Targeted Immune Modulators for Plaque Psoriasis and Psoriatic Arthritis: Update

Systematic Review

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Executive Summary

Background

Targeted immune modulators (TIMs) are a category of medications used to treat certain types of immunologic and inflammatory diseases, including plaque psoriasis and psoriatic arthritis.[1,2] Plaque psoriasis is a chronically recurring, debilitating inflammatory disease that affects the skin, scalp, and joints.[3] It is characterized by erythrosquamous, itchy, scaling lesions, and ranges in severity from mild to severe.[3] Psoriatic arthritis is a chronic inflammatory arthritis associated with psoriasis that can affect any joint in the body.[4]

TIMs work by selectively blocking mechanisms involved in the inflammatory and immune response, although the specific mechanism can vary by TIM agent.[5] The U.S. Food and Drug Administration (FDA) has approved or is currently evaluating drugs with 9 mechanisms of action in this class for treatment of plaque psoriasis or psoriatic arthritis[6,7]:

- Tumor necrosis factor alpha (TNF-α) inhibitors: adalimumab (Humira), certolizumab pegol (Cimzia), etanercept (Enbrel), golimumab (Simponi), and infliximab (Remicade)
- Interleukin (IL)-17 inhibitors: bimekizumab, brodalumab (Siliq), ixekizumab (Taltz), and secukinumab (Cosentyx)
- IL-23: inhibitors: guselkumab (Tremfya), mirikizumab, risankizumab (Skyrizi), and tildrakizumab (Ilumya)
- Janus kinase inhibitors: filgotinib, tofacitinib (Xeljanz), and upadacitinib (Rinvoq)
- IL-12/23 inhibitors: ustekinumab (Stelara)
- Phosphodiesterase 4 (PDE4) inhibitors: apremilast (Otezla)
- Selective T-cell costimulatory modulators: abatacept (Orencia)
- Dual TNF-α /IL-17 inhibitors: remtolumab
- Tyrosine kinase inhibitors: BMS-986165

The FDA has recently approved biosimilar agents for adalimumab (Amjevita, Hyrimoz, Cyltezo), etanercept (Erelzi), and infliximab (Renflexis, Inflectra, Ixifi).

PICOS and Key Questions

This report focuses on adults with plaque psoriasis or psoriatic arthritis and identifies randomized controlled trials (RCTs) that evaluated the comparative effectiveness and harms of FDA-approved TIM agents as well as cohort studies that evaluated comparative harms. Outcomes of interest were measures of clinical improvement, disease remission, quality of life, adverse events (AEs), serious adverse events (SAEs), and other health outcome measures. This report also evaluates the effectiveness and harms (compared to placebo) of selected pipeline TIM agents.

This review addresses 3 Key Questions:

1. What is the comparative effectiveness of TIMs to treat plaque psoriasis and psoriatic arthritis?
2. What are the comparative harms of TIMs to treat plaque psoriasis and psoriatic arthritis?
3. Do the included drugs differ in their effectiveness or harms in the following subgroups: age and racial groups, gender, patients with comorbidities, patients taking other commonly prescribed drugs, or in patients with early vs. established disease?

Methods

We describe our complete methods in Appendix A. Briefly, we searched Ovid MEDLINE, Embase, Cochrane Library, ClinicalTrials.gov, International Standard Randomised Controlled Trials Number (ISRCTN) registry, and several other websites to identify eligible studies published from January 1, 2017 through August 20, 2019, with active surveillance of the literature through January 31, 2020. We rated the methodological quality of eligible studies using standard instruments adapted from national and international quality standards.[8-12] We used OpenEpi (version 3.01) to calculate incident rate ratios, (IRR), absolute risk differences (ARD), risk ratios (RR), and associated 95% confidence intervals (CI) based on data provided in the study when not reported by study authors. We rated the quality of the body of evidence for each drug comparison and indication (plaque psoriasis or psoriatic arthritis) for up to 5 selected outcomes (i.e., disease remission, clinical improvement, quality of life, AEs, and SAEs) using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[13,14] The previous Drug Effectiveness Review Project (DERP) systematic review on TIMs was segmented into 3 reports. This report is an update only involving medications for indications of plaque psoriasis or psoriatic arthritis.

Key Findings

We identified 20 new studies[15-33] and carried forward 18 studies [34-49] from the previous report for a total of 38 eligible studies included in this update. Thirty studies evaluated TIM agents for plaque psoriasis,[16-21,23,26-33,35-40,42,43,46-49] and 8 studies[15,22,24,25,34,41,44,45] evaluated TIM agents for psoriatic arthritis.

Of the 38 eligible studies, 31 were RCTs[15-17,19-21,24-32,34-37,39,40,42-48] and 7 studies[18,22,23,33,38,41,49] were cohort studies.[18,22,23,33,38,41,49] Among the 31 RCTs, we rated 3 studies[15,34,37] as poor methodological quality and the rest as fair methodological quality. Among the 7 cohort studies, we rated 1 study[41] as poor methodological quality and the rest as fair methodological quality. Outcomes selected for GRADE ratings ranged from low to high quality of evidence for most efficacy outcomes, and very low to moderate for most harm outcomes. Generally, outcomes were downgraded for serious or very serious imprecision (i.e., wide confidence interval because of small sample size). We identified no findings by relevant subgroups for plaque psoriasis or psoriatic arthritis (Key Question 3).

Plaque Psoriasis

- Comparative effectiveness (Key Question 1) in plaque psoriasis
  - We identified 21 RCTs[16,17,20,21,28,29,31,32,35-37,39,40,42,43,46-48] providing direct evidence of 14 different head-to-head TIM agent comparisons. All studies enrolled participants with a history of at least 6 months of moderate-to-severe plaque psoriasis. We rated 1 RCT[37] as poor methodological quality and the rest were rated as fair methodological quality, primarily because of industry sponsorship of studies and extensive manufacturer involvement in study design, execution, and reporting, and sponsorship of studies.
  - All studies reported disease remission outcomes as a primary study endpoint; the most commonly reported outcomes were the Psoriasis Area and Severity Index (PASI) 90 and PASI 75 (reduction in PASI score of 90% and 75%, respectively). A score of 0 (no impact) or 1 (very minimal impact) on the physician's or investigator's global assessment (PGA or

IGA, respectively) measure was also commonly used as either a primary or secondary outcome for disease remission. Both measures are among the most commonly used, validated measures of clinical improvement and disease remission in clinical trials.

- Seventeen RCTs[16,17,20,21,28,29,32,35-37,40,42,46-48] reported quality of life (QoL); the Dermatology Life Quality Index (DLQI) was the mostly commonly reported quality of life (QoL) outcome. The DLQI is the most frequently used measure for evaluating QoL among persons afflicted with a variety of skin conditions. Scores on the DLQI range from 0 to 30; a score of 0 or 1 indicates no effect of the skin condition on QoL.[50] Findings from QoL outcomes typically mirrored disease remission findings in nearly all studies.
- Some studies also reported measures of clinical improvement (e.g., PASI 50); only 1 study[29] reported a measure related to work limitations.
- *Apremilast vs. etanercept* (1 RCT[47]): no significant difference in disease remission (PASI 75) or QoL (change in DLQI) at 16 weeks; low quality of evidence (QoE) for both.
- *Brodalumab vs. ustekinumab* (2 RCTs[43]): brodalumab was more effective for achieving disease remission at 12 weeks (PASI 100: ARDs, 18 and 22 percentage points; high QoE).
- *Etanercept vs. infliximab* (1 RCT[37]): etanercept was less effective for achieving disease remission at 24 weeks (PASI 75: 35% vs. 72%; very low QoE).
- *Etanercept vs. ixekizumab* (2 RCTs[40]): etanercept was less effective for achieving disease remission at 12 weeks (PASI 75: ARDs, 31 and 48 percentage points) and for improving QoL (DLQI 0 or 1: ARDs, 20 and 30 percentage points); high QoE for both remission and QoL.
- *Etanercept vs. secukinumab* (1 RCT[42]): etanercept was less effective for achieving disease remission at 12 weeks (PASI 75: 300 mg secukinumab, 44% vs. 77%; vs. 150 mg secukinumab, 67%; high QoE). Etanercept was also less effective at improving QoL (mean change DLQI: 300 mg, -7.9 vs. -10.4; vs. 150 mg, -9.7; moderate QoE). Etanercept was also less effective at maintaining remission at 52 weeks (PASI 75: 300 mg, 73% vs. 84%; vs. 150 mg, 82%; high QoE).
- *Etanercept vs. tildrakizumab* (1 RCT[28]): etanercept was less effective for disease remission at 12 weeks (PASI 75: 200 mg tildrakizumab, 48% vs. 66%; vs. 100 mg tildrakizumab, 61%) and at 28 weeks (PASI 75: both 200- and 100-mg dosages, 54% vs. 73%; high QoE for both time points). Etanercept was also less effective than both doses of tildrakizumab for improving QoL at both 12 weeks (moderate QoE) and 28 weeks (high QoE).
- *Etanercept vs. tofacitinib (not FDA-approved for psoriasis)* (1 RCT[35,51]): etanercept was more effective than 5 mg tofacitinib at achieving disease remission at 12 weeks (PASI 75: 59% vs. 40%) but similar effectiveness to tofacitinib 10 mg (PASI 75: 59% vs. 64%; moderate QoE). No significant differences in measures of clinical improvement (PASI 50, moderate QoE). Etanercept was more effective than 5 mg tofacitinib for improving QoL (DLQI 0 or 1: 75% vs. 66%, moderate QoE) but no significant differences compared to 10 mg tofacitinib (DLQI 0 or 1: 75% vs. 78%; low QoE).
- *Etanercept vs. ustekinumab* (1 RCT[39]): etanercept was less effective at 12 weeks (PASI 75: 90 mg, 57% vs. 74%; vs. 45 mg, 68%; low QoE).
- *Guselkumab vs. adalimumab* (3 RCTs[17,20,32]): guselkumab was more effective than adalimumab for disease remission at 16 weeks (PGA 0 or 1: ARD range 16 to 28 percentage points; high QoE). Guselkumab was also more effective at improving QoL (DLQI 0 or 1: ARD range 13 to 15 percentage points; moderate QoE).

- *Guselkumab vs. secukinumab* (1 RCT[31]): guselkumab was more effective than secukinumab for disease remission at 48 weeks, which was the study's primary efficacy outcome (PASI 90: 84% vs. 70%; moderate QoE); guselkumab was noninferior for disease remission at both 12 and 48 weeks (PASI 75: 85% vs. 80%; *P* < .001 for non-inferiority; *P* = .06 for superiority); a higher PASI 90 response was observed for secukinumab (69% vs. 76%) but no significance testing done to control type I error.
- *Ixekizumab vs. ustekinumab (1 RCT[48,52]):* ixekizumab was more effective than ustekinumab for disease remission at 12 weeks (PASI 90: 73% vs. 42%; moderate QoE) and at 52 weeks (PASI 90: 77% vs. 59%; moderate QoE). Ixekizumab was also more effective for improving QoL at 12 weeks (DLQI 0 or 1: 61% vs. 45%; moderate QoE).
- *Risankizumab vs. adalimumab (1 RCT[29]):* risankizumab was more effective than adalimumab for disease remission at 16 weeks (PASI 90: 72% vs. 47%; moderate QoE). Risankizumab was also more effective at improving QoL at 16 weeks (DLQI 0 or 1: 66% vs. 49%; moderate QoE).
- *Risankizumab vs. ustekinumab (3 RCTs[21,46]):* risankizumab was more effective than ustekinumab for disease remission at 12 to 16 weeks (PASI 90: ARD range 28 to 37 percentage points, moderate QoE). Risankizumab was also more effective at improving QoL at 12 to 16 weeks (DLQI 0 or 1: ARD range 19 to 23 percentage points; moderate QoE).
- *Secukinumab vs. ustekinumab (2 RCTs[16,53]):* secukinumab was more effective than ustekinumab for disease remission at 16 weeks (PASI 90: ARDs 21 and 22 percentage points; high QoE). Secukinumab was also more effective at improving QoL at 16 weeks (DLQI 0 or 1: ARDs 13 and 15 percentage points; high QoE).

- Comparative harms (Key Question 2): all 21 RCTs included for Key Question 1 also reported on harms of TIM agents; in addition we identified 5 cohort studies.[18,23,33,38,49]
  - Overall, we observed few differences in harms in head-to-head RCT comparisons of TIM agents. In the RCT body of evidence, between-agent differences were typically in just 1 of several harm outcomes reported when differences were present. The rest of this section describes findings where a statistically significant difference was observed in AEs, SAEs, or other serious harms.
  - *Apremilast vs. adalimumab (1 cohort[18]):* lower incidence of serious infection requiring hospitalization for apremilast compared to adalimumab (hazard ratio [HR], 0.31; 95% CI, 0.15 to 0.65; very low QoE).
  - *Apremilast vs. etanercept (1 RCT[47]):* lower proportion of overall AEs (RR, 0.75; 95% CI, 0.58 to 0.95; low QoE). Estimate for SAEs too imprecise to draw meaningful conclusions (RR, 0.67; 95% CI, 0.11 to 3.9; low QoE).
  - *Etanercept vs. adalimumab (2 cohorts[18,23]):* lower incidence of serious infection requiring hospitalization for etanercept (HR, 0.76; 95% CI, 0.61 to 0.94; very low QoE) in 1 study;[18] lower incidence rate of SAEs (incidence rate ratio [IRR], 0.75; 95% CI, 0.66 to 0.86; very low QoE) in other study.[23]
  - *Etanercept vs. tildrakizumab (1 RCT[28]):* fewer overall AEs for tildrakizumab compared with etanercept during weeks 13 to 28 (RR, 0.80; 95% CI, 0.68 to 0.93), but no difference in incidence during weeks 0 to 12 (moderate QoE). No difference in incidence of SAEs during both time periods (low QoE).

- *Etanercept vs. ustekinumab (1 RCT[39] and 1 cohort[23]):* no significant differences in overall AEs or SAEs observed in RCT (low QoE); higher incidence of SAEs observed for ustekinumab (IRR, 2.4; 95% CI, 1.8 to 3.1) in the cohort study in participants with clinical status that would make them ineligible to participate in clinical trials (very low QoE).
- *Infliximab vs. adalimumab (1 cohort[18]):* higher incidence of serious infection requiring hospitalization for infliximab (HR, 1.9; 95% CI, 1.01 to 3.6; very low QoE).
- *Risankizumab vs. ustekinumab (3 RCTs[21,46]):* One RCT reported no significant differences in AEs or SAEs.[46] Two RCTs reported some differences but not across all time periods evaluated. For overall AEs, fewer AEs were observed for risankizumab in the later time period (weeks 17 to 52) of 1 study (RR, 0.75; 95% CI, 0.11 to 0.77) and fewer SAEs were observed in the early time period (weeks 0 to 16) of the other study (RR, 0.29; 95% CI, 011 to 0.77).[21]
- *Ustekinumab vs. adalimumab (1 cohort[18]):* no difference in serious infection requiring hospitalization (HR, 0.70; 95% CI, 0.49 to 1.0; very low QoE); higher incidence of SAEs for ustekinumab (IRR, 1.2; 95% CI, 1.1 to 1.4, very low QoE).

- Effectiveness and harms of pipeline TIM agents were limited to 4 placebo-controlled trials. QoE ratings ranged from very low to moderate. Complete results are available in the full report.

Psoriatic Arthritis

- Comparative effectiveness (Key Question 1) in psoriatic arthritis: we identified 5 RCTs[15,24,34,44,45] evaluating the comparative effectiveness of TIMs. Of these, 2 RCTs[15,24] are new to this update.
  - All studies enrolled participants with active psoriatic arthritis; 1 study[15] specifically required active enthesitis (i.e., a common symptom in psoriatic arthritis involving inflammation of the sites where tendon or ligaments attach to bones).
  - We rated 2 RCTs[15,34] as poor methodological quality for various critical methodological flaws; we rated the rest as fair methodological quality because of industry sponsorship and extensive manufacturer involvement in study design, execution, and reporting.
  - Nearly all studies reported clinical improvement as primary study endpoints; the most commonly reported outcomes were the American College of Rheumatology 20 criteria (ACR20) response (at least 20% improvement in swollen and tender joint count, and at least 20% improvement in 3 of the following 5 outcomes: inflammatory biomarker, IGA, patient global assessment (PtGA), pain, disability). QoL outcomes were only reported in 2 of the RCTs.[15,45]
  - *Adalimumab vs. etanercept or infliximab* (1 RCT[34]): no differences in ACR20 response at 1 year (no statistical significance testing; very low QoE).
  - *Adalimumab vs. ixekizumab* (1 RCT[44]): numerically lower clinical improvement at 24 weeks compared to ixekizumab every 2 or 4 weeks (ACR20: 57% vs. 62% vs. 58%; low QoE); no statistical significance testing as the primary study aim was to compare ixekizumab to placebo. A numerically lower skin disease remission response was also observed compared to ixekizumab every 2 weeks or every 4 weeks (PASI 75: 54% vs. 80% vs. 71%; low QoE).

- *Adalimumab vs. tofacitinib* (1 RCT[45]): numerically lower clinical improvement at 12 months compared to participants treated with tofacitinib 10 mg but not compared to participants treated with tofacitinib 5 mg (ACR20: 60% vs. 70% vs. 68%; low QoE). Numerically lower skin disease remission at 12 months compared to tofacitinib 10 mg, but not 5 mg (PASI 75: 56% vs. 67% vs. 56%; low QoE). Numerically higher improvement in QoL (36-item Short Form Health Survey [SF-36] Physical Health Component Score [PCS]) compared to tofacitinib 10 mg or tofacitinib 5 mg (6.2 vs. 5.7 vs. 5.5; low QoE).
- *Adalimumab compared to remtolumab* (1 RCT[24]): no difference in clinical improvement at 12 weeks (ACR50) compared to 120-mg remtolumab dose; marginally lower proportion when compared to 240-mg remtolumab dose (ACR50: ARD, 15.9 percentage points; 95% CI, -0.07% to 31.9%; $P < .05$ as reported by study; low QoE); lower proportion with disease remission compared to 240-mg dose (ACR70: ARD,16.2%; 95% CI, 2.7% to 29.7%), but no difference in disease remission compared to 120-mg dose (low QoE).
- *Ustekinumab compared to TNF-α inhibitors* (1 RCT[15]): at 24 weeks, higher proportion achieved enthesitis remission (Spondyloarthritis Research Consortium of Canada Enthesitis Index [SPARCC EI]: 74% vs. 42%; very low QoE) and skin disease remission (PASI 90: 86% vs. 29%; very low QoE), but not arthritis remission (tender joint count, 54% vs. 46%; $P = .78$; swollen joint count, 59% vs. 46%; $P = .38$; very low QoE). Larger improvement in QoL as measured by SF-36 PCS for ustekinumab (magnitude not reported), but no statistically significant difference in improvement in QoL as measured by SF-36 Mental Health Component Score (MCS; very low QoE).

- Comparative harms (Key Question 2) in psoriatic arthritis
  - 4 (of 5) RCTs[24,34,44,45] included for Key Question 1 also reported harms; we also identified 1 cohort study[41] reporting harms. Overall, we observed few differences in harms in head-to-head comparisons of TIM agents.
  - *Adalimumab* vs. *etanercept vs. infliximab* (1 RCT[34]): fewer AEs with adalimumab compared to etanercept (RR, 0.38; 95% CI, 0.17 to 0.84); fewer AEs with adalimumab compared to infliximab (RR, 0.23; 95% CI, 0.11 to 0.49), more AEs with infliximab compared to etanercept (RR, 1.6; 95% CI, 1.1 to 2.4; very low QoE for all comparisons).

- Efficacy and harms of pipeline agents were limited to 2 placebo-controlled trials.[24,25] QoE ratings ranged from very low to moderate. Complete results are available in the full report.

- Ongoing Studies
  - We identified 30 ongoing studies (23 RCTs and 7 observational studies) evaluating the comparative effectiveness or harms of TIM agents.

Conclusions

For plaque psoriasis, the largest body of comparative evidence is for etanercept and ustekinumab compared to other TIM agents. For disease remission outcomes, high-quality evidence suggests that etanercept is less effective than ixekizumab, secukinumab, and tildrakizumab. High-quality evidence also suggests that ustekinumab is less effective than brodalumab and risankizumab and moderate quality evidence suggests it may also be less effective than ixekizumab for disease remission outcomes. High-quality evidence suggests that adalimumab is less effective than guselkumab and moderate-quality evidence suggests that it is

also less effective than risankizumab. Finally, moderate-quality evidence suggests that guselkumab is more effective than secukinumab for maintenance therapy. Few differences in harms among TIM agents were observed, based on very low- to moderate-quality evidence.

For psoriatic arthritis, limited head-to-head comparisons were available. Based on low-quality evidence, ixekizumab, tofacitinib, and remtolumab may be more effective than adalimumab with no difference in harms.

List of Brand Names and Generics

Table 1. Included Drugs and Biosimilars

Generic Name	Trade Name	Mechanism	Route	Approved Population[a]
Abatacept	Orencia	Selective T-cell costimulation modulator	IV or SC	Psoriatic arthritis
Adalimumab	Humira	TNF-α inhibitor	SC	Plaque psoriasis Psoriatic arthritis
Adalimumab-adaz	Hyrimoz	TNF-α inhibitor	SC	Plaque psoriasis Psoriatic arthritis
Adalimumab-adbm	Cyltezo	TNF-α inhibitor	SC	Plaque psoriasis Psoriatic arthritis
Adalimumab-atto	Amjevita	TNF-α inhibitor	SC	Plaque psoriasis Psoriatic arthritis
Apremilast	Otezla	PDE4 inhibitor	PO	Plaque psoriasis Psoriatic arthritis
Brodalumab	Siliq	IL-17RA inhibitor	SC	Plaque psoriasis
Certolizumab pegol	Cimzia	TNF-α inhibitor	SC	Plaque psoriasis Psoriatic arthritis
Etanercept	Enbrel	TNF-α inhibitor	SC	Plaque psoriasis Psoriatic arthritis
Etanercept-szzs	Erelzi	TNF-α inhibitor	SC	Plaque psoriasis Psoriatic arthritis
Golimumab	Simponi/ Simponi ARIA	TNF-α inhibitor	SC	Psoriatic arthritis
Guselkumab	Tremfya	IL-23 inhibitor	SC	Plaque psoriasis
Infliximab	Remicade	TNF-α inhibitor	IV	Plaque psoriasis Psoriatic arthritis
Infliximab-abda	Renflexis	TNF-α Inhibitor	IV	Plaque psoriasis Psoriatic arthritis
Infliximab-dyyb	Inflectra	TNF-α Inhibitor	IV	Plaque psoriasis Psoriatic arthritis
Infliximab-qbtx	Ixifi	TNF-α Inhibitor	IV	Plaque psoriasis Psoriatic arthritis
Ixekizumab	Taltz	IL-17A inhibitor	SC	Plaque psoriasis Psoriatic arthritis
Risankizumab	Skyrizi	IL-23 inhibitor	SC	Plaque psoriasis
Secukinumab	Cosentyx	IL-17A inhibitor	SC	Plaque psoriasis Psoriatic arthritis
Tildrakizumab	Ilumya	IL-23 inhibitor	SC	Plaque psoriasis

Generic Name	Trade Name	Mechanism	Route	Approved Population[a]
Tofacitinib	Xeljanz Xeljanz XR	JAK inhibitor	PO	Psoriatic arthritis
Upadacitinib	Rinvoq®	JAK inhibitor	PO	Rheumatoid arthritis[b]
Ustekinumab	Stelara	IL-12/23 p40 inhibitor	Initial dose IV then SC	Plaque psoriasis Psoriatic arthritis
Pipeline Drugs				
Bimekizumab	None	IL-17A and IL-17F inhibitor	IV	Not yet approved
BMS-986165	None	TYK2 inhibitor	PO	Not yet approved
Filgotinib	None	JAK inhibitor	PO	Not yet approved
Mirikizumab	None	IL-23 inhibitor	SC	Not yet approved
Remtolumab	None	Dual TNF-α/IL-17 inhibitor	SC	Not yet approved

Notes. [a] *Details of approved indications for each drug can be found in the full prescribing information. Some drugs may be approved for indications other than psoriasis or psoriatic arthritis.* [b] *Approved for rheumatoid arthritis and is currently being studied for use in psoriatic arthritis. Abbreviations. IL: interleukin; IV: intravenous; JAK: Janus kinase; PDE4: phosphodiesterase 4; PO:* per os *(oral); RA: receptor A; SC: subcutaneous; TNF-α: tumor necrosis factor alpha; TYK2: tyrosine kinase 2.*

Background

Targeted immune modulators (TIMs) are a category of medications used in the treatment of certain types of immunologic and inflammatory diseases, including rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, plaque psoriasis, and psoriatic arthritis. TIMs work by selectively blocking mechanisms involved in the inflammatory and immune response.[5] The U.S. Food and Drug Administration (FDA) approved the first TIM for psoriatic arthritis (etanercept) in 2002 and the first TIM for psoriasis (alefacept) in 2003.[6,54] Since then, the FDA has approved numerous agents for these conditions, including biosimilars.[6] Table 1 summarizes currently available TIMs approved in the U.S. for plaque psoriasis and psoriatic arthritis.[6,7]

Adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab all bind to both the circulating and transmembrane forms of tumor necrosis factor alpha (TNF-α), inhibiting its biological activity.[1,2,6] Biosimilars are available for adalimumab, etanercept, and infliximab. Adalimumab, certolizumab, etanercept, and infliximab are all FDA-approved for both plaque psoriasis and psoriatic arthritis. Golimumab is only FDA-approved for psoriatic arthritis.

Secukinumab and ixekizumab are human immunoglobulin G1 (IgG1) and IgG4 monoclonal antibodies, respectively, that selectively bind to the interleukin-17A (IL-17A) cytokine and inhibit their interaction with the IL-17 receptor, thus inhibiting the release of pro-inflammatory cytokines and chemokines.[1,2,6] Brodalumab is another human IgG monoclonal antibody to the IL-17A receptor, which inhibits the activity of IL-17F, IL-17A/F, and IL-17E in addition to IL-17A. Ixekizumab and secukinumab are FDA-approved for plaque psoriasis and psoriatic arthritis, while brodalumab is approved only for plaque psoriasis. Because of a potential risk for suicidal ideation, the FDA requires a Risk Evaluation and Mitigation Strategy program for patients and prescribers of brodalumab.[55] Finally, bimekizumab is a dual IL-17A and IL-17F inhibitor but is not yet FDA-approved.

Tildrakizumab, risankizumab, guselkumab, and mirikizumab are humanized IgG1 monoclonal antibodies that act as IL-23 antagonists by selectively binding to the P19 subunit of IL-23.[1,2,6] Tildrakizumab and risankizumab are approved for plaque psoriasis while mirikizumab is not yet FDA-approved.

Ustekinumab is a human monoclonal antibody that binds to the p40 protein subunit used by both the IL-12 and IL-23 cytokines.[1,2,6] This drug has current FDA approval for plaque psoriasis and psoriatic arthritis.

Tofacitinib, upadacitinib, and filgotinib are small molecules directed against the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) proteins pathway.[1,2,6] Unlike other biologics that may selectively block a single cytokine or integrin, JAK inhibitors block multiple cytokines, resulting in a wider effect on inflammation. Tofacitinib is approved for the treatment of psoriatic arthritis; in 2015 the FDA declined to approve tofacitinib for a plaque psoriasis pending additional efficacy and long-term safety data.[56] As of this update, we identified no evidence that the manufacturer plans to resubmit for this indication. Upadacitinib is approved for rheumatoid arthritis and is considered a pipeline drug for use in psoriasis and psoriatic arthritis. Filgotinib is not yet FDA-approved.

Apremilast is an orally available phosphodiesterase 4 (PDE4) inhibitor that modulates production of a wide range of inflammatory mediators and is FDA-approved for psoriasis and psoriatic arthritis.[1,2,6]

The immunosuppressant agent abatacept exerts immune regulation by interfering with T lymphocyte activation. Abatacept is FDA-approved for psoriatic arthritis.[1,2,6]

Two other pipeline drugs with other mechanisms of action include remtolumab, a dual TNF-α/IL-17 inhibitor, and BMS-986165, a tyrosine kinase 2 inhibitor.

Plaque Psoriasis

Plaque psoriasis is a chronically recurring, debilitating inflammatory disease that affects the skin, scalp, and joints and is characterized by erythrosquamous scaling, itchy lesions, and ranges in severity from mild to severe.[3] Patients with moderate-to-severe disease experience significant deterioration of quality of life (QoL).[57] The exact pathogenesis of plaque psoriasis is still unknown; however, pathophysiological evidence suggests that an overproduction of pro-inflammatory cytokines plays an important role.[58,59]

The severity of plaque psoriasis is most commonly classified based on the percentage of body surface area (BSA) involved. Mild psoriasis is defined as affecting less than 5% of the BSA; moderate psoriasis affects 5% to 10%; and severe psoriasis is defined as affecting more than 10% of the BSA.[57,60] The goal of plaque psoriasis treatment is to gain control of the disease process, decrease the percentage of BSA involved, and achieve and maintain long-term remission.[2]

Psoriatic Arthritis

Psoriatic arthritis is a chronic inflammatory arthritis associated with the skin disease psoriasis, but the presentation is variable.[4] In all cases, symptoms include pain and stiffness in the affected joint as well as joint-line tenderness, swelling, and sometimes loss of range of motion. Pitting of the fingernails often correlates with concurrent plaque psoriasis.[61] Dactylitis, swelling of a whole digit, is a characteristic clinical finding. Enthesitis, spondylitis, sacroiliitis, and inflammatory eye disease (uveitis) may also occur.

The etiology and pathogenesis of psoriasis and psoriatic arthritis are not completely understood, but genetic, immunological, and environmental factors are all likely to play a role.[62] The first line of treatment is nonsteroidal anti-inflammatory drugs (NSAIDs), although in most cases disease-modifying antirheumatic drugs (DMARDs) are necessary. If disease continues to be active despite the use of NSAIDs and methotrexate, then other oral DMARDs or TIMs should be employed.[1]

PICOS

Population

- Adults with plaque psoriasis
- Adults with psoriatic arthritis

Interventions

- TIMs and respective biosimilars that have FDA approval for the treatment of plaque psoriasis or psoriatic arthritis, and select pipeline drugs likely to be approved soon (Table 1)

Comparators

- FDA-approved drugs: another listed TIM intervention (head-to-head comparison)
- For pipeline drugs: any listed TIM, standard of care, placebo

Outcomes

- Health outcomes
  - Quality of life (QoL)
  - Functional capacity
  - Productivity, ability to sustain employment
  - Clinical improvement
  - Disease remission
  - Pain
  - Reduction in number of swollen or tender joints
  - Reduction in disease-related hospitalizations
  - Reduction in disease-specific mortality
  - Rebound/flare
  - Joint destruction
  - Steroid withdrawal

- Harms
  - Overall adverse events (AEs)
  - Withdrawals due to AEs
  - Serious adverse events (SAEs)
  - Specific AEs (e.g., lymphoma, all malignancies, serious infectious diseases, herpes zoster, opportunistic infections, congestive heart failure)
  - Mortality

Study Designs

- Randomized controlled trials (RCTs) with ≥ 12-week study duration
- Retrospective and prospective cohort studies comparing an intervention type to another for outcomes on harms
  - > 12-week study duration
  - Minimum total sample size of 1,000

Key Questions

1. What is the comparative effectiveness of TIMs to treat plaque psoriasis and psoriatic arthritis?
2. What are the comparative harms of TIMs to treat plaque psoriasis and psoriatic arthritis?
3. Do the included drugs differ in their effectiveness or harms in the following subgroups: age and racial groups, gender, patients with comorbidities, patients taking other commonly prescribed drugs, or in patients with early vs. established disease?

Methods

We describe our complete methods in Appendix A. Briefly, we searched Ovid MEDLINE, Embase, Cochrane Library, ClinicalTrials.gov, International Standard Randomised Controlled Trials Number (ISRCTN) registry, and several other websites to identify eligible studies published from January 1, 2017 through August 20, 2019, with active surveillance of the literature through January 31, 2020. We rated the methodological quality of eligible studies using standard instruments adapted from national and international quality standards.[8-12] We used OpenEpi (version 3.01) to calculate incident rate ratios (IRR), absolute risk differences (ARD), risk ratios (RR), and associated 95% confidence intervals (CI) based on data provided in the study when not reported by authors (calculated values are *italicized*). We rated the quality of the body of evidence for each drug comparison and indication (plaque psoriasis or psoriatic arthritis) for 5 selected outcomes (i.e., disease remission, clinical improvement, QoL, AEs, and SAEs) using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[13,14] The previous Drug Effectiveness Review Project (DERP) systematic review on TIMs was segmented into 3 reports. This report is an update only involving medications for indications for plaque psoriasis and psoriatic arthritis, and for pipelines drugs anticipating approval for one of these conditions.

Findings

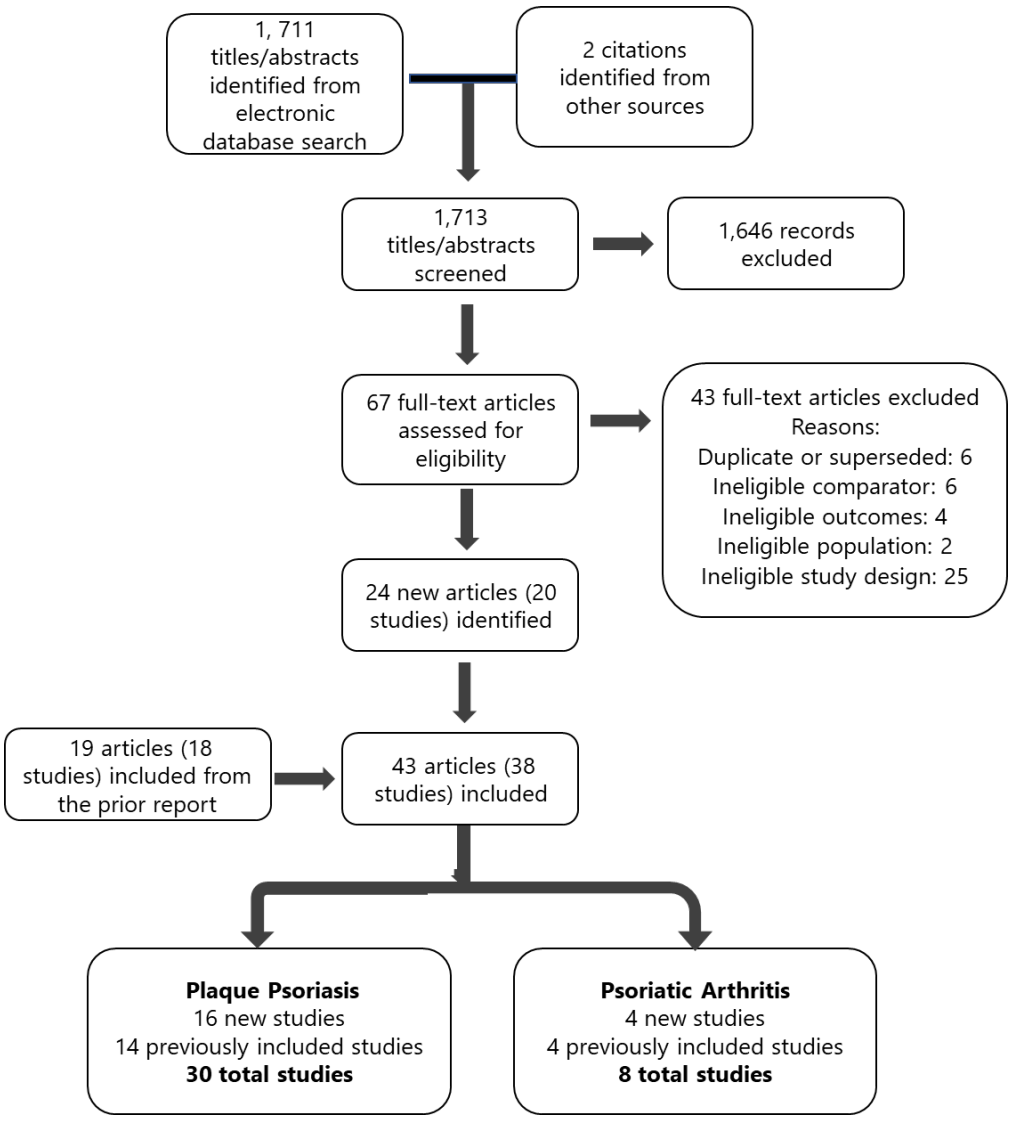
We identified 20 new studies[15-33] and carried forward 18 studies[34-49] from the previous report, for a total of 38 eligible studies in this update (Figure 2 and Appendix E). We excluded 9 observational studies that were included in the previous report because they were conducted among mixed populations that were either not specified,[63] or were conducted among patients with a broad set of clinical indications but included mostly participants with rheumatoid arthritis.[41,64-70] Appendix F provides the bibliography of studies identified in the update search but that we excluded at full-text review stage.

Thirty studies evaluated TIMs for plaque psoriasis,[16-21,23,26-33,35-40,42,43,46-49] and 8 studies evaluated TIMs for psoriatic arthritis.[15,22,24,25,34,41,44,45] We did not identify any studies that addressed differences in effectiveness or harms by subgroup (Key Question 3).

Across this body of evidence, the most common outcomes used to assess clinical improvement and disease remission for psoriasis were the Psoriasis Area and Severity Index (PASI) and the Physician's or Investigator's Global Assessment (PGA or IGA).[71] The PASI score is based on the extent of skin area involved, severity of erythema, desquamation, and plaque induration; the score can range from 0 (no disease) to 72 (maximum disease).[71] Clinical improvement and disease remission is reported based on PASI response; a PASI 50 response refers to a 50% reduction in PASI score from baseline. Likewise, a PASI 90 response refers to a 90% reduction in score from baseline. The PGA/IGA is scale where 0 represents "clear skin" and 5 or 6 represents "severe and extensive involvement."[71] The Dermatology Life Quality Index (DLQI) is the most frequently used validated measure for evaluating QoL among persons afflicted with a variety of skin conditions.[72] Scores on the DLQI range from 0 to 30; a score of 0 or 1 indicates no effect of the skin condition on QoL.[50] The most common outcome used to assess clinical improvement and disease remission in psoriatic arthritis was the American College of Rheumatology (ACR) score.[73] The ACR score is a composite measure of disease activity that considers the number of tender joints, the number

of swollen joints, a patient's global assessment, a PGA, functional ability, pain, and inflammatory markers (e.g., erythrocyte sedimentation rate, C-reactive protein). An ACR20 response is defined as a 20% improvement in the number of tender and swollen joints and a 20% improvement in at least 3 of the other score elements. The Health Assessment Questionnaire (HAQ) was the most commonly used instrument to assess QoL in psoriatic arthritis trials; additional instruments and measures used across this body of evidence are described in Appendix D.

Figure 2. Literature Flow Diagram



Plaque Psoriasis

We identified 25 RCTs[16,17,19-21,26-32,35-37,39,40,42,43,46-48] evaluating the effectiveness, comparative effectiveness, or harms of TIMs, and 5 cohort studies[18,23,33,38,49] evaluating the comparative harms of TIMs. Of these studies, 15 are new to this update.[16-21,23,26-33] Table 2 shows the Summary of Findings (GRADE) for comparative effectiveness and harms of TIMs for plaque psoriasis. Appendix C Table C1 provides detailed evidence profiles.

Table 2. Summary of Findings (GRADE) of TIMs for Plaque Psoriasis (Comparative Effectiveness and Harms)

Outcome	Quality of Evidence	Relationship[a]
Apremilast Compared to Adalimumab		
Serious infections (1 cohort)	●○○○ (very low)	Favors apremilast
Apremilast Compared to Etanercept		
Disease remission (1 RCT)	●●○○ (low)	No difference
Quality of life (1 RCT)	●●○○ (low)	No difference
AEs (1 RCT)	●●○○ (low)	Favors apremilast
SAEs (1 RCT)	●●○○ (low)	No difference
Brodalumab Compared to Ustekinumab		
Disease remission (2 RCTs)	●●●● (high)	Favors brodalumab
AEs (2 RCTs)	●●●○ (moderate)	No difference
SAEs (2 RCTs)	●○○○ (very low)	Uncertain
Etanercept Compared to Adalimumab		
Serious infection (1 cohort)	●○○○ (very low)	Favors etanercept
SAEs (1 cohort)	●○○○ (very low)	Favors etanercept
Etanercept Compared to Infliximab		
Disease remission (1 RCT)	●○○○ (very low)	Favors infliximab
Quality of life (1 RCT)	●○○○ (very low)	No difference
AEs (1 RCT)	●○○○ (very low)	No difference
SAEs (1 RCT)	●○○○ (very low)	No difference
Etanercept Compared to Ixekizumab		
Disease remission (2 RCTs)	●●●● (high)	Favors ixekizumab
Quality of life (2 RCTs)	●●●● (high)	Favors ixekizumab
AEs (2 RCTs)	●●●○ (moderate)	No difference
SAEs (2 RCTs)	●●○○ (low)	No difference

Outcome	Quality of Evidence	Relationship[a]
Etanercept Compared to Secukinumab		
Disease remission (1 RCT)	●●●● (high)	Favors secukinumab
Quality of life (1 RCT)	●●●○ (moderate)	Favors secukinumab
AEs (1 RCT)	●●●○ (moderate)	No difference
SAEs (1 RCT)	●●○○ (low)	No difference
Etanercept Compared to Tildrakizumab		
Disease remission (1 RCT)	●●●● (high)	Favors tildrakizumab
Quality of life (1 RCT)	●●●● (high)	Favors tildrakizumab
AEs (1 RCT)	●●●○ (moderate)	Favors tildrakizumab
SAEs (1 RCT)	●●○○ (low)	No difference
Etanercept Compared to Tofacitinib		
Disease remission (1 RCT)	●●●○ (moderate)	Favors etanercept
Clinical improvement (1 RCT)	●●●○ (moderate)	Favors etanercept
Quality of life (1 RCT)	●●○○ (low)	Favors etanercept
AEs (1 RCT)	●●○○ (low)	No difference
SAEs (1 RCT)	●●○○ (low)	No difference
Etanercept Compared to Ustekinumab		
Disease remission (1 RCT)	●●○○ (low)	Favors ustekinumab
AEs (1 RCT)	●●○○ (low)	No difference
SAEs (1 RCT)	●●○○ (low)	No difference
SAEs (1 Cohort)	●○○○ (very low)	Favors etanercept

Outcome	Quality of Evidence	Relationship[a]
Guselkumab Compared to Adalimumab		
Disease remission (3 RCTs)	●●●● (high)	Favors guselkumab
Quality of life (3 RCTs)	●●●○ (moderate)	Favors guselkumab
AEs (3 RCTs)	●●○○ (low)	No difference
SAEs (3 RCTs)	●●○○ (low)	No difference
Guselkumab Compared to Secukinumab		
Disease remission (1 RCT)	●●●○ (moderate)	Favors guselkumab at later timepoints[b]
AEs (1 RCT)	●●○○ (low)	No difference
SAEs (1 RCT)	●●○○ (low)	No difference
Infliximab Compared to Adalimumab		
Serious infection (1 cohort)	●○○○ (very low)	Favors adalimumab
Ixekizumab Compared to Ustekinumab		
Disease remission (1 RCT)	●●●○ (moderate)	Favors ixekizumab
Quality of life (1 RCT)	●●●○ (moderate)	Favors ixekizumab
AEs (1 RCT)	●●○○ (low)	No difference
SAEs (1 RCT)	●●○○ (low)	No difference
Risankizumab Compared to Adalimumab		
Disease remission (1 RCT)	●●●○ (moderate)	Favors risankizumab
Quality of life (1 RCT)	●●●○ (moderate)	Favors risankizumab
AEs (1 RCT)	●●○○ (low)	No difference
SAEs (1 RCT)	●●○○ (low)	No difference
Risankizumab Compared to Ustekinumab		
Disease remission (3 RCTs)	●●●● (high)	Favors risankizumab
Quality of life (3 RCTs)	●●●● (high)	Favors risankizumab
AEs (3 RCTs)	●●●○ (moderate)	No difference
SAEs (3 RCTs)	●●○○ (low)	No difference
Secukinumab Compared to Ustekinumab		
Disease remission (2 RCTs)	●●●● (high)	Favors secukinumab
Quality of life (1 RCT)	●●●● (high)	Favors secukinumab
AEs (2 RCTs)	●●○○ (low)	No difference
SAEs (2 RCTs)	●●○○ (low)	No difference
Ustekinumab Compared to Adalimumab		
Serious infection (1 cohort)	●○○○ (very low)	No difference
SAEs (1 cohort)	●○○○ (very low)	Favors ustekinumab[c]

Notes. [a] For efficacy outcomes, 'favors' refers to a larger improvement compared to the comparator; for harm outcomes, 'favors' refers to a lower incidence of harm relative to the comparator. [b] Some secondary endpoints favored secukinumab at early (12 week) timepoint. [c] For participants that would not be eligible for clinical trials. Abbreviations. AE: adverse event; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; RCT: randomized controlled trial; SAE: serious adverse event; TIM: targeted immune modulator.

Comparative Efficacy (Key Question 1)

Twenty-one RCTs[16,17,19-21,28,29,31,32,35-37,39,40,42,43,46-48] reported efficacy outcomes for 14 different head-to-head TIM agent comparisons. All studies enrolled participants with a history of at least 6 months of moderate-to-severe plaque psoriasis. We rated 1 RCT as poor methodological quality because of insufficient blinding and switching treatments.[37] We rated the rest as fair methodological quality, primarily because of industry sponsorship and extensive manufacturer involvement in study design, execution, and reporting. In this section we describe efficacy findings organized by drug comparisons. Table 3 provides a summary of this evidence base and summarizes the findings. Appendix B, Tables B1 and B2 provide detailed study characteristics and results, and Appendix D describes outcome measures used in included RCTs.

Apremilast Compared to Etanercept

We did not identify any new RCTs for this update. The previous review included 1 head-to-head fair-methodological-quality RCT (LIBERATE)[47] that compared apremilast 30 mg twice daily with etanercept 50 mg once weekly, and to placebo in 250 biologically-naïve patients with moderate-to-severe chronic plaque psoriasis for 16 weeks. This dosage of etanercept (50 mg once per week) is the standard labeled dose in Europe; however, it is less than the recommended dosage in the U.S. (twice weekly for 3 months, followed by 50 mg once a week).

The primary endpoint for the trial was the PASI 75 response rate. At week 16, patients treated with apremilast had no difference in response compared to patients receiving etanercept (40% vs. 48%; *P* = .26).[47] For key secondary outcomes some differences were observed but statistical significance testing was not reported (PGA 0 or 1, 22% vs. 29%; PASI 50, 63% vs. 83%). Similar results were seen for the PASI 90, an exploratory endpoint (15% vs. 21%; *P* value not reported [NR]). For other secondary outcomes such as the percent BSA involvement or the DLQI score, patients on apremilast or etanercept had no difference in improvements.

Brodalumab Compared to Ustekinumab

We did not identify any new RCTs for this update. The previous review included 1 publication reporting on 2 large (> 1,000 participants), phase 3, multicenter fair-methodological quality randomized trials (AMAGINE-2, AMAGINE-3) comparing brodalumab (210 mg at weeks 0, 1 and 2, then every 2 weeks) with ustekinumab (45 mg for patients with a body weight ≤ 100 kg and 90 mg for patients > 100 kg, at weeks 0 and 4) in patients with moderate-to-severe plaque psoriasis.[43] These studies also included placebo arms. The primary efficacy endpoint for the comparison of brodalumab to ustekinumab was the PASI 100 response rates at 12 weeks, and the key secondary endpoint was response rates on the PASI 75 at 12 weeks. Other secondary endpoints included the PGA (0 or 1, and 0) response.

For the primary comparative effectiveness endpoint, brodalumab resulted in a higher proportion of participants achieving a PASI 100 response compared to ustekinumab (AMAGINE-2, 44% vs. 22%; *P* < .001; AMAGINE-3, 37% vs. 19%; *P* < .001).[43] In AMAGINE-2, brodalumab 210 mg did not have significantly greater efficacy in PASI 75 response rate over ustekinumab (86% vs. 70%; *P* = .08), but it did in the second trial (85% vs. 69%, *P* = .007).[43] Those treated with brodalumab had significantly greater response when compared to those receiving ustekinumab (AMAGINE-2: 79% vs. 61%; *P* < .001; AMAGINE-3: 80% vs. 57%; *P* < .001) for achieving a 0 or 1 on the PGA.[43] Superiority was also achieved with brodalumab for a PGA score of 0.

Etanercept Compared to Infliximab

We did not identify any new RCTs for this update. The previous review included 1 RCT (PIECE) conducted among 50 participants with moderate-to-severe chronic plaque psoriasis. This study randomized participants to 24 weeks of treatment with either etanercept 50 mg twice weekly or infliximab (5 mg/kg intravenously at weeks 0, 2, 6, 14, and 22).[37] The Netherlands Organisation for Scientific Research-Medical Sciences funded the study. We rated this study as poor methodological quality; methodological flaws included insufficient blinding and switching treatments during the primary outcomes follow-up time period. Fewer participants treated with etanercept achieved a PASI 75 response compared to infliximab (35% vs. 72%; *P* = .01).[37] No statistically significant differences were observed for changes in the 36-item Short Form Health Survey (SF-36) Physical Health Component Score (PCS) or Mental Health Component Score (MCS).

Etanercept Compared to Ixekizumab

We did not identify any new RCTs for this update. The previous review included 1 publication reporting on 2 large (> 1,000 participants), phase 3 multicenter, fair-methodological quality, randomized trials (UNCOVER-2, UNCOVER-3) comparing etanercept (50 mg twice weekly) with ixekizumab (80 mg twice weekly or 80 mg every 4 weeks, both after an initial starting dose of 160 mg) in participants with moderate-to-severe plaque psoriasis of at least 6 months' duration.[40] This trial, funded by the manufacturer of ixekizumab, also included a placebo arm. Primary efficacy endpoints were the percentage of patients achieving a PGA score of 0 or 1 (with at least a 2-point reduction from baseline at week 12) and a PASI 75 response at 12 weeks. Secondary outcomes included: PGA score of 0; PASI 90; PASI 100; itch Numeric Rating Scale (NRS); and the DLQI. The FDA-approved dose for ixekizumab is 160 mg at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks.

At 12 weeks, the proportion of participants achieving a PASI 75 response was statistically significantly lower for those randomized to etanercept compared to both doses of ixekizumab (ARD range 31 to 48 percentage points across studies and doses of ixekizumab). Likewise, the percentage of patients achieving a PGA score of 0 or 1 was statistically less in patients randomized to etanercept compared to those randomized to ixekizumab (ARD range 34 to 47 percentage points). The proportion of participants achieving a 0 or 1 on the DLQI was also statistically significantly lower for etanercept compared to either dose of ixekizumab (ARD range 20 to 30 percentage points). Similar findings were observed on other secondary efficacy outcomes.

Etanercept Compared to Secukinumab

We did not identify any new RCTs for this update. The previous review included 1 fair-methodological-quality RCT (FIXTURE) that compared etanercept (50 mg twice weekly through week 12, then once weekly) with 2 doses of secukinumab (150 mg and 300 mg, both weekly for 4 weeks, then every 4 weeks) among participants with at least a 6-month history of moderate-to-severe psoriasis.[42] The study's primary endpoints were all placebo comparisons; key secondary outcomes were comparative effectiveness of etanercept compared to secukinumab as assessed by PASI 75 and PGA 0 or 1 response. Both the 150-mg and 300-mg dosages of secukinumab are FDA-approved.

Participants randomized to etanercept achieved a significantly lower response (44%) compared to participants randomized to 300 mg secukinumab (77%) or 150 mg secukinumab (67%; *P* < .001 for both secukinumab doses compared to etanercept).[42] Of those with a PASI 75 response at week 12, a statistically significant higher proportion of participants had a continued response at 52 weeks (73% vs. 84% vs. 82%; *P* < .001 for 300-mg dosage, *P* < .009 for 150-mg dosage).[42] Similar treatment effects were observed for the PGA 0 or 1 response for both the induction period (through week 12) and the maintenance period (through week 52). Etanercept was also statistically significantly less effective than either dose of secukinumab on the PASI 90 and PASI 100 response. The mean improvement in QoL as measured by the DLQI was numerically lower for participants randomized to etanercept (-7.9) compared to secukinumab 300 mg or 150 mg (-10.4 and -9.7, respectively; *P* value NR).[42]

Etanercept Compared to Tildrakizumab

We identified 1 new, fair-methodological quality RCT for this update (RESURFACE-2) that compared etanercept (50 mg twice weekly through week 12, then once weekly) to tildrakizumab (100 mg or 200 mg at week 0 and week 4, then every 12 weeks) in adults with moderate-to-severe plaque psoriasis.[28] This trial also included a placebo study group. The co-primary study endpoints were the PASI 75 and PGA 0 or 1 response at 12 weeks. Secondary remission and improvement outcomes included the PASI 90 and 100 at 12 and 28 weeks, the PASI 75 and PGA 0 or 1 at 28 weeks. QoL was assessed with the DLQI at 12 and 28 weeks. The FDA-approved dose for tildrakizumab is 100 mg at weeks 0 and 4, then every 12 weeks.

