## **REVIEW ARTICLE**



# Efficacy of Immunobiologic and Small Molecule Inhibitor Drugs for Psoriasis: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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#### **Abstract**

Background Psoriasis is an immune-mediated inflammatory disease for which treatment has evolved over the past few years due to the introduction of immunobiologic and small molecule inhibitor medications. A better understanding of the comparative efficacies of drugs may help doctors to choose the most appropriate treatment for patients.

*Objective* The aim of this study was to conduct a systematic review and meta-analysis to assess the efficacy of immunobiologic and small molecule inhibitor drugs for patients with moderate to severe psoriasis.

*Data Sources* The EMBASE, PUBMED, LILACS, Web of Science and ClinicalTrials.org databases were searched for trials published to 21 July 2016.

Study Selection Only randomized, double-blind, placebocontrolled clinical trials that evaluated the efficacy of immunobiologics or small molecule inhibitors for

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moderate to severe plaque-type psoriasis were selected by two independent authors. No restrictions were used.

Data Extraction and Synthesis Two authors independently extracted the data and a random-effects model meta-analysis was performed.

Main Outcomes and Measures The Psoriasis Area and Severity Index (PASI) 75 was considered the primary outcome, measured at the primary endpoint of each study. Results Thirty-eight studies were included in our analysis. The overall pooled effect favored biologics and small molecule inhibitors over placebo (risk difference [RD] 0.59, 95% confidence interval [CI] 0.58–0.60). Ixekizumab at a dose of 160 mg on week 0 and then every 2 weeks (RD 0.84, 95% CI 0.81–0.88), brodalumab 210 mg (RD 0.79, 95% CI 0.76–0.82), infliximab 5 mg/kg (RD 0.76, 95% CI 0.73–0.79), and secukinumab 300 mg (RD 0.76, 95% CI 0.71–0.81) showed a greater chance of response (PASI 75) when compared with placebo.

Limitations The methodology of a traditional meta-analysis does not allow for drugs to be ranked. Included studies used short-term endpoints (10–16 weeks) to evaluate the primary outcome, therefore long-term efficacy could not be determined.

Conclusions and Relevance The anti-IL-17 drugs brodalumab, ixekizumab and secukinumab showed an equal or greater chance of helping patients achieve a 75% improvement on PASI compared with other reviewed drugs.

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# **Key Points**

Anti-tumor necrosis factor and anti-interleukin (IL)-12/23 have been shown to be effective in treating patients with moderate to severe psoriasis.

Anti-IL-17 drugs showed an equal or greater chance of leading patients to a 75% improvement when compared with other biologics/small molecule inhibitors.

Ixekizumab showed higher efficacy among FDAapproved drugs when a 90 or 100% improvement over the baseline Psoriasis Area and Severity Index was analyzed.

## 1 Introduction

Psoriasis is a chronic, immune-mediated inflammatory disease, where an intricate immune process, mainly driven by the T-helper (Th) 1/Th17 branch of the immune system, leads to persistent inflammation [1–3].

The treatment of psoriasis has been revolutionized by the introduction of biologic and small molecule inhibitor targeted therapy. Several of these therapies have been released and are available for general use, such as infliximab [4], adalimumab [5], ustekinumab [6], apremilast [7], etanercept [8], ixekizumab [9], and secukinumab [10], while others are in phase II or later trials, e.g. brodalumab [11], guselkumab [12], certolizumab pegol [13], and tofacitinib [14]. On the other hand, studies on the efficacy of briakinumab were halted because of safety concerns during phase III trials [15].

Schmitt et al. [16] recently carried out a meta-analysis that included studies that evaluated systemic treatments for psoriasis (biologics or not) published before October 2012. This review did not include anti-IL-17 drugs, and infliximab 5 mg/kg was superior to ustekinumab, adalimumab and etanercept. Xiong et al. published a systematic review that only included secukinumab, one of the anti-IL-17 biologic drugs, and concluded that anti-IL-17 drugs would be more efficacious than currently available biologics [17]. Also in 2015, Chen et al. performed a meta-analysis comparing only anti-IL-17 drugs, and reported a greater chance of response of brodalumab 140 mg, followed by ixekizumab 25 mg and secukinumab 150 mg [18].

As new drugs have emerged in the last few years [9, 11, 13, 14], it is important to update previous reviews to provide the best evidence on the efficacy of recent treatments for psoriasis. This study aimed to systematically

review the evidence on the efficacy of biologic and small molecule inhibitor drugs for the treatment of moderate to severe psoriasis

## 2 Methods

This systematic review and meta-analysis was conducted using the recommendations of the Cochrane Initiative, and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [19].

## 2.1 Search Strategy/Databases Searched/Eligibility Criteria

The research question ("What is the efficacy, measured by the improvement of 75% over baseline Psoriasis Area and Severity Index (PASI), of biologic and small molecule inhibitor drugs for moderate to severe psoriasis patients when compared to placebo?") was formulated using the PICO method (Population, Intervention, Comparator, Outcome). The EMBASE, PUBMED, LILACS, Web of Science and ClinicalTrials.org databases were searched for double-blind, randomized, placebo-controlled clinical trials (RCTs) published to 21 July 2016. Search strategies involved use of the terms 'psoriasis AND (abatacept OR apremilast OR CC-10004 OR adalimumab OR D2E7 OR briakinumab OR ABT-480 OR brodalumab OR certolizumab OR etanercept OR TNF Fc OR fezakizumab OR golimumab OR guselkumab OR CNTO1959 OR infliximab OR ixekizumab OR secukinumab OR Ly-2439821 OR sifalimumab OR siplizumab OR tasocitinib OR tofacitinib OR ustekinumab OR CNTO-1275 OR AbGn-168 OR RG-4934 OR APG-2305 OR MK-3222)'. Studies published online or in print, or studies in press were reviewed. Although we considered all languages eligible for the review, only studies published in English were found to be relevant.

Initially, duplicate studies were excluded and two researchers (AVEC and RPD) independently reviewed the titles and abstracts to exclude those studies that were clearly irrelevant. The reviewers then evaluated the full text of the remaining manuscripts and relevant articles were identified. Disagreements were solved by consensus. Randomized clinical trials were eligible for inclusion in the present review if they fulfilled the following criteria: human-based, double-blind, randomized, placebo-controlled clinical trials that evaluated adult patients and used the Psoriasis Area and Severity Index (PASI) as a measurement for psoriasis severity. Phase II studies were only included if the studied drugs or doses were identified in further phase III studies, or if drugs or doses were already

approved by the US FDA. In the case of studies with multiple study arms, including approved and non-approved drugs or doses, only the arms containing approved drugs/doses were included in the meta-analysis. Head-to-head studies without a placebo arm were excluded from the analysis, and studies that evaluated the improvement of psoriatic arthritis as a primary outcome were also excluded. The reference lists of the articles included in the review were searched for additional studies.

The primary efficacy outcome was the number of patients who experienced a 75% improvement in disease status, measured by the PASI (PASI 75), at the time of the primary efficacy assessment. Secondary outcomes were 90% improvement (PASI 90) and 100% improvement (PASI 100) in disease status.

#### 2.2 Data Extraction

Using a standardized protocol [20] entirely based on the Cochrane handbook for systematic reviews and interventions, reviewers extracted the following items from each study: authors; year of publication; intervention and comparator; total number of patients randomized; trial duration; mean disease duration; mean age of patients; mean baseline PASI; number of patients achieving PASI 75, 90 and 100; and prior use of biologic or concomitant medications. Effect estimates were extracted with 95% confidence intervals (CI). Any disagreement was also solved by consensus. It was decided not to use any quality assessment of the studies (i.e. JADAD), and to evaluate its impact on the estimated pooled effect using meta-regression/sensitivity analysis. Data regarding randomization, blinding, and complete reporting of the study results were also extracted to evaluate the risk of bias [20].

## 2.3 Statistical Analysis

Effect measures were reported as the pooled risk difference (RD), and an RD >0 denoted that those subjects who received the 'new drug' showed a higher risk of presenting the outcome. The overall pooled effect of any treatment versus placebo was estimated by running a separate analysis, with all treatment patients gathered in one group and all placebo patients in another group, to avoid the unit-of-analysis error. The number needed to treat (NNT) was also calculated.

Heterogeneity among studies was assessed using the Q-test and  $I^2$ , and a random-effects model was used. Sensitivity analysis was performed excluding phase II studies when heterogeneity was found to be >50%. A funnel plot and Egger's test were used to investigate publication bias. We performed meta-regression to assess the influence of

mean baseline PASI, previous use of biologics, and duration of the disease on the heterogeneity among studies.

Meta-analysis using data extracted from the studies was performed using STATA v.14 software for Mac (StataCorp LP, College Station, TX, USA). Forest plots, funnel plots, and risk of bias assessment graphs were developed using Review Manager Version 5.3. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

#### 3 Results

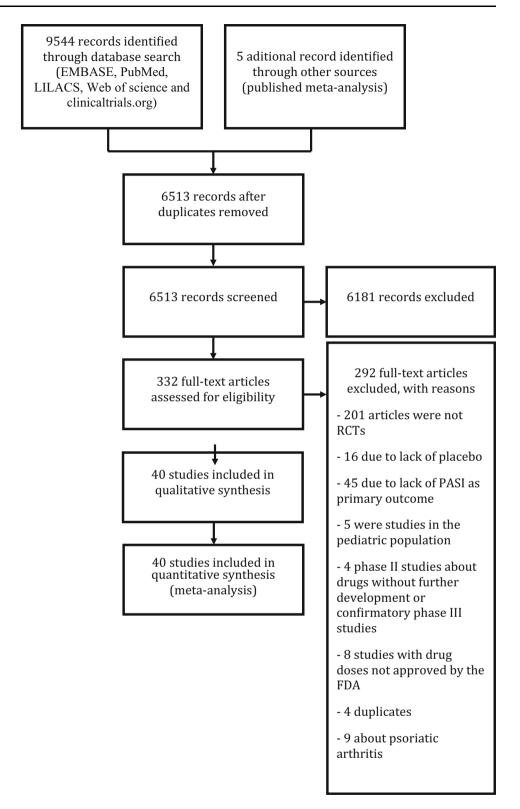
Overall, 9544 records were identified through a database search, with 5 additional records identified through a search of the bibliographical references of published meta-analyses. After removing duplicates, 6513 records were screened and 6181 were excluded (3822 were not RCTs, 2039 did not pertain to psoriasis, 122 pertained to drugs not encompassed in this review, and 198 were additional duplicates).

Among the 332 articles selected for full-text review, 292 were excluded for the following reasons: 201 were not RCTs, 16 were RCTs that did not use placebo as the comparator, 45 due to the lack of PASI as the primary outcome, 5 were studies in the pediatric population, 4 were phase II studies without further confirmatory phase III studies, 8 were studies with doses not approved by the FDA, 9 pertained to psoriatic arthritis, and 4 were additional duplicates (Fig. 1).

A total of 40 studies [4, 5, 7–9, 11, 14, 21–53] were included in the meta-analysis, providing 56 comparisons of 11 different interventions. In total, 22,884 patients were evaluated. The medications studied were adalimumab, apremilast, brodalumab, etanercept, infliximab, ixekizumab, secukinumab, tofacitinib and ustekinumab. Of the 40 studies included in the meta-analysis, 6 used a 10-week endpoint, 6 used a 16-week endpoint, and 28 used a 12-week endpoint. Primary endpoints for outcomes assessment were correlated with the induction period of the drugs and can be considered short-term therapy. All studies shared similar inclusion criteria and baseline characteristics (Table 1). Risk of bias assessment showed that high risk of bias was low among the studies (Online Resource 1 and 2).

At FDA-approved dose regimens, 1054 patients were randomized to adalimumab, 650 to apremilast, 2957 to etanercept (535–50 mg/wk, and 2422–100 mg/wk), 844 to infliximab, 1169 to ixekizumab, 691 to secukinumab, and 1678 to ustekinumab (949–45 mg, and 729–90 mg). With regard to drugs still not approved by the FDA, 2554 patients were randomized to brodalumab (1278–140 mg, and 1276–210 mg) and 2197 to tofacitinib (1124–5 mg, and 1073–10 mg).

Fig. 1 PRISMA statement diagram for database searches for meta-analysis of the efficacy of biologics and small molecule inhibitors for psoriasis. *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses, *RCTs* randomized controlled trials, *PASI* Psoriasis Area and Severity Index



Considering PASI 75 as the primary endpoint, ixekizumab (160 mg week 0 and 80 mg every 2 weeks) was the drug that achieved the higher RD (0.84, 95% CI 0.81–0.88), followed by brodalumab at a dose of 210 mg (weeks 0, 1, 2, 4, 6, 8, and 10) [RD 0.79, 95% CI

0.76–0.82). Figure 2 shows the remaining comparisons. Infliximab 5 mg/kg (RD 0.76, 95% CI 0.73–0.79) and secukinumab 300 mg (RD 0.76, 95% CI 0.71–0.81) performed comparably. The overall pooled effect favored treatment when compared with placebo (RD 0.59, 95% CI

Table 1 Clinical trial identification and summary categorized by drug<sup>a</sup>

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Drug	Author, year	Intervention/comparator	No. of patients randomized (total patients)	Total trial duration (weeks)	Mean disease duration (years)	Mean age of patients	Mean Baseline PASI	Primary outcome measure/primary endpoint
Adalimumab	Asahina, 2010 [22]	Adalimumab sc (40 mg EOW) <sup>c</sup>	38 (169)	24	14.2	47.8	25.4	PASI 75/wk 16
		Adalimumab sc (80 mg wk $0 + 40$ mg EOW starting wk 1)	43 (169)	24	14	44.2	30.2	PASI 75/wk 16
		Adalimumab sc (80 mg EOW) <sup>c</sup>	42 (169)	24	11.6	43.5	28.2	PASI 75/wk 16
		Placebo	46 (169)	24	15.5	43.9	29.1	PASI 75/wk 16
	Gordon, 2006 [5]	Adalimumab 40 mg sc (80 mg wk $0 + 40$ mg EOW starting week 1)	46 (148)	09	21	46	16.7	PASI 75/wk 12
		Adalimumab 40 mg sc (80 mg wk 0 and $1 + 40$ mg/wk starting wk 2) <sup>c</sup>	50 (148)	09	18	4	14.5	PASI 75/wk 12
		Adalimumab 40 mg sc (80 mg wk 0 and $1 + 40$ mg/wk starting wk 2) <sup>c</sup>	50 (148)	09	18	4	14.5	PASI 75/wk 12
		Placebo	52 (148)	09	19	43	16	PASI 75/wk 12
	Gordon 2015 [48]	Guselkumab 200 mg sc (wk 0, 4 and every 12 weeks) <sup>c</sup>	42 (293)	52	19.4	46	19.4	PASI 75/wk 16
		Guselkumab 100 mg sc (every 8 weeks) <sup>d</sup>	42 (293)	52	18.3	41.5	20.4	PASI 75/wk 16
		Guselkumab 50 mg sc (wk 0, 4 and every 12 weeks) <sup>c</sup>	42 (293)	52	18	5.44	22.3	PASI 75/wk 16
		Guselkumab 15 mg sc (every 8 weeks) <sup>c</sup>	41 (293)	52	17.3	45	21.5	PASI 75/wk 16
		Guselkumab 5 mg sc (wk 0, 4 and every 12 weeks) <sup>c</sup>	41 (293)	52	19.5	43	20.9	PASI 75/wk 16
		Adalimumab sc (80 mg wk 0 and 1, then EOW)	43 (293)	52	19.3	50	20,2	PASI 75/wk 16
		Placebo	42 (293)	52	18	46.5	21.8	PASI 75/wk 16
	Menter, 2008 [32]	Adalimumab 40 mg sc (80 mg wk 0 and 40 mg EOW starting week 1)	814 (1212)	52	18.1	44.1	19	PASI 75/wk 16
		Placebo	398 (1212)	52	18.4	45.4	18.8	PASI 75/wk 16
	Saurat, 2007 [39]	Adalimumab 40 mg sc (80 mg wk $0 + 40$ mg EOW starting wk 1)	108 (271)	16	17.9	42.9	20.2	PASI 75/wk 16
		Methotrexate oral (7.5 mg until 25 mg/wk) <sup>c</sup>	110 (271)	16	18.9	41.6	19.4	PASI 75/wk 16
		Placebo	53 (271)	16	18.8	40.7	19.2	PASI 75/wk 16
Apremilast	Papp, 2012 [7]	Apremilast 10 mg orally bid <sup>c</sup>	89 (352)	24	18	4.4	18.1	PASI 75/wk 16
		Apremilast 20 mg orally bid <sup>c</sup>	87 (352)	24	19.2	44.6	18.5	PASI 75/wk 16
		Apremilast 3 0 mg orally bid	88 (352)	24	19.2	44.1	19.1	PASI 75/wk 16
		Placebo	88 (352)	24	19.6	4.1	18.1	PASI 75/wk 16
	Papp, 2015 [35]	Apremilast 30 mg bid	562 (844)	52	19.8	45.8	18.7	PASI 75/wk 16
		Placebo	282 (844)	52	18.7	46.5	19.4	PASI 75/wk 16

