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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 with either skin or joints manifestations, 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. The relative benefit of these treatments remains unclear due to the limited number of trials comparing them directly head-to-head, which is why we chose to conduct a network meta-analysis.

Objectives

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

Search methods

For this update of the living systematic review, we updated our searches of the following databases monthly to October 2021: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and Embase.

Selection criteria

Randomised controlled trials (RCTs) of systemic treatments in adults over 18 years with moderate-to-severe plaque psoriasis, at any stage of treatment, compared to placebo or another active agent. The primary outcomes were: proportion of participants who achieved clear or almost clear skin, that is, at least Psoriasis Area and Severity Index (PASI) 90; proportion of participants with serious adverse events (SAEs) at induction phase (8 to 24 weeks after randomisation).

Data collection and analysis

We conducted duplicate study selection, data extraction, risk of bias assessment and analyses. We synthesised data using pairwise and network meta-analysis (NMA) to compare treatments and rank them according to effectiveness (PASI 90 score) and acceptability (inverse of SAEs).

We assessed the certainty of NMA evidence for the two primary outcomes and all comparisons using CINeMA, as very low, low, moderate, or high. We contacted study authors when data were unclear or missing.

We used the surface under the cumulative ranking curve (SUCRA) to infer treatment hierarchy, from 0% (worst for effectiveness or safety) to 100% (best for effectiveness or safety).

Main results

This update includes an additional 19 studies, taking the total number of included studies to 167, and randomised participants to 58,912, 67.2% men, mainly recruited from hospitals. Average age was 44.5 years, mean PASI score at baseline was 20.4 (range: 9.5 to 39). Most studies were placebo-controlled (57%). We assessed a total of 20 treatments. Most (140) trials were multicentric (two to 231 centres). One-third of the studies (57/167) had high risk of bias; 23 unclear risk, and most (87) low risk. Most studies (127/167) declared funding by a pharmaceutical company, and 24 studies did not report a funding source.

Network meta-analysis at class level showed that all interventions (non-biological systemic agents, small molecules, and biological treatments) showed a higher proportion of patients reaching PASI 90 than placebo. Anti-IL17 treatment showed a higher proportion of patients reaching PASI 90 compared to all the interventions, except anti-IL23. Biologic treatments anti-IL17, anti-IL12/23, anti-IL23 and anti-TNF alpha showed a higher proportion of patients reaching PASI 90 than the non-biological systemic agents.

For reaching PASI 90, the most effective drugs when compared to placebo were (SUCRA rank order, all high-certainty evidence): infliximab (risk ratio (RR) 50.19, 95% CI 20.92 to 120.45), bimekizumab (RR 30.27, 95% CI 25.45 to 36.01), ixekizumab (RR 30.19, 95% CI 25.38 to 35.93), risankizumab (RR 28.75, 95% CI 24.03 to 34.39). Clinical effectiveness of these drugs was similar when compared against each other. Bimekizumab, ixekizumab and risankizumab showed a higher proportion of patients reaching PASI 90 than other anti-IL17 drugs (secukinumab and brodalumab) and guselkumab. Infliximab, anti-IL17 drugs (bimekizumab, ixekizumab, secukinumab and brodalumab) and anti-IL23 drugs (risankizumab and guselkumab) except tildrakizumab showed a higher proportion of patients reaching PASI 90 than ustekinumab and three anti-TNF alpha agents (adalimumab, certolizumab and etanercept). Ustekinumab was superior to certolizumab; adalimumab and ustekinumab were superior to etanercept. No significant difference was shown between apremilast and two non-biological drugs: ciclosporin and methotrexate.

We found no significant difference between any of the interventions and the placebo for the risk of SAEs. The risk of SAEs was significantly lower for participants on methotrexate compared with most of the interventions. Nevertheless, the SAE analyses were based on a very low number of events with low- to moderate-certainty for all the comparisons (except methotrexate versus placebo, which was high-certainty). The findings therefore have to be viewed with caution.

For other efficacy outcomes (PASI 75 and Physician Global Assessment (PGA) 0/1), the results were 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, bimekizumab, ixekizumab, and risankizumab were the most effective treatments for achieving PASI 90 in people with moderate-to-severe psoriasis on the basis of high-certainty evidence.

This NMA evidence is limited to induction therapy (outcomes measured from 8 to 24 weeks after randomisation), and is not sufficient for evaluating longer-term outcomes in this chronic disease. Moreover, we found low numbers of studies for some of the interventions, and the young age (mean 44.5 years) and high level of disease severity (PASI 20.4 at baseline) may not be typical of patients seen in daily clinical practice.

We found no significant difference in the assessed interventions and placebo in terms of SAEs, and the safety evidence for most interventions was low to moderate quality.

More randomised trials directly comparing active agents are needed, and these should include systematic subgroup analyses (sex, age, ethnicity, comorbidities, psoriatic arthritis). To provide long-term information on the safety of treatments included in this review, an evaluation of non-randomised studies and postmarketing reports from regulatory agencies is needed.

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

Which medicines, taken by mouth or injected, work best to treat a skin condition called plaque psoriasis?

Key messages

- After six months of treatment, medicines called 'biologics' seem to work best to clear patches of psoriasis on the skin.

- Longer studies are needed to assess the benefits and potential harms of longer treatment with medicines that are injected or taken by mouth to treat psoriasis.

- More studies are needed that compare these types of medicines directly against each other.

What is psoriasis?

Psoriasis is an immune condition that affects the skin and, sometimes, the joints. Psoriasis speeds up the production of new skin cells, which build up to form raised patches on the skin known as 'plaques'. Plaques can also be flaky, scaly, itchy, and appear red on white skin, and as darker patches on darker skin tones. Plaque psoriasis is the most common form of psoriasis.

How is psoriasis treated?

Treatments for psoriasis depend on how bad the symptoms are. Around 10% to 20% of people with moderate or severe psoriasis will need to take medicines that affect their immune system, to help control the psoriasis. These medicines are called systemic treatments, because they affect the whole body. These are usually taken by mouth (orally) or injected.

Why did we do this Cochrane Review?

There are three different types of systemic medicines to treat psoriasis:

- 'biologics' – proteins, such as antibodies, that target interleukins and cytokines (parts of the immune system that affect how cells behave);
- small molecules – organic compounds that affect immune cells; examples include apremilast; and
- non-biologic medicines – medicines that have been in use for a long time to treat psoriasis, such as methotrexate, ciclosporin and retinoids.

We wanted to find out about the benefits and potential harms of taking systemic medicines to treat psoriasis, and to see if some medicines work better than others.

What did we do?

We searched for studies that tested systemic medicines to treat plaque psoriasis.

How up to date is this review?

We included evidence up to October 2021.

What did we find?

We found 167 studies, including 19 new studies since our last search (October 2021). The studies tested 20 different medicines, covering 58,912 adults with psoriasis (average age 44.5 years) and lasted from two to six months. Of 137 studies that reported their source of funding, a pharmaceutical company provided funding for 127 studies and 10 were funded by non-commercial organisations or academic institutions.

Most studies compared the systemic medicine against a placebo (a 'dummy' treatment that does not contain any medicine but looks identical to the medicine being tested). They used a common measurement scale called the PASI (Psoriasis Area and Severity Index) to compare how well each medicine cleared psoriasis plaques from the skin, looking for a 90% improvement (called 'PASI 90'). Few studies reported on participants' well-being.

We compared all the medicines with each other using a mathematical method called a network meta-analysis.

What are the main results of our review?

All the medicines tested worked better than a placebo to treat psoriasis (measured as a 90% improvement in PASI).

Biologic medicines (that targeted interleukins 17, 23 and 12/23, and the cytokine TNF-alpha) treated psoriasis better than the non-biologic medicines.

Compared with placebo, four biologic medicines worked best to treat psoriasis, with little difference between them:

- infliximab (targets TNF-alpha);

- ixekizumab and bimekizumab (targets interleukin-17); and

- risankizumab (targets interleukin-23).

We found no significant difference in the numbers of serious unwanted events for all systemic medicines tested when compared with a placebo. However, the studies did not consistently report results about safety, such as serious unwanted events. We therefore could not create a reliable risk profile of systemic medicines.

Limitations of the evidence

We are confident in our results for the four biologic medicines (infliximab, iwekizumab, bimekizumab and risankizumab) that worked best to treat psoriasis. We are less confident in our results for serious unwanted events, because of the low number of unwanted events reported.

We are also less confident in the results for the non-biologic medicines because of concerns about how some of the studies were conducted. Further research is likely to change these results.

We did not find many studies for some of the 20 medicines included in our review. Participants in the studies often had severe psoriasis at the start of the study, so our results may not be useful for people whose psoriasis is less severe. Our findings relate only to treatment with systemic medicines for up to six months at most.

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.

BACKGROUND

Please refer to our glossary (see Table 1).

Description of the condition

Psoriasis is an immune-mediated disease for which a person can have genetic susceptibility, manifesting in chronic inflammatory effects on either the skin or joints, or both, with a prevalence ranging from 0.14% (east Asia) to 1.99% (Australasia) (Armstrong 2020b; Parisi 2020; 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 of triggering or aggravating 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 (Armstrong 2020b). 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 psoriasis, their joints are also involved (Alinaghi 2019; 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. The 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.

Associated comorbiditites, impact and quality of life

Patients with severe psoriasis or those who develop psoriasis at a young age have a higher risk of cardiometabolic comorbidities than the general population (Armstrong 2020b). The association between psoriasis and metabolic syndrome was confirmed in a population-based study in the United Kingdom. Moreover, associations with obesity, hypertriglyceridaemia, and hyperglycaemia also increased with severity of psoriasis, independent of other metabolic syndrome components (Langan 2012).

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).

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 non-biological 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 (Armstrong 2020b). 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 non-biological systemic agents (French criteria).

Non-biological systemic treatments

The oldest 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; Heydendael 2003; Ho 1999; Koo 1998; 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 (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 or target therapies affect molecules inside immune cells. Recently, small molecule drugs have been developed and show potential to treat people with psoriasis not responding to non-biological treatments. These small molecule drugs include apremilast (Papp 2012c), tofacitinib, a Januse kinase 1/3 inhibitor (Bachelez 2015) and deucravacitinib (Papp 2018). FDA approval for tofacitinib was declined for psoriasis indication based on clinical efficacy and long-term safety issues, thus we removed this drug from the interventions in this update.

Deucravacitinib 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: etanercept (Leonardi 2003), infliximab (Chaudhari 2001), adalimumab (REVEAL 2008), certolizumab (Reich 2012a), ustekinumab (Lebwohl 2010), secukinumab (Reich 2015), ixekizumab (Leonardi 2012), brodalumab (Papp 2012a), bimekizumab (BE ABLE 1 2018), sonelokimab (Papp 2021), netakimab (PLANETA 2021), guselkumab (Gordon X-PLORE 2015), mirikizumab (NCT03482011), tildrakizumab (Papp 2015), and risankizumab (IMMhance 2020). Mirikizumab will no longer be submitted for approval for psoriasis (due to competitive space), so it was removed from the interventions in this update.

Sonelokimab and netakimab 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) (Armstrong 2020b).

Non-biological systemic treatments

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

Fumaric acid esters (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) and tyrosine kinase 2 (TYK2) inhibitors (deucravacitinib) (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 been approved for psoriasis; its efficacy seems to be higher than non-biological systemic therapy, but no randomised controlled trials (RCTs) assessing apremilast versus ciclosporin have been published. However, some RCTs assessing apremilast versus methotrexate or deucravacitinib or risankizumab are ongoing (CTRI/2019/07/020274; EUCTR2018-001926-25-ES; NCT04908475). 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).

Deucravacitinib

Deucravacitinib 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, and JAK2. 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. Deucravacitinib 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

Three monoclonal antibodies against tumour necrosis factor alpha (TNF-α) (infliximab, adalimumab, certolizumab) 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).

- 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, two, and six weeks followed by a maintenance regimen of 5.0 mg/kg every eight 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 approved in 2009) (Savage 2015). A 45 mg subcutaneous dose is administered initially (90 mg if body weight is over 100 kg), then 45 mg (or 90 mg) subcutaneously four weeks later, and thereafter 45 mg (or 90 mg) subcutaneously every 12 weeks (Savage 2015). Interleukin-23 plays an essential role in skin inflammation in psoriasis leading to the development of agents that selectively target the IL-23p19 subunit (Dong 2017). Drugs targeting the p19 subunit of IL-23 are guselkumab (a fully human IgG1k monoclonal IL-23 antagonist), tildrakizumab (a humanised IgG1k monoclonal antibody) and risankizumab (high-affinity humanised IgG1 monoclonal antibody) (Dong 2017). In July 2017, the FDA approved guselkumab for psoriasis. Guselkumab is given as a 100 mg subcutaneous injection every eight weeks, following two starter doses at week 0 and week four. More recently, both tildrakizumab and risankizumab were approved. The recommended dose for tildrakizumab is one 100 mg injection, followed by a further dose after four 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 four.

- 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), bimekizumab (a humanised monoclonal IgG1 antibody that potently and selectively neutralises the biological function of both human IL-17A and IL-17F), netakimab (a humanised IgG1 nanobody that targets IL-17A) and sonelokimab (a trivalent camelid nanobody binding to 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 four weeks thereafter. Ixekizumab is administered at 160 mg (2 x 80 mg injections) at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10 and 12, then 80 mg every four weeks (Dong 2017). The recommended dose for brodalumab is 210 mg given once a week for the first three weeks and then every two weeks. In August 2021, the EMA approved bimekizumab for psoriasis. The recommended dosage for bimekizumab is two injections of 160 mg each (a total of 320 mg) given once every four weeks for 16 weeks, and then every eight weeks thereafter. Netakimab and sonelokimab 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 non-biological 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; Fahrbach 2021; Gómez-García 2017; Gospodarevskaya 2009; Lin 2012; Loveman 2009; Nast 2015a; Nelson 2008; Reich 2008; Reich 2012b; Sawyer 2019; 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 recent overview of 47 network meta-analyses (NMA) evaluating the efficacy and safety of systemic treatments in moderate to severe psoriasis found that there was redundancy in the NMAs included and that the methodological quality of the systematic reviews and NMAs was low (Guelimi 2021).

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 2021 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 5 October 2021) identifying a total of 167 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 a 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. since 2017, six new biological treatments for psoriasis have 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; Sbidian 2020; Sbidian 2021).

OBJECTIVES

To compare the efficacy and safety of non-biological systemic agents (acitretin, ciclosporin, fumaric acid esters, methotrexate), small molecules (apremilast, deucravacitinib), anti-TNF alpha (etanercept, infliximab, adalimumab, certolizumab), anti-IL12/23 (ustekinumab), anti-IL17 (secukinumab, ixekizumab, brodalumab, bimekizumab, sonelokimab, netakimab), and anti-IL23 (guselkumab, tildrakizumab, risankizumab) for people with moderate-to-severe psoriasis using a network meta-analysis, and to provide a ranking of these treatments according to their efficacy and safety.

A secondary objective is to maintain the currency of the evidence, using a living systematic review approach.

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

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**. 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 contacted international experts from the EuroGuiDerm Psoriasis guideline group, who would help to provide information of new 'eligible' drugs.

Once a year, a list of all systemic drugs used for psoriasis is proposed to the 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 experts' group select from this list all the systemic drugs needed for the future network. They also add relevant new interventions not proposed in the list. **They provide a rationale for all proposed network changes (adding or removing interventions)**. The 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.

Thus, the EuroGuiDerm Psoriasis guideline expert group was contacted on 18 May 2021. At the time, the group was comprised of 22 dermatologists. A total of 15 experts stated that only drugs approved by EMA for plaque psoriasis should be included. One person disagreed and six members of the expert group did not reply to our request.

In total, taking into account experts' feedback, tofacitinib and mirikizumab were removed from the interventions as they will no longer be submitted for approval for psoriasis. However, previous but not approved interventions such as deucravacitinib were maintained in the interventions group as phase 3 RCTs are still ongoing. We also added two new anti-IL17 drugs, not yet approved but assessed in phase 3 RCTs (sonelokimab and netakimab). **An extra sensitivity analysis was performed considering only drugs that were EMA approved for plaque psoriasis (see** Sensitivity analysis**).**

For this new update, 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:

- Non-biological treatments
  - FAEs
  - Acitretin
  - Ciclosporin
  - Methotrexate
- Small molecules
  - Apremilast
  - Deucravacitinib
- Biologic treatments
  - Anti-TNF alpha
    - Infliximab
    - Etanercept
    - Adalimumab
    - Certolizumab
  - Anti-IL12/23
    - Ustekinumab
  - Anti-IL17
    - Secukinumab
    - Brodalumab
    - Ixekizumab
    - Bimekizumab
    - Sonelokimab
    - Netakimab
  - Anti-IL23
    - Tildrakizumab
    - Guselkumab
    - Risankizumab

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).

In the Data collection and analysis and Assessment of heterogeneity sections, details on what was planned to assess the transitivity assumption for studies, participants and intervention are available.

Types of outcome measures

Psoriasis is a chronic disease; treatments are symptomatic, often with a return to baseline after discontinuation. The core outcome set for psoriasis clinical trials was defined under the auspices of the International Dermatology Outcome Measures group, whereby the authors conducted a Delphi survey and identified the following 6 domains: (1) skin manifestations of psoriasis (including location), (2) an investigator global assessment, (3) an evaluation of signs and symptoms of both psoriasis and psoriatic arthritis, (4) a patient global assessment of their condition, (5) an assessment of treatment satisfaction, and (6) a measure of health-related quality of life (Callis Duffin 2018).

As a primary outcome, we chose the first domain (skin manifestations of psoriasis). Confronted with a debilitating and a socially and psychologically highly visible disease, a completely 'clear or almost clear' skin was considered to be a 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 events (SAEs) at induction phase. We used the definition of severe adverse events 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 events (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 eight 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 had 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 events, just the proportion of participants with at least one adverse event and at least one serious adverse event 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

For this living systematic review, we revised our search strategies in line with advice from the *Guidance for the production and publication of Cochrane living systematic reviews* (Living Evidence Network 2019). Details of the search strategies used in the earlier published version of this review are available in Sbidian 2020 and Sbidian 2021.

Since September 2020, the Cochrane Skin Information Specialist has searched the following databases monthly up to 5 October 2021:

- the Cochrane Central Register of Controlled Trials (CENTRAL; 2020, Issue 9) in the Cochrane Library using the strategy in Appendix 1;
- MEDLINE (via Ovid) using the strategy in Appendix 2; and
- Embase (via Ovid) using the strategy in Appendix 3.

Trials registers

We (SA and ES for this update) searched the following trials registers up to 5 October 2021 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/); and
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov).

Retractions and errata

We undertook a search to identify retraction statements or errata related to our included studies in MEDLINE and Embase on 7 December 2021. We retrieved no new relevant records.

Searching other resources

References from other studies

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

Unpublished literature

We contact corresponding authors of ongoing studies as we identify them, and ask them to advise us when trial results are available or to share early or unpublished data. We also contact pharmaceutical companies to attempt to identify unpublished and ongoing trials (see Table 2).

Once a year, we manually check additional sources (regulatory agencies and pharmaceutical company trial registries).

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) up to 5 October 2021.

Adverse events

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

Annual review of search methods for this living systematic review

Once a year, we revisit our search methods and, if necessary, update the search strategies by adding or removing intervention terms. This ensures the strategies reflect any terminology changes in the topic area, or changes to search terms available in the databases we search.

Data collection and analysis

Selection of studies

We conducted the selection process through Covidence (Covidence 2021), a web tool allowing dual screening of search results based on titles and abstracts, and then full text by independent review authors. Thus, two review authors (from SA, ES, LLC for this update) 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 listed excluded studies and documented the primary reason for exclusion.

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

Since February 2021, we have used Cochrane's Screen4Me workflow to help assess the results of the search for RCTs. Screen4Me comprises three components, of which we used two: 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 'RCT' or 'not an RCT'); and the RCT classifier (a machine-learning model that distinguishes RCTs from non-RCTs). For more information about Screen4Me and the evaluations that have been done, please go to the Screen4Me webpage on the Cochrane Information Specialist's portal. In addition, more detailed information regarding evaluations of the Screen4Me components can be found in Marshall 2018 and Noel-Storr 2021.

Data extraction and management

Two review authors (SA, ES for this update) 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 5.4 (RevMan) (Revman 2020).

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 SAE after excluding flares of psoriasis/ 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). Two review authors (SA, ES) checked and entered the data into the Review Manager 5 (Revman 2020) 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 (LLC and SA for this update) independently assessed the risk of bias, and one author (ES for this update) 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 judged 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 address 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 pairwise 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 pairwise 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 10.10 of the *Cochrane Handbook for Systematic Reviews of Interventions*) (Deeks 2021). Potential sources of heterogeneity included participants' baseline characteristics (weight, previous systemic treatment or not, 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. To better reassure the plausibility of transitivity, we excluded from the main analysis trials including biological-naïve participants, but assessing efficacy of a biological agent. Indeed, response to biologics is different depending on treatment status (systemic-naïve or not).

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 2021): 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 variance parameter (τ^2) estimated from the network meta-analysis models (Jackson 2014). 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 and each dose 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 substantial 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

Pairwise meta-analysis

We conducted pairwise meta-analyses to synthesise trials comparing one of the treatments against placebo or two treatments against each other. We performed pairwise 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 (NMA) for all outcomes and comparisons, to estimate the relative effects for all possible comparisons between any pair of treatments within a frequentist framework, using random-effects models. 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 focused on confidence intervals as a finding of uncertainty, as 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 pairwise meta-analyses using Review Manager 5.4 (Revman 2020), 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 found new evidence (i.e. studies, data or information) meeting the review inclusion criteria, we extracted the data and assessed 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 review authors contacted trialists to request complete results. Every six months, we incorporated each newly-identified trial in the network. We performed one network for each outcome (PASI-90, SAEs, PASI-75, PGA, QoL and AEs). We re-analysed the data every six months using the standard approaches outlined in this Data synthesis section, as well as the CiNeMa process. We checked the assumptions of the NMA each time we updated the analysis.

Subgroup analysis and investigation of heterogeneity

We had planned to undertake 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 we found no heterogeneity or inconsistency.

Sensitivity analysis

To assess the robustness of our results, we performed the following sensitivity analyses for the two primary outcomes:

- running the analysis at dose-level, considering that each different drug dose is a different intervention;
- excluding trials at high risk of bias;
- excluding trials with a total sample size smaller than 50 randomised participants;
- analysing only the observed participants and assuming that missing participants were missing at random;
- analysing only the studies with a short-term assessment from eight to 16 weeks (to better reassure the plausibility of the transitivity assumption);
- including all trials irrespective of the previous systemic treatments received by the participants;
- analysing only drugs approved by European Medical Agency for plaque psoriasis;
  - Non biological systemic treatments: FAEs, acitretin, ciclosporin, methotrexate;
  - Small molecules: apremilast;
  - Anti-TNF alpha: infliximab, etanercept, adalimumab, certolizumab pegol;
  - Anti-IL12/23: ustekinumab;
  - Anti-IL17: secukinumab, brodalumab, ixekizumab, bimekizumab;
  - Anti-IL23: tildrakizumab, guselkumab, risankizumab.
- lastly, we assessed SAEs after excluding flares of psoriasis.

We undertook this analysis because it has recently been reported that after excluding cases of worsening psoriasis, the risk of occurrence of SAEs is higher in the biologic (especially for anti-TNF agents) arm than in the placebo arm (Afach 2021).

Summary of findings and assessment of the certainty of the evidence

We did not include Summary of findings (SoF) tables because the format of an SoF table does not allow us to present a summary

of comparisons across the different drugs. The SoF tables in the previous versions of the review only focused on the comparisons against placebo.

We assessed the confidence of the evidence estimates for the two primary outcomes (PASI 90 and SAEs), 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 (CINeMA 2017; Salanti 2014). 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).

The confidence in each NMA RR_{AB} between two given drugs A and B was evaluated for six domains. The software required some input in each domain in order to recommend whether there were 'major concerns', 'some concerns' or 'no concerns' for the particular domain.

Thus, threshold values and evaluation rules to be decided were finalised through discussions. After determining these rules, the remaining synthesis of confidence in the evidence can be automatically calculated via CINeMA web app; hence, one review author finally input all the data and got the results.

- Within-trial bias: we estimated it as the weighted average of the overall risk of bias of all the trials contributing information to the estimation of RR_{AB}.
- Reporting bias: also known as 'publication bias'. 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.
- Indirectness: since the included studies matched the clinical question of the review, we had 'no concern' about any of the evaluated RR_{AB}.
- Imprecision: this was rated based on whether the 95% CI of RR was allowing recommendations to be made. We set the margin of equivalent effects (where none of the drugs is favoured) to between RR 0.95 and 1.05. These values were motivated by the fact that assuming 3% response rate (reaching PASI 90) for placebo, then an RR_{AB} of 1.05 indicated a response for drug A higher than those obtained with placebo, which we considered as clinically meaningful. Then, the degree of overlap between the 95% CI of RR_{AB} and the margin of equivalent effects suggests the judgement.
- Heterogeneity: this was evaluated by monitoring the agreement between confidence intervals (CIs) and prediction intervals (PIs). CINeMA judges whether the two intervals and their overlap with the margin of equivalent effects provide similar conclusions.
- Incoherence: this was evaluated by monitoring the level of disagreement between confidence intervals (CIs) of the direct and indirect RR_{AB} and their overlap with the margin of equivalent effects.

After the judgement for all the six domains, we summarised the overall confidence in evidence for each RR between any two drugs into high, moderate, low and very low. Starting with high confidence, we downgraded by one level for each 'major concern' in any of the six domains; then by two-thirds of a level down for 'some concerns' in 'within-study bias'; and one-third of a level down for each 'some concerns' in any of the other five domains. To obtain the final level, we rounded the number of downgrades to their nearest integer.

For each drug, we calculated the percentage of the four levels based on all comparisons including that drug, for efficacy and safety.

RESULTS

Description of studies

Results of the search

Recent monthly Electronic searches of databases and trials registers for this living systematic review, from 15 October 2020 to 5 October 2021 have identified an additional 1078 references to potentially eligible studies. We have also re-examined 57 studies from the previous version of this review identified as ongoing (29 studies reported in 34 references) or awaiting classification (28 reported in 38 references). We have therefore screened a total of 1150 references for this update.

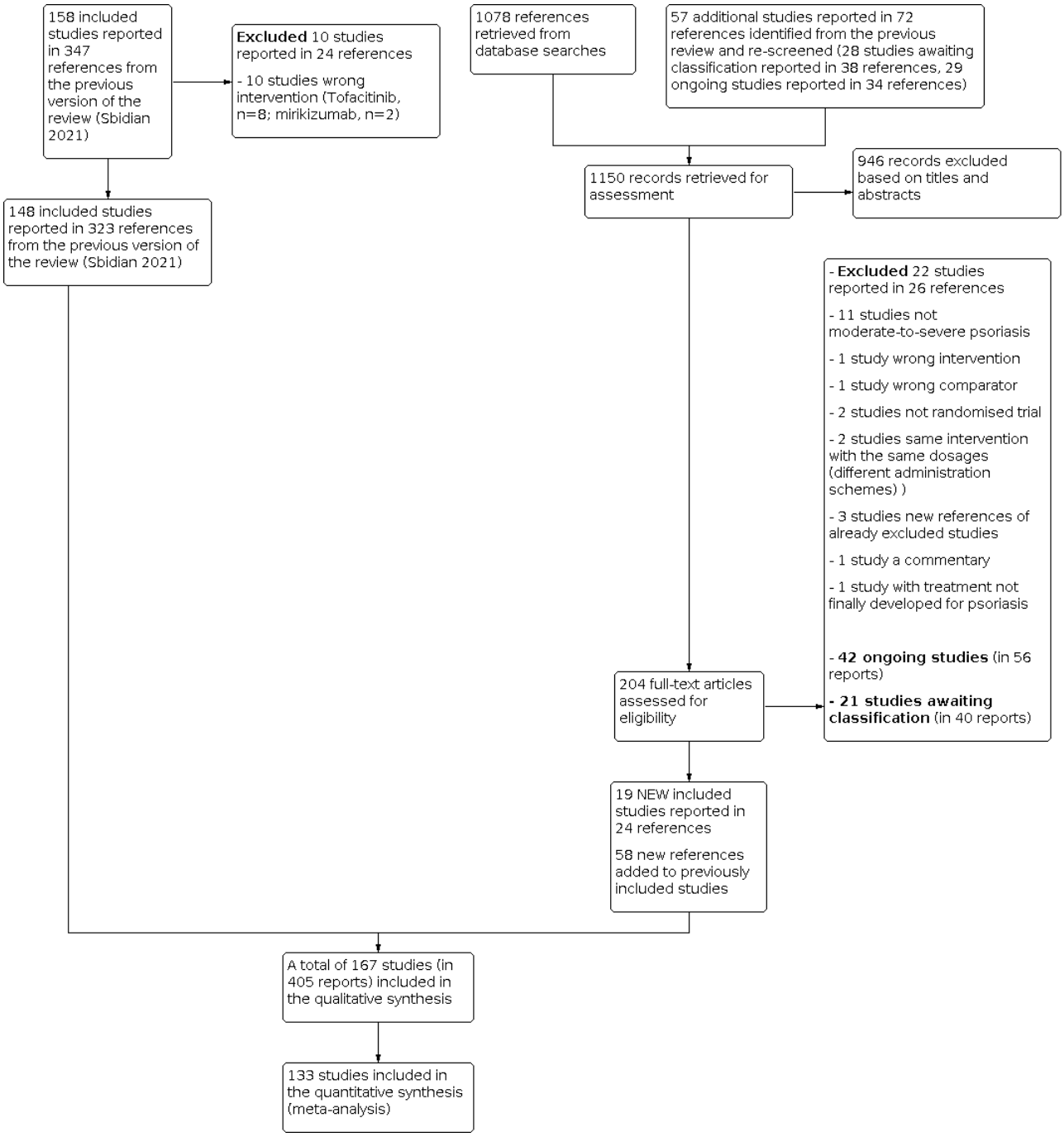
After reviewing the titles and abstracts, we discarded 946 references. We examined the full text of the remaining 204 references. Twenty-two studies (reported in 26 references) did not meet the inclusion criteria and were excluded (see Characteristics of excluded studies). This increased the total number of excluded studies across all versions of this review to 443. Twenty-one trials (reported in 40 references) were identified as studies awaiting classification (see Characteristics of studies awaiting classification). We identified 42 studies (reported in 56 references) as ongoing (see Characteristics of ongoing studies). We identified 19 new included studies (reported in 24 references) for this update. We also identified 58 references which related to studies previously included in this review.

We undertook a reassessment of included studies from the earlier version of this review, and 10 of these (reported in 24 references) are now excluded because the interventions no longer meet the inclusion criteria for the review (wrong intervention: tofacitinib and mirikizumab).

In total, we have 167 studies reported in 405 references.

For a further summary of our screening process, see the study flow diagram (Figure 1).

Figure 1. Study flow diagram



Included studies

Trial design

All trials used a parallel-group design. The mean sample size was 353 (range: 10 to 1881). In all, 140 trials were multicentric (2 to 231 centres) and 19 were single-centre trials (Akcali 2014; Al-Hamamy 2014; Asawanonda 2006; Chaudhari 2001; Chladek 2005; Dogra 2012; Dogra 2013; Dubertret 1989; Ellis 1991; Gisondi 2008; Gurel 2015; Hunter 1963; Ikonomidis 2017; Khatri 2016; Mahajan 2010; Shehzad 2004; Singh 2021; Van Bezooijen 2016; VIP-U Trial 2020); for eight trials, single-centre or multicentric status was not clear (Caproni 2009; Engst 1994; Goldfarb 1988; Olsen 1989; Rathipriyadharshini 2020; Ye 2020; Yilmaz 2002; Yu 2019). Most of the trials recruited participants from a hospital setting, but some also from physicians' offices. The trials took place worldwide (n = 68, 41%), in Europe (n = 35, 21%), in North America (n = 28, 17%), in Asia (n = 30, 18%), or in the Middle East (n = 2, 1.2%). The location was not stated for four trials (Caproni 2009; Engst 1994; Goldfarb 1988; Olsen 1989).

In total, 79 trials out of 167 were multi-arm; 64 multi-arm trials assessed the same experimental drug at multiple dose levels; 28 assessed at least two different drugs; 13 assessed both the same

experimental drug at multiple dose levels and different drugs. In total, nine trials assessed biosimilars versus original drugs for adalimumab (ADACCESS 2018; AURIEL-PsO 2020; CALYPSO 2018; NCT02581345; Papp 2017a; PsOsim 2017; VOLTAIRE-PSO 2021) and etanercept (EGALITY 2017; NCT02134210 RaPsOdy).

In total, 18 trials (Al-Hamamy 2014; Asawanonda 2006; Bissonnette 2013; Gottlieb 2012; Gurel 2015; Liu 2020; Lowe 1991; Mahajan 2010; Ruzicka 1990; Saurat 1988; Shehzad 2004; Singh 2021; Sommerburg 1993; Tanew 1991; Van Bezooijen 2016; Ye 2020; Yilmaz 2002; Yu 2019) 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 includes 167 trials (19 new trials for the updated review: AlMutairi 2021; BE RADIANT 2021; BE READY 2021; BE SURE 2021; BE VIVID 2021; Blauvelt 2021a; CALYPSO 2018; NCT02762994; NCT03364309; NCT03421197; NCT03504852; NCT03535194; NCT03589885 MATURE; Papp 2021; PLANETA 2021; Rathipriyadharshini 2020; Seo 2020; Singh 2021; Ye 2020), with a total of 58,912 randomised participants. We summarised the characteristics of the participants in the Characteristics of included studies. The participants were reported to be between 27 and 56.5 years old, with an overall mean age of 44.5; there were more men (39,591) than women (18,814). Age and gender were unreported for, respectively, 1841 and 507 participants (15 and 9 studies). The overall mean weight was 85.4 kg (range: 59 to 100.5 kg), and the overall mean Psoriasis Area and Severity Index (PASI) score at baseline was 20.4 (range: 9.5 to 39). The duration of psoriasis was 16.5 years (range 4.5 to 21.5).

Characteristics of the comparisons

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

Intervention versus placebo: 96 trials compared systemic treatments with placebo

- Twenty-five trials compared non-biological systemic treatments versus placebo
  - Acitretin (n = 10) (Goldfarb 1988; Gurel 2015; Lowe 1991; Olsen 1989; Ruzicka 1990; Saurat 1988; Sommerburg 1993; Tanew 1991; Yilmaz 2002; Ye 2020)
  - Fumaric acid esters (FAEs) (n = 4) (BRIDGE 2017; NCT03421197; Nugteren-Huying 1990; Van Bezooijen 2016)
  - Ciclosporin (n = 3) (Ellis 1991; Meffert 1997; Singh 2021)
  - Methotrexate (n = 8) (Al-Hamamy 2014; Asawanonda 2006; Gottlieb 2012; Hunter 1963; Liu 2020; Mahajan 2010; METOP 2017; Shehzad 2004)
- Seven trials compared small molecule treatments versus placebo
  - Apremilast (n = 6) (ESTEEM-1 2015; ESTEEM-2 2015; Ohtsuki 2017; Papp 2012c; Papp 2013b; STYLE 2020)
  - Oral tyrosine kinase 2 (TYK2) inhibitor (deucravacitinib) (n = 1) (Papp 2018)
- Sixty-four trials compared biological treatments versus placebo
  - Anti-TNF alpha
    - Etanercept (n = 9) (Bachelez 2015; 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; REVEAL 2008; VIP Trial 2018)
    - Infliximab (n = 6) (Chaudhari 2001; EXPRESS 2005; EXPRESS-II 2007; Gottlieb 2004a; Torii 2010; Yang 2012)
    - Certolizumab (n = 4) (CIMPASI-1 2018; CIMPASI-2 2018; Reich 2012a; Umezawa 2021)
  - Anti-IL12/23
    - Ustekinumab (n = 7) (Igarashi 2012; Krueger 2007; LOTUS 2013; PEARL 2011; PHOENIX-1 2008; PHOENIX-2 2008; VIP-U Trial 2020)
  - Anti-IL17
    - Secukinumab (n = 13) (ALLURE 2021; Cai 2020; ERASURE 2014; FEATURE 2015; JUNCTURE 2015; NCT03055494 ObePso-S; NCT03535194; NCT03589885 MATURE; Papp 2013a; Reich 2015; Rich 2013; TRANSFIGURE 2016; VIP-S trial 2020)
    - Ixekizumab (n = 3) (Leonardi 2012; NCT03364309; UNCOVER-1 2016)
    - Brodalumab (n = 4) (AMAGINE-1 2016; Nakagawa 2016; Papp 2012a; Seo 2020)
    - Bimekizumab (n = 2) (BE ABLE 1 2018; BE READY 2021)
    - Netakimab (n = 2) (NCT02762994; PLANETA 2021)
  - Anti-IL23
    - Guselkumab (n = 2) (Ohtsuki 2018; ORION 2020)
    - Tildrakizumab (n = 2) (Papp 2015; ReSURFACE-1 2017)
    - Risankizumab (n = 3) (Blauvelt 2021a; IMMhance 2020; SustaIMM 2019)

Intervention versus active comparators: 52 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 2011)
- Methotrexate versus apremilast (n = 1) (Rathipriyadharshini 2020)
- Acitretin versus etanercept (n = 4) (Caproni 2009; Gisondi 2008; Lee 2016; Yu 2019)
- FAEs versus secukinumab (n = 1) (PRIME 2017)
- FAEs versus guselkumab (n = 1) (POLARIS 2020)
- FAEs versus risankizumab (n = 1) (Thaci 2021)
- FAEs versus Brodalumab (n = 1) (CHANGE 2021)
- Etanercept versus etanercept (n = 5) (EGALITY 2017; NCT02134210 RaPsOdy; Ortonne 2013; PRESTA 2010; PRISTINE 2013)
- Etanercept versus infliximab (n = 1) (PIECE 2016)
- Etanercept versus ustekinumab (n = 1) (ACCEPT 2010)

- Adalimumab versus adalimumab (n = 7) (ADACCESS 2018; AURIEL-PsO 2020; CALYPSO 2018; NCT02581345; Papp 2017a; PsOsim 2017; VOLTAIRE-PSO 2021)
- Secukinumab versus secukinumab (n = 3) (NCT03504852; SCULPTURE 2015; SIGNATURE 2019)
- Secukinumab versus ustekinumab (n = 2) (CLARITY 2018; CLEAR 2015)
- Secukinumab versus guselkumab (n = 1) (ECLIPSE 2019)
- Ixekizumab versus ixekizumab (n = 2) (IXORA-P 2018; Khatri 2016)
- Ixekizumab versus ustekinumab (n = 1) (IXORA-S 2017)
- Ixekizumab versus guselkumab (n = 1) (IXORA-R 2020)
- Ixekizumab versus secukinumab (n = 1) (AlMutairi 2021)
- Risankizumab versus adalimumab (n = 1) (IMMvent 2019)
- Risankizumab versus ustekinumab (n = 1) (Papp 2017b)
- Risankizumab versus secukinumab (n = 1) (IMMerge 2021)
- Bimekizumab versus secukinumab (n = 1) (BE RADIANT 2021)
- Bimekizumab versus adalimumab (n = 1) (BE SURE 2021)

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

19 trials compared systemic treatments with systemic treatments and placebo.

- Methotrexate versus adalimumab versus placebo (n = 1) (CHAMPION 2008)
- Etanercept versus ixekizumab versus placebo (n = 2) (UNCOVER-2 2015; UNCOVER-3 2015)
- Etanercept versus secukinumab versus placebo (n = 1) (FIXTURE 2014)
- Etanercept versus apremilast versus placebo (n = 1) (LIBERATE 2017)
- Guselkumab versus adalimumab versus placebo (n = 3) (Gordon X-PLORE 2015; VOYAGE-1 2016; VOYAGE-2 2017)
- Brodalumab versus ustekinumab versus placebo (n = 2) (AMAGINE-2 2015; AMAGINE-3 2015)
- Certolizumab versus etanercept versus placebo (n = 1) (CIMPACT 2018)
- Ustekinumab versus etanercept versus ciclosporin (n = 1) (Ikonomidis 2017)
- Tildrakizumab versus etanercept versus placebo (n = 1) (ReSURFACE-2 2017)
- Risankizumab versus ustekinumab versus placebo (n = 2) (UltIMMa-1 2018; UltIMMa-2 2018)
- Ixekizumab versus Methotrexate versus FAEs (n = 1) (Reich 2020)
- Adalimumab versus secukinumab versus placebo (n = 1) (CARIMA 2019)
- Bimekizumab versus ustekinumab versus placebo (n = 1) (BE VIVID 2021)
- Sonelokimab versus secukinumab versus placebo (n = 1) (Papp 2021)

In total, the dataset consisted of 167 studies, which provided information on 297 direct comparisons between 36 different drug dosages, 20 different drugs, six different drug classes, and placebo. For the sensitivity analyses, the different drug doses were divided into approved dosages versus other dosages:

- 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;
- 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;
- bimekizumab, S/C, 320 mg (2 x 160 mg injections) at week 0, 4, 8, 12, 16 and every 8 weeks thereafter, or other dosages.

FAEs (taken orally), deucravacitinib (taken orally), ustekinumab (S/C 45 mg or 90 mg according to the weight), sonelokimab (S/C) and netakimab (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 (less than 24 weeks), out of the 167 trials, 135 reported PASI 90, 125 reported on Physician Global Assessment (PGA) 0/1, 141 reported PASI 75, and 74 trials reported assessment of change in quality of life. Ninety-four studies used the dermatology-specific instrument Dermatology Life Quality Index (DLQI); seven studies used other specific skin instruments (Skindex,PSI, EQ-5D5L, MGH-SFQand 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), 17 trials reported PASI 90 at one year (BE RADIANT 2021; BE VIVID 2021; CLARITY 2018; CLEAR 2015; ECLIPSE 2019; IMMerge 2021; IXORA-P 2018; IXORA-S 2017; JUNCTURE 2015; NCT02134210 RaPsOdy; NCT03055494 ObePso-S; Ohtsuki 2017; Ohtsuki 2018; SustaIMM 2019; UltIMMa-1 2018; UltIMMa-2 2018; VOYAGE-1 2016) and 15 reported PASI 75 at one year (BE RADIANT 2021; CLARITY 2018; CLEAR 2015; ECLIPSE 2019; IMMerge 2021; IXORA-P 2018; IXORA-S 2017; JUNCTURE 2015; NCT02134210 RaPsOdy; Ohtsuki 2017; Ohtsuki 2018; SustaIMM 2019; UltIMMa-1 2018; UltIMMa-2 2018; VOYAGE-1 2016).

Out of 167 trials, 126 reported the number of participants with adverse events (different from the number of adverse events), and 138 reported the number of serious adverse events.

These outcomes were evaluated between 8 and 24 weeks: eight weeks (six studies), 10 weeks (seven studies), 12 weeks (77 studies), 13 weeks (two studies), 15 weeks (one study), 16 weeks (50 studies), 24 weeks (18 studies) and 26 weeks (one study). 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 (IXORA-P 2018).

Funding

In all, 137 studies declared a source of funding: 127 studies declared a pharmaceutical company funding, 10 studies declared a unique institutional funding (Chladek 2005; Flytström 2008; Heydendael 2003; Ikonomidis 2017; Liu 2020; PIECE 2016; Reich 2020; VIP Trial 2018; VIP-U Trial 2020; Yu 2019), six studies had no funding source (Akcali 2014; AlMutairi 2021; Asawanonda 2006; Fallah Arani 2011; Gurel 2015; Singh 2021), and 24 studies did not report the source of funding (Al-Hamamy 2014; Caproni 2009; Dogra 2012; Dogra 2013; Dubertret 1989; Engst 1994; Gisondi 2008; Goldfarb 1988; Hunter 1963; Laburte 1994; Mahajan 2010; Meffert 1997; Nugteren-Huying 1990; Piskin 2003; Rathipriyadharshini 2020; Ruzicka 1990; Sandhu 2003; Saurat 1988; Shehzad 2004; Sommerburg 1993; Torii 2010; Yang 2012; Ye 2020; Yilmaz 2002).

Excluded studies

We have excluded a total of 443 studies in 475 references throughout the course of this review. We detailed all the reasons for exclusion in Characteristics of excluded studies and our study flow diagram at Figure 1.

For this update:

- We excluded 10 previously included studies (total of 24 references) from the previous review because the interventions no longer meet the inclusion criteria for the review: mirikizumab (development of the drug for psoriasis stopped, NCT03482011; Reich 2019) and tofacitinib (not approved for psoriasis, Asahina 2016; Bissonnette 2015; Jin 2017; Krueger 2016a; OPT Pivotal-1 2015; OPT Pivotal-2 2015; Papp 2012b; Zhang 2017).

- We excluded 22 studies (reported in 26 references). The reasons for exclusion were: in 11 studies, the participants did not present with moderate-to-severe psoriasis, two studies were not a randomised trial, two studies assessed the same intervention with the same dosages (different administration schemes), one study was a commentary, one study had a wrong intervention, one study had a wrong comparator, one study had a treatment not finally developed for psoriasis, and three studies were new references of already excluded studies.

From the previous reviews:

- We had excluded 411 full-text reports from the previous review. The main reasons for exclusion were that the participants did not present with moderate-to-severe psoriasis (n = 35), or that another intervention was assessed (n = 116). We excluded 46 reports because they were not trials, three did not include plaque-type psoriasis, 37 were open-label extension studies restricted to good responders; and we excluded 174 for other reasons.

- In an earlier version of this review (Sbidian 2017), we excluded a number of studies having reviewed the full text, but without creating Characteristics of excluded studies tables (n = 203). The main reason for exclusion of these studies was that the participants did not present with moderate-to-severe psoriasis.

In this update, for ten 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);
- VIP Trial 2018: 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);
- Bachelez 2015: tofacitinib versus etanercept versus placebo (tofacitinib arm was not included);
- NCT03535194: mirikizumab versus placebo versus secukinumab (mirikizumab arm 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 or in the ciclosporin < 3 mg/day group for the subgroup meta-analysis.

Studies awaiting classification

We classified 21 trials reported in 40 references as studies awaiting classification. More details are available in Studies awaiting classification and Table 2. Most of the awaiting studies compared a biological treatment versus another biological treatment or versus non-biological treatment or versus placebo (n = 12). Two studies assessed a small molecule, and seven assessed non-biological systemic treatments. Among the 21 trials, eight trials were classified as unpublished (CTRI/2016/10/007345; DRKS00000716; EUCTR2010-020168-39-DE; NCT01088165; NCT01558310; NCT02701205; NCT02714322; NCT02829424).

Ongoing studies

We classified 42 trials (reported in 56 references) as ongoing studies. More details are available in Characteristics of ongoing studies and Table 2. Most of the ongoing studies compared a biological treatment versus another biological treatment or versus non-biological treatment or versus placebo (n = 36). Six ongoing studies assessed apremilast or oral tyrosine kinase 2 (TYK2) inhibitor or phosphodiesterase type 4 (PDE4) inhibitor.

Risk of bias in included studies

Figure 2 and Figure 3 summarise risk of bias assessments. For overall risk of bias across studies, 87 (52%) trials were at low risk of bias. We categorised a third of the studies (57/167, 34%) as being at high risk of bias. We categorised the remaining 23 studies as being at unclear risk of bias. 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

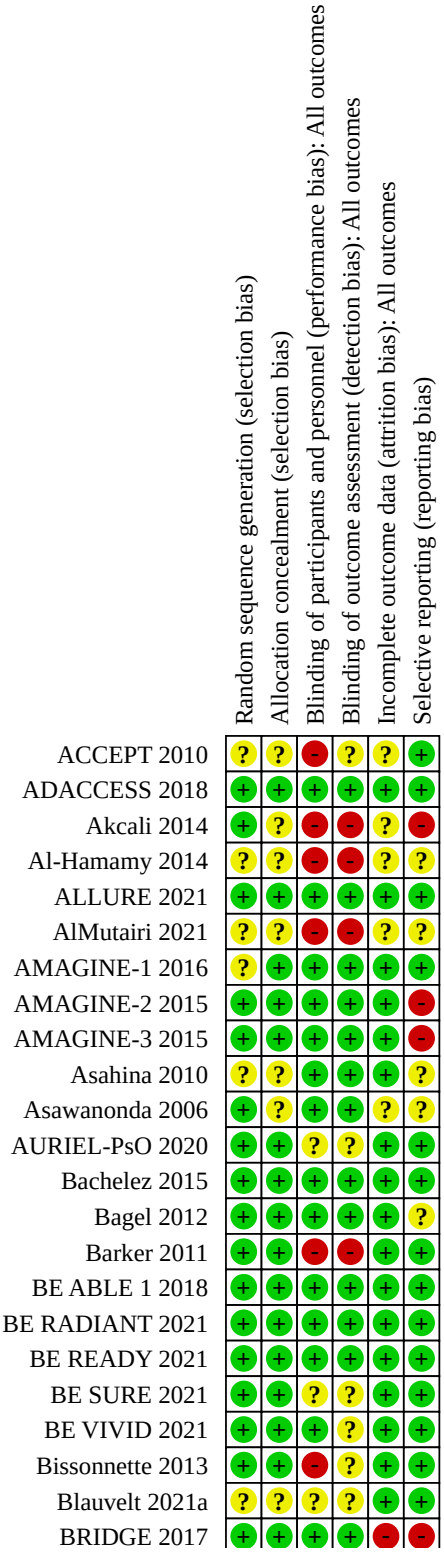
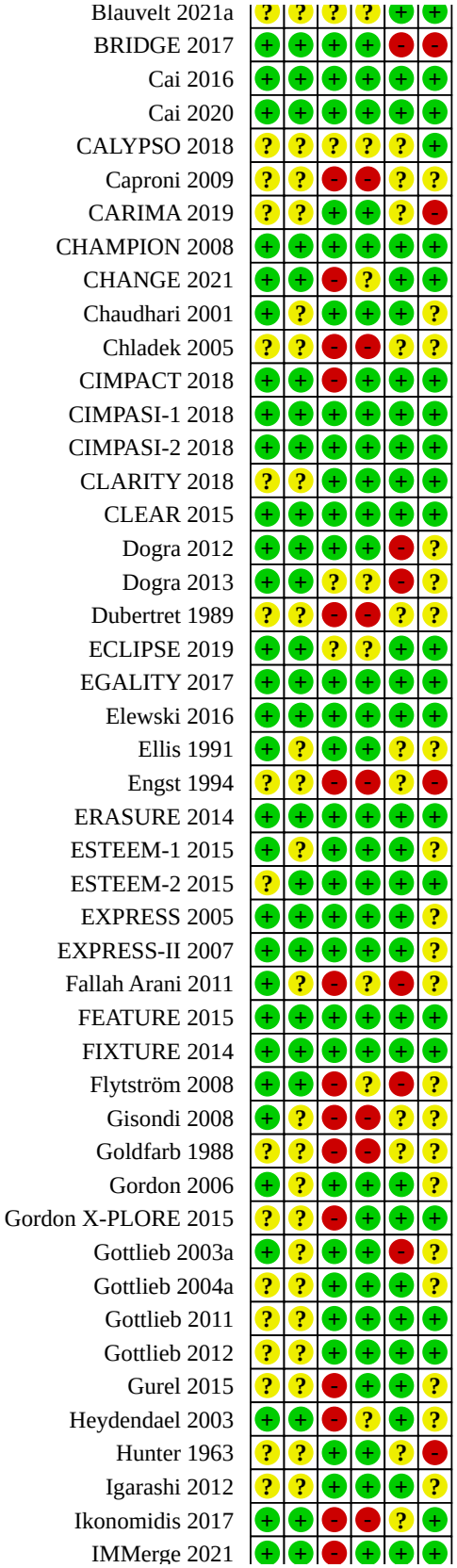


Figure 2. (Continued)



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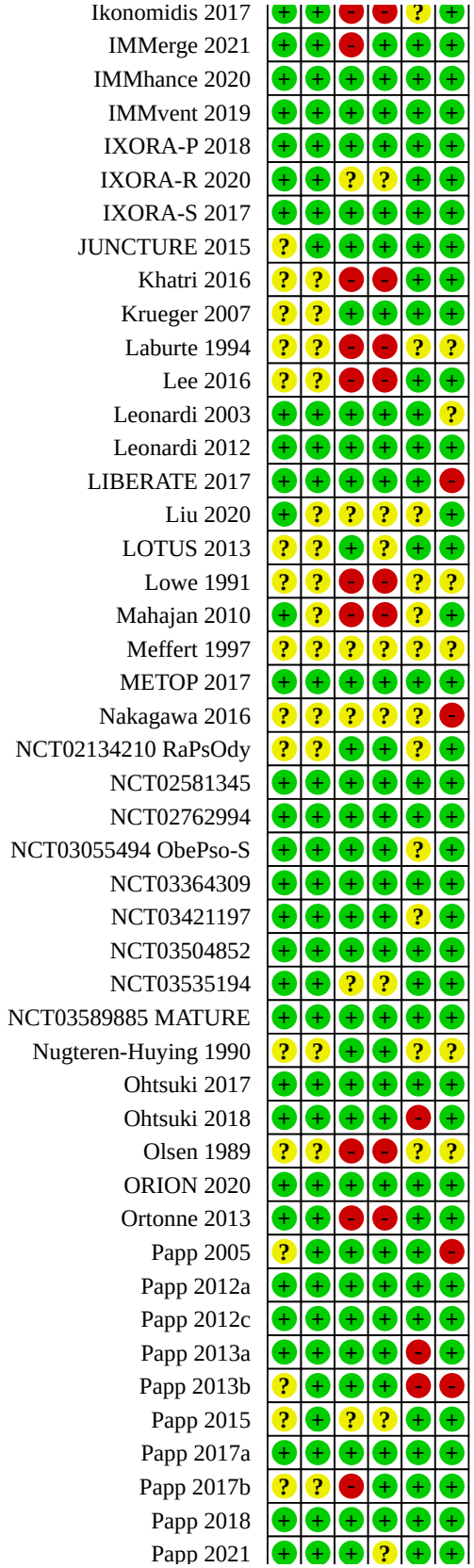

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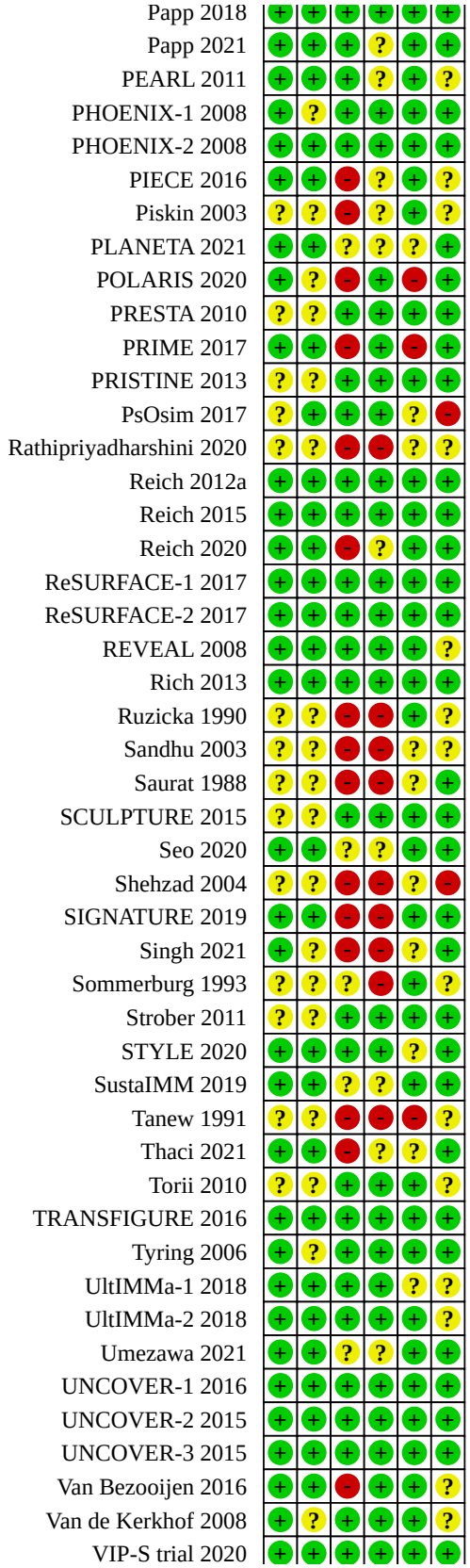

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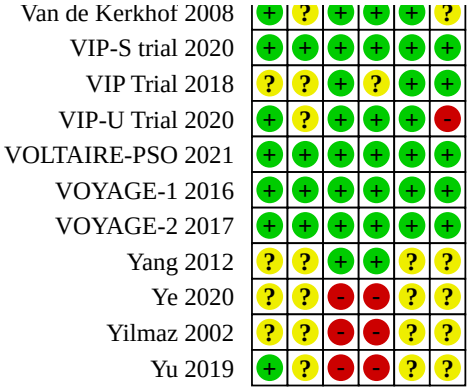
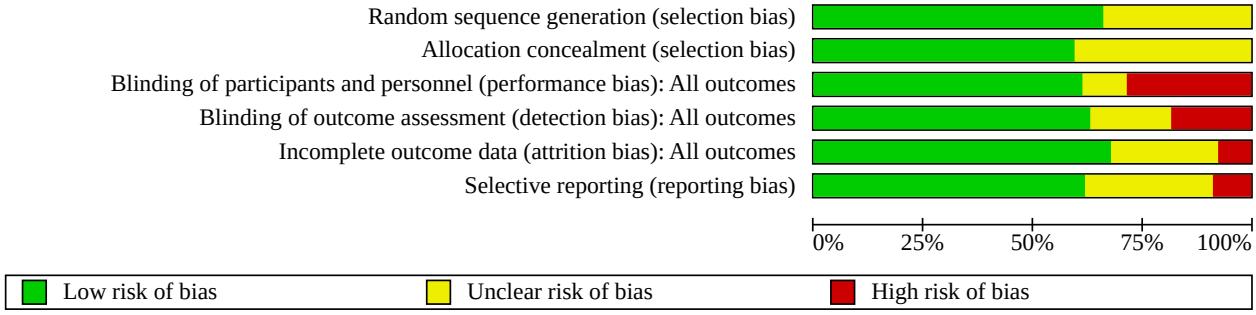


Figure 3. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies



Allocation

In 56 trials, the method of sequence generation was not described at all, or was at best unclear. The remaining studies (n = 111) described the method used to generate the allocation sequence in sufficient detail, and we therefore judged this domain as low risk of bias for these studies. For allocation concealment, most studies (n = 100) received a judgement of low risk of bias. We considered the risk unclear for the 67 remaining trials because of the absence of reporting of the method used to guarantee concealment.

Blinding

Blinding of participants and personnel was achieved in 103 studies, whereas 47 studies were at high risk of performance bias. The remaining 17 studies were at unclear risk of performance bias. Blinding of outcome assessment was reported clearly in only 106 of the 167 included studies, whereas 30 studies were at high risk of detection bias. The risk of detection bias was unclear in the remaining 31 studies.

Incomplete outcome data

In more than two-thirds of the trials (114/167), 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 12 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 41 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 14 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; AMAGINE-2 2015; AMAGINE-3 2015; BRIDGE 2017; CARIMA 2019; Engst 1994; Hunter 1963; LIBERATE 2017; Nakagawa 2016; Papp 2005; Papp 2013b; PsOsim 2017; Shehzad 2004; VIP-U Trial 2020). In all, we considered 104 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 = 49), 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 address 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

Nine 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; Rathipriyadharshini 2020; Shehzad 2004; see Table 2). The main reason we could not use their data was that these studies addressed none of our outcomes.

Eighteen studies, involving 1957 participants (3.3% 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; Liu 2020; Lowe 1991; Mahajan 2010; Ruzicka 1990; Saurat 1988; Shehzad 2004; Singh 2021; Sommerburg 1993; Tanew 1991; Van Bezooijen 2016; Ye 2020; Yilmaz 2002; Yu 2019).

Nine trials assessed biosimilars versus original drugs for adalimumab (ADACCESS 2018; AURIEL-PsO 2020; CALYPSO 2018; NCT02581345; Papp 2017a; PsOsim 2017; VOLTAIRE-PSO 2021) and etanercept (EGALITY 2017; NCT02134210 RaPsOdy). These were non-inferiority trials, assessing the same dosage and same administration schema of biosimilar and original drug.

Lowe 1991 and Shehzad 2004 had two reasons for not being included in the NMA (both no usable data and co-interventions). Thus, in total, 34 studies, involving 6381 participants, were not included in the classical or network meta-analysis (reasons are mentioned above). The interventions of the 34 studies concerned the following:

- acitretin (n = 10) (Akcali 2014; Gurel 2015; Lowe 1991; Olsen 1989; Ruzicka 1990; Saurat 1988; Sommerburg 1993; Tanew 1991; Ye 2020; Yilmaz 2002);
- methotrexate (n = 7) (Asawanonda 2006; Al-Hamamy 2014; Chladek 2005; Gottlieb 2012; Liu 2020; Mahajan 2010; Shehzad 2004);
- ciclosporin (n = 3) (Engst 1994; Piskin 2003; Singh 2021);
- adalimumab (n = 8) (ADACCESS 2018; AURIEL-PsO 2020; Bissonnette 2013; CALYPSO 2018; NCT02581345; Papp 2017a; PsOsim 2017; VOLTAIRE-PSO 2021);
- etanercept (n = 3) (EGALITY 2017; NCT02134210 RaPsOdy; Yu 2019);
- others (n = 3) (Ikonomidis 2017; Rathipriyadharshini 2020; Van Bezooijen 2016).

We included a total of 133 studies, involving 52,531 participants (89% participants of this review), in the classical or network meta-analysis for at least one of the outcomes. We used these total number of studies and participants as a denominator to calculate the proportion of trials and participants used for the quantitative synthesis of each outcome.

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

Ten studies among the 133, involving 2132 participants (3.6% of the participants in this review) included biological-naïve participants when assessing efficacy of a biological agent, and did not contribute further to the results of the main analysis, as we could not assume the plausibility of transitivity. Indeed, response to biologics is different depending on treatment status (systemic-naïve or not). However, these studies were included in the sensitivity analysis (Barker 2011; Caproni 2009; CHAMPION 2008; CHANGE 2021; Gisondi 2008; Lee 2016; POLARIS 2020; PRIME 2017; Reich 2020; Thaci 2021).

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 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. AIL12/23: anti-IL12/23; AIL17: anti-IL17; AIL23: anti-IL23, ATA: anti-TNF alpha; CSA: non-biological 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

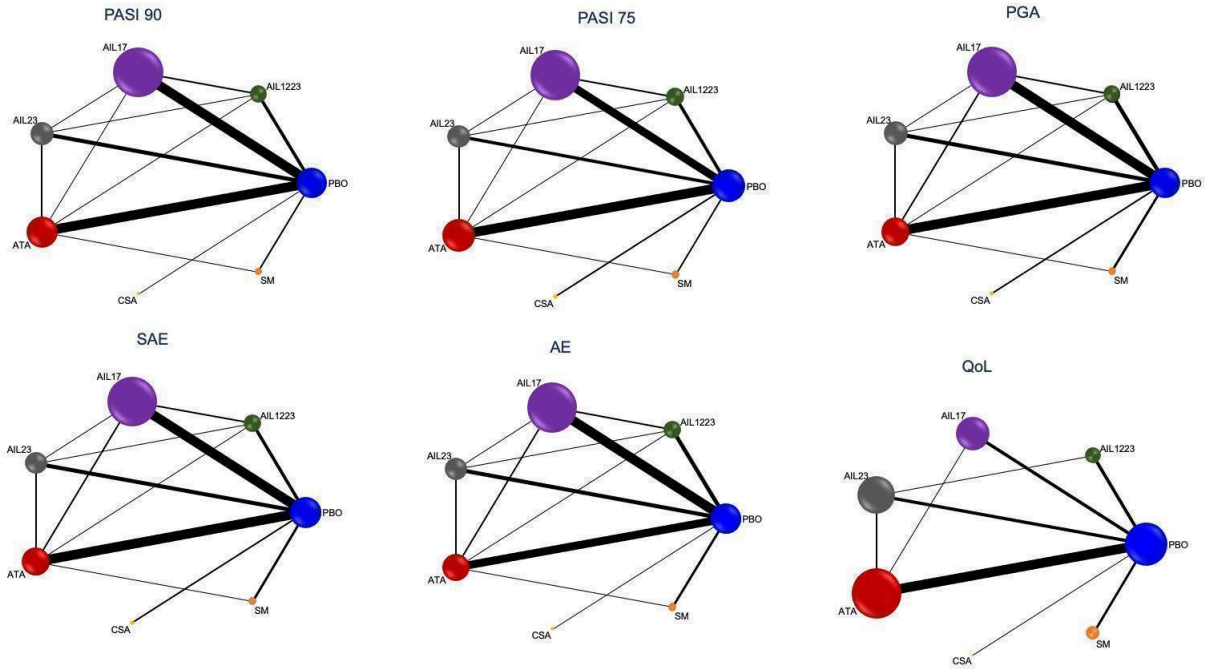


Figure 5. Network plot for all the outcomes at drug level The size of the nodes is proportional to the total number of participants allocated to each intervention and the thickness of the lines proportional to the number of studies evaluating each direct comparison. ACI: acitretin; ADA: adalimumab; APRE: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

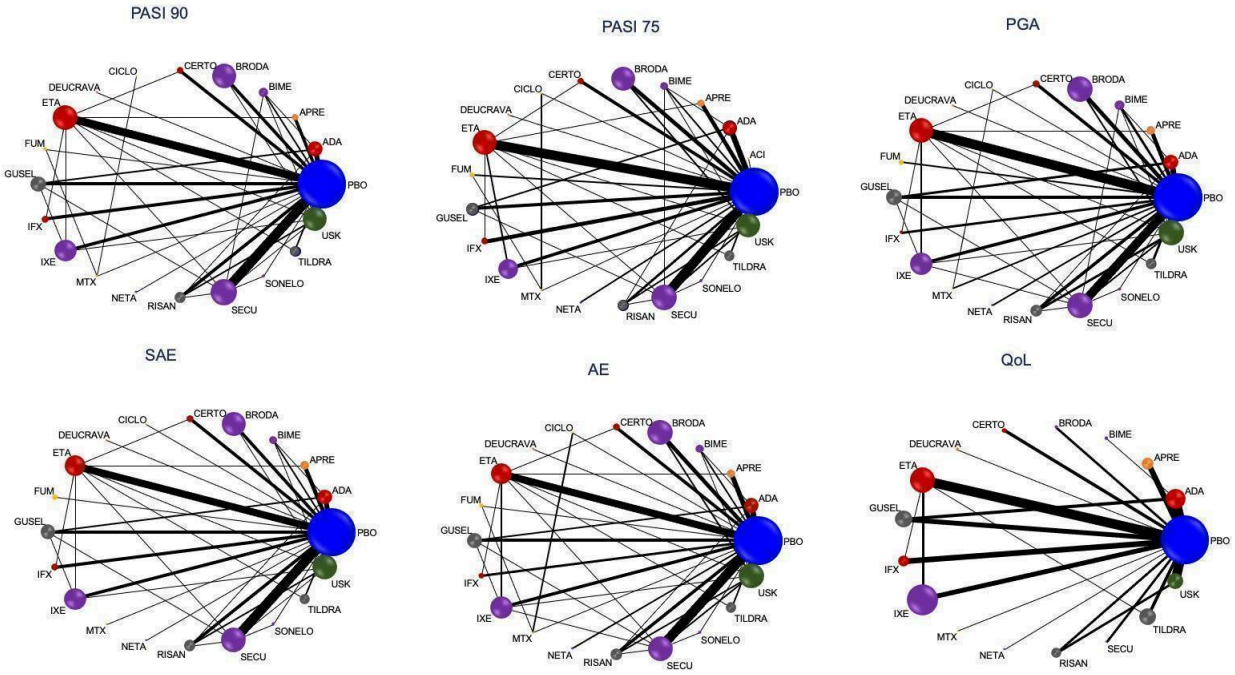


Figure 6 shows the network meta-analysis estimates of all of the outcomes for each comparison at class level.

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; SAE without worsening of psoriasis correspond to SAE after exclusion of flares of psoriasis; AIL12/23: anti-IL12/23; AIL17: anti-IL17; AIL23: anti-IL23, ATA: anti-TNF alpha; CSA: non-biological conventional systemic agents; PBO: placebo; SM: small molecules

SAE

AIL17	1.19 (0.91,1.54)	0.96 (0.70,1.33)	1.04 (0.78,1.38)	1.12 (0.63,2.01)	1.28 (0.58,2.81)	0.95 (0.76,1.20)
1.14 (0.95,1.36)	AIL23	0.81 (0.57,1.16)	0.87 (0.64,1.19)	0.94 (0.52,1.72)	1.08 (0.48,2.40)	0.80 (0.61,1.06)
1.45 (1.23,1.71)	1.27 (1.04,1.56)	AIL1223	1.07 (0.74,1.57)	1.16 (0.62,2.18)	1.33 (0.59,3.02)	0.99 (0.71,1.38)
1.95 (1.64,2.33)	1.72 (1.44,2.05)	1.35 (1.10,1.66)	ATA	1.08 (0.61,1.94)	1.24 (0.56,2.73)	0.92 (0.71,1.19)
2.96 (1.63,5.38)	2.60 (1.42,4.74)	2.04 (1.11,3.74)	1.51 (0.84,2.72)	SM	1.14 (0.45,2.88)	0.85 (0.50,1.45)
5.74 (2.40,13.73)	5.04 (2.10,12.13)	3.95 (1.64,9.53)	2.93 (1.22,7.03)	1.94 (0.69,5.45)	CSA	0.74 (0.35,1.57)
26.78 (22.07,32.49)	23.53 (19.00,29.15)	18.47 (14.82,23.02)	13.70 (11.22,16.73)	9.06 (5.06,16.23)	4.67 (1.99,10.94)	PBO

PASI90

Adverse events

AIL17	1.12 (1.05,1.19)	1.06 (1.00,1.12)	1.06 (1.01,1.12)	0.91 (0.82,1.01)	0.99 (0.86,1.15)	1.14 (1.09,1.19)
1.08 (0.97,1.20)	AIL23	0.94 (0.88,1.02)	0.95 (0.89,1.01)	0.81 (0.72,0.90)	0.89 (0.76,1.03)	1.02 (0.96,1.08)
1.18 (1.08,1.29)	1.09 (0.98,1.22)	AIL1223	1.00 (0.94,1.07)	0.86 (0.77,0.96)	0.94 (0.80,1.09)	1.08 (1.02,1.14)
1.47 (1.33,1.62)	1.36 (1.23,1.51)	1.24 (1.11,1.39)	ATA	0.85 (0.77,0.95)	0.94 (0.80,1.09)	1.07 (1.03,1.12)
2.67 (2.04,3.51)	2.48 (1.89,3.27)	2.27 (1.72,2.99)	1.82 (1.40,2.38)	SM	1.10 (0.92,1.30)	1.26 (1.15,1.39)
5.22 (3.72,7.32)	4.85 (3.44,6.83)	4.43 (3.15,6.23)	3.56 (2.54,4.99)	1.95 (1.29,2.94)	CSA	1.15 (1.00,1.33)
13.43 (12.00,15.03)	12.48 (11.03,14.11)	11.39 (10.08,12.88)	9.15 (8.20,10.21)	5.02 (3.89,6.48)	2.57 (1.87,3.54)	PBO

PASI75

Quality of life

AIL17	0.04 (-0.28,0.35)	-0.04 (-0.39,0.31)	-0.29 (-0.54,-0.03)	-0.94 (-1.32,-0.56)	-0.32 (-1.17,0.53)	-1.37 (-1.60,-1.14)
1.19 (1.01,1.41)	AIL23	-0.07 (-0.39,0.24)	-0.32 (-0.57,-0.07)	-0.97 (-1.35,-0.60)	-0.35 (-1.20,0.49)	-1.41 (-1.63,-1.18)
1.36 (1.17,1.60)	1.14 (0.95,1.37)	AIL1223	-0.25 (-0.54,0.05)	-0.90 (-1.29,-0.50)	-0.28 (-1.13,0.58)	-1.33 (-1.59,-1.07)
1.69 (1.44,1.99)	1.42 (1.21,1.67)	1.24 (1.03,1.49)	ATA	-0.65 (-0.98,-0.32)	-0.03 (-0.86,0.80)	-1.08 (-1.23,-0.94)
3.58 (2.54,5.03)	3.00 (2.12,4.23)	2.62 (1.85,3.72)	2.11 (1.51,2.94)	SM	0.62 (-0.25,1.49)	-0.43 (-0.73,-0.14)
5.56 (3.56,8.68)	4.66 (2.97,7.32)	4.08 (2.59,6.41)	3.28 (2.10,5.12)	1.55 (0.92,2.62)	CSA	-1.05 (-1.87,-0.24)
14.41 (12.32,16.85)	12.07 (10.22,14.25)	10.56 (8.90,12.54)	8.50 (7.31,9.88)	4.03 (2.95,5.49)	2.59 (1.70,3.95)	PBO

PGA

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

Figure 7. Relative effects of the intervention as estimated from the network meta-analysis model for Psoriasis Area and Severity Index (PASI) 90 and serious adverse events (SAEs) 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 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. Certainty of evidence was assessed for each comparison using CINeMA and classified in high (highlighted in green), moderate (in blue), low (in yellow) and very-low (in red). Significant results are highlighted in bold. ACI: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; DEUCRAVA: deucravacitinib; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; NETA: netakimab; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; SONELO: sonelokimab; TILDRA: tildrakizumab; USK: ustekinumab

Serious adverse events

Number of participants (studies)	1693 (6)	1730 (4)	5775 (7)	2930 (8)	8459 (20)	313 (1)	4579 (5)	4467 (7)	11342 (16)	2217 (3)	267 (1)	5440 (11)	1323 (5)	8464 (14)	127 (1)	120 (1)	2676 (7)	213 (1)	1130 (2)	-	
1693 (6)	IFX	2.26 (0.81,6.33)	1.30 (0.57,2.97)	1.62 (0.69,3.76)	1.11 (0.50,2.45)	0.95 (0.16,5.50)	1.14 (0.47,2.78)	1.31 (0.58,2.95)	1.22 (0.55,2.71)	1.49 (0.52,4.28)	1.94 (0.18,20.45)	1.17 (0.51,2.67)	1.69 (0.57,5.01)	1.48 (0.66,3.33)	0.21 (0.01,4.01)	**14.82 (1.5,143.4)**	1.38 (0.56,3.44)	1.49 (0.06,38.93)	1.35 (0.45,4.07)	1.18 (0.57,2.43)	19 per 1000
2473 (5)	1.66 (0.68,4.03)	BIME	0.58 (0.25,1.31)	0.72 (0.31,1.63)	0.49 (0.23,1.07)	0.42 (0.07,2.44)	0.51 (0.21,1.22)	0.58 (0.26,1.29)	0.54 (0.25,1.15)	0.66 (0.23,1.91)	0.86 (0.08,9.07)	0.52 (0.24,1.11)	0.75 (0.25,2.23)	0.66 (0.29,1.49)	0.09 (0.00,1.78)	6.56 (0.68,63.61)	0.61 (0.24,1.53)	0.66 (0.03,17.25)	0.60 (0.20,1.81)	0.52 (0.25,1.09)	3 per 1000
5775 (7)	1.66 (0.68,4.03)	1.00 (0.91,1.11)	IXE	1.24 (0.70,2.20)	0.85 (0.53,1.36)	0.73 (0.14,3.79)	0.88 (0.46,1.68)	1.00 (0.64,1.58)	0.94 (0.58,1.53)	1.14 (0.49,2.67)	1.49 (0.15,14.54)	0.90 (0.53,1.54)	1.30 (0.52,3.21)	1.14 (0.71,1.82)	0.16 (0.01,2.90)	**11.39 (1.3,101.6)**	1.06 (0.54,2.10)	1.14 (0.05,28.29)	1.04 (0.41,2.62)	0.91 (0.61,1.36)	16 per 1000
2930 (8)	1.75 (0.72,4.24)	1.05 (0.95,1.17)	1.05 (0.94,1.18)	RISAN	0.69 (0.42,1.11)	0.59 (0.11,3.07)	0.71 (0.37,1.37)	0.81 (0.47,1.38)	0.76 (0.48,1.20)	0.92 (0.38,2.24)	1.20 (0.12,11.78)	0.72 (0.43,1.21)	1.04 (0.41,2.63)	0.92 (0.52,1.62)	0.13 (0.01,2.34)	**9.17 (1.02,82.36)**	0.86 (0.42,1.73)	0.92 (0.04,22.88)	0.84 (0.33,2.14)	0.73 (0.47,1.13)	10 per 1000
9202 (21)	1.91 (0.79,4.63)	**1.15 (1.08,1.23)**	**1.15 (1.06,1.25)**	**1.09 (1.00,1.20)**	SECU	0.86 (0.17,4.31)	1.03 (0.57,1.86)	1.18 (0.82,1.69)	1.10 (0.75,1.61)	1.34 (0.58,3.09)	1.75 (0.18,16.83)	1.06 (0.66,1.69)	1.52 (0.63,3.65)	1.34 (0.83,2.15)	0.19 (0.01,3.36)	**13.35 (1.5,117.6)**	1.25 (0.66,2.36)	1.34 (0.05,32.88)	1.22 (0.50,2.98)	1.06 (0.77,1.47)	19 per 1000
313 (1)	1.96 (0.79,4.89)	1.18 (0.93,1.50)	1.18 (0.93,1.50)	1.12 (0.88,1.43)	1.03 (0.82,1.29)	SONELO	1.20 (0.22,6.46)	1.37 (0.27,7.06)	1.29 (0.25,6.56)	1.56 (0.26,9.27)	2.04 (0.13,32.09)	1.23 (0.24,6.40)	1.78 (0.30,10.71)	1.56 (0.30,8.09)	0.22 (0.01,5.85)	**15.61 (1.1,227.9)**	1.46 (0.27,7.93)	1.57 (0.04,55.24)	1.42 (0.23,8.64)	1.24 (0.25,6.16)	26 per 1000
4579 (5)	2.08 (0.86,5.07)	**1.26 (1.12,1.41)**	**1.25 (1.11,1.42)**	**1.19 (1.05,1.36)**	1.09 (0.98,1.21)	1.06 (0.83,1.36)	BRODA	1.14 (0.61,2.14)	1.07 (0.61,1.87)	1.30 (0.51,3.30)	1.70 (0.17,16.90)	1.02 (0.54,1.95)	1.48 (0.56,3.87)	1.30 (0.68,2.46)	0.18 (0.01,3.35)	**12.95 (1.4,118.3)**	1.21 (0.57,2.58)	1.30 (0.05,32.69)	1.18 (0.44,3.14)	1.03 (0.62,1.73)	18 per 1000
4467 (7)	2.08 (0.86,5.05)	**1.26 (1.16,1.36)**	**1.25 (1.16,1.35)**	**1.19 (1.08,1.32)**	**1.09 (1.02,1.16)**	1.06 (0.84,1.34)	1.00 (0.89,1.12)	GUSEL	0.94 (0.59,1.48)	1.14 (0.48,2.68)	1.49 (0.15,14.44)	0.90 (0.56,1.44)	1.29 (0.53,3.18)	1.14 (0.68,1.89)	0.16 (0.01,2.88)	**11.36 (1.3,101.0)**	1.06 (0.54,2.07)	1.14 (0.05,28.14)	1.03 (0.41,2.59)	0.90 (0.62,1.33)	17 per 1000
11063 (16)	**2.66 (1.09,6.44)**	**1.60 (1.48,1.73)**	**1.60 (1.46,1.74)**	**1.52 (1.38,1.67)**	**1.39 (1.31,1.47)**	**1.35 (1.07,1.71)**	**1.28 (1.17,1.39)**	**1.28 (1.18,1.38)**	USK	1.22 (0.53,2.82)	1.59 (0.16,15.33)	0.96 (0.59,1.56)	1.38 (0.57,3.33)	1.21 (0.75,1.96)	0.17 (0.01,3.06)	**12.14 (1.4,107.1)**	1.13 (0.59,2.16)	1.22 (0.05,29.92)	1.11 (0.45,2.72)	0.97 (0.69,1.36)	15 per 1000
2217 (3)	**2.70 (1.09,6.73)**	**1.63 (1.26,2.10)**	**1.63 (1.27,2.08)**	**1.55 (1.19,2.01)**	**1.41 (1.10,1.81)**	1.38 (0.98,1.93)	**1.30 (1.00,1.69)**	**1.30 (1.01,1.67)**	1.02 (0.79,1.31)	TILDRA	1.31 (0.12,14.02)	0.79 (0.33,1.89)	1.14 (0.37,3.50)	1.00 (0.46,2.18)	0.14 (0.01,2.74)	**9.98 (1.01,98.41)**	0.93 (0.36,2.41)	1.00 (0.04,26.56)	0.91 (0.29,2.85)	0.80 (0.36,1.74)	14 per 1000
267 (1)	3.59 (0.42,30.37)	2.16 (0.31,15.30)	2.16 (0.31,15.26)	2.06 (0.29,14.54)	1.88 (0.27,13.26)	1.83 (0.26,13.10)	1.72 (0.24,12.19)	1.72 (0.24,12.18)	1.35 (0.19,9.55)	1.33 (0.19,9.50)	DEUCRAVA	0.60 (0.06,5.87)	0.87 (0.08,9.43)	0.76 (0.08,7.42)	0.11 (0.00,4.08)	7.63 (0.3,170.4)	0.71 (0.07,7.17)	0.77 (0.02,37.57)	0.70 (0.06,7.59)	0.61 (0.06,5.71)	10 per 1000
5376 (10)	**2.89 (1.19,7.03)**	**1.75 (1.59,1.91)**	**1.74 (1.57,1.93)**	**1.66 (1.50,1.83)**	**1.51 (1.39,1.65)**	**1.48 (1.16,1.88)**	**1.39 (1.22,1.58)**	**1.39 (1.29,1.50)**	1.09 (0.99,1.20)	1.07 (0.83,1.38)	0.81 (0.11,5.70)	ADA	1.44 (0.58,3.56)	1.26 (0.73,2.18)	0.18 (0.01,3.21)	**12.65 (1.4,112.7)**	1.18 (0.60,2.33)	1.27 (0.05,31.39)	1.15 (0.46,2.90)	1.01 (0.68,1.50)	17 per 1000
1323 (5)	**3.77 (1.50,9.53)**	**2.28 (1.69,3.07)**	**2.27 (1.69,3.05)**	**2.16 (1.59,2.93)**	**1.98 (1.47,2.65)**	**1.93 (1.33,2.79)**	**1.81 (1.33,2.47)**	**1.81 (1.35,2.44)**	**1.42 (1.06,1.91)**	1.40 (0.98,1.99)	1.05 (0.15,7.57)	1.30 (0.96,1.77)	CERTO	0.88 (0.36,2.14)	0.12 (0.01,2.43)	8.78 (0.88,87.57)	0.82 (0.31,2.19)	0.88 (0.03,23.55)	0.80 (0.25,2.56)	0.70 (0.31,1.58)	13 per 1000
9759 (16)	**4.71 (1.94,11.44)**	**2.84 (2.50,3.22)**	**2.83 (2.54,3.16)**	**2.70 (2.35,3.10)**	**2.47 (2.20,2.76)**	**2.40 (1.87,3.10)**	**2.26 (1.96,2.61)**	**2.26 (2.01,2.54)**	**1.77 (1.58,1.99)**	**1.74 (1.39,2.18)**	1.31 (0.19,9.29)	**1.63 (1.43,1.86)**	1.25 (0.95,1.65)	ETA	0.14 (0.01,2.54)	**10.00 (1.12,89.10)**	0.93 (0.49,1.80)	1.00 (0.04,24.82)	0.91 (0.36,2.29)	0.80 (0.54,1.18)	15 per 1000
172 (2)	**7.13 (1.08,47.09)**	4.30 (0.80,23.11)	4.29 (0.80,23.05)	4.08 (0.76,21.96)	3.73 (0.69,20.03)	3.64 (0.67,19.82)	3.42 (0.64,18.42)	3.42 (0.64,18.39)	2.68 (0.50,14.42)	2.64 (0.48,14.37)	1.99 (0.15,25.89)	2.46 (0.46,13.24)	1.89 (0.34,10.37)	1.51 (0.28,8.14)	CICLO	**71.47 (2.0,2585.3)**	6.68 (0.4,124.4)	7.17 (0.1,522.0)	6.51 (0.3,129.5)	5.69 (0.3,100.6)	25 per 1000
388 (5)	**7.20 (1.17,44.37)**	4.34 (0.87,21.58)	4.33 (0.87,21.53)	4.12 (0.83,20.51)	3.77 (0.76,18.71)	3.67 (0.73,18.53)	3.46 (0.69,17.21)	3.46 (0.70,17.18)	2.71 (0.55,13.47)	2.66 (0.53,13.43)	2.01 (0.16,24.86)	2.49 (0.50,12.37)	1.91 (0.38,9.70)	1.53 (0.31,7.60)	1.01 (0.61,1.68)	MTX	0.09 (0.01,0.86)	0.10 (0.00,4.68)	0.09 (0.01,0.91)	0.08 (0.01,0.68)	7 per 1000
2113 (5)	**6.53 (2.34,18.19)**	**3.94 (2.29,6.77)**	**3.93 (2.29,6.74)**	**3.74 (2.17,6.45)**	**3.42 (1.99,5.86)**	**3.33 (1.86,5.98)**	**3.14 (1.82,5.41)**	**3.14 (1.83,5.38)**	**2.46 (1.43,4.22)**	**2.42 (1.35,4.31)**	1.82 (0.24,13.73)	**2.26 (1.31,3.88)**	1.73 (0.95,3.15)	1.39 (0.81,2.37)	0.92 (0.16,5.31)	0.91 (0.17,4.88)	APRE	1.07 (0.04,27.19)	0.98 (0.36,2.65)	0.85 (0.49,1.48)	15 per 1000
333 (2)	**11.18 (3.47,35.99)**	**6.74 (3.04,14.92)**	**6.72 (3.04,14.89)**	**6.40 (2.89,14.19)**	**5.85 (2.65,12.93)**	**5.70 (2.50,13.00)**	**5.37 (2.42,11.91)**	**5.37 (2.43,11.87)**	**4.21 (1.90,9.31)**	**4.13 (1.81,9.43)**	3.11 (0.38,25.35)	**3.86 (1.74,8.55)**	**2.96 (1.28,6.85)**	**2.37 (1.07,5.26)**	1.57 (0.25,9.91)	1.55 (0.26,9.14)	1.71 (0.67,4.40)	NETA	0.91 (0.03,24.40)	0.79 (0.03,19.17)	26 per 1000
764 (2)	**11.52 (3.58,37.11)**	**6.95 (3.14,15.39)**	**6.93 (3.13,15.35)**	**6.60 (2.98,14.63)**	**6.03 (2.73,13.33)**	**5.88 (2.58,13.40)**	**5.53 (2.49,12.28)**	**5.53 (2.50,12.24)**	**4.34 (1.96,9.59)**	**4.26 (1.87,9.72)**	3.21 (0.39,26.13)	**3.98 (1.80,8.82)**	**3.05 (1.32,7.07)**	**2.45 (1.10,5.42)**	1.62 (0.30,8.80)	1.60 (0.32,8.06)	1.76 (0.69,4.54)	1.03 (0.34,3.09)	FUM	0.87 (0.38,2.01)	17 per 1000
-	**50.19 (20.9,120.5)**	**30.27 (25.5,36.0)**	**30.19 (25.4,35.9)**	**28.75 (24.0,34.4)**	**26.26 (22.3,31.0)**	**25.60 (19.4,33.9)**	**24.10 (20.1,29.0)**	**24.11 (20.4,28.5)**	**18.90 (16.0,22.3)**	**18.57 (14.0,24.6)**	**13.99 (1.99,98.10)**	**17.35 (14.6,20.6)**	**13.30 (9.65,18.32)**	**10.65 (8.89,12.77)**	**7.04 (1.32,37.50)**	**6.97 (1.42,34.34)**	**7.69 (4.48,13.18)**	**4.49 (2.07,9.76)**	**4.36 (2.01,9.46)**	PBO	26 per 1000
	443 per 1000	880 per 1000	422 per 1000	415 per 1000	360 per 1000	210 per 1000	329 per 1000	388 per 1000	258 per 1000	256 per 1000	210 per 1000	267 per 1000	182 per 1000	146 per 1000	148 per 1000	147 per 1000	110 per 1000	123 per 1000	55 per 1000	25 per 1000	Anticipated absolute effects

PASI 90

Figure 8. Relative effects of the intervention as estimated from the network meta-analysis model for Psoriasis Area and Severity Index (PASI) 75 and adverse events (AEs) 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 75 and AEs) of the intervention in the respective column versus the comparator in the respective row. RRs larger than 1 for the lower triangle and smaller than 1 for the upper triangle favour the treatment on the left. Significant results are highlighted in grey. ACI: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; DEUCRAVA: deucravacitinib; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; NETA: netakimab; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; SONELO: sonelokimab; TILDRA: tildrakizumab; USK: ustekinumab

Adverse events

IFX	1.00 (0.87,1.14)	1.12 (0.97,1.29)	0.95 (0.80,1.12)	1.03 (0.91,1.16)	1.11 (0.96,1.27)	1.04 (0.90,1.19)	0.97 (0.72,1.30)	1.07 (0.95,1.21)	1.26 (1.07,1.48)	1.08 (0.94,1.23)	0.89 (0.63,1.26)	1.20 (1.02,1.40)	1.06 (0.95,1.20)	0.93 (0.80,1.07)	0.92 (0.69,1.22)	1.29 (0.83,2.01)	1.08 (0.89,1.32)	-	0.96 (0.78,1.17)	1.16 (1.04,1.30)
1.30 (0.86,1.98)	IXE	1.13 (1.00,1.27)	0.95 (0.82,1.10)	1.03 (0.94,1.13)	1.11 (1.00,1.23)	1.04 (0.93,1.17)	0.97 (0.73,1.29)	1.08 (0.99,1.18)	1.26 (1.10,1.46)	1.08 (0.97,1.20)	0.89 (0.63,1.25)	1.20 (1.05,1.38)	1.07 (0.98,1.17)	0.93 (0.82,1.05)	0.92 (0.70,1.21)	1.30 (0.84,2.01)	1.09 (0.90,1.30)	-	0.96 (0.80,1.16)	1.17 (1.08,1.27)
1.32 (0.86,2.00)	1.01 (0.89,1.15)	RISAN	0.84 (0.73,0.98)	0.91 (0.83,1.01)	0.99 (0.88,1.11)	0.92 (0.82,1.04)	0.86 (0.65,1.15)	0.96 (0.87,1.05)	1.12 (0.97,1.30)	0.96 (0.87,1.07)	0.79 (0.56,1.11)	1.07 (0.92,1.23)	0.95 (0.85,1.05)	0.83 (0.72,0.94)	0.82 (0.62,1.08)	1.15 (0.74,1.78)	0.96 (0.80,1.16)	-	0.85 (0.71,1.03)	1.04 (0.95,1.13)
1.32 (0.86,2.01)	1.01 (0.89,1.16)	1.00 (0.90,1.12)	BIME	1.09 (0.95,1.24)	1.17 (1.01,1.35)	1.09 (0.94,1.27)	1.03 (0.76,1.38)	1.13 (1.00,1.29)	1.33 (1.12,1.58)	1.14 (1.00,1.30)	0.94 (0.66,1.33)	1.26 (1.07,1.50)	1.13 (0.98,1.29)	0.98 (0.84,1.15)	0.97 (0.73,1.29)	1.37 (0.87,2.13)	1.14 (0.93,1.40)	-	1.01 (0.82,1.25)	1.23 (1.09,1.39)
1.39 (0.92,2.11)	1.07 (0.95,1.20)	1.06 (0.97,1.15)	1.05 (0.97,1.15)	SECU	1.08 (0.98,1.18)	1.01 (0.91,1.12)	0.94 (0.72,1.24)	1.05 (0.97,1.12)	1.23 (1.07,1.40)	1.05 (0.96,1.15)	0.86 (0.62,1.21)	1.17 (1.03,1.32)	1.04 (0.96,1.12)	0.90 (0.81,1.01)	0.89 (0.68,1.17)	1.26 (0.82,1.94)	1.05 (0.88,1.26)	-	0.93 (0.78,1.11)	1.13 (1.07,1.20)
1.43 (0.94,2.19)	1.10 (0.95,1.27)	1.09 (0.98,1.21)	1.09 (0.97,1.22)	1.03 (0.94,1.13)	GUSEL	0.94 (0.83,1.06)	0.88 (0.66,1.17)	0.97 (0.88,1.07)	1.14 (0.98,1.32)	0.97 (0.89,1.07)	0.80 (0.57,1.13)	1.08 (0.94,1.24)	0.96 (0.87,1.06)	0.84 (0.74,0.95)	0.83 (0.63,1.09)	1.17 (0.75,1.81)	0.98 (0.81,1.18)	-	0.87 (0.72,1.04)	1.05 (0.97,1.14)
1.44 (0.94,2.21)	1.11 (0.97,1.27)	1.10 (0.97,1.24)	1.10 (0.96,1.25)	1.04 (0.93,1.16)	1.01 (0.88,1.16)	BRODA	0.94 (0.70,1.25)	1.04 (0.94,1.14)	1.22 (1.05,1.41)	1.04 (0.93,1.17)	0.86 (0.61,1.20)	1.16 (1.00,1.33)	1.03 (0.92,1.14)	0.89 (0.79,1.02)	0.89 (0.67,1.17)	1.25 (0.81,1.93)	1.04 (0.87,1.26)	-	0.92 (0.77,1.12)	1.12 (1.03,1.23)
1.51 (0.97,2.37)	1.16 (0.96,1.41)	1.15 (0.96,1.38)	1.15 (0.96,1.37)	1.09 (0.93,1.27)	1.06 (0.88,1.27)	1.05 (0.87,1.27)	SONELO	1.11 (0.84,1.46)	1.30 (0.96,1.75)	1.11 (0.84,1.48)	0.91 (0.60,1.40)	1.23 (0.92,1.66)	1.10 (0.83,1.45)	0.96 (0.71,1.28)	0.95 (0.65,1.38)	1.33 (0.80,2.22)	1.11 (0.81,1.54)	-	0.99 (0.72,1.36)	1.20 (0.91,1.58)
1.59 (1.05,2.42)	1.22 (1.10,1.36)	1.21 (1.12,1.31)	1.21 (1.10,1.32)	1.15 (1.07,1.22)	1.11 (1.00,1.23)	1.10 (1.00,1.21)	1.05 (0.89,1.25)	USK	1.17 (1.03,1.34)	1.00 (0.92,1.10)	0.83 (0.59,1.15)	1.11 (0.98,1.26)	0.99 (0.92,1.07)	0.86 (0.77,0.96)	0.85 (0.65,1.12)	1.20 (0.78,1.85)	1.01 (0.84,1.20)	-	0.89 (0.75,1.06)	1.08 (1.03,1.15)
1.68 (1.08,2.61)	1.29 (1.07,1.55)	1.28 (1.05,1.55)	1.27 (1.04,1.55)	1.21 (1.00,1.46)	1.17 (0.96,1.44)	1.16 (0.95,1.43)	1.11 (0.87,1.41)	1.05 (0.88,1.26)	TILDRA	0.86 (0.74,0.99)	0.70 (0.50,1.00)	0.95 (0.81,1.12)	0.85 (0.74,0.96)	0.74 (0.63,0.86)	0.73 (0.54,0.97)	1.03 (0.66,1.60)	0.86 (0.70,1.05)	-	0.76 (0.62,0.93)	0.92 (0.82,1.04)
1.75 (1.15,2.68)	1.35 (1.17,1.55)	1.33 (1.21,1.47)	1.33 (1.20,1.48)	1.26 (1.15,1.39)	1.22 (1.13,1.33)	1.22 (1.06,1.39)	1.16 (0.97,1.39)	1.10 (1.00,1.22)	1.04 (0.86,1.28)	ADA	0.82 (0.59,1.15)	1.11 (0.97,1.27)	0.99 (0.90,1.09)	0.86 (0.76,0.97)	0.85 (0.65,1.12)	1.20 (0.78,1.85)	1.00 (0.84,1.20)	-	0.89 (0.74,1.07)	1.08 (1.00,1.16)
2.32 (0.71,7.56)	1.78 (0.59,5.43)	1.77 (0.58,5.37)	1.76 (0.58,5.37)	1.67 (0.55,5.08)	1.62 (0.53,4.94)	1.61 (0.53,4.90)	1.53 (0.50,4.71)	1.46 (0.48,4.43)	1.38 (0.45,4.25)	1.32 (0.44,4.03)	DEUCRAVA	1.35 (0.95,1.91)	1.20 (0.86,1.68)	1.04 (0.74,1.47)	1.03 (0.68,1.57)	1.46 (0.85,2.50)	1.22 (0.84,1.76)	-	1.08 (0.75,1.56)	1.31 (0.94,1.83)
1.87 (1.19,2.93)	1.44 (1.17,1.76)	1.42 (1.15,1.76)	1.42 (1.15,1.76)	1.35 (1.10,1.65)	1.31 (1.05,1.62)	1.30 (1.04,1.61)	1.23 (0.96,1.59)	1.17 (0.96,1.43)	1.11 (0.87,1.42)	1.07 (0.86,1.32)	0.81 (0.26,2.48)	CERTO	0.89 (0.79,1.01)	0.77 (0.67,0.90)	0.77 (0.57,1.02)	1.08 (0.69,1.68)	0.90 (0.74,1.11)	-	0.80 (0.65,0.98)	0.97 (0.87,1.09)
2.22 (1.47,3.36)	1.71 (1.55,1.88)	1.69 (1.51,1.89)	1.69 (1.49,1.90)	1.60 (1.45,1.76)	1.55 (1.36,1.76)	1.54 (1.35,1.75)	1.47 (1.22,1.76)	1.39 (1.27,1.53)	1.32 (1.13,1.56)	1.27 (1.12,1.43)	0.96 (0.31,2.91)	1.19 (0.99,1.42)	ETA	0.87 (0.78,0.97)	0.86 (0.66,1.13)	1.21 (0.79,1.87)	1.02 (0.85,1.21)	-	0.90 (0.75,1.07)	1.09 (1.03,1.16)
3.68 (2.30,5.89)	2.83 (2.19,3.65)	2.80 (2.17,3.61)	2.79 (2.16,3.62)	2.65 (2.06,3.40)	2.57 (1.98,3.33)	2.55 (1.96,3.32)	2.43 (1.81,3.26)	2.31 (1.80,2.96)	2.19 (1.64,2.93)	2.10 (1.62,2.71)	1.58 (0.51,4.91)	1.97 (1.46,2.66)	1.66 (1.30,2.11)	APRE	0.99 (0.75,1.31)	1.39 (0.90,2.16)	1.17 (0.96,1.41)	-	1.03 (0.85,1.25)	1.26 (1.14,1.38)
3.97 (1.73,9.12)	3.05 (1.46,6.35)	3.02 (1.45,6.28)	3.01 (1.45,6.28)	2.86 (1.38,5.94)	2.77 (1.33,5.78)	2.75 (1.32,5.74)	2.62 (1.24,5.54)	2.49 (1.20,5.18)	2.37 (1.12,5.00)	2.26 (1.09,4.71)	1.71 (0.46,6.41)	2.12 (1.00,4.50)	1.79 (0.86,3.72)	1.08 (0.50,2.31)	CICLO	1.41 (0.85,2.33)	1.18 (0.96,1.45)	-	1.04 (0.79,1.38)	1.27 (0.98,1.65)
3.92 (1.74,8.84)	3.01 (1.48,6.14)	2.98 (1.47,6.07)	2.98 (1.46,6.07)	2.82 (1.39,5.74)	2.74 (1.34,5.58)	2.72 (1.33,5.55)	2.59 (1.25,5.35)	2.46 (1.21,5.00)	2.34 (1.13,4.83)	2.24 (1.10,4.56)	1.69 (0.46,6.26)	2.10 (1.01,4.35)	1.77 (0.87,3.59)	1.07 (0.51,2.23)	0.99 (0.36,2.71)	NETA	0.84 (0.53,1.33)	-	0.74 (0.47,1.17)	0.90 (0.59,1.38)
5.09 (2.28,11.37)	3.91 (1.94,7.89)	3.87 (1.92,7.80)	3.86 (1.91,7.80)	3.66 (1.82,7.37)	3.55 (1.76,7.17)	3.53 (1.75,7.13)	3.36 (1.64,6.88)	3.20 (1.59,6.43)	3.03 (1.48,6.21)	2.90 (1.44,5.85)	2.19 (0.59,8.08)	2.72 (1.32,5.59)	2.29 (1.14,4.61)	1.38 (0.67,2.87)	1.28 (0.95,1.73)	1.30 (0.49,3.47)	MTX	-	0.89 (0.73,1.07)	1.08 (0.91,1.27)
9.78 (1.17,81.85)	7.51 (0.93,60.61)	7.43 (0.92,59.96)	7.42 (0.92,59.89)	7.04 (0.87,56.76)	6.82 (0.85,55.09)	6.77 (0.84,54.71)	6.45 (0.80,52.35)	6.14 (0.76,49.49)	5.82 (0.72,47.24)	5.57 (0.69,44.98)	4.21 (0.40,44.58)	5.23 (0.64,42.46)	4.40 (0.55,35.49)	2.66 (0.33,21.65)	2.46 (0.27,22.37)	2.49 (0.28,22.47)	1.92 (0.21,17.27)	ACI	-	-
7.44 (4.48,12.36)	5.71 (4.13,7.90)	5.65 (4.10,7.79)	5.64 (4.08,7.80)	5.35 (3.90,7.35)	5.19 (3.75,7.18)	5.15 (3.72,7.15)	4.91 (3.45,6.99)	4.67 (3.41,6.40)	4.43 (3.11,6.31)	4.24 (3.07,5.85)	3.20 (1.02,10.07)	3.98 (2.77,5.71)	3.35 (2.43,4.60)	2.02 (1.38,2.96)	1.87 (0.90,3.92)	1.90 (0.89,4.06)	1.46 (0.72,2.95)	0.76 (0.09,6.25)	FUM	1.22 (1.03,1.44)
18.05 (11.96,27.23)	13.86 (12.19,15.76)	13.72 (12.19,15.44)	13.70 (12.08,15.53)	12.99 (11.67,14.46)	12.60 (11.10,14.29)	12.51 (10.95,14.29)	11.91 (9.86,14.40)	11.33 (10.22,12.56)	10.75 (8.90,12.99)	10.29 (9.12,11.61)	7.77 (2.57,23.49)	9.65 (7.87,11.83)	8.12 (7.26,9.08)	4.90 (3.87,6.21)	4.55 (2.20,9.37)	4.60 (2.28,9.27)	3.55 (1.78,7.07)	1.85 (0.23,14.85)	2.43 (1.80,3.27)	PBO

PASI 75

Figure 9. 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; DEUCRAVA: deucravacitinib; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; NETA: netakimab; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; SONELO: sonelokimab; TILDRA: tildrakizumab; USK: ustekinumab

Quality of life

BIME	0.42 (-0.26,1.10)	-0.03 (-0.71,0.65)	0.43 (-0.30,1.16)	0.06 (-0.73,0.86)	-	-0.87 (-1.65,-0.09)	-0.10 (-0.75,0.55)	0.05 (-0.61,0.71)	-0.59 (-1.48,0.31)	-0.41 (-1.14,0.32)	-0.31 (-0.89,0.27)	0.01 (-0.69,0.72)	-0.29 (-1.23,0.65)	-0.24 (-0.90,0.41)	-	-0.51 (-1.45,0.43)	-0.96 (-1.64,-0.28)	-	-1.34 (-1.96,-0.72)
1.03 (0.86,1.24)	IXE	-0.45 (-0.84,-0.07)	0.01 (-0.46,0.48)	-0.36 (-0.93,0.21)	-	-1.29 (-1.84,-0.75)	-0.52 (-0.92,-0.13)	-0.37 (-0.73,-0.02)	-1.01 (-1.70,-0.31)	-0.84 (-1.31,-0.37)	-0.73 (-1.08,-0.38)	-0.41 (-0.83,0.01)	-0.71 (-1.46,0.05)	-0.66 (-0.96,-0.36)	-	-0.94 (-1.69,-0.18)	-1.38 (-1.77,-1.00)	-	-1.76 (-2.04,-1.49)
0.99 (0.59,1.66)	0.96 (0.58,1.59)	IFX	0.46 (-0.01,0.94)	0.09 (-0.47,0.66)	-	-0.84 (-1.38,-0.30)	-0.07 (-0.46,0.33)	0.08 (-0.28,0.44)	-0.55 (-1.25,0.14)	-0.38 (-0.85,0.09)	-0.28 (-0.63,0.07)	0.04 (-0.38,0.47)	-0.25 (-1.01,0.50)	-0.21 (-0.54,0.12)	-	-0.48 (-1.24,0.27)	-0.93 (-1.31,-0.55)	-	-1.31 (-1.58,-1.03)
1.08 (0.90,1.30)	1.05 (0.88,1.25)	1.09 (0.66,1.81)	RISAN	-0.37 (-1.00,0.26)	-	-1.30 (-1.91,-0.70)	-0.53 (-1.01,-0.06)	-0.39 (-0.76,-0.01)	-1.02 (-1.76,-0.27)	-0.85 (-1.39,-0.31)	-0.74 (-1.18,-0.30)	-0.42 (-0.92,0.08)	-0.72 (-1.52,0.08)	-0.67 (-1.11,-0.24)	-	-0.95 (-1.75,-0.15)	-1.39 (-1.86,-0.93)	-	-1.77 (-2.16,-1.39)
1.13 (0.97,1.32)	1.10 (0.95,1.26)	1.14 (0.69,1.88)	1.05 (0.90,1.21)	SECU	-	-0.93 (-1.62,-0.25)	-0.16 (-0.74,0.41)	-0.01 (-0.56,0.53)	-0.65 (-1.46,0.16)	-0.48 (-1.10,0.15)	-0.37 (-0.92,0.17)	-0.05 (-0.65,0.55)	-0.35 (-1.21,0.51)	-0.30 (-0.84,0.23)	-	-0.58 (-1.44,0.28)	-1.02 (-1.59,-0.46)	-	-1.40 (-1.90,-0.91)
1.16 (0.85,1.57)	1.12 (0.83,1.52)	1.16 (0.66,2.06)	1.07 (0.79,1.46)	1.02 (0.78,1.34)	SONELO	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1.15 (0.92,1.45)	1.12 (0.90,1.38)	1.16 (0.69,1.97)	1.07 (0.85,1.34)	1.02 (0.84,1.24)	1.00 (0.72,1.39)	BRODA	0.77 (0.22,1.32)	0.92 (0.40,1.44)	0.29 (-0.51,1.08)	0.46 (-0.15,1.06)	0.56 (0.04,1.08)	0.88 (0.31,1.46)	0.59 (-0.26,1.43)	0.63 (0.12,1.14)	-	0.36 (-0.49,1.20)	-0.09 (-0.63,0.45)	-	-0.47 (-0.94,0.00)
1.27 (1.06,1.53)	1.23 (1.05,1.44)	1.28 (0.77,2.12)	1.18 (1.00,1.38)	1.12 (0.97,1.31)	1.10 (0.81,1.50)	1.10 (0.87,1.39)	GUSEL	0.15 (-0.22,0.51)	-0.49 (-1.19,0.21)	-0.31 (-0.79,0.16)	-0.21 (-0.51,0.09)	0.11 (-0.32,0.55)	-0.19 (-0.95,0.57)	-0.14 (-0.49,0.21)	-	-0.41 (-1.17,0.34)	-0.86 (-1.25,-0.47)	-	-1.24 (-1.52,-0.96)
1.44 (1.23,1.68)	1.39 (1.21,1.60)	1.45 (0.88,2.38)	1.33 (1.17,1.52)	1.27 (1.14,1.42)	1.24 (0.93,1.66)	1.24 (1.05,1.48)	1.13 (0.97,1.32)	USK	-0.63 (-1.31,0.05)	-0.46 (-0.91,-0.02)	-0.36 (-0.67,-0.04)	-0.04 (-0.43,0.36)	-0.33 (-1.07,0.41)	-0.29 (-0.59,0.01)	-	-0.56 (-1.30,0.18)	-1.01 (-1.36,-0.66)	-	-1.39 (-1.61,-1.16)
1.86 (0.60,5.79)	1.81 (0.58,5.59)	1.88 (0.55,6.37)	1.73 (0.56,5.34)	1.65 (0.53,5.10)	1.61 (0.51,5.15)	1.61 (0.52,5.04)	1.47 (0.47,4.54)	1.30 (0.42,4.00)	DEUCRAVA	0.17 (-0.57,0.92)	0.28 (-0.40,0.95)	0.60 (-0.12,1.32)	0.30 (-0.65,1.25)	0.34 (-0.33,1.02)	-	0.07 (-0.88,1.02)	-0.38 (-1.07,0.32)	-	-0.75 (-1.40,-0.11)
1.63 (1.15,2.32)	1.58 (1.14,2.19)	1.64 (0.92,2.93)	1.51 (1.06,2.15)	1.45 (1.04,2.00)	1.41 (0.93,2.15)	1.41 (1.00,2.01)	1.29 (0.91,1.83)	1.14 (0.82,1.57)	0.88 (0.27,2.82)	CERTO	0.11 (-0.34,0.55)	0.43 (-0.08,0.93)	0.13 (-0.67,0.93)	0.17 (-0.26,0.60)	-	-0.10 (-0.90,0.70)	-0.55 (-1.01,-0.08)	-	-0.93 (-1.31,-0.54)
1.60 (1.34,1.92)	1.56 (1.30,1.86)	1.62 (0.97,2.69)	1.49 (1.28,1.73)	1.42 (1.21,1.67)	1.39 (1.01,1.91)	1.39 (1.09,1.78)	1.26 (1.11,1.43)	1.12 (0.95,1.31)	0.86 (0.28,2.67)	0.98 (0.69,1.41)	ADA	0.32 (-0.07,0.72)	0.02 (-0.72,0.76)	0.07 (-0.23,0.37)	-	-0.20 (-0.94,0.53)	-0.65 (-1.00,-0.31)	-	-1.03 (-1.25,-0.81)
1.70 (1.28,2.27)	1.65 (1.27,2.14)	1.72 (1.00,2.94)	1.58 (1.19,2.09)	1.51 (1.16,1.96)	1.47 (1.01,2.14)	1.47 (1.09,1.99)	1.34 (1.01,1.78)	1.19 (0.92,1.54)	0.91 (0.29,2.88)	1.04 (0.72,1.51)	1.06 (0.80,1.41)	TILDRA	-0.30 (-1.08,0.48)	-0.25 (-0.61,0.11)	-	-0.53 (-1.30,0.25)	-0.97 (-1.40,-0.55)	-	-1.35 (-1.68,-1.03)
2.49 (0.85,7.31)	2.42 (0.83,7.06)	2.51 (0.78,8.08)	2.31 (0.79,6.75)	2.21 (0.76,6.43)	2.16 (0.72,6.51)	2.16 (0.73,6.37)	1.96 (0.67,5.73)	1.74 (0.60,5.05)	1.34 (0.29,6.26)	1.53 (0.50,4.64)	1.55 (0.53,4.54)	1.46 (0.49,4.36)	MTX	0.05 (-0.69,0.78)	-	-0.23 (-1.22,0.77)	-0.68 (-1.43,0.08)	-	-1.05 (-1.76,-0.35)
2.09 (1.73,2.53)	2.03 (1.77,2.32)	2.11 (1.29,3.44)	1.94 (1.63,2.31)	1.85 (1.60,2.14)	1.81 (1.34,2.46)	1.81 (1.46,2.24)	1.65 (1.38,1.96)	1.46 (1.27,1.67)	1.12 (0.36,3.47)	1.28 (0.95,1.73)	1.30 (1.09,1.57)	1.23 (0.98,1.55)	0.84 (0.29,2.45)	ETA	-	-0.27 (-1.00,0.46)	-0.72 (-1.05,-0.39)	-	-1.10 (-1.30,-0.90)
2.79 (0.85,9.14)	2.71 (0.83,8.83)	2.81 (0.79,10.03)	2.59 (0.79,8.45)	2.47 (0.76,8.05)	2.42 (0.72,8.11)	2.42 (0.73,7.95)	2.20 (0.67,7.18)	1.94 (0.60,6.33)	1.50 (0.30,7.59)	1.71 (0.51,5.78)	1.74 (0.53,5.68)	1.64 (0.49,5.45)	1.12 (0.62,2.03)	1.33 (0.41,4.35)	CICLO	-	-	-	-
4.14 (2.22,7.74)	4.02 (2.17,7.44)	4.18 (1.92,9.06)	3.84 (2.07,7.14)	3.67 (1.99,6.78)	3.59 (1.84,7.01)	3.59 (1.91,6.75)	3.26 (1.76,6.07)	2.89 (1.57,5.32)	2.23 (0.62,7.93)	2.54 (1.29,5.01)	2.58 (1.39,4.81)	2.43 (1.27,4.66)	1.66 (0.49,5.62)	1.98 (1.07,3.67)	1.48 (0.40,5.54)	NETA	-0.45 (-1.20,0.30)	-	-0.83 (-1.53,-0.12)
4.13 (3.01,5.66)	4.00 (2.97,5.39)	4.16 (2.39,7.24)	3.83 (2.83,5.18)	3.65 (2.72,4.91)	3.57 (2.40,5.33)	3.58 (2.56,5.00)	3.25 (2.40,4.40)	2.88 (2.15,3.84)	2.22 (0.70,7.01)	2.53 (1.67,3.83)	2.57 (1.90,3.49)	2.43 (1.69,3.48)	1.66 (0.55,4.94)	1.97 (1.48,2.64)	1.48 (0.44,4.93)	1.00 (0.52,1.92)	APRE	-	-0.38 (-0.64,-0.11)
6.94 (4.74,10.16)	6.73 (4.66,9.73)	6.99 (3.86,12.68)	6.43 (4.44,9.31)	6.14 (4.27,8.85)	6.01 (3.82,9.45)	6.01 (4.05,8.94)	5.47 (3.78,7.91)	4.83 (3.37,6.93)	3.73 (1.16,12.00)	4.25 (2.66,6.81)	4.33 (2.99,6.26)	4.08 (2.67,6.23)	2.78 (0.92,8.47)	3.32 (2.30,4.78)	2.49 (0.73,8.43)	1.68 (0.84,3.33)	1.68 (1.09,2.58)	FUM	-
15.35 (12.83,18.38)	14.88 (12.79,17.32)	15.47 (9.47,25.26)	14.23 (12.21,16.58)	13.59 (11.79,15.66)	13.29 (9.80,18.03)	13.30 (10.76,16.44)	12.09 (10.37,14.09)	10.69 (9.40,12.16)	8.24 (2.69,25.26)	9.40 (6.75,13.10)	9.57 (8.22,11.15)	9.02 (6.97,11.67)	6.16 (2.13,17.79)	7.34 (6.35,8.48)	5.50 (1.70,17.78)	3.70 (2.03,6.75)	3.72 (2.85,4.86)	2.21 (1.58,3.10)	PBO

PGA

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 10. 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; AIL12/23: anti-IL12/23; AIL17: anti-IL17; AIL23: anti-IL23, ATA: anti-TNF alpha; CI: confidence interval; CSA: non-biological conventional systemic agents; PGA: Physician Global Assessment; PrI: predictive interval; PBO: placebo; QoL: Specific quality of life scale; RR: risk ratio; SAE: serious adverse events; SM: small molecules; SMD: standardised mean difference

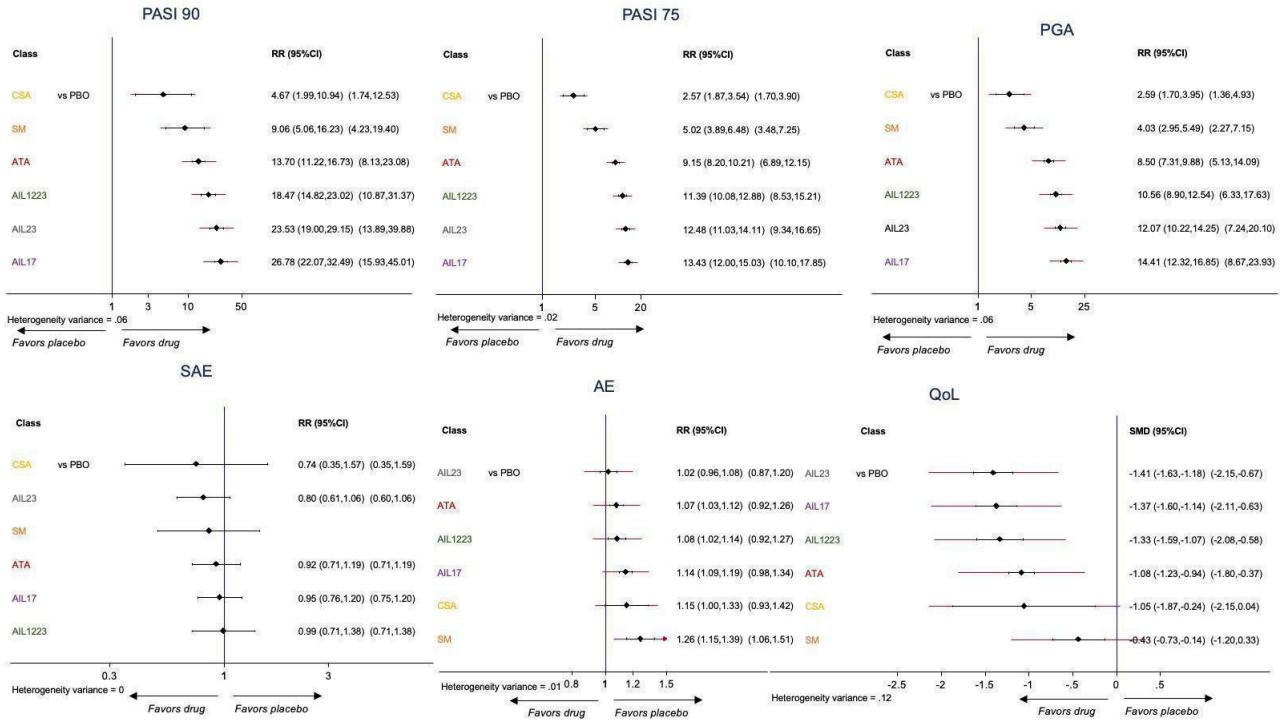


Figure 11. Interval plot. Network meta-analysis estimates of the interventions versus placebo for the primary outcomes CI: confidence interval; PrI: predictive interval; RR: risk ratio; SAE: serious adverse events; PGA: Physician Global Assessment; QoL: Specific quality of life scale; SMD: standardised mean difference ACI: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; DEUCRAVA: deucravacitinib; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; NETA: netakimab; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; SONELO: sonelokimab; TILDRA: tildrakizumab; USK: ustekinumab

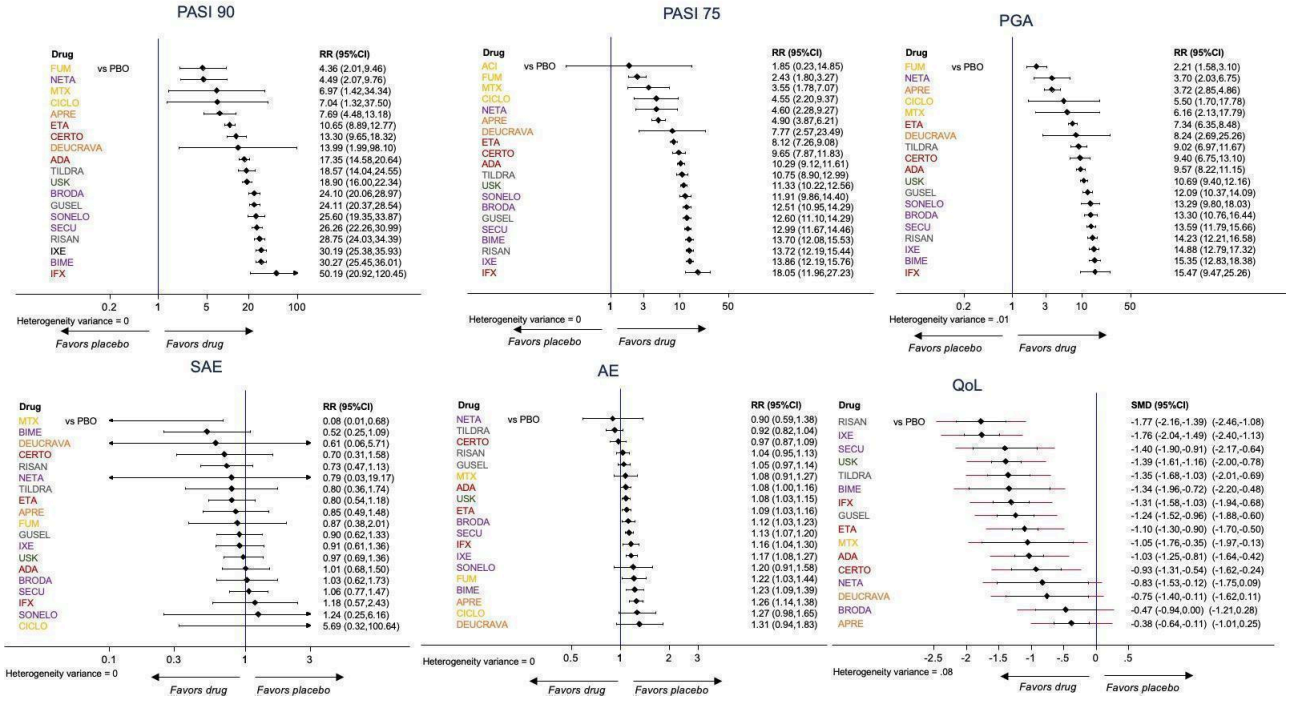


Figure 12 shows a two-dimensional ranking plot based on surface under the cumulative ranking curve (SUCRA) values for benefit (PASI 90) and acceptability (serious adverse events) at class and drug level. The different colours represent different groups of interventions considering their performance on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

Figure 12. Ranking plot. Ranking plot representing simultaneously the efficacy (x axis, PASI 90) and the acceptability (y axis, serious adverse events) of all the interventions (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 ACI: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; DEUCRAVA: deucravacitinib; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; NETA: netakimab; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; SONELO: sonelokimab; TILDRA: tildrakizumab; USK: ustekinumab PASI: Psoriasis Area and Severity Index; SAE: serious adverse events; SUCRA: surface under the cumulative ranking curve

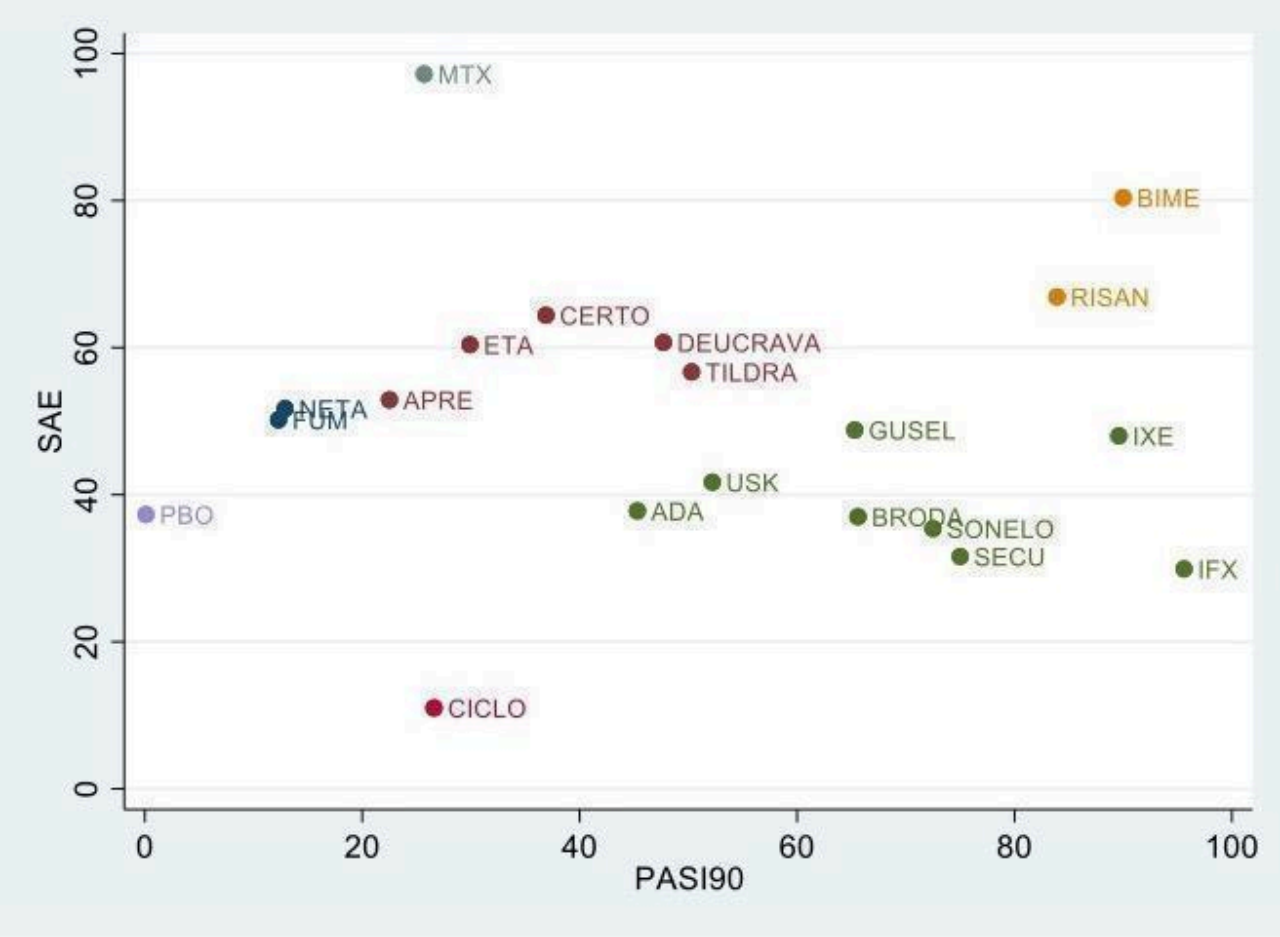


Figure 13; Figure 14 show the ranking for all the outcomes at class and drug level, respectively.

