL-23 within 6 months, systemic immunosuppressants (e.g. methotrexate, cyclosporin) within 4 weeks, or phototherapy within 4 weeks of enrolment were also excluded **Dropouts and withdrawals** • 15/192 (7.8%): Gusel 100 group (1), Gusel 50 group (2), Placebo group (12) • Participant decision: Gusel 100 group (0), Gusel 50 group (1), Placebo group (6) • AEs: Gusel 100 group (0), Gusel 50 group (1), Placebo group (6) • Others: Gusel 100 group (1), Gusel 50 group (0), Placebo group (0)
Interventions	**Intervention**: A. Guselkumab 100 mg with SC injections at weeks 0, 4, and every 8 weeks thereafter (n = 63) **Control intervention**: B. Guselkumab 50 mg with SC injections at weeks 0, 4, and every 8 weeks thereafter (n = 65) C. Placebo (n = 64)
Outcomes	**At week 16** Primary outcome: • PASI 90- IGA0/1 Secondary outcomes: • PGA 0/1 at W52 • PASI 90 at W52 • PASI 75 • DLQI total score

Ohtsuki 2018 *(Continued)*

- AEs

Notes	Funding Quote (p 883): "Funding: This study was funded by Janssen Pharmaceutical,Tokyo, Japan." Conflict of interest Quote (p 1062): "M. O. has received honoraria and/or research grants as a consultant and/or advisory board member and/or paid speaker and/or investigator from Abbvie, Boehringer-Ingelheim, Celgene, Eisai, Janssen, Kyowa-Kirin, LEO Pharma, Eli Lilly, Maruho, Novartis, Pfizer, Tanabe-Mitsubishi, Nichiiko, Torri, Bayer, Pola Pharma, Taiho, Bristol-Myers Squibb, Astellas, Otsuka, Mochida, Nippon Zoki, Actelion, Sanofi, Kaken Pharmaceuticals, Teijin Pharma, Nippon Kayaku, Shionogi, Ono and Galderma. H. N. has received honoraria and/or research grants as an advisory board member and/or speaker from ABC Pharma, Kyowa Hakko Kirin, Abbvie, Mitsubishi-Tanabe Pharma, LEO Pharma, Maruho, Eli Lilly Japan, Janssen. H. K., H. M., R. G. and R. Z. are employees of Janssen Pharmaceutical."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 1054): "Randomization was performed centrally using a computer-generated randomization scheme, balanced using randomly permuted blocks and stratified by presence of PsA." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 1054): "Randomization was performed centrally using a computer-generated randomization scheme, balanced using randomly permuted blocks and stratified by presence of PsA." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 1054): "This was a phase 3, randomized, double-blind, placebo-controlled study conducted in Japan... Study site personnel, investigators and patients were blinded to treatment allocation until week 52 database lock." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 1054): "This was a phase 3, randomized, double-blind, placebo-controlled study conducted in Japan... Study site personnel, investigators and patients were blinded to treatment allocation until week 52 database lock." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	High risk	Dealing with missing data: Quote (p 1054): "The randomized analysis set included all randomized patients for efficacy analyses, and data were analyzed by treatment groups...Last observation was carried forward for other patients with missing data." Randomised: 192; analysed: 192 Imbalance reasons and number of withdrawal: Gusel 100 group (1%), Gusel 50 group (2%), Placebo group (20%)
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02325219) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Olsen 1989

Study characteristics	
Methods	RCT, placebo-controlled, double-blind trial Date of study: not stated Setting: not stated
Participants	**Randomised**: 15 participants, age range 23 - 72 years, 11 male **Inclusion criteria** • Moderate-severe psoriasis • BSA ≥ 10 **Exclusion criteria** • Pregnancy, kidney insufficiency, liver insufficiency **Dropouts and withdrawals** • 3/15 (20%) • Disease flare-up (n = 3)
Interventions	**Intervention** A. Acitretin (n = 10), orally, 25/50 mg, daily, 8 weeks **Control intervention** B. Placebo (n = 5), orally, daily, 8 weeks
Outcomes	Assessments at 8 weeks **Primary outcomes of the trial** • Not clearly defined **Secondary outcomes of the trial** • Body surface area • Scale • Side effects
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"

Olsen 1989 *(Continued)*

		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
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 participants 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 prespecified outcomes mentioned in the Methods section were reported

Ortonne 2013

Study characteristics	
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	**Randomised**: 72 participants randomised, 69 analysed (mean age 46 years, 50 male) **Inclusion criteria** • Participants with moderate-severe psoriasis • PASI ≥ 10, PGA moderate or severe, BSA > 10, DLQI > 10 • Age 18 - 70 years • Overall NAPSI > 14 **Exclusion criteria** • TB infection; recent serious infection within 1 month of etanercept administration or active infection at screening; or known history of HIV infection • Prior exposure to any biologic treatment was prohibited **Dropouts and withdrawals** • 12/72 (17%), BIW/QW group (7), QW/QW group (5) • AEs: BIW/QW group (2), QW/QW group (1) • Participants' request or withdrawal request: BIW/QW group (1), QW/QW group (4) • Death: BIW/QW group (1) • Other: BIW/QW group (3)
Interventions	**Intervention** 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

Ortonne 2013 *(Continued)*

	Control intervention 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
Outcomes	Assessments at 24 weeks **Primary outcomes of the trial** • NAPSI **Secondary outcomes of the trial** • NAPSI 50/75 • PASI 50/75 • PGA0/1 • DLQI • AEs
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."

Risk of bias

Bias	Authors' judgement	Support for judgement
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

Ortonne 2013 *(Continued)*

		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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Papp 2005

Study characteristics	
Methods	RCT, placebo-controlled, double-blind Date of study: not stated Location: 50 centres in USA, Canada and Western Europe
Participants	**Randomised**: 611 participants (mean age 45 years, male 382 out of 583 participants who received 1 dose) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 10, BSA ≥ 10%, age ≥ 18 years) • Non-response to topical treatment • Only 1 previous systemic treatment allowed **Exclusion criteria** • Kidney insufficiency, liver insufficiency • Had received biologics (anti-TNF) • Had an active infection **Dropouts and withdrawals** • 52/611 (8.5%) • Placebo (26): refusal (7) eligibility (6) lost to follow-up (6) AE (2) lack efficacy (4) protocol requirement (1) • Etanercept 25 (13): refusal (5) eligibility (4) AE (3) lack efficacy (1) • Etanercept 50 (13): refusal (5) eligibility (2) lost to follow-up (3) AE (2) lack efficacy (1)
Interventions	**Intervention** A. Etanercept (n = 204), SC, 25 mg twice a week, 12 weeks **Control intervention** B. Etanercept (n = 203), SC, 50 mg twice a week, 12 weeks C. Placebo (n = 204), SC, twice a week, 12 weeks
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PASI 75

Papp 2005 *(Continued)*

Secondary outcomes of the trial

- Proportion of participants with PGA score of 0 or 1 at Week 12
- PASI 50 at Week 12
- PASI 90 at Week 12
- Percentage improvement from baseline at week 12 to PASI
- AEs
- QoL

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."

Risk of bias

Bias	Authors' judgement	Support for judgement
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
Incomplete outcome data (attrition bias) All outcomes	Low risk	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
Selective reporting (reporting bias)	High risk	Comment: no protocol was available. The prespecified outcomes mentioned in the Methods section appeared to have been reported except for the results of participant-reported endpoints summarised in a separate publication

Papp 2012a

Study characteristics	
Methods	RCT, placebo-controlled, double-blind trial Date of study: December 2009 – April 2010 Location: 23 centres worldwide
Participants	**Randomised**: 198 participants (mean age 42 years, 107 male) **Inclusion criteria** • Participants with moderate-severe psoriasis • PASI ≥ 12, BSA > 10% • Age 18 - 70 years **Exclusion criteria** • Pregnancy, immunosuppression • Had past history of malignant tumours **Dropouts and withdrawals** • 10/198 (5%) • Brodalumab 70: ineligible (1) • Brodalumab 140: decision (1) • Brodalumab 210: (3): deviation (1) consent withdrawn (1) decision (1) • Brodalumab 280: (2): ineligible (1), AE (1) • Placebo (3): ineligible (1), consent withdrawn (2)
Interventions	**Intervention** A. Brodalumab 70 (n = 39), SC, 70 mg, day 1-weeks 1, 2, 4, 6, 8, 10, 10 weeks **Control intervention** B. Brodalumab 140 (n = 39), SC, 140 mg, day 1 and weeks 1, 2, 4, 6, 8, 10, 10 weeks C. Brodalumab 210 (n = 40), SC, 210 mg, day 1 and weeks 1, 2, 4, 6, 8, 10, 10 weeks D. Brodalumab 280 (n = 42), SC, 280 mg, day 1 and weeks 1, 2, 4, 6, 8, 10, 10 weeks E. Placebo (n = 38), SC, day 1 and weeks 1, 2, 4, 6, 8, 10, 10 weeks
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PASI75 **Secondary outcomes of the trial** • PASI 50/90/100 at week 12 • BSA • PGA • DLQI • AEs
Notes	Funding source, quote (p 1182): "The study was funded by Amgen"

Papp 2012a *(Continued)*

Declarations of interest (pp 1188-9): "Dr. Papp reports receiving consulting fees from Abbott, Amgen, Astellas, Celgene, Centocor, Eli Lilly, Galderma, Graceway Pharmaceuticals, Janssen, Johnson & Johnson, Merck, Norvartis, 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 & 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."

Risk of bias

Bias	Authors' judgement	Support for judgement
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 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 and 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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Papp 2012b

Study characteristics	
Methods	RCT, placebo-controlled, double-blind Date of study: July 2008 - August 2009 Location: 42 centres in USA, Canada
Participants	**Randomised**: 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) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 13, BSA ≥ 15%), age ≥ 18 • Number of allowed previous biologic treatments: any **Exclusion criteria** • Had an active infection • 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) **Dropouts and withdrawals** • 48/197 (24%); • Tofacitinib 2 mg (11): AE (1), lack efficiency (2), lost to follow-up (4), decision (3), other (1) • Tofacitinib 5 mg (11): AE (2), lack efficiency (3), lost to follow-up (2), decision (4) • Tofacitinib 15 mg (6): AE (3), lack efficiency (1), other (1), decision (1) • Placebo (20): AE (3), lack efficiency (9), lost to follow-up (1), decision (7)
Interventions	**Intervention** A. Tofacitinib (n = 49), orally, 2 mg, twice a day, 12 weeks **Control intervention** B. Tofacitinib, (n = 49), orally, 5 mg, twice a day, 12 weeks C. Tofacitinib (n = 49), orally, 15 mg, twice a day, 12 weeks D. Placebo (n = 50), orally, twice a day, 12 weeks
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • Safety • Proportion of participants achieving a PASI 50 response (weeks 2, 4, 8, 12, 14 and 16) • Proportion of participants achieving a PASI 90 response week 12 • Actual and change from baseline in PASI and PASI component scores baseline/day 1 and weeks 2, 4, 8, 12, 14 and 16 • Proportion of participants with PGA of clear/almost clear, weeks 2, 4, 8, 12, 14 and 16 • Proportion of participants achieving a PASI 75 response (weeks 2, 4, 8, 14 and 16)
Notes	Funding source, quote (p 668): "This study was funded by Pfizer Inc"

Papp 2012b *(Continued)*

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, 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, Centocor/Ortho 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. "

Risk of bias

Bias	Authors' judgement	Support for judgement
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 automatedTreatment 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 done
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 done
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 received 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 2 participants out of 197 not analysed
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00678210)

Papp 2012b *(Continued)*

	The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Papp 2012c

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind Date of study: September 2008 - October 2009 Location: 35 centres in Canada and USA
Participants	**Randomised**: 352 participants (mean age 44 years, 221 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12, BSA ≥ 10%) • Age ≥ 18 years **Exclusion criteria** • Had a history of, or present, significant disease, including Mycobacterium TB or HIV infection • Had a positive screening test for hepatitis B or C • Pregnant or breastfeeding **Dropouts and withdrawals** • 65/352 (11%) at 16 weeks; • Apremilast 30 twice daily: (18): AE (10), lack efficacy (2), withdrew consent (4), lost to follow-up (1), Other (1) • Apremilast other (31): AE (9), lack efficacy (5), withdrew consent (8), protocol violation (7), other (2) • Placebo (16): AE (5), lack efficacy (4), withdrew consent (2), death (1), lost to follow-up (2), protocol deviation (1), other (1)
Interventions	**Intervention** A. Apremilast (n = 88), orally, 30 mg, twice a day, 16 weeks **Control intervention** B. Apremilast (n = 176), orally, 10 - 20 mg twice a day, 16 weeks C. Placebo (n = 88), orally, twice a day 16 weeks
Outcomes	Assessments at 16 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • PGA 0 or 1 • PASI 50/90 • DLQI • SF36
Notes	Funding source Quote (p 738): "Funding Celgene Corporation"

Papp 2012c *(Continued)*

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 & 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 & 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 & Johnson/Ortho Biotech, and Novartis; as a speaker for Abbott, Centocor, Amgen, Pfizer, Johnson & Johnson/Ortho Biotech, and Novartis; and as an adviser for Abbott, Centocor, Celgene, Amgen, Pfizer, Johnson & 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."

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 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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Papp 2013a

Study characteristics	
Methods	RCT, placebo-controlled, double-blind trial Date of study: March 2010 - February 2011 Location: 19 international centres
Participants	**Randomised**: 125 participants (mean age 46 years, 91 male) **Inclusion criteria** • Participants with moderate-severe psoriasis • PASI ≥ 12, IGA ≥ 3, BSA ≥ 10% • Age ≥ 18 years • Non-response to topical treatment • Non-response to phototherapy • Non-response to conventional systemic treatment **Exclusion criteria** • Pregnancy **Dropouts and withdrawals** • 47/125 (38%) at 36 weeks: secukinumab 25 (15): secukinumab 75 (10); secukinumab 225 (4); secukinumab 450 (7); placebo (11) • Unsatisfactory therapeutic effect: secukinumab 25 (4); secukinumab 75 (6); secukinumab 225 (2); secukinumab 450 (0); placebo (6) • Withdrew consent: secukinumab 25 (8); secukinumab 75 (2); secukinumab 225 (1); secukinumab 450 (2); placebo (3) • Administrative problems: secukinumab 25 (1); secukinumab 75 (1); secukinumab 225 (0); secukinumab 450 (2); placebo (1) • Lost to follow-up: secukinumab 25 (1); secukinumab 75 (0); secukinumab 225 (1); secukinumab 450 (2); placebo (0) • AEs: secukinumab 25 (1); secukinumab 75 (1); secukinumab 225 (0); secukinumab 450 (1); placebo (0) • Death: secukinumab 25 (0); secukinumab 75 (0); secukinumab 225 (0); secukinumab 450 (0); placebo (1)
Interventions	**Intervention** A. Secukinumab (n = 29), SC, 25 mg, 0, 4, 8 weeks, 12 weeks **Control intervention** B. Secukinumab (n = 26), SC, 3 x 25 mg, 0, 4, 8 weeks, 12 weeks C. Secukinumab (n = 21), SC, 3 x 75 mg, 0, 4, 8 weeks, 12 weeks D. Secukinumab (n = 27), SC, 3 x 150 mg, 0, 4, 8 weeks, 12 weeks E. Placebo (n = 22), SC, 0, 4, 8 weeks, 12 weeks
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PASI 75

Papp 2013a *(Continued)*

Secondary outcomes of the trial

- IGA 12 weeks
- PASI 50/90 12 weeks
- Time to relapse
- Effect on PASI over time
- ECG
- AE

Notes	Funding source (p412): "Novartis Pharm AG, Basel, Switzerland" 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 & Johnson, Eli Lilly, Fujisawa, Novartis and Pfizer, and has served as a speaker for Abbott, Amgen, Centocor/Johnson & 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."

Risk of bias

Bias	Authors' judgement	Support for judgement
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 (pp 413-4): “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 (pp 413-4): “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)

Papp 2013a *(Continued)*

	The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Papp 2013b

Study characteristics	
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	**Randomised**: 260 participants (mean age 46 years, 163 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12, BSA > 10%) • Age ≥ 18 years **Exclusion criteria** • History of clinically significant medical or psychiatric diseases • Pregnancy or lactation • History of active Mycobacterium TB infection • HIV, hepatitis B or C, history of malignancy within 5 years of screening or evidence of skin conditions • Current erythrodermic, guttate or pustular psoriasis **Dropouts and withdrawals** • 47/260 (18%) at 12 weeks; • Apremilast (28): AE (8), lack efficiency (8), withdrew consent (4), lost to follow-up (3), protocol violation (3), other (2) • Placebo (19): AE (7), lack efficiency (5), withdrew consent (2), lost to follow-up (1), protocol violation (2), other(2)
Interventions	**Intervention** A. Apremilast (n = 173), orally, 10 - 20 mg, twice a day, 12 weeks **Control intervention** B. Placebo (n = 87)
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • PGA • PASI 50/90 • BSA • AEs
Notes	Funding source quote (p 27): "This study was sponsored by Celgene Corporation"

Papp 2013b *(Continued)*

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 Thac¸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 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. "

Risk of bias

Bias	Authors' judgement	Support for judgement
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 was 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 ClinicalTrials.gov

Papp 2015

Study characteristics

Papp 2015 *(Continued)*

Methods	RCT, active/placebo-controlled, double-blind Date of study: November 2010 - June 2012 Location: 64 centres in Europe, Asia and North America
Participants	**Randomised**: 355 participants (mean age 45 years, 270 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12, BSA ≥ 10, PGA moderate, marked or severe), age ≥ 18 years **Exclusion criteria** • Active infection, past history of malignant tumours, active infection, kidney or liver insufficiency, uncontrolled cardiovascular disorder, uncontrolled diabetes, uncontrolled hypertension • Had received ≥ 2 TNF alpha antagonists with discontinuation owing to lack of efficacy • Had received anti IL12/23 **Dropouts and withdrawals** • 15/355 (4.5%) • AEs: tildrakizumab 5 (1), tildrakizumab 25 (2), tildrakizumab 100 (1), tildrakizumab 200 (1), placebo (1) • Withdrew consent: tildrakizumab 5 (0), tildrakizumab 25 (3), tildrakizumab 100 (0), tildrakizumab 200 (0), placebo (4) • Protocol noncompliance: tildrakizumab 5 (0), tildrakizumab 25 (0), tildrakizumab 100 (0), tildrakizumab 200 (1), placebo (0) • Did not meet protocol eligibility: tildrakizumab 5 (1), tildrakizumab 25 (0), tildrakizumab 100 (0), tildrakizumab 200 (0), placebo (1)
Interventions	**Intervention** A. Tildrakizumab (n = 42), SC, 5 mg weeks 0, 4, every 12 weeks **Control intervention** 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
Outcomes	Assessments at 16 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • PASI 90 • PASI 75 at week 12 • PGA 0/1 • DLQI
Notes	Funding source: Quote (p 930): “This study was funded by Merck & Co, nc., Kenilworth, NJ, USA”.

Papp 2015 *(Continued)*

Declarations of interest (Appendix 1): "E.P.B., A.M., Q.L., Y.Z. and R.S. are current or former employees of Merck & 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 & 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, Dermipsor 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 (AbbVie), 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 & Dohme, Janssen and LEO Pharma."

Risk of bias

Bias	Authors' judgement	Support for judgement
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 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

Papp 2015 *(Continued)*

		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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Papp ABP 501 2017

Study characteristics	
Methods	RCT, phase 3, randomised, double-blind, active-controlled study Date of study: August 2014 - March 2015 Location: world-wide
Participants	**Randomised**: 350 participants **Inclusion criteria** • 18 to 75 years of age who had stable moderate-to-severe plaque psoriasis for at least 6 months and were candidates for phototherapy or systemic therapy and who had inadequately responded to or were unable to tolerate or receive at least 1 conventional systemic therapy were eligible for enrolment • Patients were required to have disease involvement of 10% or more of the body surface area, a PASI score of 12 or more (scores range from 0 - 72, with higher scores indicating more severe disease),15 and a static Physician Global Assessment of at least moderate severity (6-point scale, assessment ranges from clear to very severe) • Patients must have had no evidence of active tuberculosis according to local guidelines • Women of childbearing potential were required to use contraception **Exclusion criteria** • Patients with nonplaque psoriasis, drug-induced psoriasis, or any other skin condition that might interfere with evaluation of efficacy were excluded • Patients who previously used adalimumab or a biosimilar of adalimumab, or any 2 or more biologics for psoriasis were also excluded **Dropouts and withdrawals** • 42/350 (12%): Biosimilar group (23), Humira 50 group (19) • Participant decision: Biosimilar group (3), Humira group (2) • Lost to follow-up: Biosimilar group (0), Humira group (2) • Protocol violation: Biosimilar group (1), Humira group (2) • Protocol-specified criteria: Biosimilar group (13), Humira group (8) • Others: Biosimilar group (6), Humira group (5)
Interventions	**Intervention**: A. ABP 501 at an initial loading dose of 80 mg subcutaneously on week 1/day 1, followed by 40 mg subcutaneously every other week (starting at week 2) for 16 weeks, n = 175

Papp ABP 501 2017 *(Continued)*

Control intervention:

B. Adalimumab, Humira, at an initial loading dose of 80 mg subcutaneously on week 1/day 1, followed by 40 mg subcutaneously every other week (starting at week 2) for 16 weeks, n = 175

Outcomes

At week 16

Primary outcome:

- % improvement PASI

Secondary outcomes:

- PGA 0/1
- PASI 50, 75
- AEs

Notes

Funding

Quote (p 1093): "Amgen Inc funded this study and participated in the design and conduct of the study; collection, management, analysis, and interpretation of data; and preparation, review, and approval of the manuscript. All authors were involved in the decision to submit the manuscript for publication, and had the right to accept or reject comments or suggestions. A medical writer employed by MedVal Scientific Information Services LLC and funded by Amgen Inc participated in the writing of this manuscript and is acknowledged."

Conflicts of interes t

Quote (p 1093): "Dr Papp has served as a consultant, speaker, scientific officer, steering committee member, investigator,or advisory board member for3M, Abbott, Akesis, Akros, Alza, Amgen, Astellas, Baxter, BMS, Boehringer Ingelheim, CanFite, Celgene, Cipher, Dermira, Eli Lilly, Forward Pharma, Funxional Therapeutics, Galderma, GSK, Isotechnika, Janssen, Johnson & Johnson, Kirin, Kyowa, Lypanosys, MedImmune, Merck-Serono, Mitsubishi Pharma, MSD, Novartis, Pfizer, Roche, Takeda, UCB, Valeant, and Vertex. Dr Bachelez has served as a consultant, speaker, steering committee member, investigator, or advisory board member for AbbVie, Amgen, Baxalta, Boehringer-Ingelheim, Celgene, Janssen, LEO Pharma, Lilly, MSD, Novartis, Pfizer, and Takeda, and received grant support from Pfizer. Dr Costanzo has been an investigator/consultant and speaker for AbbVie, Amgen, Celgene, Janssen, Lilly, Novartis, and Pfizer. Dr Foley has served as a consultant, investigator, speaker, and/or advisor for, and/or received travel grants from Galderma, LEOPharma/Peplin, Ascent,Clinuvel, Janssen-Cilag, Eli Lilly, Australian Ultraviolet Services, Roche, CSL, 3M/iNova/Valeant, GSK/ Stiefel, Abbott/AbbVie, Biogen Idec, Merck Serono, Schering-Plough/MSD, Wyeth/Pfizer, Amgen, Novartis, Celgene, Aspen, Boehringer Ingelheim, and BMS. Dr Gooderham has been an investigator, consultant, and/or speaker for AbbVie,Amgen, Boehringer Ingelheim, Celgene,Coherus, Dermira, Galderma, Janssen, LEO Pharma, Lilly, Medimmune, Merck Serono, Novartis, Regeneron, Roche, Sanofi Genzyme, Takeda, and Pfizer. Dr Kaur is an Amgen employee and stockholder. Dr Narbutt is an investigator for Amgen. Dr Philipp has been investigator, consultant, and/or speaker for AbbVie, Amgen, Almirall, Biogen, Boehringer-Ingelheim, BMS, Celgene, Janssen, LEO Pharma, Lilly, MSD, Novartis, Pfizer, and UCB. Dr Spelman has served on advisory boards for Galderma, Novartis, and AbbVie; undertakes sponsored clinical research for AbbVie, Amgen, Anacor, Ascend Biopharmaceuticals, Astellas, Australian Wool Innovation Limited, Blaze Bioscience, Celgene, Dermira, Eli Lilly, Galderma, Genentech, GlaxoSmith Kline, Kythera, LEO Pharma, Merck, Novartis, Phosphagenics, Regeneron, and Trius; and has received sponsored travel from Abbott, Novartis, and Janssen-Cilag. Dr Weglowska has been an investigator for Amgen, Pfizer, Novartis, Galderma, Eli Lilly, Dermira, Roche, Janssen-Cilag, Coherus, Genentech, LEO Pharma, Merck, Mylan, and Regeneron. Dr Zhang is an Amgen employee and stockholder. Dr Strober has served on a speakers bureau for AbbVie, receiving honoraria; is a consultant and advisory board member for AbbVie, Amgen, Astra Zeneca, Celgene, Dermira, Forward Pharma, Janssen, LEO Pharma, Eli Lilly, Cutanea-Maruho, Medac, Novartis, Pfizer, Sun, Stiefel/GlaxoSmithKline, UCB, and Boehringer Ingelheim, receiving honoraria for all; is an investigator for AbbVie, Amgen, GlaxoSmithKline, Novartis, Lilly, Janssen, Merck, XenoPort, Xoma, Celgene (payments to the University of Connecticut); is scientific director for Corrona Psoriasis Registry, receiving a consulting fee; received grant support to the University of Connecticut for a fellowship program fromAbbVie and Janssen."

Papp ABP 501 2017 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 1095): "This randomized, double-blind, multicenter, active-controlled phase III trial consisted of a 4-week screening period, after which eligible patients were randomized 1:1 to receive treatment with ABP 501 or adalimumab...Randomization was carried out by a computer-generated randomization schedule with stratification by prior biologic use and geographic region. Patients were allocated by an interactive voice and web response system." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 1095): "This randomized, double-blind, multicenter, active-controlled phase III trial consisted of a 4-week screening period, after which eligible patients were randomized 1:1 to receive treatment with ABP 501 or adalimumab...Randomization was carried out by a computer-generated randomization schedule with stratification by prior biologic use and geographic region. Patients were allocated by an interactive voice and web response system." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 1095): "This randomized, double-blind, multicenter, active-controlled phase III trial consisted of a 4-week screening period, after which eligible patients were randomized 1:1 to receive treatment with ABP 501 or adalimumab...During the study, the patients, investigators, study center personnel, and sponsor remained blinded to the patient's randomized treatment assignment. ABP 501 and adalimumab were administered in identical syringes" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 1095): "This randomized, double-blind, multicenter, active-controlled phase III trial consisted of a 4-week screening period, after which eligible patients were randomized 1:1 to receive treatment with ABP 501 or adalimumab...During the study, the patients, investigators, study center personnel, and sponsor remained blinded to the patient's randomized treatment assignment. ABP 501 and adalimumab were administered in identical syringes" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (p1096): "Efficacy data were analyzed using the full analysis set, which included all patients initially randomized in the study with missing values imputed using the last observation carried forward method." Randomised 350; analysed 345 (equivalence design)
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01970488) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported.

Papp AMAGINE-1 2016

Study characteristics	
Methods	RCT, placebo-controlled, double-blind Date of study: 29 August 2012 - 12 March 2014 Location: 73 centres worldwide (Europe, USA and Canada)
Participants	**Randomised**: 661 participants (mean age 46 years, 484 male) **Inclusion criteria** • Aged 18 - 75 • Participants with moderate-severe psoriasis (PASI ≥ 12, PPGA ≥ 3 and BSA ≥ 10), failed to respond to, had a contraindication to, or were intolerant to at least 1 conventional systemic treatment **Exclusion criteria** • Not plaque-type psoriasis • Active infection (TB, hepatitis B, C or HIV), had Crohn's disease and any uncontrolled significant medical condition • Had a myocardial infarction or unstable angina pectoris within 12 months before the first dose • Had active malignancy or a history of malignancy within 5 years **Dropouts and withdrawals** • 33/661(5%); brodalumab 210 (10), brodalumab 140 (11), placebo (12) • Ineligibility determined: brodalumab 210 (0), brodalumab 140 (0), placebo (2) • Not received study medication • AEs: brodalumab 210 (2), brodalumab 140 (3), placebo (3) • Death: brodalumab 210 (0), brodalumab 140 (0), placebo (0) • Lost to follow-up: brodalumab 210 (1), brodalumab 140 (1), placebo (1) • Withdrawal consent: brodalumab 210 (4), brodalumab 140 (3), placebo (3) • Other reason: brodalumab 210 (3), brodalumab 140 (4), placebo (3)
Interventions	**Intervention** A. Brodalumab (n = 222), SC, 210 mg every 2 weeks **Control intervention** B. Brodalumab (n = 219), SC, 140 mg every 2 weeks C. Placebo (n = 220)
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PASI 75 • PGA success **Secondary outcomes of the trial** • PASI 100 and PGA 0 • Participant-reported outcomes • AEs
Notes	Funding source:

Papp AMAGINE-1 2016 *(Continued)*

Quote (p 1): "This study was funded by Amgen Inc. & AstraZeneca/MedImmune."

Declarations of interest (pp 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."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (pp 2 and 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 (pp 2 and 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 (pp 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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported.

Papp BE ABLE 2018

Study characteristics

Methods	RCT, phase 2, randomised, double-blinded, placebo-controlled, parallel-group, dose-ranging study

Papp BE ABLE 2018 *(Continued)*

	Date of study: 25 August 2016 - 1 March 2017 Location: 6 countries (Canada, Czech Republic, Hungary, Japan, Poland, and USA)
Participants	**Randomised**: 250 participants (Age 44 years old, 163 males) **Inclusion criteria** • Moderate-to-severe plaque psoriasis • Patients were required to have disease involvement of 10% or more of the body surface area, a PASI score of 12 or more (scores range from 0 - 72, with higher scores indicating more severe disease),15 and a static Investigator's Global Assessment of at least moderate severity (5-point scale, assessment ranges from clear to very severe) **Exclusion criteria** • Patients were excluded if they had prior treatment with an antiIL-17 therapy or prior exposure to 1 other biologic therapy for psoriasis or PsA, a significant uncontrolled neuropsychiatric disorder, history of a suicide attempt, or suicide ideation within 6 months (assessed using the electronic Columbia Suicide Severity Rating Scale) **Dropouts and withdrawals** • 21/250 (8.4%): Bime 64 (3), Bime 160 (5), Bime 320/160 (6), Bime 320 (3), Bime 480 (4), PBO (5) • Participant decision: Bime 64 (0), Bime 160 (1), Bime 320/160 (1), Bime 320 (0), Bime 480 (1), PBO (1) • Lost to follow-up: Bime 64 (0), Bime 160 (0), Bime 320/160 (1), Bime 320 (1), Bime 480 (0), PBO (0) • AEs: Bime 64 (1), Bime 160 (1), Bime 320/160 (1), Bime 320 (0), Bime 480 (1), PBO (1) • Lack of efficacy: Bime 64 (0), Bime 160 (0), Bime 320/160 (0), Bime 320 (0), Bime 480 (0), PBO (1) • Protocol violation: Bime 64 (0), Bime 160 (0), Bime 320/160 (0), Bime 320 (0), Bime 480 (0), PBO (2) • Others: Bime 64 (2), Bime 160 (3), Bime 320/160 (3), Bime 320 (2), Bime 480 (2), PBO (1)
Interventions	**Intervention**: A. Bimekizumab every 4 weeks at doses of 64 mg, n = 39 **Control intervention**: B. Bimekizumab every 4 weeks at doses of 160 mg, n = 43 C. Bimekizumab every 4 weeks at doses of 160 mg (with 320 mg loading dose at baseline), n = 40 D. Bimekizumab every 4 weeks at doses of 320 mg, n = 43 E. Bimekizumab every 4 weeks at doses of 480 mg, n = 43 F Placebo, n = 42
Outcomes	**At week 12** Primary outcome: • PASI 90 Secondary outcomes: • IGA 0/1 • PASI 50, 75 • AEs
Notes	Funding

Papp BE ABLE 2018 *(Continued)*

Quote (p 277): "Supported by UCB Pharma."

Conflicts of interest

Quote (p 277): "Dr Papp has received consultant fees from Astellas, AstraZeneca, Baxalta, Baxter, Boehringer Ingelheim, Bristol-Myers Squibb, CanFite, Celgene, Coherus, Dermira, Dow Pharma, Eli Lilly, Forward Pharma, Galderma, Genentech, Janssen, Kyowa Hakko Kirin, LEO Pharma, Meiji, Seika Pharma, MSD, Merck Serono, Mitsubishi Pharma, Novartis, Pfizer, Regeneron, Roche, Sanofi/Genzyme, Takeda, UCB, and Valeant; investigator fees from Astellas, Baxalta, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Coherus, Dermira, Dow Pharma, Eli Lilly, Galderma, Genentech, GSK, Janssen, Kyowa Hakko Kirin, LEO Pharma, MedImmune, MSD, Merck-Serono, Novartis, Pfizer, Regeneron, Roche, Sanofi/Genzyme, Takeda, UCB, and Valeant; speaker fees from Astellas, Celgene, Eli Lilly, Galderma, Kyowa Hakko Kirin, LEO Pharma, MSD, Novartis, Pfizer, and Valeant; has participated in advisory boards for Astellas, Baxter, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dow Pharma, Eli Lilly, Galderma, Janssen, MSD, Novartis, Pfizer, Regeneron, Sanofi/Genzyme, UCB, and Valeant; is a steering committee member for Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, Kyowa Hakko Kirin, MSD, Merck-Serono, Novartis, Pfizer, Regeneron, Sanofi/Genzyme, and Valeant; and is a scientific officer for Kyowa Hakko Kirin. Dr Merola has received honoraria from AbbVie, Celgene, Eli Lilly, Janssen, Novartis, Pfizer, Samumed, and UCB. Dr Gottlieb has received consultant fees, advisory board fees, or speaker fees from AbbVie, Allergan, Beiersdorf Inc, Bristol-Myers Squibb, Celgene, Dermira, Lilly, Incyte, Janssen, Novartis, Reddy Labs, Sun Pharmaceutical Industries, UCB, and Valeant; and research grants from Allergan, Incyte, Janssen, LEO, Eli Lilly and Company, and Novartis. Dr Blauvelt has received consultant fees from Eli Lilly and Company, Janssen, Regeneron, and Sanofi Genzyme; and is a scientific adviser or clinical study investigator for AbbVie, Aclaris, Allergan, Almirall, Amgen, Boehringer Ingelheim, Celgene, Dermavant, Dermira Inc, Eli Lilly and Company, Genentech/Roche, GlaxoSmithKline, Janssen, Leo, Merck Sharp & Dohme, Novartis, Pfizer, Purdue Pharma, Regeneron, Sandoz, Sanofi Genzyme, Sienna Pharmaceuticals, Sun Pharma, UCB Pharma, Valeant, and Vidac. Dr Griffiths has received grants and personal fees from AbbVie, Celgene, LEO, Eli Lilly and Company, Janssen, Novartis, Pfizer, and UCB Pharma; grants from Sandoz; personal fees from Almirall and Galderma. Dr Griffiths has received research grants from AbbVie, Celgene, Novartis, Eli Lilly and Company, Janssen, Sandoz, Pfizer, LEO, and UCB. Mr Patterson and Dr Cioffi own stock in UCB. Dr Cross has no further conflicts to disclose.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p279): "An interactive voice or web response system was used for assigning eligible patients to a treatment regimen according to a randomization schedule produced by an independent biostatistician who was not associated with the design or analysis of the study. Treatment assignment was stratified by geographic region and prior biologic exposure." Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (p 279): "An interactive voice or web response system was used for assigning eligible patients to a treatment regimen according to a randomization schedule produced by an independent biostatistician who was not associated with the design or analysis of the study. Treatment assignment was stratified by geographic region and prior biologic exposure." Comment: Probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 279 and supplemental appendix): "Bimekizumab was provided in single-use vials containing 160 mg/mL. Due to differences in presentation and to ensure study blinding, bimekizumab and placebo injections were prepared and administered at the investigational sites by unblinded, dedicated study personnel"; "Additional details of blinding: Bimekizumab was provided in single-use vials containing 160 mg/mL. Placebo was supplied as 0.9% saline solution. Treatments were administered as 3 subcutaneous injections (lateral abdominal wall

Papp BE ABLE 2018 *(Continued)*

		and upper outer thigh). During each dosing visit, each of the 3 injections was administered at a separate injection site, and sites were rotated. Due to differences in presentation and to ensure study blinding, bimekizumab and placebo injections were prepared and administered at the investigational sites by unblinded, dedicated study personnel. The unblinded personnel were not involved in the study in any way other than assuring the medication was taken from the correct kit and administered to patients. All other study personnel remained blinded and did not have access to medication-related information. To preserve the blinding of treatment doses, each administration consisted of 3 subcutaneous injections" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 279 and supplemental appendix): "Bimekizumab was provided in single-use vials containing 160 mg/mL. Due to differences in presentation and to ensure study blinding, bimekizumab and placebo injections were prepared and administered at the investigational sites by unblinded, dedicated study personnel"; "Additional details of blinding: Bimekizumab was provided in single-use vials containing 160 mg/mL. Placebo was supplied as 0.9% saline solution. Treatments were administered as 3 subcutaneous injections (lateral abdominal wall and upper outer thigh). During each dosing visit, each of the 3 injections was administered at a separate injection site, and sites were rotated. Due to differences in presentation and to ensure study blinding, bimekizumab and placebo injections were prepared and administered at the investigational sites by unblinded, dedicated study personnel. The unblinded personnel were not involved in the study in any way other than assuring the medication was taken from the correct kit and administered to patients. All other study personnel remained blinded and did not have access to medication-related information. To preserve the blinding of treatment doses, each administration consisted of 3 subcutaneous injections" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data Quote (p281): "Efficacy analyses included patients who received 1 dose of study treatment and had a valid measurement of the primary efficacy variable at baseline (full analysis set)...Patients with missing efficacy data were imputed as nonresponders" 250 randomised, 250 analysed Comment: Done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02905006) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Papp ESTEEM-1 2015

Study characteristics	
Methods	RCT, placebo-controlled, double-blind Date of study: September 2010 - December 2012

Papp ESTEEM-1 2015 *(Continued)*

	Location: 72 centres in USA, Canada, Australia, Belgium, France, UK, Italy, Germany
Participants	**Randomised**: 844 participants (apremilast (562) mean age 46 years, 379 male; placebo (282) mean age 47 years, 194 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12, BSA ≥ 10%, PGA ≥ 3, • Age ≥ 18 years • Number of allowed previous treatment line: any (candidate for systemic/phototherapy) • Number of allowed previous biologic treatments: any **Exclusion criteria** • Pregnancy, immunodepression, clinically significant or major uncontrolled disease • Had an active infection • Clinically significant abnormality on 12-lead ECG at screening • Malignancy or history of malignancy (except for treated (i.e. cured) basal cell or squamous cell in situ skin carcinomas and treated (i.e. cured), CIN or carcinoma in situ of the cervix with no evidence of recurrence within the previous 5 years) **Dropouts and withdrawals** • 92/844 (11%) at 16w; • Apremilast (59): AE (23), lack efficiency (2), withdrew consent (12), lost to follow-up (7), deviation (7), noncompliance (7), other (1) • Placebo(33): AE (5), lack efficiency (7), withdrew consent (9), lost to follow-up (9), death (1), deviation (1), other (1)
Interventions	**Intervention** A. Apremilast (n = 562), orally, 30 mg, twice a day, 16 weeks **Control intervention** B. Placebo (n = 282), orally, twice a day, 16 weeks
Outcomes	Assessments at 16 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • Static PGA 0 or 1 • Number of participants with AEs (AE) in the placebo-controlled phase • Number of participants with a psoriasis flare or rebound during the placebo-controlled phase • Per cent change from baseline in percent of affected BSA • Per cent change from baseline in the PASI score • Per cent of participants who achieved a 50% improvement (response) in the PASI Score (PASI 50) • Change from baseline in pruritus VAS score • Change from baseline in the DLQI total score • Change from baseline in the Mental Component Summary score of the SF-36 Health Survey Version 2.0 • 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 reduction from baseline
Notes	Funding source quote (p 37): "This study was sponsored by Celgene Corporation"

Papp ESTEEM-1 2015 *(Continued)*

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.. multicenter, randomised, double-blind, placebo controlled study". Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Quote (p 38): "ESTEEM 1 was.. multicenter, 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.. multicenter, 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 (pp 38-9): "ESTEEM 1 was.. multicenter, randomised, double-blind, placebo controlled study... Blinding was maintained until all patients discontinued or completed the week 52 visit" 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 prespecified 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 NCT02054481 2017

Study characteristics

Methods	RCT, placebo-controlled, double-blind trial, phase 2 Date of study: February 2014 - July 2015 Location: world-wide
Participants	**Randomised**: 166 participants **Inclusion criteria** • BMI ≥ 18.5 and < 40 kg/m^2 • Stable moderate-severe chronic plaque-type psoriasis with or without psoriatic arthritis involving ≥ 10% body surface area, with disease severity PASI ≥ 12 and sPGA score of moderate and above (score of ≥ 3) at screening visit and visit 2 (randomisation), as assessed by the investigator • Psoriasis disease duration of ≥ 6 months prior to screening, as assessed by the investigator • Patients must be candidates for systemic psoriasis treatment or phototherapy, as assessed by the investigator • Patients must be suitable candidates for ustekinumab (Stelara®) therapy as given in the local labelling • Patient must give informed consent and sign an approved consent form prior to any study procedures in accordance with GCP and local legislation **Exclusion criteria** • Patients with guttate, erythrodermic, or pustular psoriasis and patients with drug-induced psoriasis, as diagnosed by the investigator • 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 judgement, even if other eligibility criteria are satisfied. (Psoriatic arthritis is not considered an exclusion criterion) • 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 jeopardise the safe conduct of the study • Clinically important acute or chronic infections including hepatitis and HIV With regards to TB the following applies: • 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) • Have history of latent or active TB prior to screening, except for patients who have documentation of having completed an adequate treatment regimen ≥ 6 months prior to the first administration of study agent • 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 ≥ 6 months prior to the first administration of study agent • Have had a live vaccination ≤ 12 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 1 year prior to randomisation (visit 2), during the study and for one year after last administration of study drug (according to the Stelara® SPC). • History of clinically-significant hypersensitivity to a systemically administered biologic agent or its excipient • History of malignancy in the past 5 years or suspicion of active malignant disease except treated cutaneous squamous cell or basal cell carcinoma • Has received any therapeutic agent directly targeted to IL-12, IL-23 (including ustekinumab (Stelara®))

Papp NCT02054481 2017 *(Continued)*

- 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

Dropouts and withdrawals

- 9/166 (5.4%):

Risan 18 (4), Risan 90 (2), Risan 180 (2), USK (1)

- Lost to follow-up: Risan 18 (1), Risan 90 (0), Risan 180 (0), USK (0)
- AEs: Risan 18 (1), Risan 90 (1), Risan 180 (0), USK (1)
- Others: Risan 18 (2), Risan 90 (1), Risan 180 (2), USK (0)

Interventions	**Intervention** A. Drug: Risankizumab (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), n = 43 **Control intervention** 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), n = 41 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 2eeks 4 and 16), n = 42 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 ≤ 100 kg at randomisation or 90 mg for participants with body weight > 100 kg at randomisation), n = 40
Outcomes	**At week 12** **Primary outcome** • PASI 90 **Secondary outcomes** • PASI 50, 75, 100 (weeks 12 and 24) • PGA
Notes	Funding Quote (p 1553): "The trial was funded by Boehringer Ingelheim" Conflicts of interest Quote (p 1560): "Disclosure forms provided by the authors are available with the full text of this article at NEJM.org."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p 1552): "This 48-week, multicenter, randomized, dose-ranging, phase 2 trial."

Papp NCT02054481 2017 *(Continued)*

		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	Quote (p 1552): "The trial was double blind within the risankizumab dose groups and single blind (to patients) with regard to drug (ustekinumab or risankizumab). All efficacy assessments were conducted by an assessor who was unaware of the treatment assignments." Comment: No blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 1552): "The trial was double blind within the risankizumab dose groups and single blind (to patients) with regard to drug (ustekinumab or risankizumab). All efficacy assessments were conducted by an assessor who was unaware of the treatment assignments." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data Quote (p 1553): "Primary and other end points were analyzed on an intention-to-treat basis... In the primary analyses, last observation carried forward was prespecified in the trial protocol as the method of handling missing data; a sensitivity analysis with nonresponse imputation was also performed" 166 randomised, 166 analysed Comment: Done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02054481) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported Results posted on ClinicalTrials.gov

Papp OPT Pivotal-1 2015

Study characteristics	
Methods	RCT, active/placebo-controlled, double blind Date of study: 12 January 2012–18 September 2014 Location: multicentre (74) in USA, Canda, Colombia, Germany, Japan, Hungary, Serbia, Taiwan, Ukraine
Participants	**Randomised**: 901 participants (mean age 46 years, 643 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12 or BSA ≥ 10), age ≥ 18 years **Exclusion criteria**

Papp OPT Pivotal-1 2015 *(Continued)*

- Past history of malignant tumour, active infection, uncontrolled significant medical condition
- Had received efalizumab treatment

Dropouts and withdrawals

- 136/901 (15%); tofacitinib 5 group (50), tofacitinib 10 group (40), placebo group (45)
- plus 1 participant not treated
- AEs: tofacitinib 5 group (11), tofacitinib 10 group (8), placebo group (11)
- Lack of efficacy: tofacitinib 5 group (20), tofacitinib 10 group (15), placebo group (25)
- Withdrawal consent: tofacitinib 5 group (8), tofacitinib 10 group (5), placebo group (4)
- Lost to follow-up: tofacitinib 5 group (3), tofacitinib 10 group (5), placebo group (3)
- Participant died: tofacitinib 5 group (1), tofacitinib 10 group (0), placebo group (1)
- Other reason: tofacitinib 5 group (7), tofacitinib 10 group (7), placebo group (2)

Interventions	**Intervention** A. Tofacitinib (n = 363), orally, 5 mg twice daily **Control intervention** B. Tofacitinib (n = 360), orally, 10 mg twice daily B. Placebo (n = 177), orally (same drug administration)
Outcomes	Assessments at 16 weeks **Primary outcomes of the trial** • PASI 75 • PGA 0/1 **Secondary outcomes of the trial** • PASI 75 • PGA 0/1 • PASI 90 • DLQI • AEs
Notes	Funding source: Quote (p 949): "Pfitzer Inc" 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 hono-

Papp OPT Pivotal-1 2015 *(Continued)*

raria from AbbVie, Allergan, Amgen, Boehringer Ingelheim, Convoy Technologies, Eli Lilly, Genentech, Janssen Biotech, LEO Pharma, Novartis, Pfizer Inc., Syntrix, Wyeth and XenoPort."

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)	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...Nonresponder 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.

Papp OPT Pivotal-2 2015

Study characteristics

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	**Randomised**: 960 participants (mean age 46 years, 648 male) **Inclusion criteria**

Papp OPT Pivotal-2 2015 *(Continued)*

- Participants with moderate-severe psoriasis (PASI ≥ 12 or BSA ≥ 10) age ≥ 18 years

Exclusion criteria

- Past history of malignant tumour, active infection, uncontrolled significant medical condition
- Had received efalizumab treatment

Dropouts and withdrawals

- 136/901 (15%); tofacitinib 5 group (51), tofacitinib 10 group (40), placebo group (44)
- plus 1 participant not treated
- AEs: to facitinib 5 group (11), tofacitinib 10 group (10), placebo group (5)
- Lack of efficacy: tofacitinib 5 group (15), tofacitinib 10 group (2), placebo group (24)
- Withdrawal of consent: tofacitinib 5 group (7), tofacitinib 10 group (6), placebo group (7)
- Lost to follow-up: tofacitinib 5 group (7), tofacitinib 10 group (8), placebo group (3)
- Participant died: tofacitinib 5 group (1), tofacitinib 10 group (0), placebo group (1)
- Other reason: tofacitinib 5 group (10), tofacitinib 10 group (14), placebo group (4)

Interventions

Intervention

A. Tofacitinib (n = 382), orally, 5 mg twice daily

Control intervention

B. Tofacitinib (n = 381), orally, 10 mg twice daily

C. Placebo (n = 196), orally (same drug administration)

Outcomes

Assessments at 16 weeks

Primary outcomes of the trial

- PASI 75
- PGA 0/1

Secondary outcomes of the trial

- PASI 75
- PGA 0/1
- PASI 90
- DLQI
- AEs

Notes

Funding source:

Quote (p 949): "Pfitzer Inc"

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 Ab-

Papp OPT Pivotal-2 2015 *(Continued)*

bVie, 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."

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. 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...Nonresponder 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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported.

Papp PHOENIX-2 2008

Study characteristics

Methods	RCT, placebo-controlled, double-blind trial Date of study: March 2006 – September 2007 Location: 70 centres in Europe and North America

Papp PHOENIX-2 2008 *(Continued)*

Participants	**Randomised**: 1230 participants (mean age 45 years, 840 male) **Inclusion criteria** • Participants with moderate-severe psoriasis • Authors' assessment ≥ 6 months, PASI ≥ 12, BSA > 10% • Age ≥ 18 years **Exclusion criteria** • Had received IL12/23 drug • Had an active infection • Had past history of malignant tumours **Dropouts and withdrawals** • 33/1230 (2.7%) • Ustekinumab 45 (6): AE (2), other (4) • Ustekinumab 90 (9): AE (5), death (1), other (3) • Placebo (18): lack of efficacy (2), AE (8), other (8)
Interventions	**Intervention** A. Ustekinumab (n = 409), SC, 45 mg, weeks 0 - 4 and every 12 weeks, 52 weeks **Control intervention** 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	Assessments at 12 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • PGA cleared or minimal at 12 weeks • Change of QoL from baseline at week 12 • PASI 90 at 12 weeks
Notes	Funding Centocor Inc (p 1675) Declaration of interest (p 1684): "KP has served as a consultant and advisory board member for Abbott, Alza, Amgen, Celgene, Centocor, Isotechnika, Janssen Ortho Biotech, Johnson & 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 Ingleheim, Bristol Myers Squibb, Centocor, CombinatoRx, Exelixis, Genentech, Genzyme, Isis, L'Oreal, Lupin Limited, Magen Biosciencs, 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 Ingleheim, 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,

Papp PHOENIX-2 2008 *(Continued)*

M-CH, YW, SL, and LTD are employees of Centocor. PS, NY, CG, YW, SL, and LTD own stock in Johnson and Johnson."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 1676): “Patients were randomly assigned... with bias coin assignment via a centralised interactive voice response system (ClinPhone, East Windsor, NJ, USA)” Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 1676): “Patients were randomly assigned... with bias coin assignment via a centralised interactive voice response system (ClinPhone, East Windsor, NJ, USA)” Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (pp 1676-7): “Double-blind,..., placebo-controlled...Site monitors investigators personnel 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 (pp 1676-7): “Double-blind,..., placebo-controlled...Site monitors investigators personnel 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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Papp TYK2 2018

Study characteristics

Methods	RCT, placebo-controlled, double-blind trial, phase 2 Date of study: Novermber 2016 - November 2017 Location: 82 sites In the USA, Japan, Poland, Canada, Germany, Latvia, Mexico, and Australia
Participants	**Randomised**: 267 participants **Inclusion criteria**

Papp TYK2 2018 *(Continued)*

- Men and women, ages 18 to 70 years
- Diagnosis of plaque psoriasis for 6 months
- Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test, must not be pregnant, lactating, breastfeeding or planning pregnancy
- Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment plus 5 half-lives of the study drug plus 90 days.

Exclusion criteria

- Any significant acute or chronic medical illness
- Blood transfusion within 4 weeks of study drug administration Inability to tolerate oral medication positive hepatitis-B (HBV) surface antigen
- Positive hepatitis-C (HCV) antibody
- Any history or risk for tuberculosis (TB)
- Any major illness/condition or evidence of an unstable clinical condition
- Chest X-ray findings suspicious of infection at screening has received ustekinumab, secukinumab or ixekizumab within 6 months of first administration of study medication
- Has received anti-Tumor Necrosis Factor (TNF) inhibitor(s) within 2 months of first administration of study medication Has received Rituximab within 6 months of first administration of study medication Topical medications/treatments for psoriasis within 2 weeks of the first administration of any study medication Any systemic medications/treatments for psoriasis within 4 weeks of the first administration of any study medication
- Other protocol defined inclusion/exclusion criteria could apply

Dropouts and withdrawals

- 61/267 (15.%):

BMS-986165_3EOD (10), BMS-986165_3 (8), BMS-986165_3*2 (3), BMS-986165_6*2 (6), BMS-986165_12 (2), PBO (14)

- Lost to follow-up: BMS-986165_3EOD (0), BMS-986165_3 (1), BMS-986165_3*2 (1), BMS-986165_6*2 (2), BMS-986165_12 (0), PBO (1)
- AEs: BMS-986165_3EOD (1), BMS-986165_3 (2), BMS-986165_3*2 (1), BMS-986165_6*2 (3), BMS-986165_12 (1), PBO (2)
- Lack of efficacy: BMS-986165_3EOD (4), BMS-986165_3 (3), BMS-986165_3*2 (0), BMS-986165_6*2 (0), BMS-986165_12 (1), PBO (5)
- Participant: BMS-986165_3EOD (5), BMS-986165_3 (0), BMS-986165_3*2 (1), BMS-986165_6*2 (1), BMS-986165_12 (0), PBO (5)
- Others: BMS-986165_3EOD (0), BMS-986165_3 (2), BMS-986165_3*2 (0), BMS-986165_6*2 (0), BMS-986165_12 (0), PBO (1)

Interventions	**Intervention**: A. BMS-986165 3 mg every other day (EOD) (by mouth), n = 44 **Control intervention**: B. BMS-986165 3 mg a day (by mouth), n = 44 C. BMS-986165 3 mg*2 a day (by mouth), n = 45 D. BMS-986165 6 mg*2 a day (by mouth), n = 45 E. BMS-986165 12 mg a day (by mouth), n = 44 F Placebo, n = 45
Outcomes	**At week 12** Primary outcome:

Papp TYK2 2018 *(Continued)*

- PASI 75

Secondary outcomes:

- IGA 0/1
- PASI 50, 90, 100
- DLQI 0/1
- AEs

Notes

Funding

Quote (p 1320): "Supported by Bristol-Myers Squibb."

Conflicts of interest

Quote (p 1320-21): "Dr. Papp reports receiving grant support, consulting fees, advisory board fees, and fees for serving on a speakers' bureau from Amgen, AbbVie, Boehringer Ingelheim, Eli Lilly, Janssen, Leo Pharma, Novartis, Pfizer, UCB, Valeant Pharmaceuticals, and Kyowa Hakko Kirin, grant support, consulting fees, and fees for serving as a scientific officer from Akros Pharma, consulting fees from CanFite BioPharma, grant support, consulting fees, advisory board fees, fees for serving on a speakers' bureau, and travel support from Celgene, grant support, consulting fees, and advisory board fees from Merck Sharp & Dohme, PRCL Research, and Takeda, grant support from Anacor Pharmaceuticals, GlaxoSmithKline, and Meiji Seika Pharma, and grant support and consulting fees from Coherus BioSciences and Dermira; Dr. Gordon, receiving grant support and consulting fees from AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen, Novartis, and UCB and consulting fees from Amgen, Almirall, Dermira, Leo Pharma, Pfizer, and Sun Pharma; Dr. Thaçi, receiving grant support, lecture fees, consulting fees, and advisory board fees from AbbVie, lecture fees, consulting fees, and advisory board fees from Almirall, Pfizer, Sandoz/Hexal, UCB, Regeneron Pharmaceuticals, and Sanofi, consulting fees and advisory board fees from Boehringer Ingelheim, grant support, lecture fees, consulting fees, advisory board fees, and writing assistance from Celgene and Novartis, and lecture fees, consulting fees, advisory board fees, and writing assistance from Eli Lilly, Leo Pharma, and Janssen-Cilag; Dr. Morita, receiving grant support and lecture fees from AbbVie, Esai, Kyowa Hakko Kirin, Leo Pharma, Maruho, Mitsubishi Tanabe Pharma, Novartis, and Torii Pharmaceutical and lecture fees from Celgene, Eli Lilly Japan, and Janssen Pharmaceutical; Dr. Gooderham, receiving advisory board fees, fees for serving as principal investigator, and lecture fees from AbbVie, Galderma, Leo Pharma, Pfizer, and Regeneron Pharmaceuticals, advisory board fees and lecture fees from Actelion Pharmaceuticals, fees for serving as principal investigator and consulting fees from Akros Pharma, advisory board fees, fees for serving as principal investigator, lecture fees, and consulting fees from Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, Novartis Pharmaceuticals, Sanofi Genzyme, and Valeant Pharmaceuticals, fees for serving as principal investigator from Arcutis Pharmaceuticals, Bristol-Myers Squibb, Dermira, GlaxoSmithKline, MedImmune, Merck, Roche Laboratories, and UCB, and fees for serving as principal investigator and lecture fees from Glenmark; Dr. Foley, receiving grant support, advisory board fees, fees for serving on a speakers' bureau, and travel support from AbbVie, Celgene, CSL, Galderma, iNova Pharmaceuticals, Janssen, Leo Pharma, Eli Lilly, Novartis, Pfizer, and Sanofi, grant support and advisory board fees from Amgen and Sun Pharma, grant support from Boehringer Ingelheim, Celtaxsys, Cutanea Life Sciences, Dermira, Genentech, and Regeneron Pharmaceuticals, grant support, advisory board fees, and fees for serving on a speakers' bureau from GlaxoSmithKline, grant support and consulting fees from Bristol-Myers Squibb, and grant support, fees for serving on a speakers' bureau, and travel support from Roche; Dr. Kundu, being employed by Bristol-Myers Squibb; and Dr. Banerjee, being employed by and holding stock in Bristol-Myers Squibb. No other potential conflict of interest relevant to this article was reported."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 1314):"Randomization was stratified according to previous treatment with a biologic agent (yes or no) and geographic region (Japan or the rest of the world), with the use of a central interactive Web-response system."

Papp TYK2 2018 *(Continued)*

		Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 1314):"Randomization was stratified according to previous treatment with a biologic agent (yes or no) and geographic region (Japan or the rest of the world), with the use of a central interactive Web-response system." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 1314): "Patients were randomly assigned to one of five oral doses of BMS-986165 (3 mg every other day, 3 mg daily, 3 mg twice daily, 6 mg twice daily, or 12 mg daily) or matching oral placebo in a ratio of 1:1:1:1:1:1. Capsules of the active drug (3 mg) or matched placebo were combined as appropriate to provide the required daily dose and were taken each morning and again 12 hours later...Patients, investigators, and the trial sponsor were unaware of the trial-group assignments." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 1314): "Patients were randomly assigned to one of five oral doses of BMS-986165 (3 mg every other day, 3 mg daily, 3 mg twice daily, 6 mg twice daily, or 12 mg daily) or matching oral placebo in a ratio of 1:1:1:1:1:1. Capsules of the active drug (3 mg) or matched placebo were combined as appropriate to provide the required daily dose and were taken each morning and again 12 hours later...Patients, investigators, and the trial sponsor were unaware of the trial-group assignments.'' Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data Quote (p 1315): "For the primary end point of PASI 75 and other binary end points (PASI 50, PASI 90, PASI 100, an sPGA score of 0 or 1, and a DLQI score of 0 or 1), patients who discontinued the trial regimen early or who had a missing value at any time point had outcomes imputed as a nonresponse at that time point, regardless of the status of response at the time of discontinuation." Randomised 267, analysed 267 Comment: Done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02931838) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Paul ESTEEM-2 2015

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind Date of study: 29 October 2012 – 25 March 2016 Location: 40 centres in Europe & USA
Participants	**Randomised**: 413 participants (mean age 45 years, 276 male) **Inclusion criteria**

Paul ESTEEM-2 2015 *(Continued)*

- Participants with moderate-severe psoriasis (PASI ≥ 12 or BSA ≥ 10) age ≥ 18 years

Exclusion criteria

- Pregnancy, immunosuppression, kidney insufficiency, liver insufficiency, past history of malignant tumours, active infection, uncontrolled cardiovascular disorder, uncontrolled diabetes, uncontrolled hypertension

Dropouts and withdrawals

- 62/413 (15%); apremilast group (36), placebo group (26)
- Error of randomisation, did not receive study medication; apremilast group (1), placebo group (1)
- AEs: apremilast group (12), placebo group (8)
- Lack of efficacy: apremilast group (3), placebo group (2)
- Withdrawal of consent: apremilast group (9), placebo group (7)
- Lost to follow-up: apremilast group (6), placebo group (6)
- Protocol violation: apremilast group (2), placebo group (1)
- Non-compliance: apremilast group (1), placebo group (0)
- Other reason:**a**premilast group (2), placebo group (1)

Interventions	**Intervention** A. Apremilast (n = 275), orally, 30 mg twice a day until week 32 **Control intervention** B. Placebo (n = 138), orally (same drug administration)
Outcomes	Assessments at 16 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • PASI 50 • PASI 90 • PASI 100 • PGA 0/1 • DLQI • Pruritus VAS • AEs
Notes	Funding source: Quote (p 1387): "This study was sponsored by Celgene Corporation" 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 Ab-

Paul ESTEEM-2 2015 *(Continued)*

bott/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 Xeno-Port. 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."

Risk of bias

Bias	Authors' judgement	Support for judgement
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 (pp 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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Paul JUNCTURE 2015

Study characteristics

Methods	RCT, active/placebo-controlled, double-blind Date of study: 7 June 2012 – 4 January 2013 Location: 38 centres worldwide
Participants	**Randomised**: 182 participants (mean age 45 years, 125 male) **Inclusion criteria**

Paul JUNCTURE 2015 *(Continued)*

- Participants with moderate-severe psoriasis (PASI ≥ 12, IGA 3-4 or BSA ≥ 10), age ≥ 18 years

Exclusion criteria

- Immunosuppression, active infection
- Had received anti IL17 drug

Dropouts and withdrawals

- 5/182 (2.7%)
- AEs: secukinumab 300 (0), secukinumab 150 (1), placebo (1)
- Lack of efficacy: secukinumab 300 (0), secukinumab 150 (0), placebo (1)
- Physician decision: secukinumab 300 (0), secukinumab 150 (1), placebo (0)
- Participant/guardian decision: secukinumab 300 (0), secukinumab 150 (1), placebo (0)

Interventions	**Intervention** A. Secukinumab (n = 61), SC, 150 mg weeks 0, 1, 2, 3 then monthly **Control intervention** B. Secukinumab (n = 60), SC, 300 mg weeks 0, 1, 2, 3 then monthly C. Placebo (n = 61), (same drug administration)
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PGA0/1 • PASI 75 **Secondary outcomes of the trial** • PASI 50/75/90 • DLQI
Notes	Funding source: 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”. 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."

Risk of bias

Bias	Authors' judgement	Support for judgement
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"

Paul JUNCTURE 2015 *(Continued)*

		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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Piskin 2003

Study characteristics	
Methods	RCT, active-controlled, open-label trial Date of study: not stated Location: Amsterdam and throughout the Netherlands, number not stated
Participants	**Randomised**: 10 participants (ciclosporin (5), mean age 41 years, 4 male; methotrexate (5), mean age 45 years, 3 male) **Inclusion criteria** • Participants with moderate-severe psoriasis, PASI ≥ 8 • Age ≥ 18 • Non-response to topical treatment **Exclusion criteria** • Not stated

Piskin 2003 *(Continued)*

	Dropouts and withdrawals • Not stated • All participants seemed to be evaluated at week 12
Interventions	**Intervention** A. Ciclosporin (n = 5), orally, 3 mg/kg/d, 16 weeks **Control intervention** B. Methotrexate (n = 5), orally, 15 mg/kg/week, 16 weeks
Outcomes	Assessments at 12 weeks **Primary and secondary outcomes of the trial** • Not clearly defined **Outcomes of the trial** • PASI 75 • Number of cutaneous T-cell 1-2 • Creatine kinase balance • Psoriatic skin
Notes	Funding not declared Declarations of interest: not stated

Risk of bias

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

Piskin 2003 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The prespecified outcomes mentioned in the Methods section appeared to have been reported

Reich 2012a

Study characteristics	
Methods	RCT, placebo-controlled, double-blind Date of study: October 2005 - November 2006 Location: 15 centres in France and Germany
Participants	**Randomised**: 176 participants, mean age 43 years, 123 male **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12, BSA ≥ 10), age ≥ 18 years • Non-response to conventional systemic treatment • Non-response to biologics **Exclusion criteria** • Pregnancy, kidney insufficiency, liver insufficiency • Had an active infection • Had uncontrolled cardiovascular disorder • Had uncontrolled diabetes • Had uncontrolled hypertension • Had past history of malignant tumours **Dropouts and withdrawals** • 28/176 (16%) • Placebo (19): lack efficacy (14), AE (3), lost to follow-up (2) • Certolizumab 200 (5): lack efficacy (3), AE (2) • Certolizumab 400 (4): lack efficacy (1), AE (2), pregnancy(1)
Interventions	**Intervention** A. Certolizumab (n = 59), SC, 200 mg, Certolizumab pegol (CZP) 400 mg week 0 – certolizumab 200 mg weeks 1-10, 10 weeks **Control intervention** B. Certolizumab (n = 58), SC, 400 mg, certolizumab 400 mg week 0 – certolizumab 400 mg weeks 1 - 10, 10 weeks C. Placebo (n = 59), SC, certolizumab 400 mg week 0 – placebo weeks 1 - 10, 10 weeks
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PASI 75 • PGA **Secondary outcomes of the trial**

Reich 2012a *(Continued)*

- PASI 50
- PASI 90
- Time to PASI 75 response
- Time to relapse
- Change from baseline BSA
- DLQI
- PGA week 12

Notes	Funding source quote (p 180): "This study was funded by UCB Pharma, Brussels, Belgium" 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, Dermipsor, 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."

Risk of bias

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

Reich 2012a *(Continued)*

		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). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported, except for pharmacokinetic profile of CDP870

Reich 2015

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind Date of study: December 2008 - July 2009 Location: 14 centres in the USA and Canada
Participants	**Randomised**: 100 participants (mean age 44 years, 100 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12, IGA ≥ 3 or BSA ≥ 10), age 18 - 65 years **Exclusion criteria** • Not stated **Dropouts and withdrawals** • 11/100 (11%); secukinumab 3 mg group (2), secukinumab 10 mg group (0), secukinumab 3 x 10 mg group (3), placebo group (6) • AEs: secukinumab 3 mg group (0), secukinumab 10 mg group (0), secukinumab 3 x 10 mg group (1), placebo group (0)
Interventions	**Intervention** A. Secukinumab (n = 30), SC, 3 mg/kg, 1 infusion (day 1) **Control intervention** B. Secukinumab (n = 29), SC, 10 mg/kg, 1 infusion (day 1) C. Secukinumab (n = 31), SC, 10 mg/kg, 3 infusions (says 1, 15, 29) D. Placebo (n = 10)
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • Change from baseline in PASI score at 12 weeks • (Proportion of participants who did not relapse at any time through week 56) **Secondary outcomes of the trial** • PASI 50

Reich 2015 *(Continued)*

- PASI 75
- PASI 90
- Change in DLQI score
- AEs

Notes	Funding source: Quote (p 534): "This trial and publication were found 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, Centocor, 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"

Risk of bias

Bias	Authors' judgement	Support for judgement
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 site, who then prepared and provided the study medication for the clinic in a blinded fashion... 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." Comment: probably done

Reich 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	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." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (supporting information): "To maintain data integrity, no subject-level data were circulated; therefore, blinding was maintained at the individual subject level" Comment probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	100 randomised participants, 94 analysed for PASI 75 or 90, 87 analysed for primary outcome (change in PASI) Quote (p 530): "Efficacy and pharmacodynamic parameters were evaluated in all subjects who received ≥ 1 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" Comment: low rate of loss to follow-up and reasons comparable between groups
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00805480) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Reich EXPRESS 2005

Study characteristics	
Methods	RCT, placebo-controlled, double-blind Date of study: not stated Location: 32 centres in Europe and Canada
Participants	**Randomised**: 378 participants (mean age 43 years, 268 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12, BSA ≥ 10), age ≥ 18 years **Exclusion criteria** • Immunosuppression • Had received biologics • Had an active infection • Had past history of malignant tumours **Dropouts and withdrawals** (week 24) • 41/378 (10.8%) • Discontinued study: infliximab (18), placebo (7)

Reich EXPRESS 2005 *(Continued)*

- No description of the reasons of withdrawals

Interventions	**Intervention** A. Infliximab (n = 301), IV, 5 mg/kg weeks 0, 2, 6 and every 8 weeks, 10 weeks **Control intervention** B. Placebo (n = 77), IV, equivalent, weeks 0, 2, 6 and every 8 weeks, 10 weeks
Outcomes	Assessments at 10 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • PASI90/50 • PGA • NAPSI
Notes	Funding source (p 386): This study was funded by Centocor, and Schering-Plough, Kenilworth, NJ, USA" 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)..."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 1368): "An 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 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 1368): "An 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)	Low risk	378 included / 378 analysed

Reich EXPRESS 2005 *(Continued)*

All outcomes		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 prespecified outcomes mentioned in the Methods section appeared to have been reported

Reich IXORA-S 2017

Study characteristics	
Methods	RCT, active-controlled, double-blind study Date of study: September 2015 - October 2017 Location: USA (multicentric) Phase 3
Participants	**Randomised**: 302 participants (median age 43.5, males 202) **Inclusion criteria**: • Chronic plaque psoriasis for ≥ 6 months before baseline • Failure, contraindication, or intolerability to ≥ 1 systemic therapy (including ciclosporin, methotrexate, or phototherapy) • PASI score ≥ 10 at screening and at baseline • Participant must agree to use reliable method of birth control during the study; women must continue using birth control for ≥ 15 weeks after stopping treatment **Exclusion criteria** • Predominant pattern of pustular, erythrodermic, and/or guttate forms of psoriasis • History of drug-induced psoriasis • Cannot avoid excessive sun exposure or use of tanning booths for ≥ 4 weeks before baseline and during the study • Have received systemic nonbiologic psoriasis therapy or phototherapy within 4 weeks of baseline, or have had topical psoriasis treatment within 2 weeks of baseline • Concurrent or recent use of any biologic agent within the following washout periods: etanercept < 28 days; infliximab, adalimumab, or alefacept < 60 days; golimumab < 90 days; rituximab < 12 months; or any other biologic agent < 5 half-lives prior to baseline • Have prior use of ustekinumab, or have any condition or contraindication to ustekinumab that would preclude the participant from participating in this protocol • 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 • 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 • 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 • Have a known allergy or hypersensitivity to latex • Have had any major surgery within 8 weeks of baseline or will require such during the study • Have active or history of malignant disease within 5 years prior to baseline • Significant uncontrolled disorder

Reich IXORA-S 2017 *(Continued)*

- Ongoing infection or serious infection within 12 weeks of baseline; serious bone or joint infection within 24 weeks of baseline
- Are women who are lactating or breastfeeding

Dropouts and withdrawals

- 6/302 (2%):

Ixe group (4), USK group (2)

- Discontinued before receiving 1 dose: Ixe group (1), USK group (0)
- AEs: Ixe group (2), USK group (0)
- Lack of efficacy: Ixe group (0), USK group (1)
- Patient: Ixe group (1), USK group (0)
- Other: Ixe group (0), USK group (1)

Interventions	**Intervention** 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), n = 136 **Control intervention** Ustekinumab (45 mg ustekinumab given as SC injection for participants ≤ 100 kg and 90 mg SC injection for participants > 100 kg at weeks 0, 4, 16, 28, and 40), n = 166
Outcomes	**At week 12,** **Primary outcome** • PASI 90 **Secondary outcomes** • PASI 75 • PGA • DLQI
Notes	Funding Quote (p 1014): "This study was funded in full by Eli Lilly and Company, Indianapolis, IN, U.S.A" Conflicts of interest Quote (Appendix 1): "K.R. has served as advisor and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Amgen, Biogen, Boehringer Ingelheim, Celgene, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Lilly, Medac, Merck Sharp & Dohme, Novartis, Pfizer, Regeneron, Takeda, UCB Pharma and Xenoport. A.P. has served as an advisor and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Amgen, Biogen, Boehringer Ingelheim, Celgene, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Lilly, Medac, Merck Sharp & Dohme, Novartis, Pfizer, Regeneron and UCB. J.P.L. has served as an advisor and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Amgen, Boehringer Ingelheim, Celgene, Galderma, Janssen, LEO Pharma, Lilly, Merck-Serono, Novartis, Pfizer, Regeneron, Roche and UCB Pharma. C.F. 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, Celgene, Centocor, Janssen-Cilag, LEO Pharma, Lilly, Merck Sharp & Dohme, Novartis and Pfizer. G.M. has served as an investigator for Lilly. L.E.F. has served as an advisor for and/or participated in clinical trials sponsored by AbbVie, Amgen, Celgene, Eli Lily and Company, Galderma, Janssen-Cilag and Novartis. M.L. has worked as a consultant and/or clinical trial investigator for AbbVie, Allergan Amgen, Anacor, Boehringer Ingelheim, Celgene, Dr Reddy's, Janssen, LEO Pharma, Lilly, Merck-Serono, Novartis, Oncobio- logics, Pfizer, Regeneron, Roche, Xenon Pharma, Valeant, Bayer, L'Oreal and Galderma. Y.D, C.H., S.W. and S.H. are employees of Eli Lilly and Company, and receive salary from and own stock in the company. C.P. has

Reich IXORA-S 2017 *(Continued)*

served as a consultant and/or investigator for AbbVie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, LEO Pharma, Novartis and Pfizer."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 1015): "This 52-week, phase IIIb, multicentre, controlled, double-blind, parallel-group trial (IXORA-S, NCT02561806) was conducted at 51 sites across 13 countries. Patients were randomized (1: 1) via an interactive web-response system to receive either ixekizumab or ustekinumab. Randomization was stratified by study centre and patient weight (≤ 1000 kg vs. > 1000 kg)." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 1015): "This 52-week, phase IIIb, multicentre, controlled, double-blind, parallel-group trial (IXORA-S, NCT02561806) was conducted at 51 sites across 13 countries. Patients were randomized (1: 1) via an interactive web-response system to receive either ixekizumab or ustekinumab. Randomization was stratified by study centre and patient weight (≤ 1000 kg vs. > 1000 kg)." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 1015): "To maintain the blinding, patients randomized to ixekizumab received placebo injections matching the ustekinumab dose regimen, and patients in the ustekinumab group received dummy injections of ixekizumab. Unblinded site personnel responsible for ustekinumab and ustekinumab placebo injections were involved in neither the clinical assessments nor the treatment decisions, and kept the patients and investigators blinded from treatment allocation" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 1015): "To maintain the blinding, patients randomized to ixekizumab received placebo injections matching the ustekinumab dose regimen, and patients in the ustekinumab group received dummy injections of ixekizumab. Unblinded site personnel responsible for ustekinumab and ustekinumab placebo injections were involved in neither the clinical assessments nor the treatment decisions, and kept the patients and investigators blinded from treatment allocation" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data Qjuote (p 1016): "Patients were analysed according to the treatment they were assigned at randomization (intention-to-treat population). The primary-analysis model was a logistic regression for the PASI 90 response end point after 12 weeks of treatment, with terms for treatment group, weight and geographical region. Missing data were imputed via nonresponder imputation (NRI), assuming that patients without data had no response" Patients randomized, patients analyzed Comment: Done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02561806)

Reich IXORA-S 2017 *(Continued)*

	The prespecified outcomes and those mentioned in the Methods section appeared to have been reported Results are posted on ClinicalTrials.gov

Reich LIBERATE 2017

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind Date of study: October 2012 - April 2016 Location: 82 centres worldwide (USA, Europe, Australia)
Participants	**Randomised**: 250 participants (mean age 45 years, 157 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12, PGA 3-4 or BSA ≥ 10), age ≥ 18 years • Failed to respond to, had a contraindication to, or were intolerant to at least 1 conventional systemic treatment **Exclusion criteria** • Failure of > 3 systemic agents for psoriasis • Active infection • History of known demyelinating diseases • Congestive heart failure • Significant/major uncontrolled diseases **Dropouts and withdrawals** • 17/250 (6.8%); apremilast (6), etanercept (2), placebo group (9) • AEs: apremilast (2), etanercept (1), placebo group (2) • Lack of efficacy: apremilast (0), etanercept (0), placebo group (4) • Withdrawal of consent: apremilast (3), etanercept (0), placebo group (1) • Other reason: apremilast (1), etanercept (1), placebo group (2)
Interventions	**Intervention** A. Apremilast (n = 83), orally, 30 mg twice daily **Control intervention** B. Etanercept (n = 83), SC, 50 mg weekly D. Placebo (n = 84)
Outcomes	Assessments at 16 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • PASI 50 • PASI 90

Reich LIBERATE 2017 *(Continued)*

- PGA rating of clear or almost clear
- DLQI score
- AEs

Notes	Funding source: Quote (p 2): "This study was sponsored by Celgene Corporation." Declarations of interest (p 1): "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 & 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 & Co., Inc., Novartis, Pfizer, Regeneron, Roche"

Risk of bias

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 ≥1 dose of study medication and had both baseline PASI and ≥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)

Reich LIBERATE 2017 *(Continued)*

	The prespecified outcomes and those mentioned in the Methods section have not been reported as DLQI

Reich ReSURFACE-1 2017

Study characteristics	
Methods	RCT, placebo-controlled, double-blind trial Date of study: 10 December 2012 - 28 October 2015 Location: at 118 sites (including hospital dermatology units, specialty clinics, private practices, and research sites) in Australia, Canada, Japan, the UK, and the USA Phase 3
Participants	**Randomised**: 772 participants **Inclusion criteria** • Clinical diagnosis of moderate-severe plaque psoriasis for ≥ 6 months prior to enrolment • Candidate for phototherapy or systemic therapy • 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 • For the extension study: must have completed Part 3 of the base study • For the extension study: must have achieved ≥ PASI 50 response by the end of Part 3 of the base study **Exclusion criteria** • Non-plaque forms of psoriasis • Presence or history of severe psoriatic arthritis and is well-controlled on current treatment regimen • Women of childbearing potential who are pregnant, intend to become pregnant, or are lactating • Participant is expected to require topical therapy, phototherapy, or systemic therapy during the trial • Presence of any infection or history of recurrent infection requiring treatment with systemic antibiotics • 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 • Latex allergy or sensitivity • Active or untreated latent TB **Dropouts and withdrawals** • 28/772 (3.6%): Tildra 200 (10), Tildra 100 (9), PBO (9) • Lost to follow-up: Tildra 200 (1), Tildra 100 (2), PBO (1) • AEs: Tildra 200 (5), Tildra 100 (0), PBO (0) • Lack of efficacy: Tildra 200 (0), Tildra 100 (1), PBO (2) • Participant: Tildra 200 (2), Tildra 100 (3), PBO (3) • Protocol deviation: Tildra 200 (1), Tildra 100 (0), PBO (1) • Physician decision: Tildra 200 (0), Tildra 100 (3), PBO (1) • Pregnancy: Tildra 200 (1), Tildra 100 (0), PBO (0) • Disease progression: Tildra 200 (0), Tildra 100 (0), PBO (1)
Interventions	**Intervention**