Participants randomized to etanercept had an inferior PASI 75 response at week 12 (48%) compared to participants randomized to either doses of tildrakizumab (100 mg, 61%; *P* = .001; 200 mg, 66%; *P* < .001).[28] A similar treatment effect was observed for the PGA 0 or 1, PASI 90, and PASI 100 response at week 12. Etanercept remained inferior to both doses of tildrakizumab at 28 weeks on all remission outcomes. For QoL, at 12 weeks, etanercept was inferior to 200 mg tildrakizumab; 36% of participants randomized to etanercept achieved a 0 or 1 response on the DLQI compared to 47% in the 200-mg dosage group (*P* = .003).[28] Forty-percent of participants randomized to 100 mg of tildrakizumab achieved a DLQI 0 or 1 response, which was not statistically different from the response in etanercept (*P* = .22).[28] However etanercept was inferior to both doses at 28 weeks follow-up (39% vs. 54% vs. 65%; *P* < .001 for both doses compared to etanercept).

Etanercept Compared to Tofacitinib

We did not identify any new RCTs for this update. The previous review included 1 fair-methodological quality RCT (OPT) published in 2 articles that compared etanercept (50 mg twice weekly) with 2 doses of tofacitinib (5 mg or 10 mg twice daily).[35,51] Study authors required participants enrolled in this study to have moderate-to-severe psoriasis of at least 12 months' duration. The co-primary efficacy outcomes were the PASI 75 and PGA response at 12 weeks. Secondary remission and clinical improvement outcomes included the PASI 90, PASI 50, and the itch severity item score. The DLQI and SF-36 were used to assess QoL. We note that tofacitinib is not approved for a plaque psoriasis indication; however, it is approved for psoriatic arthritis (at a dose of 5 mg twice daily) so may still be a relevant comparison to consider for this update since persons with psoriasis may also have psoriatic arthritis.

At 12 weeks, participants randomized to etanercept had a superior response on the PASI 75 (59 %) to those randomized to tofacitinib 5 mg (40%, $P < .001$) but a similar response to those randomized to tofacitinib 10 mg (64%; $P = .20$).[35] Similar findings were observed for response on the PGA and on both the PASI 50 and PASI 90. Tofacitinib 10 mg was superior to etanercept on the itch severity item score (little or no itch 57% vs. 69%; $P < .05$). The proportion of participants with a 5-point or more improvement on the DLQI was significantly higher for participants randomized to etanercept (75%) compared to tofacitinib 5 mg (66%; $P = .03$) but similar to participants randomized to tofacitinib 10 mg (78%; $P = .31$).[35] The mean change in SF-36 PCS and MCS was numerically highest among participants randomized to tofacitinib 10 mg, but study authors did not report statistical significance testing.

Etanercept Compared to Ustekinumab

We did not identify any new studies for this update. The previous review included 1 fair-methodological-quality, randomized trial that compared etanercept with ustekinumab in patients with moderate-to-severe plaque psoriasis.[39] Patients were randomized to 3 arms: 50 mg etanercept twice weekly, 45 mg ustekinumab at weeks 0 and 4, or 90 mg ustekinumab at weeks 0 and 4. In this study, patients over 90 kg received the higher dose of ustekinumab (90 mg). The trial lasted 12 weeks, and patients and study personnel administering the drugs were not blinded to treatment allocation. All other study personnel, including assessors and data managers, were blinded to treatment allocation. The FDA-approved dose is 90 mg for persons weighing > 100 kg and 45 mg for persons weighing ≤ 100 kg.

Significantly fewer patients in the etanercept group achieved the primary outcome (PASI 75 response) compared with both ustekinumab groups (etanercept 50 mg, 57%; ustekinumab 45 mg, 68%; $P = .01$; ustekinumab 90 mg, 74%; $P < .001$). Similarly, statistically significantly fewer participants in the etanercept group demonstrated cleared or minimal disease (0 or 1) on the PGA compared with both ustekinumab groups (etanercept 50 mg, 49%; ustekinumab 45 mg, 65%; $P < .001$; ustekinumab 90 mg, 71%; $P < .001$). Other secondary remission outcomes (PASI 90, PGA 0) had similar findings. No QoL or other efficacy outcomes were reported.

Guselkumab Compared to Adalimumab

We identified 3 fair-methodological quality RCTs (X-PLORE,[20] VOYAGE-1,[17,74] VOYAGE-2[32,75,76]) that were new to this update. All 3 RCTs enrolled adults with moderate-to-severe psoriasis for at least 6 months and with at least 10% BSA involvement. X-PLORE compared multiple guselkumab doses and dosing intervals to adalimumab (80 mg at week 0, then 40 mg at week 1 and every 2 weeks) whereas VOYAGE-1 and VOYAGE-2 compared 100 mg of guselkumab (at weeks 0, 4, and 12) to adalimumab (80 mg at week 0, then 40 mg at week 1 and every 2 weeks). The primary endpoint in X-PLORE was the PGA (0 or 1). No primary endpoints were designated for comparative effectiveness in either VOYAGE trials but both trials evaluated the PGA (0 or 1), PASI 90, PASI 75, DLQI (0 or 1 and mean change), and change in the Psoriasis Symptoms and Signs Diary (PSSD). VOYAGE-2 also reported SF-36 and Hospital Anxiety and Depression Scale (HADS) outcomes. The FDA-approved dose of guselkumab is 100 mg at weeks 0, 4, and every 8 weeks thereafter.

For X-PLORE, guselkumab was statistically superior to adalimumab at doses of 50 mg, 100 mg, and 200 mg for the primary endpoint, PGA 0 or 1 (58% adalimumab vs. 86% guselkumab

100 mg).[20] However, no statistical differences were observed between groups for secondary endpoints (PASI 75, DLQI). For both VOYAGE trials, guselkumab was statistically superior to adalimumab on all PGA and PASI outcomes, the DLQI, and the PSSD. The authors of VOYAGE-2 reported statistically significant larger improvements for guselkumab for the SF-36 PCS and HADS anxiety scale compared to adalimumab, but no statistical differences for the SF-36 MCS and the HADS depression scale.

Guselkumab Compared to Secukinumab

We identified 1 new fair-methodological quality RCT (ECLIPSE) for this update that compared 100 mg of guselkumab (at weeks 0, 4, and 12, then every 8 weeks) to 300 mg of secukinumab (at weeks 0, 1, 2, 3, and 4, then every 4 weeks) among participants with moderate-to-severe plaque psoriasis of at least 6 months' duration.[31] The primary study endpoint was PASI 90 response at week 48. Secondary remission outcomes include PASI 75 response at combined week 12 and week 48 endpoint, PASI 75 response at week 12, PASI 100 response at week 48, and IGA 0 and 0 or 1 response at week 48.

At week 48, guselkumab was superior to secukinumab for achieving a PASI 90 response (84% vs. 70%; $P < .001$).[31] Guselkumab was non-inferior to secukinumab for achieving a PASI 75 response at combined week 12 and week 48 endpoint (85% vs. 80%; non-inferiority $P < .001$; superiority $P = .06$).[31] Per the study's prespecified analysis plan, no further secondary endpoints were subjected to statistical significance testing once a nonsignificant finding for superiority or non-inferiority was reached. Guselkumab was numerically superior to secukinumab on the PASI 100 and IGA 0 and 0 or 1 response at week 48, whereas secukinumab was numerically superior to guselkumab on the PASI 90 and PASI 75 response at week 12.

Ixekizumab Compared to Ustekinumab

We did not identify any new RCTs for this update but we did identify a new article providing longer-term outcomes for an RCT (IXORA-S) included in the previous review.[48,52] This fair-methodological-quality RCT compared ixekizumab 80 mg (every 2 weeks through week 12, then every 4 weeks) with ustekinumab (45 mg or 90 mg depending on body weight, at weeks 0, 4, and 16) among adults with moderate-to-severe psoriasis of at least 6 months' duration and reported outcomes after a 12-week induction period[48] and after a 52-week maintenance period.[52] The primary efficacy endpoint was the PASI 90 at 12 weeks. Secondary remission and clinical improvement outcomes included the PASI 75, PASI 100, PGA, itch NRS, and skin pain as assessed with a visual analog scale (VAS). Study authors assessed QoL with the DLQI. The FDA-approved dose for ixekizumab is 160 mg at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10 and 12, then 80 mg every 4 weeks.

At 12 weeks, participants randomized to ixekizumab had a superior response on the PASI 90 (73%) compared to participants randomized to ustekinumab (42%, $P < .001$). A similar treatment effect was observed for response on the PASI 75, PASI 100, and PGA. Changes on the itch NRS and skin pain VAS were numerically higher for ixekizumab but were not statistically different from scores for ustekinumab. Sixty-one percent of participants randomized to ixekizumab reported no or minimal impact of condition on the QoL (DLQI 0 or 1) compared to 45% of participants randomized to ustekinumab ($P = .01$). Outcomes were also reported after 52

weeks.[51] Participants randomized to ixekizumab continued to have larger clinical improvement and disease remission outcomes compared to participants randomized to ustekinumab.

Risankizumab Compared to Adalimumab

We identified 1 new, fair-methodological quality RCT (IMMVENT) for this update.[29] This multicenter, phase 3 RCT compared 150 mg of risankizumab (at week 0 and 4) to 40 mg adalimumab (80 mg at week 0, then 40 mg every other week) over 16 weeks among participants with moderate-to-severe chronic plaque psoriasis. The co-primary endpoints were PASI 90 response and PGA 0 or 1 at 16 weeks. Secondary remission endpoints included the PASI 75 and PASI 100 response and PGA 0 response. The study authors assessed QoL with the DLQI 0 or 1 response, and also assessed work-related functioning with the work limitations questionnaire (WLQ).

At 16 weeks, risankizumab was superior to adalimumab on the PASI 90 response (ARD 25%; 95% CI, 18% to 32%; *P* < .001). A similar finding was observed for the PGA 0 or 1 response and on all secondary remission outcomes. For QoL, 66% of participants randomized to risankizumab achieved a 0 or 1 response on the DLQI compared with 49% of participants randomized to adalimumab (*P* < .001). Participants randomized to risankizumab also had a larger improvement (mean -2.8) on the WLQ compared to participants randomized to adalimumab (mean -1.9, *P* = .01).

Risankizumab Compared to Ustekinumab

The previous review included 1 RCT,[46] and we identified 2 new RCTs (UltIMMA-1 and UltIMMA-2) published in 1 article for this update; all were of fair-methodological quality.[21] UltIMMA-1 and UltIMMA-2 were multicenter phase 3 trials that enrolled adults with moderate-to-severe plaque psoriasis of at least 6 months' duration and randomized them to either 150 mg of risankizumab (at weeks 0 and 4, then every 12 weeks) or 45 mg or 90 mg (depending on body weight) of ustekinumab (at weeks 0 and 4, then every 12 weeks). These RCTs also included a placebo arm. The co-primary endpoints were PASI 90 and PGA (0 or 1) response at 16 weeks; both studies also reported outcomes at 52 weeks.

At 16 weeks, more participants randomized to risankizumab in UltIMMA-1 and UltIMMA-2 had disease remission compared to ustekinumab (PASI 90 75% vs. 42%; *P* < .001 in UltIMMA-1; 75% vs. 48%; *P* < .001 in UltIMMA-2). A similar treatment effect was observed for the PGA (0 or 1, and 0 only), PASI 100, and Psoriasis Symptom Scale (PSS). Participants randomized to risankizumab also demonstrated a larger improvement in QoL (DLQI 0 or 1 response, 66% vs. 43%; *P* < .001 in UltIMMA-1; 67% vs. 47%; P < .001 in UltIMMA-2).

The previously included RCT compared several dose regimens of risankizumab (single 18-mg dose, 90 mg or 180 mg at weeks 0, 4, and 16) to ustekinumab (45 mg or 90 mg depending on body weight at weeks 0, 4, and 16) in patients with moderate-to-severe plaque psoriasis of at least 6 months' duration.[46] We rated this study as fair methodological quality because of unclear allocation and insufficient blinding. Additionally, the study was sponsored by the manufacturer who had extensive involvement in study design, execution, and reporting. In this RCT, risankizumab (data pooled for 90-mg and 180-mg dosages) was more effective than ustekinumab for the PASI 90 response (77% vs. 40%; *P* < .001).[46] Similar treatment effects were observed for

the PASI 50, PASI 75, PASI 100, and PGA response. Participants randomized to either the 90-mg or 180-mg dosage of risankizumab also larger improvements in QoL (DLQI 0 or 1, 72% vs. 53%, $P < .001$).[46]

Secukinumab Compared to Ustekinumab

We identified 1 new RCT (CLARITY) comparing secukinumab 300 mg (at week 0, 1, 2, and 3, then every 4 weeks) to ustekinumab (45 mg or 90 mg depending on body weight at weeks 0 and 4, then every 12 weeks) in adult patients with chronic moderate-to-severe psoriasis for this update.[16] The previous review included 1 RCT (CLEAR) published in 3 articles that compared secukinumab 300 mg (at week 0, 1, 2, and 3, then every 4 weeks) with ustekinumab (45 mg or 90 mg depending on body weight at weeks 0 and 4, then every 12 weeks) in adults with moderate-to-severe plaque psoriasis.[36,53,77] Both studies were of fair methodological quality. Study authors reported results for CLEAR at 16 weeks and 52 weeks follow-up. The primary study endpoint in CLEAR was the PASI 90 at 16 weeks; additional remission and clinical improvement outcomes included the PASI 75, PASI 100, IGA, and symptom scores (pain, itch, and scaling). The DLQI and European Quality of Life 5-Dimensions (EQ-5D) instrument were used to assess QoL, and the Work Productivity and Activity Impairment Questionnaire-Psoriasis (WPAI-PSO) was used to assess work-related disability. The co-primary endpoints in CLARITY were the PASI 90 and IGA 0 or 1 response at 12 weeks; secondary outcomes included the PASI 75 and PASI 100 at 12 weeks and 16 weeks, the IGA 0 or 1 response at 16 weeks, and the DLQI at 12 weeks and 16 weeks.

In CLEAR and CLARITY, secukinumab was superior to ustekinumab. For the primary study outcome in CLEAR, participants randomized to secukinumab had a higher PASI 90 response (79%) compared to those randomized to ustekinumab (58%; $P < .001$) at 16 weeks.[53] Secukinumab was superior to ustekinumab on all secondary remission and clinical improvement outcomes. Secukinumab was also superior to ustekinumab for improving QoL (DLQI 0 or 1, 72% vs. 57%; $P < .001$) at 16 weeks.[53] At 52 weeks, secukinumab remained superior to ustekinumab on the PASI 90 response (75% vs. 61%; $P < .001$) and on all secondary remission, clinical improvement, and QoL outcomes.[36] For the primary study outcome in CLARITY, participants randomized to secukinumab had a higher PASI 90 response (67%) compared to those randomized to ustekinumab (48%; $P < .001$).[16] Similar treatment effects were seen for the IGA 0 or 1 response, and on the PASI 75 and PASI 100 at both 12 and 16 weeks. Participants randomized to secukinumab also had greater improvements in QoL (DLQI 0 or 1, 68%) compared to ustekinumab (56%; $P < .001$).

Table 3. Evidence Table for Efficacy Outcomes in Adults for TIMs for Plaque Psoriasis (Brief Version)

Authors, Year Trial Name	Number of Patients	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Study Quality
Apremilast Compared to Etanercept								
Reich et al., 2017[47] LIBERATE	250	16 weeks	Apremilast 30 mg twice per day vs. etanercept 50 mg once weekly	PASI 75	PGA, BSA, PASI 50, DLQI	Adult patients with moderate-to-severe plaque psoriasis ≥ 12 months duration and involving ≥ 10% BSA	No statistically significant difference between groups	Fair
Brodalumab Compared to Ustekinumab								
Lebwohl et al., 2015[43] AMAGINE-2, AMAGINE-3	1,831 and 1,881	12 weeks	Brodalumab 210 mg at weeks 0, 1, 2 then every 2 weeks vs. ustekinumab 45 mg or 90 mg[a] at weeks 0 and 4	PASI 75, PGA 0 or 1, PASI 100	PASI 100, PGA 0	Adult patients with moderate-to-severe plaque psoriasis ≥ 6 months duration and involving ≥ 10% BSA	Brodalumab was more effective than ustekinumab	Fair
Etanercept Compared to Infliximab								
De Vries et al., 2017[37] PIECE	50	24 weeks	Etanercept 50 mg twice weekly vs. infliximab 5 mg/kg at weeks 0, 2, 6,14, 22	PASI 75	PASI 75 at week 6 and 12, IGA, Skindex-17, SF-36	Adult patients with plaque psoriasis with PASI ≥ 10, BSA ≥ 10 and/or PASI ≥ 8 plus Skindex-29 ≥ 35	Infliximab was more effective than etanercept	Poor

Authors, Year Trial Name	Number of Patients	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Study Quality
Etanercept Compared to Ixekizumab								
Griffiths et al., 2015[40] UNCOVER-2, UNCOVER-3	1,224 and 1,346	12 weeks	Etanercept 50 mg twice weekly vs. ixekizumab 80 mg every 2 weeks[b] vs. ixekizumab 80 mg every 4 weeks[b]	PASI 75, PGA 0 or 1	PGA 0, PASI 90, PASI 100, NRS, DLQI	Adults with moderate-to-severe plaque psoriasis ≥ 6 months duration and involving ≥ 10% BSA	Ixekizumab was more effective than etanercept	Fair
Etanercept Compared to Secukinumab								
Langley et al., 2014[42] FIXTURE	1,306	52 weeks	Etanercept 50 mg twice weekly vs. secukinumab 300 mg or 150 mg weekly for 4 weeks then every 4 weeks	NA[c]	PASI 75, PGA, PASI 90, PASI 100, PASI 50, DLQI	Adults with plaque psoriasis of ≥6 months duration, poorly controlled with current therapies and involving at least 10% BSA	Secukinumab was more effective than etanercept	Fair
Etanercept Compared to Tildrakizumab								
Reich et al., 2017[28] RESURFACE 2	934 (without the placebo arm)	28 weeks	Etanercept 50 mg twice weekly vs. tildrakizumab 100 mg and 200 mg at weeks 0 and 4 then every 12 weeks	PASI 75, PGA 0 or 1, both at 12 weeks	PASI 90, PASI 100, DQLI at 12 weeks, PASI and DLQI at 28 weeks	Adults with moderate-to-severe plaque psoriasis involving ≥ 10% BSA	Tildrakizumab was more effective than etanercept on all primary and nearly all secondary outcomes	Fair

Authors, Year Trial Name	Number of Patients	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Study Quality
Etanercept Compared to Tofacitinib								
Bachelez et al., 2015[35] Valenzuela et al., 2016[51] OPT	1,106	12 weeks	Etanercept 50 mg twice weekly vs. tofacitinib 10 and 5 mg twice daily[d]	PASI 75, PGA	PASI 90, PASI 50, itch severity item score, DLQI, SF-36	Adults with plaque psoriasis of ≥ 12 months duration, poorly controlled with current therapies and involving at least 10% BSA	Etanercept was more effective than 5 mg twice daily but similar to 10 mg twice daily	Fair
Etanercept Compared to Ustekinumab								
Griffiths et al., 2010[39]	903	12 weeks	Etanercept 50 mg twice weekly vs. ustekinumab 45 mg and 90 mg at weeks 0 and 4	PASI 75	PGA, PASI 90	Adults with plaque psoriasis of at least 6 months duration and involving > 10% BSA	Etanercept was less effective than ustekinumab	Fair
Guselkumab Compared to Adalimumab								
Gordon et al., 2015[20] X-PLORE	251 (without the placebo arm)	16 weeks	Adalimumab 40 mg every 2 weeks[e] vs. guselkumab 5 mg, 15 mg, 50 mg, 100 mg, 200 mg[f]	PGA 0 or 1	PASI 75, DLQI	Adults with moderate-to-severe plaque psoriasis for at least 6 months and involving ≥ 10% BSA	Guselkumab was more effective than adalimumab on primary endpoint at doses of 50 mg, 100 mg, and 200 mg but no significant differences on secondary endpoints at same doses	Fair

Authors, Year Trial Name	Number of Patients	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Study Quality
Blauvelt et al., 2017 Papp et al., 2018 VOYAGE-1[17,74]	663 (without the placebo arm)	16 weeks	Adalimumab 40 mg every 2 weeks[e] vs. guselkumab 100 mg at weeks 0, 4, and 12	No primary endpoints specified	IGA 0 or 1, IGA 0, PASI 90, PASI 75, PASI 100, DLQI, PSSD	Adults with moderate-to-severe psoriasis for ≥ 6 months and involving ≥ 10% BSA	Guselkumab was more effective than adalimumab on all outcomes	Fair
Reich et al., 2017[32] Reich et al., 2019[75] Gordon et al., 2018[76] VOYAGE-2	744 (without the placebo arm)	16 weeks	Adalimumab 40 mg every 2 weeks[e] vs. guselkumab 100 mg at weeks 0, 4 and 12	No primary endpoints specified	IGA 0, IGA 0 or 1, PASI 90, PASI 75, Change in DLQI, change in PSSD score	Adults with moderate-to-severe plaque psoriasis ≥ 6 months duration and involving ≥ 10% BSA	Guselkumab was more effective than adalimumab on all psoriasis-specific outcomes, SF-36 PCS, and HADS-A, but similar on SF-36 MCS and HADS-D	Fair
Guselkumab Compared to Secukinumab								
Reich et al., 2019 ECLIPSE[31]	1,048	48 weeks	Guselkumab 100 mg at weeks 0, 4, 12 then every 8 weeks vs. secukinumab 300 mg at weeks 0, 1, 2, 3, 4 then every 4 weeks	PASI 90 at week 48	PASI 75 at week 12 and 48, PASI 90, PASI 100, IGA 0, IGA 0 or 1	Adults with moderate-to-severe psoriasis with BSA ≥ 10%, for ≥ 6 months	Guselkumab was more effective for primary endpoint and was non-inferior for the first secondary endpoint[g] Mixed results on other endpoints	Fair

Authors, Year Trial Name	Number of Patients	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Study Quality
Ixekizumab Compared to Ustekinumab								
Reich et al., 2017[48] Paul et al., 2018[52] IXORA-S	302	52 weeks	Ixekizumab 80 mg every 2 weeks through week 12 then every 4 weeks vs. ustekinumab 45 or 90 mg[a] at weeks 0, 4 and 16	PASI 90	PASI 75, PASI 100, PGA, DLQI, itch NRS, skin pain	Adults with moderate-to-severe plaque psoriasis ≥ 6 months duration, and PASI ≥10	Ixekizumab was more effective than ustekinumab on all outcomes but itch NRS and skin pain at 12 weeks and 52 weeks	Fair
Risankizumab Compared to Adalimumab								
Reich et al., 2019 IMMVENT[29]	605	16 weeks	Risankizumab 150 mg at week 0 and 4 vs. adalimumab 40 mg every 2 weeks[e]	PASI 90, PGA 0 or 1	PASI 75, PASI 100, PASI 50, DLQI, WLQ	Adults with moderate-to-severe plaque psoriasis ≥ 6 months and involving ≥ 10% BSA	Risankizumab was more effective than adalimumab on all primary and secondary outcomes	Fair
Risankizumab Compared to Ustekinumab								
Papp et al., 2017[46]	166	48 weeks	Risankizumab 90 and 180 mg[h] at weeks 0, 4 and 16 vs. ustekinumab 45 or 90 mg[a] at weeks 0, 4 and 16	PASI 90	PASI 50, PASI 75, PASI 100, PGA, NPASI, PGAR, PAI, EQ-5D, DLQI	Adults with stable moderate-to-severe plaque psoriasis ≥ 6 months, ≥ 10% BSA, and PASI ≥ 12	Risankizumab was more effective than ustekinumab	Fair

Authors, Year Trial Name	Number of Patients	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Study Quality
Gordon et al., 2018 UltIMMA-1[21]	506	52 weeks	Risankizumab 150 mg at week 0, 4 then every 12 weeks vs. ustekinumab 45 mg or 90 mg[a] at weeks 0, 4, then every 12 weeks	PASI 90, PGA 0 or 1	PGA 0, PASI 100, DLQI 0 or 1, PSS 0, PASI 75, PSS score	Adults with moderate-to-severe plaque psoriasis ≥ 6 months and involving at least 10% BSA	Risankizumab was more effective than ustekinumab on primary and nearly all secondary endpoints	Fair
Gordon et al., 2018 UltIMMA-2[21]	393	52 weeks	Risankizumab 150 mg at week 0, 4 then every 12 weeks vs. ustekinumab 45 mg or 90 mg[a] at weeks 0, 4, then every 12 weeks	PASI 90, PGA 0 or 1	PGA 0, PASI 100, DLQI 0 or 1, PSS 0, PASI 75, PSS score	Adults with moderate-to-severe plaque psoriasis ≥ 6 months and involving ≥10% BSA	Risankizumab was more effective than ustekinumab on primary endpoint and nearly all secondary endpoints	Fair
Secukinumab Compared to Ustekinumab								
Blauvelt et al., 2017[36,77] Thaci et al., 2015[53] CLEAR	676	52 weeks	Secukinumab 300 mg at weeks 0, 1, 2, 3, then every 4 weeks vs. ustekinumab 45 or 90 mg[a] at week 0, 4, then every 12 weeks	PASI 90 at 16 weeks	PASI 75, PASI 100, IGA, DLQI, EQ-5D-3L, WPAI-PSO, HAQ-DI, pain, itch scaling	Adults with moderate-to-severe plaque psoriasis ≥ 6 months and ≥ 10% BSA	Secukinumab was more effective than ustekinumab	Fair

Authors, Year Trial Name	Number of Patients	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Study Quality
Bagel et al. (2018)[16] CLARITY	1,102	16 weeks	Secukinumab 300 mg at weeks 0, 1, 2, 3, then every 4 weeks vs. ustekinumab 45 mg or 90 mg[a] at weeks 0, 4, then every 12 weeks	PASI 90, IGA 0 or 1	PASI 75, PASI 90, PASI 100, IGA 0 or 1, DLQI 0 or 1	Adults with moderate-to-severe plaque psoriasis and involving ≥ 10% BSA	Secukinumab was more effective than ustekinumab on all outcomes	Fair
Pipeline Agent: Bimekizumab Compared to Placebo								
Papp et al., 2018[26] BE-ABLE	250	12 weeks	Bimekizumab 64 mg, 160 mg, 160 mg with 320 mg loading dose, 320 mg, 480 mg, all every 4 weeks vs. placebo every 4 weeks	PASI 90 at week 12	PASI 90 at week 8, PASI 75 and PASI 100 at week 12, IGA 0 or 1 at weeks 8 and 12	Adults with moderate-to-severe plaque psoriasis ≥ 6 months and involving ≥ 10% BSA	Bimekizumab was more effective than placebo at all doses evaluated for all primary and secondary outcomes	Fair
Glatt et al., 2017[19]	39	One infusion, 20 weeks follow-up	Bimekizumab 8 mg, 40 mg, 160 mg, 480 mg, or 640 mg as a single dose vs. placebo	Adverse events	LSS, PASI, PGA 0 or 1	Adults with plaque psoriasis ≥ 6 months and involving ≥ 5% BSA	Bimekizumab demonstrated dose dependent improvement in all clinical outcomes compared to placebo for the 160 mg and higher doses	Fair

Authors, Year Trial Name	Number of Patients	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Study Quality
Pipeline Agent: BMS-986165 Compared to Placebo								
Papp et al., 2018[27]	268	12 weeks	BMS-986165 3 mg every other day, daily, twice daily, 6 mg twice daily, or 12 mg daily vs. placebo	PASI 75	PASI 50, PASI 90, PASI 100, PGA 0 or 1, DLQI 0 or 1	Adults with moderate-to-severe plaque psoriasis ≥ 6 months and involving ≥ 10% BSA	All doses 3 mg twice daily or greater were more effective than placebo on nearly all outcomes	Fair
Pipeline Agent: Mirikizumab Compared to Placebo								
Reich et al., 2019[30]	205	16 weeks	Mirikizumab 30 mg, 100 mg, or 300 mg all at weeks 0 and 8 vs. placebo at weeks 0 and 8	PASI 90	PASI 75, PASI 100, absolute PASI ≤ 5, absolute PASI ≤ 3, PGA 0 or 1, PGA 0, BSA≤1%, DLQI 0 or 1, PSSI 0, PSS 0	Adults with plaque psoriasis ≥ 6 months duration and involving ≥ 10% BSA	All doses were more effective than placebo for primary and all secondary efficacy outcomes	Fair

Notes. [a] *Dose depending on body weight, 45 mg if ≤ 100 kg and 90 mg if > 100 kg.* [b] *The FDA-approved dose for this agent is an initial 160-mg dosage, then 80 mg at weeks 2, 4, 6, 8, 10, 12, then every 4 weeks.* [c] *All primary study endpoints were placebo comparisons.* [d] *The FDA-approved dosage for this agent is 5 mg twice daily.* [e] *After initial dose of 80 mg and dose of 40 mg at week 1.* [f] *Dosing intervals varied by dose, doses administered either at weeks 0 and 4 then every 12 weeks or at week 0 and every 8 weeks.* [g] *No statistical testing done on other secondary timepoints because of hierarchical analysis but guselkumab was numerically more effective for the 3 endpoints at week 48 and secukinumab was numerically more effective for the 2 endpoints at week 12.* [h] *A single 18-mg dosage group was also included in this study. Abbreviations. BSA: Body Surface Area; DLQI: Dermatology Life Quality Index; EQ-5D-3L: European Quality of Life 5-Dimension Health Questionnaire, 3–level version; HADS-D/HADS-A: Hospital Anxiety or Depression Scale; HAQ-DI: Health Assessment Questionnaire Disability Index; IGA: Investigator Global Assessment; LSS: lesion severity score; NA: not applicable; NPASI: Nail Psoriasis Severity Index; NRS: numeric rating scale; PAI: patient's assessment of itching; PASI: Psoriasis Area and Severity Index; PGA: Physician Global Assessment; PGAR: Patient's Global Assessment Rank; PSS: psoriasis symptom scale; PSSD: Psoriasis Symptoms and Signs Diary; PSSI: Psoriasis Scalp Severity Index; SF-36: 36-item Short Form Health Survey; SF-36 PCS: 36-item Short Form Health Survey Physical Health Component Score; TIMs: targeted immune modulators; WLQ: Work Limitations Questionnaire; WPAI-PSO: Work Productivity and Activity Impairment Questionnaire-Psoriasis.*

Comparative Harms (Key Question 2)

In this section, we describe harm findings for the 21 included RCTs described for Key Question 1, plus 5 additional cohort studies reporting on eligible harms. Appendix B, Tables B1 and B2 provide detailed study characteristics and results from the included RCTs, and Table B3 provides detailed study characteristics and results from the included cohort studies.

Harms Reported in RCTs

Table 4 summarizes high-level findings for harms from included RCTs; detailed findings are summarized in Table 5. Overall, we observed few differences in harms for TIMs in head-to-head comparisons. Thus, this narrative section will only highlight comparisons for which study authors observed at least 1 statistically significant difference in a harm outcome between agents.

In the RCT comparing apremilast to etanercept over 16 weeks, a lower incidence of overall AEs was observed for apremilast (53%) compared to etanercept (71%; RR, 0.75; 95% CI, 0.58 to 0.95).47 No other significant differences in harms were observed.

In the RCT comparing etanercept to secukinumab over 12 weeks, a higher risk of injection site reactions was observed for etanercept (11%) compared to secukinumab (1%; RR, 14.9; 95% CI, 6.7 to 33.2).[42] No other significant differences in harms were observed.

In the RCT comparing etanercept to 2 doses of tildrakizumab (100 mg and 200 mg), no statistically significant differences were observed in SAEs or withdrawals due to AEs.[28] Significantly fewer AEs were observed for the 100-mg tildrakizumab dose compared to etanercept (RR, 0.82; 95% CI, 0.70 to 0.96, over weeks 0 to 12; RR, 0.81; 95% CI, 0.69 to 0.95, over weeks 13 to 28). Further, significantly fewer AEs were observed during weeks 13 to 28 for the 200-mg dose of tildrakizumab compared with etanercept (RR, 0.80; 95% CI, 0.68 to 0.93) but no difference was observed during weeks 0 to 12.[28] Significantly fewer injection site reactions were also observed for both doses of tildrakizumab compared to etanercept during weeks 0 to 12, but not during weeks 13 to 28.

In the RCT comparing etanercept to 2 doses of tofacitinib, a higher incidence of withdrawals due to AEs was observed for etanercept (3%) compared with 5 mg tofacitinib twice daily dosage (1%; RR, 3.6; 95% CI, 1.01 to 12.8).[35,51] No significant differences were observed for withdrawals for the 10 mg twice daily dosage (RR, 1.1; 95% CI, 0.39 to 3.4) or for AEs or SAEs for either dosage.

In the RCT comparing etanercept to ustekinumab, injection site reactions were more frequent with etanercept compared to ustekinumab (RR, 4.0; 95% CI, 4.0 to 9.8); however, participants in the etanercept group received more injections than participants receiving ustekinumab.[39] No significant difference in AEs, SAEs, or withdrawals due to AEs were observed.

Three RCTs compared guselkumab to adalimumab, all over 16 weeks' follow-up.[17,20,32,74-76] No significant differences in AEs, SAEs, or withdrawals due to AEs were observed. A lower incidence of injection site reactions with guselkumab compared to adalimumab was observed in 2 of the 3 studies (RR, 0.07; 95% CI, 0.01 to 0.33[20]; and RR, 0.38; 95% CI, 0.19 to 0.74[32]).

Three RCTs compared risankizumab with ustekinumab.[21,46] One of these RCTs reported no significant differences in any harms.[46] In UIttIMMA-1, significantly fewer SAEs were observed with

risankizumab over weeks 0 to 16 compared to ustekinumab (RR, 0.29; 95% CI, 0.11 to 0.77); during weeks 17 to 52, the incidence was similar.[21] In UlttIMMA-2, significantly fewer overall AEs were observed during weeks 17 to 52 for risankizumab compared to ustekinumab (RR, 0.75; 95% CI, 0.64 to 0.08), with no difference in incidence observed during weeks 0 to 16.[21] Withdrawals due to AEs were similar between groups over all time periods in both UltIMMA studies.

Harms Reported in Cohort Studies

Table 6 summarizes harm outcomes from 5 cohort studies[18,23,33,38,49] conducted among participants with plaque psoriasis. Appendix B, Table B3 provides detailed study characteristics and findings.

Two cohort studies were conducted with participants identified based on insurance claims for biologic therapy and diagnosis codes for psoriasis.[18,33] Dommasch et al. was conducted by academic researchers among 107,707 participants who were new users of adalimumab, apremilast, etanercept, infliximab, ustekinumab, and other nonbiological DMARD agents.[18] Compared to adalimumab, significantly fewer patients incurred a serious infection requiring hospitalization for apremilast (hazard ratio [HR], 0.31; 95% CI, 0.15 to 0.65) and etanercept (HR, 0.76; 95% CI, 0.61 to 0.94). Ustekinumab users had a lower risk compared to adalimumab but the upper CI included the null effect (HR, 0.70; 95% CI, 0.49 to 1.00). Infliximab users had a significantly higher risk compared to adalimumab (HR, 1.92; 95% CI, 1.01 to 3.62). In the second study, Wu et al. used insurance claims to identify participants; analyses were restricted to patients on monotherapy.[33] This analysis, supported by the manufacturer, found no statistically significant differences in "adverse medical conditions" between adalimumab and the other biological agents that were included in the analysis (etanercept, ustekinumab, infliximab).

Two studies were conducted with participants identified from the British Association of Dermatologists Biologic Interventions Register (BADBIR), a prospective registry of patients from 157 dermatology centers in the U.K. and Ireland supported by multiple drug manufacturers for pharmacovigilance activities. Mason et al. analyzed 3,812 patients with psoriasis recruited within 6 months of initiating or switching to a biologic or conventional systemic therapy.[23] The primary goal of this study was to compare the incidence of SAEs among participants in the registry who would meet criteria for typical clinical trials with those participants not meeting trial eligibility criteria. Of participants eligible for clinical trials, no significant differences in SAEs were observed between participants receiving ustekinumab compared to adalimumab (*IRR, 1.1; 95% CI, 0.89 to 1.24*); however, participants receiving ustekinumab had a statistically significant higher risk compared to participants receiving etanercept (*IRR, 1.3; 95% CI, 1.1 to 1.5).* Participants receiving adalimumab had a lower risk (IRR, 0.84; 95% CI, 0.70 to 1.003) compared to etanercept. Of participants not eligible for clinical trials, ustekinumab had a statistically significantly higher incidence of SAEs compared to both adalimumab (*IRR, 1.2; 95% CI, 1.1 to 1.4*) and etanercept (*IRR, 2.4; 95% CI, 1.8 to 3.1*). In addition, compared to adalimumab, participants receiving etanercept had a statistically significant lower risk for SAEs (IRR, 0.75; 95% CI, 0.66 to 0.86). In the second cohort study, Warren et al. also conducted analyses using the BADBIR.[78] This study reported a statistically significant higher risk for drug withdrawal for AEs with infliximab compared to adalimumab (RR, 2.8; 95% CI, 1.8 to 4.5).[78] This study also reported a statistically significant lower risk for drug withdrawal due to AEs for ustekinumab compared to adalimumab (RR, 0.60; 95% CI, 0.39 to 0.92). No significant differences in withdrawals due to AEs were observed comparing adalimumab to etanercept.

The final cohort study was conducted among participants with plaque psoriasis identified from 3 Italian referral centers and was supported by an unrestricted grant from the manufacturer.[38] The study was conducted from 2007 to 2011 and reported a statistically significant higher incidence of withdrawal due to AEs for infliximab (9%) compared to etanercept (4%; $P < .001$).[38] No differences in withdrawals due to AEs were observed between infliximab and adalimumab or between adalimumab and etanercept.

Table 4. Summary of RCTs of Adverse Events in Adults Receiving TIMs for Plaque Psoriasis

Authors, Year Trial Name	Number of Patients	Duration	Results	Study Quality
Apremilast Compared to Etanercept				
Reich et al.,[47] 2017 LIBERATE	250	16 weeks	Lower risk of AEs for etanercept than apremilast (53% vs. 71%; RR, 0.75; 95% CI, 0.58 to 0.95). No significant differences in SAEs or withdrawals due to AEs.	Fair
Brodalumab Compared to Ustekinumab				
Lebwohl et al.,[43] 2015 AMAGINE-2	1,831	52 weeks	No significant differences in AEs, SAEs, or withdrawals due to AEs.	Fair
Lebwohl et al.,[43] 2015 AMAGINE-3	1,881	52 weeks	No significant differences in AEs, SAEs, or withdrawals due to AEs.	Fair
Etanercept Compared to Infliximab				
De Vries et al.,[37] 2017 PIECE	48	24 weeks	No significant differences in AEs, SAEs, withdrawals due to AEs, or injection site reactions.	Poor
Etanercept Compared to Ixekizumab				
Griffiths et al., [40] 2015 UNCOVER-2 UNCOVER-3	2,570	12 weeks	No significant differences in AEs, SAEs, withdrawals due to AEs, or injection site reactions.	Fair
Etanercept Compared to Secukinumab				
Langley et al.,[42] 2014 FIXTURE	1,306	52 weeks	Higher risk of injection site reactions for etanercept than secukinumab 300 mg dose (11% vs. 1%; RR, 14.9; 95% CI, 6.7 to 33.2). No significant differences in AEs, SAEs or withdrawals due to AEs.	Fair
Etanercept Compared to Tildrakizumab				
Reich et al., [28] 2017 RESURFACE-2	1,090	28 weeks	No significant difference in SAEs or withdrawals due to AE during entire study period; significantly fewer AEs for 100 mg dose during entire study period; no difference in AEs for 200 mg dose during weeks 0 to12 but significantly lower AEs for 200 mg dose during weeks 13 to 28.	Fair

Authors, Year Trial Name	Number of Patients	Duration	Results	Study Quality
Etanercept Compared to Tofacitinib				
Bachelez et al.,[35] 2015 Valenzuela et al.,[51] 2016 OPT	1,106	12 weeks	Higher incidence of withdrawal due to AEs for etanercept than tofacitinib 5 mg twice daily (3% vs. 1%; RR, 3.6; 95% CI, 1.01 to 12.8). No significant difference in AEs, SAEs for either the 5 mg twice daily or 10 mg twice daily doses. No significant difference in withdrawals due to AEs for etanercept compared to the 10 mg twice daily dose.	Fair
Etanercept Compared to Ustekinumab				
Griffiths, et al.,[39] 2010	903	12 weeks	No significant differences in AEs, SAEs, or withdrawals due to AEs. Injection site reactions more frequent with etanercept than ustekinumab (RR 6.3, 95% CI, 4 to 9.8), but those participants received more injections than the ustekinumab groups.	Fair
Guselkumab Compared to Adalimumab				
Gordon et al.,[20] 2015 X-PLORE	251	16 weeks	Lower incidence of injection site reactions with guselkumab (RR, 0.07; 95% CI, 0.01 to 0.33); no significant difference in AEs, SAEs, or withdrawals due to AEs.	Fair
Blauvelt et al.,[17,74]2017 Papp et al.,[70] 2018 VOYAGE-1	663[a]	16 weeks	No significant differences in AEs, SAEs, withdrawals due to AEs, or injection site reactions.	Fair
Reich et al.,[32] 2017 Reich et al.,[75] 2019 Gordon et al.,[76] 2018 VOYAGE-2	744[a]	16 weeks	Lower incidence of injection site reactions with guselkumab (RR, 0.38; 95% CI, 0.19 to 0.74); no significant differences in AEs, SAEs, or withdrawals due to AEs.	Fair
Guselkumab Compared to Secukinumab				
Reich et al.,[31] 2019 ECLIPSE	1,048	48 weeks	No significant differences in AEs, SAEs or withdrawals due to AEs. Injection site reactions were NR.	Fair
Ixekizumab Compared to Ustekinumab				
Reich et al., [48] 2017 Paul et al.,[52] 2018 IXORA-S	302	24 weeks	No significant differences in AEs, SAEs or withdrawals due to AEs. Injection site reactions were NR.	Fair
Risankizumab Compared to Adalimumab				
Reich et al.,[29] 2019 IMMVENT	605	16 weeks	No significant differences in AEs, SAEs or withdrawals due to AEs. Injection site reactions were NR.	Fair

Authors, Year Trial Name	Number of Patients	Duration	Results	Study Quality
Risankizumab Compared to Ustekinumab				
Papp, et al.,[46] 2017	166	48 weeks	No significant differences in AEs, SAEs or withdrawals due to AEs. Injection site reactions were NR.	Fair
Gordon et al.,[21] 2018 UlttIMMA-1	506	52 weeks	Significantly fewer SAEs during weeks 0 to 16 with risankizumab compared to ustekinumab, but similar incidence during weeks 17 to 52 and similar incidence of AEs and withdrawals due to AEs.	Fair
Gordon et al.,[21] 2018 UltIMMA-2	393	52 weeks	Significantly fewer AEs during weeks 17 to 52 for risankizumab compared to ustekinumab, similar incidence of AEs during weeks 0 to 16 and similar incidence of SAEs and withdrawals due to AEs throughout study.	Fair
Secukinumab Compared to Ustekinumab				
Blauvelt et al.,[36,77] 2017 Thaci et al.,[53] 2015 CLEAR	676	16 weeks	No significant differences in AEs, SAEs or withdrawals due to AEs. Injection site reactions were NR.	Fair
Bagel et al.,[16] 2018 CLARITY	1,102	16 weeks	No significant differences in AEs, SAEs or withdrawals due to AEs. Injection site reactions were NR.	Fair
Pipeline Agent: Bimekizumab Compared to Placebo				
Papp et al.,[26] 2018 BE-ABLE	250	12 weeks	Significantly more treatment-emergent AEs with Bimekizumab compared to placebo (RR, 1.7; 95% CI, 1.1 to 2.6). No significant differences SAEs or withdrawals due to AEs. Injection site reactions were NR.	Fair
Glatt et al.,[19] 2017	39	One infusion, 20 weeks of follow-up	No significant differences in AEs, SAEs, or withdrawals due to AEs. Injection site reactions were NR.	Fair
Pipeline Agent: BMS-986165 Compared to Placebo				
Papp et al.,[27] 2018	268	12 weeks	AEs more common at higher doses of active drug compared to placebo; no significant differences in SAEs or withdrawals due to AEs for any doses. Injection site reactions were NR.	Fair
Pipeline Agent: Mirikizumab Compared to Placebo				
Reich et al.,[30] 2019	205	16 weeks	No significant differences in AEs, SAEs, or injection site reactions. Withdrawals due to AEs were NR.	Fair

Notes: [a] Not including the placebo arm. Abbreviations. AE: adverse event; CI: confidence interval; N: number of patients; NR: not reported; RCT: randomized controlled trial; RR: risk ratio; SAE: serious adverse event; TIM: targeted immune modulator;

Table 5. Comparisons of TIMs in RCTs for General Tolerability in Plaque Psoriasis

Authors, Year Trial Name	Overall Adverse Events RR (95% CI)	Withdrawal Due to Adverse Events RR (95% CI)	Serious Adverse Events RR (95% CI)	Injection Site Reactions/Infusion Reactions RR (95% CI)	Study Quality
Apremilast Compared to Etanercept					
Reich et al.,[47] 2017 LIBERATE	0.75 (0.58 to 0.95)	0.67 (0.11 to 3.9)	0.67 (0.11 to 3.9)	NA (comparing oral to injectable)	Fair
Brodalumab Compared to Ustekinumab					
Lebwohl et al.,[43] 2015 AMAGINE-2	0.98 (0.87 to 1.1)	1.47 (0.30 to 7.2)	0.74 (0.21 to 2.6)	NR	Fair
Lebwohl et al.,[43] 2015 AMAGINE-3	1.1 (0.93 to 1.2)	2.52 (0.30 to 21.4)	2.26 (0.49 to 10.4)	NR	Fair
Etanercept Compared to Infliximab					
De Vries et al.,[37] 2017 PIECE	1.04 (0.93 to 1.2)	0.72 (0.13 to 4.0)	1.09 (0.07 to 16.4)	0.36 (0.08 to 1.6)	Poor
Etanercept Compared to Ixekizumab[a]					
Griffiths et al. [40] 2015 UNCOVER-2 UNCOVER-3	0.93 (0.85 to 1.02)	0.75 (0.32 to 1.76)	0.99 (0.48 to 2.07)	1.05 (0.78 to 1.4)	Fair
Etanercept Compared to Secukinumab					
Langley et al.,[42] 2014 FIXTURE	0.97 (0.90 to 1.1)[b]	1.24 (0.58 to 2.6)[b]	1.07 (0.61 to 1.9)[b]	14.90 (6.7 to 33.2)[c]	Fair
Etanercept Compared to Tildrakizumab					
Reich et al.,[28] 2017 RESURFACE 2	*Weeks 0 to 12* Tildrakizumab 100 mg vs. etanercept: 0.82 (0.70 to 0.96) Tildrakizumab 200 mg vs. etanercept: 0.91 (0.79 to 1.06)	*Weeks 0 to 12* Tildrakizumab 100 mg vs. Etanercept: 0.51 (0.13 to 2.02) Tildrakizumab 200 mg vs. Etanercept: 0.50 (0.13 to 1.98)	*Weeks 0 to 12* Tildrakizumab 100 mg vs. etanercept: 0.58 (0.17 to 1.97) Tildrakizumab 200 mg vs. etanercept: 0.85 (0.29 to 2.51)	*Weeks 0 to 12* Tildrakizumab 100 mg vs. etanercept: 0.08 (0.02 to 0.31) Tildrakizumab 200 mg vs. etanercept: 0.07 (0.02 to 0.31)	Fair

Authors, Year Trial Name	Overall Adverse Events RR (95% CI)	Withdrawal Due to Adverse Events RR (95% CI)	Serious Adverse Events RR (95% CI)	Injection Site Reactions/Infusion Reactions RR (95% CI)	Study Quality
	Weeks 13 to 28 Tildrakizumab 100 mg vs. etanercept: 0.81 (0.69 to 0.95) Tildrakizumab 200 mg vs. etanercept: 0.80 (0.68 to 0.93)	*Weeks 13 to 28* Tildrakizumab 100 mg vs. Etanercept: 0.33 (0.03 to 3.13) Tildrakizumab 200 mg vs. Etanercept: 0.32 (0.03 to 3.08)	*Weeks 13 to 28* Tildrakizumab 100 mg vs. etanercept: 0.63 (0.28 to 1.44) Tildrakizumab 200 mg vs. etanercept: 0.41 (0.16 to 1.06)	*Weeks 13 to 28* Tildrakizumab 100 mg vs. etanercept: 0.98 (0.20 to 4.83) Tildrakizumab 200 mg vs. etanercept: 0.32 (0.03 to 3.08)	
Etanercept Compared to Tofacitinib[d]					
Bachelez et. al.,[35]2015 Valenzuela et al.,[51] 2016 OPT	5 mg: 1.1 (0.92 to 1.2) 10 mg: 0.96 (0.84 to 1.1)	5 mg: 3.6 (1.01 to 12.8) 10 mg: 1.1 (0.47 to 2.5)	5 mg: 0.98 (0.35 to 2.8) 10 mg: 1.1 (0.39 to 3.4)	NA (comparing oral to injectable)	Fair
Etanercept Compared to Ustekinumab[e]					
Griffiths, et al.,[39] 2010	1.03 (0.94 to 1.13)	1.60 (0.61 to 4.23)	0.80 (0.24 to 2.64)	6.26 (4.00 to 9.81)[f]	Fair
Guselkumab Compared to Adalimumab					
Gordon et al.,[20] 2015 X-PLORE	0.89 (0.66 to 1.20)	0.35 (0.09 to 1.39)	0.62 (0.07 to 5.85)	0.07 (0.01 to 0.33)	Fair
Blauvelt et al.,[17,74]2017 Papp et al.,[70] 2018 VOYAGE-1	1.01 (0.87 to 1.17)	1.35 (0.30 to 6.0)	1.35 (0.47 to 3.9)	0.40 (0.16 to 1.03)	Fair
Reich et al.,[32] 2017 Reich et al.,[75] 2019 Gordon et al.,[76] 2018 VOYAGE-2	0.98 (0.84 to 1.2)	0.88 (0.26 to 3.0)	0.67 (0.25 to 1.9)	0.38 (0.19 to 0.74)	Fair
Guselkumab Compared to Secukinumab					
Reich et al.,[31] 2019 ECLIPSE	0.95 (0.90 to 1.02)	0.80 (0.35 to 1.8)	0.85 (0.54 to 1.3)	NR	Fair

Authors, Year Trial Name	Overall Adverse Events RR (95% CI)	Withdrawal Due to Adverse Events RR (95% CI)	Serious Adverse Events RR (95% CI)	Injection Site Reactions/Infusion Reactions RR (95% CI)	Study Quality
Ixekizumab Compared to Ustekinumab					
Reich et al., [48] 2017 Paul et al.,[52] 2018 IXORA-S	0.92 (0.80 to 1.07)	2.46 (0.23 to 26.83)	0.74 (0.18 to 3.03)	NR	Fair
Risankizumab Compared to Adalimumab					
Reich et al.,[29] 2019 IMMVENT	0.98 (0.85 to 1.1)	0.67 (0.19 to 2.4)	1.1 (0.46 to 2.7)	NR	Fair
Risankizumab Compared to Ustekinumab					
Papp, et al.,[46] 2017	1.11 (0.87 to 1.42)	0.98 (0.06 to 15.07)	1.95 (0.52 to 7.27)	NR	Fair
Gordon et al.,[21] 2018 UlttIMMA-1	Weeks 0 to 16: 0.99 (0.79 to 1.25) Weeks 17 to 52: 0.92 (0.78 to 1.09)	Weeks 0 to 16: 0.33 (0.05 to 2.31) Weeks 17 to 52: 0.33 (0.0 to 84.9)	Weeks 0 to 16: 0.29 (0.11 to 0.77) Weeks 17 to 52: 1.33 (0.46 to 3.9)	NR	Fair
Gordon et al.,[21] 2018 UltIMMA-2	Weeks 0 to 16: 0.85 (0.68 to 1.1) Weeks 17 to 52: 0.75 (0.64 to 0.87)	Weeks 0 to 16: 1.4 (0.02 to 107.4) Weeks 17 to 52: 0.32 (0.05 to 2.3)	Weeks 0 to 16: 0.67 (0.17 to 2.64) Weeks 17 to 52: 1.05 (0.35 to 3.2)	NR	Fair
Secukinumab Compared to Ustekinumab					
Blauvelt et al.,[36,77] 2017 Thaci et al.,[53] 2015 CLEAR	1.1 (0.98 to 1.24)	0.75 (0.17 to 3.34)	1.00 (0.42 to 2.38)	NR	Fair
Bagel et al.,[16] 2018 CLARITY	1.0 (0.90 to 1.2)	1.6 (0.62 to 4.0)	1.6 (0.68 to 3.6)	NR	Fair
Pipeline Agent: Bimekizumab Compared to Placebo					
Papp et al.,[26] 2018 BE-ABLE	1.7 (1.1 to 2.6)	2.0 (0.27 to 15.4)	0.20 (0.01 to 3.2)	NR	Fair
Glatt et al.,[19] 2017	1.1 (0.78 to 1.5)	1.0 (0.004 to 249)	2.0 (0.03 to 155.1)	NR	Fair

Authors, Year Trial Name	Overall Adverse Events RR (95% CI)	Withdrawal Due to Adverse Events RR (95% CI)	Serious Adverse Events RR (95% CI)	Injection Site Reactions/Infusion Reactions RR (95% CI)	Study Quality
Pipeline agent: BMS-986165 Compared to Placebo					
Papp et al.,[27] 2018	Compared to placebo 3 mg every other day: 1.16 (0.79 to 1.7) 3 mg daily: 1.07 (0.72 to 1.6) 3 mg twice daily: 1.26 (0.88 to 1.8) 6 mg twice daily: 1.57 (1.1 to 2.2) 12 mg daily: 1.51 (1.09 to 2.10)	Compared to placebo 3 mg every other day: 0.51 (0.05 to 5.44) 3 mg daily: 1.02 (0.15 to 6.9) 3 mg twice daily: 0.50 (0.05 to 5.3) 6 mg twice daily: 1.50 (0.26 to 8.6) 12 mg daily: 0.51 (0.05 to 5.4)	Compared to placebo 3 mg every other day: 1.02 (0.70 to 15.84) 3 mg daily: 1.02 (0.70 to 15.84) 3 mg twice daily: 1 (0.065 to 15.5) 6 mg twice daily: 1.0 (.0.004 to 252) 12 mg daily: 1.0 (0.004 to 257)	NA (oral agent)	Fair
Pipeline Agent: Mirikizumab Compared to Placebo					
Reich et al.,[30] 2019	1.01 (0.73 to 1.4)	NR	0.68 (0.06 to 7.3)	2.4 (0.30 to 18.9)	Fair

Notes: indicates a calculated value. [a] Study authors reported pooled results from UNCOVER 2 and UNCOVER 3 for harms; the RRs calculated and reported in this table are for the every 2 week dose of ixekizumab. [b] RR calculated for the FDA-approved dose (300 mg) of secukinumab. [c] RR calculated for pooled data from 150 mg and 300 mg doses of secukinumab. [d] Doses are administered twice daily. The 5 mg twice daily dose is the FDA-approved dose. [e] Data are for the combined 45 mg and 90 mg doses of ustekinumab. [f] Participants in the etanercept received more injections than those in the ustekinumab group. Abbreviations. CI: confidence intervals; NA: not applicable; NR: not reported; RCT: randomized controlled trial; RR: risk ratio; TIM: targeted immune modulator.*

Table 6. Summary of Observational Studies for Harms in Adults Receiving TIMs for Plaque Psoriasis

Authors, Year	Number of Patients	Follow-up	Comparisons[a]	Population	Results	Study Quality
Dommasch et al.,[18] 2019	107,707	NR	New users of methotrexate, adalimumab, acitretin, apremilast, etanercept, infliximab, ustekinumab	Adults with psoriasis with at least 3 ICD-9-CM codes of 696.1 on separate dates identified through insurance claims 2003 to 2017	Compared to adalimumab, risk (HR; 95% CI) of serious infection requiring hospitalization: Apremilast: 0.31; 0.15 to 0.65 Etanercept: 0.76; 0.61 to 0.94 Infliximab: 1.9; 1.01 to 3.60 Ustekinumab: 0.70; 0.49 to 1.00	Fair
Esposito et al.,[38] 2013	650	At least 3 months	Infliximab vs. etanercept vs. adalimumab	Patients with plaque psoriasis	The rate of interruption due to AEs was higher with infliximab (8.8%) compared with adalimumab (4.4%) and etanercept (2.8%), the difference being significant between infliximab and etanercept (P = .002)	Fair
Mason et al.,[23] 2018	7,136	Varied	Etanercept (50 mg weekly) vs. adalimumab (40 mg every 2 weeks) vs. ustekinumab, (45 mg every 12 weeks). Primary study goal was to report outcomes among patients eligible for clinical trials vs. those who were not eligible	Adults with moderate-to-severe chronic plaque psoriasis with no comorbidities, recent infection, or previous cancer identified from a prospective dermatological pharmacovigilance patient registry throuogh 2016	Compared to adalimumab, etanercept has a lower risk (*IRR, 0.75; 95% CI, 0.66 to 0.86*) for SAEs and ustekinumab has a higher risk (*IRR, 1.23; 95% CI, 1.09 to 1.37*) for SAEs among registry patients that would not meet clinical trial eligibility criteria. Among the same population, ustekinumab has a higher risk for SAEs compared to etanercept (*IRR, 2.4; 95% CI, 1.82 TO 3.07*) Among patients eligible for clinical trials, there is no difference between between etancercept and ustekinumab compared to adlimumab, but some increased risk for ustekinumab compared to etanercept (*IRR, 1.3; 95% CI, 1.1 to 1.5*)	Fair

Authors, Year	Number of Patients	Follow-up	Comparisons[a]	Population	Results	Study Quality
Warren et al., [78] 2015	3,523	Varied	Adalimumab vs. etanercept vs. infliximab vs. ustekinumab	Biologically-naïve patients with psoriasis identified from a prospective dermatological pharmacovigilance patient registry 2007 to 2014	Discontinuation due to AEs Infliximab vs. adalimumab RR, 2.8; 95% CI, 1.8 to 4.5 Ustekinumab vs. adalimumab RR, 0.60; 95% CI, 0.39 to 0.92 Etanercept vs. adalimumab RR 0.77; 95% CI, 0.58 to 1.02	Fair
Wu et al.[33], 2018	10,065	8.3 to 11.9 months	Adalimumab, etanercept, ustekinumab, infliximab	Adults who were biologic-naïve with > 2 psoriasis diagnoses on insurance claims during the study period. Analyses restricted to patients treated with monotherapy	No statistically significant differences in the risk of adverse medical conditions between patients treated with adalimumab vs. those treated with other biologic therapies (etanercept, ustekinumab, and infliximab)	Fair

Notes. [a] Doses not reported for nearly all studies. Abbreviations. AE: adverse event; CI: confidence interval; HR: hazard ratio; ICD: international classification of disease; IRR: incidence rate ratio; NR, not reported; RR: risk ratio; SAE: serious adverse event; TIM: targeted immune modulator.