Figure 13. Ranking for all the outcomes at class level AIL12/23: anti-IL12/23; AIL17: anti-IL17; AIL23: anti-IL23, ATA: anti-TNF alpha; CSA: non-biological 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

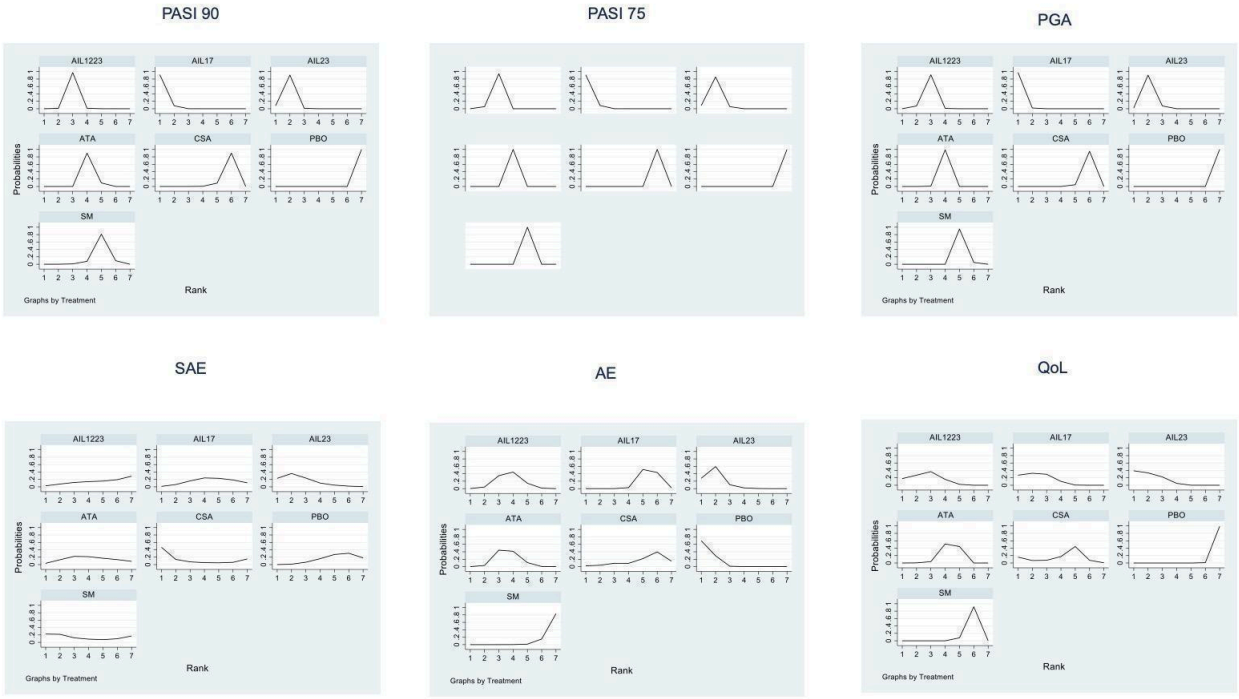


Figure 14. Ranking for all the outcomes at drug level ACI: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; DEUCRAVA: deucravacitinib; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; NETA: netakimab; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; SONELO: sonelokimab; TILDRA: tildrakizumab; USK: ustekinumab AE: adverse events; PASI: Psoriasis Area and Severity Index; PGA: Physician Global Assessment; QoL: quality of life; SAE: serious adverse events

Since this review did not include summary of findings (SoF) tables, we presented Figure 7 instead. Figure 7 includes all comparison results for the two main outcomes, but also absolute effects and assessment of the certainty of evidence using CiNeMa.

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 pairwise 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, brodalumab, bimekizumab, and sonelokimab) were more effective than placebo (risk ratio at class level (RR) 27.31, 95% confidence interval (CI) 18.94 to 39.38). No significant difference was observed between netakimab and placebo (RR 10.98, 95% CI 0.42 to 288.83). These findings were also confirmed for anti-IL23 (guselkumab, tildrakizumab, and risankizumab) (class-level RR 23.15, 95% CI 16.44 to 32.61); anti-IL12/23 (ustekinumab) (RR 18.37, 95% CI 12.56 to 26.85); anti-TNF alpha (infliximab, etanercept, adalimumab, and certolizumab) (class-level RR 13.65, 95% CI 10.71 to 17.40); and small molecules (apremilast, and oral tyrosine kinase 2 (TYK2) inhibitor) (class-level RR 7.56, 95% CI 3.84 to 14.88). Infliximab, adalimumab, and ixekizumab were more effective than methotrexate (respectively: RR 2.86, 95% CI 2.15 to 3.80; RR 3.73, 95% CI 2.25 to 6.19; and RR 2.05, 95% CI 1.43 to 2.94). Secukinumab, ixekizumab, guselkumab, risankizumab, and brodalumab were more effective than FAEs (respectively: RR 8.31, 95% CI 4.23 to 16.35; RR 8.60, 95% CI 3.69 to 20.04; RR 6.02, 95% CI 3.13 to 11.60; RR 8.33, 95% CI 3.87 to 17.95; and RR 3.00, 95% CI 2.04 to 4.42). Ustekinumab, secukinumab, infliximab, ixekizumab, and tildrakizumab were more effective than etanercept. Secukinumab, ixekizumab, brodalumab,risankizumab and bimekizumab were more effective than ustekinumab. Guselkumab, risankizumab and bimekizumab were more effective than adalimumab. Secukinumab and ixekizumab were more effective than guselkumab and bimekizumab was more effective than secukinumab. No significant difference was observed between risankizumab and secukinumab, between sonelokimab and secukinumab, between certolizumab and etanercept, or between etanercept and apremilast for this outcome (reaching PASI 90).

NETWORK META-ANALYSES

The PASI 90 outcome was available in 115 trials, involving 48,722 participants (92.7% of the participants in the meta-analysis). For two trials (Nugteren-Huying 1990; Sandhu 2003), the number of randomised participants was not available, but we added these trials in the complete-case sensitivity analyses. This outcome was reported in seven trials out of 115 (Dogra 2012; Dogra 2013; Khatri 2016; NCT03504852; PRISTINE 2013; SCULPTURE 2015; SIGNATURE 2019), comparing different dosages of the same drug in each case.

We added these trials to the sensitivity analysis at dose level. This outcome was reported in nine trials out of 115 with biological-naïve participants that were added to the sensitivity analysis for all trials, whatever previous treatments received by the participants (Barker 2011; Caproni 2009; CHAMPION 2008; CHANGE 2021; Gisondi 2008; POLARIS 2020; PRIME 2017; Reich 2020; Thaci 2021).

Sixty-eight trials, involving 23,539 participants, were placebo-controlled trials; 31 studies, involving 11,426 participants, were head-to-head comparisons; and 16 studies, involving 13,757 participants, had both a placebo and at least two active treatments arms.

PASI 90 was not reported for the remaining 18 trials including IXORA-P 2018 (only long-term assessment outcomes), and we were not able to obtain missing information from the trial authors (Table 2).

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

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. At class level (Figure 6), anti-IL17 treatment showed a higher proportion of patients reaching PASI 90 compared to all of the interventions, except anti-IL23 (RR 1.14, 95% CI 0.95 to 1.36): versus anti-IL12/23 (RR 1.45, 95% CI 1.23 to 1.71); versus anti-TNF alpha (RR 1.95, 95% CI 1.64 to 2.33); versus small molecules (RR 2.96, 95% CI 1.63 to 5.38); versus non-biological systemic agents (RR 5.74, 95% CI 2.40 to 13.73). In terms of reaching PASI 90, all of the biologic interventions (anti-IL17, anti-IL12/23, anti-IL23) except anti-TNF alpha, appeared significantly superior to the small molecule class of treatments. All of the biologic interventions (anti-IL17, anti-IL12/23, anti-IL23 and anti-TNF alpha) were significantly superior to the non-biological systemic class of treatments for reaching PASI 90.

Results of comparisons between each of the drugs are available in Figure 7. There was no significant difference between infliximab, ixekizumab, bimekizumab, and risankizumab in terms of reaching PASI 90. Bimekizumab, ixekizumab and risankizumab were significantly more likely to reach PASI 90, than other anti-IL17 drugs (secukinumab and brodalumab) and guselkumab. Infliximab, bimekizumab, ixekizumab and risankizumab were significantly more likely to reach PASI 90 than ustekinumab, tildrakizumab and the three anti-TNF alpha agents (adalimumab, certolizumab and etanercept). Anti-IL17 drugs (bimekizumab, ixekizumab, secukinumab and brodalumab) and anti-IL23 drugs (risankizumab and guselkumab) except tildrakizumab were significantly more likely to reach PASI 90 than ustekinumab and three anti-TNF alpha agents: adalimumab, certolizumab and etanercept. Ustekinumab was superior to certolizumab (RR 1.42, 95% CI 1.06 to 1.91). Adalimumab and ustekinumab were superior to etanercept (RR 1.77, 95% CI 1.58 to 1.99 and RR 1.63, 95% CI 1.43 to 1.86, respectively). No significant difference was shown between apremilast and two non-biological drugs: ciclosporin and methotrexate. We assessed the certainty of evidence for each comparison using CINeMA and classified it as high (highlighted in green), moderate (in blue), low (in yellow) and very low (in red) (Figure 7).

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

Anti-IL17 class had a better chance of reaching PASI 90 using SUCRA (versus placebo: RR 26.78, 95% CI 22.07 to 32.49; SUCRA = 98.7), followed by anti-IL23 (versus placebo: RR 23.53, 95% CI 19.00 to 29.15; SUCRA = 84.5), anti-IL12/23 (versus placebo: RR 18.47, 95% CI 14.82 to 23.02; SUCRA = 66.6), then anti-TNF alpha (versus placebo: RR 13.70, 95% CI 11.22 to 16.73; SUCRA = 48.5). The heterogeneity τ for this network overall was 0.06, which we considered to be low.

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

At drug-level, using SUCRA, infliximab had a better chance of reaching PASI 90 at drug level (versus placebo: RR 50.19, 95% CI 20.92 to 120.45; SUCRA = 95.6; high-certainty evidence), followed by bimekizumab (versus placebo: RR 30.27, 95% CI 25.45 to 36.01; SUCRA = 90; high-certainty evidence), ixekizumab (versus placebo: RR 30.19, 95% CI 25.38 to 35.93; SUCRA = 89.6; high-certainty evidence), risankizumab (versus placebo: RR 28.75, 95% CI 24.03 to 34.39; SUCRA = 83.9; high-certainty evidence), secukinumab (versus placebo: RR 26.26, 95% CI 22.26 to 30.99; SUCRA = 75; high-certainty evidence), sonelokimab (versus placebo: RR 25.60, 95% CI 19.35 to 33.87; SUCRA = 72.5; high-certainty evidence), then brodalumab (versus placebo: RR 24.10, 95% CI 20.06 to 28.97; SUCRA = 65.6; moderate-certainty evidence). The heterogeneity τ for this network overall was 0, which we considered to be low.

1.2 The proportion of participants with serious adverse events

DIRECT EVIDENCE

We report treatment estimates for pairwise 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, bimekizumab, netakimab, sonelokimab, guselkumab, tildrakizumab, risankizumab, apremilast, oral tyrosine kinase 2 (TYK2) inhibitor, and placebo in the number of participants with serious adverse events (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); Bagel 2012 (comparing etanercept with placebo); Caproni 2009 (comparing etanercept with acitretin); Chaudhari 2001 (comparing infliximab with placebo); Yu 2019 (comparing etanercept with methotrexate); Hunter 1963 (comparing methotrexate with placebo); AlMutairi 2021 (comparing ixekizumab with secukinumab); and NCT02762994 (comparing netakimab with placebo).

NETWORK META-ANALYSES

The SAE outcome was available in 120 trials, involving 49,045 participants (93.4% of the participants in the meta-analysis). For one trial (PRESTA 2010), the number of randomised participants was not available. We added this trial to the complete-cases sensitivity analyses. This outcome was reported in seven trials out of 120 (Khatri 2016; Laburte 1994; SCULPTURE 2015; Ortonne 2013; PRISTINE 2013; PRESTA 2010;SIGNATURE 2019), comparing different dosages of the same drug in each case. We added these studies to the sensitivity analysis at dose level. This outcome was reported in 10 trials out of 120 with biological-naïve participants that were added to the sensitivity analysis for all trials, whatever previous treatments received by the participants (Barker 2011; Caproni 2009; CHAMPION 2008; CHANGE 2021; Gisondi 2008; Lee 2016; POLARIS 2020; PRIME 2017; Reich 2020; Thaci 2021). Seventy-two trials, involving 23,800 participants, were placebo-controlled trials; 31, involving 11,392 participants, were head-to-head comparisons, and 17, involving 13,853 participants, had both a placebo and at least two active treatments arms.

SAEs were not reported for the 13 remaining trials, and we were not able to obtain missing information from the trial authors (Table 2).

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

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. This result was verified after excluding flares of psoriasis as SAEs (data not shown). There was no significant difference between all interventions in the number of participants with SAEs, except for methotrexate (Figure 7). The risk of SAEs was significantly lower for participants on methotrexate compared with all interventions, except bimekizumab, certolizumab, netakimab, deucravacitinib, apremilast, and FAEs. We assessed the certainty of evidence for each comparison using CINeMA and classified it as high (highlighted in green), moderate (in blue), low (in yellow) and very-low (in red) (Figure 7).

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

Anti-IL23 had the highest SUCRA at class level in terms of serious adverse events (versus placebo: RR 0.80, 95% CI 0.57 to 1.16; SUCRA = 75.4), followed by non-biological systemic treatments (versus placebo: RR 0.74, 95% CI 0.35 to 1.57; SUCRA = 69.3), small molecules (versus placebo: RR 0.85, 95% CI 0.50 to 1.45; SUCRA = 58), and then anti-TNF alpha agents (versus placebo: RR 0.92, 95% CI 0.71 to 1.19; SUCRA = 47.7). The heterogeneity τ for this network overall was 0, which we considered to be low. Placebo ranking changed from 7 (the lowest/worst SUCRA at class level) for serious adverse events to 3 (out of 7) after excluding flares of psoriasis as SAEs.

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

Methotrexate had the highest SUCRA at drug level in terms of serious adverse events (versus placebo: RR 0.08, 95% CI 0.01 to 0.68; SUCRA = 97.2; high-certainty evidence), followed by bimekizumab (versus placebo: RR 0.52, 95% CI 0.25 to 1.09; SUCRA = 80.4; moderate-certainty evidence), risankizumab (versus placebo: RR 0.73, 95% CI 0.47 to 1.13; SUCRA = 66.9; moderate-certainty evidence), certolizumab (versus placebo: RR 0.70, 95% CI 0.31 to 1.58; SUCRA = 64.4; moderate-certainty evidence), then deucravacitinib (versus placebo: RR 0.61, 95% CI 0.06 to 5.71; SUCRA = 60.7; moderate-certainty evidence). However, no significant difference was observed between drugs and placebo. The heterogeneity τ for this network overall was 0, which we considered to be low. After excluding worsening of psoriasis as a SAE, bimekizumab, risankizumab, deucravacitinib had still the highest SUCRA rank. Methotrexate could not be assessed. Placebo rose from the 15th to the 5th rank.

1.3 Relationship between PASI 90 and serious adverse events

See Figure 12.

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

At drug level, risankizumab and bimekizumab might be the overall best treatments, considering both outcomes jointly. Other highly-effective drugs (ixekizumab and infliximab) had serious adverse events.

2. Secondary outcomes

2.1 Proportion of participants who achieved PASI 75

DIRECT EVIDENCE

We report treatment estimates for pairwise 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 121 trials, involving 49,210 participants (93.7% of the participants in this review). For one trial (PRESTA 2010), the number of randomised participants was not available. We added these trials to the complete-case analyses. This outcome was reported in 10 trials out of 121 (Dogra 2012; Dogra 2013; Dubertret 1989; Khatri 2016; Laburte 1994; Ortonne 2013; PRESTA 2010; PRISTINE 2013; SCULPTURE 2015; SIGNATURE 2019), comparing different dosages of the same drug in each case. We added these trials to the sensitivity analysis at dose level. This outcome was reported in 10 trials out of 121 with biological-naïve participants that were added to the sensitivity analysis for all trials, whatever the previous treatments received by the participants (Barker 2011; Caproni 2009; CHAMPION 2008; CHANGE 2021; Gisondi 2008; Lee 2016; POLARIS 2020; PRIME 2017; Reich 2020; Thaci 2021). Seventy-one trials, involving 24,145 participants, were placebo-controlled trials; 33 trials, involving 11,212 participants, were head-to-head comparisons; and 17 trials, involving 13,853 participants, had both a placebo and at least two active treatments arms. PASI 75 was not reported for the 12 remaining trials, and we were not able to obtain missing information from the trial authors (Table 2).

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

We present the summary relative effects from the network meta-analysis in league tables for both class-level (Figure 6) and drug-level (Figure 8) analyses. All of the interventions appeared superior to placebo in terms of reaching PASI 75. At class level, the anti-IL17 class of drugs was associated with a higher chance of reaching PASI 75 compared to the other classes, except for anti-IL23 (Figure 6). All of the interventions (anti-IL17, anti-IL23, anti-IL12/23, anti-TNF alpha) appeared significantly superior to the small molecule class and the non-biological systemic class, and the small molecules appeared significantly superior to the non-biological systemic agents. Results of comparisons between each of the drugs are available in Figure 8. Infliximab, anti-IL17 drugs (ixekizumab, bimekizumab, secukinumab and brodalumab), and anti-IL23 drugs except tildrakizumab were significantly more likely to reach PASI 75, than ustekinumab, tildrakizumab and other anti-TNF alpha (adalimumab, certolizumab and etanercept).

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

Ranking analysis performed with SUCRA strongly suggested that anti-IL17 had a better chance of reaching PASI 75 at class level (versus placebo: RR 13.43, 95% CI 12.00 to 15.03; SUCRA = 98.5), followed by anti-IL23 (versus placebo: RR 12.48, 95% CI 11.03 to 14.11; SUCRA = 83.9), anti-IL12/23 (versus placebo: RR 11.39, 95% CI 10.08 to 12.88; SUCRA = 67.6), and anti-TNF alpha (versus placebo: RR 9.15, 95% CI 8.20 to 10.21; SUCRA = 50). The heterogeneity τ for this network overall was 0.02, which we considered to be low.

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

Ranking analysis performed with SUCRA strongly suggested that infliximab had the higher chance of reaching PASI 75 at drug level (versus placebo: RR 18.05, 95% CI 11.96 to 27.33; SUCRA = 96.8), followed by ixekizumab (versus placebo: RR 13.86, 95% CI 12.19 to 15.76; SUCRA = 88.4), risankizumab (versus placebo: RR 13.72, 95% CI 12.19 to 15.44; SUCRA = 87.8), bimekizumab (versus placebo: RR 13.70, 95% CI 12.08 to 15.53; SUCRA = 87.4), then secukinumab (versus placebo: RR 12.99, 95% CI 11.167 to 14.46; SUCRA = 77.6). The heterogeneity τ for this network overall was 0, which we considered to be low.

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

DIRECT EVIDENCE

We report treatment estimates for pairwise 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 111 trials, involving 48,072 participants (91.5% of the participants in this review). For three studies (Nugteren-Huying 1990; Sandhu 2003; PRESTA 2010), the number of randomised participants was not available. We added these trials to the complete-case analyses. This outcome was reported in six trials out of 111 (Khatri 2016; NCT03504852; Ortonne 2013; PRESTA 2010; PRISTINE 2013; SCULPTURE 2015), comparing different dosages of the same drug. We added these trials to the sensitivity analysis at dose level. This outcome was reported in eight trials out of 111 with biological-naïve participants that were added to the sensitivity analysis for all trials, whatever the previous treatments received by the participants (Barker 2011; CHAMPION 2008; CHANGE 2021; Gisondi 2008; Lee 2016; PRIME 2017; Reich 2020; Thaci 2021). Sixty-six trials, involving 22,532 participants, were placebo-controlled trials; 28 trials, involving 11,687 participants, were head-to-head comparisons; and 17 trials, involving 13,853 participants, had both a placebo and at least two active treatments arms. PGA 0/1 was not reported for the 22 remaining trials, and we were not able to obtain missing information from the trial authors (Table 2).

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

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 9). At class level, 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 and the non-biological systemic class of treatments. We found no significant difference between small molecule and non-biological systemic agents. Results of comparisons between each of the drugs are available in Figure 9.

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

Ranking analysis performed with SUCRA strongly suggested that anti-IL17 had a better chance of reaching PGA0/1 at class level (versus placebo: RR 14.41, 95% CI 12.32 to 16.85; SUCRA = 99.7), followed by anti-IL23 (versus placebo: RR 12.07, 95% CI 10.22 to 14.25; SUCRA = 82.4), anti-IL12/23 (versus placebo: RR 10.56, 95% CI 8.90 to 12.54; SUCRA = 67.7), and anti-TNF alpha (versus placebo: RR 8.50, 95% CI 7.31 to 9.88; SUCRA = 50.2). The heterogeneity τ for this network overall was 0.06, which we considered to be low.

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

Ranking analysis performed with SUCRA strongly suggested that bimekizumab had a better chance of reaching PGA0/1 at drug level (versus placebo: RR 15.35, 95% CI 12.83 to 18.38; SUCRA = 91.1), followed by ixekizumab (versus placebo: RR 14.88, 95% CI 12.79 to 17.32; SUCRA = 88.2), then infliximab (versus placebo: RR 15.47, 95% CI 9.47 to 25.26; SUCRA = 85.2), risankizumab (versus placebo: RR 14.23, 95% CI 12.21 to 16.58; SUCRA = 82.5), secukinumab (versus placebo: RR 13.59, 95% CI 11.71 to 15.66; SUCRA = 76.2), then sonelokimab (versus placebo: RR 13.29, 95% CI 9.8 to 18.03; SUCRA = 74.6). The heterogeneity τ for this network overall was 0.01, which we considered to be low.

Focusing on efficacy outcomes (PASI 90, PASI 75, and PGA 0/1), the results were similar at class level (Figure 10; Table 4) and at drug level (Figure 11; Table 5).

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 67 trials, involving 28,702 participants (54.6% of the participants in this review). This outcome was also reported in five trials (out of 67) (Khatri 2016; Ortonne 2013; PRISTINE 2013; SCULPTURE 2015; SIGNATURE 2019), comparing different dosages of the same drug. We added these trials to the sensitivity analyses at dose level. This outcome was reported in six trials out of 67 with biological-naïve participants that were added to the sensitivity analysis for all trials, whatever the previous treatments received by the participants (Barker 2011; CHAMPION 2008; CHANGE 2021; POLARIS 2020; Reich 2020; Thaci 2021). The quality-of-life outcome was not reported for the 66 remaining trials, and we were not able to obtain missing information from the trial authors (Table 2). Forty-three trials, involving 16,437 participants, were placebo-controlled trials; 12, involving 3563 participants, were head-to-head comparisons; and 12, involving 8702 participants, had both a placebo and at least two active treatments arms.

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

We present the summary relative effects from the network meta-analysis in league tables for both class-level (Figure 6) and drug-level (Figure 9) analyses. All classes of treatments 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 (Figure 6). These differences were statistically significant for all of the classes. No significant difference was shown between anti-IL23, anti-IL12/23 and anti-IL17. Anti-IL23 and anti-IL17 was more favourable than anti-TNF alpha. There were no significant differences between the small molecules and the non-biological agents. Results of comparisons between each of the drugs are available in Figure 9.

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

Ranking analysis performed with SUCRA strongly suggested that anti-IL23 had a better chance of improving quality of life at class level (versus placebo: standardised mean difference (SMD) −1.41, 95% confidence interval (CI) −1.63 to −1.18; SUCRA = 84.2), followed by anti-IL17 (versus placebo: SMD −1.37, 95% CI −1.60 to −1.14; SUCRA = 79.2), and anti-IL12/23 (versus placebo: SMD −1.33, 95% CI −1.59 to −1.07; SUCRA = 73.7). The heterogeneity τ for this network overall was 0.12, which we considered to be low.

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

Ranking analysis for quality of life performed with SUCRA strongly suggested that ixekizumab was the best treatment at drug level (versus placebo: SMD −1.76, 95% CI −2.04 to −1.49; SUCRA = 94.7), followed by risankizumab (versus placebo: SMD −1.77, 95% CI −2.16 to −1.39; SUCRA = 94.4), ustekinumab (versus placebo: SMD −1.39, 95% CI −1.61 to −1.16; SUCRA = 73.4), secukinumab (versus placebo: SMD −1.40, 95% CI −1.90 to −0.91; SUCRA = 72.2), then tildrakizumab (versus placebo: SMD −1.35, 95% CI −1.68 to −1.03; SUCRA = 69.9). The heterogeneity τ for this network overall was 0.08, which we considered to be low. Moreover, four interventions (acitretin, FAEs, ciclosporin, sonelokimab) were not included in the ranking at drug level, due to no available data.

In total, information on quality of life was poorly reported and lacking for almost half of the population included in the NMA, so results have to be considered with caution.

2.4 The proportions of participants with adverse events

DIRECT EVIDENCE

We report treatment estimates for pairwise 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

The adverse events (AEs) outcome was available in 110 trials, involving 46,502 participants (88.5% of the participants in this review). AEs were not reported for the 23 remaining trials, and we were not able to obtain missing information from the trial authors (Table 2). This outcome was also reported in five trials (out of 110) (Khatri 2016; Ortonne 2013; PRISTINE 2013; SCULPTURE 2015; SIGNATURE 2019), comparing different dosages of the same drug, and were added to the sensitivity analyses at dose level. This outcome was reported in nine trials out of 110 with biological-naïve participants that were added to the sensitivity analysis for all trials, whatever the previous treatments received by the participants (Barker 2011; CHAMPION 2008; CHANGE 2021; Gisondi 2008; Lee 2016; POLARIS 2020; PRIME 2017; Reich 2020; Thaci 2021). Sixty-five trials, involving 22,322 participants, were placebo-controlled trials; 28, involving 10,327 participants, were head-to-head comparisons; and 17, involving 13,853 participants, had both a placebo and at least two active treatments arms.

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

We present the summary relative effects from the network meta-analysis in league tables for both class-level (Figure 6) and drug-level (Figure 8) analyses. At class level, all of the classes of treatments had a more significant risk of AEs compared to placebo, except anti-IL23. Significant associations were found: anti-IL17 had a higher risk of AEs compared with anti-IL23, anti-IL12/23 and anti-TNF; anti-IL23, anti-IL12/23 and anti-TNF had a lower risk of AEs compared with small molecules (Figure 6). Results of comparisons between each of the drugs are available in Figure 8.

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

Placebo had the highest SUCRA (SUCRA 94.9) at class-level for all adverse events, followed by anti-IL23 (versus placebo: RR 1.02, 95% CI 0.96 to 1.08; SUCRA = 85.1), anti-TNF agents (versus placebo: RR 1.07, 95% CI 1.03 to 1.12; SUCRA = 56.3), then anti-IL12/23 (versus placebo: RR 1.08, 95% CI 1.02 to 1.14; SUCRA = 54.7). The heterogeneity τ for this network overall was 0.01, which we considered to be low.

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

Tildrakizumab had the highest SUCRA at drug-level for all adverse events (versus placebo: RR 0.93, 95% CI 0.82 to 1.04; SUCRA = 93.5), followed by certolizumab (versus placebo: RR 1.01, 95% CI 0.89 to 1.15; SUCRA = 86.6), placebo (SUCRA = 85.4), then netakimab

(versus placebo: RR 0.99, 95% CI 0.81 to 1.22; SUCRA = 81.1). The heterogeneity τ for this network overall was 0, which we considered to be low.

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

DIRECT EVIDENCE

We report treatment estimates for pairwise meta-analyses at drug level in Analysis 7.1; Analysis 7.2; and Analysis 7.3.

Nine head-to-head comparisons compared two different biologics; seven compared two different dosages of secukinumab, guselkumab, ixekizumab, risankizumab and apremilast, respectively; and one compared a biologic with placebo. We produced two meta-analyses for the comparisons risankizumab versus ustekinumab and secukinumab 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 1.23, 95% CI 1.15 to 1.31); ixekizumab was more effective than ustekinumab to reach PASI 90 at 52 weeks (RR 1.30, 95% CI 1.11 to 1.52); bimekizumab was more effective than ustekinumab to reach PASI 90 at 52 weeks (RR 1.47, 95% CI 1.27 to 1.70); risankizumab was more effective than secukinumab to reach PASI 90 at 52 weeks (RR 1.52, 95% CI 1.31 to 1.76); bimekizumab was more effective than secukinumab to reach PASI 90 at 52 weeks (RR 1.19, 95% CI 1.09 to 1.28); guselkumab was more effective than adalimumab to reach PASI 90 at 52 weeks (RR 1.59, 95% CI 1.40 to 1.81); ixekizumab every other week was more effective than ixekizumab every four weeks to reach PASI 90 at 52 weeks (RR 1.06, 95% CI 1.01 to 1.11); and secukinumab 300 mg was more effective than secukinumab 150 mg to reach PASI 90 at 52 weeks (RR 0.84, 95% CI 0.78 to 0.91).

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

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

DIRECT EVIDENCE

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

Eight head-to-head comparisons compared two different biologics; seven compared two different dosages of secukinumab, guselkumab, ixekizumab, risankizumab and apremilast, respectively. We produced one meta-analysis 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 1.13, 95% CI 1.04 to 1.22); ixekizumab was more effective than ustekinumab to reach PASI 75 at 52 weeks (RR 1.16, 95% CI 1.05 to 1.29); risankizumab was more effective than secukinumab to reach PASI 75 at 52 weeks (RR 1.28, 95% CI 1.14 to 1.44); bimekizumab was more effective than secukinumab to reach PASI 75 at 52 weeks (RR 1.09, 95% CI 1.02 to 1.16); guselkumab was more effective than adalimumab to reach PASI 75 at 52 weeks (RR 1.40, 95% CI 1.28 to 1.54); 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); and secukinumab 300 mg was more effective than secukinumab 150 mg to reach PASI 75 at 52 weeks (RR 0.90, 95% CI 0.85 to 0.94).

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: section 4. Subgroup and sensitivity analyses). The results were very similar.

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 ratio (on the right, percentage of males in the y axis) of participants across comparisons (x axis) ACI: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; DEUCRAVA: deucravacitinib; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; NETA: netakimab; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; SONELO: sonelokimab; TILDRA: tildrakizumab; USK: ustekinumab

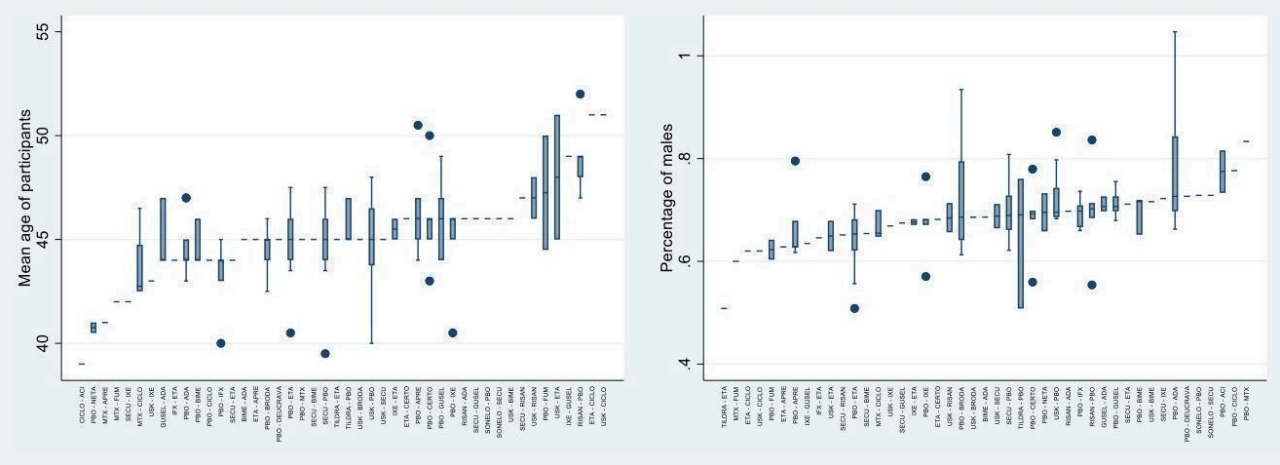
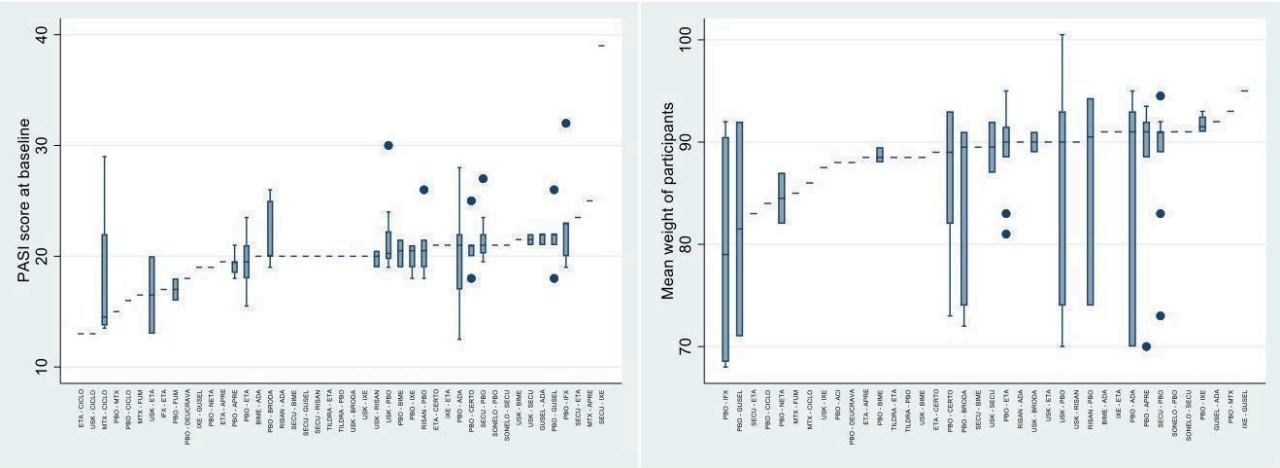


Figure 16. Distributions of PASI score at baseline (on the right, mean PASI in the y axis) and weight (on the right, mean weight in kilograms in the y axis) of participants across comparisons (x axis) ACI: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab;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



At drug-level analysis, the global test for inconsistency was not significant for any of the outcomes. 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 did not indicate inconsistency for the two primary outcomes (Figure 19; Figure 20). There were a handful of loops and comparisons with statistically significant inconsistency for secondary outcomes (PASI 75 and adverse events), but it did not 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; DEUCRAVA: deucravacitinib; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; NETA: netakimab; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; SONELO: sonelokimab; TILDRA: tildrakizumab; USK: ustekinumab

PASI 90

Side	Direct Coef.	Direct Std. Err.	Indirect Coef.	Indirect Std. Err.	Difference Coef.	Difference Std. Err.	P>|z|
PBO RISAN	3.454362	.1641107	3.330762	.0996773	.1236002	.1759488	0.482
PBO USK	2.839672	.1187746	2.987833	.0942484	-.1481604	.1229388	0.228
ADA PBO	-2.683874	.1215184	-2.982913	.1091078	.2990387	.1465307	0.041
ADA BIME	.5064654	.0802123	.5835725	.0583639	-.0771071	.0991986	0.437
ADA GUSEL	.3732888	.0469024	.2339826	.0688869	.1393063	.08328	0.094
ADA RISAN	.4245991	.0701418	.5874383	.070757	-.1628391	.0996314	0.102
APRE ETA	.3263019	.3430595	.326482	.4388423	-.0001801	.5515884	1.000
BIME PBO	-3.517977	.177119	-3.39515	.0911069	-.1228274	.1748247	0.482
BIME SECU	-.1403446	.0402006	-.1480572	.0671975	.0077126	.0783045	0.922
BIME USK	-.530614	.0820122	-.4525506	.0453381	-.0780634	.0937606	0.405
BRODA USK	-.2371073	.0456173	-.5666659	.3936842	.3295587	.3982552	0.408
CERTO ETA	-.1829234	.1478516	-.6119028	.4706197	.4289795	.493787	0.385
ETA PBO	-2.408151	.1375309	-2.320776	.1423876	-.0873756	.2099514	0.677
ETA IFX	2.219199	1.008227	1.38137	.5062205	.8378284	1.128176	0.458
ETA IXE	1.067387	.0706766	1.002844	.0872977	.0645429	.1122255	0.565
ETA SECU	.84724	.1157978	.9205185	.0664969	-.0732785	.1333633	0.583
ETA TILDRA	.5704139	.1198175	.3672879	.4360345	.203126	.4539124	0.655
ETA USK	.5889475	.1102207	.567613	.0684427	.0213345	.129742	0.869
FUM PBO	-1.497381	.4083435	-1.073687	1.600468	-.423693	1.651739	0.798
FUM MTX	.693147	1.197219	.2694549	1.137941	.423692	1.651739	0.798
GUSEL PBO	-3.388542	.1468513	-3.129053	.0914464	-.2594885	.1498629	0.083
GUSEL IXE	.2570872	.047527	.1516307	.0720756	.1054565	.0863348	0.222
GUSEL SECU	.0960834	.0425173	.0605171	.0609307	.0355663	.0742985	0.632
IFX PBO	-3.752858	.4976311	-4.590679	1.012493	.8378203	1.128175	0.458
IXE PBO	-3.562326	.1752079	-3.367727	.0968906	-.1945985	.1901061	0.306
IXE USK	-.3417531	.0753432	-.538594	.0561579	.1968409	.0939697	0.036
MTX PBO	-1.76685	1.062155	-2.190501	1.264934	.4236512	1.651736	0.798
RISAN SECU	-.1168454	.073333	-.0734009	.0588742	-.0434445	.094042	0.644
RISAN USK	-.4955189	.0759928	-.3690593	.0616197	-.1264597	.0980159	0.197
SECU USK	-.33499	.0352209	-.3159706	.0509696	-.0190194	.0619549	0.759

P value of the design-by-treatment interaction model = 0.75

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; DEUCRAVA: deucravacitinib; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; NETA: netakimab; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; SONELO: sonelokimab; TILDRA: tildrakizumab; USK: ustekinumab

SAE

Side	Direct		Indirect		Difference		
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P>|z|
PBO RISAN	-.7406052	.3372778	.0604109	.3149643	-.8010161	.473924	0.091
PBO USK	.0011927	.2324163	-.0774961	.2616697	.0786887	.3526905	0.823
ADA PBO	-.1690854	.243202	.3830229	.3856915	-.5521083	.4643227	0.234
ADA BIME	-.6962869	.6249607	-.6329063	.4947744	-.0633806	.7971058	0.937
ADA GUSEL	-.0837997	.3572239	-.1279372	.3278834	.0441376	.4847388	0.927
ADA RISAN	.1152779	.4522161	-.5458554	.3236463	.6611333	.5560992	0.234
APRE ETA	-.3893942	.8126573	-.002452	.3664432	-.3869423	.892166	0.664
BIME PBO	.5630507	.5272806	.7537333	.583345	-.1906826	.8196384	0.816
BIME USK	.6782837	.625097	.5773117	.4924959	.100972	.795512	0.899
BRODA USK	-.2834434	.4146964	.2319222	.4978652	-.5153655	.7057568	0.465
CERTO ETA	.7686644	.9566035	-.1489913	.5855099	.9176557	1.209828	0.448
ETA PBO	.3536665	.2353255	-.1309322	.3993305	.4845987	.4668157	0.299
ETA IFX	-.0833816	1.384385	.4401571	.4329992	-.5235388	1.450521	0.718
ETA IXE	.0543427	.3313905	.2146707	.3511544	-.1603279	.4846556	0.741
ETA SECU	.4649672	.6078508	.2571609	.2633766	.2078063	.6582648	0.752
ETA TILDRA	-.3538248	.4870222	.7683717	.7324077	-1.122196	.8953745	0.210
ETA USK	.2217037	.6085389	.1880333	.2685096	.0336704	.6651443	0.960
GUSEL PBO	-.0407305	.3794747	.1570344	.2354622	-.1977649	.4575264	0.666
GUSEL IXE	.0924652	.3426605	-.0786783	.3234405	.1711436	.471201	0.716
GUSEL SECU	.1525827	.2472761	.1785135	.3131889	-.0259308	.3990398	0.948
IFX PBO	-.2027733	.3823133	.3207651	1.399231	-.5235383	1.450521	0.718
IXE PBO	.0902807	.2846496	.1063318	.3310698	-.0160511	.4548076	0.972
IXE USK	.3114927	.72108	.0301952	.2647776	.2812975	.7681559	0.714
RISAN SECU	-.3993489	.5153108	.6039882	.2793189	-1.003337	.5861436	0.087
RISAN USK	.6119919	.3415955	-.0203423	.3254799	.6323341	.4719511	0.180
SECU USK	-.23463	.3051129	.001245	.2546018	-.235875	.3973864	0.553

P value of the design-by-treatment interaction model = 0.41

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. AE: adverse events; AIL12/23: anti-IL12/23; AIL17: anti-IL17; AIL23: anti-IL23, ATA: anti-TNF alpha; CSA: non-biological conventional systemic agents; PASI: Psoriasis Area and Severity Index; PBO: placebo; PGA: Physician Global Assessment; QoL: quality of life; SAE: serious adverse events; SM: small molecules

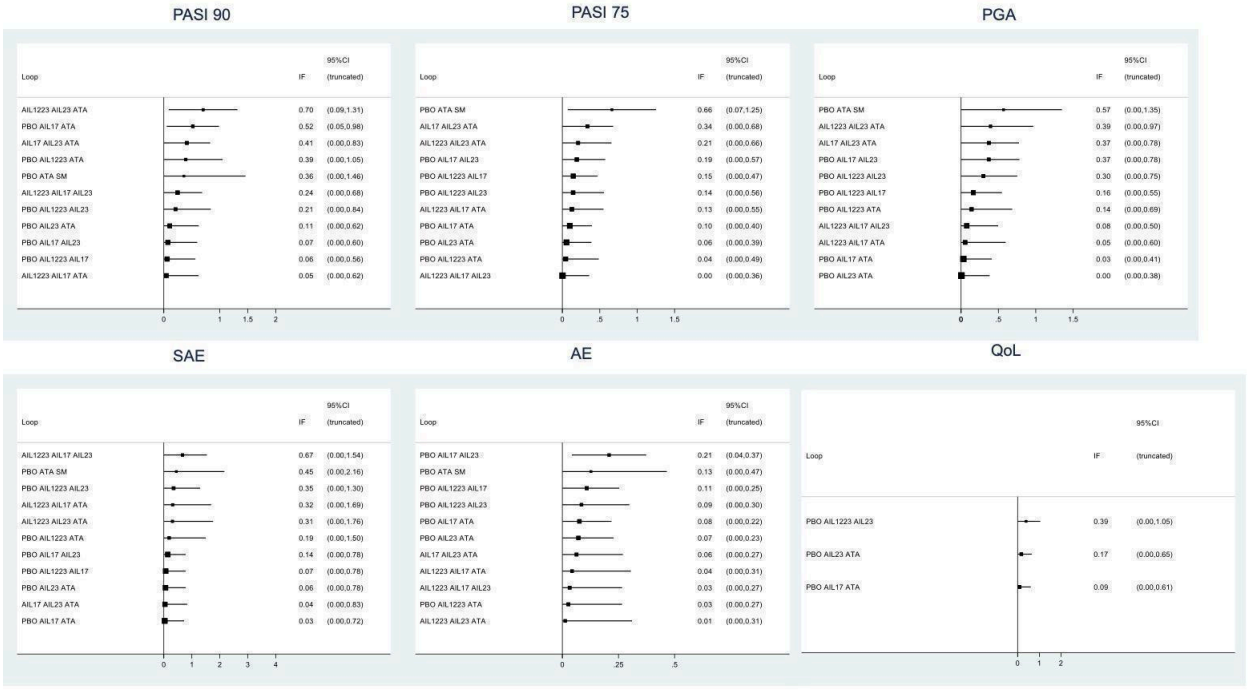
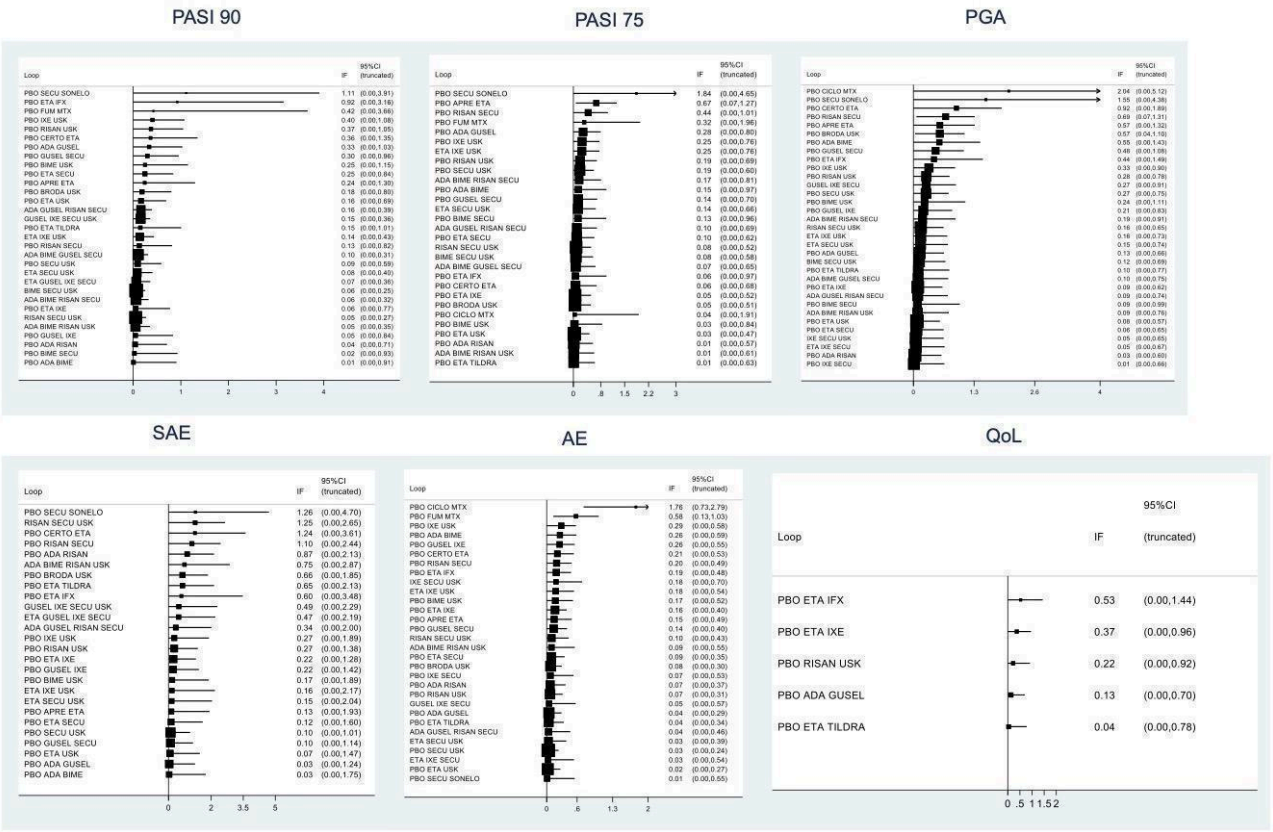


Figure 20. Inconsistency plots for all the outcomes at drug level Inconsistency factor (IF) is calculated as the risk ratio (RR)/standardised mean difference (SMD) for direct evidence over the RR/SMD for indirect evidence in the loop with its 95% confidence interval (CI). IF value close to 0 indicates the absence of evidence for disagreement between direct and indirect ACI: acitretin; ADA: adalimumab; AE: adverse events; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; DEUCRAVA: deucravacitinib; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; NETA: netakimab; PASI: Psoriasis Area and Severity Index; PBO: placebo; PGA: Physician Global Assessment; QoL: quality of life; RISAN: risankizumab; SAE: serious adverse events; SECU: secukinumab; SONELO: sonelokimab; TILDRA: tildrakizumab; USK: ustekinumab



4. Subgroup and sensitivity analyses

As we found no heterogeneity, we did not perform subgroup analyses. From a clinical point of view, it could nevertheless be interesting to have specific efficacy/safety data depending on participants' comorbidities or psoriasis characteristics. However, we did not have enough data for any of the aforementioned characteristics, 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 and 0.01 for PASI 90 and SAEs, respectively, which we considered to be low);
- completers (Figure 22) (the heterogeneity τ for this subgroup network was 0 for PASI 90 and SAEs, respectively, which we considered to be low);
- analyses at dose-level splitting approved dosages versus other dosages for each drug (Figure 23) (the heterogeneity τ for this subgroup network was 0.1 for PASI 90 and 0 for SAEs, which we considered to be low);
- 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 to be low);
- analysing only the studies with a short-term assessment from eight to 16 weeks (Figure 25): the heterogeneity τ for this subgroup network was 0 for PASI 90 and SAEs, which we considered to be low;
- analysing including 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 to be low;
- analysing only drugs approved by European Medical Agency for plaque psoriasis (Figure 27; Figure 28);
  - Non biological systemic treatments: FAEs, acitretin, ciclosporin, methotrexate;
  - Small molecules: apremilast;

- Anti-TNF alpha: infliximab, etanercept, adalimumab, certolizumab pegol;
- Anti-IL12/23: ustekinumab;
- Anti-IL17: secukinumab, brodalumab, ixekizumab, bimekizumab;
- Anti-IL23: tildrakizumab, guselkumab, risankizumab.

Figure 21. Sensitivity analyses - Interval plot. Network meta-analysis results for primary outcomes (PASI 90 and serious adverse events, left and right forest plot respectively) for trials with at least 50 participants. ACI: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; DEUCRAVA: deucravacitinib; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; NETA: netakimab; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; SONELO: sonelokimab; TILDRA: tildrakizumab; USK: ustekinumab CI: confidence interval; PASI: Psoriasis Area and Severity Index; RR: risk ratio

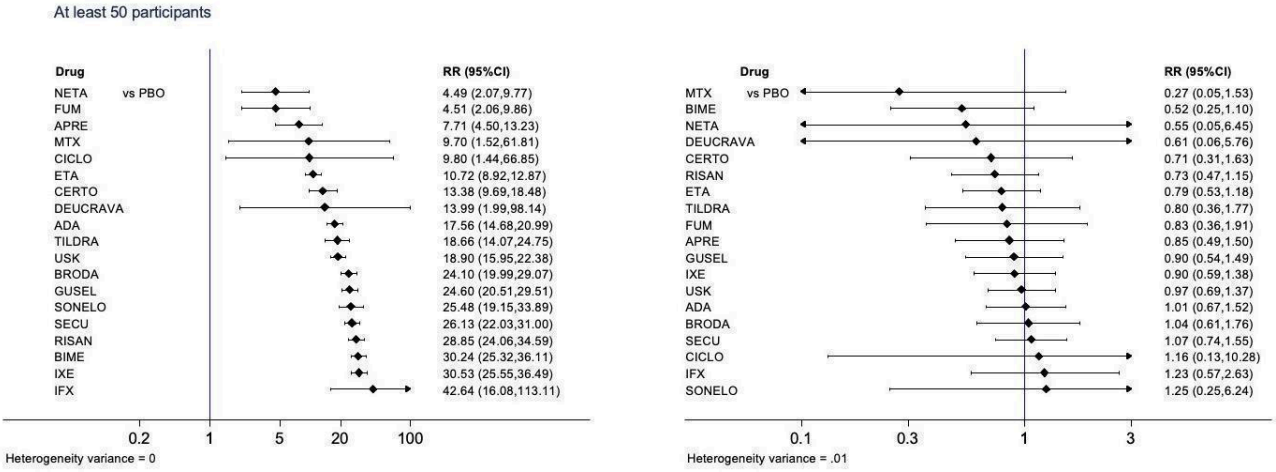


Figure 22. Sensitivity analyses - Interval plot. Network meta-analysis results for primary outcomes (PASI 90 and serious adverse events, left and right forest plot respectively) for the completers. Outcomes were measured at the induction phase (assessment from 8 to 24 weeks after randomisation). ACI: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

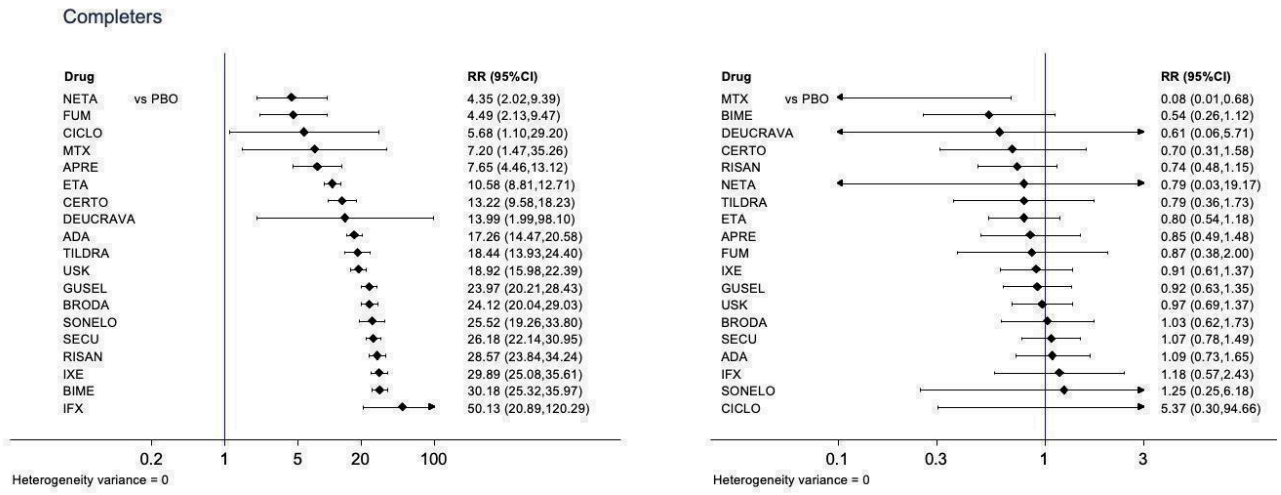


Figure 23. Sensitivity analyses - Interval plot. Network meta-analysis results for primary outcomes (PASI 90 and serious adverse events, left and right forest plot respectively) for all the interventions depending on the doses: approved dosages versus other dosages Outcomes were measured at the induction 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; 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; BIME_AMM/Other: bimekizumab, S/C, 320 mg (2 x 160 mg injections) at week 0, 4, 8, 12, 16 and every 8 weeks thereafter/other dosages. DEUCRACA (deucravacitinib), SONELO (sonelokimab) and NETA (netakimab) were grouped in one dosage whatever the dosages. CI: confidence interval; PASI: Psoriasis Area and Severity Index; RR: risk ratio; AMM: 'approved dosage'

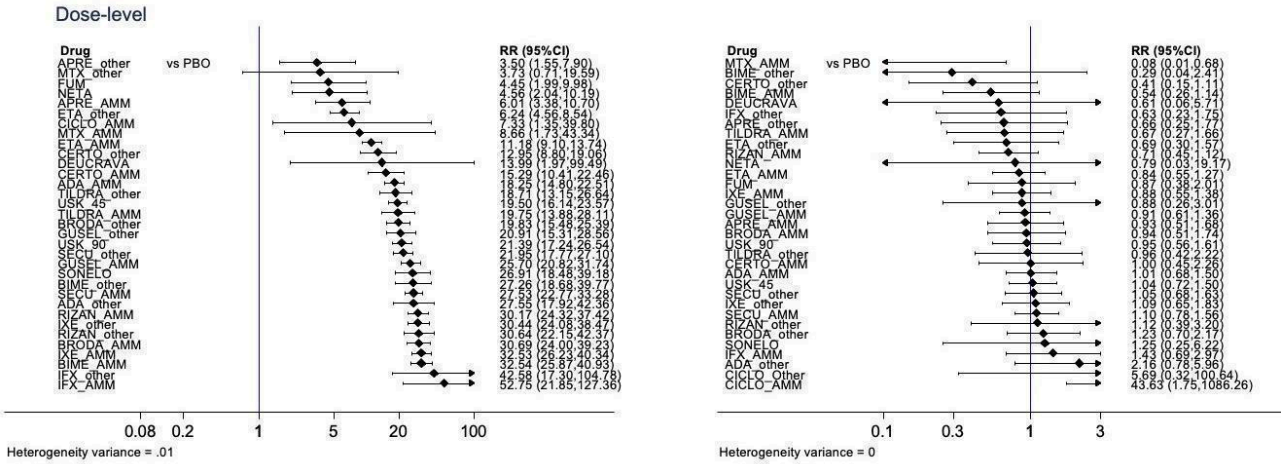


Figure 24. Sensitivity analyses - Interval plot. Network meta-analysis results for primary outcomes (PASI 90 and serious adverse events, left and right forest plot respectively) for all the interventions excluding studies at high risk of bias. Outcomes were measured at the induction phase (assessment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

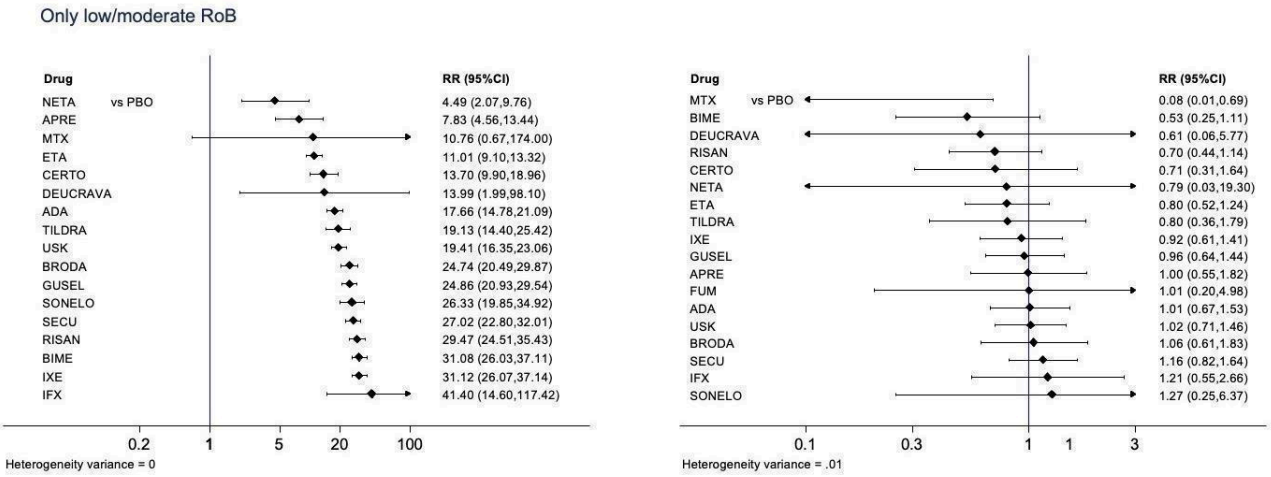


Figure 25. Sensitivity analyses - Interval plot. Network meta-analysis results for primary outcomes (PASI 90 and serious adverse events, left and right forest plot respectively) for all the interventions including studies with a short-term assessment from 8 to 16 weeks. ACI: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; DEUCRAVA: deucravacitinib; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; NETA: netakimab; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; SONELO: sonelokimab; TILDRA: tildrakizumab; USK: ustekinumab CI: confidence interval; PASI: Psoriasis Area and Severity Index; RR: risk ratio

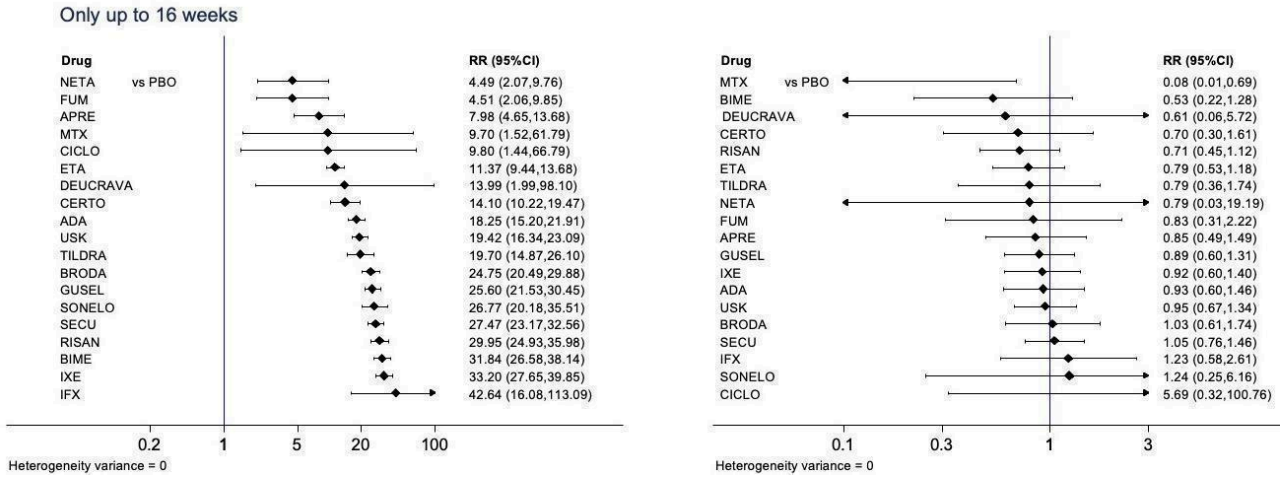


Figure 26. Sensitivity analyses - Interval plot. Network meta-analysis results for primary outcomes (PASI 90 and serious adverse events, left and right forest plot respectively) for all the interventions including studies with systemic treatment-naive participants. Outcomes were measured at the induction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

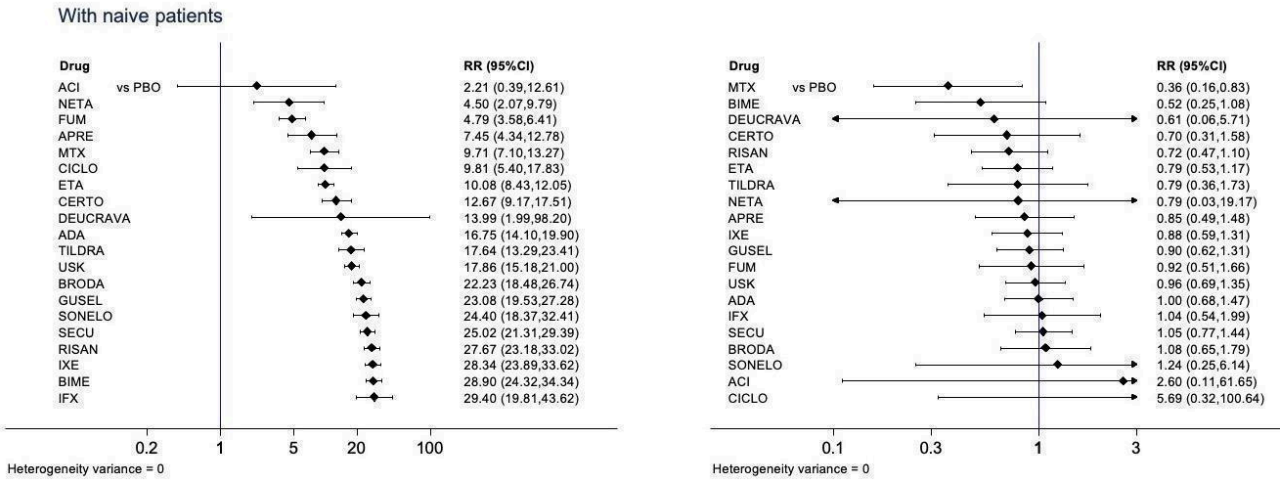
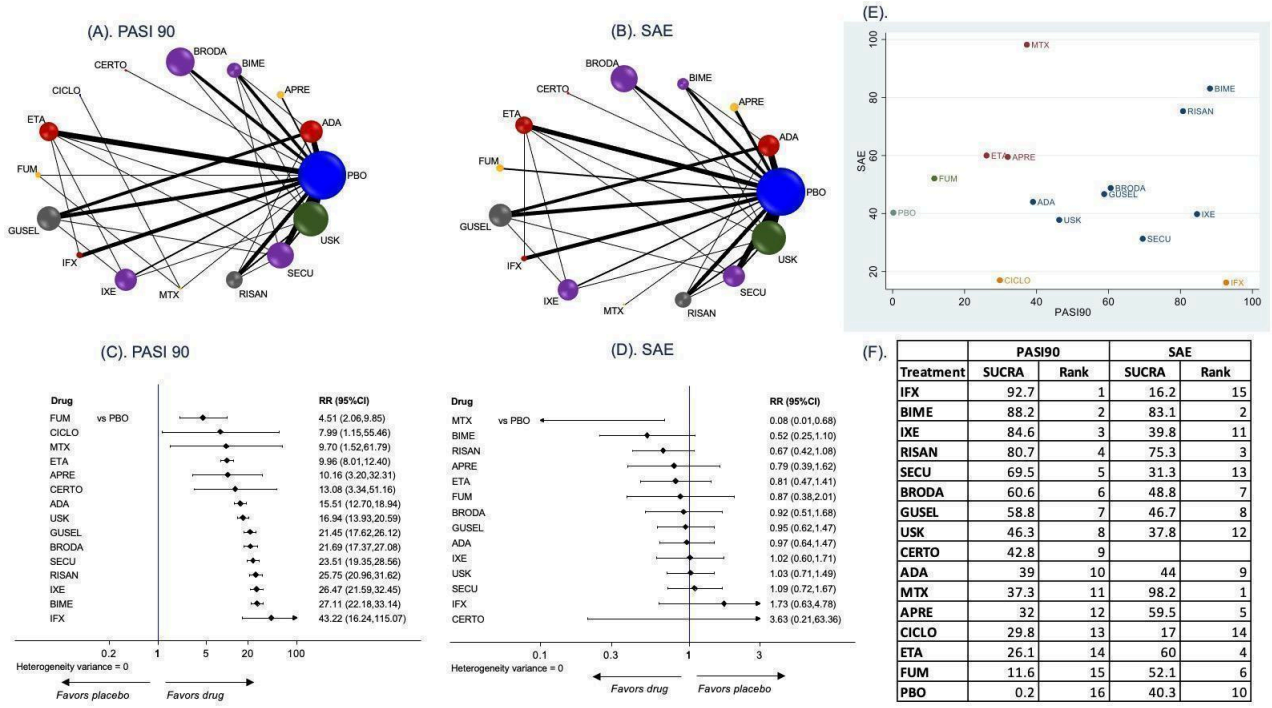


Figure 27. Network diagrams for PASI 90 (A) and SAE (B) when the analyses were restricted to drugs approved by European Medical Agency The size of the nodes is proportional to the total number of participants allocated to each intervention and the thickness of the lines proportional to the number of studies evaluating each direct comparison. Relative effects from the network meta-analyses against placebo with their 95% confidence (C&D) Interval plot. Network meta-analysis estimates of the interventions versus placebo for the primary outcomes Two-dimensional ranking plot based on surface under the cumulative ranking curve (SUCRA) values for benefit (PASI 90) and acceptability (serious adverse events) at drug level (E) 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 Ranking analysis for PASI 90 and SAE (F). PASI: Psoriasis Area and Severity Index; SAE: serious adverse events; SUCRA: surface under the cumulative ranking curve; CI: confidence interval; RR: risk ratio; SAE: serious adverse events 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; USK: ustekinumab



(F).

	PASI90		SAE	
Treatment	SUCRA	Rank	SUCRA	Rank
IFX	92.7	1	16.2	15
BIME	88.2	2	83.1	2
IXE	84.6	3	39.8	11
RISAN	80.7	4	75.3	3
SECU	69.5	5	31.3	13
BRODA	60.6	6	48.8	7
GUSEL	58.8	7	46.7	8
USK	46.3	8	37.8	12
CERTO	42.8	9		
ADA	39	10	44	9
MTX	37.3	11	98.2	1
APRE	32	12	59.5	5
CICLO	29.8	13	17	14
ETA	26.1	14	60	4
FUM	11.6	15	52.1	6
PBO	0.2	16	40.3	10

Figure 28. 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) for drugs approved by European Medical Agency for plaque psoriasis (Sensitivity analysis) 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 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. 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; USK: ustekinumab

Serious adverse events

IFX	3.30 (0.94,11.54)	1.70 (0.55,5.28)	2.58 (0.84,7.90)	1.58 (0.53,4.71)	1.88 (0.58,6.10)	1.82 (0.61,5.46)	1.68 (0.58,4.93)	0.48 (0.02,9.91)	1.79 (0.60,5.34)	**21.73 (2.01,234.42)**	2.18 (0.63,7.54)	-	2.13 (0.70,6.50)	1.98 (0.53,7.36)	1.73 (0.63,4.78)
1.59 (0.59,4.29)	BIME	0.52 (0.21,1.24)	0.78 (0.34,1.81)	0.48 (0.21,1.08)	0.57 (0.22,1.45)	0.55 (0.24,1.25)	0.51 (0.24,1.10)	0.14 (0.01,2.77)	0.54 (0.25,1.16)	6.58 (0.68,63.95)	0.66 (0.24,1.84)	-	0.64 (0.26,1.58)	0.60 (0.20,1.82)	0.52 (0.25,1.10)
1.63 (0.61,4.40)	1.02 (0.92,1.14)	IXE	1.52 (0.78,2.94)	0.93 (0.53,1.63)	1.10 (0.50,2.41)	1.07 (0.64,1.78)	0.99 (0.56,1.74)	0.28 (0.02,5.12)	1.05 (0.56,1.95)	**12.76 (1.40,116.75)**	1.28 (0.53,3.10)	-	1.25 (0.65,2.39)	1.16 (0.43,3.11)	1.02 (0.60,1.71)
1.68 (0.62,4.53)	1.05 (0.95,1.17)	1.03 (0.91,1.16)	RISAN	0.61 (0.36,1.05)	0.73 (0.34,1.54)	0.71 (0.40,1.25)	0.65 (0.39,1.08)	0.18 (0.01,3.35)	0.69 (0.40,1.19)	8.42 (0.93,76.26)	0.84 (0.36,2.00)	-	0.82 (0.41,1.64)	0.77 (0.29,2.01)	0.67 (0.42,1.08)
1.84 (0.68,4.95)	**1.15 (1.08,1.23)**	**1.13 (1.03,1.23)**	**1.10 (1.00,1.20)**	SECU	1.19 (0.58,2.42)	1.15 (0.78,1.69)	1.06 (0.70,1.62)	0.30 (0.02,5.42)	1.13 (0.67,1.90)	**13.74 (1.53,122.96)**	1.38 (0.60,3.16)	-	1.34 (0.73,2.46)	1.25 (0.49,3.18)	1.09 (0.72,1.67)
1.99 (0.74,5.40)	**1.25 (1.08,1.45)**	**1.22 (1.05,1.42)**	**1.19 (1.01,1.39)**	1.08 (0.95,1.24)	BRODA	0.97 (0.47,2.00)	0.90 (0.46,1.73)	0.25 (0.01,4.71)	0.95 (0.46,1.96)	**11.57 (1.24,107.94)**	1.16 (0.46,2.95)	-	1.13 (0.51,2.52)	1.05 (0.38,2.94)	0.92 (0.51,1.68)
2.01 (0.75,5.42)	**1.26 (1.16,1.37)**	**1.23 (1.14,1.33)**	**1.20 (1.09,1.33)**	**1.10 (1.03,1.17)**	1.01 (0.87,1.17)	GUSEL	0.93 (0.57,1.49)	0.26 (0.01,4.72)	0.98 (0.59,1.62)	**11.94 (1.33,107.19)**	1.20 (0.52,2.77)	-	1.17 (0.62,2.19)	1.09 (0.42,2.79)	0.95 (0.62,1.47)
2.55 (0.95,6.87)	**1.60 (1.48,1.73)**	**1.56 (1.43,1.71)**	**1.52 (1.38,1.67)**	**1.39 (1.31,1.47)**	**1.28 (1.13,1.45)**	**1.27 (1.17,1.37)**	USK	0.28 (0.02,5.06)	1.06 (0.64,1.76)	**12.90 (1.45,114.41)**	1.29 (0.58,2.89)	-	1.26 (0.70,2.27)	1.18 (0.47,2.92)	1.03 (0.71,1.49)
3.31 (0.62,17.72)	2.07 (0.52,8.23)	2.02 (0.51,8.04)	1.97 (0.50,7.82)	1.80 (0.45,7.13)	1.66 (0.42,6.61)	1.64 (0.41,6.51)	1.30 (0.33,5.14)	CERTO	3.75 (0.21,67.38)	**45.58 (1.27,1631.97)**	4.57 (0.24,87.13)	-	4.46 (0.24,82.00)	4.15 (0.21,81.60)	3.63 (0.21,63.36)
2.79 (1.03,7.51)	**1.75 (1.59,1.92)**	**1.71 (1.54,1.89)**	**1.66 (1.50,1.83)**	**1.52 (1.39,1.65)**	**1.40 (1.20,1.63)**	**1.38 (1.28,1.49)**	**1.09 (1.00,1.20)**	0.84 (0.21,3.35)	ADA	**12.17 (1.36,108.91)**	1.22 (0.53,2.80)	-	1.19 (0.61,2.31)	1.11 (0.44,2.82)	0.97 (0.64,1.47)
4.45 (0.55,36.16)	2.79 (0.43,17.99)	2.73 (0.42,17.56)	2.65 (0.41,17.09)	2.42 (0.38,15.59)	2.23 (0.35,14.42)	2.21 (0.34,14.23)	1.75 (0.27,11.23)	1.35 (0.14,13.43)	1.60 (0.25,10.29)	MTX	**0.10 (0.01,0.97)**	-	0.10 (0.01,0.90)	**0.09 (0.01,0.91)**	**0.08 (0.01,0.68)**
4.25 (0.93,19.36)	2.67 (0.82,8.63)	2.60 (0.80,8.43)	2.53 (0.78,8.20)	2.31 (0.72,7.47)	2.13 (0.66,6.93)	2.11 (0.65,6.82)	1.67 (0.52,5.39)	1.29 (0.22,7.69)	1.53 (0.47,4.94)	0.95 (0.11,8.47)	APRE	-	0.98 (0.40,2.40)	0.91 (0.30,2.72)	0.79 (0.39,1.62)
5.41 (0.62,47.40)	3.39 (0.48,23.79)	3.31 (0.47,23.23)	3.22 (0.46,22.60)	2.94 (0.42,20.62)	2.71 (0.39,19.07)	2.68 (0.38,18.82)	2.12 (0.30,14.85)	1.64 (0.15,17.49)	1.94 (0.28,13.61)	1.21 (0.69,2.15)	1.27 (0.13,12.14)	CICLO	-	-	-
4.34 (1.61,11.69)	**2.72 (2.37,3.12)**	**2.66 (2.34,3.01)**	**2.58 (2.23,3.00)**	**2.36 (2.08,2.67)**	**2.18 (1.83,2.60)**	**2.15 (1.89,2.45)**	**1.70 (1.50,1.93)**	1.31 (0.33,5.22)	**1.56 (1.35,1.79)**	0.97 (0.15,6.28)	1.02 (0.31,3.31)	0.80 (0.11,5.63)	ETA	0.93 (0.34,2.53)	0.81 (0.47,1.41)
9.59 (2.74,33.56)	**6.01 (2.68,13.48)**	**5.87 (2.62,13.17)**	**5.71 (2.55,12.82)**	**5.21 (2.33,11.67)**	**4.81 (2.13,10.84)**	**4.76 (2.13,10.66)**	**3.76 (1.68,8.41)**	2.90 (0.60,13.97)	**3.44 (1.54,7.71)**	2.15 (0.35,13.33)	2.25 (0.56,9.11)	1.77 (0.26,11.98)	2.21 (0.98,4.98)	FUM	0.87 (0.38,2.01)
43.22 (16.24,115.07)	**27.11 (22.18,33.14)**	**26.47 (21.59,32.45)**	**25.75 (20.96,31.62)**	**23.51 (19.35,28.56)**	**21.69 (17.37,27.08)**	**21.45 (17.62,26.12)**	**16.94 (13.93,20.59)**	**13.08 (3.34,51.16)**	**15.51 (12.70,18.94)**	**9.70 (1.52,61.79)**	**10.16 (3.20,32.31)**	**7.99 (1.15,55.46)**	**9.96 (8.01,12.40)**	**4.51 (2.06,9.85)**	PBO

PASI 90

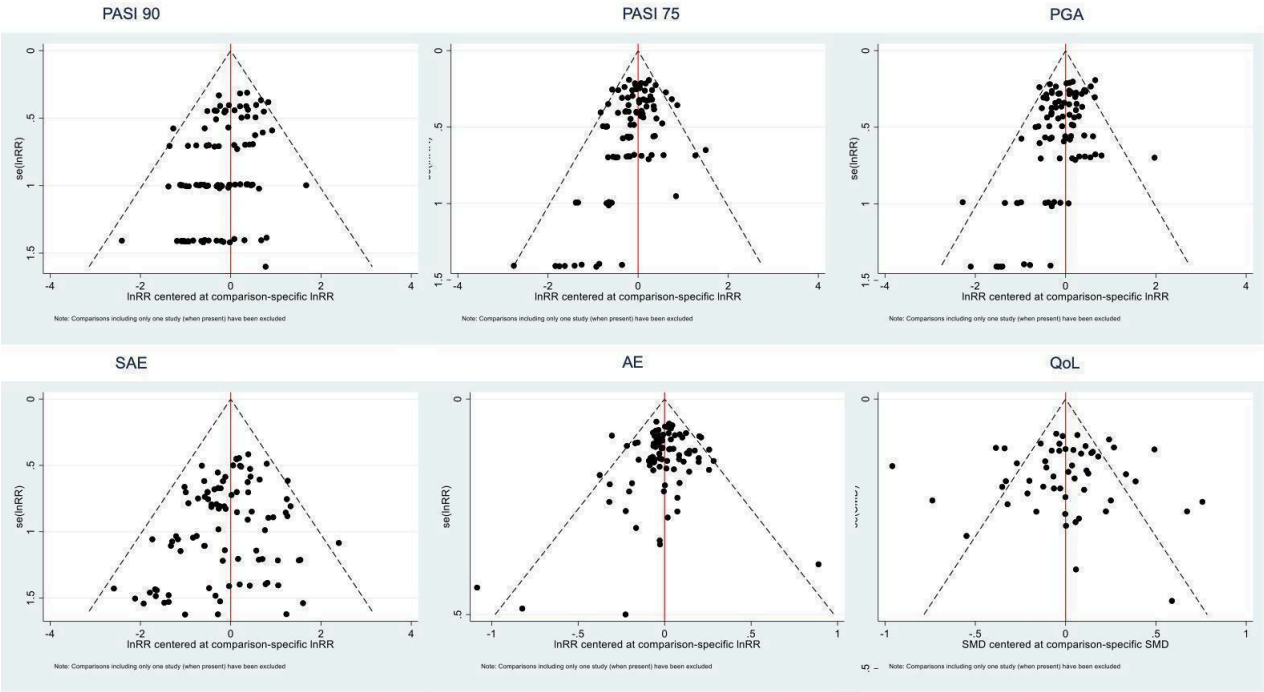
Figure 27 show the network diagrams for PASI 90 (A) and SAE (B) when the analyses were restricted to drugs approved by European Medical Agency, the relative effects from the network meta-analyses against placebo with their 95% confidence (C&D), the two-dimensional ranking plot based on surface under the cumulative ranking curve (SUCRA) values for benefit (PASI 90) and acceptability (serious adverse events) at drug level (E) and the ranking analysis for PASI 90 and SAE (F).

Figure 28 shows the network meta-analysis estimates of PASI 90 and SAE for each comparison at drug level. The heterogeneity τ for this subgroup network was 0 for PASI 90 and SAEs, which we considered to be low.

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

Figure 29. 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; SAE without worsening of psoriasis correspond to SAE after exclusion of flares of psoriasis; SMD: standardised mean difference



6. Grading of the evidence

We present results of evaluation of the certainty of evidence for the primary efficacy and safety outcomes in Table 7; Table 8 and Figure 7; Figure 30; Figure 31.

Figure 30. Certainty of evidence per drug for PASI 90 using CINeMA Each drug is presented as a bar, which indicates the composition of the 4-level confidence of evidence from all comparisons including that drug. Green: high confidence; blue: moderate confidence; yellow: low confidence; red: very low confidence. ACI: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; CINeMA: Confidence in Network Meta-Analysis; DEUCRAVA: deucravacitinib; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; NETA: netakimab; PASI: Psoriasis Area and Severity Index; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; SONELO: sonelokimab; TILDRA: tildrakizumab; USK: ustekinumab

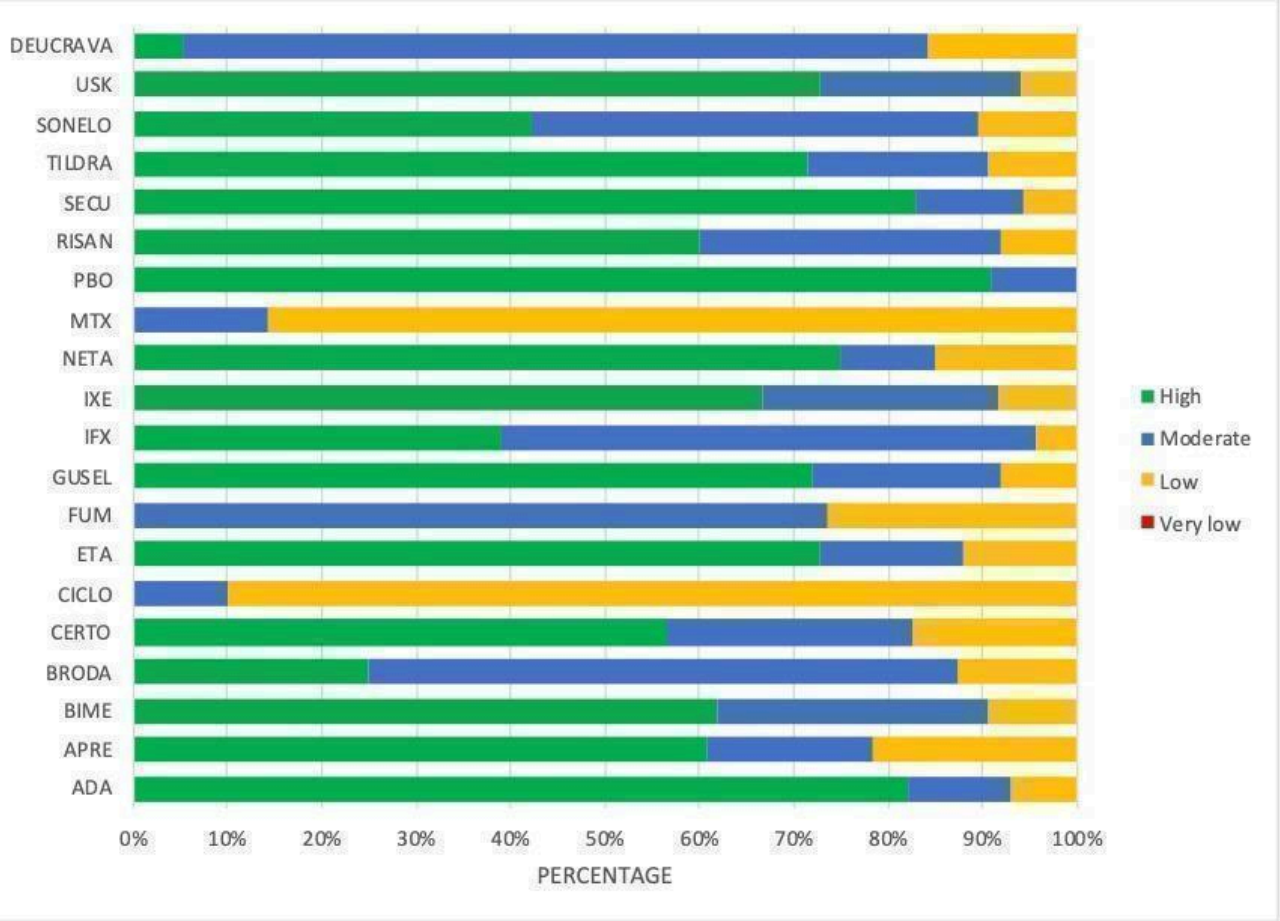


Figure 31. Certainty of evidence per drug for Serious Adverse Events using CINeMA Each drug is presented as a bar, which indicates the composition of the 4-level confidence of evidence from all comparisons including that drug. Green: high confidence; blue: moderate confidence; yellow: low confidence; red: very low confidence. ACI: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; CINeMA: Confidence in Network Meta-Analysis; DEUCRAVA: deucravacitinib; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; NETA: netakimab; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; SONELO: sonelokimab; TILDRA: tildrakizumab; USK: ustekinumab

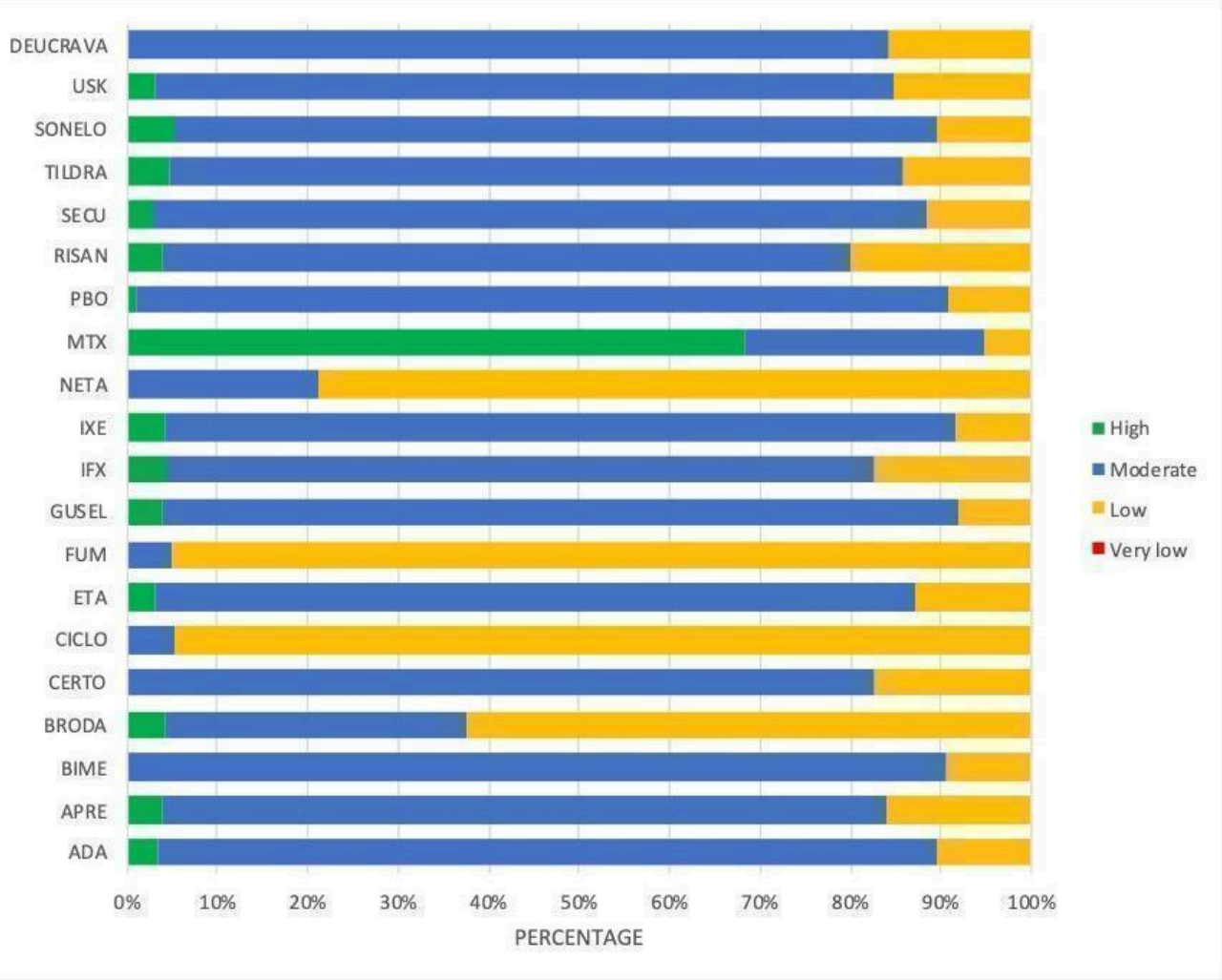


Table 7 and Table 8 represent for PASI 90 and SAEs, respectively, the evaluation of concerns (no concern, some concerns or major concerns) for each domain assessed (within-study bias, reporting bias, indirectness, imprecision, heterogeneity and incoherence). We detected no reporting bias, and there were no concerns that indirectness was present for any comparison for PASI 90 or SAEs. After the judgement for all the six domains, our overall confidence in the evidence for each comparisons is rated high, moderate, low and very low, as described in the Methods section. Results of overall confidence in evidence are available in Table 7, Table 8 and Figure 7.

Figure 30 and Figure 31 represent by drug the overall percentage of comparisons including that drug assessed as high, moderate, low and very-low certainty of evidence. For PASI 90, the overall certainty of the evidence was moderate to high. None of the comparisons were assessed as very low. For methotrexate and ciclosporin, the certainty of evidence was low for more than 80% of comparisons including these treatments. For bimekizumab, brodalumab, certolizumab, FAEs, infliximab, and oral tyrosine kinase 2 inhibitor, the certainty of evidence was moderate for most comparisons. For all other drugs, the certainty of evidence was high for most comparisons. Reasons for downgrading to moderate- or low-certainty were within-study bias or imprecision, or both. For SAEs, the overall certainty of evidence was low to moderate. None of the comparisons were assessed as very low. For tofacitinib, methotrexate, FAEs, brodalumumab and ciclosporin, the certainty of evidence was low. The certainty of evidence was moderate for all other treatments. Reasons for downgrading to moderate- or low-certainty were within-study bias or imprecision, or both.

DISCUSSION

Summary of main results

Our review and meta-analysis compares all systemic pharmacological drugs and systemic drugs undergoing phase II/III trials used for moderate-to-severe psoriasis in 2021.

This updated review included 167 studies, involving 58,912 randomised adult participants, which assessed most outcomes during the induction phase (from 8 to 24 weeks after randomisation). Participants in the included studies were young, with a mean age of 44.5 years, and had moderate-to-severe psoriasis with an overall mean PASI score at baseline of 20.4. Ninety-six trials compared systemic treatment against placebo, 52 were head-to-head trials, and 19 had both an active comparator and a placebo. Eighteen trials had a co-intervention, mainly phototherapy. Nine trials assessed biosimilars versus original drugs for adalimumab or etanercept. Finally, 127 studies declared pharmaceutical company funding, and 24 studies did not report the source of funding.

We included 133 studies (without co-intervention and without trials in biosimilar development), involving 52,531 participants (89% of the participants in this review), in the classical or network meta-analysis (NMA). Non-biological systemic agents, the oldest class-level treatment (acitretin, ciclosporin, fumaric acid esters (FAEs), methotrexate); anti-TNF alpha treatments (etanercept, infliximab, adalimumab, certolizumab); an anti-IL12/23 treatment (ustekinumab); anti-IL17 treatments (secukinumab, ixekizumab, brodalumab, bimekizumab); and anti-IL23 (guselkumab, tildrakizumab, risankizumab) have all been approved for psoriasis, except for netakimab and sonelokimab which are two new anti-IL17 drugs with ongoing phase III trials. Apart from apremilast, small molecule drugs (deucravacitinib), 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, anti-IL23, anti-IL12/23, and anti-TNF alpha outperformed the non-biological agents to reach PASI 90. Anti-IL17 treatment showed a higher proportion of patients reaching PASI 90 compared to all of the interventions, except anti-IL23.

For reaching PASI 90, the most effective drugs when compared to placebo were (in SUCRA (surface under the cumulative ranking curve) rank order): infliximab (high-certainty evidence), bimekizumab (high-certainty evidence), ixekizumab (high-certainty evidence), and risankizumab (high-certainty evidence). The clinical effectiveness of these drugs was similar when compared against each other; see Figure 7. Bimekizumab, ixekizumab and risankizumab showed a higher proportion of patients reaching PASI 90 than other anti-IL17 drugs (secukinumab and brodalumab) and guselkumab. Infliximab, bimekizumab, ixekizumab, secukinumab, brodalumab, risankizumab and guselkumab showed a higher proportion of patients reaching PASI 90 than ustekinumab, tildrakizumab and the three anti-TNF alpha agents (adalimumab, certolizumab and etanercept). Anti-IL17 drugs (bimekizumab, ixekizumab, secukinumab and brodalumab) and anti-IL23 drugs (risankizumab and guselkumab) except tildrakizumab showed a higher proportion of patients reaching PASI 90 than ustekinumab and three anti-TNF alpha agents (adalimumab, certolizumab and etanercept). Ustekinumab was superior to certolizumab; adalimumab and ustekinumab were superior to etanercept. No significant difference was shown between apremilast and two non-biological drugs: ciclosporin and methotrexate. Few trials assessed the efficacy of netakimab, sonelokimab, deucravacitinib, acitretin, ciclosporin, fumaric acid esters, and methotrexate in this network, so the results for these drugs have to be interpreted with caution. The results were similar to PASI 90 for the other efficacy outcomes (PASI 75 and PGA 0/1).

We found no significant difference between any of the interventions and the placebo for the risk of serious adverse events (SAEs). Methotrexate (high-certainty evidence), bimekizumab (moderate-certainty evidence), risankizumab (moderate-certainty evidence), certolizumab (moderate-certainty evidence) and deucravacitinib (moderate-certainty evidence) had the highest SUCRA at drug level for all the SAEs.

There was often poor reporting of information about quality of life, and these data were absent for several of the interventions.

Finally, considering both efficacy (PASI 90 outcome) and acceptability (SAE outcome), 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 they were based. Other highly-effective treatments (ixekizumab and infliximab) had SAEs.

Overall completeness and applicability of evidence

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

Participants

Participants in the included studies had a mean age of 44.5 years and had moderate-to-severe psoriasis, with an overall mean PASI score at baseline of 20.4 (range: 9.5 to 39) and a duration of psoriasis of 16.5 years (range 4.5 to 21.5). This young age and the high level of disease severity may not be typical of patients seen in daily clinical practice, or 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 (Grodner 2021).

Interventions

Evidence on 20 active treatments included in this review was derived from 167 trials (searched for up to October 2021). 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: netakimab, sonelokimab, deucravacitinib, ciclosporin, fumaric acid esters, and methotrexate, meaning we must be cautious about the conclusions drawn for these drugs. The results from the sensitivity analyses, using (i) a standard dose for each intervention and (ii) only approved drugs, were similar for PASI 90 (and SAEs) compared to the main analyses, giving us confidence in the results of the main analysis.

For drugs just approved or not yet approved for psoriasis, ongoing studies are still investigating bimekizumab and deucravacitinib (Characteristics of ongoing studies).

Comparisons

Most studies included in the review were only placebo-controlled (around 57%). Once the benefit of a treatment has been established against placebo using high-quality evidence, only head-to-head trials would be helpful to provide physicians with efficacy estimates between the different biologics, based on stronger evidence than indirect comparisons.

Outcomes

Many of the trials included in this review provided evidence for the proportion of participants who reached PASI 90, PASI 75, or Physician Global Assessment (PGA) 0/1 or who experienced 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 QOL in psoriasis trials required using the standardised mean difference (SMD) in the network. SMD shows the difference in standard deviations of the outcome. It has been suggested that values 0.2, 0.5 and 0.8 might indicate small, moderate and large magnitude of the effect size (Cohen 1988). 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. The results of our analysis assessing SAEs without psoriasis flares did not differ from those of the primary outcome. We did not summarise individual SAE types or classes of SAE in this review, in part because classification differed across different data sources. This was 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 2021).

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). Assessment of longer-term outcomes is also 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.

Due to the large number of ongoing trials (n = 42), it is important to maintain this review as a living review to increase the accuracy of the treatments being tested by incorporating new evidence as it becomes available.

Quality of the evidence

Overall, our confidence in the treatment estimates for PASI 90 is high or moderate for comparisons involving anti-IL17, anti-IL12/23, anti-IL23, or anti-TNF alpha agents, and small molecules. We judged our confidence in treatment estimates for PASI 90 as low for the comparisons involving non-biological systemic agents; we downgraded the certainty of the evidence for risk of bias and then for imprecision. We judged our confidence in the treatment estimates for SAEs to be low certainty for one-third 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 (64 out of 167). 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 25.5% (34 out of 133).
- 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 patient-reported outcomes in the main report but only in secondary publications (see Included studies). We extracted outcomes of interest both in main and secondary publications, but this disadvantaged trials that did not report all of the specified outcomes in the main report.

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

Imprecision

The number of studies included in the NMA was low for the following interventions (one or two studies for each interventions): netakimab, sonelokimab, deucravacitinib, ciclosporin, fumaric acid esters, and methotrexate, meaning we must be cautious about the conclusions drawn for these drugs. Indeed, it has been shown that treatment effect estimates differed according to trial sample size, with stronger effect estimates seen in small to moderately-sized trials than in the largest trials (Dechartres 2013). Moreover, treatment effects in randomised controlled phase II trials were better than those in matched phase III trials (Liang 2019).

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 not selecting participants on their previous systemic treatments, 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 29).

Potential biases in the review process

We performed an extensive search for relevant trials. However, we did not contact pharmaceutical companies who do not have publicly available trials databases to enquire whether they had conducted any additional relevant trials. We consider that the probability that we have missed an eligible trial is low, considering our wide search, and this view is supported by the absence of small-study effects (testing by the comparison-adjusted funnel plots). However, the fact that 21 studies are awaiting classification and 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 (i.e. before the International Committee of Medical Journal Editors issued the requirement for trial registration for publication). 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), especially excluding from the NMA analysis trials with systemic-treatment-naïve participants.

Thus, we added one new sensitivity analysis including only drugs approved by European Medical Agency for plaque psoriasis.

We used CINeMA to assess our confidence in the results.

Agreements and disagreements with other studies or reviews

We found 47 network meta-analyses assessing pharmacological systemic treatment for psoriasis published between 2006 and 2021 (last search on 25 February 2021; search strategies and sources are available in Guelimi 2021). Sixteen were published in 2020 and early 2021 (Armstrong 2020a; Blauvelt 2021b; Díaz 2020; Du 2020; Mahil 2020; Mrowietz 2021; Shear 2021; Shi 2020; Song 2021; Tada 2020; Torres 2020; Warren 2020; Warren 2020a; Xu 2021; Xue 2020; Yasmeen 2020). In total, 14/16 were funded by the pharmaceutical industry.

None of these reviews assessed all biologics, non-biological treatments, and small molecules. Two assessed both biological, non-biological treatments and small molecules, including respectively 16 and 13 interventions (Armstrong 2020a; Shear 2021); Armstrong 2020a included 60 trials in their NMA, and Shear 2021 included 52 trials in their NMA compared with 20 interventions and 167 trials in ours. Eleven NMAs assessed only biologics (Blauvelt 2021b; Díaz 2020; Du 2020; Mrowietz 2021; Shi 2020; Song 2021; Tada 2020; Warren 2020; Warren 2020a; Xu 2021; Xue 2020). Two assessed some biologics and non-biological treatments (Mahil 2020; Torres 2020), and one assessed some biologics and small molecules (Yasmeen 2020).

Among these 16 NMAs, five assessed both efficacy and safety (Du 2020; Mahil 2020; Shi 2020; Song 2021; Xu 2021); others had only safety or only efficacy outcomes.

We compared our findings with the two network meta-analyses that assessed all classes of interventions (Armstrong 2020a; Shear 2021). Armstrong 2020a included 60 trials (the number of participants is unknown) assessing biologic treatments (infliximab, adalimumab, etanercept, certolizumab, ustekinumab, secukinumab, ixekizumab, brodalumab, risankizumab, guselkumab, and tildrakizumab), apremilast and FAEs. Armstrong 2020a presented PASI 50, 75, and 90 results, and 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. Risankizumab, ixekizumab, brodalumab,

guselkumab, secukinumab and infliximab were the best treatment options in Armstrong 2020a. Our findings were close to these results for our common interventions, but differed in the ranking. One hypothesis is that the choice of time of evaluation range (from 10 to 16 weeks in Armstrong 2020a and from 8 to 24 weeks in our study) failed to include more Infliximab trials in Armstrong 2020a. We also found a higher efficacy of infliximab and ixekizumab compared with the other interventions included in their best treatment options (brodalumab, guselkumab, secukinumab, risankizumab). Lastly, our review also includes new agents (bimekizumab for biologics). Shear 2021 presented only safety results.

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 (non-biological 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 non-biological systemic agents; anti-IL17 treatment was associated with a better chance of reaching PASI 90 compared to all of the interventions, except anti-IL23.
- For reaching PASI 90, the most effective drugs when compared to placebo were (in SUCRA (surface under the cumulative ranking curve) rank order): **infliximab** (high-certainty evidence), **bimekizumab** (high-certainty evidence), **ixekizumab** (high-certainty evidence), and **risankizumab** (high-certainty evidence). The clinical effectiveness of these drugs was similar when compared against each other. Bimekizumab, ixekizumab and risankizumab were significantly more effective in reaching PASI 90 than other anti-IL17 drugs (secukinumab and brodalumab) and guselkumab. Infliximab, bimekizumab, ixekizumab, secukinumab, brodalumab, risankizumab and guselkumab were significantly more effective in reaching PASI 90 than ustekinumab, tildrakizumab and the three anti-TNF alpha agents (adalimumab, certolizumab and etanercept).
- Anti-IL17 drugs (bimekizumab, ixekizumab, secukinumab and brodalumab) and anti-IL23 drugs (risankizumab and guselkumab) except tildrakizumab were significantly more effective in reaching PASI 90 than ustekinumab and three anti-TNF alpha agents (adalimumab, certolizumab and etanercept). Ustekinumab was superior to certolizumab; adalimumab and ustekinumab were superior to etanercept.
- No significant difference was shown between apremilast and two non-biological drugs: ciclosporin and methotrexate.

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

For serious adverse events, there was no significant difference between any of the assessed interventions and placebo. Nonetheless, analyses of SAE events were based on a very low number of events with low-to-moderate certainty for the majority of the comparisons. The findings therefore have to be viewed with caution. Considering both efficacy (PASI 90 outcome) and acceptability (SAE outcome), highly-effective treatments 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 not well reported and was absent for several of the interventions.

Conservative interpretation is warranted for the results for netakimab, sonelokimab, deucravacitinib, acitretin, ciclosporin, fumaric acid esters, and methotrexate, as these drugs in the NMA have only been evaluated in few trials.

The evidence is limited to a selected trial population (participants were young (mean age of 44.5 years), had a high level of disease severity (with an overall mean score of PASI 20.4 at baseline, and were long-time sufferers), and had few major comorbidities), and the NMA evidence was limited 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 non-biological systemic agents) do not reflect the 'real life' management of patients in Europe or Canada, as an example. Currently, biological treatments (as well as apremilast) 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 non-biological systemic agents). 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 non-biological systemic agents is still in question, as the limited number of trials assessing non-biological 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 non-biological 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, race and ethnicity)?
- Which treatments offer the best combination of safety and efficacy in patients with major comorbidities (e.g. hepatitis B/C, latent tuberculosis, HIV, and renal, cardiac, and hepatic impairment) as well as pregnancy?
- 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 non-biological 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); race and ethnicity, and presence of psoriatic arthritis.
- **Interventions**: high-quality trials assessing the efficacy of non-biological 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 non-biological 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.
- **Timingassessment 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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- Managing Editor and Assistant Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Laura Prescott and Helen Scott; and Sarah Nevitt (methods guidance).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

ACCEPT 2010

Study characteristics	
Methods	RCT, active-controlled, open-label study Date of study: March 2007-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

ACCEPT 2010 *(Continued)*

Primary outcomes

- PASI 75

Secondary outcomes

- 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 source, 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

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.

ADACCESS 2018

Study characteristics	
Methods	RCT, active-controlled, double-blind study 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

ADACCESS 2018 *(Continued)*

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
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". Declarations 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

ADACCESS 2018 *(Continued)*

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." 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

Akcali 2014

Study characteristics	
Methods	RCT, active-controlled, open-label study 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**

Akcali 2014 *(Continued)*

	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** • 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 (p. 1119): "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 study Date of study: February 2010-October 2011 Location: Baghdad, Iraq (1 centre)

Al-Hamamy 2014 *(Continued)*

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 • 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 source: 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)	High risk	Comment: not stated that it was a blind trial, probably not blind

Al-Hamamy 2014 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: no independent assessor. Not stated that it was a blind trial, probably not blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Randomly assigned 120, analysed 113 Management of missing data: not stated
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available. The outcomes mentioned in the Methods section appeared to have been reported.

ALLURE 2021

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study Date of study: December 2016-June 2018 Location: worldwide (52 sites) Phase 3
Participants	**Randomised**: 214 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

ALLURE 2021 *(Continued)*

- 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

Baseline characteristics

N = 214, mean age of 43.5 years and 62% men

Dropouts and withdrawals

- 5/214 (2%): secukinumab 2 mL group (0), secukinumab 1 mL group (2), placebo group (3)
- AEs: secukinumab 2 mL group (0), secukinumab 1 mL group (1), placebo group (0)
- Lack of efficacy: secukinumab 2 mL group (0), secukinumab 1 mL group (0), placebo group (2)
- Withdrawal by subject: secukinumab 2 mL group (0), secukinumab 1 mL group (1), placebo group (1)

Interventions	**Intervention** A. 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), n = 72 **Control interventions** B. 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), n = 71 C. Placebo (2 mL + 2 x 1 mL placebo SC at randomisation, weeks 1, 3, and 4, thereafter 4-weekly until week 48), n = 71
Outcomes	**At week 12** **Primary composite outcome** • PASI 75 and IGA mod 2011 0 or 1 response **Secondary outcomes** • PASI 90, 100 at weeks 12 and 52 • PASI 75 and IGA mod 2011 0 or 1 response at week 52 • DLQI at weeks 12 and 52
Notes	Funding source: Quote (p 8) "The study was sponsored by Novartis Pharma AG, Basel, Switzerland." Declarations of interest: Quote (p 7-8) "Bardur Sigurgeirsson has consulted for Novartis and several other pharmaceutical companies. He has served on an advisory board for Novartis and several other pharmaceutical companies. Knut Sch€akel has been advisor and/or received speakers' hono- raria and/or received grants and/or participated in clinical trials of the following companies: AbbVie, Almirall-Hermal, Amgen, Biogen Idec, Boehringer-Ingelheim, Chugai Pharma, Celgene, Eli Lilly, Galderma, Janssen, Leo Pharma, Medac, Merck Serono, MSD, Novartis, Pfizer, Polichem SA, Regeneron Pharmaceutical, Sanofi-Aventis, Schering-Plough, UCB Pharma, VBL therapeutics. Chih-Ho Hong is a researcher/consultant/advisor for AbbVie, Amgen, Arcutis, Bausch Health, Boehringer Ingelheim, Bristol-Meyers Squibb, Celgene, Dermira, Dermavant, DS Biopharma, Galderma, GlaxoSmithKline, Janssen, LEO Pharma, Lilly, MedImmune, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, and UCB. Isaak Effendy reports no conflict of interest. Waldemar Placek performed clinical trials for Amgen Inc, Maruho Europe Limited, Merck Sharp and Dohme Corp, Mylan, Novartis Poland Sp. z o.o., Johnson and Johnson, Moberg Pharma AB publ, Eli Lilly, Menlo, KYMAB, Bristol Meyers, CTC Team, Boehringer Ingelheim RCV GmbH and Co KG. Phoebe Rich has participated in advisory boards and/or as an investiga- tor and/or speaker and received grants and/or honoraria from Arcutis Inc., Bristol-Myers Squibb, Centocor, Dermavant, Eli Lilly, Kadmon, Merck, Novartis, Pfizer, Sun Pharma, and UCB. Deborah Keefe is an employ-

ALLURE 2021 *(Continued)*

ee of Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA. Gerard Bruin is an employee of Novartis Institutes for Biomedical Research, Basel, Switzerland. Rong Fu is an employee of Novartis Institute for Biomedical Research, Shanghai, China. Pascal Charef, Isabelle Hampele, and Manmath Patekar are employees of Novartis Pharma AG, Basel, Switzerland."

In ClinicalTrials.gov, other prespecified outcomes" such as assess the participant usability and assessment of Dermatology Life Quality Index (DLQI) scores are exploratory in nature and are not reported in these results.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 2):"ALLURE was a 52-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study." Quote (supplemental p. 3):"At Baseline/Randomization visit, all eligible patients were randomized in a 1:1:1 ratio, to one of the 3 treatment arms; described above via Interactive Response Technology (IRT)." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 2):"ALLURE was a 52-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study." Quote (supplemental p 3):"Patients, investigators/site personnel and Novartis clinical team reviewing data remained blinded to the identity of the treatment from the time of randomization, using the following methods: (1) randomization data were kept strictly confidential until the time of unbinding, and were not accessible by anyone else involved in the study; (2) the identity of the treatments was concealed by the use of investigational treatment that are all identical in packaging, labeling, appearance, and schedule of administration". Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (supplemental p 3):"Patients, investigators/site personnel and Novartis clinical team reviewing data remained blinded to the identity of the treatment from the time of randomization, using the following methods: (1) randomization data were kept strictly confidential until the time of unbinding, and were not accessible by anyone else involved in the study; (2) the identity of the treatments was concealed by the use of investigational treatment that are all identical in packaging, labeling, appearance, and schedule of administration". Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (supplemental p. 3):"Patients, investigators/site personnel and Novartis clinical team reviewing data remained blinded to the identity of the treatment from the time of randomization, using the following methods: (1) randomization data were kept strictly confidential until the time of unbinding, and were not accessible by anyone else involved in the study; (2) the identity of the treatments was concealed by the use of investigational treatment that are all identical in packaging, labeling, appearance, and schedule of administration". Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (supplemental p. 5):"The co-primary endpoints PASI 75 and IGA 0 or 1 were analyzed based on the full analysis set (FAS) which comprised of all subjects who were randomized at baseline visit and to

ALLURE 2021 *(Continued)*

		whom study treatment was assigned...Multiple imputation was applied as the primary missing data imputation method and non-responder imputation was done for sensitivity analysis." Randomised 214; analysed 214
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02748863). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported except for DLQI. Results posted on ClinicalTrials.gov

AlMutairi 2021

Study characteristics	
Methods	RCT, active-controlled, open-label study Date of study: January 2018-August 2019 Location: Kuwait (5 sites) Phase ?
Participants	**Randomised**: 54 **Inclusion cirteria** • Age ≥ 18 with moderate-to-severe plaque psoriasis for more than 6 months having genital psoriasis • Candidates for phototherapy and/or systemic therapy, ineffectively controlled by topical therapy • Plaque psoriasis with a BSA of ≥ 10%, sPGA score of 3 or more, an sPGA of Genitalia (sPGA-G) score of 3 or more, who were either intolerant, or unresponsive to topical therapy for genital psoriasis (corticosteroid preparations, vitamin D analogs, or calcineurin inhibitors) **Exclusion criteria** • Previous history of treatment with IL-17 inhibitors • Any medical condition that might interfere with interpretation of study results • Psoriasis other than chronic plaque psoriasis (e.g. guttate or erythrodermic psoriasis) • Pregnancy • Previous history of any malignancy within the last five years **Baseline characteristics** N = 54, mean age of 42 years and 72% men **Dropouts and withdrawals** Not stated
Interventions	**Intervention** A. Secukinumab, 300 mg subcutaneous injection once weekly for first 4 weeks, followed by once every 4 weeks till week 24, n = 26 **Control intervention** B. Ixekizumab, 160 mg SC at weeks 0, and then 80 mg SC q2wks at weeks till week 12, followed by 80 mg SC q4wks till week 24, n = 82

AlMutairi 2021 *(Continued)*

Outcomes	**At week 24** • sPGA of Genitalia (sPGA-G) 0/1 • Genital Psoriasis Symptoms Scale (GPSS) • Massachusetts General Hospital-Sexual Functioning Questionnaire (MGH-SFQ)
Notes	Funding source: Quote "This paper is not funded". Declarations of interest: Quote "The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "This is a 24 week, open-label, randomized controlled study to compare the efficacy and safety of ixekizumab versus secukinumab". Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "This is a 24 week, open-label, randomized controlled study to compare the efficacy and safety of ixekizumab versus secukinumab". Comment: no description of the method used to guarantee random sequence generation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "This is a 24 week, open-label, randomized controlled study to compare the efficacy and safety of ixekizumab versus secukinumab".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "This is a 24 week, open-label, randomized controlled study to compare the efficacy and safety of ixekizumab versus secukinumab".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Randomised 54, analysed 54 Comment: methods for dealing with missing data not specified
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. The prespecified outcomes mentioned in the Methods section appeared to have been reported.

AMAGINE-1 2016

Study characteristics

Methods	RCT, placebo-controlled, double-blind study Date of study: August 2012-March 2014 Location: 73 centres worldwide (Europe, USA and Canada)
Participants	**Randomised**: 661 participants (mean age 46 years, 484 male)

AMAGINE-1 2016 *(Continued)*

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** • PASI 75 • PGA success **Secondary outcomes** • PASI 100 and PGA 0 • Participant-reported outcomes • AEs
Notes	Funding source: 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

AMAGINE-1 2016 *(Continued)*

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.

AMAGINE-2 2015

Study characteristics

Methods	RCT, active/placebo-controlled, double-blind study 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

AMAGINE-2 2015 *(Continued)*

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)

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** • PASI 75 and PGA0/1 (brodalumab compared to placebo) • % of participants who had a 100% reduction in PASI score **Secondary outcomes** • 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 reported grant support from Amgen, AbbVie, Janssen Biotech, UCB Pharma, Pfizer, Celgene, Eli Lilly, and Novartis outside the submitted work.

AMAGINE-2 2015 *(Continued)*

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...”
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.

AMAGINE-3 2015

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind study 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

AMAGINE-3 2015 *(Continued)*

- 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 interventions** 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 reported 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

AMAGINE-3 2015 *(Continued)*

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" 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.

Asahina 2010

Study characteristics	
Methods	RCT, active, placebo-controlled, double-blind study 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**

Asahina 2010 *(Continued)*

- 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 • SF-36
Notes	Funding source: 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)	Low risk	Randomly assigned 169, analysed 169

Asahina 2010 *(Continued)*

All outcomes		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.

Asawanonda 2006

Study characteristics	
Methods	RCT, active placebo-controlled, double-blind study Date of study: not stated 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** • 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 source: (quote p 1013) no funding source Declarations of interest: (quote p 1013) "None identified"
Risk of bias	

Asawanonda 2006 *(Continued)*

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.

AURIEL-PsO 2020

Study characteristics	
Methods	RCT, active-controlled, double-blind study 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

AURIEL-PsO 2020 *(Continued)*

trial; or psoralen combined with ultraviolet A phototherapy or nonbiological systemic therapies for psoriasis within 4 weeks prior to IMP administration.
- People were excluded if they had 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)
- 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 75/90/100 at 24 and 52 weeks • PGA at 24 and 52 weeks • Quality of life at 16, 24 and 52 weeks
Notes	Funding source: Quote (p 316): ''This study was sponsored by Merck. Fresenius Kabi acquired the asset from Merck KGaA''. Declarations of interest: Quote (appendix) :''J.H. has received honoraria for attendance at advisory boards for Novartis, Eli Lilly, LEO Pharma, Nordic Pharma, UCB, Sanofi Genzyme and Fresenius Kabi; as an investigator for AbbVie, Merck, Amgen, Novartis, Eli Lilly and Pfizer; and as a speaker for AbbVie, Biogen, Eli Lilly, Janssen-Cilag, LEO Pharma, L'Oréal, Nordic Pharma, Novartis, Pfizer, Pierre Fabre and Sanofi-Aventis. K.A.P. has received honoraria for attendance at advisory boards for AbbVie, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dow Pharma, Eli Lilly, Fresenius Kabi, Galderma, Janssen, Merck (MSD), Novartis, Pfizer, Regeneron, Sanofi-Aventis/Genzyme, UCB and Valeant; as a speaker for AbbVie, Amgen, Celgene, Eli Lilly, Galderma, Janssen, Kyowa Hakka Kirin, LEO, Merck (MSD), Novartis, Pfizer and Valeant; as a consultant for AbbVie, Akros, Amgen, Baxalta, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Coherus, Dermira, Dow Pharma, Eli Lilly, Galderma, Janssen, Kyowa Hakka Kirin, LEO, Merck (MSD), Merck-Serono, Novartis, Pfizer, Regeneron, Roche, Sanofi-Aventis/Genzyme, Takeda, UCB and Valeant; and for other activities for AbbVie, Akros, Amgen, Anacor, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, Kyowa Hakka Kirin, Merck (MSD), Merck-Serono, Novartis, Pfizer, Regeneron, Sanofi-Aventis/Genzyme and Valeant; and has received grants as an investigator for AbbVie, Akros, Amgen, Anacor, Baxalta, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Coherus, Dermira, Dow Pharma, Eli Lilly, Galderma, GSK, Janssen, Kyowa Hakka Kirin, LEO, Merck (MSD), Merck-Serono, Novartis, Pfizer, Regeneron, Roche, Sanofi-Aventis/Genzyme, Takeda, UCB and Valeant. V.C. is a former employee of Fresenius Kabi SwissBioSim. M.U. is an employee of Fresenius Kabi SwissBioSim. P.V. has no conflicts of interest to declare. C.J.E. has received honoraria for attendance

AURIEL-PsO 2020 *(Continued)*

	at advisory boards for AbbVie, Biogen, BMS, Celgene, Fresenius Kabi, GSK, Janssen, Lilly, Mundipharma, Roche and Sanofi; and as a consultant for Anthera, Merck and Samsung Bioepis; and has received grants as an investigator for AbbVie, Biogen and Pfizer''.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 319): "The allocation sequence was generated centrally by Cenduit (Nottingham, U.K.) using permuted blocks. The investigators enrolled patients by contacting the central interactive web response system, which assigned patients to their groups according to the allocation sequence." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 319): "The allocation sequence was generated centrally by Cenduit (Nottingham, U.K.) using permuted blocks. The investigators enrolled patients by contacting the central interactive web response system, which assigned patients to their groups according to the allocation sequence." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (p 318): "AURIEL-PsO was a multicentre, randomized, double-blind, parallel-group trial''. Comment: no description of the method used to guarantee blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (p 318): "AURIEL-PsO was a multicentre, randomized, double-blind, parallel-group trial''. Comment: no description of the method used to guarantee blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: quote (p 320): "For the per protocol set, little or no missing data were expected, so no imputation was performed. For the ITT analysis, patients with a missing PASI value at week 16 were classified as non-responders." Randomised 443, analysed 394 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. Results posted on ClinicalTrials.gov.

Bachelez 2015

Study characteristics

Methods	RCT, active placebo-controlled, double-blind study Date of study: November 2010-September 2012 Location: 122 worldwide excluding the USA and Canada

Bachelez 2015 *(Continued)*

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: tofacitinib 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** • PASI 50 • PASI 90 • Itch severity item score • Mean DLQI score • AEs
Notes	Funding source:

Bachelez 2015 *(Continued)*

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 received at least one dose of study drug... We judged patients with missing values for all binary endpoints to be non-responders in efficacy assessments". Table 2: 1101 analysed participants Comment: done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01241591).

Bachelez 2015 *(Continued)*

	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 study 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 • Participant satisfaction • AEs • PASI 50/75/90 improvement through 24 weeks • Proportion PGA 0 or 1 • Mean PASI improvement from baseline
Notes	Funding source: Amgen Inc

Bagel 2012 *(Continued)*

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: 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

Barker 2011

Study characteristics	
Methods	RCT, active-controlled, open-label study 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
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 • SF-36
Notes	Funding source: 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, Mer-

Barker 2011 *(Continued)*

ck, 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
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.

BE ABLE 1 2018

Study characteristics

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

BE ABLE 1 2018 *(Continued)*

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%): bimekizumab 64 (3), bimekizumab 160 (5), bimekizumab 320/160 (6), bimekizumab 320 (3), bimekizumab 480 (4), PBO (5)
- Participant decision: bimekizumab 64 (0), bimekizumab 160 (1), bimekizumab 320/160 (1), bimekizumab 320 (0), bimekizumab 480 (1), PBO (1)
- Lost to follow-up: bimekizumab 64 (0), bimekizumab 160 (0), bimekizumab 320/160 (1), bimekizumab 320 (1), bimekizumab 480 (0), PBO (0)
- AEs: bimekizumab 64 (1), bimekizumab 160 (1), bimekizumab 320/160 (1), bimekizumab 320 (0), bimekizumab 480 (1), PBO (1)
- Lack of efficacy: bimekizumab 64 (0), bimekizumab 160 (0), bimekizumab 320/160 (0), bimekizumab 320 (0), bimekizumab 480 (0), PBO (1)
- Protocol violation: bimekizumab 64 (0), bimekizumab 160 (0), bimekizumab 320/160 (0), bimekizumab 320 (0), bimekizumab 480 (0), PBO (2)
- Others: bimekizumab 64 (2), bimekizumab 160 (3), bimekizumab 320/160 (3), bimekizumab 320 (2), bimekizumab 480 (2), PBO (1)

Interventions	**Intervention**: A. Bimekizumab every 4 weeks at doses of 64 mg, n = 39 **Control interventions** 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 source

BE ABLE 1 2018 *(Continued)*

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

Declarations 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 (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
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. Treat-

BE ABLE 1 2018 *(Continued)*

		ments 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
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 (p. 281): "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. Results posted on ClinicalTrials.gov.