Reich ReSURFACE-1 2017 *(Continued)*

	A. Tildrakizumab 200 mg (SC on weeks 0, 4, 16, 28, 40 and 52), n = 308 **Control interventions** B. Tildrakizumab 100 mg (SC on weeks 0, 4, 16, 28, 40 and 52), n = 309 C. Placebo, n = 155
Outcomes	**At week 12** **Primary outcome (composite outcome)** • PASI 75 • PGA 0/1 **Secondary outcomes** • PASI 75 and PGA 0/1 (at weeks 28, 40, and 52) • PASI 90 (at weeks 12, 28, 40, and 52) • PASI 100 (at weeks 12, 28, 40, and 52) • DLQI (at weeks 12, 28, 40, and 52) • AEs
Notes	Funding Quote (p 276): "Funding Merck & Co" Conflicts of interest Quote (p 287): "Declaration of interests: 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, Merck & Co, Novartis, Pfizer, Vertex, and Takeda. KAP has served as a consultant or paid speaker for, or participated in clinical trials sponsored by, Amgen, Anacor, AbbVie, Active Biotech, Allergan, Astellas, AstraZeneca, Basilea, Bayer, Biogen-Idec, BMS, Boehringer-Ingelheim, CanFite, Celgene, Dermira, Eli-Lilly, Forward Pharma, Genentech, GlaxoSmithKline, Janssen, Kyowa Hako Kirin, Kythera, Leo Pharma, Merck & Co, Merck-Serono, Novartis, Pfizer, Regeneron, Rigel, Roche, Sanofi-Genzyme, Takeda, UCB, Valeant, Xenon, and Xoma. AB has served as a scientific adviser and clinical study investigator for AbbVie, Amgen, Boehringer Ingelheim, Celgene, Dermira, Genentech, GSK, Janssen, Lilly, Merck & Co, Novartis, Pfizer, Regeneron, Sandoz, Sanofi Genzyme, Sun, UCB, and Valeant, and as a paid speaker for Lilly. SKT has participated in trials supported by grants from Merck & Co. RS has served as a consultant or paid speaker for, or participated in clinical trials sponsored by, Leo Pharma, Amgen, Novartix, Merck & Co, Celgene, Coherus Biosciences, Janssen, Regeneron, MedImmune, GlaxoSmithKline, Cutanea, Samson Clinical, Boehringer Ingelheim, Pfiizer, MSD, Oncobiologics, Roche, Eli Lilly, and Bayer. DT has served as a consultant, advisory board member, or an 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 & Co, Merck-Serono, Novartis, Pfizer, Regeneron, Sandoz, Sanofi-Aventis, and Takeda. KN is a former employee of Merck & Co; AM, NC, QL, KL, CLR, and SG are current Merck & Coemployees. ABK is a consultant and investigator for Merck & Co, Amgen, AbbVie, Janssen, Novartis, Dermira, and Pfizer, a consultant for Sun Pharmaceuticals, Bristol-Myers Squibb, Lilly, and VBL, and has received fellowship funding from Janssen."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 278): "In reSURFACE 1, participants were randomly assigned (2:2:1) to tildrakizumab 200 mg, tildrakizumab 100 mg, or placebo...In reSURFACE 2, participants were randomly assigned (2:2:1:2) to tildrakizumab 200 mg, tildrakizumab 100 mg, placebo, or etanercept 50 mg...Parexel International, the contract research organisation, generated computer generated randomisation sequences, and an interactive voice-response system and interactive

Reich ReSURFACE-1 2017 *(Continued)*

		web-response system was used by Parexel to allocate participants to groups. Randomised treatment assignments on day 1 were done by region" Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (p 278): "In reSURFACE 1, participants were randomly assigned (2:2:1) to tildrakizumab 200 mg, tildrakizumab 100 mg, or placebo...In reSURFACE 2, participants were randomly assigned (2:2:1:2) to tildrakizumab 200 mg, tildrakizumab 100 mg, placebo, or etanercept 50 mg...Parexel International, the contract research organisation, generated computer generated randomisation sequences, and an interactive voice-response system and interactive web-response system was used by Parexel to allocate participants to groups. Randomised treatment assignments on day 1 were done by region" Comment: Probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 279): "Investigators, participants, and study personnel were blinded to group allocation and remained blinded until completion of the studies. A double-masking technique was used, in which tildrakizumab and its matching placebo or etanercept and its matching placebo were identical in appearance and packaging. Additional placebo doses were administered to maintain masking. The team doing the analysis was blinded until the database was locked." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 279): "Investigators, participants, and study personnel were blinded to group allocation and remained blinded until completion of the studies. A double-masking technique was used, in which tildrakizumab and its matching placebo or etanercept and its matching placebo were identical in appearance and packaging. Additional placebo doses were administered to maintain masking. The team doing the analysis was blinded until the database was locked." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data Quote (pp 280-1): "We specified full-analysis-set, intention-to-treat, and per protocol patient populations in the study protocols...Patients with missing data were treated as non-responders (non-responder imputation [NRI])." Randomised 772, Analysed 772
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01722331) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported Results are posted on ClinicalTrials.gov

Reich ReSURFACE-2 2017

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind trial Date of study: 12 February 2013 - 28 September 2015

Reich ReSURFACE-2 2017 *(Continued)*

	Location: 132 sites in Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Hungary, Italy, Israel, Netherlands, Poland, and the USA Phase 3
Participants	**Randomised**: 1090 participants **Inclusion criteria** • Clinical diagnosis of moderate-severe plaque psoriasis for ≥ 6 months prior to enrolment • Candidate for phototherapy or systemic therapy • 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 • For the extension study: must have completed Part 3 of the base study • For the extension study: must have achieved ≥ PASI 50 response by the end of Part 3 of the base study **Exclusion criteria** • Non-plaque forms of psoriasis • Presence or history of severe psoriatic arthritis and is well-controlled on current treatment regimen • Women of childbearing potential who are pregnant, intend to become pregnant, or are lactating • Participant is expected to require topical therapy, phototherapy, or systemic therapy during the trial • Presence of any infection or history of recurrent infection requiring treatment with systemic antibiotics • 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 • Latex allergy or sensitivity • Active or untreated latent TB **Dropouts and withdrawals** • 64/1090 (5.9%): Tildra 200 (14), Tildra 100 (12), ETA (24), PBO (14) • Lost to follow-up: Tildra 200 (1), Tildra 100 (2), ETA (3), PBO (3) • AEs: Tildra 200 (2), Tildra 100 (1), ETA (5), PBO (2) • Lack of efficacy: Tildra 200 (1), Tildra 100 (0), ETA (0), PBO (2) • Drug non-compliance: Tildra 200 (1), Tildra 100 (0), ETA (0), PBO (0) • Participant: Tildra 200 (5), Tildra 100 (7), ETA (6), PBO (5) • Protocol deviation: Tildra 200 (2), Tildra 100 (1), ETA (0), PBO (1) • Physician decision: Tildra 200 (0), Tildra 100 (0), ETA (4), PBO (0) • Pregnancy: Tildra 200 (0), Tildra 100 (1), ETA (1), PBO (0) • Disease progression: Tildra 200 (0), Tildra 100 (0), ETA (1), PBO (0) • Others: Tildra 200 (2), Tildra 100 (0), ETA (4), PBO (1)
Interventions	**Intervention** Tildrakizumab 200 mg (SC on weeks 0, 4, 16, 28, 40 and 52), n = 314 **Control interventions** Tildrakizumab 100 mg (SC on weeks 0, 4, 16, 28, 40 and 52), n = 307 Etanercept 50 mg (twice weekly until week 12 and once weekly from week 12 to week 28), n = 313 Placebo, n = 156
Outcomes	**At week 12** **Primary outcome (composite outcome)**

Reich ReSURFACE-2 2017 *(Continued)*

- PASI 75
- PGA 0/1

Secondary outcomes

- PASI 75 and PGA 0/1 (at weeks 28, 40, and 52)
- PASI 90 (at weeks 12, 28, 40, and 52)
- PASI 100 (at weeks 12, 28, 40, and 52)
- DLQI (at weeks 12, 28, 40, and 52)
- AEs

Notes	Funding Quote (p 276): "Funding Merck & Co" Conflicts of interest Quote (p 287): "Declaration of interests: 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, Merck & Co, Novartis, Pfizer, Vertex, and Takeda. KAP has served as a consultant or paid speaker for, or participated in clinical trials sponsored by, Amgen, Anacor, AbbVie, Active Biotech, Allergan, Astellas, AstraZeneca, Basilea, Bayer, Biogen-Idec, BMS, Boehringer-Ingelheim, CanFite, Celgene, Dermira, Eli-Lilly, Forward Pharma, Genentech, GlaxoSmithKline, Janssen, Kyowa Hako Kirin, Kythera, Leo Pharma, Merck & Co, Merck-Serono, Novartis, Pfizer, Regeneron, Rigel, Roche, Sanofi-Genzyme, Takeda, UCB, Valeant, Xenon, and Xoma. AB has served as a scientific adviser and clinical study investigator for AbbVie, Amgen, Boehringer Ingelheim, Celgene, Dermira, Genentech, GSK, Janssen, Lilly, Merck & Co, Novartis, Pfizer, Regeneron, Sandoz, Sanofi Genzyme, Sun, UCB, and Valeant, and as a paid speaker for Lilly. SKT has participated in trials supported by grants from Merck & Co. RS has served as a consultant or paid speaker for, or participated in clinical trials sponsored by, Leo Pharma, Amgen, Novartix, Merck & Co, Celgene, Coherus Biosciences, Janssen, Regeneron, MedImmune, GlaxoSmithKline, Cutanea, Samson Clinical, Boehringer Ingelheim, Pfiizer, MSD, Oncobiologics, Roche, Eli Lilly, and Bayer. DT has served as a consultant, advisory board member, or an 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 & Co, Merck-Serono, Novartis, Pfizer, Regeneron, Sandoz, Sanofi-Aventis, and Takeda. KN is a former employee of Merck & Co; AM, NC, QL, KL, CLR, and SG are current Merck & Coemployees. ABK is a consultant and investigator for Merck & Co, Amgen, AbbVie, Janssen, Novartis, Dermira, and Pfizer, a consultant for Sun Pharmaceuticals, Bristol-Myers Squibb, Lilly, and VBL, and has received fellowship funding from Janssen."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 278): "In reSURFACE 1, participants were randomly assigned (2:2:1) to tildrakizumab 200 mg, tildrakizumab 100 mg, or placebo...In reSURFACE 2, participants were randomly assigned (2:2:1:2) to tildrakizumab 200 mg, tildrakizumab 100 mg, placebo, or etanercept 50 mg...Parexel International, the contract research organisation, generated computergenerated randomisation sequences, and an interactive voice-response system and interactive web-response system was used by Parexel to allocate participants to groups. Randomised treatment assignments on day 1 were done by region" Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (p 278): "In reSURFACE 1, participants were randomly assigned (2:2:1) to tildrakizumab 200 mg, tildrakizumab 100 mg, or placebo...In reSURFACE 2, participants were randomly assigned (2:2:1:2) to tildrakizumab 200 mg, tildrakizumab 100 mg, placebo, or etanercept 50 mg...Parexel International,

Reich ReSURFACE-2 2017 *(Continued)*

		the contract research organisation, generated computergenerated randomisation sequences, and an interactive voice-response system and interactive web-response system was used by Parexel to allocate participants to groups. Randomised treatment assignments on day 1 were done by region" Comment: Probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 279): "Investigators, participants, and study personnel were blinded to group allocation and remained blinded until completion of the studies. A double-masking technique was used, in which tildrakizumab and its matching placebo or etanercept and its matching placebo were identical in appearance and packaging. Additional placebo doses were administered to maintain masking. The team doing the analysis was blinded until the database was locked." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p279): "Investigators, participants, and study personnel were blinded to group allocation and remained blinded until completion of the studies. A double-masking technique was used, in which tildrakizumab and its matching placebo or etanercept and its matching placebo were identical in appearance and packaging. Additional placebo doses were administered to maintain masking. The team doing the analysis was blinded until the database was locked." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data Quote (pp 280-1): "We specified full-analysis-set, intention-to-treat, and per protocol patient populations in the study protocols...Patients with missing data were treated as non-responders (non-responder imputation [NRI])." Randomised 1090, Analysed 1090
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01729754) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported Results are posted on ClinicalTrials.gov

Reich TRANSFIGURE 2016

Study characteristics	
Methods	RCT, active-controlled, double-blind trial, phase 3 Date of study: November 2013 - January 2017 Location: world-wide
Participants	**Randomised**: 198 participants **Inclusion criteria** • Chronic moderate-severe plaque type psoriasis for ≥ 6 months prior to randomisation, including significant nail involvement, defined as NAPSI score ≥ 16 and number of fingernails involved ≥ 4 and PASI score ≥ 12 and BSA score ≥ 10%

Reich TRANSFIGURE 2016 *(Continued)*

- 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

Exclusion criteria

- Forms of psoriasis other than chronic plaque type psoriasis (e.g. pustular psoriasis, palmoplantar pustulosis, acrodermatitis of Hallopeau, erythrodermic and guttate psoriasis)
- Drug-induced psoriasis (e.g. new onset or current exacerbation from β-blockers, calcium channel inhibitors or lithium)
- Ongoing inflammatory skin diseases other than psoriasis or any other disease affecting the fingernails that may potentially confound the evaluation of study treatment effects
- Ongoing use of prohibited treatments (e.g. topical or systemic corticosteroids (CS), UV therapy). Washout periods do apply
- Prior exposure to secukinumab (AIN457) or any other biological drug directly targeting IL-17 or the IL-17 receptor
- 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
- History of hypersensitivity to constituents of the study treatment
- Other protocol-defined inclusion/exclusion criteria do apply

Dropouts and withdrawals

- 12/198 (6.1%):

Secu 150 (4), Secu 300 (1), PBO (7)

- Lost to follow-up: Secu 150 (1), Secu 300 (0), PBO (0)
- AEs: Secu 150 (2), Secu 300 (0), PBO (0)
- Lack of efficacy: Secu 150 (0), Secu 300 (0), PBO (2)
- Participant: Secu 150 (0), Secu 300 (1), PBO (3)
- Protocol deviation: Secu 150 (1), Secu 300 (0), PBO (1)
- Physician decision: Secu 150 (0), Secu 300 (0), PBO (1)

Interventions	**Intervention** A. Biological: secukinumab 150 mg weekly for 5 weeks, then once every 4 weeks up to and including Week 128, n = 67 **Control Intervention** B. Biological: secukinumab 300 mg weekly for 5 weeks, then once every 4 weeks up to and including Week 128, n = 66 C. Biological: Placebo, n = 65
Outcomes	**At week 16** **Primary outcome** • NAPSI **Secondary outcomes** • NAPSI at 132 weeks • PASI 75 at weeks 16 and 132 • IGA 0/1 at weeks 16 and 132 • AEs
Notes	Funding Quote (p 1): "Funding sources: This study was funded by Novartis Pharma AG, Basel, Switzerland." Conflicts of interest

Reich TRANSFIGURE 2016 *(Continued)*

Quote (Appendix): "Conflicts of interest. K.R. has 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; and has served as a consultant for AbbVie, Amgen, Biogen Idec, Celgene, Centocor, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, LEO, Lilly, Medac, MSD, Novartis, Pfizer, Takeda and Vertex. J.S. has received educational grants from Novartis, AbbVie and Pfizer; and has received consultancy fees from Novartis, AbbVie, Pfizer and Eli Lilly. P.A. has received grants from Novartis. U.M. has 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; has served as an advisor for and/or received speaker honoraria and/or grants from Abbott/Abb- Vie, 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; has participated in clinical trials by Novartis, AbbVie, UCB, Valeant, Athenex, MC2 Therapeutics, Dermira, Kadmon, Boehringer Ingelheim, Galderma, Regeneron, Coherus, Tolmar, Amgen, Total, Watson, Sandoz, Xenoport, AbGenomics and Lilly; and has received consulting fees or speaker honoraria from Novartis, Celgene and AbbVie. M.A. has
received grants from and/or participated in clinical trials for AbbVie, Almirall, Amgen, Biogen Idec, Boehringer Ingelheim,
Celgene, Centocor, Eli Lilly, Janssen-Cilag, LEO, Medac, MSD (formerly Essex, Schering-Plough), Mundipharma, Novartis,
Pfizer (formerly Wyeth), Pohl Boskamp, Sandoz and Xenoport; and has served as an advisor for and/or received speaker
honoraria from AbbVie, Almirall, Amgen, Biogen Idec, Boehringer Ingelheim, Celgene, Centocor, Eli Lilly, Janssen-Cilag,
LEO, Medac, MSD (formerly Essex, Schering-Plough), Mundipharma, Novartis, Pfizer (formerly Wyeth), Pohl Boskamp,
Sandoz and Xenoport. A.P., P.R., R.Y. and M.M. are full-time employees of Novartis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 2):"Randomization was managed via a central interactive randomization system and ensured that an equal number of patients were allocated to secukinumab 300 mg, secukinumab 150 mg or placebo, stratified by body weight (< 90 kg or ≥ 90 kg). At week 16, all patients receiving placebo were rerandomized 1: 1 to receive either 300 mg or 150 mg secukinumab." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 2):"Randomization was managed via a central interactive randomization system and ensured that an equal number of patients were allocated to secukinumab 300 mg, secukinumab 150 mg or placebo, stratified by body weight (< 90 kg or ≥ 90 kg). At week 16, all patients receiving placebo were rerandomized 1: 1 to receive either 300 mg or 150 mg secukinumab." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 2): " TRANSFIGURE was a randomized, double-blind, placebo-controlled trial...Patients received subcutaneous treatments of identical appearance once a week for 5 weeks (at baseline and weeks 1, 2, 3 and 4), followed by dosing every 4 weeks, starting at week 4 (Appendixes S3 and S4; see Supporting Information)." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 2): " TRANSFIGURE was a randomized, double-blind, placebo-controlled trial...Patients received subcutaneous treatments of identical appearance once a week for 5 weeks (at baseline and weeks 1, 2, 3 and 4), followed by

Reich TRANSFIGURE 2016 *(Continued)*

		dosing every 4 weeks, starting at week 4 (Appendixes S3 and S4; see Supporting Information)." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data Quote (p 2): "Missing values for PASI and Investigator's Global Assessment (IGA) mod 2011 were imputed using multiple imputation. Missing patient reported outcome values were imputed with last observation carried forward" On ClinicalTrials.gov, randomized 198, analyzed 198
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01807520) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported REsults are posted on ClinicalTrials.gov

Reich VOYAGE-2 2017

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind Date of study: November 2014 - May 2016 Location: 115 centres world-wide
Participants	**Randomised**: 992 participants (mean age 44 years, 692 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12, IGA ≥ 3 or BSA ≥ 10), age ≥ 18 years **Exclusion criteria** • Had a history or current signs of a severe, progressive, or uncontrolled medical condition • Had current or history of malignancy, except non-melanoma skin cancer, within 5 years • Patients with history or symptoms of active TB were excluded • Patients could not participate if they received guselkumab or adalimumab previously **Dropouts and withdrawals** • 44/992 (4.4%); guselkumab (18), adalimumab (11), placebo group (15) • AEs: guselkumab (9), adalimumab (4), placebo group (2) • Lack of efficacy: guselkumab (0), adalimumab (2), placebo group (4) • Lost to follow-up: guselkumab (3), adalimumab (2), placebo group (1) • Withdrawal of consent: guselkumab (1), adalimumab (0), placebo group (7) • Non-compliance: guselkumab (1), adalimumab (2), placebo group (0) • Protocol violation: guselkumab (3), adalimumab (1), placebo group (1) • Others: guselkumab (1), adalimumab (0), placebo group (0)
Interventions	**Intervention** A. Guselkumab (n = 496), SC, 100 mg, weeks 0 and 4, then every 8 weeks

Reich VOYAGE-2 2017 *(Continued)*

	Control intervention B. Adalimumab (n = 248), 80 mg week 0, then 40 mg week 1, and every 2 weeks C. Placebo (n = 248)
Outcomes	Assessments at 16 weeks **Primary outcomes of the trial** • PASI 90 • IGA clear or almost clear **Secondary outcomes of the trial** • PASI 50/75 • Mean DLQI score • NAPSI • Scalp-specific IGA • Fingernail PGA • AEs
Notes	Funding source: Quote (p 1): "Supported by Janssen Research & 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 & 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, Boeringher Ingelheim, Eli Lilly, and Janssen, and consultant/ honoraria from AbbVie, Amgen, Boeringher Ingelheim, Celgene, Eli Lilly, Janssen, Novartis, and Pfizer. Drs Song, Wasfi, Randazzo, Li, and Shen are all employees of Janssen Research & Development, LLC (subsidiary of Johnson & Johnson) and own stock in Johnson & Johnson."

Risk of bias

Bias	Authors' judgement	Support for judgement
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 every 2 weeks through week 47. Central randomization was implemented using an interactive World Wide Web response system (Perceptive Informatics, East Windsor, NJ)."

Reich VOYAGE-2 2017 *(Continued)*

		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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Rich 2013

Study characteristics	
Methods	RCT, placebo-controlled, double-blind trial Date of study: July 2009 - December 2010 Location: 60 centres in Portland, USA
Participants	**Randomised**: 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) **Inclusion criteria** • Participants with moderate-severe psoriasis • PASI ≥ 12, IGA ≥ 3 or BSA ≥ 10 • Age ≥ 18 years • Non-response to topical treatment • Non-response to phototherapy • Non-response to conventional systemic treatment **Exclusion criteria**

Rich 2013 *(Continued)*

- Pregnancy
- Immunosuppresion
- Had an active infection
- **Dropouts and withdrawals**
- 24/404 (6%)
- Secukinimab A (5): lack efficacy (2), withdrew consent (1), AE (1), other (1)
- Secukinimab B (4): lack efficacy (1), withdrew consent (2), other (1)
- Secukinimab C (6): withdrew consent (2), AE (3), other (1)
- Placebo (9): lack efficacy (5), withdrew consent (2), AE (2)

Interventions	**Intervention** A. Secukinumab (n = 66), SC, 150 mg, week 0, 12 weeks **Control intervention** B. Secukinumab (n = 138), SC, 150 mg, weeks 0, 4, 8, 12 weeks C. Secukinumab (n = 133), SC, 150 mg, weeks 0, 1, 2, 4, 12 weeks D. Placebo (n = 67), SC, weeks 0, 1, 2, 4, 8, 12 weeks
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • PASI 75 20/28 weeks • IGA 12 weeks • PASI 90 12 weeks
Notes	Funding support quote (p 402): "Novartis Pharma AG, Basel, Switzerland" 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-Idec, 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."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (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
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

Rich 2013 *(Continued)*

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 th 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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Ruzicka 1990

Study characteristics	
Methods	RCT, placebo-controlled, double-blind Date of study: December 1986 - March 1988 Location: 7 centres in Germany
Participants	**Randomised**: 82 participants (mean age 44 years, 55 male) **Inclusion criteria** • Aged 18 - 75 • Generalised chronic plaque or exanthematic **Exclusion criteria** • Pregnancy, kidney insufficiency, liver insufficiency • Had uncontrolled cardiovascular disorder • Had uncontrolled diabetes • Had uncontrolled hypertension **Dropouts and withdrawals** • 4/82 (5%) • Acitretin (2) overweight and dyslipidaemia • Placebo (2) erythrodermia
Interventions	**Intervention** A. Acitretin, orally, 35 mg, daily, 8 weeks (n = 42)

Ruzicka 1990 *(Continued)*

	Control intervention B. Placebo, orally, daily, 8 weeks (n = 40)
Outcomes	Assessments at 8 weeks **Primary outcomes of the trial** • PASI **Secondary outcomes of the trial** • Side effects
Notes	Funding sources: not stated Declarations of interest: not stated

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 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 prespecified outcomes mentioned in the Methods section appeared to have been reported

Sandhu 2003

Study characteristics	
Methods	RCT, active-controlled, open-label Date of study: not stated Location: multicentric (number not stated) in North India
Participants	**Randomised**: 30 participants (methotrexate: mean age 39 years, 12 male; ciclosporin: mean age 46 years, 13 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (BSA > 40%), age ≥ 18 years **Exclusion criteria** • Pregnancy, kidney insufficiency, liver insufficiency • Had uncontrolled hypertension • Had past history of malignant tumours **Dropouts and withdrawals** • Not stated
Interventions	**Intervention** A. Methotrexate (n = 15), orally, 0.5 mg/kg dose tapered after PASI 75 obtained **Control intervention** 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 **Primary or secondary outcomes of the trial** • Not clearly defined **Outcomes of the trial** • PASI
Notes	Funding source: not stated Declarations of interest: not stated

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
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

Sandhu 2003 *(Continued)*

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 prespecified outcomes mentioned in the Methods section appeared to have been reported.No primary outcome declared

Saurat 1988

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind Date of study: not stated Location: 6 centres in France and Switzerland
Participants	**Randomised**: 42 participants (placebo (22) mean age 43 years, 16 male; acitretin (20), mean age 46 years, 16 male) **Inclusion criteria** • BSA > 20% **Exclusion criteria** • Kidney insufficiency, liver insufficiency, had uncontrolled cardiovascular disorder **Dropouts and withdrawals** • 7/65 (11%)
Interventions	**Intervention** A. Acitretin (n = 20), orally, 2 x 25/d 2 weeks and 25/d + UVA 3/weeks, daily, 10 weeks **Control intervention** C. Placebo, orally (n = 22), daily, 10 weeks **Co-intervention**: UVA 3/week, 10 weeks
Outcomes	Assessments not clearly stated (reported at 8 weeks) **Primary outcomes of the trial** • Not clearly stated **Outcomes of the trial**

Saurat 1988 *(Continued)*

- Change in PASI
- Time to clear
- AEs

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	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 AEs in both acitretin and etretinate groups
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 AEs 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 prespecified outcomes mentioned in the Methods section appeared to have been reported

Saurat CHAMPION 2008

Study characteristics

Methods	RCT, active/placebo-controlled, double-blind Date of study: unreported Location: multicentre (n = 28) in Europe and Canada
Participants	**Randomised**: 271 participants (mean age 42, 178 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 10 or BSA ≥ 10), age > 18 years

Saurat CHAMPION 2008 *(Continued)*

	Exclusion criteria • Pregnancy, immunosuppression, kidney insufficiency, liver insufficiency, past history of malignant tumours • Had received conventional systemic treatments for Methotrexate arm • Had received biologics **Dropouts and withdrawals** • 15/271 (5.5%): adalimumab group (4), methotrexate group (6), placebo group (5) • AEs: adalimumab group (1), methotrexate group (6), placebo group (1) • Lack of efficacy: adalimumab group (0), methotrexate group (0), placebo group (4) • Withdrawal of consent: adalimumab group (2), methotrexate group (0), placebo group (0) • Other reason:**a**dalimumab group (1), methotrexate group (0), placebo group (0)
Interventions	**Intervention** A. Adalimumab (n = 108), SC, 80 mg at week 0, 40 mg at week 1 and 40 mg eow **Control intervention** B. Methotrexate (n = 110), orally, 7.5 - 25 mg weekly C. Placebo (n = 53), SC and orally (same drug administration)
Outcomes	Assessments at 16 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • PASI 50 • PASI 90 • PASI 100 • PGA • DLQI • AEs
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. "

Risk of bias

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"

Saurat CHAMPION 2008 *(Continued)*

		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 prespecified 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

Study characteristics	
Methods	RCT, active-controlled, open-label Date of study: March 2001 - November 2001 Location: 1 centre in Karachi, Pakistan
Participants	**Randomised**: 40 participants (age from 18-50 years, % male unknown) **Inclusion criteria**

Shehzad 2004 *(Continued)*

- Participants with moderate-severe psoriasis (PASI > 10)

Exclusion criteria

- Immunosuppresion, kidney insufficiency, liver insufficiency
- Had an active infection
- Had uncontrolled cardiovascular disorder

Dropouts and withdrawals

- Not stated

Interventions	**Intervention** A. PUVA therapy (+ psoralen) (n = 20), 4 times/week **Control intervention** B. Methothrexate (n = 20), orally, 10 mg/week, 5 mg Saturday + Sunday
Outcomes	Time of assessments: not stated **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • Time to clearance • AEs
Notes	Funding source: Immunex Corporation Declarations of interest: not stated

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
Incomplete outcome data (attrition bias)	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...)

Shehzad 2004 *(Continued)*
All outcomes

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

Study characteristics	
Methods	RCT, placebo-controlled, double-blind Date of study: 1986 - 1988 Location: 7 centres in Germany
Participants	**Randomised**: 88 participants (mean age 45 years, 68 male) **Inclusion criteria** • Generalised chronic plaque psoriasis or exanthematic • Aged 19 - 75 years **Exclusion criteria** • Pregnancy, kidney insufficiency, liver insufficiency • Had uncontrolled cardiovascular disorder • Had uncontrolled diabetes • Had uncontrolled hypertension **Dropouts and withdrawals** • 5/88 (6%) • Acitretin (4), placebo (1) • Missing outcome (3) erythroderma (1)
Interventions	**Intervention** A. Acitretin (n = 44), orally, 50 mg (15 days) then 25 mg, daily, 8 weeks **Control intervention** 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 **Primary outcomes of the trial** • PSI **Secondary outcomes of the trial** • PSI 75
Notes	Funding source: not stated Declarations of interest: not stated

Sommerburg 1993 *(Continued)*

Risk of bias

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 (pp 310-1): "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 AEs in acitretin groups
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (pp 310-1): " 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 AEs 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 dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The prespecified outcomes mentioned in the Methods section appeared to have been reported

Sterry PRESTA 2010

Study characteristics

Methods	RCT, active-controlled, double-blind Date of study: December 2005 - May 2008 Location: centres (n = 98) world-wide
Participants	**Randomised**: 754 participants (mean age 46 years, 473 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PGA moderate-severe, BSA > 10) • Age ≥ 18 **Exclusion criteria**

Sterry PRESTA 2010 *(Continued)*

- Pregnancy
- Had received biologics
- Had an active infection

Dropouts and withdrawals

- 59/754 (8%)
- No drug administered (2)
- Etanercept twice a week (29): AE (14), lost to follow-up (2), deviation (4), decision (5), lack efficacy (4)
- Etanercept once a week (28): AE (10), lost to follow-up (2)

Interventions	**Intervention** A. Etanercept, SC, 50 mg, twice a week, 12 weeks (n = 379) **Control intervention** B. Etanercept, SC, 50 mg, once a week, 12 weeks (n = 373)
Outcomes	Assessments at 12 weeks **Primary and secondary outcomes of the trial** • Clear or almost clear PGA (0/1) **Outcomes of the trial** • PGA 24 weeks • PASI 75 • PASI 90 • Mean PASI • ACR (American College of Rheumatology) 20, 50 and 70 (weeks 12 and 24) • Participant-reported outcomes
Notes	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..." 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."

Risk of bias

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

Sterry PRESTA 2010 *(Continued)*

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 prespecified outcomes mentioned in the Methods section appeared to have been reported, except for the results of participant-reported end points summarised in a separate publication

Sticherling PRIME 2017

Study characteristics	
Methods	RCT, active-controlled, open-label study Date of study: June 2015 - June 2016 Location: USA (multicentric) Phase 3

Participants	**Randomised**: 202 participants
	
	Inclusion criteria
	
	• Men or women, must be ≥ 18 years of age at the time of screening
	• Chronic plaque-type psoriasis diagnosed for ≥ 6 months before randomisation
	• Patients with moderate-severe plaque psoriasis who are candidates for systemic therapy as defined at randomisation by:
	  * PASI score of > 10
	  * BSA) > 10%
	  * DLQI > 10
	• 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
	
	Exclusion criteria
	
	• Previous systemic treatment of plaque psoriasis or known contraindication for systemic therapy at baseline
	• Ongoing use of other prohibited psoriasis and non-psoriasis treatment

Sticherling PRIME 2017 *(Continued)*

- Clinically important active infections or infestations, chronic, recurrent or latent infections or infestations
- Severe liver diseases
- Severe gastrointestinal diseases including but not limited to ventricular and duodenal ulcers
- Severe kidney diseases or serum creatinine above 1 x ULN
- Known haematological disease or lab abnormalities
- Pregnancy, breast feeding, or unwillingness/inability to use appropriate measures of contraception (if necessary)

Dropouts and withdrawals

- 60/202 (2%):

Secu group (6), FAEs group (56)

- Did not receive allocated intervention: Secu group (0), FAEs group (2)
- AEs: Secu group (2), FAEs group (32)
- Patient: Secu group (2), FAEs group (13)
- Lost to follow-up: Secu group (2), FAEs group (2)
- Other: Secu group (0), FAEs group (3)

Interventions	**Intervention** A. Secukinumab (300 mg at weeks 0, 1, 2, 3, 4, 8, 12, 16 and 20), n = 105 **Control intervention** B. Fumaderm® (week 0: 1 tablet of Fumaderm® INITIAL in the evening, n =97 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® in the evening Weeks 8-24: 2 tablets of Fumaderm® in the morning, at noon and in the evening)
Outcomes	**At week 24** **Primary outcome** • PASI 75 **Secondary outcomes** • PASI 90 • IGA 0/1 • DLQI
Notes	Funding Quote (p 1024): "Novartis Pharma GmbH"

Sticherling PRIME 2017 *(Continued)*

Conflicts of interest

Quote (Appendix): " M.S. is an advisor and/or paid speaker for and/or has participated in clinical trials sponsored by AbbVie, Actelion, Almirall, Biogen, Boehringer Ingelheim, Celgene, GlaxoSmithKline, Janssen Cilag, LEO Pharma, Eli Lilly, Merck Sharp & Dohme, Mibe, Mundipharma, Novartis, Pfizer, Regeneron and Sanofi. U.M. has been an advisor for and/or received speaker honoraria and/or grants from and/or participated in clinical trials sponsored by Abbott/AbbVie, Almirall Hermal, Amgen, Biogen Idec, Boehringer Ingelheim, Celgene, Centocor, Eli Lilly, Foamix, Forward Pharma, Janssen Cilag, LEO Pharma, Medac, MSD, Miltenyi Biotech, Novartis, Pfizer, VBL and Xenoport. M.A. has served as a consultant for, or has been a paid speaker for clinical trials sponsored by AbbVie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Celgene, Centocor, Eli Lilly, GlaxoSmithKline, Janssen Cilag, LEO Pharma, Medac, Merck, MSD, Novartis, Pfizer, UCB and Xenoport. D.T. is an advisor or consultant for AbbVie, Amgen, Biogen Idec, Cel-gene, Dignity, Eli Lilly, Galapagos, GlaxoSmithKline, Janssen, LEO Pharma, Maruho, Mitsubishi, Mundipharma, Novartis, Pfizer, Sandoz and Xenoport. He has participated in clinical trials sponsored by AbbVie, Almirall, Amgen, Astellas, Biogen Idec, Boehringer Ingelheim, Celgene, Dignity, Eli Lilly, Forward Pharma, GlaxoSmithKline, LEO Pharma, Janssen Cilag, Maruho, MSD, Mitsubishi Pharma, Novartis, Pfizer, Roche and Sandoz. He has received honoraria from AbbVie, Biogen Idec, Celgene, Janssen Cilag, LEO Pharma, Pfizer, Roche Possay, Novartis and Mundipharma. K.R. has served as an advisor and/or paid speaker for, and/or has participated in clinical trials sponsored by AbbVie, Amgen, Biogen, Boehringer Ingelheim Pharma, Celgene, Centocor, Covagen, Forward Pharma, GlaxoSmithKline, Janssen Cilag, LEO Pharma, Eli Lilly, Medac, Merck Sharp & Dohme, Novartis, Ocean Pharma, Pfizer, Regeneron, Takeda, UCB Pharma and Xenoport. N.M., C.S., C.H. and J.K. are employees of and/or own stock in Novartis"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 1025): "This 24-week, randomized, open-label, active-comparator, parallel-group, superiority study was conducted... Eligible patients were randomized 1: 1 to receive subcutaneous injections of secukinumab 300 mg or oral FAEs per label, via an automated randomization list. Randomization numbers were assigned to patients by the investigators in consecutive order, who then assigned the treatment displayed on the card. Randomization lists and sealed envelopes were generated by personnel who were not otherwise involved in the trial." Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (p 1025): "This 24-week, randomized, open-label, active-comparator, parallel-group, superiority study was conducted... Eligible patients were randomized 1: 1 to receive subcutaneous injections of secukinumab 300 mg or oral FAEs per label, via an automated randomization list. Randomization numbers were assigned to patients by the investigators in consecutive order, who then assigned the treatment displayed on the card. Randomization lists and sealed envelopes were generated by personnel who were not otherwise involved in the trial." Comment: Probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (p 1025): "This 24-week, randomized, open-label, active-comparator, parallel-group, superiority study was conducted... The blinded assessor and all involved personnel were instructed to desist from any discussions regarding safety, efficacy and treatment allocation of the study and patients in the presence of the blinded assessor. Efficacy parameters were assessed by blinded assessors who were not involved in any other study procedures and who did not have access to the allocation data or case report forms." Comment: Participants not blinded

Sticherling PRIME 2017 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 1025): "This 24-week, randomized, open-label, active-comparator, parallel-group, superiority study was conducted... The blinded assessor and all involved personnel were instructed to desist from any discussions regarding safety, efficacy and treatment allocation of the study and patients in the presence of the blinded assessor. Efficacy parameters were assessed by blinded assessors who were not involved in any other study procedures and who did not have access to the allocation data or case report forms." Comment: Probably done
Incomplete outcome data (attrition bias) All outcomes	High risk	Dealing with missing data Quote (p 1026): "Efficacy end points were assessed for the full analysis set, consisting of all randomized patients who had received at least one dose of study drug. Between treatments, comparisons were made by logistic regression models adjusted for centre and baseline values of PASI scores. Odds ratios (ORs), 95% confidence intervals (CIs) and P-values were derived from these models. Patients with missing assessments were considered responders if they had already met the response criterion at the time of dropout for the primary end point and all other end points where response was investigated. Otherwise they were considered nonresponders" Randomized 202, analyzed 201 Unbalance proportion regarding discontinuation: 5.7% for Secukinumab vs 57.7% for FAE
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02474082) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported Results are posted on ClinicalTrials.gov

Strober 2011

Study characteristics	
Methods	RCT, placebo-controlled, double-blind Date of study: July 2008 - April 2009 Location: 41 centres in the USA
Participants	**Randomised**: 211 participants (mean age 45 years, 131 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PGA ≥ 3, PASI ≥ 12, BSA ≥ 10), age ≥ 18 years **Exclusion criteria** • Previous exposure to either etanercept or ABT-874 **Dropouts and withdrawals** • 18/211 (8.5%): etanercept 12, placebo 6

Strober 2011 *(Continued)*

- Time and reasons:
  - Etanercept: AE (3), lost to follow-up (1), withdrew consent (3), protocol violation (4), other (1)
  - Placebo: AE (2), lost to follow-up (1), protocol violation (2), other (1)

Interventions	**Intervention** A. Etanercept (n = 139), SC auto-administered, 50 mg twice a week, 11 weeks **Control intervention** B. Placebo (n = 72), SC auto-administered, twice a week
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PASI 75 • PGA 0/1 **Secondary outcomes of the trial** At 4, 8, 12 weeks • PASI 50 • PASI 75 • PASI 90 • DLQI • PGA • Safety • Patient global assessment of psoriasis
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."

Risk of bias

Bias	Authors' judgement	Support for judgement
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)	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

Strober 2011 *(Continued)*

All outcomes		week 8, consisting of either briakinumab or matching placebo, depending on the treatment arm. In addition, each patient also received two SC injections bi-weekly, 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 bi-weekly, 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 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 (NCT00710580) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Strohal PRISTINE 2013

Study characteristics	
Methods	RCT, active-controlled, double-blind Date of study: April 2008 - March 2012 Location: 32 centres in Europe, Latin America and Asia
Participants	**Randomised**: 273 participants (mean age 44 years, 190 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 10, BSA ≥ 10), age ≥ 18 years • Non-response to topical treatment • Non-response to phototherapy • Non-response to conventional systemic treatment **Exclusion criteria** • Had received biologics • Had an active infection **Dropouts and withdrawals** • 25/273 (9%)

Strohal PRISTINE 2013 *(Continued)*

- Time and reasons:
  - No efficacy evaluations (3)
  - Etanercept once a week (10): AE (3), lack of efficacy (1), decision (5), other (1)
  - Etanercept twice a week (12): AE (6), lack of efficacy (1), decision (2), deviation (1), other (2)

Interventions	**Intervention** A. Etanercept (n = 137), SC, 50 mg, once a week, 24 weeks **Control intervention** B. Etanercept (n = 136), SC, 50 mg, twice a week, 24 weeks
Outcomes	Assessments at 24 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • PASI 50, 75, 90 • Mean PASI • PGA (Physician Global Assessment) 0/1 • DLQI • AE
Notes	Funding source, quote (p 177): "The PRISTINE trial was sponsored by Pfizer Inc..." Declarations of interest (pp 177-8): "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."

Risk of bias

Bias	Authors' judgement	Support for judgement
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)	Low risk	Quote (p 170): "The study consisted of a 12-week double-blind treatment period"

Strohal PRISTINE 2013 *(Continued)*

All outcomes		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 prespecified outcomes mentioned in the Methods section appeared to have been reported

Tanew 1991

Study characteristics	
Methods	RCT, placebo-controlled, double-blind Date of study: not stated Location: 2 centres in Austria (Vienna, Innsbruck)

Participants	**Randomised**: 60 participants (mean age 40 years (acitretin), 49 years (placebo); 42 male)
	
	Inclusion criteria
	
	• Participants with moderate-severe psoriasis (BSA ≥ 20), age ≥ 18 years
	
	Exclusion criteria
	
	• Not stated
	
	Dropouts and withdrawals
	
	• 12/60 (20%)
	• Time and reasons:
	  * acitretin group (7): severe muscle pain (1), serum triglycerides exceeding 400 mg/dL (2), irregular drug intake (4)
	  * placebo group (5): unrelated to therapy

Interventions	**Intervention** A. Acitretin (n = 30), orally, 1 mg/kg, daily, 12 weeks or until complete clearing **Control intervention** B. Placebo (n = 30), orally, daily, 12 weeks **Co-intervention** PUVA, phototherapy, 4 times/week, 12 weeks
Outcomes	Assessments at 12 weeks

Tanew 1991 *(Continued)*

	Primary and secondary outcomes of the trial • Not defined **Outcomes of the trial** • Complete remission • Side effects
Notes	Funding: supported by a grant from Hoffma La Roche & Co Ltd Declarations of interest: not stated

Risk of bias

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

Thaçi CLEAR 2015

Study characteristics

Methods	RCT, active-controlled, double-blind Date of study: 27 February 2014 – 11 May 2015 Location: 137 centres in Europe, Australia and Asia
Participants	**Randomised**: 676 participants (mean age 46 years, 481 male)

Thaçi CLEAR 2015 *(Continued)*

Inclusion criteria

- Participants with moderate-severe psoriasis (PASI ≥ 12, BSA ≥ 10), age ≥ 18 years

Exclusion criteria

- Immunosuppression, active infection
- Had received anti IL17 drug or ustekinumab

Dropouts and withdrawals

- 32/676 (4.7%)
- Did not receive the treatment (4)
- Information consent obtained the day after study-related procedure (1, excluded from the efficacy analysis)
- AE (7)
- Lost to follow-up (3)
- Protocol deviation (5)
- Participant/guardian decision (7)
- Physician decision (1)
- Non-compliance with study treatment (1)
- Technical problem (1)

Interventions	**Intervention** A. Secukinumab (n = 334), SC, 300 mg weeks 0, 1, 2, 3 then monthly **Control intervention** B. Ustekinumab (n = 335), SC, 45/90 mg weeks 0, 4 then every 12 weeks
Outcomes	Assessments at 16 weeks **Primary outcomes of the trial** • PASI 90 **Secondary outcomes of the trial** • PASI 75 • PASI 90 at week 54 • DLQI • AEs
Notes	Funding source: Quote (p 400): "Novartis Pharma supported this study" Declarations of interest (p 400): "Dr Thaçi 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..."
Risk of bias	

Thaçi CLEAR 2015 *(Continued)*

Bias	Authors' judgement	Support for judgement
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 (p 402): “were randomised via an interactive response technology system “ Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 402) : “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 (p 402) : “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: 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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Torii 2010

Study characteristics	
Methods	RCT, placebo-controlled, double-blind Date of study: not stated Location: 28 centres in Japan
Participants	**Randomised**: 54 participants (mean age 46 years, 36 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12, BSA ≥ 10) **Exclusion criteria**

Torii 2010 *(Continued)*

- Active infection
- Past history of malignant tumours

Dropouts and withdrawals

- 7/54 (13%) at W14;
- Infliximab (3): therapeutic effect (2), adverse event (1)
- Placebo (4): AE (1), withdrawal of consent (3)

Interventions	**Intervention** A. Infliximab (n = 35), IV, 5 mg/kg, weeks 0, 2, 6; 10 weeks **Control intervention** B. Placebo (n = 19), IV, weeks 0, 2, 6; 10 weeks
Outcomes	Assessments at 10 weeks **Primary outcomes of the trial** • PASI75 **Secondary outcomes of the trial** • PASI50 • DLQI • PGA • AE
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	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 (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 allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 41): "The induction phase of the 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
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 41): "The induction phase of the 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

Torii 2010 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 54, analysed 54 Quote (p 42): "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 prespecified outcomes mentioned in the Methods section appeared to have been reported

Tsai PEARL 2011

Study characteristics	
Methods	RCT, placebo-controlled, double-blind Date of study: December 2008 - March 2010 Location: 13 centres in Taiwan and Korea
Participants	**Randomised**: 121 participants (mean age 41 years, 103 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12, BSA ≥ 10), age > 20 years **Exclusion criteria** • Had an active infection • Past history of malignant tumours **Dropouts and withdrawals** • 9/121 (7.4%): ustekinumab group (4), placebo group (5) • AEs: placebo group (3) • Unsatisfactory therapeutic effects: ustekinumab group (1), placebo group (2) • Invalid study entry criteria: ustekinumab group (2) • Withdrawal of consent: ustekinumab group (1)
Interventions	**Intervention** A. Ustekinumab, SC, 45 mg, weeks 0, 4, 16 + placebo week 12, 16 weeks (n = 61) **Control intervention** B. Placebo, SC, weeks 0 - 4 + ustekinumab 45 mg weeks 12 to 16 (n = 60)
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • PGA cleared or minimal at 12 weeks • Change from baseline in the DLQI at 12 weeks

Tsai PEARL 2011 *(Continued)*

- AEs

Notes	Funding source quote (p 162): "This study was supported by Centocore, Inc" Declarations of interest: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
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 (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...” Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 155): “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 (p 155): “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 prespecified outcomes mentioned in the Methods section appeared to have been reported

Tyring 2006

Study characteristics

Methods	RCT, placebo-controlled, double-blind Date of study: June 2003 – January 2004 Location: 39 centres in Houston, USA and Canada

Tyring 2006 *(Continued)*

Participants	**Randomised**: 620 participants (mean age 46 years, 419 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 10, BSA ≥ 10), age > 18 years **Exclusion criteria** • Kidney insufficiency, liver insufficiency, past history of malignant tumours • Had received conventional systemic treatments • Had received biologics (etanercept or anti-TNF) **Dropouts and withdrawals** • 23/620 (3.7%); etanercept group (6), placebo group (15) • AEs: etanercept group (4), placebo group (3) • Disease progression: etanercept group (1), placebo group (4) • Withdrawal of consent: etanercept group (1), placebo group (5) • Lost to follow-up: placebo group (4) • Non-compliance: placebo group (1)
Interventions	**Intervention** A. Etanercept (n = 311), 50 mg, SC, twice weekly, 12 weeks **Control intervention** B. Placebo (n = 309), SC, twice weekly, 12 weeks
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • DLQI at 12w • PASI 50 • PASI 90 • the 17-item Hamilton rating scale for depression • Beck depression inventory
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 (pp 367-8): "S Tyring has received research support from Amgen. 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

Tyring 2006 *(Continued)*

	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..."

Risk of bias

Bias	Authors' judgement	Support for judgement
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): “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” Comment: only 2 participants did not receive at least 1 dose, 618 participants should be involved in the mITT, however 617 participants were analysed for the primary outcome
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00111449) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Van Bezooijen 2016

Study characteristics

Methods	RCT, placebo-controlled, double-blind Date of study: 2013 and June 2015 Location: single centre in the Netherlands
Participants	**Randomised**: 33 participants

Van Bezooijen 2016 *(Continued)*

	Inclusion criteria • Participants with moderate-severe psoriasis (PASI ≥ 10, BSA ≥ 10), age > 18 years **Exclusion criteria** • Any other subtype of psoriasis • Previous treatment failure on etanercept or fumarates • Had a clinically significant adverse event with prior use of both drugs. • Pregnant or lactating women **Dropouts and withdrawals** • None at week 12
Interventions	**Intervention** A. Fumaric acid (n = 18), from 215 mg once daily up to a maximum of 215 mg 4 times a day, 24 weeks **Control intervention** B. Placebo **Co-intervention** Etanercept (n = 15) (50 mg SC twice weekly for 12 weeks followed by 50 mg once weekly for an additional 12 weeks)
Outcomes	Assessments at 24 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • PGA0/1 • DLQI • AEs
Notes	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." 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 Pharmaceu-ticals, Cutanea and Novartis. T. van Gelder has been on the speakers' bureau or worked as consultant for Sandoz, Novartis, Teva, Chiesi, Astellas and Roche".

Risk of bias

Bias	Authors' judgement	Support for judgement
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

Van Bezooijen 2016 *(Continued)*

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 combined 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, but 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 prespecified results mentioned in the Methods section appeared to have been reported

Van de Kerkhof 2008

Study characteristics	
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	**Randomised**: 142 participants (mean age 45 years, 84 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 10, BSA ≥ 10), age > 18 years **Exclusion criteria** • Had received biologics (etanercept, anti-TNF) • Had an active infection **Dropouts and withdrawals** • 16/143 (11%): etanercept group (6), placebo group (10) • AEs: etanercept group (3), placebo group (3) • Lack of efficacy: etanercept group (2), placebo group (4)

Van de Kerkhof 2008 *(Continued)*

- Other reason: etanercept group (1), placebo group (3)

Interventions	**Intervention** A. Etanercept, 50 mg, self-administered SC, once a week, 12 weeks (n = 96) **Control intervention** B. Placebo, self-administered SC, once a week, 12 weeks (n = 46)
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • Proportion of participants PASI 75 or greater **Secondary outcomes of the trial** • PASI 75 at other time points • PASI 50 at 12,24 • PASI 90 at 12,24 • PASI 100 at 24 • PASI improvement from baseline • PGA • DLQI
Notes	Funding source (p 1184): "This study was supported financially by Wyeth Pharmaceuticals, Collegeville, PA, USA)" Comments: 3 authors were employed by Wyeth pharmaceuticals which supported this study financially 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. "

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 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

Van de Kerkhof 2008 *(Continued)*

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, but no protocol was available

Warren METOP, 2017

Study characteristics	
Methods	RCT, placebo-controlled Date of study: 22 February 2013 - 13 May 2015 Location: 13 centres in Europe
Participants	**Randomised**: 120 participants **Inclusion criteria** • Definition moderate-severe psoriasis • Methotrexate treatment-naïve • Aged ≥ 18 years **Exclusion criteria** • Pregnancy, kidney insufficiency, liver insufficiency • Had an active infection • Had past history of malignant tumours **Dropouts and withdrawals** • 21/212 (17.5%), methotrexate n = 14, placebo, n = 7 • AEs: methotrexate (10), placebo (4) • Lost to follow-up: methotrexate (2) • Participants' choice: placebo (2) • Poor efficacy: methotrexate (1), placebo (1) • Other: methotrexate (1)
Interventions	**Intervention** A. Methotrexate (n = 91), SC, IM, 17.5 - 22.5 mg/week, 12 weeks **Control intervention** B. Placebo (n = 29)
Outcomes	16 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial**

Warren METOP, 2017 *(Continued)*

- PASI 90
- PGA
- NAPSI
- DLQI
- AEs

Notes	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" 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 & 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 & Dohme, Novartis, Pfizer, Regeneron, Takeda, UCB Pharma, and Xenoport, outside the submitted work. IZ, TMF, and NB-S declare no competing interests."

Risk of bias

Bias	Authors' judgement	Support for judgement
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)	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 ran-

Warren METOP, 2017 *(Continued)*

All outcomes		domisation 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 prespecified outcomes and those mentioned in the Methods section appeared to have been reported

Yang 2012

Study characteristics	
Methods	RCT, placebo-controlled, double-blind Date of study: February 2009 - February 2010 Location: 9 centres in China
Participants	**Randomised**: 129 participants (mean age 39 years (infliximab) and 40 years (placebo), 95 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12, BSA ≥ 10), age 18 - 65 years • Had a diagnosis of plaque psoriasis for at least 6 months • Had failed to respond to conventional systemic treatment of psoriasis including: ciclosporin, methotrexate, or acitretin as previous treatment **Exclusion criteria** • Non-plaque forms of psoriasis • A history of a chronic infectious disease or opportunistic infection • A serious infection within 2 months of enrolment • Active or latent TB • Pregnancy or planned pregnancy within 12 months of enrolment • A history of lymphoproliferative disease • An active malignancy or history of malignancy within 5 years **Dropouts and withdrawals** • 2/129 (1.55%): infliximab group (1), placebo group (1) • Withdrawal of informed consent: infliximab group (0), placebo group (1) • Adverse event: infliximab group (1), placebo group (0)
Interventions	**Intervention**

Yang 2012 *(Continued)*

	A. Infliximab (n = 84), IV, 5 mg/kg, weeks 0, 2, 6, 14, 22; 22 weeks **Control intervention** B. Placebo (n = 45), IV, weeks 0, 2, 6 then infliximab 5 mg/kg weeks 10, 12, 16
Outcomes	Assessments at 10 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • PGA • DLQI
Notes	Funding source: not stated Declarations of interest: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p 1846): "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 (p 1846): "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 (p 1846): "This randomised, double-blind, placebo controlled trial... Eligible patients were randomly assigned in a 1:2 ratio to the placebo and infliximab... Infliximab 5 mg/kg or placebo was administered 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 (p 1846): "This randomised, double-blind, placebo controlled trial... Eligible patients were randomly assigned in a 1:2 ratio to the placebo and infliximab... Infliximab 5 mg/kg or placebo was administered 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 treatment group..." Comment: no description of the method used to manage the missing data

Yang 2012 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The prespecified outcomes mentioned in the Methods section appeared to have been reported

Yilmaz 2002

Study characteristics	
Methods	RCT, placebo-controlled, open-label trial Date of study: unreported Location: Turkey
Participants	**Randomised**: 50 participants (no description of the study population) **Inclusion/exclusion criteria** • Not stated **Dropouts and withdrawals** • Not stated
Interventions	**Intervention** A. Acitretin (n = 50), orally, 0.5-0.7 mg/kg, daily **Control intervention** B. Placebo (n = 50) **Co-intervention** PUVA, twice weekly, 8-MOP at a dosage of 0.4 - 0.6 g/kg, 2 hours before UVA exposure
Outcomes	Time of assessments not stated **Primary or secondary outcomes of the trial** • Not clearly defined **Outcomes of the trial** • Complete remission
Notes	Funding source: not stated Declarations of interest: not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
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

Yilmaz 2002 *(Continued)*

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

Zhang 2017

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study Date of study: December 2013 - July 2015 Location: China (multicentric) Phase 3
Participants	**Randomised**: 266 participants (mean age 41 years, 194 men) **Inclusion criteria** • Have had a diagnosis of plaque-type psoriasis (psoriasis vulgaris) for at least 12 months prior to the first screening procedure. • Have a PASI score of 12 or greater AND a PGA score of 3 ("moderate") or 4 ("severe") at baseline (Day 1). • Considered by dermatologist investigator to be a candidate for systemic therapy or phototherapy of psoriasis (either naïve or history of previous treatment) **Exclusion criteria** • Currently have non-plaque forms of psoriasis, e.g., erythrodermic, guttate, or pustular psoriasis, with the exception of nail psoriasis which is allowed. • Have current drug-induced psoriasis, e.g. a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, antimalarial drugs or lithium. • People who cannot discontinue systemic therapies and/or topical therapies for the treatment of psoriasis and cannot discontinue phototherapy (UVB or PUVA) for the study are excluded **Dropouts and withdrawals** • 22/266 (8.3%): Tofacitinib 5 group (4), Tofacitinib 10 group (7), Placebo group (11)

Zhang 2017 *(Continued)*

- Does not meet criteria: Tofacitinib 5 group (0), Tofacitinib 10 group (2), Placebo group (0)
- Insufficient clinical response: Tofacitinib 5 group (0), Tofacitinib 10 group (2), Placebo group (4)
- Protocol violation: Tofacitinib 5 group (0), Tofacitinib 10 group (1), Placebo group (0)
- AEs: Tofacitinib 5 group (3), Tofacitinib 10 group (1), Placebo group (3)
- Patient withdrawal: Tofacitinib 5 group (0), Tofacitinib 10 group (0), Placebo group (1)
- Lost to follow-up: Tofacitinib 5 group (1), Tofacitinib 10 group (0), Placebo group (0)
- Other: Tofacitinib 5 group (0), Tofacitinib 10 group (1), Placebo group (3)

Interventions	**Intervention** A. Tofacitinib 5 mg twice a day, n = 88 **Control intervention** B. Tofacitinib 10 mg twice a day, n = 90 C. Placebo, n = 88
Outcomes	**At week 24** **Primary outcome** • PASI 75 & PGA0/1 **Secondary outcomes** • PASI 90 • PASI 75, PGA and PASI 75 week 52 • DLQI
Notes	Funding Quote (p 44): "This study was sponsored by Pfizer Inc. Medical writing support, under the guidance of the authors, was provided by Complete Medical Communications and funded by Pfizer Inc." Conflicts of interest Quote (p 44): "J.Z. Zhang conducted clinical trials or received honoraria for serving as a consultant for AbbVie, Bayer, Janssen-Cilag and Pfizer Inc. T.F. Tsai conducted clinical trials or received honoraria for serving as a consultant for AbbVie, Boehringer Ingelheim, Celgene, Eli Lilly, Galderma, Janssen-Cilag, Leo, Novartis Pharmaceuticals, Pfizer Inc, and Serono International SA (now Merck Serono International). M.G. Lee conducted clinical trials for Eli Lilly, Janssen-Cilag, Novartis Pharmaceuticals, and Pfizer Inc, and received honoraria for acting as a speaker for Janssen-Cilag. M. Zheng conducted clinical trials or received honoraria for serving as a consultant for AbbVie, Janssen-Cilag and Pfizer Inc. G. Wang has conducted clinical trials for AbbVie, Janssen-Cilag, and Pfizer Inc, and has acted as a consultant or speaker for La Roche-Posay China, LEO Pharma China, and Xian-Janssen. H.Z. Jin conducted clinical trials or received honoraria for serving as a consultant for AbbVie, Boehringer Ingelheim, Galderma, Janssen-Cilag, and Pfizer Inc. J. Gu conducted clinical trials or received honoraria for serving as a speaker for AbbVie, Galderma, Janssen-Cilag, Novartis, and Pfizer Inc. R.Y. Li conducted clinical trials or received honoraria for serving as a consultant for AbbVie, Galderma, Leo Pharma China, Novartis Pharmaceuticals, Pfizer Inc, and Xian-Janssen Pharmaceuticals. Q.Z. Liu conducted clinical trials for Bayer, Ipsen, and Pfizer Inc. J. Chen conducted clinical trials for AbbVie, AstraZeneca, and Pfizer Inc. C.X. Tu conducted clinical trials for Janssen-Cilag and Pfizer Inc, and has acted as a consultant for Astellas Pharma Inc and Janssen-Cilag. C.M. Qi, H. Zhu, W. Ports, and T. Crook are employees and shareholders of Pfizer Inc."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 37): "This was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study (NCT01815424) carried out between December

Zhang 2017 *(Continued)*

		2013 and July 2015 (Fig. 1). A computer-generated randomization schedule was developed by Pfizer and an automated telephone/web-based interactive response system was used to assign patients 2:2:1:1 to receive tofacitinib 5 mg BID, tofacitinib 10 mg BID, placebo advanced to tofacitinib 5 mg BID, or placebo advanced to tofacitinib 10 mg BID." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 37): "This was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study (NCT01815424) carried out between December 2013 and July 2015 (Fig. 1). A computer-generated randomization schedule was developed by Pfizer and an automated telephone/web-based interactive response system was used to assign patients 2:2:1:1 to receive tofacitinib 5 mg BID, tofacitinib 10 mg BID, placebo advanced to tofacitinib 5 mg BID, or placebo advanced to tofacitinib 10 mg BID." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 37): "This was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study (NCT01815424) carried ... Patients, investigators, and the sponsor were blinded to study treatment. Placebo was provided as oral tablets matching those of tofacitinib." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 37): "This was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study (NCT01815424) carried ... Patients, investigators, and the sponsor were blinded to study treatment. Placebo was provided as oral tablets matching those of tofacitinib." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	High risk	Dealing with missing data Quote (p 38): "Data were analyzed for the full analysis set: all randomized patients who received >= dose of study drug. All binary variables... were analyzed..., with non-responder imputation for missing data." 266 randomized, 266 analyzed imbalance reasons and number of withdrawal: Insufficient clinical response: Tofacitinib 5 group (0), Tofacitinib 10 group (2), Placebo group (4)
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01815424) The prespecified outcomes and those mentioned in the Methods section appeared to have been reported Results are posted on ClinicalTrials.gov

Zhu LOTUS 2013

Study characteristics	
Methods	RCT, placebo-controlled, double-blind (LOTUS) Date of study: 23 October 2009 - 07 July 2011

Zhu LOTUS 2013 *(Continued)*

	Location: 14 centres in China
Participants	**Randomised**: 322 participants (mean age 40 years, 248 male) **Inclusion criteria** • Participants with moderate-severe psoriasis (PASI ≥ 12 and BSA ≥ 10), age > 18 years **Exclusion criteria** • Severe uncontrolled or progressive medical conditions • Known to be infected with HIV, hepatitis B virus (HBV), hepatitis C virus (HCV), or syphilis **Dropouts and withdrawals** • 6/322 (1.86%): ustekinumab group (3), placebo group (3) • AEs: ustekinumab group (2), placebo group (1) • Other reasons: ustekinumab group (1), placebo group (2)
Interventions	**Intervention** A. Ustekinumab (n = 160), SC, 45 mg, week 0, week 4, 4 weeks **Control intervention** B. Placebo (n = 162), SC, week 0, week 4, 4 weeks
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PASI 75 **Secondary outcomes of the trial** • PGA 0 /1 • DLQI
Notes	Funding source: Quote (p 173): "This study was supported by Janssen Research & Development" Declarations of interest (p 173): "Drs Zhu, Zang and Wand served as investigators for this Janssen RD-sponsored study..."

Risk of bias

Bias	Authors' judgement	Support for judgement
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

Zhu LOTUS 2013 *(Continued)*

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, analysed 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 prespecified 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; eow: every other week; **CIN**: cervical intraepithelial neoplasia; **DLQI**: Dermatology Life Quality Index; **ECG**: electrocardiogram; **eow:** every other week; **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; **SAEs;** serious adverse events; **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
Abe 2017	Post hoc subgroup analyses of an already included trial
Abufarag 2010	Other treatment
Adsit 2017	Post hoc subgroup analyses of an already included trial
Akhyani 2010	Other treatment
Altmeyer 1994	Not plaque-type psoriasis
Angsten 2007	Not a trial
Anonymous 2005	Not a trial
Anonymous 2008	Not a trial
Araujo 2017	Not moderate-to-severe psoriasis
Araujo 2019	Not moderate-to-severe psoriasis
Arifov 1998	Not a randomised trial
Armati 1972	Other treatment

Study	Reason for exclusion
Augustin 2017	Dose de-escalation strategy study
Avgerinou 2011	Not a randomised trial
Bachelez 2017	Post hoc subgroup analyses of an already included trial
Bagel 2017a	Open-label extension restricted to good responders
Bagel 2017b	Not a randomised trial
Bagel 2017c	Not moderate-to-severe psoriasis
Bagel 2018	Not a randomised trial
Bagherani 2017	Commentary/editorial
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
Bhat 2017	Post hoc subgroup analyses of an already included trial
Bhuiyan 2010	Other treatment
Bian 2018	Open-label extension restricted to good responders
Bigby 2004	Not a trial
Bissonnette 2006	Other treatment
Bissonnette 2010	Other treatment
Bissonnette 2017a	Open-label extension restricted to good responders
Bissonnette 2017b	Not moderate-to-severe psoriasis
Bissonnette 2018	Not moderate-to-severe psoriasis
Bjerke 1989	Other treatment
Blauvelt 2016a	Ineligible study design
Blauvelt 2016b	Open-label extension restricted to good responders
Blauvelt 2017a	Pooled trials

Study	Reason for exclusion
Blauvelt 2017b	Open-label extension restricted to good responders
Blauvelt 2017c	Open-label extension restricted to good responders
Blauvelt 2017d	Open-label extension restricted to good responders
Blauvelt 2017e	Pooled trials
Blauvelt 2017f	Ineligible study design
Blauvelt 2017g	Open-label extension restricted to good responders
Blauvelt 2017h	Open-label extension restricted to good responders
Blauvelt 2017i	Open-label extension restricted to good responders
Blauvelt 2017j	Pooled trials
Blauvelt 2017k	Open-label extension restricted to good responders
Blauvelt 2018a	Not a randomised trial
Blauvelt 2018b	Open-label extension restricted to good responders
Blauvelt 2018c	Open-label extension restricted to good responders
Blauvelt 2018d	Pooled trials
Blauvelt 2018e	Pooled trials
Blauvelt 2018f	Pooled trials
Blauvelt 2018g	Pooled trials
Blauvelt 2018h	Pooled trials
Blauvelt 2018i	Pooled trials
Branigan 2017	Open-label extension restricted to good responders
Brasil 2012	Ineligible study design
Brasil 2013	Ineligible patient population
Brasil 2016	Ineligible patient population
Burden 2017	Commentary/editorial
Burkhardt 2017	Ineligible study design
Callis Duffin 2017	Comparison of the same drug with the same dosages
Cassano 2006	Identical dosing regimens
Cassano 2010	Not a trial

Study	Reason for exclusion
Cather 2006	Dose-ranging after remission
Cather 2018	Ineligible patient population
Chakravadhanula 2017	Ineligible intervention
Chapman 2018	Ineligible study design
Chládek 2002	Basic science (aim of study: to understand the physiopathology of the disease)
Chodorowska 1999a	Not a trial
Chodorowska 1999b	Not a trial
Choi 2017	Not moderate-to-severe psoriasis
Crowley 2018a	Not moderate-to-severe psoriasis
Crowley 2018b	Open-label extension restricted to good responders
De Jong 2003	Other treatment
De Mendizabal 2017	Post hoc subgroup analyses of an already included trial
Dubiel 1972	Not a trial
Duffin 2016	Comparison of 2 different ways of drug injection for the same drug and the same dosage
Duffin 2017	Ineligible study design
Ecker-Schlipf 2009	Other treatment
Edson-Heredia 2013	Post hoc subgroup analyses of an already included trial
Egeberg 2016	Commentary/editorial
Elewski 2007	Pooled trials
Elewski 2017	Post hoc subgroup analyses of an already included trial
Elewski 2018a	Ineligible study design
Elewski 2018b	Ineligible study design
Ellis 1986	Assessment < 8 weeks
Ellis 2001	Another intervention
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)

Study	Reason for exclusion
Ezquerra 2007	Other treatment
Feldman 2017	Not moderate-to-severe psoriasis
Fernandes 2013	Not a trial
Fernandez 2017	Not a randomised trial
Finzi 1993	Other treatment
Fitz 2018	Post hoc subgroup analyses of an already included trial
Fleischer 2005	Other treatment
Foley 2017	Pooled trials
Foley 2018	Pooled trials
Fredriksson 1971	Other treatment
Fredriksson 1978	Other treatment
Friedrich 2001	Other treatment
Gambichler 2011	Other treatment
Ganguly 2004	Pooled trials
Gil 2003	Not a randomised trial
Glatt 2017	Ineligible study design
Goerz 1978	Not a trial
Gold 2018	Ineligible study design
Goll 2017	Not moderate-to-severe psoriasis
Goll 2018	Ineligible study design
Gollnick 1988	Other treatment
Gollnick 1993	Other treatment
Gollnick 2002	Other treatment
Gordon 2014	Ineligible study design
Gordon 2015	Ineligible study design
Gordon 2018a	Open-label extension restricted to good responders
Gordon 2018b	Post hoc subgroup analyses of an already included trial
Gordon 2018c	Pooled trials

Study	Reason for exclusion
Gordon 2018d	Post hoc subgroup analyses of an already included trial
Gottlieb 2002	Other treatment
Gottlieb 2003b	Other treatment
Gottlieb 2003c	Open-label extension restricted to good responders
Gottlieb 2004b	Pooled trials
Gottlieb 2005	Other treatment
Gottlieb 2006a	Ineligible intervention
Gottlieb 2006b	Ineligible intervention
Gottlieb 2010	Cross-over trial
Gottlieb 2016	Pooled trials
Gottlieb 2017a	Not moderate-to-severe psoriasis
Gottlieb 2017b	Not moderate-to-severe psoriasis
Gottlieb 2017c	Post hoc subgroup analyses of an already included trial
Gottlieb 2017d	Pooled trials
Gottlieb 2018a	Pooled trials
Gottlieb 2018b	Pooled trials
Goupille 1995	Not a randomised trial
Goupille 2018	Not moderate-to-severe psoriasis
Griffiths 1998	Other treatment
Griffiths 2002a	Pooled trials
Griffiths 2002b	Pooled trials
Griffiths 2005	Pooled trials
Griffiths 2010	Open-label extension restricted to good responders
Griffiths 2016	Post hoc subgroup analyses of an already included trial
Griffiths 2017	Open-label extension restricted to good responders
Griffiths 2018a	Ineligible study design
Griffiths 2018b	Post hoc subgroup analyses of an already included trial
Griffiths 2018c	Pooled trials

Study	Reason for exclusion
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
Hawkes 2018	Ineligible study design
Heule 1988	Assessment < 8 weeks
Ho 2010	Other treatment
Hsu 2018	Post hoc subgroup analyses of an already included trial
Hunter 1972	Other treatment
Iest 1989	Not a randomised trial
Imafuku 2017	Post hoc subgroup analyses of an already included trial
Iversen 2018	Ineligible comparator
Jackson 2018	Ineligible study design
Jacobe 2008	Another intervention
Kaur 2018	Ineligible outcomes
Kavanaugh 2009	Not a randomised trial
Kemeny 2019	Post hoc subgroup analyses of an already included trial
Kimball 2008	Drug withdrawn for safety reasons
Kimball 2011	Drug withdrawn for safety reasons
Kimball 2018	Ineligible study design
Koo 1998	Other treatment
Kopp 2015	Phase 1 trial
Kragballe 1989	Other treatment
Krishnan 2005	Pooled trials

Study	Reason for exclusion
Krishnan 2018	Pooled trials
Kristensen 2017	Not moderate-to-severe psoriasis
Krueger 1980	Other treatment
Krueger 2002a	Another intervention
Krueger 2002b	Not a trial
Krueger 2003	Not a trial
Krueger 2012	Phase 1 trial
Krueger 2015	Phase 1 trial
Krueger 2016b	Phase I trial
Krupashankar 2014	Another intervention
Kuijpers 1998	Other treatment
Lajevardi 2015	Other treatment
Lambert 2018	Post hoc subgroup analyses of an already included trial
Langewouters 2005	Other treatment
Langley 2006	Other treatment
Langley 2010	Other treatment
Langley 2016	Open-label extension restricted to good responders
Langley 2018	Ineligible study design
Langner 2004	Not plaque-type psoriasis
Lauharanta 1989	Other treatment
Lawrence 1983	Other treatment
Leavell 1970	Other treatment
Lebwohl 2003	Another intervention
Lebwohl 2003a	Pooled trials
Lebwohl 2009	Pooled trials
Lebwohl 2012	Other treatment
Lebwohl 2013	Other treatment
Ledo 1988	Other treatment

Study	Reason for exclusion
Legat 2005	Other treatment
Leonardi 2010a	Pooled trials
Leonardi 2010b	Not a randomised trial
Leonardi 2010c	Pooled trials
Leonardi 2011a	Open-label extension restricted to good responders
Leonardi 2011b	Not plaque-type psoriasis
Levell 1995	Other treatment
Li 2018	Post hoc subgroup analyses of an already included trial
Liang 1995	Assessment < 8 weeks
Louw 2017	Open-label extension restricted to good responders
Lui 2011	Other treatment
Lui 2012	Other treatment
Lynde 2012	Other treatment
Macdonald 1972	Not a randomised trial
Mahrle 1995	Other treatment
Malik 2010	Other treatment
Marecki 2004	Other treatment
Marks 1986	Not a randomised trial
Mate 2017	Not moderate-to-severe psoriasis
Mate 2018	Open-label extension restricted to good responders
McInnes 2013	Pooled trials
McInnes 2017	Not moderate-to-severe psoriasis
Mease 2011	Drug withdrawn for safety reasons
Mease 2016a	Not moderate-to-severe psoriasis
Mease 2016b	Not moderate-to-severe psoriasis
Mease 2017a	Not moderate-to-severe psoriasis
Mease 2017b	Not moderate-to-severe psoriasis
Mease 2017c	Not moderate-to-severe psoriasis

Study	Reason for exclusion
Mease 2018	Not moderate-to-severe psoriasis
Meffert 1989	Other treatment
Mehta 2018	Not a randomised trial
Menon 2012	Basic science (aim of study: to understand the physiopathology of the disease)
Menter 2007	Pooled trials
Menter 2014	Drug withdrawn for safety reasons
Merola 2017	Post hoc subgroup analyses of an already included trial
Merola 2018	Not moderate-to-severe psoriasis
Meyer 2011	Other treatment
Mittal 2009	Other treatment
Moller 2009	Other treatment
Monk 1986	Not a randomised trial
Montgomery 1993	Other treatment
Mrowietz 1991	The 2 study arms compared the same molecule with the same dosage
Mrowietz 2012	Pooled trials
Narang 2012	Other treatment
Nash 2015	Not moderate-to-severe psoriasis
NCT00106847	Dose de-escalation strategy study
NCT00111111	Dose de-escalation strategy study
NCT00258713	Ineligible intervention
NCT00358670	Open-label extension restricted to good responders
NCT00377325	Withdrawal trial
NCT00438360	Open-label extension restricted to good responders
NCT00585650	Ineligible patient population
NCT00645892	Open-label extension restricted to good responders
NCT00646191	Open-label extension restricted to good responders
NCT00647400	Open-label extension restricted to good responders
NCT00832364	Withdrawal trial

Study	Reason for exclusion
NCT01163253	Not a randomised trial
NCT01235442	Ineligible intervention
NCT01276847	Phase I trial
NCT01412944	Open-label extension restricted to good responders
NCT01443338	Ineligible comparator
NCT01544595	Open-label extension restricted to good responders
NCT01550744	Open-label extension restricted to good responders
NCT01624233	Not a randomised trial
NCT01722214	Not moderate-to-severe psoriasis
NCT01806597	Ineligible patient population
NCT01815723	Withdrawal trial
NCT01828086	Phase I trial
NCT01936688	Withdrawal trial
NCT02362789	Withdrawal trial
NCT02409667	Open-label extension restricted to good responders
NCT02798211	Not moderate-to-severe psoriasis
NCT03010527	Open-label extension restricted to good responders
NCT03020199	Ineligible comparator
NCT03073213	Phase I trial
Nemoto 2018	Phase I trial
Nieboer 1990	Other treatment
Nijsten 2008	Not a trial
Noda 2011	Not a randomised trial
Noor 2017	Not a randomised trial
Novotny 1973	Not a trial
Nyfors 1978	Not a trial
Okubo 2019	Open-label extension restricted to good responders
Orfanos 1978	Other treatment

Study	Reason for exclusion
Orfanos 1979	Other treatment
Ortonne 2008	Comparison of 2 schemes of administration
Ortonne 2011	Other treatment
Osamu 2014	Phase 1 trial
Pakozdi 2018	Post hoc subgroup analyses of an already included trial
Papp 2001	Other treatment
Papp 2006	Other treatment
Papp 2008	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 2012d	Phase 1 trial
Papp 2012e	Pooled trials
Papp 2017	Open-label extension restricted to good responders
Papp 2018a	Ineligible outcomes
Papp 2018b	Ineligible outcomes
Park 2013	Other treatment
Paul 2012	Other treatment
Paul 2014	Other treatment
Paul 2018	Pooled trials
Perks 2017	Ineligible study design
Pettit 1979	Assessment < 8 weeks
Petzelbauer 1990	Not a randomised trial
Piascik 2003	Not a trial
Ports 2013	Other treatment
Puig 2018	Ineligible outcomes
Punwani 2012	Other treatment

Study	Reason for exclusion
Rabasseda 2012	Not a trial
Radmanesh 2011	Comparison of 2 schemes of administration
Raman 1998	Other treatment
Reich 2004	Ineligible intervention
Reich 2011	Pooled trials
Reich 2014	Other treatment
Reich 2016a	Ineligible study design
Reich 2016b	Ineligible study design
Reich 2017a	Ineligible study design
Reich 2017b	Open-label extension restricted to good responders
Reich 2017c	Pooled trials
Reich 2018a	Ineligible outcomes
Reich 2018b	Ineligible
Reich 2018c	Open-label extension restricted to good responders
Reitamo 1999	Other treatment
Reitamo 2001	Other treatment
Rim 2003	Other treatment
Rinsho Iyaku 1991	Other treatment
Ritchlin 2006a	Not a randomised trial
Ritchlin 2006b	Not a randomised trial
Romiti 2017	Post hoc subgroup analyses of an already included trial
RPCEC00000201	Ineligible intervention
Ryan 2018	Not moderate-to-severe psoriasis
Saeki 2017	Not a randomised trial
Salim 2006	Other treatment
Scholl 1981	Other treatment
Schopf 1998	Other treatment
Schulze 1991	Other treatment