Efficacy and Harms of Pipeline TIM Agents for Plaque Psoriasis

We identified 4 RCTs[19,26,27,30] that reported on the efficacy and harms of 3 pipeline TIM agents: bimekizumab, BMS-986165, and mirikizumab. All these studies are new to this update. Table 7 shows the Summary of Findings (GRADE) for the comparison of these agents to placebo. Tables 3, 4, and 5 provide a summary of this evidence and findings. Appendix B, Tables B1 and B2 provide detailed study characteristics and results, and Appendix D describes efficacy outcome measures used in included RCTs. We rated all 4 studies as of fair methodological quality because of industry sponsorship and extensive manufacturer involvement in study design, execution, and reporting.

Table 7 Summary of Findings (GRADE) of Pipeline TIMs for Plaque Psoriasis

Outcome	Quality of Evidence	Relationship[a]
Bimekizumab Compared to Placebo		
Disease remission (2 RCTs)	●●●○ (moderate)	Favors bimekizumab
AEs (2 RCTs)	●○○○ (Very low)	Uncertain
SAEs (2 RCTs)	●○○○ (Very low)	Uncertain
BMS-9865165 Compared to Placebo		
Disease remission (1 RCT)	●●●○ (moderate)	Favors BMS-9865165
Quality of life (1 RCT)	●●●○ (moderate)	Favors BMS-9865165
AEs (1 RCT)	●●○○ (low)	Favors placebo at 2 highest doses of active drug, no difference at 3 lowest doses
SAEs (1 RCT)	●●○○ (low)	Uncertain
Mirikizumab Compared to Placebo		
Disease remission (1RCT)	●●●○ (moderate)	Favors mirikizumab
Quality of life (1RCT)	●●●○ (moderate)	Favors mirikizumab
AEs (1 RCT)	●●○○ (low)	No difference
SAEs (1 RCT)	●●○○ (low)	Uncertain

Notes. [a] For efficacy outcomes, 'favors' refers to a larger improvement compared to the comparator; for harm outcomes, 'favors' refers to a lower incidence of harm relative to the comparator. Abbreviations. AE: adverse events; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; RCT: randomized controlled trial; SAE: serious adverse events; TIM: targeted immune modulator.

Bimekizumab Compared to Placebo

Two fair-methodological-quality RCTs, both new to this update, compared various doses of the pipeline TIM agent bimekizumab to placebo.[19,26] Papp et al. (BE-ABLE) evaluated various doses administered subcutaneously every 4 weeks and reported outcomes at 12 weeks.[26] Glatt et al. administered various doses between 8 mg and 640 mg as a single infusion and reported outcomes over 20 weeks.[19]

The study by Glatt et al. was a first-in-human study with AEs designated as the primary study endpoints.[19] However, clinical efficacy was evaluated and statistically significant differences between placebo and all doses evaluated were observed at all timepoints for the lesion severity

score, and for the higher doses evaluated (160 mg, 480 mg, 640 mg) at nearly all timepoints for percent change from baseline for PASI and PGA. In BE-ABLE, the proportion of participants achieving PASI 90 response varied from 46% to 79% across all bimekizumab doses and was 0% in the placebo group ($P < .001$ for all dose comparisons to placebo).[26] Similar findings were observed on all secondary remission and clinical improvement outcomes.

With respect to harms in Glatt et al., no significant differences were observed in AEs compared to placebo (all dosages were pooled).[19] Only 1 SAE occurred overall (in the bimekizumab group). No withdrawals due to AE were observed in either the bimekizumab or placebo group. In the BE-ABLE trial, a significant increased risk of AEs were observed bimekizumab doses pooled compared to a placebo (RR, 1.7; 95% CI, 1.1 to 2.6) for all.[26] No differences in SAEs or withdrawals due to AEs were observed.

BMS-986165 Compared to Placebo

One fair-methodological-quality RCT new to this update evaluated various dosages of the pipeline TIM agent BMS-98165, compared to placebo, over 12 weeks among adults with moderate-to-severe plaque psoriasis for at least 6 months.[27] Except for the lowest dose (3 mg every other day), all doses were more effective than placebo on the primary study endpoint (PASI 75: ARD range 36 to 72 percentage points) and nearly all secondary remission, clinical improvement, and QoL outcomes.

With respect to harms, overall AEs were more frequent at the higher doses of the pipeline agent (RR, 1.6; 95% CI, 1.1 to 2.2, for 6 mg twice daily and RR, 1.5; 95% CI, 1.1 to 2.1, for 12 mg daily dose) compared to placebo.[27] The incidence of SAEs and withdrawals due to AEs was not different between groups.[27]

Mirikizumab Compared to Placebo

We identified 1 new, fair-methodological quality RCT comparing the pipeline drug mirikizumab to placebo.[30] This multicenter, phase 2 RCT compared multiple doses of mirikizumab (30 mg, 100 mg, and 300 mg) to placebo among participants with at least moderate plaque psoriasis for at least 6 months. The primary study endpoint was PASI 90 response at 16 weeks. Secondary remission outcomes were PASI 75 and PASI 100 response, PGA 0 or 1 and 0 response, absolute PASI < 5 and < 3, BSA involvement < 1%, and PSS and Psoriasis Scalp Severity Index (PSSI) response of 0. QoL was assessed with the DLQI 0 or 1 response.

For the PASI 90 response, all doses of mirikizumab were superior to placebo (300 mg, 67%; 100 mg, 59%; 30 mg, 29%; 0%, placebo; $P < .001$ for 300 and 100 mg vs. placebo; $P = .009$ for 30 mg vs. placebo). Similar findings were observed for all secondary remission outcomes. For QoL, 47% of participants randomized to the 300-mg dosage achieved a 0 or 1 response on the DLQI compared with 49% (100-mg dosage), 35% (30-mg dosage), and 4% (placebo, $P < .001$ for all comparisons with placebo).

With respect to harms, no significant differences were observed in AEs or SAEs. Withdrawals due to AEs were not reported.

Psoriatic Arthritis

We identified 6 RCTs[15,24,25,34,44,45] and 2 cohort studies[22,41] evaluating the effectiveness, comparative effectiveness, or harms of TIMs. Of these studies, 4 are new to this update.[15,22,24,25] Table 8 shows the Summary of Findings (GRADE) for the head-to-head TIM agent comparisons; Appendix C, Table C2 provides detailed evidence profiles.

Table 8. Summary of Findings (GRADE) of TIMs for Psoriatic Arthritis (Comparative Effectiveness and Harms)

Outcome	Quality of Evidence	Relationship[a]
Adalimumab Compared to Etanercept and Infliximab		
Clinical improvement (1 RCT)	●○○○ (very low)	No difference
AEs (1 RCT)	●○○○ (very low)	Favors adalimumab[b]
Adalimumab Compared to Ixekizumab		
Clinical improvement (1 RCT)	●●○○ (low)	Favors ixekizumab[c]
Skin improvement (1 RCT)	●●○○ (low)	Favors ixekizumab
AEs (1 RCT)	●●○○ (low)	No difference
SAEs (1 RCT)	●●○○ (low)	No difference
Adalimumab Compared to Remtolumab		
Clinical improvement (1 RCT)	●●○○ (low)	Favors remtolumab[e]
Disease remission (1 RCT)	●●○○ (low)	Favors remtolumab[e]
Skin improvement (1 RCT)	●●○○ (low)	Favors remtolumab[e]
AEs (1 RCT)	●●○○ (low)	No difference
SAEs (1 RCT)	●○○○ (very low)	Cannot determine
Adalimumab Compared to Tofacitinib		
Clinical improvement (1 RCT)	●●○○ (low)	Favors tofacitinib
Disease remission (1 RCT)	●●○○ (low)	Favors tofacitinib[d]
Quality of life (1 RCT)	●●○○ (low)	Favors adalimumab
AEs (1 RCT)	●●○○ (low)	No difference
SAEs (1 RCT)	●●○○ (low)	No difference
Ustekinumab Compared to TNF-α Inhibitors[g]		
Enthesitis remission (1 RCT)	●○○○ (very low)	Favors ustekinumab
Arthritis remission (1 RCT)	●○○○ (very low)	No difference
Skin remission (1 RCT)	●○○○ (very low)	Favors ustekinumab
Quality of life (1 RCT)	●○○○ (very low)	Favors ustekinumab[g]
Incident atrial fibrillation or major CV events (1 cohort study)	●○○○ (very low)	No difference

Notes. [a] For efficacy outcomes, 'favors' refers to a larger improvement compared to the comparator; for harm outcomes, 'favors' refers to a lower incidence of harm relative to the comparator; [b] Adalimumab favored

compared to either etanercept of infliximab, infliximab favored compared to etanercept; [c] Favors the every 2 week dosage but no difference with the every 4 week dosage; [d] Favors the 10 mg twice daily dosage but no difference with the 5 mg twice daily dosage; [e] Favors the 240 mg dosage, no difference with the 120-mg dosage of remtolumab; [f] Among participants with active enthesitis; [g] As measured by SF-36 PCS but no difference as measured by SF-36 MCS. Abbreviations. AE: adverse event; CV: cardiovascular; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; RCT: randomized controlled trial; SAE: serious adverse event; SF-36 MCS: 36-item Short Form Health Survey Mental Health Component Score; SF-36 PCS: 36-item Short Form Health Survey Physical Health Component Score; TIM: targeted immune modulator.

Comparative Effectiveness (Key Question 1)

Five RCTs[15,24,34,44,45] reported comparative efficacy outcomes for 5 different head-to-head TIM comparisons. All studies enrolled participants with active psoriatic arthritis. We rated 1 RCT as of poor methodological quality because of inadequate reporting of methods, differences in baseline characteristics between groups, and lack of adequate statistical analysis.[34] We rated another RCT as of poor methodological quality because of inadequate reporting of randomization method and allocation concealment, unstandardized agents and doses in the comparison group, and lack of blinding.[15] We rated the remaining RCTs as fair methodological quality for industry sponsorship and extensive manufacturer involvement. In this section we describe efficacy findings organized by drug comparisons. Table 9 provides a brief summary of this evidence base and findings. Appendix B, Tables B1 and B2 provide detailed study characteristics and results, and Appendix D describes outcome measures used in included RCTs.

Adalimumab Compared to Etanercept and Infliximab

We did not identify any new RCTs for this update. The previous review included 1 poor-methodological-quality, head-to-head randomized trial comparing adalimumab with etanercept and infliximab.[34] In this 12-month trial, 100 patients were randomized to receive 40 mg adalimumab every other week, 25 mg etanercept twice per week, or 5 mg/kg infliximab every 6-to-8 weeks. An induction regimen for infliximab was not described and the source of study sponsorship was not disclosed. Dose adjustment was permitted for infliximab in this trial. Patients who had previously trialed anti-TNF-α drugs were excluded, as were patients taking more than 10 mg prednisolone daily or requiring increasing amounts of NSAIDs. The FDA-approved dose for etanercept is 50 mg twice weekly.

The methodological quality of this trial was difficult to assess because of poor reporting. Neither the method of randomization nor the method of allocation concealment is described. The authors do not declare which outcomes are primary or secondary, nor do they conduct any statistical adjustment for the baseline differences in the groups (the infliximab group had less severe joint disease at baseline, and the etanercept group had more severe skin disease).

The outcomes assessed in this trial were not designated as “primary” or “secondary” but included: ACR20 response, PASI, HAQ, tender joint count, and swollen joint count. Efficacy results indicated that the 3 groups experienced no difference in improvements. The proportion of patients achieving an ACR20 response at 12 months was: adalimumab 70%; etanercept 72%; infliximab 75% (*P* value NR). The authors report on other outcomes, but they do not say whether adjustment for multiple testing was performed, and they do not adjust for differences in baseline characteristics of the groups, so these results are not reliable. The authors observed no statistically significant differences in the median number of tender joints (*P* = .12), swollen joints

(*P* = .23), or HAQ (*P* = .60). Significant differences in median PASI at 1 year were observed (etanercept 2, adalimumab 0.1, infliximab 0; *P* < .01).

Adalimumab Compared to Ixekizumab

We did not identify any new RCTs for this update. The previous review included a phase 3 RCT (SPIRIT-P1) that compared patients treated with adalimumab (40 mg every 2 weeks) with patients receiving 1 of 2 regimens of ixekizumab (80 mg every 2 weeks or 80 mg every 4 weeks, both after initial loading dose of 160 mg) or placebo.[44] The trial enrolled 417 TIM-naïve patients with moderate-to-severe psoriatic arthritis for more than 24 weeks. More than half of the patients in each arm had concomitant use of methotrexate. The manufacturer of ixekizumab funded the study, and we rated it as of fair methodological quality because of extensive manufacturer involvement in the study design, execution, and reporting.

No statistical testing was conducted among the active treatment study groups as the primary study aim was to compare ixekizumab to placebo. The ACR20 response rate at 24 weeks (primary study endpoint) was 57% in the adalimumab group compared to 62% in the ixekizumab every 2-week group and 58% in the ixekizumab every 4-week group.[44] A similar pattern of results was observed for secondary measures of remission and improvement (ACR70, ACR50, PASI 75, PASI 90, PASI 100, and HAQ). The percent change in BSA involvement was not different across groups (-10% vs. -11% vs. -12%).

Adalimumab Compared to Remtolumab

We identified 1 new phase 2 RCT for this update.[24] This study enrolled 240 participants with psoriatic arthritis for at least 3 months and compared adalimumab (40 mg every other week) to 120 mg or 240 of remtolumab every week, or placebo. Remtolumab is a pipeline drug and is not yet FDA-approved for the treatment of psoriatic arthritis. This study was primarily designed to evaluate remtolumab compared to placebo; it was not designed for comparative effectiveness evaluation but did report comparative effectiveness outcomes. The manufacturer of remtolumab funded the study, and we rated it as fair methodological quality because of extensive manufacturer involvement in the study design, execution, and reporting. The primary study endpoints were ACR20 response; secondary endpoints included ACR50, ACR70, Disease Activity Score (DAS28-hsCRP), PASI 50, PASI 75, and HAQ-S (HAQ modified for spondyloarthritides).

Study authors observed no difference in ACR20 response between either dose of remtolumab and adalimumab (*ARD, 6.0 percentage points; 95% CI, -21.0 to 9.2* for 120-mg dosage; *ARD*, 5.9 percentage points; 95% CI, -8.5 to 19.9 for 240-mg dosage).[24] However, remtolumab 240 mg was more effective than adalimumab as measured by ACR70, ACR50 and PASI 75, but PASI 90 responses were not statistically different. Study authors observed similar changes in the HAQ-S measure from baseline across groups (-0.58 for placebo vs. -0.56 for 120-mg dosage vs. -0.55 for 240-mg dosage).

Adalimumab Compared to Tofacitinib

We did not identify any new RCTs for this update. The previous review included 1 multicenter, phase 3 RCT (OPAL Broaden) that compared adalimumab with 2 regimens of tofacitinib (5 mg twice daily and 10 mg twice daily), or placebo.[45] Patients had not previously tried TNF-α

inhibitors but had experienced treatment failure with a DMARD. More than 75% of patients used concomitant methotrexate. The manufacturer of tofacitinib funded the study, and we rated it as fair methodological quality because of extensive manufacturer involvement in the study design, execution, and reporting. The FDA-approved dose of tofacitinib is 5 mg twice daily.

This trial was designed to evaluate superiority of tofacitinib compared to placebo; it was not designed to show superiority or non-inferiority between the active drug groups and no statistical testing was conducted among active treatment groups. The ACR20 response at 12 months was 60% in the adalimumab group vs. 70% in the tofacitinib 10 mg group and 68% in the tofacitinib 5 mg group.[45] The ACR50 and ACR70 and PASI 75 responses at 12 months followed a similar pattern. Post-hoc analyses of most patient-reported outcomes at month 3 (pain VAS, SF-36, Functional Assessment of Chronic Illness Therapy [FACIT] fatigue, European Quality of Life-VAS) also showed a similar pattern.[79]

Ustekinumab Compared to TNF-α Inhibitors

We identified 1 new RCT for this update.[15] This study enrolled 47 participants with psoriatic arthritis and active enthesitis. The authors describe the study designed as "prospective observational trial"; however, authors reported that participants were randomized to either 45 or 90 mg of ustekinumab (depending on body weight at weeks 0, 4, 12, and 24) or to standard approved doses of TNF-α inhibitors (the selection of TNF-α inhibitor was left up to the participant based on preferred route and frequency of administration). German governmental agencies funded this study. We rated this study as poor methodological quality because of the paucity of information related to randomization and allocation concealment, self-selection of agents in the TNF-α inhibitors comparison group, and the lack of blinding among participants and investigators. The primary study endpoint was a change in the Spondyloarthritis Research Consortium of Canada Enthesitis Index (SPARCC EI) and complete remission (0 on the SPARCC EI) at week 24. Numerous secondary endpoints were evaluated, including other measures of enthesitis (question 4 on the Bath Ankylosing Spondylitis Disease Activity Index [BASDAI], Leeds Enthesitis Index [LEI], Maastricht Ankylosing Spondylitis Enthesitis Score[MASES]), measures of arthritis (Bath Ankylosing Spondylitis Function Index [BASFI], swollen joint count, tender joint count, Disease Activity Index for Psoriatic Arthritis [DAPSA], VAS pain and global disease), skin and nail involvement (PASI 90, PASI 100, nail psoriasis and severity index [NAPSI]), functional impairment and related symptoms (HAQ, FACIT fatigue), and QoL (SF-36 PCS and MCS).

Ustekinumab was superior to TNF-α inhibitors for achieving complete enthesitis remission at 24 weeks as measured by SPARCC EI score of 0 (74% vs. 42%; $P = .02$).[15] Similar findings were observed on other measures of enthesitis (LEI, MASES, question 4 of BASDAI). No significant differences were observed in achieving complete remission of arthritis symptoms as measured by tender or swollen joint count. Ustekinumab treated patients had a larger response on measures of psoriasis activity in skin (PASI 100: 50% vs. 29%; $P = .04$) and nails, and in the PCS component of the SF-36 (but not the MCS component).[15]

Table 9. Evidence Table for Efficacy Outcomes in Adults for TIMs for Psoriatic Arthritis (Brief Version)

Authors, Year (Trial Name)	Study Design	Number of Patients	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Study Quality
Adalimumab Compared to Etanercept Compared to Infliximab									
Atteno et al., 2010[34]	RCT	100	12 months	Adalimumab 40 mg every 2 weeks vs. etanercept 25 mg twice weekly vs. infliximab 5 mg/kg every 6 to 8 weeks	HAQ, PASI, TJC, SJC, ACR20, AEs[a]		Adults with psoriatic arthritis with an inadequate response to DMARDs	Similar ACR20, HAQ, TJC, SJC response rates between groups; some differences in median PASI response	Poor
Adalimumab Compared to Ixekizumab									
Mease et al., 2017[44] (SPIRIT-P1)	RCT	417	24 weeks	Adalimumab 40 mg every 2 weeks vs. ixekizumab 80 mg every 2 weeks[b] vs. ixekizumab 80 mg every 4 weeks[b]	ACR20	ACR50, ACR70, PASI 75, BSA, HAQ, mTSS, DAS28-CRP, PASI 90, PASI 100	TIM-naïve patients with active psoriatic arthritis	Numerically highest responses across measures for ixekizumab every 2 weeks, followed by ixekizumab every 4 weeks, then adalimumab but no statistical testing conducted[c]	Fair
Adalimumab Compared to Remtolumab Compared to Placebo									
Mease et al., 2018[24]	RCT	240	12 weeks	Adalimumab 40 mg every 2 weeks vs. remtolumab 120 mg every week vs. remtolumab 240 mg every week vs. placebo	ACR20	ACR50, ACR70, DAS28-hsCRP, PASI 50, PASI 75, HAQ-S	Adults with active psoriatic arthritis for at least 3 months	Both doses of remtolumab more effective than placebo. Larger improvements on most but not all measures for 240-mg dosage compared to adalimumab; no difference for 120-mg dosages on all outcomes.	Fair

Authors, Year (Trial Name)	Study Design	Number of Patients	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Study Quality
Adalimumab Compared to Tofacitinib									
Mease et al., 2017[45] (OPAL Broaden)	RCT	422	12 months	Adalimumab 40 mg every 2 weeks vs. tofacitinib 5 mg twice daily vs. tofacitinib 10 mg twice daily	ACR20, HAQ	ACR50, ACR70, PASI 75, LEI, BSA, mTSS, DAS28-CRP, FACIT-F, SF-36, EQ-VAS	Adults with psoriatic arthritis with an inadequate response to DMARDs	Numerically highest responses across measures for tofacitinib 10 mg group, but no statistical testing conducted[d]	Fair
Ustekinumab Compared to TNF-α Inhibitor									
Araujo et al., 2019[15] (ECLIPSA)	RCT	47	24 weeks	Ustekinumab 45 mg or 90 mg[e] vs. TNF-α inhibitor per patient's choice at standard approved doses	SPARCC EI change, SPARCC EI 0	MASES, LEI, PASI 90, TJC, SJC, DAS, DAPSA, PASI 100, NAPSI, BASDAI, BASFI, VAS pain and global disease activity, SF-36 PCS and MCS, HAQ, FACIT-F	Adults with psoriatic arthritis with active enthesitis	Ustekinumab more effective than TNF-α inhibitor therapy on measures of enthesitis and skin disease, no significant differences on measures of arthritis	Poor

Authors, Year (Trial Name)	Study Design	Number of Patients	Duration	Comparisons	Primary Outcome	Secondary Outcomes	Population	Results	Study Quality
Pipeline Agent: Filgotinib Compared to Placebo									
Mease et al.; 2018[25] (EQUATOR)	RCT	131	16 weeks	Filgotinib 200 mg daily vs. placebo daily	ACR20	ACR50, ACR70, DAS28, PsARC, MDA; SPARCC EI, PASI 75, NPASI, pruritus NRS, HAQ, FACIT-F	Adults with active moderate-to-severe psoriatic arthritis ≥12 weeks' duration	Filgotinib more effective than placebo on all outcomes	Fair

Notes. [a] *Article did not distinguish between primary and secondary outcomes.* [b] *After an initial loading dose of 160 mg at week 0.* [c] *The primary study aim was to compare ixekizumab to placebo; statistical significance testing between active arms was not conducted.* [d] *The primary study aim was to compare tofacitinib to placebo; statistical significance testing between active arms was not conducted.* [e] *Dose was 45 mg if body weight was ≤ 100 kg and dose was 90 mg if body weight > 100 kg. Abbreviations. AE: adverse event; ACR: American College of Rheumatology; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Function Index; BSA: percentage of psoriasis-affected Body Surface Area; DAPSA: Disease Activity Index for Psoriatic Arthritis; DAS: Disease Activity Score; DAS28-CRP: 28 joint Disease Activity Score using C-reactive protein; DMARD: disease-modifying antirheumatic drug; EQ-VAS: European Quality of Life - Visual Analog Scale; FACIT-F: Functional assessment of Chronic Illness Therapy-Fatigue; HAQ: Health Assessment Questionnaire; HAQ-S: Health Assessment Questionnaire for the Spondyloarthropathies; LEI: Leeds Enthesitis Index; MASES: Maastrict Ankylosing Spondylitis Enthesitis Score; MDA: Minimal Disease Activity; mTSS: modified Total Sharp Score; NAPSI: nail psoriasis severity index; PASI: Psoriasis Area and Severity Index; PsARC: Psoriatic Arthritis Response criteria; NRS: Numeric Rating Scale; RCT: randomized controlled trial; SF-36 MCS: Short Form Survey Mental Health Component Score; SF-36 PCS: Short Form Survey Physical Health Component Score; SJC: swollen joint count; SPARCC EI: Spondylarthritis Research Consortium of Canada Enthesitis Index; TIM: targeted immune modulator; TJC: tender joint count; TNF-α: tumor necrosis factor alpha.*

Comparative Harms (Key Question 2)

Four RCTs[24,34,44,45] that reported efficacy outcomes for Key Question 1 also reported comparative harm outcomes. In addition, 2 cohort studies reported harm outcomes.[22,41]

Harms Reported in RCTs

Table 10 summarizes high-level findings for harms from 4 RCTs that reported the outcomes. Detailed findings are summarized in Table 11. Overall, we observed very few differences in head-to-head comparisons of TIM agents for overall AEs, SAEs, and withdrawals due to AEs. Thus, this narrative section will only highlight comparisons for which study authors observed at least 1 statistically significant difference in a harm outcome between agents.

In 1 poor-methodological-quality RCT, adalimumab had statistically significantly fewer overall AEs compared to etanercept (RR, 0.38; 95% CI, 0.17 to 0.84) and compared to infliximab (RR, 0.23; 95% CI, 0.11 to 0.49).[34] Infliximab had more overall AEs compared to etanercept (RR, 1.6; 95% CI, 1.1 to 2.4). In this study only 2 SAEs were reported, both in the infliximab group, and withdrawals due to AEs were not reported.

Harms Reported in Cohort Studies

We identified 1 new fair-methodological-quality cohort study for this update.[22] The previous review included 1 poor-methodological-quality cohort study.[41] Findings from these studies are summarized in Table 12.

Lee et al. used insurance claims to identify adults with psoriasis or psoriatic arthritis who initiated therapy with ustekinumab or a TNF-α inhibitor between 2009 and 2015.[22] No significant differences were observed for incident atrial fibrillation or major cardiovascular events.[22] Kisacik et al. identified patients with various rheumatologic conditions, including psoriatic arthritis, from a Turkish patient registry.[41] Study authors reported a significantly higher risk for tuberculosis with infliximab (1.3%) compared to etanercept (0.3%) or adalimumab (0.6%).[41]

Table 10. Summary of Adverse Events from RCTs in Adults Receiving TIMs for Psoriatic Arthritis

Authors, Year (Trial Name)	Number of Patients	Duration	Results	Study Quality
Adalimumab Compared to Infliximab Compared to Etanercept				
Atteno et al., 2010[34]	100	12 months	Incidence of AEs (23% vs. 17% vs. 6%, *P* < .001); adalimumab with significantly lower incidence of AEs than either etanercept or infliximab; infliximab with significantly higher incidence of AEs than etanercept. Withdrawals due to AEs NR; 2 SAEs reported overall, both in the infliximab group. Injection site/infusion reactions NR.	Poor
Adalimumab Compared to Ixekizumab				
Mease et al., 2017[44] SPIRIT-P1	417	24 weeks	Injection site/infusion reactions more frequent with ixekizumab (2.0% vs. 13.9%, RR, 0.14; 95% CI, 0.03 to 0.59). No significant differences in overall AEs, SAEs, or withdrawals due to AEs.	Fair
Adalimumab Compared to Remtolumab				
Mease et al.(2018)[24]	240	12 weeks	No significant differences in AEs, SAEs, or withdrawals due to AEs. No injection site reactions reported in either group.	Fair
Adalimumab Compared to Tofacitinib				
Mease et al., 2017[45] (OPAL Broaden)	422	12 months	No significant differences in AEs, SAEs, or withdrawals due to AEs.	Fair
Filgotinib Compared to Placebo				
Mease et al.(2018)[25] (EQUATOR)	131	16 weeks	No significant differences in AEs, SAEs, or withdrawals due to AEs.	Fair

Abbreviations. AE: adverse event; CI: confidence interval; NR: not reported; RCT: randomized controlled trial; RR: risk ratio; SAE: serious adverse event; TIM: targeted immune modulator.

Table 11. Comparisons of TIMs in RCTs for General Tolerability in Adults with Psoriatic Arthritis

Authors, Year Trial Name	Overall AEs RR (95% CI)	Withdrawals Due to AEs RR (95% CI)	SAEs RR (95% CI)	Injection Site Reactions/ Infusion Reactions RR (95% CI)	Study Quality
Adalimumab Compared to Infliximab Compared to Etanercept					
Atteno et al., 2010[34]	Adalimumab vs. etanercept: 0.38 (0.17 to 0.84)* Adalimumab vs. infliximab: 0.23 (0.11 to 0.49)* Infliximab vs. etanercept: 1.6 (1.1 to 2.4)*	NR	2 events in the infliximab group	NR	Poor
Adalimumab Compared to Ixekizumab					
Mease et al., 2017[44] SPIRIT-P1	0.97 (0.82 to 1.16)	0.69 (0.14 to 3.4)	1.2 (0.40 to 3.3)	0.14 (0.03 to 0.59)	Fair
Adalimumab Compared to Remtolumab					
Mease et al., 2018[24]	Remtolumab 120 mg vs. placebo 1.01 (0.61 to 1.7)* Remtolumab 120 mg vs. adalimumab 0.88 (0.63 to 1.2)* Remtolumab 240 mg vs. placebo 0.93 (0.56 to 1.5)* Remtolumab 240 mg vs. adalimumab 0.80 (0.57 to 1.1)*	Remtolumab 120 mg vs. placebo: 2.73 (0.04 to 170.2)* Remtolumab 240 mg vs. placebo: 0.34 (0.02 to 103.8)* Remtolumab (either dose) vs. adalimumab: 1.5 (0.16 to 14.2)*	Remtolumab 120 mg vs. placebo: 0.08 (0.001 to 6.6)* Remtolumab 120 mg vs. adalimumab 1.01 (0.004 to 256.6)* Remtolumab 240 mg vs. placebo: 0.33 (0.02 to 5.1)* Remtolumab 240 mg vs. adalimumab 4.0 (0.05 to 313.0)*	0 events reported	Fair
Adalimumab Compared to Tofacitinib					
Mease et al., 2017[45] OPAL Broaden	1.1 (0.90 to 1.3)*	0.67 (0.20 to 2.3)*	1.14 (0.46 to 2.8)*	NA (oral agent)	Fair
Filgotinib Compared to Placebo					
Mease et al., 2018[25] EQUATOR	0.96 (0.72 to 1.3)	4.1 (0.05 to 320.7)	1.0 (0.0 to 15.9)	NA (oral agent)	Fair

*Notes: * indicates a calculated value. Abbreviations. AE: adverse event; CI: confidence interval; NA: not applicable; RCT: randomized controlled trial; NR: not reported; RR: risk ratio; SAE: serious adverse event; TIM: targeted immune modulator.*

Table 12. Summary of Observational Studies of AEs in Adults Receiving TIMs for Psoriatic Arthritis

Authors, Year	Number of Patients	Follow-up	Comparison[a]	Population	Results	Study Quality
Kisacik et al., 2016[41]	10,434	NR	Adalimumab Etanercept Infliximab	Ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, Behcet disease identified through a patient a Turkish patient registry	Significantly higher risk for tuberculosis with infliximab than etanercept or adalimumab	Poor
Lee et al., 2019[22]	60,028	Mean (SD) 1.4 (1.3) years, maximum 6.0 years	Ustekinumab TNF-α inhibitors	Adults with psoriasis or psoriatic arthritis who initiated therapy with ustekinumab or a TNF-α inhibitor identified through U.S. insurance claims between 2009 and 2015	No significant difference for incident atrial fibrillation or major cardiovascular events comparing ustekinumab with TNF-α inhibitors	Fair

Note. [a] Dosages not reported. Abbreviations. AE: adverse event; NR: not reported; SD: standard deviation; TIM: targeted immune modulator; TNF-α: tumor necrosis factor alpha.

Efficacy and Harms of Pipeline TIM Agents for Psoriatic Arthritis

We identified 2 RCTs,[24,25] both new to this update, that reported on the efficacy and harms of 2 pipeline TIM agent: filgotinib and remtolumab. Table 13 shows the Summary of Findings (GRADE) for the comparison of these agents to placebo. Tables 9, 10, and 11 provide a summary of this evidence base and summarizes the findings. Appendix B, Tables B1 and B2 provide detailed study characteristics and results, and Appendix D describes efficacy outcome measures used. We rated both studies as fair-methodologic quality because of industry sponsorship and extensive manufacturer involvement in study design, reporting, and execution.

Table 13. Summary of Findings (GRADE) of Pipeline TIMs in Adults for Psoriatic Arthritis

Outcome	Quality of Evidence	Relationship[a]
Filgotinib Compared to Placebo		
Clinical improvement (1 RCT)	●●○○ (low)	Favors filgotinib
Disease remission (1 RCT)	●●○○ (low)	Favors filgotinib
Skin disease remission (1 RCT)	●●○○ (low)	Favors filgotinib
AEs (1 RCT)	●●○○ (low)	No difference
SAEs (1 RCT)	●○○○ (very low)	Uncertain
Remtolumab Compared to Placebo		
Disease remission (1 RCT)	●●●○ (moderate)	Favors remtolumab
Clinical improvement (1 RCT)	●●●○ (moderate)	Favors remtolumab
Quality of life (1 RCT)	●●○○ (low)	Favors remtolumab
AEs (1 RCT)	●●○○ (low)	No difference
SAEs (1 RCT)	●○○○ (very low)	Uncertain

Note. [a] For efficacy outcomes, 'favors' refers to a larger improvement compared to the comparator; for harm outcomes, 'favors' refers to a lower incidence of harm relative to the comparator. Abbreviations. AE: adverse event; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; RCT: randomized controlled trial; SAE: serious adverse event; TIM: targeted immune modulator.

Filgotinib Compared to Placebo

We identified 1 new, fair-methodological quality, phase 2 RCT (EQUATOR) for this update.[25] This study enrolled 131 participants with moderate-to-severe psoriatic arthritis and compared 200 mg of daily filgotinib with placebo over 16 weeks. The primary study endpoint was ACR20 response at 16 weeks; secondary outcomes included ACR50 and ACR70 response, DAPSA, Psoriatic Arthritis Response Criteria (PsARC) response, Psoriatic Arthritis Disease Activity Score (PASDAS), PASI 75, SPARCC EI, itch NRS, HAQ, FACIT fatigue, and psoriatic arthritis-related pain intensity.

For efficacy outcomes, a higher proportion of participants randomized to filgotinib (80%) had an ACR20 response compared to placebo (33%; $P < .001$).[25] Filgotinib was also superior to placebo on all secondary remission and clinical improvement outcomes. For harms, no statistically significant difference was observed for overall AEs, SAEs, or withdrawals due to AEs, though findings were very imprecise for the latter 2 outcomes.

Remtolumab compared to Placebo

We identified 1 new, fair-methodological quality RCT for this update.[24] This phase 2 study enrolled 240 participants with psoriatic arthritis for at least 3 months and compared adalimumab (40 mg every other week) to 120 mg or 240 of remtolumab every week, or placebo over 12 weeks. Remtolumab is a pipeline drug and is not yet FDA-approved for the treatment of psoriatic arthritis. This study was primarily designed to evaluate remtolumab compared to placebo and we reported the findings for the adalimumab vs. remtolumab comparison in the previous section. The primary study endpoints were ACR20 response; secondary endpoints included ACR50, ACR70, DAS28-hsCRP, PASI 50, PASI 76, and HAQ-S.

Remtolumab was more effective than placebo on most all disease remission and clinical improvement outcomes reported. With respect to clinical improvement, a higher percentage of participants achieved an ACR50 response with both doses of remtolumab (37% and 53% for the 120 mg and 240 mg dosages respectively) compared to placebo (13%; $P < .05$ and $P < .001$ respectively). With respect to remission, the percentage of participants achieving an ACR70 response was higher in both doses of remtolumab (23% for 120 mg dosage, 32% for 240 mg dosage) compared to placebo (4%; $P < .05$ for 120 mg dosage and $P < .01$ for 240 mg dosage). Participants randomized to remtolumab also experienced larger improvements on the HAQ-S QoL measure compared to placebo, but statistical significance testing was not conducted by study authors. Among participants with more than 3% BSA involvement from psoriasis, participants randomized to either dose of remtolumab also achieved a larger PASI 75 response compared to placebo ($P < .01$ for both doses) but no statistically significant difference was observed in the PASI 90 response. With respect to harms no statistically significant differences were observed for either dose for treatment-emergent AEs, SAEs, or withdrawals due to AEs though findings for the latter 2 outcomes were very imprecise.

Ongoing Studies

We identified 30 ongoing studies evaluating the comparative effectiveness or harms of TIM agents (Tables 14, 15, and 16). Twenty-three of these studies are RCTs and 7 are observational studies. Seventeen RCTs are in participants with plaque psoriasis and 6 are in participants with psoriatic arthritis. Two observational studies are in participants with plaque psoriasis, 3 are in participants with psoriatic arthritis, and 2 studies include participants with either condition. Drug manufacturers are funding 27 studies, hospitals are funding 2 studies, and the NIH is funding 1 study.

Table 14. Ongoing RCTs of TIMs for Plaque Psoriasis

Registration Number Trial Name Phase	Treatment Groups; Blinded vs. Open Label	N Enrollment; Treatment Duration	Study Completion Date[a]	Primary Outcome(s)
Ustekinumab Compared to Abatacept				
NCT01999868 Efficacy of Ustekinumab Followed by Abatacept for the Treatment of Psoriasis Vulgaris (PAUSE) Phase 2	Ustekinumab Abatacept Blinded	N = 108 88 weeks	March 2018	Percentage of patients with psoriasis relapse
BI 695501 Compared to Adalimumab				
NCT02850965 Efficacy, Safety and Immunogenicity of BI 695501 Versus Humira in Patients With Moderate-to-severe Chronic Plaque Psoriasis Phase 3	BI 695501 Adalimumab Blinded	N= 318 16 weeks	January 2018	PASI 75
Mirikizumab Compared to Placebo				
NCT03482011 A Study to Evaluate the Efficacy and Safety of Mirikizumab (LY3074828) in Participants With Moderate-to-Severe Plaque Psoriasis (OASIS-1) Phase 3	Placebo Mirikizumab Blinded	N = 689 (Estimated) 16 weeks	February 2020 (Estimated)	PGA PASI 90
BMS-986165 Compared to Placebo[b]				
NCT03881059 Efficacy and Safety of BMS-986165 Compared With Placebo in Participants With Active Psoriatic Arthritis (PsA) Phase 2	Placebo BMS-986165 Blinded	N = 180 (Estimated) 16 weeks	December 2020	ACR20
BMS-986165 Compared to Apremilast				
NCT03611751 An Investigational Study to Evaluate Experimental Medication BMS-986165 Compared to Placebo and a Currently Available Treatment in Participants With Moderate-to-Severe Plaque Psoriasis (POETYK-PSO-2) Phase 3	Placebo BMS-986165 Apremilast Blinded	N = 1000 (Estimated) 16 weeks	July 2020 (Estimated)	PGA PASI 75

Registration Number Trial Name Phase	Treatment Groups; Blinded vs. Open Label	N Enrollment; Treatment Duration	Study Completion Date[a]	Primary Outcome(s)
NCT03624127 An Investigational Study to Evaluate Experimental Medication BMS-986165 Compared to Placebo and a Currently Available Treatment in Participants With Moderate-to-severe Plaque Psoriasis (POETYK-PSO-1) Phase 3	Placebo BMS-986165 Apremilast Blinded	N = 600 (Estimated) 16 weeks	July 2020 (Estimated)	PGA (0,1) PASI 75
Bimekizumab Compared to Placebo				
NCT03025542 Study to Evaluate the Pharmacokinetic (PK), Pharmacodynamics (PD), and Safety of Bimekizumab in Patients With Chronic Plaque Psoriasis Phase 2	Placebo Bimekizumab Blinded	N = 49 16 weeks	December 2017	Change in PASI from baseline Adverse events
NCT03010527 A Study to Evaluate the Long-term Safety, Tolerability and Efficacy of Bimekizumab in Patients With Chronic Plaque Psoriasis (BE-ABLE 2) Phase 2	Placebo Bimekizumab (3 doses) Blinded	N = 217 64 weeks	September 2018	Adverse events
NCT03410992 A Study With an Initial Treatment Period Followed by a Randomized-withdrawal Period to Evaluate the Efficacy and Safety of Bimekizumab in Adult Subjects With Moderate-to-severe Chronic Plaque Psoriasis (BE READY) Phase 3	Placebo Bimekizumab Blinded	N = 435 16 weeks	January 2020 (Estimated)	PASI 90 IGA
Bimekizumab Compared to Ustekinumab				
NCT03370133 A Study to Evaluate the Efficacy and Safety of Bimekizumab Compared to Placebo and an Active Comparator in Adult Subjects With Moderate to Severe Chronic Plaque Psoriasis (BE VIVID) Phase 3	Placebo Bimekizumab Ustekinumab Blinded	N = 570 52 weeks	January 2020 (Estimated)	PASI 90 IGA

Registration Number Trial Name Phase	Treatment Groups; Blinded vs. Open Label	N Enrollment; Treatment Duration	Study Completion Date[a]	Primary Outcome(s)
Bimekizumab Compared to Adalimumab[b]				
NCT03412747 A Study to Evaluate the Efficacy and Safety of Bimekizumab in Adult Subjects With Moderate to Severe Chronic Plaque Psoriasis (BE SURE) Phase 3	Bimekizumab (2 doses) Adalimumab Blinded	N = 480 16 weeks	March 2020 (Estimated)	PASI 90 IGA
NCT03895203 A Study to Test the Efficacy and Safety of Bimekizumab in the Treatment of Subjects With Active Psoriatic Arthritis (BE OPTIMAL) Phase 3	Placebo Bimekizumab Adalimumab Blinded	N = 840 (Estimated) 16 weeks	May 2022	ACR50
Bimekizumab Compared to Secukinumab				
NCT03536884 A Study to Evaluate the Efficacy and Safety of Bimekizumab Compared to an Active Comparator in Adult Subjects With Moderate to Severe Chronic Plaque Psoriasis (BE RADIANT) Phase 3	Placebo Bimekizumab (2 doses) Secukinumab Blinded	N = 743 16 weeks	May 2022 (Estimated)	PASI 100
M1095 Compared to Secukinumab				
NCT03384745 A Phase 2b Study of the Efficacy, Safety, and Tolerability of M1095 in Subjects With Moderate to Severe Psoriasis Phase 2	Placebo M1095 (30, 60, and 120-mg dosages) Secukinumab (300 mg)	N = 300 12 weeks	August 2020 (Estimated)	IGA
Risankizumab Compared to Secukinumab				
NCT03478787 Risankizumab Versus Secukinumab for Subjects With Moderate to Severe Plaque Psoriasis Phase 3	Risankizumab Secukinumab Open Label	N = 327 52 weeks	February 2020 (Estimated)	PASI 90

Registration Number Trial Name Phase	Treatment Groups; Blinded vs. Open Label	N Enrollment; Treatment Duration	Study Completion Date[a]	Primary Outcome(s)
Mirikizumab Compared to Secukinumab				
NCT03535194 A Study to Assess if Mirikizumab is Effective and Safe Compared to Secukinumab and Placebo in Moderate to Severe Plaque Psoriasis (OASIS-2) Phase 3	Placebo Mirikizumab Secukinumab	N = 1443 (Estimated) 16 weeks	December 2020 (Estimated)	PGA PASI 90
Ixekizumab Compared to Guselkumab				
NCT03573323 A Study of Ixekizumab (LY2439821) Compared to Guselkumab in Participants With Moderate-to-Severe Plaque Psoriasis (IXORA-R) Phase 4	Ixekizumab Guselkumab Blinded	N = 960 12 weeks	December 2019	PASI 100

Notes. [a] As reported in ClinicalTrials.gov registry. [b] Study included participants with plaque psoriasis and psoriatic arthritis. Abbreviations. ACR: American College of Rheumatology percentage improvement; IGA: Investigator's Global Assessment; N: number of patients; NCT: U.S. National Clinical Trial; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment; RCT: randomized controlled trial; TIM: targeted immune modulator.