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Drug	Author, year	Intervention/comparator	No. of patients randomized (total patients)	Total trial duration (weeks)	Mean disease duration (years)	Mean age of patients	Mean Baseline PASI	Primary outcome measure/primary endpoint
Brodalumab	Lebwohl, 2015	Brodalumab 210 mg sc EOW	612 (1831)	52	19	45	18.6	PASI 75/wk 12
	Amagine2 [21]	Brodalumab 140 mg sc EOW	610 (1831)	52	19	45	18.9	PASI 75/wk 12
		Ustekinumab	300 (1831)	52	19	45	18.9	PASI 75/wk 12
		Placebo	309 (1831)	52	18	44	18.6	PASI 75/wk 12
	Lebwohl, 2015	Brodalumab 210 mg sc (wks 0, 1, 2, 4, 6, 8, and 10)	624 (1881)	52	18	45	18,7	PASI 75/wk 12
	Amagmez [21]	Brodalumab 140 mg sc (wks 0, 1, 2, 4, 6, 8, and 10)	629 (1881)	52	17	45	18.1	PASI 75/wk 12
		Ustekinumab	313 (1881)	52	18	45	18.7	PASI 75/wk 12
		Placebo	315 (1881)	52	18	4	19	PASI 75/wk 12
	Papp, 2012 [11]	Brodalumab 70 mg sc (wks 0, 1, 2, 4, 6, 8, and $10)^{\circ}$	39 (198)	12	20.7	42.1	18.8	PASI 75/wk 12
		Brodalumab 140 mg sc (wks 0, 1, 2, 4, 6, 8, and 10)	39 (198)	12	19.2	4	19.4	PASI 75/wk 12
		Brodalumab 210 mg sc (wks 0, 1, 2, 4, 6, 8, and 10)	40 (198)	12	17.1	42.1	20.6	PASI 75/wk 12
		Brodalumab 280 mg sc monthly <sup>c</sup>	42 (198)	12	19.3	42.3	17.9	PASI 75/wk 12
		Placebo	38 (198)	12	18.3	41.8	18.9	PASI 75/wk 12
Etanercept	Bachelez, 2015 [45]	Tofacitinib 5 mg bid	330 (1106)	12	16	4	21	PASI 75/wk 12
		Tofacitinib 10 mg bid	332 (1106)	12	17	4	21	PASI 75/wk 12
		Etanercept 100 mg/wk	336 (1106)	12	18	42	19.4	PASI 75/wk 12
		Placebo	108 (1106)	12	17	46	19.5	PASI 75/wk 12
	Bagel, 2012 [23]	Etanercept sc (100 mg/wk)	62 (124)	24	17.5	39	15.5	PASI 75/wk 12
		Placebo	62 (124)	24	11.9	42	15.2	PASI 75/wk 12
	Gottlieb, 2003 [26]	Etanercept sc (50 mg/wk)	57 (112)	24	23	48.2	17.8	PASI 75/wk 12
		Placebo	55 (112)	24	20	46.5	19.5	PASI 75/wk 12
	Gottlieb, 2011 [49]	Etanercept sc (100 mg/wk)	141 (347)	12	17	43.1	19.4	PASI 75/wk 12
		Briakinumab 200 mg sc (wks 0 and 4 then 100 mg wk 8)	138 (347)	12	16.1	43.6	18.4	PASI 75/wk 12
		Placebo	68 (347)	12	19.1	4	18.5	PASI 75/wk 12
	Griffiths, 2015 Uncover-2 [46]	Ixekizumab sc (160 mg wk 0 and 80 mg every 4 wks) <sup>c</sup>	347 (1224)	12	18	45	19	PASI 75/wk 12
		Ixekizumab (160 mg wk 0 and 80 mg every 2 wks)	351 (1224)	12	19	45	20	PASI 75/wk 12
		Etanercept (100 mg/wk)	358 (1224)	12	19	45	19	PASI 75/wk 12
		Placebo	168 (1224)	12	19	45	21	PASI 75/wk 12

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Drug	Author, year	Intervention/comparator	No. of patients randomized (total patients)	Total trial duration (weeks)	Mean disease duration (years)	Mean age of patients	Mean Baseline PASI	Primary outcome measure/primary endpoint
	Griffiths, 2015 Uncover-3 [46]	Ixekizumab sc (160 mg wk 0 and 80 mg every 4 wks) <sup>c</sup>	385 (1346)	12	18	46	21	PASI 75/wk 12
		Ixekizumab (160 mg wk 0 and 80 mg every 2 wks)	386 (1346)	12	18	46	21	PASI 75/wk 12
		Etanercept (100 mg/wk)	382 (1346)	12	18	46	21	PASI 75/wk 12
		Placebo	193 (1346)	12	18	46	21	PASI 75/wk 12
	Langley, 2014 Fixture [29]	Secukinumab 300 mg sc (wks 0, 1, 2, 3 and 4, then wks 8 and 12)	327 (1306)	52	15.8	5.44	23.9	PASI 75/wk 12
		Secukinumab 150 mg sc (wks 0, 1, 2, 3 and 4, then wks 8 and 12) <sup>c</sup>	327 (1306)	52	17.3	45.4	23.7	PASI 75/wk 12
		Etanercept sc (100 mg/wk)	326 (1306)	52	16.4	43.8	23.2	PASI 75/wk 12
		Placebo	326 (1306)	52	16.6	44.1	24.1	PASI 75/wk 12
	Leonardi, 2003 [31]	Etanercept sc (25 mg/wk) <sup>c</sup>	160 (652)	24	19.3	4.44	18.2	PASI 75/wk 12
		Etanercept sc (50 mg/wk)	162 (652)	24	18.5	45.4	18.5	PASI 75/wk 12
		Etanercept sc (100 mg/wk)	164 (652)	24	18.6	44.8	18.4	PASI 75/wk 12
		Placebo	166 (652)	24	18.4	45.6	18.3	PASI 75/wk 12
	Mease, 2000 [8]	Etanercept sc (50 mg/wk)	19 (38)	12	19	46	10.1	PASI 75/wk 12
		Placebo	19 (38)	12	17.5	43.5	0.9	PASI 75/wk 12
	Papp, 2005 [50]	Etanercept sc (50 mg/wk)	204 (611)	24	21.5	46	16.9	PASI 75/wk 12
		Etanercept sc (100 mg/wk)	203 (611)	24	18.1	44.5	16.1	PASI 75/wk 12
		Placebo	204 (611)	24	17.5	4	16	PASI 75/wk 12
	Strober, 2011 [51]	Etanercept sc (100 mg/wk)	139 (350)	12	15.2	45.2	18.5	PASI 75/wk 12
		Briakinumab 200 mg sc (wks 0 and 4, then 100 mg wk 8)	139 (350)	12	16.3	44.9	19.4	PASI 75/wk 12
		Placebo	72 (350)	12	15.5	45	18.3	PASI 75/wk 12
	Tyring, 2007 [42]	Etanercept sc (100 mg/wk	311 (618)	96	20.2	45.8	18.3	PASI 75/wk 12
		Placebo	307 (618)	96	19.7	45.5	18.1	PASI 75/wk 12
	Van der Kerkhof, 2008 [28]	Etanercept sc (50 mg/week)	96 (142)	24	19.3	45.9	21.4	PASI 75/wk 12
		Placebo	46 (142)	24	17.3	43.6	21	PASI 75/wk 12

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Drug	Author, year	Intervention/comparator	No. of patients randomized (total patients)	Total trial duration (weeks)	Mean disease duration (years)	Mean age of patients	Mean Baseline PASI	Primary outcome measure/primary endpoint
Infliximab	Chaudari, 2001 [4]	Infliximab 5 mg/kg iv (wks 0, 2 and 6)	11 (33)	10	ND	51	22.1	PASI 75/wk 10
		Infliximab 10 mg/kg iv (wks 0, 2 and 6) <sup>c</sup>	11 (33)	10	ND	35	26.6	PASI 75/wk 10
		Placebo	11 (33)	10	ND	45	20.3	PASI 75/wk 10
	Gottlieb, 2004 [47]	Infliximab 3 mg/kg iv (wks 0, 2 and 6)	99 (249)	30	18	45	20	PASI 75/wk 10
		Infliximab 5 mg/kg iv (wks 0, 2 and 6)	99 (249)	30	16	4	20	PASI 75/wk 10
		Placebo	51 (249)	30	16	45	18	PASI 75/wk 10
	Menter, 2007 [33]	Infliximab 3 mg iv (wks 0, 2 and 6)	313 (835)	50	18.1	43.4	20.1	PASI 75/wk 10
		Infliximab 5 mg iv (wks 0, 2 and 6)	314 (835)	50	19.1	4.5	20.4	PASI 75/wk 10
		Placebo	208 (835)	50	17.8	4.4	19.8	PASI 75/wk 10
	Reich, 2005 [38]	Infliximab 5 mg iv (wks 0, 2, 6, and then every 8 wks)	301 (317)	50	19.1	42.6	22.9	PASI 75/wk 10
		Placebo	77 (317)	50	17.3	43.8	22.8	PASI 75/wk 10
	Torri, 2010 [40]	Infliximab 5 mk/kg iv (wks 0, 2, 6 and 8)	35 (54)	78	14.2	46.9	31.9	PASI 75/wk 10
		Placebo	19 (54)	78	11.1	43.3	33.1	PASI 75/wk 10
	Yang, 2012 [43]	Infliximab 5 mk/kg iv (wks 0, 2, 6, 14 and 22)	84 (129)	26	16	40.1	23.9	PASI 75/wk 10
		Placebo	45 (129)	26	16	39.4	25.3	PASI 75/wk 10
Ixekizumab	Griffiths, 2015 Uncover-2 [46]	Ixekizumab sc (160 mg wk 0 and 80 mg every 4 wks) <sup>c</sup>	347 (1224)	12	18	45	19	PASI 75/wk 12
		Ixekizumab (160 mg wk 0 and 80 mg every 2 wks)	351 (1224)	12	19	45	20	PASI 75/wk 12
		Etanercept (100 mg/wk)	358 (1224)	12	19	45	19	PASI 75/wk 12
		Placebo	168 (1224)	12	19	45	21	PASI 75/wk 12
	Griffiths, 2015 Uncover-3 [46]	Ixekizumab sc (160 mg wk 0 and 80 mg every 4 wks) <sup>c</sup>	385 (1346)	12	18	46	21	PASI 75/wk 12
		Ixekizumab (160 mg wk 0 and 80 mg every 2 wks)	386 (1346)	12	18	46	21	PASI 75/wk 12
		Etanercept (100 mg/wk)	382 (1346)	12	18	46	21	PASI 75/wk 12
		Placebo	193 (1346)	12	18	46	21	PASI 75/wk 12
	Gordon, 2016 Uncover-1 [53]	Ixekizumab sc (160 mg wk 0 and 80 mg every 4 wks) <sup>c</sup>	433 (1296)	12	19	46	20	PASI 75/wk 12
	,	Ixekizumab (160 mg wk 0 and 80 mg every 2 wks)	433 (1296)	12	20	45	20	PASI 75/wk 12
		Placebo	431 (1296)	12	20	46	20	PASI 75/wk 12

Fable 1 continued

Primary outcome measure/primary PASI 75/wk 12 PASI 75/wk12 endpoint Baseline PASI Mean 22.6 21.5 21.2 21.5 20.5 22 18.9 19.5 19.5 20.7 21.1 22.3 23.7 21.4 23.9 23.7 19.4 19.4 20.4 19.8 20.7 19.3 24.1 21 Mean age of patients 46.5 4.9 43.9 45.1 45.4 45.4 4.5 45.4 46.6 43.7 46 4 4 42 46 46 46 46 47 47 47 45 Mean disease duration (years) 9.91 50.6 19.8 16.5 6.9 18 20.4 20.2 17.5 17.3 17.3 15.8 17.3 16.4 17.2 6.9 15.7 15.2 15.2 9 91 7 ∞ 7 Total trial duration (weeks) 12 12 52 52 5252 52 552 552 552 552 552 112 112 112 116 116 116 16 16 16 16 9 No. of patients (total patients) randomized 326 (1306) 330 (1106) (1106) 245 (738) 327 (1306) 327 (1306) 327 (1306) 326 (1306) 332 (1106) 336 (1106) 177 (900) 248 (738) 49 (197) 363 (900) 360 (900) 382 (959) 196 (959) 381 (959) 59 (177) 61 (182) 60 (182) 49 (197) 59 (177) 61 (182) 49 (197) 50 (197) 59 (177) secukinumab 300 mg sc (wks 0, 1, 2, 3, 4, 8) Secukinumab 150 mg sc (wks 0, 1, 2, 3 and 4, then wks 8 and 12)<sup>c</sup> Secukinumab 300 mg sc (wks 0, 1, 2, 3 and 4, then wks 8 and 12)<sup>c</sup> Secukinumab 300 mg sc (wks 0, 1, 2, 3 and Secukinumab 150 mg sc (wks 0, 1, 2, 3 and 4, then wks 8 and 12)<sup>c</sup> Secukinumab 150 mg sc (wks 0, 1, 2, 3, 4, 8) Secukinumab 300 mg sc (wks 0, 1, 2, 3, 4, 8) Secukinumab 150 mg sc (wks 0, 1, 2, 3, 4, Tofacitinib 15 mg orally bid Fofacitinib 2 mg orally bid Tofacitinib 5 mg orally bid Fofacitinib 5 mg orally bid Fofacitinib 5 mg orally bid Etanercept sc (100 mg/wk) 4, then wks 8 and 12) Intervention/comparator Etanercept 100 mg/wk Fofacitinib 10 mg bid Tofacitinib 10 mg bid Fofacitinib 10 mg bid Tofacitinib 5 mg bid Placebo Placebo Placebo Placebo Blauvelt, 2014 [24] Papp, 2012 [14] Paul, 2014 [37] Langley, 2014 Langley, 2014 Bachelez [45] Erasure [29] Fixture [29] Author, year Papp, 2015 Papp, 2015 OPT1 [52] OPT2 [52] Secukinumab **Tofacitinib** Drug