BE RADIANT 2021

Study characteristics

BE RADIANT 2021 *(Continued)*

Methods	RCT, active-controlled, double-blind study Date of study: June 2018-May 2019 Location: world-wide (77 sites) Phase 3
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 **Baseline characteristics** N = 743, mean age of 45 years and 65% men **Dropouts and withdrawals** • 27/743 (3.6%): bimekizumab group (11), secukinumab group (16) • AEs: bimekizumab group (8), secukinumab group (6) • Withdrew consent: bimekizumab group (3), secukinumab group (4) • Lost to follow-up: bimekizumab group (0), secukinumab group (3) • Other reason: bimekizumab group (0), secukinumab group (3)
Interventions	**Intervention** A. Bimekizumab 320 mg every 4 weeks, n = 373 **Control intervention** B. Secukinumab 300 mg weekly to week 4 followed by once every 4 weeks, n = 370
Outcomes	**At week 16** **Primary outcome** • PASI 100 **Secondary outcomes**

BE RADIANT 2021 *(Continued)*

- PASI 75 and PASI 100 at week 48
- IGA and PASI 90 at week 16
- DLQI
- SAEs, AEs

Notes	Funding source: Quote (p 2) "The sponsor, UCB Pharma, funded and designed the trial with the participation of authors employed by the sponsor". Declarations of interest: Quote (disclosure forms) "Dr. Blauvelt reports personal fees and other from AbbVie, personal fees from Aligos, personal fees from Almirall, personal fees and other from Amgen, personal fees and other from Arcutis, personal fees from Arena, personal fees and other from Athenex, personal fees and other from Boehringer Ingelheim, personal fees and other from Bristol Myers Squibb, personal fees and other from Dermavant Sciences, personal fees and other from Eli Lilly, personal fees and other from Evommune, personal fees from Forte, personal fees from Galderma, personal fees and other from Incyte, personal fees and other from Janssen, personal fees and other from Leo, personal fees and other from Novartis, personal fees and other from Pfizer, personal fees from Rapt, personal fees and other from Regeneron, personal fees from Sanofi Genzyme, personal fees and other from Sun Pharma, personal fees and other from UCB Pharma, outside the submitted work."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 2) "This is a phase 3b multicenter, randomized, double-blind, active-comparator–controlled, parallel-group trial conducted across 77 sites..." Quote (p 3) "Randomization was performed with the use of an interactive response technology, stratified by region (North America, Western Europe, Central and Eastern Europe, or Asia and Australia) and previous exposure to biologic agents (yes or no)". Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 2) "This is a phase 3b multicenter, randomized, double-blind, active-comparator–controlled, parallel-group trial conducted across 77 sites..." Quote (p 3) "Randomization was performed with the use of an interactive response technology, stratified by region (North America, Western Europe, Central and Eastern Europe, or Asia and Australia) and previous exposure to biologic agents (yes or no)". Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 2) "This is a phase 3b multicenter, randomized, double-blind, active-comparator–controlled, parallel-group trial conducted across 77 sites..." Quote (p 3) "To maintain double blinding, patients randomly assigned to the bimekizumab group received placebo at relevant study visits to account for differences in dosing schedules between the treatment groups..". "All sponsor and investigator site personnel involved in the trial were unaware of the treatment assignments except site staff responsible for the preparation and administration of trial treatments and bio-analytic sample analysis". Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 2) "This is a phase 3b multicenter, randomized, double-blind, active-comparator–controlled, parallel-group trial conducted across 77 sites..." Quote (p 3) "Efficacy outcomes were assessed by the investigator, another delegated physician, or an appropriately qualified medical professional, all of whom were unaware of the patients' treatment assignments".

BE RADIANT 2021 *(Continued)*

		Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (p 5) "For efficacy and quality-of-life variables, patients with missing data were considered not to have had a response (nonresponder imputation)." Randomised 743, analysed 743
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT03536884). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. No results are posted on ClinicalTrials.gov

BE READY 2021

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study Date of study: February 2018-January 2020 Location: worldwide (77 sites in Australia, Canada, Germany, Hungary, Poland, Russia, South Korea, the UK, and the USA) 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 • Female subject of childbearing 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 judgement, would make the subject unsuitable for inclusion in the study • Presence of active suicidal ideation or positive suicide behaviour • 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 **Baseline characteristics** N = 435, mean age of 44.5 years and 72% men

BE READY 2021 *(Continued)*

Dropouts and withdrawals

- 13/435 (3%): 9/349 bimekizumab and 4/86 placebo
- AEs: bimekizumab (5), placebo (0)
- Lack of efficacy: bimekizumab (1), placebo (2)
- Lost to follow-up: bimekizumab (3), placebo (1)
- Withdrew consent: bimekizumab (0), placebo (1)

Interventions	**Intervention** A. Bimekizumab 320 mg every 4 weeks, n = 349 **Control intervention** B. Placebo every 4 weeks, n = 86
Outcomes	**At week 16** **Primary composite outcome** • PASI 90-IGA 0/1 **Secondary outcomes** • PASI 100 at week 16 • PASI 75 at week 4 • AEs, SAEs • DLQI at week 16
Notes	Funding source: Quote (p 475) "Funding UCB Pharma" Declarations of interest: Quote (p 485) "KBG has received consulting fees from AbbVie, Almirall, Amgen, Boehringer Ingelheim, BMS, Celgene, Dermira, Eli Lilly, Janssen, Novartis, Pfizer, Sun Pharma and UCB Pharma; and research support from AbbVie, BMS, Celgene, Eli Lilly, Janssen, Novartis and UCB Pharma. PF received grant support from AbbVie, Amgen, Celgene,Eli Lilly, Janssen, Merck, Novartis, Pfizer, Sun Pharma, and Sanofi; served as an investigator for AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Botanix, Celgene, Celtaxsys, CSL, Cutanea, Dermira, Eli Lilly, Galderma, Genentech, Geneseq, GSK, Hexima, Janssen, LEO Pharma, Merck, Novartis, Pfizer, Regeneron, Reistone, Roche, Sanofi Genzyme, Sun Pharma, UCB Pharma, and Valeant/Bausch Health; served on the advisory board of AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Eli Lilly, Galderma, Janssen, Kyowa Kirin, Leo Pharma, Medac, MSD, Novartis, Ocean Pharma, Pfizer, Samsung Bioepis, Sanofi, SunPharma, Takeda, UCB Pharma, and Xenoport; paid speaker for AbbVie, Almirall, Biogen-Idec, Celgene, Eli Lilly, Janssen-Cilag, Leo Pharma, Medac, MSD, Novartis, Sanofi, and Valeant; and has participated in clinical trials sponsored by AbbVie, Affibody, Almirall, Biogen-Idec, Boehringer Ingelheim, Celgene, Covagen, Eli Lilly, Forward Pharma, Fresenius Medical Care, Galapagos, Galderma, Janssen-Cilag, Kyowa Kirin, Leo Pharma, Medac, MSD, Miltenyl, Novartis, Ocean Pharma, Pfizer, Sanofi, SunPharma, Takeda, UCB Pharma, and XBiotech. RV served as a consultant, scientific adviser, investigator, or speaker for Amgen, AbbVie, Astellas, Bristol- Myers Squibb, Boehringer Ingelheim, Celgene, Dermira, Eli Lilly, Galderma, GSK, Janssen, LEO Pharma, MSD, Merck Serono, Novartis, Pfizer, Regeneron, Roche, Sanofi-Aventis/Genzyme, Sun Pharma, Takeda, UCB Pharma, and Valeant/Bausch Health. VV, CM, KW, and CC are employees and shareholders of UCB Pharma. AB has served as a scientific adviser for AbbVie, Almirall, Arena, Athenex, Boehringer Ingelheim, Bristol-Myers Squibb, Dermavant, Eli Lilly, Evommune, Forte, Galderma, Incyte, Janssen, Leo Pharma, Novartis, Pfizer, Rapt, Regeneron, Sanofi Genzyme, Sun Pharma, and UCB Pharma; and as a clinical study investigator for AbbVie, Athenex, Boehringer Ingelheim, Bristol-Myers Squibb, Dermavant, Eli Lilly, Galderma, Incyte, Janssen, Leo Pharma, Novartis, Pfizer, Regeneron, Sun Pharma, and UCB Pharma."

Risk of bias

Bias	Authors' judgement	Support for judgement

BE READY 2021 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote (p 476) "BE READY was a phase 3, multicentre, randomised, double-blind, placebo-controlled trial done across 77 sites... At week 0, patients were randomly assigned (4:1) to receive either bimekizumab dosed at 320 mg every 4 weeks or placebo every 4 weeks for initial treatment, by use of interactive response technology. The interactive response technology assigned patients on the basis of a predetermined randomisation and packaging schedule provided by the funder. Randomisation was stratified by region (North America, Western Europe, Central or Eastern Europe, and Asia and Australia) and previous biologic exposure (yes vs no)." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 476) "BE READY was a phase 3, multicentre, randomised, double-blind, placebo-controlled trial done across 77 sites... At week 0, patients were randomly assigned (4:1) to receive either bimekizumab dosed at 320 mg every 4 weeks or placebo every 4 weeks for initial treatment, by use of interactive response technology. The interactive response technology assigned patients on the basis of a predetermined randomisation and packaging schedule provided by the funder. Randomi- sation was stratified by region (North America, Western Europe, Central or Eastern Europe, and Asia and Australia) and previous biologic exposure (yes vs no)." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 476) "BE READY was a phase 3, multicentre, randomised, double-blind, placebo-controlled trial done across 77 sites... Throughout the study, patients, investigators, and sponsors remained masked to treatment assignment, with the exception of specially designated, unmasked site staff who were responsible for the preparation and administration of study treatments, safety monitoring, or bioanalytical sample analysis." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 476) "BE READY was a phase 3, multicentre, randomised, double-blind, placebo-controlled trial done across 77 sites... Throughout the study, patients, investigators, and sponsors remained masked to treatment assignment, with the exception of specially designated, unmasked site staff who were responsible for the preparation and administration of study treatments, safety monitoring, or bioanalytical sample analysis." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (p 480) "Efficacy analyses of data from the initial treatment period were done in the intention-to-treat population, including all randomised patients." Randomly assigned 435, analysed 435
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT03410992). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. No results are posted on ClinicalTrials.gov.

BE SURE 2021

Study characteristics

BE SURE 2021 *(Continued)*

Methods	RCT, active-controlled, double-blind study Date of study: January 2018-February 2020 Location: worldwide (77 sites) Phase 3
Participants	**Randomised**: 478 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 • Participant is a candidate for systemic PSO therapy and/or phototherapy • Women of childbearing potential must be willing to use highly effective method of contraception. **Exclusion criteria** • Participant has a known hypersensitivity to any excipients of bimekizumab or adalimumab. • Participant has an active infection (except common cold), a serious infection, or a history of opportunistic or recurrent chronic infections. • Participant has concurrent acute or chronic viral hepatitis B or C or human immunodeficiency virus (HIV) infection. • Participant has known tuberculosis (TB) infection, is at high risk of acquiring TB infection, or has current or history of nontuberculous mycobacterium (NTMB) infection. • Participant has any other condition, including medical or psychiatric, which, in the investigator's judgement, would make the participant unsuitable for inclusion in the study. • Participant 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 • Participant 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. **Baseline characteristics** N = 478, mean age of 45 years and 69% men **Dropouts and withdrawals** • 21/478 (4.5%): bimekizumab group (12), adalimumab group (9) • AEs: bimekizumab group (4), adalimumab group (4) • Lost to follow-up: bimekizumab group (2), adalimumab group (1) • Withdrew consent: bimekizumab group (5), adalimumab group (1) • Other reason: bimekizumab group (1), adalimumab group (0) • Lack of efficacy: bimekizumab group (0), adalimumab group (1) • Protocol violation: bimekizumab group (0), adalimumab group (2)
Interventions	**Intervention** A. Bimekizumab SC 320 mg every 4 week, n = 319 **Control intervention** B. Adalimumab SC 40 mg every 2 weeks, n = 159

BE SURE 2021 *(Continued)*

Outcomes	**At week 16** **Primary composite outcome** • PASI 90 - IGA 0/1 **Secondary outcomes** • PASI 75 at week 4 • PASI 100 at week 16, 24 • PASI 90 - IGA 0/1 at week 24 • DLQI at week 24 • AEs • SAEs
Notes	Funding source: Quote (p 2) "The trial was funded by UCB Pharma and de- signed by the ninth through the twelfth authors and UCB Pharma." Declarations of interest: Quote (disclosure forms at NEJM.org) "Dr. Warren reports receiving grant support and consulting fees from AbbVie, Almirall, Bristol-Myers Squibb, Eli Lilly, Janssen, LEO Pharma, Novartis, and UCB Pharma, consulting fees from Amgen, Arena Pharmaceuticals, Avillion, Boehringer Ingelheim, Celgene, Pfizer, Sanofi, Astellas, GlaxoSmithKline, Biogen, DiCE Molecules, Sun Pharma, and Union Therapeutics, and grant support from Medac; Dr. Blauvelt, receiving research funding and consulting fees from AbbVie, Amgen, Arcutis Biotherapeutics, Athenex, Boehringer Ingelheim, Bristol-Myers Squibb, Dermavant Sciences, Eli Lilly, Evommune, Incyte, Janssen, LEO Pharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Sun Pharma, and UCB Pharma and consulting fees from Aligos Therapeutics, Almirall, Arena Pharmaceuticals, Forte Biosciences, Galderma, Rapt Therapeutics, and Sanofi Genzyme; Dr. Bagel, receiving grant support from Arcutis Biotherapeutics, Boehringer Ingelheim, Corrona, Dermavant Sciences, Dermira, Glenmark Pharmaceuticals, Kadmon, LEO Pharma, Lycera, Menlo Therapeutics, Pfizer, Regeneron Pharmaceuticals, Taro Pharmaceutical Industries, and Ortho Dermatologics, grant support, consulting fees, and lecture fees from AbbVie, Celgene, Eli Lilly, Janssen Biotech, and Novartis, and grant support and consulting fees from Amgen, Bristol-Myers Squibb, Sun Pharmaceutical Industries, and UCB Pharma; Dr. Papp, receiving grant support, consulting fees, fees for serving on a speakers bureau, steering committee fees, and advisory board fees, all paid to his institution, and honoraria from AbbVie, Amgen, Celgene, Eli Lilly, Janssen, Merck (Merck Sharp & Dohme), Novartis, Pfizer, Sanofi Genzyme, and Bausch Health, grant support and consulting fees, all paid to his institution, and honoraria from Akros Pharma, Coherus BioSciences, Mitsubishi Pharma, Takeda, and PRCL Research, grant support, paid to his institution, from Anacor Pharmaceuticals, GlaxoSmithKline, MedImmune, Gilead Sciences, and Moberg Pharma, grant support and consulting fees, all paid to his institution, from Arcutis Biotherapeutics, Baxalta, Can-Fite BioPharma, Dermira, Genentech, Meiji Seika Pharma, Roche, Evelo Biosciences, Galapagos, Avillion, and DiCE Molecules, grant support, consulting fees, fees for serving on a speakers bureau, and advisory board fees from Astellas, grant support, consulting fees, steering committee fees, and advisory board fees, all paid to his institution, and honoraria from Boehringer Ingelheim and Regeneron Pharmaceuticals, grant support, consulting fees, and advisory board fees, all paid to his institution, from Bristol-Myers Squibb, Dow Pharma, and Dermavant Sciences, grant support, consulting fees, fees for serving on a speakers bureau, and advisory board fees, all paid to his institution, and honoraria from Galderma, grant support, consulting fees, fees for serving on a speakers bureau, and advisory board fees, all paid to his institution, and honoraria from Kyowa Hakko Kirin, grant support, consulting fees, and fees for serving on a speakers bureau, all paid to his institution, from LEO Pharma and Incyte, grant support, consulting fees, and steering committee fees, all paid to his institution, and honoraria from Merck Serono, grant support, consulting fees, and advisory board fees, all paid to his institution, and honoraria from UCB Pharma, and grant support and advisory board fees, all paid to his institution, from Sun Pharma; Dr. Yamauchi, receiving lecture fees, consulting fees, and investigator fees from AbbVie, Amgen, Eli Lilly, Janssen, Novartis, Ortho Dermatologics, Sun Pharma, and UCB Pharma; Dr. Armstrong, receiving grant support, advisory fees, and lecture fees from AbbVie and Regeneron Pharmaceuticals, grant support and advisory fees from Bristol-Myers Squibb, Dermavant Sciences, Dermira, Eli Lilly, LEO Pharma, Novartis, and UCB Pharma, advisory fees from Janssen, Modernizing Medicine, Ortho Dermatologics, Sanofi Genzyme, Sun Pharma, and Pfizer, grant support from Kyowa Kirin and Galderma, and fees for serving on a data and safety monitoring board from Boehringer Ingelheim and Parexel; Dr. Langley, receiving grant support, ad-

BE SURE 2021 *(Continued)*

visory board fees, investigator fees, and lecture fees from AbbVie, Amgen, Centocor, Eli Lilly, Janssen, LEO Pharma, Novartis, UCB Pharma, and Celgene and grant support, advisory board fees, and investigator fees from Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, and Merck; Ms. Vanvoorden, Drs. De Cuyper and Cioffi, Mr. Peterson, and Dr. Cross, being employed by and owning shares in UCB Pharma; and Dr. Reich, receiving grant support, consulting fees, and lecture fees from AbbVie, Almirall, Biogen Idec, Celgene, Eli Lilly, Janssen-Cilag, LEO Pharma, Medac, Merck Sharp & Dohme, Novartis, and Sanofi, grant support and consulting fees from Affibody, Boehringer Ingelheim, Covagen, Forward Pharma, Galderma, Kyowa Kirin, Ocean Pharma, Pfizer, Sun Pharma, Takeda, UCB Pharma, and Bristol-Myers Squibb, consulting fees from Amgen, GlaxoSmithKline, Samsung Bioepis, and XenoPort, lecture fees from Valeant Pharmaceuticals and Sandoz, and grant support from Fresenius Medical Care, Galapagos, Miltenyi Biotec, and XBiotech. 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 2) "After the screening period, patients were randomly assigned in a 1:1:1 ratio to receive subcutaneous bimekizumab at a dose of 320 mg every 4 weeks for 56 weeks..." Quote (p 3) "Randomization was carried out with the use of interactive-response technology, stratified according to geographic region (North America, Western Europe, Central and Eastern Europe, or Asia and Australia) and previous exposure to biologic agents (yes or no)." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 2) "After the screening period, patients were randomly assigned in a 1:1:1 ratio to receive subcutaneous bimekizumab at a dose of 320 mg every 4 weeks for 56 weeks..." Quote (p 3) "Randomization was carried out with the use of interactive-response technology, stratified according to geographic region (North America, Western Europe, Central and Eastern Europe, or Asia and Australia) and previous exposure to biologic agents (yes or no)." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (p 2) "This was a 56-week, phase 3, multicenter, double-blind trial of bimekizumab as compared with adalimumab..." Quote (p 3) "To maintain double blinding, patients in all groups received dummy injections at some trial visits to account for the differences in dosing schedules among the treatment groups." "The investigators, other trial-site personnel, and the sponsor (with the exception of site staff responsible for the preparation and administration of trial treatments and bioanalytic sample analysis) were unaware of the trial-group assignments." Comment: no detailled description of means used to guarentee absence of communication between blinded and unblinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (p 3) "Efficacy end points were assessed by the investigator, another delegated physician, or an appropriately qualified medical professional, all of whom were unaware of the trial-group assignments." Comment: no detailled description of means used to guarentee blinding
Incomplete outcome data (attrition bias)	Low risk	Dealing with missing data: Quote (p 4) "For efficacy variables, imputation of nonresponse was used to account for missing data."

BE SURE 2021 *(Continued)*

All outcomes		Randomised 478, analysed 478
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT03412747). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. No results are posted on ClinicalTrials.gov.

BE VIVID 2021

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind study Date of study: December 2017-December 2019 Location: worldwide (105 sites) Phase 3
Participants	**Randomised**: 567 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 • Patient is a candidate for systemic PSO therapy and/or phototherapy • Women of childbearing potential must be willing to use highly effective method of contraception. **Exclusion criteria** • Participant has an active infection (except common cold), a recent serious infection, or a history of opportunistic or recurrent chronic infections. • Participant has concurrent acute or chronic viral hepatitis B or C or human immunodeficiency virus (HIV) infection. • Participant has known tuberculosis (TB) infection, is at high risk of acquiring TB infection, or has current or history of nontuberculous mycobacterium (NTMB) infection. • Participant has any other condition, including medical or psychiatric, which, in the Investigator's judgement, would make the participant 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 • Participant 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. **Baseline characteristics** N = 567, mean age of 46 years and 72% men **Dropouts and withdrawals** • 30/567 (5.3%): placebo group (9), bimekizumab group (15), ustekinumab group (6) • AEs: placebo group (6), bimekizumab group (6), ustekinumab group (3) • Lack of efficacy: placebo group (2), bimekizumab group (1), ustekinumab group (0) • Withdrew consent: placebo group (1), bimekizumab group (2), ustekinumab group (1) • Lost to follow-up: placebo group (0), bimekizumab group (3), ustekinumab group (0)

BE VIVID 2021 *(Continued)*

- Protocol violations: placebo group (0), bimekizumab group (0), ustekinumab group (2)
- Other: placebo group (0), bimekizumab group (3), ustekinumab group (0)

Interventions	**Intervention** A. Bimekizumab 320 mg SC every 4 weeks, n = 321 **Control interventions** B. Ustekinumab 45 mg or 90 mg SC at weeks 0 and 4, then every 12 weeks, n = 163 C. Placebo SC every 4 weeks, n = 83
Outcomes	**At week 16** **Primary composite outcome** • PASI 90 - IGA 0/1 **Secondary outcomes** • PASI 75/100 • AE, SAE
Notes	Funding source: Quote (p 487) "Funding UCB Pharma" Declarations of interest: Quote (p 496-497) "KR has been an adviser for AbbVie, Affivody, Almirall, Amgen, Biogen- Idec, Boehringer Ingelheim, Celgene, Covagen, Eli Lilly, Forward Pharma, Galderma, GSK, Janssen-Cilag, Kyowa Kirin, LEO Pharma, Medac, MSD, Novartis, Ocean Pharma, Pfizer, Samsung Bioepis, Sanofi, Sun Pharma, Takeda, UCB Pharma, and Xenoport; has been a paid speaker for AbbVie, Almirall, Biogen-Idec, Celgene, Eli Lilly, Janssen- Cilag, LEO Pharma, Medac, MSD, Novartis, Sanofi, and Valeant; and has participated in clinical trials sponsored by AbbVie, Affibody, Almirall,Biogen-Idec, Boehringer Ingelheim, Celgene, Covagen, Eli Lilly, Forward Pharma, Fresenius Medical Care, Galapagos, Galderma, Janssen-Cilag, Kyowa Kirin, LEO Pharma, Medac, MSD, Miltenyl, Novartis, Ocean Pharma, Pfizer, Sanofi, Sun Pharma, Takeda, UCB Pharma, and XBiotech, all outside of the submitted work. KAP has been a consultant for AbbVie, Akros, Amgen, Arcutis, Astellas, Bausch Health/Valeant, Baxalta, Boehringer Ingelheim, Bristol Myers Squibb (BMS), Can-Fite Biopharma, Celgene, Coherus, Dermira, Dice Pharmaceuticals,Dow Pharma, Eli Lilly, Evelo, Galapagos, Galderma, Genentech, Janssen, Kyowa Hakko Kirin, LEO Pharma, Meiji Seika Pharma, MSD, Merck-Serono, Mitsubishi Pharma, Novartis, Pfizer, PRCL Research, Regeneron, Roche, Sanofi-Aventis/Genzyme, Takeda, and UCB Pharma; has been on speakers' bureau for AbbVie, Amgen, Bausch Health/ Valeant, Celgene, Eli Lilly, Galderma, Janssen, Kyowa Hakko Kirin,LEO Pharma, MSD, Novartis, Pfizer, and Sanofi-Aventis/Genzyme;has received clinical research grants from AbbVie, Akros, Amgen, Anacor, Arcutis, Astellas, Bausch Health/Valeant, Baxalta, Boehringer Ingelheim, BMS, Can-Fite Biopharma, Celgene, Coherus, Dermira, Dow Pharma, Eli Lilly, Evelo, Galapagos, Galderma, Genentech, Gilead, GSK, Janssen, Kyowa Hakko Kirin, LEO Pharma, Medimmune, MSD, Merck-Serono, Moberg Pharma, Novartis, Pfizer, PRCL Research, Regeneron, Roche, Sanofi-Aventis/Genzyme, Sun Pharma, Takeda,for Dermavent, LEO Pharma, and UCB Pharma, all outside of the submitted work. YO has received research grants from Eisai, Torii, Maruho, and Shiseido; has current consulting or advisory board agreements or speakers bureau from AbbVie, Amgen, Boehringer Ingelheim, BMS, Celgene, Eisai, Eli Lilly, Janssen Pharma, Jimro, Kyowa Kirin, LEO Pharma, Maruho, Novartis Pharma, Pfizer, Sanofi, Sun Pharma, Taiho, Tanabe-Mitsubishi, Torii, and UCB Pharma; and is involved in clinical trials sponsored by AbbVie, Amgen, Boehringer Ingelheim, BMS, Celgene, Eli Lilly, Janssen Pharma, LEO Pharma, Maruho, Pfizer, Sun Pharma, and UCB Pharma, all outside of the submitted work. MW is an employee of UCB Pharma. CM, VV,and CC are employees and shareholders in UCB Pharma. ML is an employee of Mount Sinai Hospital (New York, NY), which receives research funds from AbbVie, Amgen, Arcutis, Boehringer Ingelheim, Dermavant, Eli Lilly, Incyte, Janssen Research & Development,LEO Pharma, Ortho Dermatologics, Pfizer, and UCB Pharma. ML is also a consultant for Aditum Bio, Allergan, Almirall, Arcutis, Avotres Therapeutics, BirchBioMed, BMD Skincare, Boehringer Ingelheim, BMS, Cara Therapeutics, Castle Biosciences, Corrona, Dermavant Sciences, Evelo, Facilitate International Dermatologic Education, Foundation for Research and Education in Dermatology,

BE VIVID 2021 *(Continued)*

	Inozyme Pharma, LEO Pharma, Meiji Seika Pharma, Menlo, Mitsubishi, Neuroderm, Pfizer, Promius/Dr Reddy's Laboratories, Serono, Theravance, and Verrica, all outside of the submitted work."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 488-489) "BE VIVID was a multicentre, randomised, double-blind, active comparator and placebo controlled phase 3 trial done across 105 sites... Patients were randomly assigned (4:2:1) to receive bimekizumab, ustekinumab, or placebo, using an interactive response technology, which assigned patients on the basis of a predetermined production randomisation or packaging schedule. Randomisation was stratified by geographical region (North America, Western Europe, Central and Eastern Europe, and Asia and Australia) and previous exposure to biologics (yes or no)." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 488-489) "BE VIVID was a multicentre, randomised, double-blind, active comparator and placebo controlled phase 3 trial done across 105 sites... Patients were randomly assigned (4:2:1) to receive bimekizumab, ustekinumab, or placebo, using an interactive response technology, which assigned patients on the basis of a predetermined production randomisation or packaging schedule. Randomisation was stratified by geographical region (North America, Western Europe, Central and Eastern Europe, and Asia and Australia) and previous exposure to biologics (yes or no)." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 488-489) "BE VIVID was a multicentre, randomised, double-blind, active comparator and placebo controlled phase 3 trial done across 105 sites... To maintain double-blinding, ustekinumab-treated patients received placebo to match the bimekizumab dosing regimen (appendix p 6). Throughout the study, patients, investigators, and sponsors remained masked to treatment assignment with the exception of specially designated, unmasked site staff responsible for the preparation and administration of study treatments, safety monitoring, or bioanalytical sample analysis." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (p 488-489) "BE VIVID was a multicentre, randomised, double-blind, active comparator and placebo controlled phase 3 trial done across 105 sites... To maintain double-blinding, ustekinumab-treated patients received placebo to match the bimekizumab dosing regimen (appendix p 6). Throughout the study, patients, investigators, and sponsors remained masked to treatment assignment with the exception of specially designated, unmasked site staff responsible for the preparation and administration of study treatments, safety monitoring, or bioanalytical sample analysis." Comment: no detailled description of means used to guarentee absence of communication between blinded and unblinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (p 491) "Efficacy analyses included all randomly assigned patients (intention-to-treat population)... For the binary variables reported here, non-responder imputation was used to account for missing data." Randomly assigned 567, analysed 567

BE VIVID 2021 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT03370133). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. No results are posted on ClinicalTrials.gov.

Bissonnette 2013

Study characteristics	
Methods	RCT, placebo-controlled, single-blind study 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 source: 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.

Blauvelt 2021a

Study characteristics

Methods	RCT, active/placebo-controlled, double-blind study Date of study: May 2019-February 2020 Location: USA (38 sites) Phase 3
Participants	**Randomized:** 157 participants **Inclusion criteria**:

Blauvelt 2021a *(Continued)*

- Participant has diagnosis of chronic plaque psoriasis for at least 6 months before the baseline visit.
- Participant meets following disease activity criteria:
  - Stable moderate-to-severe chronic plaque psoriasis, defined as ≥ 10% body surface area (BSA) psoriasis involvement, static physician global assessment (sPGA) score of ≥ 3, and Psoriasis Area Severity Index (PASI) ≥ 12 at screening and baseline visit
- Candidate for systemic therapy as assessed by the investigator

Exclusion criteria:

- Participant has history of active skin disease other than psoriasis that could interfere with the assessment of psoriasis.
- Participant has history of erythrodermic psoriasis, generalised or localised pustular psoriasis, medication-induced or medication-exacerbated psoriasis, or new onset guttate psoriasis.
- Participant has previous exposure to risankizumab.

Baseline characteristics

N = 157, mean of age 49 years and 55% men

Dropouts and withdrawals

- 33/157 (21%): risankizumab (13), placebo (20)
- AEs: risankizumab (0), placebo (1)
- Withdrew consent: risankizumab (5), placebo (6)
- Lost to follow-up: risankizumab (8), placebo (2)
- Lack of efficacy: risankizumab (0), placebo (11)

Interventions	**Intervention** A. Risankizumab 150 mg SC at weeks 0, 4, and 16, n = 105 **Control intervention** B. Placebo, n = 52
Outcomes	**At week 16** **Primary outcomes** • PASI 90 • PGA 0/1 **Secondary outcomes** • PASI 100 • PGA 0
Notes	Funding source: Quote (p. 8) "This work was supported by AbbVie. AbbVie participated in the study design, research, analysis, data collection, interpretation of data, reviewing, and approval of the publication." Declarations of interest: Quote (p. 8) "Andrew Blauvelt has served as a scientific adviser and/or clinical study investigator for AbbVie, Aligos, Almirall, Amgen, Arcutis, Arena, Athenex, Boehringer Ingelheim, Bristol-Myers Squibb, Dermavant, Eli Lilly and Company, Evommune, Forte, Galderma, Incyte, Janssen, Leo, Novartis, Pfizer, Rapt, Regeneron, Sanofi Genzyme, Sun Pharma, and UCB Pharma. Kenneth B. Gordon has received honoraria and/or research support from AbbVie, Amgen, Arcutis, Arena Pharma, Bristol Myers Squibb, Dermavant, Dermira, Incyte, Janssen, Kyowa Hakko Kirin, LEO Pharma, Novartis, Pfizer, Sanofi Genzyme, Sun Pharma, and UCB. Patricia Lee does not have any conflicts of interest, but her spouse is a speaker for AbbVie. Jerry Bagel has received research funds pay- able to Psoriasis Treatment Center from AbbVie, Amgen, Arcutis Biotherapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Celgene Corporation, Corrona LLC, Dermavant Sciences Ltd, Dermira, UCB, Eli Lilly and Compa-

Blauvelt 2021a *(Continued)*

ny, Glenmark Pharmaceuticals Ltd, Janssen Biotech, Kadmon Corporation, Leo Pharma, Lycera Corp, Menlo Therapeutics, Novartis, Pfizer, Regeneron Pharmaceuticals, Sun Pharma, Taro Pharmaceutical Industries Ltd, and Ortho Dermatologics; consultant fees from AbbVie, Amgen, Celgene Corporation, Bristol-Myers Squibb, Eli Lilly and Company, Janssen Biotech, Novartis, Sun Pharmaceutical Industries Ltd, UCB; and fees for speaking from AbbVie, Celgene Corporation, Eli Lilly, Janssen Biotech, and Novartis. Howard Sofen has served as a scientific adviser and/or clinical study investigator for AbbVie, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Eli Lilly, Incyte, Janssen, Leo, Novartis, Pfizer, Sanofi Genzyme, Sun Pharma, and UCB. Benjamin Lockshin has served as a speaker, consultant and/or clinical study investigator for AbbVie, Bristol Myers Squibb, Celgene, Corrona registry, Eli Lilly, Incyte, Novartis, Regeneron, Sanofi Genzyme, Sun Pharma, and UCB. Ahmed M. Soliman, Ziqian Geng, Tianyu Zhan, and Gabriela Alperovich are employees of AbbVie Inc. and may hold stock or stock options. Linda Stein Gold has served as a scien- tific adviser, speaker and/or clinical study investigator for AbbVie, Almirall, Arcutis, Bristol Myers Squibb, Dermavant, Eli Lilly and Company, Galderma, Incyte, Leo, Novartis, Ortho Derm, Pfizer, Regeneron, Sanofi Genzyme, Sun Pharma, and UCB Pharma."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p. 2) "Study 1 (NCT03875482) was a multicenter, randomized, double-blinded, placebo-controlled, parallel-group study conducted at 38 sites in the United States..." Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (p. 2) "Study 1 (NCT03875482) was a multicenter, randomized, double-blinded, placebo-controlled, parallel-group study conducted at 38 sites in the United States..." Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (p. 2) "Study 1 (NCT03875482) was a multicenter, randomized, double-blinded, placebo-controlled, parallel-group study conducted at 38 sites in the United States..." Comment: unclear if the process guaranteed blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (p. 2) "Study 1 (NCT03875482) was a multicenter, randomized, double-blinded, placebo-controlled, parallel-group study conducted at 38 sites in the United States..." Comment: unclear if the process guaranteed the blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (p. 4) "In study 1, the intent-to-treat (ITT) population included all randomized patients; patients were analyzed according to treatment as randomized. The safety analysis population consisted of all patients who received at least one dose of study drug; patients were analyzed according to the first dose of study drug (risankizumab or placebo) received....". "For analysis of both studies, categorical efficacy variables were analyzed using non-responder imputation (NRI) to handle missing data; mixed-effect model repeat measurements (MMRMs) of additional efficacy endpoints was used for continuous variables. As observed and modified NRI (mNRI) were conducted as sensitivity analyses for efficacy endpoints (co-primary and ranked secondary efficacy endpoints in study 1) for the two studies. For mNRI, a patient was considered as a non-responder for the visit if the patient did not have an

Blauvelt 2021a *(Continued)*

		evaluation and discontinued study drug due to lack of efficacy or due to an AE of worsening of psoriasis during the visit window". Randomised 157, analysed 157
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT03875482). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. Results are posted on ClinicalTrials.gov.

BRIDGE 2017

Study characteristics	
Methods	RCT, active-controlled, double-blind study 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 **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

BRIDGE 2017 *(Continued)*

- 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
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.”

BRIDGE 2017 *(Continued)*

		DMF/DMF + MEF/placebo Randomised: 280/286/138 Safety set analysis: 279/283/137 (untreated 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

Cai 2016

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study Date of study: August 2012-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)
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

Cai 2016 *(Continued)*

	Primary outcomes • PASI 75 **Secondary outcomes** • 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 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."

Cai 2016 *(Continued)*

		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.

Cai 2020

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind study Date of study: February 2017-November 2018 Location: China, Hungary, Malaysia, Turkey, Thailand, Philippines Phase 3
Participants	**Randomised**: 441 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 • 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 **Baseline characteristics** N = 441, mean age of 39 years and 79% men **Dropouts and withdrawals** • 6/441 (1.3%): secukinumab 150 group (2), secukinumab 300 group (2), placebo group (2) • Pregnancy: secukinumab 150 group (0), secukinumab 300 group (0), placebo group (1) • Lack of efficacy: secukinumab 150 group (0), secukinumab 300 group (0), placebo group (1) • AEs: secukinumab 150 group (2), secukinumab 300 group (2), placebo group (0)

Cai 2020 *(Continued)*

Interventions	**Intervention** A. Secukinumab 150 mg: 150 mg SC at randomisation, weeks 1, 2, 3, 4 and every 4 weeks til week 48, n = 110 **Control interventions** B. Secukinumab 300 mg: 300 mg SC at randomisation, weeks 1, 2, 3, 4 and every 4 weeks til week 48, n = 221 C. Placebo, n = 110
Outcomes	**At week 12** **Primary composite outcome** • PASI 75 • IGA 0/1 **Secondary outcomes** • PASI 90/75, IGA, DLQI (12 and 52 weeks)
Notes	Funding source: Quote (p 2672) :''This study was sponsored by Novartis Pharma AG, Basel, Switzerland.'' Declarations of interest: Quote (p 2672): ''Lin Cai has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from Novartis, AbbVie, Pfizer Inc. Jian-Zhong Zhang has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from LEO Pharma China, Novartis, Sanofi, La Roche-Posay China, AbbVie, Bayer, Janssen-Cilag, Hen- lius, Kyowa Kirin, and Pfizer Inc. Xu Yao has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from LEO Pharma China, Novartis, Sanofi, AbbVie, Bayer, Janssen- Cilag, and Pfizer Inc. Jun Gu has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from LEO Pharma China, Novartis, Sanofi, La Roche-Posay China, AbbVie, Bayer, Henlius, and Pfizer Inc. Quan-Zhong Liu has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from Novartis, La Roche-Posay China, AbbVie, Bayer, Janssen- Cilag, and Pfizer Inc. Min Zheng has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from AbbVie, Janssen-Cilag, Boehringer Ingelheim, LEO Pharma China, Xian-Janssen, Novartis, and Pfizer Inc. Shi-Fa Zhang has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from LEO Pharma China, Novartis, Janssen-Cilag, Henlius. Jin- Hua Xu has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from Novartis, Sanofi, La Roche-Posay China, AbbVie, Bayer, Kyowa Kirin, and Pfizer Inc. Cheng-Xin Li has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from LEO Pharma China, Novartis, AbbVie, Bayer, Janssen-Cilag, Kyowa Kirin, and Pfizer Inc. Hao Cheng has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from LEO Pharma China, Novartis, AbbVie, Bayer, Janssen-Cilag, Henlius, and Pfizer Inc. Qing Guo has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from LEO Pharma China, Novartis, Sanofi, La Roche-Posay China, AbbVie, Bayer, Janssen-Cilag, Hen- lius, Kyowa Kirin, and Pfizer Inc. Wei-Li Pan has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from LEO Pharma China, Novartis, Sanofi, La Roche-Posay China, AbbVie, Bayer, Janssen-Cilag, Henlius, Kyowa Kirin, and Pfizer Inc. Shen-Qiu Li has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from LEO Pharma China, Novartis, Sanofi, AbbVie, Bayer, Janssen-Cilag, and Pfizer Inc. Ruo-Yu Li has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from LEO Pharma China, Novartis, Bayer, Janssen-Cilag, MSD, and Pfizer Inc. Zai-Pei Guo has participated in advisory boards and/ or as an investigator and/or speaker and received grants and/or honoraria from LEO Pharma China, Novartis, Sanofi, AbbVie, Bayer, Janssen-Cilag, and Pfizer Inc. Zhi- Qi Song has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from LEO Pharma China, Novartis, Sanofi, La Roche-Posay China, AbbVie, Bayer, Janssen-Cilag, Hen- lius, Kyowa Kirin, and Pfizer Inc. Shan-Shan Li has participated as an investigator and received

Cai 2020 *(Continued)*

honoraria from Novartis China. Xiu-Qin Dong has participated in advisory boards and/or as an investigator and/or speaker and received honoraria from LEO Pharma China, Novartis, Sanofi, AbbVie, Bayer, Janssen-Cilag. Linda Wang, Rong Fu, Pascaline Regnault, Pascal Charef, Rafal Mazur, and Manmath Patekar are employed by Novartis.''

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 2666): "This study ... was a 52-week, multicenter, randomized, double-blind, placebo- controlled, parallel-group, Phase 3 trial." Quote (p 2667): "At Baseline visit, all eligible patients were randomized via interactive response technology (IRT) to one of the treatment arms. The Investigator or his/her delegate contacted the IRT after confirming that the patient fulfilled all the inclusion/exclusion criteria. A patient randomization list was produced by the IRT provider using a validated system that automated the random assignment of patient numbers to randomization numbers. These randomization numbers were linked to the different treatment arms, which in turn were linked to medication numbers for the packages of investigational treatment to be dispensed to the patient (only the medication number, but not the randomization number)." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 2666):"This study ... was a 52- week, multicenter, randomized, double-blind, placebo- controlled, parallel-group, Phase 3 trial. ." Quote (p 2667): "At Baseline visit, all eligible patients were randomized via interactive response technology (IRT) to one of the treatment arms. The Investigator or his/her delegate contacted the IRT after confirming that the patient fulfilled all the inclusion/exclusion criteria. A patient randomization list was produced by the IRT provider using a validated system that automated the random assignment of patient numbers to randomization numbers. These randomization numbers were linked to the different treatment arms, which in turn were linked to medication numbers for the packages of investigational treatment to be dispensed to the patient (only the medication number, but not the randomization number)." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (study protocol p 29): "Subjects, investigator staff, persons performing the assessments and data analyst will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study, (2) the identity of the treatments will be concealed by the use of investigational treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor." Quote (p 2666): "This study ... was a 52-week, multicenter, randomized, double-blind, placebo- controlled, parallel-group, Phase 3 trial." Quote (p 2666): "Due to treatment blinding, patients received an additional weekly secukinumab or matching placebo dose at Weeks 13, 14, and 15." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (study protocol p 29): "Subjects, investigator staff, persons performing the assessments and data analyst will remain blind to the identity of the treatment from the time of randomization until database lock, using the following

Cai 2020 *(Continued)*

		methods: (1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study, (2) the identity of the treatments will be concealed by the use of investigational treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor." Quote (p 2666): "This study ... was a 52- week, multicenter, randomized, double-blind, placebo- controlled, parallel-group, Phase 3 trial." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (p 2667):"The co-primary endpoints were evaluated using a logistic regression model with treatment group, baseline body weight category, geographical region, and baseline PASI score as exploratory variables and a multiple imputations (MI) method was used for missing values." Randomised 441, analysed 441
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT03066609). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. Results are posted on ClinicalTrials.gov.

CALYPSO 2018

Study characteristics	
Methods	RCT, active-controlled, double-blind study Date of study: January 2017-April 2018 Location: Russia (multicentre) Phase 3
Participants	**Randomised**: 346 participants **Inclusion criteria** • Participant had written informed consent. • Age between 18 and 75 years. • Participant has moderate-to-severe plaque psoriasis with stable course of the disease for 6 months. • Participant 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 • Participant 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 pa-

CALYPSO 2018 *(Continued)*

tients who have active tuberculosis AND have no signs of tuberculosis on chest X-ray that was performed during 3 months before randomisation).

- Participants are able to perform all procedures planed by protocol.
- Participants 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 phototherapy. Subject 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 breastfeeding 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

Baseline characteristics

CALYPSO 2018 *(Continued)*

N = 346, mean of age 42.5 years and 66% men

Dropouts and withdrawals

- 19/346 (5.5%): BCD-057 (9), Humira® (10)
- Eliminated for security reasons: BCD-057 (3), Humira® (4)
- Low adherence treatment: BCD-057 (2), Humira® (0)
- Deviation from protocol: BCD-057 (0), Humira® (2)
- Withdrawal of informed consent: BCD-057 (4), Humira® (4)

Interventions	**Intervention** BCD-057 (a biosimilar of adalimumab) 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, n = 174 **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, n = 172
Outcomes	**At week 16** **Primary outcome** • PASI 75 **Secondary outcomes** • PASI improvement • PASI 50, PASI 90, PGA • SF-36 • DLQI • SAE, AE
Notes	Funding source: Quote (clinicaltrials.gov) "Biocad" Declarations of interest: not stated The filling in of the characteristics and ROB tool of this study was made from his article translated from Russian into English.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p. 74) "BCD-057-2/CALYPSO (NCT02762955) is a randomized double-blind clinical study of efficacy and safety of the drug BCD-057 (international non-proprietary name, INN: adalimumab, CJSC "BIOCAD", Russia)..." Comment: no description of the method used to guarantee random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (p. 74) "BCD-057-2 / CALYPSO (NCT02762955) is a randomized double-blind clinical study of efficacy and safety of the drug BCD-057 (international non-proprietary name, INN: adalimumab, CJSC "BIOCAD", Russia)..." Comment: no description of the method used to guarantee allocation concealment

CALYPSO 2018 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (p. 74) "BCD-057-2 / CALYPSO (NCT02762955) is a randomized double-blind clinical study of efficacy and safety of the drug BCD-057 (international non-proprietary name, INN: adalimumab, CJSC "BIOCAD", Russia)..." Comment: no description of the method used to guarantee blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (p. 74) "BCD-057-2 / CALYPSO (NCT02762955) is a randomized double-blind clinical study of efficacy and safety of the drug BCD-057 (international non-proprietary name, INN: adalimumab, CJSC "BIOCAD", Russia)..." Comment: no description of the method used to guarantee blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Randomised 346, analysed 346 Comment: methods for dealing with missing data not specified, ITT analyses
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02762955). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. Results are not posted on ClinicalTrials.gov.

Caproni 2009

Study characteristics	
Methods	RCT, active-controlled study 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**

Caproni 2009 *(Continued)*

	• Not stated **Outcomes of the trial** • Mean PASI at baseline and at 12 weeks • PASI 75, PASI 50
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. 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

CARIMA 2019

Study characteristics

Methods	RCT, placebo-controlled, double-blind study Date of study: April 2014-April 2016 Location: Germany (23 sites, multicentre) Phase 3
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

CARIMA 2019 *(Continued)*

- Inadequate response, intolerance or contraindication to ciclosporin, methotrexate and psoralen plus ultraviolet A light treatment (PUVA) as documented in the participant's medical history or reported by the participant or determined by the investigator at screening. Relative contraindications such as interference of participant'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
- Ongoing use of prohibited psoriasis and non-psoriasis treatments. Washout periods have to be adhered to.

Baseline characteristics

N = 151, mean age of 51.93 years and 67% men

Dropouts and withdrawals

- 11/151 (7.3%): secukinumab 300 group (1), secukinumab 150 group (5), placebo group (5)
- Person/guardian decision: secukinumab 300 group (1), secukinumab 150 group (2), placebo group (1)
- Progressive disease: secukinumab 300 group (0), secukinumab 150 group (1), placebo group (0)
- AEs: secukinumab 300 group (0), Secukinumab 150 group (2), placebo group (4)

Interventions

Intervention

A. Secukinumab 300 (300 mg every week for 4 weeks followed by 300 mg secukinumab every 4 weeks until week 48) (n = 48)

Control interventions

B. Secukinumab 150 (150 mg every week for 4 weeks followed by 300 mg secukinumab every 4 weeks until week 48) (n = 54)

C. Placebo (n = 49)

Outcomes

At week 12

Primary outcome

- Flow Mediated Dilation (FMD)

Secondary outcomes

- Aortic Augmentation Index at heart rate of 75 at weeks 4, 12, 24, and 52
- Pulse wave velocity
- Biomarkers at weeks 4, 12, 24, and 52
- PASI at weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, and 52
- IGA at weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, and 52

Notes

On ClinicalTrials.gov, results submitted without PASI or IGA outcomes

Funding source

Quote (p. 1061): "The CARIMA study was funded by Novartis Pharma GmbH, Germany. Medical writing assistance was provided by Evelyn Altemeyer, Novartis Ireland Ltd., and funded by Novartis Pharma GmbH, Germany, in line with Good Publication Practice 3 guidelines."

Declarations of interest

Quote (p. 1061): "EVS received grants from the Deutsche Forschungsgemeinschaft. KR has served as advisor and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Affibody, Amgen, Biogen, Boehringer Ingelheim Pharma, Celgene, Centocor, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, Kyowa Kirin, Leo, Lilly, Medac, Merck Sharp & Dohme, Novartis, Ocean

CARIMA 2019 *(Continued)*

Pharma, Pfizer, Regeneron, Sanofi, Takeda, UCB Pharma, and Xenoport. DT has received research support/acted as Principal Investigator (clinical trials) from AbbVie, Almirall, Amgen, Astellas, Biogen-Idec, Boehringer-Ingelheim, Celgene, Dignity, Eli Lilly, Forward-Pharma, GlaxoSmithKline, Leo, Janssen-Cilag, Maruho, Merck Sharp & Dohme, Mitsubishi Pharma, Novartis, Pfizer, Roche, and Sandoz; has acted as a consultant for AbbVie, Biogen-Idec, Celgene, Dignity, Maruho, Mitsubishi, Novartis, Pfizer, and Xenoport; has received honoraria from AbbVie, Biogen-Idec, Celgene, Janssen, Leo, Pfizer, Roche-Possay, Novartis, and Mundipharma; and has participated in scientific advisory boards for AbbVie, Amgen, Biogen-Idec, Celgene, Eli Lilly, GlaxoSmithKline, Pfizer, Novartis, Janssen, Mundipharma, and Sandoz. WK served on the executive steering committee of JUPITER and CANTOS; served as a consultant for Amgen, DalCor, Kowa, Novartis, Pfizer, and Sanofi; and has received fees for lectures from Amgen, AstraZeneca, Novartis, Pfizer, and Sanofi. AP is a speaker for AbbVie, Almirall-Hermal, Amgen, Biogen Idec, Celgene, Eli Lilly, Galderma, Janssen, Leo Pharma, Medac, Novartis, Pfizer, and UCB Pharma; served as an advisor for AbbVie, Almirall-Hermal, Amgen, Celgene, Eli Lilly, Janssen, Leo Pharma, and Novartis; and has participated in clinical trials funded by AbbVie, Almirall-Hermal, Amgen, Biogen Idec, Boehringer-Ingelheim, Celgene, Glax- oSmithKline, Eli Lilly, Galderma, Hexal, Janssen, Leo Pharma, Medac, Merck Serono, Mitsubishi, Merck Sharp & Dohme, Novartis, Pfizer, Tigercat Pharma, Regeneron, Roche, Sandoz Biopharmaceuticals, Schering-Plough, and UCB Pharma. AK has received honoraria from Novartis, Eli Lilly, Leo Pharma, Almirall, Janssen, UCB Pharma, Merck Sharp & Dohme, and Pfizer and has received fees for board participation from Novartis, Leo Pharma, Janssen, and Eli Lilly. TR has received fees and honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, and Novartis. DY, JF, CS, and NM are employees of Novartis. NNM is a full-time US government employee. TG has received grant support and speaker honoraria from Abbott Vascular."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p 1059): "CARIMA was a multicenter, double-blind, randomized, placebo- controlled, parallel-group, exploratory trial in patients with plaque-type psoriasis." Comment: No description
Allocation concealment (selection bias)	Unclear risk	Quote (p 1059): "CARIMA was a multicenter, double-blind, randomized, placebo- controlled, parallel-group, exploratory trial in patients with plaque-type psoriasis." Comment: No description
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 1059): "CARIMA was a multicenter, double-blind, randomized, placebo- controlled, parallel-group, exploratory trial in patients with plaque-type psoriasis." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 1059): "CARIMA was a multicenter, double-blind, randomized, placebo- controlled, parallel-group, exploratory trial in patients with plaque-type psoriasis." Quote (p 1060): " The FMD analysis was performed in a blinded fashion by a core laboratory (University Medical Center Mainz; see Supplementary Materials)." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dealing with missing data: Quote (p 1060-1): "The full analysis set comprised all randomly assigned patients to whom treatment was administered. All analyses were as observed; missing values were not imputed. "

CARIMA 2019 *(Continued)*

		Results for PASI 75 and 90 were reported as percentage number not reported; impossible to state if all randomised particiants were analysed
Selective reporting (reporting bias)	High risk	Comment: The protocol for the study was available on ClinicalTrials.gov (NCT02559622). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported except for IGA. Results posted in ClinicalTrials.gov.

CHAMPION 2008

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind study Date of study: not stated 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 **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: adalimumab 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 outcome** • PASI 75 **Secondary outcomes** • PASI 50 • PASI 90

CHAMPION 2008 *(Continued)*

- 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". 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

CHAMPION 2008 *(Continued)*

		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.

CHANGE 2021

Study characteristics	
Methods	RCT, active-controlled, open-label study with blinded assessment of the efficacy outcome Date of study: November 2017-March 2019 Location: Germany (30 sites) 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

CHANGE 2021 *(Continued)*

Baseline characteristics

N = 210, mean of age 44 years, and 69% men

Dropouts and withdrawals

- 61/210 (29%): 14/105 brodalimumab and 47/105 fumaric acid esthers
- AEs: brodalimumab group (7), fumaric acid esthers group (28)
- Lack of efficacy: brodalimumab group (1), fumaric acid esthers group (4)
- Lost to follow-up: brodalimumab group (0), fumaric acid esthers group (2)
- Withdrawal by subject: brodalimumab group (1), fumaric acid esthers group (8)
- Other: brodalimumab group (5), fumaric acid esthers group (5)

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)), n = 105 **Control intervention** 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), n = 105.
Outcomes	**At week 24** **Primary composite outcome** • PASI 75 - IGA 0/1 **Secondary outcomes** • 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) • Change From Baseline at week 24 in DLQI (time frame: baseline to week 24) • DLQI Total Score of 0 or 1 at week 24 (time frame: week 24)
Notes	Funding source: Quote (p 2) "The trial was funded in full by LEO Pharma A/S, Ballerup, Denmark." Declarations of interest: Quote (p 1-2) "A. Pinter has received honoraria as investigator and/or for consultancy and/or received speakers honoraria and/ or research grants from AbbVie, Almirall Hermal, Amgen, Biogen Idec, BioNTech, Boehringer Ingelheim, Celgene, GSK, Eli Lilly, Galderma, Hexal, Janssen, LEO Pharma, MC2, Medac, Merck Serono, Mitsubishi, MSD, Novartis, Pascoe, Pfizer, Tigercat Pharma, Regeneron, Roche, Sandoz Biopharmaceuticals, Sanofi Genzyme, Schering- Plough and UCB Pharma. M. Hoffmann has received honoraria as investigator and/or for consultancy and/or received speaker's honoraria and/or research grants from AbbVie, Almirall Hermal, Boehringer Ingelheim, Eli Lilly, Janssen, LEO Pharma, Medac, MSD, Novartis, Pfizer and UCB Pharma. K. Reich has received honoraria as investigator and/or for consultancy and/or received speaker's honoraria and/or research grants from AbbVie, Affibody, Almirall, Amgen, Biogen Idec, Boehringer Ingelheim, Bristol-Meyers Squibb, Celgene, Covagen, Eli Lilly, Forward Pharma, Fresenius Medical Care, Galapagos, GlaxoSmithKline, Janssen-Cilag, Kyowa Kirin, LEO Pharma, Medac, Merck Sharp & Dohme Corp., Miltenyi, Novartis, Ocean Pharma, Pfizer, Samsung Bioepis, Sandoz, Sanofi, Sun Pharma, Takeda, UCB Pharma, Valeant, XBiotech and XenoPort. M. Augustin has received honoraria as investigator and/or for consultancy and/or received speaker's honoraria and/or research grants AbbVie, Almirall, Amgen, Biogen, Boehringer

CHANGE 2021 *(Continued)*

Ingelheim, Celgene, Centocor, Eli Lilly, GSK, Janssen-Cilag, LEO Pharma, Medac, Merck, MSD, Novartis, Pfizer, UCB Pharma and XenoPort. U. Mrowietz has received honoraria as investigator and/or for consultancy and/or received speaker's honoraria and/or research grants from AbbVie, Almirall, Aristea, Boehringer Ingelheim, Celgene, Dr. Reddy's, Eli Lilly, Foamix, Formycon, Forward Pharma, Janssen, LEO Pharma, Medac, Novartis, Pierre Fabre, Sanofi-Aventis, UCB and Xenoport. K. Kaplan, S.D. Gudjonsdottir and T. Delvin are employees of LEO Pharma A/S."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote : (p 2) "This was a 24-week, phase 4, randomized, assessor-blinded, multi-centre, open-label, parallel-group, active-controlled trial... Two hundred ten subjects were randomized 1: 1 using an interactive web response system (Bioclinica Trident, Princeton, NJ, USA) to receive either subcutaneous, self-administered injections of 210 mg brodalumab once weekly at weeks 0, 1 and 2 followed by 210 mg every 2 weeks, or to FAE tablets (Fumaderm" Initial/Fumaderm", Biogen GmbH, Munic, Germany) up to 240 mg three times daily, with individual dose titration according to label". Coments: adequate process
Allocation concealment (selection bias)	Low risk	Quote (p 2):""This was a 24-week, phase 4, randomized, assessor-blinded, multi-centre, open-label, parallel-group, active-controlled trial... Two hundred ten subjects were randomized 1: 1 using an interactive web response system (Bioclinica Trident, Princeton, NJ, USA) to receive either subcutaneous, self-administered injections of 210 mg brodalumab once weekly at weeks 0, 1 and 2 followed by 210 mg every 2 weeks, or to FAE tablets (Fumaderm" Initial/Fumaderm", Biogen GmbH, Munic, Germany) up to 240 mg three times daily, with individual dose titration according to label". Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (p 2-3):" This was a 24-week, phase 4, randomized, assessor-blinded, multi-centre, open-label.... Assessment of PASI, static Physician's Global Assessments (sPGA), BSA and Nail Psoriasis Severity Index (NAPSI) were performed by investigators blinded to the trial treatment."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (p 2-3):" This was a 24-week, phase 4, randomized, assessor-blinded, multi-centre, open-label.... Assessment of PASI, static Physician's Global Assessments (sPGA), BSA and Nail Psoriasis Severity Index (NAPSI) were performed by investigators blinded to the trial treatment." Comment: No description of the method used to guarantee blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (p 4):"Efficacy endpoints were analysed for the intention-to-treat population (full analysis set). Safety data were analysed for subjects who were exposed to trial treatment and according to the treatment received (safety analysis set). Binary data were analysed using the Cochran–Mantel–Haenszel (CMH) test with stratification by weight group (≥ 100 or < 100 kg) and non-responder imputation for missing data". Randomised 210, analysed 210

CHANGE 2021 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT03331835). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. Results are posted on ClinicalTrials.gov.

Chaudhari 2001

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study 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 • 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 source: Y Johnson and Johnson, Centocor Inc.

Chaudhari 2001 *(Continued)*

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) 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 study 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**

Chladek 2005 *(Continued)*

	• 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 source: Czech Ministry of Education Declarations of interest: not stated

Risk of bias

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

Chladek 2005 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Comment: no primary or secondary outcomes stated

CIMPACT 2018

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind study 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), certolizumab 200 (6), certolizumab 400 (5) • AEs: placebo (0), etanercept (4), certolizumab 200 (1), certolizumab 400 (1) • Protocol violation: placebo (0), etanercept (1), certolizumab 200 (0), certolizumab 400 (0) • Participant decision: placebo (0), etanercept (2), certolizumab 200 (3), certolizumab 400 (1) • Lost to follow-up: placebo (1), etanercept (2), certolizumab 200 (1), certolizumab 400 (2) • Absence of efficacy: placebo (1), etanercept (1), certolizumab 200 (0), certolizumab 400 (0) • Others: placebo (0), etanercept (1), certolizumab 200 (1), certolizumab 400 (1)

CIMPACT 2018 *(Continued)*

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 interventions** 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." Declarations 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

Bias	Authors' judgement	Support for judgement

CIMPACT 2018 *(Continued)*

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.

CIMPASI-1 2018

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind study Date of study: December 2014-October 2016 Location: worldwide Phase 3

CIMPASI-1 2018 *(Continued)*

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

CIMPASI-1 2018 *(Continued)*

- DLQI

Notes	Funding source Quote (p 302): "Supported by Dermira Inc and UCB Inc." Declarations 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,

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.

CIMPASI-2 2018

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind study Date of study: December 2014-December 2016 Location: worldwide 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

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."

Declarations 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-

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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

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.

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

CLARITY 2018 *(Continued)*

	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
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)	Low risk	Quote (p 572): “CLARITY (NCT02826603) is a multicenter, randomized, double-blinded, active-controlled. . .”

CLARITY 2018 *(Continued)*

All outcomes		Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 572): "CLARITY (NCT02826603) is a multicenter, randomized, double-blinded, active-controlled. . ." 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.

CLEAR 2015

Study characteristics	
Methods	RCT, active-controlled, double-blind study 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) **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)

CLEAR 2015 *(Continued)*

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 outcome** • PASI 90 **Secondary outcomes** • 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 402): “were randomised via an interactive response technology system". Randomisation 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

CLEAR 2015 *(Continued)*

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.

Dogra 2012

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

Dogra 2012 *(Continued)*

- Change in PASI score

Secondary outcomes

- PASI 75
- AEs

Notes	Funding source: not stated Declarations of interest: not stated

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
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

Dogra 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.

Dogra 2013

Study characteristics	
Methods	RCT, active-controlled, double blind study 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 **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 outcome** • Change in PASI score **Secondary outcomes** • PASI 75 • % complete clearance • Time taken to achieve those parameters • AEs
Notes	Funding source (quote e305): not stated

Dogra 2013 *(Continued)*

Declarations of interest (quote e305): not stated

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
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 study 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)

Dubertret 1989 *(Continued)*

	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 outcome** • PASI 75 **Secondary outcomes** • Not stated
Notes	Funding source: not stated, but 1 out of 4 authors was a staff member of Sandoz pharmaceutical company Declarations of interest: not stated

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

Dubertret 1989 *(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.

ECLIPSE 2019

Study characteristics	
Methods	RCT, active-controlled, double-blind study Date of study: April 2017-September 2018 Location: worldwide (142 sites) 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. • 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 **Baseline characteristics** N = 1048, mean age of 46 years and 67% men **Dropouts and withdrawals** • 75/1048 (7.2%): guselkumab 100 group (27), secukinumab 300 group (48) • AEs: guselkumab 100 group (1 worsening of psoriasis and 8 other AEs), secukinumab 300 group (1 worsening of psoriasis and 10 other AEs) • Lack of perceived efficacy: guselkumab 100 group (2), secukinumab 300 group (7) • Lost to follow-up: guselkumab 100 group (2), secukinumab 300 group (2) • Not comply with study drug: guselkumab 100 group (2), secukinumab 300 group (0)

ECLIPSE 2019 *(Continued)*

- Withdrew: guselkumab 100 group (7), secukinumab 300 group (19)
- Pregnant: guselkumab 100 group (1), secukinumab 300 group (1)
- Protocol violations: guselkumab 100 group (2), secukinumab 300 group (6)
- Other: guselkumab 100 group (2), secukinumab 300 group (2)

Interventions	**Intervention** A. Guselkumab 100 mg (TREMFYA) SC injection plus placebo (one injection) at weeks 0, 4, 12, and every 8 weeks thereafter until week 44, n = 534 **Control intervention** B**.** Secukinumab 300 mg (COSENTYX) administered as two 150 mg SC injections at weeks 0, 1, 2, 3, and 4, and every 4 weeks thereafter until week 44, n = 514
Outcomes	**At week 48** **Primary outcome** • PASI 90 **Secondary outcomes** • PASI 75, PASI 90 (at weeks 12 and 48) • PASI 100 (at week 48) • IGA 0/1 (at week 48)
Notes	Funding source: Quote (p. 831):"This study was funded by Janssen Research & Development." Declarations of interest: "Quote (p. 838): "KR has served as an advisor and paid speaker and has participated in clinical trials for AbbVie, Affibody, Almirall, Amgen, Avillion, Biogen, Boehringer Ingelheim, Celgene, Covagen, Forward Pharma, Fresenius Medical Care, GlaxoSmithKline, Janssen, Janssen-Cilag, Kyowa Kirin, LEO Pharma, Eli Lilly, Medac, Merck Sharp & Dohme, Novartis, Miltenyi Biotech, Ocean Pharma, Pfizer, Regeneron, Samsung Bioepis, Sanofi, Sun Pharma, Takeda, UCB, Valeant, XBiotech, and Xenoport. AWA has served as a consultant, research investigator, speaker, or data safety board member for AbbVie, Boehringer Ingelheim/Parexel, Bristol-Myers Squibb, Celgene, Dermavant, Dermira, Eli Lilly, Genentech, GlaxoSmithKline, Janssen, Janssen-Ortho, Kyowa Hakko Kirin, LEO Pharma, Menlo Therapeutics, Merck, Modernizing Medicine, Novartis Pharmaceutical Corp, Ortho Dermatologics, Pfizer, Regeneron Pharmaceuticals, Sanofi Genzyme, Science 37, UCB Pharma, and Valeant. RGL has served as principle investigator, as a speaker, and on the scientific advisory board for and received compensation in the form of honoraria from AbbVie, Amgen, Boehringer Ingelheim, Celgene, Janssen, LEO Pharma, Eli Lilly, Merck, Novartis, Pizer, Sun, and UCB Pharma. SF, BR, SL, M-CH, and PB are all employees of Janssen Research & Development and own stock in Johnson & Johnson, of which Janssen is a subsidiary. AB has served as a scientific advisor or clinical study investigator for AbbVie, Aclaris, Allergan, Almirall, Amgen, Arena, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermavant, Dermira, Eli Lilly, FLX Bio, Galderma, Genentech/Roche, GlaxoSmithKline, Janssen, LEO Pharma, Meiji, Merck Sharp & Dohme, Novartis, Pfizer, Purdue Pharma, Regeneron, Revance, Sandoz, Sanofi Genzyme, Sienna Pharmaceuticals, Sun Pharma, UCB Pharma, Valeant, and Vidac, and as a paid speaker for Janssen, Regeneron, and Sanofi Genzyme."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p. 833): "Patients were randomly assigned (1:1) to receive either guselkumab or secukinumab. An outside vendor (Paraxel, Waltham, MA, USA) used an interactive web response system to randomly assign patients based on computer- generated permuted blocks." Comment: probably done

ECLIPSE 2019 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote (p. 833): "An outside vendor (Paraxel, Waltham, MA, USA) used an interactive web response system to randomly assign patients based on computer-generated permuted blocks." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (p. 832, 833): "A phase 3, multicentre, randomised, double-blind, comparator-controlled study (ECLIPSE)... ." "Patients, investigators, and the funder of the study were masked throughout the 56-week database lock, with the exception of the unmasked site personnel who dispensed or administered the study agent." Comment: unclear if the process guarented blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (p. 832, 833): "A phase 3, multicentre, randomised, double-blind, comparator-controlled study (ECLIPSE)... ." "Patients, investigators, and the funder of the study were masked throughout the 56-week database lock, with the exception of the unmasked site personnel who dispensed or administered the study agent." Comment: unsure that the process guarented the blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (p. 834, 835): "For efficacy analyses, we included all patients according to the random treatment allocation (intention-to-treat [ITT] population), regardless of the treatment received... Patients with missing data were considered non- responders (non-responder imputation)." Randomly assigned 1048, analysed 1048
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT03090100). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. Results are posted on ClinicalTrials.gov.

EGALITY 2017

Study characteristics	
Methods	Randomised, active-controlled, double-blind study Date of study: June 2013-March 2015 Location: 74 centres in 11 European countries and South Africa Phase 3
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

EGALITY 2017 *(Continued)*

- 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** **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." Declarations 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,

EGALITY 2017 *(Continued)*

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."

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 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-administer 50 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-administer 50 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

EGALITY 2017 *(Continued)*

		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.

Elewski 2016

Study characteristics	
Methods	Randomised, placebo-controlled, double-blind study Date of study: January 2014-April 2016 Location: worldwide
Participants	**Randomised:** 217 participants **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 • 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 breastfeeding or considering becoming pregnant during the study • History of cancer, except successfully treated skin cancer **Dropouts and withdrawals**

Elewski 2016 *(Continued)*

- 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." Declarations 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 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,

Elewski 2016 *(Continued)*

	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). 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 study Date of study: not stated

Ellis 1991 *(Continued)*

	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) • Failure to respond to at least one of the main agents for psoriasis i.e. ultraviolet B, ultraviolet A with oral psoralen, etretinate, or methotrexate. **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 source (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 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

Ellis 1991 *(Continued)*

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 physicians 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 study 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, • 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

Engst 1994 *(Continued)*

	Primary or secondary outcomes of the trial: not stated **Outcomes of the trial** • PASI score • Blood pressure • Blood count • Urine samples
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 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
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.

ERASURE 2014

Study characteristics

Methods	RCT, placebo-controlled, double-blind study Date of study: June 2011-April 2013 Location: 88 centres worldwide (Erasure)
Participants	**Randomised**: 738 participants mean age 45 years, 509 male

ERASURE 2014 *(Continued)*

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** • PASI 75 • IGA score at 0 or 1 **Secondary outcomes** • 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,

ERASURE 2014 *(Continued)*

		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.

ESTEEM-1 2015

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

ESTEEM-1 2015 *(Continued)*

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** • PASI 75 **Secondary outcomes** • Static PGA 0 or 1 • Number of participants with AEs 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". Declarations of interest: quote (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 investiga-

ESTEEM-1 2015 *(Continued)*

	tor 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.

ESTEEM-2 2015

Study characteristics

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

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: apremilast 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

- PASI 75

Secondary outcomes

- 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-

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.

EXPRESS 2005

Study characteristics

Methods	RCT, placebo-controlled, double-blind study Date of study: not stated Location: 32 centres in Europe and Canada
Participants	**Randomised**: 378 participants (mean age 43 years, 268 male) **Inclusion criteria**

EXPRESS 2005 *(Continued)*

- 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)
- 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** • PASI 75 **Secondary outcomes** • 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

EXPRESS 2005 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 1368): "The investigators, study site personnel, and patients remained blinded until the database lock at week 50... placebo group". Comment: probably done, placebo controlled trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 1368): "The investigators, study site personnel, and patients remained blinded until the database lock at week 50... placebo group". Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	378 included/378 analysed Quote (p 1368): "The primary endpoint ... as well as.. were analysed on an intention-to-treat basis... In patients who discontinued the study agent ... the patients were regarded as not achieving the endpoints for binary responses". Comment: probably done
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available. The prespecified outcomes mentioned in the Methods section appeared to have been reported.

EXPRESS-II 2007

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

EXPRESS-II 2007 *(Continued)*

	C. Placebo (n = 208), IV, weeks 0, 2, 6; 10 weeks
Outcomes	Assessments at 10 weeks **Primary outcomes** • PASI 75 **Secondary outcomes** • PASI 50/90 • DLQIAE • PGA
Notes	Funding source (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, 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

EXPRESS-II 2007 *(Continued)*

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.

Fallah Arani 2011

Study characteristics	
Methods	RCT, active-controlled, open-label study 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)
	• 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

Fallah Arani 2011 *(Continued)*

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

FEATURE 2015

Study characteristics

Methods	RCT, active/placebo-controlled, double-blind study

FEATURE 2015 *(Continued)*

	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 **Primary outcomes** • PASI 75 and IGA 0-1 **Secondary outcomes** • 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 source: 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

FEATURE 2015 *(Continued)*

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) • 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.

FIXTURE 2014

Study characteristics	
Methods	RCT, active, placebo-controlled, double-blind study 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 • 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** • PASI 75 • and a IGA score at 0 or 1 **Secondary outcomes** • 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

FIXTURE 2014 *(Continued)*

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
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.

Flytström 2008

Study characteristics

Methods	RCT, active-controlled, open-label study

Flytström 2008 *(Continued)*

	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 outcome** • PASI **Secondary outcomes** • DLQI • SF-36 • VAS for patient assessment
Notes	Funding source (p 121): "Financial support from the Swedish Psoriasis Association and the Welander foundation" 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

Flytström 2008 *(Continued)*

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 caregivers 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 study 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 • 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**

Gisondi 2008 *(Continued)*

	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 outcome** • ≥ PASI 75 improvement from baseline **Secondary outcomes** • 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 source: 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". Comment: acitretin provided 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 study 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** • Not stated **Outcomes** • 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 source, quote (p 655): "Supported in part by Hoffman-La Roche Inc., Nutley, NJ, and the Babcock Dermatologic Endowment" 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

Goldfarb 1988 *(Continued)*

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 study 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
	
	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)

Gordon 2006 *(Continued)*

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** • PASI 75 **Secondary outcomes** • PASI 50 • PASI 100 • PGA • DLQI
Notes	Funding source, 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
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%)

Gordon 2006 *(Continued)*

		• 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 X-PLORE 2015

Study characteristics	
Methods	RCT, active placebo-controlled, double-blind study 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**

Gordon X-PLORE 2015 *(Continued)*

	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 outcome** • PGA 0-1 **Secondary outcomes** • PASI 90 • PASI 75 • 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

Gordon X-PLORE 2015 *(Continued)*

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”. 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 study 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)

Gottlieb 2003a *(Continued)*

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 outcome** • PASI 75 **Secondary outcomes** At 4, 8, 12, 24 weeks • PASI 50 • PASI 75 • PASI 90 • 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 was 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"

Gottlieb 2003a *(Continued)*

		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

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 study 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

Gottlieb 2004a *(Continued)*

	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 outcome** • PASI 75 **Secondary outcomes** • PASI • PGA • DLQI • AEs
Notes	Funding source, Quote (p 534): "Supported by Centocor Inc" 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".

Gottlieb 2004a *(Continued)*

		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 study 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
	• 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** • PASI 75 and PGA 0/1 **Secondary outcomes** At 4, 8, 12 weeks • PASI 50 • PASI 75 • PASI 90 • DLQI • PGA • Safety • Patient global assessment of psoriasis

Gottlieb 2011 *(Continued)*

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

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:

Gottlieb 2011 *(Continued)*

		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 study Date of study: November 2010–December 2011 Location: Multicentre in Boston, USA

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

Gottlieb 2012 *(Continued)*

Primary outcome

- PASI 75

Secondary outcomes

- 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), 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)	Low risk	Randomly assigned 478, analysed 478 Management of missing data:

Gottlieb 2012 *(Continued)*

All outcomes		Quote (p 651): "Efficacy analyses were performed using the ITT set (all randomised patients)... Missing post-baseline 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.

Gurel 2015

Study characteristics	
Methods	RCT, placebo-controlled, single-blind study 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** A. Acitretine (0.3-0.5 mg/kg/day, 25 mg) (n = 25) **Control intervention** B. Placebo (n = 25) Co-invervention NBUVB
Outcomes	Assessment at 12 weeks **Primary outcome** • Not stated **Outcomes:** • Change in PASI scores from baseline • Change in self-PASI scores from baseline

Gurel 2015 *(Continued)*

	• Skindex 30
Notes	Funding source: 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 study 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, • 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

Heydendael 2003 *(Continued)*

- 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 outcome** • PASI **Secondary outcomes** • Side effects • SF-36
Notes	Funding source, 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
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".

Heydendael 2003 *(Continued)*

		Comment: no description of method used to guarantee no communication between caregivers 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 study 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
	
	• Not stated
	
	Outcomes
	
	• Scale:
	  ○ 0 = no improvement
	  ○ 1 = definite improvement
	  ○ 2 = marked improvement
	  ○ 3 = complete clearing

Hunter 1963 *(Continued)*

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	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 No ITT analyses
Selective reporting (reporting bias)	High risk	No prespecified outcomes mentioned in the Methods section

Igarashi 2012

Study characteristics

Methods	RCT, placebo-controlled, double-blind study 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 • 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**

Igarashi 2012 *(Continued)*

- 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 outcome** • PASI 75 **Secondary outcomes** • 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” 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

Igarashi 2012 *(Continued)*

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 effects
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 243): "double-blind placebo-control" Comment: used a placebo without visible side effects
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 numbers 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 study 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 • 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)

Ikonomidis 2017 *(Continued)*

	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) 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
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."

Ikonomidis 2017 *(Continued)*

		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 amount 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.

IMMerge 2021

Study characteristics	
Methods	RCT, active-controlled, single-blinded study (outcomes assessor) Date of study: March 2018-March 2020 Location: worldwide (64 sites) Phase 3
Participants	**Randomised**: 327 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 **Baseline characteristics** N = 327, mean age of 47 years and 65% men **Dropouts and withdrawals**

IMMerge 2021 *(Continued)*

- 46/327 (14%): risankizumab group (15), secukinumab group (31)
- Protocol deviation: risankizumab group (1), secukinumab group (3)
- Lack of efficacy: risankizumab group (1), secukinumab group (8)
- Lost to follow-up: risankizumab group (6), secukinumab group (8)
- Adverse event: risankizumab group (2), secukinumab group (8)
- Withdrew with consent: risankizumab group (5), secukinumab group (2)
- Other: risankizumab group (0), secukinumab group (3)

Interventions	**Intervention** A. Risankizumab (2 SC injections of 75 mg (150 mg total) at weeks 0 and 4, and every 12 weeks thereafter until the last dose at week 40, except for participants in France, who received additional doses at weeks 52 and 64 to allow for continuous treatment until it was commercially available for patients in France), n = 164 **Control intervention** B. Secukinumab (2 SC injections of 150 mg (300 mg total) at weeks 0, 1, 2, 3 and 4, and every 4 weeks thereafter until the last dose at week 48), n = 163
Outcomes	**At week 16** **Primary outcome** • PASI 90 **Secondary outcomes** • PASI 90 at 52 weeks • PGA 0/1 at 52 weeks • PASI 75 at 52 weeks • PASI 100 at 52 weeks
Notes	Funding source Quote (p 1): "AbbVie Inc. funded this study, and participated inthe study design, research, analysis, data collection, interpretation of data, reviewing and approval ofthe publication. All authors had access to the data and participated in the development, review, critique and approval of the manuscript throughoutthe editorial process, and approved the final manuscript draft submitted for publication. All authors agree to be accountable for all aspects of the work, ensuring the accuracy and integrity of the publication. Medical writing support was paid for by AbbVie)." Declarations of interest Quote (appendix 1): "R.B.W. has received research grants from and leads clinical trials for AbbVie, Almirall, Amgen, Bristol Myers Squibb, Celgene, Eli Lilly, Janssen, LEO Pharma, Novartis, Pfizer and UCB Pharma; and has received consulting fees from AbbVie, Almirall, Amgen, Arena Pharmaceuticals, Avillion, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Janssen, LEO Pharma, Eli, Lilly, Novartis, Pfizer, Sanofi and UCB Pharma. A.B. has served as a scientific adviser and/or clinical study investigator for AbbVie, Aclaris, Almirall, Arena, Pharmaceuticals, Athenex, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Dermira, Eli Lilly and Company, Forte, Galderma, Janssen, LEO, Novartis, Ortho, Pfizer, Rapt, Regeneron, Sandoz, Sanofi Genzyme, Sun Pharma and UCB Pharma; and as a paid speaker for AbbVie. Y.P. has received grant funding and honoraria for services as an investigator, speaker and member of advisory boards from AbbVie, Amgen, Bausch, Janssen-Ortho and UCB Pharma; and has received grant funding as an investigator from Baxter, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Galderma, Genentech, GlaxoSmithKline, Incyte, LEO Pharma, MedImmune, Merck, Novartis, Pfizer, Regeneron, Sanofi, Serono and Takeda. C.P. has received grants from and has been a consultant for AbbVie, Almirall, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, LEO Pharma, Merck, Novartis, Pfizer, Sandoz and UCB Pharma. S.B., M.K., T.W. and Z.G. are full-time employees of AbbVie Inc. and may hold AbbVie stock and/or stock options."

IMMerge 2021 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 1) : "IMMerge was a phase III, international, multicentre, randomized, ... randomized in a 1:1 ratio via a centralized Interactive Response Technology system to open-label treatment with risankizumab or secukinumab for up to 64 weeks". Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 1) : "IMMerge was a phase III, international, multicentre, randomized.....randomized in a 1:1 ratio via a centralized Interactive Response Technology system to open-label treatment with risankizumab or secukinumab for up to 64 weeks". Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (p 1) : open-label, efficacy–assessor-blinded, active-comparator study Comment: no blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 3) : "Efficacy assessments were performed by a qualified physician or designee at each study site at all appropriate study visits. The efficacy assessor was fully trained on the protocol and could not perform efficacy assessments prior to having completed all necessary training. The efficacy assessor remained blinded to each patient's treatment and clinical laboratory results, and all safety data during the course of the study. The efficacy assessor was instructed to document the dermatological assessments on paper worksheets and was not allowed access to patient electronic case report forms". Comment: clearly defined
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data Quote (p 4): "Missing efficacy data were accounted for using nonresponder imputation, whereby any patient who had a missing value at a study visit was categorized as a nonresponder for that visit, unless the patient was a responder both before and after a specific visit window. Safety analyses were performed on all intent-to-treat patients who received at least one dose of study drug (safety population)." Randomised 327, analysed 327
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT03478787). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. No results were posted on ClinicalTrials.gov on the 21 September 2020.

IMMhance 2020

Study characteristics

Methods	RCT, placebo-controlled, double-blind study

IMMhance 2020 *(Continued)*

	Date of study: March 2016-July 2018 Location: worldwide (60 sites in Australia, Belgium, Canada, Czech Republic, France, Germany, Japan, South Korea, and the US) 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 **Baseline characteristics** N = 507, mean age of 49.5 years and 70% men **Dropouts and withdrawals** • 7/507 (1.4%): risankizumab group (4), placebo group (3)

IMMhance 2020 *(Continued)*

- 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 75/100 at weeks 16 and 52 • PASI 90 at weeks 52 • PGA 0/1 at weeks 52 • DLQI 0/1 at weeks 16
Notes	Funding source: Quote (p 658) "Funding for the study was provided by AbbVie and Boehringer Ingelheim." Declarations of interest: Quote (p 657) " Dr Blauvelt has served as a scientific adviser and/or clinical study investigator for AbbVie, Aclaris, Almirall, Arena, Athenex, Boehringer Ingelheim, Bristol-Myers Squibb, Dermavant, Dermira, Eli Lilly and Company, FLX Bio, Forte, Galderma, Janssen, Leo, Novartis, Ortho, Pfizer, Regeneron, Sandoz, Sanofi Genzyme, Sun Pharma, and UCB Pharma, and as a paid speaker for AbbVie. Dr Leonardi has received honoraria or fees for serving on advisory boards,as a speaker, and as a consultant, as well as grants as an investigator from AbbVie, Actavis, Amgen, Celgene, Coherus, Dermira, Eli Lilly, Galderma, Janssen, Leo, Merck, Novartis, Pfizer, Sandoz, Stiefel, UCB, and Wyeth. Dr Gooderham has received honoraria or fees for serving on advisory boards, as a speaker, and as a consultant, as well as grants as an investigator from AbbVie, Amgen, Akros, Arcutis, Boehringer Ingelheim, BMS, Celgene, Coherus, Dermavant, Dermira, Eli Lilly, Galderma, GSK, Janssen, Kyowa Hakko Kirin Pharma, Leo Pharma, MedImmune, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, Sun Pharma, Takeda, UCB, and Valeant. Dr Papp has received honoraria or fees for serving on advisory boards, as a speaker, and as a consultant, as well as grants as principal investigator from AbbVie, Amgen, Astellas, Baxalta, Baxter, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Coherus, Dermira, Eli Lilly, Forward Pharma, Galderma, Genentech, GlaxoSmithKline, Janssen, Kyowa-Hakko Kirin, Leo Pharma, MedImmune, Merck-Serono, Merck Sharp & Dohme, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, Stiefel, Sun Pharma, Takeda, UCB, and Valeant. Dr Philipp has received honoraria or fees for serving on advisory boards, as a speaker, and as a consultant, as well as grants as an investigator from AbbVie, Almirall, Amgen, Biogen, BMS GmbH, Boehringer Ingelheim, Celgene, Dermira, Eli Lilly, GSK, Hexal, Janssen Cilag, Leo Pharma, Maruho, MSD, Merck, Mundipharma, Novartis, Pfizer,UCB Pharma, and VBL Therapeutics. Dr J. J. Wu has been an investigator for AbbVie, Amgen, Eli Lilly, Janssen, and Novartis; a paid consultant for AbbVie, Almirall, Amgen, Bristol-Myers Squibb, Celgene, Dermira, Dr Reddy's Laboratories, Eli Lilly, Janssen, LEO Pharma, Novartis, Promius Pharma, Regeneron, Sun Pharmaceutical, UCB, and Valeant Pharmaceuticals North America LLC; and a speaker for AbbVie, Amgen, Celgene, Novartis, Regeneron, Sanofi Genzyme, Sun Pharmaceutical, UCB, and Valeant Pharmaceuticals North America LLC.Dr Igarashi has received honoraria or fees for serving on advisory boards, as a speaker, and asa consultant, as well as grants as an investigator from AbbVie, Celgene, Eli Lilly, Kyowa Kirin, Janssen, Maruho and Novartis. Dr Flack is a full-time employee of Boehringer Ingelheim.Drs Geng, T. Wu, and Williams are full-time employees of AbbVie and may own stock/options. Dr Camez is a former full-time

IMMhance 2020 *(Continued)*

employee of AbbVie and may own stock/options. Dr Langley has served as principal investigator for and is a paid member of the scientific advisory board or served as a speaker for AbbVie, Amgen, Celgene, Janssen, Leo, Lilly, Merck, Novartis, Pfizer, and Boehringer Ingelheim".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 650): "The IMMhance study was a 2-year, phase 3, multinational, double-blind placebo-controlled trial with randomized withdrawal and retreatment comparing risankizumab, 150 mg, with placebo. In parts A and B, patients were randomly assigned via interactive response technology using block randomization. Randomizations were stratified by baseline weight (≤ 100 vs > 100 kg) and prior exposure to a tumor necrosis factor α inhibitor (yes vs no)." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 650) "The IMMhance study was a 2-year, phase 3, multinational, double-blind placebo-controlled trial with randomized withdrawal and retreatment comparing risankizumab, 150 mg, with placebo. In parts A and B, patients were randomly assigned via interactive response technology using block randomization. Randomizations were stratified by baseline weight (≤100 vs >100 kg) and prior exposure to a tumor necrosis factor α inhibitor (yes vs no)." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 650): "Patients, investigators, and study personnel involved in trial conduct or analysis remained blinded to randomized treatment assignments until study completion. To maintain blinding, risankizumab and its matching placebo were identical in appearance. Following a screening period (1-6 weeks), patients entered a 16-week double-blind treatment period (part A1)." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 650): "Patients, investigators, and study personnel involved in trial conduct or analysis remained blinded to randomized treatment assignments until study completion. To maintain blinding, risankizumab and its matching placebo were identical in appearance. Following a screening period (1-6 weeks), patients entered a 16-week double-blind treatment period (part A1)." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (p 651): "Efficacy was analyzed in the intention-to-treat population." Randomised 507, analysed 507
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. Results are posted on ClinicalTrials.gov.

IMMvent 2019

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind study Date of study: March 2016-August 2017 Location: worldwide Phase 3
Participants	**Randomised**: 605 participants **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 judgement • 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. • 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

IMMvent 2019 *(Continued)*

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 (5)
- 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)
- Disease worsening: risankizumab group (1), adalimumab group (2)
- 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 composite outcome** • PASI 90-PGA 0/1 **Secondary outcomes** • PASI 75, PASI 100 • DLQI • AE, SAE
Notes	Funding source: Quote (p 1) "Abbvie and Boehringer Ingelheim" Declarations of interest: Quote (p 10) "KR has served as adviser, paid speaker, or participated in clinical trials sponsored by AbbVie, Affibody, Almirall, Amgen, Biogen, Boehringer Ingelheim, Celgene, Centocor, Covagen, Forward Pharma, Fresenius Medical Care, GlaxoSmithKline, Janssen-Cilag, Kyowa Kirin, Leo, Lilly, Medac, Merck Sharp & Dohme, Novartis, Miltenyi Biotec, Ocean Pharma, Pfizer, Regeneron, Samsung Bioepis, Sanofi, Takeda, UCB, Valeant, and Xenoport. MG has received grant or research support from AbbVie, Akros, Arcutis, Boehringer Ingelheim, BMS, Celgene, Dermira, Eli Lilly, Galderma, GlaxoSmithKline, Janssen, Kyowa Kirin, Medimmune, Merck, Novartis, Pfizer, Regeneron, Roche, UCB,and Valeant; has participated in a speaker's bureau for AbbVie, Actelion, Celgene, Eli Lilly, Galderma, Janssen, Novartis, Pfizer, Regeneron, and Sanofi Genzyme; and has served as a consultant for AbbVie, Amgen, Arcutis,Akros,BoehringerIngelheim,Celgene,KyowaKirin,Novartis, Pfizer, Sanofi Genzyme, and Sun Pharmaceuticals. DT has received grant or research support from AbbVie, Celgene, and Novartis;has participated in a speaker's bureau for AbbVie, Almirall, Celgene, Eli Lilly, Janssen-Cilag, Leo Pharma, Novartis, Pfizer, Regeneron Pharmaceuticals,Sandoz/Hexal,Sanofi,andUCB;andhasservedasa consultant for AbbVie, Almirall, Boehringer Ingelheim, Celgene,Eli Lilly, Janssen-Cilag, Leo Pharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Sandoz/Hexal, Sanofi, and UCB. JJC has received compensation as a speaker, consultant, and investigator for AbbVie, Amgen, Celgene, Eli Lilly, Janssen, Novartis, Regeneron, Sanofi-Aventis, Sun Pharma, and UCB. He has been an investigator for Merck, Maruho, Pfizer, Regeneron, Boehringer Ingelheim, MC-2, Verrica, and Sandoz. CR has received compensation as a speaker or consultant, or adviser for AbbVie, Janssen, Leo, Lilly, Novartis, and UCB, and has served as a consultant or adviser for AbbVie, Boehinger Ingelheim Dermira,Dr Reddys, Janssen, Leo, Lilly, Novartis, Regeneron-Sanofi, and UCB. JGK has received honoraria and consulting fees paid to Rockefeller University from AbbVie, Acros, Amgen, BMS, BiogenMA, Boehringer, Innovoderm, Janssen, Kineta, Leo Pharma, Novan, Novartis, Paraxel, Pfizer, Regeneron, Sienna, UCB, and Vitae, and has received consulting fees from Allergan, Asana, Aurigene, BiogenIdec, Escalier, Lilly, Roche, and Valent. T-FT has served as a consultant for AbbVie, Boehringer Ingelheim, Celgene, Eli-Lilly, Janssen-Cilag, Novartis International AG, and Pfizer. MF is a full-time employee of Boehringer Ingelheim and might hold stock or stock

IMMvent 2019 *(Continued)*

options. YG and DAW are full-time employees of AbbVie and might hold stock or stock options. EHZT was a full-time employee of AbbVie when the study was done and might hold stock or stock options. CP has received grants or research support from Pierre Fabre and Sanofi-Regeneron and has served as a consultant for AbbVie, Almirall, Amgen, Boehringer Ingelheim, Celgene, Janssen Cilag, Leo, Lilly, Pfizer, Novartis, Pierre Fabre, Sanofi, and UCB."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 2): "IMMvent was a phase 3 randomised, double-blind, double-dummy, active-comparator trial..." Quote (p 3) "In part A and part B of the trial, patients were randomly assigned 1:1 via interactive response technology using block randomisation, which allocated medication to patients through medication numbers randomly generated; double-blind allocation to each patient was maintained throughout the process". Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (p 2) "IMMvent was a phase 3 randomised, double-blind, double-dummy, active-comparator trial..." Quote (p 3) "In part A and part B of the trial, patients were randomly assigned 1:1 via interactive response technology using block randomisation, which allocated medication to patients through medication numbers randomly generated; double-blind allocation to each patient was maintained throughout the process" Comment: Probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 2) "IMMvent was a phase 3 randomised, double-blind, double-dummy, active-comparator trial..." Quote (p 3) "Throughout the study, all patients, investigators, and involved study personnel remained masked to treatment assignment. A double-dummy strategy was used to maintain masking, with patients in each group receiving the same number of injections at each time point. Risankizumab and adalimumab were identical in appearance." Comment: Probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 2) "IMMvent was a phase 3 randomised, double-blind, double-dummy, active-comparator trial..." Quote (p 3) "Throughout the study, all patients, investigators, and involved study personnel remained masked to treatment assignment. A double-dummy strategy was used to maintain masking, with patients in each group receiving the same number of injections at each time point. Risankizumab and adalimumab were identical in appearance." Comment: no detailled description of means used to guarentee absence of communication between blinded and unblinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (p 5): "Missing efficacy data were handled using non-responder imputation for categorical variables and last observation carried forward for continuous variables."

IMMvent 2019 *(Continued)*

		Randomised 605, analysed 605
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. Results posted on ClinicalTrials.gov: ITT results

IXORA-P 2018

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind study 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 • 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 **Baseline characteristics** N = 1227, mean of age 47.5 years and 66% men **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)

IXORA-P 2018 *(Continued)*

- 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), ixekizumab 2-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), ixekizumab 2-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), ixekizumab 2-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 • Itch Numeric Rating Scale • DLQI
Notes	Funding source Quote (p 1315): "This study was funded in full by Eli Lilly and Company, Indianapolis, IN, U.S.A". Declarations 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 sci-

IXORA-P 2018 *(Continued)*

entific 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." 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.

IXORA-R 2020

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind study Date of study: November 2018-July 2019 Location: 124 sites, USA and Canada Phase 4
Participants	**Randomised**: 1027 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 • 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 (breastfeeding) **Baseline characteristics** N = 1027, mean of age 49 years and 63.5% men **Dropouts and withdrawals:** ixekizumab: 32/520, guselkumab 26/507 • Withdrawal participants: ixekizumab 11, guselkumab 4 • Adverse events: ixekizumab 6, guselkumab 7 • Lost of follow-up: ixekizumab 6, guselkumab 5 • Protocol deviation: ixekizumab 3, guselkumab 0 • Lack of efficacy: ixekizumab 2, guselkumab 1

IXORA-R 2020 *(Continued)*

- Screen failure: ixekizumab 1, guselkumab 1
- Other: ixekizumab 3, guselkumab 2

Interventions	**Intervention** A. Ixekizumab 160 mg at week 0 then 80 every 2 weeks from weeks 2-12, n = 520 **Control interventions** B. Guselkumab 100 mg at week 0, 4 and 12, n = 507 Participants on guselkumab received placebo injection at weeks 0, 2, 6, 8 and 10.
Outcomes	At week 12 **Primary outcome** • PASI 100 **Secondary outcomes** • PASI 75 week 2 • Proportion of participants achieving PASI 90 week 4 • Proportion of participants achieving PASI 90 week 8 • Proportion of participants achieving PASI 100 week 4 • Proportion of participants achieving PASI 100 week 8 • Proportion of participants achieving PASI 100 week 24 • Proportion of participants achieving Static Physician Global Assessment week 12 • Proportion of participants achieving PASI 50 week 1
Notes	Funding source (Quote p 1348) "Funding for this study was provided by Eli Lilly and Company, Indianapolis, IN, U.S.A. Eli Lilly and Company contributed to study design, data collection, data analysis, data interpretation, manuscript preparation and the decision to submit the paper for publication. An advisory committee was involved in the study design and data interpretation, together with authors from Eli Lilly and Company. Authors had full access to all group-level data in the study, but not individual-level data that would risk unblinding those authors who were also study investigators. Authors had final responsibility for the decision to submit for publication". Declarations of interest: Quote (Appendix 1) "A.B. has served as a scientific adviser and/or clinical study investigator for AbbVie, Aclaris, Almirall, Arena, Athenex, Boehringer Ingelheim, Bristol-Myers Squibb, Dermavant, Dermira, Eli Lilly and Company, FLX Bio, Forte, Galderma, Janssen, LEO, Novartis, Ortho, Pfizer, Regeneron, Sandoz, Sanofi Genzyme, Sun Pharma and UCB Pharma, and as a paid speaker for AbbVie. K.P. has served as a scientific adviser and/or clinical study investigator for AbbVie, Akros, Allergan, Almirall, Amgen, Arcutis, Avillion, Bausch Health, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermavant, Dermira, Eli Lilly and Company, Galderma, Genentech/Roche, GlaxoSmithKline, Janssen, Kyowa Kirin, LEO, Meiji, Merck Sharp & Dohme, Novartis, Pfizer, Regeneron, Sanofi Genzyme, Sienna Pharmaceuticals, Sun Pharma, Takeda, UCB and Valeant; and as a paid speaker for AbbVie, Akros, Allergan, Almirall, Amgen, Bausch Health, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermavant, Dermira, Eli Lilly and Company, Galderma, Genentech/Roche, Janssen, Kyowa Kirin, LEO, Meiji, Merck Sharp & Dohme, Novartis, Pfizer, Regeneron, Sanofi Genzyme, Sienna Pharmaceuticals, Sun Pharma, Takeda, UCB and Valeant. A.G. has served as a consultant or speaker for Janssen, Celgene, Beiersdorf, Bristol-Myers Squibb, AbbVie, UCB, Novartis, Incyte, Eli Lilly and Company, Allergan, Sun Pharmaceutical Industries, Xbiotech, LEO, Avotres Therapeutics and Boehringer Ingelheim; and received research/educational grants from Janssen, Incyte, Novartis, Xbiotech, UCB and Boehringer Ingelheim. A.J. has served as scientific advisor or clinical study investigator for AbbVie, Asana Biosciences, Castle Biosciences, Inc., Bristol-Myers Squibb, Celgene, Dermira, Eli Lilly and Company, Galderma, Genentech/Roche, GlaxoSmithKline, LEO Pharma, Novartis, Pfizer, Purdue Pharma, Regeneron, Sanofi Genzyme, Sienna Pharmaceuticals, Sun Pharma and UCB Pharma, and as a paid speaker for Castle Biosciences, Inc., Eli Lilly and Company, Novartis, Regeneron and Sanofi Genzyme. K.R. has served as an advisor and paid speaker and has participated in clinical trials for AbbVie, Affibody, Almirall, Amgen, Avillion, Biogen, Boehringer Ingelheim, Celgene, Covagen, Forward Pharma, Fresenius

IXORA-R 2020 *(Continued)*

Medical Care, GlaxoSmithKline, Janssen, Janssen-Cilag, Kyowa Kirin, LEO Pharma, Eli Lilly and Company, Medac, Merck Sharp & Dohme, Novartis, Miltenyi Biotech, Ocean Pharma, Pfizer, Regeneron, Samsung Bioepis, Sanofi, Sun Pharma, Takeda, UCB, Valeant, XBiotech and Xenoport. C.M. has served as principal investigator, as a speaker or on a scientific advisory board for and received compensation in the form of honoraria from AbbVie, Amgen, Celgene, Janssen, LEO Pharma, GlaxoSmithKline, Bausch Health, Eli Lilly and Company, Novartis, Pfizer and UCB Pharma. K.B.G. has consulting relationships with AbbVie, Amgen, Celgene, Eli Lilly and Company, Janssen, Novartis, Pfizer, Dermira and Boehringer Ingelheim and has received grants from AbbVie, Amgen, Celgene and Janssen. L.K.F. has been an investigator and consultant for Eli Lilly and Company, Janssen and Pfizer; a consultant for UCB; and an investigator for AbbVie, Amgen, Galderma, LEO Pharma and Regeneron. R.G. Langley has served as principal investigator, as a speaker and on the scientific advisory board for and received compensation in the form of honoraria from AbbVie, Amgen, Boehringer Ingelheim, Celgene, Janssen, LEO Pharma, Eli Lilly and Company, Merck, Novartis, Pfizer, Sun and UCB Pharma. Y.T. received grants for research from Maruho, LEO Pharma, Eisai, AbbVie, Kyowa Hakko Kirin, Taiho Pharmaceutical, Celgene, and Eli Lilly and Company, and honoraria for lectures from Torii Pharmaceutical, Maruho, LEO Pharma, Eisai, AbbVie, Kyowa Hakko Kirin, Eli Lilly and Company, Taiho Pharmaceutical, Mitsubishi Tanabe Pharma and Janssen. R.G. Lima, H.E., G.G., L.R., S.Y.P. and R.B. are employees and stockholders of Eli Lilly and Company. J.B. is a speaker and investigator for AbbVie, Celgene, Eli Lilly and Company, Janssen, Novartis and Ortho Dermatologics. He is an investigator for Amgen, Boehringer Ingelheim, Bristol-Myers Squibb and LEO Pharma."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 3): "Patients were allocated to treatment by a computer-generated random sequence." Comment: adequate process
Allocation concealment (selection bias)	Low risk	Quote: "supplementary material S2 interactive web-response system (IWRS). The IWRS was used to assign double-blind investigational product to each patient. The Unblinded Site Personnel at the site confirmed that they located the correct assigned study drug package by entering a confirmation number found on the package into the IWRS. Designated Unblinded Site Personnel were responsible for receipt of study drug shipments, dispensing study drug, administering study drug (ixekizumab, guselkumab, and placebo), recording information in the Study Drug Administration Log, and confirming treatment assignments. "Comment: interactive web-response system guaranteed allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (p 3): "Patients, investigators and all other personnel involved in the conduct of this ongoing study are to remain blinded to individual treatment assignments until all patients have completed the study." Comment: Because the syringes look different, participants were not allowed to see the syringe before, during, or after the drug administration. Comment: not sure that the method has been sufficiently efficient to guarantee blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (p 3): "Patients, investigators and all other personnel involved in the conduct of this ongoing study are to remain blinded to individual treatment assignments until all patients have completed the study. Because the syringes look different, patients were not allowed to see the syringe before, during, or after the drug administration. Unblinded Site Personnel were responsible for maintaining the blind of the patient (e.g. by means of a blindfold or other appropriate physical barrier means communicated to the sponsor for final approval). Designated Unblinded Site Personnel were not involved in any clinical

IXORA-R 2020 *(Continued)*

		aspects of the study, including clinical evaluations and adverse event assessments." Comment: no detailled description of means used to guarantee absence of communication between blinded and unblinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Analysis for primary outcome and major secondary outcome was performed as ITT. Missing data were imputed using a nonresponder imputation method. The number of withdrawals was low and reasons comparable in each group.
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT03573323). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. Results are posted on ClinicalTrials.gov.

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

IXORA-S 2017 *(Continued)*

- 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
- 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

- 12/302 (4%): IXE group (4), USK group (8)
- Lost to follow-up: IXE group (0), USK group (1)
- AEs: IXE group (2), USK group (1)
- Lack of efficacy: IXE group (0), USK group (1)
- Protocol deviation: IXE group (0), USK group (1)
- Other: IXE group (0), USK group (1)
- Subject decision: IXE group (2), USK group (3)

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 and 24 **Primary outcome** • PASI 90 **Secondary outcomes** • PASI 75/100 • PGA • DLQI • European Quality of Life - 5 Dimensions 5 Level (EQ-5D-5L)
Notes	Funding source Quote (p 1014): "This study was funded in full by Eli Lilly and Company, Indianapolis, IN, U.S.A." Declarations 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

IXORA-S 2017 *(Continued)*

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 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 (≤ 100 kg vs. > 100 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 (≤ 100 kg vs. > 100 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

IXORA-S 2017 *(Continued)*

		region. Missing data were imputed via nonresponder imputation (NRI), assuming that patients without data had no response". Patients randomized, patients analysed Comment: Done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02561806). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. Results are posted on ClinicalTrials.gov.

JUNCTURE 2015

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind study Date of study: June 2012–January 2013 Location: 38 centres worldwide
Participants	**Randomised**: 182 participants (mean age 45 years, 125 male) **Inclusion criteria** • 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** • PGA 0/1 • PASI 75

JUNCTURE 2015 *(Continued)*

Secondary outcomes

- 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 randomization number that linked the subject to a treatment arm and specified unique medication pack number". Comment: no description of the method used to guarantee the random sequence generation
Allocation concealment (selection bias)	Low risk	Quote: “Randomization was conducted via Interactive Response Technology, which assigned a randomization 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

JUNCTURE 2015 *(Continued)*

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.

Khatri 2016

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

Khatri 2016 *(Continued)*

- Itch Numeric Rating Scale
- DLQI
- PASI
- BSA
- AEs

Notes	Funding source Quote (p 33) "Funding provided by Eli Lilly and Company" Declarations 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, 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 80 mg of ixekizumab either every two (Q2W) or four (Q4W) weeks during the induction dosing period (0–12 weeks) following an initial 160 mg 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 80 mg of ixekizumab either every two (Q2W) or four (Q4W) weeks during the induction dosing period (0–12 weeks) following an initial 160 mg 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 80 mg of ixekizumab either every two (Q2W) or four (Q4W) weeks during the induction dosing period (0–12 weeks) following an initial 160 mg 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).

Khatri 2016 *(Continued)*

	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) 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

Krueger 2007 *(Continued)*

	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" Conflict of interest (p 590-1): "Dr. Krueger reports receiving fees as a consultant or advisory board member for Abbott, Almirall, Alza, Amgen, Astellas, Boehringer Ingelheim, Barrier Therapeutics, Bristol-Myers Squibb, Centocor, Connetics, and Genentech; Dr. Langley, for Centocor, Abbott, and Amgen/Wyeth; Dr. Leonardi, for Abbott, Amgen, Centocor, and Genentech; and Dr. Lebwohl, for Abbott, Amgen, Astellas, Centocor, Connetics, Galderma, Genentech, Novartis, PharmaDerm, and Warner Chilcott. Dr. Krueger reports receiving lecture fees from Abbott, Amgen, Boehringer Ingelheim, Centocor, and Connetics; Dr. Langley, from Abbott and Amgen/ Wyeth; Dr. Leonardi, from Abbott, Amgen, Centocor, and Genentech; and Dr. Lebwohl, from Abbott, Astellas, Amgen, Centocor, Connetics, Galderma, Genentech, PharmaDerm, and Warner Chilcott. Dr. Krueger reports receiving stipends for a clinical research fellowship from Amgen and Centocor; Dr. Langley, grant support from Centocor, Abbott, and Amgen/Wyeth; Dr. Leonardi, educational grants from Amgen and Genentech; and Dr. Lebwohl, grants from Abbott, Amgen, Astellas, Centocor, Connetics, Galderma, Genentech, PharmaDerm, and Warner Chilcott. Drs. Yeilding, Guzzo, Wang, and Dooley report being employees of Centocor. Dr. Krueger reports owning stock options from ZARS Pharma; Drs. Yeilding, Guzzo, and Dooley report holding stock and stock options in Johnson & 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 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	320 included, 320 analysed

Krueger 2007 *(Continued)*

		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.

Laburte 1994

Study characteristics	
Methods	RCT, active-controlled, open-label study 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** 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

Laburte 1994 *(Continued)*

Notes	Funding source 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.

Lee 2016

Study characteristics

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

Lee 2016 *(Continued)*

- 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 interventions** 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 • PGA 0/1 • 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." Declarations of interest 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

Lee 2016 *(Continued)*

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 5 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 study Date of study: December 2001-April 2002 Location: 47 centres in USA
Participants	**Randomised**: 672 participants (mean age 45 years, 672 male) **Inclusion criteria**

Leonardi 2003 *(Continued)*

- 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 interventions** 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 • 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."

Leonardi 2003 *(Continued)*

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 study Date of study: April 2010-May 2011 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%) :

Leonardi 2012 *(Continued)*

- 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
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

Leonardi 2012 *(Continued)*

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: mITT 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.

LIBERATE 2017

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind study 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**

LIBERATE 2017 *(Continued)*

	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** • PASI 75 **Secondary outcomes** • PASI 50 • PASI 90 • 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

LIBERATE 2017 *(Continued)*

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

Liu 2020

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study Date of study: August 2014-October 2016 Location: China (19 centres) Phase 4
Participants	**Randomised**: 466 participants **Inclusion criteria** • Adults of both sexes, ≥ 18 years of age • Patients who had a diagnosis of moderate-to-severe plaque psoriasis for ≥ 6 months • Patients with an affected body surface area ≥ 10% and a PASI score > 10 at screening and baseline • Patients who had failed to respond to a systemic therapy except methotrexate and were candidates for systemic therapy in the opinion of the investigator • Patients who agreed to take means of contraception during the trial and 6 months after if they had reproductive potential **Exclusion criteria** • Patients with guttate, erythrodermic, pustular psoriasis or drug-induced psoriasis or other skin diseases that may interfere with evaluation • 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)

Liu 2020 *(Continued)*

- 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
- 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.

Baseline characteristics

N = 466, mean age of 43 years and 76% men

Dropouts and withdrawals

- 24/466 (5.15%): methotrexate group (13), placebo group (11)
- AEs: methotrexate group (4), placebo group (5)
- Lost to follow-up: methotrexate group (6), placebo group (5)
- Withdrawal of consent: methotrexate group (2), placebo group (1)
- Did not meet eligibility criteria: methotrexate group (1), placebo group (0)

Interventions	**Intervention** A. Methotrexate (initial dose of 7.5 mg/week to a maximum dose of 15 mg/week or the maximum tolerated dose within 8 weeks), n = 233 **Control intervention** B. Placebo, n = 233 Co-intervention: etanercept (50 mg subcutaneously once weekly)
Outcomes	**At week 24** **Primary outcome** • PASI 75 **Secondary outcomes** • PASI 90, PASI 50 at weeks 12 and 24 • PASI 75 at weeks 12 • Patient's Global Assessment (PtGA) and static Physician's Global Assessment (sPGA) at weeks 12 and 24 • DLQI at weeks 12 and 24 • AEs
Notes	Funding source "This research was supported by Zhejiang Public Walfare Technology Research Project (Grant number: LGF20H110002). Med- ical Health Science and Technology Project of Zhejiang Provincial Health Commission (Grant Number: 2018KY088) and 3SBIO INC." Declarations of interest "The authors declare that they have no conflict of interest."

Risk of bias

Bias	Authors' judgement	Support for judgement

Liu 2020 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "All eligible patients were randomly assigned by a random number created by a computer-generated coding system to receive either the combination of rhTNFR-Fc and MTX (combination group) or rhTNFR-Fc plus placebo (monotherapy group)."
Allocation concealment (selection bias)	Unclear risk	Quote: "Then patients were randomized 1:1 to receive 50 mg rhTNFR-Fc subcutaneously once weekly and oral MTX (from an initial dose of 7.5 mg/week to a maximum dose of 15 mg/week or the maximum tolerated dose within 8 weeks) or receive rhTNFR-Fc (as that in combination group) and a matched placebo (as MTX in combination group) for 24 weeks." Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote:"This was a multicentre, randomized, double-blind, placebo-controlled trial of rhTNFR-Fc..." Comment: no description of the method used to guarantee allocation blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote:"This was a multicentre, randomized, double-blind, placebo-controlled trial of rhTNFR-Fc..." Comment: no description of the method used to assess the primary outcome
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dealing with missing data: no information on how missing data were handled Quote:"Efficacy analysis was performed using the intent-to-treat principle, in which all randomized patients who received any part of the study medication treatment and received at least one evaluation of therapeutic effectiveness were included in the analysis. All results of the efficacy analysis were analysed in the full analysis set (FAS). Safety was analysed in a safety analysis set (SAS), which included all patients who had received at least 1 dose of the study drug." Randomised 466; analysed 466
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (Liu 2020 NCT02313922). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. No results are posted on ClinicalTrials.gov.

LOTUS 2013

Study characteristics	
Methods	RCT, placebo-controlled, double-blind (LOTUS) study Date of study: 23 October 2009-07 July 2011 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

LOTUS 2013 *(Continued)*

	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** • PASI 75 **Secondary outcomes** • 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): "The LOTUS study is a phase 3, multicenter, randomized, double blind, placebo-controlled..." Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 167): "The LOTUS study is a phase 3, multicenter, randomized, double blind, placebo-controlled..." Comment: placebo-controlled study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (p 167): "The LOTUS study is a phase 3, multicenter, randomized, double blind, placebo-controlled..." Comment: no description of the method used to guarantee blinding of outcome assessment

LOTUS 2013 *(Continued)*

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.

Lowe 1991

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study 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 **Control intervention** B. Placebo (n = 18), orally, daily, 12 weeks Co-intervention: UVB (phototherapy)
Outcomes	Assessments at 12 weeks **Primary outcomes** • PASI **Secondary outcomes** • Side effects

Lowe 1991 *(Continued)*

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 were 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 were 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 study 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

Mahajan 2010 *(Continued)*

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/cm^2 **Control intervention** B. Placebo + folic acid (n = 20), orally, 5 mg/d day-1; day+1 + NBUVB 3/week max 1200 mJ/cm^2
Outcomes	Assessments at 6 months **Primary outcomes** • PASI 75 **Secondary outcomes** • 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
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

Mahajan 2010 *(Continued)*

		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 study 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) • AEs (5)
Interventions	**Intervention** A. Ciclosporin (n = 43), orally, 1.25 mg/kg/d, 10 weeks **Control intervention** 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 outcome** • PASI **Secondary outcomes** • PASI 25 • PASI 50 • PASi 75
Notes	Funding source not stated but 3 out of 4 authors from Sandoz Pharmaceuticals

Meffert 1997 *(Continued)*

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.

METOP 2017

Study characteristics

Methods	RCT, placebo-controlled study Date of study: February 2013-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

METOP 2017 *(Continued)*

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	**At 16 weeks** **Primary outcome** • PASI 75 **Secondary outcomes** • 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

METOP 2017 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote (p 3): "Eligible patients were randomly assigned (3:1), via computer-generated random numbers (RandList 1.2) in an ascending order, to receive either methotrexate or placebo injections for the first 16 weeks of the study (phase 1)." Comments: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 3): "Eligible patients were randomly assigned (3:1), via computer-generated random numbers (RandList 1.2) in an ascending order, to receive either methotrexate or placebo injections for the first 16 weeks of the study (phase 1)." Comments: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 3): "Study phase 1 was done in a double-blind manner, with group allocation concealed from participants and investigators from the time of randomisation until an interim database lock at week 16...The syringes for placebo and active drug were not distinguishable and were fully coated to prevent identification of colour differences between injections". Comments: clearly defined
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 3): "Study phase 1 was done in a double-blind manner, with group allocation concealed from participants and investigators from the time of randomisation until an interim database lock at week 16...The syringes for placebo and active drug were not distinguishable and were fully coated to prevent identification of colour differences between injections". Comments: clearly defined
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of randomised participants, n = 120, 120 analysed Quote (p 4): "All outcomes were analysed in the modified intention to-treat population of patients who had received at least one injection of study drug, with missing data treated as indicating no response (non-responder imputation)." Comment: probably done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02902861). The 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 study Date of study: October 2012–March 2013 Location: multicentre (56) in Japan
Participants	**Randomised**: 151 participants (mean age 45 years, 120 male) **Inclusion criteria**

Nakagawa 2016 *(Continued)*

- 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
- 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** • % improvement in PASI **Secondary outcomes** • 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

Nakagawa 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (p 51): "double-blind…" Comment: not stated
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.

NCT02134210 RaPsOdy

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 **Baseline characteristics** N = 521, mean of age 43.5 years and 70% men **Dropouts and withdrawals**

NCT02134210 RaPsOdy *(Continued)*

	• 25/521 (1.4%): CHS-0214 group (6), Enbrel group (19) 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 source: Quote (ClinicalTrials.gov) Coherus Biosciences, Inc. Declarations 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).

NCT02134210 RaPsOdy *(Continued)*

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

NCT02581345

Study characteristics	
Methods	RCT, active-controlled, triple-blind study Date of study: September 2015-April 2017 Location: worldwide
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

NCT02581345 *(Continued)*

- 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

Baseline characteristics

N = 572, mean of age 45 years and 66% men

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 source: Quote (ClinicalTrials.gov): Novartis Declarations 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

NCT02581345 *(Continued)*

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) All outcomes	Low risk	Quote (ClinicalTrials.gov): "Masking: Triple (Participant, Care Provider, Investigator)" 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.

NCT02762994

Study characteristics	
Methods	RCT, placebo-controlled, multicenter, double-blind study Date of study: June 2016-May 2017 Location: Russia Phase 2
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 has 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. • 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.

NCT02762994 *(Continued)*

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 than 12 weeks before signing informed consent
- Is taking corticosteroids for up to 4 weeks in a dose > 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.

Baseline characteristics

N = 114, median of age 40 years and 69% men

Dropouts and withdrawals

- 6/114 (5%): BCD-085 40 mg (1), BCD-085 80 mg (1), BCD-085 120 mg (2), placebo (2)
- Withdrawal by subject: BCD-085 40 mg (0), BCD-085 80 mg (1), BCD-085 120 mg (2), placebo (0)
- Protocol violation: BCD-085 40 mg (1), BCD-085 80 mg (0), BCD-085 120 mg (0), placebo (2)

Interventions	**Intervention** **A.** BCD-085 (Netakimab anti-IL17), 40 mg: Participant will receive 40 mg of BCD-085 subcutaneously at weeks 0, 1, 2, 4, 6, 8, 10, n = 30 **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, n = 30 C. BCD-085, 120 mg: Participant will receive 80 mg of BCD-085 subcutaneously at weeks 0, 1, 2, 4, 6, 8, 10, n = 28 D. Placebo, n = 26
Outcomes	At week 12 **Primary outcome** • PASI 75 **Secondary outcomes** • PASI 50, PASI 90 • NAPSI • VAS pruritus • PGA • DLQI • AEs/SAEs at week 14
Notes	Funding source:Quote (Clinicaltrials.gov)"Biocad"

NCT02762994 *(Continued)*

Declarations of interest: not stated

RoB completed according to protocol posted on ClinicalTrials.gov.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (study protocol p. 62) "This clinical trial was designed as a multicenter, double-blind, randomized study of the efficacy and safety...". Quote (study protocol p. 82)"."Randomization in the study will be centralized. Patient included in the study will be randomised within each stratum (block randomization)". Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (study protocol p. 85) "During randomization, the BIOCAD's clinical manager allocates the patient to an appropriate stratum, assigns her/his the first free arm number in the block and a 3-digit randomization number coding this arm (corresponds to the patient's order number in the study). After randomization, the clinical study manager assigns the patient an investigational product lot number (corresponding to treatment arm) and a patient ID. The investigator will know only the subject's ID and investigational product lot number." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (study protocol p. 86) "Neither investigators, not patients will be aware of whether the active treatment or placebo is used in each particular patient. The investigator (the principal investigator, a co-investigator responsible for the therapy of this patient) receives BCD-085/placebo in identical secondary packaging (cartons). The drugs differ only by their lot numbers. The lot number is individual for the subject. During therapy, the subject may receive the investigational product of several batches but they will be assigned the same lot number." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (study protocol p. 86) "Neither investigators, not patients will be aware of whether the active treatment or placebo is used in each particular patient. The investigator (the principal investigator, a co-investigator responsible for the therapy of this patient) receives BCD-085/placebo in identical secondary packaging (cartons). The drugs differ only by their lot numbers. The lot number is individual for the subject. During therapy, the subject may receive the investigational product of several batches but they will be assigned the same lot number." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (study protocol p. 157-158) "The safety analysis will include all patients who received at least one dose of the investigational product. Additionally, the SAE analysis will include all randomized patients starting from the ICF signing and until the end of their participation in the study. Per protocol, the efficacy analysis is to include all patients who received at least one dose of BCD-085/placebo and who attended at least one visit next visit. If no data are available at Week 12, the data from the last assessment are to be used (last-observation-carried-forward method). In addition, these patients should be considered non-responders and analyzed separately."

NCT02762994 *(Continued)*

		Randomised 120, analysed 114
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02762994). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. Results are posted on ClinicalTrials.gov.

NCT03055494 ObePso-S

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study Date of study: April 2017-February 2019 Location: USA Phase 4
Participants	**Randomised**: 102 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 **Baseline characteristics** N = 82, mean age of 44.5 years and 63% men **Dropouts and withdrawals** • 11/82 (13.4%): secukinumab group (10), placebo group (1) • Lost to follow-up: secukinumab group (6), placebo group (0) • Physician decision: secukinumab group (2), placebo group (0) • Withdrawal by subject: secukinumab group (1), placebo group (0) • Adverse event: secukinumab group (0), placebo group (1) • Non-compliance with study treatment: secukinumab group (1), placebo group (0)
Interventions	**Intervention** A. Secukinumab 300 mg SC at randomisation, weeks 1, 2, 3, and 4 followed by monthly dosing up to week 48, n = 54 **Control interventions**

NCT03055494 ObePso-S *(Continued)*

B. Placebo, n = 28

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
Notes	Funding source: Quote (ClinicalTrials.gov) Novartis Pharmaceuticals Declarations of interest: not stated RoB completed according protocol posted on ClinicalTrials.gov

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (study protocol p 18, p 19): "This study uses a randomized, double-blind, placebo-controlled, parallel-group, multicenter design. At the start of the Double-blind Treatment Period, eligible patients will be randomized via Interactive Response Technology (IRT) in a 2:1 ratio to one of two treatment arms (secukinumab 300 mg or placebo). Randomization will be stratified by body weight collected at visit 2 (<90kg or >- 90kg)." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (study protocol p 18, p 19): "This study uses a randomized, double-blind, placebo-controlled, parallel-group, multicenter desing... At the start of the Double-blind Treatment Period, eligible patients will be randomized via Interactive Response Technology (IRT) in a 2:1 ratio to one of two treatment arms (secukinumab300 mg or placebo). Randomization will be stratified by body weigth collected at visit 2 (< 90kg or >- 90kg)." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (study protocol p 32): "Patients, investigators/site staff, persons performing assessments, and Novartis study personnel will remain blinded to individual treatment assignment from the time of randomization until the final database lock at Week 53,using the following methods: 1.Randomization data will be kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions: specific vendors whose role in trial conduct requires their unblinding (e.g. IRT), Drug Supply Management (DSM); 2.The identity of secukinumab and placebo prefilled syringes (PFS) will be concealed by identical packaging,labeling, schedule of administration, and appearance." Comment: clearly defined
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (study protocol p 32): "Patients, investigators/site staff, persons performing assessments, and Novartis study personnel will remain blinded to individual treatment assignment from the time of randomization until the final database lock at Week 53,using the following methods: 1.Randomization da-

NCT03055494 ObePso-S *(Continued)*

		ta will be kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions: specific vendors whose role in trial conduct requires their unblinding (e.g. IRT), Drug Supply Management (DSM); 2. The identity of secukinumab and placebo prefilled syringes (PFS) will be concealed by identical packaging,labeling, schedule of administration, and appearance. At the Week 12 primary analysis time point, there will be a database lock after all patients have completed the Week 12 visit. At that time, only the statistician and programmer(s) from the designated CRO will be unblinded in order to perform the analysis." Comment: clearly defined
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dealing with missing data: Quote (study protocol p 65): "For the two primary efficacy variables at Week 12 (and other time points), a patient with a missing assessment will be considered as a non-responder." Randomised 102, analysed 82 In ClinicalTrials.gov (results section): "a total of 133 patients were screened for the study, with 82 (61.7%) of these completing the screening phase". We are waiting for the publication to compare the number of randomised and analysed participants.
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT03055494 ObePso-S). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. Results are posted on ClinicalTrials.gov.