Table 15. Ongoing RCTs of TIMs for Psoriatic Arthritis

Registration Number Trial Name Phase	Treatment Groups; Blinded vs. Open Label	N Enrollment Treatment Duration	Study Completion Date[a]	Primary Outcome(s)
Secukinumab Compared to Adalimumab				
NCT02745080 Efficacy of Secukinumab Compared to Adalimumab in Patients With Psoriatic Arthritis (EXCEED) Phase 3	Secukinumab (300 mg) Adalimumab (40 mg) Blinded	N = 850 52 weeks	December 2019	ACR20
BMS-986165 Compared to Placebo[b]				
NCT03881059 Efficacy and Safety of BMS-986165 Compared With Placebo in Participants With Active Psoriatic Arthritis (PsA) Phase 2	Placebo BMS-986165 Blinded	N = 180 (Estimated) 16 weeks	December 2020	ACR20
Bizmekizumab Compared to Placebo				
NCT02969525 A Multicenter Study to Evaluate the Dose Response Based on the Efficacy, Safety and Tolerability of Bimekizumab in Subjects With Active Psoriatic Arthritis Which is a Type of Inflammatory Arthritis Phase 2	Placebo Bimekizumab (4 doses)	N = 206 12 weeks	July 2018	ACR50
NCT03896581 A Study to Evaluate the Efficacy and Safety of Bimekizumab in the Treatment of Subjects With Active Psoriatic Arthritis (BE COMPLETE) Phase 3	Placebo Bimekizumab Blinded	N = 380 (Estimated) 16 weeks	May 2021 (Estimated)	ACR50
Bizmekizumab Compared to Adalimumab[b]				
NCT03412747 A Study to Evaluate the Efficacy and Safety of Bimekizumab in Adult Subjects With Moderate to Severe Chronic Plaque Psoriasis (BE SURE) Phase 3	Bimekizumab (2 doses) Adalimumab Blinded	N = 480 16 weeks	March 2020 (Estimated)	PASI 90 IGA

Registration Number Trial Name Phase	Treatment Groups; Blinded vs. Open Label	N Enrollment Treatment Duration	Study Completion Date[a]	Primary Outcome(s)
NCT03895203 A Study to Test the Efficacy and Safety of Bimekizumab in the Treatment of Subjects With Active Psoriatic Arthritis (BE OPTIMAL) Phase 3	Placebo Bimekizumab Adalimumab Blinded	N = 840 (Estimated) 16 weeks	May 2022	ACR50
Ixekizumab Compared to Adalimumab				
NCT03151551 A Study of Ixekizumab (LY2439821) Versus Adalimumab in Participants With Psoriatic Arthritis (SPIRIT-H2H) Phase 4	Ixekizumab (80 mg) Adalimumab (80 mg) Blinded	N = 566 52 weeks	September 2019	ACR50 PASI 100
Upadacitinib Compared to Placebo				
NCT03104374 A Study Comparing Upadacitinib (ABT-494) to Placebo in Participants With Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Biologic Disease-Modifying Anti-Rheumatic Drug (SELECT – PsA2 2) Phase 3	Placebo Upadacitinib	N = 642 12 weeks	April 2022 (Estimated)	ACR20 ACR50 IGA PASI 75 MDA HAQ-DI
NCT03104400 A Study Comparing Upadacitinib (ABT-494) to Placebo and to Adalimumab in Participants With Psoriatic Arthritis Who Have an Inadequate Response to at Least One Non-Biologic Disease-Modifying Anti-Rheumatic Drug (SELECT-PsA 1) Phase 3	Placebo Upadacitinib	N = 1705 12 weeks	August 2022 (Estimated)	ACR20 HAQ-DI IGA PASI 75 MDA ACR50 ACR70

Notes. [a] *As reported in ClinicalTrials.gov registry.* [b] *Study included participants with both plaque psoriasis and psoriatic arthritis. Abbreviations. ACR: American College of Rheumatology percentage improvement; HAQ-DI: Health Assessment Questionnaire-Disability Index; IGA: Investigator's Global Assessment; MDA: minimal disease activity; N: number of patients; NCT: U.S. National Clinical Trial; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; TIM: targeted immune modulator.*

Table 16. Ongoing Cohort Studies of TIMs for Plaque Psoriasis or Psoriatic Arthritis

Registration Number Study Name	Treatment Groups	N Enrollment Treatment Duration	Study Completion Date[a]	Primary Outcome(s)
Various Biologic Treatments Evaluated Through Cohort Studies				
NCT01965132 Korean College of Rheumatology Biologics Registry KOBIO	Etanercept Adalimumab Infliximab Golimumab Tolcilizumab Abatacept Rituximab Ustekinumab Secukinumab	N = 3,500 (Estimated) Up to 5 years	June 2023 (Estimated)	AEs
NCT02075697 Spanish Registry of Systemic Treatments in Psoriasis Biobadaderm	Biologic therapy, apremilast of fumarates Nonbiological systemic treatment (methotrexate, cyclosporine and acitretin)	N = 3500 (Estimated) 5 years	October 2025	SAEs
NCT03496831 Predicting Hospitalized Infection in Patients With Chronic Inflammatory Arthritis Treated With Biological Drugs	Abatacept Adalimumab Anakinra Certolizumab Etanercept Golimumab Infliximab Rituximab Secukinumab Tocilizumab Ustekinumab	N = 7500 (Estimated) 12 months	December 2017	Hospitalized infection or death
NCT00508547 Psoriasis Longitudinal Assessment and Registry PSOLAR	Guselkumab Infliximab Ustekinumab Biological therapies other than infliximab, ustekinumab, and guselkumab Conventional systemic agents	N = 16,000 (Estimated) 8 years	April 2030 (Estimated)	AEs SAEs
NCT00741793 Biologic Treatment Registry Across Canada BioTRAC	Infliximab Golimumab Ustekinumab	N = 2821 Up to 4 years	June 2018	Disease status
NCT01848028 PsoBest – The German Psoriasis Registry	Fumaric acid ester Methotrexate Cyclosporine A Etanercept Infliximab	N = 3,500 (Estimated) 10 years	July 2026 (Estimated)	PASI

Registration Number Study Name	Treatment Groups	N Enrollment Treatment Duration	Study Completion Date[a]	Primary Outcome(s)
	Adalimumab Ustekinumab Golimumab Secukinumab Apremilast Certolizumab Retinoids Leflunomids Systemic PUVA			
NCT01081730 Ustekinumab Safety and Surveillance Program Using the Ingenix NHI Database	Ustekinumab Anti-TNF biologics Non-anti-TNF biologics Nonbiological treatments	N = 2,040 Up to 8 years	September 2017	Serious infections, tuberculosis and non-TB mycobacterial infections, malignancies, and other selected outcomes

Notes. [a] As reported in ClinicalTrials.gov registry. Abbreviations. AE: adverse events; N: number of patients; NCT: U.S. National Clinical Trial; PASI: Psoriasis Area and Severity Index; PUVA: psoralen ultraviolet A therapy; SAE: serious adverse events; TB: tuberculosis; TIM: targeted immune modulator; TNF: tumor necrosis factor.

Discussion

For plaque psoriasis, the largest body of comparative evidence is for etanercept and ustekinumab compared to other TIM agents. With respect to disease remission outcomes, high-quality evidence suggests that etanercept is less effective than ixekizumab, secukinumab, and tildrakizumab. Very low- to low-quality evidence also suggests that etanercept is less effective than ustekinumab and probably not significantly different compared to apremilast with respect to disease remission. High-quality evidence suggests that ustekinumab is less effective than brodalumab and risankizumab and moderate-quality evidence suggests it may also be less effective than ixekizumab with respect to disease remission. Only 3 additional head-to-head comparisons were identified. High quality-evidence suggests that adalimumab is less effective than guselkumab and moderate-quality evidence suggests that it is also less effective than risankizumab for disease remission. Finally, moderate-quality evidence suggests that guselkumab is more effective than secukinumab for maintenance therapy. Clinical improvement and QoL outcomes typically mirrored disease remission outcomes in most, but not all, studies. With 2 exceptions, outcomes with at least low-quality evidence did not identify any differences in AEs or SAEs for any head-to-head comparisons. Moderate-quality evidence suggests that the 3 pipeline TIM agents included in this report (bimekizumab, BMS-9865165, and mirikizumab) are more effective compared to placebo, but no comparative studies were identified. With respect to harms, findings were inconsistent or imprecise across the pipeline agents.

For psoriatic arthritis, limited head-to-head comparisons were available. Ixekizumab, tofacitinib, and remtolumab may be more effective than adalimumab, though none of the efficacy outcomes were rated better than low-quality evidence. Further, very low- to low-quality evidence suggests no difference in harms between adalimumab and ixekizumab, tofacitinib, or remtolumab. The bodies of evidence for psoriatic arthritis were generally downgraded by 1 or 2 levels for imprecision, and in some cases also for study limitations. Further, several studies in this body of evidence were primarily designed to assess effectiveness compared to a placebo control and were not designed to evaluate comparative effectiveness. Two pipeline agents were evaluated for use in psoriatic arthritis: filgotinib and remtolumab. Both were more effective than placebo based on low- and moderate-quality evidence, respectively. However, no comparative studies were identified. No differences in harms were observed based on very low- and low-quality evidence. However, some harm outcomes for these pipeline agents were very imprecise precluding a definitive conclusion.

Data from Network Meta-Analyses

We identified several published network meta-analyses (NMA) providing indirect comparisons of TIM agents for plaque psoriasis; we describe findings from the 3 most recent analyses that included a methodological quality assessment for included studies. These analyses include placebo-controlled studies and studies on TIM or non-TIM drugs outside the scope of this update.

The first NMA was a 2017 Cochrane review of systemic pharmacologic treatments for plaque psoriasis which searched the literature through December 2016.[80] This review included 109 RCTs and included conventional systemic therapies (e.g., cyclosporine) in addition to TIM agents. At the class level, anti-IL-17 (secukinumab, ixekizumab, brodalumab), anti-IL-12/23

(ustekinumab), anti-IL-23 (guselkumab, tildrakizumab), and anti-TNF-α (etanercept, infliximab, adalimumab, certolizumab pegol) agents were significantly more effective than the small-molecule TIM agents (apremilast, tofacitinib) and the conventional systemic therapies for disease remission (PASI 90). At the drug level, secukinumab, ixekizumab, brodalumab, and guselkumab were significantly more effective than the anti-TNF-α agents (except for certolizumab pegol), and ustekinumab was significantly more effective than etanercept. No differences were observed between infliximab, adalimumab, and etanercept. The analysis reported that, when compared to placebo, ixekizumab, secukinumab, brodalumab, guselkumab, certolizumab, and ustekinumab outperformed other agents; ixekizumab was the most effective and secukinumab was the next most effective. The analysis also reported no differences (compared to placebo) in the risk of SAEs across all agents (TIMs and conventional medications).

The second NMA (Xu et al.[81]) was published in 2019 and focused on 13 TIM agents (adalimumab, alefacept briakinumab, brodalumab, efalizumab, etanercept, guselkumab, infliximab, itolizumab, ixekizumab, secukinumab, tildrakizumab, ustekinumab) for treatment of plaque psoriasis.[78,81] This review searched the literature through August 2018 and included 54 RCTs. Several TIM agents included in that analysis were not within the scope of this update review (i.e., alefacept, briakinumab, efalizumab, itolizumab). Brodalumab was ranked as most effective as measured by PASI 90 and PASI 100. However, the analysis identified other significant differences in pairwise comparisons; for example, guselkumab and ixekizumab were both more effective than tildrakizumab and ustekinumab as measured by PASI 90 response. This analysis only considered headache, infection, and withdrawals as harms; with 1 exception (withdrawals higher for ixekizumab compared to ustekinumab), no significant pairwise differences in harms were identified.

The third NMA[82] was published in 2019 and focused on comparing short-term efficacy of IL-17 targeted agents (brodalumab, ixekizumab, secukinumab) to IL-23 targeted agents (guselkumab, risankizumab, tildrakizumab) and other biologic and nonbiologic agents for plaque psoriasis. The search was conducted through November 2018 and the analysis included 77 RCTs. At the class level, no significant differences were observed between the IL-17 and IL-23 agents for disease remission outcomes (PASI 75 and PASI 90). At the drug level, many pairwise comparisons were statistically significant, but the magnitude of some of the differences may not be clinically meaningful. Overall, brodalumab, ixekizumab, secukinumab, guselkumab, and risankizumab were more effective than nearly all other agents. Within those 4 agents, brodalumab was more effective than secukinumab but not different from ixekizumab, guselkumab, and risankizumab. Apremilast was inferior to all other agents.

Limitations of the Evidence

Although the evidence base for head-to-head comparisons of TIM agents includes numerous studies, few comparisons were evaluated by more than 1 or 2 studies. Furthermore, gaps remain for specific head-to-head comparisons because of the number of TIM agents that are available. Most RCTs were focused on efficacy outcomes after induction, typically 12 to 16 weeks, and fewer reported outcomes from maintenance therapy. Drug manufacturers sponsored nearly all included RCTs. Although the extent to which the manufacturer's involvement influenced study execution or reporting is not definitively known, findings from a Cochrane systematic review suggest that industry sponsorship is associated with more favorable results than sponsorship by

other sources.[83] Several of the cohort studies that we included used administrative or claims data to evaluate harms, and the validity of this approach for evaluating harms is uncertain.

Limitations of this Review

This review has several limitations. First, we did not include RCTs shorter than 12 weeks in duration, cohort studies with fewer than 1,000 participants, or studies published in languages other than English. We included only studies published in the peer-reviewed literature; we did not use data presented in press releases or conference abstracts. This review represents a cumulative synthesis of the evidence. Thus, studies included in the prior DERP review on this topic were carried forward into this update if they continued to meet eligibility criteria; however, data from these studies were not rechecked against the original sources for accuracy. Further, we did not reevaluate the methodological study quality for the previously included studies, except for RCTs that were previously assessed as good quality. We reassessed these good-quality RCTs to determine the influence of manufacturer involvement on study design and execution for consistency with current Center methodology. Lastly, the previous report used a modified GRADE approach whereby the lowest quality rating was termed *insufficient*; we converted all previous insufficient strength-of-evidence ratings to *very low* for consistency with current GRADE methods.

When reviewing this report, state Medicaid administrators might consider using the findings and conclusions as a tool in their evidence-based decision making process, such as for clarifying place in therapy for TIM agents and populations of interest. Currently, the body of evidence for pipeline therapies are limited to placebo-controlled trials, which will introduce challenges for determining place in therapy, if additional evidence is not published ahead of FDA approval.

References

1. Gladman DD, Ritchlin CR. Treatment of psoriatic arthritis. 2018; www.uptodate.com/contents/treatment-of-psoriatic-arthritis. Accessed January 28, 2020.

2. Feldman SR. Treatment of psoriasis in adults. 2019; www.uptodate.com/contents/treatment-of-psoriasis-in-adults. Accessed January 28, 2020.

3. Feldman SR. Psoriasis: epidemiology, clinical manifestations, and diagnosis. 2019; www.uptodate.com/contents/psoriasis:-epidemiology-clinical-manifestations-and-diagnosis. Accessed January 28, 2020.

4. Gladman DD, Ritchlin CR. Clinical manifestations and diagnosis of psoriatic arthritis. 2020; www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-psoriatic-arthritis. Accessed January 28, 2020.

5. Manis JP. Overview of therapeutic monoclonal antibodies. 2019; www.uptodate.com/contents/overview-of-therapeutic-monoclonal-antibodies. Accessed January 28, 2020.

6. Ronholt K, Iversen L. Old and new biological therapies for psoriasis. *Int J Mol Sci*. 2017;18(11). doi: 10.3390/ijms18112297.

7. D'Angelo S, Tramontano G, Gilio M, Leccese P, Olivieri I. Review of the treatment of psoriatic arthritis with biological agents: choice of drug for initial therapy and switch therapy for non-responders. *Open Access Rheumatology*. 2017;9:21-28. doi: 10.2147/oarrr.S56073.

8. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. 2011; http://handbook.cochrane.org/ Accessed November 1, 2019.

9. National Heart, Lung, and Blood Institute. Quality assessment tool for observational cohort and cross-sectional studies. 2018; https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Accessed November 1, 2019.

10. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. *NICE*. 2014; https://www.nice.org.uk/media/default/about/what-we-do/our-programmes/developing-nice-guidelines-the-manual.pdf. Accessed November 1, 2019.

11. Scottish Intercollegiate Guidelines Network. Methodology checklist 2: randomised controlled trials. 2015; http://www.sign.ac.uk/checklists-and-notes.html. Accessed November 1, 2019.

12. Scottish Intercollegiate Guidelines Network. Methodology checklist 3: cohort studies. 2012; http://www.sign.ac.uk/checklists-and-notes.html. Accessed November 1, 2019.

13. Schünemann H, Brozek J, Guyatt G, Oxman A. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group, 2013. 2014; http://gdt.guidelinedevelopment.org/app/handbook/handbook.html. Accessed November 1, 2019.

14. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. doi: 10.1136/bmj.39489.470347.AD.

15. Araujo EG, Englbrecht M, Hoepken S, et al. Effects of ustekinumab versus tumor necrosis factor inhibition on enthesitis: results from the enthesial clearance in psoriatic arthritis (ECLIPSA) study. *Seminars in Arthritis & Rheumatism*. 2019;48(4):632-637. doi: 10.1016/j.semarthrit.2018.05.011.

16. Bagel J, Nia J, Hashim PW, et al. Secukinumab is superior to ustekinumab in clearing skin in patients with moderate to severe plaque psoriasis (16-Week CLARITY Results). *Dermatology And Therapy*. 2018;8(4):571-579. doi: 10.1007/s13555-018-0265-y.

17. Blauvelt A, Papp KA, Griffiths CEM, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator–controlled VOYAGE 1 trial. *Journal of the American Academy of Dermatology*. 2017;76(3):405-417. doi: 10.1016/j.jaad.2016.11.041.

18. Dommasch ED, Kim SC, Lee MP, Gagne JJ. Risk of serious infection in patients receiving systemic medications for the treatment of psoriasis. *JAMA Dermatology*. 2019;10:10. doi: 10.1001/jamadermatol.2019.1121.

19. Glatt S, Helmer E, Haier B, et al. First-in-human randomized study of bimekizumab, a humanized monoclonal antibody and selective dual inhibitor of IL-17A and IL-17F, in mild psoriasis. *British Journal of Clinical Pharmacology*. 2017;83(5):991-1001. doi: 10.1111/bcp.13185.

20. 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(2):136-144. doi: 10.1056/NEJMoa1501646.

21. Gordon KB, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind,

randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet*. 2018;392(10148):650-661. doi: 10.1016/S0140-6736(18)31713-6.

22. Lee MP, Desai RJ, Jin Y, Brill G, Ogdie A, Kim SC. Association of ustekinumab vs TNF inhibitor therapy with risk of atrial fibrillation and cardiovascular events in patients with psoriasis or psoriatic arthritis. *JAMA Dermatology*. 2019;155(6):700-707. doi: 10.1001/jamadermatol.2019.0001.

23. Mason KJ, Barker J, Smith CH, et al. Comparison of drug discontinuation, effectiveness, and safety between clinical trial eligible and ineligible patients in BADBIR. *JAMA Dermatology*. 2018;154(5):581-588. doi: 10.1001/jamadermatol.2018.0183.

24. Mease PJ, Genovese MC, Weinblatt ME, et al. Phase II study of ABT-122, a tumor necrosis factor- and interleukin-17A-targeted dual variable domain immunoglobulin, in patients with psoriatic arthritis with an inadequate response to methotrexate. *Arthritis & Rheumatology*. 2018;70(11):1778-1789. doi: 10.1002/art.40579.

25. Mease P, Coates LC, Helliwell PS, et al. Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active psoriatic arthritis (EQUATOR): results from a randomised, placebo-controlled, phase 2 trial. *Lancet*. 2018;392(10162):2367-2377. doi: 10.1016/S0140-6736(18)32483-8.

26. Papp KA, Merola JF, Gottlieb AB, et al. Dual neutralization of both interleukin 17A and interleukin 17F with bimekizumab in patients with psoriasis: Results from BE ABLE 1, a 12-week randomized, double-blinded, placebo-controlled phase 2b trial. *Journal of the American Academy of Dermatology*. 2018;79(2):277-286.e210. doi: 10.1016/j.jaad.2018.03.037.

27. Papp K, Gordon K, Thaçi D, et al. Phase 2 trial of selective tyrosine kinase 2 inhibition in psoriasis. *New England Journal of Medicine*. 2018;379(14):1313-1321. doi: 10.1056/NEJMoa1806382.

28. Reich K, Papp KA, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. *Lancet*. 2017;390(10091):276-288. doi: 10.1016/s0140-6736(17)31279-5.

29. Reich K, Gooderham M, Thaci D, et al. Risankizumab compared with adalimumab in patients with moderate-to-severe plaque psoriasis (IMMvent): a randomised, double-blind, active-comparator-controlled phase 3 trial. *Lancet*. 2019;04:04. doi: 10.1016/S0140-6736(19)30952-3.

30. Reich K, Rich P, Maari C, et al. Efficacy and safety of mirikizumab (LY3074828) in the treatment of moderate-to-severe plaque psoriasis: results from a randomized phase II study. *British Journal of Dermatology*. 2019;181(1):88-95. doi: 10.1111/bjd.17628.

31. Reich K, Armstrong AW, Langley RG, et al. Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): results from a phase 3, randomised controlled trial. *Lancet*. 2019;08:08. doi: 10.1016/S0140-6736(19)31773-8.

32. Reich K, Armstrong AW, Foley P, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. *J Am Acad Dermatol*. 2017;76(3):418-431. doi: 10.1016/j.jaad.2016.11.042.

33. Wu JJ, Armstrong A, Singh R, et al. Adverse medical conditions across treatment options in patients with psoriasis: a claims-based analysis. *Journal of Drugs in Dermatology: JDD*. 2018;17(11):1211-1218.

34. Atteno M, Peluso R, Costa L, et al. Comparison of effectiveness and safety of infliximab, etanercept, and adalimumab in psoriatic arthritis patients who experienced an inadequate response to previous disease-modifying antirheumatic drugs. *Clin Rheumatol*. 2010;29(4):399-403. doi: 10.1007/s10067-009-1340-7.

35. Bachelez H, van de Kerkhof PC, 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):552-561. doi: 10.1016/s0140-6736(14)62113-9.

36. Blauvelt A, Reich K, Mehlis S, et al. Secukinumab demonstrates greater sustained improvements in daily activities and personal relationships than ustekinumab in patients with moderate-to-severe plaque psoriasis: 52-week results from the CLEAR study. *J Eur Acad Dermatol Venereol*. 2017;31(10):1693-1699. doi: 10.1111/jdv.14391.

37. de Vries AC, Thio HB, de Kort WJ, et al. A prospective randomized controlled trial comparing infliximab and etanercept in patients with moderate-to-severe chronic plaque-type psoriasis: the Psoriasis Infliximab vs. Etanercept Comparison Evaluation (PIECE) study. *Br J Dermatol*. 2017;176(3):624-633. doi: 10.1111/bjd.14867.

38. Esposito M, Gisondi P, Cassano N, et al. Survival rate of antitumour necrosis factor-alpha treatments for psoriasis in routine dermatological practice: a multicentre observational study. *British Journal of Dermatology*. 2013;169(3):666-672. doi: 10.1111/bjd.12422.

39. Griffiths CE, Strober BE, van de Kerkhof P, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *New England Journal of Medicine*. 2010;362(2):118-128. doi: 10.1056/NEJMoa0810652.

40. Griffiths CE, 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*. 2015:541-551. doi: 10.1016/s0140-6736(15)60125-8.

41. Kisacik B, Pamuk ON, Onat AM, et al. Characteristics predicting tuberculosis risk under tumor necrosis factor-alpha inhibitors: report from a large multicenter cohort with high background prevalence. *J Rheumatol.* 2016;43(3):524-529. doi: 10.3899/jrheum.150177.

42. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. *New England Journal of Medicine.* 2014;371(4):326-338. doi: 10.1056/NEJMoa1314258.

43. Lebwohl M, Strober B, Menter A, et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. *New England Journal of Medicine.* 2015;373(14):1318-1328. doi: 10.1056/NEJMoa1503824.

44. Mease PJ, Van Der Heijde D, Ritchlin CT, et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: Results from the 24-week randomised, double-blind, placebocontrolled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. *Annals of the Rheumatic Diseases.* 2017;76(1):79-87. doi: 10.1136/annrheumdis-2016-209709.

45. Mease P, Hall S, FitzGerald O, et al. Tofacitinib or adalimumab versus placebo for psoriatic arthritis. *N Engl J Med.* 2017;377(16):1537-1550. doi: 10.1056/NEJMoa1615975.

46. Papp K, Blauvelt A, Bukhalo M, et al. Risankizumab versus ustekinumab for moderate-to-severe plaque psoriasis. *New England journal of medicine.* 2017;376(16):1551-1560. doi: 10.1056/NEJMoa1607017.

47. Reich K, Gooderham M, Green L, et al. The efficacy and safety of apremilast, etanercept and placebo in patients with moderate-to-severe plaque psoriasis: 52-week results from a phase IIIb, randomized, placebo-controlled trial (LIBERATE). *J Eur Acad Dermatol Venereol.* 2017;31(3):507-517. doi: 10.1111/jdv.14015.

48. Reich K, Pinter A, Lacour JP, et al. Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24-week results from IXORA-S, a phase III study. *Br J Dermatol.* 2017;177(4):1014-1023. doi: 10.1111/bjd.15666.

49. Carrascosa JM, Vanaclocha F, Caloto T, Echave M, Oyagüez I, Tencer T. Cost-utility analysis of apremilast for the treatment of moderate to severe psoriasis in Spain. *Value in Health.* 2015;18(7):A420.

50. Hongbo Y, Thomas CL, Harrison MA, Salek MS, Finlay AY. Translating the science of quality of life into practice: What do dermatology life quality index scores mean? *J Invest Dermatol.* 2005;125(4):659-664. doi: 10.1111/j.0022-202X.2005.23621.x.

51. Valenzuela F, Paul C, Mallbris L, et al. Tofacitinib versus etanercept or placebo in patients with moderate to severe chronic plaque psoriasis: patient-reported outcomes from a Phase 3 study. *J Eur Acad Dermatol Venereol.* 2016;30(10):1753-1759. doi: 10.1111/jdv.13702.

52. Paul C, Griffiths CEM, van de Kerkhof PCM, et al. Ixekizumab provides superior efficacy compared with ustekinumab over 52 weeks of treatment: Results from IXORA-S, a phase 3 study. *Journal of the American Academy of Dermatology.* 2019;80(1):70-79.e73. doi: 10.1016/j.jaad.2018.06.039.

53. Thaci D, Blauvelt A, Reich K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. *J Am Acad Dermatol.* 2015;73(3):400-409. doi: 10.1016/j.jaad.2015.05.013.

54. Immunex Corporation, Wyeth-Ayerst Laboratories. ENBREL is first therapy approved for psoriatic arthritis. 2002; https://www.eurekalert.org/pub_releases/2002-01/b-eif011602.php. Accessed January 28, 2020.

55. Mechantie E. Brodalumab approved for psoriasis with REMS required. 2017; https://www.mdedge.com/psychiatry/article/131613/psoriasis/brodalumab-approved-psoriasis-rems-required. Accessed January 28, 2020.

56. Berekmeri A, Mahmood F, Wittmann M, Helliwell P. Tofacitinib for the treatment of psoriasis and psoriatic arthritis. *Expert Rev Clin Immunol.* 2018;14(9):719-730. doi: 10.1080/1744666x.2018.1512404.

57. Krueger GG, Feldman SR, Camisa C, et al. Two considerations for patients with psoriasis and their clinicians: what defines mild, moderate, and severe psoriasis? What constitutes a clinically significant improvement when treating psoriasis? *J Am Acad Dermatol.* 2000;43(2 Pt 1):281-285. doi: 10.1067/mjd.2000.106374.

58. Gottlieb AB. Psoriasis. Immunopathology and immunomodulation. *Dermatol Clin.* 2001;19(4):649-657, viii. doi: 10.1016/s0733-8635(05)70306-5.

59. Krueger JG, Krane JF, Carter DM, Gottlieb AB. Role of growth factors, cytokines, and their receptors in the pathogenesis of psoriasis. *J Invest Dermatol.* 1990;94(6 Suppl):135S-140S. doi: 10.1111/1523-1747.ep12876121.

60. Menter A, Griffiths CE. Current and future management of psoriasis. *Lancet.* 2007;370(9583):272-284. doi: 10.1016/S0140-6736(07)61129-5.

61. Williamson L, Dalbeth N, Dockerty JL, Gee BC, Weatherall R, Wordsworth BP. Extended report: nail disease in psoriatic arthritis--clinically important, potentially treatable and

often overlooked. *Rheumatology (Oxford).* 2004;43(6):790-794. doi: 10.1093/rheumatology/keh198.

62. Anandarajah AP, Ritchlin CT. Pathogenesis of psoriatic arthritis. *Current Opinion in Rheumatology.* 2004;16(4):338-343. doi: 10.1097/01.bor.0000129718.13939.81.

63. Monemi S, Berber E, Sarsour K, et al. Incidence of gastrointestinal perforations in patients with rheumatoid arthritis treated with tocilizumab from clinical trial, postmarketing, and real-world data sources. *Rheumatol Ther.* 2016;3(2):337-352. doi: 10.1007/s40744-016-0037-z.

64. Yeung H, Wan J, Van Voorhees AS, et al. Patient-reported reasons for the discontinuation of commonly used treatments for moderate to severe psoriasis. *Journal of the American Academy of Dermatology.* 2013;68(1):64-72. doi: 10.1016/j.jaad.2012.06.035.

65. Jung SM, Ju JH, Park MS, et al. Risk of tuberculosis in patients treated with anti-tumor necrosis factor therapy: a nationwide study in South Korea, a country with an intermediate tuberculosis burden. *International Journal of Rheumatic Diseases.* 2015;18(3):323-330. doi: 10.1111/1756-185x.12530.

66. Winthrop KL, Baxter R, Liu L, et al. Mycobacterial diseases and antitumour necrosis factor therapy in USA. *Annals of the Rheumatic Diseases.* 2013;72(1):37-42. doi: 10.1136/annrheumdis-2011-200690.

67. Herrinton LJ, Harrold LR, Liu L, et al. Association between anti-TNF-(alpha) therapy and interstitial lung disease. *Pharmacoepidemiology and Drug Safety.* 2013;22(4):394-402. doi: 10.1002/pds.3409.

68. Chiu YM, Tang CH, Hung ST, Yang YW, Fang CH, Lin HY. A real-world risk analysis of biological treatment (adalimumab and etanercept) in a country with a high prevalence of tuberculosis and chronic liver disease: a nationwide population-based study. *Scand J Rheumatol.* 2017;46(3):236-240. doi: 10.1080/03009742.2016.1202318.

69. Herrinton LJ, Liu L, Chen L, et al. Association between anti-TNF-alpha therapy and all-cause mortality. *Pharmacoepidemiology and Drug Safety.* 2012;21(12):1311-1320. doi: 10.1002/pds.3354.

70. Baddley JW, Winthrop KL, Chen L, et al. Non-viral opportunistic infections in new users of tumour necrosis factor inhibitor therapy: results of the SAfety Assessment of Biologic ThERapy (SABER) study. *Annals of the Rheumatic Diseases.* 2014;73(11):1942-1948. doi: 10.1136/annrheumdis-2013-203407.

71. Feldman SR, Krueger GG. Psoriasis assessment tools in clinical trials. *Ann Rheum Dis.* 2005;64 Suppl 2:ii65-68; discussion ii69-73. doi: 10.1136/ard.2004.031237.

72. Basra MK, Fenech R, Gatt RM, Salek MS, Finlay AY. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. *Br J Dermatol.* 2008;159(5):997-1035. doi: 10.1111/j.1365-2133.2008.08832.x.

73. Mease PJ, Antoni CE, Gladman DD, Taylor WJ. Psoriatic arthritis assessment tools in clinical trials. *Ann Rheum Dis.* 2005;64 Suppl 2:ii49-54. doi: 10.1136/ard.2004.034165.

74. Papp KA, Blauvelt A, Kimball AB, et al. Patient-reported symptoms and signs of moderate-to-severe psoriasis treated with guselkumab or adalimumab: results from the randomized VOYAGE 1 trial. *Journal of the European Academy of Dermatology & Venereology.* 2018;32(9):1515-1522. doi: 10.1111/jdv.14910.

75. Reich K, Foley P, Han C, et al. Guselkumab improves work productivity in patients with moderate-to-severe psoriasis with or without depression and anxiety: results from the VOYAGE 2 comparator study versus adalimumab. *Journal of Dermatological Treatment.* 2019:1-7. doi: 10.1080/09546634.2019.1628172.

76. Gordon KB, Armstrong AW, Han C, et al. Anxiety and depression in patients with moderate-to-severe psoriasis and comparison of change from baseline after treatment with guselkumab vs. adalimumab: results from the Phase 3 VOYAGE 2 study. *Journal of the European Academy of Dermatology & Venereology.* 2018;32(11):1940-1949. doi: 10.1111/jdv.15012.

77. Blauvelt A, Reich K, Tsai T, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: results from the CLEAR study. *Journal of the american academy of dermatology.* 2017;76(1):60-69.e69. doi: 10.1016/j.jaad.2016.08.008.

78. Warren RB, Smith CH, Yiu ZZ, et al. Differential drug survival of biologic therapies for the treatment of psoriasis: a prospective observational cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *Journal of Investigative Dermatology.* 2015;135(11):2632-2640. doi: 10.1038/jid.2015.208.

79. Strand V, de Vlam K, Covarrubias-Cobos JA, et al. Tofacitinib or adalimumab versus placebo: patient-reported outcomes from OPAL Broaden-a phase III study of active psoriatic arthritis in patients with an inadequate response to conventional synthetic disease-modifying antirheumatic drugs. *RMD Open.* 2019;5(1):e000806. doi: 10.1136/rmdopen-2018-000806.

80. Sbidian E, Chaimani A, Garcia-Doval I, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. *Cochrane Database of Systematic Reviews.* 2017;12:CD011535. doi: 10.1002/14651858.CD011535.pub2.

81. Xu G, Xia M, Jiang C, et al. Comparative efficacy and safety of thirteen biologic therapies for patients with moderate or severe psoriasis: a network meta-analysis. *Journal of Pharmacological Sciences.* 2019;139(4):289-303. doi: 10.1016/j.jphs.2018.12.006.

82. Sawyer LM, Malottki K, Sabry-Grant C, et al. Assessing the relative efficacy of interleukin-17 and interleukin-23 targeted treatments for moderate-to-severe plaque psoriasis: A systematic review and network meta-analysis of PASI response. *PLoS ONE.* 2019;14(8):e0220868. doi: 10.1371/journal.pone.0220868.

83. Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. *Cochrane Database Syst Rev.* 2017(2). doi: 10.1002/14651858.MR000033.pub3.

84. !!! INVALID CITATION !!! 8-12.

Appendix A. Methods

Search Strategy

We searched Drug Effectiveness Review Project (DERP) clinical evidence sources to identify systematic reviews (with and without meta-analyses), technology assessments, randomized controlled trials (RCTs), and cohort studies (for harms) using terms for the conditions *(Plaque Psoriasis, Psoriatic Arthritis)* and the interventions *(Abatacept, Adalimumab, Adalimumab-adaz, Adalimumab-adbm, Adalimumab-atto, Apremilast, Brodalumab, Certolizumab pegol, Etanercept, Golimumab, Guselkumab, Infliximab, Infliximab-abda, Infliximab-dyyb, Infliximab-qbtx, Ixekizumab, Secukinumab, Tildrakizumab-asmn, Tofacitinib, Ustekinumab, Risankizumab, Upadacitinib, Filgotinib, Bimekizumab, PF-04965842, ABT-122, BMS-986165, Mirikizumab, M1095)* and study designs (if appropriate). We limited searches of evidence sources to citations published since January 1, 2017 through August 20, 2019. We conducted active surveillance of known ongoing studies through January 31, 2020.

The following DERP evidence sources were searched:

- Agency for Healthcare Research and Quality (AHRQ)
  - Evidence-based Practice Centers (EPC) Reports
  - Effective Health Care (EHC) Program
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Interscience)
- National Institute for Health and Care Excellence (NICE)
- Ovid MEDLINE
- Veterans Administration Evidence-based Synthesis Program (ESP)
- Embase
- Clinical Trials.gov
- ISRCTN

Ovid MEDLINE Search Strategy

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to August 20, 2019

#	Searches
1	exp Psoriasis/
2	psoriasis.ti,ab,kf.
3	psoriatic arthr*.ti,ab,kf.
4	or/1-3
5	Biological Products/
6	(biologic therap* or biologics).ti,ab.
7	Tumor Necrosis Factor-alpha/ai [Antagonists & Inhibitors]
8	((tumor necrosis factor alpha or TNF-alpha) adj2 (inhibitor? or anti or block* or antagonist?)).ti,ab.
9	exp Receptors, Interleukin/ai [Antagonists & Inhibitors]
10	(interleukin adj2 (inhibitor? or anti or block* or antagonist?)).ti,ab.
11	exp Janus Kinases/ai [Antagonists & Inhibitors]
12	((janus kinase or JAK?) adj2 (inhibitor? or anti or block* or antagonist?)).ti,ab.
13	antibodies, monoclonal/ or antibodies, monoclonal, humanized/
14	monoclonal antibod*.ti,ab.

#	Searches
15	Adalimumab/
16	(adalimumab or Humira or Amjevita or Hyrimoz or Cyltezo).mp.
17	Certolizumab Pegol/
18	(Certolizumab or Cimzia).mp.
19	(golimumab or simponi or CNTO148 or "CNTO 148").af.
20	Infliximab/
21	(infliximab or Remicade or Renflexis or Inflectra or Ixifi).mp.
22	Abatacept/
23	(Abatacept or Orencia).mp.
24	Etanercept/
25	(Etanercept or Enbrel or Erelzi).mp.
26	(Secukinumab or Cosentyx or "AIN 457" or AIN457).af.
27	(Tofacitinib or Xeljanz or "CP 690550" or CP690550).af.
28	(Apremilast or Otezla or "CC 10004" or CC10004).af.
29	(Brodalumab or Siliq or "AMG 827" or AMG827).af.
30	(Ixekizumab or Taltz or "LY 2439821" or LY2439821).af.
31	Ustekinumab/
32	(Ustekinumab or Stelara).mp.
33	or/5-32
34	limit 33 to yr="2017 -Current"
35	(Upadacitinib or ABT494 or "ABT 494").af.
36	(Guselkumab or Tremfya or "CNTO 1959" or CNTO1959).af.
37	(Tildrakizumab or Ilumya or "SCH 900222" or SCH900222 or "MK 3222" or MK3222).af.
38	(Risankizumab or Skyrizi or "BI 655066" or BI655066 or "ABBV 066" or ABBV066).af.
39	(Filgotinib or GLPG-0634 or GLPG0634 or GS-6034 or GS6034).af.
40	(Bimekizumab or UCB-4940 or UCB4940 or CDP-4940 or CDP4940).af.
41	(Abrocitinib or PF-04965842 or PF04965842).af.
42	(Remtolumab or ABT-122 or ABT122).af.
43	(BMS-986165 or BMS986165).af.
44	(Mirikizumab or LY-3074828 or LY3074828).af.
45	(M-1095 or M1095 or ALX-0761 or ALX0761 or MSB-0010841 or MSB0010841).af.
46	or/34-45
47	4 and 46
48	exp animals/ not humans/
49	47 not 48
50	exp age groups/ not exp adult/
51	49 not 50
52	Systematic Review.pt.
53	(systematic or structured or evidence or trials).ti. and ((review or overview or look or examination or update* or summary).ti. or review.pt.)
54	(0266-4623 or 1469-493X or 1366-5278 or 1530-440X).is.
55	meta-analysis.pt. or Network Meta-Analysis/ or (meta-analys* or meta analys* or metaanalys* or meta synth* or meta-synth* or metasynth*).tw,hw.
56	review.pt. and ((medline or medlars or embase or pubmed or scisearch or psychinfo or psycinfo or psychlit or psyclit or cinahl or electronic database* or bibliographic database* or computeri#ed database* or online database* or pooling or pooled or mantel haenszel or peto or dersimonian or der simonian or fixed effect or ((hand adj2 search*) or (manual* adj2 search*))).tw,hw. or (retraction of publication or retracted publication).pt.)
57	((systematic or meta) adj2 (analys* or review)).ti,kf. or ((systematic* or quantitativ* or methodologic*) adj5 (review* or overview*)).tw,hw. or (quantitativ$ adj5 synthesis$).tw,hw.

#	Searches
58	(integrative research review* or research integration).tw. or scoping review?.ti,kf. or (review.ti,kf,pt. and (trials as topic or studies as topic).hw.) or (evidence adj3 review*).ti,ab,kf.
59	or/52-58
60	59 not (case report/ or letter.pt.)
61	60 and 51
62	randomized controlled trial.pt. or random*.mp. or placebo.mp.
63	62 and 51
64	exp Antirheumatic Agents/ae [Adverse Effects]
65	exp Antibodies, Monoclonal/ae [Adverse Effects]
66	Biological Products/ae [Adverse Effects]
67	"Drug-Related Side Effects and Adverse Reactions"/
68	Long Term Adverse Effects/
69	((adverse or dangerous or harmful or indirect or injurious or secondary or side or undesirable) adj2 (effect* or event* or consequence* or impact* or outcome* or reaction*)).ti,ab.
70	(drug adj (survival or retention or longevity or adherence)).ti,ab.
71	(harms or safety or complication?).ti.
72	(toxicity or ((injection site or infusion) adj reaction?) or mortality or infection? or tuberculosis or herpes or malignan* or skin cancer? or heart failure or heart disease? or cardiovascular risk or lung disease? or ((gastrointestinal or gastro-intestinal) adj perforation?)).ti.
73	or/64-72
74	73 and 51
75	61 or 63 or 74

Cochrane Library Search Strategy

Cochrane Library (Wiley) – 21 August 2019

ID	Search
#1	[mh Psoriasis]
#2	psoriasis:ti,ab,kw
#3	(psoriatic NEXT arthr*):ti,ab,kw
#4	(or #1-#3)
#5	[mh ^"Adalimumab"]
#6	(adalimumab or Humira or Amjevita or Hyrimoz or Cyltezo):ti,ab,kw
#7	[mh ^"Certolizumab Pegol"]
#8	(Certolizumab or Cimzia):ti,ab,kw
#9	(golimumab or simponi or CNTO148 or "CNTO 148"):ti,ab,kw
#10	[mh ^"Infliximab"]
#11	(infliximab or Remicade or Renflexis or Inflectra or Ixifi):ti,ab,kw
#12	[mh ^"Abatacept"]
#13	(Abatacept or Orencia):ti,ab,kw
#14	[mh ^"Etanercept"]
#15	(Etanercept or Enbrel or Erelzi):ti,ab,kw
#16	(Secukinumab or Cosentyx or "AIN 457" or AIN457):ti,ab,kw
#17	(Tofacitinib or Xeljanz or "CP 690550" or CP690550):ti,ab,kw
#18	(Apremilast or Otezla or "CC 10004" or CC10004):ti,ab,kw
#19	(Brodalumab or Siliq or "AMG 827" or AMG827):ti,ab,kw
#20	(Ixekizumab or Taltz or "LY 2439821" or LY2439821):ti,ab,kw
#21	[mh ^"Ustekinumab"]
#22	(Ustekinumab or Stelara):ti,ab,kw

ID	Search
#23	(or #5-#12) with Cochrane Library publication date Between Oct 2017 and Aug 2019
#24	(Upadacitinib or ABT494 or "ABT 494"):ti,ab,kw
#25	(Guselkumab or Tremfya or "CNTO 1959" or CNTO1959):ti,ab,kw
#26	(Tildrakizumab or Ilumya or "SCH 900222" or SCH900222 or "MK 3222" or MK3222):ti,ab,kw
#27	(Risankizumab or Skyrizi or "BI 655066" or BI655066 or "ABBV 066" or ABBV066):ti,ab,kw
#28	(Filgotinib or GLPG-0634 or GLPG0634 or GS-6034 or GS6034):ti,ab,kw
#29	(Bimekizumab or UCB-4940 or UCB4940 or CDP-4940 or CDP4940):ti,ab,kw
#30	(Abrocitinib or PF-04965842 or PF04965842):ti,ab,kw
#31	(Remtolumab or ABT-122 or ABT122):ti,ab,kw
#32	(BMS-986165 or BMS986165):ti,ab,kw
#33	(Mirikizumab or LY-3074828 or LY3074828):ti,ab,kw
#34	(M-1095 or M1095 or ALX-0761 or ALX0761 or MSB-0010841 or MSB0010841):ti,ab,kw
#35	(or #23-#34)
#36	#4 and #35
#37	[mh "age groups"] not [mh adult]
#38	#36 not #37
#39	(clinicaltrials or trialsearch or ANZCTR or ensaiosclinicos or chictr or cris or ctri or registroclinico or clinicaltrialsregister or DRKS or IRCT or rctportal or JapicCTI or JMACCT or jRCT or UMIN or trialregister or PACTR or REPEC or SLCTR):so
#40	#38 not #39

Embase Search Strategy

Embase.com (Elsevier) – 21 August 2019

No.	Query
#1	'psoriasis'/de OR 'psoriasis vulgaris'/exp OR 'psoriatic arthritis'/exp
#2	psoriasis:ti,ab
#3	'psoriatic arthr*':ti,ab
#4	#1 OR #2 OR #3
#5	'adalimumab'/exp/mj
#6	adalimumab:ti,ab OR humira:ti,ab OR amjevita:ti,ab OR hyrimoz:ti,ab OR cyltezo:ti,ab
#7	'certolizumab pegol'/exp/mj
#8	certolizumab:ti,ab OR cimzia:ti,ab
#9	'golimumab'/exp/mj
#10	golimumab:ti,ab OR simponi:ti,ab OR cnto148:ti,ab OR 'cnto 148':ti,ab
#11	'infliximab'/exp/mj
#12	infliximab:ti,ab OR remicade:ti,ab OR renflexis:ti,ab OR inflectra:ti,ab OR ixifi:ti,ab
#13	'abatacept'/exp/mj
#14	abatacept:ti,ab OR orencia:ti,ab
#15	'etanercept'/exp/mj
#16	etanercept:ti,ab OR enbrel:ti,ab OR erelzi:ti,ab
#17	'secukinumab'/exp/mj
#18	secukinumab:ti,ab OR cosentyx:ti,ab OR 'ain 457':ti,ab OR ain457:ti,ab
#19	'tofacitinib'/exp/mj
#20	tofacitinib:ti,ab OR xeljanz:ti,ab OR 'cp 690550':ti,ab OR cp690550:ti,ab
#21	'apremilast'/exp/mj
#22	apremilast:ti,ab OR otezla:ti,ab OR 'cc 10004':ti,ab OR cc10004:ti,ab
#23	'brodalumab'/exp/mj
#24	brodalumab:ti,ab OR siliq:ti,ab OR 'amg 827':ti,ab OR amg827:ti,ab

No.	Query
#25	'ixekizumab'/exp/mj
#26	ixekizumab:ti,ab OR taltz:ti,ab OR 'ly 2439821':ti,ab OR ly2439821:ti,ab
#27	'ustekinumab'/exp/mj
#28	ustekinumab:ti,ab OR stelara:ti,ab
#29	(#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28) AND [2017-2019]/py
#30	'upadacitinib'/exp/mj
#31	upadacitinib:ti,ab OR abt494:ti,ab OR 'abt 494':ti,ab
#32	'guselkumab'/exp/mj
#33	guselkumab:ti,ab OR tremfya:ti,ab OR 'cnto 1959':ti,ab OR cnto1959:ti,ab
#34	'tildrakizumab'/exp/mj
#35	tildrakizumab:ti,ab OR ilumya:ti,ab OR 'sch 900222':ti,ab OR sch900222:ti,ab OR 'mk 3222':ti,ab OR mk3222:ti,ab
#36	'risankizumab'/exp/mj
#37	risankizumab:ti,ab OR skyrizi:ti,ab OR 'bi 655066':ti,ab OR bi655066:ti,ab OR 'abbv 066':ti,ab OR abbv066:ti,ab
#38	'filgotinib'/exp
#39	filgotinib:ti,ab OR 'glpg 0634':ti,ab OR glpg0634:ti,ab OR 'gs 6034':ti,ab OR gs6034:ti,ab
#40	'bimekizumab'/exp
#41	bimekizumab:ti,ab OR 'ucb 4940':ti,ab OR ucb4940:ti,ab OR 'cdp 4940':ti,ab OR cdp4940:ti,ab
#42	'abrocitinib'/exp
#43	abrocitinib:ti,ab OR 'pf 04965842':ti,ab OR pf04965842:ti,ab
#44	'remtolumab'/exp
#45	remtolumab:ti,ab OR 'abt 122':ti,ab OR abt122:ti,ab
#46	'bms 986165' OR bms986165
#47	'mirikizumab'/exp
#48	'm 1095' OR m1095 OR 'alx 0761' OR alx0761 OR 'msb 0010841' OR msb0010841
#49	#29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48
#50	#4 AND #49
#51	'animal'/exp NOT 'human'/exp
#52	#50 NOT #51
#53	'groups by age'/exp NOT 'adult'/exp
#54	#52 NOT #53
#55	'systematic review'/exp OR 'meta analysis'/exp
#56	(((systematic OR 'state of the art' OR scoping OR umbrella) NEXT/1 (review* OR overview* OR assessment*)):ti,ab) OR 'review* of reviews':ti,ab OR 'meta analy*':ti,ab OR metaanaly*:ti,ab OR (((systematic OR evidence) NEAR/1 assess*):ti,ab) OR 'research evidence':ti,ab OR metasynthe*:ti,ab OR 'meta synthe*':ti,ab
#57	#55 OR #56
#58	#54 AND #57
#59	'randomized controlled trial'/exp OR random*:ti,ab OR placebo:ti,ab
#60	#54 AND #59
#61	'adalimumab'/exp/dd_ae OR 'certolizumab pegol'/exp/dd_ae OR 'golimumab'/exp/dd_ae OR 'infliximab'/exp/dd_ae OR 'abatacept'/exp/dd_ae OR 'etanercept'/exp/dd_ae OR 'secukinumab'/exp/dd_ae OR 'tofacitinib'/exp/dd_ae OR 'apremilast'/exp/dd_ae OR 'brodalumab'/exp/dd_ae OR 'ixekizumab'/exp/dd_ae OR 'ustekinumab'/exp/dd_ae OR 'upadacitinib'/exp/dd_ae OR 'guselkumab'/exp/dd_ae OR 'tildrakizumab'/exp/dd_ae OR 'risankizumab'/exp/dd_ae OR 'filgotinib'/exp/dd_ae OR 'bimekizumab'/exp/dd_ae OR 'abrocitinib'/exp/dd_ae OR 'remtolumab'/exp/dd_ae OR 'mirikizumab'/exp/dd_ae

No.	Query
#62	'adverse drug reaction'/de
#63	((adverse OR dangerous OR harmful OR indirect OR injurious OR secondary OR side OR undesirable) NEAR/2 (effect* OR event* OR consequence* OR impact* OR outcome* OR reaction*)):ti,ab
#64	(drug NEXT/1 (survival OR retention OR longevity OR adherence)):ti,ab
#65	harms:ti OR safety:ti OR complication$:ti
#66	toxicity:ti OR ((('injection site' OR infusion) NEXT/1 reaction$):ti) OR mortality:ti OR infection$:ti OR tuberculosis:ti OR herpes:ti OR malignan*:ti OR "skin cancer$":ti OR 'heart failure':ti OR "heart disease$":ti OR 'cardiovascular risk':ti OR "lung disease$":ti OR (((gastrointestinal OR 'gastro intestinal') NEXT/1 perforation$):ti)
#67	#61 OR #62 OR #63 OR #64 OR #65 OR #66
#68	#54 AND #67
#69	#58 OR #60 OR #68
#70	#69 NOT 'conference abstract'/it

Ongoing Studies

We searched the following DERP sources for ongoing studies. Search terms were selected depending on the information source (see below):

- ClinicalTrials.gov – 21 August 2019

Search
psoriasis OR psoriatic | adalimumab OR Humira OR Amjevita OR Hyrimoz OR Cyltezo OR Certolizumab OR Cimzia OR golimumab OR simponi OR CNTO148 OR "CNTO 148" OR infliximab OR Remicade OR Renflexis OR Inflectra OR Ixifi OR Abatacept OR Orencia OR Etanercept OR Enbrel OR Erelzi | Adult, Older Adult | Last update posted from 11/01/2017 to 08/13/2019
psoriasis OR psoriatic | Secukinumab OR Cosentyx OR "AIN 457" OR AIN457 OR Tofacitinib OR Xeljanz OR "CP 690550" OR CP690550 OR Apremilast OR Otezla OR "CC 10004" OR CC10004 OR Brodalumab OR Siliq OR "AMG 827" OR AMG827 | Adult, Older Adult | Last update posted from 11/01/2017 to 08/13/2019
psoriasis OR psoriatic | Ixekizumab OR Taltz OR "LY 2439821" OR LY2439821 OR Ustekinumab OR Stelara OR Upadacitinib OR ABT494 OR "ABT 494" OR Guselkumab OR Tremfya OR "CNTO 1959" OR CNTO1959 | Adult, Older Adult | Last update posted from 11/01/2017 to 08/13/2019
psoriasis OR psoriatic | Tildrakizumab OR Ilumya OR "SCH 900222" OR SCH900222 OR "MK 3222" OR MK3222 OR Risankizumab OR Skyrizi OR "BI 655066" OR BI655066 OR "ABBV 066" OR ABBV066 | Adult, Older Adult | Last update posted from 11/01/2017 to 08/13/2019
psoriasis OR psoriatic | Filgotinib OR GLPG-0634 OR GLPG0634 OR GS-6034 OR GS6034 OR Bimekizumab OR UCB-4940 OR UCB4940 OR CDP-4940 OR CDP4940 OR Abrocitinib OR PF-04965842 OR PF04965842 OR Remtolumab OR ABT-122 OR ABT122 OR BMS-986165 OR BMS986165 | Adult, Older Adult | Last update posted from 11/01/2017 to 08/21/2019
psoriasis OR psoriatic | Mirikizumab OR LY-3074828 OR LY3074828 OR M-1095 OR M1095 OR ALX-0761 OR ALX0761 OR MSB-0010841 OR MSB0010841 | Adult, Older Adult | Last update posted from 11/01/2017 to 08/21/2019
Total (before internal deduplication)
Total (after deduplication)

- ISRCTN Registry – 13 August 2019

Search
adalimumab OR Humira OR Amjevita OR Hyrimoz OR Cyltezo OR Certolizumab OR Cimzia OR golimumab OR simponi OR CNTO148 OR "CNTO 148" OR infliximab OR Remicade OR Renflexis OR Inflectra OR Ixifi OR Abatacept OR Orencia OR Etanercept OR Enbrel OR Erelzi OR Secukinumab OR Cosentyx OR "AIN 457" OR AIN457 OR Tofacitinib OR Xeljanz OR "CP 690550" OR CP690550 OR Apremilast OR Otezla OR "CC 10004" OR CC10004 OR Brodalumab OR Siliq OR "AMG 827" OR AMG827 OR Ixekizumab OR Taltz OR "LY 2439821" OR LY2439821 OR Ustekinumab OR Stelara OR Upadacitinib OR ABT494 OR "ABT 494" OR Guselkumab OR Tremfya OR "CNTO 1959" OR CNTO1959 OR Tildrakizumab OR Ilumya OR "SCH 900222" OR SCH900222 OR "MK 3222" OR MK3222 OR Risankizumab OR Skyrizi OR "BI 655066" OR BI655066 OR "ABBV 066" OR ABBV066 |filter within Condition: Psoriasis OR psoriatic | filter Participant age range: Adult | filter Last edited: from: 01/11/2017 | filter Last edited: to: 21/08/2019
Filgotinib OR GLPG-0634 OR GLPG0634 OR GS-6034 OR GS6034 OR Bimekizumab OR UCB-4940 OR UCB4940 OR CDP-4940 OR CDP4940 OR Abrocitinib OR PF-04965842 OR PF04965842 OR Remtolumab OR ABT-122 OR ABT122 OR BMS-986165 OR BMS986165 OR Mirikizumab OR LY-3074828 OR LY3074828 OR M-1095 OR M1095 OR ALX-0761 OR ALX0761 OR MSB-0010841 OR MSB0010841 |filter within Condition: Psoriasis OR psoriatic | filter Participant age range: Adult | filter Last edited: from: 01/11/2017 | filter Last edited: to: 13/08/2019
Total

Inclusion Criteria

Population

- Adults with plaque psoriasis
- Adults with psoriatic arthritis

Interventions

- TIMs and respective biosimilars that the FDA has approved for the treatment of plaque psoriasis or psoriatic arthritis and select pipeline drugs likely to be approved soon

Comparators

- For FDA-approved drugs: another listed TIM intervention (head-to-head comparison)
- For pipeline drugs: any listed TIM, standard of care, placebo

Outcomes

- Health Outcomes
  - Quality of life
  - Functional capacity
  - Productivity, ability to sustain employment
  - Clinical improvement
  - Disease remission
  - Pain
  - Reduction in disease-related hospitalizations
  - Reduction in disease-specific mortality
  - Rebound/flare
  - Steroid withdrawal

- Harms
  - Overall adverse events (AEs)
  - Withdrawals due to adverse events
  - Serious adverse events (SAEs)
  - Specific adverse events (e.g., lymphoma, all malignancies, serious infectious diseases, herpes zoster, opportunistic infections, congestive heart failure)
  - Mortality

Study Designs

- RCTs with ≥ 12-week study duration
- Retrospective and prospective cohort studies comparing an intervention type to another for outcomes on harms
  - > 12-week study duration
  - Minimum total sample size of 1,000

Exclusion Criteria

We excluded studies if they were not published in English. We also excluded conference abstracts and data reported in press releases.