Study	Reason for exclusion
Shintani 2011	Comparison of 2 schemes of administration
Shiohara 1992	Not a trial
Shupack 1997	Not a trial
Simonova 2005	Other treatment
Sinclair 2017	Pooled trials
Sofen 2011	Basic science (aim of study: to understand the physiopathology of the disease)
Sofen 2014	Phase 1 trial
Spadaro 2008	Not a trial
Spuls 2012	Not a trial
Stein Gold 2018	Not moderate-to-severe psoriasis
Sticherling 1994	Not a trial
Strober 2004	Not a trial
Strober 2012	Not a randomised trial
Strober 2017a	Pooled trials
Strober 2017b	Not moderate-to-severe psoriasis
Strober 2017c	Ineligible outcomes
Strober 2018	Ineligible study design
Sweetser 2006	Cross-over trial
Talwar 1992	Not a randomised trial
Tejasvi 2012	Other treatment
Thaçi 2002	The 2 study arms compared the same molecule with the same dosage
Thaçi 2010	Other treatment
Thaçi 2018	Ineligible outcomes
Tong 2008	Other treatment
Tsakok 2018	Commentary/editorial
Vaclavkova 2014	Another intervention
Valenzuela 2017	Post hoc subgroup analyses of an already included trial
Van de Kerkhof 2017	Post hoc subgroup analyses of an already included trial

Study	Reason for exclusion
Van Joost 1988	Assessment < 8 weeks
Vena 2005	Comparison of 2 schemes of administration
Vena 2012	Other treatment
Viglioglia 1978	Not a trial
Witkamp 1995	Other treatment
Wolf 2012	Other treatment
Wright 1966	Not a randomised trial
Wu 2015	Other treatment
Yan 2011	Another intervention
Yesudian 2013	Other treatment
Yoon 2007	Dose-escalation study
Yosipovitch 2018	Not moderate-to-severe psoriasis
Zachariae 2008	Other treatment
Zhang 2007	Other treatment
Zhang 2009a	Other treatment
Zhang 2009b	Other treatment
Zhu 2009	Pooled trials
Zhuang 2016	Phase 1 trial
Zobel 1987	Not a trial

Characteristics of studies awaiting classification *[ordered by study ID]*

Chow 2015

Methods	RCT, active/placebo-controlled, double-blind Date of study: not stated Location: Canada, Germany and Poland
Participants	**Randomised**: 455 participants (mean age 43, 313 male) **Inclusion criteria** • Aged ≥ 18 years at time of screening • Diagnosed with plaque psoriasis ≥ 6 months prior to screening

Chow 2015 *(Continued)*

- Diagnosis of stable, plaque psoriasis; i.e. psoriasis must not be spontaneously improving or worsening in the 4 weeks prior to the screening visit
- Psoriasis failing ≥ 1 systemic treatment regimen or where other systemic therapies are contraindicated or where tolerability is an issue
- Plaque psoriasis involving ≥ 10% of the body surface area and a SPGA score ≥ 3 at screening and prior to randomisation at the day 0 visit
- Not pregnant or nursing
- Sexually-active women of childbearing potential or < 1 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 ≥ 3 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
- Written informed consent prior to washout and screening procedures
- Able to keep study appointments and co-operate with all study requirements, in the opinion of the Investigator

Exclusion criteria

- Has generalised erythrodermic, guttate, or pustular psoriasis
- Have other dermatoses that would interfere with the evaluation of psoriasis, at the discretion of the Investigator
- A current malignancy or history of malignancy within 5 years or a history of lymphoma at any time. Patients can be enrolled with a history of squamous or basal cell carcinoma that has been surgically excised or removed with curettage and electrodesiccation
- 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
- A known history of TB
- Serologic evidence or known latent HIV, hepatitis B or C virus
- Uncontrolled hypertension of systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 90 mmHg
- Modification of Diet in Renal Disease < 60 mL/min
- Liver enzyme serum levels ≥ 2 x upper limit of normal (ULN)
- White blood cell count ≤ 2.8 x 10^9/L
- 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
- Has used any investigational drug or device within 30 days or 10 half-lives (whichever is longer) prior to the screening visit
- Current participation in another clinical trial of any drug or biological agent
- 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
- Previous exposure to voclosporin
- A history of clinically-defined allergy to ciclosporin, constituents of Neoral or any of the constituents of the ISA247 formulation
- A history of alcoholism or drug addiction
- Weighs < 45 kg (99 lbs)
- 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

Interventions	**Interventions** (n = 366)

Chow 2015 *(Continued)*

	Drug: voclosporin 0.8 mg/kg/day Drug: ciclosporin 3.0 mg/kg/day **Control intervention** (n = 89) Drug: placebo
Outcomes	**At week 24,** **Primary outcome measures** • Superiority in the proportion of participants achieving a score of clear or almost clear in the SPGA score **Secondary outcome measures** • 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 • Superiority in de novo hypertriglyceridaemia, defined as proportion of participants developing fasting triglycerides ≥ 1.7 mmol/L • Superiority in de novo hypertension, defined as proportion of participants developing blood pressure ≥ 140 mmHg (systolic) or ≥ 90 mmHg (diastolic) • Superiority of renal function, defined as the proportion of participants experiencing a confirmed ≥ 30% rise in serum creatinine • Superiority in proportion of participants achieving a 75% reduction in the PASI score (PASI 75)
Notes	Randomised, placebo and ciclosporin controlled study of ISA247 in plaque psoriasis patients (ESSENCE), NCT00408187 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. 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 Two emails were sent without response (8 November 2016, 16 December 2016)

CTRI/2015/05/005830

Methods	Randomised, parallel-group, multiple-arm trial Date of study: 10 December 2013 (starting date) Location: India
Participants	**Total sample size**: 120 **Inclusion criteria**: • Diagnosed to be suffering exclusively from Palmo-plantar psoriasis either by clinical examination or histopathology; if required will be included in palmoplantar psoriasis group • Diagnosed to be suffering from psoriasis vulgaris having > 20% BSA will be included in psoriasis vulgaris group • Be at least 18 years of age **Exclusion criteria:** • Hypersensitivity to drug or intolerance to the study medication

CTRI/2015/05/005830 *(Continued)*

	• Pregnant and lactating • 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 • On any other systemic drugs therapy which in the judgement of investigator may interfere with interpretation of results • History of TB or chest X-ray showing evidence of any infective pathology
Interventions	**Intervention 1**: acitretin: orally, 25 - 50 mg/day, daily single dose Total duration: 90 days **Intervention 2**: ciclosporin: orally 2.5 - 5 mg/kg/day, daily in 2 divided doses Total duration: 90 days **Intervention 3**: methotrexate: orally 7.5 - 15 mg/week in 3 divided doses Total duration: 90 days **Control Intervention 1**: palmoplantar psoriasis: variant of psoriasis in which only palms and soles are affected **Control Intervention 2**: psoriasis vulgaris: variant of psoriasis in which lesions appear on body skin
Outcomes	**At 90 days** • 75% reduction in PASI or modified PASI • 75% reduction in BSA • 75% reduction in psoriasis severity index. Timepoint: 90 days • DLQI
Notes	Starting date: 10 December 2013. Recruitment status: open to recruitment We sent an email to Prof. Shah (5 and 12 January 2017) without response

DRKS00000716

Methods	Randomised, active-controlled, parallel-group, simple blind Date of study: 3 June 2008 (starting date) Location: Germany
Participants	**Total sample size**: 50 **Inclusion criteria** • Aged 18 - 65 years • Clinical diagnosis of psoriasis for > 6 months • Plaque-type psoriasis (PASI > 10) • BSA > 10% **Exclusion criteria** • Contraindications for treatment with TNF-alpha inhibitors and FAEs • Women who are pregnant or who are breast-feeding. Women of childbearing potential must follow a medically recognised form of contraception • 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 • TB anamnesis, infections (Hepatitis B, C, HIV) • History of lymphoproliferative disorders, malignancies, demyelinating disease, severe heart failure

DRKS00000716 *(Continued)*

	• 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 • 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
Interventions	**Intervention 1**: adalimumab (Humira), SC, 80 mg initially and 40 mg eow for 24 weeks **Intervention 2**: etanercept (Enbrel), SC, 50 mg twice a week for 12 weeks and 25 mg twice a week subsequently for another 12 weeks **Intervention 3**: FAEs (Fumaderm), orally, up to 6 doses/day for 24 weeks
Outcomes	**Week 8:** • PASI: clinical score of skin lesions • DLQI • skin biopsy: immunohistology • T cells in peripheral blood **Week 24:** • PASI: clinical score of skin lesions • DLQI • skin biopsy: immunohistology • T cells in peripheral blood
Notes	Starting date: 03 June 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

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	**Intervention** Recombinant human tumour necrosis factor receptor (50 mg/week) **Control intervention** Methotrexate (7.5 mg/week)
Outcomes	**At 12 weeks** Proportion of PASI 50, PASI 75, PASI 90
Notes	**Abstract in Journal of Clinical Dermatology 2007 (730-2)**

Han 2007 *(Continued)*

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)

Objective: 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). **Methods**: 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. **Results**: 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. **Conclusion**: 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" manu41.magtech.com.cn/Jwk_cmazp/EN/abstract/abstract11844.shtml#), 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 we could not find the authors' emails

Hodge 2017 PsOsim

Methods	RCT, active-controlled, double-blind study Date of study: May 2016 - Location: Multicentre Phase 4
Participants	**Randomised**: 545 participants

Hodge 2017 PsOsim *(Continued)*

	Key inclusion criteria • Men or women PsO diagnosis for 6 months • Active disease: PASI ≥ 12 • Physician's Static Global Assessment (PSGA) score ≥ 3 (based on a scale of 0 - 5) • Body Surface Area (BSA) involved with PsO ≥ 10% **Key exclusion criteria** • Forms of psoriasis other than PsO drug-induced psoriasis • Positive QuantiFERON-tuberculosis (TB) Gold Test Presence of significant comorbid conditions • Chemistry and haematology values outside protocol-specified range • Major systemic infections
Interventions	**Intervention** Adalimumab (Humira) 40 mg 2 doses at week 0/Day 0, then 1 dose every 2 weeks starting at Week 1 until week 15. At week 16 participants initially randomised to adalimumab will be reassigned (1:1) to CHS-1420 or continue adalimumab treatment, 1 dose every 2 weeks for weeks 17 - 23. At week 24 participants will switch to CHS-1420 open-label until study end **Control interventions** CHS-1420 40mg 2 doses at week 0/Day 0 then 1 dose every 2 weeks starting at week 1 for 23 weeks. At week 24 participants will continue on to CHS-1420 open label until study end
Outcomes	**At week 12,** **Primary outcome** • Difference between the percentage of participants in each treatment group achieving a 75% improvement in PASI-75 **Secondary outcomes** • Not stated
Notes	On ClinicalTrials.gov, no results submitted Waiting for the publication to contact the main author

Krishna 2016

Methods	RCT, active-controlled, double-blind trial, phase 3 Date of study: November 2013 - January 2015 Location: India
Participants	**Randomised**: 50 participants **Inclusion criteria** • Age range 18 - 65 years • Both sexes • Severe plaque-type psoriasis (BSA > 10% or PASI > 12) **Exclusion criteria** • Pregnancy

Krishna 2016 *(Continued)*

- Lactation
- Malignancy or immunosuppression including HIV
- Liver disease
- Renal disease
- Non-compliant
- Psychiatric illness
- Hypersensitivity to methotrexate in the past

Interventions	**Intervention** Methotrexate 10 mg/week **Control intervention** Methotrexate 25 mg/week
Outcomes	**At week 12** **Primary outcome** • Improvement in health-related quality of life **Secondary outcomes** • Comparison of improvement in health-related quality of life between Group A and Group B
Notes	On ClinicalTrials.gov Estimated Enrolment: 50 Study start date: November 2013 Estimated primary completion date: January 2015 (final data collection date for primary outcome measure) Emails sent to Prof. Krishna (5 and 12 January 2017)

Mrowietz 2005

Methods	RCT, placebo-controlled, double-blind trial Date of study: not stated Setting: not stated
Participants	**Randomised**: 175 participants (characteristics not stated) **Inclusion criteria** • Not stated **Exclusion criteria** • Not stated **Dropouts and withdrawals** • Not stated
Interventions	**Intervention**

Mrowietz 2005 *(Continued)*

	A. Dimethyl fumarate (n = 105), orally, 240 mg, 3 times/day; 16 weeks **Control Intervention** B. Placebo (n = 70), orally, 2 capsules, 3 times/day; 16 weeks
Outcomes	Assessments at 16 weeks **Primary outcomes of the trial** • PASI **Secondary outcomes of the trial** • PASI 50 • PASI 75 • SKINDEX-29 • Side effects
Notes	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 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 Studies awaiting classification

NCT01088165

Methods	RCT, active-controlled, triple-blind trial Date of study: May 2010 - Setting: Austria
Participants	**Randomised**: 66 participants (characteristics not stated) **Inclusion criteria** • Chronic severe plaque type psoriasis (PASI < 10) requiring systemic treatment Non-response or contraindication to previous systemic and/or light treatment • PASI ≥ 10, BSA ≥ 10 • Age 18 - 80 years **Exclusion criteria** • Women of childbearing potential not taking contraceptive measures • Pregnant or breastfeeding women • Patients with a history or ongoing malignancy, chronic infections or autoimmune disease • Patients with severe impairment of their general health • Patients who are unable to understand or comply with the study protocol

NCT01088165 *(Continued)*

	Dropouts and withdrawals • Not stated
Interventions	**Intervention** A. Adalimumab treatment arm: day 1: 2 x 40 mg SC, day 8: 40 mg SC., thereafter 40 mg SC at bi-weekly intervals **Control Intervention** B. Fumaric acid esters treatment group C. Narrow-band UVB radiation
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • The influence of adalimumab treatment in comparison to treatment with fumaric acid esters on the functional integrity of the endothelium will be monitored by flow-mediated dilatation (FMD) **Secondary outcomes of the trial** • The measurement of carotid artery intima-media thickness (IMT) by ultrasound will serve as a morphological substrate for evaluating the potential effect of adalimumab on signs of atherosclerosis within the vessel wall (Time frame: 3 and 6 months) • Influence of adalimumab in comparison to fumaric acid esters on biochemical cardiovascular and metabolic risk factors (Time frame: 3 and 6 months)
Notes	Funding, quote (ClinicalTrials.gov) by Medical University of Vienna We sent an email to Prof. Holzer to be sure this trial is still ongoing (3 June 2019) without response

NCT02559622

Methods	RCT, placebo-controlled, double-blind study Date of study: September 2015 - Location: Germany Phase 4
Participants	**Randomised**: 151 participants **Key inclusion criteria** • Chronic moderate-severe plaque type psoriasis for ≥ 6 months prior to randomisation with a PASI score ≥ 10 at randomisation • 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 **Key exclusion criteria** • Forms of psoriasis other than chronic plaque-type (e.g. pustular, erythrodermic and guttata psoriasis) at screening or randomisation

NCT02559622 *(Continued)*

	• Ongoing use of prohibited psoriasis and non-psoriasis treatments. Washout periods have to be adhered to
Interventions	**Intervention** Secukinumab 300 (300 mg every week for 4 weeks followed by 300 mg secukinumab every 4 weeks until week 48) (n = 48) **Control interventions** Secukinumab 150 (150 mg every week for 4 weeks followed by 300 mg secukinumab every 4 weeks until week 48) (n = 54) Placebo (n = 49)
Outcomes	**At week 12,** **Primary outcome** • Flow Mediated Dilation (FMD) **Secondary outcomes** • Aortic Augmentation Index at heart rate of 75 • Pulse wave velocity • Biomarkers • PASI • IGA
Notes	On ClinicalTrials.gov, results submitted without PASI or IGA outcomes No principal investigator on ClinicalTrials.gov; waiting for the publication to contact the main author

NCT02655705

Methods	RCT, placebo-controlled, open-label study Date of study: September 2015 - Location: Korea Phase 4
Participants	**Randomised**: 34 participants **Inclusion criteria** • Present with chronic plaque psoriasis based on a clinical diagnosis • Have > 5% BSA involvement at screening • Are a candidate for systemic therapy • Are men and women ≥18 years • Have given written informed consent approved by the Institutional Review Board **Exclusion criteria** • Have predominant pattern of pustular, erythrodermic, or guttate forms of psoriasis • Have had any of the systemic non-biologic psoriasis therapy (including neotigason, ciclosporin, and methotrexate) within 4 weeks prior to baseline

NCT02655705 *(Continued)*

	• Have had etanercept within 4 weeks prior to baseline • Have had adalimumab and infliximab within 8 weeks prior to baseline • Have had ustekinumab within 16 weeks prior to baseline • Presence of significant hepatic or renal disorders • Have uncontrolled arterial hypertension • Are women who are lactating, breastfeeding or planning pregnancy • Have any other condition that precludes from following and completing the protocol
Interventions	**Intervention** Ciclosporin A (men 200 mg/day, women 150 mg/day for 16 weeks) **Control intervention** Methotrexate (initial dose 10 mg/week, increasing 2.5 mg every 2 weeks up to 15 mg/week)
Outcomes	**At week 16** **Primary outcome** • Change in PASI **Secondary outcome** • PASI 75, PASI 90 • AEs
Notes	Published articles without outcomes of interest Emails sent to Pr Sang Woong Youn, Seoul National University Hospital (3 June 2019)

Reich 2017

Methods	RCT, active-controlled, double-blind study Date of study: September 2016 Location: World-wide Phase 2
Participants	**Randomised**: 200 participants **Inclusion criteria** • Present with chronic plaque psoriasis based on an investigator-confirmed diagnosis of chronic psoriasis vulgaris for at least 6 months prior to baseline and meet the following criteria:plaque psoriasis involving ≥ 10% body surface area (BSA) and absolute PASI score ≥ 12 in affected skin at screening and baselines; PGA score of ≥ 3 at screening and baseline • Candidate for biologic treatment for psoriasis **Exclusion criteria** • Have a history or presence of cardiovascular, respiratory, hepatic, gastrointestinal, endocrine, haematological, neurological, or neuropsychiatric disorders or any other serious and/or unstable illness that, in the opinion of the investigator, could constitute a risk when taking investigational product or could interfere with the interpretation of data • Breastfeeding or nursing (lactating) women • Have had serious, opportunistic, or chronic/recurring infection within 6 months prior to screening

Reich 2017 *(Continued)*

	• Have received live vaccine(s) (included attenuated live vaccines) within 1 month of screening or intend to during the study • Have any other skin conditions (excluding psoriasis) that would affect interpretation of the results • Have received systemic nonbiologic psoriasis therapy or phototherapy within 28 days prior to baseline • Have received topical psoriasis treatment within 14 days prior to baseline • Have received anti-tumour necrosis factor (TNF) biologics, or anti-interleukin (IL)-17 targeting biologics within 8 weeks prior to baseline • Have previous exposure to any biologic therapy targeting IL-23 (including ustekinumab), either licensed or investigational (previous briakinumab use is permitted)
Interventions	**Intervention** A. Mirikizumab, dose 1 **Control interventions** B. Mirikizumab, dose 2 C. Mirikizumab, dose 3 D. Placebo
Outcomes	**At week 16** **Primary outcome** PASI 90 **Secondary outcome** PASI 100, PASI 75, PASI 50 PGA 0/1 DLQI
Notes	On ClinicalTrials.gov, no results submitted. Will be included in the living network meta-analysis

AEs: adverse effects; **BMI**: body mass index; **BSA**: body surface area;**DLQI**: Dermatology Life Quality Index; **ECG**: electrocardiogram; **eow**: 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

Study name	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	**Randomised**: 350 participants

ChiCTR-INR-16009710 *(Continued)*

	Inclusion criteria • Men and women aged 18 - 75 years • Mild psoriasis vulgaris defined by the following criteria: BSA > 10% at screening and baseline and PASI > 7 at screening and baseline • Provide written informed consent and willing and able to comply with all aspects of the protocol **Main exclusion criteria** • Other types of psoriasis than mild psoriasis vulgaris e.g. guttate, pustular, erythrodermic, etc • Active infectious disease, which was hard to control • History of hepatitis B or hepatitis C, and advanced HIV infection • Laboratory data such as alanine aminotransferase (ALT), aspartate aminotransferase (AST) and blood lipid profile was 1.5 times higher than the normal limits • History of severe systemic disease or cancer • Pregnant or lactating women or planning to get pregnant in 2 years • Allergic to methotrexate and acitretin - any ingredient
Interventions	**Intervention group** A. Acitretin plus methotrexate group (n = 100) **Control intervention group** 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	**Time point outcome measured**: not stated **Primary outcome** • PASI **Secondary outcome** • DLQI
Starting date	January 2016
Contact information	Prof. Xia Yumin; xiayumin1202@163.com
Notes	Ongoing study

CTRI/2016/10/007345

Study name	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

CTRI/2016/10/007345 *(Continued)*

Participants	**Randomised**: 231 participants **Inclusion criteria** • Men and women, aged 18 - 65 years • Moderate-severe plaque psoriasis for ≥ 6 months who are candidates for phototherapy or systemic therapy **Exclusion criteria** • Pregnant or lactating women • Known hypersensitivity to the study drug or any of the excipient • History of current erythrodermic, guttate or pustular psoriasis • Psoriasis flare or rebound within 4 weeks prior to screening • Used topical therapy within 2 weeks of randomisation or systemic therapy or phototherapy (i.e. UVB, PUVA) for psoriasis within 28 days of randomisation • Used biological therapy for psoriasis within 6 months of randomisation • 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 • Evidence of skin conditions that would interfere with clinical assessments in the opinion of the investigator • Active substance abuse or a history of substance abuse within 6 months prior to screening • Bacterial infections requiring treatment with oral or injectable antibiotics, or significant viral or fungal infections • 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
Interventions	**Intervention** Apremilast 30 mg tablets: administered 1 tablet twice daily for 16 weeks **Control intervention** Placebo tablets: administered 1 tablet twice daily for 16 weeks
Outcomes	**At week 16** **Primary outcome** • Proportion of participants achieving PASI 75 responses **Secondary outcomes** • Proportion of participants achieving PGA score of clear (0) or almost clear (1) at 16 weeks • Proportion of participants achieving PASI 50 at 16 weeks • Proportion of participants achieving PASI 90 at 16 weeks • Proportion of participants who have taken rescue medication during the treatment period at 16 weeks
Starting date	20 October 2016
Contact information	Dr Piyush Agarwal, DrPiyush.Agarwal@glenmarkpharma.com
Notes	Ongoing study Last refreshed in April 2019

EUCTR2013-004918-18-NL

Study name	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	**Randomised**: number of participants not stated **Inclusion criteria** • Diagnosis of moderate-severe plaque psoriasis (PASI = 8 at time of screening) • Candidate for the treatment with biologic drugs according to the pertaining guidelines • Willing and able to use an adequate contraceptive during the study (all men and pre-menopausal women) • Adalimumab therapy will be started for the treatment of psoriasis • Signed informed consent **Exclusion criteria** • History of significant methotrexate or adalimumab toxicity, intolerability or contraindication • Prior treatment with adalimumab • Age < 18 years • Pregnant and nursing women • Other immunosuppressive medication (prednisone, mycophenolate mofetil (e.g. Cellcept), ciclosporin (e.g. Neoral), sirolimus (Rapamune), systemic tacrolimus (e.g. Prograft)
Interventions	**Intervention** Adalimumab with methotrexate **Control intervention** Adalimumab monotherapy Dosage and frequency of adalimumab and methotrexate: not stated
Outcomes	**Primary end point(s)** • Drug survival at 1 year • Drug survival by efficacy • Drug survival by adverse events **Timepoint(s) of evaluation of this end point: week 49** **Secondary end point(s)** • 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 • Change in patient global assessment and IGA • Average adalimumab serum trough concentrations and titers • Change in impact on QoL (Skindex 29 and DLQI) • Treatment satisfaction (measured by Treatment Satisfaction Questionnaire for Medication) • Occurrence of (serious) AEs;

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

	• 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) Time point(s) of evaluation of this end point: week 13, 25, 37 and 49
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

NCT01558310

Study name	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	**Randomised**: 30 participants **Inclusion criteria** • Capable of giving informed consent and the consent must be obtained prior to any study- related procedures • ≥ 18 years at the time of consent; may be male or female • Diagnosis of plaque psoriasis ≥ 6 months prior to administration of study agent • Presence of moderate or severe psoriasis on the body other than the scalp • ≥ 30% of scalp affected with erythema, induration and desquamation and s-PGA score ≥ 4 • Candidates for phototherapy or systemic treatment of psoriasis • 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 sterilisation) 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 • Be able to adhere to protocol requirements and study visit schedule • Must agree not to receive a live virus or live bacterial vaccination during the trial and 12 months after last study injection

NCT01558310 *(Continued)*

- Must agree not to receive a BCG vaccination during the trial and up to 12 months after the last injection
- Must avoid prolonged sun exposure and avoid use of tanning booths or other ultraviolet light sources during the study
- Considered eligible according to the following TB screening criteria.
  * 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.
  * Have no signs or symptoms suggestive of active TB upon medical history or physical examination, or both
  * Within 6 weeks prior to the first administration of study agent, have a negative QuantiFERON-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:
  * Haemoglobin > 10g/dL
  * White Blood Cells > 3.5 x 10^9/L
  * Neutrophils > 1.5 x 10^9/L
  * Platelets > 100 X10^9/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 D3 and analogues, psoralens, sulfasalazine, hydroxyurea, or fumaric acid derivatives) within 4 weeks of administration of study agent
- Have used topical mediations/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

NCT01558310 *(Continued)*

- 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
- Have a history of latent or active granulomatous infection, including histoplasmosis or coccidioidomycosis, prior to screening
- Have persistently indeterminate (indeterminate on repeat sampling) QuantiFERON-TB Gold test results
- Have had a Bacille Calmette-Guérin (BCG) vaccination within 12 months of screening
- 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
- Have had a non-tuberculous mycobacterial infection or opportunistic infection (e.g. cytomegalovirus, pneumocystosis, aspergillosis) within 6 months prior to screening
- Known to be infected with HIV, hepatitis B, or hepatitis C
- Have current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, haematological, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease
- Have a transplanted organ
- Have a known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and /or splenomegaly
- 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)
- 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 (< 2 weeks) course of oral corticosteroids for asthma within the previous year
- Have undergone allergy immunotherapy previously for prevention of anaphylactic reactions
- Have shown a previous immediate hypersensitivity response, including anaphylaxis, to an immunoglobulin product (e.g. plasma-derived or recombinant monoclonal antibody).
- Be known to have had a substance abuse (drug or alcohol) problem within the previous 12 months
- Be participating in another trial using an investigational agent or procedure during participation in the trial
- Use of tar shampoos within 14 days of first dose of study drug
- Use of over-the-counter shampoos for scalp psoriasis will not be allowed during study
- Use of topical corticosteroids or other topical agents for the treatment of psoriasis on the scalp will not be allowed during the study

Interventions	**Intervention** 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) **Control intervention** Placebo
Outcomes	**At week 12,** **Primary outcome** • Scalp-specific PGA

NCT01558310 *(Continued)*

	Secondary outcomes • Not stated
Starting date	August 2012
Contact information	Paul Steven Yamauchi, MD, PhD
Notes	On ClinicalTrials.govEstimated 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 you 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

NCT02187172

Study name	Vascular Inflammation in Psoriasis-Ustekinumab (VIP-U)
Methods	RCT, placebo-controlled, double-blind trial Date of study: July 2014 - Location: University of Pennsylvania, USA Phase 4
Participants	**Randomised**: 43 participants **Inclusion criteria** • Men and women 18 years of age and older • Clinical diagnosis of psoriasis for at least 6 months as determined by patient interview of his/her medical history and confirmation of diagnosis through physical examination by Investigator. • Stable plaque psoriasis for at least 2 months before screening and at baseline (week 0) as determined by patient interview of his/her medical history • Moderate-to-severe psoriasis defined by ≥ 10 percent BSA involvement at the baseline (week 0) visit • PASI score of ≥ 12 at the baseline (week 0) visit • Patient is a candidate for systemic therapy and has active psoriasis despite prior treatment with topical agents • Previous adverse event following exposure to an IL-12/IL-23 antagonist that led to discontinuation of therapy and contraindicates future treatment • Previous lack of response to an IL-12/IL-23 antagonist that led to discontinuation of therapy • Diagnosis of erythrodermic psoriasis, generalised or localised pustular psoriasis, medication-induced or medication-exacerbated psoriasis, or new onset guttate psoriasis • Diagnosis of other active skin diseases or skin infections (bacterial, fungal, or viral) that may interfere with evaluation of psoriasis

NCT02187172 *(Continued)*

	• Cannot avoid UVB phototherapy or Excimer laser for at least 14 days prior to the baseline (week 0) visit and during the study • Cannot avoid psoralen-UVA phototherapy for at least 30 days prior to the baseline (week 0) visit and during the study • Cannot discontinue systemic therapies for the treatment of psoriasis, or systemic therapies known to improve psoriasis
Interventions	**Intervention** A. Ustekinumab (Stelara) subcutaneous injection 45 mg (if person's weight is 100 kg or less) or 90 mg (if person's weight is greater than 100 kg) at day 0 and week 4 followed by every 12-week dosing thereafter **Control intervention** B. Placebo
Outcomes	**At week 52** **Primary outcome** • Vascular Inflammation and biomarkers (Time frame: Baseline - End of Study Visit (week 52 or Week 64)) **Secondary outcomes** • Change in psoriasis activity (Time frame: baseline, week 4, 8, 12, and then every 12 weeks throughout the study) • Change in psoriasis activity throughout the study • Change in participant-reported outcomes (Time frame: baseline, week 4, 8, 12, and then every 12 weeks throughout the study) • Change in participant-reported dietary and physical activity assessments (i.e. MEDFICTS and IPAQ) • Number of participants with adverse events [Time frame: Per patient report throughout the study)
Starting date	May 2014
Contact information	Joel M Gelfand, MD, MSCE
Notes	Actual study completion date: 11 September 2018 Ongoing study

NCT02258282

Study name	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	**Randomised**: 80 participants **Inclusion criteria**

NCT02258282 *(Continued)*

- Has plaque psoriasis and has shown an unsatisfactory response to traditional disease-modifying antirheumatic drugs (DMARDs)
- 18 - 75 years old
- PGA ≥ 3 at Day 0
- BSA ≥ 3% at Day 0
- Has psoriasis severe enough to be eligible for systemic therapy
- Willing to use an effective method of contraception for ≥ 30 days before day 0 and until ≥ 1 month after the last drug administration
- Capable of giving informed consent
- Normal or non-clinically significant chest X-ray within 6 months prior to day 0
- Negative Purified Protein Derivative (PPD) or Quantiferon TB Gold test within 90 days prior to day 0
- Women of childbearing potential have a negative serum pregnancy test
- Able to start etanercept per the approved product monograph

Exclusion criteria

- Used topical steroids, topical tar preparations, or other anti-psoriatic preparations within the 2 weeks prior to day 0 or during the study period
- Presence of erythrodermic, pustular or guttate psoriasis
- Significant infections within the 30 days prior to day 0
- Received investigational drugs within the 4 weeks prior to screening or during the study period
- 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
- Received systemic antibiotics within the 4 weeks prior to day 0
- Treated with UV light therapy (UVB, nbUVB) within the 2 weeks prior to day 0 or during the study period
- Used infliximab within 14 days of day 0 or during the study period
- Used other biologic agents for the treatment of psoriasis besides etanercept 8 weeks prior to day 0 or during the study period
- Had an allergic reaction to infliximab
- 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
- 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 or transient ischaemic attack within 3 months of screening visit; unstable angina pectoris
- Uncontrolled hypertension, oxygen-dependent severe pulmonary disease
- Known sero-positivity for HIV virus or history of any other immunosuppressive disease
- Active or chronic Hepatitis B or C
- Any mycobacterial disease, patient with a chest X-ray suggestive of TB or taking anti-TB medication
- Known hypersensitivity to etanercept or one of its components
- Received a live attenuated vaccine within the 12 weeks prior to day 0 or plans to receive 1 during the study
- Current pregnancy or lactation

Interventions	**Intervention** Etanercept (participants under the treatment of 50 mg etanercept) **Control intervention** Placebo
Outcomes	**At week 24** **Primary outcome**

NCT02258282 *(Continued)*

	• PGA **Secondary outcomes** • PASI • BSA
Starting date	May 2014
Contact information	Yang Min, Ph.D, Chengdu PLA General Hospital
Notes	On ClinicalTrials.gov Estimated primary completion date: December 2016 Ongoing study

NCT02313922

Study name	Optimizing psoriasis treatment of etanercept combined methotrexate
Methods	RCT, placebo-controlled, double-blind trial Date of study: December 2014 - Location: China Phase 4
Participants	**Randomised**: 488 participants **Inclusion criteria** • Adults of both sexes, ≥ 18 years of age • Stable plaque psoriasis for ≥ 6 months, psoriasis involving ≥ 10% BSA, minimal PASI of 10 at screening • Previously received phototherapy or systemic psoriasis therapy at least once or candidates for such therapy in the opinion of the investigator **Exclusion criteria** • Patients with guttate, erythrodermic, or pustular psoriasis at the time of screening • Recent infection or opportunistic infections, active TB, hepatitis B and so on • Liver and kidney dysfunction • 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 • History of significant methotrexate toxicity or total cumulative methotrexate exposure > 1000 mg (unless grade IIIb liver injury has not occurred) • 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 • 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

NCT02313922 *(Continued)*

	• 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
Interventions	**Intervention** Methotrexate (dosage not stated) **Control intervention** Co-intervention: etanercept (dosage not stated)
Outcomes	**At week 24** **Primary outcome** • PASI 75 **Secondary outcomes** • PASI 90 • DLQI • AEs
Starting date	November 2014
Contact information	Min Zheng, Director of Dermatology, Zhejiang University
Notes	On ClinicalTrials.gov Primary completion date: August 2018 Still ongoing

NCT02325219

Study name	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	**Randomised**: 226 participants **Inclusion criteria** • Have a diagnosis of plaque-type psoriasis with or without psoriatic arthritis for ≥ 6 months before screening • Have a PASI ≥ 12 at screening and at baseline • Have an IGA ≥ 3 at screening and at baseline • BSA ≥ 10% at screening and at baseline • Be a candidate for phototherapy or systemic treatment for psoriasis (either naive or history of previous treatment)

NCT02325219 *(Continued)*

	Exclusion criteria • History of or current signs or symptoms of severe, progressive, or uncontrolled cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, haematologic, psychiatric, or metabolic disturbances • Unstable cardiovascular disease, defined as a recent clinical deterioration (example, unstable angina, atrial fibrillation) in the last 3 months or a cardiac hospitalisation within the last 3 months before screening • Currently has a malignancy or has a history of malignancy within 5 years before screening (with the exception of a non-melanoma skin cancer that has been adequately treated with no evidence of recurrence for ≥ 3 months before the first study drug administration or cervical carcinoma in situ that has been treated with no evidence of recurrence for ≥ 3 months before screening • 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 • 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 non-remitting cystitis), fungal infection (mucocutaneous candidiasis), or open, draining, or infected skin wounds or ulcers
Interventions	**Intervention** CNTO 1959 50 mg (50 mg at weeks 0, 4 and then every 8 weeks thereafter) **Control interventions** CTNO 1959 100 mg (100 mg at weeks 0, 4 and then every 8 weeks thereafter) Placebo
Outcomes	**At week 16** **Primary composite outcome** • IGA 0/1 • PASI 90 **Secondary outcomes** • PASI 75 • DLQI • AEs
Starting date	Study start date: December 2014 Study final completion date: 8 February 2019 Ongoing study
Contact information	Janssen Pharmaceutical K.K.
Notes	Ongoing study

NCT02690701

Study name	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

NCT02690701 *(Continued)*

	Date of study: February 2016 - Location: USA Phase 4
Participants	**Randomised**: 84 participants **Inclusion criteria** • Men and women ≥ 18 years with moderate-severe plaque psoriasis **Exclusion criteria** • Forms of psoriasis other than chronic plaque psoriasis • Previous exposure to IL-17A or IL-17 receptor targeting agents • Other active or ongoing disease that may interfere with evaluation of psoriasis or places the participant at unacceptable risk
Interventions	**Intervention** 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) **Control intervention** Placebo
Outcomes	**At week 12** **Primary outcome** • Aortic vascular inflammation as measured by FDG-PET/CT **Secondary outcomes** • PASI 75 • PASI 90 • PASI 100 • IGA 0/1 • DLQI
Starting date	Study start date: February 2016 Study completion date: March 2018 Results submitted: April 2019
Contact information	Novartis Pharmaceuticals, 1-888-669-6682
Notes	Ongoing study

NCT02701205

Study name	Safety and efficacy study of etanercept (Qiangke®) to treat moderate to severe plaque psoriasis
Methods	RCT, placebo and active-controlled, double-blind study Date of study: January 2015 -

NCT02701205 *(Continued)*

	Location: China
Participants	**Randomised**: 216 participants **Inclusion criteria** • Men or women, age 18 - 65, Asian • Freely provides both verbal and written informed consent • Consent to use effective contraception during the trial period • Participant had a clinical diagnosis of psoriasis for at least 6 months, and had moderate-to-severe plaque psoriasis • Participant must have a PASI score ≥ 12 at the baseline visit and BSA involvement ≥ 10% at the baseline visit • Participant has previous exposure to systemic psoriasis therapy or phototherapy, but not ideal • Meet the following criteria for tuberculosis screening: A. has no prior history of occult or active tuberculosis. B. No signs or symptoms of active tuberculosis in history and/or physical examination. C. in the first 6 weeks of the trial, tuberculosis screening test meet the requirements of the trial • Laboratory screening results: Haemoglobin ≥ 110g/L; white blood cell ≥ 4 * 10^9/L. Neutrophil ≥ 1.5 * 10^9/L. Platelet ≥ 100 * 10^9/L. Serum alanine aminotransferase and/or aspartate aminotransferase not > 1.5 times of the upper limit of normal. Serum creatinine does not exceed 1.5 mg/dL (International units: ≤133 mol/L) • During the first 2 weeks of the study, participant must stop adjuvant therapy including traditional Chinese medicine and acupuncture • Hepatitis B (HBV) screening in compliance with the requirements of this test • Weight ≥ 60 Kg **Exclusion criteria** • Pustular, erythrodermic, and/or guttate forms of psoriasis • Participant was treated with TNF antagonists within 6 weeks prior to the baseline visit • Participant was treated with other biological agents within 6 weeks prior to the baseline visit • Participant was treated with phototherapy or systemic antipsoriatic treatment (such as: methotrexate, acitretin, cyclosporine, Total Glucosides of Paeony (TGP, treatment of psoriasis-related Chinese medicines, etc.) and systemic corticosteroid treatment within 4 weeks prior to the baseline visit • Participant was treated with topical corticosteroid therapy, vitamin A or D analogue or anthralin within 2 weeks prior to the baseline visit • Participant received any drug whose metabolism was less than 7 half-lives before the baseline visit • Participant plans to be pregnant or breast-feeding or become a father during the study • A history of occult or active granuloma infections, including histoplasmosis, coccidioidomycosis • Participant has suffered from non-mycobacterium tuberculosis infection or opportunistic infections (such as cytomegalovirus sense of dyeing, Pneumocystis carinii pneumonia, aspergillosis) within 6 weeks prior to the baseline visit • A close-contact history of active tuberculosis patients or tuberculosis screening results do not meet the requirements • Participant has suffered from severe infection (for example hepatitis, pneumonia, acute pyelonephritis or sepsis), or participant uses intravenous antibiotics now because of infection within 6 weeks prior to the baseline visit • Participant has suffered from chronic or recurrent infections now or earlier, including (but not limited to) chronic kidney infection disease and chronic chest infectious diseases (such as bronchial dilation), sinusitis, recurrent urinary tract infections (such as recurrent pyelonephritis and chronic non-remission cystitis), open, overflow liquid or infection of skin wound or ulcer • HIV antibody-positive • Hepatitis B virus (HBV) screening results do not meet the requirements • Hepatitis C virus (HCV) antibody-positive • Participant has demyelinating diseases such as multiple sclerosis or optic neuritis

NCT02701205 *(Continued)*

	• A history of congestive heart failure, including asymptomatic congestive heart failure • A history or sign of a lymph node hyperplasia, including lymphoma or suggestive of a possible sign such as the size and location of an enlarged lymph node or a history of clinically significant enlargement of the spleen • Participant has symptoms or signs of severe, progressive or uncontrolled kidney, liver, blood, gastrointestinal, endocrine, lung, heart, nerve, mental or brain diseases • A history of malignancy • Joint prosthesis has not yet been removed or replaced
Interventions	**Intervention** A. Recombinant Human TNF Receptor-Ig Fusion Protein for Injection 50 mg twice a week by subcutaneous injection for 12 weeks. At the end of the first 12 weeks, all subjects will be treated with Recombinant Human TNF Receptor-Ig Fusion Protein for Injection 50 mg once a week for an additional 12 weeks **Control intervention** B. Recombinant Human TNF Receptor-Ig Fusion Protein for Injection 25mg twice a week by subcutaneous injection for 12 weeks, At the end of the first 12 weeks, all participants will be treated with Recombinant Human TNF Receptor-Ig Fusion Protein for Injection 50 mg once a week for an additional 12 weeks C. Placebo
Outcomes	**At week 12** **Primary outcome** • Percentage of participants achieving a PASI ≥ 75% reduction (PASI 75) response **Secondary outcomes** • Proportion of participants achieving PASI 90 and 50 (Time frame: week 12) • Proportion of participants achieving PASI 90, 50 and 75 (Time frame: week 24) • Physician's Global Assessment (PGA) (Time frame: week 12 and 24) • NAPSI (Time frame: week 12 and 24) • DLQI (Time frame: week 12 and 24) • PGA (Time frame: week 12 and 24) • Safety profile
Starting date	Study start date: February 2016 Estimated study completion date: December 2017
Contact information	Contact: Hongzhong Jin, M.D.; jinhongzhong@263.net
Notes	Ongoing study Email sent to Prof Hongzhong Jin

NCT02714322

Study name	MYL-1401A Efficacy and Safety Comparability Study to Humira®
Methods	RCT, active-controlled, double-blind study Date of study: June 2015 -

NCT02714322 *(Continued)*

	Location: Russia, Estonia, Hungary, Poland, Bulgaria

Participants	**Randomised**: 294 participants
	
	Inclusion criteria
	
	• Has signed the informed consent form
	• Is aged 18 to 75 years, inclusive, at time of screening
	• Has had moderate-to-severe chronic plaque psoriasis for at least 6 months
	• Has involved BSA ≥ 10%, PASI ≥ 12, and sPGA ≥ 3 (moderate) at screening and at baseline
	• Has had stable disease for at least 2 months (i.e. without significant changes as defined by the investigator)
	• Is a candidate for systemic therapy
	• Has had a previous failure, inadequate response, intolerance, or contraindication to at least 1 conventional antipsoriatic systemic therapy
	• Is naïve to adalimumab therapy, approved or investigational
	• For women of childbearing potential, a negative serum pregnancy test during screening and a negative urine pregnancy test at baseline
	
	Exclusion criteria
	
	• Diagnosed with erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, other skin conditions (e.g. eczema), or other systemic autoimmune disorder inflammatory disease at the time of the screening visit that would interfere with evaluations of the effect of the study treatment on psoriasis
	• Has used any of the following medications within specified time periods or will require their use during the study:
	  * Topical medications within 2 weeks before the end of the screening period oral psoralen with ultraviolet A (PUVA) phototherapy and/or ultraviolet B (UVB) phototherapy within 4 weeks before the end of the screening period;
	  * Nonbiologic systemic therapies within 4 weeks before the end of the screening period (e.g. cyclosporine, methotrexate, and acitretin);
	  * Any prior or concomitant adalimumab therapy, approved or investigational;
	  * Any other investigational agent within 90 days or 5 half-lives of screening (whichever is longer);
	  * Any systemic steroid in the 4 weeks before the end of the screening period
	  * Note: Low-potency topical corticosteroids applied to the palms, soles, face, and intertriginous areas are permitted during study participation
	• Has received live vaccines during the 4 weeks prior to screening or has the intention of receiving a live vaccine at any time during the study
	• Has a positive test for tuberculosis (TB) during screening or a known history of active or latent TB, except documented and complete adequate treatment of TB or initiation (> 1 month) of adequate prophylaxis of latent TB, with an isoniazid-based regimen. Patients with a positive purified protein derivative (PPD) and a history of Bacillus Calmette-Guérin vaccination are allowed with a negative Interferon-γ release assays (IGRA)Patients with a positive PPD test without a history of Bacillus Calmette-Guérin vaccination or those with a positive or indeterminate IGRA are allowed if they have all of the following: No symptoms or signs of active TB, including a negative chest x-ray within 3 months prior to the first dose of study treatment; Documented history of completion of adequate treatment of TB or initiation (> 1 month) of adequate prophylaxis of latent TB, with an isoniazid-based regimen prior to receiving study treatment in accordance with local recommendations
	• Underlying condition (including, but not limited to metabolic, haematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious, or gastrointestinal) which, in the opinion of the investigator, significantly immunocompromises the person and/or places them at unacceptable risk for receiving an immunomodulatory therapy
	• Has a planned surgical intervention during the duration of the study except those related to the underlying disease and which, in the opinion of the investigator, will not put the person at further risk or hinder their ability to maintain compliance with study treatment and the visit schedule

NCT02714322 *(Continued)*

- Has an active and serious infection or history of infections as follows:
  - Any active infection for which nonsystemic anti-infectives were used within 4 weeks prior to randomisation.
  - Requiring hospitalisation or systemic anti-infectives within 8 weeks prior to randomisation
  - Recurrent or chronic infections or other active infection that, in the opinion of the investigator, might cause this study to be detrimental to the person
  - Invasive fungal infection or mycobacterial infection
  - Opportunistic infections, such as listeriosis, legionellosis, or pneumocystis
- Is positive for HIV, hepatitis C virus antibody or hepatitis B surface antigen (HBsAg) or is positive for hepatitis B core antibody and negative for HBsAg at screening
- Has a history of clinically-significant haematological abnormalities, including cytopenias (e.g. thrombocytopenia, leukopenia)
- Has severe progressive or uncontrolled, clinically-significant disease that in the judgement of the investigator renders the person unsuitable for the study
- Has history of malignancy within 5 years, except adequately-treated cutaneous squamous or basal cell carcinoma, in situ cervical cancer or in situ breast ductal carcinoma
- Has active neurological disease such as multiple sclerosis, Guillain-Barré syndrome, optic neuritis, transverse myelitis, or history of neurologic symptoms suggestive of central nervous system demyelinating disease
- Has moderate-to-severe heart failure (New York Heart Association class III/IV)
- Has a history of hypersensitivity to the active substance or to any of the excipients of Humira® or MYL-1401A
- Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a woman after conception and until the termination of gestation
- Evidence of alcohol or drug abuse or dependency at the time of screening, for the 5 years prior to screening or during the study
- Is unable to follow study instructions and comply with the protocol in the opinion of the investigator

Interventions	**Intervention** A. Biological: MYL-1401A (Adalimumab) MYL-1401A initial dose of 80 mg administered SC, followed by 40 mg SC given every other week starting 1 week after the initial dose **Control intervention** B. Humira® (Adalimumab) Humira® initial dose of 80 mg administered SC, followed by 40 mg SC given every other week starting 1 week after the initial dose
Outcomes	**At week 12** **Primary outcome** • Per cent improvement in PASI from baseline **Secondary outcomes** Proportion of participants showing at least a 75% improvement in PASI (PASI 75 response rate) (Time frame: week 12)
Starting date	Study start date: June 2015 Study completion date: March 2017
Contact information	Abhijit Barve, MD; Mylan (Sponsor)
Notes	Ongoing study No principal investigator stated on ClinicalTrials.gov; waiting for results publication

NCT02748863

Study name	Study of secukinumab with 2 mL pre-filled syringes (ALLURE)
Methods	RCT, placebo-controlled, double-blind study Date of study: April 2016 - Location: world-wide Phase 4
Participants	**Randomised**: 210 participants **Inclusion criteria** People eligible for inclusion in this study must fulfil all of the following criteria: • 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 • Men or women of ≥ 18 years of age at the time of screening • Chronic plaque-type psoriasis present for ≥ 6 months and diagnosed before randomisation • Moderate-severe psoriasis as defined at randomisation by: PASI score of ≥ 12, IGA mod 2011 score of ≥ 3 (based on a scale of 0 - 4), and BSA affected by plaque-type psoriasis of ≥ 10% • 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 **Exclusion criteria** • Forms of psoriasis other than chronic plaque-type (e.g. pustular, erythrodermic and guttate psoriasis) at screening or randomisation • 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 randomisation or during the study period is also prohibited. • Previous exposure to secukinumab (AIN457) or any other biologic drug directly targeting IL-17 or the IL-17 receptor • 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 • 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 • 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) • History of hypersensitivity to any of study drug constituent
Interventions	**Intervention** Secukinumab 2 mL form (secukinumab 300 mg/2 mL + 2 x 1 mL placebo SC. at randomisation, weeks 1, 3, 4, thereafter 4-weekly until week 48) **Control interventions** Secukinumab 1 mL form (secukinumab 150 mg/1 mL x 2 + 2 mL placebo SC. at randomisation, weeks 1, 3, 4, thereafter 4-weekly until Week 48)

NCT02748863 *(Continued)*

	Placebo (2 mL + 2 x 1 mL placebo SC at randomisation, weeks 1, 3, and 4, thereafter 4-weekly until week 48)
Outcomes	**At week 12** **Primary composite outcome** • PASI 75 and IGA mod 2011 0 or 1 response **Secondary outcome** • PASI 90, 100 at weeks 12 and 52 • PASI 75 at week 52 • DLQI at weeks 12 and 52
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

NCT02762955

Study name	Comparative clinical trial of efficacy and safety of BCD-057 and Humira® in patients with moderate to severe plaque psoriasis (CALYPSO)
Methods	RCT, active-controlled, double-blind study Date of study: December 2016 - Location: Russia
Participants	**Randomised**: 344 participants **Inclusion criteria** • Patient had written informed consent • Age between 18 and 75 years. • Patient has moderate to severe plaque psoriasis with stable course of the disease for 6 months • Patient has had at least 1 course of phototherapy or systemic treatment for psoriasis or are candidates for such treatment in opinion of Investigator • BSA affected by psoriasis ≥ 10%, PASI score ≥ 12, sPGA score ≥ 3 • Patient has haemoglobin ≥ 10 g/dl, leucocytes count ≥ 3000/mcl, thrombocytes count ≥ 100,000/mcl, neutrophil count ≥ 2000/mcl, aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase exceed 2.5 or less times the upper limit of the normal range creatinine less than 176.8 µmol/l, no serologic or virologic markers of hepatitis B virus or hepatitis C virus, negative urine pregnancy test, no signs of tuberculosis (negative tuberculosis skin test or negative quantiferon test. Patients can be included in they have positive tuberculin test, have had Bacteria Calmette-Guerin (BCG) vaccination and have negative Diaskintest or negative quantiferon test. Patients can be included if they have positive tuberculin test, have not been vaccinated with BCG and also patients with positive or uncertain quantiferon test/Diaskintest if they have documented adequate prophylaxis of tuberculosis finished before first adalimumab injection AND have documented absence of contacts with patients who have active tuberculosis AND have no signs of tuberculosis on chest X-Ray that was performed during 3 months before randomisation) • Patients are able to perform all procedures planed by protocol

NCT02762955 *(Continued)*

- Patients are ready for contraception with reliable methods starting 2 weeks before entering the study, and up to 4 weeks after the last dose of study drug

Exclusion criteria

- Diagnosed with erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, or other skin conditions at the time of the screening visit (e.g. eczema) that would interfere with evaluations of the effect of investigational product on psoriasis
- Previous receipt of adalimumab, history of use of any other biological anti-tumour necrosis factor-alpha therapy. Prior use of 2 or more biologics for treatment of psoriasis
- Previous receipt of monoclonal antibodies if they were cancelled less than 12 weeks before screening
- Taking corticosteroids for up to 4 weeks before signing informed consent and during screening, disease-modifying drugs including methotrexate, sulfasalazin and cyclosporin for up to 4 weeks before signing informed consent, leflunomide, cyclophosphamide for up to 6 months before signing informed consent, phototherapy including selective phototherapy and photochemotherapy for up to 4 weeks before signing informed consent, live or attenuated vaccines for up to 8 weeks before signing informed consent
- Cannot discontinue systemic therapies and/or topical therapies for the treatment of psoriasis and cannot avoid phototherapySubject has a planned surgical intervention during the study or had surgical intervention less than 30 days prior to study.
- Has an active infection or history of infections as follows: any active infection for which systemic anti-infectives were used within 28 days prior to signing informed consent; a serious infection, defined as requiring hospitalisation or intravenous anti-infectives within 8 weeks prior to signing informed consent; recurrent or chronic infections or other active infection that, in the opinion of the Investigator, might cause this study to be detrimental to the person
- Has known history of HIV or any other severe immunodeficiency
- Hepatitis B surface antigen or Hepatitis B core antigen or Hepatitis C antibody positivity at screening
- History of tuberculosis.
- Positive results of rapid plasma reagin-test for T. pallidum at screening
- Active ongoing diseases other than psoriasis that might confound the evaluation of the benefit of treatment of adalimumab or can increase risk of adverse reactions: acute inflammatory diseases or exacerbation of chronic diseases other than psoriasis; stable ischaemic heart disease III-IV functional class, unstable angina or history of myocardial infarction less than 1 year before the signing of informed consent; moderate-to-severe heart failure (New York Heart Association [NYHA] class III/IV); severe resistant arterial hypertension, atopic bronchial asthma, history of angio-oedema, moderate-to-severe respiratory insufficiency, chronic obstructive lung disease 3 - 4 grade, decompensated diabetes mellitus, systemic autoimmune diseases, active neurologic disorders or their symptoms, other underlying condition (including, but not limited to metabolic, haematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal) which in the opinion of the investigator significantly immunocompromises the person and/or places them at unacceptable risk for receiving an immunomodulatory therapy.
- Has history of malignancy within 5 years EXCEPT treated and considered cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, OR in situ breast ductal carcinoma
- Has a history of hypersensitivity to the active substance or to any of the excipients of adalimumab or BCD-057 or other monoclonal antibodies
- Woman who is pregnant or breast-feeding or considering becoming pregnant during the study
- Has any mental illness, including severe depressive disorders and/or suicidal thoughts in history, which, in the opinion of the investigator, may create excessive risk to the person or to influence their ability to follow the protocol
- History of drug addiction, alcoholism
- Simultaneous participation in any other clinical trial, as well as former participation in other clinical trials within 3 months before this study initiation; previous participation in this study.

Interventions	**Intervention**

NCT02762955 *(Continued)*

	BCD-057 group includes participants with moderate-to-severe plaque psoriasis, who will receive BCD-057 SC at a dose 80 mg on week 0, then at a dose 40 mg on weeks 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21 and 23 **Control interventions** Humira® group includes participants with moderate-to-severe plaque psoriasis, who will receive Humira® SC at a dose 80 mg on week 0, then at a dose 40 mg on weeks 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23
Outcomes	**At week 16** **Primary outcome** • PASI 75 **Secondary outcome** • PASI improvement • PASI 50 PASI 90 PGA • SF-36 • DLQI • SAE AE
Starting date	Study start date: December 2016 Estimated study completion date: December 2018
Contact information	Study Chair: Roman Ivanov, PhD, JCS BIOCAD
Notes	Ongoing study

NCT02762994

Study name	International clinical trial to evaluate efficacy and safety of multiple subcutaneous injections of BCD-085 in various doses in patients with moderate to severe plaque psoriasis
Methods	RCT, placebo-controlled, double-blind study Date of study: June 2016 - Location: World-wide
Participants	**Randomised**: 120 participants **Inclusion criteria** • Written informed consent • Age between 18 and 65 years • Diagnosis of plaque psoriasis with stable course of the disease during last 6 months prior to enrolment in the study • Patient has had at least 1 course of phototherapy or systemic therapy of psoriasis or are candidates for such treatment • BSA affected by psoriasis ≥ 10%, PASI score ≥ 12, sPGA score ≥ 3 • If patient have had biologic therapy for at least 3 months, there were no positive results of such treatment or patient revealed intolerance to the drug. This therapy must be discontinued at least 12 weeks before enrolment in the study • Women have negative urine pregnancy test • Patient has no history of tuberculosis

NCT02762994 *(Continued)*

- Patients have negative results of Diaskintest
- Patient has no history of alcohol or drug abuse
- Patients are able to perform all procedures planed by protocol
- Patients are ready for contraception with reliable methods starting 2 weeks before entering the study, and up to 4 weeks after the last dose of study drug

Exclusion criteria

- Diagnosed with erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, or other skin conditions at the time of the screening visit (e.g. eczema) that would interfere with evaluations of the effect of investigational product on psoriasis
- Previous receipt of anti-interleukin 17 drugs or anti-interleukin 17 receptor drugs
- Prior use of 2 or more biologics to tumour necrosis factor alfa.
- Prior use of 2 or more biologics to other targets
- Previous receipt of monoclonal antibodies if they were cancelled less that in 12 weeks before signing informed consent
- Is taking corticosteroids for up to 4 weeks in a dose more than 10 mg (recalculated to prednisolone) before signing informed consent and during screening, or in a dose less than 10 mg (recalculated to prednisolone) if it was not stable
- Prior use of disease-modifying drugs including methotrexate, sulfasalazin and cyclosporin for up to 4 weeks before signing informed consent, if their dose was not stable for up to 4 weeks before signing informed consent and during screening
- Prior use of live or attenuated vaccines for up to 8 weeks before signing informed consent
- Prior use of phototherapy including selective phototherapy and photochemotherapy for up to 4 weeks before signing informed consent.

Interventions	**Intervention** **A.** BCD-085, 40 mg: Participant will receive 40 mg of BCD-085 subcutaneously at weeks 0, 1, 2, 4, 6, 8, 10 **Control interventions** **B.** BCD-085, 80 mg: Participant will receive 80 mg of BCD-085 subcutaneously at weeks 0, 1, 2, 4, 6, 8, 10 C. BCD-085, 120 mg: Participant will receive 80 mg of BCD-085 subcutaneously at weeks 0, 1, 2, 4, 6, 8, 10 D. Placebo
Outcomes	**At week 12** **Primary outcome** • PASI 75 **Secondary outcome** • PASI 50, PASI 90 • NAPSI • VAS pruritus • PGA • DLQI
Starting date	Study start date: June 2016 Estimated study completion date: May 2017

NCT02762994 *(Continued)*

Contact information	Study Chair: Roman Ivanov, PhD, JCS BIOCAD
Notes	Ongoing study

NCT02829424

Study name	Multicenter randomized double blind controlled-study to assess the potential of methotrexate versus placebo to improve and maintain response to anti TNF- alpha agents in adult patients with moderate to severe psoriasis (METHOBIO)
Methods	RCT, active-controlled, double-blind study Date of study: April 2016 Location: Fance Pahse 4
Participants	**Randomised**: 330 participants **Inclusion criteria** • Men or women aged 18 years or older • Patients with moderate-to-severe chronic plaque psoriasis with or without psoriatic arthritis AND who had started any first line of anti-TNF alpha according to the labelling of these drugs BEFORE the study (i.e. the study will be restricted to anti-TNF alpha-naïve patients (first course). Patients who have been previously treated with any other non-anti-TNFA alpha biopharmaceutical (ustekinumab or anti IL17- secukinumab, ixekizumab, brodalumab) as a first line of biotherapy for psoriasis could be enrolled) after a washout period of at least 5 half-lifetimes of the drug i.e. 16 weeks before inclusion • No significant anomalies from a blood sampling performed within 15 days before patient selection that could lead to MTX contraindication • Patients with an EARLY start of anti-TNF alpha, i.e. within the 7 days preceding the first study drug (methotrexate or placebo) administration • Men or women agreeing to use a reliable method of birth control during the study. Men agreeing to use a reliable method of birth control during the study i.e. preservative and for at least 6 months following the last dose of investigational product, the patient's partner treated by methotrexate must be notified of the teratogenic risk of methotrexate and should be under effective contraception throughout the study. Female patients are women of childbearing potential who are negatively tested for pregnancy and agree to use a reliable method of birth control (every month) or remain abstinent during the study and for at least 6 months following the last dose of investigational product, whichever is longer. Methods of contraception considered acceptable include oral contraceptives, contraceptive patch, intrauterine device, vaginal ring. • Negative serum b-Human Chorionic Gonadotrophin (B-HCG) test at screening, or women of non-childbearing potential, defined as: women who have had a surgical sterilisation (hysterectomy, bilateral oophorectomy, or tubal ligation) Or women ≥ 60 years of age or women ≥ 40 and < 60 years who have had a cessation of menses for ≥ 12 months and a follicle stimulating hormone (FSH) test confirming non-childbearing potential • Patients with previous failure or intolerance but no absolute contraindication to previous methotrexate medication for psoriasis can be enrolled, on the condition that methotrexate (whatever the dose) has been stopped at least 2 months before the inclusion • For patients who have never been previously treated with MTX, taking a test dose of MTX (2.5 mg to 5 mg) with normality of the laboratory tests conducted for 1 week to remove a reaction idiosyncrasy before inclusion in the protocol • Patients should be affiliated to the French Social Security system • Patients who have given written consent for the study

NCT02829424 *(Continued)*

Exclusion criteria

- Patients with isolated pustular, erythrodermic and or guttate forms of psoriasis
- Patients with prior use of any anti TNF alpha
- Patients who have known active liver disease (with the exception of a simple liver steatosis, transaminases and/or alkaline phosphatases > 2 ULM) or history of liver disease in the past 2 years, whatever the related diagnosis but which could interfere with MTX safety and according to the summary of the SmPC
- Intake of restricted medications (cf section VIII.5.) or other drugs considered likely to interfere with the safe conduct of the study, as assessed by the investigator and according to the Summary of the Product Characteristics (SmPC), including any drug intakes that could interfere with methotrexate metabolism or that could enhance liver and/or haematologic toxicity and according to the SmPC
- Patient with evidence or positive test for HIV, Hepatitis C virus, Hepatitis B virus (patients who are negative for hepatitis B surface antigen but positive for anti-hepatitis B anti body (HBsAb+ and HBcAb+) and negative for serum HBV DNA may participate in the study
- High alcohol intake, defined as more than 60 g of daily intake (approx daily intake of 0.5 l of wine or equivalent)
- Patients who have a known allergy or hypersensitivity to MTX
- Patients who have a known serious adverse event with MTX prior to the trial leading to MTX discontinuation in the past
- Presence of significant haematologic or renal disorder or abnormal laboratory values at screening that, in the opinion of the investigator is associated with an unacceptable risk to the patient to participate in the study
- Clinical laboratory test results at screening that are outside a normal reference rating for the population and are considered clinically significant, or/and have any of the following specific abnormalities: Total white blood cell count < 3G/L; Neutrophil count < 1.5 G/l; Lymphocytes count < 0.5G/l. Platelet count < 100 G/l; Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 times the upper limit of normal (ULM); Haemoglobin < 8.5 g/dL (85.0 g/L); Creatinine clearance < 40 ml/min (Cockcroft formula)
- For women: pregnant or breast feeding
- Patients who have an active or serious infection or history of infections (bacterial, viral, fungal or mycobacteria), requiring hospitalisation or intravenous anti-infectives infusion within 4 weeks prior to the baseline
- Patients who have primary or secondary active immunodeficiency
- Patients who had live vaccine administration within 4 weeks prior to baseline
- Patients who have any current or active cancer (with the exception of patient with successfully treated basal cell carcinoma or in situ cervix carcinoma)
- Patients who had history of malignancy within 5 years prior to the trial that could contraindicate the use of an immunosuppressant
- Patients who will not be available for protocol which requires study visits or procedures
- Patients who is not affiliated to the French Social Security system
- Patients unable to give informed consent and/or comply with all required study procedures

Interventions	**Intervention** **A.** Methotrexate (low dose) **Control interventions** **B.** Placebo **Co-intervention**: anti-TNF agent
Outcomes	**At week 24** **Primary outcome** Loss of PASI 75

NCT02829424 *(Continued)*

	Secondary outcome PASI 75 PASI 50 Maintenance of response rates proportion DLQI
Starting date	Study start date: April 2016 Estimated study completion date: April 2020
Contact information	Prof MA Richard: mrichard@ap-hm.fr
Notes	Ongoing study

NCT02982005

Study name	A study of KHK4827 (brodalumab) in subjects with moderate to severe psoriasis in Korea
Methods	RCT, placebo-controlled, double-blind study Date of study: December 2016 - Location: Korea Phase 3
Participants	**Randomised**: 60 participants **Inclusion criteria** • Stable moderate-severe plaque psoriasis for ≥ 6 months • Involved BSA ≥ 10%, PASI ≥ 12, and sPGA ≥ 3 at screening and at baseline **Exclusion criteria** • 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 • Scheduled to undergo a surgical intervention during the study period • Any active infection or history of infections as defined in the study protocol • Known history of Crohn's disease • Any other significant concurrent medical condition or laboratory abnormalities, as defined in the study protocol • Has not stopped using certain psoriasis therapies as defined in the study protocol • Previously used any anti-IL-17 biologic therapy • Pregnant or breastfeeding, or planning to become pregnant while enrolled in the study • 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 • 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 • Severe depression based on a total score of ≥ 15 on the Patient Health Questionnaire-8 (PHQ-8) at screening or at baseline

NCT02982005 *(Continued)*

	• Known history or evidence of a psychiatric disorder that, in the opinion of the investigator, would pose a risk to participant safety or interfere with the study evaluation, procedures or completion • Known history of alcohol and/or substance abuse within the last 12 months
Interventions	**Intervention** KHK4827 (SC, dosage not stated) **Control intervention** Placebo
Outcomes	**At week 12** **Primary composite outcome** • PPGA 0/1 • PASI 75 **Secondary outcomes** • PASI 90 at weeks 12 and 64 • PASI 75 at week 64 • NAPSI score at week 64 • Psoriasis scalp severity index (PSSI) score at week 64 • DLQI at week 64 • AEs
Starting date	Study start date: 1 December 2016 Study completion date: December 2018
Contact information	Kyowa Hakko Kirin Korea Co., Ltd
Notes	Ongoing study

NCT03025542

Study name	Study to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), and safety of bimekizumab in patients with chronic plaque psoriasis
Methods	RCT, placebo-controlled, double-blind study Date of study: December 2016 Location: USA, Australia, Canada Phase 2
Participants	**Randomised**: 49 participants **Inclusion criteria** • Men or women at least 18 years of age and ≤ 70 • Chronic plaque psoriasis for at least 6 months prior to screening • PASI ≥ 12 and BSA ≥ 10% and Investigator's Global Assessment (IGA) score ≥ 3 on a 5-point scale • Candidates for systemic psoriasis therapy and/or phototherapy and/or chemophototherapy • Women must be postmenopausal, permanently sterilised or, if of childbearing potential, must be willing to use a highly effective method of contraception up til 20 weeks after last administration

NCT03025542 *(Continued)*

	of study drug, and have a negative pregnancy test at Visit 1 (screening) and immediately prior to first dose • Men with a partner of childbearing potential must be willing to use a condom when sexually active, up til 20 weeks after the last administration of study medication (anticipated 5 half-lives) **Exclusion criteria** • Previously participating in a bimekizumab study • With erythrodermic, guttate, pustular form of psoriasis, or drug-induced psoriasis • History of chronic or recurrent infections, or a serious or life-threatening infection within the 6 months prior to the baseline visit (including herpes zoster) • High risk of infection in the Investigator's opinion • Current sign or symptom that may indicate an active infection • Concurrent acute or chronic viral hepatitis B or C or HIV infection • Live (includes attenuated) vaccination within the 8 weeks prior to baseline • With concurrent malignancy or history of malignancy during the past 5 years (except for specific malignant condition as defined in the protocol) • Primary immunosuppressive conditions • TB infection, high risk of acquiring TB infection, latent TB infection (LTBI), or current or history of NTMB infection • Laboratory abnormalities, as defined in the study protocol • Any condition which, in the Investigator's judgement, would make the person unsuitable for inclusion in the study • Exposure to more than 1 biological response modifier (limited to anti-TNF or IL-12/-23) or any biologic response modifier during the 3 months prior to the baseline visit • Have received previous treatment with any anti-IL-17 therapy for the treatment of psoriasis or psoriatic arthritis • With a diagnosis of inflammatory conditions other than psoriasis or psoriatic arthritis, including but not limited to rheumatoid arthritis, sarcoidosis, or systemic lupus erythematosus. People with a diagnosis of Crohn's disease or ulcerative colitis are allowed as long as they have no active symptomatic disease at screening or baseline • Taking psoriatic arthritis medications other than nonsteroidal anti-inflammatory drugs (NSAIDs) or analgesics
Interventions	**Intervention** A. Bimekizumab **Control interventions** B. Placebo
Outcomes	**At week 16** **Primary composite outcome** Change from baseline in PASI at week 28 (Time frame: week 28)
Starting date	Study start date: December 2016 Estimated study completion date: December 2017 Last update posted: December 2018
Contact information	UCB Cares +1 844 599 22 73 (UCB)
Notes	Ongoing study

NCT03051217

Study name	A Study to Test the Efficacy and Safety of Certolizumab Pegol in Japanese Subjects With Moderate to Severe Chronic Psoriasis
Methods	RCT, active/placebo-controlled, double-blind study Date of study: February 2017 Location: Japan Pahse 2/3
Participants	**Randomised**: 149 participants **Inclusion criteria** • Men or women, ≥ 20 years of age. • Institutional Review Board-approved written informed consent form is signed and dated by the participant • Other protocol-defined inclusion criteria may apply. For patients with moderate-to-severe chronic plaque psoriasis (PSO) • Chronic plaque psoriasis for at least 6 months. • Baseline PASI ≥ 12 and BSA affected by PSO ≥ 10% and PGA score of 3 or higher • Candidates for systemic PSO therapy and/or phototherapy and/or chemophototherapy. **Exclusion criteria** • Woman who is breastfeeding, pregnant, or plans to become pregnant during the study or within 5 months following last dose of study drug. Man who is planning a partner pregnancy during the study or within 5 months following the last dose of study drug • Has guttate psoriasis or drug-induced psoriasis. For people with moderate-to-severe plaque psoriasis, erythrodermic or pustular forms of psoriasis also are excluded • History of current, chronic, or recurrent infections of viral, bacterial, or fungal origin as described in the protocol. Also, those with a high risk of infection in the Investigator's opinion • History of a lymphoproliferative disorder including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease. • History of other malignancy or concurrent malignancy as described in the protocol • Class III or IV congestive heart failure • History of, or suspected, demyelinating disease of the central nervous system (e.g. multiple sclerosis or optic neuritis) • Any other condition which, in the Investigator's judgement, would make them unsuitable for inclusion in the study • Concurrent medication restrictions as described in the protocol • Known tuberculosis (TB) infection, at high risk of acquiring TB infection, or with untreated latent tuberculosis infection (LTBI) or current or history of nontuberculous mycobacterial (NTMB) infection. • Any protocol-defined clinically significant laboratory abnormalities at the screening • Other protocol-defined exclusion criteria may apply
Interventions	**Intervention** A. Certolizumab Pegol SC injection 400 mg at weeks 0, 2, 4, followed by Certolizumab Pegol SC injection 200 mg every 2 weeks (Q2W) with PBO administered to maintain the blind, starting at week 6 **Control interventions**

NCT03051217 *(Continued)*

	B.Certolizumab Pegol SC injection 400 mg every 2 weeks (Q2W). C. Placebo SC injection every 2 weeks (Q2W)
Outcomes	**At week 16** **Primary outcome** PASI 75 **Secondary outcome** PGA 0/1 PASI 90 DLQI
Starting date	Study start date: February 2017 Actual study completion date: January 2019
Contact information	UCB Cares +1 844 599 22 73 (UCB)
Notes	Ongoing study

NCT03055494

Study name	Study to explore the effect of secukinumab, compared to placebo, on fat tissue and skin in plaque psoriasis patients (ObePso-S)
Methods	RCT, placebo-controlled, double-blind study Date of study: April 2017 Location: USA
Participants	**Randomised**: 82 participants **Inclusion criteria** • Written informed consent must be obtained before any assessment is performed • Clinical diagnosis of chronic plaque-type psoriasis at least 6 months prior to randomisation • Moderate-to-severe plaque psoriasis as defined at baseline by: ≥ 10% BSA involvement and PASI total score of ≥ 12 and IGA mod 2011 score of ≥ 3 (based on a scale of 0 - 4) **Exclusion criteria** • Forms of diagnosed psoriasis other than chronic plaque psoriasis • Medication-induced or medication-exacerbated psoriasis • Previous exposure to secukinumab or any other biologic drug directly targeting IL-17A or IL-17RA receptors • Ongoing use of prohibited treatments • Pregnant or nursing (lactating) women
Interventions	**Intervention** Secukinumab 300 mg SC at randomisation, weeks 1, 2, 3, and 4 followed by monthly dosing up to week 48

NCT03055494 *(Continued)*

	Control interventions Placebo
Outcomes	**At week 12** **Primary composite outcome** Response in skin histology/K16 expression to treatment (yes, no) PASI 90 **Secondary outcome** Vital signs (blood pressure, weight, waist circumference, body mass index), clinical laboratory variables (glucose, insulin, hs-CRP, HOMA-IR, HbA1c) Response in skin histology/K16 expression to treatment (yes, no) - 52 weeks PASI 90 (yes, no) - 52 weeks
Starting date	Study start date: April 2017 Estimated study completion date: February 2019
Contact information	Novartis Pharmaceuticals
Notes	Ongoing study

NCT03066609

Study name	Study of Efficacy and Safety of Secukinumab in Subjects With Moderate to Severe Chronic Plaque-type Psoriasis
Methods	RCT, active/placebo-controlled, double-blind study Date of study: February 2017 Location: China, Hungary, Malaysia, Turkey, Thailand, Philippines
Participants	**Randomised**: 543 participants **Inclusion criteria** • Must give a written, signed and dated informed consent. • Men or women at least 18 years of age at time of screening. • Chronic plaque-type psoriasis present for at least 6 months and diagnosed before baseline. • Moderate-to-severe psoriasis as defined at baseline by: PASI score ≥ 12, and IGA mod 2011 score ≥ 3 (based on a static scale of 0 - 4), and BSA affected by plaque-type psoriasis ≥ 10% • Candidate for systemic therapy. This is defined as a person having moderate-to-severe chronic plaque-type psoriasis that is inadequately controlled by topical treatment and/or phototherapy and/or previous systemic therapy **Exclusion criteria** • Forms of psoriasis other than chronic plaque-type (e.g. pustular, erythrodermic and guttate psoriasis) at screening or baseline • Drug-induced psoriasis • Ongoing use of prohibited treatments

NCT03066609 *(Continued)*

	• Previous exposure to secukinumab (AIN457) or any other biologic drug directly targeting IL-17 or the IL-17 receptor • 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 • 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
Interventions	**Intervention** A. Secukinumab 150 mg: 150 mg SC at randomisation, weeks 1, 2, 3, 4 and every 4 weeks til week 48 **Control interventions** B. Secukinumab 300 mg: 300 mg SC at randomisation, weeks 1, 2, 3, 4 and every 4 weeks til week 48 C. Placebo
Outcomes	**At week 12** **Primary composite outcome** PASI 75 IGA 0/1 **Secondary outcome** PASI, IGA, ACR (12 and 52 weeks)
Starting date	Study start date: February 2017 Actual study completion date: November 2018
Contact information	Novartis Pharmaceuticals
Notes	Ongoing study

NCT03090100

Study name	A study to evaluate the comparative efficacy of CNTO 1959 (Guselkumab) and secukinumab for the treatment of moderate to severe plaque-type psoriasis (ECLIPSE)
Methods	RCT, active-controlled, double-blind study Date of study: April 2017 Location: world-wide Phase 3
Participants	**Randomised**: 1048 participants **Inclusion criteria** • Have a diagnosis of plaque-type psoriasis (with or without Psoriatic Arthritis (PsA)) for at least 6 months before the first administration of study drug • A woman of childbearing potential must have a negative urine pregnancy test at screening and at week 0 and agree to urine pregnancy testing before receiving injections

NCT03090100 *(Continued)*

- 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
- Agree not to receive a Bacille Calmette-Guérin (BCG) vaccination during the study, or within 12 months after the last administration of study drug
- Agree to avoid prolonged sun exposure and avoid use of tanning booths or other ultraviolet light sources during study

Exclusion criteria

- Has a history or current signs or symptoms of severe, progressive, or uncontrolled renal, cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, haematologic, rheumatologic, psychiatric, or metabolic disturbances
- Has previously received guselkumab or secukinumab
- Has a history of chronic or recurrent infectious disease, including but not limited to chronic renal infection, chronic chest infection (example bronchiectasis), recurrent urinary tract infection (recurrent pyelonephritis or chronic nonremitting cystitis), fungal infection (mucocutaneous candidiasis), or open, draining, or infected skin wounds or ulcers
- Has a history of lymphoproliferative disease, including lymphoma; a history of monoclonal gammopathy of undetermined significance; or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy or splenomegaly
- Is unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access to veins

Interventions	**Intervention** A. Guselkumab participants will receive 1 injection of active guselkumab at weeks 0, 4, 12, 20, 28, 36, and 44 **Control interventions** B**.** Secukinumab participants will receive 2 injections of active secukinumab at weeks 0, 1, 2, 3, 4 and every 4 weeks (q4w) thereafter through week 44 C. Placebo
Outcomes	**At week 48** **Primary outcome** PASI 90 **Secondary outcome** PASI 75, PASI 90, PASI 100 IGA 0/1
Starting date	Study start date: April 2017 Actual study completion date: September 2018
Contact information	Study Director: Janssen Research & Development, LLC Clinical Trial
Notes	Ongoing study

NCT03210259

Study name	The VOLTAIRE-X trial looks at the effect of switching between Humira® and BI 695501 in patients with plaque psoriasis
Methods	RCT, active-controlled, double-blind study Date of study: July 2017 Location: world-wide
Participants	**Randomised**: 350 participants **Inclusion criteria** • Men and women aged ≥ 18 to < 80 years at screening who have a diagnosis of moderate-to-severe chronic plaque psoriasis (with or without psoriatic arthritis) for at least 6 months before the first administration of trial drug (a self-reported diagnosis confirmed by the Investigator is acceptable), and which has been stable per Investigator opinion for the last 2 months with no changes in morphology or significant flares at both screening and baseline:involved BSA ≥ 10% and PASI score ≥ 12 and sPGA score of ≥ 3 • Participants of reproductive potential (childbearing potential) must be willing and able to use highly-effective methods of birth control per International Council for Harmonisation (ICH) M3 (R2) that results in a low failure rate of < 1% a year when used consistently and correctly during the trial and for 6 months following completion or discontinuation from the trial medication. A list of contraception methods meeting these criteria is provided in patient information • Signed and dated written informed consent in accordance with Good Clinical Practice (GCP) and local legislation prior to admission to the trial • Patients who are candidates for systemic therapy or phototherapy according to Investigator judgement **Exclusion criteria** • Active ongoing inflammatory diseases other than psoriasis that might confound trial evaluations according to Investigator's judgement • Prior exposure to any biologic therapies for any auto-immune diseases (e.g.: RA, Psoriasis, Crohns Disease, etc) • A significant disease other than psoriasis and/or a significant uncontrolled disease (such as, but not limited to, nervous system, renal, hepatic, endocrine, haematological, autoimmune or gastrointestinal disorders). A significant disease is defined as a disease which, in the opinion of the Investigator, may (i) put the patient at risk because of participation in the trial, or (ii) influence the results of the trial, or (iii) cause concern about the patient's ability to participate in the trial • Major surgery (major according to the Investigator's assessment) performed within 12 weeks before enrolment or planned within 6 months after screening, e.g. total hip replacement • Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately-treated (in the opinion of the Investigator) basal cell carcinoma of the skin or in situ carcinoma of uterine cervix • Patients who must or wish to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial • Currently enrolled in another investigational device or drug trial, or < 30 days (or < 5 half-lives, whichever is longer) since ending another investigational device or drug trial(s), or receiving other investigational treatment(s) • Chronic alcohol or drug abuse or any condition that, in the Investigator's opinion, makes the patient an unreliable trial participant or unlikely to complete the trial • Women who are pregnant, nursing, or who plan to become pregnant during the course of this trial or within the period at least 6 months following completion or discontinuation from the trial medication • Forms of psoriasis (e.g. pustular, erythrodermic and guttate) other than chronic plaque psoriasis. Drug-induced psoriasis (i.e. new onset or current exacerbation from e.g. beta blockers or lithium).