NCT03364309

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind study Date of study: April 2018-June 2020 Location: China (17 sites) Phase 3
Participants	**Randomised**: 438 participants **Inclusion criteria** • Present with chronic plaque psoriasis (Ps) based on a confirmed diagnosis of chronic Ps vulgaris for at least 6 months prior to baseline • Have ≥ 10% BSA involvement at screening and baseline. • Have both an sPGA score ≥ 3 and PASI score ≥ 12 at screening and baseline • Are candidates for phototherapy and/or systemic therapy **Exclusion criteria** • Forms of psoriasis other than chronic plaque-type (e.g. pustular, erythrodermic and/or guttate psoriasis) at screening or baseline)

NCT03364309 *(Continued)*

- Drug-induced psoriasis
- Ongoing use of prohibited treatments
- Have previously completed or withdrawn from this study, or have previously been exposed to ixekizumab or any other biologic drug directly targeting interleukin-17 (IL-17) (such as secukinumab) or the IL-17 receptor
- Have concurrent or recent use of any biologic agent within washout periods or < 5 half-lives prior to baseline, whichever is longer
- 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 human chorionic gonadotropin (hCG) laboratory test

Baseline characteristics

N = 438, mean of age 40.5 years and 76.5% men

Dropouts and withdrawals

- 11/438 (2.5%): ixekizumab Q4W (4), ixekizumab Q2W (1), placebo (6)
- AEs: ixekizumab Q4W (0), ixekizumab Q2W (1), placebo (4)
- Withdrawal by subject: ixekizumab Q4W (3), ixekizumab Q2W (0), placebo (1)
- Lost to follow-up: ixekizumab Q4W (0), ixekizumab Q2W (0), placebo (1)
- Physician decision: ixekizumab Q4W (1), ixekizumab Q2W (0), placebo (0)

Interventions	**Interventions** A. Ixekizumab 160 mg at week 0 followed by 80 mg once every four weeks (Q4W) SC, n = 174 B. Ixekizumab 160 mg at week 0 followed by 80 mg once every two weeks (Q2W) SC, n = 176 **Control intervention** C. Placebo, n = 88
Outcomes	At week 12 **Primary composite outcome** • PGA0/1 - PASI 75 **Secondary outcomes** • PASI 90, PASI 100 • BSA • SF-36 • DLQI
Notes	Funding source: Quote (clinicaltrials.gov)"Eli Lilly and Company" Declarations of interest: not stated RoB completed according to ClinicalTrials.gov protocol.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (study protocol p. 48): "At Week 0 (Visit 2), patients who meet all criteria for enrollment at Visits 1/1A and 2 will be randomized at a 2:2:1 ratio to ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, or placebo. Assignment to double-blind treatment groups will be determined by a computer-generated random sequence using an interactive web response system (IWRS). The IWRS will

NCT03364309 *(Continued)*

		be used to assign double-blind investigational product to each patient. Site personnel will confirm that they have located the correct assigned investigational product package by entering a confirmation number found on the package into the IWRS." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (study protocol p. 48): "At Week 0 (Visit 2), patients who meet all criteria for enrollment at Visits 1/1A and 2 will be randomized at a 2:2:1 ratio to ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, or placebo. Assignment to double-blind treatment groups will be determined by a computer-generated random sequence using an interactive web response system (IWRS). The IWRS will be used to assign double-blind investigational product to each patient. Site personnel will confirm that they have located the correct assigned investigational product package by entering a confirmation number found on the package into the IWRS." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (study protocol p. 30) "To maintain blinding, each patient will be administered 2 injections of blinded investigational product subcutaneously at Week 0, and each patient will be administered 1 injection of blinded investigational product subcutaneously Q2W from Weeks 2 through 10 regardless of his/her assigned dose regimen (that is, placebo will be given as necessary to maintain the blind). Quote (study protocol p. 51) "This is a double-blind study; patients and study site personnel will be blinded to study treatment until all patients reach Week 60 (Visit 19) or have discontinued from the study (moved into Period 4). To preserve the blinding of the study, a minimum number of sponsor personnel not in direct contact with study sites will see the randomization table and treatment assignments before the study is unblinded." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (study protocol p. 30) "To maintain blinding, each patient will be administered 2 injections of blinded investigational product subcutaneously at Week 0, and each patient will be administered 1 injection of blinded investigational product subcutaneously Q2W from Weeks 2 through 10 regardless of his/her assigned dose regimen (that is, placebo will be given as necessary to maintain the blind). Quote (study protocol p. 51) "This is a double-blind study; patients and study site personnel will be blinded to study treatment until all patients reach Week 60 (Visit 19) or have discontinued from the study (moved into Period 4). To preserve the blinding of the study, a minimum number of sponsor personnel not in direct contact with study sites will see the randomization table and treatment assignments before the study is unblinded." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (study protocol p. 74) "Analysis of categorical efficacy and health outcome variables will be assessed using a NRI method. In both Periods 2 (Induction Dosing Period) and 3 (Maintenance Dosing Period), patients will be considered a non-responder for the NRI analysis if they do not meet the clinical response criteria or have missing clinical response data at the analysis time point." "A last observation carried forward (LOCF) analysis may be performed on all continuous efficacy and health outcome variables." Randomised 438, analysed 438

NCT03364309 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT03364309). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. Results posted on ClinicalTrials.gov

NCT03421197

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind study Date of study: January 2018-March 2020 Location: USA (76 sites) Phase 2
Participants	**Randomised**: 426 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 • Received 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) **Baseline characteristics** N = 426, mean of age 50 years, 60% men **Dropouts and withdrawals** Not stated
Interventions	**Intervention** A. Tepilamide fumarate 400 mg tablet once a day, n = 105

NCT03421197 *(Continued)*

	Control interventions B. Tepilamide fumarate 400 mg tablet twice a day, n = 107 C. Tepilamide fumarate tablets 600 mg twice a day, n = 107 D. Placebo, n = 107
Outcomes	At week 24 **Primary composite outcome** • PASI 75 and IGA 0/1 **Secondary outcomes** • PASI 50, PASI 75 • IGA • BSA
Notes	Funding source: Quote (protocol p. 1): "Dr Reddy's Laboratories" Declarations of interest: not stated RoB completed according to ClinicalTrials.gov protocol

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (protocol p. 37) "All subjects who enter into the screening period for the study (defined as the point at which the subject signs the ICF) will receive a subject identification number through the Interactive Web Response System (IWRS)." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (protocol p. 37) "All subjects who enter into the screening period for the study (defined as the point at which the subject signs the ICF) will receive a subject identification number through the Interactive Web Response System (IWRS)...This number will not be the same as the assigned randomization number." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (protocol p. 37) "This is a double-blind study. The investigator, study coordinator(s), subjects and the Sponsor study team and its representatives, will be blinded to the identity of the randomized treatment assignment from the time of randomization until database lock. Randomization data will be kept in strict confidence by the statistician who generated the randomization schedule, the IWRS provider, and the vendor involved in the IP labeling. All active and placebo IP will be of identical appearance, regardless of the dose. Study materials will be packaged and issued in a manner designed to maintain the blind." Comment: adequate process
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (protocol p. 37) "This is a double-blind study. The investigator, study coordinator(s), subjects and the Sponsor study team and its representatives, will be blinded to the identity of the randomized treatment assignment from the time of randomization until database lock. Randomization data will be kept in strict confidence by the statistician who generated the randomization sched-

NCT03421197 *(Continued)*

		ule, the IWRS provider, and the vendor involved in the IP labeling. All active and placebo IP will be of identical appearance, regardless of the dose. Study materials will be packaged and issued in a manner designed to maintain the blind." Comment: adequate process
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dealing with missing data: Quote (protocol p. 59) "The primary population for all efficacy analyses will be the FAS population. For the analyses of the primary endpoints (PASI 75 and IGA) based on the FAS population, several methods will be used to impute missing data, including, multiple imputation (MI), modified non-responder imputation (mNRI), and last-observation-carried-forward (LOCF)." Randomised 426, analysed 406
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT03421197). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. Results posted on ClinicalTrials.gov

NCT03504852

Study characteristics	
Methods	RCT, active-controlled, double-blind study Date of study: June 2018-July 2020 Location: worldwide (67 sites) Phase 3
Participants	**Randomised**: 331 participants **Inclusion criteria** • 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

NCT03504852 *(Continued)*

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

Baseline characteristics

N = 331, mean of age 47 years and 75% men

Dropouts and withdrawals

- 38/331 (11.5%): secukinumab Q2 (17), secukinumab Q4 (21)
- Withdrawal of informed consent: secukinumab Q2 (2), secukinumab Q4 (1)
- Withdrawal by subject: secukinumab Q2 (5), secukinumab Q4 (6)
- Lost to follow-up: secukinumab Q2 (4), secukinumab Q4 (1)
- New therapy for study indication: secukinumab Q2 (1), secukinumab Q4 (0)
- Lack of efficacy: secukinumab Q2 (1), secukinumab Q4 (2)
- Death: secukinumab Q2 (0), secukinumab Q4 (1)
- AEs: secukinumab Q2 (4), secukinumab Q4 (10)

Interventions	**Intervention** A. Secukinumab 300 mg every 2 weeks Q2, n = 165 **Control intervention** B. Secukinumab 300 mg every 4 weeks Q4, n = 166
Outcomes	**At week 16** **Primary outcome** • PASI 90 **Secondary outcomes** • IGA 0/1 • AE, SAE
Notes	Funding source: Quote (protocol p. 10) "Novartis" Declarations of interest: not stated RoB completed according to ClinicalTrials.gov protocol

Risk of bias

Bias	Authors' judgement	Support for judgement

NCT03504852 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote (protocol p. 18) "The investigator or his/her delegate will contact the Interactive Response Technology (IRT) after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the package of study drug to be dispensed to the subject". Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (protocol p. 26) "A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s)." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (protocol p. 27-28) "Subjects, investigator staff and persons performing the assessments, and data analysts will remain blind to the identity of the study treatment from the time of randomization until the end of study database lock: Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study. The identity of the treatments will be concealed by the use of investigational treatments that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (protocol p. 27-28) "Subjects, investigator staff and persons performing the assessments, and data analysts will remain blind to the identity of the study treatment from the time of randomization until the end of study database lock: Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study. The identity of the treatments will be concealed by the use of investigational treatments that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (protocol p. 64) "Response variables based on PASI score and IGA mod 2011 score will be imputed with multiple imputation (MI) as primary imputation method for the missing values." Randomised 331, analysed 331
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT03504852). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. Results posted on ClinicalTrials.gov

NCT03535194

Study characteristics

NCT03535194 *(Continued)*

Methods	RCT, active/placebo-controlled, double-blind study Date of study: May 2018-June 2020 Location: worldwide (178 sites) Phase 3
Participants	**Randomised**: 1484 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) **Baseline characteristics** N = 1484 and 67% men **Dropouts and withdrawals** • 47/1484 (3%): mirikizumab(28), secukinumab (11), placebo (8) • AEs: mirikizumab(4), secukinumab (3), placebo (1) • Death: mirikizumab(1), secukinumab (0), placebo (0) • Lack of efficacy: mirikizumab(4), secukinumab (2), placebo (2) • Lost to follow-up: mirikizumab(8), secukinumab (3), placebo (2) • Physician decision: mirikizumab(2), secukinumab (0), placebo (0) • Protocol violation: mirikizumab(1), secukinumab (1), placebo (0) • Screen failure: mirikizumab(1), secukinumab (0), placebo (0) • Withdrawal by subject: mirikizumab(7), secukinumab (2), placebo (3)
Interventions	**Intervention** **A.** Mirikizumab 250 mg SC at weeks 0, 4, 8, and 12, n = 905 **Control interventions** B. Secukinumab 300 mg SC at weeks 0, 1, 2, 3, 4, 8, and 12, n = 448 C. Placebo, n = 112
Outcomes	At week 16 **Primary composite outcome** • PASI 90 - IGA 0/1 **Secondary outcomes**

NCT03535194 *(Continued)*

- PASI 75
- DLQI
- SF-36
- Change from baseline in quick inventory of depressive symptomology
- PASI 90
- IGA 0/1
- Psoriasis Symptoms Scale (PSS) symptom score
- Change in Psoriasis Scalp Severity Index (PSSI) total score in participants with scalp involvement
- Change from baseline in Nail Psoriasis Severity Index (NAPSI) total score in participants with fingernail involvement

Notes	Funding source: Quote (ClinicalTrials.gov) "Eli Lilly and Company" Declarations of interest: not stated RoB completed according to ClinicalTrials.gov protocol

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (protocol p. 43) "Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign prefilled syringes containing double-blind investigational product to each patient." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (protocol p. 43) "Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign prefilled syringes containing double-blind investigational product to each patient." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (protocol p. 45) "This is a double-blind study. The blinding applies to patients, site personnel, and Sponsor personnel. To preserve the blinding of the study, a minimum number of Lilly and site personnel will see the randomization table and treatment assignments before the study is complete." Comment: no description of the method used to guarantee blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (protocol p. 45) "This is a double-blind study. The blinding applies to patients, site personnel, and Sponsor personnel. To preserve the blinding of the study, a minimum number of Lilly and site personnel will see the randomization table and treatment assignments before the study is complete." Comment:no description of the method used to guarantee blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (protocol p. 72) "The following methods for imputation of missing data will be used: Non-Responder Imputation (NRI) for binary clinical response and Mixed Model Repeated Measures (MMRM)." Randomised 1465, analysed 1465
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT03535194). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. Results posted on ClinicalTrials.gov

NCT03589885 MATURE

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind study (MATURE) Date of study: December 2018-November 2019 Location: USA, Germany, Spain, Iceland, Poland Phase 3B

Participants	**Randomised**: 122 participants
	
	Inclusion criteria
	
	• Men or women of at least 18 years of age at time of screening
	• Subjects able to understand and communicate with the investigator and comply with the requirements of the study and must have given a written, signed and dated informed consent before any study related activity was performed. Where relevant, a legal representative signed the informed study consent according to local laws and regulations.
	• Chronic plaque-type psoriasis present for at least 6 months and diagnosed before randomization
	• Moderate to severe psoriasis as defined at randomization by:
	  ◦ PASI score of 12 or greater, and
	  ◦ IGA mod 2011 score of 3 or greater (based on a scale of 0-4), and
	  ◦ Body Surface Area (BSA) affected by plaque-type psoriasis of 10% or greater
	• Candidate for systemic therapy. This is defined as a subject 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 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 constituents

Interventions	**Intervention** A. Secukinumab 300 mg provided in 2 mL auto-injector, n = 41

NCT03589885 MATURE *(Continued)*

	Control interventions B. Secukinumab 300 mg provided as 2 x 1 mL prefilled syringe of 150 mg/mL, n = 41 C. Placebo, n = 40
Outcomes	At week 12 **Primary composite outcome** • PASI 75 - IGA 0/1 **Secondary outcomes** • PASI 50, 75, 90 and 100 and IGA 0/1 at week 52 • PASI 90 at week 52 • DLQI at week 52
Notes	Funding: Quote (Clinicaltrials.gov): Novartis Pharmaceuticals Declaration of interests: not stated RoB completed according to ClinicalTrials.gov protocol

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (study protocol p. 31): "At Randomization visit, all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms."...."The IRT will assign one randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the package of study drug to be dispensed to the subject." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (study protocol p. 31): "The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the IRT using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supplies using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s)." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (study protocol p. 31-32): "A double-dummy design is used to ensure that the identity of the study drug cannot be disguised, as the drug products are visibly different. Subjects, investigator staff and persons performing the assessments, and data analysts will remain blind to the identity of the study treatment from the time of randomization until the end of study database lock, using the following methods: 1. Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study ... 2. The identity of the treatments will be concealed by the use of investigational treatments that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor."

NCT03589885 MATURE *(Continued)*

		Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (study protocol p. 31-32): "A double-dummy design is used to ensure that the identity of the study drug cannot be disguised, as the drug products are visibly different. Subjects, investigator staff and persons performing the assessments, and data analysts will remain blind to the identity of the study treatment from the time of randomization until the end of study database lock, using the following methods: 1. Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study ... 2. The identity of the treatments will be concealed by the use of investigational treatments that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (study protocol p. 68) "The following imputation methods will apply to the missing data: Response variables based on PASI score and IGA mod 2011 categories will be imputed with multiple imputations (MI) method as primary imputation method. MI is a simulation based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. These completed data sets can then be analyzed using standard methods. Within this analysis the PASI score or IGA mod 2011 categories will be imputed and response variables will be derived based on the imputed scores. In the multiple imputation analysis the response status will be imputed based on the individual treatment arm information. Non-responder imputation will be used as sensitivity method: Missing values with respect to response variables based on PASI score and IGA mod 2011 categories will be imputed with non-response regardless to the reason for missing data (e.g. premature study discontinuation, missed visit, administrative issues)". Randomised 122, analysed 122 Comment: probably done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT03589885). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. Results are posted on ClinicalTrials.gov

Nugteren-Huying 1990

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind study 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**

Nugteren-Huying 1990 *(Continued)*

- 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 outcome** • BSA **Secondary outcomes** • 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..." 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 colour”. Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Randomly assigned 39, analysed 34

Nugteren-Huying 1990 *(Continued)*

		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 study Date of study: July 2013-December 2015 Location: Japan Phase 2
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 • 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

Ohtsuki 2017 *(Continued)*

- 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 source 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." Declarations 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 BID. or apremilast 30 mg b.i.d." Comment: probably done

Ohtsuki 2017 *(Continued)*

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: January 2015-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 recur-

Ohtsuki 2018 *(Continued)*

rence 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%): guselkumab 100 group (1), guselkumab 50 group (2), placebo group (12)
- Participant decision: guselkumab 100 group (0), guselkumab 50 group (1), placebo group (6)
- AEs: guselkumab 100 group (0), guselkumab 50 group (1), placebo group (6)
- Others: guselkumab 100 group (1), guselkumab 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 interventions** 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- IGA 0/1 **Secondary outcomes** • PGA 0/1 at W52 • PASI 90 at W52 • PASI 75 • DLQI total score • AEs
Notes	Funding source Quote (p 883): "Funding: This study was funded by Janssen Pharmaceutical,Tokyo, Japan." Declarations 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."

Ohtsuki 2018 *(Continued)*

		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 study Date of study: not stated Location: 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**

Olsen 1989 *(Continued)*

- 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** • Not clearly defined **Secondary outcomes** • Body surface area • Scale • Side effects
Notes	Funding source by Hoffman-La Roche Inc Declarations of interest: not stated

Risk of bias

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

ORION 2020

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study Date of study: March 2017- February 2018 Location: worldwide 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: for 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 sterilisation (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
	
	Baselline characteristics
	
	N = 78, mean of age 46 years and 68% men
	
	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)

ORION 2020 *(Continued)*

Interventions	**Intervention** 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** B. Placebo, n = 16
Outcomes	**At week 16** **Primary outcomes** • IGA 0/1 • PASI 90 **Secondary outcomes** • PASI 75 • PASI 100
Notes	Funding source: 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." Declarations 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)."

ORION 2020 *(Continued)*

		Comment: probably done
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 PASI 90 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.

Ortonne 2013

Study characteristics	
Methods	RCT, active-controlled, open-label study Date of study: 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.

Ortonne 2013 *(Continued)*

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 **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** • NAPSI **Secondary outcomes** • NAPSI 50/75 • PASI 50/75 • PGA 0/1 • 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

Ortonne 2013 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (p 1081): “This was a multicenter, multinational, randomised, open-label study”. Comment: not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	72 included/69 analysed Quote (p 1082): "All efficacy analyses were based on the modified intent-to treat (mITT) population, which was defined as all patients who had received one or more doses of ETN and had baseline and post baseline data...The MMRM and GEE models have been developed for the analysis of longitudinal categorical data and to handle missing data without any imputation; this kind of model is preferred to the last-observation-carried-forward approach for analysis of longitudinal data". Comment: probably done
Selective reporting (reporting bias)	Low risk	Comment: The protocol for the study was available on ClinicalTrials.gov (NCT00581100). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported.

Papp 2005

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study 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**

Papp 2005 *(Continued)*

	A. Etanercept (n = 204), SC, 25 mg twice a week, 12 weeks **Control interventions** 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 outcome** • PASI 75 **Secondary outcomes** • 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

Papp 2005 *(Continued)*

		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 study 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 outcome**

Papp 2012a *(Continued)*

- PASI 75

Secondary outcomes

- PASI 50/90/100 at week 12
- BSA
- PGA
- DLQI
- AEs

Notes	Funding source, quote (p 1182): "The study was funded by Amgen". 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

Papp 2012a *(Continued)*

		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 2012c

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind study 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** • PASI 75 **Secondary outcomes**

Papp 2012c *(Continued)*

- PGA 0 or 1
- PASI 50/90
- DLQI
- SF-36

Notes	Funding source Quote (p 738): "Funding Celgene Corporation" 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

Papp 2012c *(Continued)*

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 study 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

Papp 2013a *(Continued)*

	E. Placebo (n = 22), SC, 0, 4, 8 weeks, 12 weeks
Outcomes	Assessments at 12 weeks **Primary outcomes of the trial** • PASI 75 **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

Papp 2013a *(Continued)*

		Quote (p 415): "The full analysis set consisted of all patients who were randomised... The missing score was imputed by carrying forward the last non missing post baseline PASI". Comment: very high number of withdrawals (38%)
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01071252). The 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 study 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 outcome** • PASI 75 **Secondary outcomes**

Papp 2013b *(Continued)*

- PGA
- PASI 50/90
- BSA
- AEs

Notes	Funding source quote (p 27): "This study was sponsored by Celgene Corporation". 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 Thaç 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 prespecified 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	
Methods	RCT, active/placebo-controlled, double-blind study 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 interventions** 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 outcome** • PASI 75 **Secondary outcomes** • PASI 90 • PASI 75 at week 12 • PGA 0/1 • DLQI

Papp 2015 *(Continued)*

Notes	Funding source: Quote (p 930): “This study was funded by Merck & Co, nc., Kenilworth, NJ, USA”. Declarations of interest (Appendix 1): "E.P.B., A.M., Q.L., Y.Z. and R.S. are current or former employees of Merck & 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

Papp 2015 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 355, analysed 352 Management of missing data: Quote (p 932): "The primary analysis was performed on all randomised participants who received at least one or more doses of treatment. Participants who discontinued treatment prior to week 16... were considered to not have achieved PASI 75 at week 16". Comment: low number lost to follow-up
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT01225731). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported.

Papp 2017a

Study characteristics	
Methods	RCT, phase 3, randomised, double-blind, active-controlled study Date of study: August 2014-March 2015 Location: worldwide
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), 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**

Papp 2017a *(Continued)*

	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 **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 source 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." Declarations of interest 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 di-

Papp 2017a *(Continued)*

rector for Corrona Psoriasis Registry, receiving a consulting fee; received grant support to the University of Connecticut for a fellowship program from AbbVie and Janssen."

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 (p. 1096): "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 2017b

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study Date of study: February 2014-July 2015 Location: worldwide Phase 2
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

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- 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®))
- 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%): risankizumab 18 (4), risankizumab 90 (2), risankizumab 180 (2), USK (1)
- Lost to follow-up: risankizumab 18 (1), risankizumab 90 (0), risankizumab 180 (0), USK (0)
- AEs: risankizumab 18 (1), risankizumab 90 (1), risankizumab 180 (0), USK (1)
- Others: risankizumab 18 (2), risankizumab 90 (1), risankizumab 180 (2), USK (0)

Interventions	**Intervention** A. 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. 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. BI 655066 (high dose) (180 mg BI 655066 administered by SC injection as 2 injections plus a placebo-matching BI 655066 injection at week 0, followed 180 mg BI 655066 administered as 2 injections at weeks 4 and 16), n = 42 D. 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 source Quote (p 1553): "The trial was funded by Boehringer Ingelheim". Declarations 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 2017b *(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 2018

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study Date of study: Novermber 2016-November 2017 Location: 82 sites In the USA, Japan, Poland, Canada, Germany, Latvia, Mexico, and Australia Phase 2
Participants	**Randomised**: 267 participants **Inclusion criteria** • Men and women, ages 18 to 70 years • Diagnosis of plaque psoriasis for 6 months

Papp 2018 *(Continued)*

- 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.

Baseline characteristics

N = 267, mean of age 45 years and 73% men

Dropouts and withdrawals

- 61/267 (15.%): BMS-986165_3 EOD (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_3 EOD (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_3 EOD (4), BMS-986165_3 (3), BMS-986165_3*2 (0), BMS-986165_6*2 (0), BMS-986165_12 (1), PBO (5)
- Participant: BMS-986165_3 EOD (5), BMS-986165_3 (0), BMS-986165_3*2 (1), BMS-986165_6*2 (1), BMS-986165_12 (0), PBO (5)
- Others: BMS-986165_3 EOD (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 interventions** 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 2018 *(Continued)*

- PASI 75

Secondary outcomes

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

Notes	Funding source Quote (p 1320): "Supported by Bristol-Myers Squibb" Declarations 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 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. Results are posted on ClinicalTrials.gov.

Papp 2021

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind study Date of study: August 2018-March 2015 Location: worldwide (41 sites) Phase 2b

Papp 2021 *(Continued)*

Participants	**Randomised**: 313 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 6. History of suicidal thoughts within 12 months **Baseline characteristics** N = 313, mean of age 46 years and 73% men **Dropouts and withdrawals** • 11/313 (3.5%): sonelokimab 30 (0), sonelokimab 60 (1), sonelokimab 120 Q8 (3), sonelokimab 120 Q4 (2), secukinumab (2), placebo (3) • Withdrew consent: sonelokimab 30 (0), sonelokimab 60 (0), sonelokimab 120 Q8 (0), sonelokimab 120 Q4 (0), secukinumab (1), placebo (3) • Lost to follow-up: sonelokimab 30 (0), sonelokimab 60 (1), sonelokimab 120 Q8 (1), sonelokimab 120 Q4 (0), secukinumab (1), placebo (0) • AEs: sonelokimab 30 (0), sonelokimab 60 (0), sonelokimab 120 Q8 (1), sonelokimab 120 Q4 (1), secukinumab (0), placebo (0) • Protocol deviation: sonelokimab 30 (0), sonelokimab 60 (0), sonelokimab 120 Q8 (1), sonelokimab 120 Q4 (0), secukinumab (0), placebo (0)
Interventions	**Intervention** A. M1095 (sonelokimab), 30 mg, given at week 0, 2, 4, 8, 12 and every four weeks, n = 52 **Control interventions** B. M1095, 60 mg, given at week 0, 2, 4, 8, 12 and every four weeks, n = 52 C. M1095, 120 mg, given at week 0, 2, 4, 8, 12 and every eight weeks Q8, n = 53 D. M1095, 120 mg, given at week 0, 2, 4, 8, 12 and every four weeks Q4, n = 51 E. Secukinumab 300 mg, n = 53 F. Placebo, n = 52
Outcomes	At week 12 **Primary outcome** • IGA 0/1

Papp 2021 *(Continued)*

Secondary outcomes

- PASI 75
- PASI 100
- DLQI

Notes	Funding source: Quote (p 1574) "This study was funded by Avillion." Declarations of interest: Quote (p 1574) "MAW is an employee of Avillion (Northbrook, IL, USA). AM is an employee of Avillion (London, UK). KAP reports grants and personal fees from Avillion, during the conduct of the study; personal fees and non-financial support from Meiji Seika Pharma outside the submitted work; grants and personal fees from AbbVie, Akros, Amgen, Arcutis, Astellas, Baxalta, Boehringer Ingelheim, Bristol-Myers Squibb, Canfite, Celgene, Centocor, Coherus, Dermira, Dow Pharma, Eli Lilly and Company, Forward Pharma, Galderma, Genentech, Gilead, GlaxoSmithKline, Janssen, Kyowa Hakko Kirin, LEO, MedImmune, Meiji Seika Pharma, Merck Sharpe & Dohme, Merck-Serono, Mitsubishi Pharma, Moberg Pharma, Novartis, Pfizer, PRCL Research, Regeneron, Roche, Sanofi Aventis/Genzyme, Samsung Bioepsis, Sun Pharma, Takeda, UCB Pharma, and Valeant/Bausch Health outside the submitted work; and being a consultant (no compensation) for AstraZeneca and Meiji Seika Pharma. KR reports personal fees from Avillion, during the conduct of the study; personal fees from Almirall, Amgen, Centocor, Dermira, GlaxoSmithKline, Samsung Bioepsis, Valeant, and Xenoport outside the submitted work; grants from Galapagos, Miltenyi Biotec, Sun Pharma, Regeneron, and Takeda outside the submitted work; grants and personal fees from AbbVie, Affibody, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Covagen, Forward Pharma, Fresenius Medical Care, Janssen-Cilag, Kyowa Kirin, LEO, Eli Lilly and Company, Medac, Merck Sharpe & Dohme, Novartis, Ocean Pharma, Pfizer, Sanofi, and UCB outside the submitted work; and serving as an advisor for, serving as a paid speaker for, or participating in clinical trials sponsored by AbbVie, Affibody, Almirall, Amgen, Avillion, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Centocor, Covagen, Dermira, Forward Pharma, Fresenius Medical Care, Galapagos, Galderma, GlaxoSmithKline, Janssen-Cilag, Kyowa Kirin, Leo, Lilly, Medac, Merck Sharp & Dohme, Novartis, Miltenyi Biotec, Ocean Pharma, Pfizer, Regeneron, Samsung Bioepis, Sanofi, Sun Pharma, Takeda, UCB, Valeant, and Xenoport."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 1567) "Randomisation was done at a study level via a centralised interactive response technology system, which provided blinded treatment kit numbers to the investigator". Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 1567) "Participants were enrolled by masked investigators and randomly assigned (1:1:1:1:1:1)....". "Randomisation was done at a study level via a centralised interactive response technology system, which provided blinded treatment kit numbers to the investigator". Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 1567) "Study drug was prepared and administered at the site by a designated unmasked individual at the study site, who had no other involvement in the trial. Participants and all other site personnel were masked to therapy allocation throughout the study. The study sponsor was unmasked after all participants had completed week 24 treatment and the database was locked." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (p 1567) "Study drug was prepared and administered at the site by a designated unmasked individual at the study site, who had no other involvement in the trial. Participants and all other site personnel were masked to

Papp 2021 *(Continued)*

		therapy allocation throughout the study. The study sponsor was unmasked after all participants had completed week 24 treatment and the database was locked." Comment: no detailled description of means used to guarantee absence of communication between blinded and unblinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (p 1568) "The primary outcome was analysed in the intention-to- treat (ITT) population; participants with missing data were considered as nonresponders (nonresponder imputation)." ...."Selected sensitivity analyses (missing response imputed with last observation carried forward, using randomised previous biologic use and bodyweight stratum) were done in the ITT population. The safety population was defined as all patients who received the study drug and and was identical to the defined ITT population". Randomised 313, analysed 313
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT03384745). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. Results are posted on ClinicalTrials.gov.

PEARL 2011

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study 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**

PEARL 2011 *(Continued)*

	B. Placebo, SC, weeks 0-4 + ustekinumab 45 mg weeks 12 to 16 (n = 60)
Outcomes	Assessments at 12 weeks **Primary outcome** • PASI 75 **Secondary outcomes** • PGA cleared or minimal at 12 weeks • Change from baseline in the DLQI at 12 weeks • 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.

PHOENIX-1 2008

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study 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 • 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 outcome** • PASI 75 **Secondary outcomes** • 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 Israeal 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 con-

PHOENIX-1 2008 *(Continued)*

sultant 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
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.

PHOENIX-2 2008

Study characteristics

Methods	RCT, placebo-controlled, double-blind study Date of study: March 2006–September 2007

PHOENIX-2 2008 *(Continued)*

	Location: 70 centres in Europe and North America
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 source: 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 Ab-

PHOENIX-2 2008 *(Continued)*

	bot, Biogen-Idec, Centocor, Janssen-Cilag, Schering-Plough, MerckSerono, UCB, and Wyeth. PS, NY, CG, M-CH, YW, SL, and LTD are employees of Centocor. PS, NY, CG, YW, SL, and LTD own stock in Johnson and Johnson."

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.

PIECE 2016

Study characteristics

Methods	RCT, active-controlled study Date of study: April 2009-June 2011 Location: 5 centres in The Netherlands
Participants	**Randomised**: 50 participants **Inclusion criteria**

PIECE 2016 *(Continued)*

- 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

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 outcome** • PASI 75 **Secondary outcomes** • 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 derma-

PIECE 2016 *(Continued)*

tology 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 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
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

PIECE 2016 *(Continued)*

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

Piskin 2003

Study characteristics	
Methods	RCT, active-controlled, open-label study 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 **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 source: not stated Declarations of interest: not stated

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Piskin 2003 *(Continued)*

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

PLANETA 2021

Study characteristics	
Methods	Randomised, placebo-controlled, double-blind study Date of study: December 2017-June 2019 Location: Russia (24 sites) Phase 3
Participants	**Randomised**: 213 participants **Inclusion criteria** • Subjects must give a written and signed informed consent. • Men or women at least 18 years old at the time of signing the ICF • Moderate to severe plaque psoriasis diagnosed at least 6 months before signing the informed consent form • Patients received at least one course of phototherapy or systemic therapy for psoriasis or are candidates for such treatment according to the investigator. • Body surface area (BSA) affected by psoriasis of 10% or greater, the PASI score of 10 or greater, and the sPGA score of 3 or greater at screening. • Negative pregnancy urine test in female subjects (no test is required in women who are postmenopausal for at least 2 years and in surgically sterile women). • The patient must be able to follow the Protocol procedures (in the investigator's opinion).

PLANETA 2021 *(Continued)*

- Patients of childbearing potential and their partners with preserved reproductive function must implement reliable contraceptive methods starting from signing informed consent to 20 weeks after the last dose of the study therapy. This requirement does not apply to the patients after surgical sterilisation and to females who are postmenopausal for 2 years or longer. Reliable contraception methods suggest using one barrier method in combination with one of the following: spermicides, intrauterine device/oral contraceptives

Exclusion criteria

- Baseline erythrodermic, pustular, and guttate psoriasis or any skin diseases (e.g eczema) that can affect/complicate assessment of psoriasis treatment
- Use of the following medications:
  - Prior use of monoclonal antibodies targeting IL17 or its receptor
  - Prior use of more than one drug containing monoclonal antibodies or their fragments
  - Prior use of monoclonal antibodies within 12 weeks before signing the informed consent.
  - Any systemic medications for psoriasis (including glucocorticoids, methotrexate, sulfasalazine, cyclosporine, acitretin, mycophenolate mofetil, apremilast, calcitriol derivatives, etc.) used within 4 weeks before signing the ICF. If prior systemic therapy with non-biologics was stopped due to any reasons, the screening period can be extended up to 8 weeks during which no new non-biologics are allowed.
  - Use of phototherapy within 4 weeks before signing the ICF
  - Topical medications for psoriasis used within 2 weeks before signing the ICF
  - Vaccination with live or attenuated vaccines within 8 weeks before signing the ICF
- Any active systemic infection or recurrent infection at screening/randomisation
- HIV, hepatitis B, hepatitis C, or syphilis
- Blood biochemistry abnormalities appearing as:
  - baseline creatinine > 2 × ULN
  - baseline ALT, AST or alkaline phosphatase > 2.5 × ULN
  - baseline bilirubin > 1.5 × ULN
- WBC count < 3.0 × 109/L; ANC < 2.0 × 109/L; platelet count < 100 × 109/L, or haemoglobin < 90 g/L at baseline
- Any psychiatric conditions including severe depressive disorders and/or any history of suicidal thoughts or suicidal attempts ;
- Signs of clinically significant depression (Beck's score of 16 or more at screening)
- Alcohol or substance abuse
- Tuberculosis now or in the past
- Latent TB infection (positive results of the Diaskintest or QuantiFERON test, or T-spot).
- Concurrent diseases ongoing at screening that may increase the risk of adverse events during the study or affect the evaluation of psoriasis symptoms (mask, enhance or alter the symptoms of psoriasis, or cause clinical or laboratory signs/symptoms similar to those of psoriasis):
  - active inflammatory diseases or aggravation of chronic inflammatory diseases other than psoriasis
  - Stable angina class III-IV, unstable angina or a history of myocardial infarction within 1 year before signing the informed consent
  - Cardiac failure moderate to severe (NYHA class III-IV)
  - Treatment-resistant hypertension
  - A history of severe asthma or angiooedema
  - Moderate to severe respiratory failure, COPD grade ¾
  - Diabetes mellitus with unsatisfactory glycaemic control, when the level of glycated haemoglobin HbA1c ≥ 8% (results are valid if the test was performed at the screening or within 3 months before signing the ICF)
  - The patient has thyrotoxicosis, which persists in the presence of thyreostatic medications, or hypothyroidism despite of the thyroid hormone treatment
  - Systemic autoimmune diseases (including but not limited to SLE, rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, systemic scleroderma, inflammatory myopathy, mixed connective tissue disease, intersection syndrome, etc.)

PLANETA 2021 *(Continued)*

- Any other underlying conditions (including but not limited to metabolic, haematologic, hepatic, renal, pulmonary, neurological, endocrine, cardiac, gastrointestinal conditions and infections) that, in the opinion of the investigator, may affect the course of psoriasis, affect the assessment of signs/symptoms of psoriasis, or put patients using the study treatment at additional risk.

- Malignancies with less than 5 years of remission
- Known severe allergies (anaphylaxis or drug allergy to two or more drug products)
- Known allergy or intolerance to monoclonal antibody drugs (murine, chimeric, humanised, or human) or any other components of the test drug or comparator
- Major surgery within 30 days before the screening, or a major surgery being scheduled at any time during the study
- Severe infections (including those that required hospitalisation or parenteral antibacterial/antimycotic/antiprotozoal treatment) within 6 months before signing the ICF
- Systemic antibacterial/antimycotic/antiprotozoal treatment within 2 months before the signing the ICF
- More than 4 episodes of respiratory infection within 6 months before signing the ICF
- Episodes of severe mycoses (histoplasmosis, coccidioidomycosis, blastomycosis, etc.) within 6 months before signing the ICF
- A history of epileptic attacks or seizures
- Any concurrent diseases during which, in the investigator's opinion, the study treatment can harm the patient
- Pregnancy, breastfeeding, or planning for pregnancy while participating in the study
- Participation in any other clinical study within 3 months before signing the ICF or simultaneous participation in other clinical studies
- Patients will not be re-enrolled in this study if they were randomised to this study and then discontinue the participation.

Baseline characteristics

N = 213, mean of age 61 years and 73% men

Dropouts and withdrawals

- 3/213 (1.4%): netakimab Q2W (0), netakimab Q4W (2), placebo (1)
- Withdrawal by subject: netakimab Q2W (0), netakimab Q4W (1), placebo (1)
- Lost to follow-up: netakimab Q2W (0), netakimab Q4W (1), placebo (0)

Interventions	**Interventions** A. Netakimab (BCD-085) Q2W 120 mg (two SC injections, 60 mg in 1.0 mL each) at week 0, week 1, week 2, week 4, week 6, week 8, and week 10, n = 85 B. Netakimab (BCD-085) Q4W 120 mg (two SC injections, 60 mg in 1.0 mL each) at week 0, week 1, week 2, week 6 and week 10. For the purpose of blind design, patients will receive a placebo (2 injections) at week 4 and week 8, n = 84. **Control intervention** C. Placebo, n = 44
Outcomes	At week 12 **Primary outcome** • PASI 75 **Secondary outcomes** • PASI 75 at weeks 8, 16, 24, 42 and 52 • PASI 90/100 at weeks 8, 12, 16, 24, 42 and 52 • The change from baseline in PASI at weeks 8, 12, 16, 24, 42 and 52

PLANETA 2021 *(Continued)*

- The proportion of patients with sPGA 0 or 1 and sPGA 0 at weeks 8, 12, 16, 24, 42 and 52
- The proportion of patients with DLQI 0 or 1 at weeks 24, 42 and 52
- The change from baseline in itch severity (measured by visual analogue scale [VAS], 0–100 mm) at weeks 1, 12, 24 and 52
- Nail Psoriasis Severity Index (NAPSI) at weeks 12, 24 and 52
- DLQI at weeks 8, 12, 24, 42 and 52

Notes	Funding source: Quote (p1330)"Sponsorship for this study and the Rapid Service Fee were funded by JSC BIOCAD, Ul. Italianskaya 17, St Petersburg, Russia, 191186." Declarations of interest: Quote (p1331)"Lu ́ıs. Puig has received consul- tancy/speaker's honoraria from and/or partici- pated in clinical trials sponsored by Abbvie, Almirall, Amgen, Baxalta, Biogen, Boehringer Ingelheim, Celgene, Gebro, Janssen, JSC BIO- CAD, Leo-Pharma, Lilly, Merck-Serono, MSD, Mylan, Novartis, Pfizer, Regeneron, Roche, Sandoz, Samsung-Bioepis, Sanofi and UCB. Andrey L. Bakulev has received consultancy/ speaker's honoraria from and/or participated in clinical trials sponsored by Abbvie, Amgen, Boehringer Ingelheim, Celgene, Janssen, JSC BIOCAD, Leo-Pharma, Lilly, MSD, Novartis, Pfizer, Sanofi, UCB and Zeldis Pfarma. Muza M. Kokhan has received consultancy/speaker's honoraria from and/or participated in clinical trials sponsored by Celgene, Janssen, JSC BIO- CAD, Leo-Pharma, Lilly, Novartis, Pfizer and Sanofi. Alexey V. Samtsov has received consul- tancy/speaker's honoraria from and/or partici- pated in clinical trials sponsored by Celgene, Glenmark, Jadran and JSC BIOCAD. Vladislav R. Khairutdinov has received consultancy/speak- er's honoraria from and/or partic- ipated in clin- ical trials sponsored by Abbvie, Belupo, Bosnalec, Celgene, Glenmark, Jadran, Janssen, JSC BIOCAD, Leo-Pharma, Lilly, MSD, Novartis, Pfizer, Sanofi and Sun Pharma. Maria A. Moro- zova, Antonina V. Artemeva, Arina V. Zinkina- Orikhan, Nikita A. Zolkin, Ivan V. Kuryshev and Alexey N. Petrov are JSC BIOCAD employees."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p. 1321) "The randomization was performed with random sequence using an electronic centralized randomization system." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p. 1321) "The randomization was performed with random sequence using an electronic centralized randomization system." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (p. 1321) "The study investigators, trial team and patients were blinded to the treatment allocation during the first 12 weeks of the study....During the first 3 weeks, all patients received subcutaneous injections of NTK or placebo (according to the allocation) once a week (induction phase). Patients in the NTK Q2W group then received the study drug at weeks 4, 6, 8 and 10. Subjects in the NTK Q4W group received NTK at weeks 6 and 10 and placebo at weeks 4 and 8 to preserve blinding". Comment: unclear if the process guaranteed blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (p1321)"The study investigators, trial team and patients were blinded to the treatment allocation during the first 12 weeks of the study....During the first 3 weeks, all patients received subcutaneous injections of NTK or placebo (according to the allocation) once a week (induction phase). Patients in the NTK Q2W group then received the study drug at weeks 4, 6, 8 and 10. Subjects in the NTK Q4W group received NTK at weeks 6 and 10 and placebo at weeks 4 and 8 to preserve blinding". Comment: unclear if the process guaranteed blinding of outcome assessor

PLANETA 2021 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dealing with missing data: Quote (p. 1322) "The efficacy and safety analyses were performed according to the intention-to-treat (ITT) principle and included all patients randomised in the study (n = 213). For dichotomous responder-type endpoints, missing responses at a post-baseline visit were imputed as a nonresponder. For continuous endpoints, no missing data imputation rules were applied. Randomised 213, analysed 213 Comment: no rule was applied for continuous endpoints.
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT03390101). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. Results posted on ClinicalTrials.gov

POLARIS 2020

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 • 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

POLARIS 2020 *(Continued)*

Baseline characteristics

N = 119, mean of age 42.5 years and 69% men

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 75/100 • DLQI • IGA • SF-36
Notes	Funding source:Quote (p 265) "Funding for the trial and its publication was provided by Janssen-Cilag GmbH". Declarations of interest: Quote (p 275) "D.T. has received honoraria as an investi- gator or consultant for and/or received speakers' honoraria and/or research grants from AbbVie, Almirall, Amgen, Boehringer Ingelheim, Celgene, Dignity, Dr Reddy, Galapagos, GSK, Janssen, LEO, Lilly, Morphosis, MSD, Novartis, Pfizer, Regeneron/Sanofi, Sandoz-Hexal and UCB. A.P. has received honoraria as an investigator for, and/or received speakers' honoraria from, and/or received grants from, and/or been an advisor for AbbVie, Almirall-Hermal, Amgen, Biogen Idec, Boehringer Ingelheim, Celgene, GSK, Eli Lilly, Galderma, Hexal, Janssen, LEO Pharma, Medac, Merck Serono, Mit- subishi, MSD, Novartis, Pfizer, Tigercat Pharma, Regeneron, Roche, Sandoz Biopharmaceuticals, Schering-Plough and UCB Pharma. M. Sebastian has received honoraria as an investigator for, received grants from, and been an advisor or consultant for AbbVie, Boehringer Ingelheim, Celgene, Dr Reddy, GSK, MSD, Mundipharma, Novartis, UCB Pharma, Janssen, Almirall, LEO Pharma, Galderma, Lilly and Regeneron. C.T. has received honoraria as an investigator for, and/or received speakers' honoraria and/or grants from, and/or been an advisor for Janssen, Almirall, Allergopharma, AbbVie, LEO and UCB. M. Sticherling has received honoraria as an investigator and/or speaker for, has received grants from, and/or has participated in clinical studies for AbbVie, Actelion, Almirall, Amgen Celgene, Galderma, GSK, Janssen, LEO, Lilly, MSD, Mundi- pharma, Novartis, Pfizer, Sandoz, Sanofi and UCB Pharma. S.G. has been an advisor for, and/or received speakers' hono- raria from, and/or received grants from, and/or participated in clinical trials for Abbott/AbbVie, Almirall-Hermal, Amgen, Baxalta, Bayer Health Care, Biogen Idec, Bioskin, Boehringer Ingelheim, Celgene, Centocor, Dermira, Eli Lilly, Foamix, For- ward Pharma, Galderma, Hexal AG, Isotechnika, Janssen, LEO Pharma, Medac, Merck Serono, Mitsubishi Tanabe, MSD, Novartis, Pfizer, Polichem SA, Regeneron Pharmaceuticals, Sandoz Biopharmaceuticals, Sanofi-Aventis, Schering-Plough, Sienna Biopharmaceuticals, Takeda, Teva, UCB Pharma, VBL Therapeutics and Wyeth Pharma. S.W., S.K., C.R.,

POLARIS 2020 *(Continued)*

H.B. and A.M. are employees of Janssen-Cilag GmbH, Germany. K.E. has received honoraria as an investigator for, and/or received speakers' honoraria from, and/or received grants from, and/ or been an advisor for Janssen, AbbVie, Celgene, Hexal, LEO, Lilly, Novartis and Sanofi."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p. 267): "Patients were randomized 1: 1 based on a computer-generated randomization schedule that was prepared before the start of the study. The randomization was balanced using randomly permuted blocks of four. The interactive web-based electronic case report forms assigned a unique treatment code, which dictated the treatment assignment at the baseline visit for each patient. The blinded efficacy assessors were not involved in any other study procedure and did not have access to the allocation data." Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Quote (p. 267): "Patients were randomized 1: 1 based on a computer-generated randomization schedule that was prepared before the start of the study. The randomization was balanced using randomly permuted blocks of four. The interactive web-based electronic case report forms assigned a unique treatment code, which dictated the treatment assignment at the baseline visit for each patient. The blinded efficacy assessors were not involved in any other study procedure and did not have access to the allocation data." 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 266): "This multicentre, randomized, open-label, assessor-blinded, active-comparator-controlled phase IIIb study... ".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 266-267): "This multicentre, randomized, open-label, assessor-blinded, active-comparator-controlled phase IIIb study... ". "The blinded efficacy assessors were not involved in any other study procedure and did not have access to the allocation data." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	High risk	Dealing with missing data: Quote (p 268): "For binary endpoints, all patients with missing data were considered nonresponders (nonresponder imputation analysis). For continuous endpoints, the last available observation after baseline was carried forward (last observation carried forward analysis)." 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). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. Results posted on ClinicalTrials.gov

PRESTA 2010

Study characteristics	
Methods	RCT, active-controlled, double-blind study Date of study: December 2005-May 2008 Location: centres (n = 98) worldwide
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** • 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 source, 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 Bris-

PRESTA 2010 *(Continued)*

tol-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
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.

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.

PRIME 2017 *(Continued)*

- 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
- 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, breastfeeding, or unwillingness/inability to use appropriate measures of contraception (if necessary)

Dropouts and withdrawals

- 60/202 (2%): secukinumab group (6), FAEs group (56)
- Did not receive allocated intervention: secukinumab group (0), FAEs group (2)
- AEs: secukinumab group (2), FAEs group (32)
- Patient: secukinumab group (2), FAEs group (13)
- Lost to follow-up: secukinumab group (2), FAEs group (2)
- Other: secukinumab 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

PRIME 2017 *(Continued)*

Primary outcome

- PASI 75

Secondary outcomes

- PASI 90
- IGA 0/1
- DLQI

Notes	Funding source Quote (p 1024): "Novartis Pharma GmbH" Declarations 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."

PRIME 2017 *(Continued)*

		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
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, analysed 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.

PRISTINE 2013

Study characteristics	
Methods	RCT, active-controlled, double-blind study 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**

PRISTINE 2013 *(Continued)*

- Participants with moderate-severe psoriasis (PASI ≥ 10, BSA ≥ 10), age ≥ 18 years
- Nonresponse to topical treatment
- Nonresponse to phototherapy
- Nonresponse to conventional systemic treatment

Exclusion criteria

- Had received biologics
- Had an active infection

Dropouts and withdrawals

- 25/273 (9%)
- 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".

PRISTINE 2013 *(Continued)*

		Comment: not specified
Allocation concealment (selection bias)	Unclear risk	Quote (p 170): "Subjects were randomly assigned to one of the 2 etanercept treatment groups... in 1:1 treatment allocation". Comment: not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 170): "The study consisted of a 12-week double-blind treatment period". Comment: probably done, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 170): "The study consisted of a 12-week double-blind treatment period". Comment: probably done, placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	273 enrolled and randomised, and 270 analysed Quote (p 171): "All efficacy analyses were performed using the modified intent-to-treat population which included all randomised subjects who received at least one dose of etanercept and had both baseline and on therapy PASI evaluations. The last observation-carried-forward method was used for the imputation of missing data..." Comment: mITT and only 3 of 273 participants not included in the analyses of the primary outcome
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00663052). The prespecified outcomes mentioned in the Methods section appeared to have been reported,

PsOsim 2017

Study characteristics	
Methods	RCT, active-controlled, double-blind study Date of study: May 2016-March 2017 Location: Multicentre (99 centres worldwilde) Phase 3
Participants	**Randomised**: 545 participants **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

PsOsim 2017 *(Continued)*

- Chemistry and haematology values outside protocol-specified range
- Major systemic infections

Baseline characteristics

N = 545, 72% men

Dropouts and withdrawals

Total CHS-1420: 54/274, adalimumab: 19/136

Reasons not reported

Interventions	**Intervention** A. 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, n = 274. At week 24 participants will switch to CHS-1420 open-label until study end. **Control intervention** B. CHS-1420 (Biosimilar) 40 mg 2 doses at week 0/day 0 then 1 dose every 2 weeks starting at week 1 for 23 weeks, n = 271. At week 24 participants will continue on to CHS-1420 open label until study end.
Outcomes	**Primary outcome** • PASI 75 at week 12 **Secondary outcomes** • PASI 75 at weeks 2, 4, 6, 8, 10, 16, 20, 24, 32, 40 and 48 • Percentage change from baseline in PASI at weeks 2, 4, 6, 8, 10,12, 16, 20, 24, 32, 40 and 48 • PASI 50 at weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 32, 40 and 48 • PASI 90 at weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 32, 40 and 48 • PSGA from baseline to weeks 2, 4, 6, 8, 10
Notes	Funding source: Quote (ClinicalTrials.gov) "Coherus Biosciences, Inc." Declarations of interest: not stated On ClinicalTrials.gov (NCT02489227), waiting for the publication to contact the main author RoB completed according study protocol posted on ClinicalTrials.gov.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (protocol): "Once the subject has signed the ICF at Screening, site personnel will assign a subject identification number (ID). The subject ID will include the site number (3 digits), and 3 digit subject number, assigned sequentially starting with 001." Comment: Suggest centrally with the use of computer-generated but unsure
Allocation concealment (selection bias)	Low risk	Quote (protocol): "Once the subject ID has been assigned, the site will contact the Interactive Voice Response System/Interactive Web-based Response System (IXRS) to register the subject ID". Comment: Probably done

PsOsim 2017 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "This is a double-blind study. The Humira and CHS-1420 syringes will be matched in appearance. Blinded study drug will be shipped under appropriate storage conditions to site personnel according to the regulations of the study country". Comment: Probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "This is a double-blind study. The Humira and CHS-1420 syringes will be matched in appearance. Blinded study drug will be shipped under appropriate storage conditions to site personnel according to the regulations of the study country". Comment: Probably done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Subjects who lack a PASI assessment at week 12 will be considered nonresponders in the primary analyses. As a sensitivity analysis, the last available score will be used". Comment: reasons for withdrawal not reported
Selective reporting (reporting bias)	High risk	None of the secondary outcomes were reported, but results on ClinicalTrials.gov

Rathipriyadharshini 2020

Study characteristics	
Methods	RCT, active-controlled, open-label study Date of study: 2018-2019 Location: India
Participants	**Randomised**: 40 participants **Inclusion criteria**: • 18-70 years old • With chronic plaque psoriasis involving > 10% BSA **Exclusion criteria**: • pregnancy • lactation • abnormalities in LFT, RFT, CBC • hypertension and diabetes • active tuberculosis/HIV infection • hypersensitivity to the drugs • on immunosuppressive medications **Baseline characteristics** N = 40, mean of age 41 years **Dropouts and withdrawals** Not stated

Rathipriyadharshini 2020 *(Continued)*

Interventions	**Intervention** A. Apremilast 30 mg twice a day from day 6 to 12 weeks after the recommended initial dosage titration from day 1 to day 6, n = 20 **Control intervention** B. Methotrexate 7.5 mg per week for 12 weeks along with T.Folic Acid 5 mg daily, n =20
Outcomes	At week 12 **Primary outcome** • PASI 75 **Secondary outcome** • Improvement in PASI at week 3 and week 9
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 (article) "It is an open-labelled randomized comparative clinical study". Comment: no description of the methods used to guarantee the random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote (article) "It is an open-labelled randomized comparative clinical study". Comment: no description of the methods used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (article) "It is an open-labelled randomized comparative clinical study".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (article) "It is an open-labelled randomized comparative clinical study".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no description of the methods used to manage missing data, no description of the methods used to assess the primary outcome (ITT, PP...)
Selective reporting (reporting bias)	Unclear risk	Comment: a protocol was registered (CTRI/2019/01/017362). The outcomes mentioned in the Results section were not specified in the Methods section.

Reich 2012a

Study characteristics

Reich 2012a *(Continued)*

Methods	RCT, placebo-controlled, double-blind study 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 200 (n = 59), SC Initial dose of certolizumab pegol (CZP) 400 mg at week 0, followed by 200 mg CZP every other week (Q2W) until week 10 **Control intervention** B. Certolizumab 400 (n = 58), SC Initial dose of CZP 400 mg at week 0, followed by 400 mg CZP Q2W until week 10 C. Placebo (n = 59), SC, Q2W until week 10
Outcomes	Assessments at 12 weeks **Primary outcomes** • PASI 75 • PGA **Secondary outcomes** • PASI 50 • PASI 90 • Time to PASI 75 response • Time to relapse • Change from baseline BSA • DLQI

Reich 2012a *(Continued)*

- 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 Quote (p 182): "Co-primary efficacy assessments were performed on the intention-to-treat population... Nonresponder imputations for missing values were used for the primary analysis". Comment: probably done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT00245765).

Reich 2012a *(Continued)*

	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 study 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 (days 1, 15, 29) D. Placebo (n = 10)
Outcomes	Assessments at 12 weeks **Primary outcomes** • Change from baseline in PASI score at 12 weeks • Proportion of participants who did not relapse at any time through week 56 **Secondary outcomes** • PASI 50 • 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."

Reich 2015 *(Continued)*

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
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".

Reich 2015 *(Continued)*

		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 2020

Study characteristics	
Methods	RCT, active-controlled, open-label, rater-blinded, parallel-group study Date of study:January 2016-December 2016 Location: Germany (28 centres) 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, haematologic, 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 **Baseline characteristics** N = 162, mean of age 42 years and 75% men

Reich 2020 *(Continued)*

Dropouts and withdrawals

- 37/162 (23%): IXE group (5), FAEs group (29), methotrexate group (3)
- Participant decision: IXE group (1), FAEs group (6), methotrexate group (1)
- 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** A. 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** B. FAEs (105 mg FAE given orally followed by 215 mg FAE given orally 1-3 times/day until week 24), n = 54 C. 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 outcomes** • PGA 0/1 • PASI 90/100 • DLQI
Notes	Funding source: quote (p. 869)"This study was supported by Eli Lilly (Indi- anapolis, IN, U.S.A.). This study was designed by Lilly Deutschland GmbH." Declarations of interest: quote (p878-879)"K.R. has served as an advisor and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Amgen, Biogen, Boehringer Ingelheim Pharma, Celgene, Centocor, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Eli Lilly and Company, Medac, Merck Sharp & Dohme, Novartis, Ocean Pharma, Pfizer, Regeneron, Sanofi, Takeda, UCB Pharma and Xenoport. M.A. has served as a consultant or paid speaker for clinical trials sponsored by AbbVie, Almirall, Amgen, AstraZeneca, Biogen, Boehringer Ingelheim, Celgene, Centocor, Eli Lilly and Com- pany, GSK, Hexal, Janssen, LEO Pharma, Medac, Merck, MSD, Novartis, Pfizer, UCB Pharma and Xenoport. D.T. has been an advisor for, received speaker's honoraria and grant support from, and participated in clinical trials for AbbVie, Almirall, Amgen, Biogen Idec, Bioskin, Boehringer Ingelheim, Celgene, Dignity, Dr Reddy's, Eli Lilly and Company, Galapagos, GlaxoSmithKline, LEO Pharma, Janssen-Cilag, Kymab, Merck Sharp & Dohme, Mundipharma, Morphosis, Novartis, Pfizer, Regeneron, Samsung, Sanofi-Genzyme, Sandoz and UCB Pharma. A.P. has worked as an investigator, speaker and/or advisor for AbbVie, Almirall-Hermal, Amgen, Biogen Idec, Boehringer Ingelheim, Celgene, GSK, Eli Lilly and Company, Galderma, Hexal, Janssen, LEO Pharma, Medac, Merck Serono, Mitsubishi, MSD, Novartis, Pfizer, Regeneron, Roche, Sandoz Biopharmaceuticals, Schering-Plough, Tigercat Pharma and UCB Pharma. U.M. has been an advisor for, received speakers honoraria and/or grants from, and/or participated in clinical trials for Abbott/AbbVie, Almirall-Hermal, Amgen, Biogen Idec, Boehringer Ingelheim, Celgene, Centocor, Eli Lilly and Company, Foamix, Forward Pharma, Janssen, LEO Pharma, Medac, Miltenyi Biotech, MSD, Novartis, Pfizer, VBL and Xenoport. A.L., C.H., E.S., A.S. and M.D. were employees of and minor stockholders in Eli Lilly and Company during the conduct of this study."

Risk of bias

Bias	Authors' judgement	Support for judgement

Reich 2020 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote (p 870): "Patients were randomized 1:1:1 to FAEs, methotrexate or ixekizumab via an interactive web response system." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 870-871):"To ensure that FAE and methotrexate treatments were given according to labels and according to clinical practice (e.g. dose adjustment due to adverse events), the study was conducted open-label. Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (p 871): "Both patients and investigators were unblinded to treatment allocation." Comment: open-label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (p 871): "A blinded rater assessed all clinical outcome measures to minimize bias for the clinical efficacy assessments of each treatment arm". Comment: No clear description of the process followeed to guarantee the blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: quote (p. 871) "Non- responder imputation was used to impute patients with missing data. Continuous end points were tested using ANCOVA with terms for treatment and baseline. Modified imputation using the baseline observation carried forward was used to impute missing values: patients who discontinued due to adverse events were imputed with their baseline observation." Randomised 162, analysed 162 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. Results are posted on ClinicalTrials.gov.

ReSURFACE-1 2017

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

ReSURFACE-1 2017 *(Continued)*

- 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%): tildrakizumab 200 (10), tildrakizumab 100 (9), PBO (9)
- Lost to follow-up: tildrakizumab 200 (1), tildrakizumab 100 (2), PBO (1)
- AEs: tildrakizumab 200 (5), tildrakizumab 100 (0), PBO (0)
- Lack of efficacy: tildrakizumab 200 (0), tildrakizumab 100 (1), PBO (2)
- Participant: tildrakizumab 200 (2), tildrakizumab 100 (3), PBO (3)
- Protocol deviation: tildrakizumab 200 (1), tildrakizumab 100 (0), PBO (1)
- Physician decision: tildrakizumab 200 (0), tildrakizumab 100 (3), PBO (1)
- Pregnancy: tildrakizumab 200 (1), tildrakizumab 100 (0), PBO (0)
- Disease progression: tildrakizumab 200 (0), tildrakizumab 100 (0), PBO (1)

Interventions	**Intervention** 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 source Quote (p 276): "Funding Merck & Co" Declarations of interest

ReSURFACE-1 2017 *(Continued)*

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 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

ReSURFACE-1 2017 *(Continued)*

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 nonresponders (nonresponder 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.

ReSURFACE-2 2017

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

ReSURFACE-2 2017 *(Continued)*

- 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%): tildrakizumab 200 (14), tildrakizumab 100 (12), ETA (24), PBO (14)
- Lost to follow-up: tildrakizumab 200 (1), tildrakizumab 100 (2), ETA (3), PBO (3)
- AEs: tildrakizumab 200 (2), tildrakizumab 100 (1), ETA (5), PBO (2)
- Lack of efficacy: tildrakizumab 200 (1), tildrakizumab 100 (0), ETA (0), PBO (2)
- Drug non-compliance: tildrakizumab 200 (1), tildrakizumab 100 (0), ETA (0), PBO (0)
- Participant: tildrakizumab 200 (5), tildrakizumab 100 (7), ETA (6), PBO (5)
- Protocol deviation: tildrakizumab 200 (2), tildrakizumab 100 (1), ETA (0), PBO (1)
- Physician decision: tildrakizumab 200 (0), tildrakizumab 100 (0), ETA (4), PBO (0)
- Pregnancy: tildrakizumab 200 (0), tildrakizumab 100 (1), ETA (1), PBO (0)
- Disease progression: tildrakizumab 200 (0), tildrakizumab 100 (0), ETA (1), PBO (0)
- Others: tildrakizumab 200 (2), tildrakizumab 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)** • 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 source Quote (p 276): "Funding Merck & Co" Declarations 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

ReSURFACE-2 2017 *(Continued)*

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 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 (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

ReSURFACE-2 2017 *(Continued)*

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 nonresponders (nonresponder 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.

REVEAL 2008

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study Date of study: December 2004-August 2007 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 outcome**

REVEAL 2008 *(Continued)*

- PASI 75

Secondary outcomes

- 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 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".

REVEAL 2008 *(Continued)*

		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.

Rich 2013

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study 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 • Nonresponse to topical treatment • Nonresponse to phototherapy • Nonresponse to conventional systemic treatment **Exclusion criteria** • 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

Rich 2013 *(Continued)*

	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 outcome** • PASI 75 **Secondary outcomes** • PASI 75 20/28 weeks • IGA 12 weeks • PASI 90 12 weeks
Notes	Funding source 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
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 404): “Patients, investigator staff, persons performing the assessments and data analysts were blinded to the identity of treatment from the time of randomisation until primary outcome analysis”. Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 404): “Patients, investigator staff, persons performing the assessment and data analysts were blinded to the identity of treatment from the time of randomisation until primary outcome analysis”. Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	404 included/404 analysed Quote (p 405): "Following the intent-to-treat principle, data were analysed... Missing values were replaced using the last-observation-carried-forward approach".

Rich 2013 *(Continued)*

		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 study 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) **Control intervention** B. Placebo, orally, daily, 8 weeks (n = 40)
Outcomes	Assessments at 8 weeks **Primary outcomes** • PASI **Secondary outcomes** • Side effects
Notes	Funding source: not stated Declarations of interest: not stated

Ruzicka 1990 *(Continued)*

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 study 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**

Sandhu 2003 *(Continued)*

- 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
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 study 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/week, daily, 10 weeks **Control intervention** B. 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** • Not clearly stated **Outcomes** • Change in PASI • Time to clear • AEs
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 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

Saurat 1988 *(Continued)*

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: no 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.

SCULPTURE 2015

Study characteristics	
Methods	RCT, active-controlled, double-blind study 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) **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**

SCULPTURE 2015 *(Continued)*

	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 outcome** • PASI 75 **Secondary outcomes** • PASI 50/75/90 at 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 Corporation, and Vichy. Dr Regnault, Ms Thurston, and Dr Papavassilis are employees of and/or own stock in Novartis. Dr Balki has no conflicts of interest to declare."

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)	Low risk	Quote (p 28): "administered via 2 150 mg SC injections or one 150 mg SC and one placebo SC injection respectively"

SCULPTURE 2015 *(Continued)*

All outcomes		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 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 (NCT01406938). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported.

Seo 2020

Study characteristics	
Methods	RCT, placebo-controlled, double blind, parallel arms study Date of study: January 2017-August 2018 Location: Korea (10 sites)
Participants	**Randomised**: 62 participants **Inclusion criteria** • Ages eligible: 20 to 85 years • Subject has had stable moderate to severe plaque psoriasis for at least 6 months • Subject has involved BSA ≧ 10%, PASI ≧ 12, and sPGA ≧ 3 at screening and at baseline **Exclusion criteria** • Subject 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 • Subject scheduled to undergo a surgical intervention during the study period • Subject has any active infection or history of infections as defined in the study protocol • Subject has known history of Crohn's disease • Subject has any other significant concurrent medical condition or laboratory abnormalities, as defined in the study protocol • Subject has not stopped using certain psoriasis therapies as defined in the study protocol • Subject has previously used any anti-IL-17 biologic therapy • Subject is 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 • Subject has known history or evidence of suicidal ideation (severity of 4 or 5) or any suicidal behavior based on an assessment with the Columbia-Suicide Severity Rating Scale (C-SSRS) at screening or at baseline • Subject has severe depression based on a total score of ≥ 15 on the Patient Health Questionnaire-8 (PHQ-8) at screening or at baseline • Subject has known history or evidence of a psychiatric disorder that, in the opinion of the investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion

Seo 2020 *(Continued)*

- Subject has known history of alcohol and/or substance abuse within the last 12 months

Baseline characteristics

N = 62, mean age of 44 years and 61% men

Dropouts and withdrawals

17/62 (27.5%); placebo (8), brodalumab (9)

- Eligibility criteria: placebo (2), brodalumab (0)
- Withdrawal consent: placebo (4), brodalumab (6)
- Private reasons: placebo (1), brodalumab (0)
- Removal criteria: placebo (0), brodalumab (2)
- AEs: placebo (1), brodalumab (1)

Interventions	**Intervention** A. Brodalumab 210 mg SC injection at weeks 1, 2, 4, 6, 8, 10, and Q2W thereafter, until week 62, n= 40 **Control intervention** B. Placebo SC injection at weeks 1, 2, 4, 6, 8, 10, and Q2W thereafter, until week 62, n = 22
Outcomes	**At week 12** **Primary outcomes** • PASI 75 • sPGA of "0 (clear)" or "1 (almost clear)" **Secondary outcomes** • PASI 50/75/90/100 at week 64 • sPGA of "0 (clear)" or "1 (almost clear)" at week 64 • BSA at week 64 • Nail psoriasis severity index (NAPSI) score at week 64 • Psoriasis scalp severity index (PSSI) score at week 64 • DLQI at week 64 • Treatment-emergent adverse events (TEAEs) or drug-related TEAEs at week 64 • Laboratory values at week 64 • Vital signs at week 64 • Anti-KHK4827 antibodies at week 12, 24, 48, 64 • Serum KHK4827 concentration at week 12, 24, 48, 64
Notes	Funding source: Quote (p 816) "funded by Kyowa Kirin Korea Co., Ltd." Declarations of interest: Quote (p 816) "Haeyoun Jeong is a full-time employee of Kyowa Kirin Korea Co., Ltd. The other authors 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 808) "This phase III, randomized, multicenter study consisted of a 12-week double-blind phase followed by a 52-week open-label extension phase... patients were randomized to receive brodalumab 210 mg Q2W or placebo for 12 weeks at a 2:1 ratio and were stratified by bodyweight at screening (≤ 70 kg, > 70 kg), prior use of biologic agents, and investigative site. Randomization was performed through a dynamic allocation procedure using an IWRS. The IP

Seo 2020 *(Continued)*

		was administrated after coordination with the IWRS vendor, Cenduit, an IQVIA business (Durham, NC, USA)." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 808) "This phase III, randomized, multicenter study consisted of a 12-week double-blind phase followed by a 52-week open-label extension phase... patients were randomized to receive brodalumab 210 mg Q2W or placebo for 12 weeks at a 2:1 ratio and were stratified by bodyweight at screening (≤ 70 kg, > 70 kg), prior use of biologic agents, and investigative site. Randomization was performed through a dynamic allocation procedure using an IWRS. The IP was administrated after coordination with the IWRS vendor, Cenduit, an IQVIA business (Durham, NC, USA)." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (p 808) "This phase III, randomized, multicenter study consisted of a 12-week double-blind phase followed by a 52-week open-label extension phase..." Comment: No description of the method used to guarantee blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (p 808) "This phase III, randomized, multicenter study consisted of a 12-week double-blind phase followed by a 52-week open-label extension phase..." Comment: No description of the method used to guarantee blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (p 810) "The populations analyzed were the FAS, which included all randomized patients; the PPS, which included all patients in the FAS but excluded those who had received no treatment, had no post-dosing primary efficacy data available, failed to meet major eligibility criteria, or had major protocol deviations ... investigative site to examine the treatment difference in the PASI 75 response and sPGA success at week 12 using the last observation carried forward method or non-responder imputation method for missing data." Randomised 62, analysed 62 Note high rate of dropout: 27%
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT02982005). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. No results are posted on ClinicalTrials.gov.

Shehzad 2004

Study characteristics	
Methods	RCT, active-controlled, open-label study Date of study: March 2001-November 2001 Location: 1 centre in Karachi, Pakistan

Shehzad 2004 *(Continued)*

Participants	**Randomised**: 40 participants (age from 18-50 years, % male unknown) **Inclusion criteria** • 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 outcome** • PASI 75 **Secondary outcomes** • 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)	High risk	Comment: not blinded

Shehzad 2004 *(Continued)*
All outcomes

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

SIGNATURE 2019

Study characteristics	
Methods	RCT, active-controlled, double-blind study (SIGNATURE) Date of study: October 2013-July 2016 Location: UK-Ireland (53 centres)
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 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

SIGNATURE 2019 *(Continued)*

- 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

Baseline characteristics

N = 235, mean of age 46 years and 56% men

Dropouts and withdrawals

- 25/235 (10.6%): secukinumab 150 group (13), secukinumab 300 group (12)
- Death: secukinumab 150 group (1), secukinumab 300 group (0)
- Lack of efficacy: secukinumab 150 group (1), secukinumab 300 group (2)
- Participant decision: secukinumab 150 group (2), secukinumab 300 group (1)
- Lost to follow-up: secukinumab 150 group (2), secukinumab 300 group (3)
- Protocol deviation: secukinumab 150 group (0), secukinumab 300 group (1)
- AEs: secukinumab 150 group (5), secukinumab 300 group (3)
- Others: secukinumab 150 group (2), secukinumab 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 source: Quote (p 60) "This study was funded by Novartis Pharmaceuti- cals U.K. Ltd." Declarations of interest: Quote (p 60-61) "R.B.W. has received honoraria and/or research grants from AbbVie, Almirall, Bristol-Myers Squibb, Celgene, Janssen, Leo, Lilly, MSD, Novar- tis, Sun, Xenoport and UCB Pharma. J.N.W.B. has received honoraria and/or research grants from AbbVie, Almirall, Bristol-Myers Squibb, Celgene, Janssen, Leo, Lilly, Novartis, Samsung, Sun and UCB Pharma. A.Y.F. is joint copyright owner of the Dermatology Life Quality Index (Cardiff University) and A.Y.F. receives royalties from this. A.Y.F. has also received honoraria for lecturing and consultancy from Lilly, Novartis and Sanofi. A.D.B. has received honoraria for lecturing and consultancy from AbbVie, Almirall, Boehringer Ingelheim, Celgene, Leo, Lilly, Novartis, Janssen and UCB Pharma. B.K. has received honoraria and research grants from AbbVie, Almirall, Cel- gene, Janssen, Leo, Lilly, MSD, Novartis and UCB Pharma. Y.A., R.W., C.H. and S.K. are all employees of Novartis Pharmaceuticals U.K. Ltd. C.E.M.G. has received honoraria and/or research grants from AbbVie, Almirall, Bristol-Myers Squibb, Celgene, Galderma, Janssen, Leo, Lilly, MSD, Novartis, Sandoz and UCB Pharma. C.E.M.G. is also a National Institute for Health Research Senior Investigator."

Risk of bias

Bias	Authors' judgement	Support for judgement

SIGNATURE 2019 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote (p 61): "Patients were randomized in a 1: 1 ratio to receive either secukinumab 300 mg or secukinumab 150 mg using an Interactive Response Technology randomization system." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 61): "Patients were randomized in a 1: 1 ratio to receive either secukinumab 300 mg or secukinumab 150 mg using an Interactive Response Technology randomization system." Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (p61): "This was a 72-week, multicentre, open-label, noncomparator study". Comment: not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (p61): "This was a 72-week, multicentre, open-label, noncomparator study". Comment: not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: quote (p62)"Missing values for the response variables based on a 'period-wise' analysis for PASI were imputed with nonresponse imputation (NRI), regardless of the reason for the missing data. Analyses were based on the full analysis set (i.e. all treated patients who had a baseline PASI assessment and at least one post-baseline PASI assessment)." Reasonable rate of withdrawal (10%) and number and reason comparable between groups Randomised 235, analysed 233
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. ClinicalTrials.gov: ITT analyses

Singh 2021

Study characteristics	
Methods	RCT, active-controlled, non-blinded study Date of study: August 2018-July 2019 Location: India (single centre)
Participants	**Randomised:** 140 partcipants **Inclusion criteria** • Adult patients of 18-65 years of age • Chronic plaque psoriasis with PASI > 10 • Cumulative MTX dose < 1.5 gram and were not taking systemic immunosuppressants for 1 month and topical immunosuppressant for 2 weeks prior to enrolment

Singh 2021 *(Continued)*

Exclusion criteria

- Pregnancy or lactation
- History of alcoholism or taking hepatotoxic or nephrotoxic drugs
- Hypertension defined as ≥140 mm systolic and ≥ 90 mm diastolic at baseline or rise in BP to ≥ 150 mm systolic and ≥ 100 mm diastolic during the study in two consecutive visits after the addition of amlodipine 5 mg
- Haemoglobin < 8 gram/dL, TLC < 4000 cells/mm^3, platelet count < 1 lakh/mm^3, lymphocytes < 1500 cells/ mm^3, raised aminotransferases ≥ twice the upper limit of normal at baseline and ≥ thrice the upper limit at follow-up, raised total bilirubin > 1.2 or 30% increase of baseline, serum creatinine values of > 1.4 mg/dL at baseline or more than 30% increase in baseline at two consecutive visits
- Tuberculosis and immunosuppression or any chronic disease, peptic ulcers, any reliable sign of infection and an unreliable patient

Baseline characteristics

N = 140, mean of age 38 years and 73% men

Dropouts and withdrawals

- 18/140 (13%) methotrexate (8), cyclosporine (10)
- Lost to follow-up: methotrexate (4), cyclosporine (3)
- AEs: methotrexate (4), cyclosporine (7)

Interventions	**Intervention** A. Methotrexate 0.15 mg/kg/week intramuscular injection + cyclosporine 2.5 mg/kg/day, n = 70 **Control intervention** B. Methotrexate 0.3 mg/kg/week intramuscular injection, n = 70
Outcomes	At week 12 **Primary outcome** • PASI 75 **Secondary outcomes** • PASI 50/90/100 • AEs
Notes	Funding source: Quote (p 221) "Nil" Declarations of interest: Quote (p 221) "There are no conflicts of interest."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 215) "The study was a non-blinded trial. Participants were randomised equally in a 1:1 allocation (unstratified) into two treatment groups by a computer generated random number sequence using the MS Excel software." Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Quote (p 215) "The study was a non-blinded trial. Participants were randomised equally in a 1:1 allocation (unstratified) into two treatment groups

Singh 2021 *(Continued)*

		by a computer generated random number sequence using the MS Excel software." Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (p 215) "The study was a non-blinded trial. Participants were randomised equally in a 1:1..." Comment: not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (p 215) "The study was a non-blinded trial. Participants were randomised equally in a 1:1..." Comment: not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dealing with missing data: quote (p 216) "The analysis for adverse effects included all patients excluding the ones who were lost to follow-up. Per-protocol analysis was initially done. The parameters found to be significant were also subjected to intention to treat analysis (ITT)." Randomised 140, analysed 140 Comment: no description of the method used to guarantee management of missing data
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was not available on ClinicalTrials.gov but on CTRI (CTRI/2018/07/015044). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported.

Sommerburg 1993

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study 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%)

Sommerburg 1993 *(Continued)*

- 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 outcome** • PSI **Secondary outcome** • PSI 75
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 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

Sommerburg 1993 *(Continued)*

		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.

Strober 2011

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study 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
	• 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** • PASI 75 • PGA 0/1 **Secondary outcomes** At 4, 8, 12 weeks • PASI 50 • PASI 75 • PASI 90 • DLQI • PGA • Safety

Strober 2011 *(Continued)*

- 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) All outcomes	Low risk	Quote (p 662): “Patients enrolled in the placebo arm received SC injections matching active treatment to maintain the blind. To maintain the blind, all patients received two SC injections at weeks 0 and 4 and one SC injection at week 8, consisting of either briakinumab or matching placebo, depending on the treatment arm. In addition, each patient also received two SC injections biweekly, 3 days apart, week 0 through week 11, consisting of either etanercept or matching placebo, depending on the treatment arm.” Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 662): “Patients enrolled in the placebo arm received SC injections matching active treatment to maintain the blind. To maintain the blind, all patients received two SC injections at weeks 0 and 4 and one SC injection at week 8, consisting of either briakinumab or matching placebo, depending on the treatment arm. In addition, each patient also received two SC injections biweekly, 3 days apart, week 0 through week 11, consisting of either etanercept or matching placebo, depending on the treatment arm.” Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomly assigned 211, analysed 211 Management of missing data: Quote (p 663): “The primary efficacy analysis consisted of four comparisons 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).

Strober 2011 *(Continued)*

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

STYLE 2020

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study Date of study: May 2017-January 2019 Location: 13 sites in Canada and 28 sites the USA Phase 3
Participants	**Randomised**: 303 participants **Inclusion criteria** • Patients aged ≥ 18 years with moderate-to-severe plaque psoriasis of the scalp, defined as Scalp Physician Global Assessment (ScPGA) score ≥ 3, psoriasis-involved scalp surface area (SSA) ≥ 20% • Inadequate response or intolerance to ≥ 1 topical therapy for plaque psoriasis of the scalp • Moderate-to-severe plaque psoriasis, defined as PASI score ≥ 12, BSA ≥ 10%, and sPGA ≥ 3 **Exclusion criteria** • Current or planned concurrent use of topical therapies (including medicated shampoos, coal tar, and salicylic acid preparations) within 2 weeks, or conventional systemic therapy for psoriasis within 4 weeks • Intralesional corticosteroids on the scalp within 2 weeks • Phototherapy treatment of body or scalp lesions within 4 weeks • Use of biologics within 12 to 24 weeks • Prolonged sun or ultraviolet light exposure **Baseline characteristics** N = 303, mean age of 46.9 years and 62% men **Dropouts and withdrawals** • 51/303 (17%): apremilast group (33), placebo group (18) • AEs: apremilast group (8), placebo group (3) • Lack of efficacy: apremilast group (4), palcebo group (3) • Withdrawal by subject: apremilast group (16), placebo group (6) • Lost to follow-up: apremilast group (3), placebo group (1) • Non-compliance with study drug: apremilast group (0), placebo group (3) • Protocol deviation: apremilast group (1), placebo group (2) • Miscellaneous: apremilast group (1), placebo group (0)
Interventions	**Intervention** A. Apremilast 30 mg tablets orally twice a day for 16 weeks **Control intervention** B. Placebo tablets twice a day for 16 weeks
Outcomes	At week 16

STYLE 2020 *(Continued)*

Primary composite outcome

- Percentage of participants with Scalp Physician Global Assessment (ScPGA) score of clear (0) or almost clear (1)

Secondary outcomes

- Percentage of participants with ≥ 4-point reduction (improvement) from baseline in the whole body itch numeric rating score (NRS) and scalp itch NRS scores
- Change from baseline in DLQI total score
- Number of participants with treatment emergent adverse events (TEAE)
- Proportion of participants with sPGA of 0 (clear) or 1 (almost clear) with a ≥ 2-point reduction from baseline
- Percentage change from baseline in BSA
- Percentage change from baseline in PASI score

Notes

Funding source

Quote (p 2): "The authors acknowledge financial support for this study from Celgene Corporation. The authors received editorial support in the preparation of this report from Amy Shaberman, PhD, of Peloton Advantage, LLC, an OPEN Health company, Parsippany, NJ, USA, sponsored by Celgene Corporation, Summit, NJ, USA. The authors, however, directed and are fully responsible for all content and editorial decisions for this report."

Declarations of interests

Quote (p 3-4): "ASVV: AbbVie, Allergan, Celgene Corporation, Derm Tech, Dermira, Novartis, and Valeant – honoraria for advisory board and/or consulting; Merck – pension (ex-spouse). LSG: Celgene Corporation, LEO Pharma, Novartis, Pfizer, and Stiefel/GlaxoSmithKline – investigator and/or consultant. ML: Mount Sinai (which receives funds from Boehringer Ingelheim, Celgene Corporation, Eli Lilly, Janssen/Johnson & Johnson, Kadmon, MedImmune/AstraZeneca, Novartis, Pfizer, and ViDac). BS: AbbVie, Almirall, Amgen, Arena, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene Corporation, Dermavant, Dermira, Eli Lilly, GlaxoSmithKline, Janssen, Kyowa Hakko Kirin, LEO Pharma, Medac, Meiji Seika Pharma, Menlo Therapeutics, Novartis, Ortho Dermatologics/Valeant, Pfizer, Regeneron, Sanofi-Genzyme, Sebela Pharmaceuticals, Sun Pharma, and UCB Pharma – honoraria as a consultant and advisory board member; AbbVie, Boehringer Ingelheim, Celgene Corporation, Eli Lilly,Galderma, GlaxoSmithKline, Janssen, Merck, Pfizer, and Sienna – payments (to the University of Connecticut) as an investigator; Corrona Psoriasis Registry – fees as a scientific director; AbbVie and Janssen – grant support (to the University of Connecticut for Fellowship Program). CL: AbbVie, Boehringer Ingelheim, Celgene Corporation, Eli Lilly, Janssen, Merck, Novartis, Pfizer, Sun Pharma, and Valeant – principal investigator/consultant. ST: No conflicts or potential conflicts of interest to disclose. AC: AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Celgene Corporation, Dermira, Eli Lilly, Janssen, Maruho, Novartis, Pfizer, Stiefel/ GlaxoSmithKline, Sun Pharma, and UCB – investigator; Celgene Corporation – consultant. HS: Celgene Corporation, Janssen, Lilly, and Novartis – grants received as an investigator. ZZ, MP, & YW: Celgene Corporation – employment."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 9): "For the placebo-controlled phase, study personnel randomized patients (2:1), using a permuted block randomization and centralized interactive response technology, to receive apremilast 30 mg BID or placebo for 16 weeks." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 9): "For the placebo-controlled phase, study personnel randomized patients (2:1), using a permuted block randomization and centralized interactive response technology, to receive apremilast 30 mg BID or placebo for 16 weeks."

STYLE 2020 *(Continued)*

		Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 9): "The study sponsor, site, contract research organization (CRO) personnel, and patients were blinded to treatment allocation through week 16". Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 9): "The study sponsor, site, contract research organization (CRO) personnel, and patients were blinded to treatment allocation through week 16". Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Randomly assigned 303, analysed 303 Management of missing data: Quote (p 9, 10): "missing values at week 16 were imputed using the MI method... Primary and secondary endpoints were analyzed in the intent-to-treat (ITT) population, defined as all randomized patients." Results for PASI and PGA were reported in supplementary appendix. Comment: number of analysed pateints not reported for PGA and PASI
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT03123471). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. Results are posted on ClinicalTrials.gov.

SustaIMM 2019

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind study Date of study: December 2016-September 2017 Location: multicentre, Japan Phase 2/3
Participants	**Randomised**: 182 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

SustaIMM 2019 *(Continued)*

	Baseliene characteristics N = 171, mean of age years 52 and 84% men **Dropouts and withdrawals** • 7/171 (4%): risankizumab 150 group (1), risankizumab 75 group (2), placebo group (4) • Disease worsening: risankizumab 150 group (1), risankizumab 75 group (2), placebo group (4)
Interventions	**Intervention** A. Risankizumab 150 mg by SC injection at Weeks 0 and 4 (Part A), n = 55 **Control interventions** 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 source: Quote (p 693)"AbbVie and Boehringer Ingelheim funded the SustaIMM (NCT03000075) study..." Declarations of interest: Quote (p 693) "The authors and AbbVie scien- tists designed the study and analyzed and interpreted the data. All authors contributed to the development of the content, all authors and AbbVie reviewed and approved the manuscript, and the authors main- tained control over the final content. M. O. has received honoraria or fees for serving on advisory boards, as a speaker and as a consultant, and grants as an investigator from AbbVie, Celgene, Eisai, Eli Lilly and Com- pany, Janssen, LEO Pharma, Maruho, Mitsubishi-Tanabe, Novartis and Torii. H. F. has received honoraria or fees for serving on advisory boards and as a speaker and grants as an investigator from AbbVie, Celgene, Eisai, Eli Lilly and Company, Janssen, Kyowa Hakko Kirin, LEO Pharma, Maruho, Mitsubishi-Tanabe, Novartis, Taiho and Torii. M. W., K. S. and M. F. are full-time employees of Boehringer Ingelheim. X. H., S. K. and J. V. are full-time employees of AbbVie and may own stock/options. A. I. has received honoraria or fees for serving on advisory boards, as a speaker and as a consultant, and grants as an investigator from AbbVie, Celgene, Eli Lilly, Janssen, Kyowa Hakko Kirin, Maruho and Novartis."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 687): "In this double-blinded, placebo-controlled, two-part study of risankizumab, patients were randomized 2:2:1:1 to receive risankizumab 75 mg, risankizumab 150 mg, placebo with cross-over to risankizumab 75 mg or placebo with cross-over to risankizumab 150 mg. Randomization was stratified according to concomitant psoriatic arthritis at baseline (yes vs no) and body-weight (≤ 90 vs > 90 kg)." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 687): "In this double-blinded, placebo-controlled, two-part study of risankizumab, patients were randomized 2:2:1:1 to receive risankizumab 75 mg, risankizumab 150 mg, placebo with cross-over to risankizumab 75 mg or placebo with cross-over to risankizumab 150 mg. Randomization was stratified

SustaIMM 2019 *(Continued)*

		according to concomitant psoriatic arthritis at baseline (yes vs no) and body-weight (≤ 90 vs > 90 kg)." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (p 687): "In this double-blinded, placebo-controlled, two-part study of risankizumab, patients were randomized 2:2:1:1 to receive risankizumab 75 mg, risankizumab 150 mg, placebo with cross-over to risankizumab 75 mg or placebo with cross-over to risankizumab 150 mg." Comment: no description of the method used to guarantee blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (p 687): "In this double-blinded, placebo-controlled, two-part study of risankizumab, patients were randomized 2:2:1:1 to receive risankizumab 75 mg, risankizumab 150 mg, placebo with cross-over to risankizumab 75 mg or placebo with cross-over to risankizumab 150 mg." Comment: no description of the method used to guarantee blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (p 688): "For all non-binary end-points, last observation carried forward was used for missing data. For all binary end-points, missing data were imputed as non-response." Randomised 171, analysed 171
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT03000075). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. Results posted on ClinicalTrials.gov: ITT

Tanew 1991

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study 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)

Tanew 1991 *(Continued)*

- 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 **Primary and secondary outcomes of the trial** • Not defined **Outcomes of the trial** • Complete remission • Side effects
Notes	Funding source: 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 (p. 682): "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 (p. 682): "Acitretin ... or placebo..." Comment: no description of the method used to guarantee blinding of participants and personnel as acitretin leads to visible adverse effects (cheilitis).
Incomplete outcome data (attrition bias) All outcomes	High risk	Randomly assigned 60, analysed 48 Quote (p 683): "Of the 60 patients, 48 completed the study and were included in the statistical analysis". Comment: not ITT
Selective reporting (reporting bias)	Unclear risk	No protocol available, no outcomes defined in the Method section

Thaci 2021

Study characteristics	
Methods	RCT, active-controlled, open-label study with blinded assessment of the efficacy outcome Date of study: August 2017-July 2018 Location: Germany (21 sites) Phase 3
Participants	**Randomised**: 120 participants **Inclusion criteria** • Have a diagnosis of chronic plaque psoriasis for at least 6 months before the first administration of study drug. Duration since diagnosis may be reported by the participant. • Participant has stable moderate-to-severe plaque psoriasis (body surface area [BSA] > 10, Psoriasis Area and Severity Index [PASI] > 10, and Dermatology Quality of Life Index [DLQI] > 10) with or without psoriatic arthritis at baseline • Must be naïve to and candidate for systemic therapy, as assessed by the investigator • Participant has an inadequate response, intolerance or contraindication to topical psoriasis treatment **Exclusion criteria** • Patients with non-plaque forms of psoriasis • Patient has previously received systemic therapy for psoriasis, whether biologic or non-biologic or photochemotherapy • Active systemic infection during the last 2 weeks (exception: common cold) prior to screening • 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 • Patient has any condition or contraindication to fumaderm that would preclude their participation in the present study **Baseline characteristics** N = 120, mean age of 42 years and 59% men **Dropouts and withdrawals** • 13/120 (11%): risankizumab group (0), Fumaderm 300 group (13) • AEs: risankizumab group (0), Fumaderm 300 group (3) • Lost to follow-up: risankizumab group (0), Fumaderm 300 group (2) • Withdrawal by subject: risankizumab group (0), Fumaderm 300 group (2) • Other: risankizumab group (0), Fumaderm 300 group (6)
Interventions	**Intervention** A. Risankizumab 150 mg by subcutaneous injection at weeks 0, 4, and 16, n = 60 **Control intervention** B. Fumaderm 30 mg administered as a tablet orally once daily from week 0 to week 2, then up to 240 mg, n = 60
Outcomes	At week 24 **Primary outcome**

Thaci 2021 *(Continued)*

- PASI 90

Secondary outcomes

- PASI 50, PASI 75, PASI 100 (at weeks 4, 8, 12, 16, 20 and 24)
- BSA (at weeks 4, 8, 12, 16, 20 and 24)
- SF-36, EQ-5D-5L (at weeks 16 and 24)
- PGA (at weeks 4, 8, 12, 16, 20 and 24)
- PSS (at weeks 16 and 24)
- Psoriasis Scalp Severity Index (PSSI) (at weeks 16 and 24)
- Patient Benefit index (at weeks 16 and 24)
- Clinical Severity of Nail Psoriasis (NAPPA-CLIN) (at weeks 16 and 24)
- Palmoplantar Psoriasis Severity Index (PPASI) (at weeks 16 and 24)
- DLQI (at weeks 16 and 24)
- Nail Psoriasis Severity Index (NAPSI) (at weeks 16 and 24)

Notes	Funding source: Quote (article) "AbbVie Inc. funded the research for this study and participated in the study design". Declarations of interest: Quote (article)"DT: received grant/research support from AbbVie Inc., Celgene, Novartis; has participated in a speakers bureau for AbbVie Inc., Amgen, Almirall, Biogen-Idec, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Galapagos, Janssen-Cilag, LEO Pharma, Morphosis, Novartis, Pfizer, Regeneron Pharmaceuticals, Sandoz/Hexal, Sanofi, and UCB Pharma; and has served as a consultant/member of scientific board for AbbVie Inc., Almirall, Celgene, Eli Lilly, Janssen-Cilag, LEO Pharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Sandoz/Hexal, Sanofi, and UCB Pharma. KE:Served as a speaker, investigator, and/or advisor for AbbVie Inc., Almirall, Berlin Chemie, BMS, Boehringer Ingelheim, Celgene, Eli Lilly, Galapagos, Hexal, Janssen, Novartis, Sanofi, and UCB Pharma. AP: Served as an investigator, grant recipient, advisor/consultant, and/or speaker for AbbVie Inc., Almirall-Hermal, Amgen, Biogen Idec, Boehringer Ingelheim, Celgene, Eli Lilly, Galderma, GSK, Hexal, Janssen, LEO Pharma, MC2, Medac, Merck Serono, Mitsubishi, MSD, Novartis, Pascoe, Pfizer, Regeneron Pharmaceuticals, Roche, Sandoz Biopharmaceuticals, Schering-Plough, Tigercat Pharma, and UCB Pharma."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (article) "Patients were randomly assigned via interactive response/web response technology using block randomization and a randomization schedule prepared by the statistics department of the sponsor. Randomization was stratified by prior phototherapy exposure.'' Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (article)"Patients were randomly assigned via interactive response/web response technology using block randomization and a randomization schedule prepared by the statistics department of the sponsor. Randomization was stratified by prior phototherapy exposure." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (article): "This phase 3, randomized, active-controlled, multicenter, open-label study with blinded assessment of efficacy"

Thaci 2021 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (article) "This phase 3, randomized, active-controlled, multicenter, open-label study with blinded assessment of efficacy" Comment: no description of method used to guarantee no communication between participants and assessors.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dealing with missing data: Quote (article): "Missing efficacy data were imputed using non-responder imputation (NRI) for categorical endpoints and last observation carried forward for continuous endpoints. An as-observed case (OC) analysis was used as a secondary approach in the analysis of continuous endpoints and did not impute values for missing evaluations (e.g. those patients who did not have an evaluation at a scheduled visit were excluded from the OC analysis for that visit)." Randomisd 120, analysed 120 Comment: probably done
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT03255382). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. Results are posted on ClinicalTrials.gov.

Torii 2010

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study 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** • 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**

Torii 2010 *(Continued)*

	B. Placebo (n = 19), IV, weeks 0, 2, 6; 10 weeks
Outcomes	Assessments at 10 weeks **Primary outcome** • PASI 75 **Secondary outcomes** • PASI 50 • DLQI • PGA • AE
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 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
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.

TRANSFIGURE 2016

Study characteristics	
Methods	RCT, active-controlled, double-blind study Date of study: November 2013-January 2017 Location: worldwide Phase 3
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% • 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%): secukinumab 150 (4), secukinumab 300 (1), PBO (7) • Lost to follow-up: secukinumab 150 (1), secukinumab 300 (0), PBO (0) • AEs: secukinumab 150 (2), secukinumab 300 (0), PBO (0) • Lack of efficacy: secukinumab 150 (0), secukinumab 300 (0), PBO (2) • Participant: secukinumab 150 (0), secukinumab 300 (1), PBO (3) • Protocol deviation: secukinumab 150 (1), secukinumab 300 (0), PBO (1) • Physician decision: secukinumab 150 (0), secukinumab 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 **ControlIntervention** 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

TRANSFIGURE 2016 *(Continued)*

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 source

Quote (p 1): "Funding sources: This study was funded by Novartis Pharma AG, Basel, Switzerland."

Declarations of interest

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 re-randomized 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 re-randomized 1:1 to receive either 300 mg or 150 mg secukinumab." Comment: probably done

TRANSFIGURE 2016 *(Continued)*

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 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, randomised 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.

Tyring 2006

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study Date of study: June 2003–January 2004 Location: 39 centres in Houston, USA and Canada
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)

Tyring 2006 *(Continued)*

- 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 outcome** • PASI 75 **Secondary outcomes** • DLQI at 12w • PASI 50 • PASI 90 • the 17-item Hamilton rating scale for depression • Beck depression inventory
Notes	Funding source 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 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".

Tyring 2006 *(Continued)*

		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.

UltIMMa-1 2018

Study characteristics	
Methods	RCT, placebo/active-controlled, double-blind study Date of study: February 2016-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)

UltIMMa-1 2018 *(Continued)*

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

Interventions

Intervention

A. Risankizumab, S/C, 150 mg, n = 304

Control interventions

B. Ustekinumab, SC, 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

UltIMMa-1 2018 *(Continued)*

	C. Placebo, n = 102
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" Declarations 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 in-

UltIMMa-1 2018 *(Continued)*

vestigator 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
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Randomly assigned 506

UltIMMa-1 2018 *(Continued)*

		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.

UltIMMa-2 2018

Study characteristics	
Methods	RCT, placebo/active-controlled, double-blind study Date of study: March 2016-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 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

UltIMMa-2 2018 *(Continued)*

- 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, SC, 150 mg, n = 294 **Control interventions** B. Ustekinumab, SC, 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 • PGA 0/1 at week 52
Notes	Funding source

UltIMMa-2 2018 *(Continued)*

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

Declarations 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."

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

UltIMMa-2 2018 *(Continued)*

		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 nonresponder imputation and for continuous variables with last observation carried forward". Table 2: 491 analysed participants Comment: done
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.

Umezawa 2021

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind study Date of study: February 2017-January 2019 Location: Japan (33 centres) Phase 2/3
Participants	**Randomised**: 127 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. **Baseline characteristics** N = 127, mean age of 50 years and 62% men **Dropouts and withdrawals** • 7/127 (5.5%): certolizumab pegol 200 group (2), certolizumab pegol 400 group (2), placebo group (3) • AEs: certolizumab pegol 200 group (0), certolizumab pegol 400 group (1), placebo group (2) • Protocol violation: certolizumab pegol 200 group (1), certolizumab pegol 400 group (0), placebo group (0)

Umezawa 2021 *(Continued)*

- Withdrawal by participant: certolizumab pegol 200 group (1), certolizumab pegol 400 group (1), placebo group (1)

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, n = 48 **Control interventions** B. Certolizumab pegol SC injection 400 mg every 2 weeks (Q2W), n = 53 C. Placebo SC injection every 2 weeks (Q2W), n = 26
Outcomes	At week 16 **Primary outcome** • PASI 75 **Secondary outcomes** • PGA 0/1 • PASI 90 • DLQI • Itch Numeric Rating Scale (INRS)
Notes	Funding source: Quote (p 525) "This study was sponsored by UCB Pharma." Declarations of interest: Quote (p 525-526) "Yoshinori Umezawa hasreceived consulting agreements and/or speaker fees from Maruho Co. Ltd., AbbVie GK, Janssen Pharmaceutical K.K., Kyowa Hakko Kirin Co. Ltd., and UCB Japan Co., Ltd. Shinya Sakurai and Naoki Hoshii are employees of UCB Japan Co., Ltd. Hidemi Nakagawa has received consulting agreements, honoraria and/or speaker fees from Japan Tobacco Inc., LEO Pharma, Maruho Co. Ltd., Kyowa Hakko Kirin Co. Ltd., AbbVie GK, Mitsubishi-Tanabe Pharma, Torii Pharmaceuticals Co. Ltd., Janssen Pharmaceuticals K.K., Novartis Pharma K.K., Eli Lilly Japan K.K., Bristol-Myers Squibb, and UCB Japan Co., Ltd."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 515) "This was a phase 2/3, randomized, double- blind, placebo-controlled trial ...". "Following a 2–5 week screening period to confirm eligibility, an interactive response technology (IRT) was used to randomize patients 2:2:1 to CZP 400 mg every 2 weeks (Q2W), CZP 200 mg Q2W (with a loading dose of CZP 400 mg Q2W at weeks 0, 2, and 4), and placebo, according to the randomization schedule produced by the IRT vendor (stratified by prior biologic exposure [yes/no] and concurrent PsA [yes/no])." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 515) "This was a phase 2/3, randomized, double- blind, placebo-controlled trial ...". "Following a 2–5 week screening period to confirm eligibility, an interactive response technology (IRT) was used to randomize patients 2:2:1 to CZP 400 mg every 2 weeks (Q2W), CZP 200 mg Q2W (with a loading dose of CZP 400 mg Q2W at weeks 0, 2, and 4), and placebo, according to the randomization schedule produced by the IRT vendor (stratified by prior biologic exposure [yes/no] and concurrent PsA [yes/no])." Comment: probably done

Umezawa 2021 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (p 515) "This was a phase 2/3, randomized, double-blind, placebo-controlled trial ...". "All CZP and placebo treatments were administered subcutaneously at the study site by unblinded, trained site personnel not involved in any other study procedures." Comment: uncertainty on the possibility of this process to guarantee blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (p 515) "This was a phase 2/3, randomized, double-blind, placebo-controlled trial ...". "All CZP and placebo treatments were administered subcutaneously at the study site by unblinded, trained site personnel not involved in any other study procedures." Comment: uncertainty on the possibility of this process to guarantee blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (p 517) "For PASI and PGA outcomes, missing data were imputed using Markov chain Monte Carlo (MCMC) multiple imputation methodology.". "For DLQI and INRS change from baseline values, missing data were imputed using the last observation carried forward (LOCF) approach". Randomised 127; analysed 127
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (NCT03051217). The prespecified outcomes and those mentioned in the Methods section appeared to have been reported. Results are posted on ClinicalTrials.gov.

UNCOVER-1 2016

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study Date of study: November 2011-June 2014 Location: multicentre (104) in Europe, Australia, North America Phase 3
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)

UNCOVER-1 2016 *(Continued)*

- 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** • PGA 0-1 • PASI 75 **Secondary outcomes** • 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)	Low risk	Quote (p 346): “double-blind, placebo-controlled”

UNCOVER-1 2016 *(Continued)*

All outcomes		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.

UNCOVER-2 2015

Study characteristics	
Methods	RCT, active, placebo-controlled, double-blind study Date of study: May 2012- May 2015 Location: 118 centres in Europe, Australia, North America Phase 3
Participants	**Randomised**: 1224 participants (mean age 45 years, 821 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** • 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)

UNCOVER-2 2015 *(Continued)*

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** • PGA 0-1 • PASI 75 **Secondary outcomes** • 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

UNCOVER-2 2015 *(Continued)*

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

UNCOVER-3 2015

Study characteristics	
Methods	RCT, active, placebo-controlled, double-blind study Date of study: July 2012-January 2016 Location: 101 in Europe, Asia, North and South America Phase 3
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**

UNCOVER-3 2015 *(Continued)*

- 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), ixekizumab 2-week group (8), etanercept (4), placebo (2)
- Protocol violation: ixekizumab 4-week group (8), ixekizumab 2-week group (7), etanercept (3), placebo (1)
- Participant decision: ixekizumab 4-week group (4), ixekizumab 2-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), ixekizumab 2-week group (1), etanercept (2), placebo (1)
- Absence of efficacy: ixekizumab 4-week group (2), ixekizumab 2-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** • PGA 0-1 • PASI 75 **Secondary outcomes** • 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, No-

UNCOVER-3 2015 *(Continued)*

vartis, 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 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.

Van Bezooijen 2016

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study Date of study: 2013-June 2015 Location: single centre in the Netherlands
Participants	**Randomised**: 33 participants **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 outcome** • PASI 75 **Secondary outcomes** • PGA0/1 • DLQI • AEs
Notes	Funding source: 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".

Van Bezooijen 2016 *(Continued)*

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
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 study 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

Van de Kerkhof 2008 *(Continued)*

	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) • 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** • Proportion of participants PASI 75 or greater **Secondary outcomes** • 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

Van de Kerkhof 2008 *(Continued)*

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
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.

VIP-S trial 2020

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study Date of study: February 2016-February 2018 Location: USA (12 centres) Phase 4
Participants	**Randomised**: 91 participants **Inclusion criteria** • Men and women ≥ 18 years with moderate-severe plaque psoriasis (≥ 6 months prior to randomisation), with ≥ 10% BSA involvement, PASI ≥ 12, and IGA mod 2011 score ≥ 3 (based on a scale of 0 to 4) • Eligible for systemic therapy **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 • Used cholesterol-lowering medications (unless the use of cholesterol-lowering medications involved a dose that was stable ≥ 90 days prior to randomisation and remained stable during the study) • Notable current cardiovascular or cerebrovascular disease • Significant medical problems (uncontrolled hypertension with measured systolic ≥ 180 mmHg and/or diastolic ≥ 95 mm Hg, congestive heart failure) • Serum creatinine level of > 2.0 mg/dL, a fasting blood glucose ≥150 mg/dL, or a total white blood cell (WBC) count < 2500/µl, thrombocytes < 100,000/µl, neutrophils < 1500/µl, or haemoglobin < 8.5 g/dL **Baseline characteristics**

VIP-S trial 2020 *(Continued)*

N = 91, mean age of 47.5 years and 67% men

Dropouts and withdrawals

- 5/91 (5.5%): secukinumab group (2), placebo group (3)
- AEs: secukinumab group (2), placebo group (2)
- Participant/guardian decision: secukinumab group (0), placebo group (1)

Interventions	**Intervention** A. 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), n = 46 **Control intervention** B. Placebo, n = 45
Outcomes	At week 12 **Primary outcome** • Aortic vascular inflammation as measured by FDG-PET/CT **Secondary outcomes** • Cardiometabolic biomarkers • PASI 75 • PASI 90 • PASI 100 • IGA 0/1 • DLQI
Notes	Funding source "This study is funded by Novartis Pharmaceuticals Corporation, East Hanover, NJ." Declarations of interest "Dr Gelfand served as a consultant for BMS, Boehringer Ingelheim, Janssen Biologics, Novartis Corp, UCB (DSMB), Sanofi, and Pfizer, receiving honoraria; and receives research grants (to the Trustees of the University of Pennsylvania) from AbbVie, Boehringer Ingelheim, Janssen, Novartis, Celgene, Ortho Dermatologics, and Pfizer; and received payment for continuing medical education work related to psoriasis that was supported indirectly by Lilly, Ortho Dermatologics, and Novartis. Dr Gelfand is a Deputy Editor for the Journal of Investigative Dermatology receiving honoraria from the Society for Investigative Dermatology.Dr Duffin has received research grants from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen, Novartis, Pfizer, Sienna Biopharmaceuticals, Stiefel Laboratories, and UCB; and has received consulting fees from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen, Novartis, Ortho Dermatologic, Pfizer, Sienna Biopharmaceuticals, Stiefel Laboratories, and UCB; and is on the speaker's bureau for Novartis.Dr Armstrong has served as investigator, advisor, and/or consultant to Leo, AbbVie, UCB, Janssen, Novartis, Eli Lilly, Sun, Dermavant, BMS, Regeneron Pharmaceuticals, Inc., Sanofi U.S., Dermira, Modmed, and Ortho Dermatologics, Inc.Dr Blauvelt has served as a scientific adviser and/or clinical study investigator for AbbVie, Aclaris, Akros, Allergan, Almirall, Amgen, Arena, Athenex, Boehringer Ingelheim, Bristol- Myers Squibb, Celgene, Dermavant, Dermira, Eli Lilly, FLX Bio, Forte, Galderma, Genentech/Roche, GlaxoSmithKline, Janssen, Leo, Meiji, Merck Sharp & Dohme, Novartis, Ortho, Pfizer, Purdue Pharma, Regeneron, Revance, Sandoz, Sanofi Genzyme, SiennaPharmaceuticals, Sun Pharma, UCB Pharma, and Vidac and as a paid speaker for AbbVie, Regeneron, and Sanofi Genzyme.Dr Trying has conducted studies sponsored by the producer of secukinumab.Dr Menter has received compensation from or served as an investigator, consultant, advisory board member, or speaker for Abbott Labs, AbbVie, Allergan, Amgen, Anacor, Boehringer Ingelheim, Celgene, Dermira, Eli Lilly, Galderma, Janssen, Leo, Merck & Co, Neothetics, Novartis, Pfizer, Regeneron, Sienna, Symbio/Maruho, UCB, Vitae, and Xenoport. Dr Gottlieb is currently serving as consultant, advisory board member, speaker for Janssen, Celgene, Bristol Myers Squibb, Beiersdorf, Abbvie, UCB, No-

VIP-S trial 2020 *(Continued)*

vartis, Incyte, Lilly, Reddy Labs, Valeant, Dermira, Allergan, Sun Pharmaceutical Industries, Xbiotech, Leo, Avotres Therapeutics. Research/Educational Grants: Janssen, Incyte, UCB, Novartis, Lilly Xbiotech, Boeringer Ingelheim.Dr Lockshin reports personal fees from Lilly, Novartis, Janssen, and Abbott; has served as a speaker for Novartis, Eli Lilly, and Abbvie; conducted research for Celgene, Abbvie, Novartis, Eli Lilly, and Strata, and served as a consultant for Novartis, Lilly, AstraZeneca, Abbive.Dr. Simpson reports grants from Eli Lilly, Kyowa Hakko Kirin, Leo Pharmaceutical, Merck, Pfizer, and Regeneron, and personal fees from Menlo Therapeutics, Valeant, Novartis, Eli Lilly, Galderma, Dermira, Sanofi Genzyme, Pfizer, Regeneron, and Leo Pharmaceuticals. Dr Shin, Dr Ahlman, Dr Playford, Dr Joshi, Dr Dey, Dr Werner and Dr Alavi have nothing to disclose."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "This was a randomized, double-blinded, placebo-controlled, parallel-group, multicenter study in adult patients (≥ 18 years of age) with moderate-to-severe chronic plaque psoriasis....Eligible patients were randomized via Interactive Response Technology in a 1:1 ratio to either secukinumab 300 mg or placebo."
Allocation concealment (selection bias)	Low risk	Quote: "The Investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment group and will specify a unique medication number for the first box of study treatment to be dispensed to the subject. The randomization number will not be communicated to the caller. The identity of secukinumab and placebo prefilled syringes (PFS) will be concealed by identical packaging, labeling, schedule of administration, and appearance." Comment: adequate procedure to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote:"Patients, investigators/site staff, persons performing assessments, and Novartis study personnel remained blinded to individual treatment assignment from time of randomization until the final database lock at week 52." Comment: adequate procedure to guarantee blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote:"Patients, investigators/site staff, persons performing assessments, and Novartis study personnel remained blinded to individual treatment assignment from time of randomization until the final database lock at week 52." Comment: adequate procedure to guarantee blinding of assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote:"The primary analysis was based on the full analysis set. For the primary efficacy variable, data for patients with missing post-baseline value were not imputed, and patients were included in the analysis if they had both baseline and post-baseline assessments. The primary analysis was based on the full analysis set. Changes from baseline in each cardiometabolic biomarker were analyzed at each time point using the same ANCOVA model as for the primary efficacy variable; missing data were imputed using the last-observation-carried-forward method." Randomised 91; analysed 91
Selective reporting (reporting bias)	Low risk	Comment: the protocol for the study was available on ClinicalTrials.gov (VIP-S trial 2020).

VIP-S trial 2020 *(Continued)*

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

VIP Trial 2018

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind study Date of study: February 2012-October 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 • 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 ustek-

VIP Trial 2018 *(Continued)*

inumab, 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 breastfeeding 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/mm^3. 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

Baseline characteristics

N = 96, mean of age 43 years and 70% men

Dropouts and withdrawals

- 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

VIP Trial 2018 *(Continued)*

Control intervention

B. NBUVB 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 outcomes

- 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 outcomes

- 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 source

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."

Declarations 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
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

VIP Trial 2018 *(Continued)*

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". Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomised: 96; analysed 92 Dealing with missing data: not stated but few withdrawals (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.

VIP-U Trial 2020

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study Date of study: July 2014-September 2018 Location: University of Pennsylvania, USA (40 sites, multicentre) 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 **Exclusion criteria** • 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 • 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 **Baseline characteristics** N = 43, mean age of 42.5 years and 70% men **Dropouts and withdrawals** 8/43 (18.6%): ustekinumab group (2), placebo group (6) Before cross-over • Lost to follow-up: ustekinumab group (1), placebo group (2) • Physician discretion: ustekinumab group (1), placebo group (0) After cross-over • Lack of perceived efficacy: ustekinumab group (0), placebo group (2) • Physician discretion: ustekinumab group (0), placebo group (1)

VIP-U Trial 2020 *(Continued)*

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 > 100 kg) at day 0 and week 4 followed by every 12-week dosing thereafter; participant will receive total of 52 weeks of ustekinumab (12 weeks during RCT phase, 40 weeks post-RCT phase) n = 22. **Control intervention** B. Placebo: placebo subcutaneous injection will be given according to the same dose and schedule as the active comparator until week 12 (end of RCT phase). At week 12, ustekinumab will be administered according according to the same injection schedule as the active comparator arm for 52 weeks. Patient will receive total of 52 weeks of ustekinumab (0 weeks during RCT phase, 52 weeks post RCT phase) n = 21.
Outcomes	At week 52 **Primary outcome** • Change in vascular Inflammation and biomarkers between baseline and weeks 12, 52 (only participants initially randomised to ustekinumab), and 64 (only participant initially on placebo) **Secondary outcomes** • Change in physician-reported measures of psoriasis activity (PASI 90, 75 and PGA) from baseline to weeks 12, 52, and 64 (only participant initially on placebo) • Change in participant-reported dietary and physical activity assessments (i.e. MEDFICTS and IPAQ) from baseline to weeks 12, 52, and 64 (only participant initially on placebo) • Number of participants with adverse events (time frame: per patient report throughout the study)
Notes	In ClinicalTrials.gov, the secondary outcomes are different from paper • Number of participants achieving PASI 75 [time frame: baseline - week 12; baseline - end of study visit (week 52 or week 64)] • Number of participants achieving PASI 90 [time frame: baseline - week 12; baseline - end of study visit (week 52 or week 64)] Funding source Quote (p. 92): "This study was funded by a grant to the Trustees of the University of Pennsylvania from Janssen Pharmaceuticals (JMG). JMG received additional funding from NIAMS K24AR064310. JT is funded in part by K23 AR068433. NNM received additional funding from NHLBI Intramural Research Program (HL006193-05). We thank the patients who volunteered for this study and Suzette Baez Vanderbeek for her project management expertise." Conflict of interest Quote (p. 92): "Outside of the submitted work, JMG served and received honoraria as a consultant for BMS, Boehringer Ingelheim, Janssen Biologics, Novartis Corp, UCB (DSMB), Sanofi, and Pfizer Inc.; and received research grants (to the Trustees of the University of Pennsylvania) from AbbVie, Boehringer Ingelheim, Janssen, Novartis Corp, Celgene, Ortho Dermatologics, and Pfizer Inc.; and received payment for continuing medical education work related to psoriasis that was supported indirectly by Eli Lilly, Ortho Dermatologics, and Novartis. JMG is a co-patent holder of resiquimod for treatment of cutaneous T-cell lymphoma, and is a Deputy Editor for the Journal of Investigative Dermatology receiving honoraria from the Society for Investigative Dermatology. DAT is a cofounder of Quantitative Radiology Solutions LLC. MHN receives a research grant via the Trustees of the University of Pennsylvania from Boehringer Ingelheim, and she is supported by a K23-AR073932 career development award from the National Institute of Arthritis and Musculo-skeletal and Skin Diseases. MHN has also received payments for work done as in independent contractor from UptoDate and Derm101. JT receives a grant from NIAMS K23-AR068433 and a research grant (both to the Trustees of the University of Pennsylvania) from Pfizer Inc.,

VIP-U Trial 2020 *(Continued)*

and has received payment for continuing medical education work related to psoriasis that was supported indirectly by Eli Lilly and Novartis. NNM is a full time US government employee. NNM has served as a consultant for Amgen, Eli Lilly, and Leo Pharma receiving grants and/or other payments; as a principal investigator and/or investigator for AbbVie, Celgene, Janssen Pharmaceuticals Inc, and Novartis receiving grants and/or research funding; and as a principal investigator for the National Institute of Health receiving grants and/or research funding. All the other authors state no conflict of interest."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p. 89, 91): "The study was a randomized, double-blind, placebo-controlled trial designed to enroll 42 patients with allocation ratio of 1:1 to ustekinumab subcutaneous injections or placebo injections at baseline and week 4.... Study group assignment was performed via block randomization (of four and eight), using a computerized system at the Investigational Drug Services, University of Pennsylvania." Comment: adequate procedure
Allocation concealment (selection bias)	Unclear risk	Quote (p. 89, 90):"The study was a randomized, double-blind, placebo-controlled trial designed to enroll 42 patients with allocation ratio of 1:1 to ustekinumab subcutaneous injections or placebo injections at baseline and week 4... Ustekinumab (or corresponding placebo) therapy was administered in a double-blind manner as subcutaneous injections." Comment: lack of information on appearance of ustekinumab and placebo, no information on process of treatment dispensation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p. 89, 91): "The study was a randomized, double-blind, placebo-controlled trial designed to enroll 42 patients with allocation ratio of 1:1 to ustekinumab subcutaneous injections or placebo injections at baseline and week 4....Study investigators, staff, and patients were blinded to ustekinumab or placebo status during the placebo-controlled period. All scans were read in a blinded fashion to patient characteristics, treatment allocation, and visit dates (i.e. baseline, week 12, or end of study)." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p. 89, 91): "The study was a randomized, double-blind, placebo-controlled trial designed to enroll 42 patients with allocation ratio of 1:1 to ustekinumab subcutaneous injections or placebo injections at baseline and week 4....Study investigators, staff, and patients were blinded to ustekinumab or placebo status during the placebo-controlled period. All scans were read in a blinded fashion to patient characteristics, treatment allocation, and visit dates (i.e. baseline, week 12, or end of study)." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (p. 91): "The missing data were summarized using frequencies for each outcome measure...The primary analyses were restricted to subjects who completed the trial (i.e. had primary outcome measures assessed at baseline and week 12)." "The primary analyses were restricted to subjects who completed the trial (i.e. had primary outcome measures assessed at baseline and week 12). For TBRmax, additional multivariate linear regression models were fitted to assess sensitivity to potential imbalance of covariates (which may occur by chance in smaller randomized controlled trials), such as age, sex, and major cardiovascular disease risk factors (serum glucose, systolic and diastolic blood pressure, tobacco use, family history, serum LDL, HDL, total cholesterol,

VIP-U Trial 2020 *(Continued)*

		body mass index, psoriatic arthritis, and PASI). For binary outcomes, the treatment group comparisons were assessed using logistic regression models." Randomly assigned 43
Selective reporting (reporting bias)	High risk	Comment: In clinicaltrials, the secondary outcomes are different from paper; the protocol for the study was available on ClinicalTrials.gov (NCT02187172). Results are posted on ClinicalTrials.gov.

VOLTAIRE-PSO 2021

Study characteristics	
Methods	RCT, active-controlled, double-blind study Date of study: August 2016-January 2018 Location: worldwide (54 sites) Phase 3
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 • 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

VOLTAIRE-PSO 2021 *(Continued)*

- 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 (IV) 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 m^2 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** 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 90/50/75/100 at 16 and 24 weeks • sPGA ≤ 1 (i.e. clear or almost clear of the signs of psoriasis) at 16 and 24 weeks • Quality of life DLQI at 16 and 24 weeks

VOLTAIRE-PSO 2021 *(Continued)*

- Improvement in modified Nail Psoriasis Severity Index (mNAPSI) at 16 and 24 weeks
- Patients with drug-related adverse events (AEs) (from first drug administration until 10 weeks after last drug administration, up to 34 weeks)

Notes	Funding source: Quote (p 95) "Boehringer Ingelheim provided funding and were responsible for the conduct of this study." Declarations of interest: Quote (p 95) "A Menter has held advisory board, consultant, investigator, and speaker roles with, and grants/research funding and honoraria from, Abbott Labs, Amgen, Janssen Biotech, Inc., LEO Pharma and Sienna; advisory board and investigator roles with, and grants/research funding and honoraria from, Boehringer Ingelheim; investigator roles with, and grants/research funding from, Celgene and Merck; consultant and investigator roles with, and honoraria from, Eli Lilly and Novartis; and consultant, investigator and speaker roles with, and honoraria from, UCB Pharma. S Beissert has held advisory board and speaker roles with, and has received honoraria from, AbbVie, Actelion (now part of Johnson&Johnson), Celgene, Galderma, Janssen-Cilag, Novartis, and MSD; advisory board roles with, and honoraria from, Amgen, LEO Pharma, Eli Lilly, Menlo Therapeutics, Pfizer, and UCB Pharma; speaker roles with, and honoraria from, La Roche Posay, GlaxoSmithKline and BMS; and investigator roles with, and grants/research funding from, Boehringer Ingelheim. A Cauthen has held a speaker role with Otezla (Amgen), and investigator roles with Amgen, Arcutis, AbbVie, Baxter Healthcare, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Janssen, Kadmon, Pfizer, Prothena, Therapeutics, TOLMAR, and UCB. J Soung has held speaker bureau roles with, and honoraria and travel fees from, Amgen and Celgene; investigator, speaker bureau, and advisory board roles with, and grants/research funding and honoraria from, Eli Lilly; speaker bureau and investigator roles with, and grants/research funding and honoraria from, AbbVie; investigator roles with, and grants/research funding from, Pfizer, Allergan, Galderma, Actavis, Cassiopeia, GlaxoSmithKline, Boehringer Ingelheim, Kadmon, Novan, Dr. Reddy, Kyowa Kirin, and Menlo; investigator and speaker bureau roles with, and grants/research funding from, Ortho Dermatologics; investigator and speaker bureau roles with, and grants/research funding and honoraria from, Actelion; speaker roles with, and honoraria from, the National Psoriasis Foundation; investigator and advisory board roles with, and grants/research funding and honoraria from, LEO Pharma; investigator, speaker bureau and consultant roles with, and grants/research funding and honoraria from, Novartis; speaker bureau roles with, and honoraria from, Regeneron and Dermira; investigator roles with, and grants/research funding and honoraria from, Janssen; and investigator roles with, and honoraria from, UCB Pharma. S Jazayeri has held speaker roles with Novartis and Abbvie; and grants from AbbVie, Amgen, Athenex, AbGenomics, Bausch Health Americas Valeant, Boehringer Ingelheim, Bristol Myers Squibb, Coherus Biosciences, Corrona LLC, DS Biopharma, Eli Lilly and Company, Galderma, Genentech, Health Analytics, Innovaderm, IQVIA Biotech, Janssen Biotech, Kadmon, Leo Pharmaceuticals, Novartis, Novella, Pfizer, Regeneron, Tolmar, UCB Biopharma, Xenoport (Arbor Pharmaceuticals), and Watson. P Weisenseel has held investigator roles with, and honoraria/investigator fees to his institution from, Boehringer Ingelheim; advisory board, investigator and speaker roles with, and honoraria/investigator fees to his institution from, AbbVie; advisory board and speaker roles with, and honoraria from, Hexal, Almirall and Biogen Idec; advisory board, consultant, investigator and speaker roles with, and honoraria from, Janssen; advisory board, investigator and speaker roles with, and honoraria from, Novartis and Celgene; and speaker roles and honoraria from Medac. P Arenberger reports no disclosures. S Balser, N Czeloth, and G Jayadeva are employees of Boehringer Ingelheim. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 88): "This was a randomized, double-blind, parallel-arm, multiple-dose, active comparator trial. Patients were randomized 1:1 via Interactive Response Technology (IRT; Almac Clinical Technologies, Souderton, PA, USA) to receive either BI 695501 or adalimumab RP (Humira®; AbbVie Inc., North Chicago, IL, USA). Each patient was allocated the lowest sequentially available ran-

VOLTAIRE-PSO 2021 *(Continued)*

		domization number, and the randomization code was concealed from personnel throughout the study." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (p 88): "This was a randomized, double-blind, parallel-arm, multiple-dose, active comparator trial. Patients were randomized 1:1 via Interactive Response Technology (IRT; Almac Clinical Technologies, Souderton, PA, USA) to receive either BI 695501 or adalimumab RP (Humira®; AbbVie Inc., North Chicago, IL, USA). Each patient was allocated the lowest sequentially available randomization number, and the randomization code was concealed from personnel throughout the study." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p 88): "This was a randomized, double-blind, parallel-arm, multiple-dose, active comparator trial... The packaging of syringes containing either BI 695501 or adalimumab RP was of identical appearance to ensure blinding, while unique medication identification numbers enabled each patient to receive the correct treatment." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p 88): "This was a randomized, double-blind, parallel-arm, multiple-dose, active comparator trial... The packaging of syringes containing either BI 695501 or adalimumab RP was of identical appearance to ensure blinding, while unique medication identification numbers enabled each patient to receive the correct treatment." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dealing with missing data: Quote (p 89-90) "The full analysis set (FAS) comprised all randomized patients who received at least one dose of study medication and had efficacy measures required for determining PASI 75 response or non-response... The primary efficacy analysis, performed on the FAS, was based on logistic regression and the Reeve method was used to calculate the 95% CI. A combination of non-responder imputation (NRI) and multiple imputation (MI) was used for incomplete or missing data. The per-protocol analysis set (PPS), used for sensitivity analysis of the primary endpoint, contained all patients in the FAS with no important efficacy-relevant protocol deviations. In this analysis, missing data were imputed using a combination of NRI and Last Observed Carried Forward (LOCF) ... The safety analysis set (SAF) contained all randomized patients who received at least one dose of study medication." Per-protocol analyses (non-inferiority trial) Randomly assigned 318, efficacy FAS analysed 315, safety SAF 317
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. Results are posted on ClinicalTrials.gov.