Screening

Two experienced researchers independently screened all titles and abstracts of identified documents. In cases in which there was disagreement about eligibility, the result was managed by discussion. This method was repeated for full-text review of documents that could not be excluded by title and abstract screening.

Data Abstraction

One experienced researcher abstracted and entered data from eligible studies in a standardized way using DistillerSR. A second experienced researcher reviewed all the data entered. We resolved discrepancies through discussion.

Quality Assessment

Methodological Quality of Included Studies

We assessed the methodological quality of the included RCTs and cohort studies using standard instruments developed and adapted by DERP that are modifications of instruments used by national and international standards for quality.[84] Two experienced researchers independently rated all included studies. In cases in which there was disagreement about the methodological quality of a study, the disagreement was resolved through discussion.

Randomized Controlled Trials

Good-quality RCTs include a clear description of the population, setting, intervention, and comparison groups; a random and concealed allocation of patients to study groups; low dropout rates; and intention-to-treat analyses. Good-quality RCTs also have low potential for bias from conflicts of interest and funding source(s). Fair-quality RCTs have incomplete information about methods that might mask important limitations or a meaningful conflict of interest. Poor-quality RCTs have clear flaws that could introduce significant bias.

Cohort Studies

Good-quality cohort studies include a sample that is representative of the source population, have low loss to follow-up, and measure and consider relevant confounding factors. Good-quality cohort studies also list their funding source(s) and have a low potential of bias from conflicts of interest. Fair-quality cohort studies might not have measured all relevant confounding factors or adjusted for them in statistical analyses, have loss to follow-up that could bias findings, consist of a sample that is not representative of the source population, or have potential conflicts of interest that are not addressed. Poor-quality cohort studies have a clear, high risk of bias that would affect findings.

Quality of Evidence Assessment

Overall Quality of Evidence

We assigned each outcome a summary judgment for the overall quality of evidence based on the system developed by the Grading of Recommendations, Assessment, Development, and Evaluation Working Group (GRADE).[13,14] Two independent experienced researchers assigned ratings, with disagreements resolved through discussion. The GRADE system defines the overall quality of a body of evidence for an outcome in the following manner:

- **High:** Raters are very confident that the estimate of the effect of the intervention on the outcome lies close to the true effect. Typical sets of studies are RCTs with few or no limitations, and the estimate of effect is likely stable.
- **Moderate:** Raters are moderately confident in the estimate of the effect of the intervention on the outcome. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.
- **Low:** Raters have little confidence in the estimate of the effect of the intervention on the outcome. The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.
- **Very low:** Raters have no confidence in the estimate of the effect of the intervention on the outcome. The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.
- **Not applicable:** Researchers did not identify any eligible articles.

Appendix B. Full Evidence Tables

Table B1. Evidence Table for RCTs of TIMs for Plaque Psoriasis or Psoriatic Arthritis (Study and Population Characteristics)

Author, Year Country Trial Name Registry Number Study Quality	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
Araujo et al.,[15] 2019 Germany Effects of ustekinumab versus tumor necrosis factor inhibition on enthesitis: Results from the enthesial clearance in psoriatic arthritis (ECLIPSA) study EudraCT 2017-003799-29 Poor	Adult patients (> 18 years of age) with a diagnosis of PsA according to CASPAR criteria, presence of active enthesitis defined as 1 painful entheses using the SPARCC EI, and methotrexate treatment failure for at least 3 months. Patients who had received or were receiving biological DMARD therapy were excluded from the study. Glucocorticoids of less than 5 mg prednisolone/day were allowed during the study.	Patients > 18 years of age. • Ustekinumab: 62 (18) • TNF inhibitor: 58 (21) 19* (40.2%) female Race/ethnicity: NR	Duration of PsA, Mean (SD) in years • Ustekinumab: 2 (6.0) • TNF inhibitor: 3 (4.8) N (%) with concomitant treatment Glucocorticoids • Ustekinumab: 0 (0) • TNF inhibitor: 1*(4.2) Methotrexate • Ustekinumab: 19*(82.) • TNF inhibitor: 24 (100)	Deutsche Forschungs-gemein-schaft; Bundes-ministerium fur Bildung und Forschung (govern-ment agencies)
Atteno et al.,[34] 2010 Italy Comparison of effectiveness and safety of infliximab, etanercept, and adalimumab in psoriatic arthritis patients who experienced an inadequate	Adult patients (≥ 18 years of age) with psoriatic arthritis and inadequate response to previous DMARDs therapy. Patients were excluded if they had previous used anti-TNF-α inhibitors, DMARDs (other than sulfasalazine, methotrexate, azathioprine, or	Mean (SD) age in years: 48.5 (12.5) 60 (60%) female Race/ethnicity: NR	Median (IQR) PASI: 19 (18.2) Median (IQR) HAQ: 1.2 (0.4) Median (range) duration of disease in	NR

Author, Year Country Trial Name Registry Number Study Quality	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
response to previous disease-modifying antirheumatic drugs Poor	leflunomide) within 4 weeks of enrollment, more than 10 mg prednisone daily, or had changed dosage of NSAIDs or prednisone within 2 weeks of enrollment.		months: 80 (20 to 140)	
Bachelez et. al.,[35] 2015 Valenzuela et al.,[51] 2016 Multiple countries (not U.S. or Canada) Tofacitinib versus etanercept or placebo in moderate to severe chronic plaque psoriasis: a non-inferiority trial (OPT)[35] Tofacitinib versus etanercept or placebo in patients with moderate-to-severe chronic plaque psoriasis: patient-reported outcomes from a Phase 3 study (OPT)[51] NCT01241951 Fair	18 years of age or older diagnosed with chronic (≥ 12 months) stable plaque psoriasis; candidate for systemic therapy or phototherapy; PASI score ≥ 12; IGA of moderate or severe psoriasis that involved at least 10% of BSA; failed to respond to, had a contraindication to, or were intolerant to at least 1 conventional systemic therapy (including ultraviolet therapy).	Age: NR Gender: NR Race/ethnicity: NR (most White)	NR	Pfizer
Bagel et al.,[16] 2018 U.S., Canada, Czech, Guatemala, Hungary, Iceland, Korea, Malaysia, Poland, Slovakia, Vietnam Secukinumab is superior to ustekinumab in clearing skin in patients with moderate to severe plaque psoriasis (16-week CLARITY Results) NCT02826603	Adult patients with moderate-to-severe chronic plaque psoriasis defined by PASI ≥ 12, static 5-point IGA 2011 modified version score ≥ 3, and body surface area (BSA) involvement ≥ 10%. Eligible patients were also inadequately controlled by topical treatments, phototherapy, and/or previous systemic therapy.	Patients ≥ 18 years of age Mean (SD) • Secukinumab: 45.4 (14.1) • Ustekinumab: 45.3 (14.2) 370 (33.6%) female 278 (25.2%) nonwhite population	PASI, Mean (SD) • Secukinumab: 20.8 (9.0) • Ustekinumab: 21.3 (9.2) Mean time since first diagnosis of plaque-type psoriasis, Mean (SD) in years	Novartis Pharma AG

Author, Year Country Trial Name Registry Number Study Quality	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
Fair			• Secukinumab: 16.8 (11.9) • Ustekinumab: 17.3 (13.3)	
Blauvelt et al.,[17] 2017 Papp et al.,[74] 2018 U.S., Australia, Canada, Germany, Hungary, Republic of Korea, Poland, Russian Federation, Spain, Taiwan Efficacy and safety of Guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate-to-severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE-1 trial[17] Patient-reported symptoms and signs of moderate-to-severe psoriasis treated with guselkumab or adalimumab: results from the randomized VOYAGE-1 trial[74] NCT02207231 Fair	Adults with moderate-to-severe psoriasis for ≥ 6 months, ≥ 10% BSA, ≥ 12 PASI, ≥ 3 IGA. Participants were included if they were candidates for phototherapy. Participants were excluded if they had a history of an uncontrolled medical condition or malignancy, except nonmelanoma skin cancer within 5 years. Patient were excluded if they had a history of TB, had received guselkumab or adalimumab or other anti-TNF-α therapy (within 3 months), other treatment targeting IL 12/23, IL-17 or IL-23 (6 months), or any systemic immunosuppressants or phototherapy (4 weeks).	Mean (SD) age in years • Adalimumab: 42.9 (12.6) • Guselkumab: 43.9 (12.7) N (%) female • Adalimumab: 85 (25.4) • Guselkumab: 89 (27.1) N (%) White • Adalimumab: 277 (82.9) • Guselkumab: 262 (79.6) N (%) Asian • Adalimumab: 47 (14.1) • Guselkumab: 51 (15.5) N (%) Black • Adalimumab: 8 (2.4) • Guselkumab: 6 (1.8)	Mean (SD) duration of psoriasis in years • Adalimumab: 17.0 (11.3) • Guselkumab: 17.9 (12.3) Mean (SD) PASI • Adalimumab: 22.4 (9.0) • Guselkumab: 22.1 (9.5)	Janssen Research & Development

Author, Year Country Trial Name Registry Number Study Quality	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
Blauvelt et al.,[36] 2017 Blauvelt et al.[77] 2016 Thaci et al.,[53] 2015 Worldwide Secukinumab demonstrates greater sustained improvements in daily activities and personal relationships than ustekinumab in patients with moderate-to-severe plaque psoriasis: 52-week results from the CLEAR study[36] Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: Results from the CLEAR study[77] Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis: CLEAR a randomized controlled trial[53] NCT02074982 Fair	Adult patients with moderate-to-severe plaque psoriasis ≥ 6 months' duration and ≥ 10% BSA, PASI of 12 or greater, IGA 2011 modified version 3 (moderate) or 4 (severe) and inadequate response to topical treatment, and/or phototherapy, and/or previous systemic therapy (conventional or biologic).	Age: mean age 45 Gender: 68 to 74% male Race/ethnicity: 85% to 89% white	NR	Novartis

Author, Year Country Trial Name Registry Number Study Quality	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
De Vries et al.,[37] 2017 The Netherlands A prospective randomized controlled trial comparing infliximab and etanercept in patients with moderate-to-severe chronic plaque-type psoriasis: the Psoriasis Infliximab vs. Etanercept Comparison Evaluation (PIECE) study Dutch Trials Registry 1559 Poor	Adult patients with moderate-to-severe chronic plaque psoriasis (with PASI ≥ 10, and/or BSA ≥ 10 and/or PASI ≥ 8 plus Skindex-29 ≥ 35).	Age: mean age in the 2 groups ranged from 42 to 46 years of age Gender: 28 to 44% females Race/ethnicity: NR	Patients must have failed or were contraindicated for and/or intolerant to UV therapy, and methotrexate or ciclosporin Washout period was 2 weeks for topical and UV therapy and 4 weeks for systemic therapies	The Netherlands Organization for Scientific Research-Medical Sciences
Glatt et al.,[19] 2017 United Kingdom First-in-human randomized study of bimekizumab, a humanized monoclonal antibody and selective dual inhibitor of IL-17A and IL-17F, in mild psoriasis NCT02529956 Fair	Adults (ages 18 to 70) with plaque-type psoriasis for at least 6 months involving more than 5% of BSA (excluding the scalp) and at least 2 psoriatic lesions with at least 1 plaque in a suitable biopsy site. Patients were excluded if they were using systemic nonbiological psoriasis therapy or phototherapy (within 4 weeks prior to screening), and treatment with biological agents (within 12 months prior to screening).	Mean (SD) age in years • Placebo: 38.2 (13..3) • Bimekizumab: 39.5 (10.4) N (%) female • Placebo: 1 (7.3) • Bimekizumab: 9 (23.1) N (%) Asian • Placebo: 0 (0) • Bimekizumab: 1 (2.6) N (%) Other/mixed • Placebo: 0 (0) • Bimekizumab: 1 (2.6) N (%) Caucasian • Placebo: 13 (100) • Bimekizumab: 37 (94.9)	Median (range) PASI score • Placebo 3.0 (1.8 to 6.1) • Bimekizumab: 3.5 (0.8 to 6.7)	UCB Pharma

Author, Year Country Trial Name Registry Number Study Quality	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
		N (%) Hispanic or Latino • Placebo: 0 (0) • Bimekizumab: 0 (0)		
Gordon et al.,[21] 2018 Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Japan, Mexico, Poland, Portugal, South Korea, Spain, and United States Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomized, placebo-controlled and ustekinumab-controlled phase 3 trials. NCT02684357, NCT02684370 Fair	Adult with moderate-to-severe plaque psoriasis ≥ 6 months and involving 10% BSA, PASI ≥ 12, PGA ≥ 3. Patients were included if they were candidates for systemic therapy or phototherapy and eligible for treatment with ustekinumab.	Mean (SD) age in years • Risankizumab: 48.3 (13.4) • Ustekinumab: 46.5 (13.4) N (%) female • Risankizumab: 92 (30) • Ustekinumab: 30 (30) N (%) White • Risankizumab: 200 (66) • Ustekinumab: 74 (74) N (%) Black or African American • Risankizumab: 10 (3) • Ustekinumab: 1 (1) N (%) Asian • Risankizumab: 86 (28) • Ustekinumab: 22 (22) N (%) Other • Risankizumab: 8 (3) • Ustekinumab:3 (3)	Mean (SD) PASI • Risankizumab: 20.6 (7.7) • Ustekinumab: 20.1 (6.8)	AbbVie and Boehringer Ingelheim

Author, Year Country Trial Name Registry Number Study Quality	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
Gordon et al.,[20] 2015 United States, Belgium, Germany, Poland, and Canada A phase 2 trial of guselkumab versus adalimumab for plaque psoriasis (X-PLORE) NCT01483599 Fair	Adults age 18 and older with moderate-to-severe psoriasis with at least 10% BSA involvement, ≥ 3 PGA score; ≥ 12 PASI; patients were excluded if they had previously been exposed to adalimumab or guselkumab.	Median age in years • Adalimumab: 50.0 • Guselkumab: 44.0 N (%) female • Adalimumab: 13* (30)* • Guselkumab: 59* (28)* N (%) White • Adalimumab: 39 (91) • Guselkumab: 189 (91)	Mean (SD) duration of psoriasis in years • Adalimumab: 19.3 (12.8) • Guselkumab: 18.5 (12.2) Mean (SD) PASI score • Adalimumab: 20.2 (7.6) • Guselkumab: 20.9 (8.1)	Janssen Research and Development
Griffiths et al.,[39] 2010 Worldwide Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis NCT0045484 Fair	Adults age 18 and older with moderate-to-severe plaque psoriasis ≥ 6 months' duration and involving ≥ 10% BSA, PGA score of 3 or more, PASI score of 12 or more.	Mean age in years • Etanercept: 45.7 • Ustekinumab 45 mg: 45.1 • Ustekinumab 90 mg: 44.8 N (%) female • Etanercept: 101* (29)* • Ustekinumab 45 mg: 76* (36)* • Ustekinumab 90 mg: 113* (33)* N (%) White race • Etanercept: 316 (91) • Ustekinumab 45 mg: 193 (92) • Ustekinumab 90 mg: 309 (89)	Mean (SD) duration of psoriasis in years • Etanercept: 18.8 (12.1) • Ustekinumab 45 mg: 18.9 (11.8) • Ustekinumab 90 mg: 18.7 (11.8) Mean (SD) PASI score Etanercept: 18.6 (6.2) • Ustekinumab 45 mg: 20.5 (9.2)	Centocor Research and Development

Author, Year Country Trial Name Registry Number Study Quality	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
			• Ustekinumab 90 mg: 19.9 (8.4)	
Griffiths et al.,[40] 2015 Multiple countries including United Kingdom, Germany, United States, Netherlands, France Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3) results from two phase 3 randomised trials NCT01597245, NCT01646177 Fair	Adult patients with at least moderate-to-severe plaque psoriasis ≥ 6 months' duration and involving ≥ 10% BSA, PGA score of 3 or more, PASI score of 12 or more.	Age: mean age in the 2 trials ranged from 45 to 46 years of age Gender: 63 to 71% males Race/ethnicity: White ranged from 89 to 94%	NR	Eli Lilly and Company
Langley et al.,[42] 2014 Worldwide Secukinumab in Plaque Psoriasis: Results of Two Phase 3 Trials (FIXTURE) NCT01358578 Fair	18 years of age or older with moderate-to-severe plaque psoriasis that had been diagnosed at least 6 months before randomization and that was poorly controlled with topical treatments, phototherapy, systemic therapy, or a combination. Score of 12 or higher on PASI; score of 3 or 4 on the modified IGPA, and involvement of 10% or more of the BSA. Psoriasis other than chronic plaque type (e.g., drug-induced) were excluded. Medications that might confound efficacy were not allowed.	Age: 18 years or older Gender: 71% Race/ethnicity: 67% White	14 to 27% concurrent psoriatic arthritis, BSA affected around 33%, rates of previous TNF inhibitor or biologic 4% to 30%	Novartis

Author, Year Country Trial Name Registry Number Study Quality	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
Lebwohl et al.,[43] 2015 142 sites worldwide Phase 3 Studies Comparing Brodalumab with Ustekinumab in Psoriasis (AMAGINE-2 and AMAGINE-3) NCT01708603, NCT01708629 Fair	Adult patients 18 to 75 years of age with stable moderate-to-severe plaque psoriasis ≥ 6 months' duration, ≥ 10% BSA, PASI of 12 or greater, PGA score of 3 or higher.	Age: mean age 45 Gender: 68 to 69% male Race/ethnicity: 90 to 91% White	NR	Amgen
Mease et al.,[25] 2018 Belgium, Bulgaria, Czech Republic, Estonia, Poland, Spain, and Ukraine Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active psoriatic arthritis (EQUATOR): results from a randomized, placebo-controlled, phase 2 trial NCT03101670 Fair	Eligible patients were 18 years or older, met CASPAR criteria, with a diagnosis of psoriatic arthritis for at least 12 weeks, with active moderate-to-severe disease defined as at least 5 swollen joints (from a 66 swollen joint count) and at least 5 tender joints (from a 68 tender joint count), history of plaque psoriasis, and an insufficient response or intolerance to at least 1 conventional DMARD, which were allowed during the study if they had received this treatment for at least 12 weeks and were on a stable dose for at least 4 weeks. Exclusion criteria receipt of more than 1 anti-TNF agent, or any alkylating agent, JAK inhibitor, or other investigational or approved biologic immune modulator at any time. Intramuscular or intravenous corticosteroids or intra-articular injection within 4 weeks, receipt of	Eligible patients were 18 years or older. • Placebo: 50 (10.9) • Filgotinib: 49 (12.2) 66 (50.4%) female NR	Mean (SD) duration of psoriatic arthritis, years • Placebo: 7 (6·2) • Filgotinib: 7 (6.7) N (%) with concurrent use of DMARD • Placebo: 50 (76) • Filgotinib: 47 (72) N (%) with concurrent use of steroids • Placebo: 16 (24) • Filgotinib: 17 (26)	Galapagos and Gilead Sciences

Author, Year Country Trial Name Registry Number Study Quality	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
	oral steroids (> 10 mg/day prednisone or equivalent), receipt of oral steroids (≤ 10 mg/day prednisone or equivalent) at a dose that was not stable for at least 4 weeks before baseline, or very poor functional status or inability to perform self-care.			
Mease et al.,[24] 2018 Australia, Bulgaria, Czech Republic, Germany, Hungary, Latvia, New Zealand, Poland, Romania, Spain, United States Phase II Study of ABT-122, a Tumor Necrosis Factor- and Interleukin-17A-Targeted Dual Variable Domain Immunoglobulin, in Patients with Psoriatic Arthritis With an Inadequate Response to Methotrexate NCT02349451 Fair	Adults with active psoriatic arthritis (defined as fulfilling the Classification of Psoriatic Arthritis Study Group) for at least 3 months, as well as 3 or more tender joints or swollen joints at screening, and at least 1 psoriatic plaque of at least 2 cm in diameter. Patients were included if were receiving a stable dosage of methotrexate at ≥ 10 mg/week for ≥ 4 weeks. Patients were excluded if they had prior exposure to adalimumab or another TNF inhibitor if the TNF inhibitor was discontinued for lack of efficacy or safety reasons or the drug had not been washed out for ≥ 5 half-lives; prior exposure to other non-TNF inhibitors or IL-17 inhibitor biologic DMARDs, unless washed out for > -5 half-lives; current treatment with conventional synthetic DMARDs other than methotrexate, sulfasalazine, and hydroxychloroquine; having received orally administered prednisone or its	Mean (SD) age in years • Placebo: 47.7 (13.7) • Adalimumab: 50.5 (12.0) • Remtolumab 120 mg: 51.0 (12.4) • Remtolumab: 240 mg: 47.4 (13.8) N (%) female • Placebo: 12 (50.0) • Adalimumab: 33 (45.8) • Remtolumab 120 mg: 37 (52.1) • Remtolumab 240 mg: 37 (50.7) N (%) White • Placebo: 24 (100) • Adalimumab: 70 (97.2) • Remtolumab 120 mg: 70 (98.6) • Remtolumab 240 mg: 70 (95.9)	Mean (SD) Duration of PsA in years • Placebo: 7.6 (7.2) • Adalimumab: 8.4 (9.2) • Remtolumab1 20 mg: 5.9 (7.1) • Remtolumab2 40 mg:7.5 (8.2) Mean (SD) PASI (in patient with ≥ 3% BSA) • Placebo: 8.8 (4.6) • Adalimumab: 11.9 (9.3) • Remtolumab 120 mg: 11.8 (9.5) • Remtolumab 240 mg: 14.9 (12.9)	AbbVie

Author, Year Country Trial Name Registry Number Study Quality	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
	equivalent a ≥ 10 mg/day within 30 days of the baseline visit; current pregnancy or breastfeeding; and presence of active TB, chronic recurring infections or active viral infections.			
Mease et al.,[45] 2017 Strand et al.,[79] 2019 126 centers worldwide Tofacitinib or Adalimumab versus Placebo for Psoriatic Arthritis (OPAL-Phase III)[45] Tofacitinib or adalimumab versus placebo: patient-reported outcomes from OPAL Broaden-a phase III study of active psoriatic arthritis in patients with an inadequate response to conventional synthetic disease-modifying antirheumatic drugs[79] NCT01877668 Fair	Adult patients with active psoriatic arthritis of at least 6 months, TNF-inhibitor-naïve with an inadequate response to at least 1 DMARD.	Age: mean age in the 3 active groups ranged from 47 to 49 years of age Gender: 47% to 60% were females Race/ethnicity: White ranged from 93% to 98%	88% of tofacitinib 10 mg group had concomitant use of methotrexate, 85% of tofacitinib 5 mg group, and 75% of the adalimumab group	Pfizer
Mease et al.,[44] 2017 114 study sites in 15 countries; Ixekizumab, an interleukin-17A specific mono-clonal antibody, for the treatment of biologic-naïve patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active	Adult patients with active psoriatic arthritis of at least 6 months, biologic therapy-naïve	Age: mean age in the 3 active groups ranged from 49 to 50 years of age Gender: 42 to 51% were males Race/ethnicity: White ranged from 93 to 95%;	Methotrexate use ranged from 53 to 56%	Eli Lilly

Author, Year Country Trial Name Registry Number Study Quality	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
(adalimumab)-controlled period of the phase III trial SPIRIT-P1 NCT01695239 Fair				
Papp et al.,[27]2018 United States, Japan, Poland, Canada, Germany, Latvia, Mexico, and Australia Phase 2 Trial of Selective Tyrosine Kinase 2 Inhibition in Psoriasis NCT02931838 Fair	Adults with moderate-to-severe plaque psoriasis ≥ 6 months' duration; BMI between 18 and 40; eligible for phototherapy or systemic therapy; BSA ≥ 10%; PASI ≥ 12; PGA ≥ 3.	Mean (SD) age in years • Placebo: 46 (12) • BMS-986165: 45 (13) N (%) female • Placebo: 8* (18)* • BMS-986165: 73* (27)* N (%) White • Placebo: 40 (89) • BMS-986165: 225 (84) N (%) Asian • Placebo: 5 (11) • BMS-986165: 36 (13) N (%) Other • Placebo: 0 (0) • BMS-986165: 6 (2)	Median (range) duration of disease in years • Placebo: 18 (2 to 48) • BMS-986165: 15 (1 to 61) Mean (SD) PASI score • Placebo: 19 (6) • BMS-986165: 18 (6)	Bristol-Myers Squibb
Papp et al.,[26] 2018 Canada, Czech Republic, Hungary, Japan, Poland, and United States Dual neutralization of both interleukin 17A and interleukin 17F with bimekizumab in patients with psoriasis: Results from BE ABLE 1, a 12-week, randomized, double-blinded, placebo-controlled phase 2b trial	Adults with moderate-to-severe plaque psoriasis ≥ 6 months' duration, involving ≥ 10% BSA., IGA score of ≥ 3 on a 5-point scale, and who were candidates for systemic psoriasis therapy or phototherapy. Patients were excluded if they had prior treatment with an anti-IL-17 therapy or prior exposure to > 1 other biologic therapy for psoriasis or psoriatic arthritis, a significant	Eligible patients were > 18 years of age. Mean (SD): 44.3 (13.7) 87 (34.8%) female 27 (10.8%) nonwhite	Disease duration, years, median (range), 15.0 (0 to 58.7) PASI, mean (SD), 19.1 (6.5) N (%) other characteristics	UCB Pharma

Author, Year Country Trial Name Registry Number Study Quality	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
NCT02905006 Fair	uncontrolled neuropsychiatric disorder, history of a suicide attempt, or suicide ideation within 6 months.		• Prior systemic therapy 177 (70.8) • Prior biologic therapy 58 (23.2) • Prior nonbiologic systemic therapy 90 (36.0) • Prior systemic phototherapy 122 (48.8)	
Papp et al.,[46] 2017 32 sites across North America and Europe Risankizumab versus Ustekinumab for Moderate-to-Severe Plaque Psoriasis; NCT02054481 Fair	Adult patients 18 to 75 years of age with stable moderate-to-severe chronic plaque psoriasis > 6 months' duration, with or without psoriatic arthritis, involving ≥ 10% BSA, PASI score of 12 or higher PGA score of 3 or higher, biologic-naïve.	Age: mean age 46 ± 14 Gender: 66% male Race/ethnicity: 91% White	NR	Boehringer Ingelheim

Author, Year Country Trial Name Registry Number Study Quality	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
Reich et al.,[32] 2017 Reich et al.,[75] 2019 Gordon et al.,[76] 2018 United States, Australia, Canada, Czechia, Germany, Hungary, Republic of Korea, Poland, Russia, Spain, Taiwan Anxiety and depression in patients with moderate-to-severe psoriasis and comparison of change from baseline after treatment with guselkumab vs. adalimumab: results from the Phase 3 VOYAGE 2 study Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate-to-severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE-2 trial[32] Guselkumab improves work productivity in patients with moderate-to-severe psoriasis with or without depression and anxiety: results from the VOYAGE-2 comparator study versus adalimumab[75] NCT02207244 Fair	Adults (aged ≥ 18 years) with moderate-to-severe plaque psoriasis (as per IGA score ≥ 3, PASI score ≥ 12, BSA ≥ 10%) for at least 6 months and were candidates for systemic therapy or phototherapy. Patients were ineligible if they had a history or current signs of a severe, progressive, or uncontrolled medical condition or had current or history of malignancy, except nonmelanoma skin cancer, within 5 years. Patients could not participate if they received guselkumab or adalimumab previously; other anti-TNF-α therapy (within 3 months); other treatment targeting IL-12/23, IL-17, or IL-23 (6 months); or any systemic immunosuppressants (e.g., methotrexate) or phototherapy (4 weeks).	Patients ≥ 18 years of age Mean (SD) • Adalimumab: 43.2 (11.9) • Guselkumab: 43.7 (12.2) 225 (30.2%) female *among guselkumab and adalimumab groups 11 (1.48%) African American 109 (14.7%) Asian *among guselkumab and adalimumab groups	Duration of psoriasis, Mean (SD) in years • Adalimumab: 17.6 (11.7) • Guselkumab: 17.9 (12.0) PASI score, 0 to 72, Mean (SD) • Adalimumab: 21.7 (9.0) • Guselkumab: 21.9 (8.8) Prior Biologic agents, N (%) • 150 (20.2%)	Janssen Research & Development

Author, Year Country Trial Name Registry Number Study Quality	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
Reich et al.,[31] 2019 Australia, Canada, Czech Republic, France, Germany, Hungary, Poland, Spain, United States Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): results from a phase 3, randomized controlled trial NCT03090100 Fair	Patients with moderate-to-severe psoriasis over the age of 18; PASI ≥ 12; IGA ≥ 3; BSA ≥ 10%, for ≥ 6 months who were candidates for phototherapy or systemic therapy. Patients were excluded if they had an uncontrolled medical condition, current or history of malignancy (except nonmelanoma skin cancer), inflammatory bowel disease, had previously taken guselkumab and secukinumab or any therapeutic agent directly targeted to IL12/23p40, IL-17 A, IL-17R, or IL-23 within 6 months prior to enrollment, or any systemic immunosuppressant or phototherapy within 4 weeks before enrollment.	Mean (SD) age in years • Overall: 45.8 (13.6) • Guselkumab: 46.3 (13.7) • Secukinumab: 45.3 (13.6) N (%) female • Overall: 341 (33) • Guselkumab: 169 (32) • Secukinumab: 172 (33) N (%) White: • Overall: 979 (93) • Guselkumab: 499 (93) • Secukinumab: 480 (93) N (%) Asian: • Overall: 30 (3) • Guselkumab: 18 (3) • Secukinumab: 12 (2) N (%) Black or African American: • Overall: 16 (2) • Guselkumab: 5 (1) • Secukinumab: 11 (2) N (%) Other: • Overall: 23 (2) • Guselkumab: 12 (2) • Secukinumab: 11 (2)	Mean (SD) PASI • Overall: 20.0 (7.5) • Guselkumab: 20.0 (7.4) • Secukinumab: 20.1 (7.6) Duration of psoriasis in years • Overall: 18.4 (12.4) • Guselkumab: 18.5 (12.2) • Secukinumab: 18.3 (12.7)	Janssen Research & Development
Reich et al.,[30] 2019 Canada, Germany, Japan, Poland, United States Efficacy and safety of mirikizumab (LY3074828) in the treatment of	Adults age 18 to 75 years with plaque psoriasis vulgaris for at least 6 months; ≥ 10% BSA involved; absolute PASI score ≥ 12; PGA score of ≥ 3; eligible for biologic treatment; Patients were excluded if they had	All participants ranged ages 18 to 75; mean (SD) age in years • Placebo: 46.0 (12.4) • Mirikizumab 30 mg: 49.2 (13.3)	Mean (SD) Duration of Psoriasis • Placebo: 18.0 (9.8)	Eli Lilly and Company

Author, Year Country Trial Name Registry Number Study Quality	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
moderate-to-severe plaque psoriasis: results from a randomized phase II study NCT02899988 Fair	used anti-tumor necrosis factor or anti-IL-17 in the last 8 weeks or any IL-23 targeting biologic, with the exception of briakinumab.	• Mirikizumab 100 mg: 46.0 (13.2) • Mirikizumab 300 mg: 47.5 (13.2) N(%) female • Placebo: 10* (19)* • Mirikizumab 30 mg: 12* (24)* • Mirikizumab 100 mg: 16* (31)* • Mirikizumab 300 mg: 15* (29)* NR	• Mirikizumab 30 mg: 20.4 (13.5) • Mirikizumab 100 mg: 18.6 (11.3) • Mirikizumab 300 mg: 18.1 (12.7) Mean (SD) PASI • Placebo: 19.7 (7.4) • Mirikizumab 30 mg: 21.0 (8.4) • Mirikizumab 100 mg: 20.3 (8.0) • Mirikizumab 300 mg: 18.4 (6.9) 41% of patients had been previous treated with biologics	

Author, Year Country Trial Name Registry Number Study Quality	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
Reich et al.,[29] 2019 Canada, Czech Republic, Germany, Finland, France, Mexico, Poland, Portugal, Sweden, Taiwan, United States Risankizumab compared with adalimumab in patients with moderate-to-severe plaque psoriasis (IMMvent): a randomized, double-blind, active-comparator-controlled phase 3 trial NCT02694523 Fair	Adults (aged ≥18 years) with moderate-to-severe chronic plaque psoriasis ≥ 6 months, involving ≥ 10% BSA, with a PASI of 12 or higher, and a static PGA score of 3 or higher. Patients were required to be candidates for systemic therapy or phototherapy and eligible for adalimumab treatment in accordance with local approved labeling.	Patients ≥ 18 years of age • Risankizumab: 45.3 (13.8) • Adalimumab: 47.0 (13.1) 183 (30.2%) female 17 (2.81%) Black or African American 76 (12.6%) Asian 508 (83.9%) White 4 (0.1%) Other	PASI, Mean (SD) • Risankizumab: 20.0 (7.5) • Adalimumab: 19.7 (7.5) Any previous biologic treatment, N (%) • Risankizumab: 118 (39%) • Adalimumab: 111 (37%) Previous non-TNF-α treatment, N (%) • Risankizumab: 95 (32%) • Adalimumab: 83 (27%)	AbbVie and Boehringer Ingelheim
Reich et al.,[28] 2017 Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Hungary, Italy, Israel, Netherlands, Poland, and United States Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomized controlled, phase 3 trials NCT01729754	Adults with moderate-to-severe plaque psoriasis involving ≥ 10% BSA., ≥ 3 PGA, ≥ 12 PASI, candidates for phototherapy or systemic therapy, women could not be pregnant and those of childbearing age had to practice abstinence or use contraception. Patients were excluded if they had active or latent tuberculosis, infection requiring antibiotic treatment with 2 weeks of screening, severe infection requiring hospital	Mean (SD) in years • Placebo: 46.4 (12.2) • Etanercept: 45.8 (14.0) • Tildrakizumab 100 mg: 44.6 (13.6) • Tildrakizumab 200 mg: 44.6 (13.6) N (%) female • Placebo: 89* (28)* • Etanercept: 87* (28)* • Tildrakizumab 100 mg: 91* (29)*	Mean (SD) % BSA • Placebo: 31.3 (14.8) • Etanercept: 31.6 (16.6) • Tildrakizumab 100 mg: 34.2 (18.5) • Tildrakizumab 200 mg: 31.8 (17.2) Mean (SD) PASI	Merck & Co

Author, Year Country Trial Name Registry Number Study Quality	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
Fair	admission of intravenous antibiotics within 8 weeks of study, live viral or bacterial vaccination within 4 weeks of study, HIV, hepatitis B, hepatitis C, previous malignancy, hospitalization for acute cardiovascular event, illness, or surgery within 6 months of trials, uncontrolled hypertension, uncontrolled diabetes, or previous use of tildrakizumab or etanercept.	• Tildrakizumab 200 mg: 44* (28)* N (%) White • Placebo: 144 (92) • Etanercept: 289 (92) • Tildrakizumab 100 mg: 279 (91) • Tildrakizumab 200 mg: 284 (90) N (%) Asian • Placebo: 3 (2) • Etanercept: 10 (3) • Tildrakizumab 100 mg: 9 (3) • Tildrakizumab 200 mg: 14 (4) N (%) Other • Placebo: 9 (6) • Etanercept: 14 (4) • Tildrakizumab 100 mg: 19 (6) • Tildrakizumab 200 mg: 16 (5)	• Placebo: 20.0 (7.6) • Etanercept: 20.2 (7.4) • Tildrakizumab 100 mg: 20.5 (7.6) • Tildrakizumab 200 mg: 19.8 (7.5) N (%) previously treated with biologics • Placebo: 20 (13) • Etanercept: 37 (12) • Tildrakizumab 100 mg: 39 (13) • Tildrakizumab 200 mg: 38 (12	
Reich et al.,[48] 2017 Paul et al,.[52] 2018 Multiple countries including Germany, France, Spain, Italy, Switzerland, Canada, United States (51 sites, 13 countries) Comparison of ixekizumab with ustekinumab in moderate-to-severe	Adult patients with moderate-to-severe plaque psoriasis ≥ 6 months' duration and PASI ≥ 10, PASI score ≥ 10; previously failed or had a contraindication or intolerability to at least 1 systemic therapy (including ciclosporin, methotrexate and phototherapy).	Age: mean age for both groups 43 to 44 Gender: 66 to 68% male Race/ethnicity: 93 to 96% White	NR	Eli Lilly and Company

Author, Year Country Trial Name Registry Number Study Quality	Population	Age Gender Race/Ethnicity	Other Population Characteristics	Funding
psoriasis: 24-week results from IXORA-S, a phase III study[48] Ixekizumab provides superior efficacy compared with ustekinumab over 52 weeks of treatment: Results from IXORA-S, a phase 3 study[52] NCT02561806 Fair				
Reich et al.,[47] 2017 Multiple Countries including Germany, Canada, United States, United Kingdom The efficacy and safety of apremilast, etanercept and placebo in patients with moderate-to-severe plaque psoriasis: 52-week results from a phase IIIb, randomized, placebo-controlled trial (LIBERATE) NCT01690299 Fair	Adult patients with moderate-to-severe plaque psoriasis for ≥ 12 months (BSA ≥ 10%, PASI ≥ 12, PGA ≥ 3) and inadequate response, intolerance or contraindication to ≥ 1 conventional systemic agent for treatment of psoriasis, no prior exposure to a biologic therapy.	Age: mean age in the 2 groups ranged from 46 to 47 years of age Gender: 59% to 70% males Race/ethnicity: White ranged from 90 to 95%	NR	Celgene Corporation

Abbreviations: BMI: body mass index; BMS: Bristol-Myers Squibb; BSA: body surface area; CASPAR: classification for psoriatic arthritis; DMARD: disease-modifying antirheumatic drug; HAQ: Health Assessment Questionnaire; HIV: human immunodeficiency virus; IGA: Investigator's Global Assessment; IL: interleukin; IQR: interquartile range; JAK: janus kinase; NCT: U.S. National Clinical Trial; NR: not reported; PASI: Psoriasis Area and Severity Index; NSAID: nonsteroidal anti-inflammatory drug; PGA: Physicians Global Assessment; PsA: psoriatic arthritis; RCT: randomized controlled trial; SD: standard deviation; SPARCC EI: Spondyloarthritis Research Consortium of Canada Enthesitis Index; TB: tuberculosis; TIM: targeted immune modulator; TNF-α: tumor necrosis factor alpha; UV: ultraviolet.

Table B2. Evidence Table for RCTs of TIMs for Plaque Psoriasis and Psoriatic Arthritis (Intervention and Results)

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
Araujo et al.,[15] 2019 ECLIPSA Poor	Ustekinumab 45 m SC (body weight < 100 kg) or 90 mg (body weight > 100 kg body weight) at weeks 0, 4, 12, and 24. TNF-α inhibitor at standard approved doses and frequency. The choice of TNF-α inhibitor was according to patient's preferences related to route and frequency of administration.	Ustekinumab: 23 TNF-α inhibitor: 24 (adalimumab: 10, certolizumab: 6; etanercept: 5, infliximab: 3) Total: 47	*Primary outcomes at week 24* **SPARCC EI 0** Ustekinumab: 17*(73.9) TNF-α inhibitor: 10* (41.7); *P* = .018 **SPARCC EI (repeated measures)** *P* = .007 favoring ustekinumab *Secondary outcomes at week 24* **MASES 0** Ustekinumab: 19* (82) TNF-α inhibitor: 12* (50); *P* = .002 **MASES (repeated measures)** *P* = .022 favoring ustekinumab **LEI 0** Ustekinumab: 18* (78) TNF-α inhibitor: 12*(50); *P* = .032 LEI indices (repeated measures), *P* = 0.074 **TJC 0** Ustekinumab: 12 (54) TNF-α inhibitor: 11 (46); *P** = .78 TJC score (repeated measures), *P* = .889 **SJC 0** Ustekinumab: 14* (59) TNF-α inhibitor: 11* (46); *P** = .38 SJC score (repeated measures), *P* = .957 **PASI 100** Ustekinumab: 14* (59) TNF-α inhibitor: 7* (29); *P* = .039 **PASI 90** Ustekinumab: 20*(86) TNF-α Inhibitor: 7* (29); *P* < .001 **PASI score** (repeated measures)	NR	NR

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			P = .03, favoring ustekinumab **MDA 5/7** Ustekinumab: 18* (77) TNF-α Inhibitor: 11* (45); *P* = .04 **SF-36 PCS** (repeated measures), *P* < .001, favoring ustekinumab **SF-36 MCS** (repeated measures), *P* = .509		
Atteno et al.,[34] 2010 None Poor	Infliximab 5mg/kg every 6 to 8 weeks, Etanercept 25 mg twice weekly, Adalimumab 40 mg every other week	Infliximab: 30 Etanercept: 36 Adalimumab: 34 Total: 100	*At 1 year* **Median (IQR) PASI** Etanercept: 2 (4.4) Adalimumab: 0.1 (1.90 Infliximab: 0.0 (1) Overall: 0.6 (2) *P* < .01 **Median (IQR) HAQ** Etanercept: 0.1 (0.1) Adalimumab: 0.1 (0.2) Infliximab: 0.1 (0) Overall: 0.1 (0.1) *P* = .60 **Median (IQR) tender joints** Etanercept: 1(1) Adalimumab: 1 (2) Infliximab: 1 (1.8) Overall: 1(1) *P* = .12 **Median (IQR) swollen joints** Etanercept: 0 (1) Adalimumab (0.5 (1) Infliximab: 1 (1) Overall: 0 (1) *P* = .23 **% ACR20 Response** Etanercept: 72	**% AE** Infliximab: 23 Etanercept: 17 Adalimumab: 6 *P* = .001 RR* 0.38, 95% CI, 0.17 to 0.84, for adalimumab vs. etanercept: RR*, 0.23; 95% CI, 0.11 to 0.49, for adalimumab vs. infliximab RR*, 1.6; 95% CI, 1.1 to 2.4 for Infliximab vs. etanercept **SAEs** Two SAEs occurred in the infliximab group (pneumonitis and thrombocytopenia). Both were considered drug related and resolved with drug withdrawal and	No cases of tuberculosis or demyelinating disease were reported.

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			Adalimumab: 70 Infliximab: 75	treatment.	
Bachelez et. al.,[35]2015 Valenzuela et al.,[51] 2016 OPT Fair	Tofacitinib 5 mg twice daily, Tofacitinib 10 mg twice daily, Etanercept 50 mg subcutaneously twice weekly Placebo	1,106	*Primary outcomes at week 12* **% PASI 75** 39.5% (tofacitinib 5 mg) vs. 63.6% (tofacitinib 10 mg) vs. 58.8% (etanercept 50 mg) ARD 5 mg vs. etanercept: -19.3, *P* < .001 ARD 10 mg vs. etanercept: 4.8, *P* = .20 **% PGA 0 or 1** 47.1% (tofacitinib 5 mg) 68.2% (tofacitinib 10 mg) 66.3% (etanercept) ARD 5 mg vs. etanercept: -19.2, *P* < .001 ARD 10 mg vs. etanercept: 1.9; *P* = .60 *Secondary outcomes at week 12* **% PASI 90** 21.0 % (tofacitinib 5 mg) 36.1% (tofacitinib 10 mg) 32.2% (etanercept) ARD 5 mg vs. etanercept: -11.3, *P* = .0009 ARD 10 mg vs. etanercept: 3.8; *P* = .30 **% PASI 50** 65.7% (tofacitinib 5 mg) 80.6% (tofacitinib 10 mg) 80.3% (etanercept) ARD 5 mg vs. etanercept: -14.6, *P* < .001	**% treatment-related AE** RR (95% CI compared to tofacitinib) Etanercept 50 mg: 57% Tofacitinib 5 mg: 55% 1.1 (0.92 to 1.2) Tofacitinib 10 mg: 60% 0.96 (0.84 to 1.1) **% serious treatment-related AE** Etanercept 50 mg: 2% Tofacitinib 5 mg: 2% 0.98 (0.35 to 2.8) Tofacitinib 10 mg: 2% 1.1 (0.39 to 3.4) **% severe treatment-related AE** Etanercept 50 mg: 2% Tofacitinib 5 mg: 2% Tofacitinib 10 mg: 2% **% withdrawal of treatment due to AE** Etanercept 50 mg:	**% infections and infestations** Tofacitinib 5 mg: 19% Tofacitinib 10 mg: 22% Etanercept 50 mg: 23% **% serious infections** Tofacitinib 5 mg: 1% perforated diverticulitis, extradural abscess Tofacitinib 10 mg: 1% pneumonia, paronychia Etanercept 50 mg: 1% bronchitis, perineal abscess **% gastrointestinal disorders** Tofacitinib 5 mg: 9% Tofacitinib 10

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			ARD 10 mg vs. etanercept: 0.3; *P* = .92 **% DLQI reduction ≥ 5 points** 66.3% (tofacitinib 5 mg) 78.2% (tofacitinib 10 mg) 74.7% etanercept ARD 5 mg vs. etanercept: -8.3; *P* = .03 ARD 10 mg vs. etanercept: 3.5; *P* = .31 **% DLQI 0 or 1** 30.9% (tofacitinib 5 mg) vs. 47.3% (tofacitinib 10 mg) vs. 43.6% (etanercept 50 mg), *P* = NR **Mean (SE) change SF-36 PCS** 4.0 (0.4) (tofacitinib 5 mg) vs. 5.4 (0.4) (tofacitinib 10 mg) vs. 5.0 (0.4) (etanercept 50 mg), *P* = NR **Mean (SE) change SF-36 MCS** 5.2 (0.5) (tofacitinib 5 mg) vs. 7.6 (0.5) (tofacitinib 10 mg) vs. 5.9 (0.5) (etanercept 50 mg), *P* = NR **PtGA:** 30.4% (tofacitinib 5 mg) vs. 51.8% (tofacitinib 10 mg) vs. 49.0% (etanercept 50 mg), *P* = NR, rates reported as 'similar' **% ISI (little or no itch):** 55.6% (tofacitinib 5 mg) vs. 68.6% (tofacitinib 10 mg) vs. 57.4% (etanercept 50 mg), *P* < 0.05 for 10 mg tofacitinib vs. etanercept	3% Tofacitinib 5 mg: 1% 3.6 (1.01 to 12.8) Tofacitinib 10 mg: 3% 1.1 (0.47 to 2.5)	mg: 9% Etanercept 50 mg: 9% **General disorders and administration site conditions** (among others: Injection site erythema, Injection site reaction) Tofacitinib 5 mg: 6% Tofacitinib 10 mg: 6% Etanercept 50 mg: 15% **Major cardiac events** Tofacitinib 5 mg: 0.3% Myocardial Infarction Tofacitinib 10 mg: 0 Etanercept 50 mg: 0.3%; Stroke or transient ischemic attack **Mortality** 0 in all groups

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
Bagel et al.,[16] 2018 CLARITY Fair	Secukinumab 300 mg SC at baseline, weeks 1, 2, and 3, and then every 4 weeks from weeks 4 Ustekinumab SC 45 mg (for patients weighing ≤ 100 kg) or 90 mg (for patients weighing patients > 100 kg) at baseline, week 4, and then every 12 weeks	Secukinumab 300 mg: 550 Ustekinumab 45/90 mg: 552 Total: 1,102	*Primary Outcomes at week 12* **N (%) PASI 90** Secukinumab: 366 (66.5) Ustekinumab: 264 (47.9) *P* < .001 **N (%) IGA 0 or 1** Secukinumab: 398 (72.3) Ustekinumab: 264 (55.4) *P* < .001 *Secondary outcomes* **% PASI 90 at week 16** Secukinumab: 76.6 Ustekinumab: 54.2 *P* < .001 **N (%) PASI 75 at week 12** Secukinumab: 484 (88.0) Ustekinumab: 410 (74.2) *P* < .001 **N (%) PASI 100 at week 16** Secukinumab: 249 (45.3%) Ustekinumab: 147 (26.7%) *P* < .001 **N (%) IGA 0 or 1 at week 16** Secukinumab: 432 (78.6%) Ustekinumab: 326 (59.1%) *P* < .001 **N (%) PASI 100 at week 12** Secukinumab: 210 (38.1%) Ustekinumab: 111 (20.1%) *P* < .001 **N (%) PASI 75 at week 16** Secukinumab: 504 (91.7%) Ustekinumab: 440 (79.8%) *P* < .001 **% DLQI 0 or 1 at week 12**	**N (%) TEAE** Secukinumab: 261 (47.5%) Ustekinumab: 256 (46.4%) RR*, 1.0; 95% CI, 0.90 to 1.2 **N (%) serious TEAE** Secukinumab: 14 (2.5%) Ustekinumab: 9 (1.6%) RR*, 1.6; 95% CI, 0.68 to 3.6 **N (%) withdrawal due to AEs** Secukinumab: 11 (2.0%) Ustekinumab: 7 (1.3%) RR*, 1.6; 95% CI, 0.62 to 4.0	**N (%) infections and infestations** Secukinumab: 122 (22.2%) Ustekinumab: 117 (21.2%) RR*, 1.0; 95% CI, 0.84 to 1.3 There were 2 deaths, 1 due to acute intoxication by cocaine and another due to sudden cardiac death (patient had a history of hypertension and atherosclerosis). Most frequent AEs included nasopharyngitis, upper respiratory infection diarrhea, headache, and sinusitis.