NCT03210259 *(Continued)*

- Primary or secondary immunodeficiency (history of, or currently active), including known history of HIV infection or a positive HIV test at screening (at the Investigator discretion and where mandated by local authorities)
- Known chronic or relevant acute TB; IGRA TB test or PPD skin test will be performed according to the labelling for Humira®. If the result is positive, patients may participate in the trial if further work-up (according to local practice/guidelines) establishes conclusively that the person has no evidence of active TB. If latent TB is confirmed, then treatment must have been initiated before treatment in the study and continued according to local country guidelines
- Known clinically-significant (in the Investigator's opinion) coronary artery disease, significant cardiac arrhythmias, moderate to severe congestive heart failure (New York Heart Association Classes III or IV) or interstitial lung disease observed on chest X-ray
- A history of any clinically-significant adverse reaction (including serious allergic reactions, or anaphylactic reaction, or hypersensitivity) to murine or chimeric proteins, previously-used biological drug or its excipients, or natural rubber and latex
- Positive serology for HBV or HCV
- Receipt of a live/attenuated vaccine within 12 weeks prior to the screening visit; people who are expecting to receive any live/attenuated virus or bacterial vaccinations during the trial or up to 3 months after the last dose of trial drug
- Any treatment (including biologic therapies) that, in the opinion of the Investigator, may place the person at unacceptable risk during the trial
- Known active infection of any kind (excluding fungal infections of nail beds), any major episode of infection requiring hospitalisation or treatment with intravenous (i.v.) antiinfectives within 4 weeks of the screening visit or completion of oral anti-infectives within 2 weeks of the screening visit
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 times upper limit of normal (ULN) at screening
- Haemoglobin < 8.0 g/dL at screening
- Platelets < 100,000/µL at screening
- Leukocyte count < 4000/µL at screening
- Calculated creatinine clearance < 60 mL/min at screening

Interventions	**Intervention** BI 695501 **Control interventions** Humira®
Outcomes	**At week 30** **Primary composite outcome** • AUC tau, 30 - 32 (Area under the adalimumab plasma concentration-time curve [AUC] over the dosing interval of week 30 - 32) (Time frame: Week 30 - 32) • Cmax, 30 - 32 (maximum observed adalimumab plasma concentration during the dosing interval week 30 - 32) (Time frame: week 30 - 32)
Starting date	Study start date: July 2017 Estimated study completion date: May 2020
Contact information	Boehringer Ingelheim (clintriage.rdg@boehringer-ingelheim.com)
Notes	Ongoing study

NCT03255382

Study name	A study to assess the efficacy of risankizumab compared to FUMADERM® in subjects with moderate to severe plaque psoriasis who are naïve to and candidates for systemic therapy
Methods	RCT, active-controlled, open-label study with blinded assessment of the efficacy outcome Date of study: August 2017 Location: Germany
Participants	**Randomised**: 120 participants **Inclusion criteria** **Exclusion criteria**
Interventions	**Intervention** A. risankizumab subcutaneous injection **Control interventions** B. Fumaderm (Tablet)
Outcomes	**At week 24** **Primary outcome** PASI 90 **Secondary outcomes** PASI 75 BSA SF-36; EQ-5D-5L PGA
Starting date	Study start date: August 2017 Estimated study completion date: July 2018 Results submitted May 2019
Contact information	Study director: AbbVie Inc.
Notes	Ongoing study

NCT03331835

Study name	A trial comparing the efficacy of subcutaneous injections of brodalumab to oral administrations of Fumaric Acid Esters in adults with moderate to severe plaque psoriasis
Methods	RCT, active-controlled, open-label study with blinded assessment of the efficacy outcome Date of study: November 2017 Location: Germany

NCT03331835 *(Continued)*

	Phase 4
Participants	**Randomised**: 210 participants **Inclusion criteria** • Men or women ≥ 18 years of age at the time of screening • Chronic plaque type psoriasis diagnosed at least 6 months before randomisation • Moderate-to-severe plaque psoriasis in whom topical therapy is not adequate and who are candidates for systemic therapy, defined at randomisation by PASI > 10, affected BSA > 10%, and DLQI > 10 • No known history of active tuberculosis • Negative test for tuberculosis taken at screening (negative Quantiferon test) • Participant and their designee is/are capable of administering subcutaneous injections **Exclusion criteria** • Previous or current systemic treatment of plaque psoriasis or known contraindication for systemic therapy • Previous or current PUVA (psoralens and ultraviolet A) therapy • Washouts and non-permitted drugs: Have received phototherapy (UVA light therapy without psoralens, UVB light therapy, excimer laser, tanning beds etc. within 4 weeks of baseline, or have had topical psoriasis treatment within 2 weeks of baseline (exceptions: bland emollients without urea or beta or alpha hydroxy acids); have received any biologic immune modulating treatments used for indication other than psoriasis within 4 weeks of baseline or within a period of 5 half-lives of the IMP, whichever is longer; have received any other systemic immune modulating treatment (including but not limited to oral retinoids, methotrexate, calcineurin inhibitors, oral or parenteral corticosteroids etc. used for indications other than psoriasis) within 4 weeks of baseline or within a period of 5 half-lives of the IMP, whichever is longer • Any of the following laboratory abnormalities at screening:Leukocyte cell count below 3×10^9/L or lymphocyte count below 0.7×10^9/L; Aspartate aminotransferase (AST) or alanine transferase (ALT) > 2 × ULN (upper level of normal limit); Absolute neutrophil count < 2×10^9/L; Serum creatinine > ULN • History of depressive disorder within the last 2 years including current antidepressive treatment • A history of suicidal behaviour (suicide attempt) • Any suicidal ideation of severity 4 or 5 based on the eC-SSRS questionnaire at screening • A PHQ-8 score of ≥ 10 corresponding to moderate-to-severe depression at screening
Interventions	**Intervention** A. Brodalumab (Kyntheum® (brodalumab) pre-filled syringe 210 mg/1.5 mL solution for subcutaneous injections. First 3 injections are administered weekly, and thereafter every 2 weeks (Q2W)) **Control interventions** B. Fumaric acid esters (Fumaderm® initial dose tablets (30 mg dimethyl fumarate, 67 mg ethyl hydrogen fumarate calcium salt, 5 mg ethyl hydrogen fumarate magnesium salt, 3 mg ethyl hydrogen fumarate zinc salt) Fumaderm® tablets (120 mg dimethyl fumarate, 87 mg ethyl hydrogen fumarate calcium salt, 5 mg ethyl hydrogen fumarate magnesium salt, 3 mg ethyl hydrogen fumarate zinc salt) Fumaderm® tablets are administered orally up to 3 times daily in accordance with the dosing scheme in the label)
Outcomes	**At week 24** **Primary composite outcome** PASI 75 - IGA 0/1

NCT03331835 *(Continued)*

	Secondary outcome • At least 90% improvement from baseline at week 24 in PASI (Time frame: baseline to week 24) • 100% improvement from baseline at week 24 in PASI (Time frame: baseline to week 24) • Change from baseline at week 24 in PASI score (Time frame: baseline to week 24) • PASI improvement (%) from baseline at week 24 (Time frame: baseline to week 24) • Change from baseline at week 24 in affected BSA (Time frame: baseline to week 24)
Starting date	Study start date: November 2017 Actual study completion date: March 2019
Contact information	Study director: LEO Pharma
Notes	Ongoing study

NCT03364309

Study name	A study of ixekizumab (LY2439821) in Chinese participants with moderate-to-severe plaque psoriasis
Methods	RCT, active/placebo-controlled, double-blind study Date of study: 26 April 2018 Location: China Phase 3
Participants	**Randomised**: 438 participants **Inclusion criteria** Present with chronic plaque psoriasis based on a confirmed diagnosis of chronic psoriasis vulgaris for at least 6 months prior to baseline
Interventions	**Intervention** A. Ixekizumab dose schedule 1: Ixekizumab given SC **Control interventions** B. Ixekizumab dose schedule 2: Ixekizumab given SC C. Placebo
Outcomes	**At week 12** **Primary composite outcome** PGA0/1 - PASI 75 **Secondary outcome** PASI 90, PASI 100 BSA SF-36

NCT03364309 *(Continued)*

	DLQI
Starting date	Study start date: 26 April 2018 Estimated study completion date: 30 June 2020
Contact information	Study director: Call 1-877-CTLILLY (1-877-285-4559)
Notes	Ongoing study

NCT03370133

Study name	A Study to Evaluate the Efficacy and Safety of Bimekizumab Compared to Placebo and an Active Comparator in Adult Subjects With Moderate to Severe Chronic Plaque Psoriasis (BE VIVID)
Methods	RCT, active/placebo-controlled, double-blind study Date of study: December 2017 Location: worldwide
Participants	**Randomised**: 570 participants **Inclusion criteria** • Must be at least 18 years of age • Chronic plaque psoriasis (PSO) for at least 6 months prior to the Screening Visit • Psoriasis Area Severity Index (PASI) >=12 and body surface area (BSA) affected by PSO >=10% and Investigator's Global Assessment (IGA) score >=3 on a 5-point scale • Subject is a candidate for systemic PSO therapy and/or phototherapy • Female subject of child bearing potential must be willing to use highly effective method of contraception **Exclusion criteria** • Subject has an active infection (except common cold), a recent serious infection, or a history of opportunistic or recurrent chronic infections • Subject has concurrent acute or chronic viral hepatitis B or C or human immunodeficiency virus (HIV) infection • Subject has known tuberculosis (TB) infection, is at high risk of acquiring TB infection, or has current or history of nontuberculous mycobacterium (NTMB) infection • Subject has any other condition, including medical or psychiatric, which, in the Investigator's judgment, would make the subject unsuitable for inclusion in the study • Presence of active suicidal ideation or positive suicide behavior • Presence of moderately severe major depression or severe major depression • Subject has any active malignancy or history of malignancy within 5 years prior to the Screening Visit EXCEPT treated and considered cured cutaneous squamous or basal cell carcinoma, or in situ cervical cancer
Interventions	**Intervention** A. Bimekizumab **Control interventions** B. Ustekinumab

NCT03370133 *(Continued)*

	C. Placebo
Outcomes	**At week 16** **Primary composite outcome** PASI 90 - IGA 0/1 **Secondary outcome** PASI 75 AE, SAE
Starting date	Study start date: December 2017 Estimated Study completion date: January 2020
Contact information	Study director: UCB Cares + 1 844 599 2273 (UCB)
Notes	Ongoing study

NCT03384745

Study name	A Phase 2b Study of the Efficacy, Safety, and Tolerability of M1095 in Subjects With Moderate to Severe Psoriasis
Methods	RCT, active/placebo-controlled, double-blind study Date of study: July 2018 Location: worldwide Phase 2b
Participants	**Randomised**: 300 participants **Inclusion criteria** 1. Male and female subjects between 18 and 75 years of age. 2. Moderate to severe plaque-type psoriasis for at least 6 months. 3. Subject is a candidate for systemic biologic therapy. 4. Subject has IGA ≥3, involved body surface area (BSA) ≥10%, and PASI ≥12 at screening and at baseline. 5. Subject is able to comply with the study procedures. 6. Subject must provide informed consent. **Exclusion criteria** 1. Non-plaque type psoriasis, drug-induced psoriasis, or other skin conditions (e.g., eczema). (Psoriatic arthritis is allowed). 2. Other medical conditions, including planned surgery or active infection / history of infection, as defined in the study protocol. Subjects will be screened for tuberculosis and hepatitis B / hepatitis C. 3. Laboratory abnormalities at screening, as defined in the study protocol. 4. Prior use of systemic or topical treatments for psoriasis, as defined in the study protocol. 5. Prior use of any compound targeting IL-17, more than two biologic therapies, ustekinumab within 6 months, or TNF targeting therapies within 12 weeks.

NCT03384745 *(Continued)*

	6. History of suicidal thoughts within 12 months.
Interventions	**Intervention** A. M1095, 30 mg, given at Week 0, 2, 4, 8, 12 and every four weeks. **Control interventions** B. M1095, 60 mg, given at Week 0, 2, 4, 8, 12 and every four weeks. C. M1095, 120 mg, given at Week 0, 2, 4, 8, 12 and every eight weeks. D. M1095, 120 mg, given at Week 0, 2, 4, 8, 12 and every four weeks. E. Placebo
Outcomes	**At week 12** **Primary outcome** IGA 0/1 **Secondary outcome** PASI 75 PASI 100
Starting date	Study start date: July 2018 Estimated Study completion date: August 2020
Contact information	Principal investigator: Dr Kim Papp Contact: Dr Mark Weinberg +44 (0)203 764 9530 mark@avillionllp.com
Notes	Ongoing study

NCT03410992

Study name	A Study With a Initial Treatment Period Followed by a Randomized-withdrawal Period to Evaluate the Efficacy and Safety of Bimekizumab in Adult Subjects With Moderate to Severe Chronic Plaque Psoriasis (BE READY)
Methods	RCT, placebo-controlled, double-blind study Date of study: February 2018 Location: worldwide Phase 3
Participants	**Randomised**: 435 participants **Inclusion criteria** • Must be at least 18 years of age • Chronic plaque psoriasis (PSO) for at least 6 months prior to the Screening Visit • Psoriasis Area Severity Index (PASI) >=12 and body surface area (BSA) affected by PSO >=10% and Investigator's Global Assessment (IGA) score >=3 on a 5-point scale • Subject is a candidate for systemic PSO therapy and/or phototherapy

NCT03410992 *(Continued)*

	• Female subject of child bearing potential must be willing to use highly effective method of contraception **Exclusion criteria** • Subject has an active infection (except common cold), a recent serious infection, or a history of opportunistic, recurrent, or chronic infections • Subject has concurrent acute or chronic viral hepatitis B or C or human immunodeficiency virus (HIV) infection • Subject has known tuberculosis (TB) infection, is at high risk of acquiring TB infection, or has current or history of nontuberculous mycobacterium (NTMB) infection • Subject has any other condition, including medical or psychiatric, which, in the Investigator's judgment, would make the subject unsuitable for inclusion in the study • Presence of active suicidal ideation or positive suicide behavior • Presence of moderately severe major depression or severe major depression • Subject has any active malignancy or history of malignancy within 5 years prior to the Screening Visit EXCEPT treated and considered cured cutaneous squamous or basal cell carcinoma, or in situ cervical cancer
Interventions	**Intervention** A. Bimekizumab **Control interventions** B. Placebo
Outcomes	**At week 16** **Primary composite outcome** PASI 90 1 IGA 0/1 **Secondary outcomes** PASI 100, PASI 75 AEs SAEs
Starting date	Study start date: February 2018 Estimated Study completion date: January 2020
Contact information	Study director: UCB cares +1 844 599 2273 (UCB)
Notes	Ongoing study

NCT03412747

Study name	A Study to Evaluate the Efficacy and Safety of Bimekizumab in Adult Subjects With Moderate to Severe Chronic Plaque Psoriasis (BE SURE)
Methods	RCT, active-controlled, double-blind study Date of study: January, 2018 Location: worldwide Phase 3

NCT03412747 *(Continued)*

Participants	**Randomised**: 480 participants **Inclusion criteria** • Must be at least 18 years of age • Chronic plaque PSO for at least 6 months prior to the Screening Visit • Psoriasis Area Severity Index (PASI) >=12 and body surface area (BSA) affected by PSO >=10% and Investigator's Global Assessment (IGA) score >=3 on a 5-point scale • Subject is a candidate for systemic PSO therapy and/or phototherapy • Female subject of child bearing potential must be willing to use highly effective method of contraception **Exclusion criteria** • Subject has a known hypersensitivity to any excipients of bimekizumab or adalimumab • Subject has an active infection (except common cold), a serious infection, or a history of opportunistic or recurrent chronic infections • Subject has concurrent acute or chronic viral hepatitis B or C or human immunodeficiency virus (HIV) infection • Subject has known tuberculosis (TB) infection, is at high risk of acquiring TB infection, or has current or history of nontuberculous mycobacterium (NTMB) infection • Subject has any other condition, including medical or psychiatric, which, in the Investigator's judgment, would make the subject unsuitable for inclusion in the study • Subject has had previous exposure to adalimumab • Presence of active suicidal ideation or positive suicide behavior • Presence of moderately severe major depression or severe major depression • Subject has any active malignancy or history of malignancy within 5 years prior to the Screening Visit EXCEPT treated and considered cured cutaneous squamous or basal cell carcinoma, or in situ cervical cancer
Interventions	**Intervention** A. Bimekizumab dose regimen 1 **Control interventions** B. Bimekizumab dose regimen 2 C. Adalimumab
Outcomes	**At week 16** **Primary composite outcome** PASI 90 - IGA 0/1 **Secondary outcome** PASI 75 PASI 100 AEs SAEs
Starting date	Study start date: January, 2018 Estimated Study completion date: March 2020

NCT03412747 *(Continued)*

Contact information	Study director: UCB cares +1 844 599 2273 (UCB)
Notes	Ongoing study

NCT03421197

Study name	A study to assess the efficacy and safety of PPC-06 (Tepilamide Fumarate)
Methods	RCT, active/placebo-controlled, double-blind study Date of study: January 2018 Location: USA Phase 2
Participants	**Randomised**: 400 participants **Inclusion criteria** • Generally healthy men or non-pregnant women age ≥ 18 years at the time of screening (or who have reached the state minimum legal age of consent) • Stable, moderate-to-severe plaque psoriasis diagnosed for at least 6 months prior to randomisation (no morphology changes or significant flares of disease activity in the last 6 months in the opinion of the investigator or as reported by the person) • Severity of disease meeting all 3 of the following criteria prior to randomisation (at the baseline [day 0] visit): PASI score of ≥ 12; Total BSA affected by plaque psoriasis of ≥ 10%; IGA score of > 3 • Must be a candidate for phototherapy and/or systemic therapy for psoriasis **Exclusion criteria** • Non-plaque psoriasis (i.e. predominantly inverse, erythrodermic, predominantly guttate, or pustular psoriasis) • Drug-induced psoriasis or with drug-exacerbated psoriasis that has not resolved within 4 weeks prior to screening • Rreceived systemic non-biologic psoriasis therapy or phototherapy (including either oral and topical psoralen and ultraviolet A (PUVA) light therapy, ultraviolet B, or self-treatment with tanning beds or therapeutic sunbathing) within 4 weeks prior to the baseline visit • Had topical psoriasis treatment within the previous 2 weeks prior to the baseline visit • History of concurrent or recent use of any biologic agent within the following washout periods prior to baseline visit: Etanercept - 35 days; Infliximab, adalimumab - 12 weeks; Ustekinumab - 24 weeks; Any other biologic agent < 5 half-lives prior to the baseline visit • History of use of any investigational drug within 28 days prior to randomisation, or 5 pharmacokinetic/pharmacodynamic half-lives (whichever is longer)
Interventions	**Intervention** A. Tepilamide fumarate 400 mg tablet once a day **Control interventions** B. Tepilamide fumarate 400 mg tablet twice a day C. Tepilamide fumarate tablets 600 mg twice a day D. Placebo
Outcomes	**At week 24**

NCT03421197 *(Continued)*

	Primary composite outcome PASI 75 and IGA 0/1 **Secondary outcome** PASI 50, PASI 75 IGA BSA
Starting date	Study start date: January 2018 Estimated study completion date: March 2019 Last update posted: September 2018, active not recruiting
Contact information	Dr. Reddy's Laboratories Limited
Notes	Ongoing study

NCT03478280

Study name	Effect of brodalumab compared to placebo on vascular inflammation in moderate-to-severe psoriasis
Methods	RCT, placebo-controlled, double-blind study Date of study: April 2018 Location: Aarhus University Hospital, Denmark
Participants	**Randomised**: 50 participants **Inclusion criteria** • Written informed consent obtained from the participant prior to performing any protocol-related procedures • Age 40 and above • Diagnosis of chronic plaque psoriasis confirmed by a dermatologist • PASI ≥ 10 **Exclusion criteria** Non-Danish speaking
Interventions	**Intervention** A. Participants will receive 210 mg of Kyntheum administered by subcutaneous injection at weeks 0, 1 and 2 followed by 210 mg every other week (EOW) thereafter **Control interventions** B. Placebo
Outcomes	**At week 16** **Primary outcome**

NCT03478280 *(Continued)*

	Average of maximum TBR values (MeanTBRmax) of the entire aorta at baseline and at week 16 (aortic wall inflammation) **Secondary outcome** The splenic inflammation at baseline and at week 16 in brodalumab-treated psoriasis participants compared to placebo. (Time frame: 16 weeks); the spleen-to-liver ratio (SLR) based on splenic and liver mean standardised uptake values (SUVmean)
Starting date	Study start date: April 2018 Estimated study completion date: March 2020
Contact information	Contact: Anne Bregnhøj, MD, PhD +45 2183 5720 annebreg@rm.dk
Notes	Ongoing study

NCT03478787

Study name	Risankizumab versus secukinumab for subjects with moderate to severe plaque psoriasis
Methods	RCT, active-controlled, single-blind study (outcomes assessor) Date of study: March 2018 Location: worldwide
Participants	**Randomised**: 281 participants **Inclusion criteria** • Diagnosis of chronic plaque psoriasis with or without psoriatic arthritis for at least 6 months before the baseline visit • Stable moderate-to-severe chronic plaque psoriasis with or without psoriatic arthritis • Must be a candidate for systemic therapy as assessed by the investigator • Must be an acceptable candidate to receive secukinumab according to the local label for this compound **Exclusion criteria** • History of erythrodermic psoriasis, generalised or localised pustular psoriasis, medication-induced or medication-exacerbated psoriasis, or new onset guttate psoriasis; or active skin disease other than psoriasis that could interfere with the assessment of psoriasis • Chronic infections including HIV, viral hepatitis (hepatitis B, hepatitis C), and/or active tuberculosis. People with a positive QuantiFERON®-TB /PPD) test result may participate in the study if further work-up (according to local practice/guidelines) establishes conclusively that the person has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then treatment must have been initiated and maintained according to local country guidelines • Active systemic infection during the last 2 weeks prior to baseline visit (exception: common cold) • History of any documented active or suspected malignancy or history of any malignancy within the last 5 years except for successfully-treated non-melanoma skin cancer (NMSC) or localised carcinoma in situ of the cervix • Previous exposure to risankizumab • Previous exposure to secukinumab
Interventions	**Intervention** A. Risankizumab

NCT03478787 *(Continued)*

	Control interventions B. Secukinumab
Outcomes	**At week 16** **Primary outcome** PASI 90 **Secondary outcome** PASI 90 at 52 weeks PGA PASI 75
Starting date	Study start date: March 2018 Estimated study completion date: November 2019 Last update posted: March 2019: active not yet recruiting
Contact information	Study director: AbbVie
Notes	Ongoing study

NCT03482011

Study name	A study to evaluate the efficacy and safety of mirikizumab (LY3074828) in participants with moderate-to-severe plaque psoriasis (OASIS-1)
Methods	RCT, placebo-controlled, double-blind study Date of study: April 2018 Location: world-wide
Participants	**Randomised**: 689 participants **Inclusion criteria** • Present with chronic plaque psoriasis based on an investigator-confirmed diagnosis of chronic psoriasis vulgaris for at least 6 months prior to baseline and meet the following criteria: plaque psoriasis involving ≥ 10% BSA and absolute PASI score ≥ 12 in affected skin at screening and baselines; PGA score of ≥ 3 at screening and baseline • Candidate for systemic therapy and/or phototherapy for psoriasis **Exclusion criteria** • Have an unstable or uncontrolled illness, including but not limited to a cerebro-cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, haematologic, or neurologic disease or abnormal laboratory values at screening, that in the opinion of the investigator, would potentially affect participant safety within the study or of interfering with the interpretation of data. • Breastfeeding or nursing women • Have had serious, opportunistic, or chronic/recurring infection within 3 months prior to screening • Have received a Bacillus Calmette-Guerin (BCG) vaccination within 12 months or received live vaccine(s) (including attenuated live vaccines) within 12 weeks of baseline or intend to receive either during the study

NCT03482011 *(Continued)*

	• Have any other skin conditions (excluding psoriasis) that would affect interpretation of the results • Have received systemic nonbiologic psoriasis therapy or phototherapy within 28 days prior to baseline • Have received topical psoriasis treatment within 14 days prior to baseline • Have received anti-tumour necrosis factor (TNF) biologics, or anti-interleukin (IL)-17 targeting biologics within 12 weeks prior to baseline • Have previous exposure to any biologic therapy targeting IL-23 (including ustekinumab), either licensed or investigational
Interventions	**Intervention** **A.** Mirikizumab **Control interventions** B. Placebo
Outcomes	**At week 16** **Primary composite outcome** PASI 90 - IGA 0/1 **Secondary outcome** PASI 75 DLQI SF-36 Change from baseline in quick inventory of depressive symptomology
Starting date	Study start date: April 2018 Estimated study completion date: February 2020 Last update posted: May 2019, active, not recruiting
Contact information	Study Director: call 1-877-CTLILLY (1-877-285-4559)
Notes	Ongoing study

NCT03504852

Study name	Efficacy and safety of 2 secukinumab regimens in 90 kg or higher subjects with moderate to severe chronic plaque-type psoriasis
Methods	RCT, active-controlled, double-blind study Date of study: February 2018 Location: world-wide
Participants	**Randomised**: 330 participants **Inclusion criteria**

NCT03504852 *(Continued)*

- Written informed consent must be obtained before any assessment is performed. Where relevant, a legal representative will also sign the informed study consent according to local laws and regulations
- Participants must be able to understand and communicate with the investigator and comply with the requirements of the study
- Men or women at least 18 years of age at time of screening
- Body weight of ≥ 90 kg at the time of randomisation
- Chronic plaque-type psoriasis present for at least 6 months and diagnosed before randomisation
- Moderate-to-severe psoriasis as defined at randomisation by: PASI score ≥ 12, and IGA mod 2011 score ≥ 3 (based on a static scale of 0 - 4), and BSA affected by plaque-type psoriasis ≥ 10%
- Candidate for systemic therapy. This is defined as a person having moderate-to-severe chronic plaque-type psoriasis that is inadequately controlled by:topical treatment and/or phototherapy and/or previous systemic therapy

Exclusion criteria

- Forms of psoriasis other than chronic plaque-type (e.g. pustular, erythrodermic and guttate psoriasis) at screening or randomisation
- Ongoing use of prohibited treatments. Washout periods detailed in the protocol have to be adhered to. People 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 randomisation or during the study period is also prohibited
- Previous exposure to secukinumab (AIN457) or any other biologic drug directly targeting Interleukin-17 (IL-17) or the IL-17 receptor
- Use of other investigational drugs at the time of enrolment, or within 5 half-lives of enrolment, or within 4 weeks until the expected pharmacodynamic effect has returned to baseline, whichever is longer; or longer if required by local regulations
- Pregnant or nursing (lactating) women
- 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 skin 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)
- History of hypersensitivity to any of the study drug constituents

Interventions	**Intervention** A. Secukinumab 300 mg every 2 weeks **Control interventions** B. Secukinumab 300 mg every 4 weeks
Outcomes	**At week 16** **Primary outcome** PASI 90 **Secondary outcome** IGA 0/1
Starting date	Study start date: February 2018 Estimated study completion date: August 2020
Contact information	Study Director: Novartis Pharmaceuticals

NCT03504852 *(Continued)*

Notes	Ongoing study

NCT03518047

Study name	Risankizumab therapy versus placebo for subjects with psoriasis in the Russian Federation (IMMPRESS)
Methods	RCT, active-controlled, double-blind study Date of study: May 2018 Location: Russia
Participants	**Randomised**: 50 participants **Inclusion criteria** • A diagnosis of chronic plaque psoriasis (with or without psoriatic arthritis) for at least 6 months before the first administration of study drug • Moderate-to-severe chronic plaque psoriasis at both screening and baseline (randomisation) visits • Candidates for systemic therapy or phototherapy for psoriasis treatment as assessed by the investigator **Exclusion criteria** • Prior therapy with an anti-interleukin (IL)-17 or anti-IL12/23p40 or anti-IL-23p19 inhibitor • Concurrent therapy with a biologic and/or other systemic therapy
Interventions	**Intervention** A. Risankizumab **Control interventions** B. Placebo
Outcomes	**At week 16** **Primary outcome** PASI 90 **Secondary outcome** PGA 0/1 PASI 75 DLQI
Starting date	Study start date: May 2018 Estimated study completion date: February 2020
Contact information	Study director: AbbVie Inc.
Notes	Ongoing study

NCT03535194

Study name	A study to assess if mirikizumab is effective and safe compared to secukinumab and placebo in moderate-to-severe plaque psoriasis (OASIS-2)
Methods	RCT, active/placebo-controlled, double-blind study Date of study: May 2018 Location: world-wide
Participants	**Randomised**: 1443 participants **Inclusion criteria** • Participant must have chronic plaque psoriasis for at least 6 months **Exclusion criteria** • Not be breastfeeding or nursing woman • Must not have had serious, opportunistic, or chronic/recurring infection within 3 months • Must not have received a Bacillus Calmette-Guerin (BCG) vaccination within 12 months or received live vaccine(s) (including attenuated live vaccines) within 12 weeks of baseline or intend to receive either during the study • Must not have any other skin conditions (excluding psoriasis) • Must not have previous exposure to Cosentyx and any other biologic therapy targeting IL-17 (including Taltz) • Must not have received anti-tumour necrosis factor (TNF) biologics within 8 weeks • Must not have previous exposure to any biologic therapy targeting IL-23 (including Stelara)
Interventions	**Intervention** **A.** Mirikizumab **Control interventions** B. Secukinumab C. Placebo
Outcomes	**At week 16** **Primary composite outcome** PASI 90 - IGA 0/1 **Secondary outcome** PASI 75 DLQI SF-36 Change from baseline in quick inventory of depressive symptomology
Starting date	Study start date: May 2018 Estimated study completion date: December 2020 Last update posted: May 2019, active, recruiting

NCT03535194 *(Continued)*

Contact information	Study Director: call 1-877-CTLILLY (1-877-285-4559)
Notes	Ongoing study

NCT03536884

Study name	A study to evaluate the efficacy and safety of bimekizumab compared to an active comparator in adult subjects with moderate to severe chronic plaque psoriasis (BE RADIANT)
Methods	RCT, active-controlled, double-blind study Date of study: June 2018 Location: world-wide
Participants	**Randomised**: 743 participants **Inclusion criteria** • Men or women at least 18 years of age • Must have had chronic plaque psoriasis (PSO) for at least 6 months prior to the screening visit • Must have PASI ≥ 12 and BSA affected by PSO ≥ 10% and IGA score ≥ 3 on a 5-point scale • Must be a candidate for systemic PSO therapy and/or phototherapy • Must be considered, in the opinion of the Investigator, to be a suitable candidate for treatment with secukinumab per regional labelling and has no contraindications to receive secukinumab as per the local label • Women of child-bearing potential must be willing to use highly effective method of contraception **Exclusion criteria** • Has an active infection (except common cold), a serious infection, or a history of opportunistic, recurrent or chronic infections • Has concurrent acute or chronic viral hepatitis B or C or HIV infection • Has known tuberculosis (TB) infection, is at high risk of acquiring TB infection, or has current or history of nontuberculous mycobacterium (NTMB) infection • Has any other condition, including medical or psychiatric, which, in the Investigator's judgement, would make the person unsuitable for inclusion in the study • Presence of active suicidal ideation or severe depression • Has any active malignancy or history of malignancy within 5 years prior to the screening visit EXCEPT treated and considered cured cutaneous squamous or basal cell carcinoma, or in situ cervical cancer
Interventions	**Intervention** A. Bimekizumab dosage regimen 1 **Control interventions** **B.** bimekizumab dosage regimen 2 C. Secukinumab
Outcomes	**At week 16** **Primary outcome** PASI 100

NCT03536884 *(Continued)*

	Secondary outcome PASI 75, PASI 90, PASI 100 IGA SAEs, AE
Starting date	Study start date: June 2018 Estimated study completion date: August 2020
Contact information	Study Director UCB cares +1 844 599 2273
Notes	Ongoing study

NCT03573323

Study name	A study of ixekizumab (LY2439821) compared to guselkumab in participants with moderate-to-severe plaque psoriasis (IXORA-R)
Methods	RCT, active/placebo-controlled, double-blind study Date of study: November 2018 Location: World-wide
Participants	**Randomised**: 960 participants **Inclusion criteria** • Have chronic plaque psoriasis based on a diagnosis for at least 6 months before baseline as determined by the investigator • Are a candidate for phototherapy and/or systemic therapy • Have both an sPGA score of ≥ 3 and a PASI score ≥ 12 at screening and at baseline • Have ≥ 10% BSA involvement at screening and baseline • If male, agree to use a reliable method of birth control during the study • If female, agree to use highly effective method of contraception **Exclusion criteria** • Predominant pattern of pustular, erythrodermic, and/or guttate forms of psoriasis • Have a history of drug-induced psoriasis • Had a clinically-significant flare of psoriasis during the 12 weeks before baseline • Use of tanning booths for at least 4 weeks before baseline • Concurrent or recent use of any biologic agent within the following periods prior to baseline: etanercept < 28 days; infliximab, adalimumab, certolizumab pegol, or alefacept < 60 days; golimumab < 90 days; rituximab < 12 months; secukinumab < 5 months; or any other biologic agent (e.g. ustekinumab) < 5 half- lives • Have prior use of IL-23p19 antagonists (e.g. guselkumab, tildrakizumab, risankizumab), or have any condition or contraindication as addressed in the local labelling for guselkumab that would preclude the person from participating in this protocol • Have previously completed or withdrawn from this study, participated in any other study with ixekizumab or guselkumab, have participated in any study investigating other IL-17 or IL-23p19 antagonists, or have received treatment with ixekizumab • Have previously failed to respond to an IL-17 antagonist, per investigator assessment • Have had a live vaccination within 12 weeks of baseline

NCT03573323 *(Continued)*

	• Have a known allergy or hypersensitivity to any biologic therapy • Have had any major surgery within 8 weeks of baseline • Have had a serious infection, have been hospitalised, or have received intravenous antibiotics for an infection within 12 weeks of baseline • Are women who are pregnant, or who are lactating (breast-feeding)
Interventions	**Intervention** A. Ixekizumab **Control interventions** B. Guselkumab C. Placebo
Outcomes	**At week 12** **Primary outcome** PASI 100 **Secondary outcome** PASI 75, PASI 90 IGA
Starting date	Study start date: November 2018 Estimated study completion date: December 2019
Contact information	Study Director: call 1-877-CTLILLY (1-877-285-4559)
Notes	Ongoing study

NCT03589885

Study name	Study of efficacy and safety of secukinumab 2 mL auto-injector (300 mg) in subjects with moderate to severe plaque psoriasis (MATURE)
Methods	RCT, active-controlled, double-blind study Date of study: December 2018 Location: USA, Germany Phase IIIB
Participants	**Randomised**: 120 participants **Inclusion criteria** People eligible for inclusion in this study must fulfil all of the following criteria: • 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 • Chronic plaque-type psoriasis present for at least 6 months and diagnosed before randomisation

NCT03589885 *(Continued)*

- Moderate-to-severe psoriasis as defined at randomisation by: PASI score ≥ 12, and IGA mod 2011 score ≥ 3 (based on a scale of 0 - 4), and BSA affected by plaque-type psoriasis ≥ 10%
- Candidate for systemic therapy. This is defined as a person having moderate-to-severe chronic plaque-type psoriasis that is inadequately controlled by topical treatment and/or phototherapy

Exclusion criteria

- Forms of psoriasis other than chronic plaque-type (e.g. pustular, erythrodermic and guttate psoriasis) at screening or randomisation
- Ongoing use of prohibited treatments. Washout periods detailed in the protocol have to be adhered to. People 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 randomisation or during the study period is also prohibited
- Previous exposure to secukinumab (AIN457) or any other biologic drug directly targeting IL-17 or the IL-17 receptor
- 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
- 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
- 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)
- History of hypersensitivity to any of study drug constituent

Interventions	**Intervention** A. Secukinumab 2 mL auto-injector **Control interventions** B. Secukinumab 1 mL pre-filled syringe C. Placebo
Outcomes	**At week 12** **Primary composite outcome** PASI 75 - IGA 0/1 **Secondary outcome** PASI 90 DLQI
Starting date	Study start date: December 2018 Estimated study completion date: June 2020
Contact information	Contact: Novartis Pharmaceuticals 1-888-669-6682
Notes	Ongoing study

NCT03598790

Study name	A study to assess the safety, tolerability and efficacy of bimekizumab in adult subjects with moderate to severe chronic plaque psoriasis (BE BRIGHT)
Methods	RCT, active-controlled, open-label study Date of study: July 2018 Location:
Participants	**Randomised**: 1120 participants **Inclusion criteria** Person is considered reliable and capable of adhering to the protocol (e.g. able to understand and complete diaries), visit schedule, and medication intake according to the judgement of the Investigator
Interventions	**Intervention** A. Bimekizumab dose regimen 1 **Control interventions** B. Bimekizumab dose regimen 2
Outcomes	**At week 68** **Primary composite outcome** Number of treatment-emergent adverse events **Secondary outcome** Number of SAEs PASI 90 IGA
Starting date	Study start date: July 2018 Estimated study completion date: May 2021
Contact information	Contact: UCB Cares +1844599 ext 2273
Notes	Ongoing study

NCT03611751

Study name	An investigational study to evaluate experimental medication BMS-986165 compared to placebo and a currently available treatment in participants with moderate-to-severe plaque psoriasis (POETYK-PSO-2)
Methods	RCT, active/placebo-controlled, double-blind study Date of study: August 2018 Location: world-wide
Participants	**Randomised**: 1000 participants

NCT03611751 *(Continued)*

	Inclusion criteria • Plaque psoriasis for at least 6 months • Moderate-to-severe disease • Candidate for phototherapy or systemic therapy **Exclusion criteria** • Other forms of psoriasis • History of recent infection • Prior exposure to BMS-986165 or active comparator
Interventions	**Intervention** A. BMS-986165 **Control interventions** B. Apremilast C. Placebo
Outcomes	**At week 16** **Primary composite outcome** PASI 75 - IGA 0/1 **Secondary outcome** PASI 90 (Time frame: week 16)
Starting date	Study start date: August 2018 Estimated study completion date: July 2020
Contact information	clinical.trials@bms.com (sponsor: Bristol-Myers Squibb)
Notes	Ongoing study

TCTR20161028001

Study name	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	**Randomised**: 40 participants **Inclusion criteria** • 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-

TCTR20161028001 *(Continued)*

	related activity is performed. Where relevant, a legal representative will also sign the informed study consent according to local laws and regulations • Men and women ≥ 18 years of age at the time of screening • Chronic plaque-type psoriasis present for ≥ 6 months and diagnosed before baseline • Moderate-severe psoriasis **Exclusion criteria** • Forms of psoriasis other than chronic plaque-type (e.g. pustular, erythrodermic and guttate psoriasis) at screening or baseline • Drug-induced psoriasis (i.e. new onset or current exacerbation from beta-blockers, calcium channel inhibitors or lithium) at baseline • Ongoing use of prohibited treatments. Washout periods detailed in the protocol have to be adhered to (Table 5-1). Paricipants 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 randomisation or during the study period is also prohibited • Previous exposure to secukinumab (AIN457) or any other biologic drug directly targeting IL-17 or the IL-17 receptor • 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
Interventions	**Intervention** A. Secukinumab 300 mg SC (administration not specified) **Control intervention** B. Secukinumab 150 mg SC (administration not specified) C. Placebo
Outcomes	**At week 12** **Primary outcome (composite)** • IGA 0/1 • PASI 75 **Secondary outcomes** • ACR 20/50/70 (timeframe 12 weeks and 52 weeks) • PASI 50/75/90/100 (timeframe 12 weeks and 52 weeks PASI score) • Safety and tolerability
Starting date	28 February 2017; not yet recruiting (24 April 2019)
Contact information	Kerstin Letzelter, kerstin.letzelter@novartis.com
Notes	Ongoing study

AE: Adverse events; **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; **SAE**: Serious adverse event

DATA AND ANALYSES

Comparison 1. Primary outcome - PASI 90

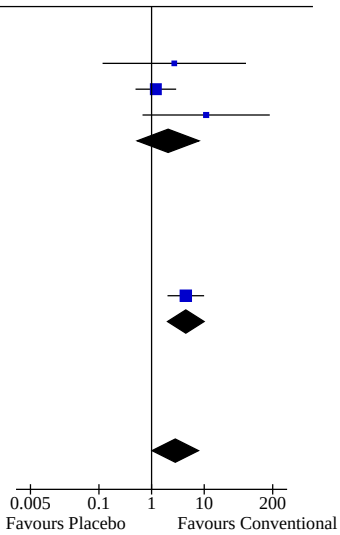
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Conventional systemic agents versus placebo	4	1022	Risk Ratio (M-H, Random, 95% CI)	2.82 [1.02, 7.78]
1.1.1 Methotrexate versus placebo	3	318	Risk Ratio (M-H, Random, 95% CI)	2.06 [0.53, 7.97]
1.1.2 Fumaric acid esters versus placebo	1	704	Risk Ratio (M-H, Random, 95% CI)	4.47 [2.01, 9.95]
1.2 Conventional systemic 1 versus conventional systemic 2	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.2.1 Ciclosporin versus methotrexate	2	172	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.47, 2.98]
1.2.2 Methotrexate versus fumaric acid esters	2	168	Risk Ratio (M-H, Random, 95% CI)	3.82 [1.65, 8.85]
1.3 Anti-TNF alpha versus placebo	31	11742	Risk Ratio (M-H, Random, 95% CI)	13.59 [10.63, 17.38]
1.3.1 Etanercept versus placebo	14	5650	Risk Ratio (M-H, Random, 95% CI)	11.68 [8.14, 16.75]
1.3.2 Adalimumab versus placebo	9	3421	Risk Ratio (M-H, Random, 95% CI)	13.13 [8.01, 21.53]
1.3.3 Certolizumab versus placebo	4	1026	Risk Ratio (M-H, Random, 95% CI)	18.54 [7.42, 46.32]
1.3.4 Infliximab versus placebo	5	1645	Risk Ratio (M-H, Random, 95% CI)	27.71 [12.52, 61.30]
1.4 Anti-IL12/23 versus placebo	9	4231	Risk Ratio (M-H, Random, 95% CI)	20.02 [13.01, 30.81]
1.4.1 Ustekinumab versus placebo	9	4231	Risk Ratio (M-H, Random, 95% CI)	20.02 [13.01, 30.81]
1.5 Anti-IL17 versus placebo	18	10532	Risk Ratio (M-H, Random, 95% CI)	30.58 [21.73, 43.03]
1.5.1 Secukinumab versus placebo	8	2905	Risk Ratio (M-H, Random, 95% CI)	27.47 [15.81, 47.71]
1.5.2 Ixekizumab versus placebo	4	3268	Risk Ratio (M-H, Random, 95% CI)	53.85 [15.34, 189.07]
1.5.3 Brodalumab versus placebo	5	4109	Risk Ratio (M-H, Random, 95% CI)	26.33 [16.77, 41.33]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5.4 Bimekizumab versus placebo	1	250	Risk Ratio (M-H, Random, 95% CI)	58.64 [3.72, 923.86]
1.6 Anti-IL23 versus placebo	12	5146	Risk Ratio (M-H, Random, 95% CI)	23.70 [16.63, 33.76]
1.6.1 Guselkumab versus placebo	5	1767	Risk Ratio (M-H, Random, 95% CI)	27.79 [16.23, 47.60]
1.6.2 Tildrakizumab versus placebo	3	1903	Risk Ratio (M-H, Random, 95% CI)	17.26 [8.27, 36.05]
1.6.3 Risankizumab versus placebo	4	1476	Risk Ratio (M-H, Random, 95% CI)	24.00 [13.04, 44.18]
1.7 Biologic versus conventional systemic treatments	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.7.1 Etanercept versus acitretin	2	102	Risk Ratio (M-H, Random, 95% CI)	4.56 [0.81, 25.79]
1.7.2 Infliximab versus methotrexate	1	868	Risk Ratio (M-H, Random, 95% CI)	2.86 [2.15, 3.80]
1.7.3 Adalimumab versus methotrexate	1	218	Risk Ratio (M-H, Random, 95% CI)	3.73 [2.25, 6.19]
1.7.4 Secukinumab versus fumaric acid esters	1	202	Risk Ratio (M-H, Random, 95% CI)	8.31 [4.23, 16.35]
1.7.5 Ixekizumab versus fumaric ester acids	1	108	Risk Ratio (M-H, Random, 95% CI)	8.60 [3.69, 20.04]
1.7.6 Ixekizumab versus methotrexate	1	108	Risk Ratio (M-H, Random, 95% CI)	2.05 [1.43, 2.94]
1.7.7 Guselkumab versus fumaric ester acids	1	119	Risk Ratio (M-H, Random, 95% CI)	6.02 [3.13, 11.60]
1.8 Biologic 1 versus biologic 2	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.8.1 Ustekinumab versus etanercept	1	903	Risk Ratio (M-H, Random, 95% CI)	1.80 [1.45, 2.24]
1.8.2 Secukinumab versus etanercept	1	980	Risk Ratio (M-H, Random, 95% CI)	2.32 [1.85, 2.92]
1.8.3 Ixekizumab versus etanercept	2	2209	Risk Ratio (M-H, Random, 95% CI)	2.98 [2.24, 3.98]
1.8.4 Secukinumab versus ustekinumab	2	1778	Risk Ratio (M-H, Random, 95% CI)	1.40 [1.30, 1.50]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.8.5 Brodalumab versus ustekinumab	2	3088	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.16, 1.39]
1.8.6 Guselkumab versus adalimumab	3	1658	Risk Ratio (M-H, Random, 95% CI)	1.43 [1.26, 1.62]
1.8.7 Risankizumab versus ustekinumab	3	965	Risk Ratio (M-H, Random, 95% CI)	1.67 [1.43, 1.93]
1.8.8 Ixekizumab versus ustekinumab	1	302	Risk Ratio (M-H, Random, 95% CI)	1.73 [1.41, 2.12]
1.8.9 Certolizumab versus etanercept	1	502	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.90, 1.61]
1.8.10 Risankizumab versus adalimumab	1	605	Risk Ratio (M-H, Random, 95% CI)	1.53 [1.33, 1.75]
1.8.11 Tildrakizumab versus etanercept	1	934	Risk Ratio (M-H, Random, 95% CI)	1.76 [1.39, 2.23]
1.8.12 Inliximab versus etanercept	1	48	Risk Ratio (M-H, Random, 95% CI)	9.20 [1.28, 66.37]
1.9 Small molecules versus placebo	11	5388	Risk Ratio (M-H, Random, 95% CI)	7.09 [5.05, 9.95]
1.9.1 Apremilast versus placebo	5	2029	Risk Ratio (M-H, Random, 95% CI)	6.94 [3.37, 14.30]
1.9.2 Tofacitinib versus placebo	5	3092	Risk Ratio (M-H, Random, 95% CI)	7.81 [4.54, 13.46]
1.9.3 TYK2 versus placebo	1	267	Risk Ratio (M-H, Random, 95% CI)	13.99 [1.99, 98.10]
1.10 Biologic versus small molecules	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.10.1 Etanercept versus tofacitinib	1	998	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.93, 1.38]
1.10.2 Etanercept versus apremilast	1	166	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.72, 2.78]

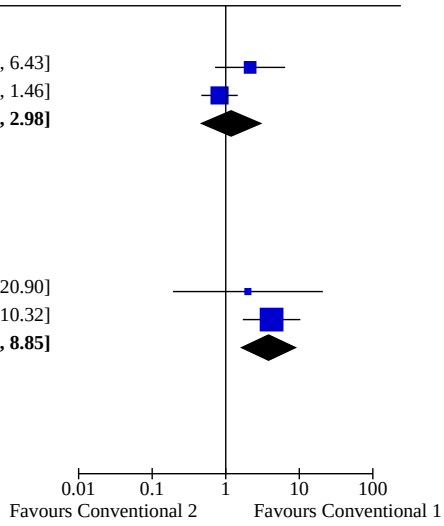
Analysis 1.1. Comparison 1: Primary outcome - PASI 90, Outcome 1: Conventional systemic agents versus placebo

Study or Subgroup	Conventional treatments Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Methotrexate versus placebo						
Hunter 1963	1	19	0	17	8.8%	2.70 [0.12 , 62.17]
Saurat CHAMPION 2008	15	110	6	53	39.1%	1.20 [0.50 , 2.93]
Warren METOP, 2017	16	90	0	29	10.7%	10.88 [0.67 , 175.90]
Subtotal (95% CI)		**219**		**99**	**58.6%**	**2.06 [0.53 , 7.97]**
Total events:	32		6			
Heterogeneity: Tau² = 0.52; Chi² = 2.81, df = 2 (P = 0.25); I² = 29%						
Test for overall effect: Z = 1.05 (P = 0.29)						
1.1.2 Fumaric acid esters versus placebo						
Mrowietz BRIDGE 2016	110	566	6	138	41.4%	4.47 [2.01 , 9.95]
Subtotal (95% CI)		**566**		**138**	**41.4%**	**4.47 [2.01 , 9.95]**
Total events:	110		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.67 (P = 0.0002)						
Total (95% CI)		**785**		**237**	**100.0%**	**2.82 [1.02 , 7.78]**
Total events:	142		12			
Heterogeneity: Tau² = 0.48; Chi² = 6.20, df = 3 (P = 0.10); I² = 52%						
Test for overall effect: Z = 2.00 (P = 0.05)						
Test for subgroup differences: Chi² = 0.93, df = 1 (P = 0.33), I² = 0%						



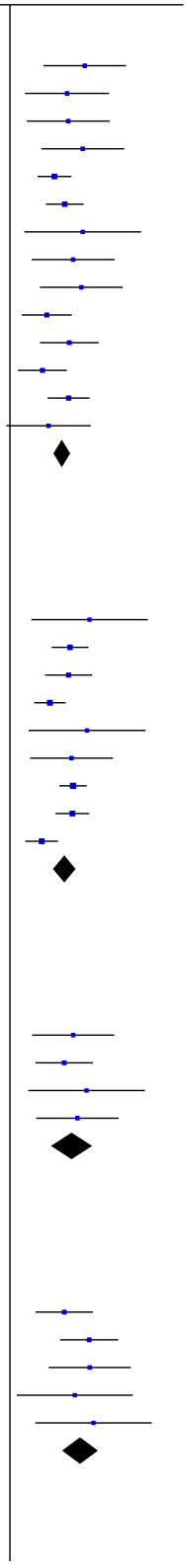
Analysis 1.2. Comparison 1: Primary outcome - PASI 90, Outcome 2: Conventional systemic 1 versus conventional systemic 2

Study or Subgroup	Conventional 1 Events	Total	Conventional 2 Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Ciclosporin versus methotrexate						
Flytström 2008	9	43	4	41	37.9%	2.15 [0.72 , 6.43]
Heydendael 2003	14	44	17	44	62.1%	0.82 [0.47 , 1.46]
Subtotal (95% CI)		**87**		**85**	**100.0%**	**1.18 [0.47 , 2.98]**
Total events:	23		21			
Heterogeneity: Tau² = 0.27; Chi² = 2.37, df = 1 (P = 0.12); I² = 58%						
Test for overall effect: Z = 0.36 (P = 0.72)						
1.2.2 Methotrexate versus fumaric acid esters						
Fallah Arani 2011	2	30	1	30	12.8%	2.00 [0.19 , 20.90]
NCT02634801	21	54	5	54	87.2%	4.20 [1.71 , 10.32]
Subtotal (95% CI)		**84**		**84**	**100.0%**	**3.82 [1.65 , 8.85]**
Total events:	23		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 1 (P = 0.56); I² = 0%						
Test for overall effect: Z = 3.13 (P = 0.002)						



Analysis 1.3. Comparison 1: Primary outcome - PASI 90, Outcome 3: Anti-TNF alpha versus placebo

Study or Subgroup	Anti-TNF Events	Anti-TNF Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Etanercept versus placebo						
Bachelez 2015	108	336	1	108	1.5%	34.71 [4.90 , 245.72]
Bagel 2012	15	62	1	62	1.4%	15.00 [2.04 , 110.11]
Gottlieb 2011	33	141	1	68	1.5%	15.91 [2.22 , 113.92]
Griffiths UNCOVER-2 2015	67	358	1	168	1.5%	31.44 [4.40 , 224.56]
Griffiths UNCOVER-3 2015	98	382	6	193	7.0%	8.25 [3.69 , 18.47]
Langley FIXTURE 2014	67	326	5	327	5.9%	13.44 [5.49 , 32.91]
Lebwohl CIMPACT 2018	46	170	0	57	0.8%	31.54 [1.98 , 503.75]
Leonardi 2003	60	504	1	168	1.5%	20.00 [2.79 , 143.20]
Papp 2005	59	407	1	204	1.5%	29.57 [4.13 , 211.91]
Reich LIBERATE 2017	17	83	3	84	3.7%	5.73 [1.75 , 18.84]
Reich ReSURFACE-2 2017	67	313	2	156	2.8%	16.70 [4.15 , 67.25]
Strober 2011	27	139	3	72	3.9%	4.66 [1.46 , 14.85]
Tyring 2006	65	311	4	309	5.0%	16.15 [5.96 , 43.77]
Van de Kerkhof 2008	13	96	1	46	1.4%	6.23 [0.84 , 46.18]
Subtotal (95% CI)		**3628**		**2022**	**39.4%**	**11.68 [8.14 , 16.75]**
Total events:	742		30			
Heterogeneity: Tau² = 0.00; Chi² = 10.49, df = 13 (P = 0.65); I² = 0%						
Test for overall effect: Z = 13.35 (P < 0.00001)						
1.3.2 Adalimumab versus placebo						
Asahina 2010	57	123	0	46	0.8%	43.59 [2.75 , 691.12]
Blauvelt VOYAGE-1 2016	166	334	5	174	6.2%	17.30 [7.24 , 41.31]
Cai 2016	188	338	3	87	4.1%	16.13 [5.28 , 49.24]
Elewski 2016	47	109	7	108	7.8%	6.65 [3.15 , 14.06]
Gordon 2006	35	96	0	52	0.8%	38.79 [2.43 , 619.78]
Gordon X-PLORE 2015	19	43	1	42	1.5%	18.56 [2.60 , 132.47]
Menter REVEAL 2008	366	814	9	398	9.5%	19.88 [10.38 , 38.10]
Reich VOYAGE-2 2017	116	248	6	248	7.1%	19.33 [8.67 , 43.09]
Saurat CHAMPION 2008	55	108	6	53	7.4%	4.50 [2.07 , 9.77]
Subtotal (95% CI)		**2213**		**1208**	**45.1%**	**13.13 [8.01 , 21.53]**
Total events:	1049		37			
Heterogeneity: Tau² = 0.25; Chi² = 16.13, df = 8 (P = 0.04); I² = 50%						
Test for overall effect: Z = 10.21 (P < 0.00001)						
1.3.3 Certolizumab versus placebo						
Gottlieb CIMPASI-1 2018	72	183	1	51	1.5%	20.07 [2.86 , 140.89]
Gottlieb CIMPASI-2 2018	95	178	2	49	2.9%	13.08 [3.34 , 51.16]
Lebwohl CIMPACT 2018	108	332	0	57	0.8%	37.80 [2.38 , 599.65]
Reich 2012a	50	118	1	58	1.5%	24.58 [3.48 , 173.49]
Subtotal (95% CI)		**811**		**215**	**6.7%**	**18.54 [7.42 , 46.32]**
Total events:	325		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 3 (P = 0.89); I² = 0%						
Test for overall effect: Z = 6.25 (P < 0.00001)						
1.3.4 Infliximab versus placebo						
Gottlieb 2004a	102	198	2	51	2.9%	13.14 [3.35 , 51.45]
Menter EXPRESS-II 2007	258	627	2	208	2.8%	42.79 [10.74 , 170.51]
Reich EXPRESS 2005	172	301	1	77	1.5%	44.00 [6.26 , 309.15]
Torii 2010	19	35	0	19	0.8%	21.67 [1.38 , 340.07]
Yang 2012	48	84	0	45	0.8%	52.49 [3.31 , 831.78]
Subtotal (95% CI)		**1245**		**400**	**8.8%**	**27.71 [12.52 , 61.30]**
Total events:	599		5			
Heterogeneity: Tau² = 0.00; Chi² = 2.10, df = 4 (P = 0.72); I² = 0%						
Test for overall effect: Z = 8.20 (P < 0.00001)						

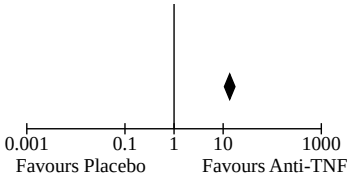


Analysis 1.3. (Continued)

Test for overall effect: Z = 8.20 (P < 0.00001)

Total (95% CI)	**7897**	**3845**	**100.0%**	**13.59 [10.63 , 17.38]**	
Total events:	2715	76			

Heterogeneity: Tau² = 0.06; Chi² = 35.15, df = 31 (P = 0.28); I² = 12%
Test for overall effect: Z = 20.80 (P < 0.00001)
Test for subgroup differences: Chi² = 4.22, df = 3 (P = 0.24), I² = 29.0%



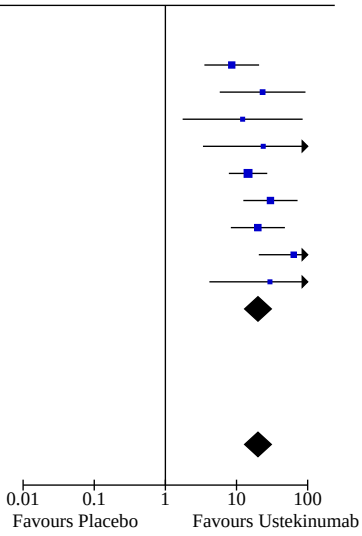
Analysis 1.4. Comparison 1: Primary outcome - PASI 90, Outcome 4: Anti-IL12/23 versus placebo

Study or Subgroup	Ustekinumab Events	Ustekinumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Ustekinumab versus placebo						
Gordon UltIMMa-1 2018	42	100	5	102	15.1%	8.57 [3.54 , 20.77]
Gordon UltIMMa-2 2018	47	99	2	98	7.8%	23.26 [5.81 , 93.14]
Igarashi 2012	48	126	1	32	4.4%	12.19 [1.75 , 84.99]
Krueger 2007	95	256	1	64	4.4%	23.75 [3.38 , 167.12]
Lebwohl AMAGINE-2 2015	141	300	10	309	22.4%	14.52 [7.80 , 27.04]
Lebwohl AMAGINE-3 2015	149	313	5	315	15.3%	29.99 [12.47 , 72.11]
Leonardi PHOENIX-1 2008	200	511	5	255	15.4%	19.96 [8.32 , 47.86]
Papp PHOENIX-2 2008	382	820	3	410	10.8%	63.67 [20.57 , 197.05]
Tsai PEARL 2011	30	61	1	60	4.3%	29.51 [4.16 , 209.54]
Subtotal (95% CI)	**2586**		**1645**		**100.0%**	**20.02 [13.01 , 30.81]**
Total events:	1134		33			

Heterogeneity: Tau² = 0.12; Chi² = 11.13, df = 8 (P = 0.19); I² = 28%
Test for overall effect: Z = 13.63 (P < 0.00001)

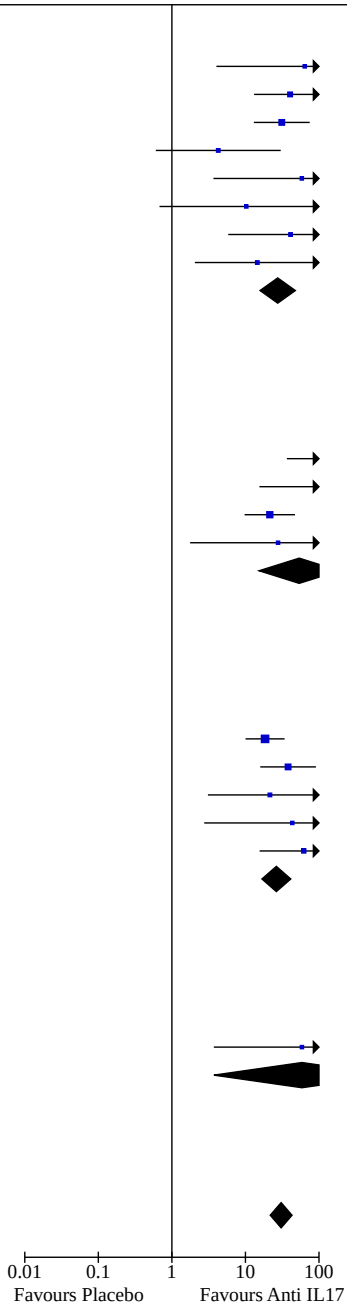
Total (95% CI)	**2586**	**1645**	**100.0%**	**20.02 [13.01 , 30.81]**	
Total events:	1134	33			

Heterogeneity: Tau² = 0.12; Chi² = 11.13, df = 8 (P = 0.19); I² = 28%
Test for overall effect: Z = 13.63 (P < 0.00001)
Test for subgroup differences: Not applicable



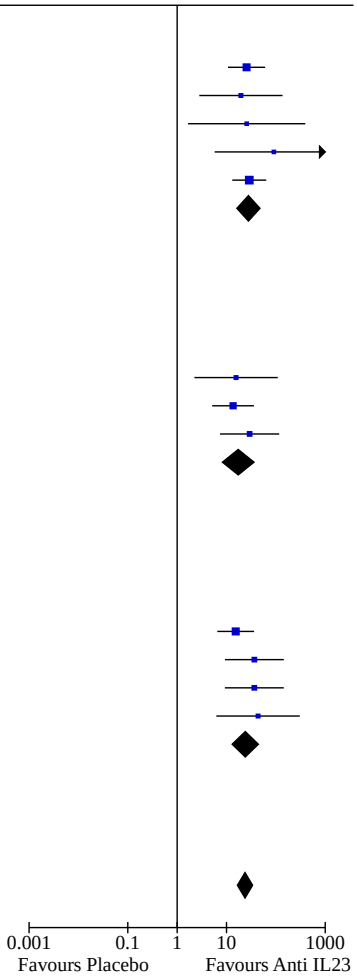
Analysis 1.5. Comparison 1: Primary outcome - PASI 90, Outcome 5: Anti-IL17 versus placebo

Study or Subgroup	Anti IL17 Events	Anti IL17 Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Secukinumab versus placebo						
Blauvelt FEATURE 2015	63	118	0	59	1.5%	64.03 [4.03 , 1017.14]
Langley ERASURE 2014	240	490	3	248	7.8%	40.49 [13.10 , 125.14]
Langley FIXTURE 2014	312	654	5	327	11.9%	31.20 [13.03 , 74.73]
Papp 2013a	20	103	1	22	2.9%	4.27 [0.60 , 30.17]
Paul JUNCTURE 2015	57	121	0	61	1.5%	58.44 [3.67 , 929.87]
Reich 2015	42	90	0	10	1.5%	10.27 [0.68 , 155.50]
Reich TRANSFIGURE 2016	84	133	1	65	2.9%	41.05 [5.85 , 288.30]
Rich 2013	73	337	1	67	2.9%	14.51 [2.05 , 102.61]
Subtotal (95% CI)		**2046**		**859**	**33.0%**	**27.47 [15.81 , 47.71]**
Total events:	891		11			
Heterogeneity: Tau² = 0.00; Chi² = 5.94, df = 7 (P = 0.55); I² = 0%						
Test for overall effect: Z = 11.76 (P < 0.00001)						
1.5.2 Ixekizumab versus placebo						
Gordon UNCOVER-1 2016	586	865	2	431	5.5%	145.99 [36.60 , 582.31]
Griffiths UNCOVER-2 2015	455	698	1	168	2.9%	109.51 [15.51 , 773.49]
Griffiths UNCOVER-3 2015	514	771	6	193	13.9%	21.44 [9.74 , 47.21]
Leonardi 2012	57	115	0	27	1.5%	27.76 [1.77 , 435.55]
Subtotal (95% CI)		**2449**		**819**	**23.8%**	**53.85 [15.34 , 189.07]**
Total events:	1612		9			
Heterogeneity: Tau² = 0.96; Chi² = 7.99, df = 3 (P = 0.05); I² = 62%						
Test for overall effect: Z = 6.22 (P < 0.00001)						
1.5.3 Brodalumab versus placebo						
Lebwohl AMAGINE-2 2015	731	1222	10	309	19.8%	18.48 [10.03 , 34.07]
Lebwohl AMAGINE-3 2015	756	1253	5	315	12.0%	38.01 [15.91 , 90.79]
Nakagawa 2016	64	113	1	38	2.9%	21.52 [3.09 , 149.88]
Papp 2012a	89	160	0	38	1.5%	43.36 [2.75 , 683.33]
Papp AMAGINE-1 2016	249	441	2	220	5.5%	62.11 [15.59 , 247.38]
Subtotal (95% CI)		**3189**		**920**	**41.7%**	**26.33 [16.77 , 41.33]**
Total events:	1889		18			
Heterogeneity: Tau² = 0.00; Chi² = 3.76, df = 4 (P = 0.44); I² = 0%						
Test for overall effect: Z = 14.21 (P < 0.00001)						
1.5.4 Bimekizumab versus placebo						
Papp BE ABLE 2018	142	208	0	42	1.5%	58.64 [3.72 , 923.86]
Subtotal (95% CI)		**208**		**42**	**1.5%**	**58.64 [3.72 , 923.86]**
Total events:	142		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.89 (P = 0.004)						
Total (95% CI)		**7892**		**2640**	**100.0%**	**30.58 [21.73 , 43.03]**
Total events:	4534		38			
Heterogeneity: Tau² = 0.06; Chi² = 19.04, df = 17 (P = 0.33); I² = 11%						
Test for overall effect: Z = 19.62 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.39, df = 3 (P = 0.71), I² = 0%						



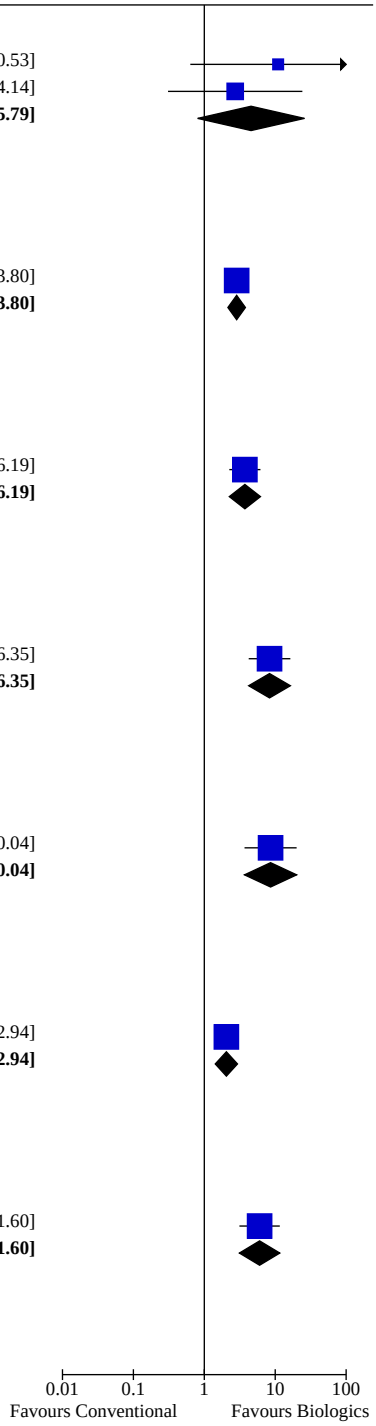
Analysis 1.6. Comparison 1: Primary outcome - PASI 90, Outcome 6: Anti-IL23 versus placebo

Study or Subgroup	Anti IL23 Events	Anti IL23 Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Guselkumab versus placebo						
Blauvelt VOYAGE-1 2016	241	329	5	174	16.7%	25.49 [10.72 , 60.62]
Gordon X-PLORE 2015	97	208	1	42	3.3%	19.59 [2.81 , 136.56]
NCT02905331 ORION	47	62	0	16	1.7%	25.63 [1.66 , 394.78]
Ohtsuki 2018	90	128	0	64	1.6%	91.20 [5.75 , 1445.91]
Reich VOYAGE-2 2017	347	496	6	248	19.9%	28.92 [13.09 , 63.88]
Subtotal (95% CI)		**1223**		**544**	**43.3%**	**27.79 [16.23 , 47.60]**
Total events:	822		12			
Heterogeneity: Tau² = 0.00; Chi² = 0.91, df = 4 (P = 0.92); I² = 0%						
Test for overall effect: Z = 12.11 (P < 0.00001)						
1.6.2 Tildrakizumab versus placebo						
Papp 2015	105	309	1	46	3.3%	15.63 [2.24 , 109.29]
Reich ReSURFACE-1 2017	216	616	4	155	13.2%	13.59 [5.13 , 35.96]
Reich ReSURFACE-2 2017	234	621	2	156	6.6%	29.39 [7.39 , 116.91]
Subtotal (95% CI)		**1546**		**357**	**23.1%**	**17.26 [8.27 , 36.05]**
Total events:	555		7			
Heterogeneity: Tau² = 0.00; Chi² = 0.84, df = 2 (P = 0.66); I² = 0%						
Test for overall effect: Z = 7.58 (P < 0.00001)						
1.6.3 Risankizumab versus placebo						
Gordon UltIMMa-1 2018	229	304	5	102	17.0%	15.37 [6.52 , 36.21]
Gordon UltIMMa-2 2018	220	294	2	98	6.6%	36.67 [9.29 , 144.77]
NCT02672852 IMMhance	298	407	2	100	6.6%	36.61 [9.27 , 144.54]
NCT03000075	85	113	1	58	3.3%	43.63 [6.23 , 305.39]
Subtotal (95% CI)		**1118**		**358**	**33.6%**	**24.00 [13.04 , 44.18]**
Total events:	832		10			
Heterogeneity: Tau² = 0.00; Chi² = 2.24, df = 3 (P = 0.52); I² = 0%						
Test for overall effect: Z = 10.21 (P < 0.00001)						
Total (95% CI)		**3887**		**1259**	**100.0%**	**23.70 [16.63 , 33.76]**
Total events:	2209		29			
Heterogeneity: Tau² = 0.00; Chi² = 5.04, df = 11 (P = 0.93); I² = 0%						
Test for overall effect: Z = 17.53 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.05, df = 2 (P = 0.59), I² = 0%						



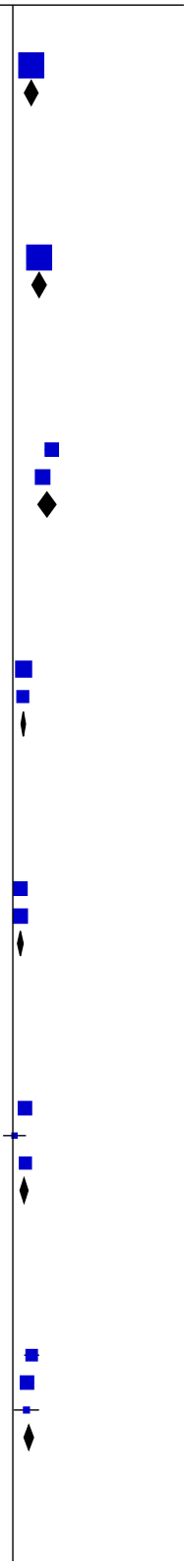
Analysis 1.7. Comparison 1: Primary outcome - PASI 90, Outcome 7: Biologic versus conventional systemic treatments

Study or Subgroup	Biologic Events	Biologic Total	Conventional systemic Events	Conventional systemic Total	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 Etanercept versus acitretin						
Caproni 2009	5	30	0	30	36.9%	11.00 [0.64 , 190.53]
Gisondi 2008	3	22	1	20	63.1%	2.73 [0.31 , 24.14]
Subtotal (95% CI)		**52**		**50**	**100.0%**	**4.56 [0.81 , 25.79]**
Total events:	8		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 1.72 (P = 0.09)						
1.7.2 Infliximab versus methotrexate						
Barker RESTORE-1 2011	356	653	41	215	100.0%	2.86 [2.15 , 3.80]
Subtotal (95% CI)		**653**		**215**	**100.0%**	**2.86 [2.15 , 3.80]**
Total events:	356		41			
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.25 (P < 0.00001)						
1.7.3 Adalimumab versus methotrexate						
Saurat CHAMPION 2008	55	108	15	110	100.0%	3.73 [2.25 , 6.19]
Subtotal (95% CI)		**108**		**110**	**100.0%**	**3.73 [2.25 , 6.19]**
Total events:	55		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.11 (P < 0.00001)						
1.7.4 Secukinumab versus fumaric acid esters						
Sticherling PRIME 2017	72	105	8	97	100.0%	8.31 [4.23 , 16.35]
Subtotal (95% CI)		**105**		**97**	**100.0%**	**8.31 [4.23 , 16.35]**
Total events:	72		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.14 (P < 0.00001)						
1.7.5 Ixekizumab versus fumaric ester acids						
NCT02634801	43	54	5	54	100.0%	8.60 [3.69 , 20.04]
Subtotal (95% CI)		**54**		**54**	**100.0%**	**8.60 [3.69 , 20.04]**
Total events:	43		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.99 (P < 0.00001)						
1.7.6 Ixekizumab versus methotrexate						
NCT02634801	43	54	21	54	100.0%	2.05 [1.43 , 2.94]
Subtotal (95% CI)		**54**		**54**	**100.0%**	**2.05 [1.43 , 2.94]**
Total events:	43		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.90 (P < 0.0001)						
1.7.7 Guselkumab versus fumaric ester acids						
NCT02951533 POLARIS	49	60	8	59	100.0%	6.02 [3.13 , 11.60]
Subtotal (95% CI)		**60**		**59**	**100.0%**	**6.02 [3.13 , 11.60]**
Total events:	49		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.37 (P < 0.00001)						



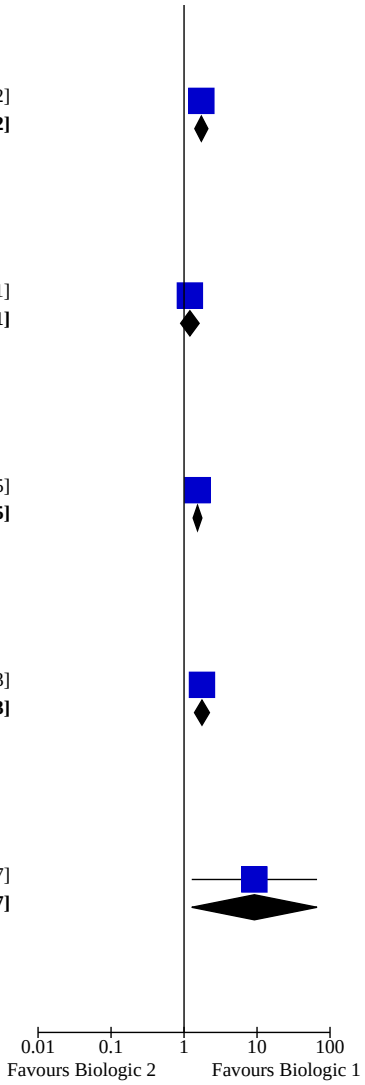
Analysis 1.8. Comparison 1: Primary outcome - PASI 90, Outcome 8: Biologic 1 versus biologic 2