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Dug Muthor, year   Intervention/comparation   Fig. 2   Fig. 1   Fi									
innumb   ligratich   Udeskinnumb 45 mg (wks 0, 4 and every   64 (157)   72   173   414   28.7    Lecenardi, 2008 [30]   Lucekinnumb 45 mg vc (wks 0, 4 and every   255 (766)   75   1.73   414   28.7    Lecenardi, 2008 [30]   Lucekinnumb 45 mg vc (wks 0, 4 and every   255 (766)   75   1.95   1.95   1.95    Lecenardi, 2008 [30]   Lucekinnumb 45 mg vc (wks 0, 4 and every   255 (766)   75   1.95   1.95   1.95    Lecenardi, 2008 [30]   Lucekinnumb 45 mg vc (wks 0, 4 and every   255 (766)   75   1.95   1.95   1.95    Lecenardi, 2008 [30]   Lucekinnumb 45 mg vc (wks 0, 4 and every   255 (766)   25   1.95   1.95   1.95    Lecenardi, 2008 [30]   Lucekinnumb 45 mg vc (wks 0, 4 and every   255 (766)   25   1.95   1.95   1.95    Lecenardi, 2008 [30]   Lucekinnumb 45 mg vc (wks 0, 4 and then   100 (121)   255 (123)   25   1.95   1.95    Lecenardi, 2008 [30]   Lucekinnumb 45 mg vc (wks 0, 4 and then   100 (121)   255 (123)   25   1.95   1.95    Lecenardi, 2008 [30]   Lucekinnumb 45 mg vc (wks 0, 4 and then   100 (121)   255 (123)   25   25   25    Lecenardi, 2008 [30]   Lucekinnumb 45 mg vc (wks 0, 4 and every 12 wks)   25   25   25    Lecenardi, 2008 [31]   Lucekinnumb 40 mg vc (80 mg wk 0 and 1 + 40 mg/wk satring wk 1)   25   25   25    Lecenardi, 2008 [31]   Lucekinnumb 40 mg vc (80 mg wk 0 and 1 + 40 mg/wk satring wk 1)   25   25   25    Lecenardi, 2008 [31]   Lucekinnumb 40 mg vc (80 mg wk 0 and 1 + 40 mg/wk satring wk 1)   25   25   25    Lecenardi, 2008 [31]   25   25   25   25   25   25    Lecenardi, 2008 [31]   25   25   25   25   25	Drug	Author, year	Intervention/comparator	nts ts)		Mean disease duration (years)	Mean age of patients		
Lecturidi, 2008 [30]   Usekinnumb 90 mg (wks 0, 4 and every 12   62 (157)   72   167   448   28.3	Ustekinumab	Igarashi, 2011 [27]	Ustekinumab 45 mg (wks 0, 4 and every 12 wks)			15.8	45	30.1	PASI 75/wk 12
Likely   Pacebo   11			Ustekinumab 90 mg (wks 0, 4 and every 12 wks)			17.3	44	28.7	PASI 75/wk 12
Leonardi, 2008 [30] Ussekinnumb 45 mg sc (wks 0, 4 and every 256 (766) 76 (197) 446 448 20.4  Usekinnumb 45 mg sc (wks 0, 4 and every 256 (766) 76 (197) 444 448 20.4  Trai, 2011 [41] Ussekinnumb 45 mg sc (wks 0, 4 and then 160 (121) 28 (119 4) 40.9 25.7  Trai, 2011 [41] Ussekinnumb 45 mg sc (wks 0, 4 and then 160 (121) 28 (119 4) 40.9 25.7  Trai, 2011 [41] Ussekinnumb 45 mg sc (wks 0, 4 and then 160 (123) 28 (146 4) 29 (123) 29 (146 4) 20.2  Zhu, 2013 [44] Ussekinnumb 45 mg sc (wks 0, 4 and then 160 (123) 28 (146 4) 20.4  Author, year Intervention/comparator 160 (123) 28 (146 7) 140 (123) 29 (146 7) 140 (123) 29 (146 7) 140 (123) 29 (146 7) 140 (123) 29 (146 7) 140 (147			Placebo			16	49	30.3	PASI 75/wk 12
Total Content   Total Conten		Leonardi, 2008 [30]	Ustekinumab 45 mg sc (wks 0, 4 and every 12 wks)			19.7	44.8	20.5	PASI 75/wk 12
Placebo			Ustekinumab 90 mg sc (wks 0, 4 and every 12 wks)			19.6	46.2	19.7	PASI 75/wk 12
Tsai, 2011 [41]   Usrekinumab 45 mg sc (wks 0, 4 and then   61 (121)   28   119   40.9   40.9   25.2     Pacebo			Placebo			20.4	44.8	20.4	PASI 75/wk 12
Sheebo		Tsai, 2011 [41]	Ustekinumab 45 mg sc (wks 0, 4 and then every 12 wks)			11.9	40.9	25.2	PASI 75/wk 12
Author, year   Piacebo   Lieu   Lie			Placebo			13.9	40.4	22.9	PASI 75/wk 12
Author, year   Placebo   162 (332)   35   142   39.2   22.7     Author, year   Intervention/comparator   Posterior   Patients   Pa		Zhu, 2013 [44]	Ustekinumab 45 mg sc (wks 0, 4 and then every 12 wks)	_		14.6	40.1	23.2	PASI 75/wk 12
Author, year Author, year Hintervention/comparator Author, year A cashina, 2010 [22] Adalimumab sc (40 mg EOW)* Asahina, 2010 [22] Adalimumab sc (80 mg wk 0 + 40 mg EOW starting wk 1) 35 27 17 PASI 50 PASI 100 and Adalimumab sc (80 mg wk 0 + 40 mg EOW starting wk 1) 185 27 17 PASI 50 PASI 100 PASI 1			Placebo			14.2	39.2	22.7	PASI 75/wk 12
Adalimumab sc (80 mg kV 0 + 40 mg EOW starting wk 1) 35 27 14 ND Adalimumab sc (80 mg kV 0 + 40 mg EOW starting wk 1) 35 27 17 ND Adalimumab sc (80 mg kV 0 + 40 mg EOW starting week 1) ND Placebo  Gordon, 2006 [5] Adalimumab 40 mg sc (80 mg wk 0 + 40 mg EOW starting week 1) ND 24 ND 5 Adalimumab 40 mg sc (80 mg wk 0 and 1 + 40 mg/wk starting wk 2) <sup>c</sup> ND 40 ND 13 Placebo  Gordon 2015 [48] Guselkumab 200 mg sc (wk 0, 4 and every 12 weeks) <sup>c</sup> ND 34 24 12 Guselkumab 50 mg sc (we 0, 4 and every 12 weeks) <sup>c</sup> ND 34 19 5 Guselkumab 50 mg sc (wk 0, 4 and every 12 weeks) <sup>c</sup> ND 34 19 5 Guselkumab 5 mg sc (wk 0, 4 and every 12 weeks) <sup>c</sup> ND 34 14 14 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4	Drug	Author, year	Intervention/comparator		No. of patients achieving PASI 50			No. of patients achieving PASI 100	Prior immunobiologic treatment/concomitant systemic medication <sup>b</sup>
Adalimumab sc (80 mg wk 0 + 40 mg EOW starting wk 1)       35       27       17       ND         Adalimumab sc (80 mg EOW) <sup>c</sup> 9       2       0       ND         Placebo       40       ND       24       ND       5         Adalimumab 40 mg sc (80 mg wk 0 and 1 + 40 mg/wk starting wk 2) <sup>c</sup> ND       40       ND       13         Adalimumab 40 mg sc (80 mg wk 0 and 1 + 40 mg/wk starting wk 2) <sup>c</sup> ND       40       ND       13         Placebo       ND       2       ND       13         Guselkumab 40 mg sc (wk 0, 4 and every 12 weeks) <sup>c</sup> ND       34       24       12         Guselkumab 100 mg sc (every 8 weeks) <sup>c</sup> ND       33       26       14         Guselkumab 50 mg sc (wk 0, 4 and every 12 weeks) <sup>c</sup> ND       31       14       5         Guselkumab 5 mg sc (wk 0, 4 and every 12 weeks) <sup>c</sup> ND       31       14       5         Guselkumab 5 mg sc (wk 0, 4 and every 12 weeks) <sup>c</sup> ND       30       19       11         Adalimumab sc (80 mg wk 0 and 1, then EOW)       ND       30       19       11         Placebo       10       10       10       11       11	Adalimumab	Asahina, 2010 [22]	Adalimumab sc (40 mg EOW) <sup>c</sup>		28	22	14	ND	No/no
Adalimumab sc (80 mg EOW)*       38       34       26       ND         Placebo       Placebo       2       0       ND         Adalimumab 40 mg sc (80 mg wk 0 and 1 + 40 mg/wk starting wk 2)*       ND       40       ND       13         Adalimumab 40 mg sc (80 mg wk 0 and 1 + 40 mg/wk starting wk 2)*       ND       40       ND       13         Adalimumab 40 mg sc (80 mg wk 0 and 1 + 40 mg/wk starting wk 2)*       ND       2       ND       13         Placebo       ND       34       24       12         Guselkumab 200 mg sc (wk 0, 4 and every 12 weeks)*       ND       33       26       14         Guselkumab 50 mg sc (every 8 weeks)*       ND       31       14       5         Guselkumab 15 mg sc (every 8 weeks)*       ND       31       14       5         Guselkumab 5 mg sc (wk 0, 4 and every 12 weeks)*       ND       31       14       4         Adalimumab sc (80 mg wk 0 and 1, then EOW)       ND       30       19       11         Placebo       19       11       9       11       11			Adalimumab sc (80 mg wk $0 + 40$ mg EOW star	ting wk 1)	35	27	17	ND	No/no
Placebo       9       2       0       ND         Adalimumab 40 mg sc (80 mg wk 0 + 40 mg EXOW starting wek 1)       ND       24       ND       5         Adalimumab 40 mg sc (80 mg wk 0 and 1 + 40 mg/wk starting wk 2) <sup>c</sup> ND       40       ND       13         Adalimumab 40 mg sc (80 mg wk 0 and 1 + 40 mg/wk starting wk 2) <sup>c</sup> ND       2       ND       13         Placebo       ND       34       24       12         Guselkumab 200 mg sc (wk 0, 4 and every 12 weeks) <sup>c</sup> ND       33       26       14         Guselkumab 50 mg sc (every 8 weeks) <sup>c</sup> ND       34       19       8         Guselkumab 15 mg sc (every 8 weeks) <sup>c</sup> ND       31       14       5         Guselkumab 5 mg sc (wk 0, 4 and every 12 weeks) <sup>c</sup> ND       31       14       4         Adalimumab sc (80 mg wk 0 and 1, then EOW)       ND       30       19       11         Placebo       ND       2       1       0			Adalimumab sc (80 mg EOW) <sup>c</sup>		38	34	26	ND	No/no
Adalimumab 40 mg sc (80 mg wk 0 + 40 mg EOW starting week 1)       ND       24       ND       5         Adalimumab 40 mg sc (80 mg wk 0 and 1 + 40 mg/wk starting wk 2)°       ND       40       ND       13         Adalimumab 40 mg sc (80 mg wk 0 and 1 + 40 mg/wk starting wk 2)°       ND       40       ND       13         Placebo       ND       2       ND       13         Guselkumab 200 mg sc (wk 0, 4 and every 12 weeks)°       ND       34       24       12         Guselkumab 50 mg sc (every 8 weeks)°       ND       34       19       8         Guselkumab 15 mg sc (every 8 weeks)°       ND       31       14       5         Guselkumab 5 mg sc (wk 0, 4 and every 12 weeks)°       ND       18       14       4         Adalimumab sc (80 mg wk 0 and 1, then EOW)       ND       30       19       11         Placebo       ND       2       1       0			Placebo		6	2	0	ND	No/no
Adalimumab 40 mg sc (80 mg wk 0 and 1 + 40 mg/wk starting wk 2)°       ND       40       ND       13         Adalimumab 40 mg sc (80 mg wk 0 and 1 + 40 mg/wk starting wk 2)°       ND       40       ND       13         Placebo       Guselkumab 200 mg sc (wk 0, 4 and every 12 weeks)°       ND       34       24       12         Guselkumab 100 mg sc (every 8 weeks)°       ND       33       26       14         Guselkumab 50 mg sc (every 8 weeks)°       ND       34       19       8         Guselkumab 15 mg sc (every 8 weeks)°       ND       31       14       5         Guselkumab 5 mg sc (wk 0, 4 and every 12 weeks)°       ND       18       14       4         Adalimumab sc (80 mg wk 0 and 1, then EOW)       ND       30       19       11         Placebo       ND       2       1       0		Gordon, 2006 [5]	Adalimumab 40 mg sc (80 mg wk 0 + 40 mg EC	W starting week 1)		24	ND	5	ND/no
Adalimumab 40 mg sc (80 mg wk 0 and 1 + 40 mg/wk starting wk 2)°       ND       40       ND       13         Placebo       Guselkumab 200 mg sc (wk 0, 4 and every 12 weeks)°       ND       34       24       12         Guselkumab 100 mg sc (every 8 weeks)°       ND       33       26       14         Guselkumab 50 mg sc (wk 0, 4 and every 12 weeks)°       ND       31       14       5         Guselkumab 15 mg sc (every 8 weeks)°       ND       18       14       4         Adalimumab sc (80 mg wk 0 and 1, then EOW)       ND       30       19       11         Placebo       ND       2       1       0			Adalimumab 40 mg sc (80 mg wk 0 and 1 + 40	ng/wk starting wk 2) <sup>c</sup>		40	ND	13	ND/no
Placebo       ND       2       ND       0         Guselkumab 200 mg sc (wk 0, 4 and every 12 weeks) <sup>c</sup> ND       34       24       12         Guselkumab 100 mg sc (every 8 weeks) <sup>c</sup> ND       33       26       14         Guselkumab 50 mg sc (wk 0, 4 and every 12 weeks) <sup>c</sup> ND       31       14       5         Guselkumab 15 mg sc (every 8 weeks) <sup>c</sup> ND       18       14       4         Adalimumab sc (80 mg wk 0 and 1, then EOW)       ND       30       19       11         Placebo       ND       2       1       0			Adalimumab 40 mg sc (80 mg wk 0 and 1 + 40	ng/wk starting wk 2) <sup>c</sup>		40	ND	13	ND/no
Guselkumab 200 mg sc (wk 0, 4 and every 12 weeks)°       ND       34       24       12         Guselkumab 100 mg sc (every 8 weeks)°       ND       33       26       14         Guselkumab 50 mg sc (wk 0, 4 and every 12 weeks)°       ND       34       19       8         Guselkumab 15 mg sc (every 8 weeks)°       ND       31       14       5         Guselkumab 5 mg sc (wk 0, 4 and every 12 weeks)°       ND       18       14       4         Adalimumab sc (80 mg wk 0 and 1, then EOW)       ND       30       19       11         Placebo       ND       2       1       0			Placebo		ND	2	ND	0	ND/no
ND       33       26       14         ND       34       19       8         ND       31       14       5         ND       18       14       4         ND       30       19       11         ND       2       1       0		Gordon 2015 [48]	Guselkumab 200 mg sc (wk 0, 4 and every 12 we	eks) <sup>c</sup>	ND	34	24	12	20 (42)/ND
ND     34     19     8       ND     31     14     5       ND     18     14     4       ND     30     19     11       ND     2     1     0			Guselkumab 100 mg sc (every 8 weeks) <sup>c</sup>		ND	33	26	14	17 (42)/ND
ND 31 14 5 ND 18 14 4 ND 30 19 11 ND 2 1 0			Guselkumab 50 mg sc (wk 0, 4 and every 12 wee	ks) <sup>c</sup>	ND	34	19	8	15 (42)/ND
ks) <sup>c</sup> ND 18 14 4 ND 30 19 11 ND 2 1 0			Guselkumab 15 mg sc (every 8 weeks) <sup>c</sup>		ND	31	14	5	14 (41)/ND
ND 30 19 11 ND 2 1 0			Guselkumab 5 mg sc (wk 0, 4 and every 12 week	s) <sub>c</sub>	ND	18	14	4	19 (41)/ND
$ND \qquad 2 \qquad 1 \qquad 0$			Adalimumab sc (80 mg wk 0 and 1, then EOW)		ND	30	19	11	26 (43)/ND
			Placebo		ND	2	1	0	15 (42)/no