VOYAGE-1 2016

Study characteristics	
Methods	RCT, active placebo-controlled, double-blind study

VOYAGE-1 2016 *(Continued)*

	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 C. Placebo (n = 174)
Outcomes	Assessment at 16 weeks **Primary outcomes** • PASI 90 and IGA clear or almost clear **Secondary outcomes** • 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 Abb-Vie, Amgen, Boehringer Ingelheim, Celgene, Dermira, Genentech, GSK, Janssen, Eli Lilly, Merck, No-vartis, Pfizer, Regeneron, Sandoz, Sanofi-Genzyme, Sun, UCB, and Valeant, and as a paid speaker for

VOYAGE-1 2016 *(Continued)*

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) All outcomes	Low risk	Quote (p 3): "To maintain the blind, matching placebos were used." Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (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 an AE 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.

VOYAGE-2 2017

Study characteristics	
Methods	RCT, active/placebo-controlled, double-blind study Date of study: November 2014-May 2016 Location: 115 centres worldwide Phase 3
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 **Control interventions** 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** • PASI 90 • IGA clear or almost clear **Secondary outcomes** • PASI 50/75 • Mean DLQI score • NAPSI • Scalp-specific IGA • Fingernail PGA • AEs

VOYAGE-2 2017 *(Continued)*

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)." 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 analysed 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."

VOYAGE-2 2017 *(Continued)*

		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.

Yang 2012

Study characteristics	
Methods	RCT, placebo-controlled, double-blind study 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** 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 outcome** • PASI 75 **Secondary outcomes**

Yang 2012 *(Continued)*

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

Ye 2020

Study characteristics

Methods	RCT, active-controlled study Date of study: August 2017-February 2019

Ye 2020 *(Continued)*

	Location: China
Participants	**Randomised**: 150 participants Inclusion criteria • Patients who met the diagnostic criteria for psoriasis vulgaris • Patients who had no other skin system diseases patients who cooperated with the treatment • Patients whose clinical data were complete. **Exclusion criteria** • Patients who were allergic to or unsuitable for the treatment • Patients who had undergone systemic psoriasis treatment within the previous weeks; patients who had received glucocorticoids or formic acid immunosuppressants within the previous two weeks • Patients who had congenital immunodeficiencies in addition to psoriasis **Baseline characteristics** N = 150, mean of age 33 years and 57% men **Dropouts and withdrawals** Not stated
Interventions	**Intervention** A. Acitretin per os initial dose 30 mg/d **Control intervention** B. No treatment Co-intervention: Narrow-band ultraviolet therapy
Outcomes	At week 8 **Primary outcomes** • Basic recovery (patients with PASI score reduction between 60% and 89%) • Significant improvement (patients with PASI score reduction over than 90%: "good curative effect") • Improvement (patients with PASI score reduction between 20% and 59%) • Ineffectual treatment (patients with PASI score reduction less than 20%) **Secondary outcomes** • Recurrence within one year after the treatment (patients were notified to revisit the clinic by telephone)
Notes	Funding source: not stated Declarations of interest: Quote (p 5074) "None"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (p 5069) "The patients were randomly divided into the control group (n = 75) and the observation group (n = 75)." Comment: no description of the method used to guarantee random sequence generation

Ye 2020 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Quote (p 5069) "The patients were randomly divided into the control group (n = 75) and the observation group (n = 75)." Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no description if the trial is blinded or open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: no description if the trial is blinded or open
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Randomised 150, analysed 150 Comment: methods for dealing with missing data not specified, 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.

Yilmaz 2002

Study characteristics	
Methods	RCT, placebo-controlled, open-label study Date of study: not stated 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

Yilmaz 2002 *(Continued)*

	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
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

Yu 2019

Study characteristics

Methods	RCT, active-controlled study Date of study: not stated Location: China
Participants	**Randomised**: 30 participants **Key inclusion criteria** • Moderate-to-severe plaque psoriasis defined by clinical features and/or with PASI score ≥ 10 • Not undergone systemic immunotherapies within the preceding 2 months • Not taken topical glucocorticoids within the preceding 2 weeks

Yu 2019 *(Continued)*

	Key exclusion criteria • Previously treated with TNF-α inhibitors • Patients with other autoimmune diseases or significant renal/hepatic disease • Patients with contraindications for phototherapy • Pregnant or breastfeeding **Baseline characteristics** N = 30, mean age of 51.93 years and 67% men **Dropouts and withdrawals** No withdrawals occured
Interventions	**Intervention** A. methotrexate (combination of etanercept, SC injection 50 mg weekly and methotrexate, PO 7.5-15 mg weekly), n = 15 **Control intervention** B. No treatment n = 15 **Co-intervention** Etanercept (SC injection 50 mg every week through week 24)
Outcomes	At week 24 **Outcomes** • PASI 90 • PASI 75 • PASI 50 • Static Physician's Global Assessment (sPGA) • Patient's Global Assessment (PtGA) • Dermatology Life Quality Index (DLQI) • Clinical and laboratory abnormalities
Notes	Funding source Quote (p 449): "This work was supported by grants from National Natural Science Foundation of China (No. 81673050, 81872522), the Program of Science and Technology Commission of Shanghai Municipality (No. 18140901800), Innovation Program of Shanghai Municipal Education Commission (No.2019-01-07-00-07-E00046), Excellent Subject Leader Program of Shanghai Municipal Commission of Health and Family Planning (No. 2018BR30), Clinical Research Program of Shanghai Hospital Development Center (No. SHDC12018X06)." Declarations of interest Quote (p 449): "There is no conflicting interest."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (p 443): "Randomization was undertaken with the use of computer-generated random numbers." Comment: adequate process

Yu 2019 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Quote (p 443): "Randomization was undertaken with the use of computer-generated random numbers." Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no description of the method used to guarantee blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (p 443): "The PASI score was determined by a dermatologist at 2, 6, 12, 18 and 24 weeks of treatment." Comment: Physicians were not blinded for for PASI evaluation.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	15 included/15 analysed 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.

8-MOP: Methoxsalen
ABP 501: adalimumab biosimilar
ACI: acitretin
ACR: American College of Rheumatology
ACT: activated clotting time
ADA: adalimumab
ADMB: adalimumab
AEs: adverse events
AIN457: secukinumab
ALT: alanine aminotransferase
ANC: absolute neutrophil count
ANCOVA: analyse of covariance
AST: aspartate aminotransferase
BI695501: adalimumab biosimilar
BCD-057: adalimumab biosimilar
BCG: bacille Calmette-Guérin
BI655066: risankizumab
BID: two times a day
Bime: bimekizumab
BIW: twice a week
BMS-986615: deucravacitinib
BSA: Body Surface Area
CBC: complete blood count
Certo: certolizumab
CHS-0214: etanercept biosimilar
CI: confidence interval
CIN: cervical intraepithelial neoplasia
CMH: Cochran-Mantel-Haenszel
COPD: chronic obstructive pulmonary disease
CRO: contract research organization
CRP: c-reactive protein
CS: systemic corticosteroid
C-SSRS: Columbia Suicide Severity Rating Scale
CTL: cytotoxic T-lymphocyte
CZP: certolizumab

DLQI: Dermatology Life Quality Index
DMF: dimethylformamide
DSM: drug supply management
ECG: electrocardiogram
eow: every other week
EQ-5D-5L: standardised measure of health-related quality of life
ETA: etanercept
ETN: etanercept
EudraCT: European Union Drug Regulating Authorities Clinical Trials
FAE: fumaric acid esters
FAS: full analysis set
FDA: food drug administration
FDG-PET/CT: fluorodeoxyglucose (FDG)-positron emission tomography
FMD: flow-mediated dilatation
FSH: follicle-stimulating hormone
GCP: good clinical practice
GPSS: genital psoriasis symptoms scale
HbA1c: haemoglobin A1c
HBV: hepatitis B virus
hCG: human chorionic gonadotropin
HCV: hepatitis C virus
HD: high dose
HDL: high-density lipoprotein
Hgb: haemoglobin
HIV: human immunodeficiency virus
HOMA-IR: Homeostatic Model Assessment for Insulin Resistance
ICF: international classification of functioning, disability and health
ICH: intracerebral brain haemorrhage
ID: identification number
IFX: infliximab
IGA: Investigator's Global Assessment
IL(-23/17/12): interleukin-23/17/12
IM: intramuscular
IMP: investigational medicinal product
INRS: itch numeric rating scale
IP: investigational product
IPAQ: international physical activity questionnaire
IRT: interactive response technology
ITT: intention-to-treat
IUD: intrauterine device
IUS: intrauterine system
IV: intravenous
IWRS: interactive web response systems
IXE: ixekizumab
IXRS: interactive voice/web response system
LD: low dose
LDL: low-density lipoprotein
LFT: live function tests
LOCF: last observation carried forward
LTBI: latent tuberculosis infection
M3(R2): guideline on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals
MCMC: markov chain *Monte Carlo*
MCS: multiple chemical sensitivity
MD: medium dose
MEDFICTS: dietary assessment instrument
MEF: monoethyl fumarate
MGH-SFQ: Massachusetts general hospital-sexual functioning questionnaire
MGUS: monoclonal gammopathy of undetermined significance
MI: multiple imputation
m-ITT: modified ITT
MK-3222: tildrakizumab
MMRM: mixed-model repeated measures

mNAPSI: modified NAPSI
mNRI: modified NRI
MTX: methotrexate
NAPPA-CLIN: nail assessment in psoriasis and psoriatic arthritis clinician-reported measure
NAPSI: Nail psoriasis severity index
NBUVB: narrow-band UVB
NMSC: non melanoma skin cancer
NRI: non responder imputation
NTK: netakimab
NTMB: nontuberculous mycobacteria
NYHA: New-York heart association
OC: oral contraceptive
OR: odds ratio
OS: overall survival
PASE: physical activity scale for the elderly
PASI: Psoriasis Area and Severity Index
PBO: placebo
PFS: progression-free survival
PGA(-G): Physician Global Assessment
PHQ-8: eight-item Patient Health Questionnaire depression scale
PP: per protocol
PPASI: palmoplantar psoriasis severity index
PPD: purified protein derivative
PPGA: physician global assessment
PPS: palliative performance scale
Ps: performance status
PsA: psoriatic arthritis
PSGA: physician static global assessment.
PSI: Psoriasis Severity Index
PSO: psoriasis
PSSD: post-SSRI sexual dysfunction
PSSI: Psoriasis Scalp Severity Index
PSSQ: Psoriasis subject satisfaction questionnaire
PtGA: patient's global assessment
PUVA: psoralen plus ultraviolet A
Q(2/4)W: every other week/every 4 week
QFT: quantiFERON-TB gold
QoL: quality of life
R2: cf M3(R2)
RA: rheumatoid arthritis
RCT: randomised controlled trial
RFT: renal function tests
rhTNFR-Fc: tumour necrosis factor receptor: fusion protein
ROB: risk of bias
SAEs: serious adverse events
SAF: safety analysis set
SAS: statistical analysis system
SC: subcutaneous
ScPGA: scalp physician global assessment
SF-36: 36-item Short Form Health Survey
SIAQ: Self-Injection Assessment Questionnaire
SSA: scalp surface area
TB: tuberculosis
TBR(max): target background ratio
TEAE: treatment emergent adverse event
Th-17: T helper-17 cell
TNFα: tumour necrosis factor alpha
ULN: upper limit of normal
USK: ustekinumab
UV: ultraviolet
UVB: ultraviolet B
VAS: visual analogue scale

W14: week 14
WBC: white blood count
WOCBP: women of childbearing potential
Please note that the term “conventional” in these tables is replaced with “non-biological treatment” in the main text of this review.

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
Anonymous 2019	Not a randomised 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
Asahina 2016	Other treatment, now excluded in this update because interventions no longer meet inclusion criteria
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 2018b	Not a randomised trial
Bagherani 2017	Commentary/editorial
Bagot 1994	Other treatment
Bartlett 2008	Not a trial

Study	Reason for exclusion
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 2015	Other treatment, now excluded in this update because interventions no longer meet inclusion criteria
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
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

Study	Reason for exclusion
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	Pooled trials
Blauvelt 2018d	Pooled trials
Blauvelt 2018e	Pooled trials
Blauvelt 2018f	Pooled trials
Blauvelt 2018g	Pooled trials
Blauvelt 2018h	Pooled trials
Blauvelt 2020	Not moderate-to-severe psoriasis (good-responders selection)
Branigan 2017	Open-label extension restricted to good responders
Brasil 2012	Ineligible study design
Brasil 2013	Ineligible patient population
Brasil 2016	Ineligible patient population
Buono 2020	Not randomised trial
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
Cather 2006	Dose-ranging after remission
Cather 2018	Ineligible patient population
Chakravadhanula 2017	Ineligible intervention
Chapman 2018	Ineligible study design
ChiCTR2000030273 2020	Phase 1 trial
ChiCTR-INR-16009710	Assessment at 4 weeks
Chládek 2002	Basic science (aim of study: to understand the physiopathology of the disease)

Study	Reason for exclusion
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
CTRI/2018/01/011373	2 different schemas of administration (same drug, same dosage)
CTRI/2020/07/026598 2020	2 different schemas of administration (same drug, same dosage)
CTRI/2020/12/029472 2020	Wrong intervention
CTRI/2020/12/029611	Same intervention
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)
EUCTR2007-004328-18-FR	Ineligible intervention

Study	Reason for exclusion
EUCTR2012-005685-35-DE	Withdrawn trial, NCT01815723
EUCTR2016-001593-15-ES	Withdrawal trial, DEEP Study
EUCTR2016-003592-21-GB	Withdrawal trial
EUCTR2018-001021-10-SE	Not moderate-to-severe psoriasis
EUCTR2019-000817-35-DE	Not moderate-to-severe psoriasis
EXCEED 2021	RCT dedicated to psoriatic arthritis. The randomisation not stratified on plaque psoriasis with BSA > 10% or PASI ≥ 10 but on psoriatic plaque of ≥ 2 cm diameter.
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
GAIN 2021	Not moderate-to-severe psoriasis
Gambichler 2011	Other treatment
Ganguly 2004	Pooled trials
Gil 2003	Not a randomised trial
Gisondi 2020	Not randomised trial
Glatt 2017	Ineligible study design
Goerz 1978	Not a trial
Gold 2018	Ineligible study design
Goll 2017	Not moderate-to-severe psoriasis

Study	Reason for exclusion
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
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

Study	Reason for exclusion
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
Grim 2000	Basic science (aim of study: to understand the physiopathology of the disease)
Grossman 1994	Other treatment
Guenther 2020	Not moderate-to-severe psoriasis
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
Holzer 2020	No efficacy or safety assessment - the study assessed cardiovascular outcomes
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

Study	Reason for exclusion
Jacobe 2008	Another intervention
JapicCTI-194706 2019	Comparison of different schemas of administraton (same drug, same dosage)
Jin 2017	Other treatment, now excluded in this update because interventions no longer meet inclusion criteria
JPRN-jRCTs041180012 2018	Not moderate-to-severe psoriasis
Kaur 2018	Not moderate-to-severe psoriasis
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
Korotaeva 2021	Not moderate-to-severe psoriasis
Kragballe 1989	Other treatment
Krishnan 2005	Pooled trials
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 2016a	Other treatment, now excluded in this update because interventions no longer meet inclusion criteria
Krueger 2016b	Phase I trial
Krupashankar 2014	Another intervention
Kuijpers 1998	Other treatment

Study	Reason for exclusion
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
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

Study	Reason for exclusion
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
Mease 2018	Not moderate-to-severe psoriasis
Mease 2020	Not moderate-to-severe psoriasis
Meffert 1989	Other treatment
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
Merola 2020	Not moderate-to-severe psoriasis
Meyer 2011	Other treatment
Mittal 2009	Other treatment

Study	Reason for exclusion
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
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

Study	Reason for exclusion
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
NCT03025542	Not moderate-to-severe psoriasis at the time of placebo use
NCT03073213	Phase I trial
NCT03210259	Not moderate to severe psoriasis
NCT03482011	Other treatment, now excluded in this update because interventions no longer meet inclusion criteria
NCT04121143	Other treatment, now excluded in this update because interventions no longer meet inclusion criteria
NCT04839016	Other treatment, now excluded in this update because interventions no longer meet inclusion criteria
NCT04882098	Not moderate-to-severe psoriasis
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
OPT Pivotal-1 2015	Other treatment, now excluded in this update because interventions no longer meet inclusion criteria
OPT Pivotal-2 2015	Other treatment, now excluded in this update because interventions no longer meet inclusion criteria

Study	Reason for exclusion
Orfanos 1978	Other treatment
Orfanos 1979	Other treatment
Ortonne 2008	Comparison of 2 schemes of administration
Ortonne 2011	Other treatment
Osamu 2014	Phase 1 trial
Page 2020	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 2012b	Other treatment, now excluded in this update because interventions no longer meet inclusion criteria
Papp 2012d	Phase 1 trial
Papp 2012e	Pooled trials
Papp 2017c	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

Study	Reason for exclusion
Piascik 2003	Not a trial
Ports 2013	Other treatment
Puig 2018	Ineligible outcomes
Punwani 2012	Other treatment
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
Reich 2019	Other treatment, now excluded in this update because interventions no longer meet inclusion criteria
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

Study	Reason for exclusion
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
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
Stein Gold 2021	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
Sun 2019	Not psoriasis
Sweetser 2006	Cross-over trial
Syversen 2020	NCT03074656 - pragmatic trial according to anti-TNF dosages
Talamonti 2021	Not randomised study

Study	Reason for exclusion
Talwar 1992	Not a randomised trial
TCTR20190705002	Comparison of 2 different schema of administration (same drug same dosage)
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
Van Joost 1988	Assessment < 8 weeks
Vena 2005	Comparison of 2 schemes of administration
Vena 2012	Other treatment
Verma 2021	Wrong comparator
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
Yiu 2020	Commentary
Yoon 2007	Dose-escalation study
Yosipovitch 2018	Not moderate-to-severe psoriasis
Zachariae 2008	Other treatment
Zhang 2007	Other treatment
Zhang 2009a	Other treatment

Study	Reason for exclusion
Zhang 2009b	Other treatment
Zhang 2017	Other treatment, now excluded in this update because interventions no longer meet inclusion criteria
Zhang 2020	Other treatment, now excluded in this update because interventions no longer meet inclusion criteria
Zhu 2009	Pooled trials
Zhuang 2016	Phase 1 trial
Zobel 1987	Not a trial

BSA: Body Surface Area
PASI: Psoriasis Area Severity Index
TNF: Tumor necrosis factor

Characteristics of studies awaiting classification *[ordered by study ID]*

ChiCTR2000034243 2020

Methods	RCT, active-controlled, double-blind study Date of study: April 2017 Location: China Phase 3
Participants	**Randomised**: 320 participants **Inclusion criteria** • Subject voluntarily signed informed consent and could be reliable and capable of adhering to the protocol • Aged 18 to 75 years at the date of signature of the informed consent • BMI:18~32 kg/m^2 • A clinical diagnosis of moderate to severe chronic plaque psoriasis for at least 6 months • Subject has a stable history of plaque psoriasis for at least 2 months before randomisation according to the judgement of the Investigator • Subject has moderate to severe psoriasis at screening and baseline, as defined below: Psoriasis Area and Severity Index (PASI) score >= 12 (0-72), and Body Surface Area (PGA) affected by psoriasis >= 10% • Study participant must be a candidate for systemic therapy. Defined as moderate-to-severe chronic plaque type with poor control through local and/or phototherapy and/or previous traditional systemic treatment psoriasis subjects (including insensitivity to the original treatment, or intolerance, or contraindications, or treatment failure) **Exclusion criteria** • Patients have non-plaque forms of psoriasis such as pustular psoriasis, erythrodermic psoriasis, guttate psoriasis • Patients have a history of drug-induced psoriasis (including but not limited to new psoriasis or exacerbations of psoriasis caused by beta-blockers, calcium channel inhibitors or lithium)

ChiCTR2000034243 2020 *(Continued)*

- Patients who are allergic to any of the components of the investigational medicinal product, or patients who have previously had an allergic reaction to drugs of the same pharmacological and biological classification
- Patients who used UVB within 2 weeks or psoralen + UVA (PUVA) within 4 weeks before randomisation
- Patients who used local treatment within 2 weeks before randomisation, including glucocorticoids, vitamin D derivatives, retinoic acid preparations, etc
- Patients had systemic treatment for psoriasis within 4 weeks before randomisation
- Patients used biologics, such as inhibitor of TNF-alpha/IL-6R/IL-12/IL-23/IL-17, within 12 weeks before randomisation
- Subjects who received any live vaccine within 2 months before randomisation or plan to receive any vaccine during the study period
- Patients who have previously been treated with infliximab, or those with positive anti-drug antibody results during the screening period
- Participants who are pregnant or nursing
- Patients have other active inflammatory diseases that may confuse treatment evaluations.
- Patients have medical, psychiatric condition or a history of mental illness, that is currently unsuitable for the trial or the investigator believes will impact the compliance.
- Patients with severe, progressive, or uncontrolled disease where participation in the study increases the risk. Including but not limited to: (1) History of myocardial infarction within 12 months before signing informed consent; (2) Unstable angina pectoris; (3) Congestive heart failure (NYHA III or IV); (4) Severe lung disease that requires hospitalisation or oxygen therapy, such as chronic bronchitis, obstructive pulmonary disease
- Patients had history of lymphoproliferative disease, or any malignancy, or any organ system malignancy in the past 5 years.
- Patients are suffering from persistent or chronic active infection, and are not suitable for participation in the study at the discretion of the investigator; patients had severe infections requiring systemic anti-infective treatment or hospitalisation within 4 weeks before randomisation.
- Patients have active tuberculosis or the history of tuberculosis, or a chest radiograph suggesting a previous infection with tuberculosis, or a positive γ-interferon release test.
- Patients have human immunodeficiency virus (HIV) antibody, treponema pallidum antibody, hepatitis C virus antibody, or hepatitis B surface antigen. When hepatitis B surface antigen is negative and core antibody is positive, patient should be tested for hepatitis B virus DNA; if it is greater than or equal to the upper limit of this hospital's reference value, the patient should be excluded.
- Patients have abnormal laboratory test results. Any results of laboratory tests that investigators consider clinical significance, the patient is not suitable to participate in this trial.
- Patients had central nervous system demyelinating disease (such as multiple sclerosis or optic neuritis) or suspected central nervous system demyelinating disease.
- Patients are unable or unwilling to undergo repeated venipuncture.
- There is evidence of a history of alcohol or drug abuse within 6 months before randomisation.
- Patients were in any clinical trials within 12 weeks before signing informed consent.
- Any circumstances that the investigator thinks is not suitable to participate

Interventions	**Intervention** HS626 (infliximab biosimilar) 5 mg/kg at weeks 0, 2, 6, 14, 22, 30, 38, 46 **Control intervention** Infliximab 5 mg/kg at weeks 0, 2, 6, 14, 22, 30, 38, 46
Outcomes	At 10, 30, and 52 weeks • Proportion of participants achieving PASI 75 responses • Proportion of participants achieving PASI 50 responses • Proportion of participants achieving PASI 90 responses

ChiCTR2000034243 2020 *(Continued)*

- Proportion of participants with improved overall PGA scores from baseline (scores reduced to 0 or 1)
- Proportion of participants who had a PGA score that had subsided (reduced to 0) from baseline
- DLQI score improved from baseline
- Degree of change in rash area (BSA) from baseline
- Physical examination, vital signs, electrocardiogram, chest X-ray gamma interferon release test, laboratory tests (including blood routine, blood biochemistry, erythrocyte sedimentation, urine routine, coagulation function, auto-antibodies), adverse events
- Immunogenicity (ADA, Nab)
- Pharmacokinetics (Ctrough)

Notes	Unpublished study Funding: Hisun Pharmaceutical (Hangzhou) Co. Ltd Date last refreshed on: June 2020 Last checked in October 2021

Chow 2015

Methods	RCT, active/placebo-controlled, double-blind study 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 • 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 postmenopausal 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

Chow 2015 *(Continued)*

- 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) A. Voclosporin 0.8 mg/kg/day B. Ciclosporin 3.0 mg/kg/day **Control intervention** B. Placebo, n = 89
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)

Chow 2015 *(Continued)*

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 study Date of study: 10 December 2013 (starting date) Location: India
Participants	**Total sample size**: 75 **Inclusion criteria**: • Diagnosed to be suffering exclusively from palmo-plantar psoriasis either by clinical examination or histopathology; if required will be included in palmo-plantar 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 • 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**: palmo-plantar 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 **Primary outcomes** • Improvement in modified PASI and psoriasis severity scale (PSS)

CTRI/2015/05/005830 *(Continued)*

- Modified PASI assessed severity

Secondary outcomes

- Visual analogue scale
- PGA
- Palmo-plantar Quality of Life Instrument scoring (PPQOL)

Notes	Starting date: 10 December 2013. Recruitment status: open to recruitment (10 January 2020) We sent an email to Prof. Shah (5 and 12 January 2017) without response. New email sent to Prof. Kale (11 February 2020) tapdia.raj@gmail.com Article published Nov. 2020: Safety and efficacy profile of oral cyclosporine vs oral methotrexate vs oral acitretin in palmo-plantar psoriasis: a hospital-based prospective investigator blind randomised controlled comparative study, Samkit Shah, 2020 Last checked in October 2021

CTRI/2016/10/007345

Methods	RCT, placebo-controlled, double-blind trial Date of study: October 2016 Location: India Phase 3
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

CTRI/2016/10/007345 *(Continued)*

Interventions	**Intervention** A. Apremilast 30 mg tablets: administered 1 tablet twice daily for 16 weeks **Control intervention** B. 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
Notes	Unpublished Last checked in October 2021 Emails sent to Dr Piyush Agarwal, Amol Pendse (11 February 2020, 30 August 2021)

CTRI/2017/09/009850

Methods	RCT, active/placebo-controlled, open-label study Date of study: August 2017-November 2018 Location: worldwide Phase 4
Participants	**Randomised**: 566 participants **Inclusion criteria** • Presents with established diagnosis of active psoriatic arthritis for at least 6 months, and currently meets Classification for Psoriatic Arthritis (CASPAR) criteria (Active PsA defined as the presence of at least 3 (out of 68) tender and at least 3 (out of 66) swollen joints • Presence of active plaque psoriasis with a BSA ≥ 3% • Men must agree to use a reliable method of birth control or remain abstinent during the study • Women must agree to use reliable birth control or remain abstinent during the study and for at least 12 weeks after stopping treatment • Have had an inadequate response when treated with 1 or more conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) **Exclusion criteria** • Current or prior use of biologic agents for treatment of Ps or PsA • Evidence of active inflammatory arthritic syndromes or spondyloarthropathies other than PsA • Have participated in any study with interleukin 17 (IL-17) antagonists, including ixekizumab • Serious disorder or illness other than psoriatic arthritis • Serious infection within the last 3 months

CTRI/2017/09/009850 *(Continued)*

- Active Crohn's disease or active ulcerative colitis
- Active vasculitis or uveitis
- Diagnosis of or history of malignant disease < 5 years prior to randomisation
- Women who are breastfeeding

Interventions	**Intervention** A. Ixekizumab 160 milligrams (mg) given subcutaneously (SC) at baseline for all participants 80 mg ixekizumab given once every 2 weeks (Q2W) SC from week 2 to week 12 and once every 4 weeks (Q4W) thereafter for participants with moderate-to-severe plaque Ps 80 mg ixekizumab given SC Q4W starting week 4 for participants not meeting criteria for moderate-to-severe plaque Ps **Control Intervention** B. Adalimumab 80 mg given SC at baseline followed by 40 mg Q2W given SC starting week 1 for participants with moderate-to-severe plaque Ps 40 mg adalimumab given Q2W SC at baseline followed by 40 mg Q2W starting at week 2 given SC for participants not meeting criteria for moderate-to-severe plaque Ps
Outcomes	At week 24 **Primary outcome** • Percentage of participants simultaneously achieving American College of Rheumatology 50 (ACR50) and PASI 100 **Secondary outcomes** • ACR 50 week 24 • PASI 100 week 24 • Change from baseline in TJC week 52 • Change from baseline in SJC week 52 • Change from baseline in Participant's Assessment of Pain VAS week 52 • Change from baseline in Participant's Global Assessment of Disease Activity week 52 • Change from baseline in Physician's Global Assessment of Disease Activity week 52 • Change from baseline in C-Reactive Protein week 52 • Change from baseline in HAQ-DI week 52 • Percentage of participants simultaneously achieving ACR50 and PASI 100 week 52 • Change from baseline in Disease Activity Score-CRP (DAS28-CRP) week 52 • Percentage of participants achieving Minimal Disease Activity (MDA) week 52 • Percentage of participants achieving Psoriatic Arthritis Response Criteria (PsARC) week 52 • Change from baseline in modified Composite Psoriatic Disease Activity Index (CPDAI) Score (modified) week 52 • Change from baseline in the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index in participants with enthesitis week 52 • Change from baseline in the Leeds Enthesitis Index (LEI) in participants with enthesitis at baseline week 52 • Change from baseline in the Leeds Dactylitis Index-Basic (LDI-B) in participants with dactylitis at baseline week 52 • Change from baseline in psoriasis Body Surface Area (BSA) week 52 • Change from baseline in the Nail Psoriasis Severity Index (NAPSI) fingernails score in the subgroup of participants with fingernail involvement at baseline week 52 • Change from baseline in the Itch NRS week 52 • Change from baseline in Fatigue Severity NRS (Fatigue NRS) Score week 52

CTRI/2017/09/009850 *(Continued)*

- Change from baseline in Medical Outcomes Study 36-item Short Form Health Survey (SF-36): Physical Component Summary (PCS) week 52 (SF-36 is a standardised participant-administered measure designed to evaluate 8 domains of functional health and well-being).
- Change from baseline in Measures of Health Utility (EuroQol-5 Dimensions 5 Level [EQ-5D 5L]) week 52
- Change from baseline in Dermatology Life Quality Index (DLQI) total score week 52
- Change from baseline on the Treatment Satisfaction Questionnaire week 52
- Change from baseline in Columbia Suicide Severity Rating Scale (C-SSRS) Week 52

Notes	NCT03151551 Lilly Article published: Multicentre, randomised, open-label, parallel-group study evaluating the efficacy and safety of ixekizumab versus adalimumab in patients with psoriatic arthritis naïve to biological disease-modifying antirheumatic drug: final results by week 52, Josef S Smolen, 2020 (email sent 30/09/2021) He responded 30/09/2021:"Hello, No such subgroups were analyzed. If you wish to receive such data, you would have to request them from Lilly. Kind regards, JS" Last checked in October 2021

CTRI/2020/10/028555 2020

Methods	RCT, active-controlled, investigator-blinded study Date of study: October 2020-August 2021 Location: India
Participants	**Randomised**: 50 participants **Inclusion criteria** • Have completed 18 years of age • Diagnosed to be suffering from moderate-to-severe psoriasis and palmo-plantar psoriasis or palmo-plantar psoriasis clinically in DERMATOLOGY OPD of a tertiary care centre in Karad • Have not taken any treatment, two months prior to the inclusion in study **Exclusion criteria** • Haemoglobin < 8 gm/dL, total leukocyte count < 3500/ mm^3, platelet count < 100,000/mm^3 • Elevation of hepatic enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) to more than twice the upper limit of normal or any deranged liver function tests • Hepatitis, active or recurrent, cirrhosis or excessive current alcohol intake • Use of other hepatotoxic drugs by the patient • Positive hepatitis B, hepatitis C or HIV serology • Pulmonary or extra-pulmonary active tuberculosis • Deranged renal function test • Pregnancy or lactation or if patient is planning to conceive during the treatment period • Patient on other immunosuppressive drugs • Recent live vaccination • Unreliable patient • Patients unwilling for monthly follow-ups • Patient with known hypersensitivity to drug. Patient with unrealistic expectation

CTRI/2020/10/028555 2020 *(Continued)*

Interventions	**Intervention 1** A. Methotrexate oral 0.3-0.5 mg/kg body weight/week **Intervention 2** B. Methotrexate injectable 0.3-0.5 mg/kg body weight/week
Outcomes	At 7th day, 30th day, 60th, 90th day **Primary outcomes** • PASI in chronic plaque psoriasis • mPASI in palmoplantar psoriasis **Secondary outcomes** • VAG in chronic plaque psoriasis • PGA in chronic plaque psoriasis • DLQI in chronic plaque psoriasis • VAG in palmoplantar psoriasis • PGA in palmoplantar psoriasis • PPQOL in palmoplantar psoriasis
Notes	Dr Pooja Kanumuru pooja.kanumuru@yahoo.com Last check in October 2021

DRKS00000716

Methods	Randomised, active-controlled, parallel-group, simple blind study Date of study: 3 June 2008 (starting date) Location: Germany
Participants	**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 breastfeeding. 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 • 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

DRKS00000716 *(Continued)*

Interventions	• Arm 1: adalimumab (Humira): 80 mg initial, then 40 mg at 2 weeks and every other week, until 24 weeks • Arm 2: etanercept (Enbrel): 50 mg 2 x week SC 12 weeks, then 25 mg 2 x week SC 12 weeks • Arm 3: Fumaderm
Outcomes	At week 8: PASI DLQI Immunohistology At week 24: PASI DLQI Immunohistology
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 Study Closing (LPLV): 2010/10/03 We emailed Prof. Jacobi (5 January 2017) without response. Last check in October 2021

EUCTR2010-020168-39-DE

Methods	Randomised, placebo-controlled, parallel-group, double-blind study Date of study: September 2010-January 2012 Location: Germany Phase 2
Participants	**Total sample size:** 252 **Inclusion criteria** • Patients of either sex at least 18 years of age • A clinical diagnosis of plaque psoriasis defined as skin areas with erythema, induration and scaling, with a body surface area of no less than 10% and in total to be scoring at least 10 on the PASI scale • The psoriasis disease has been stable for at least 6 months at randomisation • Sexually-active women of childbearing potential must be either surgically sterile (hysterectomy or tubal ligation) or use a highly effective (failure rate < 1%) medically accepted contraceptive method during the trial as well as 1 month after trial is finished such as: Systemic contraceptive (oral, implant, injection), intrauterine device (IUD) inserted for at least 1 month prior to study entrance • Willingness and ability to comply with the trial procedures • Patient is, apart from psoriasis disease, in good general health in the opinion of the investigator, as determined by medical history, physical examination, vital signs and clinical laboratory parameters (haematology, biochemistry and urinalysis). **Exclusion criteria**

EUCTR2010-020168-39-DE *(Continued)*

	• Women who are pregnant or breastfeeding or planning to become pregnant up to 7 months from treatment start as well as men planning pregnancy with their partner up to 7 months from treatment start or practise unprotected sexual relationship up to 7 months from treatment start • Known allergy to any of the constituents of the product being tested. Pustular forms of psoriasis, erythrodermic or guttate psoriasis, known immunosuppressive diseases (e.g. AIDS/HIV) • Presence of another serious or progressive disease which, according to the Investigator, may interfere with treatment outcome. Active skin disease such as atopic dermatitis, rosacea, lupus erythematosus, or other inflammatory or infectious skin disease which, according to the Investigator, may interfere with treatment outcome • Use of topical medical treatment or UVB treatment - use of systemic anti-psoriatic treatment preceding the baseline visit; methotrexate, cyclosporine, steroids or PUVA treatment; biological treatment (efalizumab, adalimumab, infliximab, etanercept); acitretin; treatment with Fumaderm® or other DMF-containing products; discontinuation of previous treatment with Fumaderm® or other DMF-containing products due to lack of efficacy or side effects; no precision was available about the length of periods without previous treatments • Use of drugs influencing the course of the psoriasis such as antimalarial drugs, beta-blockers or lithium • Has a relevant clinical history of stomach or intestinal problems (e.g. gastritis or peptic ulcer within the last 10 years) • Has liver enzyme measures (AST, ALT, Gamma-GT) higher than 2 x ULN) • Kidney failure, leucopenia, lymphopenia or hypereosinophilia • Has protein in the urine test at screening or baseline visit • Participation in another clinical trial during the last month preceding the baseline visit or participation in a trial with treatment of biologicals • Patients who are involved in the organisation of the clinical investigation or are in any way dependant on the investigator or sponsor
Interventions	**Intervention 1**: FP-187 (dimethyl fumarate) at a daily dose of 750 mg divided in 3 doses (250 mg TID) **Intervention 2**: FP-187 at a daily dose of 750 mg divided in 2 doses (375 mg BID) **Intervention 3**: FP-187 at a daily dose of 500 mg divided in 2 doses (250 mg BID) **Intervention 4**: Placebo
Outcomes	**Primary outcome**: • PASI 75 compared to placebo week 20 **Secondary outcome** • PASI 75 at week 4, 8, 12 and 16 • PASI 50 at week 4, 8, 12, 16 and 20 • PASI 90 at week 4, 8, 12, 16 and 20 • PGA (Physicians Global Assessment) at week 4, 8, 12, 16 and 20 • PaGA (Participants Global Assessment: at week 4,8,12,16 and 20 • Participants evaluation on a 5-point Likert scale • Pruritus DLQI at week 4, 8, 12, 16 and 20 • Adverse events (AEs) at week 4, 8, 12, 16 and 20
Notes	Recruitment status: completed Last update posted: December 2012 Study completion date on ClinicalTrials.gov: May 2012 Last checked in October 2021

EUCTR2010-020168-39-DE *(Continued)*

NCT01230138
Contact: Peder M Andersen, MD Forward-Pharma GmbH

EUCTR2015-005279-25-DE

Methods	Randomised, placebo-controlled, parallel-group, double-blind study Date of study: September 2016 (starting date) Location: Germany Phase 2
Participants	**Total sample size:** 36 **Inclusion criteria** • Signed and dated informed consent • Aged between 18 years and 65 • Men or women of non-childbearing potential • Clinical diagnosis of psoriasis vulgaris with or without psoriatic arthritis • Have moderate-to-severe psoriasis vulgaris • Candidates of systemic anti-psoriatic treatment and/or phototherapy **Exclusion criteria** • Patients with therapy-resistant psoriasis • Previously exposed to apremilast • Systemic treatment with biological therapies, whether marketed or not, with a possible effect on psoriasis vulgaris • Systemic treatment with all other therapies (other than biologics) with a possible effect on psoriasis vulgaris
Interventions	**Intervention** **A.** LEO 32731 (phosphodiesterase 4 inhibitor, Orismilast) 30 mg twice a day for 16 weeks **Control Intervention** **B.** Placebo
Outcomes	**Primary outcome** • Psoriasis Area and Severity Index (PASI) at week 16 **Secondary outcomes** • Proportion of participants with Physician's Global Assessment of Disease Severity (PGA) treatment success, defined as clear or almost clear at week 16 • Itch evaluated by itch Numerical Rating Scale (NRS) at week 16
Notes	Study completion date on ClinicalTrials.gov July 2017 Last update posted: August 2017 Last checked in October 2021 NCT02888236 Sandra Philipp, PhD, Charite University, Berlin, Germany hautarzt.philipp@gmail.com

EUCTR2015-005279-25-DE *(Continued)*

	Email sent to Pr Sandra Philipp (31 August 2021) without response UNION Therapeutics announces acquisition of Orismilast compound class from LEO Pharma; we will wait for more information.

Goldust 2019

Methods	RCT study, 4 were randomly assigned to receive combination therapy (efficacy assessments were performed)
Participants	**Randomised :** 48 patients with moderate-to-severe plaque psoriasis
Interventions	**Intervention 1:** adalimumab SC 80 mg at weeks 1 and 2 then 40 mg every 2 weeks **Intervention 2**: no intervention or placebo ?? Co-intervention: methotrexate 15–20 mg a week or methotrexate monotherapy
Outcomes	PASI Hospital Anxiety and Depression scale
Notes	ABSTRACT Contact author: Drmgjgoldust@gmail.com Email sent to Pr Goldust (31 August 2021)

Han 2007

Methods	Randomised, double-blind, active-controlled study Date: not stated Location: China
Participants	No statement except a total number of participants (n = 144)
Interventions	**Intervention** A. Recombinant human tumour necrosis factor receptor (50 mg/week) **Control intervention** B. 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 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 (rhTN-FR:Fc) in the treatment of moderate-to-severe plaque psoriasis on psoriasis area and severity in-

Han 2007 *(Continued)*

dex (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 PASI 50, PASI 75, PASI 90 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 score."

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, oedema 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

Krishna 2016

Methods	RCT, active-controlled, double-blind study Date of study: November 2013-January 2015 Location: India Phase 4
Participants	**Randomised**: 50 participants **Inclusion criteria** • Age range 18-65 years • Both sexes • Severe plaque-type psoriasis (BSA > 10% or PASI > 12)

Krishna 2016 *(Continued)*

	Exclusion criteria • Pregnancy • Lactation • Malignancy or immunosuppression including HIV • Liver disease • Renal disease • Non-compliant • Psychiatric illness • Hypersensitivity to methotrexate in the past
Interventions	**Intervention** A. Methotrexate 10 mg/week **Control intervention** B. 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 (NCT02248792) Recruitment status: Unknown verified September 2014 by C. V. Krishna, Narayana Medical College & Hospital. Recruitment status was: Recruiting 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; 11 February 2020)

Makavos 2020

Methods	RCT, active-controlled, open study Date of study: not stated Location: not stated
Participants	**Randomised**: 150 participants, mean age 52; 92 men **Inclusion criteria** • Plaque-type psoriasis (n = 78) • Psoriatic arthritis (n = 72) **Exclusion criteria**

Makavos 2020 *(Continued)*

- Ejection fraction ≤ 50%
- History of acute coronary syndrome
- Familial hyperlipidaemia
- Diabetes mellitus
- Moderate-to-severe valvular heart disease
- Primary cardiomyopathies
- Malignant tumours

Dropouts and withdrawals

- Not stated

Interventions	**Intervention** A. Secukinumab, 300 mg SC, W0, 1, 2, 3, 4 and 300 mg once monthly **Control intervention** B. Ciclosporin, 2.5 to 3 mg/kg daily C. Methotrexate (non-randomised controlled group, n = 50)
Outcomes	Assessments at 16 weeks **Primary outcome** • vascular function **Secondary outcomes** • coronary flow reserve of the LAD by Doppler echography • Arterial stiffness • PASI
Notes	Authors were asked whether - methotrexate group was randomised or not - included patients were moderate-to-severe psoriasis - randomisation was stratified according psoriatic arthritis or not - subgroup results for plaques psoriasis for our outcomes An email was sent without response to Pr Ikonomidis (30 October 2020, 10 September 2021)

Mrowietz 2005

Methods	RCT, placebo-controlled, double-blind study Date of study: not stated Location: not stated
Participants	**Randomised**: 175 participants (characteristics not stated) **Inclusion criteria** • Not stated

Mrowietz 2005 *(Continued)*

	Exclusion criteria • Not stated **Dropouts and withdrawals** • Not stated
Interventions	**Intervention** 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 outcome** • PASI **Secondary outcomes** • 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 study Date of study: May 2010 - end date not reported Location: 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**

NCT01088165 *(Continued)*

	• 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 **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 Interventions** 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, NCT01088165) by Medical University of Vienna Recruitment status: Unknown verified January 2012 by Gregor Holzer, Medical University of Vienna Estimated study completion date: May 2014 Last update posted: January 2012 We sent an email to Prof. Holzer to be sure this trial is still ongoing (3 June 2019 and 11 February 2020) without response. Gregor Holzer, MD gregor.holzer@meduniwien.ac.at Last check in October 2021

NCT01558310

Methods	RCT, placebo-controlled, double-blind study Date of study: March 2012 Location: USA

NCT01558310 *(Continued)*

	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 sPGA 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
	• 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 > 10 g/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

NCT01558310 *(Continued)*

- 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 sPGA/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 sPGA/PASI evaluation (e.g. corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethyl psoralens) within 2 weeks of the first administration of study agent
- Have used any systemic immunosuppressants (e.g. methotrexate, azathioprine, ciclosporin, 6-thioguanine, mercaptopurine, mycophenolate, mofetil, hydroxyurea, and tacrolimus) within 4 weeks of the first administration of study agent
- Are currently receiving lithium, anti-malarials, or intramuscular gold, or have received lithium, anti-malarials, or intramuscular gold, or have received lithium, anti-malarials, or intramuscular gold within 4 weeks of the first administration of study agent
- Have received within 3 months prior to the first injection a live virus or bacterial vaccination. Participants must agree not to receive a live virus or bacterial vaccination during the trial or up to 12 months after the last study agent injection.
- Have had a BCG vaccination within 12 months of screening. Participants must agree not to receive a BCG vaccination during the trial or up to 12 months after the last study agent injection.
- Have a history of chronic or recurrent infectious disease, including but not limited to chronic renal infection, chronic chest infections (e.g. bronchiectasis), recurrent urinary tract infections (recurrent pyelonephritis or chronic non-remitting cystitis), or open, draining, or infected skin wounds or ulcers
- Have or have had a serious infection (e.g. sepsis, pneumonia,or pyelonephritis) or have been hospitalised or received IV antibiotics for an infection during the 2 months prior to screening
- 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)

NCT01558310 *(Continued)*

	• 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** A. 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** B. Placebo
Outcomes	At week 12 **Primary outcome** • Scalp-specific PGA **Secondary outcomes** • Not stated
Notes	On ClinicalTrials.gov estimated enrolment: 30 Recruitment status: Unknown verified July 2012 by Paul Steven Yamauchi, MD, PhD, Yamauchi, Paul Steven, M.D., Ph.D. Not yet recruiting Estimated study completion date: December 2013 We emailed Dr Yamauchi (5 and 12 January 2017). Email response: "Dear Dr Sbidian, Thank you for your kind email, forwarded to me by Dr Paul Yamauchi, MD, PhD. Our 'Study to Evaluate the Effectiveness of STELARA ™ (USTEKINUMAB) in the Treatment of Scalp Psoriasis (NCT 01558310)' completed enrolment in December 2016 and the last subject will complete in December 2017; as such we do not have the final data analysis. What is your absolute cut-off for publication data? Would an interim analysis report be acceptable? Best regards, Rickie Patnaik Director, Clinical Science Institute" Will be included when published paulyamauchi@yahoo.com

NCT02655705

Methods	RCT, placebo-controlled, open-label study Date of study: September 2015 - end date not reported Location: Korea Phase 4
Participants	Inclusion criteria: • Present with chronic plaque psoriasis based on a clinical diagnosis

NCT02655705 *(Continued)*

- Have > 5% body surface area involvement at screening
- Are a candidate for systemic therapy
- Are male or female patients 18 years or older
- 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, cyclosporine, and methotrexate) within 4 weeks prior to baseline
- 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** A. Ciclosporin A (men 200 mg/day, women 150 mg/day for 16 weeks) **Control intervention** B. 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 and 11 February 2020) Last checked in October 2021

NCT02701205

Methods	RCT, placebo and active-controlled, double-blind study Date of study: January 2015 - end date not reported Location: China
Participants	**Randomised**: 216 participants **Inclusion criteria** • Men or women, age 18-65, Asian • Freely provides both verbal and written informed consent

NCT02701205 *(Continued)*

- 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 ≥ 110 g/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 breastfeeding 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
- 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

NCT02701205 *(Continued)*

	• Joint prosthesis has not yet been removed or replaced
Interventions	**Intervention** A. Recombinant Human TNF Receptor-Ig Fusion Protein for Injection (Qiangke®) 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 (Qiangke®) 50 mg once a week for an additional 12 weeks **Control intervention** B. Recombinant Human TNF Receptor-Ig Fusion Protein for Injection (Qiangke®) 25 mg 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 (Qiangke®) 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
Notes	Unpublished Emails sent to Prof Hongzhong Jin (3 June 2019 and 11 February 2020 (not delivered), 30 August 2021)

NCT02714322

Methods	RCT, active-controlled, double-blind study Date of study: June 2015 Location: Russia, Estonia, Hungary, Poland, Bulgaria Phase 3
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)

NCT02714322 *(Continued)*

- 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
- 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)

NCT02714322 *(Continued)*

	• 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) 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) 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** • Percent improvement in PASI from baseline **Secondary outcome** • Proportion of participants showing at least a 75% improvement in PASI (PASI 75 response rate) • Number of subjects achieving sPGA responses of clear (0) or almost clear (1)
Notes	Recruitment status: completed Last update posted: May 2017 Actual study completion date: March 2017 No principal investigator stated on ClinicalTrials.gov; waiting for results publication Last checked in October 2021

NCT02829424

Methods	RCT, active-controlled, double-blind study Date of study: April 2016 Location: France Phase 4
Participants	**Randomised**: 330 participants

NCT02829424 *(Continued)*

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

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 ULN) 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

NCT02829424 *(Continued)*

- 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 < 3 G/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 (ULN); Haemoglobin < 8.5 g/dL (85.0 g/L); Creatinine clearance < 40 mL/min (Cockcroft formula)
- For women: pregnant or breastfeeding
- 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 **Secondary outcomes** PASI 75 PASI 50 Maintenance of response rates proportion DLQI
Notes	End prematurely - unpublished Last checked in October 2021

NCT04488185

Methods	RCT, placebo-controlled, double-blind study Date of study: June 2020

NCT04488185 *(Continued)*

	Location: unknown Phase 4
Participants	**Inclusion criteria:** Clinical diagnosis of chronic plaque-type psoriasis confirmed through physical examination by a dermatologist, with at least 6 months of clinical history prior to the baseline visit Moderate-to-severe plaque psoriasis at baseline, defined as: • ≥ 10 % Body Surface Area (BSA) involvement, or • ≥ 3% to < 10% BSA with involvement of special regions (nails, scalp, or intertriginous skin), or with a history of psoriatic arthritis in a parent Candidate for systemic therapy, defined as having psoriasis inadequately controlled by current topical and/or systemic treatment(s) (including topical corticosteroids), phototherapy, or previous systemic therapies Presence of sonographic enthesitis at screening, in at least 1 enthesis, defined by the presence of at least abnormal thickening and hypoechogenicity of the tendon insertion, with or without presence of Doppler signal (Grade 0-3), or by the presence of grade ≥ 2 Doppler signal, independent of gray scale abnormalities **Exclusion criteria:** • Diagnosis of PsA as per CASPAR confirmed by a rheumatologist (including the presence of inflammatory pain in entheses or joints), and any other known rheumatological disease affecting the assessed joints • Exposure to any IL-17 or IL-23(p19) inhibitor for the treatment of psoriasis (approved or investigational) within 12 months prior to screening, or exposure to any inhibitors of TNF-α and IL-12/-23 within 6 months prior to screening • Previous exposure to non-biologic systemic therapy for psoriasis, including methotrexate, PDE-4 inhibitors, or systemic corticosteroids within 12 weeks or 5 half-lives (whichever is longer) prior to screening • A degree of obesity that impedes proper ultrasound examination of entheses and joints • Forms of diagnosed psoriasis other than chronic plaque psoriasis (e.g. erythrodermic, generalised or localised pustular psoriasis, or new-onset guttate psoriasis) • Other protocol-defined inclusion/exclusion criteria may apply
Interventions	**Intervention** A. Secukinumab 300 mg administered SC (2 single-use prefilled syringes of 150 mg/mL), on days 1, 8, 15, 22, 29, 57, 85 **Control intervention** B. Placebo
Outcomes	At week 16 **Primary outcome** • Change from baseline in the Outcome Measures in Rheumatology (OMERACT) ultrasound enthesitis score **Secondary outcomes** • Change from baseline in the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) ultrasound enthesitis score • Change from baseline in the PsASon13 unilateral ultrasound composite score of synovitis • Number of participants who achieve complete resolution of enthesitis based on OMERACT criteria

NCT04488185 *(Continued)*	• Number of participants who achieve Psoriasis Area and Severity Index 90 (PASI 90) • Number of participants who achieve Investigator's Global Assessment modified 2011 (IGA mod 2011) score of 0 or 1 • Change from baseline in Dermatology Life Quality Index (DLQI) score
Notes	Recruitment status: recruiting Last update posted: March 2021 Actual study completion date: April 2022 Waiting for subgroup analyses for participants with moderate-to-severe psoriasis Last checked in October 2021

ABT-874: name of a monoclonal anti–interleukin 12/23 antibody
ACR50: American College of Rheumatology response criteria, ACR 50: 50% improvement from baseline ACR
ADA: adalimumab
AEs: adverse effects
AIDS: acquired immunodeficiency syndrome
ALT: aspartate transaminase
AST: alanine transaminase
BCG: bacille Calmette-Guérin
B-HCG: beta-human chorionic gonadotropin
BID: two times a day
BMI: body mass index
BSA: body surface area
CASPAR: classification criteria for psoriatic arthritis
CIN: Cervical intraepithelial neoplasia
CPDAI: composite psoriatic disease activity index
CRP: c-reactive protein
csDMARD: conventional systemic disease-modifying antirheumatic drugs
DAS-28: disease activity score-28 (measure of disease activity in rheumatoid arthritis)
DLQI: Dermatology Life Quality Index
DMF: dimethylformamide
DNA: deoxyribonucleic acid
ECG: electrocardiogram
eow: every other week
FAEs: fumaric acid esters
FMD: flow-mediated dilatation
FP-187: forward-pharma-187 is a fumaric acid ester
FSH: follicle-stimulating hormone
GRAPPA: group for research and assessment of psoriasis and psoriatic arthritis
HAQ-DI: health assessment questionnaire disability index
HBcAb: hepatitis B core antibody
HBsAb: hepatitis B surface antibody
HBsAg: hepatitis B surface antigen
HBV: hepatitis B virus
HCV: hepatitis C virus
HIV: human immunodeficiency virus
HS626: infliximab biosimilar
ICTRP: international clinical trials registry platform
IGA: Investigator's Global Assessment
IL(-12/-17/-23): interleukin-12,-17,-23
IM: intramuscular
IMT: intima-media thickness
ISA247: voclosporin (immunosuppressive agent)
IUD: intrauterine device
IV: intravenous
LAD: left anterior descending coronary artery

LDI-B: Leeds dactylitis index-basic
LEI: Leeds enthesitis index
LEO 32731: phosphodiesterase-4 inhibitor
MDA: minimal disease activity
mPASI: modified PASI
MTX: methotrexate
MYL-1401A: adalimumab biosimilar
NAPSI: Nail Psoriasis Severity Index
NRS: numeric rating scale
NYHA: New-York heart association
OMERACT: international, informally organized network which is an independent initiative of international stakeholders interested in outcome measurement
OPD: outpatient department
PaGA: Patient Global Assessment
PASI: Psoriasis Area and Severity Index
PDE-4: phosphodiesterase-4 i
PGA: Physician's Global Assessment
PPD: purified protein derivative
PPQOL: palmoplantar quality of life instrument score
Ps: psoriasis
PsA: psoriatic arthritis
PsARC: psoriatic arthritis response criteria
PsASon13: unilateral score compromised 13 joints
PSS: psoriasis symptom scale
PUVA: psoralen plus ultraviolet A
Q2W: every other week
RCT: randomised controlled trial
rhTNFR:FC: tumour necrosis factor Receptor: fusion protein
SC: subcutaneous
SF-36: short-form 36
SJC: swollen joint count
SKINDEX: quality of life index for patients with skin diseases
SmPC: summaries of product characteristics
SPARCC: spondyloarthritis research consortium of Canada score
SPGA: static physician global assessment
TB: tuberculosis
TGP: glutamate-pyruvate transaminase
TID: three times a day
TJC: the joint commission
TNF: tumour necrosis factor
ULN: upper limit of normal
UVB: ultraviolet B
VAG: visual grading analysis
VAS: visual analogue scale
W (followed by number): week
Please note that the term “conventional” in these tables is replaced with “non-biological treatment” in the main text of this review.

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

Cestari 2021

Study name	Efficacy and safety of risankizumab vs methotrexate in patients with moderate-to-severe plaque psoriasis: results from the 28-week randomized, double-blind period of an ongoing phase 3 study in Brazil
Methods	RCT, double-blind, active controlled multicentre study Date of study: July 2018- September 2021 Location: Brazil (11 sites)

Cestari 2021 *(Continued)*

	Phase 3
Participants	**Randomised**: 98 participants **Inclusion criteria** • Have a diagnosis of plaque psoriasis (with or without concurrent psoriatic arthritis) for at least 6 months before the first administration of study drug • Have stable moderate-to-severe plaque psoriasis with or without psoriatic arthritis at both screening and baseline visits • Be a candidate for systemic therapy for plaque psoriasis as assessed by the investigator • Be a candidate for treatment with methotrexate according to local label **Exclusion criteria** • Subjects with non-plaque forms of psoriasis, current drug-induced psoriasis, or active ongoing inflammatory diseases other than psoriasis that might confound study evaluations according to investigator's judgement • Previous exposure to risankizumab • Previous exposure to methotrexate • Use of any prohibited medication or any drug considered likely to interfere with the safe conduct of the study, as assessed by the investigator • Subject has a history of clinically significant haematologic, renal, or liver disease
Interventions	**Intervention** A. Risankizumab at weeks 0, 4, and every 12 weeks thereafter SC, n = 50 **Control intervention** B. Methotrexate weekly oral 5 mg may be titrated up to 25 mg, unless achieved ≥ 90% reduction in Psoriasis Area Severity Index [PASI 90] and static Physician's Global Assessment [sPGA] of clear/almost clear [0/1] or shown poor tolerability, n = 48 All patients received 5 mg folate weekly.
Outcomes	At 28 weeks **Primary outcomes** • sPGA score of clear or almost clear (0, 1) • PASI 90 **Secondary outcomes** • PASI 100/75 • sPGA score of clear (0) • Change from baseline in EQ-5D-5L • Achievement of an increase of 0.1 or more points from baseline in European Quality of Life 5 Dimensions (EQ-5D-5L)
Starting date	Actual study start date: July 2018 Estimated primary completion date: September 2021 Last update posted: December 2020, active, not recruiting
Contact information	Not stated
Notes	Funding: Quote (clinicaltrials.gov): AbbVie

Cestari 2021 *(Continued)*

	NCT03219437

CTRI/2019/07/020274

Study name	Comparative efficacy of methotrexate, apremilast and their combination in psoriasis vulgaris
Methods	Randomised, parallel-group, multiple-arm study Date of study: July 2019 Location: India
Participants	**Randomised**: 30 participants **Inclusion criteria:** • > 18 year to 60 years • Patients with psoriasis vulgaris requiring systemic therapy (Body surface area > 10%) • PASI score > 10 or non-responsive to topical therapy **Exclusion criteria** • Patients suffering from any other significant systemic illness • History of anti-psoriatic treatment in the last 2 months • Pregnant or lactating women
Interventions	**Intervention 1**: apremilast 30 mg twice a day, starting at 10 mg/day with an increment of 10 mg/day over 5 days, for 8 weeks **Intervention 2**: oral methotrexate 0.2 mg/kg/week, maximum 25 mg/week for 8 weeks **Intervention 3: o**ral methotrexate 0.2 mg/kg/week, maximum 25 mg/week along with oral apremilast 30 mg twice a day, starting at 10 mg/day with an increment of 10 mg/day over 5 days, for 8 weeks
Outcomes	**Primary outcome:** To compare the efficacy of apremilast and methotrexate and their combination in patients with psoriasis vulgaris by comparing the PASI score before and after start of the therapy at 0, 2, 4, 6, 8 weeks **Secondary outcome:** To assess the safety of all the three treatment modalities by assessing the side effects at 0, 2, 4, 6, 8 weeks
Starting date	Date of first enrolment: July 2019 Last modified on: 22 July 2019, estimation duration of trial one year
Contact information	Dr Nainika Goel Government Medical College and Hospital, Chandigarh Address Department of Dermatology, D block, 5th floor, GMCH, sector 32, Chandigarh Chandigarh CHANDIGARH 160030 dr.nainika1311@gmail.com
Notes	Ongoing trial

CTRI/2019/07/020274 *(Continued)*

	Last checked in October 2021

CTRI/2020/02/023107 2020

Study name	Prospective, multi-center, randomized, double-blind, two-arm, parallel group, active control, comparative clinical study to evaluate efficacy and safety of R-TPR-046/Stelara® in patients with moderate-to-severe plaque psoriasis
Methods	Randomized, parallel-group, active controlled trial Date of trial approval: 2019 Location: India
Participants	Randomised: 220 **Inclusion criteria:** • Male or female between 18 and 65 years of age • Patients with diagnosis of plaque-type psoriasis at least 6 months prior to first administration of study drug • Patients with moderate-to-severe plaque psoriasis with > 10% BSA involvement and PASI score >12 at screening • Patients who are potential candidates for phototherapy or systemic treatment of psoriasis **Exclusion criteria** • Patients with non-plaque forms of psoriasis (e.g. erythrodermatic, guttate, or pustular) • Patients with current drug-induced psoriasis (e.g. a new onset of psoriasis or an exacerbation of psoriasis from beta-blockers, calcium channel blockers, or lithium) • Pregnant, nursing females or planning pregnancy (both males and females) during the study period until 12 months after receiving the last injection of study drug • Use of any therapeutic agent targeted at reducing lL-12 or IL-23, including but not limited to ustekinumab • Patients who have received phototherapy or any systemic medications/treatments that could affect psoriasis or PASI evaluation (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 prior to first administration of study drug • Use of topical medications/treatments that could affect psoriasis or PASI evaluation (e.g. corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralens) within 2 weeks prior to first administration of study drug
Interventions	**Intervention** R-TPR-046 (ustekinumab biosimilar) at week 0, week 4, week 16, week 28 and week 40 **Control intervention** Ustekinumab at week 0, week 4, week 16, week 28 and week 40
Outcomes	At week 12 **Primary outcome** • Proportion of participants achieving PASI 75 responses At week 52 **Secondary outcomes**

CTRI/2020/02/023107 2020 *(Continued)*

- Proportion of participants achieving PASI 50
- Proportion of participants achieving PASI 75
- Proportion of participants achieving PASI 90
- Proportion of participants achieving PASI 100
- Proportion of participants achieving Physician Global Assessment (PGA) score of 'cleared' or 'minimal'
- Change in DLQI from baseline
- Proportion of participants achieving DLQI score of 0 or 1
- Improvement in Short Form-36 Health Survey Questionnaire (SF-36) score from baseline
- Single dose and multiple dose pharmacokinetic assessment of R-TPR-046 and Stelara

Starting date	September 2020 Last modified: August 2021
Contact information	Dr Supriya Sonowal Reliance Life Sciences Pvt. Ltd. Address : RLS Bio - Product Trials Group, Dhirubhai Ambani Life Sciences Centre (DALC) R-282, TTC Area of MIDC, Thane - Belapur Road, Rabale, Navi Mumbai - 400701, India Thane MAHARASHTRA 400701, India Thane MAHARASHTRA 400701 India supriya.sonowal@relbio.com
Notes	Ongoing trial Last checked in October 2021

Dong 2020

Study name	Pharmacokinetics, tolerability, immunogenicity, dose increasing safety and evaluate of preliminary effect clinical trial on GR1501 injection in patients with plaque psoriasis
Methods	Randomised, parallel, double-blind study Date of study: August 2018-August 2020 Location: China Phase I/II
Participants	**Randomised**: 46 participants **Inclusion criteria:** • Male or female between 18 and 65 years of age • Body index (BMI) 18-32 kg/m^2 • Plaque psoriasis history ≥ 6 months • Psoriasis BSA ≥ 10% • The grade of psoriasis area and severity index (PASI) ≥ 12 • The poor treatment effect on patients with moderate-to-severe plaque psoriasis • Consent to participate in the research study and sign the informed consent form

Dong 2020 *(Continued)*

	Exclusion criteria • At baseline or screening, patients with pustular psoriasis, erythroderma psoriasis and/or drip psoriasis • Drug psoriasis on baseline • Systemic therapy on the whole body within 4 weeks prior to the baseline • Received any biological agents directly targeting IL-17 • Participate in other clinical trials within 3 months prior to the baseline • Received live vaccine within 4 weeks prior to the baseline • Patients with active tuberculosis • Drug and biological agents allergies • Received a major operation within 8 weeks prior to the baseline or study period • Subjects with history of lymphoproliferative disease or with malignant tumour previously or concurrently • Subjects with active infection previously or concurrently • Subjects with hepatitis B surface antigen-positive hepatitis C antibody-positive human immunodeficiency virus (HIV) antibody-positive or TPPA positive • ECG abnormalities with clinical significance • Unstable cardiovascular disease • Hypertensive patients with unstable blood pressure • Subjects with abnormal function of liver and kidney or blood routine abnormality • Blood donation ≥ 400mL or blood loss ≥ 400 mL within 4 weeks prior to the baseline • Women who have fertility refusal to adopt contraception from the screening period to the last time after the end of the drug delivery • Pregnancy or lactation • Patients who have a history of smoking, alcohol abuse or drug abuse • Subjects with history or family history of severe psychosis • Other subjects judged by the investigator to be ineligible for enrolment in the study
Interventions	**Intervention** A. GR1501 (monoclonal antibody IL-17A) **Control intervention** B. Placebo
Outcomes	**Primary outcomes** • Adverse events • Laboratory tests, vital signs and physical examinations At week 12 **Secondary outcomes** • Proportion of participants achieving PASI 75, PASI 90 responses • Proportion of participants whose sPGA is 0 or 1 • The immunogenicity evaluation criteria will include the antidrug antibody positive rate before and after administration. • t1/2, Cmax, Tmax, AUC0-t, AUC0-∞, AUCss, Cav, CL
Starting date	Starting date: August 2018 Date last refreshed on: August 2018 (recruiting status: recruiting)
Contact information	Yi Fang phaseistudy@163.com

Dong 2020 *(Continued)*

Notes	Funding: Chinese Society of Academic Degrees and Graduate Education 'the Project of Research of Degree and Master Education' (No:2019YX01) and Genrix (Shanghai) Biopharmaceutical Co Completed according to the protocol ChiCTR1800017956 Last checked in October 2020

DRKS00022104 2020

Study name	Influence of psychological factors on the response to therapy with secukinumab in psoriasis patients on the subjective and objective level (PSOPSYCH)
Methods	RCT, parallel, double-blind, active-control study Date of study: September 2020 Location: Germany Phase 3b
Participants	Randomised: 120 participants **Inclusion criteria:** • Adults >= 18 years of age • Subject has had diagnosis of moderate-to-severe chronic plaque psoriasis for at least 6 months • Psoriasis Area and Severity Index (PASI) > 12 and Body Surface Area (BSA) affected by plaque psoriasis of 10% or greater • Patient is a candidate for systemic therapy (this is defined as a patient having moderate-to-severe chronic plaque psoriasis that is inadequately controlled by topical treatment and/or phototherapy and/or previous systemic therapy) • Women must not be pregnant and, if of childbearing potential, must have a negative serum pregnancy test before entering the study. • Women of childbearing potential must agree to use a highly effective method of contraception throughout the therapy. **Exclusion criteria** • Age < 18 years • Forms of psoriasis other than chronic plaque (e.g. pustular, erythrodermic, guttate or drug-induced) psoriasis • Existing contraindication to therapy with secukinumab according to the summary of product characteristics like history of hypersensitivity to secukinumab or its excipients or to drugs of similar chemical classes or clinically relevant (chronic or acute) infections, e.g. untreated (latent) tuberculosis or HIV infection • Significant medical problems, which in the opinion of the investigator, significantly immunocompromises the subject and/or places the subject at unacceptable risk for receiving therapy with secukinumab • History of, respectively active, inflammatory bowel disease (IBD) • Administration of live vaccines < 6 weeks before first injection of secukinumab • Any medical or psychiatric condition which, in the investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol • Previous exposure to secukinumab • Ongoing use of systemic anti-psoriatic treatments (concomitant topical treatment is allowed)

DRKS00022104 2020 *(Continued)*

	• History or evidence of ongoing alcohol or drug abuse, within the last six months before start of the study • Subject is lacking capacity to consent.
Interventions	**Intervention 1**: 300 mg secukinumab (as in clinical routine consisting of two SC injections with 150 mg) for 5 weeks (weeks 0-4) followed by additional injections four (week 8) and eight (week 12) weeks later **Intervention 2**: one injection with 75 mg secukinumab and one injection with NaCl during all treatment weeks. **Intervention 3**: 75 mg secukinumab and an additional positive verbal instruction (cover story, see below) to strengthen their expectation towards the benefits of this "exceptional new drug." In addition, the salience of this verbal instruction will be reinforced by combining each injection with the ingestion of a new tasting beverage together with the detailed information, that "… studies showed that this combination (drug & drink) induces significant additional beneficial effects on disease symptomatology and disease activity."
Outcomes	At week 16 **Primary outcomes** • Impairment of quality of life caused by the skin disease as measured with the DLQI • Pruritus and skin pain as measured with the Numeric Rating Scale (NRS) and the Visual Analogue Scale (VAS) **Secondary outcome** • Severity of skin lesions as measured with the PASI
Starting date	September 2020 Recruitment status: recruiting in progress
Contact information	Ms. Dr. Wiebke Sondermann Universitätsklinikum Essen (AöR)Allgemeine Poliklinik, PsoriasisKlinik für Dermatologie, Venerologie und Allergologie Hufelandstraße 55 45122 Essen Germany wiebke.sondermann@uk-essen.de
Notes	Ongoing study DRKS00022104 Last checked in October 2021

EUCTR2013-004918-18-NL

Study name	Optimising adalimumab treatment in psoriasis with concomitant methotrexate - OPTIMAP
Methods	Phase 4 RCT, placebo-controlled, open-label trial

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

	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 premenopausal 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 endpoint: 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) • Occurence of (serious) AEs • Participant 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 by biologic), trial medication and potential other covariates (e.g. genetic polymorphisms) Time point(s) of evaluation of this endpoint: week 13, 25, 37 and 49
Starting date	12 December 2013

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

	Date of the global end of the trial: 2020-06-04
Contact information	Prof 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 Trial status: prematurely ended Last checked in July 2021

EUCTR2017-001615-36-DE

Study name	Study to evaluate ABY-035 in subjects with moderate-to-severe plaque psoriasis (AFFIRM-35)
Methods	Randomised, placebo-controlled, parallel-group, double-blind study (AFFIRM-35) Date of study: March 2018 (starting date) Location: Germany Phase 2
Participants	**Inclusion criteria:** • Diagnosed with plaque psoriasis of at least 6 months prior to screening, without clinically significant flares during the 12 weeks before randomisation, with or without psoriatic arthritis • Having precedent failure, intolerance or contraindication to at least 2 standard therapies for moderate-to-severe plaque psoriasis • Moderate-to-severe plaque psoriasis at screening and at baseline as defined by: i. Psoriasis involving ≥ 10% BSA; ii. PASI score of ≥ 12; iii. sPGA score of ≥ 3 • Use of highly effective contraceptive measure, woman of non-childbearing potential or sterilised man **Exclusion criteria:** • Current forms of psoriasis other than chronic plaque-type • Current drug-induced psoriasis • History of recurrent or medically important infections requiring intervention and/or systemic treatment in the last 12 months, including infections with e.g. candida and Staphylococcus aureus • Autoimmune disease of relevance • Inflammatory bowel disease requiring treatment within the past 12 months • Significantly immunocompromised • Blood pressure out of range • Laboratory values out of range, including ALT, AST, eGFR • Positive to HIV, hepatitis B, hepatitis C or tuberculosis

EUCTR2017-001615-36-DE *(Continued)*

	• Numerous recent previous psoriasis treatments,with defined washout periods • Prior exposure to systemic psoriasis treatments with anti-IL-17 biological therapies • Live vaccination within defined time restrictions • Inability or unwillingness to limit ultraviolet (UV) light exposure during the course of the study • Pregnancy, breastfeeding • Drug and/or alcohol abuse or dependence
Interventions	**Intervention 1:** 2 mg ABY-035 (izokibep anti-IL17A) SC 12 weeks **Intervention 2:** 20 mg ABY-035 SC 12 weeks **Intervention 3:** 80 mg ABY-035 SC 12 weeks **Intervention 4:** 160 mg ABY-035 SC 12 weeks **Intervention 5:** placebo 12 weeks After the first 12 weeks of treatment, the participants randomised to placebo will receive active treatment. The dose levels and dosing intervals are adjusted depending on the absolute PASI score, to obtain an individualised treatment regimen
Outcomes	**Primary outcome** • PASI 90 at week 12 **Secondary outcome measures** • Number of treatment-related adverse events at 52 weeks • PASI 90 at week 24 • PASI 90 at week 52 • PASI 75 at week 12 • PASI 100 at week 12 • Proportion of participants with an absolute PASI score ≤ 1 at week 12 • Proportion of participants with an absolute PASI score ≤ 1 at week 24 • Proportion of participants with an absolute PASI score ≤ 1 at week 52 • Proportion of participants with Static Physician's Global Assessment (sPGA) 1 or 0 at week 12 • Proportion of participants with Dermatology Life Quality Index (DLQI) of 0 or 1 at week 12 • Proportion of participants with DLQI of 0 or 1 at week 24 • Proportion of subjects with DLQI of 0 or 1 at week 52 • Change from baseline in target nail Nail Psoriasis Severity Index (NAPSI) at week 12 • Change from baseline in pain-Visual Analogue Scale (VAS) at week 12 • Change from baseline in itch-Visual Analogue Scale (VAS) at week 12 • Pharmacokinetics: Area Under the Curve (AUC) of ABY-035 • Levels of anti-ABY-035 antibodies in serum week 52
Starting date	Actual study start date: March 2018 Actual primary completion date: April 2020 Estimated study completion date: December 2022 Last update posted: July 2020, active, not recruiting
Contact information	sgerdes@dermatology.uni-kiel.de Sascha Gerdes, Dr. Med
Notes	NCT03591887 Last checked in October 2021

EUCTR2017-003367-35-PL

Study name	Efficacy, safety, and immunogenicity of AVT02 with moderate-to-severe chronic plaque psoriasis
Methods	RCT, active-controlled, double-blind Date of study: February 2019 Location: Poland, Estonia, Georgia, Ukraine Phase 3
Participants	**Randomised**: 413 participants **Inclusion criteria** • Patient with moderate-to-severe chronic plaque psoriasis • Patient has had stable psoriatic disease for at least 2 months • Patient is a candidate for systemic therapy and the patient has a previous failure, inadequate response, intolerance, or contraindication to at least 1 systemic anti-psoriatic therapy including, but not limited to, methotrexate, cyclosporine, psoralen plus ultraviolet light A (PUVA), and ultraviolet light B (UVB). **Exclusion criteria** • Patient has prior use of 2 or more biologics for treatment of PsO • 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 • Patient has prior use of any of the following medications within specified time periods or will require use during the study: Topical medications within 2 weeks of BL (week 1). PUVA phototherapy and/or UVB phototherapy within 4 weeks prior to the BL visit • Nonbiologic psoriasis systemic therapies (e.g. cyclosporine, methotrexate, and acitretin) within 4 weeks prior to the BL visit. Any prior or concomitant or biosimilar adalimumab therapy, either approved or investigational • Any systemic steroid in the 4 weeks prior to BL
Interventions	**Intervention** AVT02 (adalimumab biosimilar) 80 mg (2 × 40 mg) administered subcutaneously (SC), followed by 40 mg given SC once every other week (eow) until week 48 **Control intervention** Humira 80 mg (2 × 40 mg) administered SC, followed by 40 mg given SC eow until week 48
Outcomes	**Primary outcome measures** : Psoriasis Area and Severity Index (PASI) [time frame: baseline to week 16] Percent (%) change in PASI **Secondary outcome measures**: PASI [time frame: Percent improvement in PASI from BL to week 8, 12, 24, 32, 42, and 50] Percent (%) change in PASI
Starting date	Study start date: February 2019 Actual study completion date: July 2020 Last update posted: July 2020, completed

EUCTR2017-003367-35-PL *(Continued)*

Contact information	Investigator: Steve Feldman, MD PhD, Wake Forest University Health Sciences
Notes	NCT03849404 Funding: Alvotech Swiss AG (Alvotech) Last checked in October 2021

EUCTR2018-001238-16-FR

Study name	A study to evaluate further therapeutic strategies with guselkumab in participants with moderate-to-severe plaque-type psoriasis (GUIDE)
Methods	Phase 3b RCT, double-blind, parallel-group, multicentre study Date of study: February 2019 Location: France, Germany
Participants	**Randomised**: 888 participants **Inclusion criteria**: • disease duration of plaque psoriasis of either ≤ 2 years or > 2 years • moderate-to-severe plaque-psoriasis • no signs or symptoms suggestive of active tuberculosis **Exclusion criteria**: • Has previously received any therapeutic agent directly targeted to interleukin (IL) -23 (including but not limited to guselkumab, tildrakizumab [MK3222], risankizumab [BI-655066]) • Has received any systemic immunosuppressant (for example (e.g.) methotrexate, azathioprine, cyclosporin, 6-thioguanine, mercaptopurine, mycophenolate mofetil, tacrolimus), or anakinra within 4 weeks of the first administration of study drug • Tests positive for hepatitis B virus (HBV) infection or who are seropositive for antibodies to hepatitis C virus (HCV), unless they have 2 negative HCV RNA test results 6 months apart after completing antiviral treatment and prior to baseline and have a third negative HCV RNA test result at baseline • Has received natalizumab, belimumab, or agents that modulate B cells or T cells (e.g., rituximab, alemtuzumab, abatacept, or visilizumab) within 12 months of the first administration of study drug • Has received any anti-tumour necrosis factor (TNF)-α biologic therapy within 3 months before the first administration of study drug
Interventions	**Intervention**: guselkumab 100 mg subcutaneously at weeks 0, 4, 12 and 20 **Control intervention**: placebo then re-randomisation
Outcomes	**Primary outcome**: • Group (2a and 2b): percentage of participants who achieve an absolute psoriasis area and severity index (PASI) score < 3 at week 68 **Secondary outcome:** • Group (1, 2a, 2b, 2c): time to improvement from baseline (week 0) in PASI score

EUCTR2018-001238-16-FR *(Continued)*

- Group (1, 2a, 2b, 2c, 3a and 3b): percentage of participants who achieve an absolute PASI score of 0, ≤ 1 and < 3 at weeks 20, 28, 68 and 116
- Group (1, 2a, 2b, 2c, 3a and 3b): percentage of participants who achieve a PASI 75/90/100 response at weeks 20, 28, 68 and 116
- Group 1: percentage of participants with an absolute PASI score = 0 at weeks 12, 16, 20 and 28
- Group (1, 2a, 2b, and 2c): change from baseline (week 0) in Dermatology Life Quality Index (DLQI) score at baseline (week 0), week 28 and week 68
- Group (1, 2a, 2b, and 2c): percentage of participants who achieve a DLQI Score 0/1 and < 5 week 28 and week 68
- Percent change from baseline (week 0) in psoriasis-affected body surface area (BSA) at weeks 12, 28, 52, 68, 80, and 104
- Change from baseline in Nail Assessment in Psoriasis and Psoriatic Arthritis-Quality of Life (NAPPA-QOL) at weeks 28, 68 and 116
- Group (1, 2a, 2b, 2c, 3a, and 3b): change from baseline in Nail Assessment in Psoriasis and Psoriatic Arthritis- Patient Benefit Index (NAPPA-PBI) at weeks 28, 68 and 116
- Group (1, 2a, 2b, 2c, 3a, and 3b): change from baseline in Nail Assessment in Psoriasis and Psoriatic Arthritis- Clinical (NAPPA-CLIN) at weeks 28, 68 and 116
- Group (1, 2a, 2b, 2c, 3a and 3b): change from baseline (week 0) in the signs and symptoms aggregate scores of the Psoriasis Symptoms and Signs Diary (PSSD) at weeks 28, 68 and 116
- Group (2a, 2b and 2c): percentage of participants who achieve a PSSD sign score = 0 at week 68 in participants with a PSSD sign score ≥ 1 at week 28
- Group 1, 2a, 2b and 2c: relationship between trough serum concentration and efficacy or serum biomarker level
- Group (2a and 2b): relationship between trough serum guselkumab levels at weeks 20, 28, 36 and 68 and achieving PASI score < 3 at week 68
- Group (2d and 3c): percentage of participants who were re-treated due to loss of disease control (PASI > 5) and regain control of disease (PASI < 3) 24 weeks after start of re-treatment [re-treatment period: week 0 up to week 24]
- Group (1, 2a, 2b, 2c, 2d, 3a, 3b, and 3c): number of participants with adverse events as a measure of safety and tolerability up to week 116
- Group (1, 2a, 2b, 2c, 2d, 3a, 3b, and 3c): number of participants with clinically significant laboratory abnormalities

Starting date	Study start date: February 2019 Estimated primary completion: August 2022) Estimated study completion date: June 2025 Last update posted:September 2021, active, not recruiting
Contact information	JNJ.CT@sylogent.com
Notes	NCT03818035 Funding: Jansssen-Cilag Germany Ongoing study Last checked in October 2021

EUCTR2018-001926-25-ES

Study name	Effectiveness and safety of BMS-986165 compared to placebo and active comparator in participants with psoriasis (POETYK-PSO-1)

EUCTR2018-001926-25-ES *(Continued)*

Methods	RCT, double-blind, parallel-group, placebo and active comparator, multicentre study Date of study: August 2018-September 2020 Location: Worldwide Phase 3b
Participants	**Randomised**: 666 participants **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 (deucravacitinib) 6 mg once daily, n = 332 **Control interventions** B. Apremilast 30 mg twice daily, n = 168 C. Placebo, n = 166
Outcomes	**Primary outcomes** • Percentage of participants who achieve sPGA score of 0 to 1 response at week 16 • Percentage of participants who achieve PASI 75 at week 16 **Secondary outcomes** • Percentage of participants who achieve PASI 90 at week 16 • Percentage of participants who achieve PASI 100 at week 16 • Change from baseline in Psoriasis Symptoms and Signs Diary (PSSD) score between baseline and week 16 • Percentage of participants who achieve scalp specific Physician's Global Assessment (ssPGA) score 0 or 1 among participants with a baseline ssPGA score ≥ 3 (baseline to week 16) • Change from baseline in DLQI score (baseline to week 16) • Percentage of participants who achieve Physician Global Assessment-Fingernails (PGA-F) score 0 or 1 among participants with a baseline PGA-F score ≥ 3 (baseline to week 16) • Percentage of participants who achieve palmoplantar Physician's Global Assessment (ppPGA) score 0 or 1 among participants with a baseline ppPGA score ≥ 3 (baseline to week 16) • Percentage of participants who achieve PASI 75 /PASI 90/sPGA score of 0 or 1 response at week 52
Starting date	Actual study start date: August 2018 Actual study completion date: September 2020 Last update posted: September 2021, completed
Contact information	Not stated
Notes	Funding: Quote (clinicaltrials.gov) Bristol Myers Squibb

EUCTR2018-001926-25-ES *(Continued)*

	NCT03624127

EUCTR2020-005205-42-DE

Study name	A study to investigate interchangeability of ABP 654 for the treatment of subjects with moderate-to-severe plaque psoriasis
Methods	RCT, active-controlled, double-blind study Date of study: March 2021 - completion date not reported Location: worldwide Phase 3

Participants	**Randomised**: 352 participants
	Inclusion criteria
	• Participant has stable moderate to severe plaque psoriasis for at least 6 months
	• Participant has a baseline score of PASI ≥ 12, involvement of ≥ 10% body surface area and static Physician Global Assessment ≥ 3 at screening and at baseline
	• Participant is a candidate for phototherapy or systemic therapy
	• Participant has previous failure, inadequate response, intolerance, or contraindication to at least 1 conventional anti-psoriatic systemic therapy
	• Female participant should have a negative serum pregnancy test during screening and a negative urine pregnancy test at baseline
	• Participant or legally acceptable representative is capable of giving signed Institutional Review Board (IRB)/Independent Ethics Committee (IEC) informed consent
	• Participant has no known history of latent or active tuberculosis
	• Participant with a positive purified protein derivative (PPD) test and a history of Bacillus Calmette-Guérin (BCG) vaccination is allowed with a negative Quantiferon/T-spot test
	• Participant with a positive PPD test or participant with a positive or indeterminate Quantiferon/T-spot test is allowed if he/she has all the following:
	  ◦ No symptoms per tuberculosis worksheet provided by the sponsor, Amgen Inc.
	  ◦ Documented history of adequate prophylaxis initiation prior to receiving investigational product in accordance with local recommendations
	  ◦ No known exposure to a case of active tuberculosis after most recent prophylaxis
	  ◦ No evidence of active tuberculosis on chest radiograph within 3 months prior to the first dose of investigational product
	Exclusion criteria
	• Participant has erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, or other skin conditions at the time of screening (e.g. eczema) that would interfere with evaluations of the effect of investigational product of psoriasis
	• Participant has an active infection or history of infections
	• Participant has uncontrolled, clinically significant systemic disease, such as uncontrolled diabetes mellitus, cardiovascular disease, renal disease, liver disease, or hypertension
	• Participant has moderate-to-severe heart failure (New York Heart Associate class III/IV)
	• Participant has known hypersensitivity to the investigational product or to any of the excipients
	• Participant has laboratory abnormalities at screening
	• Participant has had previous treatment with any agent specifically targeting interleukin (IL)-12 or IL-23 within 1 year prior to enrolment
	• Participant has received biologic treatment for psoriasis within the previous month or 5 drug half-lives (whichever is longer) prior to enrolment

EUCTR2020-005205-42-DE *(Continued)*

	• Participant has received any investigational agents within the previous month or 5 half-lives (whichever is longer) prior to enrolment • Participant has received non-biologic systemic psoriasis therapy within 4 weeks prior to enrolment • Participant has received ultraviolet A phototherapy (with or without psoralen) or excimer laser within 4 weeks prior to enrolment, or ultraviolet B phototherapy within 2 weeks prior to enrolment • Participant has received topical psoriasis treatment within 2 weeks prior to enrolment • Participant has received other investigational procedures within 4 weeks prior to enrolment and during the course of the study • Female participant is pregnant or breastfeeding or planning to become pregnant while participating in the study and for at least 15 weeks after the last dose of investigational product • Sexually active participants and their partners who are of childbearing potential and not agreeing to use adequate protocol-defined contraception methods while participating in the study and for 5 months after the last dose of investigational product
Interventions	**Intervention** A. Switching group (ustekinumab - ABP 654); participants will initially receive injection of ustekinumab up to week 16. Thereafter, starting from week 28, participants will switch between ABP 654 and ustekinumab every 12 weeks up to week 52. **Control intervention** B. Continued-use group ustekinumab SC from day 1 to week 52
Outcomes	**Primary outcomes** • Area Under the Curve from time 0 over the dosing interval (AUCtau) [time frame: week 52 (pre-dose and post-dose) until week 64] • Maximum concentration (Cmax) [time frame: week 52 (pre-dose and post-dose) until week 64] **Secondary outcomes** • Time of maximum concentration (tmax) [time frame: week 52 (pre-dose and post-dose) until week 64] • Trough concentration at steady state (Ctrough,ss) [time frame: week 28 (pre-dose and post-dose) until week 52 (pre-dose and post-dose)] • Percent improvement in PASI from baseline to week 64 • Percentage of participants with PASI 75 response at week 64 • Percentage of participants with PASI 100 response at week 64 • Number of participants with treatment-emergent adverse events and serious adverse events [time frame: week 28 until week 64] • Number of participants with events of interest [time frame: week 28 until week 64] • Number of participants with positive anti-drug antibodies to ABP 654 [time frame: week 28 until week 64 (Pre-dose)]
Starting date	Study start date: March 2021 Estimated study completion date: March 2023 Last update posted: September 2021, recruiting
Contact information	Amgen Call Center 866-572-6436medinfo@amgen.com
Notes	NCT04761627 Ongoing study

EUCTR2020-005205-42-DE *(Continued)*

	Last check in October 2021

Holsken 2021

Study name	Expectation-induced enhancement of pain, itch and quality of life in psoriasis patients
Methods	RCT, active-controlled study Date of study: November 2020 - end date not reported Location: Sweden
Participants	**Randomised**: 120 participants **Inclusion criteria** • Diagnosis of moderate-to-severe chronic plaque psoriasis for at least 6 months • Psoriasis Area and Severity Index > 12 and body surface area affected by plaque psoriasis ≥ 10% • Patient is a candidate for systemic therapy (this is defined as a patient having moderate-to-severe chronic plaque psoriasis that is inadequately controlled by topical treatment and/or phototherapy and/or previous systemic therapy). • Women must not be pregnant and, if of childbearing potential, must have a negative serum pregnancy test before entering the study. • Women of childbearing potential must agree to use a highly effective method of contraception throughout the therapy. **Exclusion criteria** • Age <18 years • Forms of psoriasis other than chronic plaque (e.g. pustular, erythrodermic, guttate or drug-induced) psoriasis • Existing contraindication to therapy with secukinumab according to the summary of product characteristics like history of hypersensitivity to secukinumab or its excipients or to drugs of similar chemical classes or clinically relevant (chronic or acute) infections, for example, untreated (latent) tuberculosis or HIV infection • Significant medical problems, which in the opinion of the investigator significantly immunocompromise the subject and/or place the subject at unacceptable risk for receiving therapy with secukinumab • History of, respectively active, inflammatory bowel disease • Administration of live vaccines < 6 weeks before first injection of secukinumab • Any medical or psychiatric condition which, in the investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol • Previous exposure to secukinumab • Ongoing use of systemic antipsoriatic treatments (concomitant topical treatment is allowed) • History or evidence of ongoing alcohol or drug abuse, within the last 6 months before start of the study • Subject is lacking capacity to consent
Interventions	**Group 1 pharmacological control**: secukinumab (as in clinical routine consisting of two subcutaneous injections with 150 mg) for 5 weeks (weeks 0–4), followed by two additional injections four (week 8) and eight (week 12) weeks later, n = 40 **Expectation-LOW group 2**: secukinumab 75 mg as one injection and one injection with NaCl, n = 40

Holsken 2021 *(Continued)*

	Expectation-HIGH group 3: secukinumab 75 mg as one injection and an additional positive verbal instruction presented in a standardised manner by the main study physician to strengthen their expectation towards the benefits of the treatment. The salience of this verbal instruction will be reinforced by combining each injection with the ingestion of a newly tasting beverage together with detailed information about the potential beneficial effects of this combination, n = 40
Outcomes	At 16 weeks **Primary outcomes** • Skin pain, itch and skin-related QoL **Secondary outcomes** • Lesion severity • Immunological markers
Starting date	Date of study: November 2020-2023
Contact information	Dr. Wiebke Sondermann; wiebke.sondermann@uk-essen.de
Notes	Funding: "Gefördert durch die Deutsche Forschungsgemeinschaft (DFG)— Projektnummer 422744262—TRR 289—Funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation)—Project-ID 422744262—TRR 289)." Declarations of interest: "WS reports grants from medi Bayreuth, personal fees from Janssen, grants and personal fees from Novartis, personal fees from Lilly UCB, Almirall, LEO Pharma and Sanofi Genzyme, outside the submitted work. The other authors declare that they have no competing interests."

IRCT20120524009844N 2020

Study name	Therapeutic effects of adalimumab in patients with resistant psoriasis patients by DLQI and PASI questionnaires
Methods	Randomised, parallel, open, active controlled study Date of study: July 2020 Location: Iran Phase 3
Participants	**Randomised**: 60 participants **Inclusion criteria**: • Adults from 18 years old • Confirmed psoriasis • Accepted patients without response to previous treatments • Don’t use of other drugs and herbal supplements • Resistance to at least one systemic treatment • No signs or symptoms suggestive of active tuberculosis **Exclusion criteria**: • Allergy to adalimumab having active inflammation such as tuberculosis, malignancies etc. • Neurological disorders; haematological disorders

IRCT20120524009844N 2020 *(Continued)*

	• Moderate-to-severe heart failure • Pregnant and breastfeeding woman • Mentally retarded patients
Interventions	**Intervention** A. Adalimumab 80 mg. The next dose will be one week later (40 mg) and then every two weeks (40 mg) (the total duration of treatment will be two months). **Control intervention** B. Methotrexate and cyclosporine at a specific dose determined by a dermatologist
Outcomes	**Primary outcomes** • PASI at 4, 8, 12 and 16 weeks • DLQI at 16 weeks
Starting date	Actual recruitment start date: July 2020 Trial completion date: November 2020, recruitment complete
Contact information	Pr Mehdi Amirnia amirniam@tbzmed.ac.ir
Notes	Ongoing study Funding: Tabriz University of Medical Sciences Last checked in October 2021

NCT02258282

Study name	Safety and efficacy of etanercept in patients with psoriasis
Methods	RCT, placebo-controlled, double-blind trial Date of study: May 2014 Location: China Phase 4
Participants	**Randomised**: 80 participants **Inclusion criteria** • 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

NCT02258282 *(Continued)*

- 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** A. Etanercept (participants under the treatment of 50 mg etanercept) **Control intervention** B. Placebo
Outcomes	At week 24 **Primary outcome** • PGA **Secondary outcomes** • PASI • BSA
Starting date	Study start date: May 2014 Estimated primary completion date: December 2022

NCT02258282 *(Continued)*

	Last update posted: April 2017, active, not recruiting
Contact information	Yang Min, Ph.D, Chengdu PLA General Hospital
Notes	Ongoing study Last checked in October 2021

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: September 2018 Location: Aarhus University Hospital, Denmark Phase 4
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** Average of maximum TBR values (mean TBRmax) 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: September 2018 Estimated study completion date: March 2020

NCT03478280 *(Continued)*

	Last update posted: July 2019, unknown
Contact information	Contact: Anne Bregnhøj, MD, PhD Aarhus University Hospital. +45 2183 5720 annebreg@rm.dk Email sent to Pr Anne Bregnhøj (31 August 2020)
Notes	Ongoing study Last checked in October 2021

NCT03518047

Study name	Risankizumab therapy versus placebo for subjects with psoriasis in the Russian Federation (IMMPRESS)
Methods	RCT, placebo-controlled, double-blind study (IMMPRESS) Date of study: July 2018 Location: Russia Phase 3
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-IL-12/23p40 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 outcomes** • PGA 0/1 • PASI 75 • PASI 100 • DLQI

NCT03518047 *(Continued)*

Starting date	Starting date: July 2018 Recruitment status: completed Last update posted: January 2021, completed Actual study completion date: February 2020
Contact information	No principal investigator stated on ClinicalTrials.gov
Notes	Waiting for results publication Ongoing study Last checked in October 2021

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 multicentre study Date of study: September 2018 Location: worldwide Phase 3

Participants	**Randomised**: 1355 participants
	Inclusion criteria
	• Subject 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
	• Subject completes the feeder study (PS0008 [NCT03412747], PS0009 [NCT03370133], PS0013 [NCT03410992]) without meeting any withdrawal criteria
	• Female subjects must be:
	  ◦ Postmenopausal: Menopause is defined as 12 consecutive months of amenorrhoea, for which there is no other obvious pathological or physiological cause
	  ◦ Permanently sterilised (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy)
	  ◦ Or, if of childbearing potential (and engaged in sexual activity that could result in procreation), must be willing to use a highly effective method of contraception throughout the duration of the study until 20 weeks after last administration of investigational medicinal product (IMP), and have a negative pregnancy test at the feeder study in final visit/baseline visit in PS0014
	Exclusion criteria
	• Subject has previously participated in this study
	• Female subjects who plan to become pregnant during the study or within 20 weeks following last dose of study medication
	• Subject has any medical or psychiatric condition that, in the opinion of the Investigator, could jeopardise or would compromise the subject's ability to participate in this study. Note: For any subject with an ongoing Serious Adverse Event (SAE), or a history of serious infections in the feeder study, the Medical Monitor must be consulted prior to the subject's entry into PS0014, although the decision on whether to enrol the subject remains with the investigator

NCT03598790 *(Continued)*

	• Subject has a positive or indeterminate interferon gamma release assay (IGRA) in a feeder study, unless appropriately evaluated and treated • Subject may not participate in another study of a medicinal product or device under investigation other than the substudy • Subject has a history of chronic alcohol or drug abuse within 6 months prior to baseline as assessed by medical history, site interview, and/or results of the specified urine drug screen
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: September 2018 Estimated study completion date: January 2023 Last update posted: August 2021, active, not recruiting
Contact information	Contact: UCB Cares +1844599 ext 2273
Notes	Ongoing study Last checked in October 2021

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: worldwide Phase 3
Participants	**Randomised**: 1000 participants **Inclusion criteria** • Plaque psoriasis for at least 6 months • Moderate-to-severe disease

NCT03611751 *(Continued)*

	• 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 (deucravacitinib: selective tyrosine kinase 2 (TYK2) inhibitor) **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 Actual study completion date: November 2020 Last update posted: June 2021, completed
Contact information	clinical.trials@bms.com (sponsor: Bristol-Myers Squibb)
Notes	Ongoing study Last checked in October 2021

NCT03897075

Study name	Efficacy and safety study of tildrakizumab in the treatment of nail psoriasis
Methods	RCT, parallel-arm, double-blind, multicentric study Date of study: May 2021 Location: USA Phase 3
Participants	**Randomised:** 146 participants **Inclusion criteria**: • 18 years or older • Patients with a chronic moderate-to-severe plaque-type psoriasis for at least 6 months • Patients must have moderate-to-severe nail psoriasis at screening and baseline

NCT03897075 *(Continued)*

- Patients must be considered candidates for systemic therapy, meaning psoriasis inadequately controlled by topical treatments (corticosteroids), and/or phototherapy, and/or previous systemic therapy
- Patients have a negative evaluation for tuberculosis within 4 weeks before initiating study treatment, defined as a negative QuantiFERON® test
- Participants with a positive or 2 successive indeterminate QuantiFERON® tests
- Participants must have results of a physical examination within normal limits or clinically acceptable limits to the investigator prior to day 1

Exclusion criteria:

- Patients who have predominantly non-plaque forms of psoriasis specifically erythrodermic psoriasis, predominantly pustular psoriasis, medication-induced or medication-exacerbated psoriasis, or new-onset guttate psoriasis
- Patients with ongoing inflammatory skin diseases other than psoriasis or any other disease affecting the fingernails which may potentially confound the evaluation of study treatment
- Patients with fungal nail infection should be excluded from the study
- Women of childbearing potential who are pregnant, intend to become pregnant (within 6 months of completing the study), or are lactating
- Patients with any infection or history of recurrent infection requiring treatment with systemic antibiotics within 2 weeks prior to screening, or severe infection (e.g. pneumonia, cellulitis, bone or joint infections) requiring hospitalisation or treatment with intravenous antibiotics within 6 weeks prior to screening
- Patients with any previous use of tildrakizumab or other IL-23/Th-17 pathway inhibitors, including p40, p19 and IL-17 antagonists for psoriasis
- Prior use of TNF-alpha inhibitors with a washout period of 12 weeks would be allowed. However, the number of patients with prior use of TNF-alpha inhibitors would be capped at 40% and the analysis will be stratified based on prior use of these biologics
- Patients with a positive human immunodeficiency virus test result, hepatitis B surface antigen, or hepatitis C virus test result
- Patients with a prior malignancy or concurrent malignancy (excluding successfully-treated basal cell carcinoma, squamous cell carcinoma of the skin in situ, squamous cell carcinoma of skin with no evidence of recurrence within 5 years or carcinoma in situ of the cervix that has been adequately treated)
- Patients who have received live viral or bacterial vaccination within 4 weeks prior to baseline or who intend to receive live viral or bacterial vaccination during the study
- Patients who were hospitalised due to an acute cardiovascular event (such as myocardial infarction, cerebrovascular accident, cardiovascular illness [e.g. angina pectoris], or cardiovascular surgery [such as coronary artery bypass]) within 6 months before screening
- Patients who have a history of alcohol or drug abuse in the previous year
- Patients who have high risk of suicidality at the screening assessment based on investigator's judgement or, if appropriate, as indicated by a response of "yes" within the last 12 months to Questions 4 or 5 in the suicidal ideation section, or any positive response in the behavioural section of the Columbia-Suicide Severity Rating Scale

Interventions	**Intervention** A. Tildrakizumab **Comparator** B. Placebo
Outcomes	**Primary Outcomes** • The proportion of participants who achieve "clear" or "minimal" with a ≥ 2-grade improvement from baseline on the Physician's Global Assessment of Finger Nail Psoriasis scale at week 28 • The percentage of participants with incidence, seriousness, and severity of all adverse events week 52

NCT03897075 *(Continued)*

- The percentage of participants with severe infections, whether or not reported as a serious event defined as any infection meeting the regulatory definition of a serious adverse event, or any infection requiring intravenous antibiotics week 52
- The percentage of participants with malignancies (excluding carcinoma in situ of the cervix) week 52
- The percentage of participants with non-melanoma skin cancer week 52
- The percentage of participants with melanoma skin cancer week 52
- The percentage of participants with major adverse cardiovascular events week 52
- The percentage of participants with study treatment-related hypersensitivity reactions (e.g. anaphylaxis, urticaria, angioedema, etc.) week 52
- The percentage of participants with injection site reactions week 52

Secondary Outcomes

- The proportion of participants who achieve at least a 75% improvement from baseline in total-modified Nail Psoriasis Severity Index week 28
- The proportion of participants achieving total-fingernail total-modified Nail Psoriasis Severity Index I90, and total-modified Nail Psoriasis Severity Index 100 week 28
- The proportion of participants achieving total-fingernail Nail Psoriasis Severity Index 75, Nail Psoriasis Severity Index 90, and Nail Psoriasis Severity Index 100 week 28
- Mean percentage change in total-fingernail modified Nail Psoriasis Severity Index score from baseline week 28
- Mean percentage change in total-fingernail Nail Psoriasis Severity Index score from baseline week 28
- Mean change in participant-reported nail pain numeric rating scale score from baseline week 28
- The proportion of participants with a 4-point decrease in Nail Pain numeric rating scale score from baseline, among those with baseline Nail Pain NRS of ≥ 4 week 28
- The proportion of participants achieving Psoriasis Area and Severity Index 75, Psoriasis Area and Severity Index 90, and Psoriasis Area and Severity Index 100 week 28
- The proportion of participants achieving Physician's Global Assessment score of "clear" or "almost clear" with at least 2-point reduction from baseline week 28
- Mean percentage change in total body surface area involvement from baseline week 28

Other Outcomes

- Change from baseline in modified Nail Psoriasis Severity Index week 52
- Change from baseline in Dermatology Life Quality Index score, Nail Psoriasis Functional Severity Score, and Nail Assessment in Psoriasis and Psoriatic Arthritis QoL score week 52

Starting date	Actual study start date: May 2021 Estimated study completion date: March 2024 Last update posted: July 2021, recruiting
Contact information	Head, Clinical development; 91 2266455645clinical.trials@sparcmail.com
Notes	Funding: Sun Pharma Global FZE Ongoing study Last checked in October 2021

NCT03897088

Study name	Efficacy and safety of tildrakizumab in the treatment of scalp psoriasis

NCT03897088 *(Continued)*

Methods	RCT, multicentre, double-blind, placebo-controlled study Date of study: May 2019 Location: USA, Australia Phase 3
Participants	**Randomised**: 136 participants **Inclusion criteria**: • 18 years or older • Patients with a chronic plaque-type psoriasis for at least 6 months • Patients must have moderate-to-severe plaque psoriasis of the scalp at screening and at baseline • Patients must be considered candidates for systemic therapy, meaning psoriasis inadequately controlled by topical treatments (corticosteroids), and/or phototherapy, and/or previous systemic therapy • Patients has a negative evaluation for tuberculosis within 4 weeks before initiating study treatment, defined as a negative QuantiFERON® test • Patients with a positive or 2 successive indeterminate QuantiFERON® test • Patients must have results of a physical examination within normal limits or clinically acceptable limits to the investigator prior to day 1 **Exclusion criteria:** • Patients who have predominantly non-plaque forms of psoriasis specifically erythrodermic psoriasis, predominantly pustular psoriasis, medication-induced or medication-exacerbated psoriasis, or new-onset guttate psoriasis • Patients with ongoing inflammatory skin diseases other than psoriasis or any other disease affecting the fingernails which may potentially confound the evaluation of study treatment • Women of childbearing potential who are pregnant, intend to become pregnant (within 6 months of completing the study), or are lactating • Patients with any infection or history of recurrent infection requiring treatment with systemic antibiotics within 2 weeks prior to screening, or severe infection (e.g. pneumonia, cellulitis, bone or joint infections) requiring hospitalisation or treatment with intravenous antibiotics within 6 weeks prior to screening • Patients with any previous use of tildrakizumab or other IL-23/Th-17 pathway inhibitors, including p40, p19 and IL-17 antagonists for psoriasis • Prior use of TNF-alpha inhibitors with a washout period of 12 weeks would be allowed. However, the number of patients with prior use of TNF-alpha inhibitors would be capped at 40% and the analysis will be stratified based on prior use of these biologics • Patients with a positive human immunodeficiency virus test result, hepatitis B surface antigen, or hepatitis C virus test result • Patients with a prior malignancy or concurrent malignancy (excluding successfully treated basal cell carcinoma, squamous cell carcinoma of the skin in situ, squamous cell carcinoma of skin with no evidence of recurrence within 5 years or carcinoma in situ of the cervix that has been adequately treated) • Patients who have received live viral or bacterial vaccination within 4 weeks prior to baseline or who intend to receive live viral or bacterial vaccination during the study • Patients who were hospitalised due to an acute cardiovascular event (such as myocardial infarction, cerebrovascular accident, cardiovascular illness [e.g. angina pectoris], or cardiovascular surgery [such as coronary artery bypass]) within 6 months before screening • Patients who have a history of alcohol or drug abuse in the previous year • Patients who have high risk of suicidality at the screening assessment based on investigator's judgement or, if appropriate, as indicated by a response of "yes" within the last 12 months to Questions 4 or 5 in the suicidal ideation section, or any positive response in the behavioral section of the Columbia-Suicide Severity Rating Scale

NCT03897088 *(Continued)*

Interventions	**Intervention** A. Tildrakizumab **Comparator** B. Placebo
Outcomes	**Primary outcome**: • The proportion of participants with Investigator Global Assessment mod 2011 (scalp) score of "clear" and "almost clear" with at least 2-point reduction from baseline at week 16 • The percentage of participants with incidence, seriousness and severity of all adverse events week 52 • The percentage of participants with severe infections, whether or not reported as a serious event defined as any infection meeting regulatory definition of serious adverse event, or any infection requiring intravenous antibiotics week 52 • The percentage of participants with malignancies (excluding carcinoma in situ of the cervix) week 52 • The percentage of participants with melanoma skin cancer week 52 • The percentage of participants with major adverse cardiovascular events week 52 • The percentage of participants with study treatment-related hypersensitivity reactions week 52 • The percentage of participants with injection site reactions week 52 **Secondary outcome**: • The proportion of participants with at least 90% improvement from baseline in the Psoriasis Scalp Severity Index at week 16 • Mean percentage change in Psoriasis Scalp Severity Index score from baseline to week 16 • The proportion of participants achieving Psoriasis Scalp Severity Index 75 at week 16 • The proportion of participants achieving Psoriasis Scalp Severity Index 100 at week 16 • Mean percentage change in scalp surface area involvement from baseline to week 16 • Time to 75% reduction in Psoriasis Scalp Severity Index during 16-week placebo-controlled treatment period week 16 • Time to Investigator Global Assessment mod 2011 (scalp) response during the 16-week placebo-controlled treatment period • Proportion of participants achieving a 4-point reduction in Itch Numeric Rating Scale score from baseline to week 16 • The proportion of participants achieving Psoriasis Area and Severity Index 75, Psoriasis Area and Severity Index 90, and Psoriasis Area and Severity Index 100 at week 16 • The proportion of participants with Investigator Global Assessment mod 2011 score (whole body) and Physician's Global Assessment score (whole body) score of "clear" or "almost clear" with at least a 2-point reduction from baseline to week 16 • Mean percentage change in total body surface area involvement from baseline to week 16 • The proportion of participants with Investigator Global Assessment (scalp only) score of "clear" and "almost clear" with at least 2-point reduction from baseline at week 16 • Investigator Global Assessment mod 2011 (scalp and whole body), Psoriasis Scalp Severity Index, Investigator Global Assessment (scalp only), Scalp Itch NRS, Psoriasis Area and Severity Index, Physician Global Assessment for skin (whole body) **Other outcome**: • Change from baseline in Dermatology Life Quality Index score (total and 6 domain scores) at measured time points through week 52
Starting date	Actual study start date: May 2019 Estimated study completion date: February 2022

NCT03897088 *(Continued)*

	Last update posted: June 2021, active, not recruiting
Contact information	Head, Clinical development; 91 2266455645clinical.trials@sparcmail.com
Notes	Funding: Sun Pharma Global FZE Ongoing study Last checked in October 2021

NCT03927352

Study name	A phase 3, randomized, double-blind study evaluating the efficacy and safety of SCT630 compared with adalimumab in subjects with moderate to severe plaque psoriasis
Methods	RCT, phase 3, parallel-arm, double-blind study Date of study: September 2019 Location: China Phase 3
Participants	Randomised: 330 participants **Inclusion criteria**: • Men or women ≥ 18 and ≤ 70 years of age at time of screening • History of psoriasis for at least 6 months, and stable moderate-to-severe plaque psoriasis within 2 months prior to being randomised • Moderate-to-severe psoriasis defined at screening and baseline • Negative test for Interferon-gamma-release assay an chest X-ray at time of screening • Participant is a candidate for systemic therapy or phototherapy procedures • Women must have a negative pregnancy test; are not planning to become pregnant; and must not be lactating • From the screening period to the end (6 months after the last administration), women must agree to use a highly effective contraceptive measure **Exclusion criteria**: • Other forms of psoriasis,skin conditions (e.g. eczema) or systemic autoimmune diseases which affect the evaluation of treatment outcomes • Received local anti-psoriasis drugs within 2 weeks prior to baseline • Received PUVA ,UVB or non-biologics within 4 weeks prior to baseline,including methotrexate, cyclosporine,tretinoins, traditional Chinese medicine, and so on • Received etanercept or its biosimilars within 4 weeks prior to baseline • Received other anti-TNF, IL-12/23 inhibitors or IL-17 inhibitors within 12 months prior to baseline • Be receiving or had received any biologics ≤ 5 half-lives • Patients who previously used adalimumab or a biosimilar of adalimumab ineffectively or intolerantly • History of tuberculosis, active tuberculosis or latent tuberculosis infection • Suffering from active infection or history of infection: Systemic anti-infective therapy was performed 4 weeks before screening, severe infections with hospitalisation or intravenous anti-infective treatment within 8 weeks before screening or recurrent, chronic or other active infections which were assessed by researchers to increase the risk of participants • Participants were known to have malignant tumours or a history of malignant tumours (except for skin squamous cell carcinoma in situ, basal cell carcinoma, cervical cancer in situ, or skin squa-

NCT03927352 *(Continued)*

mous cell carcinoma with no evidence of recurrence after thorough treatment, or 5 years prior to investigational product administration)
- Moderate-to-severe congestive heart failure (New York Heart Association Classes III or IV)
- Participants 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), and which were assessed by researchers to increase the risk of participants
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 times upper limit of normal (ULN), haemoglobin < 90 g/L, leukocyte count < 3.5 × 109/L, platelets < 100 × 109/L, serum creatinine > 2.5 times upper limit of normal (ULN) at screening
- Received any live vaccines ≤ 4 weeks prior to investigational product administration, or patients who are expecting to receive any live vaccines during the trial
- Participants had hypersensitivity to test drugs and their excipients, or drugs with the same pharmacological and biological classification as test drugs, and had a history of allergy to active substances or excipients of adalimumab or SCT630
- Positive test for anti-nuclear antibody (ANA) or anti-double-stranded DNA antibody at screening
- Participants were accompanied by active neuropathy, including but not limited to multiple sclerosis, Guillain-Barre syndrome, optic neuritis, transverse myelitis, or neurological symptoms suggesting demyelinating lesions of the central nervous system
- Positive test for HIV antibodies, hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibodies, or treponema pallidum antibody at screening
- The results of 5 tests for hepatitis B virus infection should be further tested for hepatitis B virus DNA, if it is ≥ the upper limit of the reference value of each hospital
- Women who are pregnant or nursing

Interventions

Intervention

A. SCT630 (biosimilair adalimumab) 80 mg subcutaneously on week 1/day 1 (initial loading dose) and 40 mg at week 2 and every 2 weeks thereafter until week 16
Participants with a PASI 50 response at week 16 continued to receive 40 mg SCT630 until week 48

Control Intervention

B. Adalimumab 80 mg subcutaneously on week 1/day 1 (initial loading dose) and 40 mg at week 2 and every 2 weeks thereafter until week 16
At week 16 participants with a PASI 50 response were re-randomised to treatment with adalimumab or were transitioned to SCT630 until week 48

Outcomes

Primary outcome

- Percent improvement from baseline in Psoriasis Area and Severity Index (PASI) at week 16

Secondary outcomes

- Percent improvement from baseline in PASI at week 4, 8, 12, 24, 32, 48, 50
- Percent improvement from baseline with a PASI 75 response at week 4, 8, 12, 24, 32, 48, 50
- Percent improvement from baseline with a PASI 50 response at week 4, 8, 12, 24, 32,, 48, 50
- Percent improvement from baseline with a PASI 90 response at week 4, 8, 12, 24, 32,, 48, 50
- Percent improvement from baseline with a PASI 100 response at week 4, 8, 12, 24, 32,, 48, 50
- Percent of participants with a Static Physician's Global Assessment (sPGA) response at week 4, 8, 12, 24, 32, 48, 50
- Change from baseline in the percentage of Body Surface Area (BSA) involved with psoriasis at week 4, 8, 12, 24, 32, 48, 50
- Change from baseline of dermatology life quality index (DLQI) at week 4, 8, 12, 24, 32, 48, 50
- Positive rate of ADA and NAb week 1, 4, 16, 32, 48, 50, 52
- Number of participants with adverse events week 2, 4, 8, 12, 16, 24, 32, 40, 48, 52
- Minimum concentration of SCT630 and EU-licensed Humira: week 1, 4, 16, 32, 48, 50

NCT03927352 *(Continued)*

Starting date	Actual study start date: September 2019 Estimated study completion date: December 2022 Last update posted: January 2021, active, not recruiting
Contact information	Guo Ming +86-10-58628288-9138; ming_guo@sinocelltech.com
Notes	Funding: Sinocelltech Ltd. Ongoing study Last checked in October 2021

NCT04102241

Study name	Efficacy and safety study of hemay005 in subjects with moderate to severe plaque psoriasis
Methods	RCT, double-blind, placebo-controlled, parallel-arm study Location: China Phase 2
Participants	**Randomised**: 216 participants **Inclusion criteria** • Male or female at least 18 years of age and less than or equal to 75 • Diagnosed with plaque psoriasis more than 6 months • Screening and baseline PSAI ≥ 12, sPGA ≥ 3 (moderate-to-severe, affected body surface area BSA ≥ 10%) • Investigator determined suitable for systemic treatment of psoriasis • All subjects must agree and commit to the use of a reliable contraceptive regimen. Women of childbearing potential must undergo monthly pregnancy testing during the study and agree to use two of the following methods of contraception throughout the study and for 90 days after the last dose of study drug. Reliable contraceptive regimen: vasectomy, abstinence, the use of condoms, intrauterine contraceptives (IUD) (oral administration, patch, ring, injection, implantation), barrier methods (diaphragm with spermicide, condom with spermicide) • Ability to understand and be willing to sign a written informed consent before study entry **Exclusion criteria** • Forms of psoriasis other than chronic plaque-type (i.e. erythrodermic and guttate psoriasis, palmar, plantar or nail disease) at screening, investigator-diagnosed with drug-induced psoriasis (i.e. from beta-blockers, calcium channel inhibitors or lithium) prior to randomisation • A history of chronic infection (i.e. tuberculosis) • A condition of any skin disease (i.e. dermatitis) • History of systemic autoimmune inflammatory disease that affects drug evaluation • Patients with an active infection who are assessed by the investigator as at increased risk • TB infection, high risk of acquiring TB infection, latent TB infection (LTBI), or current or history of NTMB infection • Subjects who used any of the following treatments: 2 weeks before randomisation (including but not limited to local use of glucocorticoids, topical retinoic acid preparations, vitamin D derivatives, tacrolimus, pimeklimus, dianthranol, etc.) except for the following situations: In the face, armpit and groin psoriasis skin lesions using weak or inefficient local use of glucocorticoid (efficacy grade 6-7) or scalp psoriasis skin lesions with coal tar shampoo, salicylic acid topical prepara-

NCT04102241 *(Continued)*

	tions, selenium disulfide, the use of non-pharmaceutical emollients (such as silicone cream, vitamin E cream, etc.); 4 weeks before randomisation, non-biological drug systemic therapy (including but not limited to systemic glucocorticoids, leflunomide, cyclophosphamide, methotrexate, cyclosporine, retinoic acid, traditional Chinese medicine decoction, proprietary Chinese medicine for the treatment of psoriasis, etc.), 2 weeks before randomisation with UVB treatment, 4 weeks before randomisation with psoralen and long wave ultraviolet (PUVA) therapy, 12 weeks before randomisation with biological agents such as adamuzumab, enasip or infliximab, 24 weeks before randomisation with alefacept, briakinumab, ustekinumab, secukinumab; subjects with psoriasis worsen or rebound 4 weeks before screening • Subjects with congenital or acquired immunodeficiency • Subjects couldn't limit their UV exposure during the study period (e.g. sunbathing and/or tanning devices) • History of apremilast • Subjects with conditions that may affect oral drug absorption, such as subtotal gastrectomy, clinically significant diabetic gastroenteropathy, or certain types of weight-loss surgery, such as gastric bypass surgery, do not include surgery that simply separates the stomach into separate chambers, such as gastric banding surgery • sCr ≥ 1.5 upper limit of normal (ULN); AST ≥ 2 ULN; ALT ≥ 2 ULN • WBC < 3.0 × 109/L or WBC > 14 × 109/L, PLT < 100 × 109/L, Hb < 85 g/L • Subjects with a malignant tumour, or any history of malignancy within 5 years (except skin squamous cell carcinoma in situ, basal cell carcinoma or cervical carcinoma in situ that has been treated and has no evidence of recurrence in the past 12 weeks) • Subjects with positive blood screen for human immunodeficiency virus (HIV antibody), hepatitis B virus surface antigen, or hepatitis C virus antibody at screening • Has a history of alcohol or drug abuse or dependence, or a history of mental illness • Has committed suicide (includes active attempts, discontinued attempts or attempted attempts) or suicidal thoughts within the past 6 months • Pregnant or lactating women or planning pregnancy during the study period • Know allergic to active ingredient or excipient of the investigational product • 4 weeks before randomisation, participated in a clinical trial and use of the study drug • Accompanied by severe, progressive, or uncontrolled disease or in the investigator's opinion unsuitable to be enrolled
Interventions	**Interventions** A. Hemay005 15 mg BID for 16 weeks B. Hemay005 30 mg BID for 16 weeks C. Hemay005 60 mg BID for 16 weeks **Control intervention** D. Placebo
Outcomes	At 16 weeks **Primary outcome** • PASI 75 **Secondary outcomes** • Severity of AEs and SAEs at week 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56 • Cmax of Hemay005 at week 8 • sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at week 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56
Starting date	Actual study start date: May 2019

NCT04102241 *(Continued)*

	Estimated study completion date: August 2021 Last update posted: December 2020, active, not recruiting
Contact information	Principal Investigator: Min Zheng, Dr Second Affiliated Hospital, School of Medicine, Zhejiang University
Notes	Funding: Tianjin Hemay Pharmaceutical Co., Ltd Last check in October 2021

NCT04167462

Study name	An investigational study to evaluate experimental medication BMS-986165 compared to placebo in participants with plaque psoriasis (POETYK-PSO-3) in mainland China, Taiwan, and South Korea (POETYK-PSO-3)
Methods	RCT, double-blind, placebo-controlled, parallel-arm, multicentric study Location: China, Taiwan, Korea Phase 3
Participants	**Randomised:** 180 participants **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
Interventions	**Intervention** A. BMS-986165 (deucravacitinib: selective tyrosine kinase 2 (TYK2) inhibitor) **Control intervention** B. Placebo
Outcomes	**Primary outcomes** • Static Physician Global Assessment (sPGA) 0/1 response week 16 • Psoriasis Area and Severity Index (PASI) 75 response week 16 **Secondary outcome measures** : • PASI 90,100 at 16 weeks • sPGA 0 at 16 weeks • Scalp specific Physician's Global Assessment (ssPGA) 0/1 response at 16 weeks • Change from baseline in Psoriasis Symptoms and Signs Diary (PSSD) symptom score at 16 weeks • PSSD symptom score of 0 assessed as a proportion of participants with a PSSD symptom score of 0 among participants with a baseline PSSD symptom score ≥ 1 at 16 weeks • Change from baseline in PSSD sign score at 16 weeks

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	• PSSD sign score of 0 assessed as a proportion of participants with a PSSD sign score of 0 among participants with a baseline PSSD sign score ≥ 1 at 16 weeks • Physician Global Assessment- Fingernails (PGA-F) 0/1 at 16 weeks • Dermatology Life Quality Index (DLQI) 0/1 assessed as a proportion of participants with a DLQI score of 0 or 1 among participants with a baseline DLQI score ≥ 2 at 16 weeks • Change from baseline in DLQI score at 16 weeks • Palmoplantar PGA (ppPGA) 0/1 assessed as a proportion of participants with a ppPGA score of 0 or 1 among participants with a baseline ppPGA score ≥ 3 at 16 weeks
Starting date	Actual study start date: November 2019 Estimated study completion date: January 2022 Last update posted: September 2020, recruiting
Contact information	-
Notes	Funding: Bristol-Myers Squibb Ongoing study Last checked in October 2021