Study or Subgroup	Biologic 1 Events	Biologic 1 Total	Biologic 2 Events	Biologic 2 Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Ustekinumab versus etanercept						
Griffiths ACCEPT 2010	231	556	80	347	100.0%	1.80 [1.45 , 2.24]
Subtotal (95% CI)		**556**		**347**	**100.0%**	**1.80 [1.45 , 2.24]**
Total events:	231		80			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.34 (P < 0.00001)						
1.8.2 Secukinumab versus etanercept						
Langley FIXTURE 2014	312	654	67	326	100.0%	2.32 [1.85 , 2.92]
Subtotal (95% CI)		**654**		**326**	**100.0%**	**2.32 [1.85 , 2.92]**
Total events:	312		67			
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.24 (P < 0.00001)						
1.8.3 Ixekizumab versus etanercept						
Griffiths UNCOVER-2 2015	455	698	67	358	47.3%	3.48 [2.79 , 4.35]
Griffiths UNCOVER-3 2015	514	771	98	382	52.7%	2.60 [2.18 , 3.10]
Subtotal (95% CI)		**1469**		**740**	**100.0%**	**2.98 [2.24 , 3.98]**
Total events:	969		165			
Heterogeneity: Tau² = 0.03; Chi² = 4.10, df = 1 (P = 0.04); I² = 76%						
Test for overall effect: Z = 7.44 (P < 0.00001)						
1.8.4 Secukinumab versus ustekinumab						
Bagel CLARITY 2018	421	550	299	552	59.4%	1.41 [1.29 , 1.55]
Thaçi CLEAR 2015	264	337	193	339	40.6%	1.38 [1.23 , 1.53]
Subtotal (95% CI)		**887**		**891**	**100.0%**	**1.40 [1.30 , 1.50]**
Total events:	685		492			
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%						
Test for overall effect: Z = 9.51 (P < 0.00001)						
1.8.5 Brodalumab versus ustekinumab						
Lebwohl AMAGINE-2 2015	731	1222	141	300	48.4%	1.27 [1.12 , 1.45]
Lebwohl AMAGINE-3 2015	758	1253	149	313	51.6%	1.27 [1.12 , 1.44]
Subtotal (95% CI)		**2475**		**613**	**100.0%**	**1.27 [1.16 , 1.39]**
Total events:	1489		290			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 5.27 (P < 0.00001)						
1.8.6 Guselkumab versus adalimumab						
Blauvelt VOYAGE-1 2016	241	329	166	334	47.8%	1.47 [1.30 , 1.67]
Gordon X-PLORE 2015	97	208	19	43	10.6%	1.06 [0.73 , 1.52]
Reich VOYAGE-2 2017	347	496	116	248	41.6%	1.50 [1.29 , 1.73]
Subtotal (95% CI)		**1033**		**625**	**100.0%**	**1.43 [1.26 , 1.62]**
Total events:	685		301			
Heterogeneity: Tau² = 0.00; Chi² = 3.14, df = 2 (P = 0.21); I² = 36%						
Test for overall effect: Z = 5.55 (P < 0.00001)						
1.8.7 Risankizumab versus ustekinumab						
Gordon UltIMMa-1 2018	229	304	42	102	38.8%	1.83 [1.44 , 2.33]
Gordon UltIMMa-2 2018	220	294	47	99	47.5%	1.58 [1.27 , 1.96]
Papp NCT02054481 2017	78	126	16	40	13.8%	1.55 [1.03 , 2.32]
Subtotal (95% CI)		**724**		**241**	**100.0%**	**1.67 [1.43 , 1.93]**
Total events:	527		105			
Heterogeneity: Tau² = 0.00; Chi² = 0.96, df = 2 (P = 0.62); I² = 0%						
Test for overall effect: Z = 6.67 (P < 0.00001)						

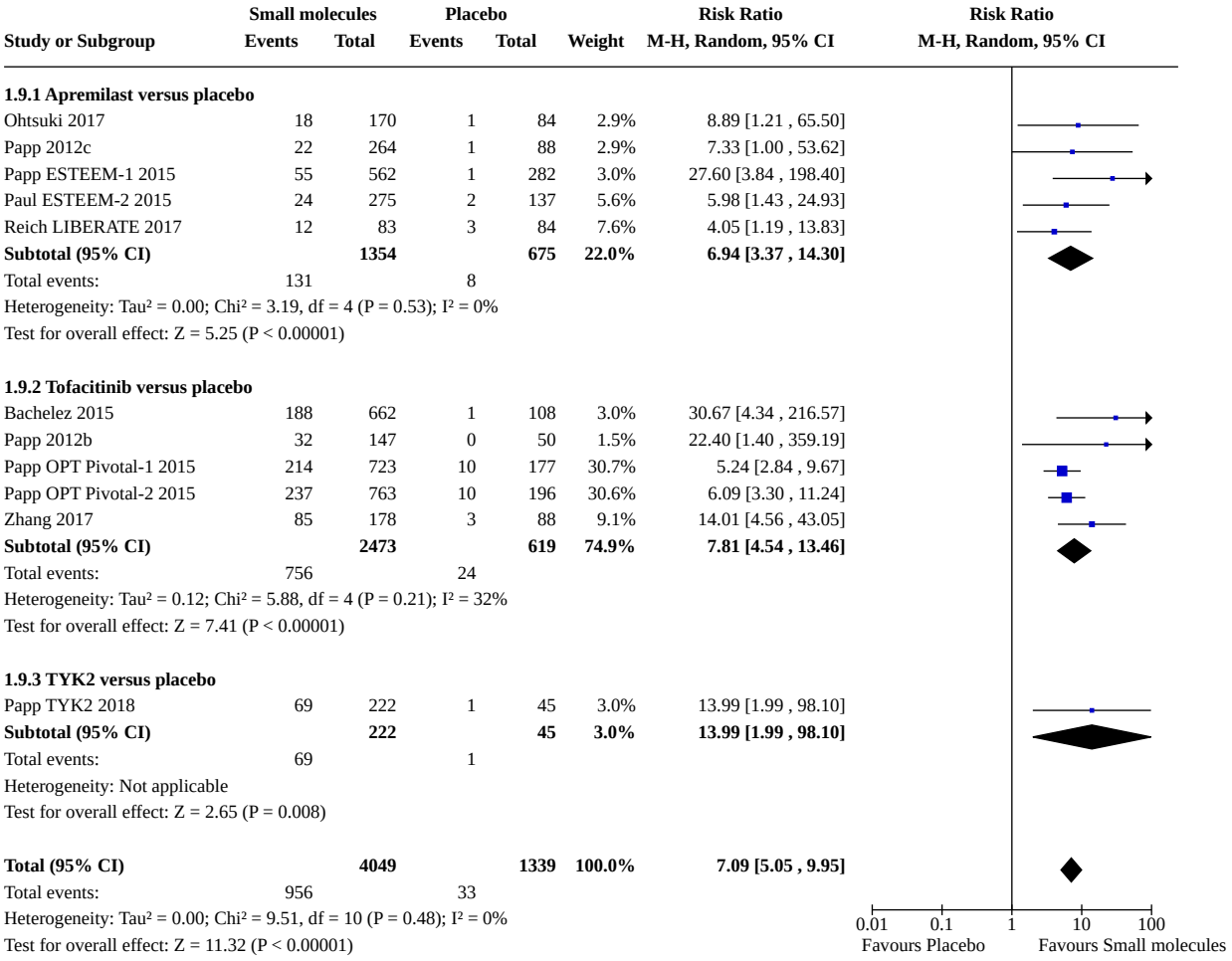


Analysis 1.8. (Continued)

Test for overall effect: Z = 6.67 (P < 0.00001)						
1.8.8 Ixekizumab versus ustekinumab						
Reich IXORA-S 2017	99	136	70	166	100.0%	1.73 [1.41 , 2.12]
Subtotal (95% CI)		**136**		**166**	**100.0%**	**1.73 [1.41 , 2.12]**
Total events:	99		70			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.20 (P < 0.00001)						
1.8.9 Certolizumab versus etanercept						
Lebwohl CIMPACT 2018	108	332	46	170	100.0%	1.20 [0.90 , 1.61]
Subtotal (95% CI)		**332**		**170**	**100.0%**	**1.20 [0.90 , 1.61]**
Total events:	108		46			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.24 (P = 0.22)						
1.8.10 Risankizumab versus adalimumab						
EUCTR2015-003623-65-DE	218	301	144	304	100.0%	1.53 [1.33 , 1.75]
Subtotal (95% CI)		**301**		**304**	**100.0%**	**1.53 [1.33 , 1.75]**
Total events:	218		144			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.05 (P < 0.00001)						
1.8.11 Tildrakizumab versus etanercept						
Reich ReSURFACE-2 2017	234	621	67	313	100.0%	1.76 [1.39 , 2.23]
Subtotal (95% CI)		**621**		**313**	**100.0%**	**1.76 [1.39 , 2.23]**
Total events:	234		67			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.71 (P < 0.00001)						
1.8.12 Inliximab versus etanercept						
De Vries PIECE 2016	10	25	1	23	100.0%	9.20 [1.28 , 66.37]
Subtotal (95% CI)		**25**		**23**	**100.0%**	**9.20 [1.28 , 66.37]**
Total events:	10		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.20 (P = 0.03)						

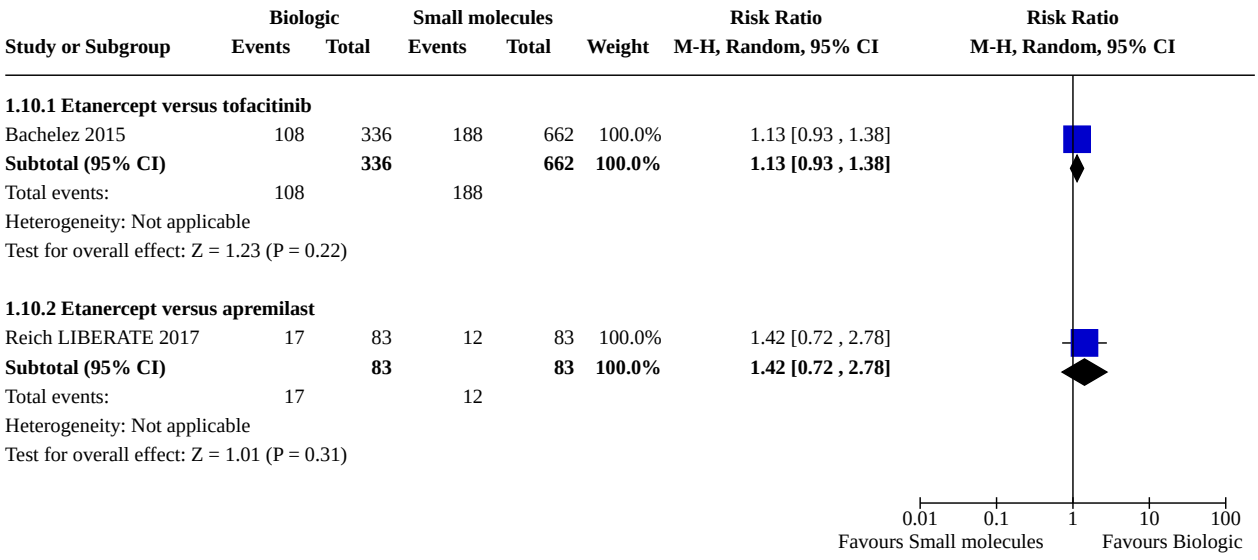


Analysis 1.9. Comparison 1: Primary outcome - PASI 90, Outcome 9: Small molecules versus placebo



Study or Subgroup	Small molecules Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 Apremilast versus placebo						
Ohtsuki 2017	18	170	1	84	2.9%	8.89 [1.21 , 65.50]
Papp 2012c	22	264	1	88	2.9%	7.33 [1.00 , 53.62]
Papp ESTEEM-1 2015	55	562	1	282	3.0%	27.60 [3.84 , 198.40]
Paul ESTEEM-2 2015	24	275	2	137	5.6%	5.98 [1.43 , 24.93]
Reich LIBERATE 2017	12	83	3	84	7.6%	4.05 [1.19 , 13.83]
Subtotal (95% CI)		**1354**		**675**	**22.0%**	**6.94 [3.37 , 14.30]**
Total events:	131		8			
Heterogeneity: Tau² = 0.00; Chi² = 3.19, df = 4 (P = 0.53); I² = 0%						
Test for overall effect: Z = 5.25 (P < 0.00001)						
1.9.2 Tofacitinib versus placebo						
Bachelez 2015	188	662	1	108	3.0%	30.67 [4.34 , 216.57]
Papp 2012b	32	147	0	50	1.5%	22.40 [1.40 , 359.19]
Papp OPT Pivotal-1 2015	214	723	10	177	30.7%	5.24 [2.84 , 9.67]
Papp OPT Pivotal-2 2015	237	763	10	196	30.6%	6.09 [3.30 , 11.24]
Zhang 2017	85	178	3	88	9.1%	14.01 [4.56 , 43.05]
Subtotal (95% CI)		**2473**		**619**	**74.9%**	**7.81 [4.54 , 13.46]**
Total events:	756		24			
Heterogeneity: Tau² = 0.12; Chi² = 5.88, df = 4 (P = 0.21); I² = 32%						
Test for overall effect: Z = 7.41 (P < 0.00001)						
1.9.3 TYK2 versus placebo						
Papp TYK2 2018	69	222	1	45	3.0%	13.99 [1.99 , 98.10]
Subtotal (95% CI)		**222**		**45**	**3.0%**	**13.99 [1.99 , 98.10]**
Total events:	69		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.65 (P = 0.008)						
Total (95% CI)		**4049**		**1339**	**100.0%**	**7.09 [5.05 , 9.95]**
Total events:	956		33			
Heterogeneity: Tau² = 0.00; Chi² = 9.51, df = 10 (P = 0.48); I² = 0%						
Test for overall effect: Z = 11.32 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.44, df = 2 (P = 0.80), I² = 0%						

Analysis 1.10. Comparison 1: Primary outcome - PASI 90, Outcome 10: Biologic versus small molecules



Study or Subgroup	Biologic Events	Total	Small molecules Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.10.1 Etanercept versus tofacitinib						
Bachelez 2015	108	336	188	662	100.0%	1.13 [0.93 , 1.38]
Subtotal (95% CI)		**336**		**662**	**100.0%**	**1.13 [0.93 , 1.38]**
Total events:	108		188			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.23 (P = 0.22)						
1.10.2 Etanercept versus apremilast						
Reich LIBERATE 2017	17	83	12	83	100.0%	1.42 [0.72 , 2.78]
Subtotal (95% CI)		**83**		**83**	**100.0%**	**1.42 [0.72 , 2.78]**
Total events:	17		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.01 (P = 0.31)						

Comparison 2. Primary outcome - serious adverse events (SAE)

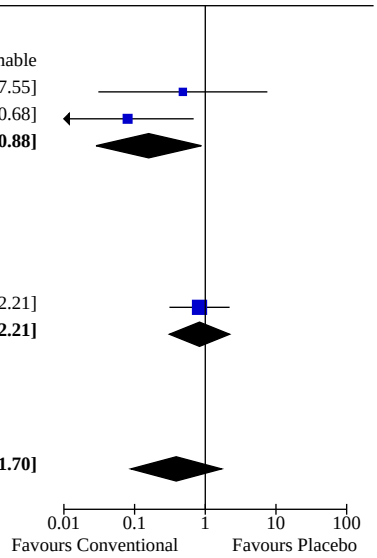
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Conventional systemic agents versus placebo	4	1023	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.09, 1.70]
2.1.1 Methotrexate versus placebo	3	319	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.03, 0.88]
2.1.2 Fumaric acid esters versus placebo	1	704	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.31, 2.21]
2.2 Conventional systemic agents versus conventional agents	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.2.1 Methotrexate versus fumaric ester acids	1	108	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.04, 3.10]
2.3 Anti-TNF alpha versus placebo	32	10454	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.77, 1.49]
2.3.1 Etanercept versus placebo	13	4265	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.53, 1.60]
2.3.2 Adalimumab versus placebo	10	3485	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.72, 1.84]
2.3.3 Certolizumab versus placebo	4	1026	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.19, 7.50]
2.3.4 Infliximab versus placebo	6	1678	Risk Ratio (M-H, Random, 95% CI)	1.99 [0.82, 4.78]
2.4 Anti-IL12/23 versus placebo	10	4553	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.59, 1.54]
2.4.1 Ustekinumab versus placebo	10	4553	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.59, 1.54]
2.5 Anti-IL17 versus placebo	18	10531	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.73, 1.42]
2.5.1 Secukinumab versus placebo	8	2904	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.63, 1.89]
2.5.2 Ixekizumab versus placebo	4	3268	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.63, 2.13]
2.5.3 Brodalumab versus placebo	5	4109	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.52, 1.61]
2.5.4 Bimekizumab versus placebo	1	250	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 3.16]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.6 Anti-IL23 versus placebo	12	5147	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.49, 1.25]
2.6.1 Guselkumab versus placebo	5	1767	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.50, 2.28]
2.6.2 Tildrakizumab versus placebo	3	1904	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.37, 2.77]
2.6.3 Risankizumab versus placebo	4	1476	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.24, 2.10]
2.7 Biologic versus conventional systemic treatments	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.7.1 Etanercept versus acitretin	3	142	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.01, 7.02]
2.7.2 Infliximab versus methotrexate	1	868	Risk Ratio (M-H, Random, 95% CI)	2.41 [1.04, 5.59]
2.7.3 Adalimumab versus methotrexate	1	218	Risk Ratio (M-H, Random, 95% CI)	2.04 [0.19, 22.14]
2.7.4 Secukinumab versus fumaric acid esters	1	202	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.16, 1.75]
2.7.5 Ixekizumab versus fumaric ester acids	1	108	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.04, 3.10]
2.7.6 Ixekizumab versus methotrexate	1	108	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.06, 15.58]
2.7.7 Guselkumab versus fumaric ester acids	1	119	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.26, 8.51]
2.8 Biologic 1 versus biologic 2	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.8.1 Ustekinumab versus etanercept	1	903	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.38, 4.11]
2.8.2 Secukinumab versus etanercept	1	980	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.41, 2.82]
2.8.3 Ixekizumab versus etanercept	2	2209	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.55, 2.06]
2.8.4 Secukinumab versus ustekinumab	2	1778	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.70, 2.30]
2.8.5 Brodalumab versus ustekinumab	2	3088	Risk Ratio (M-H, Random, 95% CI)	1.51 [0.64, 3.56]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.8.6 Guselkumab versus adalimumab	3	1658	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.45, 1.84]
2.8.7 Risankizumab versus ustekinumab	3	965	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.24, 1.32]
2.8.8 Ixekizumab versus ustekinumab	1	302	Risk Ratio (M-H, Random, 95% CI)	1.83 [0.67, 5.02]
2.8.9 Certolizumab versus etanercept	1	502	Risk Ratio (M-H, Random, 95% CI)	2.56 [0.30, 21.74]
2.8.10 Risankizumab versus adalimumab	1	605	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.46, 2.72]
2.8.11 Tildrakizumab versus etanercept	1	934	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.28, 1.87]
2.8.12 Infliximab versus etanercept	1	48	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.06, 13.87]
2.9 Small molecules versus placebo	14	5679	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.60, 1.44]
2.9.1 Apremilast versus placebo	6	2290	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.44, 1.68]
2.9.2 Tofacitinib versus placebo	7	3122	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.57, 2.11]
2.9.3 TYK2 versus placebo	1	267	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.06, 5.71]
2.10 Biologic versus small molecules	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.10.1 Etanercept versus tofacitinib	1	998	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.46, 2.89]
2.10.2 Etanercept versus apremilast	1	166	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.04, 3.14]

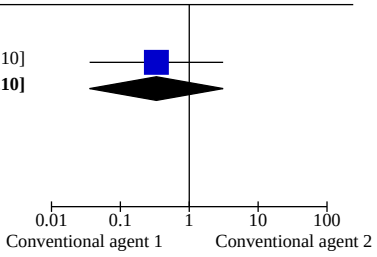
Analysis 2.1. Comparison 2: Primary outcome - serious adverse events (SAE), Outcome 1: Conventional systemic agents versus placebo

Study or Subgroup	Conventional treatment Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Methotrexate versus placebo						
Hunter 1963	0	19	0	17		Not estimable
Saurat CHAMPION 2008	1	110	1	53	20.2%	0.48 [0.03 , 7.55]
Warren METOP, 2017	1	91	4	29	27.8%	0.08 [0.01 , 0.68]
Subtotal (95% CI)		**220**		**99**	**47.9%**	**0.16 [0.03 , 0.88]**
Total events:	2		5			
Heterogeneity: Tau² = 0.03; Chi² = 1.02, df = 1 (P = 0.31); I² = 2%						
Test for overall effect: Z = 2.11 (P = 0.04)						
2.1.2 Fumaric acid esters versus placebo						
Mrowietz BRIDGE 2016	17	566	5	138	52.1%	0.83 [0.31 , 2.21]
Subtotal (95% CI)		**566**		**138**	**52.1%**	**0.83 [0.31 , 2.21]**
Total events:	17		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.38 (P = 0.71)						
Total (95% CI)		**786**		**237**	**100.0%**	**0.39 [0.09 , 1.70]**
Total events:	19		10			
Heterogeneity: Tau² = 0.84; Chi² = 3.82, df = 2 (P = 0.15); I² = 48%						
Test for overall effect: Z = 1.26 (P = 0.21)						
Test for subgroup differences: Chi² = 2.70, df = 1 (P = 0.10), I² = 63.0%						



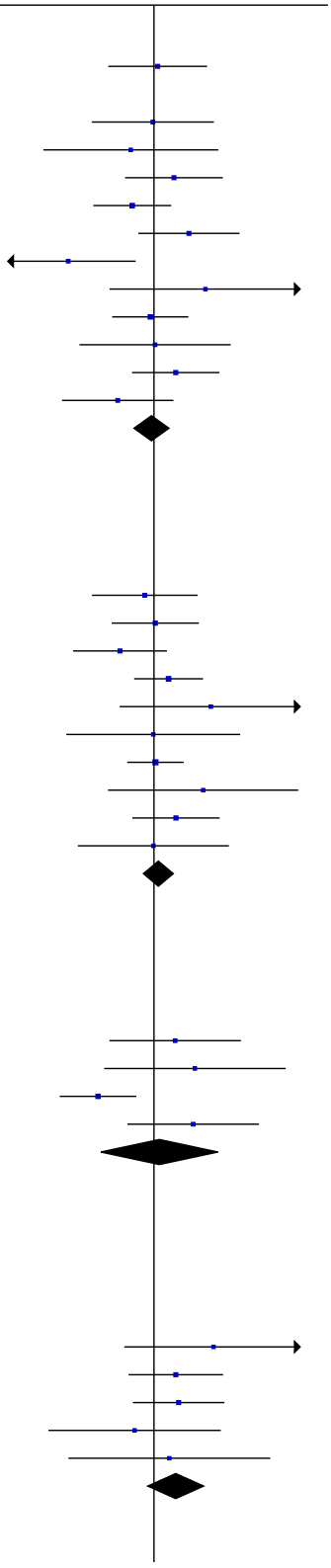
Analysis 2.2. Comparison 2: Primary outcome - serious adverse events (SAE), Outcome 2: Conventional systemic agents versus conventional agents

Study or Subgroup	Conventional agent 1 Events	Total	Conventional agent 2 Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Methotrexate versus fumaric ester acids						
NCT02634801	1	54	3	54	100.0%	0.33 [0.04 , 3.10]
Subtotal (95% CI)		**54**		**54**	**100.0%**	**0.33 [0.04 , 3.10]**
Total events:	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.96 (P = 0.33)						



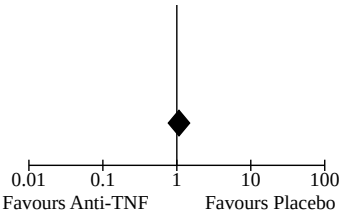
Analysis 2.3. Comparison 2: Primary outcome - serious adverse events (SAE), Outcome 3: Anti-TNF alpha versus placebo

Study or Subgroup	Anti-TNF Events	Anti-TNF Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Etanercept versus placebo						
Bachelez 2015	7	336	2	108	3.8%	1.13 [0.24 , 5.33]
Bagel 2012	0	62	0	62		Not estimable
Gottlieb 2003a	2	57	2	55	2.6%	0.96 [0.14 , 6.61]
Gottlieb 2011	1	141	1	68	1.4%	0.48 [0.03 , 7.59]
Griffiths UNCOVER-2 2015	8	358	2	168	3.8%	1.88 [0.40 , 8.74]
Griffiths UNCOVER-3 2015	5	382	5	193	5.5%	0.51 [0.15 , 1.72]
Langley FIXTURE 2014	6	326	2	327	3.6%	3.01 [0.61 , 14.80]
Lebwohl CIMPACT 2018	1	170	5	57	2.2%	0.07 [0.01 , 0.56]
Reich LIBERATE 2017	2	83	0	84	1.1%	5.06 [0.25 , 103.82]
Reich ReSURFACE-2 2017	7	169	4	86	5.7%	0.89 [0.27 , 2.96]
Strober 2011	2	139	1	72	1.8%	1.04 [0.10 , 11.23]
Tyring 2006	6	311	3	309	4.6%	1.99 [0.50 , 7.87]
Van de Kerkhof 2008	2	96	3	46	3.1%	0.32 [0.06 , 1.85]
Subtotal (95% CI)		**2630**		**1635**	**39.1%**	**0.92 [0.53 , 1.60]**
Total events:	49		30			
Heterogeneity: Tau² = 0.19; Chi² = 13.80, df = 11 (P = 0.24); I² = 20%						
Test for overall effect: Z = 0.28 (P = 0.78)						
2.3.2 Adalimumab versus placebo						
Asahina 2010	4	123	2	46	3.4%	0.75 [0.14 , 3.95]
Blauvelt VOYAGE-1 2016	6	334	3	174	4.6%	1.04 [0.26 , 4.12]
Cai 2016	4	338	3	87	4.1%	0.34 [0.08 , 1.51]
Elewski 2016	8	109	5	108	6.6%	1.59 [0.54 , 4.69]
Gordon 2006	5	96	0	52	1.2%	6.01 [0.34 , 106.60]
Gordon X-PLORE 2015	1	43	1	42	1.4%	0.98 [0.06 , 15.11]
Menter REVEAL 2008	15	814	7	398	8.6%	1.05 [0.43 , 2.55]
NCT01553058 VIP trial	2	33	0	31	1.2%	4.71 [0.23 , 94.31]
Reich VOYAGE-2 2017	6	248	3	248	4.6%	2.00 [0.51 , 7.91]
Saurat CHAMPION 2008	2	108	1	53	1.8%	0.98 [0.09 , 10.58]
Subtotal (95% CI)		**2246**		**1239**	**37.4%**	**1.15 [0.72 , 1.84]**
Total events:	53		25			
Heterogeneity: Tau² = 0.00; Chi² = 6.10, df = 9 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.58 (P = 0.56)						
2.3.3 Certolizumab versus placebo						
Gottlieb CIMPASI-1 2018	7	183	1	51	2.3%	1.95 [0.25 , 15.49]
Gottlieb CIMPASI-2 2018	6	178	0	49	1.3%	3.63 [0.21 , 63.36]
Lebwohl CIMPACT 2018	5	332	5	57	5.6%	0.17 [0.05 , 0.57]
Reich 2012a	7	118	1	58	2.3%	3.44 [0.43 , 27.31]
Subtotal (95% CI)		**811**		**215**	**11.5%**	**1.19 [0.19 , 7.50]**
Total events:	25		7			
Heterogeneity: Tau² = 2.46; Chi² = 10.64, df = 3 (P = 0.01); I² = 72%						
Test for overall effect: Z = 0.18 (P = 0.86)						
2.3.4 Infliximab versus placebo						
Chaudhari 2001	0	22	0	11		Not estimable
Gottlieb 2004a	12	198	0	51	1.3%	6.53 [0.39 , 108.53]
Menter EXPRESS-II 2007	12	627	2	208	4.0%	1.99 [0.45 , 8.82]
Reich EXPRESS 2005	17	301	2	77	4.3%	2.17 [0.51 , 9.21]
Torii 2010	1	35	1	19	1.4%	0.54 [0.04 , 8.20]
Yang 2012	1	84	0	45	1.0%	1.62 [0.07 , 39.06]
Subtotal (95% CI)		**1267**		**411**	**12.0%**	**1.99 [0.82 , 4.78]**
Total events:	43		5			
Heterogeneity: Tau² = 0.00; Chi² = 1.66, df = 4 (P = 0.80); I² = 0%						



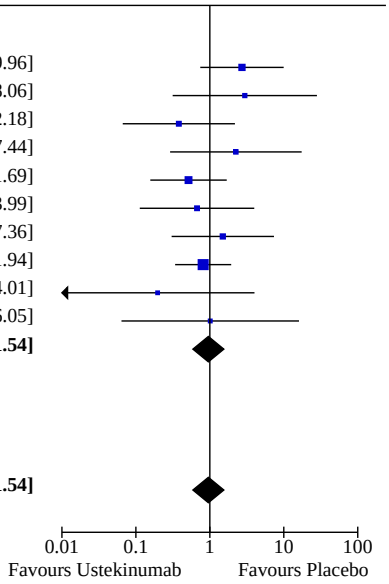
Analysis 2.3. (Continued)

Total events:	43		5			
Heterogeneity: Tau² = 0.00; Chi² = 1.66, df = 4 (P = 0.80); I² = 0%						
Test for overall effect: Z = 1.53 (P = 0.13)						
Total (95% CI)		**6954**		**3500**	**100.0%**	**1.07 [0.77 , 1.49]**
Total events:	170		67			
Heterogeneity: Tau² = 0.13; Chi² = 35.26, df = 30 (P = 0.23); I² = 15%						
Test for overall effect: Z = 0.40 (P = 0.69)						
Test for subgroup differences: Chi² = 2.09, df = 3 (P = 0.55), I² = 0%						



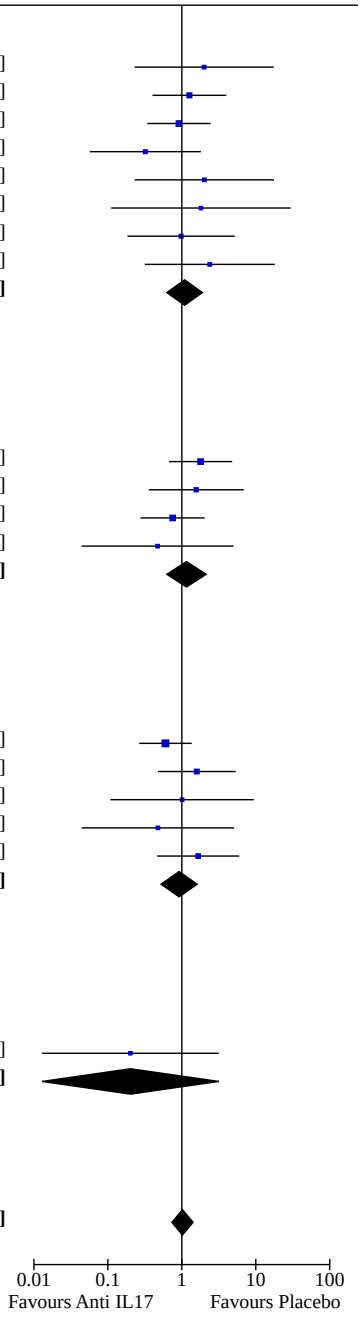
Analysis 2.4. Comparison 2: Primary outcome - serious adverse events (SAE), Outcome 4: Anti-IL12/23 versus placebo

Study or Subgroup	Ustekinumab Events	Ustekinumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 Ustekinumab versus placebo						
Gordon UltIMMa-1 2018	8	100	3	102	13.7%	2.72 [0.74 , 9.96]
Gordon UltIMMa-2 2018	3	99	1	98	4.6%	2.97 [0.31 , 28.06]
Igarashi 2012	3	126	2	32	7.6%	0.38 [0.07 , 2.18]
Krueger 2007	9	256	1	64	5.5%	2.25 [0.29 , 17.44]
Lebwohl AMAGINE-2 2015	4	300	8	309	16.3%	0.52 [0.16 , 1.69]
Lebwohl AMAGINE-3 2015	2	313	3	315	7.3%	0.67 [0.11 , 3.99]
Leonardi PHOENIX-1 2008	6	511	2	255	9.1%	1.50 [0.30 , 7.36]
Papp PHOENIX-2 2008	13	820	8	410	30.3%	0.81 [0.34 , 1.94]
Tsai PEARL 2011	0	61	2	60	2.5%	0.20 [0.01 , 4.01]
Zhu LOTUS 2013	1	160	1	162	3.0%	1.01 [0.06 , 16.05]
Subtotal (95% CI)		**2746**		**1807**	**100.0%**	**0.96 [0.59 , 1.54]**
Total events:	49		31			
Heterogeneity: Tau² = 0.00; Chi² = 7.91, df = 9 (P = 0.54); I² = 0%						
Test for overall effect: Z = 0.19 (P = 0.85)						
Total (95% CI)		**2746**		**1807**	**100.0%**	**0.96 [0.59 , 1.54]**
Total events:	49		31			
Heterogeneity: Tau² = 0.00; Chi² = 7.91, df = 9 (P = 0.54); I² = 0%						
Test for overall effect: Z = 0.19 (P = 0.85)						
Test for subgroup differences: Not applicable						



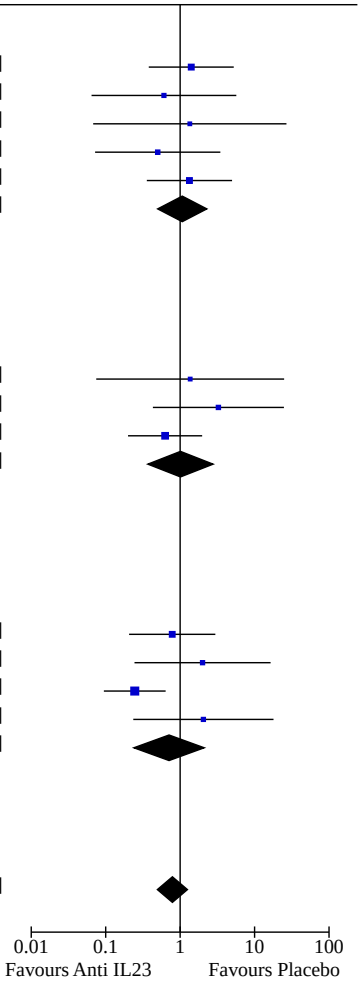
Analysis 2.5. Comparison 2: Primary outcome - serious adverse events (SAE), Outcome 5: Anti-IL17 versus placebo

Study or Subgroup	Anti IL17 Events	Anti IL17 Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 Secukinumab versus placebo						
Blauvelt FEATURE 2015	4	118	1	59	2.3%	2.00 [0.23 , 17.50]
Langley ERASURE 2014	10	490	4	248	8.2%	1.27 [0.40 , 3.99]
Langley FIXTURE 2014	11	654	6	326	11.1%	0.91 [0.34 , 2.45]
Papp 2013a	3	103	2	22	3.6%	0.32 [0.06 , 1.81]
Paul JUNCTURE 2015	4	121	1	61	2.3%	2.02 [0.23 , 17.65]
Reich 2015	7	90	0	10	1.4%	1.81 [0.11 , 29.62]
Reich TRANSFIGURE 2016	4	133	2	65	3.9%	0.98 [0.18 , 5.20]
Rich 2013	12	337	1	67	2.6%	2.39 [0.32 , 18.04]
Subtotal (95% CI)		**2046**		**858**	**35.4%**	**1.09 [0.63 , 1.89]**
Total events:	55		17			
Heterogeneity: Tau² = 0.00; Chi² = 3.51, df = 7 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.30 (P = 0.76)						
2.5.2 Ixekizumab versus placebo						
Gordon UNCOVER-1 2016	18	865	5	431	11.2%	1.79 [0.67 , 4.80]
Griffiths UNCOVER-2 2015	13	698	2	168	4.9%	1.56 [0.36 , 6.87]
Griffiths UNCOVER-3 2015	15	771	5	193	10.8%	0.75 [0.28 , 2.04]
Leonardi 2012	2	115	1	27	1.9%	0.47 [0.04 , 4.99]
Subtotal (95% CI)		**2449**		**819**	**28.9%**	**1.16 [0.63 , 2.13]**
Total events:	48		13			
Heterogeneity: Tau² = 0.00; Chi² = 2.23, df = 3 (P = 0.53); I² = 0%						
Test for overall effect: Z = 0.46 (P = 0.64)						
2.5.3 Brodalumab versus placebo						
Lebwohl AMAGINE-2 2015	19	1222	8	309	16.2%	0.60 [0.27 , 1.36]
Lebwohl AMAGINE-3 2015	19	1253	3	315	7.4%	1.59 [0.47 , 5.35]
Nakagawa 2016	3	113	1	38	2.2%	1.01 [0.11 , 9.41]
Papp 2012a	2	160	1	38	1.9%	0.47 [0.04 , 5.10]
Papp AMAGINE-1 2016	10	441	3	220	6.6%	1.66 [0.46 , 5.98]
Subtotal (95% CI)		**3189**		**920**	**34.3%**	**0.92 [0.52 , 1.61]**
Total events:	53		16			
Heterogeneity: Tau² = 0.00; Chi² = 3.02, df = 4 (P = 0.56); I² = 0%						
Test for overall effect: Z = 0.29 (P = 0.77)						
2.5.4 Bimekizumab versus placebo						
Papp BE ABLE 2018	1	208	1	42	1.4%	0.20 [0.01 , 3.16]
Subtotal (95% CI)		**208**		**42**	**1.4%**	**0.20 [0.01 , 3.16]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.14 (P = 0.25)						
Total (95% CI)		**7892**		**2639**	**100.0%**	**1.02 [0.73 , 1.42]**
Total events:	157		47			
Heterogeneity: Tau² = 0.00; Chi² = 10.46, df = 17 (P = 0.88); I² = 0%						
Test for overall effect: Z = 0.12 (P = 0.90)						
Test for subgroup differences: Chi² = 1.68, df = 3 (P = 0.64), I² = 0%						



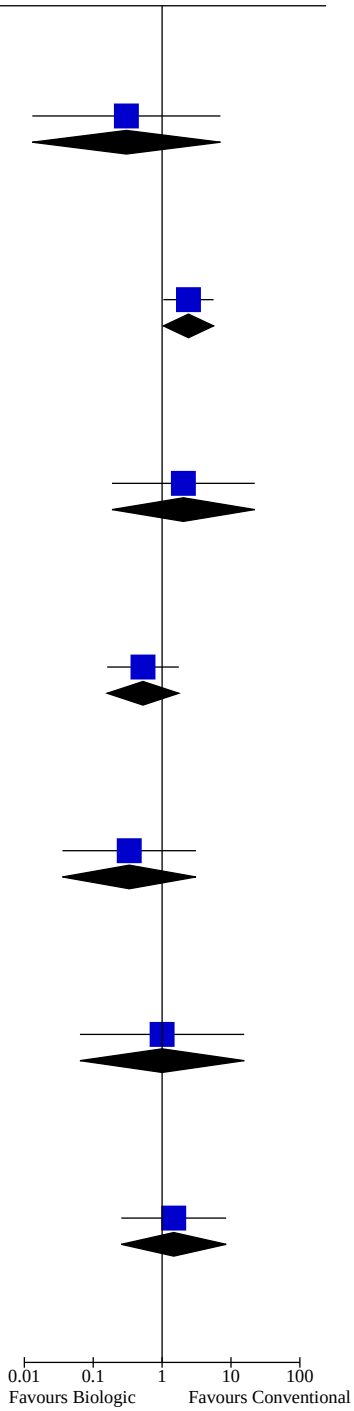
Analysis 2.6. Comparison 2: Primary outcome - serious adverse events (SAE), Outcome 6: Anti-IL23 versus placebo

Study or Subgroup	Anti IL23 Events	Anti IL23 Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.6.1 Guselkumab versus placebo						
Blauvelt VOYAGE-1 2016	8	329	3	174	11.7%	1.41 [0.38 , 5.25]
Gordon X-PLORE 2015	3	208	1	42	4.2%	0.61 [0.06 , 5.68]
NCT02905331 ORION	2	62	0	16	2.4%	1.35 [0.07 , 26.80]
Ohtsuki 2018	2	128	2	64	5.6%	0.50 [0.07 , 3.47]
Reich VOYAGE-2 2017	8	496	3	248	11.7%	1.33 [0.36 , 4.98]
Subtotal (95% CI)		**1223**		**544**	**35.6%**	**1.07 [0.50 , 2.28]**
Total events:	23		9			
Heterogeneity: Tau² = 0.00; Chi² = 1.14, df = 4 (P = 0.89); I² = 0%						
Test for overall effect: Z = 0.17 (P = 0.87)						
2.6.2 Tildrakizumab versus placebo						
Papp 2015	4	309	0	46	2.5%	1.36 [0.07 , 24.94]
Reich ReSURFACE-1 2017	13	617	1	155	5.1%	3.27 [0.43 , 24.77]
Reich ReSURFACE-2 2017	10	621	4	156	15.1%	0.63 [0.20 , 1.98]
Subtotal (95% CI)		**1547**		**357**	**22.8%**	**1.01 [0.37 , 2.77]**
Total events:	27		5			
Heterogeneity: Tau² = 0.07; Chi² = 2.14, df = 2 (P = 0.34); I² = 6%						
Test for overall effect: Z = 0.02 (P = 0.98)						
2.6.3 Risankizumab versus placebo						
Gordon UltIMMa-1 2018	7	304	3	102	11.4%	0.78 [0.21 , 2.97]
Gordon UltIMMa-2 2018	6	294	1	98	4.7%	2.00 [0.24 , 16.41]
NCT02672852 IMMhance	8	407	8	100	21.1%	0.25 [0.09 , 0.64]
NCT03000075	4	113	1	58	4.5%	2.05 [0.23 , 17.95]
Subtotal (95% CI)		**1118**		**358**	**41.7%**	**0.71 [0.24 , 2.10]**
Total events:	25		13			
Heterogeneity: Tau² = 0.60; Chi² = 6.06, df = 3 (P = 0.11); I² = 51%						
Test for overall effect: Z = 0.62 (P = 0.54)						
Total (95% CI)		**3888**		**1259**	**100.0%**	**0.79 [0.49 , 1.25]**
Total events:	75		27			
Heterogeneity: Tau² = 0.03; Chi² = 11.48, df = 11 (P = 0.40); I² = 4%						
Test for overall effect: Z = 1.01 (P = 0.31)						
Test for subgroup differences: Chi² = 0.38, df = 2 (P = 0.83), I² = 0%						



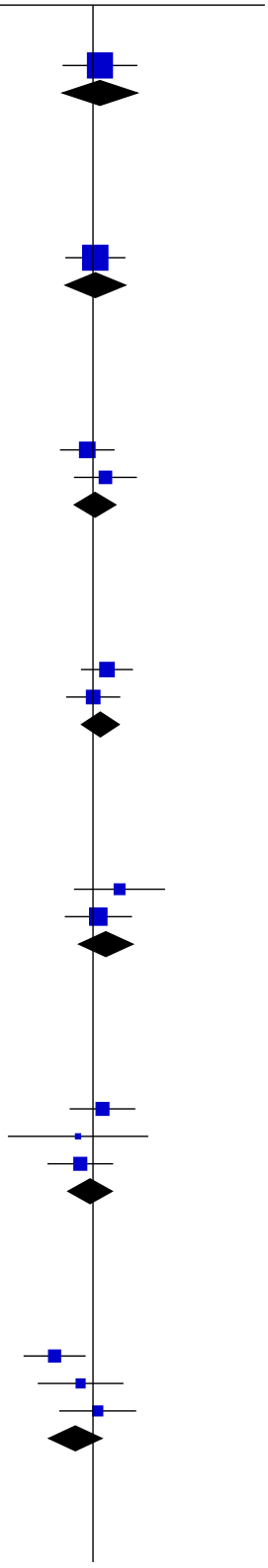
Analysis 2.7. Comparison 2: Primary outcome - serious adverse events (SAE), Outcome 7: Biologic versus conventional systemic treatments

Study or Subgroup	Biologic Events	Biologic Total	Conventional systemic Events	Conventional systemic Total	Weight	Risk Ratio M-H, Random, 95% CI
2.7.1 Etanercept versus acitretin						
Caproni 2009	0	30	0	30		Not estimable
Gisondi 2008	0	22	0	20		Not estimable
Lee 2016	0	21	1	19	100.0%	0.30 [0.01 , 7.02]
Subtotal (95% CI)		**73**		**69**	**100.0%**	**0.30 [0.01 , 7.02]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.74 (P = 0.46)						
2.7.2 Infliximab versus methotrexate						
Barker RESTORE-1 2011	44	653	6	215	100.0%	2.41 [1.04 , 5.59]
Subtotal (95% CI)		**653**		**215**	**100.0%**	**2.41 [1.04 , 5.59]**
Total events:	44		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.06 (P = 0.04)						
2.7.3 Adalimumab versus methotrexate						
Saurat CHAMPION 2008	2	108	1	110	100.0%	2.04 [0.19 , 22.14]
Subtotal (95% CI)		**108**		**110**	**100.0%**	**2.04 [0.19 , 22.14]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
2.7.4 Secukinumab versus fumaric acid esters						
Sticherling PRIME 2017	4	105	7	97	100.0%	0.53 [0.16 , 1.75]
Subtotal (95% CI)		**105**		**97**	**100.0%**	**0.53 [0.16 , 1.75]**
Total events:	4		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.30)						
2.7.5 Ixekizumab versus fumaric ester acids						
NCT02634801	1	54	3	54	100.0%	0.33 [0.04 , 3.10]
Subtotal (95% CI)		**54**		**54**	**100.0%**	**0.33 [0.04 , 3.10]**
Total events:	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.96 (P = 0.33)						
2.7.6 Ixekizumab versus methotrexate						
NCT02634801	1	54	1	54	100.0%	1.00 [0.06 , 15.58]
Subtotal (95% CI)		**54**		**54**	**100.0%**	**1.00 [0.06 , 15.58]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
2.7.7 Guselkumab versus fumaric ester acids						
NCT02951533 POLARIS	3	60	2	59	100.0%	1.48 [0.26 , 8.51]
Subtotal (95% CI)		**60**		**59**	**100.0%**	**1.48 [0.26 , 8.51]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.43 (P = 0.66)						



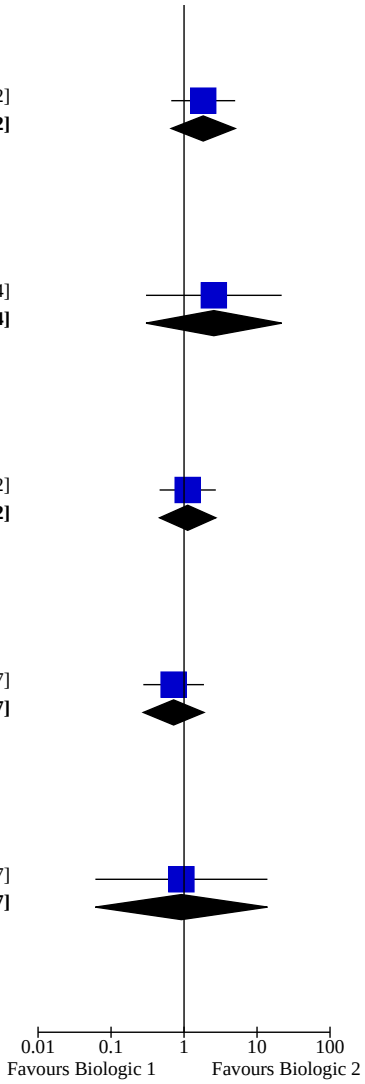
Analysis 2.8. Comparison 2: Primary outcome - serious adverse events (SAE), Outcome 8: Biologic 1 versus biologic 2

Study or Subgroup	Biologic 1 Events	Biologic 1 Total	Biologic 2 Events	Biologic 2 Total	Weight	Risk Ratio M-H, Random, 95% CI
2.8.1 Ustekinumab versus etanercept						
Griffiths ACCEPT 2010	8	556	4	347	100.0%	1.25 [0.38 , 4.11]
Subtotal (95% CI)		**556**		**347**	**100.0%**	**1.25 [0.38 , 4.11]**
Total events:	8		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.36 (P = 0.72)						
2.8.2 Secukinumab versus etanercept						
Langley FIXTURE 2014	13	654	6	326	100.0%	1.08 [0.41 , 2.82]
Subtotal (95% CI)		**654**		**326**	**100.0%**	**1.08 [0.41 , 2.82]**
Total events:	13		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.16 (P = 0.87)						
2.8.3 Ixekizumab versus etanercept						
Griffiths UNCOVER-2 2015	13	698	8	358	57.1%	0.83 [0.35 , 1.99]
Griffiths UNCOVER-3 2015	15	771	5	382	42.9%	1.49 [0.54 , 4.06]
Subtotal (95% CI)		**1469**		**740**	**100.0%**	**1.07 [0.55 , 2.06]**
Total events:	28		13			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.73$, df = 1 (P = 0.39); $I^2 = 0\%$						
Test for overall effect: Z = 0.20 (P = 0.84)						
2.8.4 Secukinumab versus ustekinumab						
Bagel CLARITY 2018	14	550	9	552	52.0%	1.56 [0.68 , 3.58]
Thaçi CLEAR 2015	10	337	10	339	48.0%	1.01 [0.42 , 2.39]
Subtotal (95% CI)		**887**		**891**	**100.0%**	**1.26 [0.70 , 2.30]**
Total events:	24		19			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.52$, df = 1 (P = 0.47); $I^2 = 0\%$						
Test for overall effect: Z = 0.77 (P = 0.44)						
2.8.5 Brodalumab versus ustekinumab						
Lebwohl AMAGINE-2 2015	19	1222	2	300	35.3%	2.33 [0.55 , 9.96]
Lebwohl AMAGINE-3 2015	19	1253	4	313	64.7%	1.19 [0.41 , 3.46]
Subtotal (95% CI)		**2475**		**613**	**100.0%**	**1.51 [0.64 , 3.56]**
Total events:	38		6			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.55$, df = 1 (P = 0.46); $I^2 = 0\%$						
Test for overall effect: Z = 0.93 (P = 0.35)						
2.8.6 Guselkumab versus adalimumab						
Blauvelt VOYAGE-1 2016	8	329	6	334	45.1%	1.35 [0.47 , 3.86]
Gordon X-PLORE 2015	3	208	1	43	9.9%	0.62 [0.07 , 5.82]
Reich VOYAGE-2 2017	8	496	6	248	45.1%	0.67 [0.23 , 1.90]
Subtotal (95% CI)		**1033**		**625**	**100.0%**	**0.91 [0.45 , 1.84]**
Total events:	19		13			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.01$, df = 2 (P = 0.60); $I^2 = 0\%$						
Test for overall effect: Z = 0.26 (P = 0.79)						
2.8.7 Risankizumab versus ustekinumab						
Gordon UltIMMa-1 2018	7	304	8	102	41.2%	0.29 [0.11 , 0.79]
Gordon UltIMMa-2 2018	6	294	3	99	27.2%	0.67 [0.17 , 2.64]
Papp NCT02054481 2017	11	126	3	40	31.6%	1.16 [0.34 , 3.97]
Subtotal (95% CI)		**724**		**241**	**100.0%**	**0.57 [0.24 , 1.32]**
Total events:	24		14			
Heterogeneity: $Tau^2 = 0.20$; $Chi^2 = 3.08$, df = 2 (P = 0.21); $I^2 = 35\%$						
Test for overall effect: Z = 1.31 (P = 0.19)						



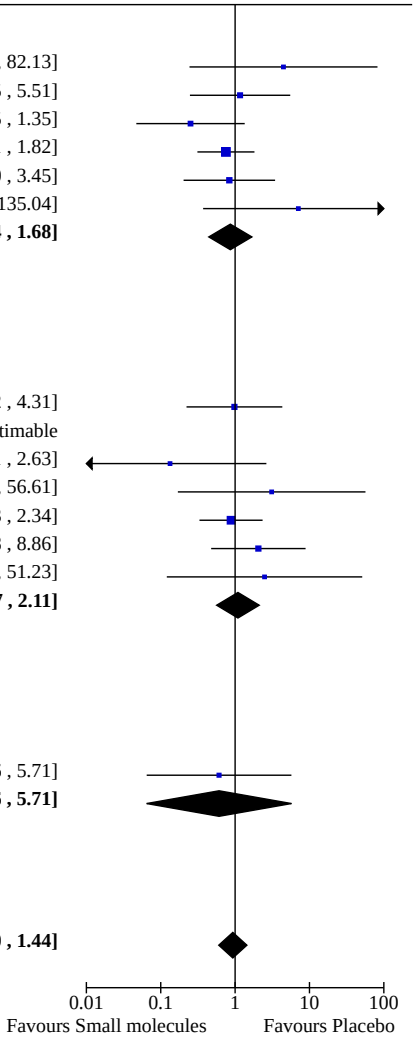
Analysis 2.8. (Continued)

Test for overall effect: Z = 1.31 (P = 0.19)						
2.8.8 Ixekizumab versus ustekinumab						
Reich IXORA-S 2017	9	136	6	166	100.0%	1.83 [0.67 , 5.02]
Subtotal (95% CI)		**136**		**166**	**100.0%**	**1.83 [0.67 , 5.02]**
Total events:	9		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.18 (P = 0.24)						
2.8.9 Certolizumab versus etanercept						
Lebwohl CIMPACT 2018	5	332	1	170	100.0%	2.56 [0.30 , 21.74]
Subtotal (95% CI)		**332**		**170**	**100.0%**	**2.56 [0.30 , 21.74]**
Total events:	5		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.86 (P = 0.39)						
2.8.10 Risankizumab versus adalimumab						
EUCTR2015-003623-65-DE	10	301	9	304	100.0%	1.12 [0.46 , 2.72]
Subtotal (95% CI)		**301**		**304**	**100.0%**	**1.12 [0.46 , 2.72]**
Total events:	10		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.25 (P = 0.80)						
2.8.11 Tildrakizumab versus etanercept						
Reich ReSURFACE-2 2017	10	621	7	313	100.0%	0.72 [0.28 , 1.87]
Subtotal (95% CI)		**621**		**313**	**100.0%**	**0.72 [0.28 , 1.87]**
Total events:	10		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
2.8.12 Infliximab versus etanercept						
De Vries PIECE 2016	1	25	1	23	100.0%	0.92 [0.06 , 13.87]
Subtotal (95% CI)		**25**		**23**	**100.0%**	**0.92 [0.06 , 13.87]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.06 (P = 0.95)						

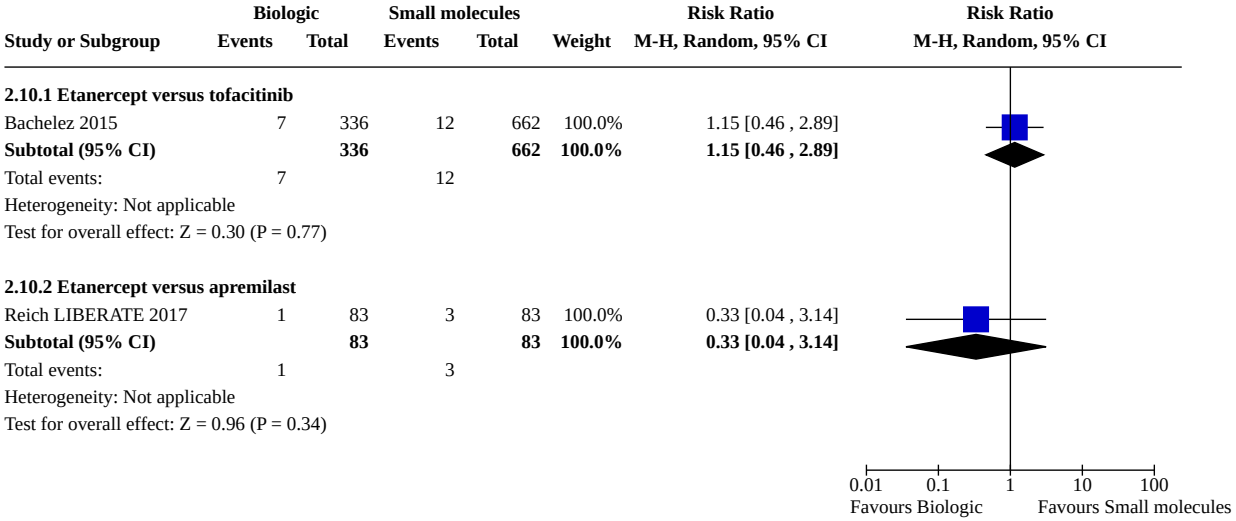


Analysis 2.9. Comparison 2: Primary outcome - serious adverse events (SAE), Outcome 9: Small molecules versus placebo

Study or Subgroup	Small molecules Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.9.1 Apremilast versus placebo						
Ohtsuki 2017	4	170	0	84	2.2%	4.47 [0.24 , 82.13]
Papp 2012c	7	264	2	88	7.8%	1.17 [0.25 , 5.51]
Papp 2013b	2	173	4	87	6.7%	0.25 [0.05 , 1.35]
Papp ESTEEM-1 2015	12	562	8	282	24.2%	0.75 [0.31 , 1.82]
Paul ESTEEM-2 2015	5	275	3	138	9.4%	0.84 [0.20 , 3.45]
Reich LIBERATE 2017	3	83	0	84	2.2%	7.08 [0.37 , 135.04]
Subtotal (95% CI)		**1527**		**763**	**52.6%**	**0.86 [0.44 , 1.68]**
Total events:	33		17			
Heterogeneity: Tau² = 0.08; Chi² = 5.63, df = 5 (P = 0.34); I² = 11%						
Test for overall effect: Z = 0.43 (P = 0.66)						
2.9.2 Tofacitinib versus placebo						
Bachelez 2015	12	662	2	108	8.6%	0.98 [0.22 , 4.31]
Jin 2017	0	12	0	6		Not estimable
Krueger 2016a	0	9	1	3	2.1%	0.13 [0.01 , 2.63]
Papp 2012b	4	147	0	50	2.2%	3.10 [0.17 , 56.61]
Papp OPT Pivotal-1 2015	18	723	5	177	19.8%	0.88 [0.33 , 2.34]
Papp OPT Pivotal-2 2015	16	763	2	196	8.8%	2.06 [0.48 , 8.86]
Zhang 2017	2	178	0	88	2.1%	2.49 [0.12 , 51.23]
Subtotal (95% CI)		**2494**		**628**	**43.6%**	**1.09 [0.57 , 2.11]**
Total events:	52		10			
Heterogeneity: Tau² = 0.00; Chi² = 3.65, df = 5 (P = 0.60); I² = 0%						
Test for overall effect: Z = 0.26 (P = 0.79)						
2.9.3 TYK2 versus placebo						
Papp TYK2 2018	3	222	1	45	3.8%	0.61 [0.06 , 5.71]
Subtotal (95% CI)		**222**		**45**	**3.8%**	**0.61 [0.06 , 5.71]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.44 (P = 0.66)						
Total (95% CI)		**4243**		**1436**	**100.0%**	**0.93 [0.60 , 1.44]**
Total events:	88		28			
Heterogeneity: Tau² = 0.00; Chi² = 9.75, df = 12 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.32 (P = 0.75)						
Test for subgroup differences: Chi² = 0.40, df = 2 (P = 0.82), I² = 0%						



Analysis 2.10. Comparison 2: Primary outcome - serious adverse events (SAE), Outcome 10: Biologic versus small molecules



Comparison 3. Secondary outcome - PASI 75

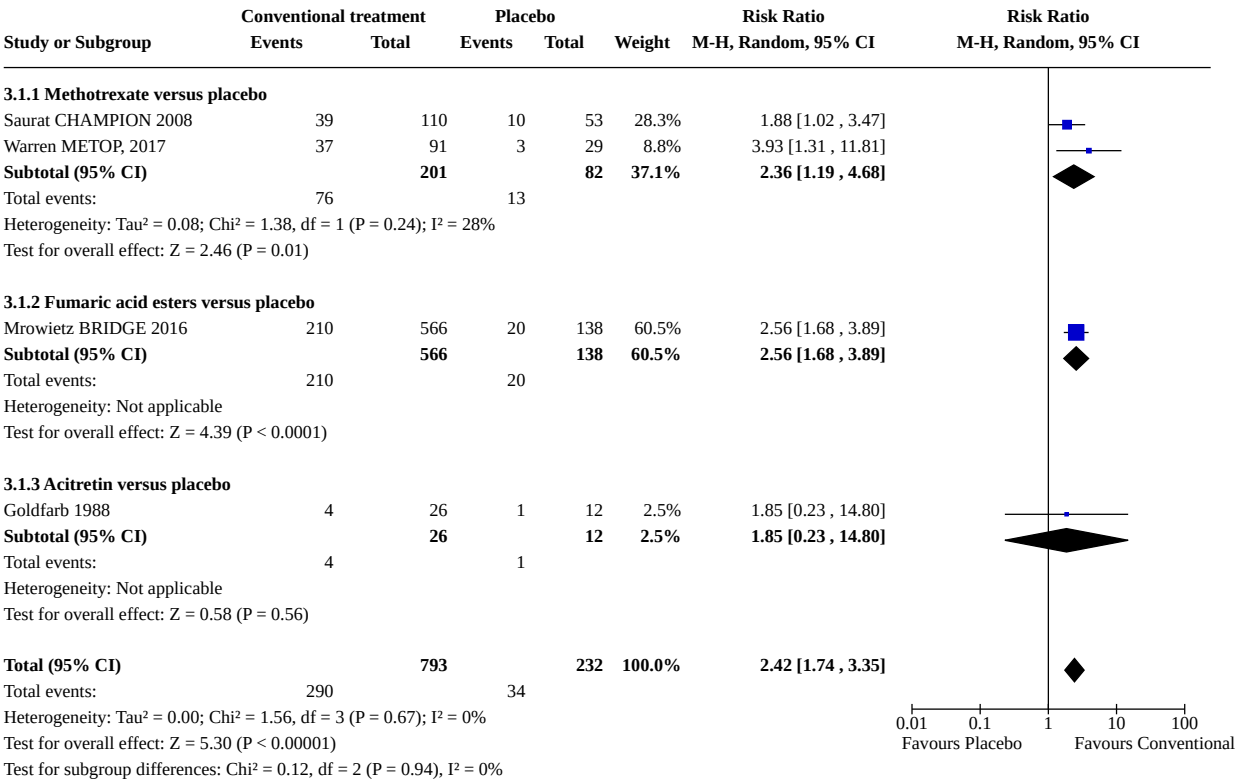
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Conventional systemic agents versus placebo	4	1025	Risk Ratio (M-H, Random, 95% CI)	2.42 [1.74, 3.35]
3.1.1 Methotrexate versus placebo	2	283	Risk Ratio (M-H, Random, 95% CI)	2.36 [1.19, 4.68]
3.1.2 Fumaric acid esters versus placebo	1	704	Risk Ratio (M-H, Random, 95% CI)	2.56 [1.68, 3.89]
3.1.3 Acitretin versus placebo	1	38	Risk Ratio (M-H, Random, 95% CI)	1.85 [0.23, 14.80]
3.2 Conventional systemic 1 versus conventional systemic 2	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.2.1 Ciclosporin versus methotrexate	2	172	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.84, 2.23]
3.2.2 Methotrexate versus fumaric acid esters	2	168	Risk Ratio (M-H, Random, 95% CI)	2.30 [0.74, 7.19]
3.3 Anti-TNF alpha versus placebo	34	11951	Risk Ratio (M-H, Random, 95% CI)	9.22 [7.75, 10.95]
3.3.1 Etanercept versus placebo	15	5762	Risk Ratio (M-H, Random, 95% CI)	8.56 [7.07, 10.36]
3.3.2 Adalimumab versus placebo	10	3485	Risk Ratio (M-H, Random, 95% CI)	8.25 [6.03, 11.29]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3.3 Certolizumab versus placebo	4	1026	Risk Ratio (M-H, Random, 95% CI)	9.45 [5.90, 15.12]
3.3.4 Infliximab versus placebo	6	1678	Risk Ratio (M-H, Random, 95% CI)	18.87 [8.53, 41.75]
3.4 Anti-IL12/23 versus placebo	10	4553	Risk Ratio (M-H, Random, 95% CI)	11.71 [8.78, 15.63]
3.4.1 Ustekinumab versus placebo	10	4553	Risk Ratio (M-H, Random, 95% CI)	11.71 [8.78, 15.63]
3.5 Anti-IL17 versus placebo	18	10532	Risk Ratio (M-H, Random, 95% CI)	14.79 [11.79, 18.57]
3.5.1 Secukinumab versus placebo	8	2905	Risk Ratio (M-H, Random, 95% CI)	15.22 [11.03, 21.01]
3.5.2 Ixekizumab versus placebo	4	3268	Risk Ratio (M-H, Random, 95% CI)	17.44 [10.45, 29.10]
3.5.3 Brodalumab versus placebo	5	4109	Risk Ratio (M-H, Random, 95% CI)	12.80 [8.46, 19.36]
3.5.4 Bimekizumab versus placebo	1	250	Risk Ratio (M-H, Random, 95% CI)	17.06 [4.41, 66.09]
3.6 Anti-IL23 versus placebo	12	5147	Risk Ratio (M-H, Random, 95% CI)	11.87 [9.66, 14.58]
3.6.1 Guselkumab versus placebo	5	1767	Risk Ratio (M-H, Random, 95% CI)	12.65 [9.24, 17.31]
3.6.2 Tildrakizumab versus placebo	3	1904	Risk Ratio (M-H, Random, 95% CI)	11.24 [7.33, 17.23]
3.6.3 Risankizumab versus placebo	4	1476	Risk Ratio (M-H, Random, 95% CI)	11.36 [7.95, 16.21]
3.7 Biologic versus conventional systemic treatments	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.7.1 Etanercept versus acitretin	3	142	Risk Ratio (M-H, Random, 95% CI)	1.98 [1.26, 3.12]
3.7.2 Infliximab versus methotrexate	1	868	Risk Ratio (M-H, Random, 95% CI)	1.86 [1.58, 2.19]
3.7.3 Adalimumab versus methotrexate	1	218	Risk Ratio (M-H, Random, 95% CI)	2.25 [1.72, 2.94]
3.7.4 Secukinumab versus fumaric acid esters	1	202	Risk Ratio (M-H, Random, 95% CI)	3.30 [2.36, 4.62]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.7.5 Ixekizumab versus fumaric ester acids	1	108	Risk Ratio (M-H, Random, 95% CI)	4.08 [2.46, 6.77]
3.7.6 Ixekizumab versus methotrexate	1	108	Risk Ratio (M-H, Random, 95% CI)	1.29 [1.06, 1.56]
3.7.7 Guselkumab versus fumaric acid esters	1	118	Risk Ratio (M-H, Random, 95% CI)	3.26 [2.13, 4.99]
3.8 Biologic 1 versus biologic 2	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.8.1 Ustekinumab versus etanercept	1	903	Risk Ratio (M-H, Random, 95% CI)	1.26 [1.13, 1.40]
3.8.2 Secukinumab versus etanercept	1	980	Risk Ratio (M-H, Random, 95% CI)	1.64 [1.44, 1.88]
3.8.3 Ixekizumab versus etanercept	2	2209	Risk Ratio (M-H, Random, 95% CI)	1.79 [1.43, 2.24]
3.8.4 Secukinumab versus ustekinumab	2	1778	Risk Ratio (M-H, Random, 95% CI)	1.14 [1.10, 1.19]
3.8.5 Brodalumab versus ustekinumab	2	3088	Risk Ratio (M-H, Random, 95% CI)	1.10 [1.04, 1.17]
3.8.6 Guselkumab versus adalimumab	3	1658	Risk Ratio (M-H, Random, 95% CI)	1.23 [1.14, 1.32]
3.8.7 Risankizumab versus ustekinumab	3	965	Risk Ratio (M-H, Random, 95% CI)	1.23 [1.13, 1.33]
3.8.8 Ixekizumab versus ustekinumab	1	302	Risk Ratio (M-H, Random, 95% CI)	1.24 [1.09, 1.41]
3.8.9 Certolizumab versus etanercept	1	502	Risk Ratio (M-H, Random, 95% CI)	1.19 [1.01, 1.40]
3.8.10 Risankizumab versus adalimumab	1	605	Risk Ratio (M-H, Random, 95% CI)	1.26 [1.17, 1.37]
3.8.11 Tildrakizumab versus etanercept	1	934	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.16, 1.50]
3.8.12 Infliximab versus etanercept	1	48	Risk Ratio (M-H, Random, 95% CI)	2.07 [1.12, 3.81]
3.9 Small molecules versus placebo	14	5679	Risk Ratio (M-H, Random, 95% CI)	4.96 [3.77, 6.51]
3.9.1 Apremilast versus placebo	6	2290	Risk Ratio (M-H, Random, 95% CI)	3.86 [2.59, 5.74]

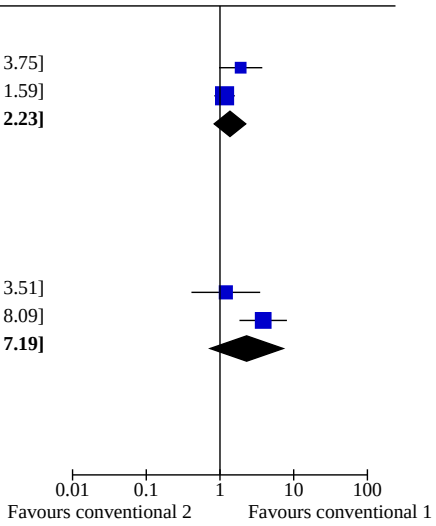
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.9.2 Tofacitinib versus placebo	7	3122	Risk Ratio (M-H, Random, 95% CI)	6.14 [4.31, 8.73]
3.9.3 TYK2 versus placebo	1	267	Risk Ratio (M-H, Random, 95% CI)	7.77 [2.59, 23.36]
3.10 Biologic versus small molecules	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.10.1 Etanercept versus tofacitinib	1	998	Risk Ratio (M-H, Random, 95% CI)	1.14 [1.02, 1.28]
3.10.2 Etanercept versus apremilast	1	166	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.86, 1.71]

Analysis 3.1. 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

Study or Subgroup	Conventional 1 Events	Conventional 1 Total	Conventional 2 Events	Conventional 2 Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Ciclosporin versus methotrexate						
Flytström 2008	18	43	9	41	33.6%	1.91 [0.97 , 3.75]
Heydendael 2003	30	44	26	44	66.4%	1.15 [0.84 , 1.59]
Subtotal (95% CI)		**87**		**85**	**100.0%**	**1.37 [0.84 , 2.23]**
Total events:	48		35			
Heterogeneity: Tau² = 0.07; Chi² = 1.94, df = 1 (P = 0.16); I² = 49%						
Test for overall effect: Z = 1.24 (P = 0.21)						
3.2.2 Methotrexate versus fumaric acid esters						
Fallah Arani 2011	6	30	5	30	44.3%	1.20 [0.41 , 3.51]
NCT02634801	27	54	7	54	55.7%	3.86 [1.84 , 8.09]
Subtotal (95% CI)		**84**		**84**	**100.0%**	**2.30 [0.74 , 7.19]**
Total events:	33		12			
Heterogeneity: Tau² = 0.46; Chi² = 3.09, df = 1 (P = 0.08); I² = 68%						
Test for overall effect: Z = 1.43 (P = 0.15)						

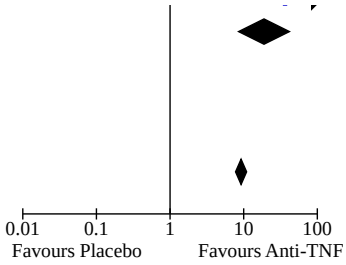


Analysis 3.3. Comparison 3: Secondary outcome - PASI 75, Outcome 3: Anti-TNF alpha versus placebo

Study or Subgroup	Anti-TNF Events	Anti-TNF Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 Etanercept versus placebo						
Bachelez 2015	197	336	6	108	3.2%	10.55 [4.82 , 23.09]
Bagel 2012	36	62	3	62	1.9%	12.00 [3.90 , 36.92]
Gottlieb 2003a	17	57	1	55	0.7%	16.40 [2.26 , 119.10]
Gottlieb 2011	79	141	5	68	2.8%	7.62 [3.24 , 17.94]
Griffiths UNCOVER-2 2015	149	358	4	168	2.3%	17.48 [6.59 , 46.39]
Griffiths UNCOVER-3 2015	204	382	14	193	5.1%	7.36 [4.41 , 12.30]
Langley FIXTURE 2014	142	326	16	327	5.3%	8.90 [5.43 , 14.58]
Lebwohl CIMPACT 2018	91	170	3	57	1.9%	10.17 [3.35 , 30.87]
Leonardi 2003	159	504	6	168	3.1%	8.83 [3.98 , 19.58]
Papp 2005	160	407	6	204	3.1%	13.37 [6.02 , 29.67]
Reich LIBERATE 2017	40	83	10	84	4.2%	4.05 [2.17 , 7.55]
Reich ReSURFACE-2 2017	151	313	9	156	4.1%	8.36 [4.39 , 15.93]
Strober 2011	55	139	5	72	2.8%	5.70 [2.39 , 13.60]
Tyring 2006	147	311	15	309	5.2%	9.74 [5.86 , 16.17]
Van de Kerkhof 2008	36	96	1	46	0.7%	17.25 [2.44 , 121.93]
Subtotal (95% CI)		**3685**		**2077**	**46.4%**	**8.56 [7.07 , 10.36]**
Total events:	1663		104			
Heterogeneity: Tau² = 0.00; Chi² = 12.40, df = 14 (P = 0.57); I² = 0%						
Test for overall effect: Z = 22.03 (P < 0.00001)						
3.3.2 Adalimumab versus placebo						
Asahina 2010	83	123	2	46	1.4%	15.52 [3.98 , 60.53]
Blauvelt VOYAGE-1 2016	244	334	10	174	4.3%	12.71 [6.94 , 23.28]
Cai 2016	263	338	10	87	4.5%	6.77 [3.77 , 12.16]
Elewski 2016	63	109	13	108	4.9%	4.80 [2.81 , 8.19]
Gordon 2006	64	96	2	52	1.4%	17.33 [4.42 , 67.96]
Gordon X-PLORE 2015	30	43	1	42	0.7%	29.30 [4.18 , 205.23]
Menter REVEAL 2008	578	814	26	398	6.5%	10.87 [7.48 , 15.80]
NCT01553058 VIP trial	15	33	2	31	1.3%	7.05 [1.75 , 28.33]
Reich VOYAGE-2 2017	170	248	20	248	5.9%	8.50 [5.54 , 13.05]
Saurat CHAMPION 2008	86	108	10	53	4.7%	4.22 [2.40 , 7.44]
Subtotal (95% CI)		**2246**		**1239**	**35.6%**	**8.25 [6.03 , 11.29]**
Total events:	1596		96			
Heterogeneity: Tau² = 0.11; Chi² = 18.54, df = 9 (P = 0.03); I² = 51%						
Test for overall effect: Z = 13.22 (P < 0.00001)						
3.3.3 Certolizumab versus placebo						
Gottlieb CIMPASI-1 2018	130	183	3	51	1.9%	12.08 [4.01 , 36.34]
Gottlieb CIMPASI-2 2018	146	178	6	49	3.4%	6.70 [3.16 , 14.22]
Lebwohl CIMPACT 2018	212	332	3	57	1.9%	12.13 [4.02 , 36.61]
Reich 2012a	92	118	4	58	2.4%	11.31 [4.37 , 29.24]
Subtotal (95% CI)		**811**		**215**	**9.7%**	**9.45 [5.90 , 15.12]**
Total events:	580		16			
Heterogeneity: Tau² = 0.00; Chi² = 1.36, df = 3 (P = 0.72); I² = 0%						
Test for overall effect: Z = 9.35 (P < 0.00001)						
3.3.4 Infliximab versus placebo						
Chaudhari 2001	17	22	2	11	1.5%	4.25 [1.19 , 15.19]
Gottlieb 2004a	158	198	3	51	1.9%	13.57 [4.52 , 40.75]
Menter EXPRESS-II 2007	457	627	4	208	2.4%	37.90 [14.34 , 100.15]
Reich EXPRESS 2005	242	301	2	77	1.4%	30.95 [7.87 , 121.68]
Torii 2010	24	35	0	19	0.4%	27.22 [1.75 , 424.16]
Yang 2012	68	84	1	45	0.7%	36.43 [5.23 , 253.71]
Subtotal (95% CI)		**1267**		**411**	**8.3%**	**18.87 [8.53 , 41.75]**
Total events:	966		12			

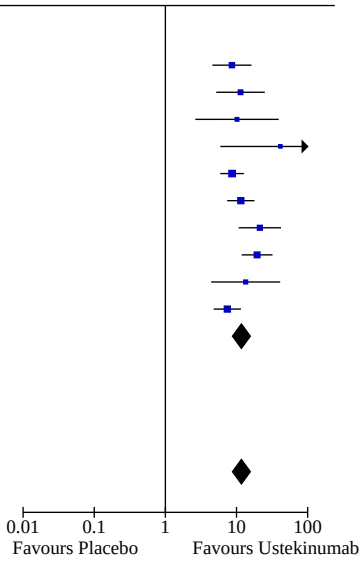
Analysis 3.3. (Continued)

Subtotal (95% CI)		**1267**		**411**	**8.3%**	**18.87 [8.53 , 41.75]**
Total events:	966		12			
Heterogeneity: Tau² = 0.45; Chi² = 9.61, df = 5 (P = 0.09); I² = 48%						
Test for overall effect: Z = 7.25 (P < 0.00001)						
Total (95% CI)		**8009**		**3942**	**100.0%**	**9.22 [7.75 , 10.95]**
Total events:	4805		228			
Heterogeneity: Tau² = 0.08; Chi² = 52.85, df = 34 (P = 0.02); I² = 36%						
Test for overall effect: Z = 25.21 (P < 0.00001)						
Test for subgroup differences: Chi² = 3.88, df = 3 (P = 0.28), I² = 22.6%						



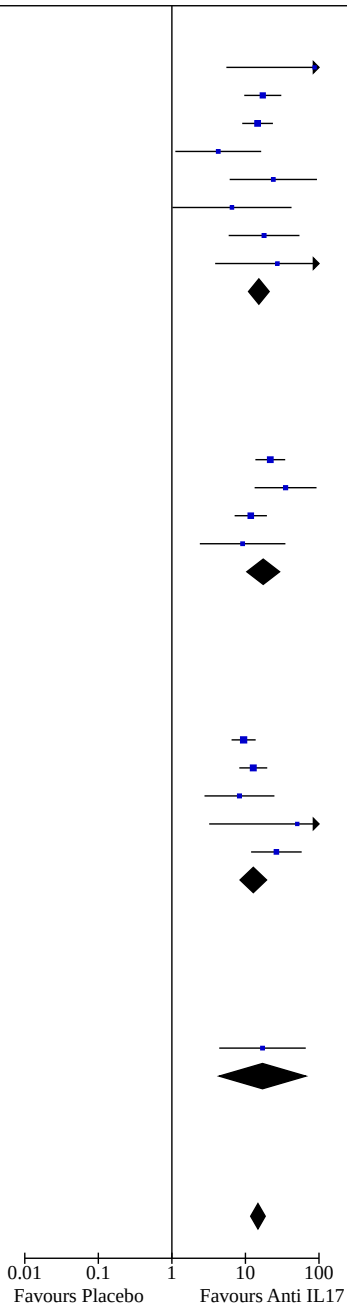
Analysis 3.4. Comparison 3: Secondary outcome - PASI 75, Outcome 4: Anti-IL12/23 versus placebo