Prior immunobiologic treatment/concomitant systemic medication<sup>b</sup> 160 (629)/yes 157 (624)/yes 177 (612)/no 79 (610)/no 162 (562)/no 75 (313)/yes 76 (315)/yes 30 (282)/no 84 (300)/no 90 (309)/no 97 (814)/no 53 (398)/no 10 (39)/no 17 (40)/no 16 (39)/no 19 (42)/no 16 (38)/no ND/no ND/no ND/no ND/no No/no No/no No/no achieving PASI 100 patients No. of ND ND ND 272 272 157 65 2 2 2 2 2 2 2 2 3 170 170 28 achieving PASI 90 patients No. of achieving PASI 75 patients No. of 217 19 13 30 33 28 achieving PASI 50 patients N 89 16 20 35 Adalimumab 40 mg sc (80 mg wk 0 and 40 mg EOW starting week 1) Adalimumab 40 mg sc (80 mg wk 0 + 40 mg EOW starting wk 1) Brodalumab 210 mg sc (wks 0, 1, 2, 4, 6, 8, and 10) Brodalumab 140 mg sc (wks 0, 1, 2, 4, 6, 8, and 10) Brodalumab 140 mg sc (wks 0, 1, 2, 4, 6, 8, and 10) Brodalumab 210 mg sc (wks 0, 1, 2, 4, 6, 8, and 10) Brodalumab 70 mg sc (wks 0, 1, 2, 4, 6, 8, and 10)<sup>c</sup> Methotrexate oral (7.5 mg until 25 mg/wk)<sup>c</sup> Brodalumab 280 mg sc monthly<sup>c</sup> Brodalumab 210 mg sc EOW Brodalumab 140 mg sc EOW Apremilast 20 mg orally bid<sup>c</sup> Apremilast 10 mg orally bid<sup>c</sup> Apremilast 3 0 mg orally bid Intervention/comparator Apremilast 30 mg bid Ustekinumab Ustekinumab Placebo Placebo Placebo Placebo Placebo Placebo Menter, 2008 [32] Saurat, 2007 [39] Papp, 2015 [35] Papp, 2012 [11] Amagine 3 [21] Amagine2 [21] Lebwohl, 2015 Lebwohl, 2015 Papp, 2012 [7] Author, year Fable 1 continued Brodalumab Apremilast Drug

Prior immunobiologic treatment/concomitant systemic medication<sup>b</sup> 84 (347)/yes 85 (351)/yes 58 (385)/yes 58 (386)/yes 60 (382)/yes 76 (358)/yes 43 (168)/yes 33 (193)/yes 20 (141)/no 39 (138)/no 35 (330)/no 29 (332)/no 37 (336)/no 12 (108)/no ou/(89) 01 6 (62)/no 7 (62)/no No/no No/no achieving PASI 100 patients No. of ΩN 145 61 achieving PASI 90 patients No. of 262 108 16 achieving PASI 75 patients No. of 197 17 1 79 113 5 315 269 149 336 37 patients achieving PASI 50 No. of ND 266 N N R R Briakinumab 200 mg sc (wks 0 and 4 then 100 mg wk 8) Ixekizumab sc (160 mg wk 0 and 80 mg every 4 wks)<sup>c</sup> Exekizumab sc (160 mg wk 0 and 80 mg every 4 wks)<sup>c</sup> (xekizumab (160 mg wk 0 and 80 mg every 2 wks) Ixekizumab (160 mg wk 0 and 80 mg every 2 wks) Etanercept sc (100 mg/wk) Etanercept sc (100 mg/wk) Etanercept sc (50 mg/wk) Etanercept (100 mg/wk) Etanercept (100 mg/wk) Intervention/comparator Etanercept 100 mg/wk Tofacitinib 10 mg bid Tofacitinib 5 mg bid Placebo Placebo Placebo Placebo Bachelez, 2015 [45] Gottlieb, 2003 [26] Gottlieb, 2011 [49] Bagel, 2012 [23] Uncover-2 [46] Uncover-3 [46] Griffiths, 2015 Griffiths, 2015 Author, year 
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 Etanercept Drug

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Drug	Author, year	Intervention/comparator	No. of patients achieving PASI 50	No. of patients achieving PASI 75	No. of patients achieving PASI 90	No. of patients achieving PASI 100	Prior immunobiologic treatment/concomitant systemic medication <sup>b</sup>
	Langley, 2014 Fixture [29]	Secukinumab 300 mg sc (wks 0, 1, 2, 3 and 4, then wks 8 and 12) Secukinumab 150 mg sc (wks 0, 1, 2, 3 and 4, then wks 8 and 12) <sup>c</sup> Etanercept sc (100 mg/wk)	ND ON ON ON	249 219 142	175 137 67	78 47 14	38 (327)/no 45 (327)/no 45 (326)/no
	Leonardi, 2003 [31]		ND 65 94 121	16 23 55 81	5 5 19 36	0 ND ND ND	35 (326)/no No/no No/no No/no
	Mease, 2000 [8] Papp, 2005 [50]		24 ND ND 124	9 2 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9	1 ND ND 20		No/no ND/yes ND/yes No/no
	Strober, 2011 [51]	Etanercept sc (100 mg/wk) Placebo Etanercept sc (100 mg/wk) Briakinumab 200 mg sc (wks 0 and 4, then 100 mg wk 8) Placebo	81 N ON O	94 6 55 112 5	39 1 19 3	0 ND 8 8 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	No/no No/no 1 (139)/no 15 (139)/no 3 (72)/no
Infliximab	Tyring, 2007 [42]  Van der Kerkhof, 2008 [28]  Chaudari, 2001 [4]	Etanercept sc (100 mg/wk Placebo Etanercept sc (50 mg/week) Placebo Infliximab 5 mg/kg iv (wks 0, 2 and 6)	230 43 66 4 ND	146 15 36 1 9	65 3 13 ND		ND/no ND/no ND/no ND/no No/no
	Gottlieb, 2004 [47] Menter, 2007 [33]	Infliximab 10 mg/kg iv (wks 0, 2 and 6) <sup>c</sup> Placebo Infliximab 3 mg/kg iv (wks 0, 2 and 6) Infliximab 5 mg/kg iv (wks 0, 2 and 6) Placebo Infliximab 3 mg iv (wks 0, 2 and 6)	N N N N N N N N N N N N N N N N N N N	8 8 2 2 711 87 3 3 220	ND ND S7 1 116		No/no No/no 32 (99)/no 33 (99)/no 16 (51)/no 49 (313) No
	Reich, 2005 [38] Torri, 2010 [40]	Infliximab 5 mg iv (wks 0, 2 and 6) Placebo Infliximab 5 mg iv (wks 0, 2, 6, and then every 8 wks) Placebo Infliximab 5 mk/kg iv (wks 0, 2, 6 and 8)	ND 274 6 ND	237 4 242 2 242	142 1 172 1 ND		45 (314)/no 27 (208)/no No/no No/no ND/no
	Yang, 2012 [43]	Placebo Infliximab 5 mk/kg iv (wks 0, 2, 6, 14 and 22) Placebo	ND 79 6	0 68	ND 48 0	ND ND ND	ND/no ND/no ND/no

ranie 1	continued						
Drug	Author, year	Intervention/comparator	No. of	No. of	No. of	No. of	Prior immunobiolog
			patients		patients	patients	treatment/concomit
			achieving	achieving	achieving	achieving	systemic medication
			DACI 50		DACI OO	DACI 100	

Drug	Author, year	Intervention/comparator	No. of patients achieving PASI 50	No. of patients achieving PASI 75	No. of patients achieving PASI 90	No. of patients achieving PASI 100	Prior immunobiologic treatment/concomitant systemic medication <sup>b</sup>
Ixekizumab	Griffiths, 2015 Uncover-2 [46] Griffiths, 2015 Uncover-3 [46] Gordon, 2016 Uncover-1 [53]	Ixekizumab sc (160 mg wk 0 and 80 mg every 4 wks) <sup>c</sup> Ixekizumab (160 mg wk 0 and 80 mg every 2 wks) Etanercept (100 mg/wk) Placebo Ixekizumab sc (160 mg wk 0 and 80 mg every 4 wks) <sup>c</sup> Ixekizumab (160 mg wk 0 and 80 mg every 2 wks) Etanercept (100 mg/wk) Placebo Ixekizumab sc (160 mg wk 0 and 80 mg every 4 wks) <sup>c</sup> Ixekizumab sc (160 mg wk 0 and 80 mg every 4 wks) <sup>c</sup> Ixekizumab (160 mg wk 0 and 80 mg every 2 wks) Placebo		315 269 149 4 336 325 204 14 357 386	248 207 67 1 1 262 252 98 6 279	142 107 19 11 145 135 28 0 0 145 153	84 (347)/yes 85 (351)/yes 76 (358)/yes 43 (168)/yes 58/ (385)/yes 58 (386)/yes 60 (382)/yes 33 (193)/yes 168 (432)/no 173 (433)/no
Secukinumab	Blauvelt, 2014 [24]  Langley, 2014  Erasure [29]  Langley, 2014  Fixture [29]  Paul, 2014 [37]	Secukinumab 300 mg sc (wks 0, 1, 2, 3, 4, 8) Secukinumab 150 mg sc (wks 0, 1, 2, 3, 4, 8) Placebo Secukinumab 150 mg sc (wks 0, 1, 2, 3 and 4, then wks 8 and 12) <sup>c</sup> Secukinumab 150 mg sc (wks 0, 1, 2, 3 and 4, then wks 8 and 12) <sup>c</sup> Placebo Secukinumab 300 mg sc (wks 0, 1, 2, 3 and 4, then wks 8 and 12) Secukinumab 150 mg sc (wks 0, 1, 2, 3 and 4, then wks 8 and 12) Etanercept sc (100 mg/wk) Placebo Secukinumab 150 mg sc (wks 0, 1, 2, 3, 4, 8) Secukinumab 300 mg sc (wks 0, 1, 2, 3, 4, 8)	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	45 41 0 0 174 219 219 249 142 16 53	36 27 0 95 137 175 175 67 5	25 5 0 0 4 4 7 8 7 8 0 0 10 10 10 10 10 10 10 10 10 10 10 10	23 (59)/no 28 (59)/no 26 (59)/no 73 (245)/no 45 (327)/no 73 (248)/no 38 (327)/no 45 (327)/no 45 (326)/no 15 (61)/no
Tofacitinib	Bachelez [45] Papp, 2012 [14]	Placebo Tofacitinib 5 mg bid Tofacitinib 10 mg bid Etanercept 100 mg/wk Placebo Tofacitinib 2 mg orally bid Tofacitinib 5 mg orally bid Tofacitinib 15 mg orally bid Placebo	ND 216 266 269 22 ND ND ND	2 130 210 197 6 12 20 33	0 69 119 ND ND ND ND		15 (01)/no 35 (330)/no 29 (332)/no 37 (336)/no 12 (108)/no 10 (49)/no 15 (49)/no 16 (50)/no

Table 1 continued

Drug	Author, year	Intervention/comparator	No. of patients achieving PASI 50	No. of patients achieving PASI 75	No. of patients achieving PASI 90	No. of patients achieving PASI 100	Prior immunobiologic treatment/concomitant systemic medication <sup>b</sup>
	Papp, 2015	Tofacitinib 5 mg orally bid	ND	145	72	ND	113 (363)/no
	OPT1 [52]	Tofacitinib 10 mg bid	ND	213	140	ND	113 (360)/no
		Placebo	ND	11	_	ND	53 (177)/no
	Papp, 2015	Tofacitinib 5 mg orally bid	ND	173	93	ND	92 (382)/no
	OPT2 [52]	Tofacitinib 10 mg bid	ND	223	148	ND	97 (381)/no
		Placebo	ND	22	10	ND	47 (196)/no
Ustekinumab	Ustekinumab Igarashi, 2011 [27]	Ustekinumab 45 mg (wks 0, 4 and every 12 wks)	53	38	21	ND	1 (64)/no
		Ustekinumab 90 mg (wks 0, 4 and every 12 wks)	52	42	27	ND	No/no
		Placebo	4	2	_	ND	No/no
	Leonardi, 2008 [30]	Ustekinumab 45 mg sc (wks 0, 4 and every 12 wks)	213	171	106	32	134 (255)/no
		Ustekinumab 90 mg sc (wks 0, 4 and every 12 wks)	220	170	94	28	130 (256)/no
		Placebo	26	∞	5	0	128 (255)/no
	Tsai, 2011 [41]	Ustekinumab 45 mg sc (wks 0, 4 and then every 12 wks)	51	41	30	5	13 (61)/no
		Placebo	8	3	1	0	9 (61)/no
	Zhu, 2013 [44]	Ustekinumab 45 mg sc (wks 0, 4 and then every 12 wks)	146	132	107	38	19 (160)/no
		Placebo	32	18	5	1	11 (162)/no

EOW every other week, bid twice daily, sc subcutaneous, iv intravenous, ND not disclosed, PASI Psoriasis Area and Severity Index

<sup>a</sup> Studies with multiple treatment arms were included more than once in the table

<sup>b</sup> Number of patients who received prior biologic or small molecule therapy (total number of patients on study drug)