NCT04237116

Study name	A study of secukinumab treatment in patients with plaque psoriasis and co-existing non-alcoholic fatty liver disease (NAFLD) (pINPOINt)
Methods	RCT, double-blind, parallel-arm, multicentric study Date of study: February 2020 Location: Germany, Spain Phase 3
Participants	**Randomized:** 90 participants **Inclusion criteria**: • Male/female patients, 18 years or older • Moderate-to-severe plaque-type psoriasis, candidate for systemic therapy • Diagnosis of NAFLD by either ultrasound at screening or liver histology within 6 months before Baseline BMI > 25 kg/m^2 ALT 1.2 to 3.0 × ULN • MRI confirmed liver fat ≥ 8% at screening **Exclusion criteria**: • Forms of psoriasis other than chronic plaque-type psoriasis • Drug-induced psoriasis • Pregnant or nursing (lactating) women • Women of childbearing potential using effective methods of contraception • Ongoing use of prohibited treatments • Previous treatment with biological drug targeting IL-17 or the IL-17 receptor • Known immunosuppression (e.g. AIDS) at screening • Unstable weight over the last 6 months prior to screening • Type I diabetes, or uncontrolled diabetes (type I or type II) defined as HbAlc ≥ 10% at screening

NCT04237116 *(Continued)*

	• Evidence of hepatic decompensation or severe liver impairment or cirrhosis • History of liver transplantation or planned liver transplant or biliary diversion • Presence or history of other liver disease • Current, or history of, significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening • Prior or planned bariatric surgery • Inability or unwillingness to undergo MRI of the abdomen
Interventions	**Intervention** A. Secukinumab 300 mg SC weekly in first 4 weeks, followed by every 4 weeks up to week 20; and placebo 300 mg SC at weeks 13, 14 and 15 to maintain the blind **Control Intervention** B. Placebo 300 mg SC weekly in first 4 weeks, followed by every 4 weeks up to week 8; and secukinumab 300 mg SC weekly for 4 weeks starting at week 12, followed by every 4 weeks up to week 20
Outcomes	**Primary outcome** • Percentage of participants achieving ≥ 90% improvement (reduction) in PASI score compared to baseline at 12 weeks **Secondary outcomes** • Serum Alanine Aminotransferase (ALT) level at 12 weeks • Percentage of participants achieving DLQI 0/1 at week 12
Starting date	Actual study start date: February 2020 Estimated study completion date: July 2021 Last update posted: July 2021, recruiting
Contact information	Novartis Pharmaceuticals novartis.email@novartis.com
Notes	Funding: Novartis Pharmaceuticals Ongoing study Last checked in October 2021

NCT04306315

Study name	Adjusted brodalumab dose compared with standard brodalumab dose in subjects with moderate-to-severe plaque psoriasis and ≥ 120 kg body weight (ADJUST)
Methods	RCT, placebo-controlled, double-blind trial, parallel-arm Date of location: June 2022 Location: ? Phase 4
Participants	**Randomised**: 384 participants **Inclusion criteria:**

NCT04306315 *(Continued)*

- Signed and dated informed consent has been obtained prior to any protocol-related procedures
- Age ≥ 18 to < 75 years at the time of screening
- Diagnosed with chronic plaque psoriasis at least 6 months before randomisation
- Body weight ≥ 120 kg at the time of screening
- Moderate-to-severe plaque psoriasis as defined by: BSA ≥ 10% and PASI ≥ 12 at screening and baseline
- No current active tuberculosis

Exclusion criteria:

- Diagnosed with erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, or other skin conditions (e.g. eczema) that would interfere with evaluations of the effect of the investigational medicinal product (IMP) on participants with plaque psoriasis
- Clinically important active infections or infestations, chronic, recurrent or latent infections or infestations, or is immunocompromised (e.g. human immunodeficiency virus, hepatitis B, and hepatitis C)
- Any systemic disease considered by the investigator to be uncontrolled and either immunocompromising the participants and/or placing the participant at undue risk of intercurrent diseases (including, but not limited to, renal failure, heart failure, liver disease, diabetes, and anaemia)
- History of Crohn's disease
- Myocardial infarction or stroke, or unstable angina pectoris within the past 12 months
- Any active malignancy
- History of malignancy within 5 years, except for treated and considered cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, or in situ breast ductal carcinoma
- History of suicidal behaviour (i.e. 'actual suicide attempt', 'interrupted attempt', 'aborted attempt', or 'preparatory acts or behaviour') based on the Columbia-Suicide Severity Rating Scale (C-SSRS) questionnaire at screening or at baseline
- Any suicidal ideation of category 4 or 5 ('active suicidal ideation with some intent to act, without specific plan' or ' active suicidal ideation with specific plan and intent') based on the C-SSRS questionnaire at screening or at baseline
- A Patient Health Questionnaire (PHQ)-8 score of ≥ 10 corresponding to moderate-to-severe depression at screening or at baseline

Interventions

Intervention

A. Brodalumab 210 mg + brodalumab 70 mg add-on (subcutaneously at week 0, week 1, and week 2, and then once every 2 weeks. Participants not fulfilling a predefined response at any visit with efficacy assessments after week 16 will receive a dose adjustment to 280 mg brodalumab every 2 weeks)

Control intervention

B. Brodalumab 210 mg + placebo add-on (subcutaneously at week 0, week 1, and week 2, and then once every 2 weeks. Participants not fulfilling a predefined response at any time visit with efficacy assessments week 16 will receive a dose adjustment to 210 mg brodalumab + placebo every 2 weeks)

Outcomes

Primary outcome :

- Having at least 90% lower PASI score relative to baseline (PASI 90 response) at week 40

Secondary outcomes :

- Having static Physician's Global Assessment (sPGA) score of 0 or 1 at week 40
- Having PASI 90 response at week 52
- Having sPGA score of 0 or 1 at week 52
- Having sPGA of genitalia (sPGA-G) score of 0 or 1 at both week 40 and week 52
- Having PASI 100 response at week 40 and week 52
- Change from baseline at weeks 40 and 52 in PASI score

NCT04306315 *(Continued)*

	• Change from baseline at weeks 40 and 52 in affected BSA • Having DLQI total score of 0 or 1 at week 40 and week 52 • Having DLQI total score of 0 or 1 at week 52 • Change from baseline at weeks 40 and 52 in DLQI total score
Starting date	Estimated study start date: June 2021 Estimated study completion date: November 2025 Last update posted: August 2021, not yet recruiting
Contact information	LEO Pharma raleodk@leo-pharma.com
Notes	Ongoing study Funding: LEO Pharma Last checked in October 2021

NCT04394936

Study name	An explorative psoriasis biomarker study
Methods	RCT, double-blind, parallel-arm study Date of study: September 2020 Location: Netherlands
Participants	**Randomised**: 50 participants **Inclusion criteria:** • Male or non-pregnant female subjects, 18 to 75 years of age (inclusive) • Healthy as defined by the absence of any uncontrolled active or uncontrolled chronic disease following a medical and surgical history, documentation of general symptoms, and a symptom-directed physical examination including vital signs
Interventions	**Intervention** A. Guselkumab 100 mg/mL, subcutaneous injection, administered on day 0, 28 and 84 **Control intervention** B. Placebo SC, administered on day 0, 28 and 84
Outcomes	**Primary outcomes** • Psoriasis Area and Severity Index (PASI) Assessment (time frame: from day 14 to day 168) • Physicians Global Assesment (PGA) Assessment (time frame: from day 14 to day 168) • Percentage body surface affected (% BSA) assessment (time frame: from day 14 to day 168) • Digital PASI (time frame: from day 14 to day 168) • Erythema measurement of the skin (time frame: from day 14 to day 168) • Multispectral imaging (time frame: from day 14 to day 168) • Laser Speckle Contrast imaging Thermography (time frame: from day 14 to day 168) • Activity Tracking Heartrate (time frame: from day 14 to day 168) • Activity Tracking Steps (time frame: from day 14 to day 168)

NCT04394936 *(Continued)*

- Cells/mL; circulating immune cell subsets (time frame: from day 14 to day 168)
- Circulating protein biomarkers (time frame: from day 14 to day 168)
- Anti-drug antibodies (time frame: from day 14 to day 168)
- Immunohistochemistry of biopsies (time frame: from day 14 to day 112)
- Blister immune cell subsets (time frame: from day 14 to day 112)
- Transcriptome of biopsies (time frame: from day 14 to day 112)
- Skin barrier function (time frame: from day 14 to day 168)
- Patient genotyping (time frame: day 14)
- Lipidomics of the stratum corneum (time frame: from day 14 to day 112)
- Skin surface biomarkers (time frame: from day 14 to day 112)
- Fecal microbiome (time frame: from day 14 to day 112)
- Cutaneous microbiome (time frame: from day 14 to day 112)

Starting date	Actual study start date: September 2020 Estimated study completion date: December 2022 Last update posted: June 2021, recruiting
Contact information	Robert Rissmann, PhD, Centre for Human Drug Research clintrials@chdr.nl
Notes	Ongoing study Funding Janssen Pharmaceuticals Last checked in October 2021

NCT04453137

Study name	Multicentre, double-blind, randomised, parallel- group, study evaluating PK efficacy, safety, and immunogenicity in patients with plaque psoriasis receiving Humira or AVT02 followed by safety extension phase of AVT02
Methods	RCT, active-controlled, double-blind trial, parallel arms Date of study: June 2020 Location: Georgia, Iceland, Poland, Russian Federation, Ukraine Phase 3
Participants	**Randomised**: 448 participants **Inclusion criteria:** • Participant has signed the informed consent form and documentation as required by relevant competent authorities and is able to understand and adhere to the visit schedule and study requirements • Participant is male or female aged 18 to 75 years, inclusive, at the time of screening • Participants with moderate-to-severe chronic plaque psoriasis who has involved body surface area (BSA) ≥ 10% (Palm Method), ≥ 12 on the PASI, and static Physicians Global Assessments (sPGA) ≥ 3 (moderate) at screening and at baseline (week 1/day 1) • Participant has had stable disease for at least 2 months (i.e. without significant changes as defined by the Investigator or designee)

NCT04453137 *(Continued)*

- Participants with moderate-to-severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate
- Participant is naïve to adalimumab therapy, approved or investigational
- Participant has a negative QuantiFERON test for tuberculosis (TB) during screening. Note: Patients with an indeterminate QuantiFERON test are allowed if they have all of the following:
  - No evidence of active TB on chest radiograph within 3 months prior to the first dose of study drug
  - Documented history of treatment of TB or adequate prophylaxis initiation with an isoniazid-based regimen > 1 month prior to receiving study drug in accordance with local recommendations
  - No known exposure to active TB after most recent prophylaxis
  - Asymptomatic at screening and baseline. Investigators should check with the medical monitor before enrolling such subjects.
- Women of childbearing potential (except those who are postmenopausal for more than 2 years or if surgically sterile) must have a negative serum pregnancy test during screening and negative urine pregnancy test at baseline (week 1/day 1)
- Sexually-active women of childbearing potential must agree to use highly effective contraception (sterilisation, hormonal contraception pills or injection or implants, sterilisation and abstinence) for the duration of the study and until 6 months after the last dose of the study drug. Men must agree to use contraception for the duration of the study and agree not to donate sperm during and for 6 months after the last dose of study drug

Exclusion criteria

- Patient 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 of psoriasis
- Patient has prior use of any of the following medications within specified time periods or will require use during the study:
  - Topical medications within 2 weeks of baseline (week 1/day 1)
  - PUVA phototherapy and/or UVB phototherapy within 4 weeks prior to the baseline (week 1/day 1)
  - Nonbiologic psoriasis systemic therapies (e.g. cyclosporine, methotrexate, and acitretin) within 4 weeks prior to the baseline (week 1/day 1)
  - Any prior or concomitant adalimumab therapy, either approved or investigational
  - Any systemic steroid in the 4 weeks prior to screening
  - Investigational agent(s) within 90 days or 5 half-lives (whichever is longer) before baseline (week 1/day 1)

Interventions	**Intervention** A. AVT02 (adalimimab biosimilar) **Control intervention** B. Adalimumab (initial dose of 80 mg (2 × 40 mg) administered SC, followed by 40 mg SC given every other week starting 1 week after the initial dose
Outcomes	At 26 weeks to 28 weeks **Primary outcome** : • Area under the concentration-time curve over the dosing interval (measurement of area under the plasma concentration-time curve (AUCtau, 26-28) of AVT02 and Humira in venous blood samples) • Maximum concentration over the dosing interval (measurement of serum concentration of AVT02 and Humira in venous blood samples) **Secondary outcomes :**

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	• PASI from week 1 to week 28 and from week 12 to week 28
Starting date	Actual study start date: June 2020 Estimated study completion date: February 2022 Last update posted: June 2021, active, not recruiting
Contact information	Roshan Dias, MSc roshan.dias@alvotech.com Heimo Stroissnig, MD heimo.stroissnig@alvotech.com Principal investigator: Steven Feldman, MD, PhD Wake Forest University Health Sciences
Notes	Ongoing study Funding: Alvotech Swiss AG Last checked in October 2021

NCT04533737

Study name	Efficacy and safety of brodalumab compared with guselkumab in the treatment of plaque psoriasis after inadequate response to ustekinumab (COBRA)
Methods	RCT, active-controlled, double-blind, parallel-arm study Date of study: November 2020 Location: worldwide Phase 4
Participants	**Randomised**: 260 participants **Inclusion criteria:** • Participant has a diagnosis of plaque psoriasis for at least 6 months before the first administration of investigational medicinal product (IMP) as determined by the investigator • Participant has inadequately controlled plaque psoriasis currently treated with ustekinumab, and fulfils ALL of the following criteria: ustekinumab administered at least 3 times at or higher than the approved dose or frequency for at least 24 weeks; IGA ≥ 2 at screening and baseline; absolute PASI > 3 at screening and baseline; the last administration of ustekinumab was ≥12 weeks before randomisation. • Participant has no active tuberculosis at screening (negative QuantiFERON® or purified protein derivative [PPD] test). Participants with adequately treated latent tuberculosis are eligible. **Exclusion criteria** • Participant was diagnosed with erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, or other skin conditions (e.g. eczema) that would interfere with evaluations of the effect of IMP on plaque psoriasis • Participant has clinically important active infections or infestations, chronic, recurrent, or latent infections or infestations, or is immunocompromised (e.g. human immunodeficiency virus) • Participant has any systemic disease (e.g. renal failure, heart failure, hypertension, liver disease, diabetes, anaemia) considered by the investigator to be clinically significant and uncontrolled • Participant has a known history of Crohn's disease • Participant has any active malignancy, including evidence of cutaneous basal or squamous cell carcinoma or melanoma

NCT04533737 *(Continued)*

	• Participant has a history of malignancy within 5 years, except for treated and considered cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, or in situ breast ductal carcinoma • Participant has a known history of active tuberculosis • Participant has a history of suicidal behaviour (i.e. 'actual suicide attempt', 'interrupted attempt', 'aborted attempt', or 'preparatory acts or behaviour') based on the Columbia-Suicide Severity Rating Scale (C-SSRS) questionnaire at screening or baseline • Participant has any suicidal ideation of severity 4 or 5 ('some intent to act, no plan' or 'specific plan and intent') based on the C-SSRS questionnaire at screening or baseline • Participant has a Patient Health Questionnaire-8 (PHQ-8) score of ≥ 10, corresponding to moderate-to-severe depression at screening or baseline • Participant has previously received more than 1 tumour necrosis factor α (TNF-α) inhibitor • Participant has previously been treated with any anti-interleukin (IL)-17A, anti-IL-17 receptor subunit A, or anti-IL-23 besides ustekinumab. Participant has known or suspected hypersensitivity to any component(s) of the IMPs
Interventions	**Intervention** A. Brodalumab 210 mg (1.5 mL) at weeks 0, 1, 2, and then every 2 weeks + dummy 1 (placebo 1.0 mL) at weeks 0, 4, and then every 8 weeks **Control intervention** B. Guselkumab 100 mg (1.0 mL) at weeks 0, 4, and then every 8 weeks + dummy 2 (placebo 1.5 mL) at weeks 0, 1, 2, and then every 2 weeks.
Outcomes	**Primary outcome** : • Having Psoriasis Area and Severity Index (PASI) 100 response at week 16 **Secondary outcomes:** • Time to PASI 100 response at week 28 • Time to PASI 90 response at week 28 • Having PASI 100 response, assessed separately at weeks 4, 8, and 28 • Having PASI 90 response, assessed separately at weeks 4, 8, 16, and 28 • Having Investigator's Global Assessment (IGA) of 0, assessed separately at week 16 and week 28 • Having IGA of 0 or 1, assessed separately at week 16 and week 28 • Having Dermatology Life Quality Index (DLQI) total score of 0 or 1, assessed separately at weeks 4, 8, 12, 16, 20, 24, and 28 • Change in 36-Item Short Form Health Survey version 2 (SF-36v2) score from baseline, assessed separately at weeks 4, 8, 16, and 28 • Occurrence of treatment-emergent adverse events (AEs) from baseline to week 28
Starting date	Actual study start date: November 2020 Estimated study completion date: October 2022 Last update posted: August 2021, recruiting
Contact information	-
Notes	Ongoing study Funding LEO Pharma Last checked in October 2021

NCT04595409

Study name	A double-blind study to compare the efficacy, safety, and immunogenicity of the proposed biosimilar ustekinumab FYB202 to Stelara® in patients with moderate-to-severe plaque psoriasis (VESPUCCI)
Methods	RCT, active-controlled, double-blind, parallel-arm study Date of study: November 2020 Location: Poland Phase 3
Participants	**Randomised**: 392 participants **Inclusion criteria** • Patients who provided written informed consent and who are able to complete study procedures • Patients who are at least 18 years of age at time of screening • Patients with PASI score of at least 12 at screening and at baseline • Patients with involved body surface area of at least 10% at screening and at baseline • Patients with a Physician's Global Assessment (PGA) score of at least 3 at screening and at baseline by means of a 5-point scoring scale • Patients who are candidates for systemic therapy or phototherapy • Previous failure, inadequate response in the opinion of the investigator, intolerance, or contraindication to at least 1 conventional anti-psoriatic systemic therapy • For female patients (except those at least 2 years postmenopausal or surgically sterilised): a negative serum pregnancy test at screening and at baseline • Female patients of childbearing potential with a fertile male sexual partner must use adequate contraception from screening until 4 months after the last dose of study intervention. Adequate contraception is defined as using hormonal contraceptives or an intrauterine device (IUD), combined with at least one of the following forms of contraception: a diaphragm, cervical cap, or a condom. Total abstinence from heterosexual activity, in accordance with the lifestyle of the patient, is acceptable. Female patients must not donate ova starting at screening and throughout the clinical study period and for 4 months after study intervention administration. • Male patients who are sexually active with women of childbearing potential must agree they will use adequate contraception if not surgically sterilised and will not donate sperm from the time of screening until 6 months after the last dose of study intervention. Adequate contraception for the male patient and his female partner of childbearing potential is defined as using hormonal contraceptives or an IUD combined with at least one of the following forms of contraception: a diaphragm, cervical cap, or a condom. Total abstinence from heterosexual activity, in accordance with the lifestyle of the patient, is acceptable. **Exclusion criteria** • Patients diagnosed with erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, any other skin disease, or other systemic inflammatory autoimmune disorder at the time of the screening and baseline visits that would interfere with evaluations of the effect of study intervention on psoriasis • Patients who have received any topical psoriasis treatment including corticosteroids • Patients who have received the following treatments for psoriasis: PUVA phototherapy and/or ultraviolet B phototherapy and/or laser therapy. Non-biologic psoriasis systemic therapies, tofacitinib, or apremilast; adalimumab. Etanercept or secukinumab. Infliximab, brodalumab, certolizumab pegol, ixekizumab, golimumab, or alefacept • Patients taking drugs that may cause new onset or exacerbation of psoriasis • Patients who have received ustekinumab or any biologics directly targeting interleukin (IL)-12 or IL-23 • Patients with active infection or history of infections as follows: Any active infection for which systemic anti-infectives were used within 4 weeks prior to randomisation. A serious infection, de-

NCT04595409 *(Continued)*

	fined as requiring hospitalisation or intravenous anti-infectives, within 8 weeks prior to randomisation. Evidence of any clinically relevant bacterial, viral, fungal, or parasitic infection. Recurrent or chronic infections or other active infection that, in the opinion of the investigator, might cause this study to be detrimental to the patient
Interventions	**Intervention** A. FYB202 (ustekinumab biosimilar), 1 SC injection at week 0 and week 4, followed by 1 SC injection every 12 weeks thereafter for the next 3 consecutive doses **Control intervention** B. Ustekinumab, 1 SC injection at week 0 and week 4, followed by 1 SC injection every 12 weeks thereafter for the next 3 consecutive doses
Outcomes	At week 12 **Primary outcome** • Percent improvement in PASI score **Secondary outcomes** • Percent improvement in PASI score [time frame: through study completion, approximately 1 year] • Raw PASI score [time frame: through study completion, approximately 1 year] • Proportion of patients with PASI 75 and PASI 90 [time frame: through study completion, approximately 1 year] • Change per Physician's Global Assessment (PGA) [time frame: through study completion, approximately 1 year] • Improvement of DLQI total score [time frame: through study completion, approximately 1 year] • Itching Visual Analogue Scale [time frame: through study completion, approximately 1 year] • Relative frequency, nature, and severity of AEs and SAEs [time frame: through study completion, approximately 1 year] • Serum trough levels of ustekinumab [time frame: through study completion, approximately 1 year] • Number of patients with antibodies to ustekinumab [time frame: through study completion, approximately 1 year]
Starting date	Actual study start date: November 2020 Estimated study completion date: Mach 2022 Last update posted: August 2021, active not recruiting
Contact information	vespucci@bioeq.com
Notes	Ongoing study Funding Bioeq GmbH Last checked in October 2021

NCT04607980

Study name	A study to investigate ABP 654 for the treatment of participants with moderate-to severe plaque psoriasis
Methods	RCT, active-controlled, double-blind, parallel-arm study

NCT04607980 *(Continued)*

	Date of study: November 2020 Location: worldwide Phase 3
Participants	**Randomised**: 542 participants **Inclusion criteria** • Men or women between 18 and 75 years old • Stable moderate to severe plaque psoriasis for at least 6 months • Baseline score of PASI >= 12, involvement of >= 10% BSA, and sPGA >= 3 at screening and at baseline • Candidate for phototherapy or systemic therapy • Previous failure, inadequate response, intolerance, or contraindication to at least 1 conventional anti-psoriatic systemic therapy • Female participants should have negative serum pregnancy test during screening and a negative urine pregnancy test at baseline • No known history of latent or active tuberculosis (TB), and has a negative test for TB during screening (with negative purified protein derivative (PPD), and Negative Quantiferon®/T-spot test) • Participants with a positive purified protein derivative and a history of Bacillus Calmette-Guérin (BCG) vaccination are allowed with a negative Quantiferon®/T-spot® • Participants with a positive PPD test (without history of BCG vaccination) or participants with a positive or indeterminate Quantiferon®/T-spot test are allowed if they have all of the following: No symptoms per TB worksheet provided by the sponsor. Documented history of adequate prophylaxis initiation prior to receiving investigational product (IP) in accordance with local recommendations. No known exposure to a case of active TB after most recent prophylaxis. No evidence of active TB on chest radiograph within 3 months prior to the first dose of IP. **Exclusion criteria** • Skin disease related conditions such as, erythrodermic psoriasis (PsO), pustular PsO, guttate PsO, medication induced PsO, or other skin conditions at the time of the screening visit (e.g. eczema) that would interfere with evaluations of the effect of IP on PsO • Participant has an active infection, recurrent or chronic infections, serious infection or history of infections • Known history of human immunodeficiency virus • Hepatitis B surface antigen or hepatitis C virus antibody positivity at screening • Uncontrolled, clinically significant systemic disease such as uncontrolled diabetes mellitus, cardiovascular disease, renal disease, liver disease, or hypertension • Moderate to severe heart failure (New York Heart Associate class III/IV) • Known hypersensitivity to the IP or to any of the excipients • Any abnormal laboratory parameters at screening, as defined in protocol • Previous treatment with any agent specifically targeting interleukin (IL)-12 or IL-23 • Received biologic treatment for psoriasis within the previous month or 5 drug half-lives prior to randomisation • Received non-biologic systemic psoriasis therapy within 4 weeks prior to randomisation • Received Ultra-violet A (UVA) phototherapy (with or without psoralen) or excimer laser within 4 weeks prior to randomisation, or ultra-violet B (UVB) phototherapy within 2 weeks prior to randomisation • Received topical psoriasis treatment within 2 weeks prior to randomisation (exception: upper mid-strength to least potent [class III to VII] topical steroids permitted on the palms, soles, face, and intertriginous areas; bland emollients) • Received live viral or live bacterial vaccination within 2 weeks prior to randomisation • Received BCG vaccination within 1 year prior to randomisation • Other investigational procedures within 4 weeks prior to randomisation and during the study

NCT04607980 *(Continued)*

	• Participants not agreeing to follow protocol-defined contraceptive procedures • Participants likely not to be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures
Interventions	**Intervention** A. ABP 654 (ustekinumab biosimilar), SC, 45 mg (baseline BW less than equal to <= 100 kg) or 90 mg (baseline BW greater than > 100 kg) at weeks 0, 4, and 16. Further from week 28, participants will receive ABP 654 (same dose) every 12 weeks (Q12W) at weeks 28 and 40 or may receive dose intensification Q8W at weeks 28, 36, and 44, depending on PASI score. **Control intervention** B. Ustekinumab, SC, 45 mg (baseline BW <= 100 kg) or 90 mg (baseline BW > 100 kg) at weeks 0, 4, and 16. At week 28, participants will be re-randomised to continue on ustekinumab (treatment group B1), or to receive ABP 654 (treatment group B2) on weeks 28 and 40. Depending on PASI score, some participants may not be re-randomised and may receive dose intensification with ustekinumab Q8W at weeks 28, 36, and 44.
Outcomes	At week 12 **Primary outcome** • Percent improvement in PASI **Secondary outcomes** • Percent improvement in PASI at other time points [time frame: baseline (day 1 [week 0]), weeks 4, 12, 16, 28, 36, 40, 44 and week 52 (end of study [EOS])] • Percentage of participants with PASI 75 response throughout the study [time frame: baseline (day 1 [week 0]), weeks 4, 12, 16, 28, 36, 40, 44 and week 52 (EOS)] • Percentage of participants with PASI 100 response throughout the study [time frame: baseline (day 1 [week 0]), weeks 4, 12, 16, 28, 36, 40, 44 and week 52 (EOS)] • Percentage of participants with static Physician's Global Assessment (sPGA) responses (0/1) at week 12 and week 52 [time frame: week 12 and week 52] • Change from baseline in percentage of BSA affected with psoriasis at week 12 and week 52 [time frame: week 12 and week 52] • Number of participants with treatment emergent Adverse Events and Serious Adverse Events [time Frame: from screening day until week 52 (EOS)] • Events of Interests (EOIs) [time frame: from screening day until week 52 (EOS)] • Number of participants with Anti-drug Antibodies (ADAs) to ABP 654 [time frame: pre-dose on weeks 0 (day 1), 4, 12, 28, 32, 40, and on week 52 (EOS)]
Starting date	Actual study start date: November 2020 Estimated study completion date: June 2022 Last update posted: August 2021, active not recruiting
Contact information	medinfo@amgen.com
Notes	Ongoing study Funding Amgen Last checked in October 2021

NCT04614298

Study name	A phase 4 study of brodalumab (KHK4827) in subjects with moderate to severe plaque psoriasis
Methods	RCT, double-blind, placebo-controlled, parallel-arm study Date of study: January 2021 Location: China Phase 4
Participants	**Randomised**: 0 participants **Inclusion criteria** • Those who are ≥ 18 and ≤ 70 years of age at the time of signing the written informed consent form • Those who have involved BSA (the percentage (%) of body surface area involved with lesion) ≥ 10%, PASI (Psoriasis Area and Severity Index) ≥ 12 and sPGA (static Physician's global assessment) ≥ 3 at screening and at baseline **Exclusion criteria** • Those who diagnosed with erythrodermic psoriasis, pustular psoriasis, guttate psoriasis or medication-induced psoriasis • Those who have skin conditions other than psoriasis including eczema at the time of the screening that would interfere with evaluations of the study drug
Interventions	**Intervention** A. KHK4827 210 mg SC **Control intervention** B. Placebo SC
Outcomes	At week 12 **Primary outcome** • Proportion of participants achieving 75% improvement from baseline in PASI (PASI 75) **Secondary outcomes** • Proportion of participants achieving 100% improvement from baseline in PASI (PASI 100) • Static physician's global assessment (sPGA) of "clear" or "almost clear" (0 or 1) • Number of participants with treatment-emergent adverse events (TEAEs) or drug-related TEAEs [time frame: after received an investigational product until last visit 1 year]
Starting date	Estimated study start date: January 2021 Estimated study completion date: November 2022 Last update posted: September 2021, withdrawn (due to the reconsideration of KHK4827's business in China, it. was decided to withdraw this clinical trial prior to enrolment of first participant)
Contact information	clinical.info.jp@kyowakirin.com
Notes	Ongoing study Funding Kyowa Kirin Co., Ltd. Last checked in October 2021

NCT04673786

Study name	A study to compare the efficacy and safety of CT-P43 to Stelara in patients with plaque psoriasis
Methods	RCT, active-controlled, double-blind, parallel-arm study Date of study: January 2021 Location: Estonia Phase 3
Participants	**Randomised**: 509 participants **Inclusion criteria** • Men or women between 18 and 80 years old • Patient has had diagnosis of plaque-type psoriasis for at least 24 weeks **Exclusion criteria** • Patients diagnosed with forms of psoriasis other than plaque-type • Patients previously received ustekinumab or a biosimilar of ustekinumab • Patient who has allergies to the active substance or any of the excipients of ustekinumab or study drug, or patients with a hypersensitivity to immunoglobulin products or natural rubber and latex
Interventions	**Intervention** A. CT-P43 (ustekinumab biosimilar) 45 mg or 90 mg dose SC **Control intervention** B. Ustekinumab 45 mg or 90 mg dose SC
Outcomes	At week 12 **Primary outcome** • Mean percent improvement in PASI score
Starting date	Actual study start date: January 2021 Estimated study completion date: May 2022 Last update posted: June 2021, active, not recruiting
Contact information	-
Notes	Ongoing study Funding Celltrion Last checked in October 2021

NCT04713592

Study name	Study of subcutaneous (injected under the skin) risankizumab to assess change in disease symptoms in adult participants with moderate-to-severe plaque psoriasis with palmoplantar involvement (IMMprint)

NCT04713592 *(Continued)*

Methods	RCT, placebo-controlled, double-blind, parallel-arm study Date of study: February 2021 Location: worldwide Phase 3
Participants	**Randomised**: 168 participants **Inclusion criteria** • Diagnosis of chronic palmoplantar plaque psoriasis (PPPsO) (with or without psoriatic arthritis) for at least 6 months before baseline and a palmoplantar Investigator's Global Assessment (ppIGA) of moderate or severe, at screening and baseline • Must have at screening and baseline a plaque psoriasis (PsO) body surface area (BSA) involvement of greater than or equal to one percent, a static Physician's Global Assessment (sPGA) score of moderate to severe (greater than or equal to three), a PPASI moderate to severe (greater than or equal to eight), at least one additional PsO plaque outside of the palms and soles • Must be a candidate for systemic therapy as assessed by the investigator • Previously had inadequately controlled disease by topicals, phototherapy and/or systemic treatments **Exclusion criteria** • History of PsO other than chronic plaque-type PsO • History of current drug-induced PsO or a drug-induced exacerbation of pre-existing psoriasis • Ongoing inflammatory skin diseases other than PsO and psoriatic arthritis that could interfere with PsO assessments • Evidence of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, human immunodeficiency virus (HIV), active tuberculosis, active systemic infection/clinically important infections in the last two weeks prior to baseline • Prior exposure to risankizumab
Interventions	**Intervention** A. Risankizumab SC for 52 weeks **Control intervention** B. Placebo SC for 16 weeks followed by risankizumab for 36 weeks
Outcomes	At week 16 **Primary outcome** • Percentage of participants achieving palmoplantar investigator's Global Assessment (ppIGA) of "clear" or "almost clear" (0 or 1) **Seconday outcomes** • Percentage of participants achieving >= 75% improvement in Palmoplantar Psoriasis Area and Severity Index (PPASI 75) response • Percentage of participants achieving >= 90% improvement in PPASI 90 response • Percentage of participants achieving static Physician's Global Assessment (sPGA) of "clear" or "almost clear" (0 or 1) with at least a 2-point reduction from baseline • Percentage of participants achieving 100% improvement in PPASI 100 response
Starting date	Actual study start date: February 2021 Estimated study completion date: April 2023

NCT04713592 *(Continued)*

	Last update posted: September 2021, recruiting
Contact information	abbvieclinicaltrials@abbvie.com
Notes	Ongoing trial Funding AbbVie Last checked in October 2021

NCT04728360

Study name	Comparative study of BAT2206 with Stelara® in patients with moderate-to-severe plaque psoriasis
Methods	RCT, active-controlled, double-blind, parallel-arm study Date of study: February 2021 Location: not stated Phase 3
Participants	**Randomised**: 406 participants **Inclusion criteria** • Male or female ≥ 18 years old with a diagnosis of plaque-type psoriasis for at least 24 weeks before screening • Have moderate-to-severe plaque-type psoriasis as defined at screening and baseline by: PASI ≥ 12, sPGA ≥ 3, and body surface area affected by chronic plaque-type psoriasis ≥ 10% • Failed to respond to, or has a contraindication to, or is intolerant to other systemic therapies including cyclosporine, methotrexate or psoralen and ultraviolet (UV) A • Female patients of childbearing potential and male patients with a female partner of childbearing potential must be willing to use a highly effective contraceptive precaution throughout the study period and continuing for at least 15 weeks after the last dose of study drug. See Appendix 1 for the acceptable highly effective contraceptive methods. Abstinence from heterosexual intercourse is accepted when this is the usual lifestyle of the patient and must be continued for at least 15 weeks after the last dose of study drug. A female patient is considered not of childbearing potential when postmenopausal (at least 12 consecutive months without menses without an alternative medical cause) or surgically sterilised (hysterectomy, bilateral salpingectomy, and bilateral oophorectomy). • If female of childbearing potential, patient should have a negative pregnancy test result at screening and baseline visits. • Must be willing to provide written consent and to comply with the requirements of the study protocol **Exclusion criteria** • Have any forms of psoriasis at the time of the screening visit other than plaque-type such as erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis or other skin conditions (e.g. eczema) that would interfere with evaluations of the effect of investigational product on psoriasis • Have previously received ustekinumab, a biosimilar of ustekinumab, or any drug that targets interleukin-12 or interleukin-23 • Have received any biologic agents other than those prohibited (see exclusion #2) within 12 weeks or 5 half-lives (whichever is longer) before the baseline visit • Have received topical therapies for the treatment of psoriasis (such as corticosteroids, vitamin D analogs, or retinoids) within 2 weeks before baseline visit

NCT04728360 *(Continued)*

- Have received UVA phototherapy (with or without oral psoralen), UVB phototherapy, any systemic steroids or nonbiological drugs for the treatment of psoriasis within 4 weeks before baseline visit
- Have received any investigational drug within 8 weeks or 5 half-lives (whichever is longer) before baseline visit
- Have received any herbal remedies or traditional medicines used to treat psoriasis within 4 weeks before baseline visit
- History of allergy to the active substance or any of the excipients of study drugs, or of hypersensitivity to late
- History of invasive infection (e.g. histoplasmosis, coccidioidomycosis, blastomycosis)
- Presence of active infection at screening, history of infection requiring intravenous antibiotics and/or hospitalisation ≤ 8 weeks before baseline visit or oral antibiotics ≤ 2 weeks before baseline visit. Minor fungal infections may be allowed.
- Any recurrent bacterial, fungal, or viral infection that, (based on the investigator´s clinical assessment), makes the patient unsuitable for the study, including recurrent/disseminated herpes zoster
- Meet any of the following criteria relative to latent or active tuberculosis (TB) infection
- Evidence of malignancy, lung infection, or abnormalities suggestive of active TB on chest radiography (x-ray or computed tomography) performed within 12 weeks before the screening visit or during the screening period
- Any history of malignancy or lymphoproliferative disease at any time, except curative treatment for non-melanoma skin cancer or resected carcinoma in situ of the cervix
- Have a transplanted organ/tissue or stem cell transplantation
- Have an underlying metabolic, haematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious, or gastrointestinal condition, which in the opinion of the investigator places the patient at unacceptable risk
- Have a history of demyelinating diseases (including myelitis) or neurologic symptoms suggestive of demyelinating disease
- Any major surgical procedure within 12 weeks of the baseline visit or planned during the study
- History of clinically significant drug or alcohol abuse in the last 12 months as judged by the investigator
- Pregnant or breastfeeding (lactating) women
- Patient is considered by the investigator, for any reason, to be an unsuitable candidate for the study
- Patients participating in another investigational drug or device (a device is an instrument, apparatus, implement, machine, contrivance, or implant, including a component part or accessory intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease), trial or planning on participating in another clinical trial during the course of the study

Interventions	**Intervention** A. BAT2206 (ustekinumab biosimilar). Patients who weigh ≤ 100 kg: BAT2206 45 mg (1 injection of 45 mg/0.5 mL) by SC injection via PFS. Patients who weigh > 100 kg: EU-sourced Stelara 90 mg (2 injections of 45 mg/0.5 mL each) by SC injection via PFS **Control intervention** B. Ustekinumab (EU-sourced Stelara). Patients who weigh ≤ 100 kg: EU-sourced Stelara 45 mg (1 injection of 45 mg/0.5 mL) by SC injection via PFS. Patients who weigh > 100 kg: EU-sourced Stelara 90 mg (2 injections of 45 mg/0.5 mL each) by SC injection via PFS
Outcomes	At week 12 **Primary outcome** • Percent improvement from baseline in PASI **Secondary outcomes**

NCT04728360 *(Continued)*

	• Percent improvement from baseline in PASI score to weeks 4, 8, 16, 20, 28, 40, and 52 • Proportion of participants who achieve at least 50/75/90/100% improvement from baseline in PASI (PASI 50/75/90/100) at weeks 4, 8, 12, 16, 20, 28, 40, and 52 • Change from baseline in static Physician's Global Assessment (sPGA) score to weeks 4, 8, 12, 16, 20, 28, 40, and 52
Starting date	Actual study start date: July 2021 Estimated study completion date: May 2023 Last update posted: October 2021, recruiting
Contact information	Min Zheng, Second Affiliated Hospital, School of Medicine, Zhejiang University
Notes	Ongoing trial Funding Bio-Thera Solutions Last checked in October 2021

NCT04785326

Study name	Efficacy, safety, and immunogenicity of subcutaneous DMB-3115 versus Stelara® in patients with moderate-to-severe chronic plaque psoriasis (Opportuniti)
Methods	RCT, active-controlled, double-blind, parallel-arm study Date of study: April 2021 Location: USA Phase 3
Participants	**Randomised**: 406 participants **Inclusion criteria** • Men or women between 18 and 75 years old • Patients who have a diagnosis of plaque-type psoriasis for at least 6 months **Exclusion criteria** • Patients with hypersensitivity to ustekinumab or any of the product excipients
Interventions	**Intervention** A. DMB-3115 45 mg or 90 mg SC **Control intervention** B. Ustekinumab 45 mg or 90 mg SC. Patients randomised to receive ustekinumab at the beginning of the study will be re-randomised at week 28 in a 1:1 ratio to either continue on Stelara or will be transitioned to receive DMB-3115.
Outcomes	At weeks 8 and 12 **Primary outcome** • Percent change in the PASI score

NCT04785326 *(Continued)*

Starting date	Actual study start date: April 2021 Estimated study completion date: November 2022 Last update posted: May 2021, recruiting
Contact information	Ji-Su Song songjs@donga.co.kr
Notes	Ongoing study Funding Dong-A ST Co., Ltd. Last checked in October 2021

NCT04839328

Study name	A phase Ⅲ efficacy and safety study of Hemay005 in subjects with moderate-to-severe plaque psoriasis
Methods	RCT, placebo-controlled, double-blind, multicentre study Date of study: March 2021 Location: Phase 3
Participants	**Randomised:** 306 participants **Inclusion criteria** • At the time of signing the informed consent, the age was more than or equal to 18 years old, regardless of gender • Stable plaque psoriasis with a history of more than 6 months (from the time of randomisation) • Screening and baseline PSAI ≥ 12, sPGA ≥ 3 (moderate-to-severe, affected body surface area BSA ≥ 10% • All subjects must agree and commit to the use of a reliable contraceptive regimen. Women of childbearing potential must undergo monthly pregnancy testing during the study and agree to use two of the following methods of contraception throughout the study and for 90 days after the last dose of study drug. Reliable contraceptive regimen: vasectomy, abstinence, the use of condoms, intrauterine contraceptives (IUD) (oral administration, patch, ring, injection, implantation), barrier methods (diaphragm with spermicide, condom with spermicide) • The subjects voluntarily participated in the study and signed the informed consent. **Exclusion criteria** • Forms of psoriasis other than chronic plaque-type (i.e. erythrodermic and guttate psoriasis, palmar, plantar or nail disease) at screening • Investigator-diagnosed as drug-induced psoriasis (including but not limited to new onset or aggravation of psoriasis caused by beta-blockers, calcium channel inhibitors or lithium preparations) • Skin diseases, chronic diarrhoea, serious digestive system diseases (such as active gastric ulcer, gastrointestinal bleeding, etc.), or other autoimmune inflammatory diseases that may interfere with clinical evaluation, according to the investigator • The screening period was accompanied with active infection (such as bacterial infection, viral infection, fungal infection, etc., which required oral or intravenous treatment), and the investigator assessed that participation in this study may increase the risk of subjects

NCT04839328 *(Continued)*

- Subjects with a history of tuberculosis or active tuberculosis (there were signs or symptoms of active tuberculosis judged by the researcher at the time of screening)
- Use of prohibited treatments of this study
- History of congenital or acquired immunodeficiency
- Subjects couldn't limit their UV exposure during the study period
- History of apremilast or Hemay005 tablets
- Subjects with conditions that may affect oral drug absorption, such as subtotal gastrectomy, clinically significant diabetic gastroenteropathy, or certain types of weight-loss surgery, such as gastric bypass surgery, not including surgery that simply separates the stomach into separate chambers, such as gastric banding surgery
- Subjects with tumour or history of malignancy (solid organ tumour or haematological tumour including myelodysplastic syndrome) in the past 5 years
- History of alcohol or drug abuse or dependence in the past year
- Subjects with a history of mental illness, suicidal behavior (including positive attempt, interrupted attempt or attempted suicide) or suicidal thoughts in the past 6 months who were not suitable for clinical trials after the evaluation of the investigator; subjects with severe anxiety or depression during the screening period being assessed as having severe anxiety or depression
- Clinically serious, progressive or uncontrollable diseases in the screening period, including but not limited to respiratory system, cardiovascular system, endocrine system, blood system, musculoskeletal system and nervous system. According to the assessment of investigator, participating in this study may increase the risk of subjects or interfere with data interpretation
- In the screening period, human immunodeficiency virus (HIV) serological positive (i.e. HIV antibody-positive); evidence of hepatitis B virus infection: hepatitis B surface antigen (HBsAg)-positive, or hepatitis B core antibody (HBcAb)-positive and HBV-DNA above the upper limit of the normal range, or hepatitis B E antibody (HBeAb) positive and HBV-DNA above the upper limit of the normal range; evidence of hepatitis C virus (HCV) infection: HCV antibody-positive
- During the screening period, there were any of the following laboratory abnormalities:
  - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 times the upper limit of normal value, or total bilirubin > 1.5 times the upper limit of normal value
  - Serum creatinine > 1.2 times the upper limit of normal value
  - The haemoglobin of male patients was less than 8.5 g/dL (85.0 g/L), and that of female patients was less than 8.0 g/dL (80.0 g/L)
  - WBC count < 3.0 × 109/L or ≥ 14 × 109/L
  - Platelet count < 100 × 109/L
- Females who were pregnant during lactation or pregnancy, or during the planned study period, or subjects who had sperm/egg donation plans during the study period
- Known to be allergic to active ingredient or excipient of the investigational product
- Participated in any other interventional clinical trial within 4 weeks or 5 pharmacokinetic/pharmacodynamic half-lives before randomisation (whichever is longer)
- The investigator considered that there are any other conditions that are not suitable for participating in the study.

Interventions	**Intervention** A. Hemay005 60 mg BID for 16 weeks **Control intervention** B. Placebo
Outcomes	At 16 weeks **Primary outcome** • PASI 75 **Secondary outcomes**

NCT04839328 *(Continued)*

	• sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at 16 weeks, 1 year • PASI 75/90 at 1 year
Starting date	Estimated study start date: May 2021 Estimated study completion date: April 2023 Last update posted: April 2021, not yet recruiting
Contact information	Junitng Wu +8615822778207 hemay1834@126.com
Notes	Funding: Tianjin Hemay Pharmaceutical Co. Ltd. Last check in October 2021

NCT04908475

Study name	Study of subcutaneous risankizumab injection compared to oral apremilast tablets to assess change in disease activity and adverse events in adult participants with moderate plaque psoriasis who are candidates for systemic therapy
Methods	RCT, active-controlled, open-label, assessor-blinded study Date of study: June 2021 Location: worldwide Phase 3

Participants	**Randomised**: 330 participants
	Inclusion criteria
	• Candidates for systemic therapy with moderate chronic plaque psoriasis (PsO) (with or without psoriatic arthritis) at screening and baseline for at least 6 months prior to baseline defined as:
	  ◦ Body Surface Area (BSA) >= 10% and <= 15%; and
	  ◦ Psoriasis Area and Severity Index (PASI) >= 12; and
	  ◦ Static Physician Global Assessment (sPGA) = 3 (moderate) based on a 5-point scale (0 to 4).
	Exclusion criteria
	• Participant has any form of PsO other than chronic plaque PsO (e.g. pustular PsO, palmoplantar pustulosis, acrodermatitis of Hallopeau, erythrodermic, or guttate PsO)
	• History of current drug-induced PsO or a drug-induced exacerbation of pre-existing psoriasis
	• History of active ongoing inflammatory skin diseases other than PsO and psoriatic arthritis that could interfere with the assessment of PsO (e.g. hyperkeratotic eczema)
	• Prior exposure to risankizumab or apremilast

Interventions	**Intervention** A. Risankizumab **Control intervention** B. Apremilast
Outcomes	At week 16

NCT04908475 *(Continued)*

	Primary outcomes • PASI 90 • sPGA **Secondary outcome** • PASI 75
Starting date	Study start date: June 2021 Estimated study completion date: April 2023 Last update posted: October 2021, recruiting
Contact information	ABBVIE CALL CENTER 844-663-3742 abbvieclinicaltrials@abbvie.com
Notes	Ongoing study Funding AbbVie Last check in October 2021

NCT04914429

Study name	A study of guselkumab (TREMFYA) in Chinese participants with moderate-to-severe plaque psoriasis
Methods	RCT, placebo-controlled, double-blind study Date of study: August 2021 Location: China Phase 4
Participants	**Randomised**: 300 participants **Inclusion criteria** • Have a diagnosis of plaque psoriasis with or without psoriatic arthritis for at least 6 months before screening • A woman of childbearing potential must have a negative urine pregnancy test 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 • Agree to avoid prolonged sun exposure and avoid use of tanning booths or other ultraviolet (UV) light sources during study • Must sign an informed consent form (ICF) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study **Exclusion criteria** • Has a non-plaque form of psoriasis (example, erythrodermic, guttate, or pustular) • Has a history of or current signs or symptoms of liver or renal insufficiency (estimated creatinine clearance below 60 millilitre/minute [mL/min]); significant, progressive, or uncontrolled cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, haematologic, rheumatologic, psychiatric, or metabolic disturbances

NCT04914429 *(Continued)*

	• Currently has a history of malignancy within 5 years before screening (exceptions are non-melanoma skin cancer that has been adequately treated with no evidence of recurrence for at least 3 months before the first study drug administration and cervical carcinoma in situ that has been treated with no evidence of recurrence for at least 3 months before screening, or malignancy, which is considered cured with minimal risk of recurrence) • History of, or ongoing, chronic or recurrent infectious disease, including but not limited to, recurrent sinopulmonary infections, bronchiectasis, recurrent renal/urinary tract infection (for example, recurrent pyelonephritis, recurrent cystitis), fungal infection (mucocutaneous candidiasis), an open, draining, or infected skin wound, or an ulcer • Has previously received guselkumab
Interventions	**Intervention** A. Guselkumab 100 mg SC injection at weeks 0, 4, and then every 8 weeks (Q8W) **Control intervention** B. Placebo
Outcomes	At week 16 **Primary outcomes** • PASI 90 • IGA • AEs up to week 56 • SAEs up to week 56 • AEs leading to discontinuation of study intervention up to week 56 • Participants with infections up to week 56 • Participants with serious hypersensitivity reactions up to week 56 • Participants with injection-site reactions up to week 56 • Change from baseline in laboratory abnormalities up to week 56 • Laboratory abnormalities with maximum toxicity grades up to week 56 • Change from baseline in vital signs up to week 56 **Secondary outcomes** • PASI 100, PASI 90, PASI 75, and PASI 50 at week 0, 4, 12, 16, 20, 28, 36, 44, 48 • IGA at week 0, 4, 12, 16, 20, 28, 36, 44, 48 • DLQI at week 0, 4, 12, 16, 20, 28, 36, 44, 48 • Percentage of participants who maintain PASI 90 response at week 48 among participants who were PASI 90 responders at week 16 in guselkumab group at week 48 • Percentage of participants who maintain IGA score of cleared (0) or minimal (1) at week 48 among participants who achieved IGA 0/1 at week 16 in guselkumab group at week 48 • Percentage of participants who achieve an IGA score of cleared (0) and an IGA score of mild or better (less than or equal to [<=] 2) over time at week 0, 4, 12, 16, 20, 28, 36, 44, 48 • Percentage of participants who achieve a DLQI score of 0 or 1 over time among participants with baseline DLQI greater than (>) 1 at week 0, 4, 16, 28, 48 • Percentage of participants with an scalp-specific Investigator Global Assessment (ss-IGA) score of absence of disease (0) or very mild disease (1) over time among participants with scalp psoriasis and an ss-IGA Score >= 2 at baseline at week 0, 16, 28, 36, 48 • Serum concentration of guselkumab over time at week 0, 4, 16, 20, 36, 44, 56 • Number of participants with antibodies to guselkumab at week 0, 16, 44, 56
Starting date	Study start date: August 2021 Estimated study completion date: December 2023

NCT04914429 *(Continued)*

	Last update posted: September 20201, recruiting
Contact information	Study Contact 844-434-4210 JNJ.CT@sylogent.com Investigators Study Director:Janssen Research & Development, LLC Clinical Trial
Notes	Ongoing study Funding Janssen Research & Development, LLC Last check in October 2021

NCT04930042

Study name	Efficacy, safety, and immunogenicity of AVT04 with moderate-to-severe chronic plaque psoriasis
Methods	RCT, active-controlled, double-blind study Date of study: June 2021 Location: Estonia Phase 3
Participants	**Randomised**: 543 participants **Inclusion criteria** • Patient has signed the informed consent form (ICF) and documentation as required by relevant competent authorities and is able to understand and adhere to the visit schedule and study requirements. • Chinese patients shall be recruited in Mainland China. • Patient is male or female, aged 18 to 75 years old, inclusive, at time of Screening. • Patient weighs ≤100 kg at Screening and at BL. • Patient has had moderate to severe chronic PsO for at least 6 months. • Patient has involved body surface area (BSA) ≥10%, PASI ≥12, and sPGA ≥3 (moderate) at Screening and at BL. • Patient has had stable psoriatic disease for at least 2 months (i.e. without significant changes as defined by the investigator or designee) prior to Screening. • Patient is a candidate for systemic therapy because the patient has had a previous failure, inadequate response, intolerance, or contraindication to at least 1 systemic antipsoriatic therapy including, but not limited to, methotrexate, cyclosporine, psoralen plus ultraviolet light A (PUVA), and ultraviolet light B (UVB). 1. Patient has a negative QuantiFERON test for tuberculosis (TB) during screening. 2. Note: Patients with an indeterminate QuantiFERON test are allowed if they have all of the following: • No evidence of active TB on chest radiograph within 3 months prior to the first dose of study drug. • Documented history of adequate prophylaxis initiation prior to receiving study drug in accordance with local recommendations. • No known exposure to active TB after most recent prophylaxis. • Asymptomatic at Screening and BL. Investigators should check with the medical monitor before enrolling such patients. • Patient is naïve to ustekinumab therapy, approved or investigational. • Women of childbearing potential (except those who are postmenopausal for more than 2 years or if surgically sterile) must have a negative serum pregnancy test during Screening and negative urine pregnancy test at BL.

NCT04930042 *(Continued)*

Exclusion criteria

- Patient diagnosed with psoriatic arthritis, 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 drug on psoriasis.
- Patient has prior use of any of the following medications within specified time periods or will require use during the study: Topical medications within 2 weeks of BL visit (except low- to mid-potency topical corticosteroids on face, eyes, scalp, palms, soles, and genital area; only).

1. PUVA phototherapy and/or UVB phototherapy within 4 weeks prior to the BL visit.
2. Nonbiologic psoriasis systemic therapies (e.g. cyclosporine, methotrexate, and acitretin) within 4 weeks prior to the BL visit.
3. Any systemic steroid in the 4 weeks prior to the BL visit.
4. Any oral traditional Chinese medicine (TCM) 4 weeks prior to the BL visit or any topical TCM 2 weeks prior to the BL visit.
5. Investigational agent(s) within 90 days or 5 half-lives (whichever is longer) before BL visit.
6. Other systemic biologics within 90 days or 5 half-lives (whichever is the longer) before BL visit.
7. Any therapeutic agent targeting IL-12, IL-17 or IL-23 at any time. Specified washout periods for approved/marketed products are provided in Table 5.1.

Table 5.1:
Approved/marketed products medication or therapy washout before BL biologic therapies, including but limited to: adalimumab 12 weeks, etanercept 8 weeks, secukinumab 12 weeks, infliximab 12 weeks, certolizumab pegol 24 weeks, alefacept 24 weeks, briakinumab 24 weeks, guselkumab 13 weeks, brodalumab 13 weeks
Any kinase inhibitor for any reason (e.g. tofacitinib citrate) 1 day
Any phosphodiesterase type 4 inhibitor (e.g. apremilast [Otezla]) 4 weeks
Cyclosporine 4 weeks
Methotrexate 4 weeks
PUVA-UVA/UVB 4 weeks
Topical psoriasis treatments (examples include vitamin D analogs, topical steroids, polifenols, etc) (except low- to mid-potency topical corticosteroids on face, eyes, scalp, palms, soles, and genital area; only) 2 weeks
Oral retinoids 4 weeks
Corticosteroids IM - IV - oral - intraarticular 4 weeks
Drugs that may cause new onset or exacerbation of psoriasis (including, but not limited to, beta blockers, lithium, and anti-malarials) 6 months[1]
TCM (oral) 4 weeks
TCM (topical) 2 weeks
Abbreviations: BL = Baseline; IM = intramuscular; IV = intravenous; PUVA = psoralen plus ultraviolet light A; TCM = traditional Chinese medicine; UVA = ultraviolet light A; UVB = ultraviolet light B.
[1] Unless the patient has been on a stable dose for at least 6 months prior to BL visit without exacerbation of psoriasis.

Patient has received live or attenuated vaccines during the 4 weeks prior to BL visit or has the intention of receiving a live or attenuated vaccine at any time during the study.

Note: Inactivated (non-live and non-attenuated) vaccines are allowed.

1. Patient has an underlying condition (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious, or gastrointestinal) which, in the opinion of the investigator or designee, significantly immunocompromises the patient and/or places the patient at unacceptable risk for receiving an immunomodulatory therapy.
2. Patient 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 or designee, will not put the patient at further risk or hinder the patient's ability to maintain compliance with study drug and the visit schedule.

Patient has an active and serious infection or history of infections as follows:

NCT04930042 *(Continued)*

a. Any active infection (including Severe Acute Respiratory Syndrome-Coronavirus-2 [SARS-CoV-2] infection) i. For which non-systemic anti-infectives were used within 4 weeks prior to BL visit. Note: patients receiving topical antibiotics for facial acne do not need to be excluded.

ii. Which required hospitalisation/quarantine or systemic anti-infective within 8 weeks prior to BL visit

b. Recurrent or chronic infections or other active infection that, in the opinion of the investigator or designee, might cause this study to be detrimental to the patient

c. Invasive fungal infection or mycobacterial infection

d. Opportunistic infections, such as listeriosis, legionellosis, or pneumocystis

- Patient is positive for human immunodeficiency virus (HIV), hepatitis C virus (HCV) antibody, hepatitis B surface antigen (HBsAg), or hepatitis B core antibody (HBcAb)
- Patient has severe progressive or uncontrolled, clinically significant disease that in the judgement of the investigator or designee renders the patient unsuitable for the study
- Patient has a history of malignancy within 5 years except for adequately treated cutaneous squamous or basal cell carcinoma, in situ cervical cancer or in situ breast ductal carcinoma.
- Patient 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.
- Patient has moderate to severe heart failure (New York Heart Association class III/IV).
- Patient has uncontrolled diabetes mellitus type 1 or 2.
- Patient has a history of hypersensitivity to the active substance or to any of the excipients of Stelara or AVT04.
- Patient is pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation.
- Patient has evidence (as assessed by the investigator or designee using good clinical judgement) of alcohol or drug abuse or dependency at the time of Screening, for the 5 years prior to Screening, or during the study.
- Patient is unable to follow study instructions and comply with the protocol in the opinion of the investigator or designee.
- Patient has a history of clinically significant hematological abnormalities, including cytopenia (e.g. thrombocytopenia, leukopenia).
- Patient has a laboratory abnormality that, in the opinion of the investigator or designee, could cause this study to be detrimental to the patient. The following laboratory abnormalities should be excluded:

1. Haemoglobin < 9 g/dL
2. Platelet count < 100,000/mm^3
3. White blood cell count < 3000 cells/mm^3
4. Aspartate aminotransferase and/or alanine aminotransferase that is persistently ≥ 2 × the upper limit of normal (persistently indicates at least on 2 occasions separated by a number of days, per the rescreening procedure)
5. Creatinine clearance < 50 mL/min (Cockcroft-Gault formula)

Interventions	**Intervention** A. AVT04 (ustekinumab biosimilar) Initial loading dose of 45 mg followed by 45 mg SC once every 12 weeks starting 4 weeks after the initial loading dose administered SC **Control intervention** B. EU Stelara (ustekinumab) Initial loading dose of 45 mg followed by 45 mg SC once every 12 weeks starting 4 weeks after the initial loading dose administered SC.
Outcomes	**At week 28**

NCT04930042 *(Continued)*

	Primary outcome • Percent (%) change in PASI 75 **Secondary outcome** • PASI 50, 75, 90, and 100 response rates at weeks 4, 8, 12, 16, 28, 40, and 52 • Percent improvement in PASI from baseline to week 4, 8, 16, 28, 40, and 52
Starting date	Study start date: June 2021 Estimated study completion date: May 2023 Last update posted: June 2021, recruiting
Contact information	Jaak Talli, MD +3726109434 jaak.talli@innomedica.ee
Notes	Ongoing study Funding Alvotech Swiss AG Last check in October 2021

NCT04967508

Study name	A study to compare SB17 (proposed ustekinumab biosimilar) to Stelara® in subjects with moderate to severe plaque psoriasis
Methods	RCT, active-controlled, double blind study Date of study: July 2021 Location: Estonia and Lithuania Phase 3
Participants	**Randomised**: 464 participants **Inclusion criteria** • Aged 18 years or older at Screening. • Have plaque psoriasis diagnosed at least 6 months, with or without psoriatic arthritis. • Have plaque psoriasis with the involvement and severity of total affected BSA ≥ 10%, PASI score of ≥ 12 and PGA score of ≥ 3 (moderate). • Considered to be a candidate for phototherapy or systemic therapy for psoriasis • Less than 95 kg of body weight. • Adequate hematological, renal and hepatic function by central lab. • Non-childbearing potential female, or childbearing potential female subjects or male subjects with their partners who agree to use at least two forms of appropriate contraception method from Screening until 15 weeks after the last dose of IP. **Exclusion criteria** • Have nonplaque forms of psoriasis, including erythrodermic, pustular, guttate, or drug-induced psoriasis. • Have other skin disease than psoriasis that requires topical or systemic corticosteroids. • Prior biologic use as any TNF inhibitors within the previous 6 months; any IL-12 or IL-23 inhibitor biologics, IL-17 inhibitor, rituximab, or integrin inhibitor biologics at any time; or other biologics within the longer of either 5 half-lives or 3 months prior to randomisation.

NCT04967508 *(Continued)*

	• Known allergic reactions or hypersensitivity to ustekinumab or to any ingredients of Stelara® or SB17 • History of exfoliative dermatitis, reversible posterior leukoencephalopathy syndrome, facial palsy, allergic alveolitis, or non-infectious pneumonia. • Have received phototherapy or conventional systemic therapy for psoriasis within 4 weeks prior to Randomisation. • Have received topical therapy for psoriasis within 2 weeks prior to Randomisation. • Women who are pregnant or nursing at Screening, or men and women planning pregnancy during the study period and until 15 weeks after the last dose of IP. • Have received a live or live attenuated viral vaccine or a live bacterial vaccine within 4 weeks (for BCG, 12 months) prior to Randomisation. • Have active or latent tuberculosis. • History of ongoing infection or a positive test of HBV, HCV, or HIV infection • History of sepsis, chronic or recurrent infection • History of malignancy within the last 5 years • History of lymphoproliferative disease or leukaemia • History of myocardial infarction, NYHA III/IV congestive heart failure, or stroke within 12 months • Have uncontrolled hypertension or diabetes • History of uncontrolled psychiatric disorders or risk of suicide
Interventions	**Intervention** A. SB17 (proposed ustekinumab biosimilar) 45mg SC at Week 0, 4, and then every 12 weeks **Control intervention** B. Stelara® (ustekinumab) 45mg SC at week 0, 4, and then every 12 weeks
Outcomes	**At week 12** **Primary outcome** • Percent change from baseline in PASI
Starting date	Study start date: July 2021 Estimated study completion date: March 2023 Last update posted: July 2021, recruiting
Contact information	Samsung Bioepis +82 32 728 0371 sbregistry@samsung.com
Notes	Ongoing study Funding Samsung Bioepis Co., Ltd. Last check in October 2021

NCT05004727

Study name	Multi-center PAMPA study (PAMPA)
Methods	RCT, double blind, placebo-controlled, multicenter study Date of study: September 2021 Location: USA, Canada

NCT05004727 *(Continued)*

	Phase 4
Participants	**Randomised**: 350 participants **Inclusion criteria** • 18 years old or older; • Both male & female; • Psoriasis diagnosis (per dermatologist) for at least 2 years (in at least 30% of participants); • Willing and able to provide informed consent; • Fulfillment of HR-PsO criteria (Psoriasis (PsO) patients will meet the definition of HR if they fulfil the following criteria: a) PsO duration >2 years and BSA >3% and positive imaging findings in MSKPDUS defined as a RM-PsASon score of >3.36 **Exclusion criteria** • Evidence of inflammatory joint pain, enthesitis and/or dactylitis on exam; • Current systemic immunosuppressive medication use (i.e., methotrexate, apremilast) at the time of enrolment or biologic therapy (ever); • RA seropositivity (mid-high RF/ACPA titers); • Current active malignancy; • History of symptomatic polyarticular OA or other joint conditions (such as RA, gout, etc) that may impair the ability to assess for PsA development • Conditions where initiation of guselkumab is prohibited in the prescribing information, including clinically important active infection and untreated latent tuberculosis; • Known hypersensitivity to the study agent.
Interventions	**Intervention** A. Guselkumab 100 mg 1 mL liquid formulation in a single-dose pre-filled syringe administered by subcutaneous injection at Week 0, Week 4 and every 8 weeks thereafter (month 0 to month 24 for arm 1; week 24 to month 24 for arm 2). **Control intervention** B. Placebo
Outcomes	**Primary outcomes** • Change in Musculoskeletal, Power Doppler Ultrasound (MSK-PDUS) composite score at week 24 • Percentage of patients transitioning to psoriatic arthritis (PsA) by modified CASPAR criteria at year 2 **Secondary outcomes** • Percentage of patients transitioning to psoriatic arthritis (PsA) by Modified CASPAR Criteria at year 1 • Severity of PsA at the time of synovio-entheseal development at year 2 • Change in the ultrasound composite score of synovitis at week 24 • Change in Madrid Sonographic Enthesis Index (MASEI) score at week 24 • BSA at week 24 • Achieved IGA mod 2011 score at week 24 • Change in Functional Assessment of Chronic Illness Therapy (FACIT) scale at week 24 • Change in EuroQol-5D (EQ-5D) score at week 24 • Change in EuroQol-5D (EQ-5D) score at year 2
Starting date	Estimated Study Start Date: October 2021 Estimated Study Completion Date: September 2025

NCT05004727 *(Continued)*

	Last Update Posted: August 2021, not yet recruiting
Contact information	Jose Scher, MD Jose.Scher@nyulangone.org Courtney Pike Courtney.Pike@nyulangone.org
Notes	Funding: NYU Langone Health Last check in October 2021

NCT05020249

Study name	A study to evaluate the efficacy and safety of bimekizumab in adult Korean study participants with moderate to severe plaque psoriasis
Methods	RCT, placebo-controlled, double-blind study Date of study: September 2021 Location: Korea (5 sites) Phase 3
Participants	**Randomised**: 45 participants **Inclusion criteria** • Study participant must be at least 19 years of age at the time of signing the informed consent • Study participant must be a Korean adult with a diagnosis of moderate to severe psoriasis (PSO) • Study participant must have had plaque PSO for at least 6 months prior to the Screening Visit • Study participant must have Psoriasis Area and 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 • Study participant must be a candidate for systemic PSO therapy and/or phototherapy • Study participant agrees not to change their usual sun exposure during the course of the study and to use ultraviolet A/ultraviolet B sunscreens if unavoidable exposure occurs • A female study participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies: • Not a female of childbearing potential (FOCBP) OR A FOCBP who agrees to follow the contraceptive guidance during the Treatment Period and for at least 20 weeks after the last dose of study treatment **Exclusion criteria** • 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 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 • Study participant has a presence of active suicidal ideation or positive suicide behavior • Study participant has a presence of moderately severe major depression or severe major depression • Subject has a known hypersensitivity to any excipients of bimekizumab

NCT05020249 *(Continued)*

	• 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
Interventions	**Intervention** A. Bimekizumab **Control intervention** B. Placebo
Outcomes	**At week 16** **Primary outcomes** • PASI 90 • IGA 0/1 **Secondary outcomes** • PASI 100 • IGA 0 • PASI 75 at week 4 • Patient Symptom Diary (PSD) (P-SIM) response for itch • PSD (P-SIM) response for pain • Scalp IGA response • DLQI 1/0 • AEs • SAEs • Change from Baseline in Patient Health Questionnaire 9 (PHQ-9)
Starting date	Study start date: September 2021 Estimated primary completion date: June 2022 Last update posted: October 2021, recruiting
Contact information	Not stated
Notes	Last checked in October 2021

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
SAE: Serious adverse event
SC: subcutaneous
sPGA: static physician global assessment
TB: tuberculosis
UVA/B: ultraviolet A/B

DATA AND ANALYSES

Comparison 1. Primary outcome - PASI 90

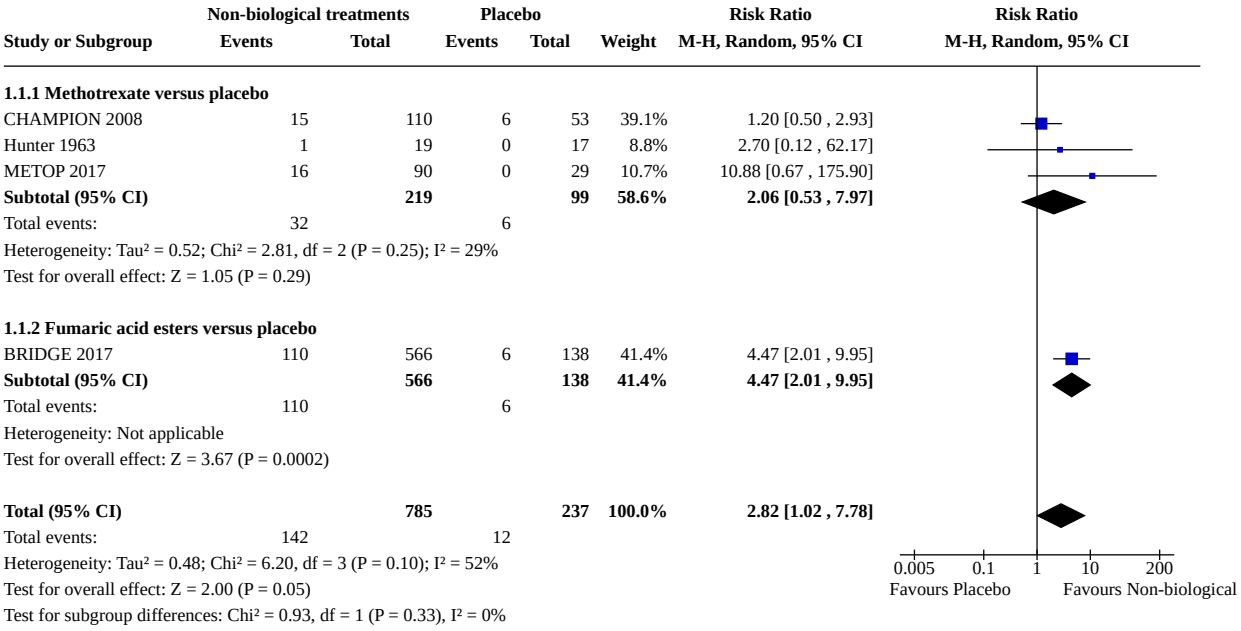
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Non-biological treatments versus placebo	4	1022	Risk Ratio (M-H, Random, 95% CI)	2.82 [1.02, 7.78]
1.1.1 Methotrexate versus placebo	3	318	Risk Ratio (M-H, Random, 95% CI)	2.06 [0.53, 7.97]
1.1.2 Fumaric acid esters versus placebo	1	704	Risk Ratio (M-H, Random, 95% CI)	4.47 [2.01, 9.95]
1.2 Non-biological treatment 1 versus non-biological treatment 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	32	11869	Risk Ratio (M-H, Random, 95% CI)	13.65 [10.71, 17.40]
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	5	1153	Risk Ratio (M-H, Random, 95% CI)	19.77 [8.29, 47.12]
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	11	4520	Risk Ratio (M-H, Random, 95% CI)	18.37 [12.56, 26.85]
1.4.1 Ustekinumab versus placebo	11	4520	Risk Ratio (M-H, Random, 95% CI)	18.37 [12.56, 26.85]
1.5 Anti-IL17 versus placebo	30	14119	Risk Ratio (M-H, Random, 95% CI)	27.31 [18.94, 39.38]
1.5.1 Secukinumab versus placebo	15	4622	Risk Ratio (M-H, Random, 95% CI)	22.70 [15.53, 33.19]
1.5.2 Ixekizumab versus placebo	5	3706	Risk Ratio (M-H, Random, 95% CI)	47.03 [18.81, 117.59]
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	3	1089	Risk Ratio (M-H, Random, 95% CI)	29.43 [10.30, 84.15]
1.5.5 Netakimab versus placebo	2	333	Risk Ratio (M-H, Random, 95% CI)	10.98 [0.42, 288.23]
1.5.6 Sonelokimab versus placebo	1	260	Risk Ratio (M-H, Random, 95% CI)	65.68 [4.15, 1038.50]
1.6 Anti-IL23 versus placebo	13	5303	Risk Ratio (M-H, Random, 95% CI)	23.15 [16.44, 32.61]
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	5	1633	Risk Ratio (M-H, Random, 95% CI)	22.51 [12.90, 39.30]
1.7 Biologic versus non-biological treatment	9		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 Ixekizumab versus methotrexate	1	108	Risk Ratio (M-H, Random, 95% CI)	2.05 [1.43, 2.94]
1.7.5 Secukinumab versus fumaric acid esters	1	202	Risk Ratio (M-H, Random, 95% CI)	8.31 [4.23, 16.35]
1.7.6 Ixekizumab versus fumaric acid esters	1	108	Risk Ratio (M-H, Random, 95% CI)	8.60 [3.69, 20.04]
1.7.7 Guselkumab versus fumaric ester acids	1	119	Risk Ratio (M-H, Random, 95% CI)	6.02 [3.13, 11.60]
1.7.8 Risankizumab versus fumaric ester acids	1	120	Risk Ratio (M-H, Random, 95% CI)	8.33 [3.87, 17.95]
1.7.9 Brodalumab versus fumaric acid esters	1	210	Risk Ratio (M-H, Random, 95% CI)	3.00 [2.04, 4.42]
1.8 Biologic 1 versus biologic 2	26		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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 Infliximab versus etanercept	1	48	Risk Ratio (M-H, Random, 95% CI)	9.20 [1.28, 66.37]
1.8.4 Ixekizumab versus etanercept	2	2209	Risk Ratio (M-H, Random, 95% CI)	2.98 [2.24, 3.98]
1.8.5 Tildrakizumab versus etanercept	1	934	Risk Ratio (M-H, Random, 95% CI)	1.76 [1.39, 2.23]
1.8.6 Certolizumab versus etanercept	1	502	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.90, 1.61]
1.8.7 Secukinumab versus ustekinumab	2	1778	Risk Ratio (M-H, Random, 95% CI)	1.40 [1.30, 1.50]
1.8.8 Ixekizumab versus ustekinumab	1	302	Risk Ratio (M-H, Random, 95% CI)	1.41 [1.21, 1.63]
1.8.9 Brodalumab versus ustekinumab	2	3088	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.16, 1.39]
1.8.10 Risankizumab versus ustekinumab	3	965	Risk Ratio (M-H, Random, 95% CI)	1.67 [1.43, 1.93]
1.8.11 Bimekizumab versus ustekinumab	1	484	Risk Ratio (M-H, Random, 95% CI)	1.71 [1.46, 2.01]
1.8.12 Guselkumab versus adalimumab	3	1658	Risk Ratio (M-H, Random, 95% CI)	1.43 [1.26, 1.62]
1.8.13 Risankizumab versus adalimumab	1	605	Risk Ratio (M-H, Random, 95% CI)	1.53 [1.33, 1.75]
1.8.14 Bimekizumab versus adalimumab	1	478	Risk Ratio (M-H, Random, 95% CI)	1.66 [1.42, 1.94]
1.8.15 Ixekizumab versus guselkumab	1	1027	Risk Ratio (M-H, Random, 95% CI)	1.29 [1.18, 1.42]
1.8.16 Risankizumab versus secukinumab	1	327	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.97, 1.30]
1.8.17 Bimekizumab versus secukinumab	1	743	Risk Ratio (M-H, Random, 95% CI)	1.15 [1.07, 1.24]
1.8.18 Guselkumab versus secukinumab	1	1048	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.84, 0.98]

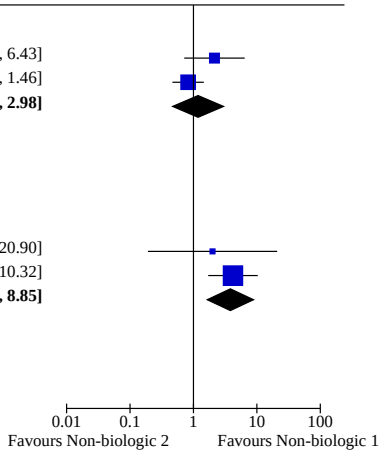
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.8.19 Sonelokimab versus secukinumab	1	261	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.77, 1.21]
1.9 Small molecules versus placebo	6	2296	Risk Ratio (M-H, Random, 95% CI)	7.56 [3.84, 14.88]
1.9.1 Apremilast versus placebo	5	2029	Risk Ratio (M-H, Random, 95% CI)	6.94 [3.37, 14.30]
1.9.2 TYK2 versus placebo	1	267	Risk Ratio (M-H, Random, 95% CI)	13.99 [1.99, 98.10]
1.10 Biologic versus small molecules	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.10.1 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: Non-biological treatments versus placebo



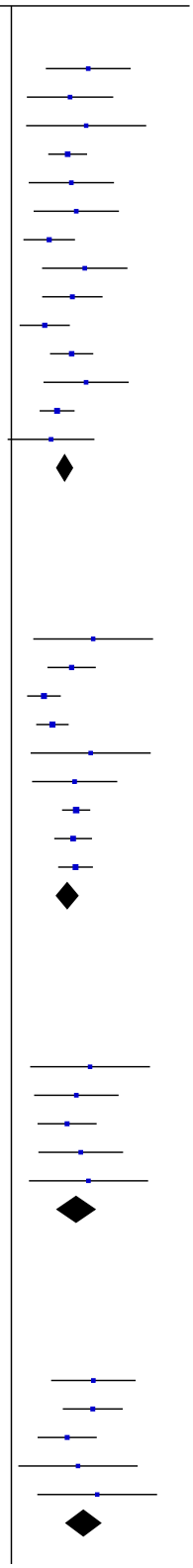
Analysis 1.2. Comparison 1: Primary outcome - PASI 90, Outcome 2: Non-biological treatment 1 versus non-biological treatment 2

Study or Subgroup	Non-biological treatment 1 Events	Total	Non-biological treatment 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]
Reich 2020	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)						



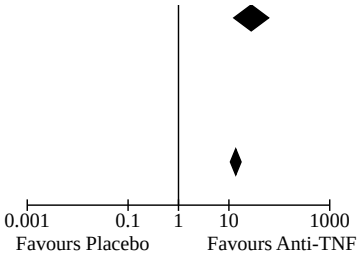
Analysis 1.3. Comparison 1: Primary outcome - PASI 90, Outcome 3: Anti-TNF alpha versus placebo

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]
CIMPACT 2018	46	170	0	57	0.7%	31.54 [1.98 , 503.75]
FIXTURE 2014	67	326	5	327	5.9%	13.44 [5.49 , 32.91]
Gottlieb 2011	33	141	1	68	1.4%	15.91 [2.22 , 113.92]
Leonardi 2003	60	504	1	168	1.4%	20.00 [2.79 , 143.20]
LIBERATE 2017	17	83	3	84	3.7%	5.73 [1.75 , 18.84]
Papp 2005	59	407	1	204	1.4%	29.57 [4.13 , 211.91]
ReSURFACE-2 2017	67	313	2	156	2.8%	16.70 [4.15 , 67.25]
Strober 2011	27	139	3	72	3.8%	4.66 [1.46 , 14.85]
Tyring 2006	65	311	4	309	5.0%	16.15 [5.96 , 43.77]
UNCOVER-2 2015	67	358	1	168	1.5%	31.44 [4.40 , 224.56]
UNCOVER-3 2015	98	382	6	193	7.0%	8.25 [3.69 , 18.47]
Van de Kerkhof 2008	13	96	1	46	1.4%	6.23 [0.84 , 46.18]
Subtotal (95% CI)		**3628**		**2022**	**38.9%**	**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]
Cai 2016	188	338	3	87	4.1%	16.13 [5.28 , 49.24]
CHAMPION 2008	55	108	6	53	7.4%	4.50 [2.07 , 9.77]
Elewski 2016	47	109	7	108	7.8%	6.65 [3.15 , 14.06]
Gordon 2006	35	96	0	52	0.7%	38.79 [2.43 , 619.78]
Gordon X-PLORE 2015	19	43	1	42	1.5%	18.56 [2.60 , 132.47]
REVEAL 2008	366	814	9	398	9.6%	19.88 [10.38 , 38.10]
VOYAGE-1 2016	166	334	5	174	6.2%	17.30 [7.24 , 41.31]
VOYAGE-2 2017	116	248	6	248	7.1%	19.33 [8.67 , 43.09]
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						
CIMPACT 2018	108	332	0	57	0.8%	37.80 [2.38 , 599.65]
CIMPASI-1 2018	72	183	1	51	1.5%	20.07 [2.86 , 140.89]
CIMPASI-2 2018	95	178	2	49	2.9%	13.08 [3.34 , 51.16]
Reich 2012a	50	118	1	58	1.5%	24.58 [3.48 , 173.49]
Umezawa 2021	66	101	0	26	0.8%	35.21 [2.25 , 550.54]
Subtotal (95% CI)		**912**		**241**	**7.3%**	**19.77 [8.29 , 47.12]**
Total events:	391		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.82, df = 4 (P = 0.94); I² = 0%						
Test for overall effect: Z = 6.73 (P < 0.00001)						
1.3.4 Infliximab versus placebo						
EXPRESS 2005	172	301	1	77	1.5%	44.00 [6.26 , 309.15]
EXPRESS-II 2007	258	627	2	208	2.8%	42.79 [10.74 , 170.51]
Gottlieb 2004a	102	198	2	51	2.9%	13.14 [3.35 , 51.45]
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**	**8.6%**	**27.71 [12.52 , 61.30]**
Total events:	599		5			



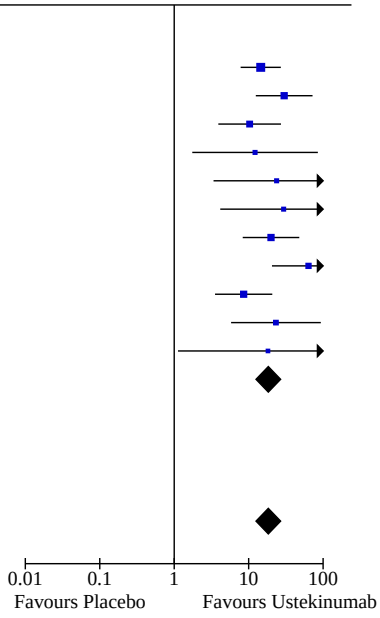
Analysis 1.3. (Continued)

Subtotal (95% CI)		**1245**		**400**	**8.6%**	**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)						
Total (95% CI)		**7998**		**3871**	**100.0%**	**13.65 [10.71 , 17.40]**
Total events:	2781		76			
Heterogeneity: Tau² = 0.05; Chi² = 35.74, df = 32 (P = 0.30); I² = 10%						
Test for overall effect: Z = 21.12 (P < 0.00001)						
Test for subgroup differences: Chi² = 4.48, df = 3 (P = 0.21), I² = 33.0%						



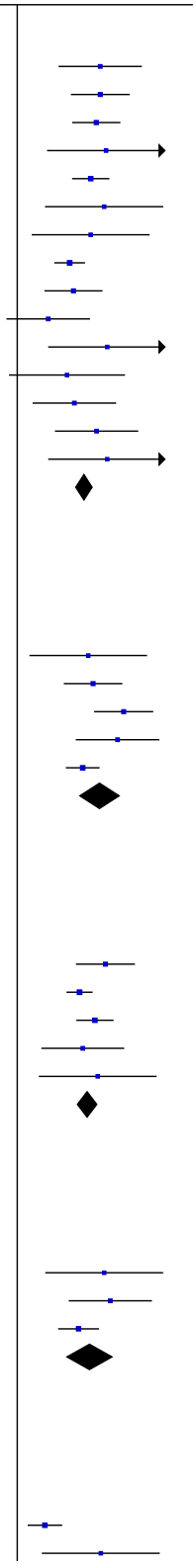
Analysis 1.4. Comparison 1: Primary outcome - PASI 90, Outcome 4: Anti-IL12/23 versus placebo

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						
AMAGINE-2 2015	141	300	10	309	20.7%	14.52 [7.80 , 27.04]
AMAGINE-3 2015	149	313	5	315	13.3%	29.99 [12.47 , 72.11]
BE VIVID 2021	81	163	4	83	11.5%	10.31 [3.91 , 27.16]
Igarashi 2012	48	126	1	32	3.5%	12.19 [1.75 , 84.99]
Krueger 2007	95	256	1	64	3.5%	23.75 [3.38 , 167.12]
PEARL 2011	30	61	1	60	3.5%	29.51 [4.16 , 209.54]
PHOENIX-1 2008	200	511	5	255	13.4%	19.96 [8.32 , 47.86]
PHOENIX-2 2008	382	820	3	410	9.1%	63.67 [20.57 , 197.05]
UltIMMa-1 2018	42	100	5	102	13.2%	8.57 [3.54 , 20.77]
UltIMMa-2 2018	47	99	2	98	6.5%	23.26 [5.81 , 93.14]
VIP-U Trial 2020	9	22	0	21	1.8%	18.17 [1.12 , 293.86]
Subtotal (95% CI)		**2771**		**1749**	**100.0%**	**18.37 [12.56 , 26.85]**
Total events:	1224		37			
Heterogeneity: Tau² = 0.08; Chi² = 12.60, df = 10 (P = 0.25); I² = 21%						
Test for overall effect: Z = 15.01 (P < 0.00001)						
Total (95% CI)		**2771**		**1749**	**100.0%**	**18.37 [12.56 , 26.85]**
Total events:	1224		37			
Heterogeneity: Tau² = 0.08; Chi² = 12.60, df = 10 (P = 0.25); I² = 21%						
Test for overall effect: Z = 15.01 (P < 0.00001)						
Test for subgroup differences: Not applicable						



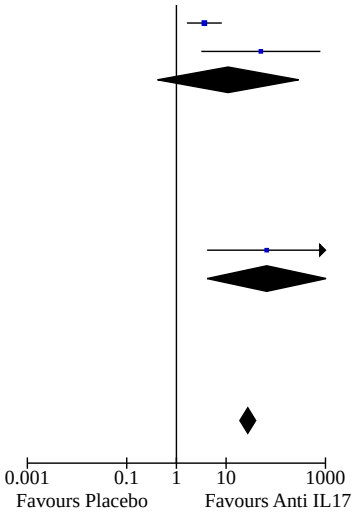
Analysis 1.5. Comparison 1: Primary outcome - PASI 90, Outcome 5: Anti-IL17 versus placebo

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						
ALLURE 2021	98	143	1	71	2.5%	48.66 [6.93 , 341.75]
Cai 2020	295	408	2	135	3.9%	48.81 [12.32 , 193.40]
ERASURE 2014	240	490	3	248	4.7%	40.49 [13.10 , 125.14]
FEATURE 2015	63	118	0	59	1.5%	64.03 [4.03 , 1017.14]
FIXTURE 2014	312	654	5	327	5.7%	31.20 [13.03 , 74.73]
JUNCTURE 2015	57	121	0	61	1.5%	58.44 [3.67 , 929.87]
NCT03055494 ObePso-S	29	54	0	28	1.5%	31.11 [1.97 , 490.92]
NCT03535194	326	448	7	112	6.4%	11.64 [5.67 , 23.91]
NCT03589885 MATURE	57	82	2	40	3.9%	13.90 [3.57 , 54.08]
Papp 2013a	20	103	1	22	2.5%	4.27 [0.60 , 30.17]
Papp 2021	34	53	0	52	1.5%	67.72 [4.26 , 1076.42]
Reich 2015	42	90	0	10	1.5%	10.27 [0.68 , 155.50]
Rich 2013	73	337	1	67	2.5%	14.51 [2.05 , 102.61]
TRANSFIGURE 2016	84	133	1	65	2.5%	41.05 [5.85 , 288.30]
VIP-S trial 2020	34	46	0	45	1.5%	67.53 [4.27 , 1069.20]
Subtotal (95% CI)		**3280**		**1342**	**43.4%**	**22.70 [15.53 , 33.19]**
Total events:	1764		23			
Heterogeneity: Tau² = 0.00; Chi² = 13.86, df = 14 (P = 0.46); I² = 0%						
Test for overall effect: Z = 16.12 (P < 0.00001)						
1.5.2 Ixekizumab versus placebo						
Leonardi 2012	57	115	0	27	1.5%	27.76 [1.77 , 435.55]
NCT03364309	277	350	2	88	3.9%	34.82 [8.84 , 137.19]
UNCOVER-1 2016	586	865	2	431	3.8%	145.99 [36.60 , 582.31]
UNCOVER-2 2015	455	698	1	168	2.5%	109.51 [15.51 , 773.49]
UNCOVER-3 2015	514	771	6	193	6.1%	21.44 [9.74 , 47.21]
Subtotal (95% CI)		**2799**		**907**	**17.8%**	**47.03 [18.81 , 117.59]**
Total events:	1889		11			
Heterogeneity: Tau² = 0.50; Chi² = 7.87, df = 4 (P = 0.10); I² = 49%						
Test for overall effect: Z = 8.24 (P < 0.00001)						
1.5.3 Brodalumab versus placebo						
AMAGINE-1 2016	249	441	2	220	3.9%	62.11 [15.59 , 247.38]
AMAGINE-2 2015	731	1222	10	309	6.9%	18.48 [10.03 , 34.07]
AMAGINE-3 2015	756	1253	5	315	5.8%	38.01 [15.91 , 90.79]
Nakagawa 2016	64	113	1	38	2.5%	21.52 [3.09 , 149.88]
Papp 2012a	89	160	0	38	1.5%	43.36 [2.75 , 683.33]
Subtotal (95% CI)		**3189**		**920**	**20.5%**	**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						
BE ABLE 1 2018	142	208	0	42	1.5%	58.64 [3.72 , 923.86]
BE READY 2021	317	349	1	86	2.5%	78.11 [11.13 , 548.40]
BE VIVID 2021	273	321	4	83	5.4%	17.65 [6.78 , 45.96]
Subtotal (95% CI)		**878**		**211**	**9.4%**	**29.43 [10.30 , 84.15]**
Total events:	732		5			
Heterogeneity: Tau² = 0.22; Chi² = 2.52, df = 2 (P = 0.28); I² = 21%						
Test for overall effect: Z = 6.31 (P < 0.00001)						
1.5.5 Netakimab versus placebo						
NCT02762994	60	92	5	28	6.0%	3.65 [1.63 , 8.20]
PLANETA 2021	94	169	0	44	1.5%	50.03 [3.17 , 790.17]



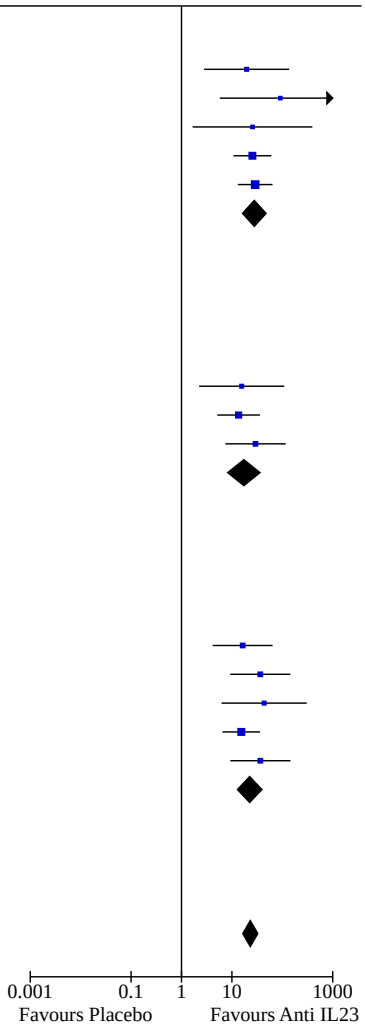
Analysis 1.5. (Continued)

NCT02762994	60	92	5	28	6.0%	3.65 [1.63 , 8.20]
PLANETA 2021	94	169	0	44	1.5%	50.03 [3.17 , 790.17]
Subtotal (95% CI)		**261**		**72**	**7.5%**	**10.98 [0.42 , 288.23]**
Total events:	154		5			
Heterogeneity: Tau² = 4.63; Chi² = 5.30, df = 1 (P = 0.02); I² = 81%						
Test for overall effect: Z = 1.44 (P = 0.15)						
1.5.6 Sonelokimab versus placebo						
Papp 2021	129	208	0	52	1.5%	65.68 [4.15 , 1038.50]
Subtotal (95% CI)		**208**		**52**	**1.5%**	**65.68 [4.15 , 1038.50]**
Total events:	129		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.97 (P = 0.003)						
Total (95% CI)		**10615**		**3504**	**100.0%**	**27.31 [18.94 , 39.38]**
Total events:	6557		62			
Heterogeneity: Tau² = 0.41; Chi² = 56.54, df = 30 (P = 0.002); I² = 47%						
Test for overall effect: Z = 17.70 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.85, df = 5 (P = 0.72), I² = 0%						



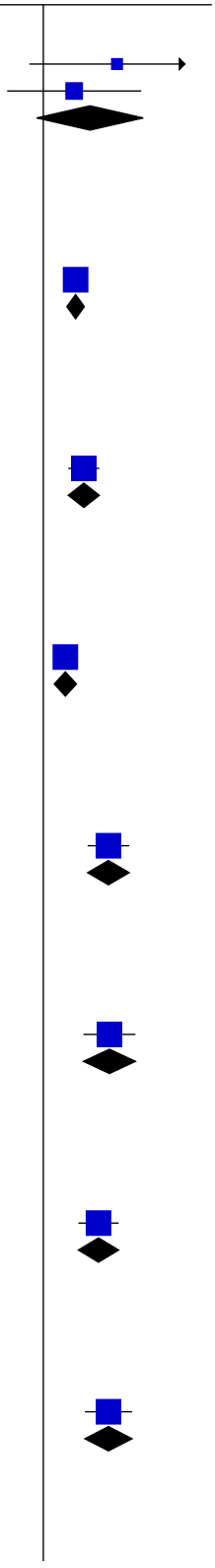
Analysis 1.6. Comparison 1: Primary outcome - PASI 90, Outcome 6: Anti-IL23 versus placebo

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						
Gordon X-PLORE 2015	97	208	1	42	3.1%	19.59 [2.81 , 136.56]
Ohtsuki 2018	90	128	0	64	1.5%	91.20 [5.75 , 1445.91]
ORION 2020	47	62	0	16	1.6%	25.63 [1.66 , 394.78]
VOYAGE-1 2016	241	329	5	174	15.6%	25.49 [10.72 , 60.62]
VOYAGE-2 2017	347	496	6	248	18.7%	28.92 [13.09 , 63.88]
Subtotal (95% CI)		**1223**		**544**	**40.5%**	**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	3.1%	15.63 [2.24 , 109.29]
ReSURFACE-1 2017	216	616	4	155	12.4%	13.59 [5.13 , 35.96]
ReSURFACE-2 2017	234	621	2	156	6.2%	29.39 [7.39 , 116.91]
Subtotal (95% CI)		**1546**		**357**	**21.7%**	**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						
Blauvelt 2021a	66	105	2	52	6.3%	16.34 [4.17 , 64.12]
IMMhance 2020	298	407	2	100	6.2%	36.61 [9.27 , 144.54]
SustaIMM 2019	85	113	1	58	3.1%	43.63 [6.23 , 305.39]
UltIMMa-1 2018	229	304	5	102	16.0%	15.37 [6.52 , 36.21]
UltIMMa-2 2018	220	294	2	98	6.2%	36.67 [9.29 , 144.77]
Subtotal (95% CI)		**1223**		**410**	**37.8%**	**22.51 [12.90 , 39.30]**
Total events:	898		12			
Heterogeneity: Tau² = 0.00; Chi² = 2.53, df = 4 (P = 0.64); I² = 0%						
Test for overall effect: Z = 10.95 (P < 0.00001)						
Total (95% CI)		**3992**		**1311**	**100.0%**	**23.15 [16.44 , 32.61]**
Total events:	2275		31			
Heterogeneity: Tau² = 0.00; Chi² = 5.32, df = 12 (P = 0.95); I² = 0%						
Test for overall effect: Z = 17.98 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.06, df = 2 (P = 0.59), I² = 0%						



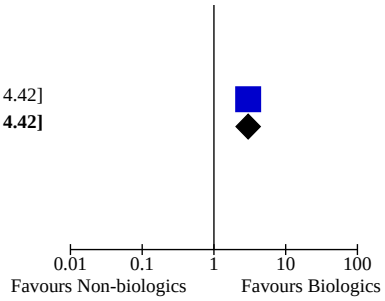
Analysis 1.7. Comparison 1: Primary outcome - PASI 90, Outcome 7: Biologic versus non-biological treatment

Study or Subgroup	Biologic Events	Biologic Total	Non-biological treatment Events	Non-biological treatment 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 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						
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 Ixekizumab versus methotrexate						
Reich 2020	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)						
1.7.5 Secukinumab versus fumaric acid esters						
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)						
1.7.6 Ixekizumab versus fumaric acid esters						
Reich 2020	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)						
1.7.7 Guselkumab versus fumaric ester acids						
POLARIS 2020	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)						
1.7.8 Risankizumab versus fumaric ester acids						
Thaci 2021	50	60	6	60	100.0%	8.33 [3.87 , 17.95]
Subtotal (95% CI)		**60**		**60**	**100.0%**	**8.33 [3.87 , 17.95]**
Total events:	50		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.41 (P < 0.00001)						



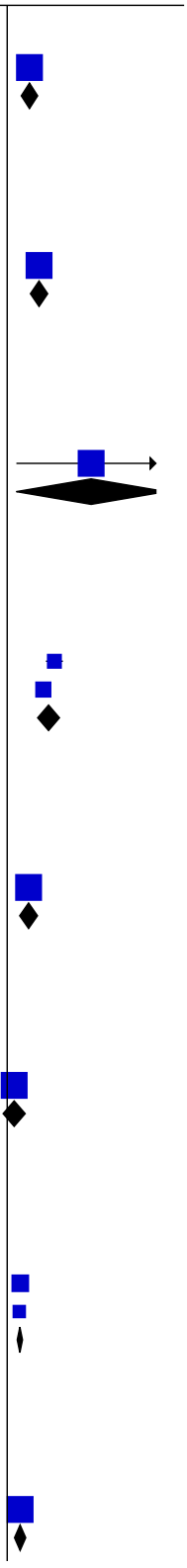
Analysis 1.7. (Continued)

Test for overall effect: Z = 5.41 (P < 0.00001)						
1.7.9 Brodalumab versus fumaric acid esters						
CHANGE 2021	69	105	23	105	100.0%	3.00 [2.04 , 4.42]
Subtotal (95% CI)		**105**		**105**	**100.0%**	**3.00 [2.04 , 4.42]**
Total events:	69		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.57 (P < 0.00001)						



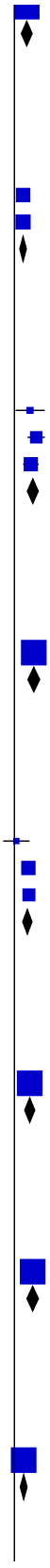
Analysis 1.8. Comparison 1: Primary outcome - PASI 90, Outcome 8: Biologic 1 versus biologic 2

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						
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						
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 Infliximab versus etanercept						
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)						
1.8.4 Ixekizumab versus etanercept						
UNCOVER-2 2015	455	698	67	358	47.3%	3.48 [2.79 , 4.35]
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)						
1.8.5 Tildrakizumab versus etanercept						
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)						
1.8.6 Certolizumab versus etanercept						
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)						
1.8.7 Secukinumab versus ustekinumab						
CLARITY 2018	421	550	299	552	59.4%	1.41 [1.29 , 1.55]
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)						
1.8.8 Ixekizumab versus ustekinumab						
IXORA-S 2017	113	136	98	166	100.0%	1.41 [1.21 , 1.63]
Subtotal (95% CI)		**136**		**166**	**100.0%**	**1.41 [1.21 , 1.63]**
Total events:	113		98			



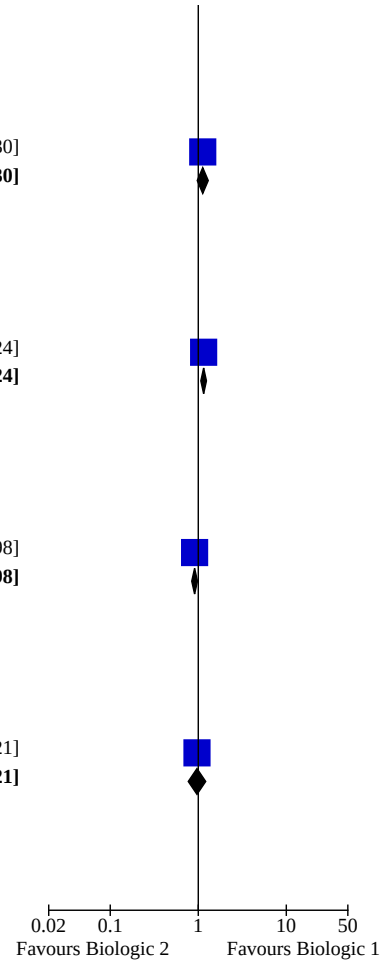
Analysis 1.8. (Continued)

Subtotal (95% CI)		**136**		**166**	**100.0%**	**1.41 [1.21 , 1.63]**
Total events:	113		98			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.54 (P < 0.00001)						
1.8.9 Brodalumab versus ustekinumab						
AMAGINE-2 2015	731	1222	141	300	48.4%	1.27 [1.12 , 1.45]
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)						
1.8.10 Risankizumab versus ustekinumab						
Papp 2017b	78	126	16	40	13.8%	1.55 [1.03 , 2.32]
UltIMMa-1 2018	229	304	42	102	38.8%	1.83 [1.44 , 2.33]
UltIMMa-2 2018	220	294	47	99	47.5%	1.58 [1.27 , 1.96]
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)						
1.8.11 Bimekizumab versus ustekinumab						
BE VIVID 2021	273	321	81	163	100.0%	1.71 [1.46 , 2.01]
Subtotal (95% CI)		**321**		**163**	**100.0%**	**1.71 [1.46 , 2.01]**
Total events:	273		81			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.54 (P < 0.00001)						
1.8.12 Guselkumab versus adalimumab						
Gordon X-PLORE 2015	97	208	19	43	10.6%	1.06 [0.73 , 1.52]
VOYAGE-1 2016	241	329	166	334	47.8%	1.47 [1.30 , 1.67]
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)						
1.8.13 Risankizumab versus adalimumab						
IMMvent 2019	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)						
1.8.14 Bimekizumab versus adalimumab						
BE SURE 2021	273	319	82	159	100.0%	1.66 [1.42 , 1.94]
Subtotal (95% CI)		**319**		**159**	**100.0%**	**1.66 [1.42 , 1.94]**
Total events:	273		82			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.31 (P < 0.00001)						
1.8.15 Ixekizumab versus guselkumab						
IXORA-R 2020	378	520	285	507	100.0%	1.29 [1.18 , 1.42]
Subtotal (95% CI)		**520**		**507**	**100.0%**	**1.29 [1.18 , 1.42]**
Total events:	378		285			
Heterogeneity: Not applicable						

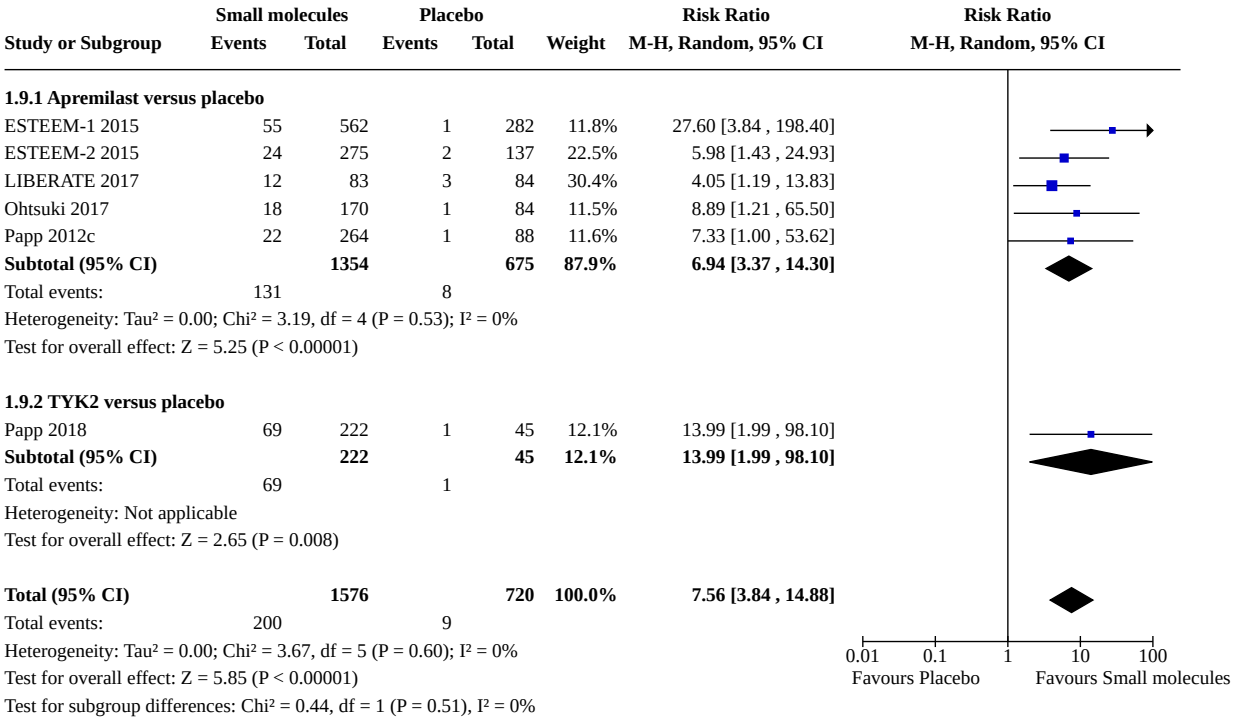


Analysis 1.8. (Continued)

Total events:	378		283			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.41 (P < 0.00001)						
1.8.16 Risankizumab versus secukinumab						
IMMerge 2021	121	164	107	163	100.0%	1.12 [0.97 , 1.30]
Subtotal (95% CI)		**164**		**163**	**100.0%**	**1.12 [0.97 , 1.30]**
Total events:	121		107			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.59 (P = 0.11)						
1.8.17 Bimekizumab versus secukinumab						
BE RADIANT 2021	319	373	275	370	100.0%	1.15 [1.07 , 1.24]
Subtotal (95% CI)		**373**		**370**	**100.0%**	**1.15 [1.07 , 1.24]**
Total events:	319		275			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.77 (P = 0.0002)						
1.8.18 Guselkumab versus secukinumab						
ECLIPSE 2019	369	534	391	514	100.0%	0.91 [0.84 , 0.98]
Subtotal (95% CI)		**534**		**514**	**100.0%**	**0.91 [0.84 , 0.98]**
Total events:	369		391			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.52 (P = 0.01)						
1.8.19 Sonelokimab versus secukinumab						
Papp 2021	129	208	34	53	100.0%	0.97 [0.77 , 1.21]
Subtotal (95% CI)		**208**		**53**	**100.0%**	**0.97 [0.77 , 1.21]**
Total events:	129		34			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.29 (P = 0.77)						

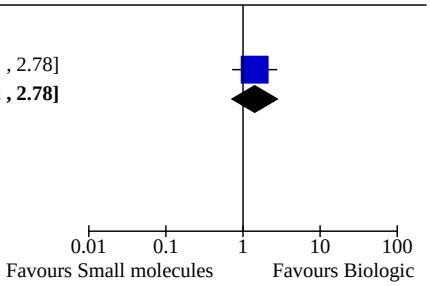


Analysis 1.9. Comparison 1: Primary outcome - PASI 90, Outcome 9: Small molecules versus placebo



Study or Subgroup	Small molecules Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 Apremilast versus placebo						
ESTEEM-1 2015	55	562	1	282	11.8%	27.60 [3.84 , 198.40]
ESTEEM-2 2015	24	275	2	137	22.5%	5.98 [1.43 , 24.93]
LIBERATE 2017	12	83	3	84	30.4%	4.05 [1.19 , 13.83]
Ohtsuki 2017	18	170	1	84	11.5%	8.89 [1.21 , 65.50]
Papp 2012c	22	264	1	88	11.6%	7.33 [1.00 , 53.62]
Subtotal (95% CI)		**1354**		**675**	**87.9%**	**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 TYK2 versus placebo						
Papp 2018	69	222	1	45	12.1%	13.99 [1.99 , 98.10]
Subtotal (95% CI)		**222**		**45**	**12.1%**	**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)		**1576**		**720**	**100.0%**	**7.56 [3.84 , 14.88]**
Total events:	200		9			
Heterogeneity: Tau² = 0.00; Chi² = 3.67, df = 5 (P = 0.60); I² = 0%						
Test for overall effect: Z = 5.85 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.44, df = 1 (P = 0.51), 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 apremilast						
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 Non-biological treatments versus placebo	5	1449	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.21, 1.49]
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	2	1130	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.38, 2.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Non-biological treatment 1 versus non-biological treatment 2	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	33	10581	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.76, 1.46]
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	5	1153	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.22, 4.24]
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	12	4842	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.62, 1.55]
2.4.1 Ustekinumab versus placebo	12	4842	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.62, 1.55]
2.5 Anti-IL17 versus placebo	30	13726	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.70, 1.26]
2.5.1 Secukinumab versus placebo	15	4229	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.64, 1.69]
2.5.2 Ixekizumab versus placebo	5	3706	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.45, 1.80]
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	3	1089	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.20, 1.65]
2.5.5 Netakimab versus placebo	2	333	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.03, 19.17]
2.5.6 Sonelokimab versus placebo	1	260	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.15, 10.47]
2.6 Anti-IL23 versus placebo	13	5304	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.50, 1.22]
2.6.1 Guselkumab versus placebo	5	1767	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.50, 2.28]

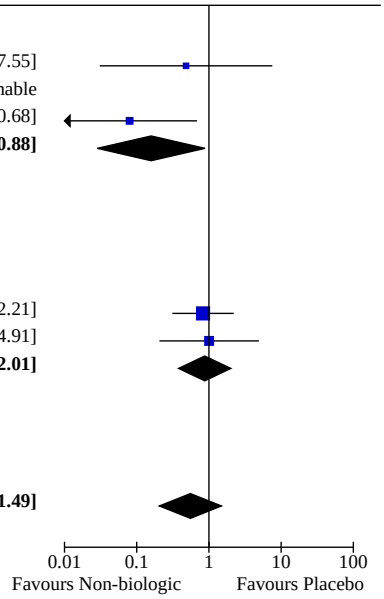
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.6.2 Tildrakizumab versus placebo	3	1904	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.37, 2.77]
2.6.3 Risankizumab versus placebo	5	1633	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.28, 1.90]
2.7 Biologic versus non-biological treatments	10		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 Ixekizumab versus methotrexate	1	108	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.06, 15.58]
2.7.5 Secukinumab versus fumaric acid esters	1	202	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.16, 1.75]
2.7.6 Ixekizumab versus fumaric ester acids	1	108	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.04, 3.10]
2.7.7 Guselkumab versus fumaric ester acids	1	119	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.26, 8.51]
2.7.8 Risankizumab versus fumaric ester acids	1	120	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.05, 5.37]
2.7.9 Brodalumab versus fumaric acid esters	1	300	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.32, 28.52]
2.8 Biologic 1 versus biologic 2	26		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 Infliximab versus etanercept	1	48	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.06, 13.87]
2.8.4 Ixekizumab versus etanercept	2	2209	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.55, 2.06]
2.8.5 Tildrakizumab versus etanercept	1	934	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.28, 1.87]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.8.6 Certolizumab versus etanercept	1	502	Risk Ratio (M-H, Random, 95% CI)	2.56 [0.30, 21.74]
2.8.7 Secukinumab versus ustekinumab	2	1778	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.70, 2.30]
2.8.8 Ixekizumab versus ustekinumab	1	302	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.18, 3.01]
2.8.9 Brodalumab versus ustekinumab	2	3088	Risk Ratio (M-H, Random, 95% CI)	1.51 [0.64, 3.56]
2.8.10 Risankizumab versus ustekinumab	3	965	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.24, 1.32]
2.8.11 Bimekizumab versus ustekinumab	1	484	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.15, 1.73]
2.8.12 Guselkumab versus adalimumab	3	1658	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.45, 1.84]
2.8.13 Risankizumab versus adalimumab	1	605	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.46, 2.72]
2.8.14 Bimekizumab versus adalimumab	1	478	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.15, 1.70]
2.8.15 Ixekizumab versus guselkumab	1	1027	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.57, 2.13]
2.8.16 Risankizumab versus secukinumab	1	327	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.54, 4.09]
2.8.17 Ixekizumab versus secukinumab	1	54	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.8.18 Guselkumab versus secukinumab	1	1048	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.55, 1.35]
2.8.19 Sonelokimab versus secukinumab	1	261	Risk Ratio (M-H, Random, 95% CI)	2.84 [0.16, 50.61]
2.9 Small molecules versus placebo	8	2860	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.47, 1.46]
2.9.1 Apremilast versus placebo	7	2593	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.48, 1.52]
2.9.2 TYK2 versus placebo	1	267	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.06, 5.71]
2.10 Biologic versus small molecules	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.10.1 Etanercept versus apremilast	1	166	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.04, 3.14]

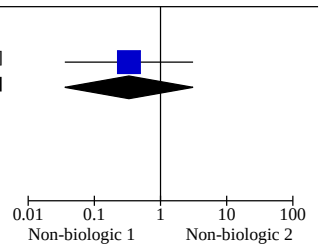
Analysis 2.1. Comparison 2: Primary outcome - serious adverse events (SAE), Outcome 1: Non-biological treatments versus placebo

Study or Subgroup	Non-biological treatment Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Methotrexate versus placebo						
CHAMPION 2008	1	110	1	53	11.2%	0.48 [0.03 , 7.55]
Hunter 1963	0	19	0	17		Not estimable
METOP 2017	1	91	4	29	16.8%	0.08 [0.01 , 0.68]
Subtotal (95% CI)		**220**		**99**	**28.0%**	**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						
BRIDGE 2017	17	566	5	138	45.6%	0.83 [0.31 , 2.21]
NCT03421197	6	319	2	107	26.4%	1.01 [0.21 , 4.91]
Subtotal (95% CI)		**885**		**245**	**72.0%**	**0.87 [0.38 , 2.01]**
Total events:	23		7			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%						
Test for overall effect: Z = 0.32 (P = 0.75)						
Total (95% CI)		**1105**		**344**	**100.0%**	**0.55 [0.21 , 1.49]**
Total events:	25		12			
Heterogeneity: Tau² = 0.31; Chi² = 4.25, df = 3 (P = 0.24); I² = 29%						
Test for overall effect: Z = 1.17 (P = 0.24)						
Test for subgroup differences: Chi² = 3.09, df = 1 (P = 0.08), I² = 67.6%						



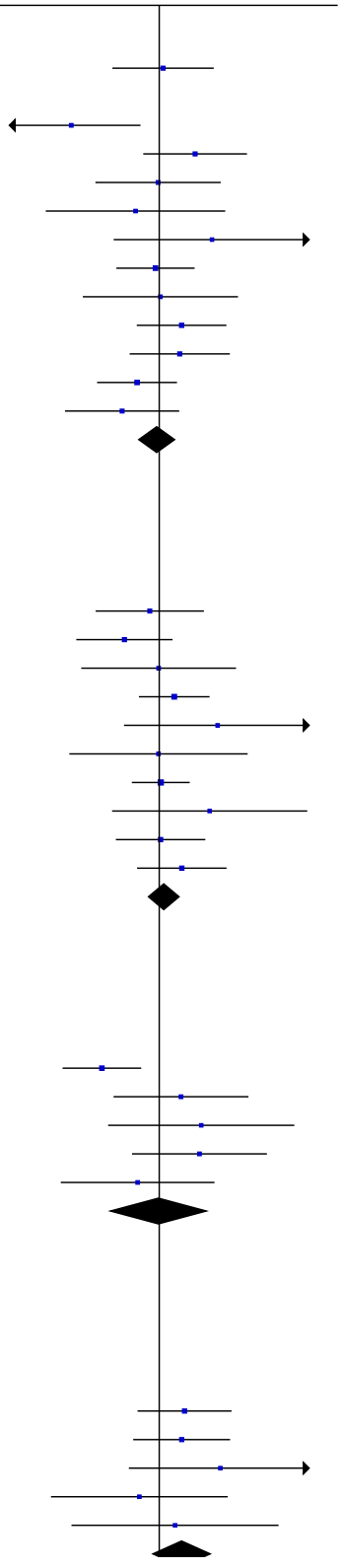
Analysis 2.2. Comparison 2: Primary outcome - serious adverse events (SAE), Outcome 2: Non-biological treatment 1 versus non-biological treatment 2

Study or Subgroup	Non-biological treatment 1 Events	Total	Non-biological treatment 2 Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Methotrexate versus fumaric ester acids						
Reich 2020	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	3.7%	1.13 [0.24 , 5.33]
Bagel 2012	0	62	0	62		Not estimable
CIMPACT 2018	1	170	5	57	2.1%	0.07 [0.01 , 0.56]
FIXTURE 2014	6	326	2	327	3.5%	3.01 [0.61 , 14.80]
Gottlieb 2003a	2	57	2	55	2.5%	0.96 [0.14 , 6.61]
Gottlieb 2011	1	141	1	68	1.3%	0.48 [0.03 , 7.59]
LIBERATE 2017	2	83	0	84	1.1%	5.06 [0.25 , 103.82]
ReSURFACE-2 2017	7	169	4	86	5.6%	0.89 [0.27 , 2.96]
Strober 2011	2	139	1	72	1.7%	1.04 [0.10 , 11.23]
Tyring 2006	6	311	3	309	4.5%	1.99 [0.50 , 7.87]
UNCOVER-2 2015	8	358	2	168	3.8%	1.88 [0.40 , 8.74]
UNCOVER-3 2015	5	382	5	193	5.4%	0.51 [0.15 , 1.72]
Van de Kerkhof 2008	2	96	3	46	3.0%	0.32 [0.06 , 1.85]
Subtotal (95% CI)		**2630**		**1635**	**38.3%**	**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	3.3%	0.75 [0.14 , 3.95]
Cai 2016	4	338	3	87	4.0%	0.34 [0.08 , 1.51]
CHAMPION 2008	2	108	1	53	1.7%	0.98 [0.09 , 10.58]
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	1.3%	0.98 [0.06 , 15.11]
REVEAL 2008	15	814	7	398	8.7%	1.05 [0.43 , 2.55]
VIP Trial 2018	2	33	0	31	1.1%	4.71 [0.23 , 94.31]
VOYAGE-1 2016	6	334	3	174	4.5%	1.04 [0.26 , 4.12]
VOYAGE-2 2017	6	248	3	248	4.5%	2.00 [0.51 , 7.91]
Subtotal (95% CI)		**2246**		**1239**	**36.9%**	**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						
CIMPACT 2018	5	332	5	57	5.6%	0.17 [0.05 , 0.57]
CIMPASI-1 2018	7	183	1	51	2.2%	1.95 [0.25 , 15.49]
CIMPASI-2 2018	6	178	0	49	1.2%	3.63 [0.21 , 63.36]
Reich 2012a	7	118	1	58	2.2%	3.44 [0.43 , 27.31]
Umezawa 2021	2	101	1	26	1.7%	0.51 [0.05 , 5.46]
Subtotal (95% CI)		**912**		**241**	**13.0%**	**0.97 [0.22 , 4.24]**
Total events:	27		8			
Heterogeneity: Tau² = 1.69; Chi² = 10.64, df = 4 (P = 0.03); I² = 62%						
Test for overall effect: Z = 0.04 (P = 0.97)						
2.3.4 Infliximab versus placebo						
Chaudhari 2001	0	22	0	11		Not estimable
EXPRESS 2005	17	301	2	77	4.2%	2.17 [0.51 , 9.21]
EXPRESS-II 2007	12	627	2	208	4.0%	1.99 [0.45 , 8.82]
Gottlieb 2004a	12	198	0	51	1.3%	6.53 [0.39 , 108.53]
Torii 2010	1	35	1	19	1.3%	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**	**11.7%**	**1.99 [0.82 , 4.78]**



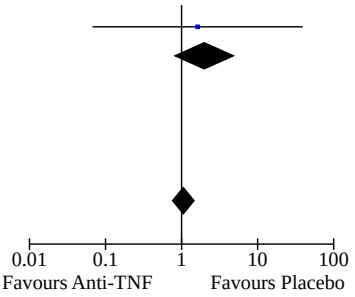
Analysis 2.3. (Continued)

Yang 2012	1	84	0	45	1.0%	1.62 [0.07 , 39.06]
Subtotal (95% CI)		**1267**		**411**	**11.7%**	**1.99 [0.82 , 4.78]**
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)		**7055**		**3526**	**100.0%**	**1.05 [0.76 , 1.46]**
Total events:	172		68			

Heterogeneity: Tau² = 0.11; Chi² = 35.63, df = 31 (P = 0.26); I² = 13%
Test for overall effect: Z = 0.32 (P = 0.75)
Test for subgroup differences: Chi² = 2.13, df = 3 (P = 0.55), I² = 0%



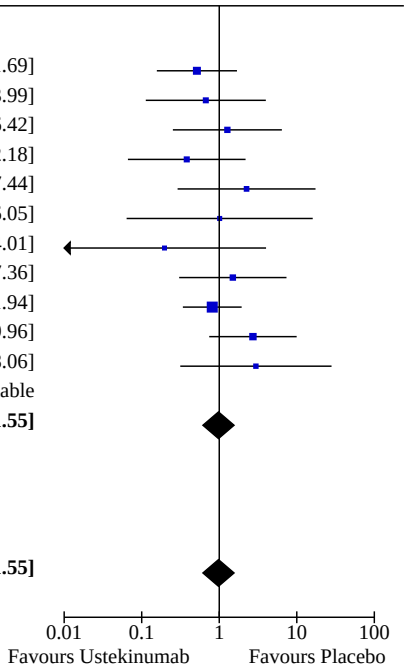
Analysis 2.4. Comparison 2: Primary outcome - serious adverse events (SAE), Outcome 4: Anti-IL12/23 versus placebo

	Ustekinumab		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
2.4.1 Ustekinumab versus placebo							
AMAGINE-2 2015	4	300	8	309	15.0%	0.52 [0.16 , 1.69]	
AMAGINE-3 2015	2	313	3	315	6.7%	0.67 [0.11 , 3.99]	
BE VIVID 2021	5	163	2	83	8.1%	1.27 [0.25 , 6.42]	
Igarashi 2012	3	126	2	32	7.0%	0.38 [0.07 , 2.18]	
Krueger 2007	9	256	1	64	5.1%	2.25 [0.29 , 17.44]	
LOTUS 2013	1	160	1	162	2.8%	1.01 [0.06 , 16.05]	
PEARL 2011	0	61	2	60	2.3%	0.20 [0.01 , 4.01]	
PHOENIX-1 2008	6	511	2	255	8.4%	1.50 [0.30 , 7.36]	
PHOENIX-2 2008	13	820	8	410	27.9%	0.81 [0.34 , 1.94]	
UltIMMa-1 2018	8	100	3	102	12.6%	2.72 [0.74 , 9.96]	
UltIMMa-2 2018	3	99	1	98	4.2%	2.97 [0.31 , 28.06]	
VIP-U Trial 2020	0	22	0	21		Not estimable	
Subtotal (95% CI)		**2931**		**1911**	**100.0%**	**0.98 [0.62 , 1.55]**	
Total events:	54		33				

Heterogeneity: Tau² = 0.00; Chi² = 8.02, df = 10 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.10 (P = 0.92)

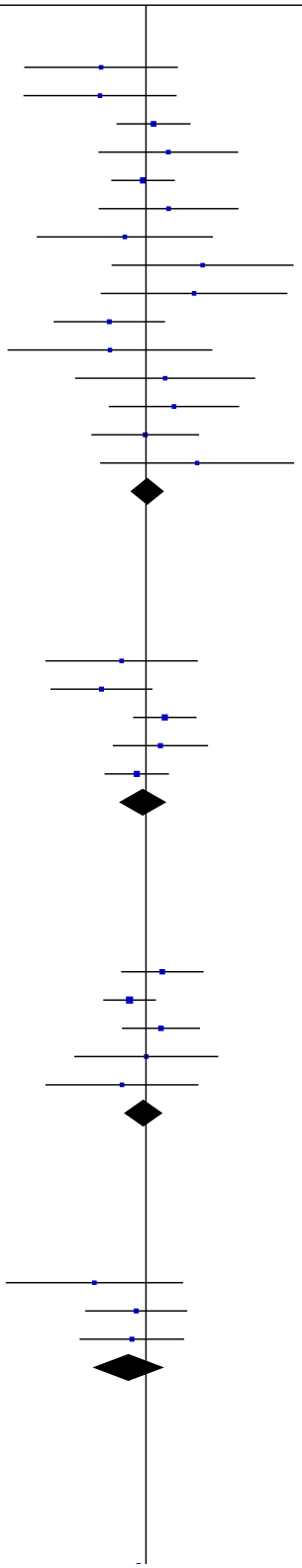
Total (95% CI)		**2931**		**1911**	**100.0%**	**0.98 [0.62 , 1.55]**
Total events:	54		33			