Study or Subgroup	Ustekinumab Events	Ustekinumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.4.1 Ustekinumab versus placebo						
Gordon UltIMMa-1 2018	76	100	9	102	10.9%	8.61 [4.57 , 16.23]
Gordon UltIMMa-2 2018	69	99	6	98	8.5%	11.38 [5.19 , 24.98]
Igarashi 2012	80	126	2	32	3.8%	10.16 [2.64 , 39.12]
Krueger 2007	166	256	1	64	2.0%	41.50 [5.92 , 290.72]
Lebwohl AMAGINE-2 2015	210	300	25	309	16.3%	8.65 [5.90 , 12.69]
Lebwohl AMAGINE-3 2015	217	313	19	315	14.9%	11.49 [7.39 , 17.88]
Leonardi PHOENIX-1 2008	341	511	8	255	10.0%	21.27 [10.73 , 42.19]
Papp PHOENIX-2 2008	584	820	15	410	13.6%	19.47 [11.82 , 32.05]
Tsai PEARL 2011	41	61	3	60	5.2%	13.44 [4.40 , 41.07]
Zhu LOTUS 2013	132	160	18	162	14.9%	7.42 [4.78 , 11.54]
Subtotal (95% CI)		**2746**		**1807**	**100.0%**	**11.71 [8.78 , 15.63]**
Total events:	1916		106			
Heterogeneity: Tau² = 0.09; Chi² = 17.91, df = 9 (P = 0.04); I² = 50%						
Test for overall effect: Z = 16.71 (P < 0.00001)						
Total (95% CI)		**2746**		**1807**	**100.0%**	**11.71 [8.78 , 15.63]**
Total events:	1916		106			
Heterogeneity: Tau² = 0.09; Chi² = 17.91, df = 9 (P = 0.04); I² = 50%						
Test for overall effect: Z = 16.71 (P < 0.00001)						
Test for subgroup differences: Not applicable						



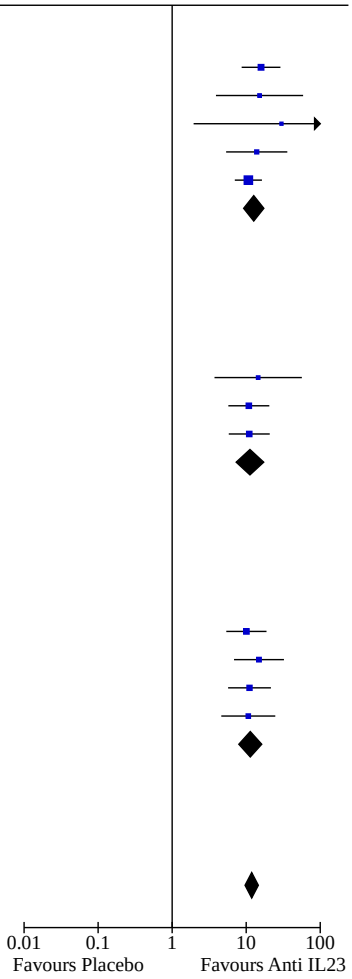
Analysis 3.5. Comparison 3: Secondary outcome - PASI 75, Outcome 5: Anti-IL17 versus placebo

Study or Subgroup	Anti IL17 Events	Anti IL17 Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.5.1 Secukinumab versus placebo						
Blauvelt FEATURE 2015	86	118	0	59	0.7%	87.23 [5.51 , 1381.52]
Langley ERASURE 2014	374	490	11	248	9.1%	17.21 [9.64 , 30.73]
Langley FIXTURE 2014	468	654	16	327	11.2%	14.63 [9.05 , 23.64]
Papp 2013a	40	103	2	22	2.5%	4.27 [1.11 , 16.37]
Paul JUNCTURE 2015	95	121	2	61	2.5%	23.95 [6.11 , 93.88]
Reich 2015	59	90	1	10	1.4%	6.56 [1.02 , 42.34]
Reich TRANSFIGURE 2016	110	133	3	65	3.5%	17.92 [5.92 , 54.26]
Rich 2013	137	337	1	67	1.3%	27.24 [3.88 , 191.36]
Subtotal (95% CI)		**2046**		**859**	**32.1%**	**15.22 [11.03 , 21.01]**
Total events:	1369		36			
Heterogeneity: Tau² = 0.00; Chi² = 7.07, df = 7 (P = 0.42); I² = 1%						
Test for overall effect: Z = 16.56 (P < 0.00001)						
3.5.2 Ixekizumab versus placebo						
Gordon UNCOVER-1 2016	743	865	17	431	11.5%	21.78 [13.66 , 34.73]
Griffiths UNCOVER-2 2015	584	698	4	168	4.4%	35.14 [13.34 , 92.59]
Griffiths UNCOVER-3 2015	661	771	14	193	10.6%	11.82 [7.13 , 19.59]
Leonardi 2012	78	115	2	27	2.5%	9.16 [2.40 , 34.95]
Subtotal (95% CI)		**2449**		**819**	**29.1%**	**17.44 [10.45 , 29.10]**
Total events:	2066		37			
Heterogeneity: Tau² = 0.13; Chi² = 6.24, df = 3 (P = 0.10); I² = 52%						
Test for overall effect: Z = 10.95 (P < 0.00001)						
3.5.3 Brodalumab versus placebo						
Lebwohl AMAGINE-2 2015	934	1222	25	309	13.8%	9.45 [6.48 , 13.77]
Lebwohl AMAGINE-3 2015	966	1253	19	315	12.2%	12.78 [8.26 , 19.78]
Nakagawa 2016	74	113	3	38	3.6%	8.29 [2.78 , 24.78]
Papp 2012a	104	160	0	38	0.7%	50.63 [3.22 , 796.97]
Papp AMAGINE-1 2016	317	441	6	220	6.0%	26.36 [11.95 , 58.15]
Subtotal (95% CI)		**3189**		**920**	**36.3%**	**12.80 [8.46 , 19.36]**
Total events:	2395		53			
Heterogeneity: Tau² = 0.09; Chi² = 7.13, df = 4 (P = 0.13); I² = 44%						
Test for overall effect: Z = 12.08 (P < 0.00001)						
3.5.4 Bimekizumab versus placebo						
Papp BE ABLE 2018	169	208	2	42	2.5%	17.06 [4.41 , 66.09]
Subtotal (95% CI)		**208**		**42**	**2.5%**	**17.06 [4.41 , 66.09]**
Total events:	169		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.11 (P < 0.0001)						
Total (95% CI)		**7892**		**2640**	**100.0%**	**14.79 [11.79 , 18.57]**
Total events:	5999		128			
Heterogeneity: Tau² = 0.06; Chi² = 24.24, df = 17 (P = 0.11); I² = 30%						
Test for overall effect: Z = 23.24 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.94, df = 3 (P = 0.82), I² = 0%						



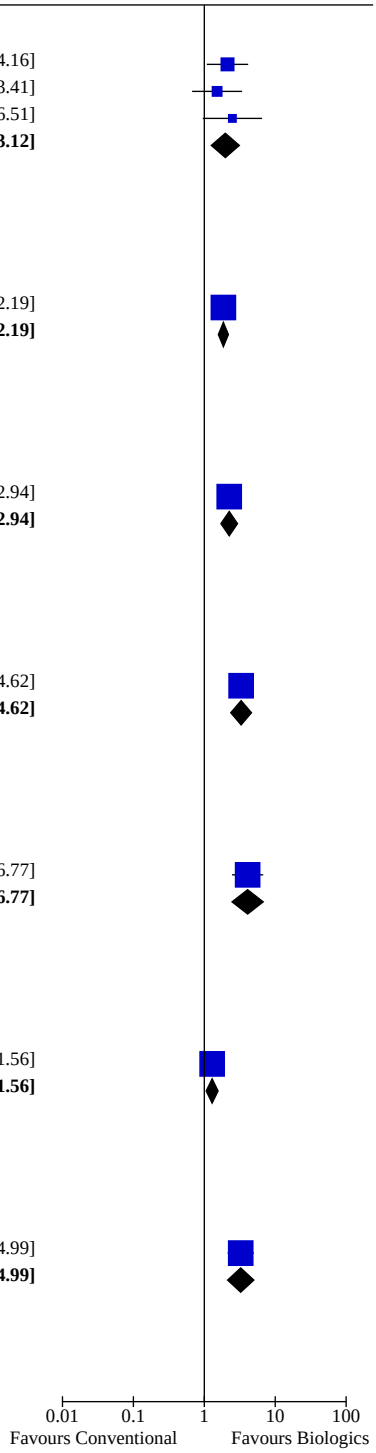
Analysis 3.6. Comparison 3: Secondary outcome - PASI 75, Outcome 6: Anti-IL23 versus placebo

Study or Subgroup	Anti IL23 Events	Anti IL23 Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.6.1 Guselkumab versus placebo						
Blauvelt VOYAGE-1 2016	300	329	10	174	11.7%	15.87 [8.68 , 28.99]
Gordon X-PLORE 2015	150	208	2	42	2.3%	15.14 [3.91 , 58.72]
NCT02905331 ORION	55	62	0	16	0.6%	29.95 [1.95 , 460.29]
Ohtsuki 2018	111	128	4	64	4.7%	13.88 [5.36 , 35.92]
Reich VOYAGE-2 2017	428	496	20	248	23.9%	10.70 [7.02 , 16.31]
Subtotal (95% CI)		**1223**		**544**	**43.2%**	**12.65 [9.24 , 17.31]**
Total events:	1044		36			
Heterogeneity: Tau² = 0.00; Chi² = 1.67, df = 4 (P = 0.80); I² = 0%						
Test for overall effect: Z = 15.85 (P < 0.00001)						
3.6.2 Tildrakizumab versus placebo						
Papp 2015	195	309	2	46	2.3%	14.51 [3.73 , 56.45]
Reich ReSURFACE-1 2017	389	617	9	155	10.5%	10.86 [5.74 , 20.53]
Reich ReSURFACE-2 2017	394	621	9	156	10.5%	11.00 [5.82 , 20.79]
Subtotal (95% CI)		**1547**		**357**	**23.3%**	**11.24 [7.33 , 17.23]**
Total events:	978		20			
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 2 (P = 0.93); I² = 0%						
Test for overall effect: Z = 11.09 (P < 0.00001)						
3.6.3 Risankizumab versus placebo						
Gordon UltIMMa-1 2018	270	304	9	102	10.9%	10.07 [5.39 , 18.81]
Gordon UltIMMa-2 2018	268	294	6	98	7.1%	14.89 [6.85 , 32.35]
NCT02672852 IMMhance	361	407	8	100	9.6%	11.09 [5.70 , 21.57]
NCT03000075	104	113	5	58	6.0%	10.68 [4.61 , 24.72]
Subtotal (95% CI)		**1118**		**358**	**33.6%**	**11.36 [7.95 , 16.21]**
Total events:	1003		28			
Heterogeneity: Tau² = 0.00; Chi² = 0.64, df = 3 (P = 0.89); I² = 0%						
Test for overall effect: Z = 13.38 (P < 0.00001)						
Total (95% CI)		**3888**		**1259**	**100.0%**	**11.87 [9.66 , 14.58]**
Total events:	3025		84			
Heterogeneity: Tau² = 0.00; Chi² = 2.73, df = 11 (P = 0.99); I² = 0%						
Test for overall effect: Z = 23.52 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.28, df = 2 (P = 0.87), I² = 0%						



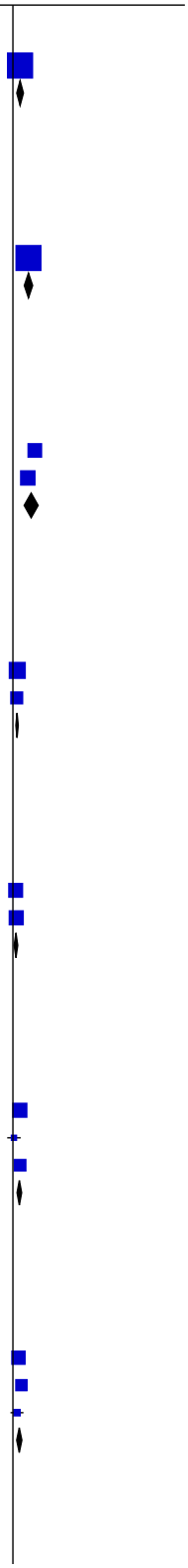
Analysis 3.7. Comparison 3: Secondary outcome - PASI 75, Outcome 7: Biologic versus conventional systemic treatments

Study or Subgroup	Biologic Events	Biologic Total	Conventional systemic Events	Conventional systemic Total	Weight	Risk Ratio M-H, Random, 95% CI
3.7.1 Etanercept versus acitretin						
Caproni 2009	17	30	8	30	46.1%	2.13 [1.09 , 4.16]
Gisondi 2008	10	22	6	20	31.5%	1.52 [0.67 , 3.41]
Lee 2016	11	21	4	19	22.4%	2.49 [0.95 , 6.51]
Subtotal (95% CI)		**73**		**69**	**100.0%**	**1.98 [1.26 , 3.12]**
Total events:	38		18			
Heterogeneity: Tau² = 0.00; Chi² = 0.68, df = 2 (P = 0.71); I² = 0%						
Test for overall effect: Z = 2.94 (P = 0.003)						
3.7.2 Infliximab versus methotrexate						
Barker RESTORE-1 2011	508	653	90	215	100.0%	1.86 [1.58 , 2.19]
Subtotal (95% CI)		**653**		**215**	**100.0%**	**1.86 [1.58 , 2.19]**
Total events:	508		90			
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.46 (P < 0.00001)						
3.7.3 Adalimumab versus methotrexate						
Saurat CHAMPION 2008	86	108	39	110	100.0%	2.25 [1.72 , 2.94]
Subtotal (95% CI)		**108**		**110**	**100.0%**	**2.25 [1.72 , 2.94]**
Total events:	86		39			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.88 (P < 0.00001)						
3.7.4 Secukinumab versus fumaric acid esters						
Sticherling PRIME 2017	93	105	26	97	100.0%	3.30 [2.36 , 4.62]
Subtotal (95% CI)		**105**		**97**	**100.0%**	**3.30 [2.36 , 4.62]**
Total events:	93		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.97 (P < 0.00001)						
3.7.5 Ixekizumab versus fumaric ester acids						
NCT02634801	49	54	12	54	100.0%	4.08 [2.46 , 6.77]
Subtotal (95% CI)		**54**		**54**	**100.0%**	**4.08 [2.46 , 6.77]**
Total events:	49		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.45 (P < 0.00001)						
3.7.6 Ixekizumab versus methotrexate						
NCT02634801	49	54	38	54	100.0%	1.29 [1.06 , 1.56]
Subtotal (95% CI)		**54**		**54**	**100.0%**	**1.29 [1.06 , 1.56]**
Total events:	49		38			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.58 (P = 0.010)						
3.7.7 Guselkumab versus fumaric acid esters						
NCT02951533 POLARIS	54	60	16	58	100.0%	3.26 [2.13 , 4.99]
Subtotal (95% CI)		**60**		**58**	**100.0%**	**3.26 [2.13 , 4.99]**
Total events:	54		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.45 (P < 0.00001)						



Analysis 3.8. Comparison 3: Secondary outcome - PASI 75, Outcome 8: Biologic 1 versus biologic 2

Study or Subgroup	Biologic 1 Events	Biologic 1 Total	Biologic 2 Events	Biologic 2 Total	Weight	Risk Ratio M-H, Random, 95% CI
3.8.1 Ustekinumab versus etanercept						
Griffiths ACCEPT 2010	397	556	197	347	100.0%	1.26 [1.13 , 1.40]
Subtotal (95% CI)		**556**		**347**	**100.0%**	**1.26 [1.13 , 1.40]**
Total events:	397		197			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.25 (P < 0.0001)						
3.8.2 Secukinumab versus etanercept						
Langley FIXTURE 2014	468	654	142	326	100.0%	1.64 [1.44 , 1.88]
Subtotal (95% CI)		**654**		**326**	**100.0%**	**1.64 [1.44 , 1.88]**
Total events:	468		142			
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.33 (P < 0.00001)						
3.8.3 Ixekizumab versus etanercept						
Griffiths UNCOVER-2 2015	584	698	149	358	48.4%	2.01 [1.77 , 2.28]
Griffiths UNCOVER-3 2015	661	771	204	382	51.6%	1.61 [1.46 , 1.77]
Subtotal (95% CI)		**1469**		**740**	**100.0%**	**1.79 [1.43 , 2.24]**
Total events:	1245		353			
Heterogeneity: Tau² = 0.02; Chi² = 7.73, df = 1 (P = 0.005); I² = 87%						
Test for overall effect: Z = 5.12 (P < 0.00001)						
3.8.4 Secukinumab versus ustekinumab						
Bagel CLARITY 2018	504	550	440	552	59.2%	1.15 [1.09 , 1.21]
Thaçi CLEAR 2015	311	337	277	339	40.8%	1.13 [1.06 , 1.20]
Subtotal (95% CI)		**887**		**891**	**100.0%**	**1.14 [1.10 , 1.19]**
Total events:	815		717			
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 6.86 (P < 0.00001)						
3.8.5 Brodalumab versus ustekinumab						
Lebwohl AMAGINE-2 2015	934	1222	210	300	49.5%	1.09 [1.01 , 1.18]
Lebwohl AMAGINE-3 2015	966	1253	217	313	50.5%	1.11 [1.03 , 1.20]
Subtotal (95% CI)		**2475**		**613**	**100.0%**	**1.10 [1.04 , 1.17]**
Total events:	1900		427			
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%						
Test for overall effect: Z = 3.37 (P = 0.0008)						
3.8.6 Guselkumab versus adalimumab						
Blauvelt VOYAGE-1 2016	300	329	244	334	50.3%	1.25 [1.16 , 1.34]
Gordon X-PLORE 2015	150	208	30	43	10.4%	1.03 [0.83 , 1.28]
Reich VOYAGE-2 2017	428	496	170	248	39.3%	1.26 [1.15 , 1.38]
Subtotal (95% CI)		**1033**		**625**	**100.0%**	**1.23 [1.14 , 1.32]**
Total events:	878		444			
Heterogeneity: Tau² = 0.00; Chi² = 2.92, df = 2 (P = 0.23); I² = 31%						
Test for overall effect: Z = 5.53 (P < 0.00001)						
3.8.7 Risankizumab versus ustekinumab						
Gordon UltIMMa-1 2018	270	304	76	102	46.8%	1.19 [1.06 , 1.34]
Gordon UltIMMa-2 2018	268	294	69	99	37.4%	1.31 [1.14 , 1.50]
Papp NCT02054481 2017	104	126	29	40	15.8%	1.14 [0.93 , 1.40]
Subtotal (95% CI)		**724**		**241**	**100.0%**	**1.23 [1.13 , 1.33]**
Total events:	642		174			
Heterogeneity: Tau² = 0.00; Chi² = 1.59, df = 2 (P = 0.45); I² = 0%						
Test for overall effect: Z = 4.83 (P < 0.00001)						



Analysis 3.8. (Continued)

Test for overall effect: Z = 4.83 (P < 0.00001)

3.8.8 Ixekizumab versus ustekinumab

Reich IXORA-S 2017	114	136	112	166	100.0%	1.24 [1.09 , 1.41]
Subtotal (95% CI)		**136**		**166**	**100.0%**	**1.24 [1.09 , 1.41]**
Total events:	114		112			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.30 (P = 0.0010)

3.8.9 Certolizumab versus etanercept

Lebwohl CIMPACT 2018	212	332	91	170	100.0%	1.19 [1.01 , 1.40]
Subtotal (95% CI)		**332**		**170**	**100.0%**	**1.19 [1.01 , 1.40]**
Total events:	212		91			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.14 (P = 0.03)

3.8.10 Risankizumab versus adalimumab

EUCTR2015-003623-65-DE	273	301	218	304	100.0%	1.26 [1.17 , 1.37]
Subtotal (95% CI)		**301**		**304**	**100.0%**	**1.26 [1.17 , 1.37]**
Total events:	273		218			

Heterogeneity: Not applicable
Test for overall effect: Z = 5.80 (P < 0.00001)

3.8.11 Tildrakizumab versus etanercept

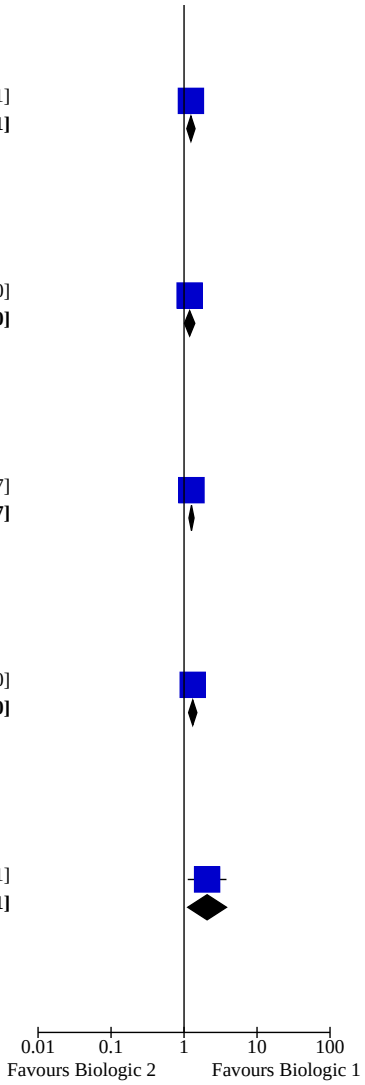
Reich ReSURFACE-2 2017	394	621	151	313	100.0%	1.32 [1.16 , 1.50]
Subtotal (95% CI)		**621**		**313**	**100.0%**	**1.32 [1.16 , 1.50]**
Total events:	394		151			

Heterogeneity: Not applicable
Test for overall effect: Z = 4.15 (P < 0.0001)

3.8.12 Infliximab versus etanercept

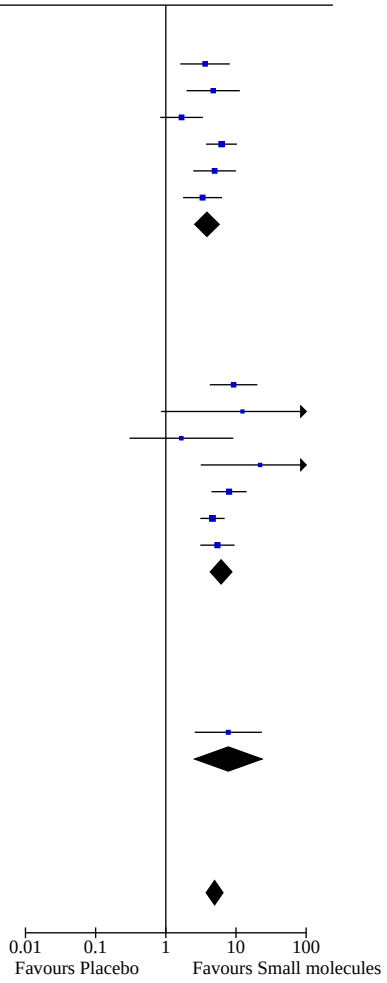
De Vries PIECE 2016	18	25	8	23	100.0%	2.07 [1.12 , 3.81]
Subtotal (95% CI)		**25**		**23**	**100.0%**	**2.07 [1.12 , 3.81]**
Total events:	18		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.34 (P = 0.02)

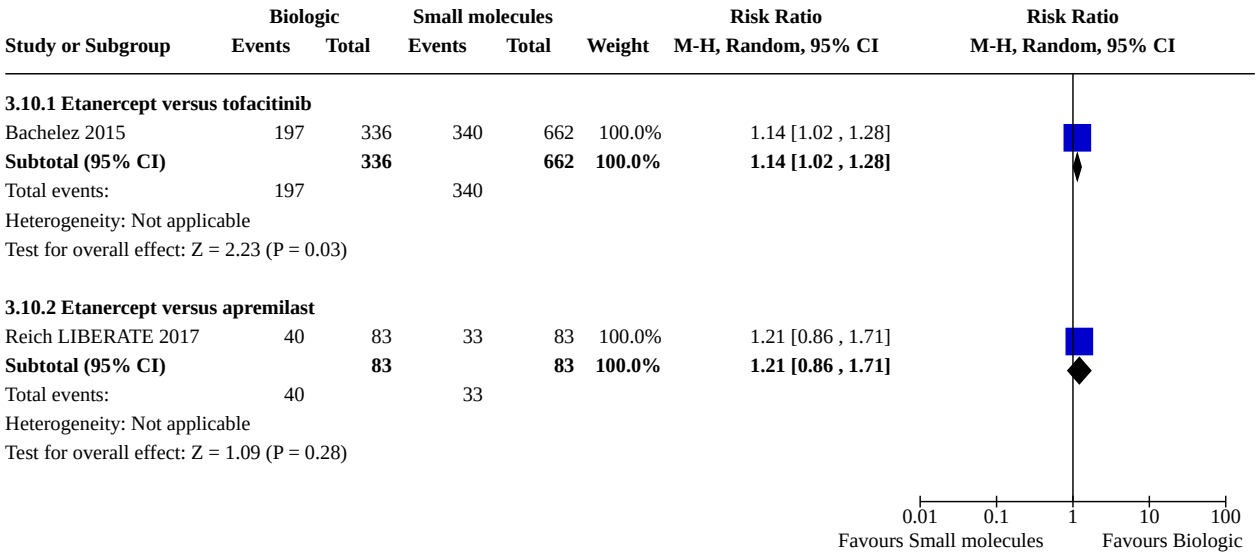


Analysis 3.9. Comparison 3: Secondary outcome - PASI 75, Outcome 9: Small molecules versus placebo

Study or Subgroup	Small molecules Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.9.1 Apremilast versus placebo						
Ohtsuki 2017	44	170	6	84	6.9%	3.62 [1.61 , 8.16]
Papp 2012c	71	264	5	88	6.3%	4.73 [1.97 , 11.35]
Papp 2013b	30	173	9	87	8.3%	1.68 [0.83 , 3.37]
Papp ESTEEM-1 2015	186	562	15	282	11.1%	6.22 [3.75 , 10.32]
Paul ESTEEM-2 2015	79	275	8	138	8.3%	4.96 [2.47 , 9.96]
Reich LIBERATE 2017	33	83	10	84	9.1%	3.34 [1.76 , 6.33]
Subtotal (95% CI)		**1527**		**763**	**50.0%**	**3.86 [2.59 , 5.74]**
Total events:	443		53			
Heterogeneity: Tau² = 0.12; Chi² = 10.06, df = 5 (P = 0.07); I² = 50%						
Test for overall effect: Z = 6.63 (P < 0.00001)						
3.9.2 Tofacitinib versus placebo						
Bachelez 2015	340	662	6	108	7.3%	9.24 [4.23 , 20.19]
Jin 2017	11	12	0	6	1.0%	12.38 [0.85 , 180.30]
Krueger 2016a	5	9	1	3	2.2%	1.67 [0.30 , 9.16]
Papp 2012b	65	147	1	50	1.8%	22.11 [3.15 , 155.20]
Papp OPT Pivotal-1 2015	358	723	11	177	10.0%	7.97 [4.47 , 14.19]
Papp OPT Pivotal-2 2015	396	763	22	196	13.0%	4.62 [3.10 , 6.90]
Zhang 2017	121	178	11	88	10.2%	5.44 [3.10 , 9.54]
Subtotal (95% CI)		**2494**		**628**	**45.4%**	**6.14 [4.31 , 8.73]**
Total events:	1296		52			
Heterogeneity: Tau² = 0.06; Chi² = 8.47, df = 6 (P = 0.21); I² = 29%						
Test for overall effect: Z = 10.09 (P < 0.00001)						
3.9.3 TYK2 versus placebo						
Papp TYK2 2018	115	222	3	45	4.6%	7.77 [2.59 , 23.36]
Subtotal (95% CI)		**222**		**45**	**4.6%**	**7.77 [2.59 , 23.36]**
Total events:	115		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.65 (P = 0.0003)						
Total (95% CI)		**4243**		**1436**	**100.0%**	**4.96 [3.77 , 6.51]**
Total events:	1854		108			
Heterogeneity: Tau² = 0.11; Chi² = 23.64, df = 13 (P = 0.03); I² = 45%						
Test for overall effect: Z = 11.49 (P < 0.00001)						
Test for subgroup differences: Chi² = 3.51, df = 2 (P = 0.17), I² = 43.1%						



Analysis 3.10. Comparison 3: Secondary outcome - PASI 75, Outcome 10: Biologic versus small molecules



Comparison 4. Secondary outcome - PGA 0/1

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Conventional systemic agents versus placebo	4	1023	Risk Ratio (M-H, Random, 95% CI)	2.87 [1.97, 4.18]
4.1.1 Methotrexate versus placebo	3	319	Risk Ratio (M-H, Random, 95% CI)	3.19 [1.66, 6.16]
4.1.2 Fumaric acid esters versus placebo	1	704	Risk Ratio (M-H, Random, 95% CI)	2.73 [1.72, 4.32]
4.2 Conventional systemic 1 versus conventional systemic 2	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.2.1 Ciclosporin versus methotrexate	1	88	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.47, 1.46]
4.2.2 Methotrexate versus fumaric acid esters	1	108	Risk Ratio (M-H, Random, 95% CI)	3.86 [1.84, 8.09]
4.3 Anti-TNF alpha versus placebo	28	10067	Risk Ratio (M-H, Random, 95% CI)	8.84 [7.32, 10.67]
4.3.1 Etanercept versus placebo	13	5030	Risk Ratio (M-H, Random, 95% CI)	8.11 [6.35, 10.37]
4.3.2 Adalimumab versus placebo	9	3337	Risk Ratio (M-H, Random, 95% CI)	7.89 [6.13, 10.16]
4.3.3 Certolizumab versus placebo	4	1139	Risk Ratio (M-H, Random, 95% CI)	27.48 [11.53, 65.49]

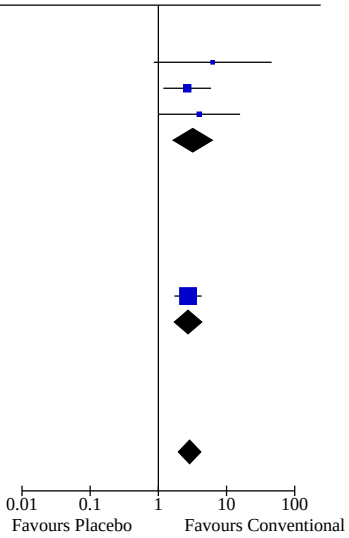
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.3.4 Infliximab versus placebo	3	561	Risk Ratio (M-H, Random, 95% CI)	13.11 [6.69, 25.69]
4.4 Anti-IL12/23 versus placebo	10	4553	Risk Ratio (M-H, Random, 95% CI)	10.94 [7.69, 15.55]
4.4.1 Ustekinumab versus placebo	10	4553	Risk Ratio (M-H, Random, 95% CI)	10.94 [7.69, 15.55]
4.5 Anti-IL17 versus placebo	16	10234	Risk Ratio (M-H, Random, 95% CI)	18.13 [13.71, 23.97]
4.5.1 Secukinumab versus placebo	6	2607	Risk Ratio (M-H, Random, 95% CI)	17.16 [7.48, 39.36]
4.5.2 Ixekizumab versus placebo	4	3268	Risk Ratio (M-H, Random, 95% CI)	17.46 [9.87, 30.90]
4.5.3 Brodalumab versus placebo	5	4109	Risk Ratio (M-H, Random, 95% CI)	18.78 [13.29, 26.55]
4.5.4 Bimekizumab versus placebo	1	250	Risk Ratio (M-H, Random, 95% CI)	15.35 [3.96, 59.49]
4.6 Anti-IL23 versus placebo	12	5147	Risk Ratio (M-H, Random, 95% CI)	10.92 [8.91, 13.39]
4.6.1 Guselkumab versus placebo	5	1767	Risk Ratio (M-H, Random, 95% CI)	10.87 [8.11, 14.57]
4.6.2 Tildrakizumab versus placebo	3	1904	Risk Ratio (M-H, Random, 95% CI)	10.26 [6.62, 15.91]
4.6.3 Risankizumab versus placebo	4	1476	Risk Ratio (M-H, Random, 95% CI)	11.50 [7.95, 16.66]
4.7 Biologic versus conventional systemic treatments	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.7.1 Infliximab versus methotrexate	1	868	Risk Ratio (M-H, Random, 95% CI)	1.99 [1.67, 2.37]
4.7.2 Adalimumab versus methotrexate	1	218	Risk Ratio (M-H, Random, 95% CI)	2.44 [1.79, 3.32]
4.7.3 Secukinumab versus fumaric acid esters	1	202	Risk Ratio (M-H, Random, 95% CI)	6.16 [3.59, 10.57]
4.7.4 Etanercept versus acitretin	2	82	Risk Ratio (M-H, Random, 95% CI)	4.98 [1.15, 21.49]
4.7.5 Ixekizumab versus fumaric acid esters	1	108	Risk Ratio (M-H, Random, 95% CI)	6.43 [3.19, 12.96]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.7.6 Ixekizumab versus methotrexate	1	108	Risk Ratio (M-H, Random, 95% CI)	1.67 [1.24, 2.23]
4.8 Biologic 1 versus biologic 2	18		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.8.1 Ustekinumab versus etanercept	1	903	Risk Ratio (M-H, Random, 95% CI)	1.40 [1.24, 1.58]
4.8.2 Secukinumab versus etanercept	1	980	Risk Ratio (M-H, Random, 95% CI)	2.09 [1.73, 2.53]
4.8.3 Ixekizumab versus etanercept	2	2209	Risk Ratio (M-H, Random, 95% CI)	2.01 [1.74, 2.31]
4.8.4 Secukinumab versus ustekinumab	2	1778	Risk Ratio (M-H, Random, 95% CI)	1.28 [1.19, 1.38]
4.8.5 Brodalumab versus ustekinumab	2	3088	Risk Ratio (M-H, Random, 95% CI)	1.17 [1.07, 1.27]
4.8.6 Guselkumab versus adalimumab	3	1658	Risk Ratio (M-H, Random, 95% CI)	1.26 [1.19, 1.34]
4.8.7 Risankizumab versus ustekinumab	3	965	Risk Ratio (M-H, Random, 95% CI)	1.37 [1.23, 1.52]
4.8.8 Ixekizumab versus ustekinumab	1	302	Risk Ratio (M-H, Random, 95% CI)	1.44 [1.24, 1.68]
4.8.9 Risankizumab versus adalimumab	1	605	Risk Ratio (M-H, Random, 95% CI)	1.39 [1.25, 1.54]
4.8.10 Tildrakizumab versus etanercept	1	934	Risk Ratio (M-H, Random, 95% CI)	1.20 [1.05, 1.37]
4.8.11 Infliximab versus etanercept	1	48	Risk Ratio (M-H, Random, 95% CI)	2.50 [1.30, 4.81]
4.9 Small molecules versus placebo	12	5401	Risk Ratio (M-H, Random, 95% CI)	4.02 [3.19, 5.05]
4.9.1 Apremilast versus placebo	5	2030	Risk Ratio (M-H, Random, 95% CI)	3.68 [2.22, 6.11]
4.9.2 Tofacitinib versus placebo	6	3104	Risk Ratio (M-H, Random, 95% CI)	4.17 [3.37, 5.17]
4.9.3 TYK2 versus placebo	1	267	Risk Ratio (M-H, Random, 95% CI)	8.24 [2.74, 24.76]
4.10 Biologic versus small molecules	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

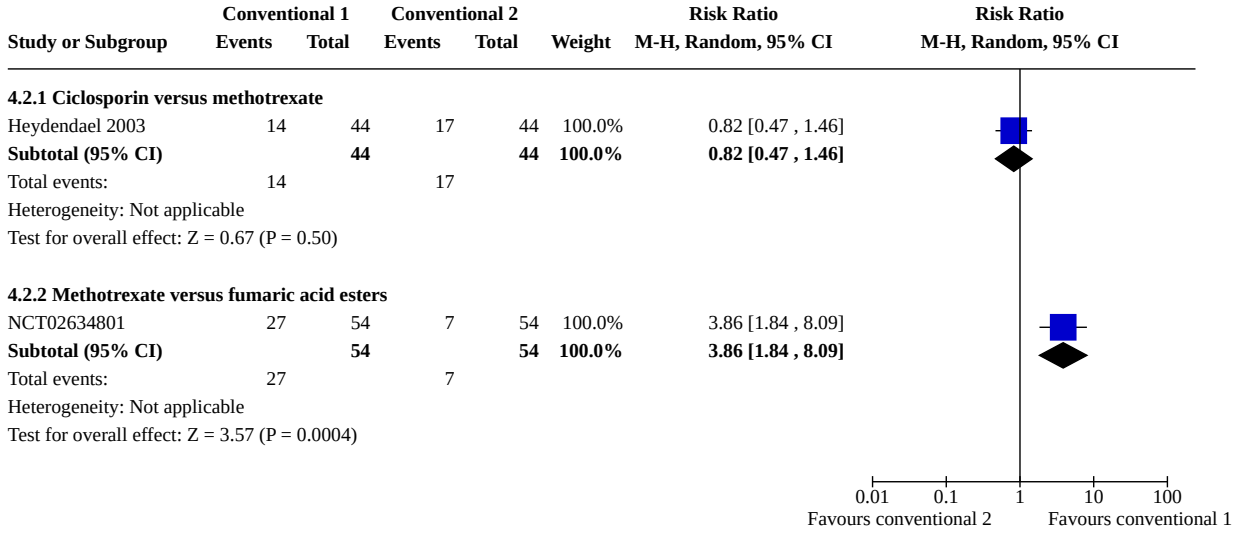
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.10.1 Etanercept versus tofacitinib	1	998	Risk Ratio (M-H, Random, 95% CI)	1.15 [1.04, 1.27]
4.10.2 Etanercept versus apremilast	1	166	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.78, 2.27]

Analysis 4.1. Comparison 4: Secondary outcome - PGA 0/1, Outcome 1: Conventional systemic agents versus placebo

Study or Subgroup	Conventional treatment Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 Methotrexate versus placebo						
Hunter 1963	7	19	1	17	3.6%	6.26 [0.86 , 45.84]
Saurat CHAMPION 2008	33	110	6	53	21.9%	2.65 [1.18 , 5.93]
Warren METOP, 2017	25	91	2	29	7.5%	3.98 [1.00 , 15.81]
Subtotal (95% CI)		**220**		**99**	**32.9%**	**3.19 [1.66 , 6.16]**
Total events:	65		9			
Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 2 (P = 0.69); I² = 0%						
Test for overall effect: Z = 3.46 (P = 0.0005)						
4.1.2 Fumaric acid esters versus placebo						
Mrowietz BRIDGE 2016	190	566	17	138	67.1%	2.73 [1.72 , 4.32]
Subtotal (95% CI)		**566**		**138**	**67.1%**	**2.73 [1.72 , 4.32]**
Total events:	190		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.27 (P < 0.0001)						
Total (95% CI)		**786**		**237**	**100.0%**	**2.87 [1.97 , 4.18]**
Total events:	255		26			
Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 3 (P = 0.83); I² = 0%						
Test for overall effect: Z = 5.49 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.15, df = 1 (P = 0.70), I² = 0%						

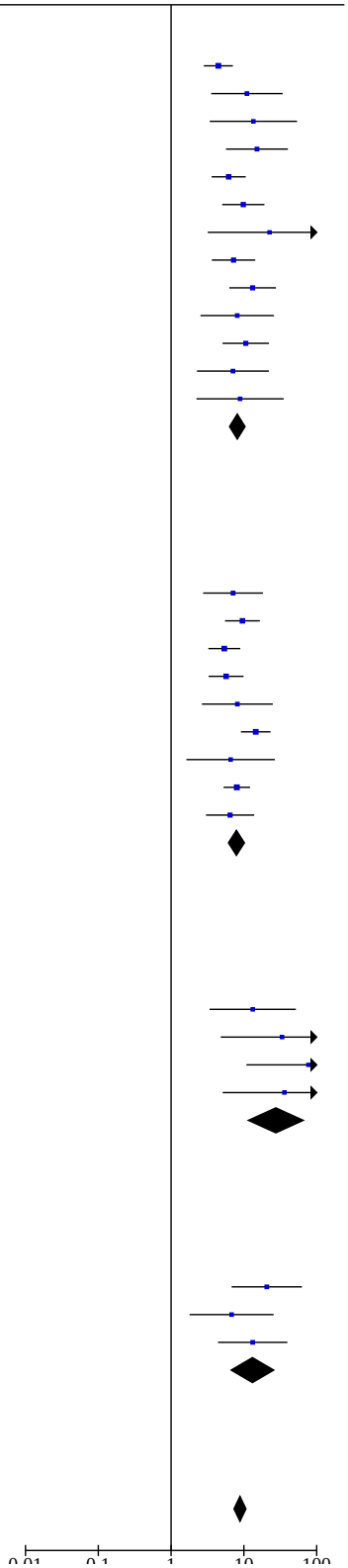


Analysis 4.2. Comparison 4: Secondary outcome - PGA 0/1, Outcome 2: Conventional systemic 1 versus conventional systemic 2



Analysis 4.3. Comparison 4: Secondary outcome - PGA 0/1, Outcome 3: Anti-TNF alpha versus placebo

Study or Subgroup	Anti-TNF Events	Anti-TNF Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.3.1 Etanercept versus placebo						
Bachelez 2015	222	336	16	108	7.1%	4.46 [2.82 , 7.06]
Bagel 2012	33	62	3	62	2.3%	11.00 [3.56 , 33.99]
Gottlieb 2011	56	141	2	68	1.6%	13.50 [3.40 , 53.70]
Griffiths UNCOVER-2 2015	129	358	4	168	2.9%	15.13 [5.69 , 40.24]
Griffiths UNCOVER-3 2015	159	382	13	193	6.1%	6.18 [3.61 , 10.59]
Langley FIXTURE 2014	88	326	9	327	4.8%	9.81 [5.03 , 19.14]
Lebwohl CIMPACT 2018	67	170	1	57	0.9%	22.46 [3.19 , 158.15]
Leonardi 2003	173	504	8	168	4.7%	7.21 [3.63 , 14.33]
Papp 2005	184	407	7	204	4.3%	13.18 [6.31 , 27.50]
Reich LIBERATE 2017	24	83	3	84	2.2%	8.10 [2.53 , 25.86]
Reich ReSURFACE-2 2017	149	313	7	156	4.3%	10.61 [5.10 , 22.09]
Strober 2011	41	139	3	72	2.3%	7.08 [2.27 , 22.07]
Van de Kerkhof 2008	37	96	2	46	1.6%	8.86 [2.23 , 35.19]
Subtotal (95% CI)		**3317**		**1713**	**45.1%**	**8.11 [6.35 , 10.37]**
Total events:	1362		78			
Heterogeneity: Tau² = 0.03; Chi² = 13.99, df = 12 (P = 0.30); I² = 14%						
Test for overall effect: Z = 16.70 (P < 0.00001)						
4.3.2 Adalimumab versus placebo						
Asahina 2010	76	123	4	46	3.0%	7.11 [2.76 , 18.31]
Blauvelt VOYAGE-1 2016	220	334	12	174	6.0%	9.55 [5.50 , 16.58]
Cai 2016	272	338	13	87	6.5%	5.39 [3.25 , 8.92]
Elewski 2016	69	109	12	108	6.0%	5.70 [3.28 , 9.90]
Gordon X-PLORE 2015	25	43	3	42	2.3%	8.14 [2.66 , 24.93]
Menter REVEAL 2008	506	814	17	398	7.0%	14.55 [9.11 , 23.24]
NCT01553058 VIP trial	14	33	2	31	1.6%	6.58 [1.62 , 26.62]
Reich VOYAGE-2 2017	168	248	21	248	7.7%	8.00 [5.27 , 12.15]
Saurat CHAMPION 2008	79	108	6	53	4.1%	6.46 [3.02 , 13.85]
Subtotal (95% CI)		**2150**		**1187**	**44.2%**	**7.89 [6.13 , 10.16]**
Total events:	1429		90			
Heterogeneity: Tau² = 0.04; Chi² = 11.48, df = 8 (P = 0.18); I² = 30%						
Test for overall effect: Z = 16.02 (P < 0.00001)						
4.3.3 Certolizumab versus placebo						
Gottlieb CIMPASI-1 2018	95	183	2	51	1.7%	13.24 [3.38 , 51.87]
Gottlieb CIMPASI-2 2018	122	178	1	49	0.9%	33.58 [4.81 , 234.27]
Lebwohl CIMPACT 2018	150	332	1	170	0.9%	76.81 [10.84 , 544.07]
Reich 2012a	73	118	1	58	0.9%	35.88 [5.11 , 251.73]
Subtotal (95% CI)		**811**		**328**	**4.3%**	**27.48 [11.53 , 65.49]**
Total events:	440		5			
Heterogeneity: Tau² = 0.00; Chi² = 2.45, df = 3 (P = 0.48); I² = 0%						
Test for overall effect: Z = 7.48 (P < 0.00001)						
4.3.4 Infliximab versus placebo						
Reich EXPRESS 2005	242	301	3	77	2.3%	20.64 [6.80 , 62.66]
Torii 2010	25	35	2	19	1.7%	6.79 [1.80 , 25.59]
Yang 2012	74	84	3	45	2.4%	13.21 [4.42 , 39.54]
Subtotal (95% CI)		**420**		**141**	**6.5%**	**13.11 [6.69 , 25.69]**
Total events:	341		8			
Heterogeneity: Tau² = 0.00; Chi² = 1.72, df = 2 (P = 0.42); I² = 0%						
Test for overall effect: Z = 7.50 (P < 0.00001)						
Total (95% CI)		**6698**		**3369**	**100.0%**	**8.84 [7.32 , 10.67]**
Total events:	3572		181			
Heterogeneity: Tau² = 0.08; Chi² = 41.49, df = 28 (P = 0.05); I² = 33%						



Analysis 4.3. (Continued)

Total events:	3572	181

Heterogeneity: Tau² = 0.08; Chi² = 41.49, df = 28 (P = 0.05); I² = 33%
Test for overall effect: Z = 22.60 (P < 0.00001)
Test for subgroup differences: Chi² = 9.04, df = 3 (P = 0.03), I² = 66.8%

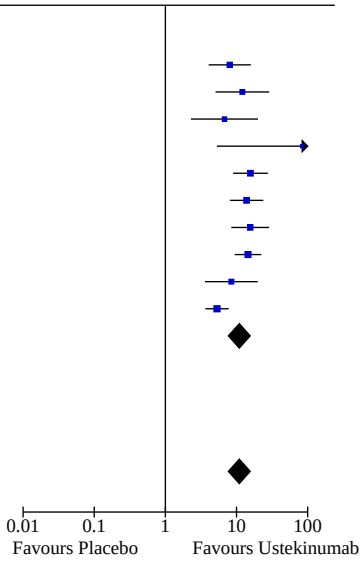
Analysis 4.4. Comparison 4: Secondary outcome - PGA 0/1, Outcome 4: Anti-IL12/23 versus placebo

Study or Subgroup	Ustekinumab Events	Ustekinumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.4.1 Ustekinumab versus placebo						
Gordon UltIMMa-1 2018	63	100	8	102	10.6%	8.03 [4.06 , 15.89]
Gordon UltIMMa-2 2018	61	99	5	98	8.5%	12.08 [5.07 , 28.77]
Igarashi 2012	80	126	3	32	6.6%	6.77 [2.29 , 20.05]
Krueger 2007	165	256	0	64	1.5%	83.72 [5.28 , 1326.17]
Lebwohl AMAGINE-2 2015	183	300	12	309	12.1%	15.71 [8.95 , 27.55]
Lebwohl AMAGINE-3 2015	179	313	13	315	12.4%	13.86 [8.07 , 23.80]
Leonardi PHOENIX-1 2008	312	511	10	255	11.4%	15.57 [8.45 , 28.70]
Papp PHOENIX-2 2008	580	820	20	410	13.9%	14.50 [9.44 , 22.28]
Tsai PEARL 2011	43	61	5	60	8.6%	8.46 [3.60 , 19.89]
Zhu LOTUS 2013	126	160	24	162	14.5%	5.32 [3.64 , 7.76]
Subtotal (95% CI)		**2746**		**1807**	**100.0%**	**10.94 [7.69 , 15.55]**
Total events:	1792		100			

Heterogeneity: Tau² = 0.18; Chi² = 25.52, df = 9 (P = 0.002); I² = 65%
Test for overall effect: Z = 13.32 (P < 0.00001)

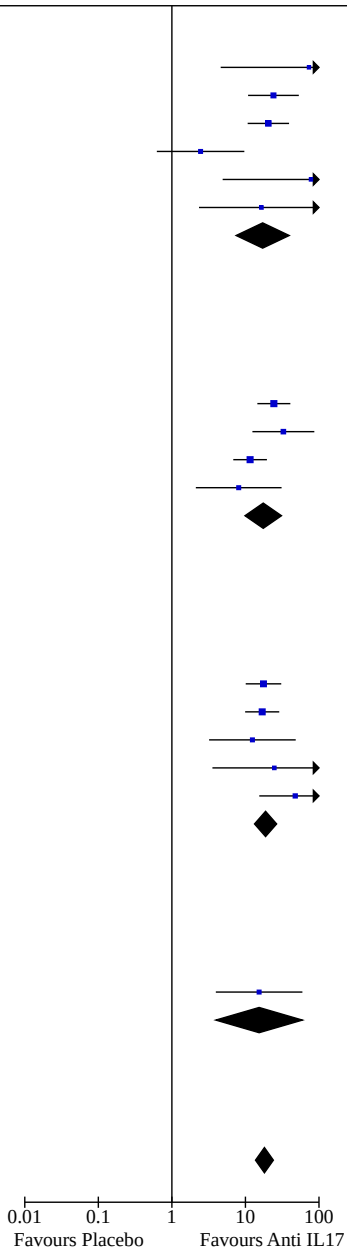
Total (95% CI)		**2746**		**1807**	**100.0%**	**10.94 [7.69 , 15.55]**
Total events:	1792		100			

Heterogeneity: Tau² = 0.18; Chi² = 25.52, df = 9 (P = 0.002); I² = 65%
Test for overall effect: Z = 13.32 (P < 0.00001)
Test for subgroup differences: Not applicable



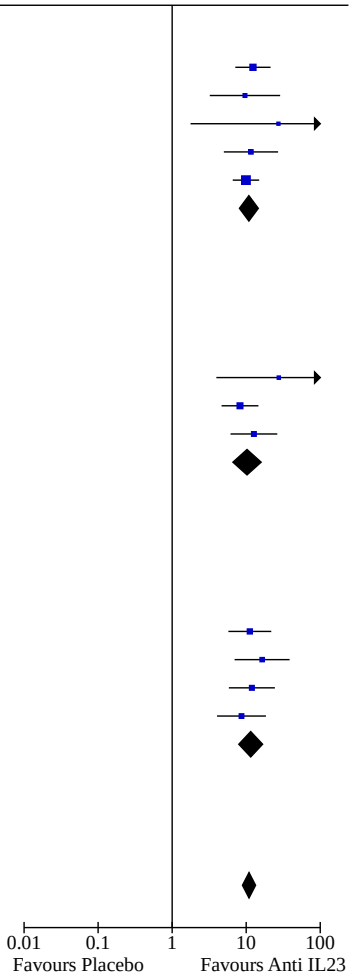
Analysis 4.5. Comparison 4: Secondary outcome - PGA 0/1, Outcome 5: Anti-IL17 versus placebo

Study or Subgroup	Anti IL17 Events	Anti IL17 Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.5.1 Secukinumab versus placebo						
Blauvelt FEATURE 2015	72	118	0	59	1.0%	73.11 [4.61 , 1159.72]
Langley ERASURE 2014	285	490	6	248	8.1%	24.04 [10.87 , 53.18]
Langley FIXTURE 2014	369	654	9	327	10.3%	20.50 [10.73 , 39.18]
Papp 2013a	23	103	2	22	3.5%	2.46 [0.62 , 9.66]
Paul JUNCTURE 2015	76	121	0	61	1.0%	77.75 [4.90 , 1233.42]
Rich 2013	83	337	1	67	1.9%	16.50 [2.34 , 116.48]
Subtotal (95% CI)		**1823**		**784**	**25.8%**	**17.16 [7.48 , 39.36]**
Total events:	908		18			
Heterogeneity: Tau² = 0.51; Chi² = 11.49, df = 5 (P = 0.04); I² = 56%						
Test for overall effect: Z = 6.71 (P < 0.00001)						
4.5.2 Ixekizumab versus placebo						
Gordon UNCOVER-1 2016	684	865	14	431	13.0%	24.34 [14.53 , 40.80]
Griffiths UNCOVER-2 2015	545	698	4	168	6.1%	32.79 [12.44 , 86.43]
Griffiths UNCOVER-3 2015	601	771	13	193	12.8%	11.57 [6.84 , 19.59]
Leonardi 2012	69	115	2	27	3.7%	8.10 [2.12 , 30.99]
Subtotal (95% CI)		**2449**		**819**	**35.5%**	**17.46 [9.87 , 30.90]**
Total events:	1899		33			
Heterogeneity: Tau² = 0.18; Chi² = 7.06, df = 3 (P = 0.07); I² = 57%						
Test for overall effect: Z = 9.82 (P < 0.00001)						
4.5.3 Brodalumab versus placebo						
Lebwohl AMAGINE-2 2015	835	1222	12	309	12.1%	17.60 [10.09 , 30.68]
Lebwohl AMAGINE-3 2015	874	1253	13	315	12.6%	16.90 [9.91 , 28.82]
Nakagawa 2016	74	113	2	38	3.6%	12.44 [3.21 , 48.26]
Papp 2012a	104	160	1	38	1.9%	24.70 [3.56 , 171.42]
Papp AMAGINE-1 2016	286	441	3	220	4.9%	47.56 [15.43 , 146.63]
Subtotal (95% CI)		**3189**		**920**	**35.1%**	**18.78 [13.29 , 26.55]**
Total events:	2173		31			
Heterogeneity: Tau² = 0.00; Chi² = 3.32, df = 4 (P = 0.51); I² = 0%						
Test for overall effect: Z = 16.61 (P < 0.00001)						
4.5.4 Bimekizumab versus placebo						
Papp BE ABLE 2018	152	208	2	42	3.6%	15.35 [3.96 , 59.49]
Subtotal (95% CI)		**208**		**42**	**3.6%**	**15.35 [3.96 , 59.49]**
Total events:	152		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.95 (P < 0.0001)						
Total (95% CI)		**7669**		**2565**	**100.0%**	**18.13 [13.71 , 23.97]**
Total events:	5132		84			
Heterogeneity: Tau² = 0.09; Chi² = 21.78, df = 15 (P = 0.11); I² = 31%						
Test for overall effect: Z = 20.32 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.13, df = 3 (P = 0.99), I² = 0%						



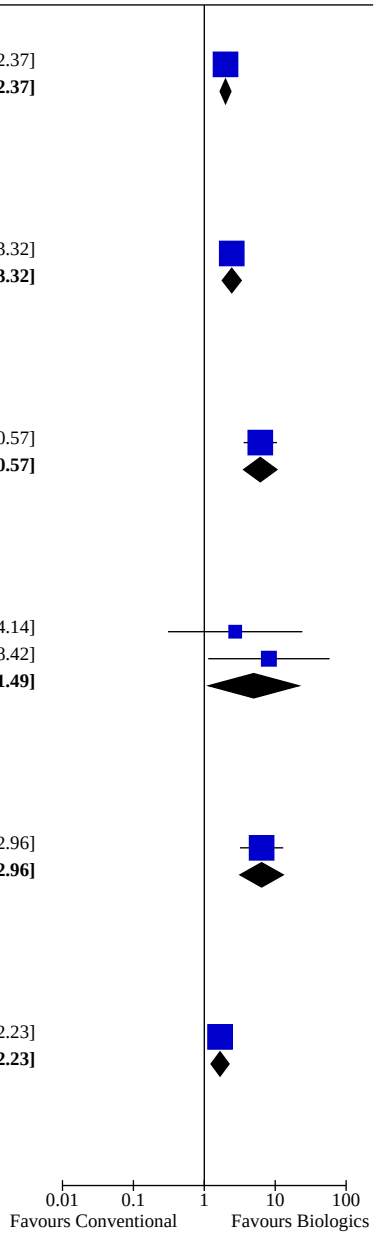
Analysis 4.6. Comparison 4: Secondary outcome - PGA 0/1, Outcome 6: Anti-IL23 versus placebo

Study or Subgroup	Anti IL23 Events	Anti IL23 Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.6.1 Guselkumab versus placebo						
Blauvelt VOYAGE-1 2016	280	329	12	174	13.8%	12.34 [7.14 , 21.34]
Gordon X-PLORE 2015	143	208	3	42	3.5%	9.63 [3.22 , 28.75]
NCT02905331 ORION	50	62	0	16	0.6%	27.25 [1.77 , 419.35]
Ohtsuki 2018	116	128	5	64	5.8%	11.60 [4.99 , 26.96]
Reich VOYAGE-2 2017	417	496	21	248	24.5%	9.93 [6.58 , 14.98]
Subtotal (95% CI)		**1223**		**544**	**48.2%**	**10.87 [8.11 , 14.57]**
Total events:	1006		41			
Heterogeneity: Tau² = 0.00; Chi² = 0.91, df = 4 (P = 0.92); I² = 0%						
Test for overall effect: Z = 15.95 (P < 0.00001)						
4.6.2 Tildrakizumab versus placebo						
Papp 2015	185	309	1	46	1.1%	27.54 [3.95 , 191.78]
Reich ReSURFACE-1 2017	361	617	11	155	12.6%	8.24 [4.65 , 14.63]
Reich ReSURFACE-2 2017	354	621	7	156	7.8%	12.70 [6.14 , 26.29]
Subtotal (95% CI)		**1547**		**357**	**21.5%**	**10.26 [6.62 , 15.91]**
Total events:	900		19			
Heterogeneity: Tau² = 0.00; Chi² = 1.98, df = 2 (P = 0.37); I² = 0%						
Test for overall effect: Z = 10.40 (P < 0.00001)						
4.6.3 Risankizumab versus placebo						
Gordon UltIMMa-1 2018	267	304	8	102	9.3%	11.20 [5.75 , 21.81]
Gordon UltIMMa-2 2018	246	294	5	98	5.7%	16.40 [6.97 , 38.58]
NCT02672852 IMMhance	340	407	7	100	8.1%	11.93 [5.83 , 24.41]
NCT03000075	101	113	6	58	7.2%	8.64 [4.04 , 18.48]
Subtotal (95% CI)		**1118**		**358**	**30.3%**	**11.50 [7.95 , 16.66]**
Total events:	954		26			
Heterogeneity: Tau² = 0.00; Chi² = 1.25, df = 3 (P = 0.74); I² = 0%						
Test for overall effect: Z = 12.94 (P < 0.00001)						
Total (95% CI)		**3888**		**1259**	**100.0%**	**10.92 [8.91 , 13.39]**
Total events:	2860		86			
Heterogeneity: Tau² = 0.00; Chi² = 4.25, df = 11 (P = 0.96); I² = 0%						
Test for overall effect: Z = 23.02 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.15, df = 2 (P = 0.93), I² = 0%						



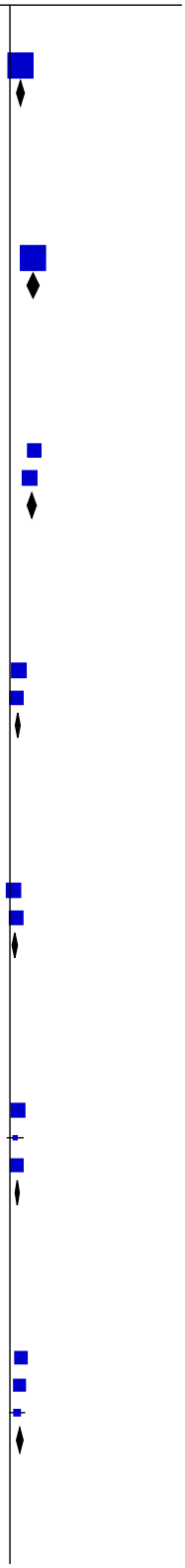
Analysis 4.7. Comparison 4: Secondary outcome - PGA 0/1, Outcome 7: Biologic versus conventional systemic treatments

Study or Subgroup	Biologic Events	Biologic Total	Conventional systemic Events	Conventional systemic Total	Weight	Risk Ratio M-H, Random, 95% CI
4.7.1 Infliximab versus methotrexate						
Barker RESTORE-1 2011	496	653	82	215	100.0%	1.99 [1.67 , 2.37]
Subtotal (95% CI)		**653**		**215**	**100.0%**	**1.99 [1.67 , 2.37]**
Total events:	496		82			
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.69 (P < 0.00001)						
4.7.2 Adalimumab versus methotrexate						
Saurat CHAMPION 2008	79	108	33	110	100.0%	2.44 [1.79 , 3.32]
Subtotal (95% CI)		**108**		**110**	**100.0%**	**2.44 [1.79 , 3.32]**
Total events:	79		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.68 (P < 0.00001)						
4.7.3 Secukinumab versus fumaric acid esters						
Sticherling PRIME 2017	80	105	12	97	100.0%	6.16 [3.59 , 10.57]
Subtotal (95% CI)		**105**		**97**	**100.0%**	**6.16 [3.59 , 10.57]**
Total events:	80		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.59 (P < 0.00001)						
4.7.4 Etanercept versus acitretin						
Gisondi 2008	3	22	1	20	45.0%	2.73 [0.31 , 24.14]
Lee 2016	9	21	1	19	55.0%	8.14 [1.13 , 58.42]
Subtotal (95% CI)		**43**		**39**	**100.0%**	**4.98 [1.15 , 21.49]**
Total events:	12		2			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.55$, df = 1 (P = 0.46); $I^2 = 0\%$						
Test for overall effect: Z = 2.15 (P = 0.03)						
4.7.5 Ixekizumab versus fumaric acid esters						
NCT02634801	45	54	7	54	100.0%	6.43 [3.19 , 12.96]
Subtotal (95% CI)		**54**		**54**	**100.0%**	**6.43 [3.19 , 12.96]**
Total events:	45		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.20 (P < 0.00001)						
4.7.6 Ixekizumab versus methotrexate						
NCT02634801	45	54	27	54	100.0%	1.67 [1.24 , 2.23]
Subtotal (95% CI)		**54**		**54**	**100.0%**	**1.67 [1.24 , 2.23]**
Total events:	45		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.43 (P = 0.0006)						



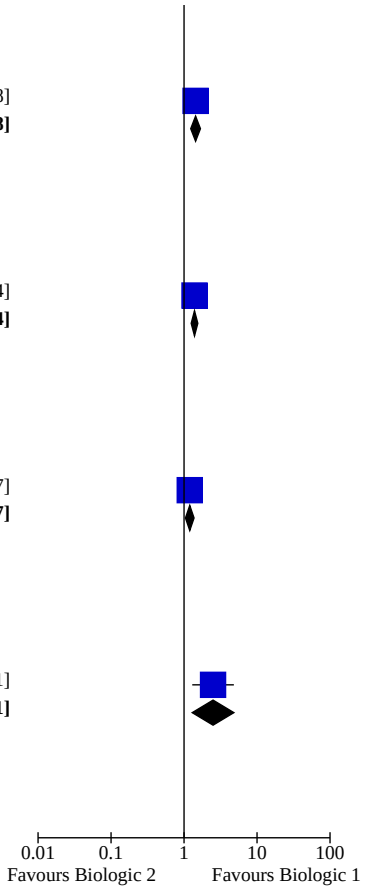
Analysis 4.8. Comparison 4: Secondary outcome - PGA 0/1, Outcome 8: Biologic 1 versus biologic 2

Study or Subgroup	Biologic 1 Events	Biologic 1 Total	Biologic 2 Events	Biologic 2 Total	Weight	Risk Ratio M-H, Random, 95% CI
4.8.1 Ustekinumab versus etanercept						
Griffiths ACCEPT 2010	381	556	170	347	100.0%	1.40 [1.24 , 1.58]
Subtotal (95% CI)		**556**		**347**	**100.0%**	**1.40 [1.24 , 1.58]**
Total events:	381		170			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.42 (P < 0.00001)						
4.8.2 Secukinumab versus etanercept						
Langley FIXTURE 2014	369	654	88	326	100.0%	2.09 [1.73 , 2.53]
Subtotal (95% CI)		**654**		**326**	**100.0%**	**2.09 [1.73 , 2.53]**
Total events:	369		88			
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.57 (P < 0.00001)						
4.8.3 Ixekizumab versus etanercept						
Griffiths UNCOVER-2 2015	545	698	129	358	46.9%	2.17 [1.88 , 2.50]
Griffiths UNCOVER-3 2015	601	771	159	382	53.1%	1.87 [1.65 , 2.12]
Subtotal (95% CI)		**1469**		**740**	**100.0%**	**2.01 [1.74 , 2.31]**
Total events:	1146		288			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 2.27$, df = 1 (P = 0.13); $I^2 = 56\%$						
Test for overall effect: Z = 9.54 (P < 0.00001)						
4.8.4 Secukinumab versus ustekinumab						
Bagel CLARITY 2018	432	550	326	552	53.1%	1.33 [1.23 , 1.44]
Thaçi CLEAR 2015	277	337	226	339	46.9%	1.23 [1.13 , 1.35]
Subtotal (95% CI)		**887**		**891**	**100.0%**	**1.28 [1.19 , 1.38]**
Total events:	709		552			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.50$, df = 1 (P = 0.22); $I^2 = 33\%$						
Test for overall effect: Z = 6.57 (P < 0.00001)						
4.8.5 Brodalumab versus ustekinumab						
Lebwohl AMAGINE-2 2015	835	1222	183	300	51.6%	1.12 [1.02 , 1.24]
Lebwohl AMAGINE-3 2015	874	1253	179	313	48.4%	1.22 [1.10 , 1.35]
Subtotal (95% CI)		**2475**		**613**	**100.0%**	**1.17 [1.07 , 1.27]**
Total events:	1709		362			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.38$, df = 1 (P = 0.24); $I^2 = 28\%$						
Test for overall effect: Z = 3.63 (P = 0.0003)						
4.8.6 Guselkumab versus adalimumab						
Blauvelt VOYAGE-1 2016	280	329	220	334	49.6%	1.29 [1.18 , 1.41]
Gordon X-PLORE 2015	143	208	25	43	5.5%	1.18 [0.90 , 1.55]
Reich VOYAGE-2 2017	417	496	168	248	44.9%	1.24 [1.13 , 1.36]
Subtotal (95% CI)		**1033**		**625**	**100.0%**	**1.26 [1.19 , 1.34]**
Total events:	840		413			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.62$, df = 2 (P = 0.73); $I^2 = 0\%$						
Test for overall effect: Z = 7.26 (P < 0.00001)						
4.8.7 Risankizumab versus ustekinumab						
Gordon UltIMMa-1 2018	267	304	63	102	43.1%	1.42 [1.21 , 1.67]
Gordon UltIMMa-2 2018	246	294	61	99	40.5%	1.36 [1.15 , 1.60]
Papp NCT02054481 2017	99	126	25	40	16.4%	1.26 [0.97 , 1.63]
Subtotal (95% CI)		**724**		**241**	**100.0%**	**1.37 [1.23 , 1.52]**
Total events:	612		149			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.65$, df = 2 (P = 0.72); $I^2 = 0\%$						
Test for overall effect: Z = 5.90 (P < 0.00001)						



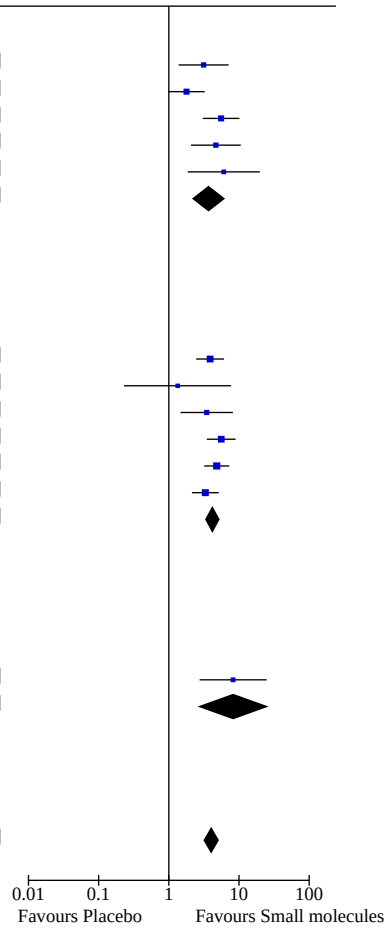
Analysis 4.8. (Continued)

Test for overall effect: Z = 5.90 (P < 0.00001)						
4.8.8 Ixekizumab versus ustekinumab						
Reich IXORA-S 2017	112	136	95	166	100.0%	1.44 [1.24 , 1.68]
Subtotal (95% CI)		**136**		**166**	**100.0%**	**1.44 [1.24 , 1.68]**
Total events:	112		95			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.67 (P < 0.00001)						
4.8.9 Risankizumab versus adalimumab						
EUCTR2015-003623-65-DE	252	301	183	304	100.0%	1.39 [1.25 , 1.54]
Subtotal (95% CI)		**301**		**304**	**100.0%**	**1.39 [1.25 , 1.54]**
Total events:	252		183			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.21 (P < 0.00001)						
4.8.10 Tildrakizumab versus etanercept						
Reich ReSURFACE-2 2017	354	621	149	313	100.0%	1.20 [1.05 , 1.37]
Subtotal (95% CI)		**621**		**313**	**100.0%**	**1.20 [1.05 , 1.37]**
Total events:	354		149			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.62 (P = 0.009)						
4.8.11 Infliximab versus etanercept						
De Vries PIECE 2016	19	25	7	23	100.0%	2.50 [1.30 , 4.81]
Subtotal (95% CI)		**25**		**23**	**100.0%**	**2.50 [1.30 , 4.81]**
Total events:	19		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.73 (P = 0.006)						

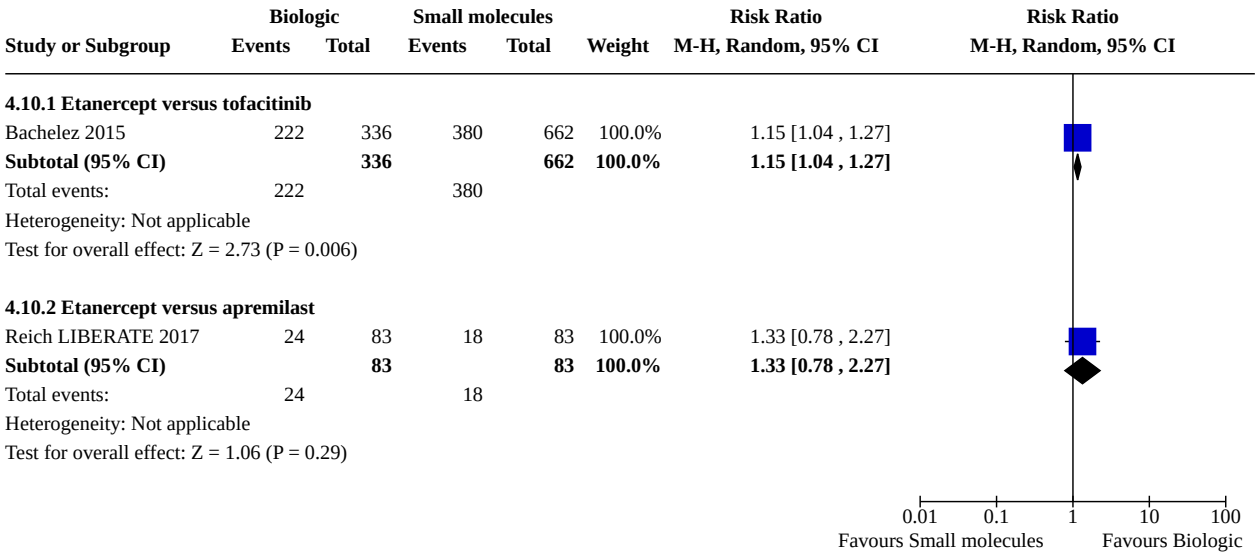


Analysis 4.9. Comparison 4: Secondary outcome - PGA 0/1, Outcome 9: Small molecules versus placebo

Study or Subgroup	Small molecules Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.9.1 Apremilast versus placebo						
Ohtsuki 2017	38	170	6	84	6.1%	3.13 [1.38 , 7.11]
Papp 2012c	59	264	11	88	9.6%	1.79 [0.98 , 3.25]
Papp ESTEEM-1 2015	122	562	11	282	9.6%	5.57 [3.05 , 10.14]
Paul ESTEEM-2 2015	56	275	6	138	6.1%	4.68 [2.07 , 10.60]
Reich LIBERATE 2017	18	83	3	84	3.3%	6.07 [1.86 , 19.84]
Subtotal (95% CI)		**1354**		**676**	**34.7%**	**3.68 [2.22 , 6.11]**
Total events:	293		37			
Heterogeneity: Tau² = 0.18; Chi² = 8.79, df = 4 (P = 0.07); I² = 54%						
Test for overall effect: Z = 5.04 (P < 0.00001)						
4.9.2 Tofacitinib versus placebo						
Bachelez 2015	380	662	16	108	13.2%	3.87 [2.45 , 6.12]
Krueger 2016a	4	9	1	3	1.6%	1.33 [0.23 , 7.74]
Papp 2012b	51	147	5	50	5.6%	3.47 [1.47 , 8.20]
Papp OPT Pivotal-1 2015	365	723	16	177	12.7%	5.58 [3.48 , 8.96]
Papp OPT Pivotal-2 2015	394	763	21	196	14.7%	4.82 [3.20 , 7.26]
Zhang 2017	114	178	17	88	13.7%	3.32 [2.13 , 5.15]
Subtotal (95% CI)		**2482**		**622**	**61.6%**	**4.17 [3.37 , 5.17]**
Total events:	1308		76			
Heterogeneity: Tau² = 0.00; Chi² = 5.01, df = 5 (P = 0.41); I² = 0%						
Test for overall effect: Z = 13.12 (P < 0.00001)						
4.9.3 TYK2 versus placebo						
Papp TYK2 2018	122	222	3	45	3.7%	8.24 [2.74 , 24.76]
Subtotal (95% CI)		**222**		**45**	**3.7%**	**8.24 [2.74 , 24.76]**
Total events:	122		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.76 (P = 0.0002)						
Total (95% CI)		**4058**		**1343**	**100.0%**	**4.02 [3.19 , 5.05]**
Total events:	1723		116			
Heterogeneity: Tau² = 0.05; Chi² = 16.28, df = 11 (P = 0.13); I² = 32%						
Test for overall effect: Z = 11.91 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.71, df = 2 (P = 0.43), I² = 0%						



Analysis 4.10. Comparison 4: Secondary outcome - PGA 0/1, Outcome 10: Biologic versus small molecules



Comparison 5. Secondary outcome - quality of life

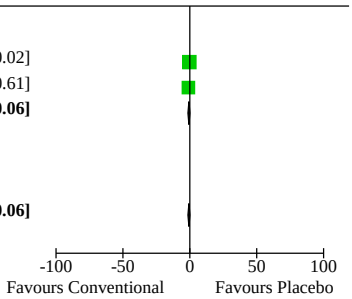
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Conventional systemic agents versus placebo	2	283	Std. Mean Difference (IV, Random, 95% CI)	-0.67 [-1.40, 0.06]
5.1.1 Methotrexate veruss placebo	2	283	Std. Mean Difference (IV, Random, 95% CI)	-0.67 [-1.40, 0.06]
5.2 Conventional systemic 1 versus conventional systemic 2	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.2.1 Methotrexate versus fumaric acid esters	1	108	Mean Difference (IV, Fixed, 95% CI)	-7.44 [-9.47, -5.41]
5.3 Anti-TNF alpha versus placebo	24	8407	Std. Mean Difference (IV, Random, 95% CI)	-1.07 [-1.18, -0.96]
5.3.1 Etanercept versus placebo	8	3246	Std. Mean Difference (IV, Random, 95% CI)	-1.11 [-1.34, -0.88]
5.3.2 Adalimumab versus placebo	9	3055	Std. Mean Difference (IV, Random, 95% CI)	-0.98 [-1.11, -0.85]
5.3.3 Certolizumab versus placebo	2	461	Std. Mean Difference (IV, Random, 95% CI)	-0.91 [-1.14, -0.68]
5.3.4 Infliximab versus placebo	5	1645	Std. Mean Difference (IV, Random, 95% CI)	-1.29 [-1.48, -1.10]
5.4 Ustekinumab versus placebo	8	3316	Std. Mean Difference (IV, Random, 95% CI)	-1.32 [-1.51, -1.13]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.5 Anti-IL17 versus placebo	5	3475	Std. Mean Difference (IV, Random, 95% CI)	-1.47 [-1.84, -1.10]
5.5.1 Ixekizumab versus placebo	3	3126	Std. Mean Difference (IV, Random, 95% CI)	-1.76 [-2.09, -1.43]
5.5.2 Brodalumab versus placebo	2	349	Std. Mean Difference (IV, Random, 95% CI)	-0.96 [-1.44, -0.47]
5.6 Anti-IL23 versus placebo	8	4146	Std. Mean Difference (IV, Random, 95% CI)	-1.46 [-1.62, -1.30]
5.6.1 Guselkumab versus placebo	3	1444	Std. Mean Difference (IV, Random, 95% CI)	-1.36 [-1.54, -1.18]
5.6.2 Tildrakizumab versus placebo	3	1904	Std. Mean Difference (IV, Random, 95% CI)	-1.36 [-1.48, -1.23]
5.6.3 Risankizumab versus placebo	2	798	Std. Mean Difference (IV, Random, 95% CI)	-1.82 [-2.04, -1.60]
5.7 Biologic versus conventional systemic treatments	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.7.1 Adalimumab versus methotrexate	1	218	Mean Difference (IV, Fixed, 95% CI)	-3.40 [-5.75, -1.05]
5.7.2 Ixekizumab versus fumaric acid esters	1	108	Mean Difference (IV, Fixed, 95% CI)	-7.71 [-9.74, -5.68]
5.7.3 Ixekizumab versus methotrexate	1	108	Mean Difference (IV, Fixed, 95% CI)	-0.27 [-2.31, 1.77]
5.7.4 Guselkumab versus fumaric acid esters	1	119	Mean Difference (IV, Fixed, 95% CI)	-5.80 [-8.06, -3.54]
5.8 Biologic 1 versus biologic 2	8		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.8.1 Ixekizumab versus etanercept	2	2209	Mean Difference (IV, Fixed, 95% CI)	-1.99 [-2.39, -1.59]
5.8.2 Guselkumab versus adalimumab	2	1407	Mean Difference (IV, Fixed, 95% CI)	-1.73 [-2.50, -0.97]
5.8.3 Risankizumab versus ustekinumab	2	799	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-1.50, -0.50]
5.8.4 Tildrakizumab versus etanercept	1	932	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-2.20, -0.60]
5.8.5 Infliximab versus etanercept	1	48	Mean Difference (IV, Fixed, 95% CI)	-1.60 [-2.93, -0.27]
5.9 Small molecules versus placebo	8	4758	Std. Mean Difference (IV, Random, 95% CI)	-0.83 [-1.03, -0.62]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.9.1 Apremilast versus placebo	4	1863	Std. Mean Difference (IV, Random, 95% CI)	-0.60 [-0.73, -0.47]
5.9.2 Tofacitinib versus placebo	4	2895	Std. Mean Difference (IV, Random, 95% CI)	-1.08 [-1.23, -0.93]
5.10 Biologic versus small molecules	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
5.10.1 Etanercept versus tofacitinib	1	998	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.19, 0.07]