<sup>c</sup> Drugs or doses not included in the final analysis

Fig. 2 Meta-analysis (random-effects model) of the Psoriasis Area and Severity Index 75% response rate of biologic and small molecule inhibitor therapies for moderate to severe psoriasis in randomized, placebo-controlled trials. CI confidence interval, M-H Mantel–Haenszel, EOW every other week, df degrees of freedom, bid twice daily

udy or Subgroup 1.1 Adalimumab load (80mg wk 0 -	40mg wk 1) + 4	Placebo Events Total Weight Omg eow		Risk Difference M-H, Random, 95% CI
sahina 2010c ordon 2006a	27 43 24 46	2 46 8.2% 2 52 8.5%	0.58 [0.43, 0.74] 0.48 [0.33, 0.64]	
ordon 2015 Ada. enter, 2008	30 43 578 814	2 42 8.7% 26 398 63.1%	0.65 [0.50, 0.80] 0.64 [0.61, 0.68]	<u> </u>
iurat, 2007 ibtotal (95% CI)	86 108 1054	10 53 11.5% 591 100.0%	0.61 [0.48, 0.74] 0.62 [0.58, 0.67]	•
otal events eterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 4.6 est for overall effect: Z = 26.25 (P < 0	745 0, df = 4 (P = 0.33 .00001)	42 ); I <sup>2</sup> = 13%		
1.2 Apremilast 30mg/bid				
app 2012 Lancet app 2015 30mg/bid	36 88 183 562	5 88 26.4% 14 282 73.6%	0.35 [0.24, 0.47] 0.28 [0.23, 0.32]	
ubtotal (95% CI) otal events	219	370 100.0%	0.30 [0.23, 0.36]	•
eterogeneity: $Tau^2 = 0.00$ ; $Chi^2 = 1.5$ est for overall effect: $Z = 8.73$ (P < 0.0	1, df = 1 (P = 0.22 00001)	); I <sup>2</sup> = 34%		
1.3 Brodalumab 140mg bwohl 2015 AMAGINE-2 140mg	406 610	25 309 40.9%	0.58 [0.54, 0.63]	_
bwohl 2015 AMAGINE-3 140mg ipp 2012 140mg	435 629 30 39	19 315 42.2% 0 38 16.9%	0.63 [0.59, 0.68] 0.77 [0.63, 0.91]	•
ubtotal (95% CI) otal events	1278 871	662 100.0% 44	0.64 [0.57, 0.70]	•
eterogeneity: $Tau^2 = 0.00$ ; $Chi^2 = 6.9$ est for overall effect: $Z = 18.19$ (P < 0	2, df = 2 (P = 0.03)			
1.4 Brodalumab 210mg				
bwohl 2015 AMAGINE-2 210mg bwohl 2015 AMAGINE-3 210mg	528 612 531 624	25 309 44.6% 19 315 50.5%	0.78 [0.74, 0.82] 0.79 [0.75, 0.83]	
upp 2012 210mg ubtotal (95% CI)	33 40 1276	0 38 4.9% 662 100.0%	0.82 [0.70, 0.95] 0.79 [0.76, 0.82]	<b>→</b>
otal events eterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.4	1092 5, df = 2 (P = 0.80	44		
est for overall effect: Z = 56.66 (P < 0 1.5 Etanercept 50mg/wk	.00001)			
otlieb 2003	17 57	1 55 11.5%	0.28 [0.16, 0.40]	
eonardi 2003 50mg/wk ease 2000	55 162 5 19	6 166 28.8% 0 19 4.1%	0.30 [0.23, 0.38] 0.26 [0.06, 0.47]	
ipp 2005 50mg/wk an der Kerkhof 2008 ubtotal (95% CI)	66 204 36 93 535	6 204 37.9% 1 166 17.7% 610 100.0%	0.29 [0.23, 0.36] 0.38 [0.28, 0.48] 0.31 [0.27, 0.35]	🔭
ibtotai (95% Ci) otal events eterogeneity: Tau² = 0.00; Chi² = 2.6	179	14	0.31 [0.27, 0.33]	•
eterogeneity: Tau* = 0.00; Chi* = 2.6 est for overall effect: Z = 14.44 (P < 0	.00001)	A . = UM		
1.6 Etanercept 100mg/wk schelez 2015 100mg/wk	197 336	6 108 11.0%	0.53 [0.46, 0.60]	<u>-</u>
igel 2012 optlieb 2011 100mg/wk	37 62 79 141	3 62 5.3% 5 68 7.4%	0.55 [0.42, 0.68] 0.49 [0.38, 0.59]	=
riffiths 2011 UNCOVER-2 Etan. riffiths 2015 UNCOVER-3 Etan.	149 358 204 382	4 168 12.6% 14 193 11.8%	0.49 [0.38, 0.39] 0.39 [0.34, 0.45] 0.46 [0.40, 0.52]	_
ingley 2014 fixture ionardi 2003 100mg/wk	142 326 81 164	16 326 12.2% 6 166 9.5%	0.39 [0.33, 0.45] 0.46 [0.38, 0.54]	<u> </u>
upp 2005 100mg/wk rober 2011 et	94 203 55 139	6 204 10.5% 5 72 7.6%	0.43 [0.36, 0.51] 0.33 [0.23, 0.43]	
ring 2007 ibtotal (95% CI)	146 311 2422	15 307 12.0% 1674 100.0%	0.42 [0.36, 0.48] 0.44 [0.40, 0.48]	₹
otal events eterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 21.	1184 94, df = 9 (P = 0.0	80 (09); I <sup>2</sup> = 59%		
est for overall effect: Z = 23.48 (P < 0	.00001)			
1.7 Infliximab 5mg/kg haudari 2001 5mg/kg	9 11 87 99	2 11 1.0% 3 51 12.5%	0.64 [0.31, 0.96]	
ottlieb 2004 5mg/kg enter 2007 5mg/kg	237 314 242 301	4 208 39.6%	0.82 [0.73, 0.91] 0.74 [0.68, 0.79]	-   €
eich 2005 orri 2010	24 35	0 19 3.7%	0.78 [0.72, 0.84] 0.69 [0.52, 0.85]	
ang 2012 ubtotal (95% CI) otal events	844	1 45 11.6% 411 100.0%	0.79 [0.69, 0.88] 0.76 [0.73, 0.79]	•
otal events eterogeneity: Tau² = 0.00; Chi² = 4.6 est for overall effect: Z = 46.47 (P < 0	667 5, df = 5 (P = 0.46 .00001)			
1.8				
ordon 2016 UNCOVER-1 riffiths 2015 UNCOVER-2 every 2 wks	386 433 315 351	17 431 37.2% 4 168 34.3%	0.85 [0.82, 0.89] 0.87 [0.83, 0.91]	
riffiths 2015 UNCOVER-2 every 2 wks riffiths 2015 UNCOVER-3 every 2 wks ribtotal (95% CI)	336 385 1169	14 193 28.5% 792 100.0%	0.87 [0.83, 0.91] 0.80 [0.75, 0.85] 0.84 [0.81, 0.88]	-
otal events eterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 5.4	1037	35		ĺ
est for overall effect: Z = 42.53 (P < 0	.00001)	•		
1.9 Secukinumab 300mg auvelt 2014 300mg	45 59	0 59 14.7%	0.76 [0.65, 0.87]	_
ingley 2014 300mg erasure ingley 2014 300mg fixture	200 245 249 327	11 246 33.0% 16 326 34.6%	0.77 [0.72, 0.83] 0.71 [0.66, 0.76]	
ul 2014 300mg ibtotal (95% CI)	52 60 <b>691</b>	2 61 17.7% 692 100.0%	0.83 [0.74, 0.93] 0.76 [0.71, 0.81]	•
otal events eterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 5.6	546 0, df = 3 (P = 0.13	29 ); I <sup>2</sup> = 46%		
est for overall effect: Z = 30.18 (P < 0 1.10 Tofacitinib 5mg BID	.00001)			
schelez 2015 5mg	130 330	6 108 28.6%	0.34 [0.27, 0.41]	-
upp 2012 5mg upp 2015 OPT1 5mg	20 49 145 363	1 50 6.5% 11 177 35.0%	0.39 [0.25, 0.53] 0.34 [0.28, 0.40]	<del>-</del>
app 2015 OPT2 5mg abtotal (95% CI)	173 382 1124	22 196 29.9% 531 100.0%	0.34 [0.27, 0.41] 0.34 [0.31, 0.38]	🕇
etal events eterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.4 est for overall effect: 7 = 18.38 (B = 0	468 4, df = 3 (P = 0.93	40 ); I <sup>2</sup> = 0%		
st for overall effect: $Z = 18.38$ (P < 0 1.11 Tofacitinib 10mg BID	.00001)			
achelez 2015 10mg no 2015 OPT1 10mg	210 332 213 360	6 108 32.4% 11 177 34.7%	0.58 [0.51, 0.64]	
pp 2015 OPT1 10mg pp 2015 OPT2 10mg ibtotal (95% CI)	213 360 223 381 1073	22 196 32.9% 481 100.0%	0.53 [0.47, 0.59] 0.47 [0.41, 0.54] 0.53 [0.47, 0.58]	
tal events terogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 4.7	646	39	, 0.303	
st for overall effect: Z = 17.71 (P < 0	.00001)			
1.12 Ustekinumab 45mg arashi 2011 45mg	38 64	2 31 7.4%	0.53 [0.38, 0.68]	
onardi 2008 45mg pp 2008 45mg	171 255 273 409	8 255 27.5% 15 410 34.6%	0.64 [0.58, 0.70] 0.63 [0.58, 0.68]	
ai 2011 nu 2013	41 61 132 160	3 60 9.3% 18 162 21.1%	0.62 [0.49, 0.75] 0.71 [0.64, 0.79]	<u> </u>
ibtotal (95% CI) otal events	949 655	918 100.0% 46	0.64 [0.60, 0.69]	•
eterogeneity: $Tau^2 = 0.00$ ; $Chi^2 = 5.9$ st for overall effect: $Z = 29.33$ (P < 0	3, df = 4 (P = 0.20	); I <sup>2</sup> = 33%		
1.13 Ustekinumab 90mg				
arashi 2011 90mg onardi 2008 90mg	42 62 170 256	2 31 17.1% 8 255 38.6%	0.61 [0.47, 0.76] 0.63 [0.57, 0.69]	-
	311 411	15 410 44.3%	0.72 [0.67, 0.77] 0.67 [0.60, 0.74]	
ipp 2008 90mg ibtotal (95% CI)	729	696 100.0%	0.07 [0.00, 0.74]	
	523	25	0.67 [0.60, 0.74]	

0.58–0.60) [Fig. 3]. When analyzing PASI 75 as an outcome, the estimated NNT for ixekizumab, brodalumab 210 mg, infliximab and secukinumab was 1.19, 1.26, 1.31 and 1.31, respectively. A summary of comparisons is reported in Table 2.

When PASI 90 was used as an outcome, both doses of brodalumab—210 mg (RD 0.75, 95% CI 0.61–0.89) and 140 mg (RD 0.72, 95% CI 0.57–0.86—achieved a higher chance of improvement, followed by ixekizumab (RD 0.69, 95% CI 0.65–0.72). Secukinumab and infliximab showed

the same RD, with exactly the same CI (RD 0.53, 95% CI 0.46–0.60). The remaining comparisons are reported in Fig. 4. The overall pooled effect favored treatment in relation to placebo (RD 0.39, 95% CI 0.38–0.40) [Fig. 5].

Brodalumab 210 mg was also the drug that achieved higher RD if PASI 100 was used as the outcome (RD 0.44, 95% CI 0.35–0.53). The approved drugs performed as follows: ixekizumab (RD 0.37, 95% CI 0.35–0.40), secukinumab (RD 0.28, 95% CI 0.22–0.34), adalimumab (RD 0.18, 95% CI 0.12–0.24), and ustekinumab 45 mg

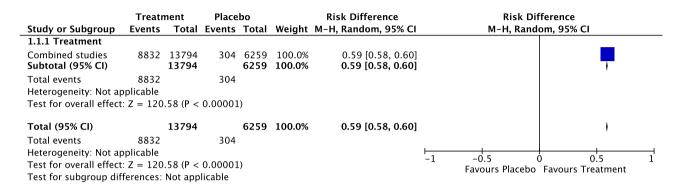


Fig. 3 Meta-analysis (random-effects model) of the Psoriasis Area and Severity Index 75% response rate of all treatments combined for moderate to severe psoriasis in randomized, placebo-controlled trials (overall pooled effect). CI confidence interval, M-H Mantel—Haenszel

Table 2 Summary of results for drugs and doses sorted by drug class

Drug class	Drug/dose	PASI 75		PASI 90		PASI 100		Primary endpoint
		RD (95% CI)	NNT	RD (95% CI)	NNT	RD (95% CI)	NNT	(weeks)
Anti-TNF	Adalimumab load (80 mg week 0 + 40 mg week 1) + 40 mg EOW	0.62 (0.58–0.67)	1.61	0.43 (0.39–0.46)	2.32	0.18 (0.12–0.24)	5.55	12–16
	Etanercept 100 mg/wk	0.44 (0.40-0.48)	2.27	0.22 (0.18-0.25)	4.54	0.05 (0.04-0.07)	20	12
	Etanercept 50 mg/wk	0.31 (0.27-0.35)	3.22	0.10 (0.07-0.13)	10	0.06 (0.01-0.10)	16.6	12
	Infliximab 5 mg/kg	0.76 (0.73-0.79)	1.31	0.53 (0.46-0.60)	1.88	ND	ND	10
	Overall pooled effect	0.54 (0.47-0.60)	1.85	0.28 (0.21-0.35)	3.57	0.10 (0.04-0.16)	10	_
Anti-IL-12/23	Ustekinumab 90 mg	0.67 (0.60-0.74)	1.49	0.42 (0.30-0.54)	2.38	0.15 (0.07-0.22)	6.66	12
	Ustekinumab 45 mg	0.64 (0.60-0.69)	1.56	0.45 (0.35-0.55)	2.22	0.16 (0.10-0.21)	6.25	12
	Overall pooled effect	0.65 (0.62-0.69)	1.53	0.44 (0.37-0.51)	2.27	0.15 (0.11-0.19)	6.66	_
Anti-IL-17	Brodalumab 210 mg	0.79 (0.76-0.82)	1.26	0.75 (0.61-0.89)	1.33	0.44 (0.35-0.53)	2.27	12
	Brodalumab 140 mg	0.64 (0.57-0.70)	1.56	0.72 (0.57-0.86)	1.38	0.26 (0.23-0.30)	3.84	12
	Ixekizumab 160 mg week 0 and 80 mg every 2 weeks	0.84 (0.81–0.88)	1.19	0.69 (0.65–0.72)	1.44	0.37 (0.35–0.40)	2.70	12
	Secukinumab 300 mg	0.76 (0.71–0.81)	1.31	0.53 (0.46-0.60)	1.88	0.28 (0.22-0.34)	3.57	12
	Overall pooled effect	0.76 (0.70-0.82)	1.31	0.61 (0.54-0.68)	1.63	0.35 (0.30-0.40)	2.85	_
Small molecule	Tofacitinib 10 mg	0.53 (0.47-0.58)	1.88	0.36 (0.33-0.39)	2.77	ND	ND	12
inhibitors	Tofacitinib 5 mg	0.34 (0.31-0.38)	2.94	0.19 (0.17-0.22)	5.26	ND	ND	12
(anti-JAK/anti-PD4)	Apremilast 30 mg bid	0.30 (0.23-0.36)	3.33	ND	ND	ND	ND	16
	Overall pooled effect	0.43 (0.30–0.55)	2.32	0.27 (0.13–0.42)	3.7	ND	ND	-

PASI Psoriasis Area and Severity Index, RD risk difference, CI confidence interval, NNT number needed to treat, EOW every other week, bid twice daily, JAK Janus kinase, PD4 phosphodiesterase 4, ND not determined, TNF tumor necrosis factor, IL interleukin

Fig. 4 Meta-analysis (random-effects model) of the Psoriasis Area and Severity Index 90% response rate of biologic and small molecule inhibitor therapies for moderate to severe psoriasis in randomized, placebo-controlled trials. CI confidence interval, M-H Mantel–Haenszel, EOW every other week, df degrees of freedom, bid twice daily