Heterogeneity: Tau² = 0.00; Chi² = 8.02, df = 10 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.10 (P = 0.92)
Test for subgroup differences: Not applicable



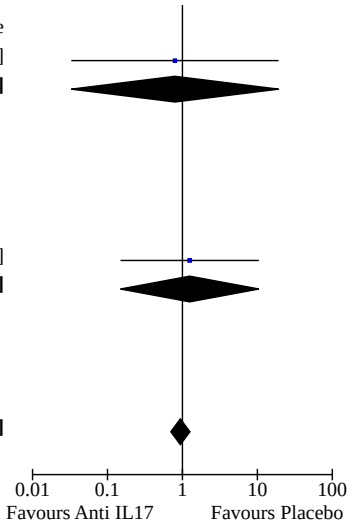
Analysis 2.5. Comparison 2: Primary outcome - serious adverse events (SAE), Outcome 5: Anti-IL17 versus placebo

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						
ALLURE 2021	1	143	2	71	1.5%	0.25 [0.02 , 2.69]
CARIMA 2019	1	102	2	49	1.5%	0.24 [0.02 , 2.59]
ERASURE 2014	10	490	4	248	6.5%	1.27 [0.40 , 3.99]
FEATURE 2015	4	118	1	59	1.8%	2.00 [0.23 , 17.50]
FIXTURE 2014	11	654	6	326	8.8%	0.91 [0.34 , 2.45]
JUNCTURE 2015	4	121	1	61	1.8%	2.02 [0.23 , 17.65]
NCT03055494 ObePso-S	1	54	1	28	1.1%	0.52 [0.03 , 7.98]
NCT03535194	11	448	0	112	1.1%	5.79 [0.34 , 97.49]
NCT03589885 MATURE	4	82	0	40	1.0%	4.45 [0.25 , 80.61]
Papp 2013a	3	103	2	22	2.9%	0.32 [0.06 , 1.81]
Papp 2021	0	53	1	52	0.8%	0.33 [0.01 , 7.85]
Reich 2015	7	90	0	10	1.1%	1.81 [0.11 , 29.62]
Rich 2013	12	337	1	67	2.1%	2.39 [0.32 , 18.04]
TRANSFIGURE 2016	4	133	2	65	3.1%	0.98 [0.18 , 5.20]
VIP-S trial 2020	2	46	0	45	0.9%	4.89 [0.24 , 99.18]
Subtotal (95% CI)		**2974**		**1255**	**36.1%**	**1.04 [0.64 , 1.69]**
Total events:	75		23			
Heterogeneity: Tau² = 0.00; Chi² = 10.77, df = 14 (P = 0.70); I² = 0%						
Test for overall effect: Z = 0.15 (P = 0.88)						
2.5.2 Ixekizumab versus placebo						
Leonardi 2012	2	115	1	27	1.5%	0.47 [0.04 , 4.99]
NCT03364309	3	350	3	88	3.4%	0.25 [0.05 , 1.22]
UNCOVER-1 2016	18	865	5	431	8.8%	1.79 [0.67 , 4.80]
UNCOVER-2 2015	13	698	2	168	3.9%	1.56 [0.36 , 6.87]
UNCOVER-3 2015	15	771	5	193	8.6%	0.75 [0.28 , 2.04]
Subtotal (95% CI)		**2799**		**907**	**26.3%**	**0.90 [0.45 , 1.80]**
Total events:	51		16			
Heterogeneity: Tau² = 0.16; Chi² = 5.38, df = 4 (P = 0.25); I² = 26%						
Test for overall effect: Z = 0.29 (P = 0.77)						
2.5.3 Brodalumab versus placebo						
AMAGINE-1 2016	10	441	3	220	5.2%	1.66 [0.46 , 5.98]
AMAGINE-2 2015	19	1222	8	309	12.8%	0.60 [0.27 , 1.36]
AMAGINE-3 2015	19	1253	3	315	5.8%	1.59 [0.47 , 5.35]
Nakagawa 2016	3	113	1	38	1.7%	1.01 [0.11 , 9.41]
Papp 2012a	2	160	1	38	1.5%	0.47 [0.04 , 5.10]
Subtotal (95% CI)		**3189**		**920**	**27.1%**	**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						
BE ABLE 1 2018	1	208	1	42	1.1%	0.20 [0.01 , 3.16]
BE READY 2021	6	349	2	86	3.4%	0.74 [0.15 , 3.60]
BE VIVID 2021	5	321	2	83	3.3%	0.65 [0.13 , 3.27]
Subtotal (95% CI)		**878**		**211**	**7.8%**	**0.58 [0.20 , 1.65]**
Total events:	12		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.67, df = 2 (P = 0.71); I² = 0%						
Test for overall effect: Z = 1.02 (P = 0.31)						
2.5.5 Netakimab versus placebo						
NCT02762994	0	92	0	28		Not estimable
PLANETA 2021	1	169	0	44	0.8%	0.79 [0.03 , 19.17]



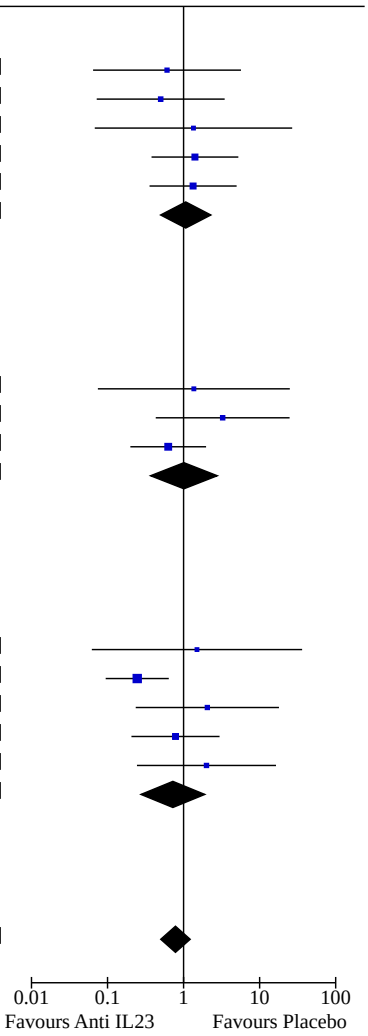
Analysis 2.5. (Continued)

NCT02762994	0	92	0	28		Not estimable
PLANETA 2021	1	169	0	44	0.8%	0.79 [0.03 , 19.17]
Subtotal (95% CI)		**261**		**72**	**0.8%**	**0.79 [0.03 , 19.17]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.14 (P = 0.89)						
2.5.6 Sonelokimab versus placebo						
Papp 2021	5	208	1	52	1.9%	1.25 [0.15 , 10.47]
Subtotal (95% CI)		**208**		**52**	**1.9%**	**1.25 [0.15 , 10.47]**
Total events:	5		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.21 (P = 0.84)						
Total (95% CI)		**10309**		**3417**	**100.0%**	**0.94 [0.70 , 1.26]**
Total events:	197		61			
Heterogeneity: Tau² = 0.00; Chi² = 20.95, df = 29 (P = 0.86); I² = 0%						
Test for overall effect: Z = 0.43 (P = 0.67)						
Test for subgroup differences: Chi² = 1.07, df = 5 (P = 0.96), I² = 0%						



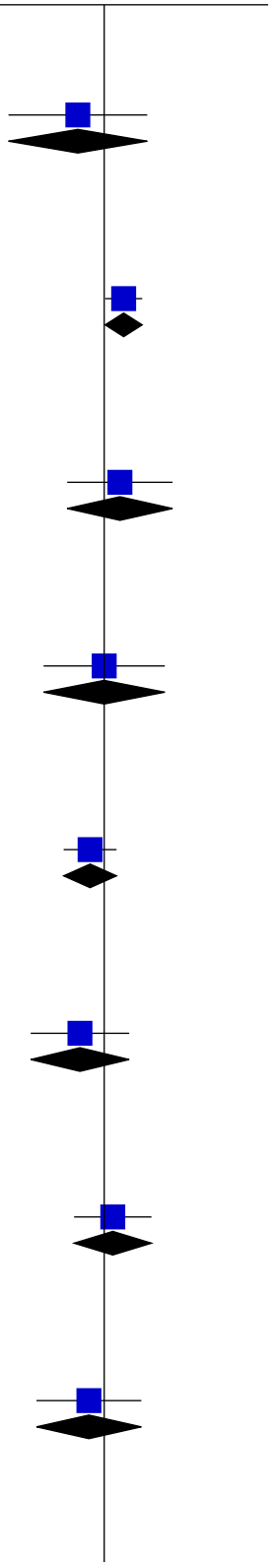
Analysis 2.6. Comparison 2: Primary outcome - serious adverse events (SAE), Outcome 6: Anti-IL23 versus placebo

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						
Gordon X-PLORE 2015	3	208	1	42	4.0%	0.61 [0.06 , 5.68]
Ohtsuki 2018	2	128	2	64	5.3%	0.50 [0.07 , 3.47]
ORION 2020	2	62	0	16	2.2%	1.35 [0.07 , 26.80]
VOYAGE-1 2016	8	329	3	174	11.5%	1.41 [0.38 , 5.25]
VOYAGE-2 2017	8	496	3	248	11.4%	1.33 [0.36 , 4.98]
Subtotal (95% CI)		**1223**		**544**	**34.3%**	**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	2.3%	1.36 [0.07 , 24.94]
ReSURFACE-1 2017	13	617	1	155	4.8%	3.27 [0.43 , 24.77]
ReSURFACE-2 2017	10	621	4	156	15.1%	0.63 [0.20 , 1.98]
Subtotal (95% CI)		**1547**		**357**	**22.2%**	**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						
Blauvelt 2021a	1	105	0	52	2.0%	1.50 [0.06 , 36.20]
IMMhance 2020	8	407	8	100	21.7%	0.25 [0.09 , 0.64]
SustaIMM 2019	4	113	1	58	4.2%	2.05 [0.23 , 17.95]
UltIMMa-1 2018	7	304	3	102	11.1%	0.78 [0.21 , 2.97]
UltIMMa-2 2018	6	294	1	98	4.5%	2.00 [0.24 , 16.41]
Subtotal (95% CI)		**1223**		**410**	**43.5%**	**0.72 [0.28 , 1.90]**
Total events:	26		13			
Heterogeneity: Tau² = 0.44; Chi² = 6.47, df = 4 (P = 0.17); I² = 38%						
Test for overall effect: Z = 0.66 (P = 0.51)						
Total (95% CI)		**3993**		**1311**	**100.0%**	**0.78 [0.50 , 1.22]**
Total events:	76		27			
Heterogeneity: Tau² = 0.00; Chi² = 11.64, df = 12 (P = 0.48); I² = 0%						
Test for overall effect: Z = 1.08 (P = 0.28)						
Test for subgroup differences: Chi² = 0.41, df = 2 (P = 0.81), I² = 0%						



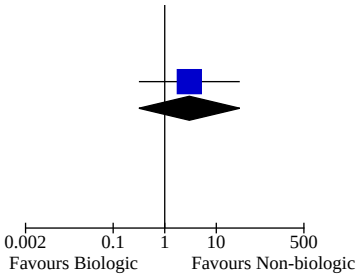
Analysis 2.7. Comparison 2: Primary outcome - serious adverse events (SAE), Outcome 7: Biologic versus non-biological treatments

Study or Subgroup	Biologic Events	Biologic Total	Non-biological treatment Events	Non-biological treatment 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 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						
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 Ixekizumab versus methotrexate						
Reich 2020	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)						
2.7.5 Secukinumab versus fumaric acid esters						
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)						
2.7.6 Ixekizumab versus fumaric ester acids						
Reich 2020	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)						
2.7.7 Guselkumab versus fumaric ester acids						
POLARIS 2020	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)						
2.7.8 Risankizumab versus fumaric ester acids						
Thaci 2021	1	60	2	60	100.0%	0.50 [0.05 , 5.37]
Subtotal (95% CI)		**60**		**60**	**100.0%**	**0.50 [0.05 , 5.37]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
2.7.9 Brodalumab versus fumaric acid esters						

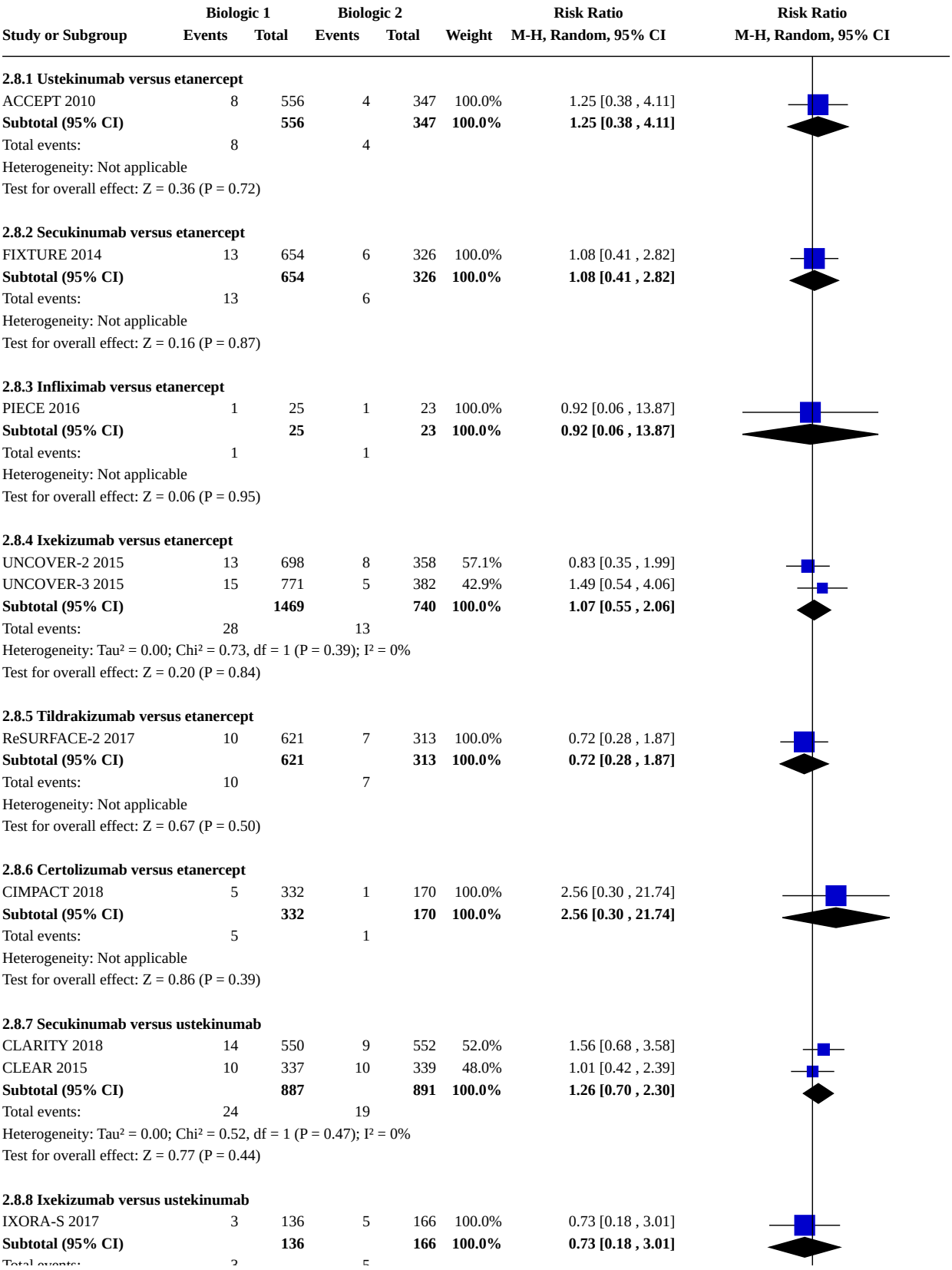


Analysis 2.7. (Continued)

2.7.9 Brodalumab versus fumaric acid esters						
CHANGE 2021	3	150	1	150	100.0%	3.00 [0.32 , 28.52]
Subtotal (95% CI)		**150**		**150**	**100.0%**	**3.00 [0.32 , 28.52]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.96 (P = 0.34)						

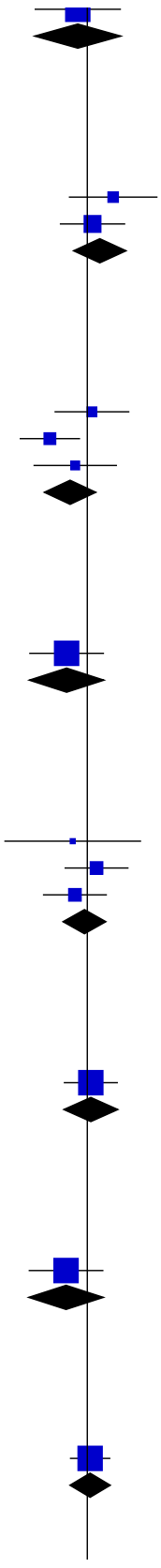


Analysis 2.8. Comparison 2: Primary outcome - serious adverse events (SAE), Outcome 8: Biologic 1 versus biologic 2



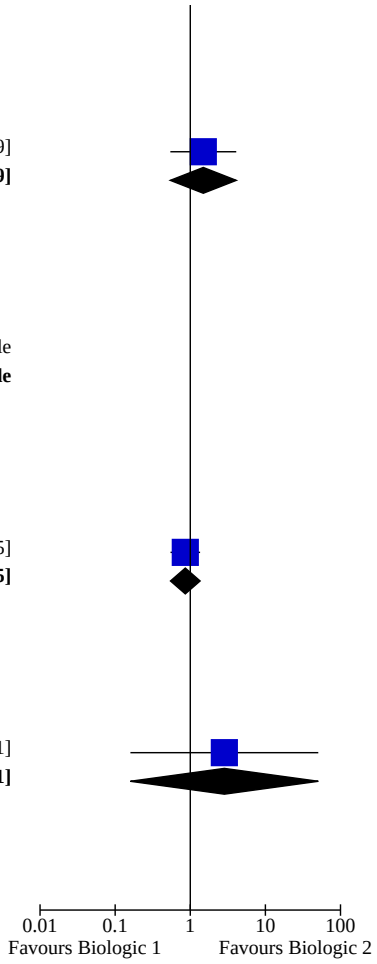
Analysis 2.8. (Continued)

Subtotal (95% CI)		**136**		**166**	**100.0%**	**0.73 [0.18 , 3.01]**
Total events:	3		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.43 (P = 0.67)						
2.8.9 Brodalumab versus ustekinumab						
AMAGINE-2 2015	19	1222	2	300	35.3%	2.33 [0.55 , 9.96]
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: Tau² = 0.00; Chi² = 0.55, df = 1 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.93 (P = 0.35)						
2.8.10 Risankizumab versus ustekinumab						
Papp 2017b	11	126	3	40	31.6%	1.16 [0.34 , 3.97]
UltIMMa-1 2018	7	304	8	102	41.2%	0.29 [0.11 , 0.79]
UltIMMa-2 2018	6	294	3	99	27.2%	0.67 [0.17 , 2.64]
Subtotal (95% CI)		**724**		**241**	**100.0%**	**0.57 [0.24 , 1.32]**
Total events:	24		14			
Heterogeneity: Tau² = 0.20; Chi² = 3.08, df = 2 (P = 0.21); I² = 35%						
Test for overall effect: Z = 1.31 (P = 0.19)						
2.8.11 Bimekizumab versus ustekinumab						
BE VIVID 2021	5	321	5	163	100.0%	0.51 [0.15 , 1.73]
Subtotal (95% CI)		**321**		**163**	**100.0%**	**0.51 [0.15 , 1.73]**
Total events:	5		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.08 (P = 0.28)						
2.8.12 Guselkumab versus adalimumab						
Gordon X-PLORE 2015	3	208	1	43	9.9%	0.62 [0.07 , 5.82]
VOYAGE-1 2016	8	329	6	334	45.1%	1.35 [0.47 , 3.86]
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: Tau² = 0.00; Chi² = 1.01, df = 2 (P = 0.60); I² = 0%						
Test for overall effect: Z = 0.26 (P = 0.79)						
2.8.13 Risankizumab versus adalimumab						
IMMvent 2019	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)						
2.8.14 Bimekizumab versus adalimumab						
BE SURE 2021	5	319	5	159	100.0%	0.50 [0.15 , 1.70]
Subtotal (95% CI)		**319**		**159**	**100.0%**	**0.50 [0.15 , 1.70]**
Total events:	5		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.11 (P = 0.27)						
2.8.15 Ixekizumab versus guselkumab						
IXORA-R 2020	18	520	16	507	100.0%	1.10 [0.57 , 2.13]
Subtotal (95% CI)		**520**		**507**	**100.0%**	**1.10 [0.57 , 2.13]**
Total events:	18		16			
Heterogeneity: Not applicable						



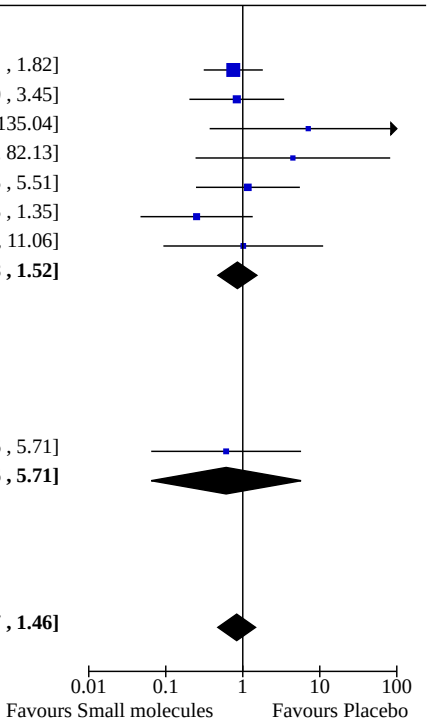
Analysis 2.8. (Continued)

Total events:	10		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.78)						
2.8.16 Risankizumab versus secukinumab						
IMMerge 2021	9	164	6	163	100.0%	1.49 [0.54 , 4.09]
Subtotal (95% CI)		**164**		**163**	**100.0%**	**1.49 [0.54 , 4.09]**
Total events:	9		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.77 (P = 0.44)						
2.8.17 Ixekizumab versus secukinumab						
AlMutairi 2021	0	28	0	26		Not estimable
Subtotal (95% CI)		**28**		**26**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.8.18 Guselkumab versus secukinumab						
ECLIPSE 2019	33	534	37	514	100.0%	0.86 [0.55 , 1.35]
Subtotal (95% CI)		**534**		**514**	**100.0%**	**0.86 [0.55 , 1.35]**
Total events:	33		37			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
2.8.19 Sonelokimab versus secukinumab						
Papp 2021	5	208	0	53	100.0%	2.84 [0.16 , 50.61]
Subtotal (95% CI)		**208**		**53**	**100.0%**	**2.84 [0.16 , 50.61]**
Total events:	5		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						



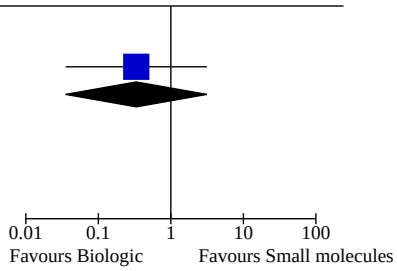
Analysis 2.9. Comparison 2: Primary outcome - serious adverse events (SAE), Outcome 9: Small molecules versus placebo

Study or Subgroup	Small molecules Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.9.1 Apremilast versus placebo						
ESTEEM-1 2015	12	562	8	282	40.6%	0.75 [0.31 , 1.82]
ESTEEM-2 2015	5	275	3	138	15.8%	0.84 [0.20 , 3.45]
LIBERATE 2017	3	83	0	84	3.6%	7.08 [0.37 , 135.04]
Ohtsuki 2017	4	170	0	84	3.7%	4.47 [0.24 , 82.13]
Papp 2012c	7	264	2	88	13.1%	1.17 [0.25 , 5.51]
Papp 2013b	2	173	4	87	11.2%	0.25 [0.05 , 1.35]
STYLE 2020	2	201	1	102	5.5%	1.01 [0.09 , 11.06]
Subtotal (95% CI)		**1728**		**865**	**93.7%**	**0.85 [0.48 , 1.52]**
Total events:	35		18			
Heterogeneity: Tau² = 0.00; Chi² = 5.64, df = 6 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.54 (P = 0.59)						
2.9.2 TYK2 versus placebo						
Papp 2018	3	222	1	45	6.3%	0.61 [0.06 , 5.71]
Subtotal (95% CI)		**222**		**45**	**6.3%**	**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)		**1950**		**910**	**100.0%**	**0.83 [0.47 , 1.46]**
Total events:	38		19			
Heterogeneity: Tau² = 0.00; Chi² = 5.73, df = 7 (P = 0.57); I² = 0%						
Test for overall effect: Z = 0.63 (P = 0.53)						
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%						



Analysis 2.10. Comparison 2: Primary outcome - serious adverse events (SAE), Outcome 10: Biologic versus small molecules

Study or Subgroup	Biologic Events	Total	Small molecules Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.10.1 Etanercept versus apremilast						
LIBERATE 2017	1	83	3	83	100.0%	0.33 [0.04 , 3.14]
Subtotal (95% CI)		**83**		**83**	**100.0%**	**0.33 [0.04 , 3.14]**
Total events:	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.96 (P = 0.34)						



Comparison 3. Secondary outcome - PASI 75

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Non-biological treatments versus placebo	5	1451	Risk Ratio (M-H, Random, 95% CI)	2.34 [1.81, 3.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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	2	1130	Risk Ratio (M-H, Random, 95% CI)	2.39 [1.78, 3.21]
3.1.3 Acitretin versus placebo	1	38	Risk Ratio (M-H, Random, 95% CI)	1.85 [0.23, 14.80]
3.2 Non-biological treatment 1 versus non-biological treatment 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	35	12078	Risk Ratio (M-H, Random, 95% CI)	9.21 [7.78, 10.91]
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]
3.3.3 Certolizumab versus placebo	5	1153	Risk Ratio (M-H, Random, 95% CI)	9.55 [6.13, 14.88]
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	12	4842	Risk Ratio (M-H, Random, 95% CI)	11.36 [8.84, 14.61]
3.4.1 Ustekinumab versus placebo	12	4842	Risk Ratio (M-H, Random, 95% CI)	11.36 [8.84, 14.61]
3.5 Anti-IL17 versus placebo	29	13664	Risk Ratio (M-H, Random, 95% CI)	14.33 [11.45, 17.93]
3.5.1 Secukinumab versus placebo	14	4540	Risk Ratio (M-H, Random, 95% CI)	15.32 [11.36, 20.66]
3.5.2 Ixekizumab versus placebo	5	3706	Risk Ratio (M-H, Random, 95% CI)	15.99 [10.44, 24.47]
3.5.3 Brodalumab versus placebo	6	4171	Risk Ratio (M-H, Random, 95% CI)	13.09 [8.75, 19.57]
3.5.4 Bimekizumab versus placebo	2	654	Risk Ratio (M-H, Random, 95% CI)	13.66 [6.99, 26.71]

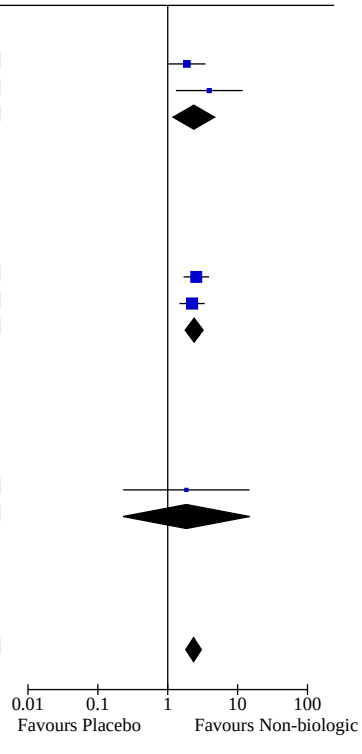
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.5.5 Netakimab versus placebo	2	333	Risk Ratio (M-H, Random, 95% CI)	14.12 [0.26, 778.45]
3.5.6 Sonelokimab versus placebo	1	260	Risk Ratio (M-H, Random, 95% CI)	86.98 [5.51, 1373.50]
3.6 Anti-IL23 versus placebo	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 non-biological treatments	10		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 Ixekizumab versus methotrexate	1	108	Risk Ratio (M-H, Random, 95% CI)	1.29 [1.06, 1.56]
3.7.5 Secukinumab versus fumaric acid esters	1	202	Risk Ratio (M-H, Random, 95% CI)	3.30 [2.36, 4.62]
3.7.6 Ixekizumab versus fumaric ester acids	1	108	Risk Ratio (M-H, Random, 95% CI)	4.08 [2.46, 6.77]
3.7.7 Guselkumab versus fumaric acid esters	1	118	Risk Ratio (M-H, Random, 95% CI)	3.26 [2.13, 4.99]
3.7.8 Risankizumab versus fumaric acid esters	1	120	Risk Ratio (M-H, Random, 95% CI)	2.95 [2.06, 4.23]
3.7.9 Brodalumab versus fumaric acid esters	1	210	Risk Ratio (M-H, Random, 95% CI)	2.12 [1.64, 2.76]
3.8 Biologic 1 versus biologic 2	25		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]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.8.2 Secukinumab versus etanercept	1	980	Risk Ratio (M-H, Random, 95% CI)	1.64 [1.44, 1.88]
3.8.3 Infliximab versus etanercept	1	48	Risk Ratio (M-H, Random, 95% CI)	2.07 [1.12, 3.81]
3.8.4 Ixekizumab versus etanercept	2	2209	Risk Ratio (M-H, Random, 95% CI)	1.79 [1.43, 2.24]
3.8.5 Tildrakizumab versus etanercept	1	934	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.16, 1.50]
3.8.6 Certolizumab versus etanercept	1	502	Risk Ratio (M-H, Random, 95% CI)	1.19 [1.01, 1.40]
3.8.7 Secukinumab versus ustekinumab	2	1778	Risk Ratio (M-H, Random, 95% CI)	1.14 [1.10, 1.19]
3.8.8 Ixekizumab versus ustekinumab	1	302	Risk Ratio (M-H, Random, 95% CI)	1.11 [1.02, 1.22]
3.8.9 Brodalumab versus ustekinumab	2	3088	Risk Ratio (M-H, Random, 95% CI)	1.10 [1.04, 1.17]
3.8.10 Risankizumab versus ustekinumab	3	965	Risk Ratio (M-H, Random, 95% CI)	1.23 [1.13, 1.33]
3.8.11 Bimekizumab versus ustekinumab	1	484	Risk Ratio (M-H, Random, 95% CI)	1.26 [1.14, 1.39]
3.8.12 Guselkumab versus adalimumab	3	1658	Risk Ratio (M-H, Random, 95% CI)	1.23 [1.14, 1.32]
3.8.13 Risankizumab versus adalimumab	1	605	Risk Ratio (M-H, Random, 95% CI)	1.26 [1.17, 1.37]
3.8.14 Bimekizumab versus adalimumab	1	478	Risk Ratio (M-H, Random, 95% CI)	1.34 [1.20, 1.49]
3.8.15 Risankizumab versus secukinumab	1	327	Risk Ratio (M-H, Random, 95% CI)	1.15 [1.05, 1.26]
3.8.16 Bimekizumab versus secukinumab	1	743	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.98, 1.07]
3.8.17 Guselkumab versus secukinumab	1	1048	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.94, 1.01]
3.8.18 Sonelokimab versus secukinumab	1	261	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.82, 1.01]
3.9 Small molecules versus placebo	8	3327	Risk Ratio (M-H, Random, 95% CI)	4.52 [3.06, 6.66]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.9.1 Apremilast versus placebo	6	2290	Risk Ratio (M-H, Random, 95% CI)	3.86 [2.59, 5.74]
3.9.2 Tofacitinib versus placebo	1	770	Risk Ratio (M-H, Random, 95% CI)	9.24 [4.23, 20.19]
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	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.10.1 Etanercept versus apremilast	1	166	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.86, 1.71]

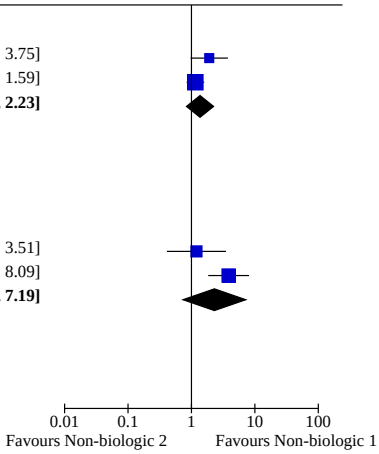
Analysis 3.1. Comparison 3: Secondary outcome - PASI 75, Outcome 1: Non-biological treatments versus placebo

Study or Subgroup	Non-biological treatment Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Methotrexate versus placebo						
CHAMPION 2008	39	110	10	53	17.5%	1.88 [1.02 , 3.47]
METOP 2017	37	91	3	29	5.4%	3.93 [1.31 , 11.81]
Subtotal (95% CI)		**201**		**82**	**23.0%**	**2.36 [1.19 , 4.68]**
Total events:	76		13			
Heterogeneity: Tau² = 0.08; Chi² = 1.38, df = 1 (P = 0.24); I² = 28%						
Test for overall effect: Z = 2.46 (P = 0.01)						
3.1.2 Fumaric acid esters versus placebo						
BRIDGE 2017	210	566	20	138	37.5%	2.56 [1.68 , 3.89]
NCT03421197	133	319	20	107	38.0%	2.23 [1.47 , 3.38]
Subtotal (95% CI)		**885**		**245**	**75.5%**	**2.39 [1.78 , 3.21]**
Total events:	343		40			
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 5.78 (P < 0.00001)						
3.1.3 Acitretin versus placebo						
Goldfarb 1988	4	26	1	12	1.5%	1.85 [0.23 , 14.80]
Subtotal (95% CI)		**26**		**12**	**1.5%**	**1.85 [0.23 , 14.80]**
Total events:	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
Total (95% CI)		**1112**		**339**	**100.0%**	**2.34 [1.81 , 3.03]**
Total events:	423		54			
Heterogeneity: Tau² = 0.00; Chi² = 1.65, df = 4 (P = 0.80); I² = 0%						
Test for overall effect: Z = 6.51 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.06, df = 2 (P = 0.97), I² = 0%						



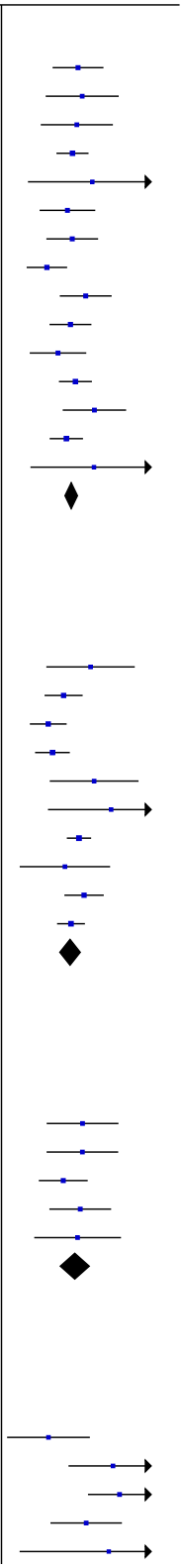
Analysis 3.2. Comparison 3: Secondary outcome - PASI 75, Outcome 2: Non-biological treatment 1 versus non-biological treatment 2

Study or Subgroup	Non-biological treatment 1 Events	Total	Non-biological treatment 2 Events	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]
Reich 2020	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)						



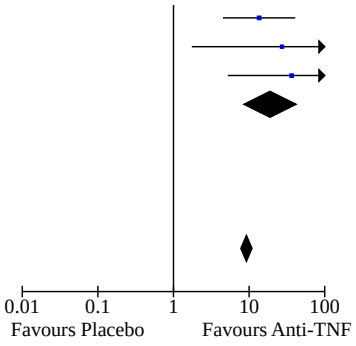
Analysis 3.3. Comparison 3: Secondary outcome - PASI 75, Outcome 3: Anti-TNF alpha versus placebo

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	3.1%	10.55 [4.82 , 23.09]
Bagel 2012	36	62	3	62	1.8%	12.00 [3.90 , 36.92]
CIMPACT 2018	91	170	3	57	1.9%	10.17 [3.35 , 30.87]
FIXTURE 2014	142	326	16	327	5.3%	8.90 [5.43 , 14.58]
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]
Leonardi 2003	159	504	6	168	3.1%	8.83 [3.98 , 19.58]
LIBERATE 2017	40	83	10	84	4.2%	4.05 [2.17 , 7.55]
Papp 2005	160	407	6	204	3.1%	13.37 [6.02 , 29.67]
ReSURFACE-2 2017	151	313	9	156	4.0%	8.36 [4.39 , 15.93]
Strober 2011	55	139	5	72	2.7%	5.70 [2.39 , 13.60]
Tyring 2006	147	311	15	309	5.1%	9.74 [5.86 , 16.17]
UNCOVER-2 2015	149	358	4	168	2.3%	17.48 [6.59 , 46.39]
UNCOVER-3 2015	204	382	14	193	5.1%	7.36 [4.41 , 12.30]
Van de Kerkhof 2008	36	96	1	46	0.7%	17.25 [2.44 , 121.93]
Subtotal (95% CI)		**3685**		**2077**	**45.8%**	**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	1.3%	15.52 [3.98 , 60.53]
Cai 2016	263	338	10	87	4.5%	6.77 [3.77 , 12.16]
CHAMPION 2008	86	108	10	53	4.6%	4.22 [2.40 , 7.44]
Elewski 2016	63	109	13	108	4.9%	4.80 [2.81 , 8.19]
Gordon 2006	64	96	2	52	1.3%	17.33 [4.42 , 67.96]
Gordon X-PLORE 2015	30	43	1	42	0.7%	29.30 [4.18 , 205.23]
REVEAL 2008	578	814	26	398	6.5%	10.87 [7.48 , 15.80]
VIP Trial 2018	15	33	2	31	1.3%	7.05 [1.75 , 28.33]
VOYAGE-1 2016	244	334	10	174	4.3%	12.71 [6.94 , 23.28]
VOYAGE-2 2017	170	248	20	248	5.9%	8.50 [5.54 , 13.05]
Subtotal (95% CI)		**2246**		**1239**	**35.3%**	**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						
CIMPACT 2018	212	332	3	57	1.9%	12.13 [4.02 , 36.61]
CIMPASI-1 2018	130	183	3	51	1.9%	12.08 [4.01 , 36.34]
CIMPASI-2 2018	146	178	6	49	3.3%	6.70 [3.16 , 14.22]
Reich 2012a	92	118	4	58	2.4%	11.31 [4.37 , 29.24]
Umezawa 2021	81	101	2	26	1.4%	10.43 [2.74 , 39.62]
Subtotal (95% CI)		**912**		**241**	**10.8%**	**9.55 [6.13 , 14.88]**
Total events:	661		18			
Heterogeneity: Tau² = 0.00; Chi² = 1.37, df = 4 (P = 0.85); I² = 0%						
Test for overall effect: Z = 9.96 (P < 0.00001)						
3.3.4 Infliximab versus placebo						
Chaudhari 2001	17	22	2	11	1.5%	4.25 [1.19 , 15.19]
EXPRESS 2005	242	301	2	77	1.3%	30.95 [7.87 , 121.68]
EXPRESS-II 2007	457	627	4	208	2.3%	37.90 [14.34 , 100.15]
Gottlieb 2004a	158	198	3	51	1.9%	13.57 [4.52 , 40.75]
Torii 2010	24	35	0	19	0.4%	27.22 [1.75 , 424.16]



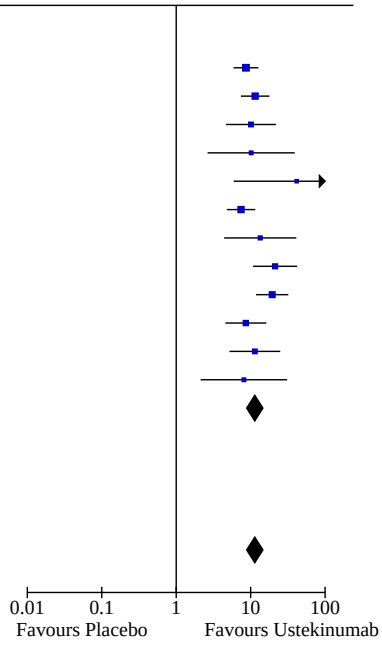
Analysis 3.3. (Continued)

Gottlieb 2004a	158	198	3	51	1.9%	13.57 [4.52 , 40.75]
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**	**8.1%**	**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)		**8110**		**3968**	**100.0%**	**9.21 [7.78 , 10.91]**
Total events:	4886		230			
Heterogeneity: Tau² = 0.08; Chi² = 52.87, df = 35 (P = 0.03); I² = 34%						
Test for overall effect: Z = 25.70 (P < 0.00001)						
Test for subgroup differences: Chi² = 3.92, df = 3 (P = 0.27), I² = 23.4%						



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						
AMAGINE-2 2015	210	300	25	309	15.5%	8.65 [5.90 , 12.69]
AMAGINE-3 2015	217	313	19	315	13.8%	11.49 [7.39 , 17.88]
BE VIVID 2021	119	163	6	83	7.3%	10.10 [4.65 , 21.95]
Igarashi 2012	80	126	2	32	3.0%	10.16 [2.64 , 39.12]
Krueger 2007	166	256	1	64	1.6%	41.50 [5.92 , 290.72]
LOTUS 2013	132	160	18	162	13.8%	7.42 [4.78 , 11.54]
PEARL 2011	41	61	3	60	4.2%	13.44 [4.40 , 41.07]
PHOENIX-1 2008	341	511	8	255	8.6%	21.27 [10.73 , 42.19]
PHOENIX-2 2008	584	820	15	410	12.4%	19.47 [11.82 , 32.05]
UltIMMa-1 2018	76	100	9	102	9.5%	8.61 [4.57 , 16.23]
UltIMMa-2 2018	69	99	6	98	7.2%	11.38 [5.19 , 24.98]
VIP-U Trial 2020	17	22	2	21	3.1%	8.11 [2.13 , 30.91]
Subtotal (95% CI)		**2931**		**1911**	**100.0%**	**11.36 [8.84 , 14.61]**
Total events:	2052		114			
Heterogeneity: Tau² = 0.07; Chi² = 18.03, df = 11 (P = 0.08); I² = 39%						
Test for overall effect: Z = 18.96 (P < 0.00001)						
Total (95% CI)		**2931**		**1911**	**100.0%**	**11.36 [8.84 , 14.61]**
Total events:	2052		114			
Heterogeneity: Tau² = 0.07; Chi² = 18.03, df = 11 (P = 0.08); I² = 39%						
Test for overall effect: Z = 18.96 (P < 0.00001)						
Test for subgroup differences: Not applicable						

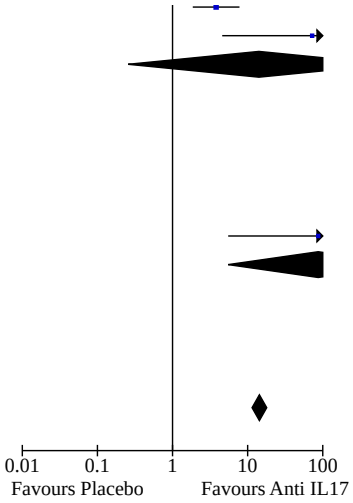


Analysis 3.5. Comparison 3: Secondary outcome - PASI 75, Outcome 5: Anti-IL17 versus placebo

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						
ALLURE 2021	122	143	1	71	1.2%	60.57 [8.64 , 424.60]
Cai 2020	366	408	6	135	4.5%	20.18 [9.23 , 44.16]
ERASURE 2014	374	490	11	248	6.0%	17.21 [9.64 , 30.73]
FEATURE 2015	86	118	0	59	0.6%	87.23 [5.51 , 1381.52]
FIXTURE 2014	468	654	16	327	6.8%	14.63 [9.05 , 23.64]
JUNCTURE 2015	95	121	2	61	2.1%	23.95 [6.11 , 93.88]
NCT03535194	401	448	9	112	5.6%	11.14 [5.95 , 20.86]
NCT03589885 MATURE	73	82	4	40	3.7%	8.90 [3.50 , 22.63]
Papp 2013a	40	103	2	22	2.2%	4.27 [1.11 , 16.37]
Papp 2021	48	53	0	52	0.6%	95.20 [6.02 , 1504.45]
Reich 2015	59	90	1	10	1.3%	6.56 [1.02 , 42.34]
Rich 2013	137	337	1	67	1.2%	27.24 [3.88 , 191.36]
TRANSFIGURE 2016	110	133	3	65	2.9%	17.92 [5.92 , 54.26]
VIP-S trial 2020	39	46	0	45	0.6%	77.32 [4.90 , 1221.04]
Subtotal (95% CI)		**3226**		**1314**	**39.2%**	**15.32 [11.36 , 20.66]**
Total events:	2418		56			
Heterogeneity: Tau² = 0.05; Chi² = 15.40, df = 13 (P = 0.28); I² = 16%						
Test for overall effect: Z = 17.88 (P < 0.00001)						
3.5.2 Ixekizumab versus placebo						
Leonardi 2012	78	115	2	27	2.2%	9.16 [2.40 , 34.95]
NCT03364309	317	350	7	88	5.0%	11.39 [5.59 , 23.19]
UNCOVER-1 2016	743	865	17	431	7.0%	21.78 [13.66 , 34.73]
UNCOVER-2 2015	584	698	4	168	3.5%	35.14 [13.34 , 92.59]
UNCOVER-3 2015	661	771	14	193	6.6%	11.82 [7.13 , 19.59]
Subtotal (95% CI)		**2799**		**907**	**24.2%**	**15.99 [10.44 , 24.47]**
Total events:	2383		44			
Heterogeneity: Tau² = 0.10; Chi² = 7.38, df = 4 (P = 0.12); I² = 46%						
Test for overall effect: Z = 12.76 (P < 0.00001)						
3.5.3 Brodalumab versus placebo						
AMAGINE-1 2016	317	441	6	220	4.4%	26.36 [11.95 , 58.15]
AMAGINE-2 2015	934	1222	25	309	7.8%	9.45 [6.48 , 13.77]
AMAGINE-3 2015	966	1253	19	315	7.2%	12.78 [8.26 , 19.78]
Nakagawa 2016	74	113	3	38	3.0%	8.29 [2.78 , 24.78]
Papp 2012a	104	160	0	38	0.6%	50.63 [3.22 , 796.97]
Seo 2020	37	40	0	22	0.6%	42.07 [2.71 , 653.61]
Subtotal (95% CI)		**3229**		**942**	**23.7%**	**13.09 [8.75 , 19.57]**
Total events:	2432		53			
Heterogeneity: Tau² = 0.08; Chi² = 8.00, df = 5 (P = 0.16); I² = 37%						
Test for overall effect: Z = 12.52 (P < 0.00001)						
3.5.4 Bimekizumab versus placebo						
BE ABLE 1 2018	169	208	2	42	2.1%	17.06 [4.41 , 66.09]
BE VIVID 2021	295	321	6	83	4.6%	12.71 [5.88 , 27.49]
Subtotal (95% CI)		**529**		**125**	**6.7%**	**13.66 [6.99 , 26.71]**
Total events:	464		8			
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%						
Test for overall effect: Z = 7.65 (P < 0.00001)						
3.5.5 Netakimab versus placebo						
NCT02762994	75	92	6	28	4.9%	3.80 [1.86 , 7.78]
PLANETA 2021	136	169	0	44	0.6%	72.26 [4.59 , 1138.77]
Subtotal (95% CI)		**261**		**72**	**5.6%**	**14.12 [0.26 , 778.45]**

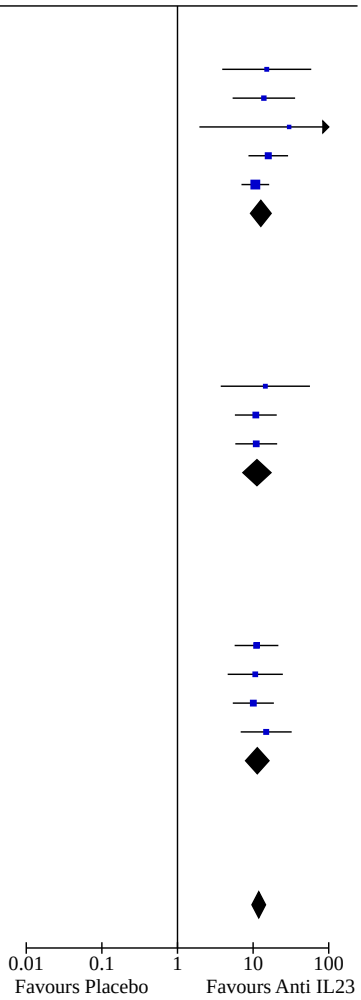
Analysis 3.5. (Continued)

PLANETA 2021	136	169	0	44	0.6%	72.26 [4.59 , 1138.77]
Subtotal (95% CI)		**261**		**72**	**5.6%**	**14.12 [0.26 , 778.45]**
Total events:	211		6			
Heterogeneity: Tau² = 7.41; Chi² = 8.02, df = 1 (P = 0.005); I² = 88%						
Test for overall effect: Z = 1.29 (P = 0.20)						
3.5.6 Sonelokimab versus placebo						
Papp 2021	171	208	0	52	0.6%	86.98 [5.51 , 1373.50]
Subtotal (95% CI)		**208**		**52**	**0.6%**	**86.98 [5.51 , 1373.50]**
Total events:	171		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.17 (P = 0.002)						
Total (95% CI)		**10252**		**3412**	**100.0%**	**14.33 [11.45 , 17.93]**
Total events:	8079		167			
Heterogeneity: Tau² = 0.13; Chi² = 51.02, df = 29 (P = 0.007); I² = 43%						
Test for overall effect: Z = 23.28 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.17, df = 5 (P = 0.82), I² = 0%						



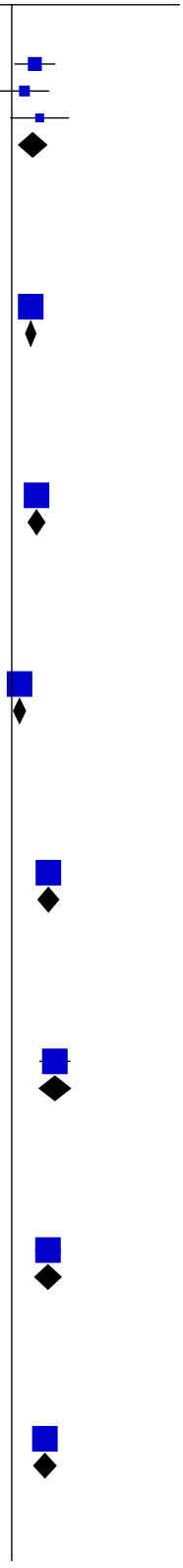
Analysis 3.6. Comparison 3: Secondary outcome - PASI 75, Outcome 6: Anti-IL23 versus placebo

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						
Gordon X-PLORE 2015	150	208	2	42	2.3%	15.14 [3.91 , 58.72]
Ohtsuki 2018	111	128	4	64	4.7%	13.88 [5.36 , 35.92]
ORION 2020	55	62	0	16	0.6%	29.95 [1.95 , 460.29]
VOYAGE-1 2016	300	329	10	174	11.7%	15.87 [8.68 , 28.99]
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]
ReSURFACE-1 2017	389	617	9	155	10.5%	10.86 [5.74 , 20.53]
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						
IMMhance 2020	361	407	8	100	9.6%	11.09 [5.70 , 21.57]
SustaIMM 2019	104	113	5	58	6.0%	10.68 [4.61 , 24.72]
UltIMMa-1 2018	270	304	9	102	10.9%	10.07 [5.39 , 18.81]
UltIMMa-2 2018	268	294	6	98	7.1%	14.89 [6.85 , 32.35]
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%						



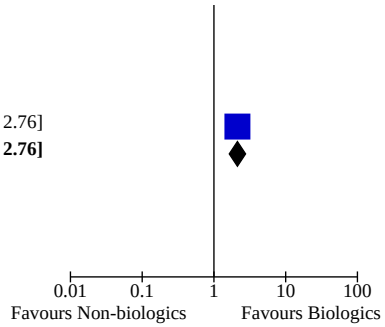
Analysis 3.7. Comparison 3: Secondary outcome - PASI 75, Outcome 7: Biologic versus non-biological treatments

Study or Subgroup	Biologic Events	Biologic Total	Non-biological treatment Events	Non-biological treatment 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 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						
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 Ixekizumab versus methotrexate						
Reich 2020	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)						
3.7.5 Secukinumab versus fumaric acid esters						
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)						
3.7.6 Ixekizumab versus fumaric ester acids						
Reich 2020	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)						
3.7.7 Guselkumab versus fumaric acid esters						
POLARIS 2020	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)						
3.7.8 Risankizumab versus fumaric acid esters						
Thaci 2021	59	60	20	60	100.0%	2.95 [2.06 , 4.23]
Subtotal (95% CI)		**60**		**60**	**100.0%**	**2.95 [2.06 , 4.23]**
Total events:	59		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.90 (P < 0.00001)						



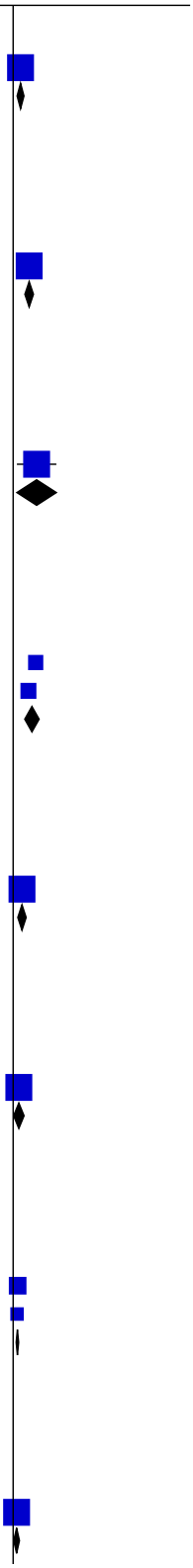
Analysis 3.7. (Continued)

Heterogeneity: Not applicable						
Test for overall effect: Z = 5.90 (P < 0.00001)						
3.7.9 Brodalumab versus fumaric acid esters						
CHANGE 2021	85	105	40	105	100.0%	2.13 [1.64 , 2.76]
Subtotal (95% CI)		**105**		**105**	**100.0%**	**2.13 [1.64 , 2.76]**
Total events:	85		40			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.66 (P < 0.00001)						



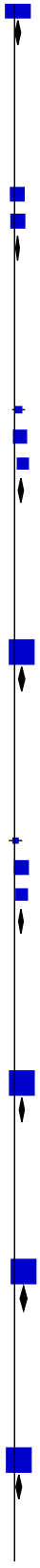
Analysis 3.8. Comparison 3: Secondary outcome - PASI 75, Outcome 8: Biologic 1 versus biologic 2

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						
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						
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 Infliximab versus etanercept						
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)						
3.8.4 Ixekizumab versus etanercept						
UNCOVER-2 2015	584	698	149	358	48.4%	2.01 [1.77 , 2.28]
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: $Tau^2 = 0.02$; $Chi^2 = 7.73$, df = 1 (P = 0.005); $I^2 = 87\%$						
Test for overall effect: Z = 5.12 (P < 0.00001)						
3.8.5 Tildrakizumab versus etanercept						
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)						
3.8.6 Certolizumab versus etanercept						
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)						
3.8.7 Secukinumab versus ustekinumab						
CLARITY 2018	504	550	440	552	59.2%	1.15 [1.09 , 1.21]
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: $Tau^2 = 0.00$; $Chi^2 = 0.21$, df = 1 (P = 0.65); $I^2 = 0\%$						
Test for overall effect: Z = 6.86 (P < 0.00001)						
3.8.8 Ixekizumab versus ustekinumab						
IXORA-S 2017	124	136	136	166	100.0%	1.11 [1.02 , 1.22]
Subtotal (95% CI)		**136**		**166**	**100.0%**	**1.11 [1.02 , 1.22]**
Total events:	124		136			



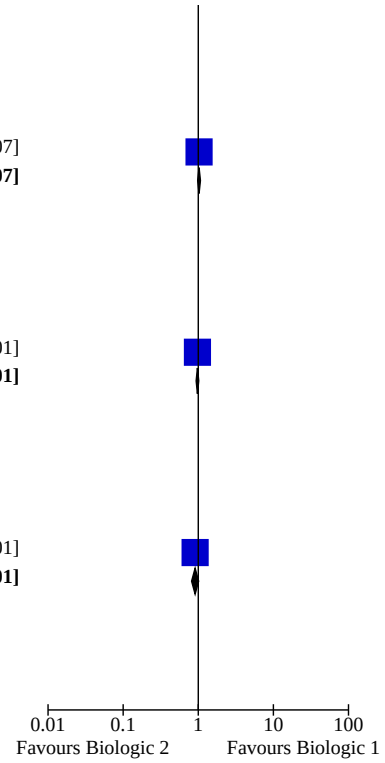
Analysis 3.8. (Continued)

Subtotal (95% CI)		**136**		**166**	**100.0%**	**1.11 [1.02 , 1.22]**
Total events:	124		136			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.37 (P = 0.02)						
3.8.9 Brodalumab versus ustekinumab						
AMAGINE-2 2015	934	1222	210	300	49.5%	1.09 [1.01 , 1.18]
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)						
3.8.10 Risankizumab versus ustekinumab						
Papp 2017b	104	126	29	40	15.8%	1.14 [0.93 , 1.40]
UltIMMa-1 2018	270	304	76	102	46.8%	1.19 [1.06 , 1.34]
UltIMMa-2 2018	268	294	69	99	37.4%	1.31 [1.14 , 1.50]
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)						
3.8.11 Bimekizumab versus ustekinumab						
BE VIVID 2021	295	321	119	163	100.0%	1.26 [1.14 , 1.39]
Subtotal (95% CI)		**321**		**163**	**100.0%**	**1.26 [1.14 , 1.39]**
Total events:	295		119			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.56 (P < 0.00001)						
3.8.12 Guselkumab versus adalimumab						
Gordon X-PLORE 2015	150	208	30	43	10.4%	1.03 [0.83 , 1.28]
VOYAGE-1 2016	300	329	244	334	50.3%	1.25 [1.16 , 1.34]
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)						
3.8.13 Risankizumab versus adalimumab						
IMMvent 2019	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)						
3.8.14 Bimekizumab versus adalimumab						
BE SURE 2021	295	319	110	159	100.0%	1.34 [1.20 , 1.49]
Subtotal (95% CI)		**319**		**159**	**100.0%**	**1.34 [1.20 , 1.49]**
Total events:	295		110			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.25 (P < 0.00001)						
3.8.15 Risankizumab versus secukinumab						
IMMerge 2021	150	164	130	163	100.0%	1.15 [1.05 , 1.26]
Subtotal (95% CI)		**164**		**163**	**100.0%**	**1.15 [1.05 , 1.26]**
Total events:	150		130			
Heterogeneity: Not applicable						



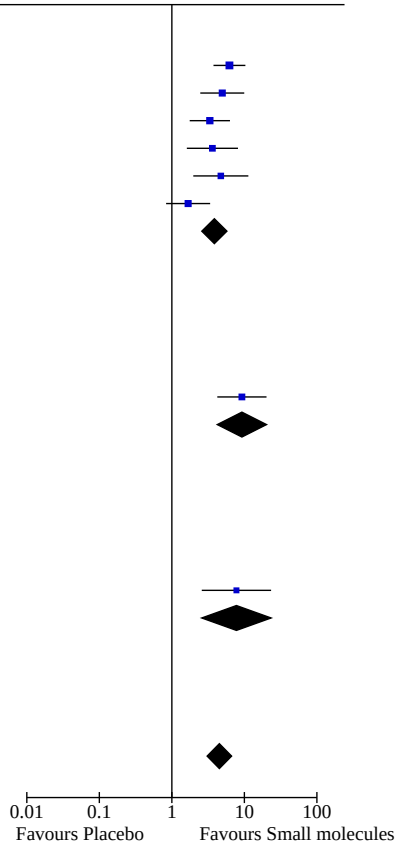
Analysis 3.8. (Continued)

Total events:	156		156			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.97 (P = 0.003)						
3.8.16 Bimekizumab versus secukinumab						
BE RADIANT 2021	348	373	337	370	100.0%	1.02 [0.98 , 1.07]
Subtotal (95% CI)		**373**		**370**	**100.0%**	**1.02 [0.98 , 1.07]**
Total events:	348		337			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.12 (P = 0.26)						
3.8.17 Guselkumab versus secukinumab						
ECLIPSE 2019	477	534	471	514	100.0%	0.97 [0.94 , 1.01]
Subtotal (95% CI)		**534**		**514**	**100.0%**	**0.97 [0.94 , 1.01]**
Total events:	477		471			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.27 (P = 0.20)						
3.8.18 Sonelokimab versus secukinumab						
Papp 2021	171	208	48	53	100.0%	0.91 [0.82 , 1.01]
Subtotal (95% CI)		**208**		**53**	**100.0%**	**0.91 [0.82 , 1.01]**
Total events:	171		48			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.77 (P = 0.08)						



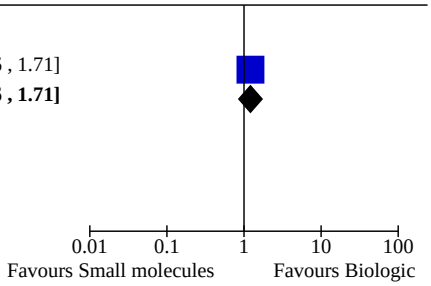
Analysis 3.9. Comparison 3: Secondary outcome - PASI 75, Outcome 9: Small molecules versus placebo

Study or Subgroup	Small molecules Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.9.1 Apremilast versus placebo						
ESTEEM-1 2015	186	562	15	282	16.7%	6.22 [3.75 , 10.32]
ESTEEM-2 2015	79	275	8	138	13.3%	4.96 [2.47 , 9.96]
LIBERATE 2017	33	83	10	84	14.3%	3.34 [1.76 , 6.33]
Ohtsuki 2017	44	170	6	84	11.6%	3.62 [1.61 , 8.16]
Papp 2012c	71	264	5	88	10.7%	4.73 [1.97 , 11.35]
Papp 2013b	30	173	9	87	13.3%	1.68 [0.83 , 3.37]
Subtotal (95% CI)		**1527**		**763**	**79.9%**	**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	12.0%	9.24 [4.23 , 20.19]
Subtotal (95% CI)		**662**		**108**	**12.0%**	**9.24 [4.23 , 20.19]**
Total events:	340		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.58 (P < 0.00001)						
3.9.3 TYK2 versus placebo						
Papp 2018	115	222	3	45	8.1%	7.77 [2.59 , 23.36]
Subtotal (95% CI)		**222**		**45**	**8.1%**	**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)		**2411**		**916**	**100.0%**	**4.52 [3.06 , 6.66]**
Total events:	898		62			
Heterogeneity: Tau² = 0.17; Chi² = 15.65, df = 7 (P = 0.03); I² = 55%						
Test for overall effect: Z = 7.61 (P < 0.00001)						
Test for subgroup differences: Chi² = 4.60, df = 2 (P = 0.10), I² = 56.5%						



Analysis 3.10. Comparison 3: Secondary outcome - PASI 75, Outcome 10: Biologic versus small molecules

Study or Subgroup	Biologic Events	Total	Small molecules Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.10.1 Etanercept versus apremilast						
LIBERATE 2017	40	83	33	83	100.0%	1.21 [0.86 , 1.71]
Subtotal (95% CI)		**83**		**83**	**100.0%**	**1.21 [0.86 , 1.71]**
Total events:	40		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.09 (P = 0.28)						



Comparison 4. Secondary outcome - PGA 0/1

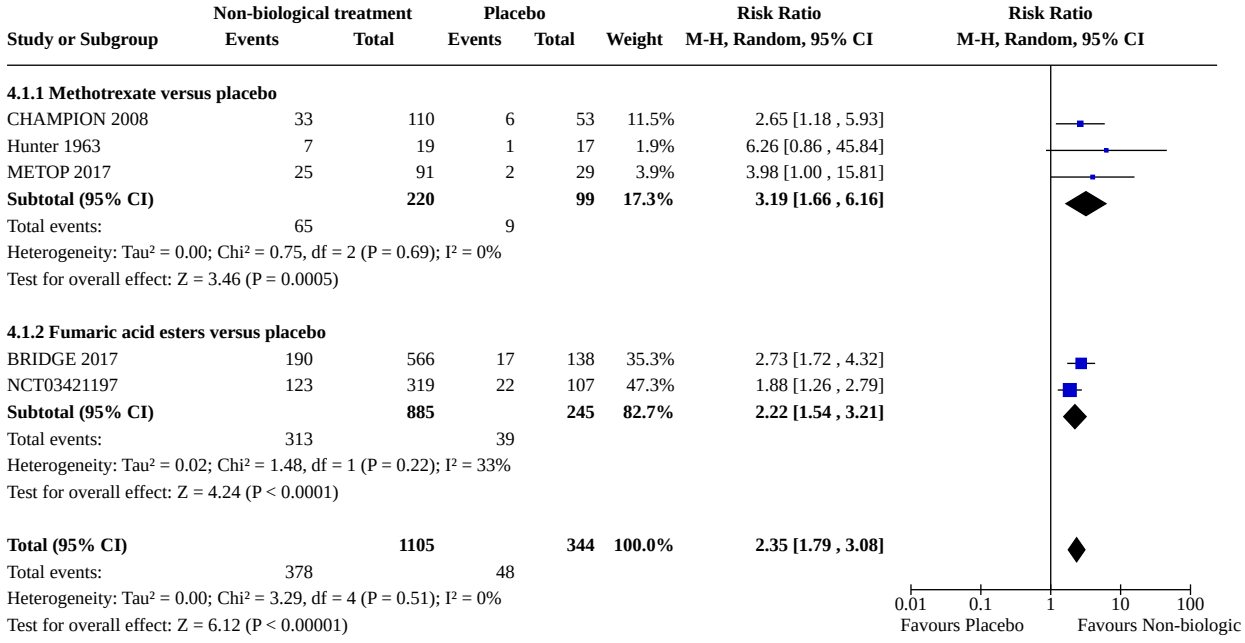
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Non-biological treatment versus placebo	5	1449	Risk Ratio (M-H, Random, 95% CI)	2.35 [1.79, 3.08]
4.1.1 Methotrexate versus placebo	3	319	Risk Ratio (M-H, Random, 95% CI)	3.19 [1.66, 6.16]
4.1.2 Fumaric acid esters versus placebo	2	1130	Risk Ratio (M-H, Random, 95% CI)	2.22 [1.54, 3.21]
4.2 Non-biological treatment 1 versus non-biological treatment 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	29	10194	Risk Ratio (M-H, Random, 95% CI)	8.89 [7.36, 10.74]
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	5	1266	Risk Ratio (M-H, Random, 95% CI)	27.86 [12.17, 63.79]
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	12	4842	Risk Ratio (M-H, Random, 95% CI)	10.70 [7.82, 14.66]
4.4.1 Ustekinumab versus placebo	12	4842	Risk Ratio (M-H, Random, 95% CI)	10.70 [7.82, 14.66]
4.5 Anti-IL17 versus placebo	28	13801	Risk Ratio (M-H, Random, 95% CI)	18.05 [13.08, 24.90]
4.5.1 Secukinumab versus placebo	12	4242	Risk Ratio (M-H, Random, 95% CI)	18.26 [11.34, 29.40]
4.5.2 Ixekizumab versus placebo	5	3706	Risk Ratio (M-H, Random, 95% CI)	18.29 [11.30, 29.61]
4.5.3 Brodalumab versus placebo	6	4171	Risk Ratio (M-H, Random, 95% CI)	19.02 [13.49, 26.81]
4.5.4 Bimekizumab versus placebo	3	1089	Risk Ratio (M-H, Random, 95% CI)	21.60 [9.32, 50.08]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.5.5 Netakimab versus placebo	2	333	Risk Ratio (M-H, Random, 95% CI)	9.20 [0.36, 232.36]
4.5.6 Sonelokimab versus placebo	1	260	Risk Ratio (M-H, Random, 95% CI)	78.87 [4.99, 1245.88]
4.6 Anti-IL23 versus placebo	13	5304	Risk Ratio (M-H, Random, 95% CI)	10.74 [8.81, 13.09]
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	5	1633	Risk Ratio (M-H, Random, 95% CI)	10.87 [7.75, 15.25]
4.7 Biologic versus non-biological treatments	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.7.1 Etanercept versus acitretin	2	82	Risk Ratio (M-H, Random, 95% CI)	4.98 [1.15, 21.49]
4.7.2 Infliximab versus methotrexate	1	868	Risk Ratio (M-H, Random, 95% CI)	1.99 [1.67, 2.37]
4.7.3 Adalimumab versus methotrexate	1	218	Risk Ratio (M-H, Random, 95% CI)	2.44 [1.79, 3.32]
4.7.4 Ixekizumab versus methotrexate	1	108	Risk Ratio (M-H, Random, 95% CI)	1.67 [1.24, 2.23]
4.7.5 Secukinumab versus fumaric acid esters	1	202	Risk Ratio (M-H, Random, 95% CI)	6.16 [3.59, 10.57]
4.7.6 Ixekizumab versus fumaric acid esters	1	108	Risk Ratio (M-H, Random, 95% CI)	6.43 [3.19, 12.96]
4.7.7 Risankizumab versus fumaric acid esters	1	120	Risk Ratio (M-H, Random, 95% CI)	2.43 [1.75, 3.38]
4.7.8 Brodalumab versus fumaric acid esters	1	210	Risk Ratio (M-H, Random, 95% CI)	3.24 [2.15, 4.87]
4.8 Biologic 1 versus biologic 2	26		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]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.8.3 Infliximab versus etanercept	1	48	Risk Ratio (M-H, Random, 95% CI)	2.50 [1.30, 4.81]
4.8.4 Ixekizumab versus etanercept	2	2209	Risk Ratio (M-H, Random, 95% CI)	2.01 [1.74, 2.31]
4.8.5 Tildrakizumab versus etanercept	1	934	Risk Ratio (M-H, Random, 95% CI)	1.20 [1.05, 1.37]
4.8.6 Secukinumab versus ustekinumab	2	1778	Risk Ratio (M-H, Random, 95% CI)	1.28 [1.19, 1.38]
4.8.7 Ixekizumab versus ustekinumab	1	302	Risk Ratio (M-H, Random, 95% CI)	1.23 [1.09, 1.39]
4.8.8 Brodalumab versus ustekinumab	2	3088	Risk Ratio (M-H, Random, 95% CI)	1.17 [1.07, 1.27]
4.8.9 Risankizumab versus ustekinumab	3	965	Risk Ratio (M-H, Random, 95% CI)	1.37 [1.23, 1.52]
4.8.10 Bimekizumab versus ustekinumab	1	484	Risk Ratio (M-H, Random, 95% CI)	1.58 [1.35, 1.83]
4.8.11 Guselkumab versus adalimumab	3	1658	Risk Ratio (M-H, Random, 95% CI)	1.26 [1.19, 1.34]
4.8.12 Risankizumab versus adalimumab	1	605	Risk Ratio (M-H, Random, 95% CI)	1.39 [1.25, 1.54]
4.8.13 Bimekizumab versus adalimumab	1	478	Risk Ratio (M-H, Random, 95% CI)	1.50 [1.30, 1.72]
4.8.14 Ixekizumab versus guselkumab	1	1027	Risk Ratio (M-H, Random, 95% CI)	1.33 [1.21, 1.46]
4.8.15 Risankizumab versus secukinumab	1	327	Risk Ratio (M-H, Random, 95% CI)	1.23 [1.10, 1.37]
4.8.16 Ixekizumab versus secukinumab	1	54	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.81, 1.27]
4.8.17 Bimekizumab versus secukinumab	1	743	Risk Ratio (M-H, Random, 95% CI)	1.09 [1.02, 1.16]
4.8.18 Guselkumab versus secukinumab	1	1048	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.95, 1.05]
4.8.19 Sonelokimab versus secukinumab	1	261	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.82, 1.14]
4.9 Small molecules versus placebo	7	2600	Risk Ratio (M-H, Random, 95% CI)	3.81 [2.58, 5.63]

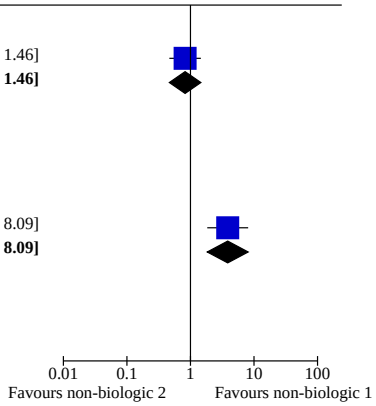
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.9.1 Apremilast versus placebo	6	2333	Risk Ratio (M-H, Random, 95% CI)	3.52 [2.40, 5.16]
4.9.2 TYK2 versus placebo	1	267	Risk Ratio (M-H, Random, 95% CI)	8.24 [2.74, 24.76]
4.10 Biologic versus small molecules	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.10.1 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: Non-biological treatment versus placebo



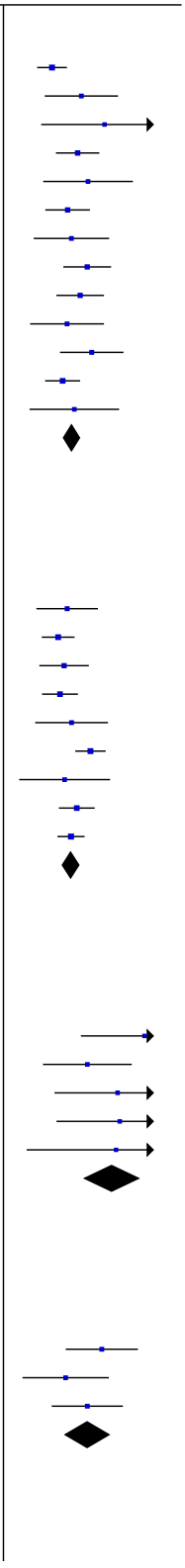
Analysis 4.2. Comparison 4: Secondary outcome - PGA 0/1, Outcome 2: Non-biological treatment 1 versus non-biological treatment 2

Study or Subgroup	Non-biological treatment 1 Events	Total	Non-biological treatment 2 Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 Ciclosporin versus methotrexate						
Heydendael 2003	14	44	17	44	100.0%	0.82 [0.47 , 1.46]
Subtotal (95% CI)		**44**		**44**	**100.0%**	**0.82 [0.47 , 1.46]**
Total events:	14		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
4.2.2 Methotrexate versus fumaric acid esters						
Reich 2020	27	54	7	54	100.0%	3.86 [1.84 , 8.09]
Subtotal (95% CI)		**54**		**54**	**100.0%**	**3.86 [1.84 , 8.09]**
Total events:	27		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.57 (P = 0.0004)						



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]
CIMPACT 2018	67	170	1	57	0.9%	22.46 [3.19 , 158.15]
FIXTURE 2014	88	326	9	327	4.8%	9.81 [5.03 , 19.14]
Gottlieb 2011	56	141	2	68	1.6%	13.50 [3.40 , 53.70]
Leonardi 2003	173	504	8	168	4.7%	7.21 [3.63 , 14.33]
LIBERATE 2017	24	83	3	84	2.2%	8.10 [2.53 , 25.86]
Papp 2005	184	407	7	204	4.3%	13.18 [6.31 , 27.50]
ReSURFACE-2 2017	149	313	7	156	4.3%	10.61 [5.10 , 22.09]
Strober 2011	41	139	3	72	2.2%	7.08 [2.27 , 22.07]
UNCOVER-2 2015	129	358	4	168	2.9%	15.13 [5.69 , 40.24]
UNCOVER-3 2015	159	382	13	193	6.1%	6.18 [3.61 , 10.59]
Van de Kerkhof 2008	37	96	2	46	1.6%	8.86 [2.23 , 35.19]
Subtotal (95% CI)		**3317**		**1713**	**44.9%**	**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]
Cai 2016	272	338	13	87	6.5%	5.39 [3.25 , 8.92]
CHAMPION 2008	79	108	6	53	4.1%	6.46 [3.02 , 13.85]
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]
REVEAL 2008	506	814	17	398	7.0%	14.55 [9.11 , 23.24]
VIP Trial 2018	14	33	2	31	1.6%	6.58 [1.62 , 26.62]
VOYAGE-1 2016	220	334	12	174	6.0%	9.55 [5.50 , 16.58]
VOYAGE-2 2017	168	248	21	248	7.6%	8.00 [5.27 , 12.15]
Subtotal (95% CI)		**2150**		**1187**	**44.0%**	**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						
CIMPACT 2018	150	332	1	170	0.9%	76.81 [10.84 , 544.07]
CIMPASI-1 2018	95	183	2	51	1.7%	13.24 [3.38 , 51.87]
CIMPASI-2 2018	122	178	1	49	0.9%	33.58 [4.81 , 234.27]
Reich 2012a	73	118	1	58	0.9%	35.88 [5.11 , 251.73]
Umezawa 2021	60	101	0	26	0.5%	32.03 [2.05 , 501.39]
Subtotal (95% CI)		**912**		**354**	**4.7%**	**27.86 [12.17 , 63.79]**
Total events:	500		5			
Heterogeneity: Tau² = 0.00; Chi² = 2.44, df = 4 (P = 0.65); I² = 0%						
Test for overall effect: Z = 7.87 (P < 0.00001)						
4.3.4 Infliximab versus placebo						
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)						

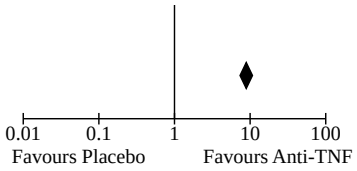


Analysis 4.3. (Continued)

Test for overall effect: Z = 7.50 (P < 0.00001)

Total (95% CI)	**6799**	**3395**	**100.0%**	**8.89 [7.36 , 10.74]**	
Total events:	3632	181			

Heterogeneity: Tau² = 0.08; Chi² = 42.64, df = 29 (P = 0.05); I² = 32%
Test for overall effect: Z = 22.68 (P < 0.00001)
Test for subgroup differences: Chi² = 9.89, df = 3 (P = 0.02), I² = 69.7%



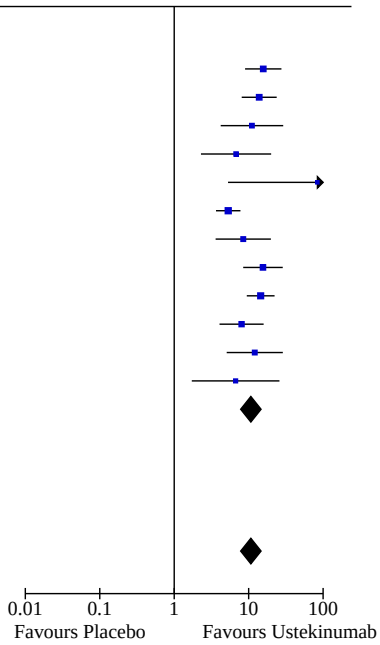
Analysis 4.4. Comparison 4: Secondary outcome - PGA 0/1, Outcome 4: Anti-IL12/23 versus placebo

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						
AMAGINE-2 2015	183	300	12	309	10.9%	15.71 [8.95 , 27.55]
AMAGINE-3 2015	179	313	13	315	11.2%	13.86 [8.07 , 23.80]
BE VIVID 2021	87	163	4	83	6.5%	11.08 [4.21 , 29.12]
Igarashi 2012	80	126	3	32	5.6%	6.77 [2.29 , 20.05]
Krueger 2007	165	256	0	64	1.2%	83.72 [5.28 , 1326.17]
LOTUS 2013	126	160	24	162	13.4%	5.32 [3.64 , 7.76]
PEARL 2011	43	61	5	60	7.5%	8.46 [3.60 , 19.89]
PHOENIX-1 2008	312	511	10	255	10.2%	15.57 [8.45 , 28.70]
PHOENIX-2 2008	580	820	20	410	12.7%	14.50 [9.44 , 22.28]
UltIMMa-1 2018	63	100	8	102	9.4%	8.03 [4.06 , 15.89]
UltIMMa-2 2018	61	99	5	98	7.4%	12.08 [5.07 , 28.77]
VIP-U Trial 2020	14	22	2	21	4.1%	6.68 [1.72 , 25.92]
Subtotal (95% CI)	**2931**		**1911**		**100.0%**	**10.70 [7.82 , 14.66]**
Total events:	1893		106			

Heterogeneity: Tau² = 0.15; Chi² = 25.88, df = 11 (P = 0.007); I² = 57%
Test for overall effect: Z = 14.77 (P < 0.00001)

Total (95% CI)	**2931**		**1911**		**100.0%**	**10.70 [7.82 , 14.66]**
Total events:	1893		106			

Heterogeneity: Tau² = 0.15; Chi² = 25.88, df = 11 (P = 0.007); I² = 57%
Test for overall effect: Z = 14.77 (P < 0.00001)
Test for subgroup differences: Not applicable

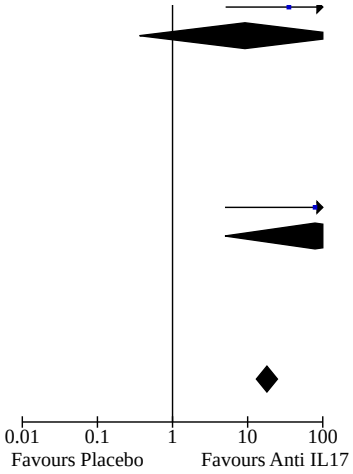


Analysis 4.5. Comparison 4: Secondary outcome - PGA 0/1, Outcome 5: Anti-IL17 versus placebo

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						
ALLURE 2021	104	143	1	71	2.0%	51.64 [7.36 , 362.46]
Cai 2020	306	408	4	135	4.4%	25.31 [9.62 , 66.57]
ERASURE 2014	285	490	6	248	5.0%	24.04 [10.87 , 53.18]
FEATURE 2015	72	118	0	59	1.1%	73.11 [4.61 , 1159.72]
FIXTURE 2014	369	654	9	327	5.6%	20.50 [10.73 , 39.18]
JUNCTURE 2015	76	121	0	61	1.1%	77.75 [4.90 , 1233.42]
NCT03535194	342	448	7	112	5.3%	12.21 [5.95 , 25.07]
NCT03589885 MATURE	59	82	3	40	3.9%	9.59 [3.20 , 28.72]
Papp 2013a	23	103	2	22	3.1%	2.46 [0.62 , 9.66]
Papp 2021	41	53	0	52	1.1%	81.46 [5.14 , 1290.43]
Rich 2013	83	337	1	67	2.0%	16.50 [2.34 , 116.48]
VIP-S trial 2020	36	46	0	45	1.1%	71.45 [4.52 , 1129.94]
Subtotal (95% CI)		**3003**		**1239**	**35.8%**	**18.26 [11.34 , 29.40]**
Total events:	1796		33			
Heterogeneity: Tau² = 0.23; Chi² = 18.04, df = 11 (P = 0.08); I² = 39%						
Test for overall effect: Z = 11.95 (P < 0.00001)						
4.5.2 Ixekizumab versus placebo						
Leonardi 2012	69	115	2	27	3.2%	8.10 [2.12 , 30.99]
NCT03364309	291	350	3	88	3.9%	24.39 [8.01 , 74.24]
UNCOVER-1 2016	684	865	14	431	6.1%	24.34 [14.53 , 40.80]
UNCOVER-2 2015	545	698	4	168	4.4%	32.79 [12.44 , 86.43]
UNCOVER-3 2015	601	771	13	193	6.0%	11.57 [6.84 , 19.59]
Subtotal (95% CI)		**2799**		**907**	**23.6%**	**18.29 [11.30 , 29.61]**
Total events:	2190		36			
Heterogeneity: Tau² = 0.13; Chi² = 7.38, df = 4 (P = 0.12); I² = 46%						
Test for overall effect: Z = 11.83 (P < 0.00001)						
4.5.3 Brodalumab versus placebo						
AMAGINE-1 2016	286	441	3	220	3.8%	47.56 [15.43 , 146.63]
AMAGINE-2 2015	835	1222	12	309	5.9%	17.60 [10.09 , 30.68]
AMAGINE-3 2015	874	1253	13	315	6.0%	16.90 [9.91 , 28.82]
Nakagawa 2016	74	113	2	38	3.2%	12.44 [3.21 , 48.26]
Papp 2012a	104	160	1	38	2.0%	24.70 [3.56 , 171.42]
Seo 2020	37	40	0	22	1.2%	42.07 [2.71 , 653.61]
Subtotal (95% CI)		**3229**		**942**	**22.1%**	**19.02 [13.49 , 26.81]**
Total events:	2210		31			
Heterogeneity: Tau² = 0.00; Chi² = 3.66, df = 5 (P = 0.60); I² = 0%						
Test for overall effect: Z = 16.81 (P < 0.00001)						
4.5.4 Bimekizumab versus placebo						
BE ABLE 1 2018	152	208	2	42	3.2%	15.35 [3.96 , 59.49]
BE READY 2021	323	349	1	86	2.0%	79.59 [11.34 , 558.74]
BE VIVID 2021	270	321	4	83	4.4%	17.45 [6.70 , 45.46]
Subtotal (95% CI)		**878**		**211**	**9.5%**	**21.60 [9.32 , 50.08]**
Total events:	745		7			
Heterogeneity: Tau² = 0.11; Chi² = 2.47, df = 2 (P = 0.29); I² = 19%						
Test for overall effect: Z = 7.16 (P < 0.00001)						
4.5.5 Netakimab versus placebo						
NCT02762994	77	92	8	28	5.8%	2.93 [1.62 , 5.30]
PLANETA 2021	136	169	1	44	2.0%	35.41 [5.09 , 246.15]
Subtotal (95% CI)		**261**		**72**	**7.8%**	**9.20 [0.36 , 232.36]**
Total events:	213		9			

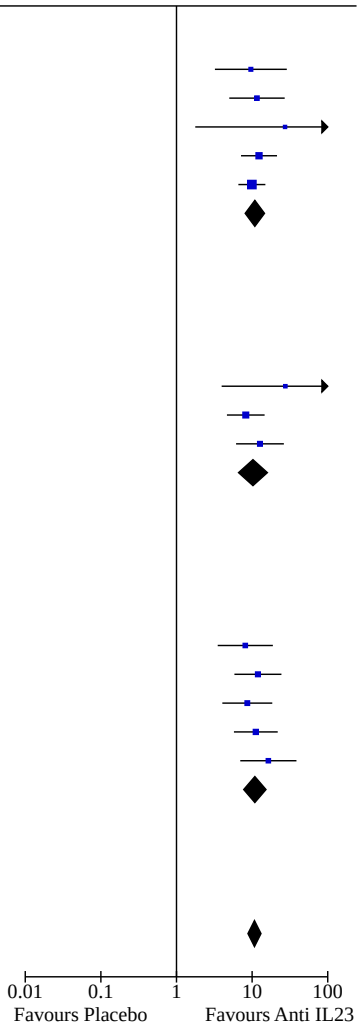
Analysis 4.5. (Continued)

Subtotal (95% CI)		**261**		**72**	**7.8%**	**9.20 [0.36 , 232.36]**
Total events:	213		9			
Heterogeneity: Tau² = 4.93; Chi² = 10.21, df = 1 (P = 0.001); I² = 90%						
Test for overall effect: Z = 1.35 (P = 0.18)						
4.5.6 Sonelokimab versus placebo						
Papp 2021	155	208	0	52	1.1%	78.87 [4.99 , 1245.88]
Subtotal (95% CI)		**208**		**52**	**1.1%**	**78.87 [4.99 , 1245.88]**
Total events:	155		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.10 (P = 0.002)						
Total (95% CI)		**10378**		**3423**	**100.0%**	**18.05 [13.08 , 24.90]**
Total events:	7309		116			
Heterogeneity: Tau² = 0.37; Chi² = 71.67, df = 28 (P < 0.0001); I² = 61%						
Test for overall effect: Z = 17.62 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.36, df = 5 (P = 0.93), I² = 0%						



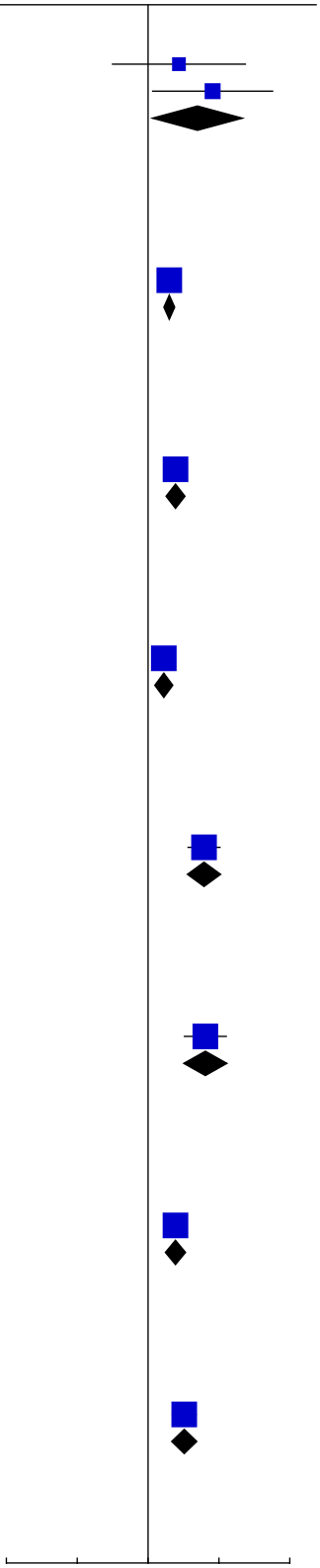
Analysis 4.6. Comparison 4: Secondary outcome - PGA 0/1, Outcome 6: Anti-IL23 versus placebo

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						
Gordon X-PLORE 2015	143	208	3	42	3.3%	9.63 [3.22 , 28.75]
Ohtsuki 2018	116	128	5	64	5.5%	11.60 [4.99 , 26.96]
ORION 2020	50	62	0	16	0.5%	27.25 [1.77 , 419.35]
VOYAGE-1 2016	280	329	12	174	13.0%	12.34 [7.14 , 21.34]
VOYAGE-2 2017	417	496	21	248	23.2%	9.93 [6.58 , 14.98]
Subtotal (95% CI)		**1223**		**544**	**45.5%**	**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	1.0%	27.54 [3.95 , 191.78]
ReSURFACE-1 2017	361	617	11	155	11.9%	8.24 [4.65 , 14.63]
ReSURFACE-2 2017	354	621	7	156	7.4%	12.70 [6.14 , 26.29]
Subtotal (95% CI)		**1547**		**357**	**20.3%**	**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						
Blauvelt 2021a	82	105	5	52	5.6%	8.12 [3.51 , 18.80]
IMMhance 2020	340	407	7	100	7.6%	11.93 [5.83 , 24.41]
SustaIMM 2019	101	113	6	58	6.8%	8.64 [4.04 , 18.48]
UltIMMa-1 2018	267	304	8	102	8.8%	11.20 [5.75 , 21.81]
UltIMMa-2 2018	246	294	5	98	5.4%	16.40 [6.97 , 38.58]
Subtotal (95% CI)		**1223**		**410**	**34.1%**	**10.87 [7.75 , 15.25]**
Total events:	1036		31			
Heterogeneity: Tau² = 0.00; Chi² = 1.83, df = 4 (P = 0.77); I² = 0%						
Test for overall effect: Z = 13.81 (P < 0.00001)						
Total (95% CI)		**3993**		**1311**	**100.0%**	**10.74 [8.81 , 13.09]**
Total events:	2942		91			
Heterogeneity: Tau² = 0.00; Chi² = 4.73, df = 12 (P = 0.97); I² = 0%						
Test for overall effect: Z = 23.52 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.05, df = 2 (P = 0.97), I² = 0%						



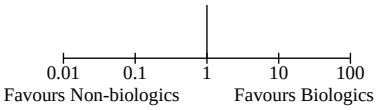
Analysis 4.7. Comparison 4: Secondary outcome - PGA 0/1, Outcome 7: Biologic versus non-biological treatments

Study or Subgroup	Biologic Events	Biologic Total	Non-biological treatment Events	Non-biological treatment Total	Weight	Risk Ratio M-H, Random, 95% CI
4.7.1 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: Tau² = 0.00; Chi² = 0.55, df = 1 (P = 0.46); I² = 0%						
Test for overall effect: Z = 2.15 (P = 0.03)						
4.7.2 Infliximab versus methotrexate						
Barker 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)						
4.7.3 Adalimumab versus methotrexate						
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)						
4.7.4 Ixekizumab versus methotrexate						
Reich 2020	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)						
4.7.5 Secukinumab versus fumaric acid esters						
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)						
4.7.6 Ixekizumab versus fumaric acid esters						
Reich 2020	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)						
4.7.7 Risankizumab versus fumaric acid esters						
Thaci 2021	56	60	23	60	100.0%	2.43 [1.75 , 3.38]
Subtotal (95% CI)		**60**		**60**	**100.0%**	**2.43 [1.75 , 3.38]**
Total events:	56		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.32 (P < 0.00001)						
4.7.8 Brodalumab versus fumaric acid esters						
CHANGE 2021	68	105	21	105	100.0%	3.24 [2.15 , 4.87]
Subtotal (95% CI)		**105**		**105**	**100.0%**	**3.24 [2.15 , 4.87]**
Total events:	68		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.65 (P < 0.00001)						



Analysis 4.7. (Continued)

Test for overall effect: Z = 5.65 (P < 0.00001)

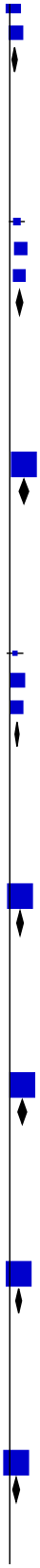


Analysis 4.8. Comparison 4: Secondary outcome - PGA 0/1, Outcome 8: Biologic 1 versus biologic 2

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						
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						
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 Infliximab versus etanercept						
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)						
4.8.4 Ixekizumab versus etanercept						
UNCOVER-2 2015	545	698	129	358	46.9%	2.17 [1.88 , 2.50]
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)						
4.8.5 Tildrakizumab versus etanercept						
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)						
4.8.6 Secukinumab versus ustekinumab						
CLARITY 2018	432	550	326	552	53.1%	1.33 [1.23 , 1.44]
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)						
4.8.7 Ixekizumab versus ustekinumab						
IXORA-S 2017	116	136	115	166	100.0%	1.23 [1.09 , 1.39]
Subtotal (95% CI)		**136**		**166**	**100.0%**	**1.23 [1.09 , 1.39]**
Total events:	116		115			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.31 (P = 0.0009)						
4.8.8 Brodalumab versus ustekinumab						
AMAGINE-2 2015	835	1222	183	300	51.6%	1.12 [1.02 , 1.24]
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]**

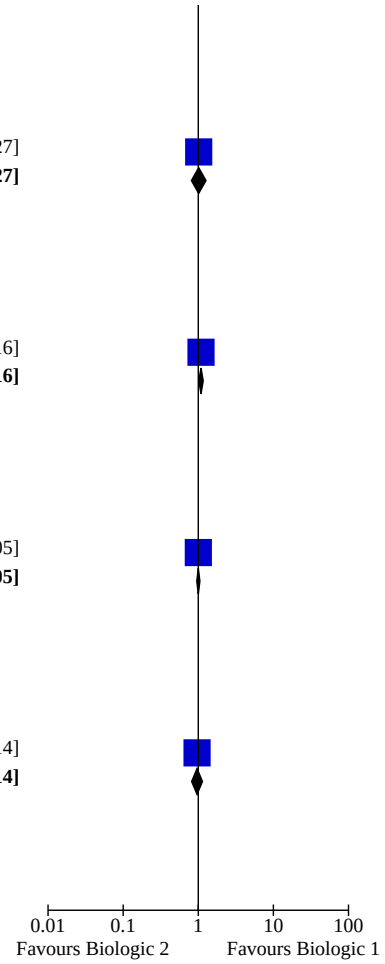
Analysis 4.8. (Continued)

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: Tau² = 0.00; Chi² = 1.38, df = 1 (P = 0.24); I² = 28%						
Test for overall effect: Z = 3.63 (P = 0.0003)						
4.8.9 Risankizumab versus ustekinumab						
Papp 2017b	99	126	25	40	16.4%	1.26 [0.97 , 1.63]
UltIMMa-1 2018	267	304	63	102	43.1%	1.42 [1.21 , 1.67]
UltIMMa-2 2018	246	294	61	99	40.5%	1.36 [1.15 , 1.60]
Subtotal (95% CI)		**724**		**241**	**100.0%**	**1.37 [1.23 , 1.52]**
Total events:	612		149			
Heterogeneity: Tau² = 0.00; Chi² = 0.65, df = 2 (P = 0.72); I² = 0%						
Test for overall effect: Z = 5.90 (P < 0.00001)						
4.8.10 Bimekizumab versus ustekinumab						
BE VIVID 2021	270	321	87	163	100.0%	1.58 [1.35 , 1.83]
Subtotal (95% CI)		**321**		**163**	**100.0%**	**1.58 [1.35 , 1.83]**
Total events:	270		87			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.90 (P < 0.00001)						
4.8.11 Guselkumab versus adalimumab						
Gordon X-PLORE 2015	143	208	25	43	5.5%	1.18 [0.90 , 1.55]
VOYAGE-1 2016	280	329	220	334	49.6%	1.29 [1.18 , 1.41]
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: Tau² = 0.00; Chi² = 0.62, df = 2 (P = 0.73); I² = 0%						
Test for overall effect: Z = 7.26 (P < 0.00001)						
4.8.12 Risankizumab versus adalimumab						
IMMvent 2019	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)						
4.8.13 Bimekizumab versus adalimumab						
BE SURE 2021	276	319	92	159	100.0%	1.50 [1.30 , 1.72]
Subtotal (95% CI)		**319**		**159**	**100.0%**	**1.50 [1.30 , 1.72]**
Total events:	276		92			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.65 (P < 0.00001)						
4.8.14 Ixekizumab versus guselkumab						
IXORA-R 2020	389	520	285	507	100.0%	1.33 [1.21 , 1.46]
Subtotal (95% CI)		**520**		**507**	**100.0%**	**1.33 [1.21 , 1.46]**
Total events:	389		285			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.11 (P < 0.00001)						
4.8.15 Risankizumab versus secukinumab						
IMMerge 2021	147	164	119	163	100.0%	1.23 [1.10 , 1.37]
Subtotal (95% CI)		**164**		**163**	**100.0%**	**1.23 [1.10 , 1.37]**
Total events:	147		119			
Heterogeneity: Not applicable						

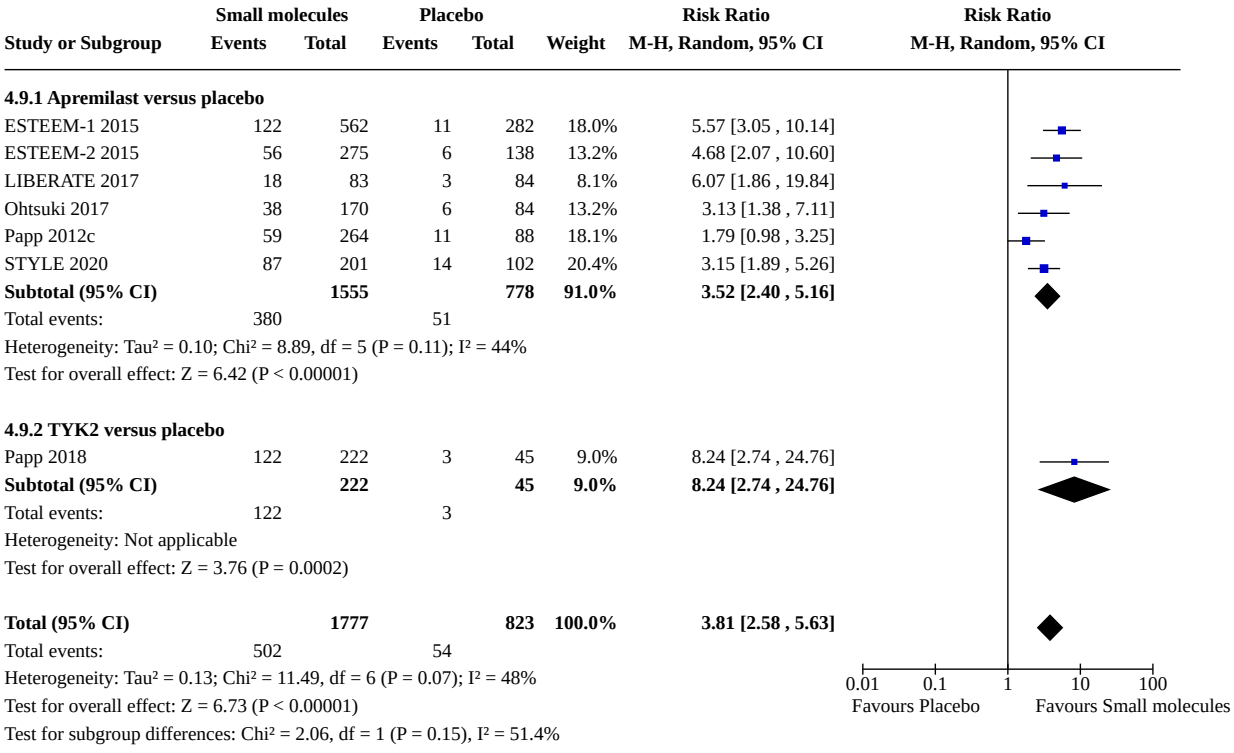


Analysis 4.8. (Continued)

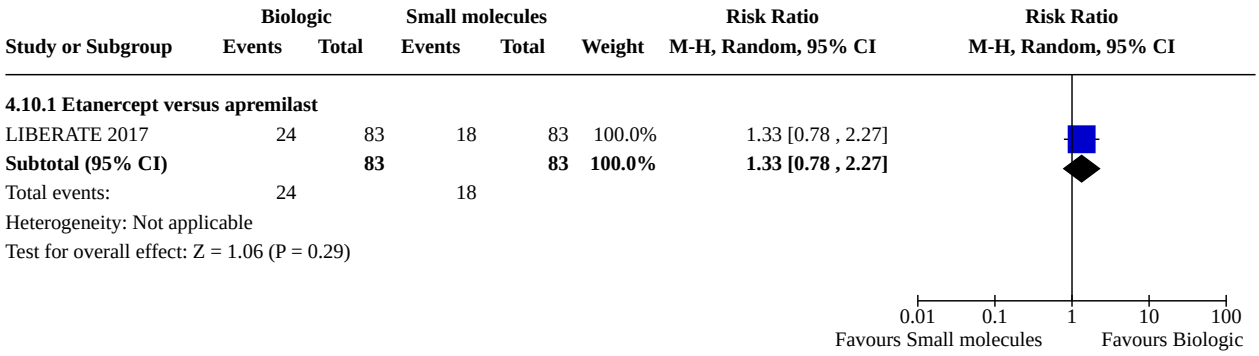
Total events:	147		115			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.76 (P = 0.0002)						
4.8.16 Ixekizumab versus secukinumab						
AlMutairi 2021	24	28	22	26	100.0%	1.01 [0.81 , 1.27]
Subtotal (95% CI)		**28**		**26**	**100.0%**	**1.01 [0.81 , 1.27]**
Total events:	24		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.11 (P = 0.91)						
4.8.17 Bimekizumab versus secukinumab						
BE RADIANT 2021	319	373	291	370	100.0%	1.09 [1.02 , 1.16]
Subtotal (95% CI)		**373**		**370**	**100.0%**	**1.09 [1.02 , 1.16]**
Total events:	319		291			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.43 (P = 0.02)						
4.8.18 Guselkumab versus secukinumab						
ECLIPSE 2019	463	534	445	514	100.0%	1.00 [0.95 , 1.05]
Subtotal (95% CI)		**534**		**514**	**100.0%**	**1.00 [0.95 , 1.05]**
Total events:	463		445			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.06 (P = 0.95)						
4.8.19 Sonelokimab versus secukinumab						
Papp 2021	155	208	41	53	100.0%	0.96 [0.82 , 1.14]
Subtotal (95% CI)		**208**		**53**	**100.0%**	**0.96 [0.82 , 1.14]**
Total events:	155		41			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.44 (P = 0.66)						



Analysis 4.9. Comparison 4: Secondary outcome - PGA 0/1, Outcome 9: Small molecules versus placebo



Analysis 4.10. Comparison 4: Secondary outcome - PGA 0/1, Outcome 10: Biologic versus small molecules



Comparison 5. Secondary outcome - quality of life

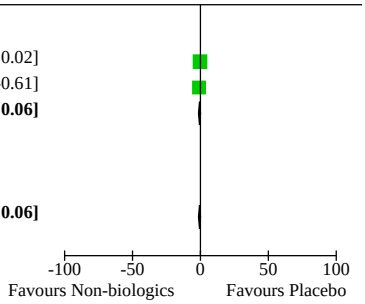
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Non-biological treatments versus placebo	2	283	Std. Mean Difference (IV, Random, 95% CI)	-0.67 [-1.40, 0.06]
5.1.1 Methotrexate versus placebo	2	283	Std. Mean Difference (IV, Random, 95% CI)	-0.67 [-1.40, 0.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2 Non-biological treatment 1 versus non-biological treatment 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	25	8534	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	3	588	Std. Mean Difference (IV, Random, 95% CI)	-0.92 [-1.13, -0.72]
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	9	3359	Std. Mean Difference (IV, Random, 95% CI)	-1.35 [-1.54, -1.16]
5.5 Anti-IL17 versus placebo	9	4246	Std. Mean Difference (IV, Random, 95% CI)	-1.47 [-1.76, -1.18]
5.5.1 Ixekizumab versus placebo	4	3564	Std. Mean Difference (IV, Random, 95% CI)	-1.85 [-2.14, -1.55]
5.5.2 Brodalumab versus placebo	2	349	Std. Mean Difference (IV, Random, 95% CI)	-0.96 [-1.44, -0.47]
5.5.3 Secukinumab versus placebo	2	213	Std. Mean Difference (IV, Random, 95% CI)	-1.40 [-1.71, -1.09]
5.5.4 Netakimab versus placebo	1	120	Std. Mean Difference (IV, Random, 95% CI)	-0.83 [-1.26, -0.39]
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 non-biological treatment	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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]
5.7.5 Risankizumab versus fumaric acid esters	1	120	Mean Difference (IV, Fixed, 95% CI)	-7.60 [-9.97, -5.23]
5.7.6 Brodalumab versus fumaric acid esters	1	210	Mean Difference (IV, Fixed, 95% CI)	-2.57 [-4.27, -0.87]
5.8 Biologic 1 versus biologic 2	9		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 Tildrakizumab versus etanercept	1	932	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-2.20, -0.60]
5.8.3 Infliximab versus etanercept	1	48	Mean Difference (IV, Fixed, 95% CI)	-1.60 [-2.93, -0.27]
5.8.4 Guselkumab versus adalimumab	2	1407	Mean Difference (IV, Fixed, 95% CI)	-1.73 [-2.50, -0.97]
5.8.5 Bimekizumab versus adalimumab	1	478	Mean Difference (IV, Fixed, 95% CI)	-1.95 [-3.15, -0.75]
5.8.6 Risankizumab versus ustekinumab	2	799	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-1.50, -0.50]
5.9 Small molecules versus placebo	5	2166	Std. Mean Difference (IV, Random, 95% CI)	-0.59 [-0.70, -0.47]
5.9.1 Apremilast versus placebo	5	2166	Std. Mean Difference (IV, Random, 95% CI)	-0.59 [-0.70, -0.47]

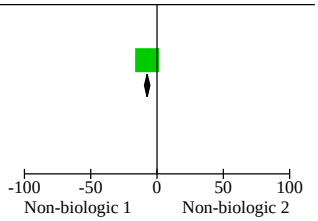
Analysis 5.1. Comparison 5: Secondary outcome - quality of life, Outcome 1: Non-biological treatments versus placebo

Study or Subgroup	Non-biological treatment Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
5.1.1 Methotrexate versus placebo								
CHAMPION 2008	-5.7	6.1	110	-3.4	9.63	53	52.0%	-0.31 [-0.64 , 0.02]
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								



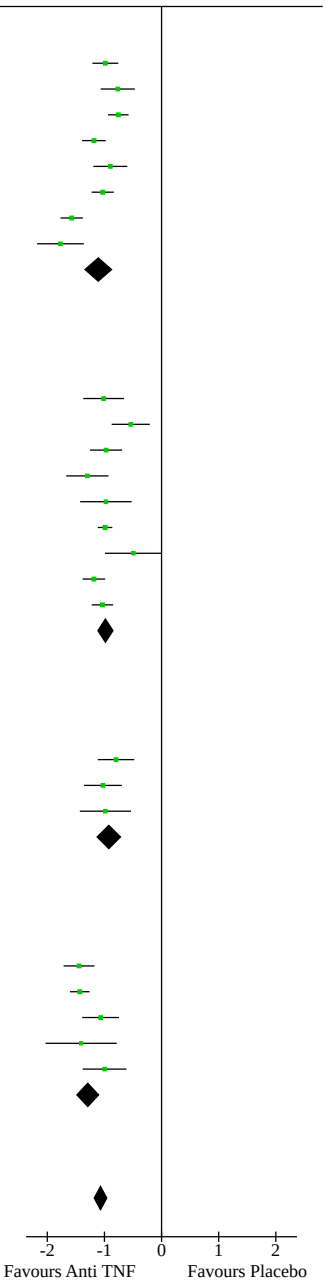
Analysis 5.2. Comparison 5: Secondary outcome - quality of life, Outcome 2: Non-biological treatment 1 versus non-biological treatment 2

Study or Subgroup	Non-biological treatment 1 Mean	SD	Total	Non-biological treatment 2 Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
5.2.1 Methotrexate versus fumaric acid esters								
Reich 2020	-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

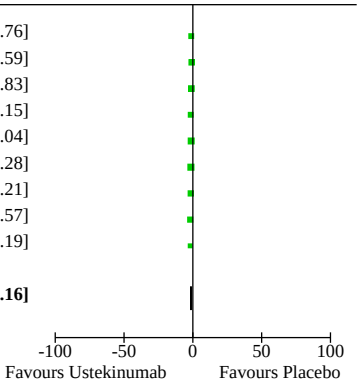
Study or Subgroup	anti TNF Mean	anti TNF SD	anti TNF Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
5.3.1 Etanercept versus placebo								
Bachelez 2015	-8.97	7.33	336	-1.85	6.86	108	4.6%	-0.98 [-1.21 , -0.76]
Gottlieb 2011	-8.01	6.18	141	-3.3	6	68	4.0%	-0.77 [-1.07 , -0.47]
Leonardi 2003	-6.37	6.02	504	-1.4	7.96	168	5.0%	-0.76 [-0.94 , -0.58]
ReSURFACE-2 2017	-8.9	5.86	311	-2	5.74	156	4.8%	-1.18 [-1.39 , -0.98]
Strober 2011	-9.09	7.43	139	-2.89	5.69	72	4.0%	-0.90 [-1.19 , -0.60]
UNCOVER-2 2015	-7.7	5.68	358	-2	5.18	168	4.9%	-1.03 [-1.22 , -0.84]
UNCOVER-3 2015	-8	3.91	382	-1.7	4.17	193	4.9%	-1.57 [-1.77 , -1.38]
Van de Kerkhof 2008	-7.4	5.34	96	1.2	3.53	46	3.2%	-1.77 [-2.18 , -1.36]
Subtotal (95% CI)			**2267**			**979**	**35.3%**	**-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	3.6%	-1.01 [-1.37 , -0.66]
CHAMPION 2008	-9.1	10.92	108	-3.4	9.63	53	3.7%	-0.54 [-0.87 , -0.21]
Elewski 2016	-8	6.26	109	-1.9	6.24	108	4.2%	-0.97 [-1.25 , -0.69]
Gordon 2006	-11.2	7.7	96	-1.3	7.36	52	3.5%	-1.30 [-1.67 , -0.93]
Gordon X-PLORE 2015	-10.1	8.9	43	-2.3	6.8	42	2.9%	-0.97 [-1.43 , -0.52]
REVEAL 2008	-8.4	6.55	814	-1.9	6.62	398	5.3%	-0.99 [-1.11 , -0.86]
VIP Trial 2018	-7.9	8.8	33	-3.7	8	31	2.6%	-0.49 [-0.99 , 0.01]
VOYAGE-1 2016	-9.3	7.8	329	-0.6	6.36	174	4.8%	-1.18 [-1.38 , -0.99]
VOYAGE-2 2017	-9.7	6.8	248	-2.6	6.9	248	4.9%	-1.03 [-1.22 , -0.85]
Subtotal (95% CI)			**1903**			**1152**	**35.6%**	**-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								
CIMPASI-1 2018	-9.2	7.5	183	-3.3	6.9	51	3.9%	-0.80 [-1.12 , -0.48]
CIMPASI-2 2018	-10.6	7.7	178	-2.9	6.6	49	3.8%	-1.03 [-1.36 , -0.70]
Umezawa 2021	-6.8	6.45	101	-0.7	4.9	26	2.9%	-0.98 [-1.43 , -0.53]
Subtotal (95% CI)			**462**			**126**	**10.6%**	**-0.92 [-1.13 , -0.72]**
Heterogeneity: Tau² = 0.00; Chi² = 1.04, df = 2 (P = 0.59); I² = 0%								
Test for overall effect: Z = 8.86 (P < 0.00001)								
5.3.4 Infliximab versus placebo								
EXPRESS 2005	-10.3	7.1	301	-0.4	5.7	77	4.3%	-1.44 [-1.72 , -1.17]
EXPRESS-II 2007	-10	7	627	-0.6	5	208	5.0%	-1.43 [-1.60 , -1.26]
Gottlieb 2004a	-9.6	7.2	198	-2	6.7	51	3.8%	-1.07 [-1.39 , -0.74]
Torii 2010	-9.9	7.1	35	-0.4	5.7	19	2.0%	-1.41 [-2.03 , -0.79]
Yang 2012	-8	7.1	84	-1.5	5.1	45	3.4%	-1.00 [-1.38 , -0.61]
Subtotal (95% CI)			**1245**			**400**	**18.5%**	**-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)			**5877**			**2657**	**100.0%**	**-1.07 [-1.18 , -0.96]**
Heterogeneity: Tau² = 0.05; Chi² = 104.06, df = 24 (P < 0.00001); I² = 77%								
Test for overall effect: Z = 19.09 (P < 0.00001)								
Test for subgroup differences: Chi² = 8.92, df = 3 (P = 0.03), I² = 66.4%								



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
Igarashi 2012	-7.7	6.5	126	-0.3	5.3	32	9.3%	-1.17 [-1.58 , -0.76]
Krueger 2007	-8.95	8.4	256	-2.2	4.2	64	12.0%	-0.87 [-1.15 , -0.59]
LOTUS 2013	-9.3	7.18	160	-1.9	6.63	162	13.1%	-1.07 [-1.30 , -0.83]
PEARL 2011	-11.2	7.1	61	-0.5	6.5	60	9.3%	-1.56 [-1.97 , -1.15]
PHOENIX-1 2008	-8.4	6.7	511	-0.6	5.97	255	14.6%	-1.21 [-1.37 , -1.04]
PHOENIX-2 2008	-9.7	6.9	820	-0.5	5.66	410	15.1%	-1.41 [-1.54 , -1.28]
UltIMMa-1 2018	-4.4	3	100	0.2	3.03	102	11.3%	-1.52 [-1.83 , -1.21]
UltIMMa-2 2018	-5.6	2.98	99	0	2.88	98	10.7%	-1.90 [-2.24 , -1.57]
VIP-U Trial 2020	-15.72	7.44	22	-2.34	6.09	21	4.7%	-1.93 [-2.66 , -1.19]
Total (95% CI)			**2155**			**1204**	**100.0%**	**-1.35 [-1.54 , -1.16]**

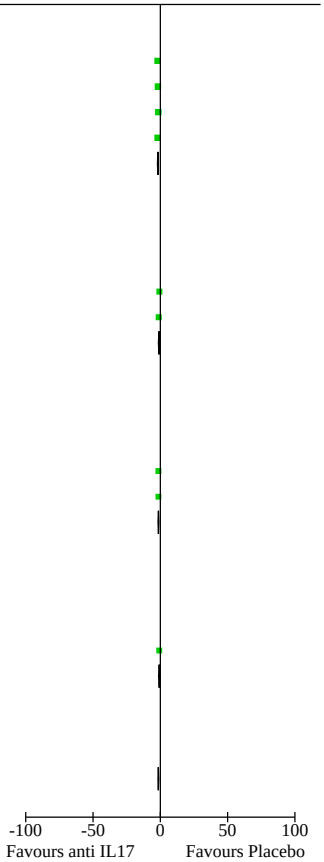
Heterogeneity: Tau² = 0.06; Chi² = 35.56, df = 8 (P < 0.0001); I² = 78%
Test for overall effect: Z = 13.99 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 5.5. Comparison 5: Secondary outcome - quality of life, Outcome 5: Anti-IL17 versus placebo

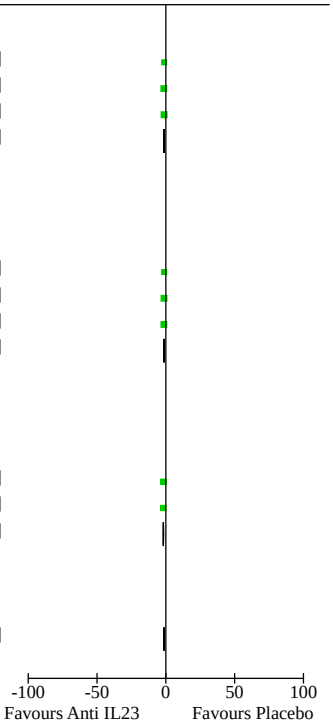
Study or Subgroup	Anti IL17 Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
5.5.1 Ixekizumab versus placebo								
NCT03364309	-8.73	4.52	350	0.92	4.48	88	11.6%	-2.14 [-2.41 , -1.86]
UNCOVER-1 2016	-10.9	5.5	865	-1	5.6	431	12.6%	-1.79 [-1.92 , -1.65]
UNCOVER-2 2015	-9.9	5.6	698	-2	5.18	168	12.3%	-1.43 [-1.61 , -1.25]
UNCOVER-3 2015	-9.9	3.9	771	-1.7	4.17	193	12.3%	-2.07 [-2.25 , -1.89]
Subtotal (95% CI)			**2684**			**880**	**48.9%**	**-1.85 [-2.14 , -1.55]**
Heterogeneity: Tau² = 0.08; Chi² = 30.25, df = 3 (P < 0.00001); I² = 90%								
Test for overall effect: Z = 12.38 (P < 0.00001)								
5.5.2 Brodalumab versus placebo								
Nakagawa 2016	-7.1	7.3	113	-2	6.7	38	10.6%	-0.71 [-1.09 , -0.33]
Papp 2012a	3.6	4.95	160	10.3	7.6	38	10.6%	-1.20 [-1.58 , -0.83]
Subtotal (95% CI)			**273**			**76**	**21.2%**	**-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)								
5.5.3 Secukinumab versus placebo								
NCT03589885 MATURE	-12.58	7.78	82	-1.97	6.96	40	10.2%	-1.40 [-1.82 , -0.98]
VIP-S trial 2020	-9.4	7.91	46	-0.5	3.97	45	9.7%	-1.41 [-1.87 , -0.94]
Subtotal (95% CI)			**128**			**85**	**19.9%**	**-1.40 [-1.71 , -1.09]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%								
Test for overall effect: Z = 8.88 (P < 0.00001)								
5.5.4 Netakimab versus placebo								
NCT02762994	-12	7.7	92	-5.65	7.4	28	10.0%	-0.83 [-1.26 , -0.39]
Subtotal (95% CI)			**92**			**28**	**10.0%**	**-0.83 [-1.26 , -0.39]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.71 (P = 0.0002)								
Total (95% CI)			**3177**			**1069**	**100.0%**	**-1.47 [-1.76 , -1.18]**

Heterogeneity: Tau² = 0.16; Chi² = 87.57, df = 8 (P < 0.00001); I² = 91%
Test for overall effect: Z = 10.06 (P < 0.00001)
Test for subgroup differences: Chi² = 18.82, df = 3 (P = 0.0003), I² = 84.1%



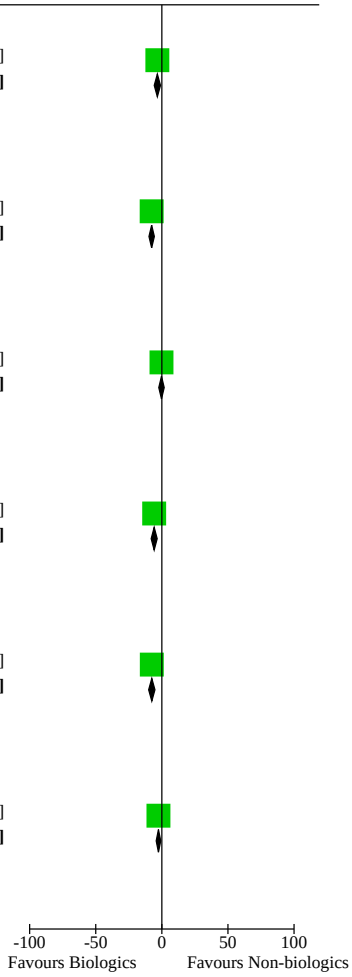
Analysis 5.6. Comparison 5: Secondary outcome - quality of life, Outcome 6: Anti-IL23 versus placebo

Study or Subgroup	Anti IL23 Mean	Anti IL23 SD	Anti IL23 Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
5.6.1 Guselkumab versus placebo								
Ohtsuki 2018	-8.4	6.4	128	-0.8	5.4	64	10.0%	-1.24 [-1.57 , -0.92]
VOYAGE-1 2016	-11.2	7.24	334	-0.6	6.36	174	13.5%	-1.52 [-1.73 , -1.32]
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]
ReSURFACE-1 2017	-9.9	5.83	617	-2.3	5.07	155	14.0%	-1.34 [-1.52 , -1.15]
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								
UltIMMa-1 2018	-5.6	3.49	304	0.2	3.03	102	12.0%	-1.71 [-1.97 , -1.46]
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%								



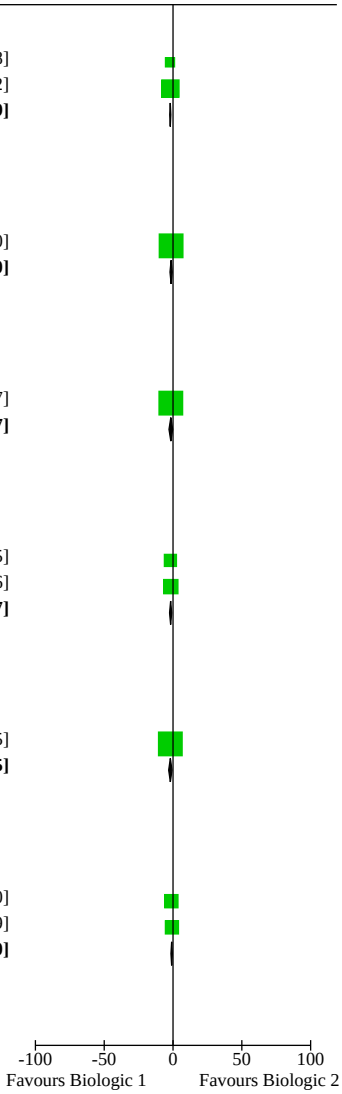
Analysis 5.7. Comparison 5: Secondary outcome - quality of life, Outcome 7: Biologic versus non-biological treatment