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			Secukinumab: 64.0% Ustekinumab: 51.7% *P* < .001 **N (%) DLQI 0 or 1 at week 16** Secukinumab: 376 (68.4%) Ustekinumab: 309 (55.9%) *P* < .001		
Blauvelt et al.,[17]2017 Papp et al.,[74] 2018 VOYAGE-1 Fair	Guselkumab 100 mg SC at 0, 4, 12 weeks Adalimumab 80 mg SC at week 0 and 40 mg at weeks 1 and every 2 weeks after This study also included a placebo arm.	Guselkumab: 329 Adalimumab: 334 Total: 837	*Primary outcomes at week 16* **N (%) IGA 0 or 1** Guselkumab: 280 (85.1) Adalimumab: 220 (65.9) ARD*. 19.2%; 95% CI, 12.9% to 25.6% RR*, 1.3; 95 %CI, 1.2 to 1.4 **N (%) PASI 90** Guselkumab: 241 (73.3) Adalimumab: 166 (49.7) ARD*, 23.6%; 95% CI, 16.4% to 30.7% RR*, 1.5; 95 %CI, 1.3 to 1.7 *Secondary outcomes at week 16* **N (%) PASI 100** Guselkumab: 123 (37.4) Adalimumab: 57 (17.1) ARD*, 20.3%; 95% CI, 13.7% to 26.9% RR*, 2.2; 95 %CI, 1.7 to 2.9 **N (%) IGA 0** Guselkumab: 157 (47.7) Adalimumab: 88 (26.3) ARD*, 21.4%; 95% CI, 14.2% to 28.6%	*At 16 weeks* **N (%) AEs** Guselkumab: 170 (51.7) Adalimumab: 170 (51.1) RR* 1.01 (95% CI, 0.87 to 1.17) **N (%) SAEs** Guselkumab: 8 (2.4) Adalimumab: 6 (1.8) RR*, 1.35 (95% CI, 0.47 to 3.9) **N (%) withdrawal because of AE** Guselkumab: 4 (1.2) Adalimumab: 3 (0.9) RR*, 1.35; 95 % CI, 0.30 to 6.0	*At 16 weeks* **N (%) infections** Guselkumab: 85 (25.8) Adalimumab: 85 (25.5) RR*, 1.01; 95 % CI, 0.78 to 1.3 **N (%) injection site erythema** Guselkumab: 6 (1.8) Adalimumab: 15 (4.5) RR*, 0.40; 95% CI, 0.16 to 1.03

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			RR* 1.8 (95 %CI, 1.5 to 2.2) **N (%) PASI 75** Guselkumab: 300 (91.2) Adalimumab: 244 (73.1) ARD*, 18.1%; 95% CI, 12.5% to 23.8% RR*, 1.2; 95 %CI, 1.2 to 1.3 **Mean (SD) change in DLQI** Guselkumab: -11.2 (7.2) Adalimumab: -9.3 (7.8) AMD, -1.9; 95% CI, -3.1 to -0.74; *P* = .001 **Mean (SD) change in PSSD symptom score** Guselkumab: -41.9 (24.6) Adalimumab: -35.4 (28.5) AMD, -6.5; 95% CI, -11.1 to -1.9; *P* = .006 **Mean (SD) change in PSSD sign score** Guselkumab: -44.6 (22) Adalimumab: -39.7 (26.4) AMD, -4.9; 95% CI, -9.1 to -0.70; *P* = .02		
Blauvelt et al.,[36] 2017 Blauvelt et al.,[77] 2016 Thaci et al.,[53] 2015 CLEAR Fair	Secukinumab 300 mg SC at weeks 0, 1, 2, and 3 then every 4 weeks Ustekinumab SC 45 mg or 90 mg (if patient weight more than 100 kg) at weeks 0, 4, and then every 12 weeks 52 weeks	Secukinumab: 337 Ustekinumab: 339 Total: 676	*Primary outcome at week 16* **PASI 90** 79.0% (secukinumab) vs. 57.6% (ustekinumab), *P* < .001 *Secondary outcomes at week 16* **PASI 100** 44.3% (secukinumab) vs. 28.4% (ustekinumab); *P* < .001 **PASI 75** 93.1% (secukinumab) vs. 82.8% (ustekinumab); *P* < .001 **IGA 0 or + an improvement of ≥ 2 points** 82.9% (secukinumab) vs. 67.5% (ustekinumab); *P* < .001	**% AE** Secukinumab: 64% (215 of 335) Ustekinumab: 58% (196 of 336) **% nonfatal SAE** Secukinumab: 3% (10 of 335) Ustekinumab: 3% (10 of 336) **% withdrawals because of AE**	**Infections and infestations** Secukinumab: 29% (98 of 335) Ustekinumab: 25% (85 of 336) **Most common AEs** (headache,

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			DLQI 0 or 1 71.9% (secukinumab) vs. 57.4% (ustekinumab); *P* < .001 **Change in mean (SD) symptom scores** **Pain** Secukinumab: -3.3 (0.8) vs. ustekinumab: -2.8 (1.0); *P* = .0414 **Itching** Secukinumab -5.0 (1.2) vs. ustekinumab -4.6 (1.6); *P* = .0053 **Scaling** Secukinumab -5.7 (0.8) vs. ustekinumab -5.2 (1.3); *P* < .001 *Outcomes at week 52* **PASI 90** 74.9% (secukinumab) vs. 60.6% (ustekinumab); *P* < .001 **PASI 100** 44.9% (secukinumab) vs. 36.7% (ustekinumab); *P* = .03 **IGA 0 or 1** Actual values NR, but secukinumab > ustekinumab (*P* < .001) **PASI 75** Actual values NR, but secukinumab > ustekinumab (*P* < .001) **DLQI (0 or 1)** 71.6% (secukinumab) vs. 59.2% (ustekinumab); *P* = .008 **Change in mean (SD) symptoms scores**, pain, itching, scaling only reported on figures, all were reported as statistically significant differences favoring secukinumab **EQ-5D-3L Visual Analog Scale (mean change)** 13.8 (secukinumab) vs. 10.6 (ustekinumab); *P* = .03	Secukinumab: 1% (3 of 335) Ustekinumab: 1% (4 of 336)	nasopharyngitis, diarrhea, fatigue, arthralgia) **Mortality** 0 in all groups

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			WPAI-PSO subscales **Absenteeism** -53% (secukinumab) vs. -39% (ustekinumab); *P* NS **Presenteeism** -89% (secukinumab) vs. -65% (ustekinumab); *P* < .01 **Work productivity loss** -81% (secukinumab) vs. -57% (ustekinumab); *P* < .01 **Overall daily activity impairment** -87% (secukinumab) vs. -76% (ustekinumab); *P* < .01)		
De Vries et al.,[37] 2017 PIECE Poor	Etanercept 50 mg subcutaneous twice weekly Infliximab 5 mg /kg intravenously at weeks 0, 2, 6 and every 8 weeks thereafter 24 weeks (induction phase)	Etanercept: 23 Infliximab: 25 Total: 48	*Primary outcome at week 24* **PASI 75** 72% (infliximab) vs. 35% (etanercept), *P* = .01 *Secondary outcomes at 24 weeks* **Skindex-17 relative reduction of symptoms** 29.9% (infliximab) vs. 25.1% (etanercept), *P* = .01 **Relative improvement on SF-36 PCS** 6.7% (infliximab) vs. 9.9% (etanercept), *P* = .32 **Relative improvement on SF-36 MCS** 0.6% (infliximab) vs. 2.2% (etanercept), *P* = .58	**% AE** Infliximab: 96 Etanercept: 100 SAEs: Infliximab: 0.5 Etanercept: 0.7 **% AE leading to drug withdrawal** Infliximab: 12.0 Etanercept: 8.7	**% injection site or infusion reactions** Infliximab: 24 Etanercept: 9
Glatt et al.,[19]2017 NCT02529956 Fair	Patients were randomized to receive a one-time infusion of placebo, bimekizumab 8 mg, 40 mg, 160 mg, 480 mg, or 640 mg over 60 minutes duration	Placebo: 13 Bimekizumab 8 mg: 4 Bimekizumab 40 mg: 4 Bimekizumab 160 mg: 6 Bimekizumab 480 mg: 6 Bimekizumab 640 mg: 6	**Mean lesion severity score** reduction of >80% was observed in the 640 mg and 480 mg bimekizumab groups by week 2. Maximal reductions for most doses achieved by week 8 and maintained through week 16. The 95 % CI for placebo and bimekizumab 40 mg, 160 mg, 480 mg, and 640 mg groups did not overlap by week 2; at did not overlap for the 640 mg at any timepoint.	**N (%) TEAE** Placebo: 10 (76.9) Bimekizumab: 22 (84.6) RR*, 1.1; 95% CI, 0.78 to 1.5 **N (%) with treatment-related TEAE** Placebo: 4 (30.8) Bimekizumab: 12	**N (%) deaths:** 0 (0) Commonly reported AEs occurring in >10% of all subjects receiving bimekizumab: headache, oropharyngeal

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
		Total: 39	**PASI and PGA:** statistically significant % change from baseline for 160 mg, 480 mg, and 640-mg dosages compared to placebo at nearly all timepoints. (actual values NR, depicted on a figure)	(46.2) **N (%) with serious TEAEs** Placebo: 0 (0) Bimekizumab: 1 (3.8) **N (%) with severe TEAEs** Placebo: 0 (0) Bimekizumab: 0 (0) RR*, 1.6; 95% CI, 0.68 to 3.6 **N (%) withdrawals due to TEAEs** Placebo: 0 (0) Bimekizumab: 0(0) RR*, 1.0; 95% CI, 0.0004 to 249	pain, nasopharyngitis
Gordon et al.,[21] 2018 UltIMMa-1 UltIMMa-2 Fair	Risankizumab 150 mg SC at weeks 0, 4, 16, 28 and 40, Ustekinumab 90 mg (if body weight >100kg) or 45 mg (if body weight ≤100 kg) at week 0, 4, 16, 28, and 40	Risankizumab: 304 Ustekinumab: 100 Total: 506 (including 102 randomized to placebo)	***UltIMMA-1*** *Primary outcomes at 16 weeks* **N (%) PASI 90** Risankizumab: 229 (75.3) Ustekinumab: 42 (42.0) Difference from ustekinumab (95% CI) 33.5% (22.7% to 44.3%), *P* < .001 **N (%) PGA 0 or 1** Risankizumab: 267 (87.8) Ustekinumab: 63 (63.0) Difference from ustekinumab (95% CI) 25.1% (15.2% to 35.0%), *P* < .001 *Secondary outcomes at 16 weeks* **N (%) PGA 0** Risankizumab: 112 (36.8) Ustekinumab: 14 (14.0) Difference from ustekinumab (95% CI) 22.9% (14.3% to 31.6%), *P* < .001	***UltIMMA-1*** *Weeks 0 to 16* **N (%) AE** Risankizumab: 151 (49.7) Ustekinumab: 50 (50.0) *RR* (95% CI) 0.99 (0.79 to 1.2) **N (%) SAE** Risankizumab: 7 (2.3) Ustekinumab: 8 (8.0) *RR* (95% CI) 0.29 (0.11 to 0.77) **N (%) severe AE** Risankizumab: 6 (2.0) Ustekinumab: 3 (3.0) **N (%) AE leading to**	***UltIMMA-1*** *Weeks 0 to 16* **N (%) infections** Risankizumab: 75 (24.7) Ustekinumab: 20 (20.0) **N (%) deaths** Risankizumab: 0 (0) Ustekinumab: 0 (0) *Weeks 17 to 52* **N (%) infections**

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			N (%) PASI 100 Risankizumab: 109 (35.9) Ustekinumab: 12 (12.0), Difference from ustekinumab (95% CI) 23.8% (15.5% to 32.1%), *P* < .001 **N (%) DLQI 0 or 1** Risankizumab: 200 (65.8) Ustekinumab: 43 (43.0) Difference from ustekinumab (95% CI), 23.0% (11.9% to 34.0%), *P* < .001 **N (%) PSS 0** Risankizumab: 89 (29.3) Ustekinumab: 15 (15.0) Difference from ustekinumab (95% CI) 14.3% (5.8% to 22.8%), *P* = .001 **Mean (SD) change in PSS**, Risankizumab: -5.6 (0.2) Ustekinumab: -4.4 (0.3) Difference (95% CI) -1.2 (-1.9 to -0.4) *Outcomes at 52 weeks* **N (%) PASI 90** Risankizumab: 249 (81.9) Ustekinumab: 44 (44.0) Difference from ustekinumab (95% CI) 38.3% (27.9% to 48.6%), *P* < .001 **N (%) PASI 100** Risankizumab: 171 (56.3) Ustekinumab: 21 (21.0) Difference from ustekinumab (95% CI) 35.1% (25.7% to 44.6%), *P* < .001 **N (%) PGA 0** Risankizumab: 175 (57.6) Ustekinumab: 21 (21.0) Difference from ustekinumab (95%	**withdrawal** Risankizumab: 2 (0.7) Ustekinumab: 2 (2.0) *RR* (95% CI) 0.33 (0.05 to 2.3) *Weeks 17 to 52* **N (%) AE** Risankizumab: 182 (61.3) Ustekinumab: 66 (66.7) *RR* (95% CI) 0.92 (0.78 to 1.1) **N (%) SAE** Risankizumab: 16 (5.4) Ustekinumab: 4 (4.0) *RR* (95% CI) 1.3 (0.46 to 3.9) **N (%) severe AE** Risankizumab: 13 (4.4) Ustekinumab: 1 (1.0) **N (%) AE leading to drug withdrawal** Risankizumab: 0 (0) Ustekinumab: 0 (0) *RR* (95% CI) 0.33 (0.001 to 84.9) ***UltIMMA-2*** *Weeks 0 to 16* **N (%) AE** Risankizumab: 134 (45.6)	Risankizumab: 112 (37.7) Ustekinumab: 41 (41.4) **N (%) deaths** Risankizumab: 0 (0) Ustekinumab: 0 (0) ***UltIMMA-2*** *Weeks 0 to 16* **N (%) infections** Risankizumab: 56 (19.0) Ustekinumab: 20 (20.2) **N (%) deaths** Risankizumab: 1 (0.3) Ustekinumab: 0 (0) *Weeks 17 to 52* **N (%) infections** Risankizumab: 101 (34.7) Ustekinumab: 46 (48.9) **N (%) deaths** Risankizumab: 1 (0.3) Ustekinumab:

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			CI) 36.5% (27.0% to 45.9%), *P* < .001 ***UltIMMA-2*** *Primary outcome at week 16* **N (%) PASI 90** Risankizumab: 220 (74.8) Ustekinumab: 47 (47.5) Difference from ustekinumab (95% CI), *P* value 27.6% (16.7% to 38.5%), <.001 **N (%) PGA 0 or 1** Risankizumab: 246 (83.7) Ustekinumab: 61 (61.6) Difference from ustekinumab (95% CI), *P* value 22.3% (12.0% to 32.5%), <.001 *Secondary outcomes at week 16* **N (%) PGA 0** Risankizumab: 150 (51.0) Ustekinumab: 25 (25.3) Difference from ustekinumab (95% CI), *P* value 26.3% (16.1% to 36.4%), < .001 **N (%) PASI 100** Risankizumab: 149 (50.7) Ustekinumab: 24 (24.2) Difference from ustekinumab (95% CI), *P* value 27.0% (17.0% to 37.0%), <.001 **N (%) DLQI 0 or 1** Risankizumab: 196 (66.7) Ustekinumab: 46 (46.5) Difference from ustekinumab (95% CI), *P* value 20.2% (9.1% to 31.4%), <.001	Ustekinumab: 53 (53.5) *RR* (95% CI) 0.85 (0.68 to 1.1) **N (%) SAE** Risankizumab: 6 (2.0) Ustekinumab: 3 (3.0) *RR* (95% CI) 0.67 (0.17 to 2.6) **N (%) severe AE** Risankizumab: 7 (2.4) Ustekinumab: 6 (6.1) **N (%) AE leading to drug withdrawal** Risankizumab: 1 (0.3) Ustekinumab: 0 (0) *RR* (95% CI) 1.4 (0.02 to 107.4) *Weeks 17 to 52* **N (%) AE** Risankizumab: 162 (55.7) Ustekinumab: 70 (74.5) *RR* (95% CI) 0.75 (0.64 to 0.87) **N (%) SAE** Risankizumab: 13 (4.5), Ustekinumab: 4 (4.3) *RR* (95% CI) 1.1 (0.35 to 3.1) **N (%) severe AE** Risankizumab: 5 (1.7) Ustekinumab: 1 (1.1)	0 (0)

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			N (%) PSS 0 Risankizumab: 92 (31.3) Ustekinumab: 15 (15.2) Difference from ustekinumab (95% CI), *P* value 16.1% (7.5% to 24.8%), .0003 **Mean (SD) change in PSS**, difference (95% CI) Risankizumab: -6.4 (0.2) Ustekinumab: -5.6 (0.3) -0.8 (-1.6 to -0.1) *At 52 weeks* **N (%) PASI 90**, difference from ustekinumab (95% CI), *P* value Risankizumab: 237 (80.6) Ustekinumab: 50 (50.5) 30.2% (19.6% to 40.9%), <.001 **N (%) PASI 100**, difference from ustekinumab (95% CI), *P* value Risankizumab: 175 (59.5) Ustekinumab: 30 (30.3) 29.5% (18.9% to 40.1%), <.001 **N (%) PGA 0**, difference from ustekinumab (95% CI), *P* value Risankizumab: 175 (59.5) Ustekinumab: 30 (30.3) 29.5% (18.9% to 40.1%), <.001	**N (%) AE leading to drug withdrawal** Risankizumab: 2 (0.7) Ustekinumab: 2 (2.1) *RR* (95% CI) 0.32 (0.05 to 2.3)	
Gordon et al.,[20] 2015 X-PLORE Fair	Adalimumab 80 mg at week 0 and 40 mg at week 1 and every other week through week 39 Guselkumab 5 mg at weeks 0 and 4 and every 12 weeks	Placebo: 42 Adalimumab 40 mg: 43 Guselkumab 5 mg: 41 Guselkumab 15 mg: 41	*Primary outcomes at week 16 At 16 weeks* **N (%) PGA score 0 or 1** Between group difference in percentage points (95% CI) vs. adalimumab Adalimumab: 25 (58); NA Guselkumab 5 mg: 14 (34); NR	**N (%) AE** Guselkumab: 103 (50) Adalimumab: 24 (56) RR*, 0.89; 95% CI, 0.66 to 1.2 **N (%) SAE**	**N (%) infection** Guselkumab: 41 (20) Adalimumab: 5 (12) RR*, 1.7 (95%

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
	thereafter Guselkumab 15 mg every 8 weeks Guselkumab 50 mg at weeks 0 and 4 and every 12 weeks thereafter Guselkumab 100 mg every 8 weeks Guselkumab 200 mg at weeks 0 and 4 and every 12 weeks thereafter. This trial also included a placebo arm.	Guselkumab 50 mg: 42 Guselkumab 100 mg: 42 Guselkumab 200 mg: 42 Total: 293	Guselkumab 15 mg: 25 (61); NR Guselkumab 50 mg: 33 (79); 20% (2% to 39%) Guselkumab 100 mg: 36 (86); 28% (10% to 46%) Guselkumab 200 mg: 35 (83); 25% (7% to 44%) *Secondary outcomes at week 16* **N (%) PASI 75** Between group difference in percentage points (95%CI)* vs. adalimumab Adalimumab: 30 (70); NA Guselkumab 5 mg: 18 (44); NR Guselkumab 15 mg: 31 (76); NR Guselkumab 50 mg: 34 (81); 11.2% (-7.0% to 29.3%) Guselkumab 100 mg: 33 (79); 8.8% (-9.7% to 27.3%) Guselkumab 200 mg: 34 (81); 11.2% (-7.0% to 29.3%) **N (%) PASI 90** Between group difference in percentage points (95%CI)* vs. adalimumab Adalimumab: 19 (44); NA Guselkumab 5 mg: 14 (34); NR Guselkumab 15 mg; 14 (34); NR Guselkumab 50 mg: 19 (45); 1.1% (-20.1% to 22.2%) Guselkumab 100 mg: 26 (62); 17.7% (-3.2% to 38.6%) Guselkumab 200 mg: 24 (57); 13.0% (-8.1% to 34.0%) **N (%) PASI 100**	Guselkumab: 3 (1) Adalimumab: 1 (2) RR*, 0.62; 95% CI, 0.07 to 5.9 **N (%) withdrawal due to AE** Guselkumab: 5 (2) Adalimumab: 3 (7) RR*, 0.35; 95% CI, 0.09 to 1.39	CI, 0.72 to 4.1) **N (%) injection site reaction** Guselkumab: 2 (1.0) Adalimumab: 6 (14) RR* 0.07 (95% CI, 0.01 to 0.33)

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			Between group difference in percentage points (95% CI)* vs. adalimumab Adalimumab: 11 (26); NA Guselkumab 5 mg: 4 (10); NR Guselkumab 15 mg: 5 (12); NR Guselkumab 50 mg: 8 (19); -6.5% (-24.2% to 11.1%) Guselkumab 100 mg: 14 (33); 7.8% (-11.6% to 27.1%) Guselkumab 200 mg: 12 (29); 3.0% (-15.9% to 21.9%) **N (%) with DLQI score 0 or 1** Between group difference in percentage points (95% CI)* vs. adalimumab Adalimumab: 19 (44); NA Guselkumab 5 mg: 10 (26) Guselkumab 15 mg: 14 (34) Guselkumab 50 mg: 17 (41); -3.7% (-24.7% to 17.3%) Guselkumab 100 mg: 25 (60); 15.3% (-5.7% to 36.3%) Guselkumab 200 mg: 26 (62); 17.7% (-3.2% to 38.6%) **Mean (SD) change in DLQI score** Adalimumab: -10.1 (9.0) Guselkumab 5 mg: -6.2 (5.2) Guselkumab 15 mg: -10.3 (5.5) Guselkumab 50 mg: -11.1 (7.4) Guselkumab 100 mg: -10.8 (7.3) Guselkumab 200 mg: -11.4 (6.8)		
Griffiths et al.,[39] 2010	Ustekinumab 45 mg or 90 mg at weeks 0 and 4 Etanercept 50 mg twice	Ustekinumab 45mg: 209 Ustekinumab 90 mg:	*Primary outcomes at week 12* **% PASI 75** 56.8% (etanercept) vs.	**N (%) AE** Etanercept: 243 (70) Ustekinumab 45 mg:	**N (%) 1 infection** Etanercept:

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
None Fair	weekly	347 Etanercept 50 mg: 347	67.5% (ustekinumab 45 mg); *P* = .01 56.8% (etanercept) vs. 73.8% (ustekinumab 90 mg); *P* < .001 *Secondary outcomes at week 12* **% PASI 90** 23.1% (etanercept) vs. 36.4% (ustekinumab 45 mg); *P* < .001 23.1% (etanercept) vs. 44.7% (ustekinumab 90 mg); *P* = .01 **% PGA 0 or 1** 49.0% (etanercept) vs. 65.1% (ustekinumab 45 mg); *P* < .001 49.0% (etanercept) vs. 70.6% (ustekinumab 90 mg); *P* < .001 **% PGA 0** 8.6% (etanercept) vs. 16.3% (ustekinumab 45 mg); *P* = .006 8.6% (etanercept) vs. 26.2% (ustekinumab 90 mg); *P* < .001	138 (66) Ustekinumab 90 mg: 240 (69.2) RR, 1.03; 955 CI, 0.94 to 1.13 for etanercept vs. ustekinumab (combined dosages) **N (%) SAE** Etanercept: 4 (1.2) Ustekinumab 45 mg: 4 (1.9) Ustekinumab 90 mg: 4 (1.2) RR, 0.80; 95% CI, 0.35 to 2.77 for etanercept vs. ustekinumab **N (%) withdrawal due to AE** Etanercept: 8 (2.3) Ustekinumab 45 mg: 4 (1.9) Ustekinumab 90 mg: 4 (1.2) RR*, 1.6; 95% CI, 0.61 to 4.23 for etanercept vs. ustekinumab	101 (29.1) Ustekinumab 45 mg: 64 (30.6) Ustekinumab 90 mg: 103 (29.7) **N (%) injection site reaction** Etanercept: 86 (24.8) Ustekinumab 45 mg: 9 (4.3) Ustekinumab 90 mg: 13 (3.7) RR, 6.26; 95% CI, 4.0 to 9.81 for etanercept vs. ustekinumab, however, participants in etanercept group received more injections than those in the ustekinumab groups.
Griffiths et al.,[40] 2015 UNCOVER-2	UNCOVER-2 Ixekizumab 80 mg every 2 weeks[a] Ixekizumab 80 mg	UNCOVER-2 Ixekizumab 2-wk: 351 Ixekizumab 4-wk:	*Primary outcomes at week 12* **% PASI 75** U2: 89.7% (ixekizumab 2-wk) vs. 77.5% (ixekizumab 4-wk) vs. 41.6%	*AEs for UNCOVER-2 and UNCOVER-3 were pooled by study authors*	*AEs for UNCOVER-2 and UNCOVER-3*

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
UNCOVER-3 Fair	every 4 weeks[a] Etanercept 50 mg twice weekly Placebo (n = 168) UNCOVER-3 Ixekizumab 80 mg every 2 weeks[a] Ixekizumab 80 mg every 4 weeks[a] Etanercept 50 mg twice weekly Placebo	347 Etanercept: 358 Placebo: 168 UNCOVER-3 Ixekizumab 2-wk: 385 Ixekizumab 4-wk: 386 Etanercept: 382 Placebo: 193	(etanercept); effect size ixekizumab 2-wk vs. etanercept: 48.1%; (97.5% CI: 41.2% to 55.0%); effect size ixekizumab 4wk vs. etanercept: 35.9% (97.5% CI, 28.2% to 43.6%) U3: 87.3% (ixekizumab 2-wk) vs. 84.2% (ixekizumab 4-wk) vs. 53.4% (etanercept); effect size ixekizumab 4-wk vs. etanercept: 30.8% (97.5% CI, 23.7% to 37.9%), effect size ixekizumab 2-wk vs. etanercept: 33·9% (97.5% CI, 27.0% to 40.7%) **% PGA 0 or 1** U2: 83.2% (ixekizumab 2-wk) vs. 72.9% (ixekizumab 4-wk) vs. 36.0% (etanercept) U3: 80.5% (ixekizumab 2-wk) vs. 75.4% (ixekizumab 4-wk) vs. 41.6% (etanercept), Ixekizumab 2-wk vs. etanercept effect size U2: 47.2% (97.5% CI, 39.9% to 54.4%); U3: 38.9% (97.5% CI, 31.7% to 46.1%) Ixekizumab 4-wk vs. etanercept effect size U 2: 36.9% (97.5% CI, 29.1% to 44.7%); U3: 33.8% (97.5% CI, 26.3% to 41.3%) *Secondary outcomes* **% PGA 0** U2: 42% vs. 32% vs. 6%, effect size ixekizumab 4-wk vs. etanercept: 26.4% (97.5% CI, 20.1% to 32.7%); effect size ixekizumab 2-wk vs. etanercept: 36.0% (97.5% CI, 29.5% to 42.5%)	**% (N) Any TEAE** Ixekizumab 2-wk: 58% (424/734) Ixekizumab 4-wk: 58% (419/729) Etanercept: 54% (399/739) **% (N) Nonfatal SAE** Ixekizumab 2-wk: 1.9% (14/734) Ixekizumab 4-wk: 1.9% (14/729) Etanercept: 2% (15/739) **% (N) Withdrawal due to AE** Ixekizumab 2-wk: 1.6% (12/736) Ixekizumab 4-wk: 1.9% (14/733) Etanercept: 1.2% (9/740)	*were pooled by study authors* **% (N) Injection site reactions** Ixekizumab 2-wk: 10% (76/734) Ixekizumab 4-wk: 9% (62/729) Etanercept: 11% (80/739) The most common AEs (≥2% of all patients given ixekizumab): nasopharyngitis, upper respiratory tract infection, injection site reaction, injection site erythema, injection site pain, pruritus, headache, and arthralgia. Most treatment-emergent AEs were mild or moderate in severity.

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			U3: 40% vs. 36% vs. 9%, effect size ixekizumab 4-wk vs. etanercept: 27.4% (97.5% CI, 21.0% to 33.7%); effect size ixekizumab 2-wk vs. etanercept: 31.6% (97.5% CI, 25.2% to 38.1%) **% PASI 90** U2: 71% vs. 60% vs. 19%, effect size ixekizumab 4-wk vs. etanercept: 40.9% (97.5% CI, 33.4% to 48.4%); ixekizumab 2-wk vs. etanercept: 51.9% (97.5% CI, 44.8% to 59.1%) U3: 68% vs. 65% vs. 26%, effect size ixekizumab 4-wk vs. etanercept: 39.6% (97.5% CI, 32.2% to 47.0%); ixekizumab 2- wk. vs. etanercept: 42.4% (97.5% CI, 35.1% to 49.7%) **% PASI 100** U2: 41% vs. 31% vs. 5%, effect size ixekizumab 4-wk vs. etanercept: 25.5% (97.5% CI, 19.4% to 31.7%); effect size ixekizumab 2-wk vs. etanercept: 35.1% (97.5% CI, 28.7% to 41.6%) U3: 38% vs. 35% vs. 7%, effect size ixekizumab 4-wk vs. etanercept: 27.6% (97.5% CI, 21.4% to 33.9%) **Itch NRS** % of patients with a 4-point improvement from baseline U2: 85% vs. 77% vs. 58% U3: 83% vs. 80% vs. 64% **% DLQI 0 or 1** U2: 64% vs. 60% vs. 34%; effect size ixekizumab 2-wk vs. etanercept: 30.3% (97.5% CI, 22.3% to 38.3%);		No deaths.

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			effect size ixekizumab 4-wk vs. etanercept: 26.1% (97.5% CI, 18.0% to 34.3%); U3: 65% vs. 64% vs. 44%; effect size ixekizumab 4-wk vs. etanercept: 20.0% (97.5% CI, 12.1% to 27.9%); effect size ixekizumab 2-wk vs. etanercept: 21.0% (97.5% CI, 13.1% to 28.8%).		
Langley et al.,[42] 2014 FIXTURE Fair	Secukinumab 300 mg weekly (induction of 4 weeks) then every 4 weeks Secukinumab 150 mg weekly (induction of 4 weeks) then every 4 weeks Etanercept 50 mg (twice weekly 1-12 weeks, then once weekly through week 51) Placebo	Secukinumab 300 mg: 327 Secukinumab 150 mg: 327 Etanercept: 326 Placebo: 326 Total: 1,306	*Primary study endpoints were all efficacy of secukinumab vs. placebo outcomes.* *Key comparative effectiveness outcomes (secondary study endpoints)* **% PASI 75 at week 12** 77.1% (secukinumab 300 mg) vs. 67.0% (secukinumab 150 mg) vs. 44.0% (etanercept 50 mg) *P* < .001 for both doses secukinumab compared to etanercept **% PGA 0 or 1 at week12** 62.5% (secukinumab 300 mg) vs. 51.1% (secukinumab 150 mg) vs. 27.2% (etanercept 50 mg) *P* < .001 for both doses secukinumab compared to etanercept *Other secondary outcomes* **% PASI 90 at week 12** 54.2% (secukinumab 300 mg) vs. 41.9% (secukinumab 150 mg) vs. 20.7% (etanercept 50 mg) *P* < .001 for both doses secukinumab compared to etanercept **% PASI 75 response at week 12 that continued to have response at week**	**% (N) AE** Secukinumab 300 mg: 81% (376 of 467); 252 events per 100 patient-years Secukinumab 150 mg: 78% (364 of 469); 236 events per 100 patient-years Etanercept: 78% (253 of 323); 234 events per 100 patient-years **% (N) nonfatal SAE** Secukinumab 300 mg: 6% (27 of 467); 7 events per 100 patient-years Secukinumab 150 mg: 5% (24 of 469); 6 events per 100 patient-years Etanercept: 6% (20 of 323); 7 events per 100 patient-years **% (N) withdrawal**	**% (N) injection site reaction** Combined Secukinumab groups: 1% (7 of 936) Etanercept: 11% (36 of 323)

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			52 84.3% (secukinumab 300 mg) vs. 82.2% (secukinumab 150 mg) vs. 72.5% (etanercept 50 mg) *P* < .001 for 300 mg vs. etanercept; *P* = .009 for 150 mg vs. etanercept **% PGA 0 or 1 response at week 12 that continued to have response at week 52** 79.7% (secukinumab 300 mg) vs. 67.7% (secukinumab 150 mg) vs. 56.8% (etanercept 50 mg) *P* < .001 for 300 mg vs. etanercept; *P* = .002 for 150 mg vs. etanercept **% PASI 100 at week 12** 24.1% (secukinumab 300 mg) vs. 14.4% (secukinumab 150 mg) vs. 4.3% (etanercept 50 mg) *P* < .001 for both doses secukinumab compared to etanercept **DLQI change in mean score at 12 weeks** -10.4 (secukinumab 300 mg) -9.7 (secukinumab 150 mg) -7.9 (etanercept 50 mg) (No *P* reported)	**due to AE** Secukinumab 300 mg: 3% (14 of 467) Secukinumab 150 mg: 2% (10 of 469) Etanercept: 4% (12 of 323)	
Lebwohl et al.,[43] 2015 AMAGINE-2 AMAGINE-3 Fair	Brodalumab 210 mg SC on day 1, weeks 1, 2, 4, 6, 8, 10 Brodalumab 140 mg SC on day 1, week 1, then every 2 weeks Ustekinumab 45 mg subcutaneous for patients with a body	Brodalumab 210 mg A2: 612 A3:624 Brodalumab 140 mg A2: 610 A3: 629 Ustekinumab A2:300	*Primary outcome for comparative effectiveness at 12 weeks* **% ASI 100** A2: brodalumab 210 mg: 44%, ustekinumab: 22%, *P* < .001 A3: brodalumab 210 mg 37%, ustekinumab: 19% *P* < .001 *Key secondary outcome for comparative effectiveness at 12 weeks*	*At 12 weeks* **% (N) AE** A2: Brodalumab 210 mg: 57.8% (354) Ustekinumab: 59%, (177) A3: Brodalumab 210 mg: 56.8% (353) Ustekinumab: 53.7%	One death (from stroke) occurred during the induction phase (in the AMAGINE-2 study, in a patient in the

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
	weight ≤100 kg and 90 mg for patients >100 kg on day 1 and week 4 Placebo Induction phase: 12 weeks Maintenance phase: 40 weeks	A3: 313 Placebo A2: 309 A3: 315	**% PASI 75** A2: brodalumab 210 mg: 86%, ustekinumab: 70%, *P* = .08 A3: brodalumab 210 mg: 85%, ustekinumab: 69%, *P* = .007 *Other secondary outcomes at 12 weeks* **% PGA 0 or1** A2: brodalumab 210 mg: 79%, ustekinumab: 61%, *P* < .001 A3: brodalumab 210 mg 80%, ustekinumab: 57%, *P* < .001 **% PGA 0** A2: brodalumab 210 mg: 45%, ustekinumab: 22%, *P* < .001 A3: brodalumab 210 mg 37%, ustekinumab: 19%, *P* < .001 Results for brodalumab 140 mg group not extracted as dose not FDA-approved.	(168) **% (N) SAE** A2: Brodalumab 210 mg: 1.0% (6) Ustekinumab: 1.3% (4) A3: Brodalumab 210 mg: 1.4% (9) Ustekinumab: 0.6% (2) **% (N) discontinued study due to AE** A2: Brodalumab 210 mg: 1.0% (6) Ustekinumab: 0.7% (2) A3: Brodalumab 210 mg: 0.8% (5) Ustekinumab: 0.3% (1) **% (N) discontinued drug due to AE** A2: Brodalumab 210 mg: 1.0% (6) Ustekinumab: 1.3% (4) A3: Brodalumab 210 mg: 1.1% (7) Ustekinumab: 0.6% (2)	210 mg brodalumab group, 20 days after the last dose)
Mease et al.,[25] 2018 EQUATOR Fair	Placebo orally once daily for 16 weeks Filgotinib 200 mg orally once daily for 16 weeks	Overall N = 131 Filgotinib 200 mg: n = 65 Placebo: n = 66	*Primary outcome at week 16* **N (%) with ACR20** Placebo: 22 (33) Filgotinib: 52 (80) ARD 47% (95% CI, 30·2 to 59·6), *P* <	**N (%) TEAE** Placebo: 39 (59) Filgotinib: 37 (57) RR* 0.96; 95% CI, 0.72 to 1.3	**N (%) serious infections** Placebo: 0 (0) Filgotinib: 1 (2) Deaths due to

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			·0001 *Secondary outcomes at week 16* **N (%) with ACR50** Placebo: 10* (15.2) Filgotinib: 31* (47.7) ARD 33% (95% CI, 16·8% to 46·2%); *P* < ·0001 **N (%) with ACR70** Placebo: 4* 6.1 Filgotinib: 15*(23.1) ARD 17% (95% CI, 4·9% to 29·2%); *P* = .0037 **Mean (SD) change in DAPSA** Placebo: −18·1 (19·9) Filgotinib: −27·9 (13·6) Mean difference: −12·5 (95% CI, −17·0 to −8·0); *P* < ·0001 **N (%) with DAPSA remission or low disease activity (score ≤14)** Placebo: 10 (15) Filgotinib: 32 (49) ARD, 34%; 95% CI, 18·3 to 47·7; *P* < .001 **N (%) PsARC response** Placebo: 31 (47·) Filgotinib: 52 (80·0) ARD 33% (95% CI, 16·7 to 47·0); *P* < 001 **MDA** ARD, 14%; 95% CI, 1·3 to 26·5; *P* = .021 **Mean difference in mean change from baseline in PASDAS** −1·3; 95% CI, −1·7 to −0·9; *P* < .001 **% PASI 75** (among those with >3% BSA involvement at baseline)	**N (%) serious TEAE** Placebo: 1 (2) Filgotinib: 1 (2) RR* 1.0; 95% CI, 0.0 to 15.9 **N (%) withdrawal due to AEs** Placebo: 0 (0) Filgotinib: 1 (2) RR*, 4.1; 95% CI, 0.05 to 320.7	treatment-emergent adverse event Placebo: 0 (0) Filgotinib: 1 (2) The most common treatment-emergent AEs were nasopharyngitis and headache, the incidences of which were similar between the 2 groups.

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			ARD, 30%; 95% CI, 10·4 to 47·0; *P* = ·003 **Mean difference in mean change from baseline in SPARCC EI** (among those with enthesitis at baseline) −1·4; 95% CI, −2·6 to −0·1; *P* = ·031 **Mean difference in mean change in pruritis numeric rating scale** −2·2; 95% CI, −3·1 to −1·4; *P* < .001 **Mean change (SD) in HAQ-DI** Placebo: -0·28 (0.5) Filgotinib: -0·57 (0.5) Mean difference, −0·28; 95% CI, −0·44 to −0·12; *P* < ·001 **Mean change (SD) in FACIT-F** Placebo: Filgotinib: 8·2 (7·3) Placebo: 5·5 (8·1) Mean difference, 3·2; 95% CI, 0·8 to 5·5; *P* = .009 **Mean change (SD) in psoriatic arthritis-related pain intensity (VAS in mm)** Placebo: −11·1 (29·7) Filgotinib: −31·6 (21·3) Mean difference, −18·9; 95% CI, −26·7 to −11·1; *P* < .001		
Mease et al.,[24] 2018 NCT02349451 Fair	Placebo SC Adalimumab 40 mg SC every other week Remtolumab 120 mg SC every week Remtolumab 240 mg SC every week	Placebo: 24 Adalimumab: 72 Remtolumab 120 mg: 71 Remtolumab 240 mg: 73 Total: 240	*Primary outcome at week 12* **% ACR20** Placebo: 25.0 Adalimumab: 68.1 Remtolumab 120 mg: 64.8, *P* < .001 vs. placebo ARD* vs. adalimumab, -3.3%; 95 %CI, -18.7% to 12.2%	**N (%) TEAE** Placebo: 11 (45.8) Adalimumab: 38 (52.8) Remtolumab: 120 mg: 33 (46.5) RR*. 1.01; 95% CI, 0.61 to 1.7 vs.	**N (%) infection** Placebo: 5 (20.8) Adalimumab: 20 (27.8) Remtolumab 120 mg: 14

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			Remtolumab 240 mg: 75.3, *P* < .001 vs. placebo, ARD* vs. adalimumab, 7.3%; 95% CI, -7.3% to 21.9% *Secondary outcomes at week 12* **% ACR50** Placebo: 12.5 Adalimumab: 37.5 Remtolumab 120 mg: 36.6, *P* < .05 vs. placebo ARD* vs. adalimumab, -0.8%; 95% CI, -16.7% to 15.0% Remtolumab 240 mg: 53.4, *P* < .001 vs. placebo ARD* vs. adalimumab, 15.9%; 95 % CI, -0.07% to 31.9%; P < .05 as reported by study **% with ACR70** Placebo: 4.2 Adalimumab: 15.3, Remtolumab 120 mg: 22.5, *P* < .05 vs. placebo ARD* vs. adalimumab, 7.3%; 95 %CI, -5.5 to 20.0 Remtolumab 240 mg: 31.5, *P* <.01 vs. placebo ARD* vs. adalimumab, 16.2%; 95 %CI 2.7% to 29.7% **Mean change in HAQ-S** Placebo: -0.28 Adalimumab: -0.58 Remtolumab 120 mg: -0.56 Remtolumab 240 mg: -0.55 No statistical testing conducted. **% PASI 75** (among those with >3%	placebo RR*, 0.88; 95 %CI, 0.63 to 1.2 vs. adalimumab Remtolumab 240 mg: 31 (42.5) RR*, 0.93; 95% CI, 0.56 to 1.5 vs. placebo RR*, 0.80; 95 % CI, 0.57 to 1.1 vs. adalimumab **N (%) SAE** Placebo: 1 (4.2) Adalimumab: 0 (0) Remtolumab 120 mg: 0 (0) RR*, 0.33; 95% CI, 0.02 to 5.1 vs. placebo RR*, 1.01; 95 % CI, 0.004 to 256.6 vs. adalimumab Remtolumab 240 mg: 1 (1.4) RR*, 0.08; 95% CI, 0.001 to 6.6 vs. placebo RR*, 4.0; 95% CI, 0.05 to 313 vs. adalimumab **N (%) severe AE** Placebo: 0 (0) Adalimumab: 1 (1.4) Remtolumab 120	(19.7) Remtolumab 240 mg: 15 (20.5) No deaths reported. No injection site reactions were reported across all groups.

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			BSA at baseline) Placebo: 27 Adalimumab: 58 Remtolumab 120 mg: 74, *P* < .01 vs. placebo ARD* vs. adalimumab, 16.8%; 95% CI, -4.5% to 38.2% Remtolumab 240 mg: 78, *P* < .01 vs. placebo ARD* vs. adalimumab, 20.0%; 95% CI, -0.5% to 40.5%, *P* < .05 as reported by study **% PASI 90** (among those with >3% BSA at baseline) Placebo: 18 Adalimumab: 46 Remtolumab 120 mg: 49, *P* NS vs. placebo ARD* vs. adalimumab, 3.4%; 95% CI, -19.2% to 26.0% Remtolumab 240 mg: 47, *P* NS vs. placebo ARD* vs. adalimumab. 1.5; 95% CI, -20.5% to 23.5%	mg: 0 (0) Remtolumab 240 mg: 1 (1.4) **N (%) withdrawals due to AEs** Placebo: 0 (0) Adalimumab: 1 (1.4) Remtolumab 120 mg: 2(2.8) Remtolumab 240 mg: 1 (1.4) Remtolumab 120 mg v. placebo: RR*, 2.7; 95% CI, 0.04 to 170.2 Remtolumab 240 mg v. placebo: RR, 0.34 95% CI, 0.02 to 103.8* Remtolumab (either dose) v. adalimumab: RR*, 1.5; 95% CI, 0.16 to 14.2	
Mease et al.,[45] 2017 Strand et al.,[79] 2019 OPAL- Broaden Fair	Tofacitinib 5 mg taken orally twice daily; Tofacitinib 10 mg taken orally twice daily; Adalimumab 40 mg subcutaneously every 2 weeks; or Placebo (with a switch to the 5-mg dosage of tofacitinib at month 3, or placebo with a	Tofacitinib 5 mg bid: 107 Tofacitinib 10 mg bid: 104; Adalimumab: 106 Placebo: 105 Total: 422	*Primary outcome at 3 months* Results by adalimumab vs. tofacitinib 10 mg vs. tofacitinib 5 mg; no statistical testing between active arms **ACR20** 52% vs. 61% vs. 50% **HAQ-DI** -0.38 vs. -0.40 vs. -0.35 *At 12 months* **ACR20** 60% vs. 70% vs. 68% **HAQ-DI** -0.45 vs. -0.51 vs. -0.54 *Secondary outcomes*	**% (N) AE** (reported through month 3) Tofacitinib 10 mg: 45% (47/104) Tofacitinib 5 mg: 39% (42/107) Adalimumab 46% (49/106) **% (N) withdrawals due to AE** Tofacitinib 10 mg: 0	Minimal cases of AEs of special interest Tofacitinib 10 mg: 1 case of nonmelanoma ski cancer, Tofacitinib 5 mg: 4 incidents: 1

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
	switch to the 10-mg dosage of tofacitinib at month 3)		*At 3 months* **PASI 75** 39% vs. 44% vs. 43% **ACR50** 33% vs. 40%. vs. 28% **ACR70** 19% vs. 14%. vs. 17% *At 12 months* **PASI 75** 56% vs. 67% vs. 56% **ACR50** 41% vs. 48%. vs. 45% **ACR70** 29% vs. 31%. vs. 23% **Modified total Sharp score** 98% vs. 95% vs. 96% *Post-hoc analyses of PROs* *At 3 months, mean (SE) change* Tofacitinib 5 mg **PtGA VAS** -20.08 (2.28) **Pain VAS** -21.49 (2.33) **SF-36 PCS:** 5.51 (0.73) **SF-36 MCS:** 4.35 (0.91) **FACIT-F** 7.0 (0.85) **EQ VAS** 14.00 (2.10) Tofacitinib 10 mg **PtGA-VAS** -25.50 (2.29) **Pain VAS** -27.10 (2.34) **SF-36 PCS** 5.69 (0.74) **SF-36 MCS** 4.20 (0.91) **FACIT-F** 6.0 (0.85) **EQ-VAS** 15.83 (2.09) Adalimumab 40 mg **PtGA-VAS** -21.47 (2.33) **Pain VAS** -21.87 (2.39) **SF-36 PCS:** 6.23 (0.75) **SF-36 MCS:** 3.13 (0.94) **FACIT-F**: 6.0 (0.87) **EQ-VAS:** 13.10 (2.14)	Tofacitinib 5 mg: 3% (3/107) Adalimumab: 2% (2/106) **% (N) SAE** Tofacitinib 10 mg: 1% (1/104) Tofacitinib 5 mg: 3% (3/107) Adalimumab: 1% (1/106)	herpes zoster infection, 1 opportunistic infection, and 2 cases of cancer (excluding nonmelanoma skin cancer)
Mease et al.,[44] 2017	Ixekizumab 80 mg once every 2 weeks[b];	Ixekizumab 80 mg every 2 weeks: 103	*Primary outcome at 24 weeks* Results presented by adalimumab,	*At 24 weeks* **% (N) treatment-**	**Injection site reactions**

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
SPIRIT-P1 Fair	Ixekizumab 80 mg once every 4 weeks; Adalimumab 40 mg once every 2 weeks; Placebo Stable doses of DMARDs, oral corticosteroids, opiates and/or NSAIDs/COX2 inhibitors allowed. At 16 weeks inadequate responders got concomitant medications, but if on adalimumab were reassigned to ixekizumab at week 24.	Ixekizumab 80 mg every 4 weeks: 107 Adalimumab: 101 Placebo: 106 Total: 417	ixekizumab 2-wk, ixekizumab 4-wk. No statistical testing between the active arms. **ACR20** 57% vs. 62% vs. 58% *Secondary outcomes at 24 weeks* **ACR50** 39% vs. 47% vs. 40% **ACR70** 26% vs. 34% vs. 23% **% BSA** -10% vs. -11% vs. -12% **DAS-CRP** −1.74 vs. −2.04 vs. -1.96 **PASI 75** 54% vs. 80% vs. 71% **PASI 90** 37% vs. 68% vs. 56% **PASI 100** 24% vs. 53% vs. 43% **HAQ DI** -0.37 vs. -0.50 vs. -0.44	**emergent AE** Adalimumab: 64% (65/101) Ixekizumab 2-wk: 66% (67/102) Ixekizumab 4-wk: 66% (71/107) **% (N) SAE** Adalimumab: 5% (5/101) Ixekizumab 2-wk: 3% (3/102) Ixekizumab 4-wk: 6% (6/107) **% (N) withdrawal due to AE** Adalimumab: 2% (2/101) Ixekizumab 2-wk: 4% (4/102) Ixekizumab 4-wk: 2% (2/107)	Adalimumab: 2% (2/101) Ixekizumab 2-wk: 16% (16/102) Ixekizumab 4wk: 12% (13/107) Infection: Adalimumab: 26% (26/101) Ixekizumab 2-wk: 24% (24/102) Ixekizumab 4-wk: 28% (30/107)
Papp et al.,[27] 2018 NCT02931838 Fair	Placebo 5 oral doses of BMS-986165 (3 mg every other day, 3 mg daily, 3 mg twice daily, 6 mg twice daily, or 12 mg daily).	Placebo: 45 BMS-986165 3 mg every other day: 44 BMS-986165 3 mg daily: 44 BMS-986165 3 mg twice daily: 45 BMS-986165 6 mg twice daily: 45 BMS-986165 12 mg daily: 44 Total: 268 randomized/267	*Primary outcome at week 12* **N (%) PASI 75**; *P* value vs. placebo Placebo: 3 (7) BMS-986165 3 mg every other day: 4 (9); *P* = .49 BMS-986165 3 mg daily: 17 (39); *P* < .001 BMS-986165 3 mg twice daily: 31 (69); *P* < .001 BMS-986165 6 mg twice daily: 30 (67); *P* < .001 BMS-986165 12 mg daily: 33 (75); *P* < .001	**N (%) AE**, RR* (95% CI) compared to placebo Placebo: 23 (51) BMS-986165 3 mg every other day: 26 (59) 1.16 (0.79 to 1.69) BMS-986165 3 mg daily: 24 (55) 1.07 (0.72 to 1.58) BMS-986165 3 mg twice daily: 29 (64)	**N (%) deaths**: 0 (0) Most frequent AEs: Nasopharyngitis, headache, diarrhea, nausea, upper respiratory infection SAE included 2 events in 1 patient in the

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
		analyzed	*Secondary outcomes at week 12* **N (%) PASI 90**; difference vs. Placebo (95% CI) Placebo: 1 (2) BMS-986165 3 mg every other day: 3 (7); 5% (-16% to 25%) BMS-986165 3 mg daily: 7 (16). 14& (-7% to 33%) BMS-986165 3 mg twice daily: 20 (44); 42% (21% to 60%) BMS-986165 6 mg twice daily: 20 (44); 42% (21% to 60%) BMS-986165 12 mg daily: 19 (43); 41% (20% to 58%) **N (%) PASI 100**; difference vs. placebo (95% CI) Placebo: 0 (0) BMS-986165 3 mg every other day: 1 (2) 2% (-18% to 23%) BMS-986165 3 mg daily: 0 (0); 0% BMS-986165 3 mg twice daily: 4 (9); 9% (-13% to 30%) BMS-986165 6 mg twice daily: 8 (18); 18% (-4% to 38%) BMS-986165 12 mg daily: 11 (25); 25% (4% to 44%) **N (%) PGA 0 or 1**; difference vs. placebo (95% CI) Placebo: 3 (7) BMS-986165 3 mg every other day: 9 (20); 14% (-7% to 33%) BMS-986165 3 mg daily: 17 (39); 32% (11% to 50%) BMS-986165 3 mg twice daily: 34 (76); 69% (51% to 83%)	1.26 (0.88 to 1.81) BMS-986165 6 mg twice daily: 36 (80) 1.57 (1.14 to 2.16) BMS-986165 12 mg daily: 34 (77) 1.51 (1.09 to 2.10) **N (%) SAE** RR* (95% CI) compared to placebo Placebo: 1 (2) BMS-986165 3 mg every other day: 1 (2) 1.02 (0.70 to 15.84) BMS-986165 3 mg daily: 1 (2) 1.02 (0.70 to 15.84) BMS-986165 3 mg twice daily: 1 (2) 1 (0.065 to 15.5) BMS-986165 6 mg twice daily: 0 (0) 1.0 (.0.004 to 252) BMS-986165 12 mg daily: 0 (0) 1.0 (0.004 to 257) **N (%) AE leading to withdrawal**; RR*(95% CI) compared to placebo Placebo: 2 (4) BMS-986165 3 mg every other day: 1 (2)	placebo group (hemorrhagic anemia and hemorrhoidal hemorrhage), 1 event in 1 patient in the 3 mg every other day group (gastroenteritis due to rotavirus), 1 patient in the 3 mg daily group (accidental eye injury), and 1 patient in the 3 mg twice daily group (dizziness due to vestibular dysfunction). In addition, 1 case of in situ melanoma was diagnosed on skin biopsy of an atypical nevus at day 96 after the first doses of 3 mg daily.