1.13.1 Additionable load (Dillony Act 4. doing with 11-40m) gew 12-5. Sec. 3.0.0 (1) 25. 6.0.7 (1)	Study or Subgroup 1.1.3 Adalimumab load (80mg wk 0 +			Weight	Risk Difference M-H, Random, 95% CI	Risk Difference M-H, Random, 95% CI
The first control effect 2 = 2.4.5 (P o 0.00001)  Page 2012 (100)  Page 2012 (100)  1.18 Encolaration 2 = 3	Gordon 2015 Ada. Menter, 2008 Subtotal (95% CI) Total events	19 43 366 814 <b>857</b> 385	1 42 8 398 440 9	94.7%	0.43 [0.39, 0.47]	•
Sabrotal (1955) CD   39   38   100.0%   0.72   (0.47, 0.86)   Test for excell effect 2 = 9.73 pt 0.00001 Test for excell effect 2 = 9.73 pt 0.00001 Test for excell effect 2 = 9.73 pt 0.00001 Test for excell effect 2 = 9.73 pt 0.00001 Test for excell effect 2 = 9.73 pt 0.00001 Test for excell effect 2 = 10.64 pt 0.000001 Test for excell effect 2 = 10.64 pt 0.000001 Test for excell effect 2 = 10.64 pt 0.000001 Test for excell effect 2 = 10.64 pt 0.000001 Test for excell effect 2 = 10.64 pt 0.000001 Test for excell effect 2 = 10.64 pt 0.000001 Test for excell effect 2 = 7.74 pt 0.000001 Test for excell effect 2 = 1.76 pt 0.000001 Test for excell effect 2 = 1.76 pt 0.000001 Test for excell effect 2 = 1.76 pt 0.000001 Test for excell effect 2 = 1.76 pt 0.000001 Test for excell effect 2 = 1.76 pt 0.000001 Test for excell effect 2 = 1.77 pt 0.000001 Test for excell effect 2 = 1.77 pt 0.000001 Test for excell effect 2 = 1.77 pt 0.000001 Test for excell effect 2 = 1.77 pt 0.000001 Test for excell effect 2 = 1.77 pt 0.000001 Test for excell effect 2 = 1.77 pt 0.000001 Test for excell effect 2 = 1.77 pt 0.000001 Test for excell effect 2 = 1.77 pt 0.000001 Tes	Test for overall effect: Z = 23.45 (P < 0 1.1.7 Brodalumab 140mg	.00001)				_
1.1.	Subtotal (95% CI) Total events Heterogeneity: Not applicable	<b>39</b> 28	38		0.72 [0.57, 0.86] 0.72 [0.57, 0.86]	-
Subtool (1995) C. (1996) C. (1996) C. (1996) C. (1995) C. (1995) C. (1996) C	1.1.8 Brodalumab 210mg		0 38	100.0%	0.75 [0.61, 0.89]	_
Learnard 2003 Sompywk	Total events Heterogeneity: Not applicable	30		100.0%	0.75 [0.61, 0.89]	•
Van der Krichel 2008 13 9 6 1 46 12.05 0.11 (0.01.0.19)  **Survival (1952 C) 7 601 488 10.05	Leonardi 2003 50mg/wk					
Tack for overall effect. Z = 7,14 (P < 0.000001)  Bachelez 2,071 St00mg/week 108 336 1 108 13,1% 0.31 (0.26, 0.37)  Bagle 2012  Griffins (MCOVIR-2 2015 Eam. 67 358 1 1 168 13,1% 0.24 (0.13, 0.36)  Griffins (MCOVIR-2 2015 Eam. 67 358 1 1 168 13,2% 0.24 (0.13, 0.36)  Griffins (MCOVIR-2 2015 Eam. 67 358 1 1 168 13,2% 0.24 (0.13, 0.36)  Griffins (MCOVIR-2 2015 Eam. 67 358 1 1 168 13,2% 0.24 (0.13, 0.36)  Hearward 2003 100mg/wh 36 164 1 1 166 11,1% 0.21 (0.15, 0.28)  Leanward 2003 100mg/wh 36 164 1 1 166 11,1% 0.21 (0.15, 0.28)  Hearward 2003 100mg/wh 37 120 11 204 12,7% 0.19 (0.13, 0.24)  Hearward 2003 100mg/wh 36 164 1 1 166 11,1% 0.21 (0.15, 0.28)  Hearward 2003 100mg/wh 36 164 1 1 169 11,1% 0.21 (0.15, 0.28)  Hearward 2003 100mg/wh 36 164 1 1 169 11,1% 0.21 (0.15, 0.28)  Hearward 2003 100mg/wh 36 120 11 204 12,7% 0.19 (0.13, 0.24)  Hearward 2003 100mg/wh 36 124 13 1 204 12,7% 0.19 (0.13, 0.24)  Hearward 2003 100mg/wh 36 124 13 1 20 20 30 0.05 (0.56, 0.57)  Grotal events  Tactro overall effect 2 = 11,8.7 of 0.00 (0.17 - 9.38, 6f - 3 of - 0.01); F = 68x  Test for overall effect 2 = 14,9.5 of - 0.00 21; F = 68x  Test for overall effect 2 = 14,9.5 of - 0.00 21; F = 68x  Test for overall effect 2 = 14,9.5 of - 0.00 21; F = 68x  Test for overall effect 2 = 14,9.5 of - 0.00 21; F = 68x  Test for overall effect 2 = 14,9.5 of - 0.00 21; F = 68x  Test for overall effect 2 = 14,9.5 of - 0.00 21; F = 68x  Test for overall effect 2 = 40,9.5 of - 0.00 21; F = 68x  Test for overall effect 2 = 40,9.5 of - 0.00 21; F = 68x  Test for overall effect 2 = 40,9.5 of - 0.00 21; F = 68x  Test for overall effect 2 = 40,9.5 of - 0.00 21; F = 68x  Test for overall effect 2 = 40,9.5 of - 0.00 21; F = 68x  Test for overall effect 2 = 40,9.5 of - 0.00 21; F = 68x  Test for overall effect 2 = 40,9.5 of - 0.00 21; F = 68x  Test for overall effect 2 = 40,9.5 of - 0.00 21; F = 68x  Test for overall effect 2 = 40,9.5 of - 0.00 21; F = 68x  Test for overall effect 2 = 40,9.5 of - 0.00 21; F = 0.00;	Van der Kerkhof 2008 Subtotal (95% CI)	13 96 <b>601</b>	1 46 488	12.0%	0.11 [0.03, 0.19]	<del>-</del>
Bachelez 2015 100mg/week 108 336 1 108 13.1% 0.31 0.24 0.370 13.6	Test for overall effect: Z = 7.14 (P < 0.0		; I <sup>2</sup> = 0%			
Pape 2005 150mg/mk	Bachelez 2015 100mg/week Bagel 2012 Griffiths UNCOVER-2 2015 Etan. Griffiths UNCOVER-3 2015 Etan.	16 62 67 358 98 382	1 62 1 168 6 193	5.5% 15.2% 13.6%	0.24 [0.13, 0.36] 0.18 [0.14, 0.22] 0.23 [0.18, 0.28]	<del>-</del>
Test for overall effect: Z = 1,8.7 (P < 0.00001)  L12.5 Inflixing Sing	Papp 2005 100mg/wk Tyring 2007 Subtotal (95% CI) Total events	39 203 65 311 <b>2142</b> 496	1 204 3 307 <b>1534</b>	12.7% 14.3%	0.19 [0.13, 0.24] 0.20 [0.15, 0.25]	<del>=</del>
Gartlieb 2004 Simglykg	Test for overall effect: Z = 13.67 (P < 0		1); I* = 62%			
Test for overall effect: Z = 14.95 (P < 0.00001)  1.1.31 Ixekizumab 160mg wk0 + 80mg every 2 wks  Cordrol 2016 (JNCOVER-1  307 433 2 431 38.4% 0.70 [0.66, 0.75]  Cordrifts 2015 UNCOVER-2 every 2 wks 262 385 6 193 29.3% 0.65 [0.60, 0.70]  (Affiffs 2015 UNCOVER-2 every 2 wks 262 385 6 193 29.3% 0.65 [0.60, 0.70]  Total event  Total event  Heterogeneity. Tau² = 0.00. Chi² = 2.87, df = 2 (P = 0.24); i² = 30%  Test for overall effect: Z = 40.53 (P < 0.00001)  1.1.35 Secukinumab 300mg  Blauwelt 2014 300mg 3 6 59 0 59 17.6% 0.61 [0.48, 0.74]  Langley 2014 300mg future 175 327 5 326 33.3% 0.55 [0.46, 0.58]  Paul 2014 300mg asure 145 245 3 248 31.4% 0.58 [0.52, 0.64]  Langley 2014 300mg future 175 327 5 326 33.3% 0.55 [0.46, 0.58]  Paul 2014 300mg control and the state of the state	Gottlieb 2004 5mg/kg Menter 2007 5mg/kg Reich 2005 Yang 2012 Subtotal (95% CI) Total events	142 314 172 301 48 84 798 419	1 208 1 77 0 45 381	30.6% 29.4% 19.5%	0.45 [0.39, 0.50] 0.56 [0.50, 0.62] 0.57 [0.46, 0.68]	**
Griffing 2015 UNCOVER-2 every 2 wks 248 351 1 168 32.4% 0.70 (0.65, 0.75) (affifing 2015 UNCOVER-3 every 2 wks 262 385 6 193 29.3% 0.65 (0.60, 0.70) (0.65 (0.75) (0.65 (0.75) (0.65 (0.72) (0.65 (0.	1.1.31 lxekizumab 160mg wk0 + 80m	ng every 2 wks				
1.1.35 Secukinumab 300mg   Salauvelt 2014 300mg   36 59 0 59 17.6%   0.61 [0.48, 0.74]   1.1.20	Griffiths 2015 UNCOVER-2 every 2 wks Griffiths 2015 UNCOVER-3 every 2 wks Subtotal (95% CI) Total events	248 351 262 385 1169 817	1 168 6 193 <b>792</b> 9	32.4% 29.3%	0.70 [0.65, 0.75] 0.65 [0.60, 0.70]	•
Blauvelt 2014 300mg 36 59 0 59 17.6% 0.61 [0.48, 0.74] Langley 2014 300mg arsure 145 245 3 248 31.4% 0.58 [0.52, 0.64] Langley 2014 300mg fixture 175 327 5 326 33.3% 0.52 [0.46, 0.58] Paul 2014 300mg fixture 175 327 5 326 33.3% 0.52 [0.46, 0.58] Paul 2014 300mg fixture 175 327 5 326 33.3% 0.52 [0.46, 0.60] Total events 380 8 8 Heterogeneity; Tau² = 0.01; Chi² = 8.04, df = 3 (P = 0.05); i² = 63% Test for overall effect; Z = 15.17 (P < 0.00001)  1.1.36 Tofactitinib 5mg BID  Bachelez 2015 5mg 69 330 1 108 32.8% 0.20 [0.15, 0.25] Papp 2015 0PT1 5mg 72 363 1 177 40.9% 0.19 [0.15, 0.24] Papp 2015 0PT2 5mg 93 382 10 196 26.3% 0.19 [0.14, 0.25] Subtoatid (95% CD) 1075 481 100.0% 0.19 [0.17, 0.22] Total events 124 12	Test for overall effect: Z = 40.53 (P < 0		; I <sup>2</sup> = 30%			
Test for overall effect: Z = 15.17 (P < 0.00001)  1.1.36 Tofactitinib Smg BIO  Bachelez 2015 Smg 69 330 1 108 32.8% 0.20 [0.15, 0.25] Papp 2015 OPT1 Smg 72 363 1 177 40.9% 0.19 [0.15, 0.24] Papp 2015 OPT2 Smg 93 382 10 196 26.3% 0.19 [0.15, 0.24] Papp 2015 OPT2 Smg 93 382 10 1075 481 100.0% 0.19 [0.17, 0.22]  Total events  Test for overall effect: Z = 14.07 (P < 0.00001)  1.1.37 Tofactitinib 10mg BIO  Bachelez 2015 10mg 119 332 1 108 33.1% 0.35 [0.29, 0.40] Papp 2015 OPT1 10mg 140 360 1 177 37.2% 0.38 [0.33, 0.43] Papp 2015 OPT1 10mg 148 381 10 196 25.6% 0.34 [0.28, 0.40] Papp 2015 OPT2 10mg 148 381 10 196 25.6% 0.34 [0.33, 0.39]  Total events  1.1.39 Ustekinumab 45mg  Igarashi 2011 45mg 21 64 1 31 17.1% 0.30 [0.17, 0.43]  Leonardi 2008 45mg 173 409 3 410 22.7% 0.48 [0.33, 0.46] Papp 2008 45mg 173 409 3 410 22.7% 0.48 [0.33, 0.46] Papp 2008 45mg 173 409 3 410 22.7% 0.48 [0.33, 0.66] Papp 2008 45mg 173 409 3 410 22.7% 0.48 [0.35, 0.60] Papp 2008 45mg 173 409 3 410 22.7% 0.48 [0.35, 0.60] Papp 2008 45mg 173 409 3 410 22.7% 0.48 [0.35, 0.60] Papp 2008 45mg 173 409 3 410 22.7% 0.48 [0.35, 0.60] Papp 2008 45mg 173 409 3 410 22.7% 0.48 [0.35, 0.60] Papp 2008 45mg 173 409 3 410 22.7% 0.48 [0.35, 0.60] Papp 2008 45mg 173 409 3 410 22.7% 0.48 [0.35, 0.60] Papp 2008 45mg 173 409 3 410 22.7% 0.48 [0.35, 0.60] Papp 2008 45mg 173 409 3 410 22.7% 0.48 [0.35, 0.60] Papp 2008 45mg 173 409 3 410 22.7% 0.48 [0.35, 0.60] Papp 2008 45mg 173 409 3 410 22.7% 0.48 [0.35, 0.60] Papp 2008 45mg 173 409 3 410 22.7% 0.48 [0.35, 0.60] Papp 2008 45mg 173 409 3 410 22.7% 0.48 [0.35, 0.60] Papp 2008 45mg 173 409 4 256 5 255 36.5% 0.35 [0.29, 0.41] Papp 2008 45mg 27 62 1 31 25.6% 0.40 [0.27, 0.54] Papp 2008 45mg 29 4 256 5 255 36.5% 0.35 [0.29, 0.41] Papp 2008 45mg 29 4 256 5 255 36.5% 0.35 [0.29, 0.41] Papp 2008 45mg 29 4 256 5 255 36.5% 0.35 [0.29, 0.41] Papp 2008 45mg 29 4 256 5 255 36.5% 0.35 [0.29, 0.41] Papp 2008 45mg 29 4 256 5 255 36.5% 0.35 [0.29, 0.41] Papp 2008 45mg 29 4 256 5 255 36.5% 0.35 [0.29, 0.41] Papp 2008 45mg 29 4 256 5 2	Blauvelt 2014 300mg Langley 2014 300mg erasure Langley 2014 300mg fixture Paul 2014 300mg Subtotal (95% Ci)	145 245 175 327 24 60 <b>691</b>	3 248 5 326 0 61 694	31.4% 33.3% 17.7%	0.58 [0.52, 0.64] 0.52 [0.46, 0.58] 0.40 [0.27, 0.53]	- <del>-</del>
Bachelez 2015 Smg 69 330 1 108 32.8% 0.20 [0.15, 0.25]   Papp 2015 OPT1 Smg 72 363 1 177 40.9% 0.19 [0.15, 0.25]   Papp 2015 OPT2 Smg 93 382 10 196 26.3% 0.19 [0.14, 0.25]   Subtotal (95% CI) 1075 481 100.0% 0.19 [0.17, 0.22]    1	Test for overall effect: Z = 15.17 (P < 0		; I <sup>2</sup> = 63%			
Heterogeneity: Tau² = 0,00; Ch² = 0.06, df = 2 (P = 0.97); l² = 0%  Test for overall effect: Z = 14.07 (P < 0.00001)  1.1.37 Tofactinih 10mg BID  Bachelez 2015 10mg 119 332 1 108 33.1% 0.35 [0.29, 0.40]  Papp 2015 0PT1 10mg 140 360 1 177 37.2% 0.38 [0.33, 0.43]  Papp 2015 0PT2 10mg 148 381 10 196 29.6% 0.34 [0.28, 0.40]  Subtotal (95% CD) 1073 481 100.0% 0.36 [0.33, 0.39]  Total events 407 12  Heterogeneity: Tau² = 0.00; Chì² = 1.52, df = 2 (P = 0.47); l² = 0%  Test for overall effect: Z = 22.32 (P < 0.00001)  1.1.39 Ustekinumab 45mg  Igarashi 2011 45mg 21 64 1 31 17.1% 0.30 [0.17, 0.43]  Leonardi 2008 45mg 173 409 3 410 22.7% 0.48 [0.33, 0.46]  Papp 2008 45mg 173 409 3 410 22.7% 0.48 [0.35, 0.66]  Papp 2008 45mg 173 409 3 410 22.7% 0.48 [0.35, 0.66]  Papp 2008 45mg 173 409 3 410 22.7% 0.48 [0.35, 0.65]  Total events 437 15  Total events 437 15  Total events 437 15  Total events 437 15  Test for overall effect: Z = 8.68 (P < 0.00001)  1.1.40 Ustekinumab 90mg  Igarashi 2011 90mg 2 7 62 1 31 25.6% 0.40 [0.27, 0.54]  Leonardi 2008 90mg 9 4 256 5 255 36.5% 0.35 [0.29, 0.41]  Papp 2008 90mg 209 411 3 410 379 0.05 [0.45, 0.55]  Heterogeneity: Tau² = 0.01; Chì² = 14.95, df = 2 (P = 0.0006); l² = 87%  Total events 400 0.05 (P = 0.00001)  Total events 400 0	Bachelez 2015 5mg Papp 2015 OPT1 5mg Papp 2015 OPT2 5mg <b>Subtotal (95% CI)</b>	72 363 93 382 <b>1075</b>	1 177 10 196 <b>481</b>	40.9% 26.3%	0.19 [0.15, 0.24] 0.19 [0.14, 0.25]	# # +
Bachelez 2015 10mg 119 332 1 1 108 33.1% 0.35 [0.29, 0.40]  Papp 2015 0PT1 10mg 140 360 1 177 37.2% 0.38 [0.33, 0.43]  Papp 2015 0PT2 10mg 148 381 10 196 29.6% 0.34 [0.28, 0.40]  Subtotal (95% CD) 1073 481 100.0% 0.36 [0.33, 0.39]  Heterogeneity: Tau² = 0.00: Chi² = 1.52, df = 2 (P = 0.47); l² = 0%    12	Heterogeneity: $Tau^2 = 0.00$ ; $Chi^2 = 0.0$ Test for overall effect: $Z = 14.07$ (P < 0	6, df = 2 (P = 0.97)	; I <sup>2</sup> = 0%			
Heterogeneity: Tau² = 0.01; Chî² = 1.52, df = 2 (P = 0.47); l² = 0%  Test for overall effect: Z = 22.32 (P < 0.00001)  1.1.39 Ustekinumab 45mg  Ugarashi 2011 45mg  21 64 1 31 17.1% 0.30 [0.17, 0.43]  Leonardi 2008 45mg 106 255 5 255 21.9% 0.40 [0.33, 0.46]  **Papp 2008 45mg 173 409 3 410 22.7% 0.48 [0.35, 0.60]  **Tasi 2011 30 61 1 60 17.2% 0.48 [0.35, 0.60]  **Pup 2013 107 160 5 162 21.0% 0.64 [0.56, 0.72]  **Subtotal (95% Cl) 949 918 100.0% 0.45 [0.35, 0.55]  **Total events  Heterogeneity: Tau² = 0.01; Chî² = 32.66, df = 4 (P < 0.00001); l² = 88%  Test for overall effect: Z = 8.68 (P < 0.00001)  1.1.40 Ustekinumab 90mg  27 62 1 31 25.6% 0.40 [0.27, 0.54]  1.1.40 Ustekinumab 90mg  29 4255 5 255 36.5% 0.35 [0.29, 0.41]  **Papp 2008 90mg 29 411 3 410 37.9% 0.55 [0.45, 0.55]  **Upapp 2008 90mg 20 411 3 410 37.9% 0.55	Bachelez 2015 10mg Papp 2015 OPT1 10mg Papp 2015 OPT2 10mg Subtotal (95% CI)	140 360 148 381 <b>1073</b>	1 177 10 196 <b>481</b>	37.2% 29.6%	0.38 [0.33, 0.43] 0.34 [0.28, 0.40]	-
	Heterogeneity: $Tau^2 = 0.00$ ; $Chi^2 = 1.5$ : Test for overall effect: $Z = 22.32$ (P < 0	2, df = 2 (P = 0.47)				
Zhu 2013 107 160 5 162 21.0% 0.64 [0.56, 0.72]   Subtotal (95% CI) 949 918 100.0% 0.45 [0.35, 0.55]    Total events 437 15  Heterogeneity: Tau² = 0.01; Ch₁² = 32.66, df = 4 (P < 0.00001); l² = 88%  Test for overall effect: Z = 8.68 (P < 0.00001)  1.1.40 Ustekinumab 90mg  1.1.40 Ustekinumab 90mg  27 62 1 31 25.6% 0.40 [0.27, 0.54]  Leonard 2008 90mg 94 256 5 255 36.5% 0.35 [0.29, 0.41]  Papp 2008 90mg 20 411 3 410 37.9% 0.50 [0.45, 0.55]  Subtotal (95% CI) 729 696 100.0% 0.42 [0.30, 0.54]  Total events 330 9  Heterogeneity: Tau² = 0.01; Ch₁² = 14.95, df = 2 (P = 0.0006); l² = 87%  Test for overall effect: Z = 7.15 (P < 0.00001)	lgarashi 2011 45mg Leonardi 2008 45mg Papp 2008 45mg	106 255 173 409	5 255 3 410	21.9% 22.7%	0.40 [0.33, 0.46] 0.42 [0.37, 0.46]	÷
1.1-40 Ustekinumab 90mg   1	Zhu 2013 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 32.	107 160 949 437 66, df = 4 (P < 0.00	5 162 918 15	21.0% <b>100.0%</b>	0.64 [0.56, 0.72]	<b>◆</b> <sup>+</sup>
Papp 2008 90mg 209 411 3 410 37.9% 0.50 [0.45, 0.55]    **Subtotal (95% CI) 729 696 100.0% 0.42 [0.30, 0.54]    Total events 330 99 100.0% 0.42 [0.30, 0.54]    Heterogeneity: Tau² = 0.01; Chi² = 14.95, df = 2 (P = 0.0006); l² = 87%    Test for overall effect: Z = 7.15 (P < 0.00001)	1.1.40 Ustekinumab 90mg Igarashi 2011 90mg	27 62				-
	Papp 2008 90mg Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 14.	209 411 729 330 95, df = 2 (P = 0.00	3 410 <b>696</b> 9	37.9%	0.50 [0.45, 0.55]	•
-1 -0.5 0 0.5 Favours treatment Favours placebo	restroi overan enect: $Z = 7.15$ (P < 0.0	,0001)				-1 -0.5 0 0.5 1 Favours treatment Favours placebo