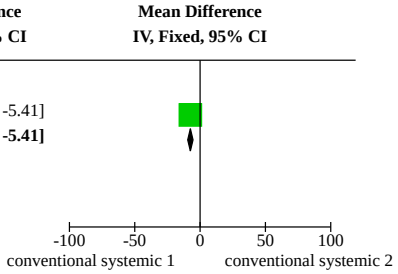
Analysis 5.1. Comparison 5: Secondary outcome - quality of life, Outcome 1: Conventional systemic agents versus placebo

Study or Subgroup	Conventional systemic Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
5.1.1 Methotrexate veruss placebo								
Saurat CHAMPION 2008	-5.7	6.1	110	-3.4	9.63	53	52.0%	-0.31 [-0.64 , 0.02]
Warren METOP, 2017	-9.4	6.58	91	-2.6	5.83	29	48.0%	-1.05 [-1.49 , -0.61]
Subtotal (95% CI)			**201**			**82**	**100.0%**	**-0.67 [-1.40 , 0.06]**
Heterogeneity: Tau² = 0.24; Chi² = 7.08, df = 1 (P = 0.008); I² = 86%								
Test for overall effect: Z = 1.79 (P = 0.07)								
Total (95% CI)			**201**			**82**	**100.0%**	**-0.67 [-1.40 , 0.06]**
Heterogeneity: Tau² = 0.24; Chi² = 7.08, df = 1 (P = 0.008); I² = 86%								
Test for overall effect: Z = 1.79 (P = 0.07)								
Test for subgroup differences: Not applicable								



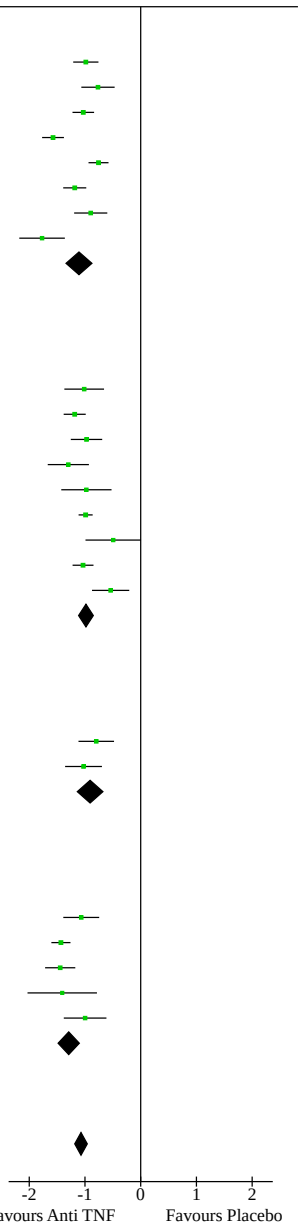
Analysis 5.2. Comparison 5: Secondary outcome - quality of life, Outcome 2: Conventional systemic 1 versus conventional systemic 2

Study or Subgroup	Conventional systemic 1 Mean	SD	Total	conventional systemic 2 Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
5.2.1 Methotrexate versus fumaric acid esters								
NCT02634801	-12.81	5.41	54	-5.37	5.34	54	100.0%	-7.44 [-9.47 , -5.41]
Subtotal (95% CI)			**54**			**54**	**100.0%**	**-7.44 [-9.47 , -5.41]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 7.19 (P < 0.00001)								



Analysis 5.3. Comparison 5: Secondary outcome - quality of life, Outcome 3: Anti-TNF alpha versus placebo

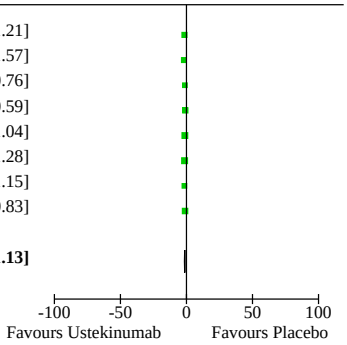
Study or Subgroup	anti TNF Mean	anti TNF SD	anti TNF Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
5.3.1 Etanercept versus placebo								
Bachelez 2015	-8.97	7.33	336	-1.85	6.86	108	4.7%	-0.98 [-1.21 , -0.76]
Gottlieb 2011	-8.01	6.18	141	-3.3	6	68	4.1%	-0.77 [-1.07 , -0.47]
Griffiths UNCOVER-2 2015	-7.7	5.68	358	-2	5.18	168	5.0%	-1.03 [-1.22 , -0.84]
Griffiths UNCOVER-3 2015	-8	3.91	382	-1.7	4.17	193	5.0%	-1.57 [-1.77 , -1.38]
Leonardi 2003	-6.37	6.02	504	-1.4	7.96	168	5.1%	-0.76 [-0.94 , -0.58]
Reich ReSURFACE-2 2017	-8.9	5.86	311	-2	5.74	156	4.9%	-1.18 [-1.39 , -0.98]
Strober 2011	-9.09	7.43	139	-2.89	5.69	72	4.2%	-0.90 [-1.19 , -0.60]
Van de Kerkhof 2008	-7.4	5.34	96	1.2	3.53	46	3.3%	-1.77 [-2.18 , -1.36]
Subtotal (95% CI)			**2267**			**979**	**36.3%**	**-1.11 [-1.34 , -0.88]**
Heterogeneity: Tau² = 0.10; Chi² = 55.41, df = 7 (P < 0.00001); I² = 87%								
Test for overall effect: Z = 9.36 (P < 0.00001)								
5.3.2 Adalimumab versus placebo								
Asahina 2010	-5.3	5.9	123	1	6.9	46	3.7%	-1.01 [-1.37 , -0.66]
Blauvelt VOYAGE-1 2016	-9.3	7.8	329	-0.6	6.36	174	5.0%	-1.18 [-1.38 , -0.99]
Elewski 2016	-8	6.26	109	-1.9	6.24	108	4.3%	-0.97 [-1.25 , -0.69]
Gordon 2006	-11.2	7.7	96	-1.3	7.36	52	3.6%	-1.30 [-1.67 , -0.93]
Gordon X-PLORE 2015	-10.1	8.9	43	-2.3	6.8	42	3.0%	-0.97 [-1.43 , -0.52]
Menter REVEAL 2008	-8.4	6.55	814	-1.9	6.62	398	5.5%	-0.99 [-1.11 , -0.86]
NCT01553058 VIP trial	-7.9	8.8	33	-3.7	8	31	2.7%	-0.49 [-0.99 , 0.01]
Reich VOYAGE-2 2017	-9.7	6.8	248	-2.6	6.9	248	5.0%	-1.03 [-1.22 , -0.85]
Saurat CHAMPION 2008	-9.1	10.92	108	-3.4	9.63	53	3.9%	-0.54 [-0.87 , -0.21]
Subtotal (95% CI)			**1903**			**1152**	**36.7%**	**-0.98 [-1.11 , -0.85]**
Heterogeneity: Tau² = 0.02; Chi² = 17.35, df = 8 (P = 0.03); I² = 54%								
Test for overall effect: Z = 14.61 (P < 0.00001)								
5.3.3 Certolizumab versus placebo								
Gottlieb CIMPASI-1 2018	-9.2	7.5	183	-3.3	6.9	51	4.0%	-0.80 [-1.12 , -0.48]
Gottlieb CIMPASI-2 2018	-10.6	7.7	178	-2.9	6.6	49	3.9%	-1.03 [-1.36 , -0.70]
Subtotal (95% CI)			**361**			**100**	**7.9%**	**-0.91 [-1.14 , -0.68]**
Heterogeneity: Tau² = 0.00; Chi² = 0.95, df = 1 (P = 0.33); I² = 0%								
Test for overall effect: Z = 7.76 (P < 0.00001)								
5.3.4 Infliximab versus placebo								
Gottlieb 2004a	-9.6	7.2	198	-2	6.7	51	4.0%	-1.07 [-1.39 , -0.74]
Menter EXPRESS-II 2007	-10	7	627	-0.6	5	208	5.2%	-1.43 [-1.60 , -1.26]
Reich EXPRESS 2005	-10.3	7.1	301	-0.4	5.7	77	4.4%	-1.44 [-1.72 , -1.17]
Torii 2010	-9.9	7.1	35	-0.4	5.7	19	2.1%	-1.41 [-2.03 , -0.79]
Yang 2012	-8	7.1	84	-1.5	5.1	45	3.5%	-1.00 [-1.38 , -0.61]
Subtotal (95% CI)			**1245**			**400**	**19.1%**	**-1.29 [-1.48 , -1.10]**
Heterogeneity: Tau² = 0.02; Chi² = 7.55, df = 4 (P = 0.11); I² = 47%								
Test for overall effect: Z = 13.32 (P < 0.00001)								
Total (95% CI)			**5776**			**2631**	**100.0%**	**-1.07 [-1.18 , -0.96]**
Heterogeneity: Tau² = 0.06; Chi² = 103.86, df = 23 (P < 0.00001); I² = 78%								
Test for overall effect: Z = 18.69 (P < 0.00001)								
Test for subgroup differences: Chi² = 8.90, df = 3 (P = 0.03), I² = 66.3%								



Analysis 5.4. Comparison 5: Secondary outcome - quality of life, Outcome 4: Ustekinumab versus placebo

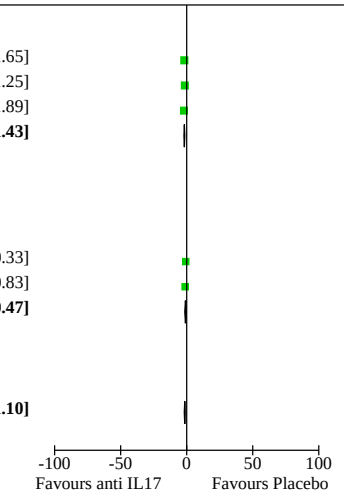
Study or Subgroup	Ustekinumab Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Gordon UltIMMa-1 2018	-4.4	3	100	0.2	3.03	102	11.8%	-1.52 [-1.83 , -1.21]
Gordon UltIMMa-2 2018	-5.6	2.98	99	0	2.88	98	11.2%	-1.90 [-2.24 , -1.57]
Igarashi 2012	-7.7	6.5	126	-0.3	5.3	32	9.6%	-1.17 [-1.58 , -0.76]
Krueger 2007	-8.95	8.4	256	-2.2	4.2	64	12.6%	-0.87 [-1.15 , -0.59]
Leonardi PHOENIX-1 2008	-8.4	6.7	511	-0.6	5.97	255	15.4%	-1.21 [-1.37 , -1.04]
Papp PHOENIX-2 2008	-9.7	6.9	820	-0.5	5.66	410	16.0%	-1.41 [-1.54 , -1.28]
Tsai PEARL 2011	-11.2	7.1	61	-0.5	6.5	60	9.7%	-1.56 [-1.97 , -1.15]
Zhu LOTUS 2013	-9.3	7.18	160	-1.9	6.63	162	13.7%	-1.07 [-1.30 , -0.83]
Total (95% CI)			**2133**			**1183**	**100.0%**	**-1.32 [-1.51 , -1.13]**

Heterogeneity: Tau² = 0.05; Chi² = 32.88, df = 7 (P < 0.0001); I² = 79%
Test for overall effect: Z = 13.59 (P < 0.00001)
Test for subgroup differences: Not applicable



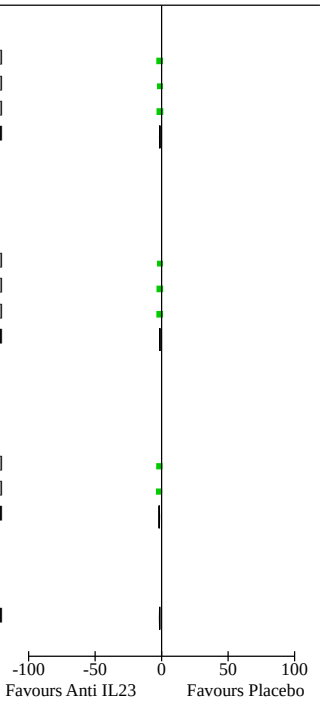
Analysis 5.5. Comparison 5: Secondary outcome - quality of life, Outcome 5: Anti-IL17 versus placebo

Study or Subgroup	Anti IL17 Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
5.5.1 Ixekizumab versus placebo								
Gordon UNCOVER-1 2016	-10.9	5.5	865	-1	5.6	431	21.6%	-1.79 [-1.92 , -1.65]
Griffiths UNCOVER-2 2015	-9.9	5.6	698	-2	5.18	168	21.1%	-1.43 [-1.61 , -1.25]
Griffiths UNCOVER-3 2015	-9.9	3.9	771	-1.7	4.17	193	21.1%	-2.07 [-2.25 , -1.89]
Subtotal (95% CI)			**2334**			**792**	**63.9%**	**-1.76 [-2.09 , -1.43]**
Heterogeneity: Tau² = 0.08; Chi² = 24.02, df = 2 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 10.45 (P < 0.00001)								
5.5.2 Brodalumab versus placebo								
Nakagawa 2016	-7.1	7.3	113	-2	6.7	38	18.0%	-0.71 [-1.09 , -0.33]
Papp 2012a	3.6	4.95	160	10.3	7.6	38	18.1%	-1.20 [-1.58 , -0.83]
Subtotal (95% CI)			**273**			**76**	**36.1%**	**-0.96 [-1.44 , -0.47]**
Heterogeneity: Tau² = 0.09; Chi² = 3.33, df = 1 (P = 0.07); I² = 70%								
Test for overall effect: Z = 3.87 (P = 0.0001)								
Total (95% CI)			**2607**			**868**	**100.0%**	**-1.47 [-1.84 , -1.10]**
Heterogeneity: Tau² = 0.16; Chi² = 59.22, df = 4 (P < 0.00001); I² = 93%								
Test for overall effect: Z = 7.86 (P < 0.00001)								
Test for subgroup differences: Chi² = 7.27, df = 1 (P = 0.007), I² = 86.3%								



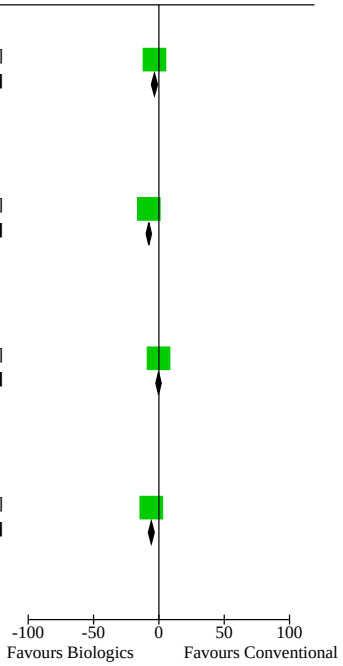
Analysis 5.6. Comparison 5: Secondary outcome - quality of life, Outcome 6: Anti-IL23 versus placebo

Study or Subgroup	Anti IL23 Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
5.6.1 Guselkumab versus placebo								
Blauvelt VOYAGE-1 2016	-11.2	7.24	334	-0.6	6.36	174	13.5%	-1.52 [-1.73 , -1.32]
Ohtsuki 2018	-8.4	6.4	128	-0.8	5.4	64	10.0%	-1.24 [-1.57 , -0.92]
Reich VOYAGE-2 2017	-11.3	6.8	496	-2.6	6.9	248	14.7%	-1.27 [-1.44 , -1.11]
Subtotal (95% CI)			**958**			**486**	**38.2%**	**-1.36 [-1.54 , -1.18]**
Heterogeneity: Tau² = 0.01; Chi² = 3.96, df = 2 (P = 0.14); I² = 49%								
Test for overall effect: Z = 14.78 (P < 0.00001)								
5.6.2 Tildrakizumab versus placebo								
Papp 2015	-8.3	7.6	309	1	7.1	46	10.1%	-1.23 [-1.55 , -0.91]
Reich ReSURFACE-1 2017	-9.9	5.83	617	-2.3	5.07	155	14.0%	-1.34 [-1.52 , -1.15]
Reich ReSURFACE-2 2017	-10.3	5.84	621	-2	5.74	156	14.0%	-1.42 [-1.61 , -1.24]
Subtotal (95% CI)			**1547**			**357**	**38.1%**	**-1.36 [-1.48 , -1.23]**
Heterogeneity: Tau² = 0.00; Chi² = 1.13, df = 2 (P = 0.57); I² = 0%								
Test for overall effect: Z = 21.57 (P < 0.00001)								
5.6.3 Risankizumab versus placebo								
Gordon UltIMMa-1 2018	-5.6	3.49	304	0.2	3.03	102	12.0%	-1.71 [-1.97 , -1.46]
Gordon UltIMMa-2 2018	-6.4	3.43	294	0	2.88	98	11.7%	-1.93 [-2.20 , -1.67]
Subtotal (95% CI)			**598**			**200**	**23.7%**	**-1.82 [-2.04 , -1.60]**
Heterogeneity: Tau² = 0.01; Chi² = 1.40, df = 1 (P = 0.24); I² = 29%								
Test for overall effect: Z = 16.38 (P < 0.00001)								
Total (95% CI)			**3103**			**1043**	**100.0%**	**-1.46 [-1.62 , -1.30]**
Heterogeneity: Tau² = 0.04; Chi² = 26.50, df = 7 (P = 0.0004); I² = 74%								
Test for overall effect: Z = 18.27 (P < 0.00001)								
Test for subgroup differences: Chi² = 14.22, df = 2 (P = 0.0008), I² = 85.9%								



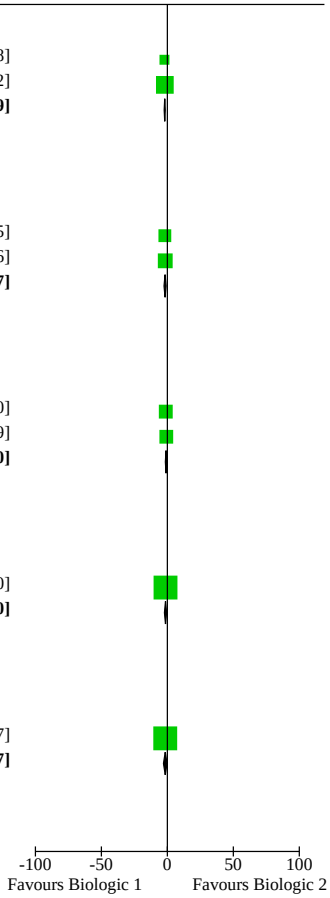
Analysis 5.7. Comparison 5: Secondary outcome - quality of life, Outcome 7: Biologic versus conventional systemic treatments

Study or Subgroup	Biologics Mean	SD	Total	Conventional systemic Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
5.7.1 Adalimumab versus methotrexate								
Saurat CHAMPION 2008	-9.1	10.92	108	-5.7	6.1	110	100.0%	-3.40 [-5.75 , -1.05]
Subtotal (95% CI)			**108**			**110**	**100.0%**	**-3.40 [-5.75 , -1.05]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.83 (P = 0.005)								
5.7.2 Ixekizumab versus fumaric acid esters								
NCT02634801	-13.08	5.43	54	-5.37	5.34	54	100.0%	-7.71 [-9.74 , -5.68]
Subtotal (95% CI)			**54**			**54**	**100.0%**	**-7.71 [-9.74 , -5.68]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 7.44 (P < 0.00001)								
5.7.3 Ixekizumab versus methotrexate								
NCT02634801	-13.08	5.43	54	-12.81	5.41	54	100.0%	-0.27 [-2.31 , 1.77]
Subtotal (95% CI)			**54**			**54**	**100.0%**	**-0.27 [-2.31 , 1.77]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.26 (P = 0.80)								
5.7.4 Guselkumab versus fumaric acid esters								
NCT02951533 POLARIS	-15.2	5.2	60	-9.4	7.2	59	100.0%	-5.80 [-8.06 , -3.54]
Subtotal (95% CI)			**60**			**59**	**100.0%**	**-5.80 [-8.06 , -3.54]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.03 (P < 0.00001)								



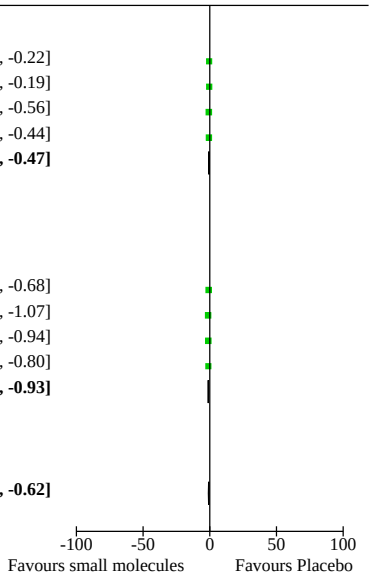
Analysis 5.8. Comparison 5: Secondary outcome - quality of life, Outcome 8: Biologic 1 versus biologic 2

Study or Subgroup	Biologic 1 Mean	Biologic 1 SD	Biologic 1 Total	Biologic 2 Mean	Biologic 2 SD	Biologic 2 Total	Weight	Mean Difference IV, Fixed, 95% CI
5.8.1 Ixekizumab versus etanercept								
Griffiths UNCOVER-2 2015	-9.9	5.6	698	-7.7	5.68	358	30.7%	-2.20 [-2.92 , -1.48]
Griffiths UNCOVER-3 2015	-9.9	3.9	771	-8	3.91	382	69.3%	-1.90 [-2.38 , -1.42]
Subtotal (95% CI)			**1469**			**740**	**100.0%**	**-1.99 [-2.39 , -1.59]**
Heterogeneity: Chi² = 0.46, df = 1 (P = 0.50); I² = 0%								
Test for overall effect: Z = 9.79 (P < 0.00001)								
5.8.2 Guselkumab versus adalimumab								
Blauvelt VOYAGE-1 2016	-11.2	7.24	334	-9.3	7.8	329	45.0%	-1.90 [-3.05 , -0.75]
Reich VOYAGE-2 2017	-11.3	6.8	496	-9.7	6.8	248	55.0%	-1.60 [-2.64 , -0.56]
Subtotal (95% CI)			**830**			**577**	**100.0%**	**-1.73 [-2.50 , -0.97]**
Heterogeneity: Chi² = 0.14, df = 1 (P = 0.70); I² = 0%								
Test for overall effect: Z = 4.42 (P < 0.00001)								
5.8.3 Risankizumab versus ustekinumab								
Gordon UltIMMa-1 2018	-5.6	3.49	304	-4.4	3	102	50.3%	-1.20 [-1.90 , -0.50]
Gordon UltIMMa-2 2018	-6.4	3.43	294	-5.6	2.98	99	49.7%	-0.80 [-1.51 , -0.09]
Subtotal (95% CI)			**598**			**201**	**100.0%**	**-1.00 [-1.50 , -0.50]**
Heterogeneity: Chi² = 0.62, df = 1 (P = 0.43); I² = 0%								
Test for overall effect: Z = 3.94 (P < 0.0001)								
5.8.4 Tildrakizumab versus etanercept								
Reich ReSURFACE-2 2017	-10.3	5.84	621	-8.9	5.86	311	100.0%	-1.40 [-2.20 , -0.60]
Subtotal (95% CI)			**621**			**311**	**100.0%**	**-1.40 [-2.20 , -0.60]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.44 (P = 0.0006)								
5.8.5 Infliximab versus etanercept								
De Vries PIECE 2016	-4.6	2.5	25	-3	2.2	23	100.0%	-1.60 [-2.93 , -0.27]
Subtotal (95% CI)			**25**			**23**	**100.0%**	**-1.60 [-2.93 , -0.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.36 (P = 0.02)								



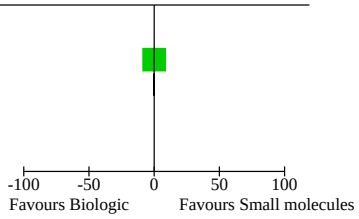
Analysis 5.9. Comparison 5: Secondary outcome - quality of life, Outcome 9: Small molecules versus placebo

Study or Subgroup	Small molecules Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
5.9.1 Apremilast versus placebo								
Ohtsuki 2017	-1.3	5.15	170	1.3	5.7	84	11.6%	-0.49 [-0.75 , -0.22]
Papp 2012c	-4.5	6.02	264	-1.9	5.91	88	12.0%	-0.43 [-0.68 , -0.19]
Papp ESTEEM-1 2015	-6.6	6.66	562	-2.1	5.69	282	13.5%	-0.71 [-0.85 , -0.56]
Paul ESTEEM-2 2015	-6.7	6.14	275	-2.7	6.23	138	12.6%	-0.65 [-0.86 , -0.44]
Subtotal (95% CI)			**1271**			**592**	**49.6%**	**-0.60 [-0.73 , -0.47]**
Heterogeneity: Tau² = 0.01; Chi² = 4.68, df = 3 (P = 0.20); I² = 36%								
Test for overall effect: Z = 8.98 (P < 0.00001)								
5.9.2 Tofacitinib versus placebo								
Bachelez 2015	-8.5	7.6	662	-1.85	6.86	108	12.6%	-0.89 [-1.09 , -0.68]
Papp OPT Pivotal-1 2015	-7.9	4.9	723	-1.9	4.4	177	13.1%	-1.25 [-1.42 , -1.07]
Papp OPT Pivotal-2 2015	-8.1	4.9	763	-2.8	4.44	196	13.2%	-1.10 [-1.27 , -0.94]
Zhang 2017	-8.07	5.99	178	-1.57	6.19	88	11.5%	-1.07 [-1.34 , -0.80]
Subtotal (95% CI)			**2326**			**569**	**50.4%**	**-1.08 [-1.23 , -0.93]**
Heterogeneity: Tau² = 0.01; Chi² = 6.86, df = 3 (P = 0.08); I² = 56%								
Test for overall effect: Z = 14.11 (P < 0.00001)								
Total (95% CI)			**3597**			**1161**	**100.0%**	**-0.83 [-1.03 , -0.62]**
Heterogeneity: Tau² = 0.07; Chi² = 57.19, df = 7 (P < 0.00001); I² = 88%								
Test for overall effect: Z = 7.99 (P < 0.00001)								
Test for subgroup differences: Chi² = 23.00, df = 1 (P < 0.00001), I² = 95.7%								



Analysis 5.10. Comparison 5: Secondary outcome - quality of life, Outcome 10: Biologic versus small molecules

Study or Subgroup	Biologic Mean	SD	Total	Samll molecules Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
5.10.1 Etanercept versus tofacitinib								
Bachelez 2015	-8.97	7.33	336	-8.5	7.6	662	100.0%	-0.06 [-0.19 , 0.07]
Subtotal (95% CI)			**336**			**662**	**100.0%**	**-0.06 [-0.19 , 0.07]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.93 (P = 0.35)								



Comparison 6. Secondary outcome - adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Conventional systemic agents versus placebo	4	1023	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.78, 1.50]
6.1.1 Methotrexate versus placebo	3	319	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.81, 1.10]
6.1.2 Fumaric acid esters versus placebo	1	704	Risk Ratio (M-H, Random, 95% CI)	1.40 [1.22, 1.62]
6.2 Conventional systemic 1 versus conventional systemic 2	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.2.1 Ciclosporin versus methotrexate	2	172	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.90, 1.34]

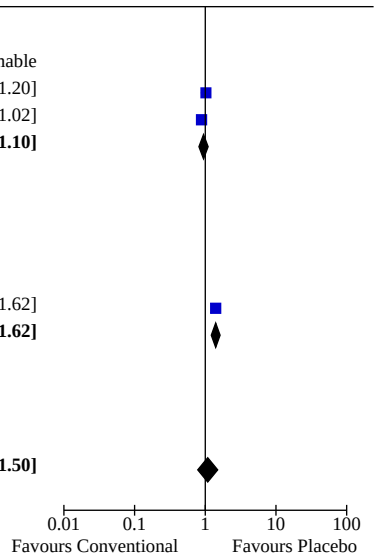
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2.2 Methotrexate versus fumaric acid esters	2	168	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.90, 1.24]
6.3 Anti-TNF alpha versus placebo	27	9856	Risk Ratio (M-H, Random, 95% CI)	1.06 [1.02, 1.10]
6.3.1 Etanercept versus placebo	11	4225	Risk Ratio (M-H, Random, 95% CI)	1.08 [1.00, 1.16]
6.3.2 Adalimumab versus placebo	9	3338	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.99, 1.12]
6.3.3 Certolizumab versus placebo	4	1026	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.86, 1.09]
6.3.4 Infliximab versus placebo	4	1267	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.93, 1.36]
6.4 Ustekinumab versus placebo	10	4553	Risk Ratio (M-H, Random, 95% CI)	1.06 [1.01, 1.13]
6.5 Anti-IL17 versus placebo	17	10334	Risk Ratio (M-H, Random, 95% CI)	1.19 [1.10, 1.28]
6.5.1 Secukinumab versus placebo	7	2707	Risk Ratio (M-H, Random, 95% CI)	1.15 [1.02, 1.29]
6.5.2 Ixekizumab versus placebo	4	3268	Risk Ratio (M-H, Random, 95% CI)	1.24 [1.07, 1.45]
6.5.3 Brodalumab versus placebo	5	4109	Risk Ratio (M-H, Random, 95% CI)	1.15 [1.00, 1.32]
6.5.4 Bimekizumab versus placebo	1	250	Risk Ratio (M-H, Random, 95% CI)	1.70 [1.11, 2.58]
6.6 Anti-IL23 versus placebo	12	5147	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.85, 1.00]
6.6.1 Guselkumab versus placebo	5	1767	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.90, 1.11]
6.6.2 Tildrakizumab versus placebo	3	1904	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.72, 1.02]
6.6.3 Risankizumab versus placebo	4	1476	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.77, 1.07]
6.7 Biologic versus conventional systemic treatments	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.7.1 Infliximab versus methotrexate	1	868	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.97, 1.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.7.2 Adalimumab versus methotrexate	1	218	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.78, 1.05]
6.7.3 Secukinumab versus fumaric acid esters	1	202	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.71, 0.94]
6.7.4 Etanercept versus acitretin	2	82	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.72, 1.96]
6.7.5 Ixekizumab versus fumaric acid esters	1	108	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.74, 1.21]
6.7.6 Ixekizumab versus methotrexate	1	108	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.76, 1.25]
6.7.7 Guselkumab versus fumaric acid esters	1	119	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.65, 0.89]
6.8 Biologic 1 versus biologic 2	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.8.1 Ustekinumab versus etanercept	1	903	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.89, 1.06]
6.8.2 Secukinumab versus etanercept	1	980	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.89, 1.12]
6.8.3 Ixekizumab versus etanercept	2	2209	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.97, 1.15]
6.8.4 Secukinumab versus ustekinumab	2	1778	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.98, 1.16]
6.8.5 Brodalumab versus ustekinumab	2	3088	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.93, 1.09]
6.8.6 Guselkumab versus adalimumab	3	1658	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.09]
6.8.7 Risankizumab versus ustekinumab	3	965	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.85, 1.11]
6.8.8 Ixekizumab versus ustekinumab	1	302	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.93, 1.13]
6.8.9 Certolizumab versus etanercept	1	502	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.86, 1.28]
6.8.10 Risankizumab versus adalimumab	1	605	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.82, 1.43]
6.8.11 Tildrakizumab versus etanercept	1	934	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.65, 0.86]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.8.12 Infliximab versus etanercept	1	48	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.86, 1.08]
6.9 Small molecules versus placebo	13	5482	Risk Ratio (M-H, Random, 95% CI)	1.25 [1.12, 1.38]
6.9.1 Apremilast versus placebo	6	2290	Risk Ratio (M-H, Random, 95% CI)	1.23 [1.10, 1.37]
6.9.2 Tofacitinib versus placebo	6	2925	Risk Ratio (M-H, Random, 95% CI)	1.28 [1.01, 1.63]
6.9.3 TYK2 versus placebo	1	267	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.97, 1.77]
6.10 Biologic versus small molecules	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.10.1 Etanercept versus tofacitinib	1	998	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.89, 1.12]
6.10.2 Etanercept versus apremilast	1	166	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.03, 1.69]

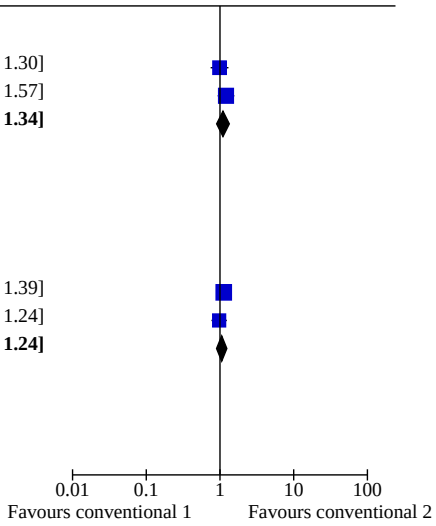
Analysis 6.1. Comparison 6: Secondary outcome - adverse events, Outcome 1: Conventional systemic agents versus placebo

Study or Subgroup	Conventional treatment Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 Methotrexate versus placebo						
Hunter 1963	0	19	0	17		Not estimable
Saurat CHAMPION 2008	89	110	42	53	32.8%	1.02 [0.87 , 1.20]
Warren METOP, 2017	75	91	27	29	33.7%	0.89 [0.77 , 1.02]
Subtotal (95% CI)		**220**		**99**	**66.5%**	**0.94 [0.81 , 1.10]**
Total events:	164		69			
Heterogeneity: Tau² = 0.01; Chi² = 1.95, df = 1 (P = 0.16); I² = 49%						
Test for overall effect: Z = 0.75 (P = 0.45)						
6.1.2 Fumaric acid esters versus placebo						
Mrowietz BRIDGE 2016	472	566	82	138	33.5%	1.40 [1.22 , 1.62]
Subtotal (95% CI)		**566**		**138**	**33.5%**	**1.40 [1.22 , 1.62]**
Total events:	472		82			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.66 (P < 0.00001)						
Total (95% CI)		**786**		**237**	**100.0%**	**1.08 [0.78 , 1.50]**
Total events:	636		151			
Heterogeneity: Tau² = 0.08; Chi² = 28.81, df = 2 (P < 0.00001); I² = 93%						
Test for overall effect: Z = 0.48 (P = 0.63)						
Test for subgroup differences: Chi² = 14.15, df = 1 (P = 0.0002), I² = 92.9%						



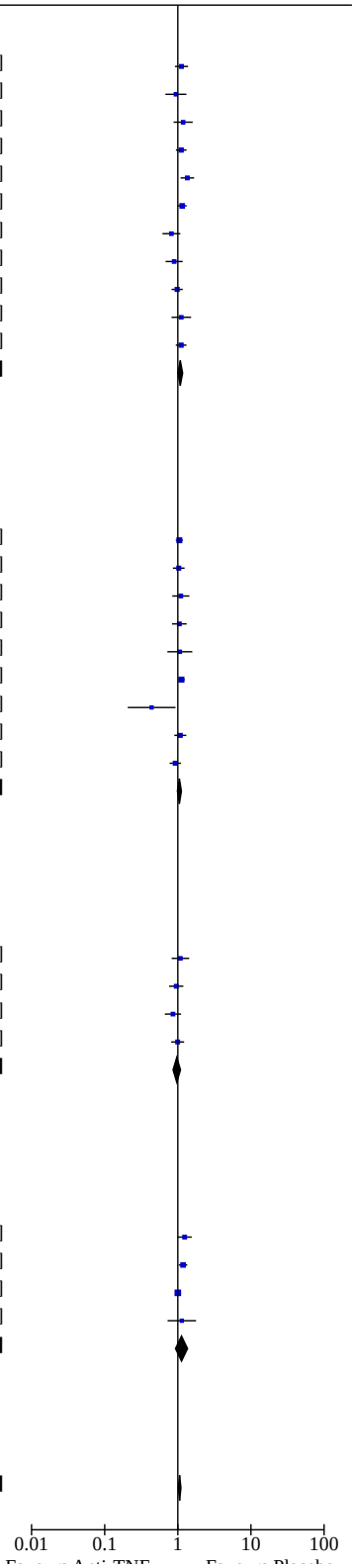
Analysis 6.2. Comparison 6: Secondary outcome - adverse events, Outcome 2: Conventional systemic 1 versus conventional systemic 2

Study or Subgroup	Conventional 1 Events	Conventional 1 Total	Conventional 2 Events	Conventional 2 Total	Weight	Risk Ratio M-H, Random, 95% CI
6.2.1 Ciclosporin versus methotrexate						
Flytström 2008	30	43	29	41	46.8%	0.99 [0.75 , 1.30]
Heydendael 2003	35	44	29	44	53.2%	1.21 [0.93 , 1.57]
Subtotal (95% CI)		**87**		**85**	**100.0%**	**1.10 [0.90 , 1.34]**
Total events:	65		58			
Heterogeneity: Tau² = 0.00; Chi² = 1.08, df = 1 (P = 0.30); I² = 7%						
Test for overall effect: Z = 0.93 (P = 0.35)						
6.2.2 Methotrexate versus fumaric acid esters						
Fallah Arani 2011	27	30	24	30	55.3%	1.13 [0.91 , 1.39]
NCT02634801	38	54	39	54	44.7%	0.97 [0.77 , 1.24]
Subtotal (95% CI)		**84**		**84**	**100.0%**	**1.06 [0.90 , 1.24]**
Total events:	65		63			
Heterogeneity: Tau² = 0.00; Chi² = 0.84, df = 1 (P = 0.36); I² = 0%						
Test for overall effect: Z = 0.66 (P = 0.51)						



Analysis 6.3. Comparison 6: Secondary outcome - adverse events, Outcome 3: Anti-TNF alpha versus placebo

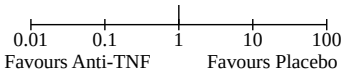
Study or Subgroup	Anti-TNF Events	Anti-TNF Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
6.3.1 Etanercept versus placebo						
Bachelez 2015	192	336	55	108	3.3%	1.12 [0.91 , 1.38]
Bagel 2012	32	62	34	62	1.4%	0.94 [0.68 , 1.31]
Gottlieb 2011	76	141	31	68	1.7%	1.18 [0.87 , 1.60]
Griffiths UNCOVER-2 2015	211	358	89	168	4.6%	1.11 [0.94 , 1.31]
Griffiths UNCOVER-3 2015	187	382	70	193	3.1%	1.35 [1.09 , 1.67]
Langley FIXTURE 2014	186	326	163	327	5.7%	1.14 [0.99 , 1.32]
Lebwohl CIMPACT 2018	78	170	32	57	1.9%	0.82 [0.62 , 1.08]
Reich LIBERATE 2017	44	83	50	84	2.1%	0.89 [0.68 , 1.16]
Reich ReSURFACE-2 2017	169	313	86	156	4.3%	0.98 [0.82 , 1.17]
Strober 2011	69	139	32	72	1.6%	1.12 [0.82 , 1.52]
Tyring 2006	153	311	137	309	4.5%	1.11 [0.94 , 1.31]
Subtotal (95% CI)		**2621**		**1604**	**34.2%**	**1.08 [1.00 , 1.16]**
Total events:	1397		779			
Heterogeneity: Tau² = 0.00; Chi² = 13.24, df = 10 (P = 0.21); I² = 24%						
Test for overall effect: Z = 2.04 (P = 0.04)						
6.3.2 Adalimumab versus placebo						
Asahina 2010	115	123	41	46	7.9%	1.05 [0.94 , 1.17]
Blauvelt VOYAGE-1 2016	170	334	86	174	4.0%	1.03 [0.86 , 1.24]
Cai 2016	158	338	37	87	2.1%	1.10 [0.84 , 1.44]
Elewski 2016	64	109	61	109	2.8%	1.05 [0.83 , 1.32]
Gordon X-PLORE 2015	24	43	22	42	1.0%	1.07 [0.72 , 1.58]
Menter REVEAL 2008	506	814	221	398	8.6%	1.12 [1.01 , 1.24]
NCT01553058 VIP trial	7	33	15	31	0.3%	0.44 [0.21 , 0.93]
Reich VOYAGE-2 2017	120	248	111	248	3.8%	1.08 [0.90 , 1.31]
Saurat CHAMPION 2008	79	108	42	53	4.1%	0.92 [0.77 , 1.10]
Subtotal (95% CI)		**2150**		**1188**	**34.5%**	**1.05 [0.99 , 1.12]**
Total events:	1243		636			
Heterogeneity: Tau² = 0.00; Chi² = 8.93, df = 8 (P = 0.35); I² = 10%						
Test for overall effect: Z = 1.53 (P = 0.13)						
6.3.3 Certolizumab versus placebo						
Gottlieb CIMPASI-1 2018	109	183	28	51	2.0%	1.08 [0.82 , 1.43]
Gottlieb CIMPASI-2 2018	114	178	33	49	2.9%	0.95 [0.76 , 1.19]
Lebwohl CIMPACT 2018	160	332	32	57	2.3%	0.86 [0.67 , 1.11]
Reich 2012a	83	118	41	58	3.4%	1.00 [0.81 , 1.22]
Subtotal (95% CI)		**811**		**215**	**10.5%**	**0.97 [0.86 , 1.09]**
Total events:	466		134			
Heterogeneity: Tau² = 0.00; Chi² = 1.60, df = 3 (P = 0.66); I² = 0%						
Test for overall effect: Z = 0.55 (P = 0.58)						
6.3.4 Infliximab versus placebo						
Gottlieb 2004a	154	198	32	51	2.9%	1.24 [0.99 , 1.55]
Menter EXPRESS-II 2007	412	627	116	208	6.3%	1.18 [1.03 , 1.35]
Torii 2010	35	35	19	19	10.9%	1.00 [0.92 , 1.08]
Yang 2012	36	84	17	45	0.8%	1.13 [0.72 , 1.78]
Subtotal (95% CI)		**944**		**323**	**20.8%**	**1.12 [0.93 , 1.36]**
Total events:	637		184			
Heterogeneity: Tau² = 0.03; Chi² = 14.98, df = 3 (P = 0.002); I² = 80%						
Test for overall effect: Z = 1.20 (P = 0.23)						
Total (95% CI)		**6526**		**3330**	**100.0%**	**1.06 [1.02 , 1.10]**
Total events:	3743		1733			
Heterogeneity: Tau² = 0.00; Chi² = 34.41, df = 27 (P = 0.15); I² = 22%						



Analysis 6.3. (Continued)

Total events:	3743		1733				

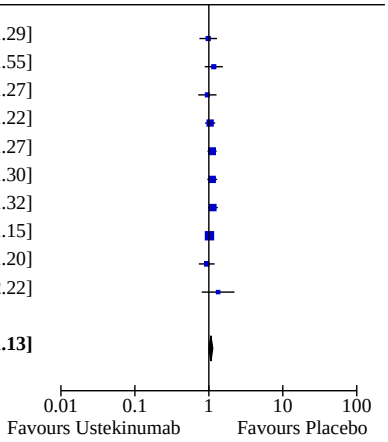
Heterogeneity: Tau² = 0.00; Chi² = 34.41, df = 27 (P = 0.15); I² = 22%
Test for overall effect: Z = 2.70 (P = 0.007)
Test for subgroup differences: Chi² = 2.91, df = 3 (P = 0.41), I² = 0%



Analysis 6.4. Comparison 6: Secondary outcome - adverse events, Outcome 4: Ustekinumab versus placebo

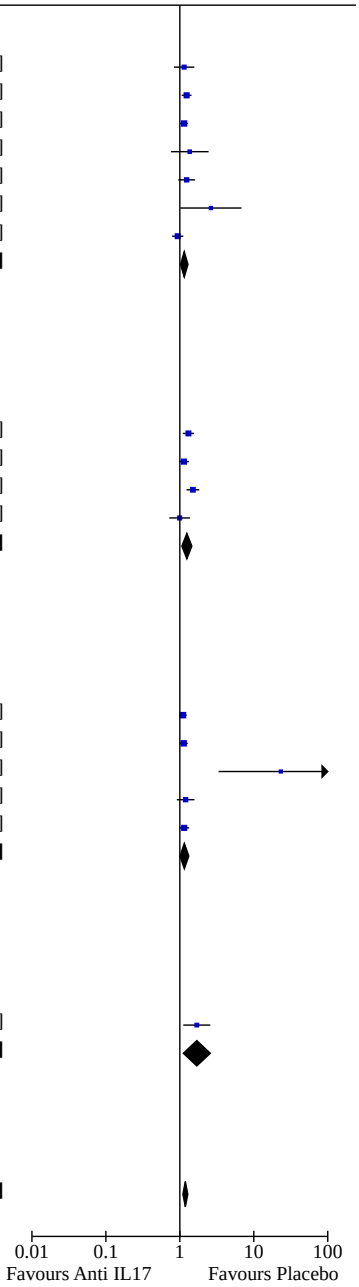
Study or Subgroup	Ustekinumab Events	Ustekinumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Gordon UltIMMa-1 2018	50	100	52	102	4.4%	0.98 [0.75 , 1.29]
Gordon UltIMMa-2 2018	53	99	45	98	4.1%	1.17 [0.88 , 1.55]
Igarashi 2012	79	126	21	32	4.0%	0.96 [0.72 , 1.27]
Krueger 2007	200	256	48	64	13.5%	1.04 [0.89 , 1.22]
Lebwohl AMAGINE-2 2015	177	300	165	309	16.5%	1.10 [0.96 , 1.27]
Lebwohl AMAGINE-3 2015	168	313	152	315	13.8%	1.11 [0.95 , 1.30]
Leonardi PHOENIX-1 2008	277	511	122	255	14.3%	1.13 [0.97 , 1.32]
Papp PHOENIX-2 2008	412	820	202	410	22.8%	1.02 [0.90 , 1.15]
Tsai PEARL 2011	40	61	42	60	5.4%	0.94 [0.73 , 1.20]
Zhu LOTUS 2013	29	160	22	162	1.3%	1.33 [0.80 , 2.22]
Total (95% CI)		**2746**		**1807**	**100.0%**	**1.06 [1.01 , 1.13]**
Total events:	1485		871			

Heterogeneity: Tau² = 0.00; Chi² = 4.97, df = 9 (P = 0.84); I² = 0%
Test for overall effect: Z = 2.15 (P = 0.03)
Test for subgroup differences: Not applicable



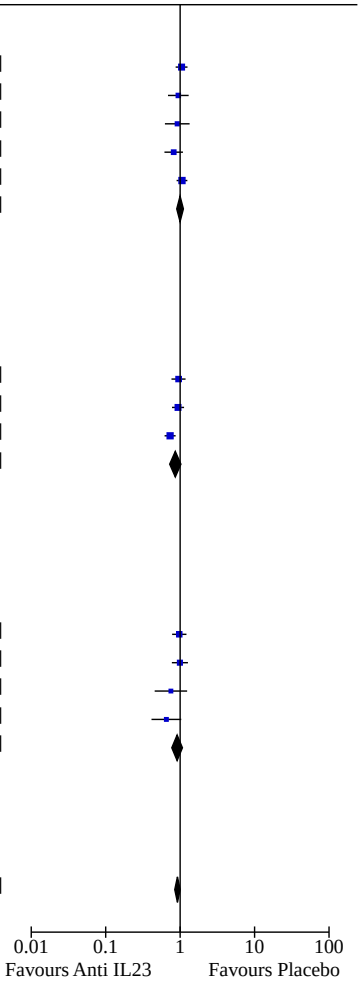
Analysis 6.5. Comparison 6: Secondary outcome - adverse events, Outcome 5: Anti-IL17 versus placebo

Study or Subgroup	Anti IL17 Events	Anti IL17 Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
6.5.1 Secukinumab versus placebo						
Blauvelt FEATURE 2015	64	118	28	59	4.0%	1.14 [0.83 , 1.57]
Langley ERASURE 2014	283	490	116	248	8.5%	1.23 [1.06 , 1.44]
Langley FIXTURE 2014	372	654	163	327	9.6%	1.14 [1.00 , 1.30]
Papp 2013a	51	103	8	22	1.5%	1.36 [0.76 , 2.45]
Paul JUNCTURE 2015	81	121	33	61	5.1%	1.24 [0.95 , 1.61]
Reich 2015	71	90	3	10	0.6%	2.63 [1.01 , 6.82]
Rich 2013	221	337	47	67	7.7%	0.93 [0.79 , 1.11]
Subtotal (95% CI)		**1913**		**794**	**37.0%**	**1.15 [1.02 , 1.29]**
Total events:	1143		398			
Heterogeneity: Tau² = 0.01; Chi² = 10.09, df = 6 (P = 0.12); I² = 41%						
Test for overall effect: Z = 2.33 (P = 0.02)						
6.5.2 Ixekizumab versus placebo						
Gordon UNCOVER-1 2016	320	865	122	431	7.8%	1.31 [1.10 , 1.55]
Griffiths UNCOVER-2 2015	420	698	89	168	8.5%	1.14 [0.97 , 1.33]
Griffiths UNCOVER-3 2015	420	771	70	193	6.9%	1.50 [1.23 , 1.83]
Leonardi 2012	72	115	17	27	3.9%	0.99 [0.72 , 1.37]
Subtotal (95% CI)		**2449**		**819**	**27.1%**	**1.24 [1.07 , 1.45]**
Total events:	1232		298			
Heterogeneity: Tau² = 0.01; Chi² = 7.24, df = 3 (P = 0.06); I² = 59%						
Test for overall effect: Z = 2.76 (P = 0.006)						
6.5.3 Brodalumab versus placebo						
Lebwohl AMAGINE-2 2015	719	1222	165	309	10.1%	1.10 [0.98 , 1.24]
Lebwohl AMAGINE-3 2015	682	1253	152	315	9.7%	1.13 [1.00 , 1.28]
Nakagawa 2016	69	113	1	38	0.2%	23.20 [3.34 , 161.40]
Papp 2012a	116	160	23	38	4.8%	1.20 [0.91 , 1.58]
Papp AMAGINE-1 2016	257	441	112	220	8.6%	1.14 [0.98 , 1.33]
Subtotal (95% CI)		**3189**		**920**	**33.3%**	**1.15 [1.00 , 1.32]**
Total events:	1843		453			
Heterogeneity: Tau² = 0.01; Chi² = 10.75, df = 4 (P = 0.03); I² = 63%						
Test for overall effect: Z = 2.02 (P = 0.04)						
6.5.4 Bimekizumab versus placebo						
Papp BE ABLE 2018	126	208	15	42	2.6%	1.70 [1.11 , 2.58]
Subtotal (95% CI)		**208**		**42**	**2.6%**	**1.70 [1.11 , 2.58]**
Total events:	126		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.46 (P = 0.01)						
Total (95% CI)		**7759**		**2575**	**100.0%**	**1.19 [1.10 , 1.28]**
Total events:	4344		1164			
Heterogeneity: Tau² = 0.01; Chi² = 34.87, df = 16 (P = 0.004); I² = 54%						
Test for overall effect: Z = 4.45 (P < 0.00001)						
Test for subgroup differences: Chi² = 3.64, df = 3 (P = 0.30), I² = 17.7%						

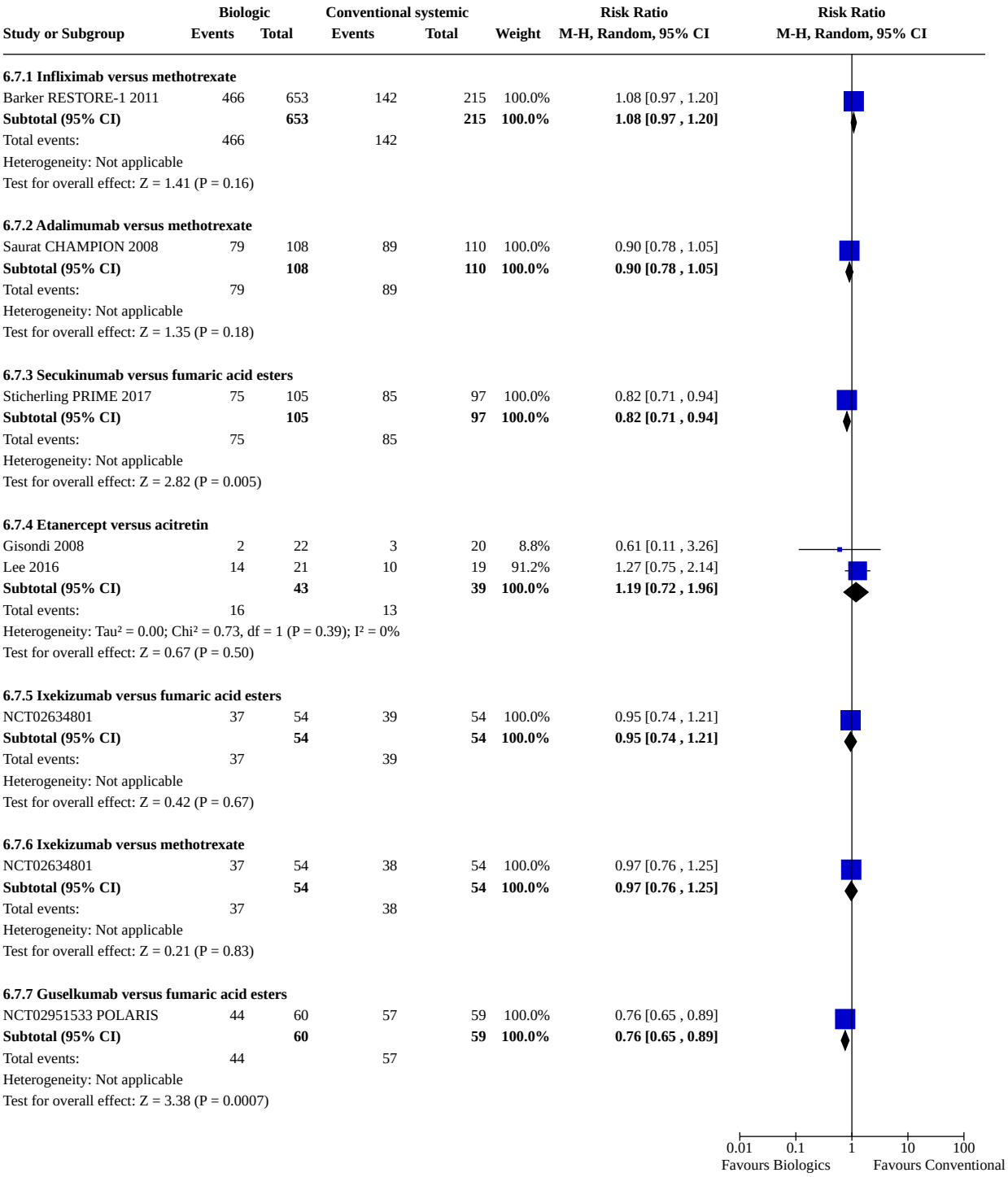


Analysis 6.6. Comparison 6: Secondary outcome - adverse events, Outcome 6: Anti-IL23 versus placebo

Study or Subgroup	Anti IL23 Events	Anti IL23 Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
6.6.1 Guselkumab versus placebo						
Blauvelt VOYAGE-1 2016	170	329	86	174	12.2%	1.05 [0.87 , 1.26]
Gordon X-PLORE 2015	103	208	22	42	5.5%	0.95 [0.69 , 1.30]
NCT02905331 ORION	39	62	11	16	4.1%	0.91 [0.62 , 1.34]
Ohtsuki 2018	59	128	36	64	6.6%	0.82 [0.62 , 1.09]
Reich VOYAGE-2 2017	235	496	111	248	13.6%	1.06 [0.90 , 1.25]
Subtotal (95% CI)		**1223**		**544**	**41.9%**	**1.00 [0.90 , 1.11]**
Total events:	606		266			
Heterogeneity: Tau² = 0.00; Chi² = 2.88, df = 4 (P = 0.58); I² = 0%						
Test for overall effect: Z = 0.04 (P = 0.97)						
6.6.2 Tildrakizumab versus placebo						
Papp 2015	198	309	31	46	9.8%	0.95 [0.76 , 1.18]
Reich ReSURFACE-1 2017	276	617	74	155	11.9%	0.94 [0.78 , 1.13]
Reich ReSURFACE-2 2017	251	621	86	156	13.2%	0.73 [0.62 , 0.87]
Subtotal (95% CI)		**1547**		**357**	**34.9%**	**0.86 [0.72 , 1.02]**
Total events:	725		191			
Heterogeneity: Tau² = 0.01; Chi² = 4.95, df = 2 (P = 0.08); I² = 60%						
Test for overall effect: Z = 1.69 (P = 0.09)						
6.6.3 Risankizumab versus placebo						
Gordon UltIMMa-1 2018	151	304	52	102	9.6%	0.97 [0.78 , 1.22]
Gordon UltIMMa-2 2018	134	294	45	98	8.1%	0.99 [0.77 , 1.27]
NCT02672852 IMMhance	52	407	17	100	2.5%	0.75 [0.45 , 1.24]
NCT03000075	28	113	22	58	2.9%	0.65 [0.41 , 1.03]
Subtotal (95% CI)		**1118**		**358**	**23.1%**	**0.91 [0.77 , 1.07]**
Total events:	365		136			
Heterogeneity: Tau² = 0.00; Chi² = 3.42, df = 3 (P = 0.33); I² = 12%						
Test for overall effect: Z = 1.12 (P = 0.26)						
Total (95% CI)		**3888**		**1259**	**100.0%**	**0.92 [0.85 , 1.00]**
Total events:	1696		593			
Heterogeneity: Tau² = 0.01; Chi² = 15.52, df = 11 (P = 0.16); I² = 29%						
Test for overall effect: Z = 1.97 (P = 0.05)						
Test for subgroup differences: Chi² = 2.37, df = 2 (P = 0.31), I² = 15.5%						

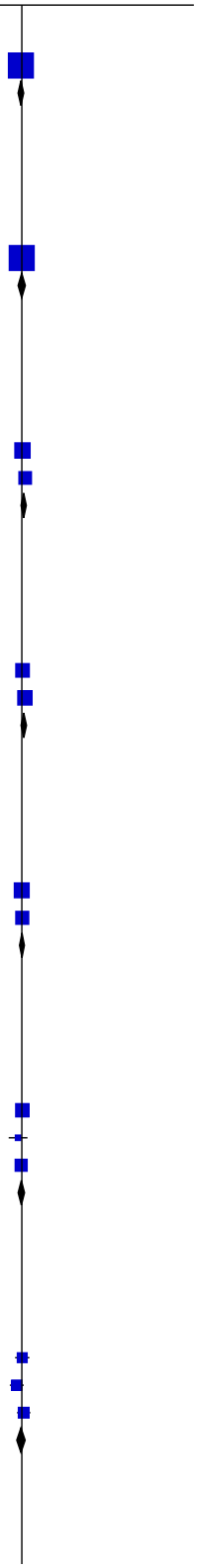


Analysis 6.7. Comparison 6: Secondary outcome - adverse events, Outcome 7: Biologic versus conventional systemic treatments



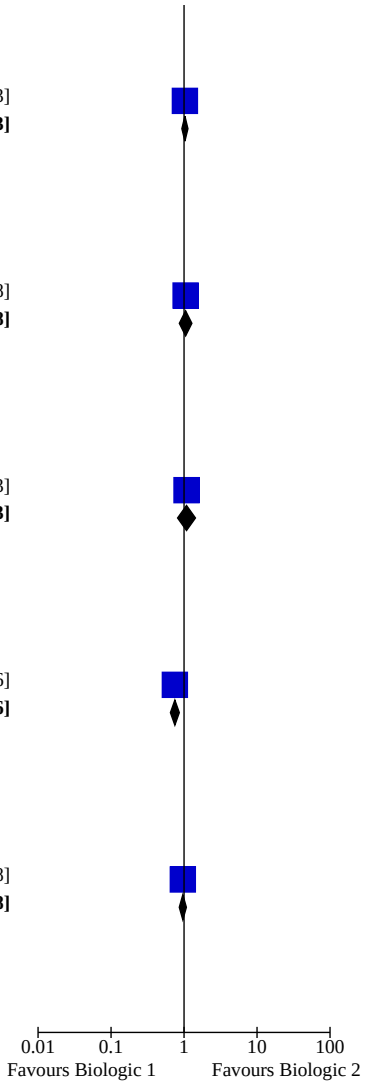
Analysis 6.8. Comparison 6: Secondary outcome - adverse events, Outcome 8: Biologic 1 versus biologic 2

Study or Subgroup	Biologic 1 Events	Biologic 1 Total	Biologic 2 Events	Biologic 2 Total	Weight	Risk Ratio M-H, Random, 95% CI
6.8.1 Ustekinumab versus etanercept						
Griffiths ACCEPT 2010	378	556	243	347	100.0%	0.97 [0.89 , 1.06]
Subtotal (95% CI)		**556**		**347**	**100.0%**	**0.97 [0.89 , 1.06]**
Total events:	378		243			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
6.8.2 Secukinumab versus etanercept						
Langley FIXTURE 2014	372	654	186	326	100.0%	1.00 [0.89 , 1.12]
Subtotal (95% CI)		**654**		**326**	**100.0%**	**1.00 [0.89 , 1.12]**
Total events:	372		186			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
6.8.3 Ixekizumab versus etanercept						
Griffiths UNCOVER-2 2015	420	698	211	358	56.1%	1.02 [0.92 , 1.13]
Griffiths UNCOVER-3 2015	420	771	187	382	43.9%	1.11 [0.99 , 1.26]
Subtotal (95% CI)		**1469**		**740**	**100.0%**	**1.06 [0.97 , 1.15]**
Total events:	840		398			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.12$, df = 1 (P = 0.29); $I^2 = 11\%$						
Test for overall effect: Z = 1.36 (P = 0.17)						
6.8.4 Secukinumab versus ustekinumab						
Bagel CLARITY 2018	261	550	256	552	48.3%	1.02 [0.90 , 1.16]
Thaçi CLEAR 2015	215	337	196	339	51.7%	1.10 [0.98 , 1.25]
Subtotal (95% CI)		**887**		**891**	**100.0%**	**1.06 [0.98 , 1.16]**
Total events:	476		452			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.73$, df = 1 (P = 0.39); $I^2 = 0\%$						
Test for overall effect: Z = 1.39 (P = 0.16)						
6.8.5 Brodalumab versus ustekinumab						
Lebwohl AMAGINE-2 2015	719	1222	177	300	54.3%	1.00 [0.90 , 1.11]
Lebwohl AMAGINE-3 2015	682	1253	168	313	45.7%	1.01 [0.90 , 1.14]
Subtotal (95% CI)		**2475**		**613**	**100.0%**	**1.00 [0.93 , 1.09]**
Total events:	1401		345			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.04$, df = 1 (P = 0.83); $I^2 = 0\%$						
Test for overall effect: Z = 0.12 (P = 0.90)						
6.8.6 Guselkumab versus adalimumab						
Blauvelt VOYAGE-1 2016	170	329	170	334	47.1%	1.02 [0.88 , 1.18]
Gordon X-PLORE 2015	103	208	24	43	11.6%	0.89 [0.66 , 1.20]
Reich VOYAGE-2 2017	235	496	120	248	41.3%	0.98 [0.84 , 1.15]
Subtotal (95% CI)		**1033**		**625**	**100.0%**	**0.98 [0.89 , 1.09]**
Total events:	508		314			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.63$, df = 2 (P = 0.73); $I^2 = 0\%$						
Test for overall effect: Z = 0.30 (P = 0.77)						
6.8.7 Risankizumab versus ustekinumab						
Gordon UltIMMa-1 2018	151	304	50	102	31.5%	1.01 [0.81 , 1.27]
Gordon UltIMMa-2 2018	134	294	53	99	33.0%	0.85 [0.68 , 1.06]
Papp NCT02054481 2017	97	126	29	40	35.5%	1.06 [0.86 , 1.31]
Subtotal (95% CI)		**724**		**241**	**100.0%**	**0.97 [0.85 , 1.11]**
Total events:	382		132			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.20$, df = 2 (P = 0.33); $I^2 = 9\%$						
Test for overall effect: Z = 0.41 (P = 0.68)						



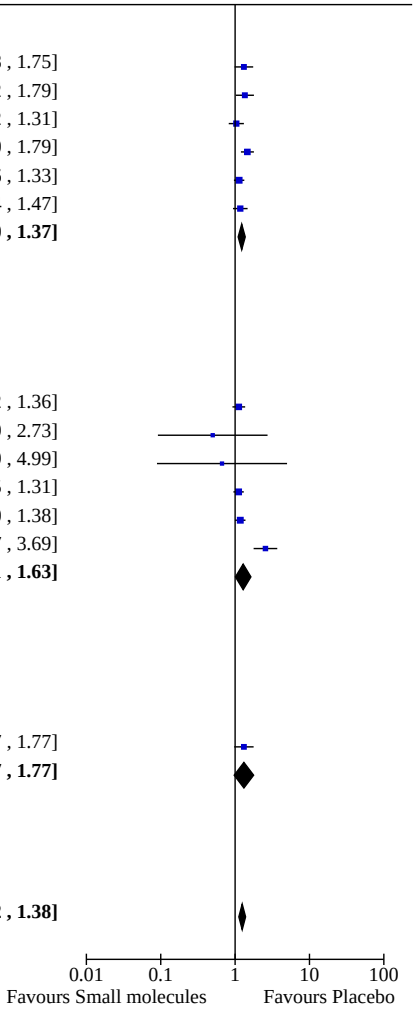
Analysis 6.8. (Continued)

Test for overall effect: Z = 0.41 (P = 0.68)						
6.8.8 Ixekizumab versus ustekinumab						
Reich IXORA-S 2017	117	136	139	166	100.0%	1.03 [0.93 , 1.13]
Subtotal (95% CI)		**136**		**166**	**100.0%**	**1.03 [0.93 , 1.13]**
Total events:	117		139			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.58)						
6.8.9 Certolizumab versus etanercept						
Lebwohl CIMPACT 2018	160	332	78	170	100.0%	1.05 [0.86 , 1.28]
Subtotal (95% CI)		**332**		**170**	**100.0%**	**1.05 [0.86 , 1.28]**
Total events:	160		78			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.49 (P = 0.63)						
6.8.10 Risankizumab versus adalimumab						
EUCTR2015-003623-65-DE	76	301	71	304	100.0%	1.08 [0.82 , 1.43]
Subtotal (95% CI)		**301**		**304**	**100.0%**	**1.08 [0.82 , 1.43]**
Total events:	76		71			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
6.8.11 Tildrakizumab versus etanercept						
Reich ReSURFACE-2 2017	251	621	169	313	100.0%	0.75 [0.65 , 0.86]
Subtotal (95% CI)		**621**		**313**	**100.0%**	**0.75 [0.65 , 0.86]**
Total events:	251		169			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.06 (P < 0.0001)						
6.8.12 Infliximab versus etanercept						
De Vries PIECE 2016	24	25	23	23	100.0%	0.96 [0.86 , 1.08]
Subtotal (95% CI)		**25**		**23**	**100.0%**	**0.96 [0.86 , 1.08]**
Total events:	24		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						

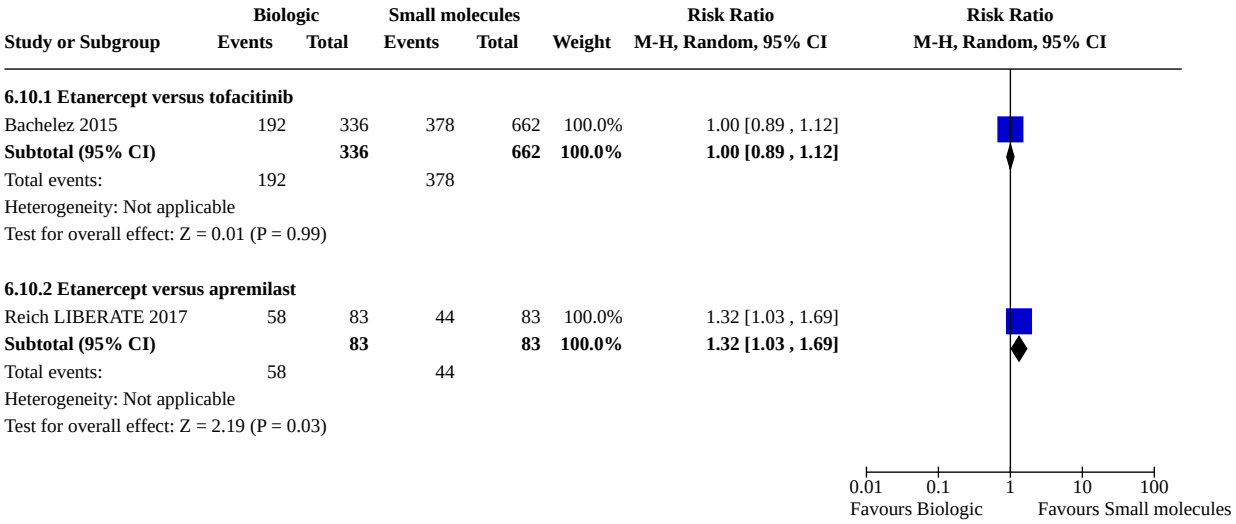


Analysis 6.9. Comparison 6: Secondary outcome - adverse events, Outcome 9: Small molecules versus placebo

Study or Subgroup	Small molecules Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
6.9.1 Apremilast versus placebo						
Ohtsuki 2017	93	170	35	84	7.2%	1.31 [0.98 , 1.75]
Papp 2012c	142	264	35	88	7.4%	1.35 [1.02 , 1.79]
Papp 2013b	97	173	47	87	8.8%	1.04 [0.82 , 1.31]
Papp ESTEEM-1 2015	248	562	85	282	10.0%	1.46 [1.20 , 1.79]
Paul ESTEEM-2 2015	185	275	82	138	11.5%	1.13 [0.96 , 1.33]
Reich LIBERATE 2017	58	83	50	84	9.1%	1.17 [0.94 , 1.47]
Subtotal (95% CI)		**1527**		**763**	**53.9%**	**1.23 [1.10 , 1.37]**
Total events:	823		334			
Heterogeneity: Tau² = 0.01; Chi² = 7.09, df = 5 (P = 0.21); I² = 30%						
Test for overall effect: Z = 3.69 (P = 0.0002)						
6.9.2 Tofacitinib versus placebo						
Bachelez 2015	378	662	55	108	10.1%	1.12 [0.92 , 1.36]
Jin 2017	2	12	2	6	0.4%	0.50 [0.09 , 2.73]
Krueger 2016a	2	9	1	3	0.3%	0.67 [0.09 , 4.99]
Papp OPT Pivotal-1 2015	405	723	89	177	11.6%	1.11 [0.95 , 1.31]
Papp OPT Pivotal-2 2015	425	763	93	196	11.5%	1.17 [1.00 , 1.38]
Zhang 2017	119	178	23	88	5.3%	2.56 [1.77 , 3.69]
Subtotal (95% CI)		**2347**		**578**	**39.2%**	**1.28 [1.01 , 1.63]**
Total events:	1331		263			
Heterogeneity: Tau² = 0.05; Chi² = 19.59, df = 5 (P = 0.001); I² = 74%						
Test for overall effect: Z = 2.05 (P = 0.04)						
6.9.3 TYK2 versus placebo						
Papp TYK2 2018	149	222	23	45	6.8%	1.31 [0.97 , 1.77]
Subtotal (95% CI)		**222**		**45**	**6.8%**	**1.31 [0.97 , 1.77]**
Total events:	149		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.78 (P = 0.08)						
Total (95% CI)		**4096**		**1386**	**100.0%**	**1.25 [1.12 , 1.38]**
Total events:	2303		620			
Heterogeneity: Tau² = 0.02; Chi² = 26.99, df = 12 (P = 0.008); I² = 56%						
Test for overall effect: Z = 4.15 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.26, df = 2 (P = 0.88), I² = 0%						



Analysis 6.10. Comparison 6: Secondary outcome - adverse events, Outcome 10: Biologic versus small molecules

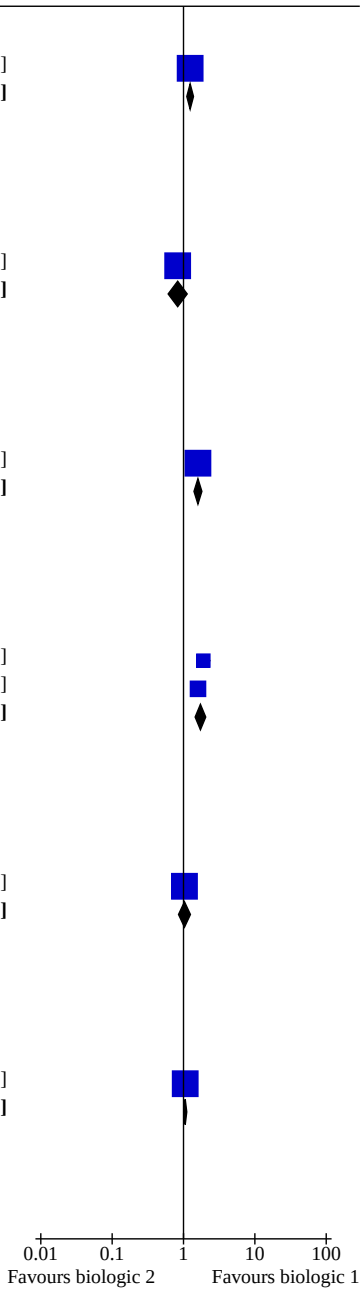


Comparison 7. Secondary outcome - PASI 90 at 52 weeks

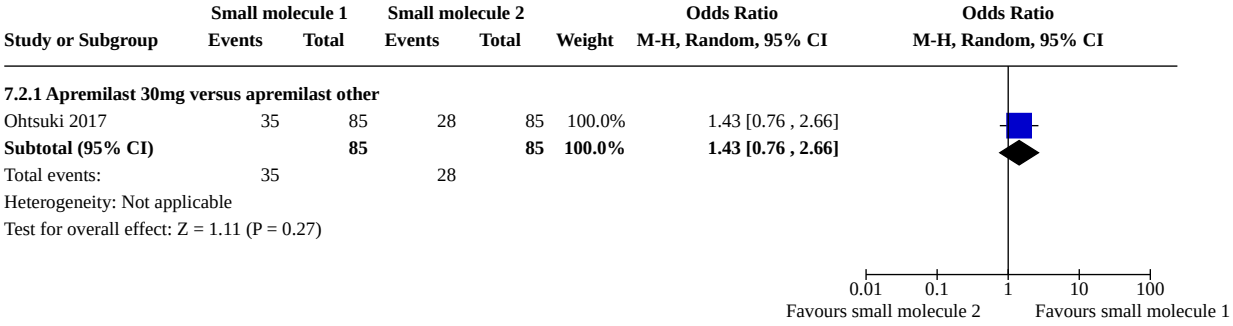
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Biologic 1 versus biologic 2	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1.1 Secukinumab versus ustekinumab	1	676	Risk Ratio (M-H, Random, 95% CI)	1.24 [1.11, 1.38]
7.1.2 Secukinumab 150 versus secukinumab 300	1	121	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.61, 1.13]
7.1.3 Guselkumab versus adalimumab	1	663	Risk Ratio (M-H, Random, 95% CI)	1.59 [1.40, 1.81]
7.1.4 Risankizumab versus ustekinumab	2	799	Risk Ratio (M-H, Random, 95% CI)	1.73 [1.46, 2.05]
7.1.5 Guselkumab 100 versus guselkumab 50	1	128	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.85, 1.25]
7.1.6 Ixekizumab Q2W versus Ixekizumab Q4W	1	1227	Risk Ratio (M-H, Random, 95% CI)	1.06 [1.01, 1.11]
7.2 Small molecule 1 versus small molecule 2	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
7.2.1 Apremilast 30mg versus apremilast other	1	170	Odds Ratio (M-H, Random, 95% CI)	1.42 [0.76, 2.66]

Analysis 7.1. Comparison 7: Secondary outcome - PASI 90 at 52 weeks, Outcome 1: Biologic 1 versus biologic 2

Study or Subgroup	Biologic 1 Events	Biologic 1 Total	Biologic 2 Events	Biologic 2 Total	Weight	Risk Ratio M-H, Random, 95% CI
7.1.1 Secukinumab versus ustekinumab						
Thaçi CLEAR 2015	250	337	203	339	100.0%	1.24 [1.11 , 1.38]
Subtotal (95% CI)		**337**		**339**	**100.0%**	**1.24 [1.11 , 1.38]**
Total events:	250		203			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.90 (P < 0.0001)						
7.1.2 Secukinumab 150 versus secukinumab 300						
Paul JUNCTURE 2015	32	61	38	60	100.0%	0.83 [0.61 , 1.13]
Subtotal (95% CI)		**61**		**60**	**100.0%**	**0.83 [0.61 , 1.13]**
Total events:	32		38			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.20 (P = 0.23)						
7.1.3 Guselkumab versus adalimumab						
Blauvelt VOYAGE-1 2016	251	329	160	334	100.0%	1.59 [1.40 , 1.81]
Subtotal (95% CI)		**329**		**334**	**100.0%**	**1.59 [1.40 , 1.81]**
Total events:	251		160			
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.18 (P < 0.00001)						
7.1.4 Risankizumab versus ustekinumab						
Gordon UltIMMa-1 2018	249	304	44	102	45.2%	1.90 [1.51 , 2.39]
Gordon UltIMMa-2 2018	237	294	50	99	54.8%	1.60 [1.30 , 1.96]
Subtotal (95% CI)		**598**		**201**	**100.0%**	**1.73 [1.46 , 2.05]**
Total events:	486		94			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.25$, df = 1 (P = 0.26); $I^2 = 20\%$						
Test for overall effect: Z = 6.29 (P < 0.00001)						
7.1.5 Guselkumab 100 versus guselkumab 50						
Ohtsuki 2018	49	63	49	65	100.0%	1.03 [0.85 , 1.25]
Subtotal (95% CI)		**63**		**65**	**100.0%**	**1.03 [0.85 , 1.25]**
Total events:	49		49			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.32 (P = 0.75)						
7.1.6 Ixekizumab Q2W versus Ixekizumab Q4W						
Langley IXORA-P 2018	525	611	501	616	100.0%	1.06 [1.01 , 1.11]
Subtotal (95% CI)		**611**		**616**	**100.0%**	**1.06 [1.01 , 1.11]**
Total events:	525		501			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.17 (P = 0.03)						



Analysis 7.2. Comparison 7: Secondary outcome - PASI 90 at 52 weeks, Outcome 2: Small molecule 1 versus small molecule 2