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			BMS-986165 6 mg twice daily: 29 (64); 58% (38% to 74%) BMS-986165 12 mg daily: 33 (75); 68% (50% to 82%) **N (%) DQLI 0 or 1;** difference vs. placebo (95% CI) Placebo: 2 (4) BMS-986165 3 mg every other day: 7 (16); 12% (-2% to 26%) BMS-986165 3 mg daily: 7 (16); 12% (-2% to 26%) BMS-986165 3 mg twice daily: 19 (42); 38% (20% to 54%) BMS-986165 6 mg twice daily: 27 (60); 56% (38% to 71%) BMS-986165 12 mg daily: 28 (64); 59% (41% to 74%)	0.51 (0.05 to 5.44) BMS-986165 3 mg daily: 2 (5) 1.02 (0.15 to 6.9) BMS-986165 3 mg twice daily: 1 (2) 0.50 (0.05 to 5.3) BMS-986165 6 mg twice daily: 3 (7) 1.57 (1.1 to 2.2) BMS-986165 12 mg daily: 1 (2) 0.51 (0.05 to 5.4)	
Papp et al.,[26] 2018 BE ABLE-1 Fair	Bimekizumab administered SC every 4 weeks at doses of 64 mg, 160 mg, 160 mg (with 320 mg loading dose at baseline), 320 mg, 480 mg, or placebo. Treatment was administered at baseline, week 4, and week 8 for a total of 3 injections.	Placebo = 42, Bimekizumab 64 mg = 39 Bimekizumab 160 mg = 43 Bimekizumab 160 mg (320 mg at baseline) = 40 Bimekizumab 320 mg = 43 Bimekizumab 480 mg = 43 Total = 250	*Primary outcome at week 12* **% PASI 90** All bimekizumab doses: 46.2% to 79.1% Placebo: 0%; *P* < .001, all comparisons *Secondary outcomes* **% PASI 90 at week 8** All bimekizumab doses: 41.0% to 86.0% Placebo: 0%; *P* < .001, all comparisons **% PAS I75 at week 12** All bimekizumab doses: 61.5% to 93.0% Placebo: 4.8%; *P* < .001, all comparisons **% PASI 100 at week 12**	**N (%) TEAE** All bimekizumab doses: 126 (61) Placebo: 15 (36) RR*, 1.7; 95% CI, 1.1 to 2.6 **N (%) SAE** All bimekizumab doses: 1 (0.5) polyp and colon cancer Placebo: 1(2.3) viral meningitis RR*, 0.20; 95% CI, 0.01 to 3.2 None of the SAEs were considered related to the study treatment by study	Deaths: 0 (0) Most common AEs were nasopharyngitis, upper respiratory infection, arthritis, elevated liver enzyme, hypertension

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			All bimekizumab doses: 27.9% to 60.0% Placebo: 0%; *P* ≤ .001, all comparisons **% IGA 0 or 1 at week 8** All bimekizumab doses: 46.2% to 86.0% Placebo: 4.8%; *P* < .001, all comparisons **% IGA 0 or 1 at week 12** All bimekizumab doses: 51.3% to 86.0% Placebo: 4.8%; *P* ≤ .001, all comparisons	investigators **N (%) severe AE** [severe was undefined] All bimekizumab doses: 2 (4.7) Placebo: 0(0) **N (%) withdrawals due to AE** All bimekizumab doses: 10 (4.8) Placebo: 1 (2.4) RR*, 2.0; 95% CI, 0.27 to 15.4	
Papp et al., [46] 2017 None Fair	Risankizumab 18 mg SC once on day 0 Risankizumab 90 mg SC at weeks 0, 4 and 16 Risankizumab 180 mg SC at weeks 0, 4, and 16 Ustekinumab 45 or 90 mg (if patient weight more than 100 kg) at weeks 0, 4, and 16 48 weeks	Risankizumab once: 43 Risankizumab 90 mg: 41 Risankizumab 180 mg: 42 Ustekinumab: 40 Total: 166	*Primary outcome at week 12* *Study authors pooled the 90-mg and 190-mg risankizumab dosages.* **% PASI 90** 77% (risankizumab) vs. 40% (ustekinumab), *P* < .001 *Secondary outcomes at week 12* **% PASI 50** 96% (risankizumab) vs. 82% (ustekinumab), *P* < .001 **% PASI 75** 93% (risankizumab) vs. 88% (ustekinumab), *P* < .001 **% PASI 100** 45% (risankizumab) vs. 18% (ustekinumab), *P* < .001 **% PGA 0 or 1** 89% (risankizumab) vs. 62% (ustekinumab), *P* < .001 **% DLQI 0 or 1** 72% (risankizumab) vs. 53% (ustekinumab), *P* < .001	*Safety data is through week 48* **% AE** 81% risankizumab 18 mg 80% risankizumab 90 mg 69% risankizumab 180 mg 72% ustekinumab, *P* = NR Treatments did not differ with regard to overall incidences of adverse events (*P* = 0. 299) **% SAE** 5 (12%) risankizumab 18 mg 6 (15%) risankizumab 90 mg 0 risankizumab 180	Most common AE (occurring in > 10% of the patients) in all treatment groups: nasopharyngitis. No deaths reported

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
				mg 3 (8%) ustekinumab **% withdrawals due to AE** 1 risankizumab 18 mg, 1 risankizumab 90 mg 0 risankizumab 180 mg 1 ustekinumab	
Reich et al.,[32] 2017 Reich et al.,[75] 2019 Gordon et al.[76] 2018 VOYAGE-2 Fair	Adalimumab SC 80 mg at week 0, 40 mg at week 1 and every 2 weeks Guselkumab SC 100 mg at weeks 0, 4, 12 This study also included a placebo arm.	Placebo: 248 Adalimumab 40 mg: 248, Guselkumab 100 mg: 496 Total: 992	*Primary outcomes at week 16* **N (%) IGA 0 or 1** Guselkumab: 417 (84.1) Adalimumab: 168 (67.7) ARD*, 16.3%; 95% CI, 9.7% to 23.0% RR*, 1.2; 95% CI, 1.1 to 1.4 **N (%) PASI 90** Guselkumab: 347 (70.0) Adalimumab: 116 (46.8) ARD* 23.2%; 95% CI, 15.8% to 30.6% RR*, 1.5; 95% CI, 1.3 to 1.7 *Secondary outcomes at week 16* **N (%) IGA 0** Guselkumab: 215 (43.3) Adalimumab: 71 (28.6) ARD* 14.7%; 95% CI, 7.6% to 21.8% RR*, 1.5; 95% CI, 1.2 to 1.9 **N (%) PASI 100** Guselkumab: 169 (34.1) Adalimumab: 51 (20.6) ARD*, 13.5%; 95% CI, 7.0% to 20.1% RR*, 1.7; 95% CI, 1.3 to 2.2 **N (%) PASI 75**	**N (%) AE** Guselkumab: 235 (47.6) Adalimumab: 120 (48.4) RR* 0.98 (95% CI, 0.84 to 1.2) **N (%) SAE** Guselkumab: 8 (1.6) Adalimumab: 6 (2.4) RR* 0.67 (95% CI, 0.25 to 1.9) **N (%) withdrawal due to AEs** Guselkumab: 7 (1.4) Adalimumab: 4 (1.6) RR* 0.88 (95% CI, 0.26 to 3.0)	**N (%) infections** Guselkumab: 106 (21.5) Adalimumab: 58 (23.4) RR* 0.92 (95% CI, 0.69 to 1.2) **N (%) with injection site reactions** Guselkumab: 13*(2.6) Adalimumab: 21* (6.9) RR* 0.38 (0.19 to 0.74) The most common AEs include nasopharyngitis, headache, and upper respiratory

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			Guselkumab: 428 (86.3) Adalimumab: 170 (68.5) ARD*, 17.7%; 95% CI, 11.2% to 24.3% RR*, 1.3; 95% CI, 1.1 to 1.4 **Mean (SD) change in SF-36 PCS** Guselkumab: 5.46 (7.8) Adalimumab: 3.92 (6.6) AMD*, 1.54; 95% CI, 0.40 to 2.7; *P* = .008 **Mean (SD) change in SF-36 MCS** Guselkumab: 5.66 (9.5) Adalimumab: 4.57 (9.4) AMD* 1.09; 95% CI, -0.36 to 2.54; *P* = .14 **Mean (SD) change in DLQI** Guselkumab: -11.3 (6.8) Adalimumab: -9.7 (6.8) AMD*, -1.6; 95% CI, -2.6 to -0.6; *P* = .003 **N (%) DLQI 0 or 1** Guselkumab: 254 (51.7) Adalimumab: 96 (39.0) ARD*, 13.0%; 95% CI, 5.5% to 20.5% RR*, 1.3; 95% CI, 1.1 to 1.6 **Mean (SD) change in PSSD symptom score** Guselkumab: -40.4 (26.5) Adalimumab: -32.8 (24.9) AMD, -7.6; 95% CI, -12.0 to -3.2; *P* < .001 **Mean (SD) change in PSSD sign score** Guselkumab: -42.9 (23.7) Adalimumab: -34.6 (23.5)		tract infection.

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			AMD*, -8.3; 95% CI, -12.3 to -4.3; *P* < .001 **Mean (SD) change in HADS-A** Guselkumab: -1.7 (3.4) Adalimumab: -1.1 (3.4) AMD*, -0.6; 95% CI, -1.1 to -0.08; *P* = .02 **Mean (SD) change in HADS-D** Guselkumab: -1.6 (3.6) Adalimumab: -1.2 (3.4) AMD*, -0.4; 95% CI, -0.94 to 0.14; *P* = .14		
Reich et al.,[31] 2019 ECLIPSE Fair	Guselkumab 100 mg SC at 0, 4, 12, weeks and then every 8 weeks until week 44. Secukinumab 300 mg as 2 150-mg SC injections at 0, 1, 2, 3, and 4, and then every 4 weeks until week 44. The guselkumab group received placebo injection to match the number of injections in the secukinumab group.	Guselkumab: 534 Secukinumab: 514 Total: 1,048	*Primary outcome at week 48* **N (%) PASI 90** Guselkumab: 451 (84) Secukinumab: 360 (70) Non-inferiority *P* < .001 Superiority *P* < .001 *Secondary outcomes* **N (%) PASI 75 at both week 12 and week 48** Guselkumab: 452 (85) Secukinumab: 412 (80) Non-inferiority *P* < .001 Superiority *P* = .062 **N (%) PASI 90 at week 12** Guselkumab: 369 (69) Secukinumab: 391 (76) No significance testing done to control for type I error. **N (%) PASI 75 at week 12** Guselkumab: 477 (89) Secukinumab: 471 (92) No significance testing done to control for type I error.	**N (%) AE** Guselkumab: 416 (78) Secukinumab: 417 (82) RR*, 0.95; 95% CI, 0.90 to 1.02 **N (%) SAE** Guselkumab: 33 (6) Secukinumab: 37 (7) RR*, 0.85; 95% CI, 0.54 to 1.3 **N (%) withdrawal because of AE** Guselkumab: 10 (2) Secukinumab: 12 (2) RR*, 0.80; 95% CI< 0.35 to 1.8	**N (%) infections** Guselkumab: 313 (59) Secukinumab: 331 (65) The most common AEs were nasopharyngitis, upper respiratory tract infection, headache, arthralgia, back pain, diarrhea.

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			N (%) PASI 100 at week 48 Guselkumab: 311 (58) Secukinumab: 249 (48) No significance testing done to control for type I error. **N (%) IGA 0 at week 48** Guselkumab: 332 (62) Secukinumab: 259 (50) No significance testing done to control for type I error. **N (%) IGA 0 or 1 at week 48** Guselkumab: 454 (85) Secukinumab: 385 (75) No significance testing done to control for type I error.		
Reich et al.,[30] 2019 NCT02899988 Fair	Placebo Mirikizumab 30 mg SC Mirikizumab 100 mg SC Mirikizumab 300 mg SC All at 0 and 8 weeks.	Placebo: 52 Mirikizumab 30 mg: 51 Mirikizumab 100 mg: 51 Mirikizumab 300 mg: 51 Total: 205	*Primary outcome at week 16* *All P values vs. placebo* **N (%) PASI 90** Placebo: 0 (0) Mirikizumab 30 mg: 15 (29); *P* = .009 Mirikizumab 100 mg: 30 (59); *P* < .001 Mirikizumab 300 mg: 34 (67); *P* < .001 *Secondary outcomes at week 16* **Mean (SD) PASI score** Placebo: 19.5 (8.4) Mirikizumab 30 mg: 6.0 (5.6); *P* < .001 Mirikizumab 100 mg: 2.7 (4.2); *P* < .001 Mirikizumab 300 mg: 2.5 (4.2); *P* < .001 **N (%) PASI 100**	**N (%) TEAE** Placebo: 25 (48) Mirikizumab: 74 (48) RR*, 1.01; 95% CI, 0.73 to 1.4 **N (%) SAE** Placebo: 1 (2) Mirikizumab: 2 (1) RR*, 0.68; 95% CI, 0.06 to 7.3 **N (%) severe TEAE** Placebo: 1 (2) Mirikizumab: 4 (3) RR*, 1.4; 95% CI, 0.1 to 11.9	**N (%) infection** Placebo: 12 (23) Mirikizumab: 40 (26) RR*, 1.1; 95% CI, 0.65 to 2.0 **N (%) injection site pain** Placebo: 1 (2) Mirikizumab: 7 (5) RR*, 2.4; 95% CI, 0.30 to 18.9 The most common TEAE reported were viral upper and

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			Placebo: 0 (0) Mirikizumab 30 mg: 8 (16); *P* < .05 Mirikizumab 100 mg: 16 (31); *P* < .01 Mirikizumab 300 mg: 16 (31); *P* < .01 **N (%) PASI 75** Placebo: 2 (4) Mirikizumab 30 mg: 27 (53); *P* < .001 Mirikizumab 100 mg: 40 (78); *P* < .001 Mirikizumab 300 mg: 38 (75); *P* < .001 **N (%) PGA 0 or 1** Placebo: 1 (2) Mirikizumab 30 mg: 19 (37); *P* < .001 Mirikizumab 100 mg: 36 (71); *P* < .001 Mirikizumab 300 mg: 35 (69); *P* < .001 **N (%) PGA 0** Placebo: 0 (0) Mirikizumab 30 mg: 8 (16); *P* < .05 Mirikizumab 100 mg: 16 (31); *P* < .01 Mirikizumab 300 mg: 16 (31); *P* < .01 **N (%) PSSI 0** Placebo: 3 (6) Mirikizumab 30 mg: 22 (43); *P* < .001		other respiratory tract infections, injection site pain, hypertension, and diarrhea. No deaths were reported. Two patients (1 assigned to placebo and 1 assigned to a mirikizumab group) with a history of psychiatric illness reported suicidal ideation. Another patient with a history of hypercholesterolemia and past alcohol abuse reported increased alanine aminotransferase and aspartate

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			Mirikizumab 100 mg: 38 (75); *P* < .001 Mirikizumab 300 mg: 26 (51); *P* < .001 **N (%) DLQI 0 or 1** Placebo: 2 (4) Mirikizumab 30 mg: 18 (35); *P* < .001 Mirikizumab 100 mg: 25 (49); *P* < .001 Mirikizumab 300 mg: 24 (47); *P* < .001		aminotransferase.
Reich et al.,[29] 2019 IMMVent Fair	Risankizumab 150 mg SC at weeks 0 and 4; Adalimumab 80 mg SC at week 0 and then 40 mg every other week from week 1 up to the end of week 15.	Risankizumab 150 mg: 301 Adalimumab 40 mg: 304 Total: 605	*Primary outcomes at week 16* **N (%) PASI 90** Adalimumab: 144 (47%) Risankizumab: 218 (72%) ARD, 24.9%; 95% CI, 17.5% to 32.4%; *P* < .001 **N (%) PGA 0 or 1** Adalimumab: 183 (60%) Risankizumab: 252 (84%) ARD, 23.3%; 95% CI, 16.6% to 30.1%; *P* < .001 *Secondary outcomes at week 16* **N (%) PGA 0** Adalimumab: 71 (23%) Risankizumab: 124 (41%) ARD, 17.7%; 95% CI, 10.4% to 24.9%; *P* < .001 **N (%) PASI 100** Adalimumab: 70 (23%) Risankizumab: 120 (40%) ARD, 16.7%; 95% CI, 9.5% to 23.9%; *P* < .001 **N (%) PASI 75**	**N (%) AE** Adalimumab: 173 (57%) Risankizumab: 168 (56%) RR* 0.98 (95% CI, 0.85 to 1.1) **N (%) SAE** Adalimumab: 9 (3%) Risankizumab: 10 (3%) RR* 1.1 (95% CI, 0.46 to 2.7) **N (%) withdrawal due to AE** Adalimumab: 6 (2%) Risankizumab: 4 (1%) RR* 0.67 (95% CI, 0.19 to 2.4)	**N (%) infection** Adalimumab: 74 (24%) Risankizumab: 88 (29%) RR*, 1.2; 95% CI, 0.92 to 1.6 The most frequently reported AEs (occurring in ≥5% of patients in either group) were viral upper respiratory tract infection, upper respiratory tract infection, and headache.

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			Adalimumab: 218 (72%) Risankizumab: 273 (91%) ARD, 18.9%; 95% CI, 13.0% to 24.9%; *P* < .001 **N (%) DLQI 0 or 1** Adalimumab: 148 (49%) Risankizumab: 198 (66%) *P* < .001 **Mean change in WLQ** Adalimumab: -1.9 Risankizumab: -2.8 *P* = .0123		Deaths occurred in 1 patient in the risankizumab group (acute myocardial infarction on day 73) and in 2 patients in the adalimumab group (stage IV gallbladder cancer, abdominal abscess, sepsis, and gastric perforation following gallbladder surgery). None of the deaths were considered to be related to the study drug by investigators.
Reich et al.[28] 2017 RESURFACE-2 Fair	Placebo (through week 12 only, then re-randomized to tildrakizumab through week 28 Etanercept 50 mg twice	Placebo: 156 Etanercept: 313 Tildrakizumab 100 mg: 307 Tildrakizumab 200 mg: 314	*Primary outcome at week 12* **N (%) PASI 75** Etanercept: 151 (48) Tildrakizumab 100 mg: 188 (61) Tildrakizumab 200 mg: 206 (66) ARD vs. etanercept (95% CI,	*Weeks 0 to 12* **N (%) AE**; RR* (95% CI) compared to etanercept Etanercept: 169 (45) Tildrakizumab 100	*Weeks 0 to 12* **N (%) deaths** Etanercept: 0 (0) Tildrakizumab 100 mg: 1 (<1)

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
	weekly through week 12 then 1 dose weekly Tildrakizumab 200 mg at baseline and week 4 and then every 12 weeks Tildrakizumab 100 mg at baseline and week 4 and then every 12 weeks	Total: 1,090	*P* value) Tildrakizumab 100 mg: 13.1% (5.3% to 20.7%, .001) Tildrakizumab 200 mg: 17.4% (9.7% to 24.9%, < .001) **N (%) PGA 0 or 1** Etanercept: 149 (48) Tildrakizumab 100 mg: 168 (55) Tildrakizumab 200 mg: 186 (59) ARD vs. etanercept (95% CI, *P* value) Tildrakizumab 100 mg: 7.3% (-0.5% to 15.0%, .066) Tildrakizumab 200 mg: 11.7% (4.0% to 19.3%, .003) *Secondary outcomes at week 12* **N (%) PASI 100** Etanercept: 15 (5) Tildrakizumab 100 mg: 38 (12) Tildrakizumab 200 mg: 37 (12) ARD vs. etanercept (95% CI, *P* value) Tildrakizumab 100 mg: 7.6% (3.3% to 12.3%, .0006) Tildrakizumab 200 mg: 7.0% (2.8% to 11.6%, .0014) **N (%) PASI 90** Etanercept: 67 (21) Tildrakizumab 100 mg: 119 (39) Tildrakizumab 200 mg: 115 (37) ARD vs. etanercept (95% CI, *P* value) Tildrakizumab 100 mg: 17.4% (10.3% to 24.4%, < .001) Tildrakizumab 200 mg: 15.2% (8.3%	mg: 136 (44); 0.82 (0.70 to 0.96) Tildrakizumab 200 mg: 155 (49); 0.91 (0.79 to 1.1) N (%) **N (%) SAE**; RR* (95% CI) compared to etanercept Etanercept: 7 (2) Tildrakizumab 100 mg: 4 (1); 0.58 (0.17 to 2.0) Tildrakizumab 200 mg: 6 (2); 0.85 (0.29 to 2.5) **N (%) withdrawal due to AE**; RR* (95% CI) compared to etanercept Etanercept: 6 (2) Tildrakizumab 100 mg: 3 (1); 0.51 (0.13 to 2.0) Tildrakizumab 200 mg: 3 (1); 0.50 (0.13 to 2.0) *Weeks 13 to 28* **N (%) AE;** RR* (95% CI) compared to etanercept Etanercept: 164 (57) Tildrakizumab 100 mg: 135 (46); 0.81 (0.69 to 0.95)	Tildrakizumab 200 mg: 0 (0) **N (%) severe infections** Etanercept: 0 (0) Tildrakizumab 100 mg: 0 (0) Tildrakizumab 200 mg: 1 (<1) **N (%) injection site erythema**, RR* (95% CI) compared to etanercept Etanercept: 27 (9) Tildrakizumab 100 mg: 2 (1), 0.08 (0.02 to 0.31) Tildrakizumab 200 mg: 2 (1), 0.07 (0.02 to 0.31) *Weeks 13 to 28* **N (%) deaths** Etanercept: 0 (0) Tildrakizumab 100 mg: 0 (0) Tildrakizumab 200 mg: 0 (0) **N (%) severe**

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			to 22.1%, < .001) **N (%) DLQI 0 or 1** Etanercept: 108 (36) Tildrakizumab 100 mg: 119 (40) Tildrakizumab 200 mg: 145 (47) ARD vs. etanercept (95% CI, *P* value) Tildrakizumab 100 mg: 4.8% (-2.9% to 12.5%, .221) Tildrakizumab 200 mg: 11.9% (4.1% to 19.5%, .003) *Outcomes at 28 weeks* **N (%) PASI 75** Etanercept: 155 (54) Tildrakizumab 100 mg: 216 (73) Tildrakizumab 200 mg: 217 (73) ARD vs. etanercept (95% CI, *P* value) Tildrakizumab 100 mg: 20.1% (12.4% to 27.6%, < .001) Tildrakizumab 200 mg: 19.2% (11.5% to 26.7%, < .001) **N (%) PGA 0 or 1** Etanercept: 131 (45) Tildrakizumab 100 mg: 190 (65) Tildrakizumab 200 mg: 207 (69) ARD vs. etanercept (95% CI, *P*-value) Tildrakizumab 100 mg: 19.6% (11.7% to 27.3%, < .001) Tildrakizumab 200 mg: 24.1% (16.2% to 31.7%, < .001) **N (%) PASI 90** Etanercept: 85 (29) Tildrakizumab 100 mg: 161 (55)	Tildrakizumab 200 mg: 135 (45); 0.80 (0.68 to 0.93) **N (%) SAE**; RR* (95% CI) compared to etanercept Etanercept: 14 (5) Tildrakizumab 100 mg: 9 (3); 0.63 (0.28 to 1.4) Tildrakizumab 200 mg: 6 (2); 0.41 (0.16 to 1.1) **N (%) withdrawal due to AE** RR* (95% CI) compared to etanercept Etanercept: 3 (1) Tildrakizumab 100 mg: 1 (<1); 0.33 (0.03 to 3.1) Tildrakizumab 200 mg: 1 (<1); 0.32 (0.03 to 3.1)	**infections** Etanercept: 3 (1) Tildrakizumab 100 mg: 1 (<1) Tildrakizumab 200 mg: 2 (1) **N (%) injection site erythema**, RR* (95% CI) compared to etanercept Etanercept: 3 (1) Tildrakizumab 100 mg: 3 (1), 0.98 (0.20 to 4.8) Tildrakizumab 200 mg: 1 (<1), 0.32 (0.03 to 3.1) Most common AEs included injection site erythema, nasopharyngitis, upper respiratory tract infection.

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			Tildrakizumab 200 mg: 169 (57) ARD vs, etanercept (95% CI, *P* value) Tildrakizumab 100 mg: 25.5% (17.6% to 33.0%, < .001) Tildrakizumab 200 mg: 27.3% (19.5% to 34.7%, < .001) **N (%) PASI 100** Etanercept: 31 (11) Tildrakizumab 100 mg: 66 (22) Tildrakizumab 200 mg: 79 (26) ARD vs, etanercept (95% CI, *P* value) Tildrakizumab 100 mg: 11.8% (5.9% to 17.9%, < .001) Tildrakizumab 200 mg: 15.7% (9.6% to 22.0%, .001) **N (%) DLQI 0 or1** Etanercept: 111 (39) Tildrakizumab 100 mg: 157 (54) Tildrakizumab 200 mg: 193 (65) ARD vs. etanercept (95% CI, *P* value) Tildrakizumab 100 mg: 15.0% (6.9% to 22.9%, .0003) Tildrakizumab 200 mg: 25.7% (17.7% to 33.4%, <.001)		

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
Reich et al.[48] 2017 Paul et al;.[52] 2018 IXORA-S Fair	Ixekizumab 80 mg[a] SC every 2 weeks through week 12, every 4 weeks thereafter Ustekinumab 45 or 90 mg SC (if patient weight more than 100 kg) at weeks 0, 4, and 16 Induction period: 12 weeks Maintenance period: 52 weeks	Ixekizumab: 136 Ustekinumab: 166 Total: 302	*Primary outcome at week 12* **% PASI 90** 72.8% (ixekizumab) vs. 42.2% (ustekinumab), *P* < .001 *Secondary outcomes at week 12* **% PASI 75** 88.2% (ixekizumab) vs. 68.7% (ustekinumab), *P* < .001 **% PASI 100** 36.0% (ixekizumab) vs. 14.5% (ustekinumab), *P* < .001 **% PGA 0 or 1** 83.6% (ixekizumab) vs. 57.2% (ustekinumab), *P* < .001 **% DLQI 0 or 1** 61.0% (ixekizumab) vs. 44.6% (ustekinumab), *P* = 0.012 **% Itch NRS ≥ 4-point improvement** 76.4% (ixekizumab) vs. 74.3% (ustekinumab), *P* = .70 **Skin pain VAS mean (SD) change** -35.4 (32.1) (ixekizumab) vs. -29.1 (30.7) (ustekinumab), *P* = .07 *Outcomes at 52 weeks:* **PASI 75** 89.2% (ixekizumab) vs. 76.3% (ustekinumab), *P* = .006 RR*, 1.2; 95% CI, 1.05 to 1.3). **PASI 90** 77.4% (Ixekizumab) vs. 59.2% (ustekinumab), *P* = .003, RR*, 1.3; 95% CI, 1.1 to 1.5) **PASI 100** 52.7% (ixekizumab) vs. 35.2% (ustekinumab), *P* = .014; RR*. 1.5; 95% CI, (1.1 to 1.9 **PGA 0 or 1** 83.6% (ixekizumab) vs.	*At week 12* **% (N) TEAEs** Ixekizumab 69.6% (94/135) vs. Ustekinumab 75.3% (125/166), *P* = .299 **% (N) Nonfatal SAE** Ixekizumab 2.2% (3/135) vs. Ustekinumab 3.0% (5/166), *P* = .735 **% (N) Severe TEAE** Ixekizumab 4.4% (6/135) vs. Ustekinumab 6.0% (10/166), *P* = .613 % (N) Withdrawal due to AEs Ixekizumab 1.5% (2/135) vs. ustekinumab 0.6% (1/166), *P* = .589 *At 52 weeks* **% (N) TEAEs** Ixekizumab 86.7% (117/135) vs ustekinumab 83.7% (139/166), *P* = .519, RR*, 1.04 (95% CI< 0.94 to 1.1) **% (N) SAE** Ixekizumab 6.7% (9/135) vs ustekinumab 3.6% (6/166), *P* = .289,	**Most common TEAE** nasopharyngitis 24.4% Ixekizumab vs. 27.1% Ustekinumab No deaths reported at 12 or 52 weeks. **Infections at 52 weeks:** 61.5% Ixekizumab vs. 64.5% Ustekinumab, *P* = .632 **Injection site reactions at 52 weeks:** 16.3% Ixekizumab vs. 1.2% Ustekinumab, *P* ≤ .001, RR* = 13.53; 95% CI, 3.2, 56.5

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
			65.8% (ustekinumab), *P* = .002, RR*, 1.3; 95% CI, (1.1 to 1.4 **PGA 0** 53.5% (ixekizumab) vs. 35.8% (ustekinumab), *P* = .013; RR*. 1.5; 95% CI, 1.1 to 1.9	RR*, 1.8; 95% CI, 0.67 to 5.1 **% (N) withdrawal due to an AE** Ixekizumab 2.2% (3/135) vs ustekinumab 1.2% (2/166), *P* = .66, RR*. 1.8; 95% CI, 0.31 to 10.9 **Death** Ixekizumab 0% (0/135) vs ustekinumab 0% (0/166)	
Reich et al.,[47] 2017 LIBERATE Fair	Etanercept 50 mg subcutaneous twice weekly Apremilast 30 mg oral tablet twice per day Placebo Duration 16 weeks, after which there was an extension phase which is not included here	Etanercept: 83) Apremilast: 83 Placebo: 84 Total: 250	*Primary outcome at 16 weeks* **% PASI 75** 39.8% (apremilast) vs. 48.2% (etanercept), *P* = .26 (post-hoc) *Secondary outcomes at 16 weeks* **% PGA 0 or 1** 21.7% (apremilast) vs. 28.9% (etanercept), *P* NR **% PASI 50** 62.7% (apremilast) vs. 83.1% (etanercept), *P* NR **Mean (SD) BSA change** -48.3 (35.1) (apremilast) vs. -56.5 (31.6) (etanercept), *P* NR **Mean (SD) DLQI change** -8.3 (7.7) (apremilast) vs. -7.8 (6.5) (etanercept) *Exploratory Outcome* **% PASI 90** 14.5% (apremilast) vs. 20.5% (etanercept), *P* NR	**% AEs** Apremilast: 71.1% Etanercept: 53.0%, *P* NR ≥ 95% of AEs were mild or moderate in severity RR, 0.75; 95% CI, 0.58 to 0.95 **% SAEs** Apremilast: 3.6% Etanercept: 2.4%, *P* NR RR, 0.67; 95% CI, 0.11 to 3.9 **% severe AEs** Apremilast: 3.6% Etanercept: 3.6%, *P* NR **% withdrawals due to AE**	Most common AEs (in ≥ 5% of patients in any treatment group): nausea, diarrhea, upper respiratory tract infection, nasopharyngitis, tension headache and headache Triglycerides > 3.4 mmol/L: 12% apremilast, 17% etanercept, *P* NR

Author, Year Trial Name Study Quality	Interventions	N	Efficacy/Effectiveness Outcomes	AE General	AE Specific
				Apremilast: 3.6% Etanercept: 2.4%, *P* NR RR, 0.67; 95% CI, 0.11 to 3.9	

Notes. An asterisk "" indicates a calculated value. [a] After 160-mg initial dose. [b] The Ixekizumab group was administered a starting dose of 160 mg given as 2 injections at Week 0. Abbreviations. A2: Amagine-2 study; A3: Amagine-3 study; ACR: American College of Rheumatology percentage improvement; AE: adverse event; AMD: absolute mean difference; ARD: absolute risk difference; BMS: Bristol-Myers Squibb; BSA: body surface area; cDMARD: conventional disease-modifying antirheumatic drugs; CI: confidence interval; COX-2: cyclooxygenase-2; DAPSA: Disease Activity Index for Psoriatic Arthritis; DAS-CRP: Disease Activity Score including c-reactive protein; DLQI: Dermatology Life Quality Index; EQ-5D: European Quality of Life 5-item measure of health utility; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; FDA: U.S. Food and Drug Administration; HADS-D/HADS-A: Hospital Anxiety or Depression Scale; HAQ-DI: Health Assessment Questionnaire Disability Index; HAQ-S: Health Assessment Questionnaire for the Spondyloarthropathies; IGA: Investigator's Global Assessment; IQR: interquartile range; IV: intravenous; ISI: Itch Severity Index; LEI: Leeds Enthesitis Index; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; MDA: Minimal Disease Activity; NA: not applicable; NCT: U.S. National Clinical Trial; NR: not reported; NRS: Numeric Rating Scale; NS: not statistically significant as reported by study authors; NSAID: nonsteroidal inflammatory drug; PASDAS: Psoriatic Arthritis Disease Activity Score; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment; PRO: patient-reported outcomes; PsARC: Psoriatic Arthritis Response criteria; PSS: Psoriasis Symptom Scale; PSSD: Psoriasis Symptoms and Signs Diary; PSSI: Psoriasis Scalp Severity Index; PtGA: Patient's Global Assessment; RCT: randomized controlled trial; RR: risk ratio; SAE: serious adverse event; SC: subcutaneous; SD: standard deviation; SE: standard error; SF-36 MCS: Short Form Survey Mental Health Component Score; SF-36 PCS: Short Form Survey Physical Health Component Score; SJC: swollen joint count; SPARCC EI: Spondyloarthritis Research Consortium of Canada Enthesitis Index; TEAE: treatment-emergent adverse event; TIM: targeted immune modulator; TJC: tender joint count: TNF-α: tumor necrosis factor alpha; U2: Uncover-2 study; U3: Uncover-3 study; VAS: visual analog scale; wk: weeks; WLQ: Work Limitations Questionnaire; WPAI-PSO: Work Productivity and Activity Impairment Questionnaire-Psoriasis.*

Table B3. Evidence Table for Cohort Studies of TIMs in Plaque Psoriasis and Psoriatic Arthritis

Author, Year Country Study Quality	Drug Dosage Duration of Exposure	Sample Time Frame, Data Source	Sample Size	Population Characteristics	Harms	Funder
Dommasch et al.,[18] 2019 United States Fair	Methotrexate Adalimumab Acitretin Apremilast Etanercept Infliximab Ustekinumab Study was conducted from January 1, 2003 to September 30, 2017.	Insurance beneficiaries within the Optum Clinformatics Data Mart between January 1, 2004 to September 30, 2017 and Truven MarketScan between January 1, 2003 to January 1, 2017. Outcomes based on ICD-9-CM codes. Serious infection defined as primary inpatient diagnosis code for pneumonia, meningitis/encephalitis, bacteremia/sepsis, cellulitis, soft-tissue	*Optum Clinformatics Data Mart* Methotrexate: N = 8,470 Adalimumab: 7,181 Acitretin: N = 2,726 Apremilast: N = 1,623 Etanercept: N = 7,102 Infliximab: N = 408 Ustekinumab: 4,085 Total: N = 31, 585 *Truven MarketScan* Methotrexate: 20,609 Adalimumab: N = 17,912 Acitretin: N = 7,456 Apremilast: N = 4,476 Etanercept: N = 16,791 Infliximab: N = 1,027 Ustekinumab: N = 7,841 Total: N = 76,112	Psoriasis patients with at least 3 ICD-9-CM codes of 696.1 on separate dates. Patients were included if they had a prescription claim for acitretin, adalimumab, apremilast, etanercept, infliximab, ustekinumab, or methotrexate. Patients were required to have continuous medical and prescription coverage during the 180 days prior to and on the cohort entry data. Patients were excluded if they had a claim for any study drug during the 180 days prior to the cohort entry date, were younger than 18 years, or a prescription for the index study drug with day supply of 0. If patient had 1 of the following within 180 days of the cohort entry date the participant was excluded, a claim for more than 1 systemic medication for psoriasis	**Serious infection requiring hospitalization** HR, 95% CI (compared to adalimumab) Apremilast: 0.31, 0.15 to 0.65 Etanercept: 0.76, 0.61 to 0.94 Infliximab: 1.92,1.01 to 3.62 Ustekinumab: 0.70, 0.49 to 1.00	The Division of Pharmaco-epidemiology and Pharmaco-economics, Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School

Author, Year Country Study Quality	Drug Dosage Duration of Exposure	Sample Time Frame, Data Source	Sample Size	Population Characteristics	Harms	Funder
		infection, endocarditis, pyelonephritis, and septic arthritis/osteoarthritis.		or other immunosuppressive medications, history of any malignancy, history of any serious infection, or a diagnosis of another immune mediated inflammatory disorder for which biologics may be used. Mean age: varied from 46 to 53across agents N (%) female: 51,008(47.3)		
Esposito et al.,[38] 2013 Italy Fair	Infliximab Etanercept Adalimumab In patients with psoriatic arthritis, etanercept given as 50 mg weekly or 25 mg biweekly, while in patients with plaque psoriasis alone 50 mg given twice weekly might also have been used for the first 12 weeks, followed by 25 mg twice weekly or 50 mg once weekly. In patients affected by psoriatic arthritis and psoriasis,	2007-2011 Three Italian referral centers (Bari, Roma, Verona)	Adalimumab:114 Etanercept:389 Infliximab:147 Total: 650	Patients with plaque psoriasis	**Withdrawals due to AEs** Infliximab (8.8%) Adalimumab (4.4%) Etanercept (2.8%), the difference was significant between infliximab and etanercept (*P* < .001)	Unrestricted grant from Pfizer

Author, Year Country Study Quality	Drug Dosage Duration of Exposure	Sample Time Frame, Data Source	Sample Size	Population Characteristics	Harms	Funder
	adalimumab given as SC initial dose 80 mg followed by 40 mg every other week, while infliximab was administered IV at a dosage of 5 mg/kg at weeks 0, 2, and 6, and then every 8 weeks/ Duration at least 3 months.					
Kisacik et al.,[41] 2016 Turkey Poor	Infliximab Etanercept Adalimumab	September 2002 to 2012	N = 10,434 (7,695 used) Infliximab: N = 2,684 (without TB), N = 46 with Adalimumab: N = 2,238 (without), N = 14 with Etanercept: N = 2,773 (without), N = 13 with	Patients from member centers of the Turkish Multicentered Investigators Platform in Rheumatology Mean age (SD): 43.4 (13.6) without TB, 43.6 (13) with Gender: N = 3,634 males/4,061 females without, N = 39 males/34 females with	**Incidence of TB** Infliximab (1.27%) Etanercept (0.3%) and Adalimumab (0.57%) *P* < .001 and *P* = .008, respectively compared to infliximab Adalimumab vs. etanercept, *P* = .08	
Lee et al.,[22] 2019 United States Fair	Ustekinumab (dose unspecified) TNF-α inhibitors (specifically adalimumab, etanercept, infliximab, certolizumab, or golimumab) Mean (SD) follow-up: 1.4 (1.3) years,	Adult patients between 25 September 2009 and 30 September 2015. Data was acquired from Optum and MarketScan databases, which contains	Ustekinumab: N = 9,071 TNF-α inhibitors: N = 50,957 Total: N = 60,028	Adults with at least 1 visit coded for psoriasis or psoriatic arthritis who initiated therapy with ustekinumab or a TNF-α inhibitor (i.e., adalimumab, etanercept, infliximab, certolizumab, or golimumab) with at least 12 months of	**N Incident atrial fibrillation** Ustekinumab: 60 TNF-α: 323 adjusted HR, 1.08; 95% CI, 0.76 to 1.54for ustekinumab compared to TNF-α inhibitor **N incident major cardiovascular event**	Division of Pharmaco-epidemiology and Pharmaco-economics at the Brigham and Women's Hospital

Author, Year Country Study Quality	Drug Dosage Duration of Exposure	Sample Time Frame, Data Source	Sample Size	Population Characteristics	Harms	Funder
	Maximum followup: 6 years	a nationwide sample of commercially insured patients.		continuous enrollment in the health plan before the index date. The cohort entry date (i.e., index date) was defined as the date of ustekinumab or TNF-α inhibitor therapy initiation, and treatment initiation was defined as the absence of the pertinent drug exposure within the last 12 months of the index date. Patients who had a previous diagnosis of atrial fibrillation (ICD-9-CM diagnosis code 427.3x) or received antiarrhythmic or anticoagulant therapy during the baseline period. N (%) male: 29,495 (49.1%) Mean Age (SD) Ustekinumab (Optum cohort): 46.0 (12.6) Ustekinumab (MarketScan cohort): 46.7 (12.9) TNF-α inhibitor (Optum cohort): 47.3 (13.0) TNF-α inhibitor	Ustekinumab: 74 TNF-α inhibitor: 421 adjusted HR,1.10; 95% CI, 0.80 to 1.52 for ustekinumab compared to TNF-α inhibitor	

Author, Year Country Study Quality	Drug Dosage Duration of Exposure	Sample Time Frame, Data Source	Sample Size	Population Characteristics	Harms	Funder
				(MarketScan cohort): 47.3 (12.6)		
Mason et al.,[23] 2018 United Kingdom and Republic of Ireland Fair	Doses after loading doses were completed: Etanercept: 50 mg weekly, dose missing for 17%) Adalimumab: 40 mg every 2 weeks, dose missing for 17% Ustekinumab: 45 mg every 12-week, dose missing for 15%	BAD Biologic Interventions Register; Patients receiving etanercept (Enbrel only), adalimumab, or ustekinumab who completed at least 1 follow-up up to December 1, 2016, were included in the analysis. Follow-up assessments are conducted at 6-month intervals. Medical records are reviewed for adverse events. SAEs	Etanercept: N = 1,509 Adalimumab: N = 2,219 Ustekinumab: N = 754 Total: N = 3,812	Patients identified from the prospective pharmacovigilance registry, a registry of patients with psoriasis recruited from 157 dermatology centers in United Kingdom and Ireland. Patients were recruited for the registry during routine appointments within 6 months of initiating or switching to a biologic or conventional systemic therapy. Median (IQR) age, in years Etanercept: 45 (36 to 54) Adalimumab: 45 (36 to 54) Ustekinumab: 46 (37 to 55) N (%) female Etanercept: 635 (42)	*Of those eligible for clinical trials:* **SAE IR per 1,000 (95% CI)** Adalimumab: 269 (227 to 319) Etanercept: 226 (167 to 305) Ustekinumab: 282 (207 to 384) **SAE IRR (95% CI)*** Etanercept vs. Adalimumab: 0.84 (0.70 to 1.003); *P* = .05 Ustekinumab vs. Adalimumab: 1.1 (0.89 to 1.24); *P* = .58 Ustekinumab vs. Etanercept: 1.25 (1.1 to 1.49); *P* = .01 *Of those not eligible for clinical trials:188* **SAE IR per 1,000 (95% CI)** Adalimumab: 514 (367 to 719)	BAD receives income from by AbbVie, Janssen Cilag, Novartis, Samsung Bioepis, Eli Lilly, and Pfizer for providing pharmaco-vigilance services.

Author, Year Country Study Quality	Drug Dosage Duration of Exposure	Sample Time Frame, Data Source	Sample Size	Population Characteristics	Harms	Funder
		included death, or resulted in overnight hospitalization, immediately life-threatening event, intravenous medication administration, loss of function or disability, or congenital malformation/birth defect, or medically important event.		Adalimumab: 1,645 (41) Ustekinumab: 644 (40) Disease duration, median (IQR) in years Etanercept: 21 (13 to 30) Adalimumab: 21 (13 to 30) Ustekinumab: 21 (12 to 31) The study authors further divided the cohort into those that would meet eligibility criteria for the phase 3 licensing clinical trials, and those that would not. Eligible: Etanercept: 839 (56) Adalimumab: 2,219 (56) Ustekinumab: 754 (46)	Etanercept: 386 (279 to 536) Ustekinumab: 630 (490 to 809) **SAE IRR (95% CI)*** Etanercept vs. adalimumab: 0.75 (0.66 to 0.86); *P* < .001 Ustekinumab vs. adalimumab: 1.23 (1.09 to 1.38); *P* < .001 Ustekinumab vs. etanercept: 2.44 (1.82 to 3.07); *P* < .001	
Warren et al., [78] 2015 United Kingdom Fair	Adalimumab Etanercept Infliximab Ustekinumab NR NR	2007-2014 BAD Biologic Interventions Register	Adalimumab: 1,879 Etanercept: 1,098 Infliximab: 96 Ustekinumab: 450 Total: 3,523	Biologically-naïve patients with chronic plaque psoriasis. Mean (SD) Age: 45.3 (12.8) years Disease duration: 22.0 (12.4) years Age of onset: 23.3 (12.9) years 39.7% female. BMI 31.1 kg/m^2 (7.3) Overall, 60.9% of patients had 1 or more	**Withdrawal due to AEs** Compared to adalimumab: Etanercept: RR 0.77; 95% CI, 0.58 to 1.02 Infliximab: RR, 2.82; 95% CI, 1.79 to 4.45; *P* < 0.05 Ustekinumab: RR, 0.60; 95% CI, 0.39 to 0.92	BAD receives income from by AbbVie, Janssen Cilag, Novartis, Samsung Bioepis, Eli Lilly, and Pfizer for providing pharmacovig-ilance services.

Author, Year Country Study Quality	Drug Dosage Duration of Exposure	Sample Time Frame, Data Source	Sample Size	Population Characteristics	Harms	Funder
				comorbidities (hypertension (27.7%), depression (23.3%), and psoriatic arthritis (20.1%) being the most common).		
Wu et al., [33] 2018 United States Fair	Dose not reported Mean (SD) duration in months: Adalimumab: 11.0 (7.5) Etanercept: 11.9 (11.3) Ustekinumab: 8.3 (8.5) Infliximab: NR	Adult patients with claims between 1 September 2008 and 30 September 2015. Data acquired from the Truven Health Analytics MarketScan Commercial Claims and Encounters database, a large U.S. administrative claims database. AEs were defined based on FDA labels, postmarketing surveillance registries, and included abnormal lab results,	Overall: 10,065 Adalimumab: 5,197 Other biologic agents: 4,868 Etanercept: 3,311 Ustekinumab: 1,370 Infliximab:187	Adults who were biologic-naïve with ≥ 2 psoriasis diagnoses on claims, with at least 1 recorded during a dermatologist encounter. Inclusion based on (1) continuous healthcare plan enrollment during the baseline period and ≥1 month after the index date, (2) ≥2 prescription fills, administrations, or sessions for ≥1 of the studied biologics, and (3) were initiated on their index treatment in monotherapy. The index date was defined as the initiation date of the first biologic therapy Median age Adalimumab: 46 years Etanercept: 46 years Ustekinumab: 47 years Infliximab: NR % female	There were no statistically significant differences in the risk of adverse medical conditions between patients treated with adalimumab and other biologic therapies. Adjusted HR, (95% CI), *P*-value Abnormal lab results: 0.96 (0.85 to 1.09); .57 Infection: 1.02 (0.96 to 1.08); .57 Mental disorder: 1.03 (0.93 to 1.13); .59 Cardiovascular disease: 1.14 (0.95 to 1.35); .15 Malignancy: 0.87 (0.67 to 1.13); .29 Respiratory disease: 1.23 (0.99 to 1.54); .06	AbbVie

Author, Year Country Study Quality	Drug Dosage Duration of Exposure	Sample Time Frame, Data Source	Sample Size	Population Characteristics	Harms	Funder
		infections, metal disorders, cardiovascular disease, malignancies, and respiratory disease. Only medical claims recorded during an inpatient or ED visit were considered for cardiovascular and respiratory conditions.		Adalimumab: 47.0 Etanercept: 48.4 Ustekinumab: 46.2% Infliximab: NR		

Abbreviations. AE: adverse event; BAD: British Association of Dermatologists; BMI: body mass index; CI: confidence intervals; ED: emergency department; FDA: U.S. Food and Drug Administration; HR: hazard ratio; ICD-9: international classification of disease-9th revision; IQR: interquartile range; IR: incidence rate; IRR: incidence rate ratio; IV: intravenous; NR: not reported; RR: risk ratio; SAE: serious adverse event; SC: subcutaneous; SD: standard deviation; TB: tuberculosis; TIM: targeted immune modulator; TNF-α: tumor necrosis factor alpha.