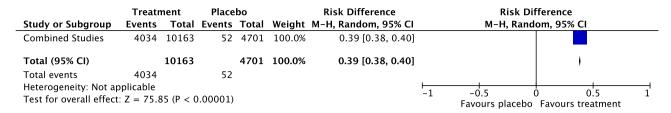


Fig. 5 Meta-analysis (random-effects model) of the Psoriasis Area and Severity Index 90% response rate of all treatments combined for moderate to severe psoriasis in randomized, placebo-controlled trials (overall pooled effect). CI confidence interval, M-H Mantel—Haenszel

(RD 0.16, 95% CI 0.10–0.21). Other comparisons are reported in Fig. 6. The overall pooled effect of treatment versus placebo was also favorable towards treatment (RD 0.24, 95% CI 0.23–0.25) [Fig. 7].

Heterogeneity ( $I^2$ ) on the PASI 75 outcome analysis was below 40% in the following drugs: adalimumab ( $I^2 = 13\%$ ), apremilast ( $I^2 = 34\%$ ), brodalumab 210 mg ( $I^2 = 0\%$ ), etanercept 50 mg ( $I^2 = 0\%$ ), infliximab ( $I^2 = 0\%$ ), tofacitinib 5 mg ( $I^2 = 0\%$ ), and ustekinumab 45 mg ( $I^2 = 33\%$ ). Moderate heterogeneity was found in the etanercept 100 mg ( $I^2 = 59\%$ ), secukinumab ( $I^2 = 46\%$ ), and tofacitinib 10 mg ( $I^2 = 58\%$ ) groups. In addition, substantial heterogeneity was seen in the following groups: brodalumab 140 mg ( $I^2 = 71\%$ ), ixekizumab ( $I^2 = 64\%$ ), and ustekinumab 90 mg ( $I^2 = 67\%$ ) [Fig. 2]. Heterogeneity for remaining outcomes (PASI 90 and 100) have been reported in Figs. 4 and 6.

The funnel plot of the PASI 75 outcome did not disclose discrepancies with regard to the magnitude of the effect measured and study size. PASI 90 and PASI 100 funnel plots are not typical, and the lack of symmetry observed may be an indication of publication bias (Online Resource 3, 4, and 5).

Meta-regression was performed to evaluate the contribution of mean baseline PASI, previous use of biologics, and duration of the disease to the heterogeneity among studies (Online Resource 6). None of these variables explained the heterogeneity.

## 4 Discussion

In the present review, anti-IL-17 drugs performed very well. Ixekizumab presented the higher RD in the primary outcome (PASI 75), while brodalumab (210 mg) performed well, following ixekizumab on the primary outcome and achieving a higher RD on both secondary outcomes (PASI 90 and PASI 100). Nevertheless, as the CI overlapped, ixekizumab, brodalumab 210 mg, and secukinumab should be considered as having similar performances, even with different RDs. On the other hand, ixekizumab and brodalumab 210 mg were superior to all remaining drugs, with the exception of infliximab and

secukinumab, when PASI 75 was the outcome (no overlapping of the CI).

When analyzing PASI 90 as an outcome, brodalumab (both doses) had the higher RD, but the performance of ixekizumab was similar to the overlapped CI. Nevertheless, it is important to emphasize that only one brodalumab study [11] (both dosages) could be identified that used PASI 90 as an outcome; however, a low number of patients were enrolled in this study. Therefore, the results regarding brodalumab at this particular outcome should be considered with caution. Ixekizumab was also the best performing drug, and was superior than all the remaining approved medications (no overlapping of the CI). Ixekizumab also showed the highest RD among approved drugs at PASI 100, and was superior to all remaining medications (no overlapping of the CI) when drugs were compared with placebo. At the same outcome, brodalumab 210 mg achieved a higher RD than ixekizumab, but effectiveness was comparable as the CI overlapped. The number of studies included in the analysis of PASI 100 outcome for brodalumab was higher, enrolling more than 1200 patients, which makes these findings more robust than the findings for brodalumab when PASI 90 was analyzed.

Among the newer small molecule inhibitor drugs, tofacitinib, an anti-Janus kinase 1, also performed well at a dose of 10 mg, being superior to lower-dose etanercept when compared with placebo, and comparable to higher-dose etanercept and adalimumab and low-dose brodalumab (overlapping CI), considering PASI 75 as the primary outcome.

On the other hand, apremilast, an anti-phosphodiesterase 4 drug, performed poorly. Nevertheless, it is comparable to low-dose etanercept (50 mg/week) and low-dose tofacitinib (5 mg) at the primary outcome. PASI 90 and 100 analyses could not be performed for apremilast as no studies that could supply the appropriate data were identified.

In accordance with previous meta-analyses [16, 52], infliximab also performed well among approved biologics. At both dosages (45 and 90 mg), ustekinumab had basically the same performance, which may be explained by the fact that the included studies did not stratify the analysis by patient weight and dosage. The order of

Study or Subgroup	Treatn Events		Placeb ents		Weight	Risk Difference M-H, Random, 95% CI	Risk Difference M-H, Random, 95% CI
.1.2 Adalimumab load (80mg wk0 + 4	-		-				
ordon 2006 LOAD+40mg/2wk	5	46	0	52	25.5%	0.11 [0.01, 0.20]	-
ordon 2015 Ada.	11	43	0	42	16.0%	0.26 [0.12, 0.39]	-
lenter, 2008	163	814	4	398	58.5%	0.19 [0.16, 0.22] <b>0.18 [0.12, 0.24]</b>	
ubtotal (95% CI)	179	903	4	492	100.0%	0.10 [0.12, 0.24]	▼
otal events eterogeneity: $Tau^2 = 0.00$ ; $Chi^2 = 3.66$ , est for overall effect: $Z = 5.76$ (P < 0.00	df = 2 (F	P = 0.16);		%			
.1.6 Brodalumab 140mg							
ebwohl 2015 AMAGINE-2 140mg	157	610	2	309	47.4%	0.25 [0.22, 0.29]	<u> </u>
ebwohl 2015 AMAGINE-3 140mg	170	629	1	315	48.2%	0.27 [0.23, 0.30]	
app 2012 140mg	15	39	0	38	4.4%	0.38 [0.23, 0.54]	
ubtotal (95% CI)	2.42	1278	-	662	100.0%	0.26 [0.23, 0.30]	▼
otal events eterogeneity: $Tau^2 = 0.00$ ; $Chi^2 = 2.88$ , est for overall effect: $Z = 15.64$ (P < 0.0		P = 0.24);	$1^2 = 31$	%			
.1.7 Brodalumab 210mg							
ebwohl 2015 AMAGINE-2 210mg	272	612	2	309	40.2%	0.44 [0.40, 0.48]	•
ebwohl 2015 AMAGINE-3 210mg	229	624	1	315	40.5%	0.36 [0.33, 0.40]	-
app 2012 210mg	25	40	0	38	19.3%	0.63 [0.47, 0.78]	
ubtotal (95% CI)		1276	_	662	100.0%	0.44 [0.35, 0.53]	<b>—</b>
otal events leterogeneity: $Tau^2 = 0.00$ ; $Chi^2 = 15.08$ est for overall effect: $Z = 9.69$ (P < 0.00		(P = 0.000)	3 )5); l <sup>2</sup> =	= 87%			
1.9 Etanercept 50mg/wk							
trober 2011	8	139	0		100.0%	0.06 [0.01, 0.10]	
ubtotal (95% CI)	-	139	_	72	100.0%	0.06 [0.01, 0.10]	◆
otal events leterogeneity: Not applicable est for overall effect: Z = 2.57 (P = 0.01	.)		0				
.1.10 Etanercept 100mg/wk							
Griffiths 2015 UNCOVER-2 Etan.	19	358	1	168	32.0%	0.05 [0.02, 0.07]	•
iriffiths 2015 UNCOVER-3 Etan.	28	382	0	193	30.1%	0.07 [0.05, 0.10]	=
angley 2014 fixture	14	326	0	326	37.9%	0.04 [0.02, 0.07]	<u>.</u>
ubtotal (95% CI)		1066		687	100.0%	0.05 [0.04, 0.07]	◆
otal events leterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3.10, fest for overall effect: Z = 5.78 (P < 0.00		P = 0.21);	1 = 35	%			
.1.23 Ixekizumab 160mg wk0 + 80mg	every 2	wks					
iordon 2016 UNCOVER-1	153	433	0	431	38.7%	0.35 [0.31, 0.40]	-
Griffiths 2015 UNCOVER-2 every 2 wks	142	351	1	168	28.4%	0.40 [0.35, 0.45]	-
riffiths 2015 UNCOVER-3 every 2 wks	145	385	0	193	32.9%	0.38 [0.33, 0.43]	
ubtotal (95% CI)		1169		792	100.0%	0.37 [0.35, 0.40]	•
otal events leterogeneity: $Tau^2 = 0.00$ ; $Chi^2 = 1.69$ , lest for overall effect: $Z = 26.13$ (P < 0.0		P = 0.43);	$I^2 = 0\%$	5			
.1.26 Secukinumab 300mg							
lauvelt 2014 300mg	25	59 245	0	59	15.0%	0.42 [0.30, 0.55]	
angley 2014 300mg erasure	70 70	245	2 0	248	32.0%	0.28 [0.22, 0.34]	
angley 2014 300mg fixture aul 2014 300mg	78 16	327 60	0	326 61	35.7% 17.3%	0.24 [0.19, 0.28] 0.27 [0.15, 0.38]	
ubtotal (95% CI)	10	691	U		100.0%	0.28 [0.22, 0.34]	•
	189		2			, 1	Ţ
otal events leterogeneity: Tau² = 0.00; Chi² = 7.47,			1 = 00				
fotal events leterogeneity: $Tau^2 = 0.00$ ; $Chi^2 = 7.47$ , lest for overall effect: $Z = 9.22$ (P < 0.00			1 = 00				
otal events leterogeneity: $Tau^2 = 0.00$ ; $Chi^2 = 7.47$ , lest for overall effect: $Z = 9.22$ (P < 0.00 .1.27 Ustekinumab 45mg	0001)			זרר	20.20/	0.12 [0.00 0.17]	
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◄ Fig. 6 Meta-analysis (random-effects model) of the Psoriasis Area and Severity Index 100% response rate of biologic and small molecule inhibitor therapies for moderate to severe psoriasis in randomized, placebo-controlled trials. CI confidence interval, M-H Mantel-Haenszel, EOW every other week, df degrees of freedom

effectiveness, measured by RD, in which infliximab 5 mg/kg, ustekinumab 90 mg, ustekinumab 45 mg, adalimumab, etanercept 100 mg, and etanercept 50 mg were positioned in this meta-analysis, was the same as that reported by Schmitt et al. in a recent meta-analysis [16]. Using a different meta-analysis methodology (Bayesian, network meta-analysis), Reich et al. [54] identified a similar ranking with regard to the chance of a PASI 75 response, with the exception of the etanercept 100 mg response rate, which was not contemplated in the study. It is important to note that a rank of RD is somewhat deceiving as the CI may overlap. Nevertheless, the concordance of the rank seen in the work of Reich et al., which used a Bayesian analysis, and the RD rank found in this work, indicates a consistent trend [54].