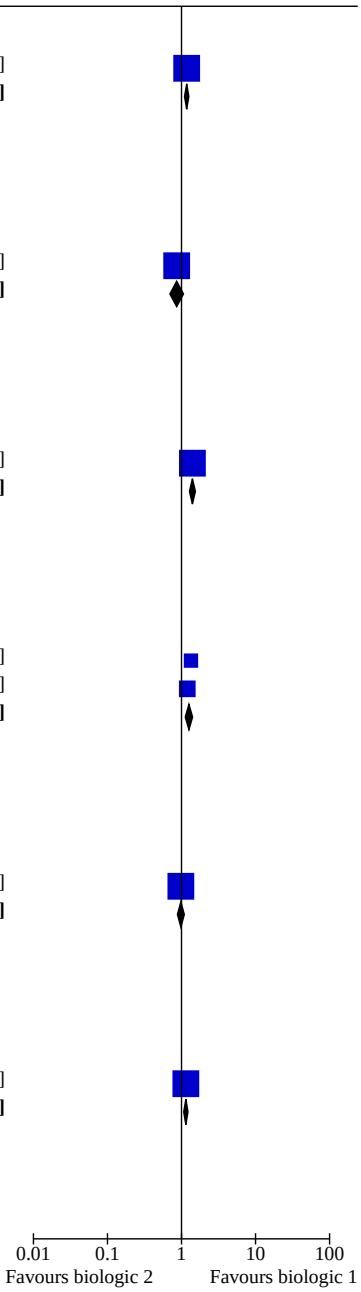


Comparison 8. Secondary outcome - PASI 75 at 52 weeks

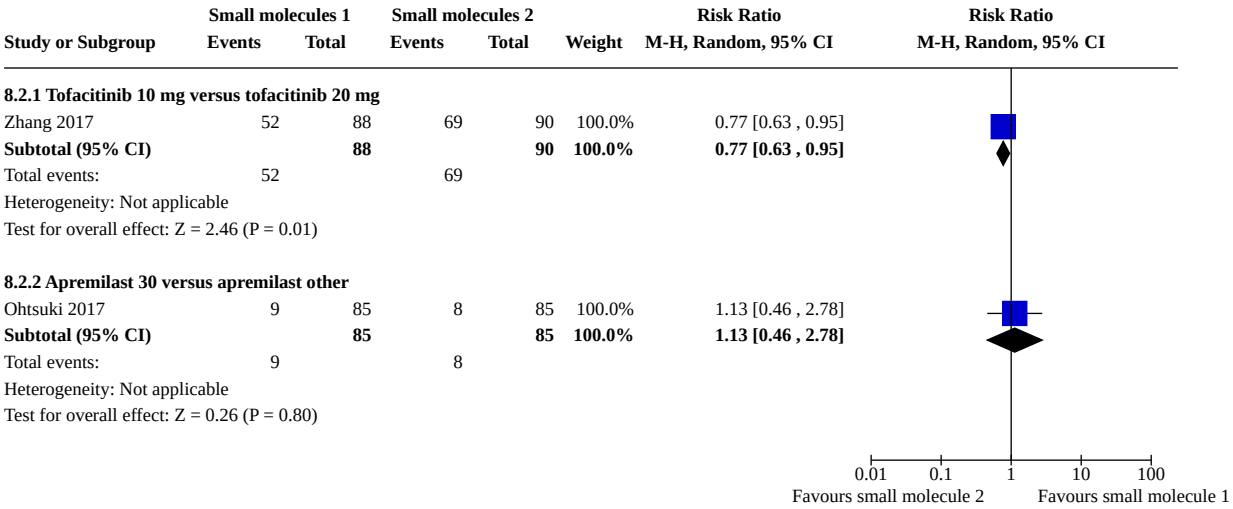
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Biologic 1 versus biologic 2	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1.1 Secukinumab versus ustekinumab	1	676	Risk Ratio (M-H, Random, 95% CI)	1.17 [1.10, 1.26]
8.1.2 Secukinumab 150 versus secukinumab 300	1	121	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.70, 1.06]
8.1.3 Guselkumab versus adalimumab	1	663	Risk Ratio (M-H, Random, 95% CI)	1.40 [1.28, 1.54]
8.1.4 Risankizumab versus ustekinumab	2	799	Risk Ratio (M-H, Random, 95% CI)	1.26 [1.12, 1.41]
8.1.5 Guselkumab 100 versus guselkumab 50	1	128	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.88, 1.09]
8.1.6 Ixekizumab Q2W versus ixekizumab Q4W	1	1227	Risk Ratio (M-H, Random, 95% CI)	1.14 [1.07, 1.22]
8.2 Small molecules 1 versus small molecules 2	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.2.1 Tofacitinib 10 mg versus tofacitinib 20 mg	1	178	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.63, 0.95]
8.2.2 Apremilast 30 versus apremilast other	1	170	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.46, 2.78]

Analysis 8.1. Comparison 8: Secondary outcome - PASI 75 at 52 weeks, Outcome 1: Biologic 1 versus biologic 2

Study or Subgroup	Biologic 1 Events	Biologic 1 Total	Biologic 2 Events	Biologic 2 Total	Weight	Risk Ratio M-H, Random, 95% CI
8.1.1 Secukinumab versus ustekinumab						
Thaçi CLEAR 2015	306	337	262	339	100.0%	1.17 [1.10 , 1.26]
Subtotal (95% CI)		**337**		**339**	**100.0%**	**1.17 [1.10 , 1.26]**
Total events:	306		262			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.72 (P < 0.00001)						
8.1.2 Secukinumab 150 versus secukinumab 300						
Paul JUNCTURE 2015	42	61	48	60	100.0%	0.86 [0.70 , 1.06]
Subtotal (95% CI)		**61**		**60**	**100.0%**	**0.86 [0.70 , 1.06]**
Total events:	42		48			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.39 (P = 0.16)						
8.1.3 Guselkumab versus adalimumab						
Blauvelt VOYAGE-1 2016	289	329	209	334	100.0%	1.40 [1.28 , 1.54]
Subtotal (95% CI)		**329**		**334**	**100.0%**	**1.40 [1.28 , 1.54]**
Total events:	289		209			
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.21 (P < 0.00001)						
8.1.4 Risankizumab versus ustekinumab						
Gordon UltIMMa-1 2018	280	304	70	102	44.8%	1.34 [1.17 , 1.54]
Gordon UltIMMa-2 2018	270	294	76	99	55.2%	1.20 [1.07 , 1.34]
Subtotal (95% CI)		**598**		**201**	**100.0%**	**1.26 [1.12 , 1.41]**
Total events:	550		146			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.67$, df = 1 (P = 0.20); $I^2 = 40\%$						
Test for overall effect: Z = 3.98 (P < 0.0001)						
8.1.5 Guselkumab 100 versus guselkumab 50						
Ohtsuki 2018	57	63	60	65	100.0%	0.98 [0.88 , 1.09]
Subtotal (95% CI)		**63**		**65**	**100.0%**	**0.98 [0.88 , 1.09]**
Total events:	57		60			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.37 (P = 0.71)						
8.1.6 Ixekizumab Q2W versus ixekizumab Q4W						
Langley IXORA-P 2018	486	611	428	616	100.0%	1.14 [1.07 , 1.22]
Subtotal (95% CI)		**611**		**616**	**100.0%**	**1.14 [1.07 , 1.22]**
Total events:	486		428			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.02 (P < 0.0001)						



Analysis 8.2. Comparison 8: Secondary outcome - PASI 75 at 52 weeks, Outcome 2: Small molecules 1 versus small molecules 2



ADDITIONAL TABLES

Table 1. Glossary

Term	Definition
Antagonist	A substance that interferes with or inhibits the physiological action of another.
Antigen	A molecule capable of inducing an immune respons
Anti-TNF alpha	A pharmaceutical drug that suppresses the physiologic response to tumor necorsis factor (TNF)
Biological agent	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
CD6	Cluster of differentiation (CD) 6 is a protein encoded by the CD6 gene
Cheilitis	An inflammation of the lips
Chimeric protein	A chimeric protein can be made by combining two different genes
Complex cyclophilin-ciclosporin	Cyclophilins are a family of proteins that bind to ciclosporin, an immunosuppressant agent
Creatinine	A compound that is produced by metabolism of creatine and excreted in the urine
Cyclic adenosine monophosphate	It is a second messenger important in many biological processes
Cytokines	Small proteins produced by a broad range of cells that are important in cell signalling; they are immunomodulating agents
Dendritic cells	Antigen-presenting cells of the immune system
Dermis	It is a layer of the skin

Table 1. Glossary *(Continued)*

Epitope	It is a part of an antigen
Erythematous	Redness of the skin
Folic acid	B vitamin
Humanised antibody	Antibodies from non-human species whose protein sequences have been modified to increase their similarity to antibody variants produced naturally in humans
IL-17A	A pro-inflammatory cytokine
IL-23R	A cytokine receptor
Immune-mediated	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
Immunogenicity	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
Immunoglobulin 1 Fc	An antibody
Interferon (IFN)-c	A protein released by cells, usually in response to a pathogen
Interleukin	A kind of cytokine
Janus kinase (JAK) inhibitors	A pharmaceutical drug that inhibits the activity of one or more of the Janus kinase family of enzymes
Keratinocytes	Epidermal cells that constitute 95% of the epidermis
Lymphocyte	A subtype of a white blood cell
Lymphoid organ	Part of the body that defends the body against invading pathogens that cause infections or the spread of tumours
Metalloproteinases	A protease enzyme
Monoclonal antibodies	Antibodies that are made by identical immune cells that are all clones of a unique parent cell
Murine sequence	Mouse genomic sequencing
Neutrophils	Type of white blood cell involved in the innate immune system
p40	Subunit beta of interleukin 12 and 23
Periumbilical	Around the navel
Pharmacological treatments	Drugs
Phase I	First-in-man studies
Phase II	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
Phase III	Randomised controlled multicenter trials on large patient groups and are aimed at being the definitive assessment of how effective the drug is

Table 1. Glossary *(Continued)*

Phase IV	Post-marketing trials involve the safety surveillance
Phosphodiesterase 4 inhibitors	A pharmaceutical drug used to block the degradative action of phosphodiesterase 4
Progressive multifocal leukoencephalopathy	A rare viral neurological disease characterised by progressive damage of the white matter of the brain at multiple locations
Receptor	A protein molecule that receives chemical signals from outside a cell
Small molecules	Chemically manufactured molecules (or SMOLs for short)
Sphingosine 1-phosphate receptor agonists	A class of protein-coupled receptors that are targets of the lipid signalling molecule Sphingosine-1-phosphate
T cells/CD4 T cells	A type of white blood cell that is of key importance to the immune system
Th1 and Tc1 cells	A type of T cell
Th17 and Tc17 cells	A type of T cell
TNF-alpha	A protein that is part of the inflammatory response
Tumour necrosis factor antagonists	Class of biological agents
Umbilic	Navel
Xerosis	Dry skin

Table 2. Investigators contacted

	Contact	Requested Information	Contacted	Reply
Missing data				
Akcali 2014	Prof. Akcali	Outcomes: PASI 90, PASI 75, PGA 0/1, QoL scale, AEs & SAEs	8 and 21 November 2016	No response
Al-Hamamy 2014	Prof. Al-Hamamy	Outcomes: PASI 75, PGA 0/1, QoL scale, AEs and SAEs	8 and 21 November 2016	No response
Asahina 2010	Prof. Asahina	Outcome: PASI 90	8 November 2016	Asahina 2010 detailed report
Asahina 2016	Prof. Asahina Pfizer	Outcomes: AEs and SAEs	3 and 12 January 2017	Additional data to the publication not provided
Asawanonda 2006	Prof. Asawanonda	Outcomes: PASI 75, PGA 0/1, AEs and SAEs	21 November 2016	Asawanonda 2006 sent detailed report for PASI 75 and AEs. PGA was not collected during this study

Table 2. Investigators contacted *(Continued)*

			15 December 2016	
Bissonnette 2015	Prof. Bisonnette Innovaderm Recherches Inc.	Outcomes: PASI 90, PGA 0/1, AEs	8 and 21 November 2016	Additional data to the publication not provided
Blauvelt FEATURE 2015	Dr Blauvelt Novartis	Outcome: QoL scale	8 and 21 November 2016	Additional data to the publication not provided
Caproni 2009	Prof. Fabri	Outcomes: PASI 90, PASI 75, PGA 0/1, QoL scale, AEs and 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 and SAEs	8 and 21 November 2016	No response
Dogra 2012	Prof. Dogra	Outcomes: PGA 0/1, QoL scale, AEs and SAEs	8 November 2016	PGA & QoL scale not collected during this study. AEs and 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. Flytström	Outcomes: PGA 0/1	12 and 19 January 2017	Additional data to the publication not provided
Gisondi 2008	Prof. Gisondi	Outcomes: PASI 90, PGA 0/1, QoL scale, AEs and SAEs	8 November 2016	Gisondi 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 and SAEs	8 November 2016	Gottlieb 2011 sent detailed report for the requested outcomes
Griffiths ACCEPT 2010	Prof. Griffiths Janssen	Outcome: QoL scale	16 December 2016	QoL was not collected during this study
Krueger 2016a	Pfizer	Outcomes: PASI 90, QoL scale	3 and 12 January 2017	No response
Lebwohl AMAGINE-2 2015	Prof. Lebwohl Valeant Pharmaceuticals NA LLC	Outcomes: PASI 90 and QoL scale	8 and 21 November 2016	Lebwohl AMAGINE-2 2015 sent detailed report for PASI 90; individual scores and median difference from baseline of QoL were not available

Table 2. Investigators contacted *(Continued)*

Lebwohl AMAGINE-3 2015	Prof. Lebwohl Valeant Pharmaceuticals NA LLC	Outcomes: PASI 90 and QoL scale	8 and 21 November 2016	Lebwohl AMAGINE-3 2015 sent detailed report for PASI 90, individual scores and median difference from baseline of QoL were not available
Leonardi 2012	Prof. Leonardi	Outcomes: QoL scale and AEs	8 and 21 November 2016	No response
Mahajan 2010	Prof. Kaur	Outcomes: PASI 90, PGA 0/1, QoL scale, AEs and SAEs	8 and 21 November 2016	No response
Menter REVEAL 2008	Prof. Menter	Outcome: PGA 0/1	8 and 21 November 2016	No response
Menter EXPRESS-II 2007	Prof. Menter	Outcome: PGA 0/1	8 and 21 November 2016	No response
Mrowietz BRIDGE 2016	Prof. Mrowietz	Outcome: QoL scale	3 and 12 January 2017	Additional data to the publication not provided
Ortonne 2013	Prof. Paul Novartis	Outcome: PASI 90	3 January 2017	Additional data to the publication not provided
Papp 2013a	Prof. Papp	Outcome: QoL scale	22 November 2016 13 December 2016	Additional data to the publication not provided
Papp AMAGINE-1 2016	Prof. Papp	Outcome: QoL scale	22 November 2016 13 December 2016	Additional data to the publication not provided
Papp 2005	Prof. Papp	Outcome: QoL scale, AEs and SAEs	22 November 2016 13 December 2016	Additional data to the publication not provided
Papp 2012b	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
Paul JUNCTURE 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 and 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

Table 2. Investigators contacted *(Continued)*

Sterry PRESTA 2010	Prof. Sterry	Outcomes: PASI 90 and 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
Thaçi 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 and PGA0/1	21 November 2016	Torii sent detailed report for the requested outcomes
Tyring 2006	Prof. Tyring	Outcomes: PGA 0/1 and 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 Kherkhof Pfizer	Outcome: AEs	8 and 21 November 2016	Additional data to the publication not provided
Zhu LOTUS 2013	No contact	Outcome: PASI 90	No	Authors' email not found
Bagel CLARITY 2018	Prof Bagel	Outcome: QoL Scale	24 June 2019	Email response 01 july 2019 Dear Dr. Sbidian, It is a pleasure to e-meet you – i am the medical director assigned to the CLARITY trial for Novartis, and I am responding on behalf of Dr. Bagel to your request of data. Thanks for your interest in the CLARITY: we published the 16w data and we are currently working on the final manuscript. The 52w manuscript will include updated PROs and clinical outcomes – unfortunately, those data are embargoed until the final manuscript is release. Once published, we'd be happy to re-connect to see how the CLARITY data will support your meta-analysis. Please feel free to reach out directly to me if you need any further assistance. Best regards, Elisa Muscianisi
Blauvelt ADACCESS 2018	Prof Blauvelt	Outcome: QoL Scale	24 June and 1st July 2019	Email response: 2 July 2019 'Cc'ing the person who should be able to help you.'
Griffiths EGALITY 2017	Prof Gerdes	Outcomes: QoL Scale, AEs, SAEs	24 June 2019	Email response 27 June 2019

Table 2. Investigators contacted *(Continued)*

				Dear Dr. Sbidian, On behalf of SANDOZ Global Medical Affairs team, I wanted to thank you for your interest to the EGALITY study and for considering it for your ongoing meta-analysis. I'm also happy to share with you on behalf of the authors and the team who worked on the study, the requested information that you can find here attached We would highly appreciate if you can keep us informed when the meta-analysis will be published, meanwhile, please feel free to revert back to us in case you would need any further information Thank you and have a nice afternoon Best regards *Sohaib* Dr. med. Sohaib HACHAICHI Global Medical Affairs Manager Immunology
Ikonomidis 2017	Prof Ikonomidis	Outcomes: PASI 90, 75, PGA0/1, QoL Scale, AES, SAEs	24 June and 1st July 2019	No response
Jin 2017	Prof Zhao	Outcomes: PASI 90, PGA0/1, QoL Scale	24 June and 1st July 2019	No response
NCT01553058 VIP trial	Prof Gelfand	Outcome: PASI 90	24 June	Email response 24 June 2019 "Yes we can do this. I propose that we have this data approved for release to you by September 30 2019" We will add the new data for the next update (living review).
NCT01961609 SIGNATURE	No contact	Outcomes: PASI 90, PGA0/1, AES, SAEs	24 June 2019	We will contact the authors when the article is published
NCT02581345	Dr Caminis	Outcome: QoL Scal	24 June 2019	Authors' email not found (SHIRE pharmaceutics). We will contact the authors when the article is published
NCT02660580 AURIEL-PsO	Sponsors and collaborators: Fresenius Kabi SwissBioSim GmbH Merck KGaA, Darmstadt, Germany	Outcomes: QoL Scale, AEs	24 June 2019	No contact; We will contact the authors when the article is published

Table 2. Investigators contacted *(Continued)*

NCT02850965	Sponsors: Boehringer Ingelheim	Outcomes: PASI 90, QoL Scale, AEs	24 June 2019	No contact. We will contact the authors when the article is published
NCT02905331 ORION	Pr Ferris	Outcome: DLQI	24 June and 2nd July 2019	No response
NCT02951533 POLARIS	Janssen-Cilag G.m.b.H, Germany Clinical Tria	Outcome: PGA0/1	24 June 2019	No contact. We will contact the authors when the article is published
NCT03000075	Sponsors and collaborators: AbbVie Boehringer Ingelheim	Outcome: DLQI	24 June 2019	No contact. We will contact the authors when the article is published
Papp ABP 501 2017	Prof. Papp	Outcome: DLQI	24 June 2019	Email answer 24 June 2019 "I am not at liberty to release results that are not in the public domain. Regards, k"
Papp BE ABLE 2018	Prof. Papp	Outcome: DLQI	24 June 2019	Email answer 24 June 2019 "I am not at liberty to release results that are not in the public domain. Regards, k"
Papp NCT02054481 2017	Prof. Papp	Outcome: DLQI	24 June 2019	Email answer 24 June 2019 "I am not at liberty to release results that are not in the public domain. Regards, k"
Papp TYK2 2018	Prof. Papp	Outcome: DLQI	24 June 2019	Email answer 24 June 2019 "I am not at liberty to release results that are not in the public domain. Regards, k"
Reich IXORA-S 2017	Prof. Reich	Outcome: DLQI	24 June and 1st July 2019	E-mails not received (email: kreich@dermatologikum.de; kreich@jeruocon.com)
Reich TRANSFIGURE 2016	Prof. Reich	Outcomes: PGA0/1, DLQI	24 June and 1st July 2019	E-mails not received (email: kreich@dermatologikum.de; kreich@jeruocon.com)

Table 2. Investigators contacted *(Continued)*

Sticherling PRIME 2017	Prof. Sticherling	Outcome: DLQI	24 June and 1st July 2019	Email answer 02 July 2019 "Dear Dr. Sbidian, thank you very much for your mail. We are currently checking the data for your table to respond in due time. Yours, Michael Sticherling"
Lebwohl CIM-PACT 2018	Prof. Lebwohl	Outcome: DLQI	24 June and 1st July 2019	No response
Lee 2016		Outcomes: PASI 90, DLQI	24 June and 1st July 2019	No response
NCT02672852 IMMhance	Sponsors and collaborators: AbbVie Boehringer Ingelheim	Outcome: DLQI	24 June 2019	No contact. We will contact the authors when the article is published
NCT02134210 CHS-0214	Barbara K Finck, M.D.; Coherus Biosciences, Inc	Outcome: DLQI	24 June 2019	No contact. We will contact the authors when the article is published
Awaiting classification studies				
Chow 2015	Prof. Chow	outcomes: PASI 90, PASI 75, PGA 0/1, QoL scale, AEs and 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 and 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 and SAEs	No	Authors' email not found
Krishna 2016	Prof. Krishna	Asking for study protocol and efficacy/safety results	5 and 12 January 2017	No response
DRKS00000716	Prof. Jacobi	Asking for study protocol and efficacy/safety results	12 and 19 January 2017	No response
CTRI/2015/05/005837	Prof. Shah	Asking for study protocol and efficacy/safety results	12 and 19 January 2017	No response
NCT01088165	Prof. Holzer	Asking for study protocol and efficacy/safety results	3 and 24 June 2019	No response

Table 2. Investigators contacted *(Continued)*

NCT02655705	Prof. Youn	Asking for study protocol and efficacy/safety results	3 and 24 June 2019	No response
Abstracts				
Mrowietz 2005	Prof. Mrowietz	Study's protocol and outcomes: PASI 90, PASI 75, PGA 0/1, QoL scale, AEs and SAEs	16 December 2016, 3 January 2017	Additional data to the publication not provided. Finally Mrowietz study was classified in the 'Awaiting classification' section.
Ongoing studies				
NCT01558310	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) 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 you 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
EUC-TR2013-004918-18-NL	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
NCT02701205	Prof Hongzhong Jin	Asking for study protocol and efficacy/safety results	3 June 2019	Email response "This is the mail system at host mta-8_BSR. Your message could not be delivered to one or more recipients."

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

	Network meta-analysis			Direct evidence			Indirect evidence		
Comparisons*	**RR**	**LCI**	**UCI**	**RR**	**LCI**	**UCI**	**RR**	**LCI**	**UCI**
Adalimumab versus placebo	17.82	14.62	21.72	14.38	10.62	19.46	21.14	16.15	27.68
Apremilast versus placebo	7.30	4.26	12.51	6.95	3.38	14.33	8.30	2.05	33.70
Bimekizumab versus placebo	58.64	3.72	923.86	58.64	3.72	923.86	.	.	.
Brodalumab versus placebo	21.96	18.17	26.53	26.32	16.77	41.33	16.98	9.23	31.26
Certolizumab versus placebo	12.11	8.78	16.71	18.54	7.42	46.32	7.04	2.25	21.99
Etanercept versus placebo	9.72	8.12	11.63	10.56	8.05	13.86	8.89	6.70	11.80
Fumaric ester acids versus placebo	3.65	2.49	5.36	4.47	2.01	9.95	3.44	2.22	5.33
Guselkumab versus placebo	25.84	20.90	31.95	29.04	18.30	46.07	22.41	13.01	38.60
Infliximab versus placebo	29.52	19.94	43.70	42.64	16.08	113.09	27.49	17.91	42.20
Ixekizumab versus placebo	28.12	23.17	34.12	32.47	22.51	46.84	26.10	20.30	33.56
Methotrexate versus placebo	9.78	7.15	13.37	1.60	0.74	3.45	15.47	10.79	22.18
Risankizumab versus placebo	27.67	22.86	33.49	29.26	19.90	43.02	26.91	20.88	34.67
Secukinumab versus placebo	23.97	20.03	28.70	23.44	15.87	34.64	24.10	19.80	29.32
Tildrakizumab versus placebo	17.08	12.93	22.56	17.25	8.26	36.02	16.86	6.57	43.27
Tofacitinib versus placebo	8.19	6.53	10.29	6.94	4.69	10.27	11.43	5.80	22.55
Tyrosine kinase 2 inhibitor versus placebo	13.99	1.99	98.10	13.99	1.99	98.10	.	.	.
Ustekinumab versus placebo	17.17	14.44	20.42	18.59	13.82	25.00	16.43	13.21	20.44
Etanercept versis acitretin	4.56	0.81	25.79	4.56	0.81	25.79			.
Guselkumab versus adalimumab	1.45	1.32	1.59	1.45	1.32	1.59	1.35	0.70	2.60

Table 3. Direct and indirect evidences and network meta-analysis results summary table for PASI 90 *(Continued)*

Methotrexate versus adalimumab	0.55	0.40	0.75	0.35	0.21	0.57	0.71	0.49	1.05
Risankizumab versus adalimumab	1.55	1.37	1.76	1.53	1.33	1.75	1.70	1.22	2.38
Etanercept versus apremilast	1.33	0.78	2.27	1.39	0.71	2.72	1.25	0.53	2.94
Ustekinumab versus brodalumab	0.78	0.72	0.85	0.79	0.72	0.86	0.49	0.23	1.07
Etanercept versus certolizumab	0.80	0.61	1.06	0.83	0.62	1.11	0.53	0.20	1.41
Methotrexate versus ciclosporin	0.99	0.60	1.64	0.99	0.60	1.64			.
Infliximab versus etanercept	3.04	2.07	4.45	9.20	1.28	66.37	2.91	1.97	4.29
Ixekizumab versus etanercept	2.89	2.57	3.26	2.91	2.54	3.34	2.84	2.24	3.59
Tildrakizumab versus etanercept	1.76	1.40	2.20	1.77	1.40	2.24	1.60	0.68	3.77
Tofacitinib versus etanercept	0.84	0.70	1.01	0.89	0.73	1.08	0.66	0.42	1.03
Ustekinumab versus etanercept	1.77	1.56	2.00	1.80	1.45	2.24	1.75	1.50	2.04
Guselkumab versus FAEs	7.07	4.82	10.37	6.02	3.13	11.60	7.68	4.79	12.31
Ixekizumab versus FAEs	7.69	5.25	11.27	4.67	2.32	9.43	8.97	5.88	13.70
Methotrexate versus FAEs	2.68	1.71	4.20	5.46	2.68	11.10	1.61	0.89	2.93
Secukinumab versus FAEs	6.56	4.51	9.54	8.31	4.23	16.35	5.91	3.77	9.26
Methotrexate versus infliximab	0.33	0.25	0.43	0.35	0.26	0.46	0.19	0.07	0.47
Methotrexate versus ixekizumab	0.35	0.26	0.46	0.48	0.33	0.68	0.21	0.13	0.33
Ustekinumab versus ixekizumab	0.61	0.53	0.70	0.58	0.47	0.71	0.64	0.53	0.77
Ustekinumab versus risankizumab	0.62	0.54	0.71	0.61	0.52	0.71	0.68	0.49	0.95
Ustekinumab versus secukinumab	0.72	0.67	0.77	0.72	0.67	0.77	0.73	0.57	0.93

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	SUCRA PASI 90	Rank PASI 90	SUCRA SAE	Rank SAE	SUCRA PASI 75	Rank PASI 75	SUCRA AE	Rank AE	SUCRA PGA	Rank PGA	SUCRA QoL	Rank QoL
Anti-IL17	99.5	1	16.7	7	99.4	1	27.6	5	100	1	78.1	2
Anti-IL23	83	2	81.1	2	79.7	2	98.9	1	79.8	2	91.3	1
Anti-IL12/23	67.5	3	46.5	3	70.9	3	60.1	3	70.3	3	77.6	3
Anti-TNF alpha	49.9	4	42.6	5	50	4	54.3	4	50	4	52.2	4
Other biologics	33.5	5	45.1	4	33.2	5	4.6	7	31.9	5	27.6	5
Conventional systemic treatments	16.7	6	87.9	1	16.8	6	20.6	6	18.1	6	23.2	6
Placebo	0	7	30.1	6	0	7	83.9	2	0	7	0	7

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	SUCRA PASI 90	Rank PASI 90	SUCRA SAE	Rank SAE	SUCRA PASI 75	Rank PASI 75	SUCRA AE	Rank AE	SUCRA PGA	Rank PGA	SUCRA QoL	Rank QoL
Acitretin	8.1	19	31.2	19	16.6	17	73.5	6	7	19	-	-
Adalimumab	58.1	8	42.6	12	50.5	11	72.6	7	51.1	12	44.6	9
Apremilast	21.9	17	54.5	7	14.2	18	17	18	17.9	17	15.7	13
Bimekizumab	83.5	4	84.3	2	80.3	4	4.2	20	76.9	6	19.5	12
Brodalumab	68.7	7	38.4	15	78.2	5	43.4	12	84.7	3	-	-
Certolizumab	42.5	12	62.4	4	51.6	10	74.5	5	58.8	9	39.4	11
Ciclosporin	33.4	13	32	18	41.8	13	20.4	16	30.5	15	-	-

Table 5. Ranking findings for all outcomes at drug level *(Continued)*

Etanercept	33	14	52.6	9	38.3	14	49.1	10	38.9	13	50.1	8
FAEs	9.8	18	43.5	10	6.3	19	14.1	19	9.6	18	6.2	14
Guselkumab	81	5	43.2	11	70	7	83.1	2	67.4	7	63.3	6
Infliximab	88.5	1	33.9	16	77.2	6	48.8	11	79	5	73.1	5
Ixekizumab	88.3	2	33	17	86.4	1	28.5	15	87.5	1	91.5	2
Methotrexate	32.9	15	87.6	1	26.1	16	57.6	9	32	14	41.8	10
Placebo	1.1	20	40.4	14	0	20	81.5	3	1.6	20	3.3	15
Risankizumab	87.5	3	79.9	3	80.5	3	79.6	4	80.4	4	97.3	1
Secukinumab	75.4	6	30.4	20	83.6	2	42.5	13	87.2	2	-	-
Tildrakizumab	55.8	9	54.6	6	63.2	9	97.5	1	52.9	10	76	4
Tofacitinib	23.4	16	41.2	13	26.5	15	33	14	23.4	16	51.1	7
Tyrosine kinase 2 inhibitor	51.5	11	61.6	5	45	12	19.6	17	51.3	11	-	-
Ustekinumab	55.6	10	52.7	8	63.7	8	59.5	8	61.9	8	77.3	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. Direct and indirect evidence and network meta-analysis results summary table for serious adverse events

	Network meta-analysis			Direct evidence			Indirect evidence		
Comparisons*	**RR**	**LCI**	**UCI**	**RR**	**LCI**	**UCI**	**RR**	**LCI**	**UCI**
Adalimumab versus placebo	0.98	0.65	1.49	1.18	0.74	1.89	0.47	0.18	1.22
Apremilast versus placebo	0.86	0.48	1.51	0.84	0.46	1.53	1.12	0.04	28.61
Bimekizumab versus placebo	0.20	0.01	3.16	0.20	0.01	3.16	-	-	-

Table 6. Direct and indirect evidence and network meta-analysis results summary table for serious adverse events *(Continued)*

Brodalumab versus placebo	1.04	0.62	1.73	0.93	0.53	1.62	2.45	0.38	15.96
Certolizumab versus placebo	0.74	0.31	1.75	0.62	0.26	1.51	36.57	0.57	2353.06
Ciclosporin versus placebo	1.47	0.19	11.22	5.69	0.32	100.64	0.38	0.02	6.75
Etanercept versus placebo	0.89	0.61	1.31	0.75	0.48	1.19	1.40	0.65	3.02
Fumaric ester acids versus placebo	0.98	0.50	1.94	0.83	0.31	2.21	1.15	0.45	2.94
Guselkumab versus placebo	0.98	0.54	1.79	1.02	0.48	2.17	0.89	0.25	3.13
Infliximab versus placebo	1.11	0.59	2.07	1.18	0.57	2.43	0.92	0.26	3.21
Ixekizumab versus placebo	1.09	0.69	1.73	1.09	0.60	1.99	1.10	0.47	2.53
Methotrexate versus placebo	0.43	0.20	0.95	0.21	0.04	0.99	0.56	0.23	1.38
Risankizumab versus placebo	0.60	0.37	0.96	0.46	0.23	0.90	0.82	0.39	1.71
Secukinumab versus placebo	1.12	0.74	1.70	1.10	0.64	1.92	1.15	0.61	2.16
Tildrakizumab versus placebo	0.84	0.39	1.83	0.97	0.38	2.50	0.50	0.07	3.77
Tofacitinib versus placebo	1.01	0.57	1.77	1.13	0.59	2.15	0.50	0.07	3.80
Tyrosine kinase 2 inhibitor versus placebo	0.61	0.06	5.71	0.61	0.06	5.71	-	-	-
Ustekinumab versus placebo	0.89	0.63	1.27	0.96	0.60	1.55	0.82	0.49	1.37
Etanercept versis acitretin	0.58	0.07	4.59	0.58	0.07	4.59	-	-	-
Guselkumab versus adalimumab	1.00	0.55	1.81	0.91	0.45	1.84	1.27	0.40	4.11
Methotrexate versus adalimumab	0.44	0.19	1.05	0.49	0.05	5.10	0.44	0.17	1.10
Risankizumab versus adalimumab	0.61	0.35	1.06	1.12	0.46	2.72	0.41	0.20	0.83
Etanercept versus apremilast	1.04	0.54	2.02	0.68	0.14	3.34	1.14	0.55	2.36
Ustekinumab versus brodalumab	0.86	0.49	1.51	0.76	0.34	1.70	1.02	0.39	2.67

Table 6. Direct and indirect evidence and network meta-analysis results summary table for serious adverse events *(Continued)*

Etanercept versus certolizumab	1.21	0.48	3.09	2.37	0.36	15.66	0.86	0.24	3.02
Methotrexate versus ciclosporin	0.29	0.04	2.23	1.02	0.07	16.11	0.07	0.00	1.36
Infliximab versus etanercept	1.24	0.60	2.56	0.92	0.06	13.87	1.27	0.60	2.69
Ixekizumab versus etanercept	1.23	0.75	2.01	1.03	0.54	1.97	1.57	0.73	3.40
Secukinumab versus etanercept	1.26	0.74	2.14	1.54	0.47	5.08	1.20	0.66	2.17
Tildrakizumab versus etanercept	0.94	0.43	2.06	0.70	0.27	1.82	1.81	0.43	7.53
Tofacitinib versus etanercept	1.13	0.61	2.08	0.87	0.35	2.19	1.39	0.61	3.15
Ustekinumab versus etanercept	1.00	0.62	1.61	1.25	0.38	4.11	0.96	0.57	1.61
Guselkumab versus FAEs	1.00	0.43	2.33	1.47	0.26	8.51	0.89	0.34	2.33
Ixekizumab versus FAEs	1.11	0.50	2.46	0.36	0.04	3.10	1.34	0.57	3.16
Methotrexate versus FAEs	0.44	0.17	1.17	0.35	0.05	2.32	0.48	0.16	1.48
Secukinumab versus FAEs	1.14	0.55	2.39	0.92	0.24	3.59	1.25	0.52	3.01
Methotrexate versus infliximab	0.39	0.19	0.80	0.41	0.18	0.96	0.34	0.09	1.28
Methotrexate versus ixekizumab	0.40	0.16	0.97	1.00	0.06	15.58	0.36	0.14	0.92
Ustekinumab versus ixekizumab	0.82	0.48	1.37	0.55	0.20	1.50	0.94	0.51	1.73
Ustekinumab versus risankizumab	1.50	0.91	2.47	1.84	0.94	3.60	1.15	0.54	2.44
Ustekinumab versus secukinumab	0.80	0.52	1.23	0.79	0.43	1.44	0.80	0.43	1.51

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.

Table 7. Study bias distribution for PASI 90 using CINeMA

Comparison	Number of studies	Within-study bias	Across-studies bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating

Table 7. Study bias distribution for PASI 90 using CINeMA *(Continued)*

ACI:ETA	2	Major concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Low
ADA:GUSEL	3	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
ADA:MTX	1	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
ADA:PBO	9	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
ADA:RISAN	1	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
APRE:ETA	1	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
APRE:PBO	5	No concerns	Undetected	Some concerns	No concerns	No concerns	No concerns	Moderate
BIME:PBO	1	No concerns	Undetected	Some concerns	No concerns	No concerns	Some concerns	Low
BRODA:PBO	5	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
BRODA:USK	2	Some concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Moderate
CERTO:ETA	1	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
CERTO:PBO	4	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
CICLO:MTX	2	Major concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
ETA:IFX	1	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
ETA:IXE	2	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
ETA:PBO	14	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
ETA:SECU	1	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
ETA:TILDRA	1	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
ETA:TOFA	1	No concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Moderate
ETA:USK	1	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
FUM:GUSEL	1	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate

Table 7. Study bias distribution for PASI 90 using CINeMA *(Continued)*

FUM:IXE	1	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
FUM:MTX	2	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
FUM:PBO	1	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
FUM:SECU	1	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
GUSEL:PBO	5	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
IFX:MTX	1	Major concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Low
IFX:PBO	5	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
IXE:MTX	1	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
IXE:PBO	4	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
IXE:USK	1	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
MTX:PBO	3	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
PBO:RISAN	4	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
PBO:SECU	8	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
PBO:TILDRA	3	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
PBO:TOFA	5	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
PBO:TYK2	1	No concerns	Undetected	Some concerns	No concerns	No concerns	Some concerns	Moderate
PBO:USK	9	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
RISAN:USK	3	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
SECU:USK	2	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
ACI:ADA	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
ACI:APRE	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low

Table 7. Study bias distribution for PASI 90 using CINeMA *(Continued)*

ACI:BIME	0	Some concerns	Undetected	No concerns	No concerns	Some concerns	Some concerns	Moderate
ACI:BRODA	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
ACI:CERTO	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
ACI:CICLO	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
ACI:FUM	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
ACI:GUSEL	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
ACI:IFX	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Low
ACI:IXE	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
ACI:MTX	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
ACI:PBO	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
ACI:RISAN	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
ACI:SECU	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
ACI:TILDRA	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
ACI:TOFA	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
ACI:TYK2	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
ACI:USK	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
ADA:APRE	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
ADA:BIME	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	Some concerns	Low
ADA:BRODA	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
ADA:CERTO	0	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
ADA:CICLO	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate

Table 7. Study bias distribution for PASI 90 using CINeMA *(Continued)*

ADA:ETA	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
ADA:FUM	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
ADA:IFX	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Low
ADA:IXE	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
ADA:SECU	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
ADA:TILDRA	0	No concerns	Undetected	No concerns	No concerns	Some concerns	Some concerns	Moderate
ADA:TOFA	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
ADA:TYK2	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	Some concerns	Low
ADA:USK	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
APRE:BIME	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	Some concerns	Low
APRE:BRODA	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
APRE:CERTO	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
APRE:CICLO	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
APRE:FUM	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
APRE:GUSEL	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
APRE:IFX	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Low
APRE:IXE	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
APRE:MTX	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
APRE:RISAN	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
APRE:SECU	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate

Table 7. Study bias distribution for PASI 90 using CINeMA *(Continued)*

APRE:TIL-DRA	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
APRE:TOFA	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
APRE:TYK2	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	Some concerns	Low
APRE:USK	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
BIME:BRO-DA	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
BIME:CERTO	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
BIME:CICLO	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
BIME:ETA	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	Some concerns	Low
BIME:FUM	0	Some concerns	Undetected	Some concerns	Some concerns	No concerns	Some concerns	Low
BIME:GUSEL	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
BIME:IFX	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
BIME:IXE	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
BIME:MTX	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
BIME:RISAN	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
BIME:SECU	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
BIME:TIL-DRA	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
BIME:TOFA	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	Some concerns	Low
BIME:TYK2	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	Some concerns	Low
BIME:USK	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	Some concerns	Low

Table 7. Study bias distribution for PASI 90 using CINeMA *(Continued)*

BRODA:CERTO	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
BRODA:CICLO	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
BRODA:ETA	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
BRODA:FUM	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
BRODA:GUSEL	0	No concerns	Undetected	No concerns	No concerns	Some concerns	Some concerns	Moderate
BRODA:IFX	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Low
BRODA:IXE	0	Some concerns	Undetected	No concerns	No concerns	Some concerns	Some concerns	Moderate
BRODA:MTX	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
BRODA:RISAN	0	Some concerns	Undetected	No concerns	No concerns	Some concerns	Some concerns	Moderate
BRODA:SECU	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
BRODA:TILDRA	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
BRODA:TOFA	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
BRODA:TYK2	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
CERTO:CICLO	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
CERTO:FUM	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
CERTO:GUSEL	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate

Table 7. Study bias distribution for PASI 90 using CINeMA *(Continued)*

CERTO:IFX	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Low
CERTO:IXE	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
CERTO:MTX	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
CERTO:RISAN	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
CERTO:SECU	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
CERTO:TILDRA	0	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
CERTO:TOFA	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
CERTO:TYK2	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
CERTO:USK	0	Some concerns	Undetected	No concerns	No concerns	Some concerns	Some concerns	Moderate
CICLO:ETA	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
CICLO:FUM	0	Major concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Low
CICLO:GUSEL	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
CICLO:IFX	0	Major concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Low
CICLO:IXE	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
CICLO:PBO	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
CICLO:RISAN	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Low
CICLO:SECU	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
CICLO:TILDRA	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate

Table 7. Study bias distribution for PASI 90 using CINeMA *(Continued)*

CICLO:TOFA	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
CICLO:TYK2	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
CICLO:USK	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
ETA:FUM	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
ETA:GUSEL	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
ETA:MTX	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
ETA:RISAN	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
ETA:TYK2	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	Some concerns	Low
FUM:IFX	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
FUM:RISAN	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
FUM:TILDRA	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
FUM:TOFA	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
FUM:TYK2	0	Some concerns	Undetected	Some concerns	Major concerns	No concerns	Some concerns	Very low
FUM:USK	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
GUSEL:IFX	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Low
GUSEL:IXE	0	No concerns	Undetected	No concerns	No concerns	Some concerns	Some concerns	Moderate
GUSEL:MTX	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
GUSEL:RISAN	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
GUSEL:SECU	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
GUSEL:TILDRA	0	No concerns	Undetected	No concerns	No concerns	Some concerns	Some concerns	Moderate

Table 7. Study bias distribution for PASI 90 using CINeMA *(Continued)*

GUSEL:TOFA	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
GUSEL:TYK2	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
GUSEL:USK	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
IFX:IXE	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Low
IFX:RISAN	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Low
IFX:SECU	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Low
IFX:TILDRA	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Low
IFX:TOFA	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Low
IFX:TYK2	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
IFX:USK	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Low
IXE:RISAN	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
IXE:SECU	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
IXE:TILDRA	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
IXE:TOFA	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
IXE:TYK2	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
MTX:RISAN	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
MTX:SECU	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
MTX:TILDRA	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
MTX:TOFA	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
MTX:TYK2	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
MTX:USK	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate

Table 7. Study bias distribution for PASI 90 using CINeMA *(Continued)*

RISAN:SECU	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
RISAN:TIL-DRA	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
RISAN:TOFA	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
RISAN:TYK2	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
SECU:TIL-DRA	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
SECU:TOFA	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
SECU:TYK2	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
TILDRA:TO-FA	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
TIL-DRA:TYK2	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Low
TILDRA:USK	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
TOFA:TYK2	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	Some concerns	Low
TOFA:USK	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
TYK2:USK	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	Some concerns	Low

Table 8. Study bias distribution for serious adverse events using CINeMA

Comparison	Number of studies	Within-study bias	Across-studies bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
ACI:ETA	3	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
ADA:GUSEL	3	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ADA:MTX	1	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate

Table 8. Study bias distribution for serious adverse events using CINeMA *(Continued)*

ADA:PBO	10	No concerns	Undetected	Some concerns	Some concerns	Some concerns	Major concerns	Very low
ADA:RISAN	1	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Moderate
APRE:ETA	1	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
APRE:PBO	6	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
BIME:PBO	1	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
BRODA:PBO	5	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
BRODA:USK	2	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
CERTO:ETA	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
CERTO:PBO	4	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
CICLO:MTX	2	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
CICLO:PBO	1	Major concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Very low
ETA:IFX	1	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
ETA:IXE	2	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
ETA:PBO	13	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
ETA:SECU	1	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
ETA:TILDRA	1	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ETA:TOFA	1	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ETA:USK	1	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
FUM:GUSEL	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
FUM:IXE	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
FUM:MTX	2	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate

Table 8. Study bias distribution for serious adverse events using CINeMA *(Continued)*

FUM:PBO	1	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
FUM:SECU	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
GUSEL:PBO	5	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
IFX:MTX	1	Major concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Low
IFX:PBO	7	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
IXE:MTX	1	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
IXE:PBO	4	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
IXE:USK	1	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
MTX:PBO	3	Some concerns	Undetected	Some concerns	No concerns	No concerns	No concerns	Moderate
PBO:RISAN	4	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
PBO:SECU	8	No concerns	Undetected	Some concerns	Some concerns	No concerns	No concerns	Moderate
PBO:TILDRA	3	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
PBO:TOFA	7	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
PBO:TYK2	1	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
PBO:USK	10	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
RISAN:USK	3	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
SECU:USK	2	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
ACI:ADA	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ACI:APRE	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ACI:BIME	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ACI:BRODA	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low

Table 8. Study bias distribution for serious adverse events using CINeMA *(Continued)*

ACI:CERTO	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ACI:CICLO	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ACI:FUM	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ACI:GUSEL	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ACI:IFX	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ACI:IXE	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ACI:MTX	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ACI:PBO	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ACI:RISAN	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ACI:SECU	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ACI:TILDRA	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ACI:TOFA	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ACI:TYK2	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ACI:USK	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ADA:APRE	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
ADA:BIME	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
ADA:BRODA	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ADA:CERTO	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
ADA:CICLO	0	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
ADA:ETA	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ADA:FUM	0	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low

Table 8. Study bias distribution for serious adverse events using CINeMA *(Continued)*

ADA:IFX	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
ADA:IXE	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ADA:SECU	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
ADA:TILDRA	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ADA:TOFA	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
ADA:TYK2	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
ADA:USK	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
APRE:BIME	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
APRE:BRODA	0	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
APRE:CERTO	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
APRE:CICLO	0	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
APRE:FUM	0	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
APRE:GUSEL	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
APRE:IFX	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
APRE:IXE	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
APRE:MTX	0	Some concerns	Undetected	Some concerns	Some concerns	No concerns	No concerns	Moderate
APRE:RISAN	0	No concerns	Undetected	Some concerns	Some concerns	No concerns	No concerns	Moderate
APRE:SECU	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
APRE:TILDRA	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
APRE:TOFA	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
APRE:TYK2	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low

Table 8. Study bias distribution for serious adverse events using CINeMA *(Continued)*

APRE:USK	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
BIME:BRODA	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
BIME:CERTO	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
BIME:CICLO	0	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
BIME:ETA	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
BIME:FUM	0	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
BIME:GUSEL	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
BIME:IFX	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
BIME:IXE	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
BIME:MTX	0	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
BIME:RISAN	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
BIME:SECU	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
BIME:TILDRA	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
BIME:TOFA	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
BIME:TYK2	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
BIME:USK	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
BRODA:CERTO	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
BRODA:CICLO	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
BRODA:ETA	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
BRODA:FUM	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low

Table 8. Study bias distribution for serious adverse events using CINeMA *(Continued)*

BRODA:GUSEL	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
BRODA:IFX	0	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
BRODA:IXE	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
BRODA:MTX	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
BRODA:RISAN	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
BRODA:SECU	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
BRODA:TILDRA	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
BRODA:TOFA	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
BRODA:TYK2	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
CERTO:CICLO	0	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
CERTO:FUM	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
CERTO:GUSEL	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
CERTO:IFX	0	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
CERTO:IXE	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
CERTO:MTX	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
CERTO:RISAN	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
CERTO:SECU	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
CERTO:TILDRA	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
CERTO:TOFA	0	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
CERTO:TYK2	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low

Table 8. Study bias distribution for serious adverse events using CINeMA *(Continued)*

CERTO:USK	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
CICLO:ETA	0	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
CICLO:FUM	0	Major concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Very low
CICLO:GUSEL	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
CICLO:IFX	0	Major concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Very low
CICLO:IXE	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
CICLO:RISAN	0	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
CICLO:SECU	0	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
CICLO:TILDRA	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
CICLO:TOFA	0	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
CICLO:TYK2	0	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
CICLO:USK	0	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
ETA:FUM	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ETA:GUSEL	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ETA:MTX	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
ETA:RISAN	0	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
ETA:TYK2	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
FUM:IFX	0	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
FUM:RISAN	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
FUM:TILDRA	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
FUM:TOFA	0	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low

Table 8. Study bias distribution for serious adverse events using CINeMA *(Continued)*

FUM:TYK2	0	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
FUM:USK	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
GUSEL:IFX	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
GUSEL:IXE	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
GUSEL:MTX	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
GUSEL:RISAN	0	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
GUSEL:SECU	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
GUSEL:TIL-DRA	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
GUSEL:TOFA	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
GUSEL:TYK2	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
GUSEL:USK	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
IFX:IXE	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
IFX:RISAN	0	No concerns	Undetected	Some concerns	Some concerns	No concerns	No concerns	Moderate
IFX:SECU	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
IFX:TILDRA	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
IFX:TOFA	0	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
IFX:TYK2	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
IFX:USK	0	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
IXE:RISAN	0	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	High
IXE:SECU	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
IXE:TILDRA	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low

Table 8. Study bias distribution for serious adverse events using CINeMA *(Continued)*

IXE:TOFA	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
IXE:TYK2	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
MTX:RISAN	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
MTX:SECU	0	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
MTX:TILDRA	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
MTX:TOFA	0	Some concerns	Undetected	Some concerns	Some concerns	No concerns	No concerns	Moderate
MTX:TYK2	0	Some concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
MTX:USK	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
RISAN:SECU	0	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
RISAN:TILDRA	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
RISAN:TOFA	0	No concerns	Undetected	Some concerns	Some concerns	No concerns	No concerns	Moderate
RISAN:TYK2	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
SECU:TILDRA	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
SECU:TOFA	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
SECU:TYK2	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
TILDRA:TOFA	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
TILDRA:TYK2	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
TILDRA:USK	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
TOFA:TYK2	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
TOFA:USK	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low
TYK2:USK	0	No concerns	Undetected	Some concerns	Major concerns	No concerns	No concerns	Low

APPENDICES

Appendix 1. 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 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 guselkumab or tofacitinib or BMS-986165 or certolizumab or tildrakizumab or Bimekizumab or Rizankizumab or risankizumab or Mirikizumab)

Appendix 2. Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library, search strategy

#1 MeSH descriptor: [Psoriasis] this term only
#2 psoria*:ti,ab,kw
#3 palmoplantar* pustulosis:ti,ab,kw
#4 pustulosis palmaris et plantaris:ti,ab,kw
#5 pustulosis and palms and soles:ti,ab,kw
#6 #1 or #2 or #3 or #4 or #5
#7 MeSH descriptor: [Methotrexate] explode all trees
#8 MeSH descriptor: [Fumarates] explode all trees
#9 MeSH descriptor: [Etretinate] explode all trees
#10 MeSH descriptor: [Acitretin] explode all trees
#11 MeSH descriptor: [Isotretinoin] explode all trees
#12 MeSH descriptor: [Retinoids] explode all trees
#13 MeSH descriptor: [Antibodies, Monoclonal] explode all trees
#14 MeSH descriptor: [Interleukin-12] explode all trees
#15 MeSH descriptor: [Interleukin-23] explode all trees
#16 MeSH descriptor: [Interleukin-12 Subunit p40] explode all trees
#17 MeSH descriptor: [Tumor Necrosis Factors] explode all trees
#18 MeSH descriptor: [Tumor Necrosis Factor-alpha] explode all trees
#19 MeSH descriptor: [Receptors, Tumor Necrosis Factor, Type II] explode all trees
#20 MeSH descriptor: [Receptors, Tumor Necrosis Factor] explode all trees
#21 MeSH descriptor: [Receptors, Tumor Necrosis Factor, Type I] explode all trees
#22 MeSH descriptor: [TNF-Related Apoptosis-Inducing Ligand] explode all trees
#23 MeSH descriptor: [Antibodies, Monoclonal] explode all trees
#24 MeSH descriptor: [Immunoglobulin Fab Fragments] explode all trees
#25 MeSH descriptor: [Phototherapy] explode all trees
#26 MeSH descriptor: [Ultraviolet Therapy] explode all trees
#27 MeSH descriptor: [PUVA Therapy] explode all trees
#28 MeSH descriptor: [Photochemotherapy] explode all trees
#29 MeSH 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 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 guselkumab or tofacitinib or certolizumab or tildrakizumab or BMS-986165 or bimekizumab or rizankizumab or risankizumab or mirikizumab):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$.mp.
27. acitretin.mp.
28. Retinoids/
29. Ustekinumab.mp.
30. stelara.mp.
31. secukinumab.mp.
32. apremilast.mp.
33. guselkumab.mp.
34. tofacitinib.mp.
35. BMS-986165.mp.
36. Ri?ankizumab.mp.
37. CNTO 1275.mp.
38. exp antibodies, monoclonal/
39. monoclonal antibod$.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. Bimekizumab.mp.
80. brodalumab.mp.
81. ixekizumab.mp.
82. certolizumab.mp.
83. tildrakizumab.mp.
84. mirikizumab.mp.
85. or/6-84
86. randomized controlled trial.pt.
87. controlled clinical trial.pt.
88. randomized.ab.
89. placebo.ab.
90. clinical trials as topic.sh.
91. randomly.ab.
92. trial.ti.
93. 86 or 87 or 88 or 89 or 90 or 91 or 92
94. exp animals/ not humans.sh.
95. 93 not 94
96. 5 and 85 and 95

[Lines 86-95: 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$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
3. palmoplantar$ 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 word, candidate term word]
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. ampremilast.ti,ab.
35. guselkumab/
36. guselkumab.ti,ab.
37. tofacitinib/
38. tofacitinib.ti,ab.
39. "CNTO 1275".ti,ab.
40. monoclonal antibod$.ti,ab.
41. exp monoclonal antibody/
42. interleukin 23/
43. interleukin 12/
44. interleukin 12p40/
45. p40 subunit.ti,ab.
46. exp tumor necrosis factor/
47. tumor necrosis factor alpha/
48. tumor necrosis factor receptor 2/
49. tumor necrosis factor receptor/
50. tumor necrosis factor related apoptosis inducing ligand/
51. (anti tumour necrosis factor or anti tumor necrosis factor).ti,ab.
52. (tumor necrosis factor-alpha or tumour necrosis factor-alpha).ti,ab.
53. anti tnf.ti,ab.
54. (tnf antibod$ or tnf alpha antibod$).ti,ab.
55. (tumour necrosis factor antibod$ or tumor necrosis factor antibod$).ti,ab.
56. (antitumor necrosis factor or antitumour necrosis factor).ti,ab.
57. "immunoglobulin F(ab) fragment"/
58. (infliximab$ or monoclonal antibody cA2 or remicade).ti,ab.
59. cdp571.ti,ab.
60. (etanercept$ or enbrel).ti,ab.
61. (adalimumab$ or d2e7 or humira).ti,ab.
62. (golimumab or simponi).ti,ab.
63. (Briakinumab or ABT-874).ti,ab.
64. exp phototherapy/
65. PUVA/
66. photochemotherapy/
67. photodynamic therap$.ti,ab.
68. phototherap$.ti,ab.
69. photochemotherap$.ti,ab.
70. puva.ti,ab.
71. ultraviolet.ti,ab.
72. light therap$.ti,ab.
73. photoradiation therap$.ti,ab.
74. BBUVB.ti,ab.
75. NBUVB.ti,ab.
76. BB-UVB.ti,ab.
77. NB-UVB.ti,ab.
78. broad band uvb.ti,ab.
79. broad band ultraviolet b.ti,ab.

80. narrow band uvb.ti,ab.
81. narrow band ultraviolet b.ti,ab.
82. psoralen ultraviolet a.ti,ab.
83. psoralen uva.ti,ab.
84. cyclosporin/
85. (Ciclosporin or cyclosporine or cyclosporin).ti,ab.
86. brodalumab.ti,ab.
87. ixekizumab.ti,ab.
88. ixekizumab/
89. brodalumab/
90. certolizumab.mp.
91. tildrakizumab.mp.
92. BMS-986165.ti,ab.
93. bimekizumab/
94. Bimekizumab.ti,ab.
95. risankizumab/
96. Ri?ankizumab.ti,ab.
97. mirikizumab/
98. Mirikizumab.ti,ab.
99. or/7-98
100. crossover procedure.sh.
101. double-blind procedure.sh.
102. single-blind procedure.sh.
103. (crossover$ or cross over$).tw.
104. placebo$.tw.
105. (doubl$ adj blind$).tw.
106. allocat$.tw.
107. trial.ti.
108. randomized controlled trial.sh.
109. random$.tw.
110. or/100-109
111. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
112. human/ or normal human/
113. 111 and 112
114. 111 not 113
115. 110 not 114
116. 6 and 99 and 115

Appendix 5. LILACS search strategy

psoria$

We searched using the term above and the Controlled clinical trials topic-specific query filter.

Appendix 6. Living systematic review protocol

Living systematic reviews (LSRs) and living network meta-analyses (Living NMAs) offer a new approach to review updating in which the review is continually updated, incorporating relevant new evidence as it becomes available (Elliott 2017).

The methods outlined below are specific to maintaining this review as a living systematic review on the Cochrane Library. They will be used immediately upon publication of this update. Core review methods, such as the criteria for considering studies in the review and assessment of risk of bias, are unchanged. As such, below we outline only those areas of the Methods for which additional activities or rules apply.

Six methodological steps will be repeated at regular intervals to update the NMA over time: adaptive search for treatments and trials, screening of reports and selection of trials, data extraction, assessment of risk of bias, update of the network of trials and synthesis, and finally dissemination.

1. Adaptive search for treatments and trials

(1) As a living systematic review, we aim to identify all relevant RCTs, regardless of language or publication status (published, unpublished, in press, or in progress).

Bibliographic databases The Cochrane Skin Information Specialist (ED) will search the following databases every month:

- We will limit the *Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library*. Searches of this database by the date a record was added to the database.
- *MEDLINE via Ovid*. We will limit Results sets from this database using two different methods: Results will first be limited by the Create Date (date when the record was added to the database). Results will also be limited by the Entry Date (the date processing of the record was completed). Using two date-limiting fields and combining the results is recommended by the Living Systematic Review Methods Group. See example search syntax below showing limiting with the Create Date (dt) and the Entry Date (ed):
  - 96. 5 and 85 and 95
  - 97. limit 96 to dt=20181031-20190416
  - 98. limit 96 to ed=20181031-20190416
  - 99. 97 or 98
- *Embase via Ovid*. We will limit results from this database by the Date Delivered field (date the citation XML file is created for delivery to Ovid and has a state='new'). The Date Delivered field is recommended for date limiting in Embase in the **Cochrane Information Specialists' Handbook, section 6.6 Updating sear ches.** See example search syntax below (dd=date delivered):
  - 116. 6 and 99 and 115
  - 117. limit 116 to dd=20181031-20190416
- Note that different limit options are proposed for MEDLINE and Embase, because their record fields are different.

For all date-limiting of bibliographic databases described above, we will apply an overlap of three months with previous searches. This approach is recommended by the Living Systematic Review Methods Group and aims to minimise the risk of missing relevant trials.

The search strategies for these three databases are displayed in Appendix 3 (MEDLINE) and Appendix 4 (Embase). The CENTRAL strategy has been slightly amended and is shown below:

#1 MeSH descriptor: [Psoriasis] this term only
#2 psoria*:ti,ab,kw
#3 (palmoplantar* next pustulosis):ti,ab,kw
#4 pustulosis palmaris et plantaris:ti,ab,kw
#5 (pustulosis and palms and soles):ti,ab,kw
#6 #1 or #2 or #3 or #4 or #5
#7 MeSH descriptor: [Methotrexate] explode all trees
#8 MeSH descriptor: [Fumarates] explode all trees
#9 MeSH descriptor: [Etretinate] explode all trees
#10 MeSH descriptor: [Acitretin] explode all trees
#11 MeSH descriptor: [Isotretinoin] explode all trees
#12 MeSH descriptor: [Retinoids] explode all trees
#13 MeSH descriptor: [Antibodies, Monoclonal] explode all trees
#14 MeSH descriptor: [Interleukin-12] explode all trees
#15 MeSH descriptor: [Interleukin-23] explode all trees
#16 MeSH descriptor: [Interleukin-12 Subunit p40] explode all trees
#17 MeSH descriptor: [Tumor Necrosis Factors] explode all trees
#18 MeSH descriptor: [Tumor Necrosis Factor-alpha] explode all trees
#19 MeSH descriptor: [Receptors, Tumor Necrosis Factor, Type II] explode all trees
#20 MeSH descriptor: [Receptors, Tumor Necrosis Factor] explode all trees
#21 MeSH descriptor: [Receptors, Tumor Necrosis Factor, Type I] explode all trees
#22 MeSH descriptor: [TNF-Related Apoptosis-Inducing Ligand] explode all trees
#23 MeSH descriptor: [Antibodies, Monoclonal] explode all trees
#24 MeSH descriptor: [Immunoglobulin Fab Fragments] explode all trees
#25 MeSH descriptor: [Phototherapy] explode all trees
#26 MeSH descriptor: [Ultraviolet Therapy] explode all trees
#27 MeSH descriptor: [PUVA Therapy] explode all trees
#28 MeSH descriptor: [Photochemotherapy] explode all trees
#29 MeSH 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 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

next antibod*) or remicade or interleukin* or "anti tumour necrosis factor" or "anti tumor necrosis factor" or ("tumour necrosis factor" next antibod*) or ("tumor necrosis factor" next antibod*) or "tnf antibod*" or ("tnf alpha" next antibod*) or "anti tnf" or ("immunoglobulin fab" next fragment*) or "p40 subunit" or "tumor necrosis factor*" or tnf or ("antitumor necrosis" next factor*) or ("antitumour necrosis" next factor*) or ampremilast or guselkumab or tofacitinib or certolizumab or tildrakizumab or BMS-986165 or bimekizumab or rizankizumab or risankizumab or mirikizumab):ti,ab,kw
#31 {or #7-#30}
#32 #6 and #31

Deduplication and preparation the results for primary screening will be performed by the Cochrane Skin Information Specialist (ED)

Trials registers We will search records of RCTs from ClinicalTrials.gov and the WHO's International Clinical Trials Registry Platform (ICTRP) through CENTRAL, which now includes trial records from these resources. Records are added to CENTRAL on a monthly basis (see relevant sections of 'How CENTRAL is created'). CENTRAL therefore has a short lag period behind the individual registries.

Unpublished literature

We will search reviews submitted to the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for drug registration (using www.accessdata.fda.gov/scripts/cder/drugsatfda and www.ema.europa.eu/ema) yearly.

Review of search methods We will review search methods and strategies approximately yearly, ensuring they reflect any terminology changes in the topic area or in the databases searched.

(2) As a living systematic review, we aim to continually identify new evidence for interventions already in the network of trials but **also for novel interventions**. Indeed, for the 2019 review update, we identified several new interventions in the ongoing trials section that were not part of the initial network (e.g. risankizumab). To provide an update and useful network of interventions for physicians, we need first to identify new interventions but also, to **drop old interventions**, which are no longer of interest.

To achieve these goals:

(1) We will create a research community in psoriasis, including international experts in the field who will help to provide information of new 'eligible' drugs.

Once a year, a list of all systemic drugs used for psoriasis will be proposed by the scientific steering committee to the international experts' group, including:

- Drugs already involved in the network
- Marketed drugs, which will be identified using the U.S. FDA and the EMA websites (www.accessdata.fda.gov/scripts/cder/drugsatfda and www.ema.europa.eu/ema, respectively).
- Drugs under development, which will be identified using the World Health Organization International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) and ISRCTN registry (www.isrctn.com).

The international experts' group will select from this list all the systemic drugs needed for the future network. They will also add new interventions not proposed in the list. **They will provide a rationale for all proposed network changes (adding or removing interventions)**. The international experts' group is necessary also to determine which drugs have to be deleted from the network, with clinical practice and market authorisation being different in each country.

It will be sufficient to update the interventions network once a year, as we will include phase II and III RCTs. Indeed, the timing between the phase I and the phase II/III for a promising intervention is over one year.

(2) At the same time, we will search the different data sources described for the initial NMA with the latest updated search strategy. The Cochrane Skin Group will perform the electronic search.

2.1. **Every month**, we will re-run the search from the date of the last iteration to the following one (covering a 1-month interval), on an automated basis, for electronic searches, trial registries and conference proceedings. We will use a script file (html extraction by automated http requests) to automatically and simultaneously search multiple sources every month. We will manually screen the reference lists of any newly-included studies and identified systematic reviews.

2.2. **Every year**, two authors (ES, LLC) will check other sources (regulatory agencies and industry trial registries) on a manual basis. We will also update the search strategy by adding or removing interventions. We will also review search methods and strategies approximately yearly, to ensure they reflect any terminology changes in the topic area, or in the databases.

As additional steps to inform the living systematic review, one author (ES) contacts corresponding authors of ongoing studies as they are identified and asks them to advise when results are available, or to share early or unpublished data.

2 Screening of reports and selection of trials

We will immediately screen any new citations retrieved by the monthly searches. We will pay attention to duplicate studies, i.e. the same trial reported in several articles. We will consider using Cochrane's Screen4Me workflow to help assess the search results, depending on the volume of search results we identify in the first few months. Screen4Me comprises three components: known assessments – a service that matches records in the search results to records that have already been screened in Cochrane Crowd and been labelled as 'an RCT' or as 'Not an RCT'; the RCTclassifier – a machine learning model that distinguishes RCTs from non-RCTs; and if appropriate, CochraneCrowd (crowd.cochrane.org) – Cochrane's citizen science platform where the Crowd help to identify and describe health evidence.

Selection process will then be done through Covidence (Covidence 2019), a web tool allowing a double selection on title, abstract and then full text by independent reviewers.

3 Data synthesis

Whenever we find new evidence (i.e. studies, data or information) meeting the review inclusion criteria, we will extract the data and assess risks of bias. For trials identified as completed in clinical trial registries but without posted results or those identified only by a conference proceeding, and for missing outcome data, trained reviewers will contact trialists to request complete results.

Every three months, we will incorporate each newly-identified trial in the network. We will perform one network for each outcome (PASI-90, SAEs, PASI-75, PGA, QoL and AEs). We will re-analyse the data every three months using the standard approaches outlined in the Data synthesis section as well as the GRADE process.

4 Dissemination

The general principle is that an update is published on the Cochrane Library with an open access each time new findings that impact on review conclusions have been identified.

We will present the results with sufficient information so that the live cumulative NMA becomes a useful tool to help medical decision-making, taking into account the safety and efficacy of all systemic treatments for chronic plaque psoriasis. The live cumulative NMA will also provide evidence for future guidelines (and updates) on moderate-to-severe psoriasis treatment in France but also in Europe (European Dermatology Guidelines) and world-wide.

We will present :

- Network graphs for each outcome and at each iteration how the networks of evidence evolves over time
- Treatment effects in forest plots, league tables and reporting of treatment rankings
- Assessments of NMA assumptions and risks of bias for each included trial, to allow readers to assess their level of confidence in the results
- Characteristics and results of included trials, to allow for an evaluation of clinical diversity and transitivity.

We will make publicly available in open access to ensure a transparent process:

- The protocol (and its amendments)
- Statistical programmes
- The screening and selection elements (flow diagram, list of included trials, list of excluded trials with reasons for exclusion)

WHAT'S NEW

Date	Event	Description
8 March 2021	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Search results up to 31 January 2019 are included in the current update (published January 2020, 140 included studies). In addition, the team have found a further 18 new included studies and 13 new ongoing studies from searches up to 8 September 2020, to be published in an updated network meta-analysis. In further searches (up to 20 January 2021) for a future update, the team have found 3 new studies to be included and 14 ongoing studies.

HISTORY

Protocol first published: Issue 2, 2015
Review first published: Issue 12, 2017

Date	Event	Description
26 January 2021	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Search results up to 31 January 2019 are included in the current update (published January 2020, 140 included studies). In addition, the team have found a further 18 new included studies and 13 new ongoing studies from searches up to 8 September 2020, to be published in an updated network meta-analysis. In further searches (up to 14 December 2020) for a future update, the team have found 1 new study to be included and 13 ongoing studies.
13 October 2020	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Search results up to 31 January 2019 are included in the current update (published January 2020). In addition, the team continues with the monthly screening (last search date 8 September 2020) and has found a further 15 new studies and 13 new ongoing studies that will be included in the next update which is underway.
3 September 2020	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Search results up to 31 January 2019 are included in the current update (published January 2020). In addition, the team continues with the monthly screening (last search date 22 July 2020) and has found a further 15 new studies and 12 new ongoing studies that will be included in the next update which is underway.
20 July 2020	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Search results up to 31 January 2019 are included in the current update (published January 2020). In addition, the team continues with the monthly screening (last search date 24 June 2020) and has found a further 14 new studies and 12 new ongoing studies that will be included in the next update which is underway.
6 July 2020	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Search results up to 31 January 2019 are included in the current update (published January 2020). In addition, the team continues with the monthly screening (last search date 27 May 2020) and has found a further 14 new studies and 12 new ongoing studies that will be included in the next update which is underway.
17 April 2020	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Search results up to 31 January 2019 are included in the current update (published January 2020). In addition, the team continues with the monthly screening (last search date 10 March 2020) and has found a further 14 new studies and 11 new ongoing studies that will be included in the next update which is underway.
4 March 2020	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Search results up to 31 January 2019 are included in the current update (published January 2020). In addi-

Date	Event	Description
		tion, the team continues with the monthly screening (last search date 12 February 2020) and has found a further 14 new studies and 7 new ongoing studies that will be included in the next update which is underway.
12 February 2020	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Search results up to 31 January 2019 are included in the current update (published January 2020). In addition, the team continues with the monthly screening (last search date 15 January 2020) and has found a further 13 new studies and 7 new ongoing studies that will be included in the next update which is underway.
2 January 2020	New citation required and conclusions have changed	This update included studies of more interventions, assessing new anti-IL17 and anti-IL23 agents.
2 January 2020	New search has been performed	This update included 31 new studies with 11,867 additional participants. We updated the review in line with the MECIR standards.

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.
LD performed the search.
LLC, SA, CM, CP, CD, IGD, and ES screened papers against eligibility criteria.
ES obtained data on ongoing and unpublished studies.
LLC, SA, CM, CP, CD, IGD, and ES appraised the quality of papers.
LLC, SA, CM, CP, CD, IGD, 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.
All the authors read and amended the manuscript.
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.APHP180680). 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: none known.
Sivem Afach: none known.
Liz Doney: none known.
Corinna Dressler: My institution received an unrestricted research grant from Eli Lilly for a time-effectiveness analysis of psoriasis treatments, and a grant from the European Dermatology Forum to fund a European Guideline Development Centre.
Camille Hua: nothing to declare.
Canelle Mazaud: nothing to declare.
Céline Phan; none known.
Carolyn Hughes: none known.
Dru Riddle: I serve as a speaker for Merck Pharmaceuticals speaking about sugammadex. Sugammadex is an anesthesia medication, so unrelated to this review.
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.

Ignacio Garcia-Doval: I received money from Novartis for a presentation unrelated to psoriasis, and Janssen for meeting expenses for the Spanish Academy of Dermatology annual Congress.
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).

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. I am a founder and part owner of Causa Research, a company dedicated to enhancing patients' adherence to treatment."

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Internal sources

- No sources of support supplied

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- 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, France

  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.
- French Ministry of Health, France, Other

  Grant support was from the Programme Hospitalier de Recherche Clinique (DGOS n°APHP-180680).

  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

A. Between the previous review (Sbidian 2017) and the first update search (January 2019)

1. Background: Why it is important to do this review

We provided a rationale for maintaining the review as a living systematic review (LSR).

This review includes some new methods relevant for living systematic reviews, which are included in the Methods section, and also described in Appendix 6.

2. Methods: Search methods for identification of studies

Changes between search methods in the existing review and the LSR Older versions of this review included searches of the Cochrane Skin Specialised Register and LILACS. The Skin Register is no longer being maintained so we will not search it separately for the LSR. The Cochrane Skin Information Specialist has analysed the results of previous searches for this review and has established that no unique studies were identified through LILACS. We will not therefore search LILACS for the LSR.

We did not identify unique trials through our previous searches of the trial results databases of various pharmaceutical companies. We will therefore not search these resources for the LSR.

For the existing review, we searched five trials registries:

- the ISRCTN registry (www.isrctn.com);
- ClinicalTrials.gov (www.clinicaltrials.gov);
- the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au);
- the World Health Organization International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/); and
- the EU Clinical Trials Register (www.clinicaltrialsregister.eu).

For the LSR we will search only those that are mandatory under the MECIR standards, i.e. ClinicalTrials.gov and WHO ICTRP. WHO ICTRP is an aggregator of the other three trials registries listed.

3. Interventions

Interventions belonging to the systemic conventional treatments, anti-TNF alpha, and anti IL12/23 classes were identical to the previous review.

Ponesimod (belonging to the small molecules class), itolizumab and alefacept (belonging to other biologics class) were withdrawn from the updated review as they are no longer used as systemic treatment for psoriasis.

Bimekizumab (anti-IL17 class), risankizumab and mirikizumab (anti-IL23 class) and BMS-986165 (small molecules class) are new included drugs for the updated review.

We added new molecules to the search strategy for the update and the LSR searches.

4. Outcomes

Primary and secondary outcomes are identical to the previous review, except for one secondary endpoint: 'Proportion of participants who achieve PASI 75 at 52 weeks' and 'Proportion of participants who achieve PASI 90 at 52 weeks'. These replace 'Proportion of participants with at least one relapse in the maintenance phase (between 52 to 104 weeks)' because this outcome was never available in the maintenance-phase trials, and our replacement outcomes answer the same question.

Secondary endpoints

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 at induction phase

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) at induction phase

4. Proportions of participants with adverse effects (AEs) at induction phase

5. Proportion of participants who achieve PASI 75 at 52 weeks

6. Proportion of participants who achieve PASI 90 at 52 weeks

To avoid selection of good responders from participants entering into long-term extension, we selected participants who have been randomised since the induction phase.

The timing of outcomes was also slightly edited: primary outcomes were restricted to only being measured during induction phase (from 8 to 24 weeks after randomisation). All secondary outcomes, except proportion of participants who achieve PASI 75 at 52 weeks and proportion of participants who achieve PASI 90 at 52 weeks, were also restricted to the induction phase. We did not include timings outside these ranges. We also clarified that if there were multiple time points within a phase we would use the longest one.

By expanding the timings (in the previous review, we only analysed trials with short-term assessment defined as 12 to 16 weeks), we aimed to include more trials.

We also clarified that 'Proportions of participants with adverse effects (AE) at induction phase' did not include serious adverse events.

5. Data collection and analysis: Selection of studies

We used Covidence (Covidence 2019) to screen the titles, abstracts and full texts.

5. Data collection and analysis: Assessement of heterogeneity

For the network meta-analysis, to further assure the plausibility of the transitivity assumption, we only excluded from our analyses trials involving co-interventions. We kept in our analyses all trials with a short-term outcome assessment from 8 to 24 weeks, and not only from 12 to 16 weeks as we had previously. We performed sensitivity analyses including only studies with a short-term outcome assessment from 12 to 16 weeks. We also performed sensitivity analyses excluding trials of systemic-treatment-naïve participants.

6. Data collection and analysis: 'Summary of findings' table

We used another method to assess confidence in the our results.

"We also performed full evaluation of the confidence in the results using the web application CINeMA (CINeMA 2017). CINeMA (Confidence in Network Meta-Analysis) is a web application that simplifies the evaluation of confidence in the findings from network meta-analysis. It is based on six domains: within-study bias (referring to the impact of risk of bias in the included studies), across-studies bias (publication or reporting bias), indirectness (relevance to the research question and transitivity), imprecision (comparing the range of treatment effects included in the 95% confidence interval with the range of equivalence), heterogeneity (predictive intervals) and incoherence (if estimates

from direct and indirect evidence disagree) (Salanti 2014).Judgements across the six domains are then summarised to obtain four levels of confidence for each relative treatment effect, corresponding to the usual GRADE approach: very low, low, moderate or high."

7. Data collection and analysis: Dealing with missing data

We clarified out approach for dealing with missing data for safety outcomes: “For the main analysis, we assumed that any participant with missing outcome data did not experience clearance (for efficacy outcomes) or did not experience AEs (for safety outcomes), whatever the group."

B. Between the first protocol submission (January 2014) and the first search (February 2015)

1. We identified and added in the protocol new systemic therapeutics for psoriasis.

- Background: Description of the intervention
  - Oral treatment
  - Biological therapies
- Background: How the intervention might work?
  - Oral 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 treatments include the following: fumaric acid esters, retinoids (acitretin), ciclosporin, methotrexate, infliximab, etanercept, adalimumab, ustekinumab, briakinumab, alefacept, brodalumab, ixekizumab" to the following:

"Systemic 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
  - Alefacept

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 on 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 had 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 2015b defined the induction period as being of a duration less than 24 weeks.

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 criterion 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 about the data extraction (outcome data, other data) for greater clarity and added the sentence, "We extracted the data from the reports of the US Food and Drug Administration (FDA) when available, if not from the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov), and finally from the published reports."

6. Methods: Assessment of risk of bias in included studies

We added information about 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 fewer 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 fewer 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 about 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 of 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 2017). 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.

In the classical meta-analyses, we assessed statistical heterogeneity by visual inspection of the forest plots and using the Q-test and the I^2 statistic. We interpreted the I^2 statistic according to the following thresholds (section 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions*; Higgins 2017): 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 (τ) estimated from the network meta-analysis models (Jackson 2014). We inferred on the presence or absence of important heterogeneity by comparing the magnitude of τ 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 uncertainly 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) and 'network graphs' packages (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 and 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 replaced by Anna Chaimani).

NOTES

This is a Living Systematic Review. Searches are run and screened monthly. Search results up to 31 January 2019 are included in the current update (published January 2020, 140 included studies). In addition, the team have found a further 18 new included studies and 13 new ongoing studies from searches up to 8 September 2020, to be published in an updated network meta-analysis. In further searches (up to 20 January 2021) for a future update, the team have found 3 new studies to be included and 14 ongoing studies.

INDEX TERMS

Medical Subject Headings (MeSH)

Antibodies, Monoclonal [*therapeutic use]; Antibodies, Monoclonal, Humanized; Chronic Disease; Cytokines [antagonists & inhibitors] [metabolism]; Immunosuppressive Agents [*therapeutic use]; Molecular Targeted Therapy; Network Meta-Analysis; Psoriasis [*drug therapy]; Randomized Controlled Trials as Topic; Remission Induction; Severity of Illness Index; Treatment Outcome; Tumor Necrosis Factor-alpha [antagonists & inhibitors]

MeSH check words

Humans