Study or Subgroup	Biologics Mean	SD	Total	Non-biological treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
5.7.1 Adalimumab versus methotrexate								
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								
Reich 2020	-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								
Reich 2020	-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								
POLARIS 2020	-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)								
5.7.5 Risankizumab versus fumaric acid esters								
Thaci 2021	-18.8	6.73	60	-11.2	6.51	60	100.0%	-7.60 [-9.97 , -5.23]
Subtotal (95% CI)			**60**			**60**	**100.0%**	**-7.60 [-9.97 , -5.23]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.29 (P < 0.00001)								
5.7.6 Brodalumab versus fumaric acid esters								
CHANGE 2021	-16.67	6.07	105	-14.1	6.49	105	100.0%	-2.57 [-4.27 , -0.87]
Subtotal (95% CI)			**105**			**105**	**100.0%**	**-2.57 [-4.27 , -0.87]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.96 (P = 0.003)								



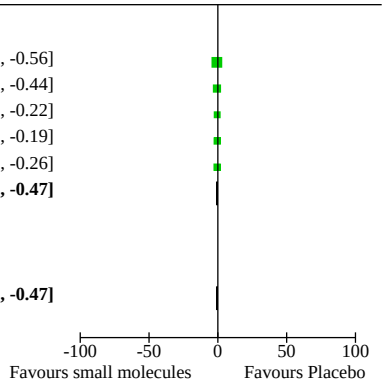
Analysis 5.8. Comparison 5: Secondary outcome - quality of life, Outcome 8: Biologic 1 versus biologic 2

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								
UNCOVER-2 2015	-9.9	5.6	698	-7.7	5.68	358	30.7%	-2.20 [-2.92 , -1.48]
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 Tildrakizumab versus etanercept								
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)								
5.8.3 Infliximab versus etanercept								
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)								
5.8.4 Guselkumab versus adalimumab								
VOYAGE-1 2016	-11.2	7.24	334	-9.3	7.8	329	45.0%	-1.90 [-3.05 , -0.75]
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)								
5.8.5 Bimekizumab versus adalimumab								
BE SURE 2021	-9.35	6.31	319	-7.4	6.3	159	100.0%	-1.95 [-3.15 , -0.75]
Subtotal (95% CI)			**319**			**159**	**100.0%**	**-1.95 [-3.15 , -0.75]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.19 (P = 0.001)								
5.8.6 Risankizumab versus ustekinumab								
UltIMMa-1 2018	-5.6	3.49	304	-4.4	3	102	50.3%	-1.20 [-1.90 , -0.50]
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)								



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								
ESTEEM-1 2015	-6.6	6.66	562	-2.1	5.69	282	32.6%	-0.71 [-0.85 , -0.56]
ESTEEM-2 2015	-6.7	6.14	275	-2.7	6.23	138	20.5%	-0.65 [-0.86 , -0.44]
Ohtsuki 2017	-1.3	5.15	170	1.3	5.7	84	14.2%	-0.49 [-0.75 , -0.22]
Papp 2012c	-4.5	6.02	264	-1.9	5.91	88	16.3%	-0.43 [-0.68 , -0.19]
STYLE 2020	-6.7	5.81	201	-3.8	5.65	102	16.5%	-0.50 [-0.74 , -0.26]
Subtotal (95% CI)			**1472**			**694**	**100.0%**	**-0.59 [-0.70 , -0.47]**
Heterogeneity: Tau² = 0.00; Chi² = 5.41, df = 4 (P = 0.25); I² = 26%								
Test for overall effect: Z = 10.36 (P < 0.00001)								
Total (95% CI)			**1472**			**694**	**100.0%**	**-0.59 [-0.70 , -0.47]**
Heterogeneity: Tau² = 0.00; Chi² = 5.41, df = 4 (P = 0.25); I² = 26%								
Test for overall effect: Z = 10.36 (P < 0.00001)								
Test for subgroup differences: Not applicable								



Comparison 6. Secondary outcome - adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Non-biological treatments 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 Non-biological treatment 1 versus non-biological treatment 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]
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	28	9983	Risk Ratio (M-H, Random, 95% CI)	1.05 [1.01, 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	5	1153	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.84, 1.04]
6.3.4 Infliximab versus placebo	4	1267	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.93, 1.36]

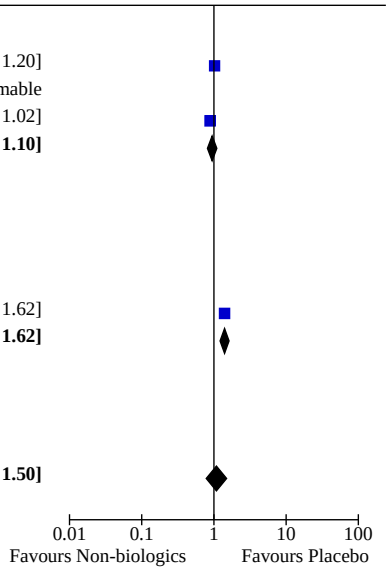
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.4 Ustekinumab versus placebo	12	4842	Risk Ratio (M-H, Random, 95% CI)	1.07 [1.01, 1.13]
6.5 Anti-IL17 versus placebo	30	14052	Risk Ratio (M-H, Random, 95% CI)	1.21 [1.13, 1.31]
6.5.1 Secukinumab versus placebo	14	4493	Risk Ratio (M-H, Random, 95% CI)	1.19 [1.05, 1.35]
6.5.2 Ixekizumab versus placebo	5	3706	Risk Ratio (M-H, Random, 95% CI)	1.31 [1.10, 1.56]
6.5.3 Brodalumab versus placebo	6	4171	Risk Ratio (M-H, Random, 95% CI)	1.14 [1.01, 1.30]
6.5.4 Bimekizumab versus placebo	3	1089	Risk Ratio (M-H, Random, 95% CI)	1.39 [1.15, 1.69]
6.5.5 Netakimab versus placebo	2	333	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.59, 1.37]
6.5.6 Sonelokimab versus placebo	1	260	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.86, 1.71]
6.6 Anti-IL23 versus placebo	13	5304	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.88, 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	5	1633	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.86, 1.08]
6.7 Biologic versus non-biological treatments	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.7.1 Etanercept versus acitretin	2	82	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.72, 1.96]
6.7.2 Infliximab versus methotrexate	1	868	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.97, 1.20]
6.7.3 Adalimumab versus methotrexate	1	218	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.78, 1.05]
6.7.4 Secukinumab versus fumaric acid esters	1	202	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.71, 0.94]
6.7.5 Ixekizumab versus methotrexate	1	108	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.76, 1.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.7.6 Ixekizumab versus fumaric acid esters	1	108	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.74, 1.21]
6.7.7 Guselkumab versus fumaric acid esters	1	119	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.65, 0.89]
6.7.8 Risankizumab versus fumaric acid esters	1	120	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.75, 0.98]
6.7.9 Brodalumab versus fumaric acid esters	1	210	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.62, 0.87]
6.8 Biologic 1 versus biologic 2	26		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 Infliximab versus etanercept	1	48	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.86, 1.08]
6.8.5 Tildrakizumab versus etanercept	1	934	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.65, 0.86]
6.8.6 Certolizumab versus etanercept	1	502	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.86, 1.28]
6.8.7 Secukinumab versus ustekinumab	2	1778	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.98, 1.16]
6.8.8 Ixekizumab versus ustekinumab	1	302	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.80, 1.06]
6.8.9 Brodalumab versus ustekinumab	2	3088	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.93, 1.09]
6.8.10 Risankizumab versus ustekinumab	3	965	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.85, 1.11]
6.8.11 Bimekizumab versus ustekinumab	1	484	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.93, 1.32]
6.8.12 Guselkumab versus adalimumab	3	1658	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.09]
6.8.13 Risankizumab versus adalimumab	1	605	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.85, 1.13]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.8.14 Bimekizumab versus adalimumab	1	478	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.90, 1.16]
6.8.15 Ixekizumab versus guselkumab	1	1027	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.92, 1.15]
6.8.16 Risankizumab versus secukinumab	1	327	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.87, 1.15]
6.8.17 Ixekizumab versus secukinumab	1	54	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.71, 1.52]
6.8.18 Guselkumab versus secukinumab	1	1048	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.90, 1.02]
6.8.19 Sonelokimab versus secukinumab	1	261	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.77, 1.42]
6.9 Small molecules versus placebo	8	2860	Risk Ratio (M-H, Random, 95% CI)	1.24 [1.14, 1.35]
6.9.1 Apremilast versus placebo	7	2593	Risk Ratio (M-H, Random, 95% CI)	1.24 [1.13, 1.36]
6.9.2 TYK2 versus placebo	1	267	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.97, 1.77]
6.10 Biologic versus small molecules	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.10.1 Etanercept versus apremilast	1	166	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.03, 1.69]

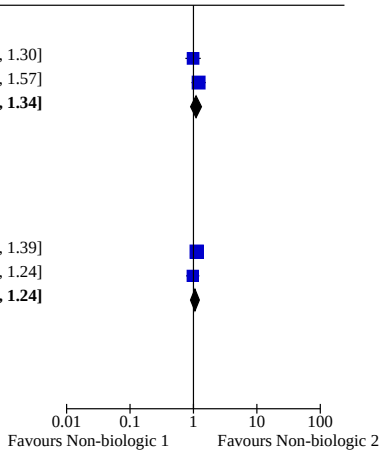
Analysis 6.1. Comparison 6: Secondary outcome - adverse events, Outcome 1: Non-biological treatments versus placebo

Study or Subgroup	Non-biological treatment Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 Methotrexate versus placebo						
CHAMPION 2008	89	110	42	53	32.8%	1.02 [0.87 , 1.20]
Hunter 1963	0	19	0	17		Not estimable
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						
BRIDGE 2017	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%						



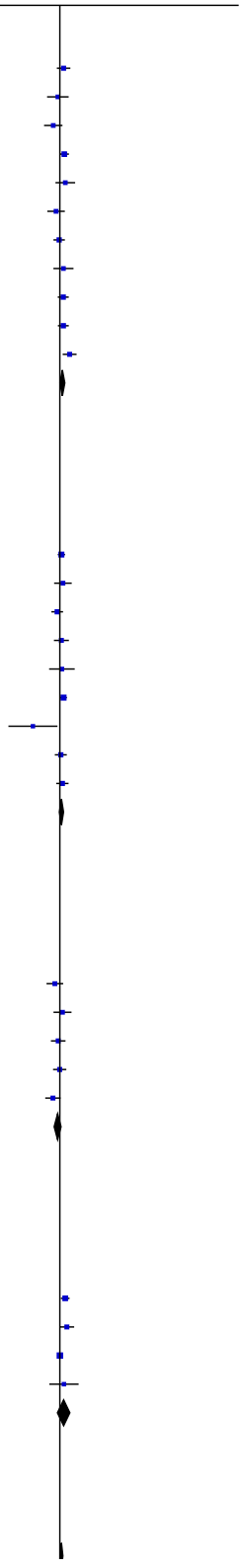
Analysis 6.2. Comparison 6: Secondary outcome - adverse events, Outcome 2: Non-biological treatment 1 versus non-biological treatment 2

Study or Subgroup	Non-biological treatment 1 Events	Total	Non-biological treatment 2 Events	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]
Reich 2020	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

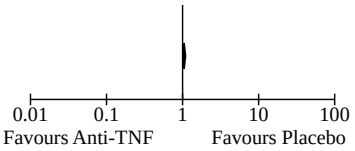
Study or Subgroup	Anti-TNF Events	Anti-TNF Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
6.3.1 Etanercept versus placebo						
Bachelez 2015	192	336	55	108	3.3%	1.12 [0.91 , 1.38]
Bagel 2012	32	62	34	62	1.5%	0.94 [0.68 , 1.31]
CIMPACT 2018	78	170	32	57	2.0%	0.82 [0.62 , 1.08]
FIXTURE 2014	186	326	163	327	5.4%	1.14 [0.99 , 1.32]
Gottlieb 2011	76	141	31	68	1.8%	1.18 [0.87 , 1.60]
LIBERATE 2017	44	83	50	84	2.2%	0.89 [0.68 , 1.16]
ReSURFACE-2 2017	169	313	86	156	4.2%	0.98 [0.82 , 1.17]
Strober 2011	69	139	32	72	1.7%	1.12 [0.82 , 1.52]
Tyring 2006	153	311	137	309	4.4%	1.11 [0.94 , 1.31]
UNCOVER-2 2015	211	358	89	168	4.5%	1.11 [0.94 , 1.31]
UNCOVER-3 2015	187	382	70	193	3.2%	1.35 [1.09 , 1.67]
Subtotal (95% CI)		**2621**		**1604**	**34.4%**	**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	7.1%	1.05 [0.94 , 1.17]
Cai 2016	158	338	37	87	2.2%	1.10 [0.84 , 1.44]
CHAMPION 2008	79	108	42	53	4.1%	0.92 [0.77 , 1.10]
Elewski 2016	64	109	61	109	2.8%	1.05 [0.83 , 1.32]
Gordon X-PLORE 2015	24	43	22	42	1.1%	1.07 [0.72 , 1.58]
REVEAL 2008	506	814	221	398	7.7%	1.12 [1.01 , 1.24]
VIP Trial 2018	7	33	15	31	0.3%	0.44 [0.21 , 0.93]
VOYAGE-1 2016	170	334	86	174	4.0%	1.03 [0.86 , 1.24]
VOYAGE-2 2017	120	248	111	248	3.8%	1.08 [0.90 , 1.31]
Subtotal (95% CI)		**2150**		**1188**	**33.1%**	**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						
CIMPACT 2018	160	332	32	57	2.4%	0.86 [0.67 , 1.11]
CIMPASI-1 2018	109	183	28	51	2.1%	1.08 [0.82 , 1.43]
CIMPASI-2 2018	114	178	33	49	2.9%	0.95 [0.76 , 1.19]
Reich 2012a	83	118	41	58	3.4%	1.00 [0.81 , 1.22]
Umezawa 2021	66	101	21	26	2.7%	0.81 [0.64 , 1.02]
Subtotal (95% CI)		**912**		**241**	**13.6%**	**0.93 [0.84 , 1.04]**
Total events:	532		155			
Heterogeneity: Tau² = 0.00; Chi² = 3.43, df = 4 (P = 0.49); I² = 0%						
Test for overall effect: Z = 1.28 (P = 0.20)						
6.3.4 Infliximab versus placebo						
EXPRESS-II 2007	412	627	116	208	5.9%	1.18 [1.03 , 1.35]
Gottlieb 2004a	154	198	32	51	2.9%	1.24 [0.99 , 1.55]
Torii 2010	35	35	19	19	9.2%	1.00 [0.92 , 1.08]
Yang 2012	36	84	17	45	0.9%	1.13 [0.72 , 1.78]
Subtotal (95% CI)		**944**		**323**	**18.9%**	**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)		**6627**		**3356**	**100.0%**	**1.05 [1.01 , 1.10]**



Analysis 6.3. (Continued)

Total (95% CI)	**6627**	**3356**	**100.0%**	**1.05 [1.01 , 1.10]**	
Total events:	3809	1754			

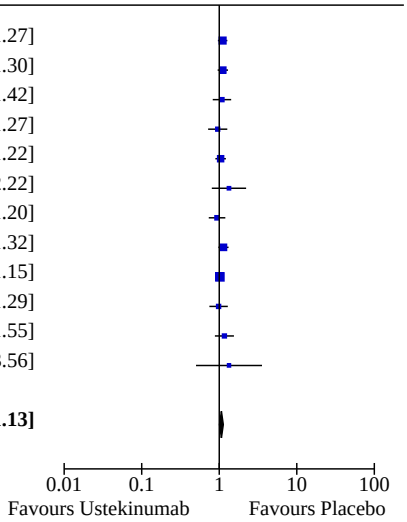
Heterogeneity: Tau² = 0.00; Chi² = 39.58, df = 28 (P = 0.07); I² = 29%
Test for overall effect: Z = 2.20 (P = 0.03)
Test for subgroup differences: Chi² = 5.77, df = 3 (P = 0.12), I² = 48.0%



Analysis 6.4. Comparison 6: Secondary outcome - adverse events, Outcome 4: Ustekinumab versus placebo

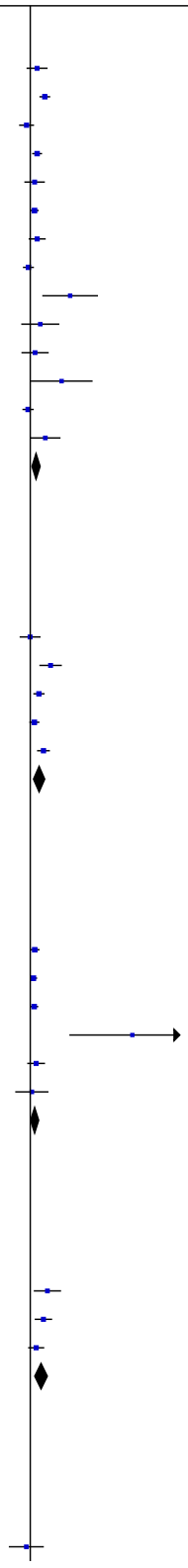
Study or Subgroup	Ustekinumab Events	Ustekinumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
AMAGINE-2 2015	177	300	165	309	15.8%	1.10 [0.96 , 1.27]
AMAGINE-3 2015	168	313	152	315	13.2%	1.11 [0.95 , 1.30]
BE VIVID 2021	83	163	39	83	4.2%	1.08 [0.82 , 1.42]
Igarashi 2012	79	126	21	32	3.8%	0.96 [0.72 , 1.27]
Krueger 2007	200	256	48	64	12.9%	1.04 [0.89 , 1.22]
LOTUS 2013	29	160	22	162	1.2%	1.33 [0.80 , 2.22]
PEARL 2011	40	61	42	60	5.1%	0.94 [0.73 , 1.20]
PHOENIX-1 2008	277	511	122	255	13.7%	1.13 [0.97 , 1.32]
PHOENIX-2 2008	412	820	202	410	21.8%	1.02 [0.90 , 1.15]
UltIMMa-1 2018	50	100	52	102	4.2%	0.98 [0.75 , 1.29]
UltIMMa-2 2018	53	99	45	98	3.9%	1.17 [0.88 , 1.55]
VIP-U Trial 2020	7	22	5	21	0.3%	1.34 [0.50 , 3.56]
Total (95% CI)	**2931**		**1911**		**100.0%**	**1.07 [1.01 , 1.13]**
Total events:	1575		915			

Heterogeneity: Tau² = 0.00; Chi² = 5.19, df = 11 (P = 0.92); I² = 0%
Test for overall effect: Z = 2.25 (P = 0.02)
Test for subgroup differences: Not applicable



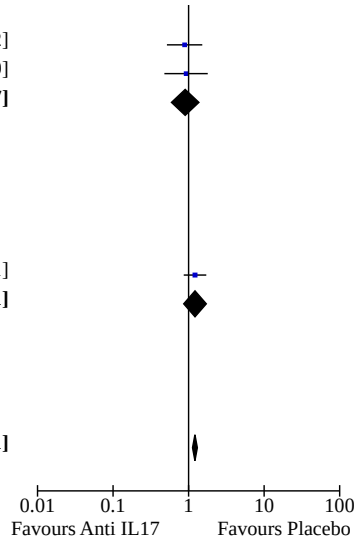
Analysis 6.5. Comparison 6: Secondary outcome - adverse events, Outcome 5: Anti-IL17 versus placebo

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						
ALLURE 2021	72	143	29	71	2.9%	1.23 [0.89 , 1.70]
Cai 2020	336	408	71	135	4.9%	1.57 [1.33 , 1.85]
CARIMA 2019	65	102	35	49	4.0%	0.89 [0.71 , 1.12]
ERASURE 2014	283	490	116	248	5.1%	1.23 [1.06 , 1.44]
FEATURE 2015	64	118	28	59	2.9%	1.14 [0.83 , 1.57]
FIXTURE 2014	372	654	163	327	5.4%	1.14 [1.00 , 1.30]
JUNCTURE 2015	81	121	33	61	3.5%	1.24 [0.95 , 1.61]
NCT03535194	257	448	68	112	4.8%	0.94 [0.80 , 1.12]
NCT03589885 MATURE	35	82	5	40	0.7%	3.41 [1.45 , 8.05]
Papp 2013a	51	103	8	22	1.3%	1.36 [0.76 , 2.45]
Papp 2021	26	53	22	52	2.1%	1.16 [0.76 , 1.76]
Reich 2015	71	90	3	10	0.5%	2.63 [1.01 , 6.82]
Rich 2013	221	337	47	67	4.8%	0.93 [0.79 , 1.11]
VIP-S trial 2020	26	46	16	45	1.8%	1.59 [1.00 , 2.54]
Subtotal (95% CI)		**3195**		**1298**	**44.6%**	**1.19 [1.05 , 1.35]**
Total events:	1960		644			
Heterogeneity: Tau² = 0.03; Chi² = 42.56, df = 13 (P < 0.0001); I² = 69%						
Test for overall effect: Z = 2.79 (P = 0.005)						
6.5.2 Ixekizumab versus placebo						
Leonardi 2012	72	115	17	27	2.9%	0.99 [0.72 , 1.37]
NCT03364309	186	350	25	88	2.6%	1.87 [1.32 , 2.64]
UNCOVER-1 2016	320	865	122	431	4.8%	1.31 [1.10 , 1.55]
UNCOVER-2 2015	420	698	89	168	5.0%	1.14 [0.97 , 1.33]
UNCOVER-3 2015	420	771	70	193	4.4%	1.50 [1.23 , 1.83]
Subtotal (95% CI)		**2799**		**907**	**19.8%**	**1.31 [1.10 , 1.56]**
Total events:	1418		323			
Heterogeneity: Tau² = 0.02; Chi² = 12.36, df = 4 (P = 0.01); I² = 68%						
Test for overall effect: Z = 3.09 (P = 0.002)						
6.5.3 Brodalumab versus placebo						
AMAGINE-1 2016	257	441	112	220	5.1%	1.14 [0.98 , 1.33]
AMAGINE-2 2015	719	1222	165	309	5.6%	1.10 [0.98 , 1.24]
AMAGINE-3 2015	682	1253	152	315	5.5%	1.13 [1.00 , 1.28]
Nakagawa 2016	69	113	1	38	0.1%	23.20 [3.34 , 161.40]
Papp 2012a	116	160	23	38	3.4%	1.20 [0.91 , 1.58]
Seo 2020	21	40	11	22	1.6%	1.05 [0.63 , 1.75]
Subtotal (95% CI)		**3229**		**942**	**21.3%**	**1.14 [1.01 , 1.30]**
Total events:	1864		464			
Heterogeneity: Tau² = 0.01; Chi² = 10.81, df = 5 (P = 0.06); I² = 54%						
Test for overall effect: Z = 2.10 (P = 0.04)						
6.5.4 Bimekizumab versus placebo						
BE ABLE 1 2018	126	208	15	42	2.1%	1.70 [1.11 , 2.58]
BE READY 2021	213	349	35	86	3.5%	1.50 [1.15 , 1.96]
BE VIVID 2021	181	321	39	83	3.7%	1.20 [0.94 , 1.54]
Subtotal (95% CI)		**878**		**211**	**9.3%**	**1.39 [1.15 , 1.69]**
Total events:	520		89			
Heterogeneity: Tau² = 0.01; Chi² = 2.55, df = 2 (P = 0.28); I² = 22%						
Test for overall effect: Z = 3.37 (P = 0.0007)						
6.5.5 Netakimab versus placebo						
NCT02762994	32	92	11	28	1.4%	0.89 [0.52 , 1.52]



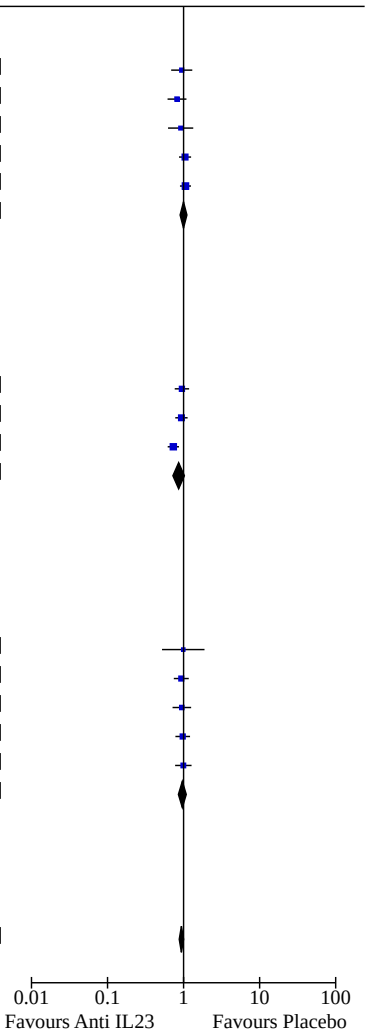
Analysis 6.5. (Continued)

6.5.5 Netakimab versus placebo						
NCT02762994	32	92	11	28	1.4%	0.89 [0.52 , 1.52]
PLANETA 2021	32	169	9	44	1.0%	0.93 [0.48 , 1.79]
Subtotal (95% CI)		**261**		**72**	**2.5%**	**0.90 [0.59 , 1.37]**
Total events:	64		20			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%						
Test for overall effect: Z = 0.49 (P = 0.63)						
6.5.6 Sonelokimab versus placebo						
Papp 2021	107	208	22	52	2.7%	1.22 [0.86 , 1.71]
Subtotal (95% CI)		**208**		**52**	**2.7%**	**1.22 [0.86 , 1.71]**
Total events:	107		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.11 (P = 0.27)						
Total (95% CI)		**10570**		**3482**	**100.0%**	**1.21 [1.13 , 1.31]**
Total events:	5933		1562			
Heterogeneity: Tau² = 0.02; Chi² = 79.48, df = 30 (P < 0.00001); I² = 62%						
Test for overall effect: Z = 5.19 (P < 0.00001)						
Test for subgroup differences: Chi² = 5.65, df = 5 (P = 0.34), I² = 11.5%						



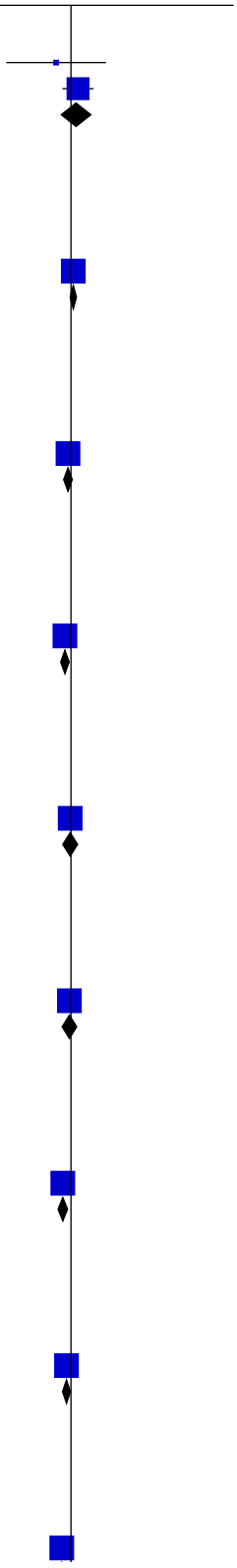
Analysis 6.6. Comparison 6: Secondary outcome - adverse events, Outcome 6: Anti-IL23 versus placebo

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						
Gordon X-PLORE 2015	103	208	22	42	4.1%	0.95 [0.69 , 1.30]
Ohtsuki 2018	59	128	36	64	5.1%	0.82 [0.62 , 1.09]
ORION 2020	39	62	11	16	2.9%	0.91 [0.62 , 1.34]
VOYAGE-1 2016	170	329	86	174	11.8%	1.05 [0.87 , 1.26]
VOYAGE-2 2017	235	496	111	248	14.0%	1.06 [0.90 , 1.25]
Subtotal (95% CI)		**1223**		**544**	**37.8%**	**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	8.5%	0.95 [0.76 , 1.18]
ReSURFACE-1 2017	276	617	74	155	11.4%	0.94 [0.78 , 1.13]
ReSURFACE-2 2017	251	621	86	156	13.4%	0.73 [0.62 , 0.87]
Subtotal (95% CI)		**1547**		**357**	**33.2%**	**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						
Blauvelt 2021a	22	105	11	52	1.0%	0.99 [0.52 , 1.88]
IMMhance 2020	186	407	49	100	7.9%	0.93 [0.74 , 1.17]
SustaIMM 2019	61	113	33	58	5.2%	0.95 [0.72 , 1.26]
UltIMMa-1 2018	151	304	52	102	8.2%	0.97 [0.78 , 1.22]
UltIMMa-2 2018	134	294	45	98	6.6%	0.99 [0.77 , 1.27]
Subtotal (95% CI)		**1223**		**410**	**29.0%**	**0.96 [0.86 , 1.08]**
Total events:	554		190			
Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 4 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.63 (P = 0.53)						
Total (95% CI)		**3993**		**1311**	**100.0%**	**0.94 [0.88 , 1.00]**
Total events:	1885		647			
Heterogeneity: Tau² = 0.00; Chi² = 12.64, df = 12 (P = 0.40); I² = 5%						
Test for overall effect: Z = 1.97 (P = 0.05)						
Test for subgroup differences: Chi² = 2.06, df = 2 (P = 0.36), I² = 2.9%						



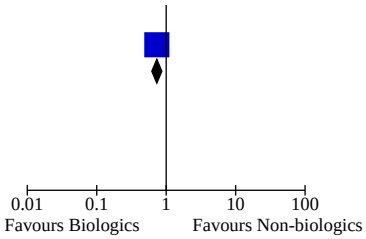
Analysis 6.7. Comparison 6: Secondary outcome - adverse events, Outcome 7: Biologic versus non-biological treatments

Study or Subgroup	Biologic Events	Biologic Total	Non-biological treatment Events	Non-biological treatment Total	Weight	Risk Ratio M-H, Random, 95% CI
6.7.1 Etanercept versus acitretin						
Gisondi 2008	2	22	3	20	8.8%	0.61 [0.11 , 3.26]
Lee 2016	14	21	10	19	91.2%	1.27 [0.75 , 2.14]
Subtotal (95% CI)		**43**		**39**	**100.0%**	**1.19 [0.72 , 1.96]**
Total events:	16		13			
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 1 (P = 0.39); I² = 0%						
Test for overall effect: Z = 0.67 (P = 0.50)						
6.7.2 Infliximab versus methotrexate						
Barker 2011	466	653	142	215	100.0%	1.08 [0.97 , 1.20]
Subtotal (95% CI)		**653**		**215**	**100.0%**	**1.08 [0.97 , 1.20]**
Total events:	466		142			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.41 (P = 0.16)						
6.7.3 Adalimumab versus methotrexate						
CHAMPION 2008	79	108	89	110	100.0%	0.90 [0.78 , 1.05]
Subtotal (95% CI)		**108**		**110**	**100.0%**	**0.90 [0.78 , 1.05]**
Total events:	79		89			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.35 (P = 0.18)						
6.7.4 Secukinumab versus fumaric acid esters						
PRIME 2017	75	105	85	97	100.0%	0.82 [0.71 , 0.94]
Subtotal (95% CI)		**105**		**97**	**100.0%**	**0.82 [0.71 , 0.94]**
Total events:	75		85			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.82 (P = 0.005)						
6.7.5 Ixekizumab versus methotrexate						
Reich 2020	37	54	38	54	100.0%	0.97 [0.76 , 1.25]
Subtotal (95% CI)		**54**		**54**	**100.0%**	**0.97 [0.76 , 1.25]**
Total events:	37		38			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.21 (P = 0.83)						
6.7.6 Ixekizumab versus fumaric acid esters						
Reich 2020	37	54	39	54	100.0%	0.95 [0.74 , 1.21]
Subtotal (95% CI)		**54**		**54**	**100.0%**	**0.95 [0.74 , 1.21]**
Total events:	37		39			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.42 (P = 0.67)						
6.7.7 Guselkumab versus fumaric acid esters						
POLARIS 2020	44	60	57	59	100.0%	0.76 [0.65 , 0.89]
Subtotal (95% CI)		**60**		**59**	**100.0%**	**0.76 [0.65 , 0.89]**
Total events:	44		57			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.38 (P = 0.0007)						
6.7.8 Risankizumab versus fumaric acid esters						
Thaci 2021	49	60	57	60	100.0%	0.86 [0.75 , 0.98]
Subtotal (95% CI)		**60**		**60**	**100.0%**	**0.86 [0.75 , 0.98]**
Total events:	49		57			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.23 (P = 0.03)						
6.7.9 Brodalumab versus fumaric acid esters						
CHANGE 2021	66	105	90	105	100.0%	0.73 [0.62 , 0.87]



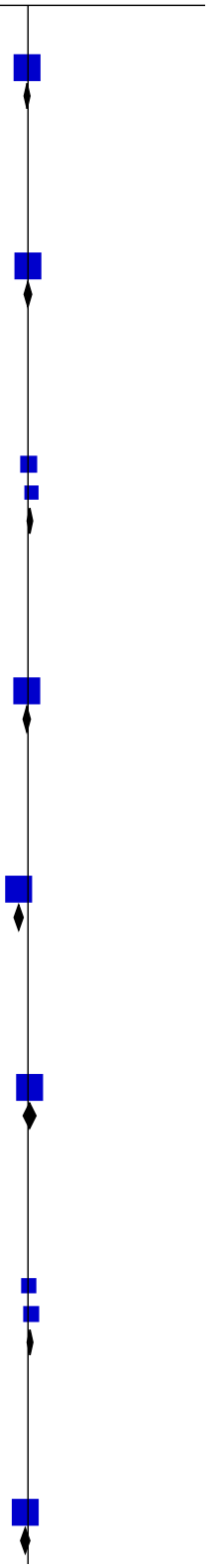
Analysis 6.7. (Continued)

6.7.9 Brodalumab versus fumaric acid esters						
CHANGE 2021	66	105	90	105	100.0%	0.73 [0.62 , 0.87]
Subtotal (95% CI)		**105**		**105**	**100.0%**	**0.73 [0.62 , 0.87]**
Total events:	66		90			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.65 (P = 0.0003)						



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						
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						
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						
UNCOVER-2 2015	420	698	211	358	56.1%	1.02 [0.92 , 1.13]
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 Infliximab versus etanercept						
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)						
6.8.5 Tildrakizumab versus etanercept						
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)						
6.8.6 Certolizumab versus etanercept						
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)						
6.8.7 Secukinumab versus ustekinumab						
CLARITY 2018	261	550	256	552	48.3%	1.02 [0.90 , 1.16]
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)						
6.8.8 Ixekizumab versus ustekinumab						
IXORA-S 2017	94	136	125	166	100.0%	0.92 [0.80 , 1.06]
Subtotal (95% CI)		**136**		**166**	**100.0%**	**0.92 [0.80 , 1.06]**
Total events:	94		125			

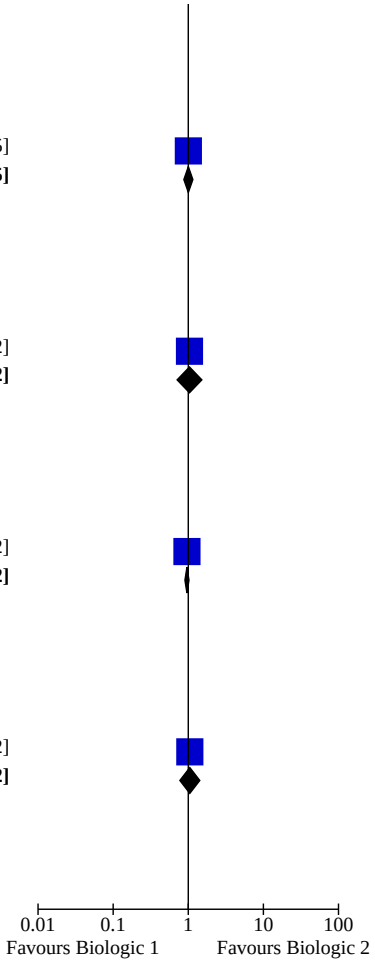


Analysis 6.8. (Continued)

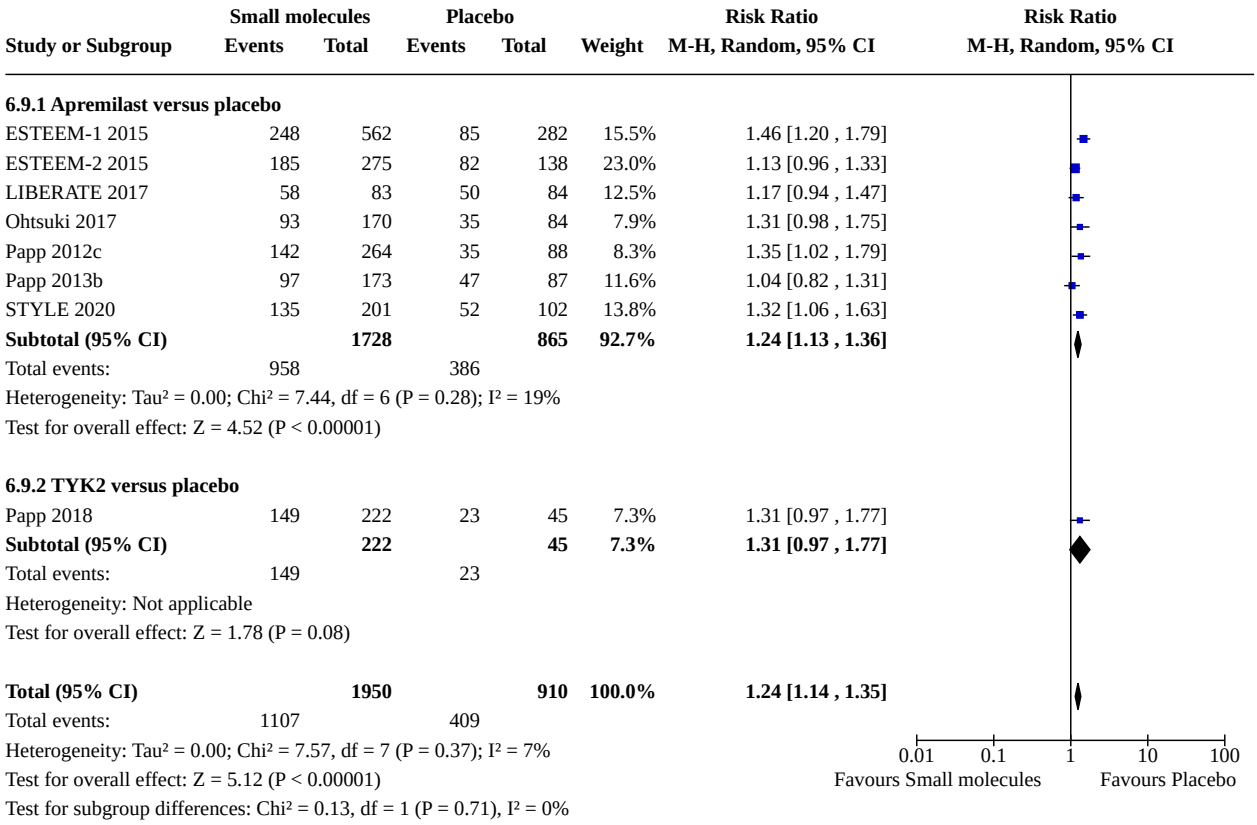
IXORA-S 2017	94	136	125	166	100.0%	0.92 [0.80 , 1.06]
Subtotal (95% CI)		**136**		**166**	**100.0%**	**0.92 [0.80 , 1.06]**
Total events:	94		125			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.18 (P = 0.24)						
6.8.9 Brodalumab versus ustekinumab						
AMAGINE-2 2015	719	1222	177	300	54.3%	1.00 [0.90 , 1.11]
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: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.12 (P = 0.90)						
6.8.10 Risankizumab versus ustekinumab						
Papp 2017b	97	126	29	40	35.5%	1.06 [0.86 , 1.31]
UltIMMa-1 2018	151	304	50	102	31.5%	1.01 [0.81 , 1.27]
UltIMMa-2 2018	134	294	53	99	33.0%	0.85 [0.68 , 1.06]
Subtotal (95% CI)		**724**		**241**	**100.0%**	**0.97 [0.85 , 1.11]**
Total events:	382		132			
Heterogeneity: Tau² = 0.00; Chi² = 2.20, df = 2 (P = 0.33); I² = 9%						
Test for overall effect: Z = 0.41 (P = 0.68)						
6.8.11 Bimekizumab versus ustekinumab						
BE VIVID 2021	181	321	83	163	100.0%	1.11 [0.93 , 1.32]
Subtotal (95% CI)		**321**		**163**	**100.0%**	**1.11 [0.93 , 1.32]**
Total events:	181		83			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.12 (P = 0.26)						
6.8.12 Guselkumab versus adalimumab						
Gordon X-PLORE 2015	103	208	24	43	11.6%	0.89 [0.66 , 1.20]
VOYAGE-1 2016	170	329	170	334	47.1%	1.02 [0.88 , 1.18]
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: Tau² = 0.00; Chi² = 0.63, df = 2 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.30 (P = 0.77)						
6.8.13 Risankizumab versus adalimumab						
IMMvent 2019	168	301	173	304	100.0%	0.98 [0.85 , 1.13]
Subtotal (95% CI)		**301**		**304**	**100.0%**	**0.98 [0.85 , 1.13]**
Total events:	168		173			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.79)						
6.8.14 Bimekizumab versus adalimumab						
BE SURE 2021	228	319	111	159	100.0%	1.02 [0.90 , 1.16]
Subtotal (95% CI)		**319**		**159**	**100.0%**	**1.02 [0.90 , 1.16]**
Total events:	228		111			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.37 (P = 0.71)						
6.8.15 Ixekizumab versus guselkumab						
IXORA-R 2020	293	520	277	507	100.0%	1.03 [0.92 , 1.15]
Subtotal (95% CI)		**520**		**507**	**100.0%**	**1.03 [0.92 , 1.15]**
Total events:	293		277			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.55 (P = 0.58)						

Analysis 6.8. (Continued)

Total events:	293		277			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.55 (P = 0.58)						
6.8.16 Risankizumab versus secukinumab						
IMMerge 2021	117	164	116	163	100.0%	1.00 [0.87 , 1.15]
Subtotal (95% CI)		**164**		**163**	**100.0%**	**1.00 [0.87 , 1.15]**
Total events:	117		116			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.04 (P = 0.97)						
6.8.17 Ixekizumab versus secukinumab						
AlMutairi 2021	19	28	17	26	100.0%	1.04 [0.71 , 1.52]
Subtotal (95% CI)		**28**		**26**	**100.0%**	**1.04 [0.71 , 1.52]**
Total events:	19		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.19 (P = 0.85)						
6.8.18 Guselkumab versus secukinumab						
ECLIPSE 2019	416	534	417	514	100.0%	0.96 [0.90 , 1.02]
Subtotal (95% CI)		**534**		**514**	**100.0%**	**0.96 [0.90 , 1.02]**
Total events:	416		417			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.29 (P = 0.20)						
6.8.19 Sonelokimab versus secukinumab						
Papp 2021	107	208	26	53	100.0%	1.05 [0.77 , 1.42]
Subtotal (95% CI)		**208**		**53**	**100.0%**	**1.05 [0.77 , 1.42]**
Total events:	107		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.31 (P = 0.76)						

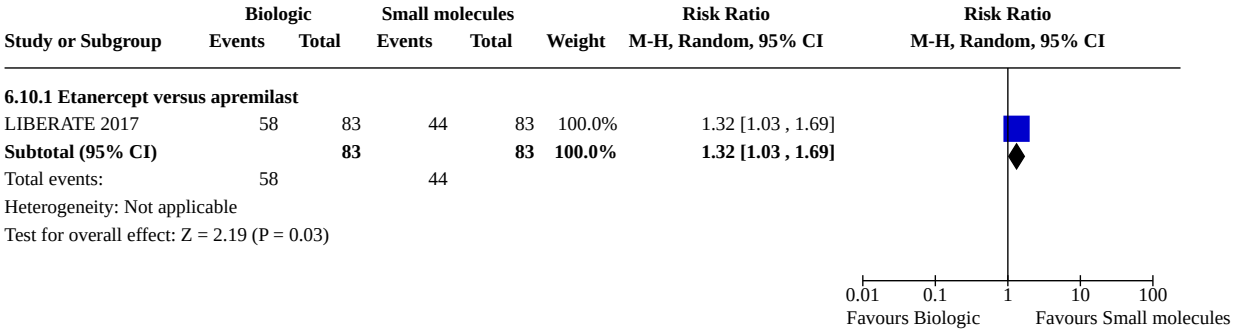


Analysis 6.9. Comparison 6: Secondary outcome - adverse events, Outcome 9: Small molecules versus placebo



Study or Subgroup	Small molecules Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
6.9.1 Apremilast versus placebo						
ESTEEM-1 2015	248	562	85	282	15.5%	1.46 [1.20 , 1.79]
ESTEEM-2 2015	185	275	82	138	23.0%	1.13 [0.96 , 1.33]
LIBERATE 2017	58	83	50	84	12.5%	1.17 [0.94 , 1.47]
Ohtsuki 2017	93	170	35	84	7.9%	1.31 [0.98 , 1.75]
Papp 2012c	142	264	35	88	8.3%	1.35 [1.02 , 1.79]
Papp 2013b	97	173	47	87	11.6%	1.04 [0.82 , 1.31]
STYLE 2020	135	201	52	102	13.8%	1.32 [1.06 , 1.63]
Subtotal (95% CI)		**1728**		**865**	**92.7%**	**1.24 [1.13 , 1.36]**
Total events:	958		386			
Heterogeneity: Tau² = 0.00; Chi² = 7.44, df = 6 (P = 0.28); I² = 19%						
Test for overall effect: Z = 4.52 (P < 0.00001)						
6.9.2 TYK2 versus placebo						
Papp 2018	149	222	23	45	7.3%	1.31 [0.97 , 1.77]
Subtotal (95% CI)		**222**		**45**	**7.3%**	**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)		**1950**		**910**	**100.0%**	**1.24 [1.14 , 1.35]**
Total events:	1107		409			
Heterogeneity: Tau² = 0.00; Chi² = 7.57, df = 7 (P = 0.37); I² = 7%						
Test for overall effect: Z = 5.12 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.71), I² = 0%						

Analysis 6.10. Comparison 6: Secondary outcome - adverse events, Outcome 10: Biologic versus small molecules



Study or Subgroup	Biologic Events	Total	Small molecules Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
6.10.1 Etanercept versus apremilast						
LIBERATE 2017	58	83	44	83	100.0%	1.32 [1.03 , 1.69]
Subtotal (95% CI)		**83**		**83**	**100.0%**	**1.32 [1.03 , 1.69]**
Total events:	58		44			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.19 (P = 0.03)						

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	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1.1 Secukinumab versus ustekinumab	2	1778	Risk Ratio (M-H, Random, 95% CI)	1.23 [1.15, 1.31]

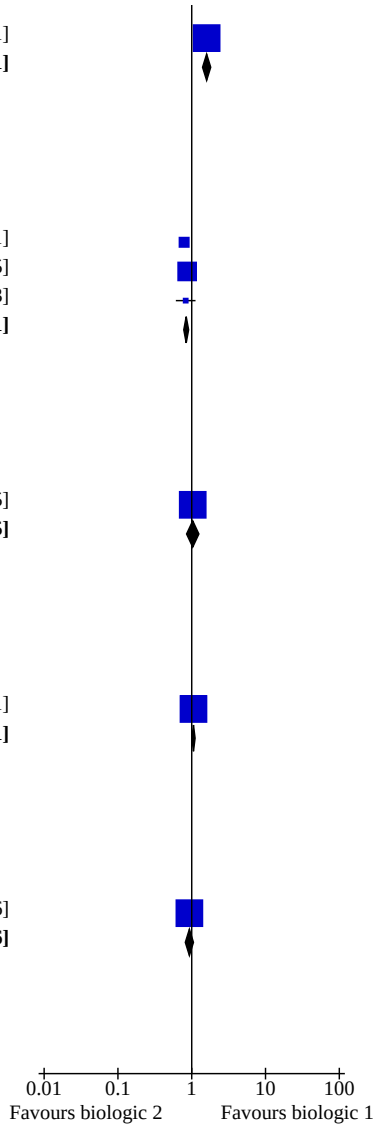
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1.2 Risankizumab versus ustekinumab	2	799	Risk Ratio (M-H, Random, 95% CI)	1.73 [1.46, 2.05]
7.1.3 Ixekizumab versus ustekinumab	1	302	Risk Ratio (M-H, Random, 95% CI)	1.30 [1.11, 1.52]
7.1.4 Bimekizumab versus ustekinumab	1	484	Risk Ratio (M-H, Random, 95% CI)	1.47 [1.27, 1.70]
7.1.5 Risankizumab versus secukinumab	1	327	Risk Ratio (M-H, Random, 95% CI)	1.52 [1.31, 1.76]
7.1.6 Bimekizumab versus secukinumab	1	743	Risk Ratio (M-H, Random, 95% CI)	1.19 [1.09, 1.28]
7.1.7 Guselkumab versus secukinumab	1	1048	Risk Ratio (M-H, Random, 95% CI)	1.21 [1.13, 1.29]
7.1.8 Guselkumab versus adalimumab	1	663	Risk Ratio (M-H, Random, 95% CI)	1.59 [1.40, 1.81]
7.1.9 Secukinumab 150 versus secukinumab 300	3	1017	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.78, 0.91]
7.1.10 Guselkumab 100 versus guselkumab 50	1	128	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.85, 1.25]
7.1.11 Ixekizumab Q2W versus Ixekizumab Q4W	1	1227	Risk Ratio (M-H, Random, 95% CI)	1.06 [1.01, 1.11]
7.1.12 Risankizumab 75 versus risankizumab 150	1	113	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.82, 1.06]
7.2 Small molecule 1 versus small molecule 2	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.2.1 Apremilast 30mg versus apremilast other	1	170	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.84, 1.86]
7.3 Biologic versus placebo	1	82	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.58, 1.12]
7.3.1 Secukinumab versus placebo	1	82	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.58, 1.12]

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						
CLARITY 2018	402	550	330	552	61.4%	1.22 [1.12 , 1.33]
CLEAR 2015	250	337	203	339	38.6%	1.24 [1.11 , 1.38]
Subtotal (95% CI)		**887**		**891**	**100.0%**	**1.23 [1.15 , 1.31]**
Total events:	652		533			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%						
Test for overall effect: Z = 6.05 (P < 0.00001)						
7.1.2 Risankizumab versus ustekinumab						
UltIMMa-1 2018	249	304	44	102	45.2%	1.90 [1.51 , 2.39]
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: Tau² = 0.00; Chi² = 1.25, df = 1 (P = 0.26); I² = 20%						
Test for overall effect: Z = 6.29 (P < 0.00001)						
7.1.3 Ixekizumab versus ustekinumab						
IXORA-S 2017	104	136	98	166	100.0%	1.30 [1.11 , 1.52]
Subtotal (95% CI)		**136**		**166**	**100.0%**	**1.30 [1.11 , 1.52]**
Total events:	104		98			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.22 (P = 0.001)						
7.1.4 Bimekizumab versus ustekinumab						
BE VIVID 2021	263	321	91	163	100.0%	1.47 [1.27 , 1.70]
Subtotal (95% CI)		**321**		**163**	**100.0%**	**1.47 [1.27 , 1.70]**
Total events:	263		91			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.15 (P < 0.00001)						
7.1.5 Risankizumab versus secukinumab						
IMMerge 2021	142	164	93	163	100.0%	1.52 [1.31 , 1.76]
Subtotal (95% CI)		**164**		**163**	**100.0%**	**1.52 [1.31 , 1.76]**
Total events:	142		93			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.59 (P < 0.00001)						
7.1.6 Bimekizumab versus secukinumab						
BE RADIANT 2021	312	373	261	370	100.0%	1.19 [1.09 , 1.28]
Subtotal (95% CI)		**373**		**370**	**100.0%**	**1.19 [1.09 , 1.28]**
Total events:	312		261			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.19 (P < 0.0001)						
7.1.7 Guselkumab versus secukinumab						
ECLIPSE 2019	451	534	360	514	100.0%	1.21 [1.13 , 1.29]
Subtotal (95% CI)		**534**		**514**	**100.0%**	**1.21 [1.13 , 1.29]**
Total events:	451		360			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.46 (P < 0.00001)						
7.1.8 Guselkumab versus adalimumab						
VOYAGE-1 2016	251	329	160	334	100.0%	1.59 [1.40 , 1.81]

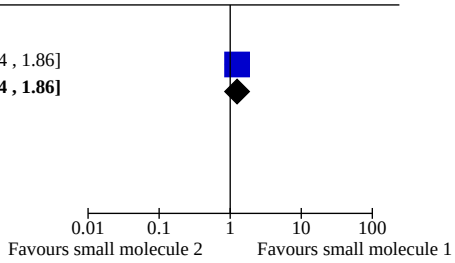
Analysis 7.1. (Continued)

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)						
7.1.9 Secukinumab 150 versus secukinumab 300						
Cai 2020	86	136	218	272	28.5%	0.79 [0.69 , 0.91]
ERASURE 2014	178	243	207	245	65.5%	0.87 [0.79 , 0.95]
JUNCTURE 2015	32	61	38	60	6.0%	0.83 [0.61 , 1.13]
Subtotal (95% CI)		**440**		**577**	**100.0%**	**0.84 [0.78 , 0.91]**
Total events:	296		463			
Heterogeneity: Tau² = 0.00; Chi² = 1.26, df = 2 (P = 0.53); I² = 0%						
Test for overall effect: Z = 4.49 (P < 0.00001)						
7.1.10 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)						
7.1.11 Ixekizumab Q2W versus Ixekizumab Q4W						
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)						
7.1.12 Risankizumab 75 versus risankizumab 150						
SustaIMM 2019	50	58	51	55	100.0%	0.93 [0.82 , 1.06]
Subtotal (95% CI)		**58**		**55**	**100.0%**	**0.93 [0.82 , 1.06]**
Total events:	50		51			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.13 (P = 0.26)						

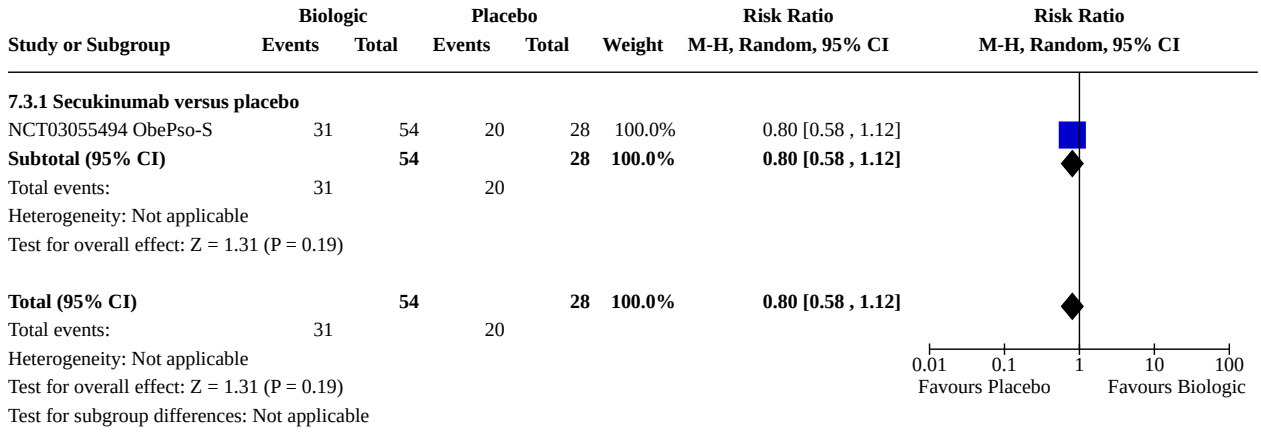


Analysis 7.2. Comparison 7: Secondary outcome - PASI 90 at 52 weeks, Outcome 2: Small molecule 1 versus small molecule 2

Study or Subgroup	Small molecule 1 Events	Small molecule 1 Total	Small molecule 2 Events	Small molecule 2 Total	Weight	Risk Ratio M-H, Random, 95% CI
7.2.1 Apremilast 30mg versus apremilast other						
Ohtsuki 2017	35	85	28	85	100.0%	1.25 [0.84 , 1.86]
Subtotal (95% CI)		**85**		**85**	**100.0%**	**1.25 [0.84 , 1.86]**
Total events:	35		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.11 (P = 0.27)						



Analysis 7.3. Comparison 7: Secondary outcome - PASI 90 at 52 weeks, Outcome 3: Biologic versus placebo



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	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1.1 Secukinumab versus ustekinumab	2	1778	Risk Ratio (M-H, Random, 95% CI)	1.13 [1.04, 1.22]
8.1.2 Risankizumab versus ustekinumab	2	799	Risk Ratio (M-H, Random, 95% CI)	1.26 [1.12, 1.41]
8.1.3 Ixekizumab versus ustekinumab	1	302	Risk Ratio (M-H, Random, 95% CI)	1.16 [1.05, 1.29]
8.1.4 Risankizumab versus secukinumab	1	327	Risk Ratio (M-H, Random, 95% CI)	1.28 [1.14, 1.44]
8.1.5 Bimekizumab versus secukinumab	1	743	Risk Ratio (M-H, Random, 95% CI)	1.09 [1.02, 1.16]
8.1.6 Guselkumab versus secukinumab	1	1048	Risk Ratio (M-H, Random, 95% CI)	1.06 [1.00, 1.12]
8.1.7 Guselkumab versus adalimumab	1	663	Risk Ratio (M-H, Random, 95% CI)	1.40 [1.28, 1.54]
8.1.8 Secukinumab 150 versus secukinumab 300	3	1017	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.85, 0.94]
8.1.9 Guselkumab 100 versus guselkumab 50	1	128	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.88, 1.09]
8.1.10 Ixekizumab Q2W versus ixekizumab Q4W	1	1227	Risk Ratio (M-H, Random, 95% CI)	1.14 [1.07, 1.22]

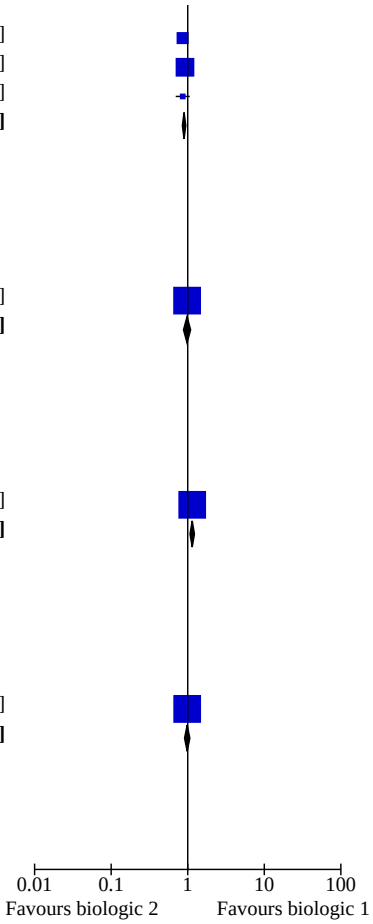
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1.11 Risankizumab 75 versus risankizumab 150	1	113	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.91, 1.07]
8.2 Small molecules 1 versus small molecules 2	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.2.1 Apremilast 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						
CLARITY 2018	490	550	453	552	54.4%	1.09 [1.03 , 1.14]
CLEAR 2015	306	337	262	339	45.6%	1.17 [1.10 , 1.26]
Subtotal (95% CI)		**887**		**891**	**100.0%**	**1.13 [1.04 , 1.22]**
Total events:	796		715			
Heterogeneity: Tau² = 0.00; Chi² = 3.51, df = 1 (P = 0.06); I² = 71%						
Test for overall effect: Z = 3.00 (P = 0.003)						
8.1.2 Risankizumab versus ustekinumab						
UltIMMa-1 2018	280	304	70	102	44.8%	1.34 [1.17 , 1.54]
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: Tau² = 0.00; Chi² = 1.67, df = 1 (P = 0.20); I² = 40%						
Test for overall effect: Z = 3.98 (P < 0.0001)						
8.1.3 Ixekizumab versus ustekinumab						
IXORA-S 2017	120	136	126	166	100.0%	1.16 [1.05 , 1.29]
Subtotal (95% CI)		**136**		**166**	**100.0%**	**1.16 [1.05 , 1.29]**
Total events:	120		126			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.80 (P = 0.005)						
8.1.4 Risankizumab versus secukinumab						
IMMerge 2021	147	164	114	163	100.0%	1.28 [1.14 , 1.44]
Subtotal (95% CI)		**164**		**163**	**100.0%**	**1.28 [1.14 , 1.44]**
Total events:	147		114			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.29 (P < 0.0001)						
8.1.5 Bimekizumab versus secukinumab						
BE RADIANT 2021	330	373	301	370	100.0%	1.09 [1.02 , 1.16]
Subtotal (95% CI)		**373**		**370**	**100.0%**	**1.09 [1.02 , 1.16]**
Total events:	330		301			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.70 (P = 0.007)						
8.1.6 Guselkumab versus secukinumab						
ECLIPSE 2019	452	534	412	514	100.0%	1.06 [1.00 , 1.12]
Subtotal (95% CI)		**534**		**514**	**100.0%**	**1.06 [1.00 , 1.12]**
Total events:	452		412			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.90 (P = 0.06)						
8.1.7 Guselkumab versus adalimumab						
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)						
8.1.8 Secukinumab 150 versus secukinumab 300						
Cai 2020	111	136	259	272	32.8%	0.86 [0.79 , 0.93]
ERASURE 2014	211	242	231	245	61.5%	0.92 [0.87 , 0.98]

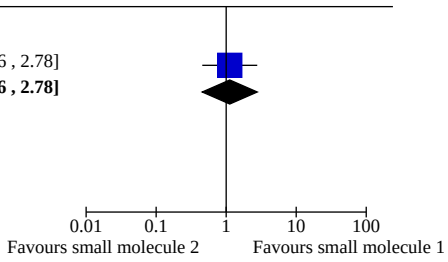
Analysis 8.1. (Continued)

Cai 2020	111	136	259	272	32.8%	0.86 [0.79 , 0.93]
ERASURE 2014	211	243	231	245	61.5%	0.92 [0.87 , 0.98]
JUNCTURE 2015	42	61	48	60	5.8%	0.86 [0.70 , 1.06]
Subtotal (95% CI)		**440**		**577**	**100.0%**	**0.90 [0.85 , 0.94]**
Total events:	364		538			
Heterogeneity: Tau² = 0.00; Chi² = 2.20, df = 2 (P = 0.33); I² = 9%						
Test for overall effect: Z = 4.21 (P < 0.0001)						
8.1.9 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)						
8.1.10 Ixekizumab Q2W versus ixekizumab Q4W						
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)						
8.1.11 Risankizumab 75 versus risankizumab 150						
SustaIMM 2019	55	58	53	55	100.0%	0.98 [0.91 , 1.07]
Subtotal (95% CI)		**58**		**55**	**100.0%**	**0.98 [0.91 , 1.07]**
Total events:	55		53			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.40 (P = 0.69)						



Analysis 8.2. Comparison 8: Secondary outcome - PASI 75 at 52 weeks, Outcome 2: Small molecules 1 versus small molecules 2

Study or Subgroup	Small molecules 1 Events	Total	Small molecules 2 Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
8.2.1 Apremilast 30 versus apremilast other						
Ohtsuki 2017	9	85	8	85	100.0%	1.13 [0.46 , 2.78]
Subtotal (95% CI)		**85**		**85**	**100.0%**	**1.13 [0.46 , 2.78]**
Total events:	9		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.26 (P = 0.80)						



ADDITIONAL TABLES

Table 1. Glossary

Term	Definition
Antagonist	A substance that interferes with or inhibits the physiological action of another.

Table 1. Glossary *(Continued)*

Antigen	A molecule capable of inducing an immune response
Anti-TNF alpha	A pharmaceutical drug that suppresses the physiologic response to tumour necrosis 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
Biosimilar	Biological agent highly similar to another already-approved biological medicine
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
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

Table 1. Glossary *(Continued)*

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
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

Table 1. Glossary *(Continued)*

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
Asawanonda 2006	Prof. Asawanonda	Outcomes: PASI 75, PGA 0/1, AEs and SAEs	21 November 2016 15 December 2016	Asawanonda 2006 sent detailed report for PASI 75 and AEs. PGA was not collected during this study
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

Table 2. Investigators contacted *(Continued)*

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
ACCEPT 2010	Prof. Griffiths Janssen	Outcome: QoL scale	16 December 2016	QoL was not collected during this study
AMAGINE-2 2015	Prof. Lebwohl Valeant Pharmaceuticals NA LLC	Outcomes: PASI 90 and QoL scale	8 and 21 November 2016	AMAGINE-2 2015 sent detailed report for PASI 90; individual scores and median difference from baseline of QoL were not available
AMAGINE-3 2015	Prof. Lebwohl Valeant Pharmaceuticals NA LLC	Outcomes: PASI 90 and QoL scale	8 and 21 November 2016	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
REVEAL 2008	Prof. Menter	Outcome: PGA 0/1	8 and 21 November 2016	No response
EXPRESS-II 2007	Prof. Menter	Outcome: PGA 0/1	8 and 21 November 2016	No response
BRIDGE 2017	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
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 2013b	Prof. Papp	Outcome: PASI 90, PGA0/1, QoL scale	3 January 2017	Additional data to the publication not provided
JUNCTURE 2015	Prof. Paul Novartis	Outcome: QoL scale	15 December 2016, 2 January 2017	Additional data to the publication not provided

Table 2. Investigators contacted *(Continued)*

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
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
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	Prof Strober sent detailed report for the requested outcomes
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	Prof 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
LOTUS 2013	No contact	Outcome: PASI 90	No	Authors' email not found
CLARITY 2018	Prof Bagel	Outcome: QoL Scale	24 June 2019	Email response 01 July 2019 Additional data to the publication not provided
ADACCESS 2018	Prof Blauvelt	Outcome: QoL Scale	24 June and 1st July 2019	Email response: 2 July 2019 Additional data to the publication not provided
EGALITY 2017	Prof Gerdes	Outcomes: QoL Scale, AEs, SAEs	24 June 2019	Email response 27 June 2019 Additional data to the publication not provided
Ikonomidis 2017	Prof Ikonomidis	Outcomes: PASI 90, 75, PGA0/1, QoL Scale, AES, SAEs	24 June and 1st July 2019, 17 August 2020, 8 September 2020	No response
VIP Trial 2018	Prof Gelfand	Outcome: PASI 90	24 June	Email response 24 June 2019

Table 2. Investigators contacted *(Continued)*

				Additional data to the publication not provided
SIGNATURE 2019	Prof. Warren	Outcomes: PGA0/1, SAEs	24 June 2019, 21 October 2021	No response
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
VOLTAIRE-PSO 2021	Prof. Menter	Outcome: QoL Scale	24 June 2019, 21 October 2021	No response
ORION 2020	Prof. Ferris	Outcome: DLQI	24 June and 2nd July 2019	No response
POLARIS 2020	Prof. Thaçi	Outcome: PGA0/1	24 June 2019, 21 October 2021	No response
SustaIMM 2019	Prof. Kitamura	Outcome: DLQI	24 June 2019, 21 October 2021	Email not received: " The following message to <susumu.kitamura@abbvie.com> was undeliverable."
Papp 2017a	Prof. Papp	Outcome: DLQI	24 June 2019	Email answer 24 June 2019 Additional data to the publication not provided
BE ABLE 1 2018	Prof. Papp	Outcome: DLQI	24 June 2019	Email answer 24 June 2019 Additional data to the publication not provided
Papp 2017b	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 2018	Prof. Papp	Outcome: DLQI	24 June 2019	Email answer 24 June 2019 Additional data to the publication not provided
IXORA-S 2017	Prof. Reich	Outcome: DLQI	24 June and 1st July 2019	E-mails not received (email: kreich@dermatologikum.de; kreich@jeruocon.com)
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)
PRIME 2017	Prof. Sticherling	Outcome: DLQI	24 June and 1st July 2019	Email answer 02 July 2019

Table 2. Investigators contacted *(Continued)*

				Additional data to the publication not provided
CIMPACT 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
IMMhance 2020	Prof. Blauvelt	Outcome: DLQI	24 June 2019, 21 October 2021	Email answer 22 October 2021: Additional data to the publication not provided
NCT02134210 RaPsOdy	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
Yu 2019	Prof. Shi	Outcomes: PGA 0/1, DLQI	12 August 2020, 8 September 2020	No response
CARIMA 2019	Prof. von Stebut	Outcomes: PASI 90, 75, IGA 0/1, QoL Scale	12 August 2020, 8 September 2020	No response
PsOsim 2017	Prof. Hodge	Outcomes: PASI 90, PGA 0/1, QoL Scale	12 August 2020, 8 September 2020	No response
VIP-U Trial 2020	Prof. Gelfand	Outcome: QoL Scale	12 August 2020	Email answer 17 August 2020 VIP-U Trial 2020 sent detailed report for the requested outcome.
Liu 2020	Prof. Liu	Outcome: QoL Scale	12 August 2020	Email answer 13 August 2020 Liu 2020 sent detailed report for the requested outcome.
ECLIPSE 2019	Prof. Reich	Outcomes: QoL Scale, AEs, SAEs	12 August 2020, 8 September 2020	Email answer 11 September 2020: Additional data to the publication not provided
IXORA-R 2020	Prof. Blauvelt	Outcomes: PASI 90/75, PGA 0/1, DLQI	12 August 2020, 15 October 2021 (outcomes at week 24)	Email answer 13 August 2020 Sent detailed report for the requested outcomes except for PASI 75 and DLQI (not disclosed yet).
ALLURE 2021	Prof. Sigurgeirsson	Outcome: DLQI	12 August 2020, 21 October 2021	Email answer 25 August 2020 Additional data to the publication not provided
Cai 2020	Prof. Zhang	Outcome: DLQI	21 October 2021	No response

Table 2. Investigators contacted *(Continued)*

NCT03055494 ObePso-S	Sponsors: Novartis	Outcomes: PASI 75, PGA 1/0, QoL Scale, AEs, SAEs	8 September 2020	No contact. We will contact the authors when the article is published
IMMerge 2021	Prof. Warren	Outcome: QoL Scale	8 September 2020, 21 October 2021	No response
AlMutairi 2021	Prof. Almutairi	Outcomes: PASI 90/75, QoL	20 September 2021	No response
BE READY 2021	Prof. Gordon	Outcomes: QoL, SAE, PASI 75	20 September 2021	No response
BE VIVID 2021	Prof. Reich	Outcomes: QoL, SAE	20 September 2021	No response
BE RADIANT 2021	Prof. Reich	Outcomes: QoL, AE, SAE	20 September 2021	No response
BE SURE 2021	Prof. Warren	Outcomes: PASI 75, SAE, QoL	20 September 2021	Email answer 20 October 2021: Sent detailed report for the requested outcome
Seo 2020	Prof. Lee	Outcomes: SAE, QoL, PASI 90	20 September 2021	No response
Ye 2020	Prof. Chengzhong Zhang	Outcomes: PGA 1/0, AE, SAE, QoL	20 September 2021	No response
Rathipriyadharshini 2020	Prof. Srinivasan	Outcomes: PASI 90/75, PGA 1/0, AE, QoL	20 September 2021	No response
CALYPSO 2018	Prof. Korotaeva	Outcomes: PGA 1/0, SAE, QoL	20 September 2021	Email answer 23 September 2021: CALYPSO 2018 sent detailed report for the requested outcome.
Singh 2021	Prof. Sermili Rini Singnarpi	Outcomes: PGA 1/0, SAE, AE, QoL	20 September 2021	No response
Blauvelt 2021a	Prof. Blauvelt	Outcomes: PASI 75, QoL	20 September 2021	Email answer 20 September 2021: "Neither was done".
PLANETA 2021	Prof. Morozova	Outcomes: PGA 1/0, QoL	20 September 2021	Email answer 27 September 2021: PLANETA 2021 sent detailed report for the requested outcome.
Papp 2021	Prof. Papp	Outcome: QoL	20 September 2021	Email answer 20 September 2021: Additional data to the publication not provided
NCT03421197	Sponsor: Dr. Reddy's Laboratories Limited	Outcomes: PASI 90, QoL, AE	20 September 2021	No contact. We will contact the authors when the article is published

Table 2. Investigators contacted *(Continued)*

NCT03504852	Sponsor: Novartis Pharmaceuticals	Outcomes: PASI 75, QoL, AE, SAE	20 September 2021	No contact. We will contact the authors when the article is published
NCT03535194	Sponsor: Eli Lilly and Company	Outcome: QoL	20 September 2021	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 11 February 2020	No response
DRKS00000716	Prof. Jacobi	Asking for study protocol and efficacy/safety results	12 and 19 January 2017	No response
CTRI/2015/05/005830	Prof. Shah	Asking for study protocol and efficacy/safety results	12 and 19 January 2017 11 February 2020	No response
NCT01088165	Prof. Holzer	Asking for study protocol and efficacy/safety results	3 and 24 June 2019 11 February 2020	No response
NCT02655705	Prof. Youn	Asking for study protocol and efficacy/safety results	3 and 24 June 2019 11 February 2020	No response
CTRI/2017/09/009859	Prof. Smolen	Asking for subgroup analysis for moderate-to severe psoriasis and their efficacy/safety results	17 Ausgut 2020, 8 September 2020, 30 September 2021	Email answer 30 September 2021: Additional data to the publication not provided
EUC-TR2010-020168-39-DE	Prof. Anderson	Asking for study protocol and efficacy/safety results	17 August 2020, 8 September 2020	No response
EUC-TR2015-005279-25-DE	Prof. Philipp	Asking for study protocol and efficacy/safety results	17 August 2020, 8 September 2020, 31 August 2021	No response
Makavos 2020	Prof. Ikonomidis	Asking for study protocol and efficacy/safety results	30 October 2020, 10 September 2021	No response

Table 2. Investigators contacted *(Continued)*

CTRI/2016/10/007345	Dr Piyush Agarwal, general manager Glenmark Pharmaceuticals Ltd DrPiyush.Agarwal@glenmarkpharma.com Amol.Pendse@glenmarkpharma.com	Asking for study protocol and efficacy/safety results	11 February 2020, 30 August 2021	No response
Goldust 2019	Prof. Goldust	Asking for study protocol and efficacy/safety results	31 August 2021	No response
NCT01558310	Dr Yamauchi, Dr Patnaik, Director, Clinical Science Institute	Asking for study protocol and efficacy/safety results	5 January 2017	Email response: Additional data to the publication not provided
NCT02701205	Prof Hongzhong Jin	Asking for study protocol and efficacy/safety results	3 June 2019 11 February 2020, 30 August 2021	Email response "This is the mail system at host mta-8_BSR. Your message could not be delivered to one or more recipients."
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				
EUCTR2013-004918-18-NL	Prof. Spuls	Asking for study protocol and efficacy/safety results	5 January 2017	Email response Additional data to the publication not provided
EUCTR2017-001615-36-DE	Prof. Gerdes	Asking for study protocol and efficacy/safety results	17 August 2020, 8 September 2020	Email answer 8 September 2020: Additional data to the publication not provided

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	17.35	14.58	20.64	14.64	11.54	18.58	19.75	15.94	24.45
Apremilast versus placebo	7.69	4.48	13.18	6.95	3.38	14.33	10.06	2.48	40.85
Bimekizumab versus placebo	30.27	25.45	36.01	33.72	23.83	47.71	29.82	24.94	35.65
Brodalumab versus placebo	24.10	20.06	28.97	26.60	16.95	41.77	21.02	11.53	38.33
Certolizumab versus placebo	13.30	9.65	18.32	19.77	8.29	47.12	7.92	2.63	23.87
Etanercept versus placebo	10.65	8.89	12.77	11.11	8.49	14.55	10.18	7.70	13.46
FAEs versus placebo	4.36	2.01	9.46	4.47	2.01	9.95	2.93	0.13	67.39
Guselkumab versus placebo	24.11	20.37	28.54	29.62	22.21	39.50	22.85	19.10	27.34
Infliximab versus placebo	50.19	20.92	120.45	42.64	16.08	113.09	98.56	13.55	717.04
Ixekizumab versus placebo	30.19	25.38	35.93	35.25	25.00	49.69	29.01	23.99	35.08
Methotrexate versus placebo	6.97	1.42	34.34	5.85	0.73	46.93	8.94	0.75	106.67
Risankizumab versus placebo	28.75	24.03	34.39	31.64	22.94	43.64	27.96	23.00	33.99
Secukinumab versus placebo	26.26	22.26	30.99	22.81	16.73	31.08	27.37	22.81	32.85
Sonelokimab versus placebo	25.60	19.35	33.87	65.68	4.15	1038.50	9.81	0.59	162.87
Tildrakizumab versus placebo	18.57	14.04	24.55	17.25	8.26	36.02	20.46	7.96	52.59
Ustekinumab versus placebo	18.90	16.00	22.34	17.11	13.56	21.60	19.84	16.50	23.87
Bimekizumab versus adalimumab	1.75	1.59	1.91	1.66	1.42	1.94	1.79	1.60	2.01
Guselkumab versus adalimumab	1.39	1.29	1.50	1.45	1.32	1.59	1.26	1.10	1.45
Risankizumab versus adalimumab	1.66	1.50	1.83	1.53	1.33	1.75	1.80	1.57	2.07

Table 3. Direct and indirect evidences and network meta-analysis results summary table for PASI 90 *(Continued)*

Etanercept versus apremilast	1.39	0.81	2.37	1.39	0.71	2.71	1.39	0.59	3.28
Secukinumab versus bimekizumab	0.87	0.81	0.92	0.87	0.80	0.94	0.86	0.76	0.98
Ustekinumab versus bimekizumab	0.62	0.58	0.67	0.59	0.50	0.69	0.64	0.58	0.70
Ustekinumab versus brodalumab	0.78	0.72	0.86	0.79	0.72	0.86	0.57	0.26	1.23
Etanercept versus certolizumab	0.80	0.61	1.06	0.83	0.62	1.11	0.54	0.22	1.36
Methotrexate versus ciclosporin	0.99	0.60	1.64	0.99	0.60	1.64	45.79	0.00	.
Infliximab versus etanercept	4.71	1.94	11.44	9.20	1.28	66.37	3.98	1.48	10.74
Ixekizumab versus etanercept	2.83	2.54	3.16	2.91	2.53	3.34	2.73	2.30	3.23
Secukinumab versus etanercept	2.47	2.20	2.76	2.33	1.86	2.93	2.51	2.20	2.86
Tildrakizumab versus etanercept	1.74	1.39	2.18	1.77	1.40	2.24	1.44	0.61	3.39
Ustekinumab versus etanercept	1.77	1.58	1.99	1.80	1.45	2.24	1.76	1.54	2.02
Methotrexate versus FAEs	1.60	0.32	8.06	2.00	0.19	20.90	1.31	0.14	12.18
Ixekizumab versus guselkumab	1.25	1.16	1.35	1.29	1.18	1.42	1.16	1.01	1.34
Secukinumab versus guselkumab	1.09	1.02	1.16	1.10	1.01	1.20	1.06	0.94	1.20
Secukinumab versus risankizumab	0.91	0.83	1.00	0.89	0.77	1.03	0.93	0.83	1.04
Ustekinumab versus risankizumab	0.66	0.60	0.72	0.61	0.52	0.71	0.69	0.61	0.78
Sonelokimab versus secukinumab	0.97	0.78	1.22	0.97	0.77	1.22	6.49	0.03	1640.30
Ustekinumab versus secukinumab	0.72	0.68	0.76	0.72	0.67	0.77	0.73	0.66	0.81

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 4. Ranking findings for all outcomes at class level

Class-level interventions	SUCRA PASI 90	Rank PASI 90	SUCRA SAE	Rank SAE	SUCRA SAE excluded flare of psoriasis	Rank SAE excluded flare of psoriasis	SUCRA PASI 75	Rank PASI 75	SUCRA AE	Rank AE	SUCRA PGA	Rank PGA	SUCRA QoL	Rank QoL
Anti-IL17	98.7	1	39.6	5	35.5	5	98.5	1	25.8	6	99.7	1	79.2	2
Anti-IL23	84.5	2	75.4	1	66.8	2	83.9	2	85.1	2	82.4	2	84.2	1
Anti-IL12/23	66.6	3	33	6	27.3	7	67.6	3	54.7	4	67.7	3	73.7	3
Anti-TNF alpha	48.5	4	47.7	4	28.8	6	50	4	56.3	3	50.2	4	43.3	5
Small molecules	33.2	5	58	3	76.6	1	33.3	5	3	7	32.5	5	18	6
Non-biological treatments	18.6	6	69.3	2	52.3	4	16.7	6	30.2	5	17.5	6	51.4	4
Placebo	0	7	27.1	7	62.6	3	0	7	94.9	1	0	7	0.1	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 SAE excluded flare of psoriasis	Rank SAE excluded flare of psoriasis	SUCRA PASI 75	Rank PASI 75	SUCRA AE	Rank AE	SUCRA PGA	Rank PGA	SUCRA QoL	Rank QoL
Infliximab	95.6	1	29.9	19	51.3	8	96.8	1	33.8	13	85.2	3	66.3	7

Table 5. Ranking findings for all outcomes at drug level *(Continued)*

Bimekizumab	90	2	80.4	2	83.7	1	87.4	4	19.8	18	91.1	1	66.9	6
Ixekizumab	89.6	3	48	12	36.1	16	88.4	2	31	15	88.2	2	94.7	1
Risankizumab	83.9	4	66.9	3	73.5	2	87.8	3	72.6	5	82.5	4	94.4	2
Secukinumab	75	5	31.6	18	39.9	15	77.6	5	40.5	12	76.2	5	72.2	4
Sonelokimab	72.5	6	35.4	17	42.2	13	65.4	8	32.5	14	74.6	6	-	-
Brodalumab	65.6	7	37	16	46	11	71.6	7	44.5	11	74.3	7	14.1	15
Guselkumab	65.3	8	48.8	11	48.2	10	72.4	6	68.2	6	63.9	8	60.2	8
Ustekinumab	52.2	9	41.7	13	42.1	14	58.3	9	58.3	9	53.6	9	73.4	3
Tildrakizumab	50.3	10	56.7	7	21.4	18	54	10	93.5	1	42.1	13	69.9	5
Deucravacitinib	47.7	11	60.7	5	66.8	3	45.7	12	19.6	19	46.1	10	27.5	14
Adalimumab	45.3	12	37.8	14	43.8	12	48.8	11	59.2	8	45	12	40.1	11
Certolizumab	36.9	13	64.4	4	25	17	45.5	13	86.6	2	45.3	11	34.5	12
Etanercept	29.9	14	60.4	6	48.2	9	36.8	14	55.1	10	30.6	15	46.3	10
Ciclosporin	26.6	15	11	20	-	-	24.8	16	20.8	17	29.5	16	-	-
Methotrexate	25.7	16	97.2	1	-	-	16.3	18	59.3	7	33.5	14	46.4	9
Apremilast	22.5	17	52.9	8	66.7	4	24.9	15	14.7	20	15.9	18	10.6	16
Netakimab	12.9	18	51.7	9	56.5	6	23.6	17	81.1	4	16	17	32.1	13
FAEs	12.3	19	50.2	10	51.9	7	9.3	20	24.8	16	6.3	19	-	-
Placebo	0.1	20	37.3	15	56.6	5	1.4	21	84.3	3	0	20	0.3	17
Acitretine	-	-	-	-	-	-	13.3	19	-	-	-	-	-	-

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	1.01	0.68	1.50	1.18	0.74	1.91	0.68	0.32	1.45
Apremilast versus placebo	0.85	0.49	1.48	0.85	0.48	1.52	0.88	0.03	22.45
Bimekizumab versus placebo	0.52	0.25	1.09	0.57	0.20	1.60	0.47	0.15	1.48
Brodalumab versus placebo	1.03	0.62	1.73	0.89	0.51	1.58	2.99	0.46	19.24
Certolizumab versus placebo	0.70	0.31	1.58	0.61	0.26	1.39	29.23	0.45	1889.32
Etanercept versus placebo	0.80	0.54	1.18	0.70	0.44	1.11	1.14	0.52	2.49
Guselkumab versus placebo	0.90	0.62	1.33	1.04	0.50	2.19	0.85	0.54	1.36
Infliximab versus placebo	1.18	0.57	2.43	1.22	0.58	2.59	0.73	0.05	11.26
Ixekizumab versus placebo	0.91	0.61	1.36	0.91	0.52	1.60	0.90	0.47	1.72
Risankizumab versus placebo	0.73	0.47	1.13	0.48	0.25	0.92	1.06	0.57	1.97
Secukinumab versus placebo	1.06	0.77	1.47	1.13	0.71	1.80	1.00	0.63	1.58
Sonelokimab versus placebo	1.24	0.25	6.16	0.93	0.16	5.51	10.08	0.03	3446.81
Tildrakizumab versus placebo	0.80	0.36	1.74	0.97	0.38	2.50	0.39	0.05	2.94
Ustekinumab versus placebo	0.97	0.69	1.36	1.00	0.63	1.58	0.93	0.55	1.55
Bimekizumab versus adalimumab	0.52	0.24	1.11	0.50	0.15	1.70	0.53	0.20	1.40
Guselkumab versus adalimumab	0.90	0.56	1.44	0.92	0.46	1.85	0.88	0.46	1.67
Risankizumab versus adalimumab	0.72	0.43	1.21	1.12	0.46	2.72	0.58	0.31	1.09
Etanercept versus apremilast	0.93	0.49	1.80	0.68	0.14	3.33	1.00	0.49	2.05

Table 6. Direct and indirect evidence and network meta-analysis results summary table for serious adverse events *(Continued)*

Ustekinumab versus bimekizumab	1.85	0.87	3.95	1.97	0.58	6.71	1.78	0.68	4.68
Ustekinumab versus brodalumab	0.94	0.53	1.65	0.75	0.33	1.70	1.26	0.48	3.35
Etanercept versus certolizumab	1.14	0.47	2.78	2.16	0.33	14.06	0.86	0.27	2.71
Infliximab versus etanercept	1.48	0.66	3.33	0.92	0.06	13.87	1.55	0.66	3.63
Ixekizumab versus etanercept	1.14	0.71	1.82	1.06	0.55	2.02	1.24	0.62	2.47
Secukinumab versus etanercept	1.34	0.83	2.15	1.59	0.48	5.24	1.29	0.77	2.17
Tildrakizumab versus etanercept	1.00	0.46	2.18	0.70	0.27	1.82	2.16	0.51	9.06
Ustekinumab versus etanercept	1.21	0.75	1.96	1.25	0.38	4.11	1.21	0.71	2.04
Ixekizumab versus guselkumab	1.00	0.64	1.58	1.10	0.56	2.15	0.92	0.49	1.74
Secukinumab versus guselkumab	1.18	0.82	1.69	1.16	0.72	1.89	1.20	0.65	2.21
Ustekinumab versus ixekizumab	1.07	0.65	1.73	1.37	0.33	5.61	1.03	0.61	1.73
Secukinumab versus risankizumab	1.46	0.90	2.36	0.67	0.24	1.84	1.83	1.06	3.16
Ustekinumab versus risankizumab	1.32	0.83	2.10	1.84	0.94	3.60	0.98	0.52	1.85
Sonelokimab versus secukinumab	1.17	0.23	5.89	2.84	0.16	50.61	0.26	0.00	19.73
Ustekinumab versus secukinumab	0.91	0.62	1.33	0.79	0.43	1.44	1.00	0.61	1.65

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	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
ADA:BIME	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]

Table 7. Study Bias distribution for PASI 90 using CINeMA *(Continued)*

ADA:GUSEL	3	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
ADA:PBO	8	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
ADA:RISAN	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
APRE:ETA	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
APRE:PBO	5	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
BIME:PBO	3	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
BIME:SECU	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
BIME:USK	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
BRODA:PBO	5	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
BRODA:USK	2	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
CERTO:ETA	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CERTO:PBO	5	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
CICLO:MTX	2	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
DEUCRAVA:PBO	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
ETA:IFX	1	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
ETA:IXE	2	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
ETA:PBO	14	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
ETA:SECU	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]

Table 7. Study Bias distribution for PASI 90 using CINeMA *(Continued)*

ETA:TILDRA	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
ETA:USK	1	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
FUM:MTX	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
FUM:PBO	1	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
GUSEL:IXE	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
GUSEL:PBO	5	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
GUSEL:SECU	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
IFX:PBO	5	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
IXE:PBO	5	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
IXE:USK	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
MTX:PBO	2	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
NETA:PBO	2	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
PBO:RISAN	5	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
PBO:SECU	16	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
PBO:SONELO	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
PBO:TILDRA	3	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
PBO:USK	11	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]

Table 7. Study Bias distribution for PASI 90 using CINeMA *(Continued)*

RISAN:SECU	1	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	High	["Heterogeneity"]
RISAN:USK	3	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
SECU:SONELO	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
SECU:USK	2	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
ADA:APRE	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
ADA:BRODA	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
ADA:CERTO	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High	["Imprecision"]
ADA:CICLO	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
ADA:DEUCRAVA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
ADA:ETA	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
ADA:FUM	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
ADA:IFX	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
ADA:IXE	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
ADA:MTX	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
ADA:NETA	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
ADA:SECU	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
ADA:SONELO	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
ADA:TILDRA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]

Table 7. Study Bias distribution for PASI 90 using CINeMA *(Continued)*

ADA:USK	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High	["Imprecision"]
APRE:BIME	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
APRE:BRODA	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
APRE:CERTO	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
APRE:CICLO	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
APRE:DEUCRAVA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
APRE:FUM	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
APRE:GUSEL	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
APRE:IFX	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
APRE:IXE	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
APRE:MTX	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
APRE:NETA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
APRE:RISAN	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
APRE:SECU	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
APRE:SONELO	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
APRE:TILDRA	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
APRE:USK	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]

Table 7. Study Bias distribution for PASI 90 using CINeMA *(Continued)*

BIME:BRODA	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
BIME:CERTO	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
BIME:CICLO	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
BIME:DEUCRAVA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BIME:ETA	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
BIME:FUM	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
BIME:GUSEL	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
BIME:IFX	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BIME:IXE	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BIME:MTX	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
BIME:NETA	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
BIME:RISAN	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BIME:SONELO	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BIME:TILDRA	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
BRODA:CERTO	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
BRODA:CICLO	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]

Table 7. Study Bias distribution for PASI 90 using CINeMA *(Continued)*

BRODA:DEUCRAVA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BRODA:ETA	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
BRODA:FUM	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
BRODA:GUSEL	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BRODA:IFX	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
BRODA:IXE	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
BRODA:MTX	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
BRODA:NETA	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
BRODA:RISAN	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
BRODA:SECU	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High	["Imprecision"]
BRODA:SONELO	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BRODA:TILDRA	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High	["Imprecision"]
CERTO:CICLO	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CERTO:DEUCRAVA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]

Table 7. Study Bias distribution for PASI 90 using CINeMA *(Continued)*

CERTO:FUM	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
CERTO:GUSEL	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
CERTO:IFX	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
CERTO:IXE	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
CERTO:MTX	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CERTO:NETA	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
CERTO:RISAN	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
CERTO:SECU	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
CERTO:SONELO	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
CERTO:TILDRA	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High	["Imprecision"]
CERTO:USK	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
CICLO:DEUCRAVA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CICLO:ETA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CICLO:FUM	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CICLO:GUSEL	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]

Table 7. Study Bias distribution for PASI 90 using CINeMA *(Continued)*

CICLO:IFX	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
CICLO:IXE	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CICLO:NETA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CICLO:PBO	0	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
CICLO:RISAN	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CICLO:SECU	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CICLO:SONELO	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CICLO:TILDRA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CICLO:USK	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
DEUCRAVA:ETA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
DEUCRAVA:FUM	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
DEUCRAVA:GUSEL	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
DEUCRAVA:IFX	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
DEUCRAVA:IXE	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]

Table 7. Study Bias distribution for PASI 90 using CINeMA *(Continued)*

DEUCRAVA:MTX	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
DEUCRAVA:NETA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
DEUCRAVA:RISAN	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
DEUCRAVA:SECU	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
DEUCRAVA:SONELO	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
DEUCRAVA:TILDRA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
DEUCRAVA:USK	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
ETA:FUM	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
ETA:GUSEL	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
ETA:MTX	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
ETA:NETA	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
ETA:RISAN	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
ETA:SONELO	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
FUM:GUSEL	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
FUM:IFX	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]

Table 7. Study Bias distribution for PASI 90 using CINeMA *(Continued)*

FUM:IXE	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
FUM:NETA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
FUM:RISAN	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
FUM:SECU	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
FUM:SONELO	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
FUM:TILDRA	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
FUM:USK	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
GUSEL:IFX	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
GUSEL:MTX	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
GUSEL:NETA	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
GUSEL:RISAN	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
GUSEL:SONELO	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
GUSEL:TILDRA	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
GUSEL:USK	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
IFX:IXE	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IFX:MTX	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]

Table 7. Study Bias distribution for PASI 90 using CINeMA *(Continued)*

IFX:NETA	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
IFX:RISAN	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IFX:SECU	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IFX:SONE-LO	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IFX:TILDRA	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
IFX:USK	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
IXE:MTX	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IXE:NETA	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
IXE:RISAN	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IXE:SECU	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
IXE:SONE-LO	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IXE:TILDRA	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
MTX:NETA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
MTX:RISAN	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
MTX:SECU	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
MTX:SONE-LO	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
MTX:TILDRA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]

Table 7. Study Bias distribution for PASI 90 using CINeMA *(Continued)*

MTX:USK	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
NETA:RISAN	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
NETA:SECU	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
NETA:SONELO	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
NETA:TILDRA	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
NETA:USK	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
RISAN:SONELO	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
RISAN:TILDRA	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
SECU:TILDRA	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
SONELO:TILDRA	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High	["Imprecision"]
SONELO:USK	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
TILDRA:USK	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]

ACI: acitretin; **ADA**: adalimumab; **APRE**: apremilast; **BIME**: bimekizumab; **BRODA**: brodalumab; **CERTO**: certolizumab; **CICLO**: ciclosporin; **DEUCRAVA**: deucravacitinib; **ETA**: etanercept; **FUM**: fumaric acid; **IFX**: infliximab; **IXE**: ixekizumab; **GUSEL**: guselkumab; **MTX**: methotrexate; **NETA**: netakimab; **PBO**: placebo; **RISAN**: risankizumab; **SECU**: secukinumab; **SONELO**: sonelokimab; **TILDRA**: tildrakizumab; **USK**: ustekinumab

Table 8. Study bias distribution for serious adverse events using CINeMA

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
ADA:BIME	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
ADA:GUSEL	3	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
ADA:PBO	9	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
ADA:RISAN	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
APRE:ETA	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
APRE:PBO	7	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BIME:PBO	3	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BIME:USK	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BRODA:PBO	5	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
BRODA:USK	2	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CERTO:ETA	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
CERTO:PBO	5	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
CICLO:PBO	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Imprecision"]
DEUCRAVA:PBO	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
ETA:IFX	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
ETA:IXE	2	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]

Table 8. Study bias distribution for serious adverse events using CINeMA *(Continued)*

ETA:PBO	12	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
ETA:SECU	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
ETA:TIL-DRA	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
ETA:USK	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
FUM:PBO	2	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
GUSEL:IXE	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
GUSEL:PBO	5	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
GUSEL:SECU	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IFX:PBO	5	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IXE:PBO	5	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IXE:USK	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
MTX:PBO	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
NETA:PBO	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
PBO:RISAN	5	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
PBO:SECU	16	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
PBO:SONELO	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
PBO:TIL-DRA	3	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
PBO:USK	11	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]

Table 8. Study bias distribution for serious adverse events using CINeMA *(Continued)*

RISAN:SECU	1	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Low	["Imprecision","Incoherence"]
RISAN:USK	3	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
SECU:SONELO	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
SECU:USK	2	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
ADA:APRE	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
ADA:BRODA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
ADA:CERTO	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
ADA:CICLO	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
ADA:DEUCRAVA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
ADA:ETA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
ADA:FUM	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
ADA:IFX	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
ADA:IXE	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
ADA:MTX	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
ADA:NETA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
ADA:SECU	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]

Table 8. Study bias distribution for serious adverse events using CINeMA *(Continued)*

ADA:SONELO	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
ADA:TILDRA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
ADA:USK	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
APRE:BIME	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
APRE:BRODA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
APRE:CERTO	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
APRE:CICLO	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
APRE:DEUCRAVA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
APRE:FUM	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
APRE:GUSEL	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
APRE:IFX	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
APRE:IXE	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
APRE:MTX	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
APRE:NETA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
APRE:RISAN	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
APRE:SECU	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]

Table 8. Study bias distribution for serious adverse events using CINeMA *(Continued)*

APRE:SONELO	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
APRE:TILDRA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
APRE:USK	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BIME:BRODA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BIME:CERTO	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BIME:CICLO	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
BIME:DEUCRAVA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BIME:ETA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BIME:FUM	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
BIME:GUSEL	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BIME:IFX	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BIME:IXE	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BIME:MTX	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BIME:NETA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BIME:RISAN	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BIME:SECU	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]

Table 8. Study bias distribution for serious adverse events using CINeMA *(Continued)*

BIME:SONELO	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BIME:TILDRA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BRODA:CERTO	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
BRODA:CICLO	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
BRODA:DEUCRAVA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BRODA:ETA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
BRODA:FUM	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
BRODA:GUSEL	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BRODA:IFX	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
BRODA:IXE	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BRODA:MTX	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
BRODA:NETA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
BRODA:RISAN	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
BRODA:SECU	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]

Table 8. Study bias distribution for serious adverse events using CINeMA *(Continued)*

BRODA:SONELO	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
BRODA:TILDRA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
CERTO:CICLO	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CERTO:DEUCRAVA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
CERTO:FUM	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CERTO:GUSEL	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
CERTO:IFX	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
CERTO:IXE	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
CERTO:MTX	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
CERTO:NETA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CERTO:RISAN	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
CERTO:SECU	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
CERTO:SONELO	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]

Table 8. Study bias distribution for serious adverse events using CINeMA *(Continued)*

CERTO:TILDRA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
CERTO:USK	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
CICLO:DEUCRAVA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CICLO:ETA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CICLO:FUM	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CICLO:GUSEL	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CICLO:IFX	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CICLO:IXE	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CICLO:MTX	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
CICLO:NETA	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CICLO:RISAN	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CICLO:SECU	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CICLO:SONELO	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]

Table 8. Study bias distribution for serious adverse events using CINeMA *(Continued)*

CI-CLO:TIL-DRA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CI-CLO:USK	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
DEUCRA-VA:ETA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
DEUCRA-VA:FUM	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
DEUCRA-VA:GUSEL	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
DEUCRA-VA:IFX	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
DEUCRA-VA:IXE	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
DEUCRA-VA:MTX	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
DEUCRA-VA:NETA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
DEUCRA-VA:RISAN	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
DEUCRA-VA:SECU	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
DEUCRA-VA:SONELO	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
DEUCRA-VA:TIL-DRA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]

Table 8. Study bias distribution for serious adverse events using CINeMA *(Continued)*

DEUCRAVA:USK	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
ETA:FUM	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
ETA:GUSEL	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
ETA:MTX	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
ETA:NETA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
ETA:RISAN	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
ETA:SONELO	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
FUM:GUSEL	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
FUM:IFX	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
FUM:IXE	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
FUM:MTX	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
FUM:NETA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
FUM:RISAN	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
FUM:SECU	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
FUM:SONELO	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]

Table 8. Study bias distribution for serious adverse events using CINeMA *(Continued)*

FUM:TILDRA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
FUM:USK	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
GUSEL:IFX	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
GUSEL:MTX	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
GUSEL:NETA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
GUSEL:RISAN	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
GUSEL:SONELO	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
GUSEL:TILDRA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
GUSEL:USK	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IFX:IXE	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IFX:MTX	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
IFX:NETA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
IFX:RISAN	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IFX:SECU	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IFX:SONELO	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IFX:TILDRA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IFX:USK	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]

Table 8. Study bias distribution for serious adverse events using CINeMA *(Continued)*

IXE:MTX	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
IXE:NETA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IXE:RISAN	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IXE:SECU	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IXE:SONELO	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
IXE:TILDRA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
MTX:NETA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
MTX:RISAN	0	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	High	["Heterogeneity"]
MTX:SECU	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
MTX:SONELO	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
MTX:TILDRA	0	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	High	["Heterogeneity"]
MTX:USK	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	[]
NETA:RISAN	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
NETA:SECU	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
NETA:SONELO	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
NETA:TILDRA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]

Table 8. Study bias distribution for serious adverse events using CINeMA *(Continued)*

NETA:USK	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
RISAN:SONELO	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
RISAN:TILDRA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
SECU:TILDRA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
SONELO:TILDRA	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
SONELO:USK	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]
TILDRA:USK	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Imprecision"]

ACI: acitretin; **ADA**: adalimumab; **APRE**: apremilast; **BIME**: bimekizumab; **BRODA**: brodalumab; **CERTO**: certolizumab; **CICLO**: ciclosporin; **DEUCRAVA**: deucravacitinib; **ETA**: etanercept; **FUM**: fumaric acid; **IFX**: infliximab; **IXE**: ixekizumab; **GUSEL**: guselkumab; **MTX**: methotrexate; **NETA**: netakimab; **PBO**: placebo; **RISAN**: risankizumab; **SECU**: secukinumab; **SONELO**: sonelokimab; **TILDRA**: tildrakizumab; **USK**: ustekinumab

APPENDICES

Appendix 1. 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* 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 certolizumab or tildrakizumab or BMS-986165 or bimekizumab or rizankizumab or risankizumab or deucravacitinib or hemay005 or sonelokimab or MSB0010841 or netakimab or BCD-085 or vunakizumab or SHR-1314):ti,ab,kw
#31 {or #7-#30}

Searches were date limited by the date a record was added to the database.

Appendix 2. MEDLINE (Ovid) search strategy

Ovid MEDLINE(R) ALL <1946 to December 15, 2021>

1 exp Psoriasis/ or psoria$.ti,ab. 59743
2 palmoplantar$ pustulosis.ti,ab. 621
3 pustulosis palmaris et plantaris.ti,ab. 172
4 (pustulosis and palms and soles).ti,ab. 100
5 or/1-4 59979
6 Deucravacitinib.ti,ab. 6
7 Hemay005.ti,ab. 1
8 (Sonelokimab or MSB0010841).ti,ab. 2
9 (netakimab or BCD-085).ti,ab. 10

10 (vunakizumab or SHR-1314).ti,ab. 1
11 exp Methotrexate/ 39648
12 methotrexate$.mp. 57368
13 amethopterin.mp. 399
14 mtx.ti,ab. 13729
15 mexate.mp. 2
16 exp Fumarates/ 5052
17 (fumar$ and esters).mp. 448
18 dimethylfumarate.mp. 196
19 fae.ti,ab. 975
20 dmf.ti,ab. 8970
21 fumarate$1.mp. 19546
22 fumaderm.mp. 54
23 Etretinate/ 1350
24 Acitretin/ 1226
25 Tegison.mp. 16
26 (Soriatane or Neotigason).mp. 39
27 ((oral or orally or systemic) and retinoid$).ti,ab. 2842
28 Isotretinoin/ 3783
29 Accutane.mp. 200
30 isotretinoin.ti,ab. 3494
31 etretin$.mp. 1739
32 acitretin.mp. 1912
33 Retinoids/ 6148
34 Ustekinumab.mp. 2551
35 stelara.mp. 46
36 secukinumab.mp. 1546
37 apremilast.mp. 870
38 guselkumab.mp. 391
39 BMS-986165.mp. 8
40 ri?ankizumab.mp. 236
41 CNTO 1275.mp. 16
42 exp antibodies, monoclonal/ 257056
43 monoclonal antibod$.mp. 197471
44 exp Interleukin-23/ or exp Interleukin-12/ 16879
45 exp Interleukin-12 Subunit p40/ or p40 subunit.mp. 1841
46 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/ 187882
47 (anti tumour necrosis factor or anti tumor necrosis factor).mp. 5805
48 (tumor necrosis factor-alpha or tumour necrosis factor-alpha).mp. 179299
49 anti tnf.mp. 11804
50 (tnf antibod$ or tnf alpha antibod$).mp. 2334
51 (tumour necrosis factor antibod$ or tumor necrosis factor antibod$).mp. 159
52 (antitumor necrosis factor or antitumour necrosis factor).mp. 863
53 exp Immunoglobulin Fab Fragments/ 28497
54 (infliximab$ or monoclonal antibody cA2 or remicade).mp. 16359
55 cdp571.mp. 43
56 (etanercept$ or enbrel).mp. 9268
57 (adalimumab$ or d2e7 or humira).mp. 9776
58 (golimumab or simponi).mp. 1445
59 (Briakinumab or ABT-874).mp. 75
60 exp Phototherapy/ 47867
61 exp Ultraviolet Therapy/ 8900
62 exp PUVA Therapy/ 4458
63 exp Photochemotherapy/ 23154
64 photodynamic therap$.mp. 23692
65 phototherap$.mp. 17356
66 photochemotherap$.mp. 24110
67 puva.mp. 4665
68 ultraviolet.mp. 187319
69 light therap$.mp. 8939
70 photoradiation therap$.mp. 173

71 BBUVB.mp. 5
72 NBUVB.mp. 194
73 BB-UVB.mp. 43
74 NB-UVB.mp. 610
75 broad band uvb.mp. 61
76 broad band ultraviolet b.mp. 13
77 narrow band uvb.mp. 395
78 narrow band ultraviolet b.mp. 424
79 psoralen ultraviolet a.mp. 205
80 psoralen uva.mp. 138
81 Cyclosporine/ 29991
82 (Ciclosporin or cyclosporine or cyclosporin).mp. 58379
83 Bimekizumab.mp. 68
84 brodalumab.mp. 434
85 ixekizumab.mp. 768
86 certolizumab.mp. 1452
87 tildrakizumab.mp. 190
88 or/6-87 964992
89 randomized controlled trial.pt. 553558
90 controlled clinical trial.pt. 94606
91 randomized.ab. 544046
92 placebo.ab. 224015
93 clinical trials as topic.sh. 198432
94 randomly.ab. 372078
95 trial.ti. 253075
96 89 or 90 or 91 or 92 or 93 or 94 or 95 1413998
97 exp animals/ not humans.sh. 4931018
98 96 not 97 1300832
99 5 and 88 and 98 2965
100 limit 99 to dt=20210508-20211005 60
101 limit 99 to ed=20210508-20211005 144
102 100 or 101 193

[Lines 89-98: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format, from section 3.6.1 in Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Rader T, Shokraneh F, Thomas J, Wieland LS. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (eds). Cochrane Handbook for Systematic Reviews of Interventions Version 6. Cochrane, 2019. Available from: www.training.cochrane.org/handbook]

We time limited results from this database using two different methods: Results were limited by the Create Date (date when the record was added to the database). Results were also 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 Cochrane Living Evidence Network. 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

Searches are generally run monthly with an overlap of three months to ensure no records are missed.

Appendix 3. Embase (Ovid) search strategy

Embase <1974 to 2021 December 15>

1 exp PSORIASIS/ 97707
2 psoria$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] 106162
3 palmoplantar$ pustulosis.mp. 880
4 pustulosis palmaris et plantaris.mp. 212
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 heading word, floating subheading word, candidate term word] 296

6 1 or 2 or 3 or 4 or 5 107474
7 exp deucravacitinib/ 56
8 hemay005.ti,ab. 1
9 exp sonelokimab/ 5
10 exp netakimab/ 53
11 exp vunakizumab/ 5
12 (deucravacitinib or sonelokimab or MSB0010841 or netakimab or BCD-085 or vunakizumab or SHR-1314).ti,ab. 63
13 methotrexate/ 190525
14 methotrexate$.ti,ab. 73204
15 amethopterin.ti,ab. 210
16 mtx.ti,ab. 26398
17 mexate.ti,ab. 1
18 fumaric acid derivative/ 1395
19 (fumar$ and esters).ti,ab. 624
20 dimethylfumarate.ti,ab. 430
21 fae.ti,ab. 1220
22 dmf.ti,ab. 12252
23 fumarate$1.ti,ab. 15846
24 fumaderm.ti,ab. 116
25 etretinate/ 4627
26 acitretin.ti,ab. 2570
27 tegison.ti,ab. 16
28 (Soriatane or Neotigason).ti,ab. 65
29 ((oral or orally or systemic) and retinoid$).ti,ab. 4116
30 isotretinoin/ 13500
31 isotretinoin.ti,ab. 5032
32 Accutane.ti,ab. 218
33 etretin$.ti,ab. 1677
34 retinoid/ 15017
35 ustekinumab.ti,ab. 5167
36 ustekinumab/ 9240
37 stelara.ti,ab. 74
38 secukinumab/ 5147
39 secukinumab.ti,ab. 3129
40 ampremilast.ti,ab. 2
41 guselkumab/ 1299
42 guselkumab.ti,ab. 706
43 "CNTO 1275".ti,ab. 20
44 monoclonal antibod$.ti,ab. 242042
45 exp monoclonal antibody/ 657311
46 interleukin 23/ 16120
47 interleukin 12/ 50609
48 interleukin 12p40/ 7665
49 p40 subunit.ti,ab. 709
50 exp tumor necrosis factor/ 176513
51 tumor necrosis factor alpha/ 230800
52 tumor necrosis factor receptor 2/ 4471
53 tumor necrosis factor receptor/ 11694
54 tumor necrosis factor related apoptosis inducing ligand/ 11513
55 (anti tumour necrosis factor or anti tumor necrosis factor).ti,ab. 8268
56 (tumor necrosis factor-alpha or tumour necrosis factor-alpha).ti,ab. 109922
57 anti tnf.ti,ab. 24317
58 (tnf antibod$ or tnf alpha antibod$).ti,ab. 3042
59 (tumour necrosis factor antibod$ or tumor necrosis factor antibod$).ti,ab. 215
60 (antitumor necrosis factor or antitumour necrosis factor).ti,ab. 1144
61 "immunoglobulin F(ab) fragment"/ 8803
62 (infliximab$ or monoclonal antibody cA2 or remicade).ti,ab. 28842
63 cdp571.ti,ab. 51
64 (etanercept$ or enbrel).ti,ab. 16088
65 (adalimumab$ or d2e7 or humira).ti,ab. 20918
66 (golimumab or simponi).ti,ab. 4253
67 (Briakinumab or ABT-874).ti,ab. 111

68 exp phototherapy/ 99752
69 PUVA/ 10150
70 photochemotherapy/ 9015
71 photodynamic therap$.ti,ab. 26880
72 phototherap$.ti,ab. 14260
73 photochemotherap$.ti,ab. 2692
74 puva.ti,ab. 4488
75 ultraviolet.ti,ab. 79701
76 light therap$.ti,ab. 3136
77 photoradiation therap$.ti,ab. 194
78 BBUVB.ti,ab. 15
79 NBUVB.ti,ab. 421
80 BB-UVB.ti,ab. 59
81 NB-UVB.ti,ab. 965
82 broad band uvb.ti,ab. 79
83 broad band ultraviolet b.ti,ab. 17
84 narrow band uvb.ti,ab. 625
85 narrow band ultraviolet b.ti,ab. 540
86 psoralen ultraviolet a.ti,ab. 268
87 psoralen uva.ti,ab. 183
88 cyclosporin/ 83639
89 (Ciclosporin or cyclosporine or cyclosporin).ti,ab. 73037
90 brodalumab.ti,ab. 588
91 ixekizumab.ti,ab. 1391
92 ixekizumab/ 2510
93 brodalumab/ 1431
94 certolizumab.mp. 8479
95 tildrakizumab.mp. 720
96 BMS-986165.ti,ab. 43
97 bimekizumab/ 210
98 Bimekizumab.ti,ab. 112
99 risankizumab/ 727
100 Ri?ankizumab.ti,ab. 337
101 or/7-100 1570359
102 crossover procedure.sh. 68907
103 double-blind procedure.sh. 190430
104 single-blind procedure.sh. 44590
105 (crossover$ or cross over$).tw. 115480
106 placebo$.tw. 335424
107 (doubl$ adj blind$).tw. 225791
108 allocat$.tw. 175009
109 trial.ti. 345044
110 randomized controlled trial.sh. 687002
111 random$.tw. 1732195
112 or/102-111 2196680
113 exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ 29835404
114 human/ or normal human/ 23020899
115 113 and 114 23020899
116 113 not 115 6814505
117 112 not 116 1944616
118 6 and 101 and 117 6216
119 limit 118 to dd=20210508-20211005 203

[Lines 102-117: Based on terms suggested for identifying RCTs in Embase (section 3.6.2) in Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Rader T, Shokraneh F, Thomas J, Wieland LS. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (eds). Cochrane Handbook for Systematic Reviews of Interventions Version 6. Cochrane, 2019. Available from: www.training.cochrane.org/handbook]

We time-limited 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 searches.** See example search syntax below (dd=date delivered):

- 116. 6 and 99 and 115
- 117. limit 116 to dd=20181031-20190416

Searches are generally run monthly with an overlap of three months to ensure no records are missed.

Appendix 4. 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 searches.** 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 2 (MEDLINE) and Appendix 3 (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. We will also revisit yearly our serach methods, and if necessary update the search strategies by adding or removing intervention terms.

(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 2021), 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
12 August 2022	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Search results up to 5 October 2021 are included in the current update (published May 2022, 167 included studies). In addition, the team continues with the monthly screening (last search date 29 July 2022) and have found a further 7 new studies and 13 ongoing studies that will be included in a future update.

HISTORY

Protocol first published: Issue 2, 2015
Review first published: Issue 12, 2017

Date	Event	Description
20 May 2022	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Search results up to 5 October 2021 are included in the current update (published May 2022, 167 included studies). In addition, the team continues with the monthly screening (last search date 21 April 2022) and have found a further 5 new studies and 7 ongoing studies that will be included in a future update.
29 April 2022	New citation required and conclusions have changed	This update included studies of more interventions, assessing two new anti-IL17 agents (netakimab, sonelokimab). **Network meta-analysis showed that infliximab, bimekizumab, ixekizumab and risankizumab outperformed other drugs when compared to placebo in reaching PASI 90. The clinical effectiveness of these drugs was similar.**
29 April 2022	New search has been performed	This is a Living Systematic Review. Searches are run and screened monthly. **Search results up to 5 October 2021** are included in the current update (167 included studies). In this update, we have fully incorporated a further **19 new included studies with 5695 additional participants**. Ten included studies from the earlier version of this review are excluded because the interventions no longer meet the inclusion criteria (tofacitinib and mirikizumab).
8 October 2021	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Search results up to 8 September 2020 are included in the current update (published April 2021, 158 included studies). In addition, the team continues with the monthly screening (last search date 5 October 2021) and have found a further 18 new studies and 31 ongoing studies that will be included in a forthcoming update.

Date	Event	Description
28 May 2021	Amended	There was a mistake in Figure 24 (PASI 90), which we have now rectified.
13 April 2021	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Search results up to 8 September 2020 are included in the current update (published April 2021, 158 included studies). In addition, the team continues with the monthly screening (last search date 17 March 2021) and have found a further 8 new studies and 15 ongoing studies that will be included in a future update.
13 April 2021	New search has been performed	In this update, we have fully incorporated a further 18 new included studies and 13 new ongoing studies from searches up to 8 September 2020, which have been incorporated in an updated network meta-analysis. This update includes a new biological agent in the network: mirikizumab.
13 April 2021	New citation required and conclusions have changed	This update includes more interventions, including a new anti-IL23. Network meta-analysis showed that infliximab, ixekizumab, risankizumab, bimekizumab, secukinumab, guselkumab, and brodalumab outperformed other drugs when compared to placebo in reaching PASI 90. The clinical effectiveness of these drugs was similar, except for ixekizumab which had a better chance of reaching PASI 90 compared with secukinumab, guselkumab and brodalumab.
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.
27 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	Event	Description
		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 addition, 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 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.
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.

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, CD, IGD, and ES screened papers against eligibility criteria.

ES obtained data on ongoing and unpublished studies.
LLC, SA, and ES appraised the quality of papers.
LLC, SA, and ES extracted data for the review and sought additional information about papers.
LLC, SA, and 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. She also wrote the Plain Language Summary.
All of the authors read and amended the manuscript.
ES is the guarantor of the update.

Department of Health Disclaimer

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

DECLARATIONS OF INTEREST

Emilie Sbidian: has declared that they have no conflict of interest.

Anna Chaimani: has declared that they have no conflict of interest.

Ignacio Garcia-Doval: reports payment from Novartis for a presentation unrelated to psoriasis; personal payment. IG-D also reports receiving meeting expenses from Janssen for the Spanish Academy of Dermatology annual Congress, personal payment; and payment from UCB (Union Chimique Belge), personal payment.

Liz Doney: has declared that they have no conflict of interest. Liz is the Information Specialist with Cochrane Skin but was not involved in the editorial process.

Corinna Dressler: has declared that they have no conflict of interest.

Camille Hua: has declared that they have no conflict of interest.

Carolyn Hughes: has declared that they have no conflict of interest.

Luigi Naldi: has declared that they have no conflict of interest.

Sivem Afach: has declared that they have no conflict of interest.

Laurence Le Cleach: has declared that they have no conflict of interest.

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Internal sources

- No sources of support provided

External sources

- The National Institute for Health Research (NIHR), UK

  The NIHR, UK, is the largest single funder of the Cochrane Skin Group.
- The French Society of Dermatology (SFD), France

  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

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  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 (September 2020) and the last update search (October 2021)

1. Methods: Data collection and analysis > Sensitivity analysis

We added a new sensitivity analysis:

- analysing only drugs approved by European Medical Agency for plaque psoriasis;
  - Non biological systemic treatments: FAEs, acitretin, ciclosporin, methotrexate;
  - Small molecules: apremilast;
  - Anti-TNF alpha: infliximab, etanercept, adalimumab, certolizumab pegol;
  - Anti-IL12/23: ustekinumab;
  - Anti-IL17: secukinumab, brodalumab, ixekizumab, bimekizumab;
  - Anti-IL23: tildrakizumab, guselkumab, risankizumab.

2. Methods: Search methods for identification of studies

In September 2021 following review, we removed from the search strategies the drug names tofacitinib and mirikizumab as these drugs were no longer applicable to psoriasis. We added the following new drug names to the search strategies: deucravacitinib, hemay005, sonelokimab (MSB0010841), netakimab (BCD-085), vunakizumab (SHR-1314).

From February 2021, we have used Screen4Me functionality to remove records unlikely to be RCTs from our search results, increasing the efficiency of our screening process.

B. Between the previous review (January 2019) and the last update search (September 2020)

1. Methods: Data collection and analysis > Data synthesis > Network meta-analysis

We will provide new networks and re-analyse the data every six months instead of three months, to have enough new data to integrate.

2. Methods: Data collection and analysis > Assessment of heterogeneity

To better reassure the plausibility of transitivity, we excluded from the main analysis trials including biological-naïve participants, but assessing efficacy of a biological agent.

3. Methods: Data collection and analysis > Sensitivity analysis

We added two new sensitivity analyses: (1) including trials irrespective of the previous treatments received by the participants, and (2) using another definition of the safety primary outcomes: SAEs after excluding flares of psoriasis.

4. Methods: Data collection and analysis > Summary of Findings and Assessment of certainty of the evidence

We did not include summary of findings (SoF) tables because the format of an SoF table does not allow us to present a summary of comparisons across the different drugs. The SoF tables in the last version of the review only focused on the comparisons against placebo.

We did not use GRADE assessment for the new update of this review, but CiNeMa is a tool specifically dedicated to network meta-analysis.

We therefore explained the methodology, and added in the Methods section:

We assessed the confidence of the evidence estimates from network meta-analysis, based on the CINeMA approach which relies on the contributions of the direct comparisons to the estimation in the network meta-analysis (CINeMA 2017; Salanti 2014). 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).

The confidence in each NMA (network meta-analysis) RR (risk ratio)$_{AB}$ between two given drugs A and B was evaluated for six domains. The software required some input in each domain in order to recommend whether there were 'major concerns', 'some concerns' or 'no concerns' for the particular domain.

Thus, threshold values and evaluation rules to be decided were finalised through discussions. After determining these rules, the remaining synthesis of confidence in the evidence can automatically be calculated with the CINeMA web app. One review author input all the data and obtained the results.

- Within-trial bias: we estimated it as the weighted average of the overall risk of bias of all the trials contributing information to the estimation of RR_{AB}.
- Reporting bias: also known as 'publication bias'. 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 judgements.
- Indirectness: since the included studies matched the clinical question of the review, we had 'no concern' about any of the evaluated RR_{AB}.
- Imprecision: was rated based on whether the 95% CI of RR allowed recommendations to be made. We set the margin of equivalent effects (where none of the drugs is favoured) to between RR 0.95 and 1.05. These values were motivated by the fact that assuming 3% response rate (reaching PASI 90) for placebo, then an RR_{AB} of 1.05 indicated a response for drug A higher than those obtained with placebo, which we considered as clinically meaningful. Then, the degree of overlap between the 95% CI of RR_{AB} and the margin of equivalent effects suggests the judgement.
- Heterogeneity: this was evaluated by monitoring the agreement between confidence intervals (CIs) and prediction intervals (PIs). CINeMA judges whether the two intervals and their overlap with the margin of equivalent effects provide similar conclusions.
- Incoherence: this was evaluated by monitoring the level of disagreement between confidence intervals (CIs) of the direct and indirect RR_{AB} and their overlap with the margin of equivalent effects.

After the judgement for all the six domains, we summarised our overall confidence in evidence for each or between any two drugs into high, moderate, low and very low ratings. Starting with high confidence, we downgraded by one level for each ‘major concern’ in any of the six domains; then two-thirds of a level down for ‘some concerns’ in ‘within-study bias’; and one-third of a level down for each rating of ‘some concerns’ in any of the other five domains. To obtain the final level, we rounded the number of downgrades to their nearest integer.

For each drug, we calculated the percentage of the four levels based on all comparisons including that drug, combining both efficacy and acceptability.

It is important to note that the CiNeMa tool was also used in the previous version of our review and results were presented with those from GRADE scoring. Evaluation rules were not the same, however, especially for the margin of equivalent effects which was RR = 1.5. We discussed this point and because the margin of effect was too large, we have changed this rule for this update.

C. 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 4.

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 regularly 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 timing 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 timing (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 2021) 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."

D. 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 2

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.

Timing

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 timing for induction and maintenance therapy to include the relevant short- or long-term remission classification. We also removed the timing 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 timing 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 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 pairwise meta-analyses using Review Manager 5 (RevMan 5) (Revman 2020), 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 5 October 2021 are included in the current update (published May 2022, 167 included studies). In addition, the team continues with the monthly screening (last search date 29 July 2022) and have found a further 7 new studies and 13 ongoing studies that will be included in a future update.

INDEX TERMS

Medical Subject Headings (MeSH)

Adalimumab [adverse effects]; *Biological Products [therapeutic use]; Etanercept [therapeutic use]; Infliximab [therapeutic use]; Methotrexate [therapeutic use]; Network Meta-Analysis; *Psoriasis [drug therapy]; Systematic Reviews as Topic; Tumor Necrosis Factor-alpha; Ustekinumab [therapeutic use]

MeSH check words

Adult; Female; Humans; Male