It is important to emphasize that the objective of this meta-analysis was to compare active treatments against placebo. A limitation to this work is that it is not inherently designed to make indirect comparisons of active treatments and, as previously stated, overlapping CIs determine that drugs are equally effective. A further Bayesian network meta-analysis should be performed to address this issue and, eventually, allow indirect comparisons to rank active treatments.

Considering approved doses and PASI 75 as an outcome, heterogeneity inside each group has been found to be low ( $I^2 \le 40\%$ ) or moderate ( $I^2 > 40$ ,  $\le 60\%$ ) [20] for all comparisons, except for ustekinumab 90 mg ( $I^2 = 67\%$ ), brodalumab ( $I^2 = 71\%$ ), and ixekizumab ( $I^2 = 64\%$ ). The heterogeneity of ustekinumab at a higher dose may be explained by the grouped analysis of populations of different weights (>100 or <100 kg). After performing sensitivity analysis, the heterogeneity found in the brodalumab subgroup was found to be due to a phase II study [11] with a low number of participants; heterogeneity for the brodalumab subgroup decreased to 48% after exclusion of this

particular study. No reason was found to account for heterogeneity in the ixekizumab group, neither in meta-regression (Online Resource 6) nor in the sensitivity analysis. Heterogeneity of the pooled overall efficacy of active treatments compared with placebo was high, but this intergroup heterogeneity was expected due to the number of different treatments analyzed and the unit of analysis error. Meta-regression was performed to analyze the impact of PASI score prior to treatment, duration of psoriasis, or previous use of biologic or small molecule inhibitor drugs on heterogeneity. None of the pre-defined variables influenced the results. Random-effects meta-analysis was performed as an attempt to incorporate heterogeneity.

Risk of bias assessment showed a small percentage of high risk of bias categorization among the included studies. On the other hand, 50% of the studies did not explicitly disclose the random sequence generation or allocation concealment (selection bias) well enough, although being categorized as having an unclear risk of bias.

The funnel plot of the primary outcome (PASI 75) was interpreted as being symmetrical and therefore it is less likely that publication bias may have been present. Larger studies are based on the mean RD at the top of the plot. The lack of smaller studies is responsible for the empty space found at the bottom of the plot, but one can assume this is due to the inclusion and exclusion criteria of the systematic review (only placebo-controlled RCTs). Two smaller studies are found on the plot but they are symmetrically positioned on each side of the mean RD. PASI 90 and 100 funnel plot were asymmetric, and both showed smaller studies to be highly efficacious, resulting in a plot that had an empty lower left quadrant. One explanation for this asymmetry is that studies that evaluated less effective drugs may have chosen not to report PASI 90 and 100, while studies evaluating more effective drugs tend to report these outcomes. Therefore, publication bias cannot be ruled out.

The time of outcomes assessment may also be a limitation in the interpretation of the results. As the majority of RCTs used a 12-week timeframe, extrapolation of the results for longer periods may not be appropriate.

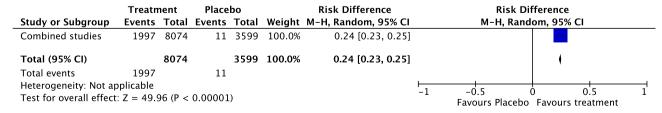


Fig. 7 Meta-analysis (random-effects model) of the Psoriasis Area and Severity Index 100% response rate of all treatments combined for moderate to severe psoriasis in randomized, placebo-controlled trials (overall pooled effect). CI confidence interval, M-H Mantel—Haenszel

#### 5 Conclusions

This meta-analysis showed that biologics and small molecule inhibitors are highly effective for the treatment of moderate to severe psoriasis, and that anti-IL-17 drugs have the same, or even greater, efficacy than anti-tumor necrosis factor (TNF) and anti-IL-12/23 drugs when PASI 75 or PASI 90 are used as the outcome. If PASI 100 is used as the outcome, newer drugs such as anti-IL-17 tend to perform better than anti-TNF and anti-IL-12/23 drugs. As the number of newer biologic and small molecule inhibitor drugs increases, the efficacy of these drugs compared with placebo, found in this meta-analysis, can help doctors to choose what the most appropriate treatment is for each particular patient.

#### **Compliances with Ethical Standards**

#### Funding None.

Conflict of interest André Vicente Esteves de Carvalho has received research support and is a speaker/advisory board program participant receiving honoraria for Abvie, Jansen, Novartis and Leo Pharma. Rodrigo Pereira Duquia, Bernardo Lessa Horta and Renan Rangel Bonamigo have no conflicts of interest.

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## References

- Durham LE, Kirkham BW, Taams LS. Contribution of the IL-17 pathway to psoriasis and psoriatic arthritis. Curr Rheumatol Rep. 2015;17(8):55.
- Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. J Am Acad Dermatol. 2008;58(5):826–50.
- Gelfand JM, Neimann AL, Shin DB, et al. Risk of myocardial infarction in patients with psoriasis. JAMA. 2006;296(14): 1735–41.
- Chaudhari U, Romano P, Mulcahy LD, et al. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. Lancet. 2001;357(9271):1842–7.
- Gordon KB, Langley RG, Leonardi C, et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. J Am Acad Dermatol. 2006;55(4):598–606.
- Krueger GG, Langley RG, Leonardi C, et al. A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. N Engl J Med. 2007;356(6):580–92.
- Papp K, Cather JC, Rosoph L, et al. Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial. Lancet. 2012;380(9843):738–46.

 Mease PJ, Goffe BS, Metz J, et al. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet. 2000;356(9227):385–90.

- Leonardi C, Matheson R, Zachariae C, et al. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. N Engl J Med. 2012;366(13):1190–9.
- Rich P, Sigurgeirsson B, Thaci DP, et al. Secukinumab induction and maintenance therapy in moderate-to-severe plaque psoriasis: a randomised, double-blind, placebo-controlled, phase II regimen-finding study. Br J Dermatol. 2013;168:402–11.
- Papp KA, Leonardi C, Menter A, et al. Brodalumab, an antiinterleukin-17-receptor antibody for psoriasis. N Engl J Med. 2012;366(13):1181–9.
- Sofen H, Li K, Smith S, et al. Guselkumab (an IL-23–specific mAb) demonstrates clinical and molecular response in patients with moderate-to-severe psoriasis. J Allergy Clin Immunol. 2014;133(4):1032–40.
- Reich K, Ortonne JP, Gottlieb AB, et al. Successful treatment of moderate to severe plaque psoriasis with the PEGylated Fab' certolizumab pegol: results of a phase II randomized, placebocontrolled trial with a re-treatment extension. Br J Dermatol. 2012;167(1):180–90.
- 14. Papp KA, Menter A, Strober B, et al. Efficacy and safety of tofacitinib, an oral Janus kinase inhibitor, in the treatment of psoriasis: a phase 2b randomized placebo-controlled dose-ranging study. Br J Dermatol. 2012;167(3):668–77.
- Gordon KB, Langley RG, Gottlieb AB, et al. A phase iii, randomized, controlled trial of the fully human IL-12/23 mAb briakinumab in moderate-to-severe psoriasis. J Invest Dermatol. 2011;132(2):304–14.
- Schmitt J, Rosumeck S, Thomaschewski G, et al. Efficacy and safety of systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. Br J Dermatol. 2014;170(2):274–303.
- 17. Xiong H-Z, Gu J-Y, He Z-G, et al. Efficacy and safety of secukinumab in the treatment of moderate to severe plaque psoriasis: a meta-analysis of randomized controlled trials. Int J Clin Exp Med. 2015;8(3):3156–72.
- Chen Y, Qian T, Zhang D, et al. Clinical efficacy and safety of anti-IL-17 agents for the treatment of patients with psoriasis. Immunotherapy. 2015;7(9):1023–37.
- Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6(7):e1000100–28.
- Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available at: http://www.cochrane-handbook.org. Accessed 21 July 2016
- Lebwohl M, Strober B, Menter A, et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. N Engl J Med. 2015;373(14):1318–28.
- Asahina A, Nakagawa H, Etoh T, et al. Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: efficacy and safety results from a phase II/III randomized controlled study. J Dermatol. 2010;37(4):299–310.
- Bagel J, Lynde C, Tyring S. Moderate to severe plaque psoriasis with scalp involvement: a randomized, double-blind, placebocontrolled study of etanercept. J Am Acad Dermatol. 2012;67(1):86–92.
- Blauvelt A, Prinz JC, Gottlieb AB, et al. Secukinumab administration by pre-filled syringe: efficacy, safety and usability results from a randomized controlled trial in psoriasis (FEATURE). Br J Dermatol. 2015;172(2):484–93.
- 25. Gottlieb A, Menter A, Mendelsohn A, et al. Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic

- arthritis: randomised, double-blind, placebo-controlled, crossover trial. Lancet. 2009;373(9664):633–40.
- Gottlieb AB, Matheson RT, Lowe N, et al. A randomized trial of etanercept as monotherapy for psoriasis. Arch Dermatol. 2003;139(12):1627–32.
- Igarashi A, Kato T, Kato M, et al. Efficacy and safety of ustekinumab in Japanese patients with moderate-to-severe plaque-type psoriasis: long-term results from a phase 2/3 clinical trial. J Dermatol. 2011;39(3):242–52.
- 28. Van De Kerkhof P, Segaert S, Lahfa M, et al. Once weekly administration of etanercept 50 mg is efficacious and well tolerated in patients with moderate-to-severe plaque psoriasis: a randomized controlled trial with open-label extension. Br J Dermatol. 2008;159(5):1177–85.
- Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis: results of two phase 3 trials. N Engl J Med. 2014;371(4):326–38.
- Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet. 2008;371(9625):1665–74.
- Leonardi CL, Powers JL, Matheson RT, et al. Etanercept as monotherapy in patients with psoriasis. N Engl J Med. 2003;349(21):2014–22.
- Menter A, Tyring SK, Gordon K, et al. Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. J Am Acad Dermatol. 2008;58(1):106–15.
- 33. Menter A, Feldman SR, Weinstein GD, et al. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. J Am Acad Dermatol. 2007;56(1):31.e1–15.
- 34. Papp KA, Langley RG, Sigurgeirsson B, et al. Efficacy and safety of secukinumab in the treatment of moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled phase II dose-ranging study. Br J Dermatol. 2013;168(2):412–21.
- 35. Papp K, Reich K, Leonardi CL, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). J Am Acad Dermatol. 2015;73(1):37–49.
- Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet. 2008;371(9625):1675–84.
- Paul C, Lacour JP, Tedremets L, et al. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). J Eur Acad Dermatol Venereol. 2015;29(6):1082–90.
- Reich K, Nestle FO, Papp K, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. Lancet. 2005;366(9494): 1367–74.
- Saurat JH, Stingl G, Dubertret L, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br J Dermatol. 2007;158(3):558–66.

- Torii H, Nakagawa H. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-controlled multicenter trial. J Dermatol Sci. 2010;59(1):40–9.
- 41. Tsai T-F, Ho J-C, Song M, et al. Efficacy and safety of ustek-inumab for the treatment of moderate-to-severe psoriasis: a phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL). J Dermatol Sci. 2011;63(3):154–63.
- 42. Tyring S, Gordon KB, Poulin Y, et al. Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. Arch Dermatol. 2007;143(6):719–26.
- 43. Yang HZ, Wang K, Jin H-Z, et al. Infliximab monotherapy for Chinese patients with moderate to severe plaque psoriasis: a randomized, double-blind, placebo-controlled multicenter trial. Chin Med J. 2012;125(11):1845–51.
- 44. Zhu X, Zheng M, Song M, et al. Efficacy and safety of ustek-inumab in Chinese patients with moderate to severe plaque-type psoriasis: results from a phase 3 clinical trial (LOTUS). J Drugs Dermatol. 2013;12(2):166–74.
- 45. Bachelez H, van de Kerkhof P, Strohal R, et al. Tofacitinib versus etanercept or placebo in moderate-to- severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial. Lancet. 2015;386(9993):552–61.
- 46. Griffiths CEM, Reich K, Lebwohl M, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. Lancet. 2015;386(9993):541–51.
- 47. Gottlieb AB, Evans R, Li S, et al. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol. 2004;51(4):534–42.
- Gordon KB, Duffin KC, Bissonnette R, et al. A phase 2 trial of guselkumab versus adalimumab for plaque psoriasis. N Engl J Med. 2015;373:136–44.
- Gottlieb AB, Leonardi C, Kerdel F, et al. Efficacy and safety of briakinumab vs. etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. Br J Dermatol. 2011;165:652–60.
- Papp KA, Tyring S, Lahfa M, et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br J Dermatol. 2005;152:1304–12.
- 51. Strober BE, Crowley JJ, Yamauchi PS, et al. Efficacy and safety results from a phase III, randomized controlled trial comparing the safety and efficacy of briakinumab with etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. Br J Dermatol. 2011;165:661–8.
- 52. Papp KA, Menter MA, Abe M, et al. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: results from two randomized, placebo-controlled, phase III trials. Br J Dermatol. 2015;173:949–61.
- 53. Gordon KB, Blauvelt A, Papp KA, et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. N Engl J Med. 2016;375:345–56.
- 54. Reich K, Burden AD, Eaton JN, et al. Efficacy of biologics in the treatment of moderate to severe psoriasis: a network meta-analysis of randomized controlled trials. Br J Dermatol. 2011;166(1):179–88.