Appendix C. Evidence Grade Profiles

Table C1. Evidence Profile of Comparisons of TIMs for Treatment of Plaque Psoriasis

Number of Studies/ Patients	Design	Quality	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
Apremilast Compared to Adalimumab							
Serious infection requiring hospitalization							
1 study[18]/107,707	Cohort	Fair	NA	Indirect	Imprecise	HR, 0.31 (95% CI, 0.15 to 0.65)	Very low[a]
Apremilast Compared to Etanercept							
Disease remission at 16 weeks (PASI 75)							
1 study[47]/166	RCT	Fair	NA	Direct	Imprecise	40% vs. 48%; post-hoc (*P* = .26); similar findings on secondary remission and clinical improvement endpoints	Low[b]
Quality of life at 16 weeks (DLQI change)							
1 study[47]/166	RCT	Fair	NA	Direct	Imprecise	Mean (SD): -8.3 (7.7) vs. -7.8 (6.5); *P*, NR	Low[b]
Adverse events							
1 study[47]/166	RCT	Fair	NA	Direct	Imprecise	RR, 0.75; 95% CI, 0.58 to 0.95	Low[b]
Serious adverse events							
1 study[47]/166	RCT	Fair	NA	Direct	Imprecise	RR, 0.67; 95% CI, 0.11 to 3.9	Low[b]
Bimekizumab Compared to Placebo (pipeline drug)							
Disease remission at 12 to 20 weeks (% change in PASI and PASI 90)							
2 studies[19,26]/289	RCT	Fair	Consistent	Direct	Imprecise	Higher proportion achieved remission with bimekizumab compared to placebo (46% to 70% across various doses compared to 0% for placebo)[26] Percent change from baseline in PASI score higher for 160-mg, 480-mg, and 640-mg dosages compared to placebo[19]	Moderate[c]
Adverse events							
2 studies[19,26]/289	RCT	Fair	Inconsistent	Direct	Imprecise	Higher incidence of AE in 1 study (RR, 1.7; 95% CI, 1.1 to 2.6) but no significant difference in the other study	Very low[b,d]

Number of Studies/ Patients	Design	Quality	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
Serious adverse events							
2 studies[19,26]/289	RCT	Fair	Inconsistent	Direct	Imprecise	No significant differences observed but effect estimates on opposite sides of the null effect (RR, 0.20 and 2.0); relationship cannot be determined	Very low[b,d]
BMS-9865165 Compared to Placebo (pipeline drug)							
Disease remission at 12 weeks (PASI 75)							
1 study[27]/268	RCT	Fair	NA	Direct	Imprecise	Higher proportion achieved remission for all but lowest of 5 different doses	Moderate[c]
Quality of life at 12 weeks (DLQI 0 or 1)							
1 study[27]/268	RCT	Fair	NA	Direct	Imprecise	Higher proportion with no effect of psoriasis on QoL for all but the 2 lowest of 5 different doses	Moderate[c]
Adverse events							
1 study[27]/268	RCT	Fair	NA	Direct	Imprecise	Higher proportion at 2 highest doses (RRs 1.6 and 1.5), no difference at 3 lowest doses	Low[b]
Serious adverse events							
1 study[27]/268	RCT	Fair	NA	Direct	Imprecise	Too imprecise for definitive conclusion, RRs for all doses very close to 1.0, but extremely wide CIs	Low[b]
Brodalumab Compared to Ustekinumab							
Disease remission at 12 weeks (PASI 100)							
2 studies[43]/3,712	RCT	Fair	Consistent	Direct	Precise	Higher proportion achieved remission (ARDs 18 and 22 percentage points)	High
Adverse events							
2 studies[43]/3,712	RCT	Fair	Consistent	Direct	Imprecise	RRs 0.98 and 1.1, CIs of both include null effect	Moderate[c]
Serious adverse events							
2 studies[43]/3,712	RCT	Fair	Inconsistent	Direct	Imprecise	RR, 0.74; 95% CI, 0.21 to 2.6 and RR, 2.3; 95% CI, 0.49 to 10.4; relationship cannot be determined	Very low[b,d]

Number of Studies/ Patients	Design	Quality	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
Etanercept Compared to Adalimumab							
Serious infection requiring hospitalization							
1 study[18]/107,707	Cohort	Fair	NA	Indirect	Imprecise	HR, 0.76; 95% CI, 0.61 to 0.94	Very low[a]
Serious adverse events							
1 study[23]/7,136	Cohort	Fair	NA	Direct	Imprecise	IRR, 0.75; 95% CI, 0.66 to 0.86 of those not eligible for clinical trials	Very low[e]
Etanercept Compared to Infliximab							
Disease remission at 24 weeks (PASI 75)							
1 study[37]/50	RCT	Poor	NA	Direct	Imprecise	Lower proportion achieved remission (35% vs. 72%)	Very low[b,f]
Quality of life at 24 weeks (Relative change in SF-36 Physical Health and Mental Health Component Score)							
1 study[37]/50	RCT	Poor	NA	Direct	Imprecise	No difference between agents.	Very low[b,f]
Adverse events							
1 study[37]/50	RCT	Poor	NA	Direct	Imprecise	RR, 1.04; 95% CI, 0.93 to 1.2	Very low[b,f]
Serious adverse events							
1 study[37]/50	RCT	Poor	NA	Direct	Imprecise	RR, 0.36; 95% CI, 0.08 to 1.6	Very low[b,f]
Etanercept Compared to Ixekizumab							
Disease remission at 12 weeks (PASI 75)							
2 studies[40]/2,570	RCT	Fair	Consistent	Direct	Precise	Lower proportion achieved remission (ARD range 31 to 48 percentage points across doses and studies)	High
Disease remission at 12 weeks (PGA 0 or 1)							
2 studies[40]/2,570	RCT	Fair	Consistent	Direct	Precise	Lower proportion achieved remission (ARD range 34 to 47 percentage points across doses and studies)	High
Quality of life at 12 weeks (DLQI 0 or 1)							
2 studies[40]/2,570	RCT	Fair	Consistent	Direct	Precise	Lower proportion achieved no or minimal effect of psoriasis on QoL (ARD 20 to 30 percentage points)	High

Number of Studies/ Patients	Design	Quality	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
Adverse events							
2 studies[40]/2,570	RCT	Fair	NA (only pooled result provided)	Direct	Imprecise	Pooled RR, 0.93; 95% CI, 0.85 to 1.02	Moderate[c]
Serious adverse events							
2 studies[40]/2,570	RCT	Fair	NA (only pooled result provided)	Direct	Imprecise	Pooled RR, 0.99; 95% CI, 0.48 to 2.1	Low[b]
Etanercept Compared to Secukinumab							
Disease remission at 12 weeks (PASI 75)							
1 study[42]/1,306	RCT	Fair	NA	Direct	Precise	Lower proportion (44%) achieved response with etanercept compared to 300 mg secukinumab (77%) or 150 mg secukinumab (67%)	High
Disease remission at 12 weeks (PGA 0 or 1)							
1 study[42]/1,306	RCT	Fair	NA	Direct	Precise	Lower proportion (27%) achieved response with etanercept compared to 300 mg secukinumab (63%) or 150 mg secukinumab (51%)	High
Maintenance of disease remission at 52 weeks (continued PASI 75 response among initial responders)							
1 study[42]/1,306	RCT	Fair	NA	Direct	Precise	Lower proportion (73%) achieved response with compared to 300 mg secukinumab (84%) or 150 mg secukinumab (82%)	High
Quality of life at 12 weeks (mean change in DLQI)							
1 study[42]/1,306	RCT	Fair	NA	Direct	Imprecise	Lower improvement in quality of life (7.9 points) for etanercept compared to 300 mg secukinumab (10.4 points) or 150 mg secukinumab (9.7 points)	Moderate[c]

Number of Studies/ Patients	Design	Quality	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
Adverse events							
1 study[42]/1,306	RCT	Fair	NA	Direct	Imprecise	RR, 0.97; 95% CI, 0.90 to 1.1	Moderate[c]
Serious adverse events							
1 study[42]/1,306	RCT	Fair	NA	Direct	Imprecise	RR, 1.1; 95% CI, 0.61 to 1.9	Low[b]
Etanercept Compared to Tildrakizumab							
Disease remission at 12 weeks (PASI 75)							
1 study[28]/1,090	RCT	Fair	NA	Direct	Precise	Lower proportion (48%) compared to 100 mg tildrakizumab (61%) or 200 mg tildrakizumab (66%)	High
Disease remission at 28 weeks (PASI 75)							
1 study[28]/1,090	RCT	Fair	NA	Direct	Precise	Lower proportion (54%) compared to 100 mg tildrakizumab (73%) or 200 mg tildrakizumab (73%)	High
Quality of life at 12 weeks (DLQI 0 or 1)							
1 study[28]/1,090	RCT	Fair	NA	Direct	Imprecise	Lower proportion (36%) with no effect of psoriasis on QoL compared to 200 mg tildrakizumab (47%), no difference compared to 100 mg tildrakizumab (40%)	Moderate[c]
Quality of life at 28 weeks (DLQI 0 or 1)							
1 study[28]/1,090	RCT	Fair	NA	Direct	Precise	Lower proportion (39%) with no effect of psoriasis on QoL compared to 100 mg tildrakizumab (54%) or 200 mg tildrakizumab (65%)	High
Adverse events							
1 study[28]/1,090	RCT	Fair	NA	Direct	Imprecise	Reported for 2 time periods: Weeks 0 to 12: RR, 0.82; 95% CI, 0.70 to 0.96 for 100-mg dosage; RR, 0.91; 95% CI, 0.79 to 1.1 for 200-mg dosage; both compared to etanercept. Weeks 13 to 28: RR, 0.81; 95% CI, 0.69 to 0.95 for 100-mg dosage; RR, 0.80; 95% CI, 0.68 to 0.93 for 200-mg dosage.	Moderate[c]

Number of Studies/ Patients	Design	Quality	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
Serious adverse events							
1 study[28]/1,090	RCT	Fair	NA	Direct	Imprecise	Reported for 2 time periods Weeks 0 to 12: RR, 0.58; 95% CI, 0.17 to 2.0 for 100-mg dosage; RR, 0.85; 95% CI, 0.29 to 2.5 for 200-mg dosage; both compared to etanercept. Weeks 13 to 28: RR, 0.63; 95% CI, 0.28 to 1.4 for 100-mg dosage; RR, 0.41; 95% CI, 0.16 to 1.1 for 200-mg dosage.	Low[b]
Etanercept Compared to Tofacitinib (not FDA-approved for plaque psoriasis)							
Disease remission at 12 weeks (PASI 75)							
1 study[35,51]/1,106	RCT	Fair	NA	Direct	Imprecise	Higher proportion (59%) achieved response compared to 5 mg tofacitinib (40%) but similar response compared to 10 mg tofacitinib (64%)	Moderate[c]
Disease remission at 12 weeks (PGA 0 or 1)							
1 study[35,51]/1,106	RCT	Fair	NA	Direct	Imprecise	Higher proportion (66%) achieved response compared to 5 mg tofacitinib (47%) but similar response compared to 10 mg tofacitinib (68%)	Moderate[c]
Clinical improvement (PASI 50) at 12 weeks							
1 study[35,51]/1,106	RCT	Fair	NA	Direct	Imprecise	Higher proportion (80%) achieved response compared to 5 mg tofacitinib (66%) but similar response compared to 10 mg tofacitinib (81%)	Moderate[c]
Quality of life (Change in DLQI of 5 points or more) at 12 weeks							
1 study[35,51]/1,106	RCT	Fair	NA	Direct	Imprecise	Higher proportion (75%) achieved response compared to 5 mg tofacitinib (66%) but similar response compared to 10 mg tofacitinib (78%)	Low[b] for 10-mg dosage Moderate[c] for 5-mg dosage
Adverse events							
1 study[35,51]/1,106	RCT	Fair	NA	Direct	Imprecise	RR, 1.1; 95% CI, 0.92 to 1.2	Low[b]

Number of Studies/ Patients	Design	Quality	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
Serious adverse events							
1 study[35,51]/1,106	RCT	Fair	NA	Direct	Imprecise	RR, 0.98; 95% CI, 0.35 to 2.8	Low[b]
Etanercept Compared to Ustekinumab							
Disease remission (PASI 75) at 12 weeks							
1 study[39]/903	RCT	Fair	NA	Direct	Imprecise	Lower proportion achieved remission with etanercept (57%) compared to either 45 mg ustekinumab (68%) or 90 mg ustekinumab (74%).	Low[c,f]
Adverse events							
1 study[39]/903	RCT	Fair	NA	Direct	Imprecise	RR, 1.03; 95% CI, 0.94 to 1.1	Low[c,f]
Serious adverse events							
1 study[39]/903	RCT	Fair	NA	Direct	Imprecise	RR, 0.80; 95% CI, 0.24 to 2.6	Low[c,f]
Serious adverse events							
1 study[23]/7,136	Cohort	Fair	NA	Direct	Imprecise	IRR, 2.4; 95% CI, 1.8 to 3.1 for ustekinumab compared to etanercept (among participants with a clinical status that would make them ineligible to participate in clinical trials).	Very low[e]
Guselkumab Compared to Adalimumab							
Disease remission at 16 weeks (PGA 0 or 1)							
3 studies[17,20,32]/1,658	RCT	Fair	Consistent	Direct	Precise	Higher proportion achieve remission with guselkumab 100 mg compared to adalimumab (ARD range 16 to 28 percentage points)	High
Quality of life at 16 weeks (mean change in DLQI or DLQI 0 or 1)							
3 studies[17,20,32]/1,658	RCT	Fair	Consistent	Direct	Imprecise	Higher proportion with no effect of psoriasis on QoL for guselkumab (ARD range 13 to 15 percentage points, but only statistically significant in 1 of the 2 studies reporting this outcome)	Moderate[c]

Number of Studies/ Patients	Design	Quality	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
						Mean difference in change: from baseline: range -0.7 to -1.6 across the 3 studies.	
Adverse Events							
3 studies[17,20,32]/1,658	RCT	Fair	Consistent	Direct	Imprecise	RR, range from 0.89 to 1.01; all CIs include null effect.	Low[b]
Serious Adverse Events							
3 studies[17,20,32]/1,658	RCT	Fair	Consistent	Direct	Imprecise	RR, range from 0.62 to 1.4; all CIs include null effect.	Low[b]
Guselkumab Compared to Secukinumab							
Disease remission at 12 and 48 weeks (PASI 75, PASI 90)							
1 study[31]/1,048	RCT	Fair	NA	Direct	Precise	Higher proportion (84%) achieved PASI 90 response compared to secukinumab (70%) at 48 weeks; proportion achieving PASI 75 response at both 12 and 48 weeks was similar (85% guselkumab vs. 80% secukinumab; $P < .001$ for non-inferiority and $P = .06$ for superiority), lower proportion (69%) achieved PASI 90 response compared to secukinumab (76%) at 12 weeks but no significance testing conducted to control type I error.	Moderate[d]
Adverse events							
1 study[31]/1,048	RCT	Fair	NA	Direct	Imprecise	RR, 0.95; 95% CI, 0.90 to 1.0	Low[b]
Serious adverse events							
1 study[31]/ 1,048	RCT	Fair	NA	Direct	Imprecise	RR, 0.85; 95% CI, 0.54 to 1.3	Low[b]
Infliximab Compared to Adalimumab							
Serious infection requiring hospitalization							
1 study[18]/107,707	Cohort	Fair	NA	Indirect	Imprecise	HR, 1.9; 95% CI, 1.01 to 3.6	Very low[a]

Number of Studies/ Patients	Design	Quality	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
Ixekizumab Compared to Ustekinumab							
Disease remission at 12 weeks (PASI 90)							
1 study[48,52]/302	RCT	Fair	NA	Direct	Imprecise	Higher proportion (73%) achieved response compared to ustekinumab (42%)	Moderate[c]
Disease remission at 52 weeks (PASI 90)							
1 study[48,52]/302	RCT	Fair	NA	Direct	Imprecise	Higher proportion (77%) maintained response compared to ustekinumab (59%)	Moderate[c]
Quality of life at 12 weeks (DLQI 0 or 1)							
1 study[48,52]/302	RCT	Fair	NA	Direct	Imprecise	Higher proportion (61%) achieved response compared to ustekinumab (45%)	Moderate[c]
Adverse events							
1 study[48,52]/302	RCT	Fair	NA	Direct	Imprecise	RR, 0.92; 95% CI, 0.80 to 1.1	Low[b]
Serious adverse events							
1 study[48,52]/302	RCT	Fair	NA	Direct	Imprecise	RR, 0.74; 95% CI, 0.18 to 3.0	Low[b]
Mirikizumab Compared to Placebo							
Disease remission at 16 weeks PASI 90)							
1 study[30]/205	RCT	Fair	NA	Direct	Imprecise	Higher proportion (67% 300 mg, 59% 100 mg, 29%, 30 mg) achieved response compared to placebo (0%)	Moderate[c]
Change in quality of life at 16 weeks (DLQI 0 or 1)							
1 study[30]/205	RCT	Fair	NA	Direct	Imprecise	Higher proportion (47% 300 mg, 49% 100 mg, 35%, 30 mg) achieved response compared to placebo (4%)	Moderate[c]
Adverse events							
1 study[30]/205	RCT	Fair	NA	Direct	Imprecise	RR, 1.01; 95% CI, 0.73 to 1.4	Low[b]
Serious adverse events							
1 study[30]/205	RCT	Fair	NA	Direct	Imprecise	RR, 0.68; 95% CI, 0.06 to 7.3	Low[b]

Number of Studies/ Patients	Design	Quality	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
Risankizumab Compared to Adalimumab							
Disease remission at 16 weeks (PASI 90)							
1 study[29]/605	RCT	Fair	NA	Direct	Imprecise	Higher proportion (72%) achieved response compared to adalimumab (47%)	Moderate[c]
Disease remission at 16 weeks (PGA 0 or 1)							
1 study[29]/605	RCT	Fair	NA	Direct	Imprecise	Higher proportion (84%) achieved response compared to adalimumab (60%)	Moderate[c]
Quality of life at 16 weeks (DLQI 0 or 1)							
1 study[29]/605	RCT	Fair	NA	Direct	Imprecise	Higher proportion (66%) achieved response compared to adalimumab (49%)	Moderate[c]
Adverse events							
1 study[29]/605	RCT	Fair	NA	Direct	Imprecise	RR, 0.98; 95% CI, 0.85 to 1.1	Low[b]
Serious adverse events							
1 study[29]/605	RCT	Fair	NA	Direct	Imprecise	RR, 1.1; 95% CI, 0.46 to 2.7	Low[b]
Risankizumab Compared to Ustekinumab							
Disease remission at 12 to 16 weeks (PASI 90)							
3 studies[21,46]/1,065	RCT	Fair	Consistent	Direct	Precise	Higher proportion achieved response compared to ustekinumab (ARD range 28 to 37 percentage points)	High
Disease remission at 12 to 16 weeks (PGA 0 or 1)							
3 studies[21,46]/1,065	RCT	Fair	Consistent	Direct	Precise	Higher proportion achieved response compared to ustekinumab (ARD range 22 to 27 percentage points)	High
Quality of life at 12 to 16 weeks (DLQI 0 or 1)							
3 studies[21,46]/1,065	RCT	Fair	Consistent	Direct	Precise	Higher proportion achieved response compared to ustekinumab (ARD range 19 to 23 percentage points)	High
Adverse events							
3 studies[21,46]/1,065	RCT	Fair	Inconsistent	Direct	Imprecise	Fewer AEs were observed for risankizumab in the later time period (weeks 17 to 52) of 1 study (RR, 0.75;	Low[c,d]

Number of Studies/ Patients	Design	Quality	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
						95% CI, 0.11 to 0.77). No significant differences in the other 2 studies.	
Serious adverse events							
3 studies[21,46]/1,065	RCT	Fair	Inconsistent	Direct	Imprecise	Fewer SAEs were observed in the early time period (weeks 0 to 16) of the 1 study (RR, 0.29; 95% CI, 011 to 0.77). No significant differences in the other 2 studies.	Low[c,d]
Secukinumab Compared to Ustekinumab							
Disease remission at 16 weeks (PASI 90)							
2 studies[16,53]/1,778	RCT	Fair	Consistent	Direct	Precise	Higher proportion achieved response compared to ustekinumab (ARDs 21 and 23 percentage points)	High
Quality of life at 16 weeks (DLQI 0 or 1)							
2 studies[16,53]/1,778	RCT	Fair	Consistent	Direct	Precise	Higher proportion achieved response compared to ustekinumab (ARDs 12 and 15 percentage points)	High
Disease remission at 52 weeks (PASI 90)							
1 study[53]/676	RCT	Fair	NA	Direct	Imprecise	Higher proportion (75%) achieved response compared to ustekinumab (61%)	Moderate[c]
Change in quality of life at 52 weeks (DLQI 0 or 1)							
1 study[53]/676	RCT	Fair	NA	Direct	Imprecise	Higher proportion (72%) achieved response compared to ustekinumab (59%).	Moderate[c]
Adverse events							
2 studies[16,53]/1,778	RCT	Fair	Consistent	Direct	Imprecise	RR, 1.1 and 1.0, CIs include the null effect	Low[b]
Serious adverse events							
2 studies[16,53]/1,778	RCT	Fair	Consistent	Direct	Imprecise	RR, 1.0 and 1.6, CIs include then null effect	Low[b]

Number of Studies/ Patients	Design	Quality	Consistency	Directness	Precision	Magnitude of Effect	Quality of Evidence
Ustekinumab Compared to Adalimumab							
Serious infection requiring hospitalization							
1 study[18]/107,707	Cohort	Fair	NA	Indirect	Imprecise	HR, 0.70; 95% CI, 0.49 to 1.0	Very low[a]
Serious adverse events							
1 study[23]/7,136	Cohort	Fair	NA	Direct	Imprecise	IRR, 1.2; 95% CI, 1.1 to 1.4 (of those not eligible for clinical trials)	Very low[e]

Notes: [a] Started at low and downgraded for indirectness and imprecision. [b] Downgraded 2 levels for imprecision. [c] Downgraded 1 level for imprecision. [d] Downgraded 1 level for inconsistency across timepoints. [e] Started at low for study design and downgraded for imprecision. [f] Downgraded 1 level for study limitations. Abbreviations: AE: adverse event; ARD: absolute risk difference; BMS: Bristol-Myers Squibb; CI: confidence interval; DLQI: Dermatology Life Quality Index; FDA: U.S. Food and Drug Administration; HR: hazard ratio; IRR: incidence rate ratio; NA: not applicable; NR: not reported; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment; QoL: quality of life; RCT: randomized controlled trial; RR: risk ratio; SAE: serious adverse event; SD: standard deviation; TIM: targeted immune modulator.

Table C2. Evidence Profile of Comparisons of TIMs for Treatment of Psoriatic Arthritis

Number of Studies/ Patients	Design	Quality	Consistency	Directness	Precision	Magnitude of Effect	Overall Quality of the Evidence
Adalimumab Compared to Etanercept and Infliximab							
Clinical improvement at 1 year (ACR20)							
1 study[34]/100	RCT	Poor	NA	Direct	Imprecise	70% vs. 72% vs. 75% (*P* NR)	Very low[a,b]
Adverse events							
1 study[34]/100	RCT	Poor	NA	Direct	Imprecise	RR*, 0.38; 95% CI, 0.17 to 0.84 for adalimumab vs. etanercept RR*, 0.23; 95% CI, 0.11 to 0.49 for adalimumab vs. infliximab RR*, 1.6; 95% CI, 1.1 to 2.4 for infliximab vs. etanercept	Very low[a,b]
Adalimumab Compared to Ixekizumab							
Clinical improvement at 24 weeks (ACR20)							
1 study[44]/417	RCT	Fair	NA	Direct	Imprecise	57% vs. 62% (ixekizumab every 2 weeks) vs. 58% (ixekizumab every 4 weeks) (*P* NR)	Low[b]
Skin disease remission at 24 weeks (PASI 75)							
1 study[44]/417	RCT	Fair	NA	Direct	Imprecise	54% vs. 80% (ixekizumab every 2 weeks) vs. 71% (ixekizumab every 4 weeks) (*P* NR)	Low[b]
Adverse events							
1 study[44]/417	RCT	Fair	NA	Direct	Imprecise	RR*, 0.97; 95% CI, 0.82 to 1.2	Low[b]
Serious adverse events							
1 study[44]/417	RCT	Fair	NA	Direct	Imprecise	RR*, 1.2; 95% CI, 0.40 to 3.3	Low[b]
Adalimumab Compared to Tofacitinib							
Clinical improvement at 12 months (ACR20)							
1 study[45]/422	RCT	Fair	NA	Direct	Imprecise	60% vs. 70% (tofacitinib 10 mg) vs. 68% (tofacitinib 5 mg) (*P* NR)	Low[b]

Number of Studies/ Patients	Design	Quality	Consistency	Directness	Precision	Magnitude of Effect	Overall Quality of the Evidence
Skin disease remission at 12 months (PASI 75)							
1 study[45]/422	RCT	Fair	NA	Direct	Imprecise	56% vs. 67% (tofacitinib 10 mg) vs. 56% (tofacitinib 5 mg) (*P* NR)	Low[b]
Quality of life at 3 months (mean change in SF-36 PCS from baseline)							
1 study[45]/422	RCT	Fair	NA	Direct	Imprecise	6.2 points vs. 5.7 (tofacitinib 10 mg) vs. 5.5 (tofacitinib 5 mg) (*P* NR)	Low[b]
Adverse events							
1 study[45]/422	RCT	Fair	NA	Direct	Imprecise	RR*, 1.1; 95% CI, 0.90 to 1.3	Low[b]
Serious adverse events							
1 study[45]/422	RCT	Fair	NA	Direct	Imprecise	RR*, 1.1; 95% CI, 0.46 to 2.8	Low[b]
Adalimumab Compared to Remtolumab							
Disease remission at 12 weeks (ACR70)							
1 study[24]/240	RCT	Fair	NA	Direct	Imprecise	Compared to adalimumab: 120-mg dosage ARD*, 7.3 percentage points; 95 %CI, -5.5 to 20.0 240-mg dosage ARD*, 16.2 percentage points; 95 %CI 2.7% to 29.7%	Low[b]
Clinical improvement at 12 weeks (ACR50)							
1 study[24]/240	RCT	Fair	NA	Direct	Imprecise	Compared to adalimumab: 120-mg dosage: ARD*, -0.8 percentage points; 95% CI, -16.7% to 15.0% 240-mg dosage: ARD*, 15.9 percentage points; 95% CI, -0.07% to 31.9%; study reported *P* < .05	Low[b]
Skin disease remission at 12 weeks among persons with BSA involvement greater than 3% (PASI 75)							
1 study[24]/240	RCT	Fair	NA	Direct	Imprecise	Compared to adalimumab: 120-mg dosage: ARD*, 16.8 percentage points; 95% CI, -4.5% to 38.2%	Low[b]

Number of Studies/ Patients	Design	Quality	Consistency	Directness	Precision	Magnitude of Effect	Overall Quality of the Evidence
						240-mg dosage: ARD*, 20.0 percentage points; 95% CI, -0.5% to 40.5%; study reported *P* < .05	
Adverse events							
1 study[24]/240	RCT	Fair	NA	Direct	Imprecise	RR*, 0.88; 95% CI, 0.63 to 1.2 for 120-mg dosage compared to adalimumab; RR*, 0.80; 95% CI, 0.57 to 1.1 for 240-mg dosage compared to adalimumab	Low[b]
Serious adverse events							
1 study[24]/240	RCT	Fair	NA	Direct	Imprecise	RR*, 1.01; 95% CI, 0.004 to 256.6 for 120-mg dosage compared to adalimumab; RR*, 4.0 (95% CI, 0.05 to 313.0 for 240-mg dosage compared to adalimumab; relationship cannot be determined.	Very low[c]
Ustekinumab Compared to TNF-α Inhibitors[d]							
Enthesitis remission at 24 weeks (SPARCC EI 0)							
1 study[15]/47	RCT	Poor	NA	Direct	Imprecise	Higher proportion achieved response (74%) compared to TNF-*α* inhibitors (42%)	Very low[a,b]
Arthritis remission at 24 weeks (tender and swollen joint count of 0)							
1 study[15]/47	RCT	Poor	NA	Direct	Imprecise	Tender joint count (54% vs. 46%, *P* = .78) Swollen joint count (59% vs. 46%, *P* = .38)	Very low[a,b]
Skin disease remission at 24 weeks (PASI 90)							
1 study[15]/47	RCT	Poor	NA	Direct	Imprecise	Higher proportion achieved response (86%) compared to TNF-*α* inhibitors (29%)	Very low[a,b]
Quality of life over 24 weeks (SF-36 PCS and MCS)							
1 study[15]/47	RCT	Poor	NA	Direct	Imprecise	Statistically significantly larger improvements in SF-36 PCS	Very low[a,b]

Number of Studies/ Patients	Design	Quality	Consistency	Directness	Precision	Magnitude of Effect	Overall Quality of the Evidence
						compared to TNF-α inhibitors; no difference in SF-36 MCS compared to TNF-α inhibitors.	
Incident atrial fibrillation or major cardiovascular effects							
1 study[22]/60,028	Cohort	Fair	NA	Indirect	Imprecise	Adjusted HR, for incident atrial fibrillation 1.08; 95% CI, 0.76 to 1.5; adjusted HR for incident major cardiovascular event 1.1; 95% CI, 0.80 to 1.5	Very low[e]
Filgotinib Compared to Placebo (pipeline agent)							
Clinical improvement at 16 weeks (ACR20)							
1 study[25]/131	RCT	Fair	NA	Direct	Imprecise	Higher proportion achieved response (80%) compared to placebo (33%)	Low[b]
Disease remission at 16 weeks (DAPSA remission or low disease activity score < 14)							
1 study[25]/131	RCT	Fair	NA	Direct	Imprecise	Higher proportion achieved response (49%) compared to placebo (15%)	Low[b]
Skin disease remission at 16 weeks among those with > 3% BSA involvement at baseline (PASI 75)							
1 study[25]/131	RCT	Fair	NA	Direct	Imprecise	ARD, 30 percentage points (95% CI, 10.4 to 47.0)	Low[b]
Adverse events							
1 study[25]/131	RCT	Fair	NA	Direct	Imprecise	RR*, 0.96; 95% CI, 0.72 to 1.3	Low[b]
Serious adverse events							
1 study[25]/131	RCT	Fair	NA	Direct	Imprecise	RR*, 1.0; 95% CI, 0.0 to 15.9	Very low[c]
Remtolumab Compared to Placebo (pipeline agent)							
Disease remission at week 12 (ACR70)							
1 study[24]/ 240	RCT	Fair	NA	Direct	Imprecise	120 mg dosage: 15% vs. 4%; *P* < .05 240 mg dosage: 32% vs. 4%; *P* < .01	Moderate[f]

Number of Studies/ Patients	Design	Quality	Consistency	Directness	Precision	Magnitude of Effect	Overall Quality of the Evidence
Clinical improvement at week 12 (ACR50)							
1 study[24]/ 240	RCT	Fair	NA	Direct	Imprecise	120 mg dosage: 37% vs. 13%; *P* < .05 240 mg dosage: 53% vs. 13%; *P* < .001	Moderate[f]
Change in quality of life at week 12 (HAQ-S)							
1 study[24]/ 240	RCT	Fair	NA	Direct	Imprecise	No significance testing: Placebo: -0.28 120 mg dosage: -0.56 240 mg dosage: -0.55	Low[b]
Adverse events							
1 study[24]/ 240	RCT	Fair	NA	Direct	Imprecise	120 mg dosage: RR*. 1.01; 95% CI, 0.61 to 1.7 240 mg dosage: RR*, 0.93; 95% CI, 0.56 to 1.5	Low[b]
Serious adverse events							
1 study[24]/ 240	RCT	Fair	NA	Direct	Imprecise	120 mg dosage: RR*, 0.33; 95% CI, 0.02 to 5.1 240 mg dosage: RR*, 0.08; 95% CI, 0.001 to 6.6	Very low[c]

Notes: An asterisk ("") represents a calculated value. [a] Downgraded 1 level for study limitations. [b] Downgraded 2 levels for imprecision. [c] Downgraded 3 levels for very serious imprecision. [d] Enrolled only participants with active enthesitis. [e] Started at low for study design and downgraded 1 level for indirectness and imprecision. [f] Downgraded 1 level for precision. Abbreviations: ACR: American College of Rheumatology Response Index; ARD: absolute risk difference; BSA: body surface area; CI: confidence interval; DAPSA: Disease Activity Index for Psoriatic Arthritis; HAQ-S: Health Assessment Questionnaire for the Spondyloarthropathies; HR: hazard ratio; NA: not applicable; NR: not reported; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; RR: risk ratio; SF-36 MCS: short form 36 survey mental health component score; SF-36 PCS: short form survey 36 physical health component score; SPARCC EI: Spondyloarthritis Research Consortium of Canada Enthesitis Index; TIM: targeted immune modulator; TNF-α: tumor necrosis factor alpha.*

Appendix D. Instruments Used to Measure Outcomes in Trials of TIMs

Table D1. Instruments Used to Measure Outcomes in Trials of TIMs

Abbreviation	Name	Condition(s) used in	General description	Range and direction
ACR 20/50/70	American College of Rheumatology, numbers refer to percentage improvement	PsA	Improvement is defined by at least 20%/50%/70% improvement in TJC and in SJC, and at least 20%/50%/70% improvement in 3 of the 5 measures: ESR or CRP, PGA of disease activity, PtGA of disease activity, patient assessment of pain (VAS), and disability (HAQ).	Larger % improvement is better
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index	PsA	Based on response to 6 questions assessing 5 major symptoms including fatigue, spinal pain, arthralgia, enthesitis, morning stiffness duration, and morning stiffness severity.	0 to 10, higher is worse
BASFI	Bath Ankylosing Spondylitis Function Index	PsA	Based on 8 performance-based tests including climbing stairs, bending, reaching up, putting on socks, reclining and declining from a chair, getting up from the floor, looking over the shoulder, and a physically demanding activity.	0 to 10, higher is worse
BSA	Body Surface Area	PP	Percent of total body surface area affected by psoriasis, where handprint equates to about 1% body surface area.	0 to 100, higher is worse
DAPSA	Disease Activity Index for Psoriatic Arthritis	PsA	Composite measure of disease activity that uses tender joint count, swollen joint count, patient assessment of disease activity (scale of 0 to 10) and pain (scale of 0 to 10).	0 to 4, remission; 5 to 14, low; 15 to 28, moderate; > 28, high
DAS-CRP	Disease Activity Score with C-reactive protein	PsA	Measure of disease activity based on tender or swollen joint counts, patient's global assessment of disease, and C-reactive protein levels.	0 to 100, higher is worse
DLQI	Dermatology Life Quality Index	PP	10-item questionnaire covering 6 dimensions (symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment) that assesses the overall impact of skin disorders and current treatments on the patient's functioning and well-being.	0 to 30, higher is worse
DQOLS	Dermatology Quality of Life Scales	PP	Psychosocial, activities and symptoms scale consisting, respectively, of 17 psychosocial items grouped into 4 categories (embarrassment, despair, irritability, and distress); 12 activity items in 4 categories (everyday activities, summer activities, social activities, and sexual	0 to 100, higher is worse

Abbreviation	Name	Condition(s) used in	General description	Range and direction
			activity); and a 12-item symptom scale including redness, itching, scarring, flaking, rawness, change in skin color, pain, tiredness, swelling, bleeding, aching, and burning.	
EQ-5D	European Quality of Life - 5 Dimensions	All	Descriptive system of health-related quality of life states consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each of which can take 1 of 3 responses. The responses record 3 levels of severity (no problems/some or moderate problems/extreme problems) within a particular EQ-5D dimension.	0 to 1, higher is better
EQ-VAS	European Quality of Life - Visual Analog Scale	All	Patient-reported description of health status measured on a vertical visual analog scale.	0 to 100, higher is better
FACIT-F	Functional Assessment of Chronic Illness Therapy - Fatigue	All	Thirteen items to measure fatigue during usual daily activities over the past week.	0 to 52, higher is better
HAQ	Health Assessment Questionnaire	All	Five generic patient-centered health dimensions: (1) to avoid disability; (2) to be free of pain and discomfort; (3) to avoid adverse treatment effects; (4) to keep dollar costs of treatment low; and (5) to postpone death.	Depends on which version used; Full HAQ vs. 2 page version.
HAQ-DI	Health Assessment Questionnaire - Disability Index	All	Patient's level of functional ability; includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. There are 20 questions in 8 categories of functioning which represent a comprehensive set of functional activities – dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. Each item is scored from 0 (no difficulty) to 3 (unable to do).	0 to 60, higher is worse
ISI	Itch Severity Index	PP	Assess severity of itching due to psoriasis.	0 to 10, higher is worse
LEI	Leeds Enthesitis Index	PsA	Measures pain and tenderness at lateral elbow epicondyle, medial femoral condyle, and Achilles tendon insertion; measures are bilateral.	0 to 6, higher is worse
MASES	Maastrict Ankylosing	PsA	Based on clinical examination by assessor of 13 sites.	0 to 13, higher is worse

Abbreviation	Name	Condition(s) used in	General description	Range and direction
	Spondylitis Enthesitis Score			
mSHARP	Modified Sharp Score	PsA	Assesses radiographic progression based on erosions and joint space evaluation (as is done for rheumatoid arthritis) and additional evaluated shaft periostitis, juxta-articular periostitis, and tuft resorption. Scoring is done across multiple joints in the hands and feet.	0 to 270 erosion, 0 to 160 joint space, additional ranges for the other elements
NAPSI	Nail Psoriasis And Severity Index	PP	The nail plate, including nail pitting, leukonychia, red spots in the lunula, and crumbling in each quadrant of the nail. Nail bed psoriasis, including onycholysis, oil drop (salmon patch) dyschromia, splinter hemorrhages, and nail bed hyperkeratosis in each quadrant of the nail. 0 if the findings are not present, 1 if they are present in 1 quadrant of the nail, 2 if present in 2 quadrants of a nail, 3 if present in 3 quadrants of a nail, and 4 if present in 4 quadrants of a nail. Thus, each nail has a matrix score (0 to 4) and a nail bed score (0 to 4), and the total nail score is the sum of those 2 (0 to 8).	0 to 8, higher is worse
PASDAS	Psoriatic Arthritis Disease Activity Score	PsA	Patient and physician global scores of skin and joint disease, in addition to assessment of dactylitis, enthesitis, physical function, quality of life, acute-phase response.	0 to 10; higher is worse
PASI	Psoriasis Area and Severity Index	PP	Based on the extent of the skin-surface area involved and the severity of erythema, desquamation, and plaque induration. Response to treatment can be reported by change in absolute PASI score, or more commonly by proportion of participants achieving a 50% reduction in score (PASI 50), 75% reduction in score (PASI 75), 90% reduction in score (PASI 90) or 100% reduction in score (PASI 100).	0 to 72, higher is worse
PGA/IGA	Physician or Investigator Global Assessment	PP	A 5- or 6-point assessment assigned by physician or investigator based on the extent of skin involvement.	0 to 5 (or 6), with 0 representing clear skin, and 5 (or 6) representing severe and extensive involvement

Abbreviation	Name	Condition(s) used in	General description	Range and direction
PGPA	Patient's Global Psoriasis Assessment	PP	Single self-explanatory item to be completed by the patient, evaluating overall cutaneous disease at a specific point in time.	0 to 10, higher is worse
PsARC	Psoriatic Arthritis Response Criteria	PsA	Response is defined by improvement in at least 2 of the 4 following measures, 1 of which must be joint swelling or tenderness, and no worsening in any of the 4 measures: PtGA of articular disease (1–5) and PGA of articular disease (1–5), improvement being a decrease by 1 category, worsening being an increase by 1 category; joint pain/tenderness score and joint swelling score, improvement being a decrease by 30%, worsening being an increase by 30%.	0 to 100, higher is better
PSS	Psoriasis Symptom Scale	PP	Uses 4 items to measure the severity of pain, itching, redness, and burning during the previous 24 hours.	0 to 5; higher is worse
PSSD	Psoriasis Symptoms and Signs Diary	PP	Measures 6 symptoms (itch, skin tightness, burning, stinging, and pain) and 6 signs (dryness, cracking, scaling, shedding/flaking, redness, and bleeding).	0 to 100; higher is worse
PtGA	Patient Global Assessment	All	A 5- or 6-point assessment assigned by patient based on the extent of skin involvement.	0 to 5, with 0 representing clear skin, and 5 representing severe and extensive involvement
SF–36 MOS	Short Form 36 Health Survey - Medical Outcomes Study	All	Measures the general level of well-being, consists of 8 domains reflecting 8 dimensions of life: PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF – social functioning; RE, role emotional; and MH, mental health. PCS is a subscale for physical health dimensions and MCS is a subscale for mental health dimensions.	0 to 100, higher is worse
SPARCC EI	Spondyloarthritis Research Consortium of Canada Enthesitis Index	PsA	Based on clinical assessment by evaluator on 9 bilateral sites, but inferior patella and tibial tuberosity are considered 1 site for scoring purposes.	0 to 16; higher is worse

Abbreviation	Name	Condition(s) used in	General description	Range and direction
WLQ	Work Limitations Questionnaire	All	Twenty-five items that aggregate into 4 scales : time management, physical demands, mental-interpersonal demands, and output demands.	0 to 100, higher is worse
WPAI-PSO	Work Productivity and Activity Impairment - Psoriasis	PP	Assesses 4 dimensions: absenteeism, presenteeism, work productivity loss, and activity impairment; scores expressed as percentages.	0 to 100%, higher is worse

Abbreviations. CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PGA: Physician Global Assessment; PP: plaque psoriasis; PsA: psoriatic arthritis; SJC: swollen joint count; TIM: targeted immune modulator; TJC: tender joint count; VAS: visual analog scale.

Appendix E. Bibliography of Included Studies

- Araujo EG, Englbrecht M, Hoepken S, et al. Effects of ustekinumab versus tumor necrosis factor inhibition on enthesitis: results from the enthesial clearance in psoriatic arthritis (ECLIPSA) study. *Semin Arthritis Rheum.* 2019;48(4):632-637. doi: 10.1016/j.semarthrit.2018.05.011.
- Atteno M, Peluso R, Costa L, et al. Comparison of effectiveness and safety of infliximab, etanercept, and adalimumab in psoriatic arthritis patients who experienced an inadequate response to previous disease-modifying antirheumatic drugs. *Clin Rheumatol.* 2010;29(4):399-403. doi: 10.1007/s10067-009-1340-7.
- Bachelez H, van de Kerkhof PC, 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):552-561. doi: 10.1016/s0140-6736(14)62113-9.
- Bagel J, Nia J, Hashim PW, et al. Secukinumab is superior to ustekinumab in clearing skin in patients with moderate to severe plaque psoriasis (16-Week CLARITY Results). *Dermatol Ther.* 2018;8(4):571-579. doi: 10.1007/s13555-018-0265-y.
- Blauvelt A, Papp KA, Griffiths CEM, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator–controlled VOYAGE 1 trial. *J Am Acad Dermatol.* 2017;76(3):405-417. doi: 10.1016/j.jaad.2016.11.041.
- Blauvelt A, Reich K, Mehlis S, et al. Secukinumab demonstrates greater sustained improvements in daily activities and personal relationships than ustekinumab in patients with moderate-to-severe plaque psoriasis: 52-week results from the CLEAR study. *J Eur Acad Dermatol Venereol.* 2017;31(10):1693-1699. doi: 10.1111/jdv.14391.
- Blauvelt A, Reich K, Tsai T, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: results from the CLEAR study. *J Am Acad Dermatol.* 2017;76(1):60-69.e69. doi: 10.1016/j.jaad.2016.08.008.
- de Vries AC, Thio HB, de Kort WJ, et al. A prospective randomized controlled trial comparing infliximab and etanercept in patients with moderate-to-severe chronic plaque-type psoriasis: the Psoriasis Infliximab vs. Etanercept Comparison Evaluation (PIECE) study. *Br J Dermatol.* 2017;176(3):624-633. doi: 10.1111/bjd.14867.
- Dommasch ED, Kim SC, Lee MP, Gagne JJ. Risk of serious infection in patients receiving systemic medications for the treatment of psoriasis. *JAMA Dermatology.* 2019;10:10. doi: 10.1001/jamadermatol.2019.1121.
- Esposito M, Gisondi P, Cassano N, et al. Survival rate of antitumour necrosis factor-alpha treatments for psoriasis in routine dermatological practice: a multicentre observational study. *Br J Dermatol.* 2013;169(3):666-672. doi: 10.1111/bjd.12422.
- Glatt S, Helmer E, Haier B, et al. First-in-human randomized study of bimekizumab, a humanized monoclonal antibody and selective dual inhibitor of IL-17A and IL-17F, in mild psoriasis. *Br J Clin Pharmacol.* 2017;83(5):991-1001. doi: 10.1111/bcp.13185.
- Gordon KB, Armstrong AW, Han C, et al. Anxiety and depression in patients with moderate-to-severe psoriasis and comparison of change from baseline after treatment with guselkumab vs. adalimumab: results from the Phase 3 VOYAGE 2 study. *J Eur Acad Dermatol Venereol.* 2018;32(11):1940-1949. doi: 10.1111/jdv.15012.

- 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(2):136-144. doi: 10.1056/NEJMoa1501646.
- Gordon KB, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet*. 2018;392(10148):650-661. doi: 10.1016/S0140-6736(18)31713-6.
- Griffiths CE, 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*. 2015:541-551. doi: 10.1016/s0140-6736(15)60125-8.
- Griffiths CE, Strober BE, van de Kerkhof P, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *N Engl J Med*. 2010;362(2):118-128. doi: 10.1056/NEJMoa0810652.
- Kisacik B, Pamuk ON, Onat AM, et al. Characteristics predicting tuberculosis risk under tumor necrosis factor-alpha inhibitors: report from a large multicenter cohort with high background prevalence. *J Rheumatol*. 2016;43(3):524-529. doi: 10.3899/jrheum.150177.
- 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):326-338. doi: 10.1056/NEJMoa1314258.
- Lebwohl M, Strober B, Menter A, et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. *N Engl J Med*. 2015;373(14):1318-1328. doi: 10.1056/NEJMoa1503824.
- Lee MP, Desai RJ, Jin Y, Brill G, Ogdie A, Kim SC. Association of ustekinumab vs TNF inhibitor therapy with risk of atrial fibrillation and cardiovascular events in patients with psoriasis or psoriatic arthritis. *JAMA Dermatology*. 2019;155(6):700-707. doi: 10.1001/jamadermatol.2019.0001.
- Mason KJ, Barker J, Smith CH, et al. Comparison of drug discontinuation, effectiveness, and safety between clinical trial eligible and ineligible patients in BADBIR. *JAMA Dermatology*. 2018;154(5):581-588. doi: 10.1001/jamadermatol.2018.0183.
- Mease P, Coates LC, Helliwell PS, et al. Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active psoriatic arthritis (EQUATOR): results from a randomised, placebo-controlled, phase 2 trial. *Lancet*. 2018;392(10162):2367-2377. doi: 10.1016/S0140-6736(18)32483-8.
- Mease P, Hall S, FitzGerald O, et al. Tofacitinib or adalimumab versus placebo for psoriatic arthritis. *N Engl J Med*. 2017;377(16):1537-1550. doi: 10.1056/NEJMoa1615975.
- Mease PJ, Genovese MC, Weinblatt ME, et al. Phase II study of ABT-122, a tumor necrosis factor- and interleukin-17A-targeted dual variable domain immunoglobulin, in patients with psoriatic arthritis with an inadequate response to methotrexate. *Arthritis Rheum*. 2018;70(11):1778-1789. doi: 10.1002/art.40579.
- Mease PJ, Van Der Heijde D, Ritchlin CT, et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebocontrolled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. *Ann Rheum Dis*. 2017;76(1):79-87. doi: 10.1136/annrheumdis-2016-209709.
- Papp K, Blauvelt A, Bukhalo M, et al. Risankizumab versus ustekinumab for moderate-to-severe plaque psoriasis. *N Engl J Med*. 2017;376(16):1551-1560. doi: 10.1056/NEJMoa1607017.

- Papp K, Gordon K, Thaçi D, et al. Phase 2 trial of selective tyrosine kinase 2 inhibition in psoriasis. *N Engl J Med*. 2018;379(14):1313-1321. doi: 10.1056/NEJMoa1806382.
- Papp KA, Blauvelt A, Kimball AB, et al. Patient-reported symptoms and signs of moderate-to-severe psoriasis treated with guselkumab or adalimumab: results from the randomized VOYAGE 1 trial. *J Eur Acad Dermatol Venereol*. 2018;32(9):1515-1522. doi: 10.1111/jdv.14910.
- Papp KA, Merola JF, Gottlieb AB, et al. Dual neutralization of both interleukin 17A and interleukin 17F with bimekizumab in patients with psoriasis: results from BE ABLE 1, a 12-week randomized, double-blinded, placebo-controlled phase 2b trial. *J Am Acad Dermatol*. 2018;79(2):277-286.e210. doi: 10.1016/j.jaad.2018.03.037.
- Paul C, Griffiths CEM, van de Kerkhof PCM, et al. Ixekizumab provides superior efficacy compared with ustekinumab over 52 weeks of treatment: Results from IXORA-S, a phase 3 study. *J Am Acad Dermatol*. 2019;80(1):70-79.e73. doi: 10.1016/j.jaad.2018.06.039.
- Reich K, Armstrong AW, Foley P, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. *J Am Acad Dermatol*. 2017;76(3):418-431. doi: 10.1016/j.jaad.2016.11.042.
- Reich K, Armstrong AW, Langley RG, et al. Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): results from a phase 3, randomised controlled trial. *Lancet*. 2019;08:08. doi: 10.1016/S0140-6736(19)31773-8.
- Reich K, Foley P, Han C, et al. Guselkumab improves work productivity in patients with moderate-to-severe psoriasis with or without depression and anxiety: results from the VOYAGE 2 comparator study versus adalimumab. *J Dermatol Treat*. 2019:1-7. doi: 10.1080/09546634.2019.1628172.
- Reich K, Gooderham M, Green L, et al. The efficacy and safety of apremilast, etanercept and placebo in patients with moderate-to-severe plaque psoriasis: 52-week results from a phase IIIb, randomized, placebo-controlled trial (LIBERATE). *J Eur Acad Dermatol Venereol*. 2017;31(3):507-517. doi: 10.1111/jdv.14015.
- Reich K, Gooderham M, Thaci D, et al. Risankizumab compared with adalimumab in patients with moderate-to-severe plaque psoriasis (IMMvent): a randomised, double-blind, active-comparator-controlled phase 3 trial. *Lancet*. 2019;04:04. doi: 10.1016/S0140-6736(19)30952-3.
- Reich K, Papp KA, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. *Lancet*. 2017;390(10091):276-288. doi: 10.1016/s0140-6736(17)31279-5.
- Reich K, Pinter A, Lacour JP, et al. Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24-week results from IXORA-S, a phase III study. *Br J Dermatol*. 2017;177(4):1014-1023. doi: 10.1111/bjd.15666.
- Reich K, Rich P, Maari C, et al. Efficacy and safety of mirikizumab (LY3074828) in the treatment of moderate-to-severe plaque psoriasis: results from a randomized phase II study. *Br J Dermatol*. 2019;181(1):88-95. doi: 10.1111/bjd.17628.
- Strand V, de Vlam K, Covarrubias-Cobos JA, et al. Tofacitinib or adalimumab versus placebo: patient-reported outcomes from OPAL Broaden-a phase III study of active psoriatic arthritis

in patients with an inadequate response to conventional synthetic disease-modifying antirheumatic drugs. *RMD Open.* 2019;5(1):e000806. doi: 10.1136/rmdopen-2018-000806.
- Thaci D, Blauvelt A, Reich K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. *J Am Acad Dermatol.* 2015;73(3):400-409. doi: 10.1016/j.jaad.2015.05.013.
- Valenzuela F, Paul C, Mallbris L, et al. Tofacitinib versus etanercept or placebo in patients with moderate to severe chronic plaque psoriasis: patient-reported outcomes from a Phase 3 study. *J Eur Acad Dermatol Venereol.* 2016;30(10):1753-1759. doi: 10.1111/jdv.13702.
- Warren RB, Smith CH, Yiu ZZ, et al. Differential drug survival of biologic therapies for the treatment of psoriasis: a prospective observational cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *J Invest Dermatol.* 2015;135(11):2632-2640. doi: 10.1038/jid.2015.208.
- Wu JJ, Armstrong A, Singh R, et al. Adverse medical conditions across treatment options in patients with psoriasis: a claims-based analysis. *J Drugs Dermatol.* 2018;17(11):1211-1218.

Appendix F. Bibliography of Excluded Studies

- Correction: Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. *J Am Acad Dermatol.* 2017;76(6):1226. doi: 10.1016/j.jaad.2017.03.013.
- Erratum: Risankizumab compared with adalimumab in patients with moderate-to-severe plaque psoriasis (IMMvent): a randomised, double-blind, active-comparator-controlled phase 3 trial. *Lancet*. 2019;394(10198):564. doi: 10.1016/S0140-6736(19)31664-2.
- Erratum: Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. *Lancet*. 2017;390(10091):230. doi: 10.1016/S0140-6736%2817%2931834-2.
- Ballegaard C, Hojgaard P, Dreyer L, et al. Impact of comorbidities on tumor necrosis factor inhibitor therapy in psoriatic arthritis: a population-based cohort study. *Arthritis Care Res (Hoboken).* 2018;70(4):592-599. doi: 10.1002/acr.23333.
- Blauvelt A, Lomaga M, Burge R, et al. Greater cumulative benefits from ixekizumab versus ustekinumab treatment over 52 weeks for patients with moderate-to-severe psoriasis in a randomized, double-blinded phase 3b clinical trial. *J Dermatol Treat*. 2019:1-6. doi: 10.1080/09546634.2019.1587146.
- Calip GS, Patel PR, Adimadhyam S, et al. Tumor necrosis factor-alpha inhibitors and risk of non-Hodgkin lymphoma in a cohort of adults with rheumatologic conditions. *Int J Cancer.* 2018;143(5):1062-1071. doi: 10.1002/ijc.31407.
- Egeberg A, Bryld LE, Skov L. Drug survival of secukinumab and ixekizumab for moderate-to-severe plaque psoriasis. *J Am Acad Dermatol.* 2019;03:03. doi: 10.1016/j.jaad.2019.05.082.
- Fitz L, Zhang W, Soderstrom C, et al. Association between serum interleukin-17A and clinical response to tofacitinib and etanercept in moderate to severe psoriasis. *Clin Exp Dermatol.* 2018;43(7):790-797. doi: 10.1111/ced.13561.
- Foley P, Gordon K, Griffiths CEM, et al. Efficacy of guselkumab compared with adalimumab and placebo for psoriasis in specific body regions: a secondary analysis of 2 randomized clinical trials. *JAMA Dermatology*. 2018;154(6):676-683. doi: 10.1001/jamadermatol.2018.0793.
- Genovese MC, Combe B, Kremer JM, et al. Safety and efficacy of ixekizumab in patients with PsA and previous inadequate response to TNF inhibitors: week 52 results from SPIRIT-P2. *Rheumatology*. 2018;57(11):2001-2011. doi: 10.1093/rheumatology/key182.
- Genovese MC, Weinblatt ME, Mease PJ, et al. Dual inhibition of tumour necrosis factor and interleukin-17A with ABT-122: open-label long-term extension studies in rheumatoid arthritis or psoriatic arthritis. *Rheumatology*. 2018;57(11):1972-1981. doi: 10.1093/rheumatology/key173.
- Georgakopoulos JR, Phung M, Ighani A, Lam K, Yeung J. Biologic switching between interleukin 17A antagonists secukinumab and ixekizumab: a 12-week, multicenter, retrospective study. *J Eur Acad Dermatol Venereol.* 2019;33(1):e7-e8. doi: 10.1111/jdv.15100.

- Gerdes S, Pinter A, Biermann M, Papavassilis C, Reinhardt M. Adiponectin levels in a large pooled plaque psoriasis study population. *J Dermatol Treat.* 2019:1-4. doi: 10.1080/09546634.2019.1621979.
- Glatt S, Baeten D, Baker T, et al. Dual IL-17A and IL-17F neutralisation by bimekizumab in psoriatic arthritis: Evidence from preclinical experiments and a randomised placebo-controlled clinical trial that IL-17F contributes to human chronic tissue inflammation. *Ann Rheum Dis.* 2018;77(4):523-532. doi: 10.1136/annrheumdis-2017-212127.
- Glatt S, Helmer E, Haier B, et al. First-in-human randomized study of bimekizumab, a humanized monoclonal antibody and selective dual inhibitor of IL-17A and IL-17F, in mild psoriasis. *Br J Clin Pharmacol.* 2017;83(5):991-1001. doi: 10.1111/bcp.13185.
- Gottlieb AB, Gordon K, Hsu S, et al. Improvement in itch and other psoriasis symptoms with brodalumab in phase 3 randomized controlled trials. *J Eur Acad Dermatol Venereol.* 2018;32(8):1305-1313. doi: 10.1111/jdv.14913.
- Gottlieb AB, Strand V, Kishimoto M, et al. Ixekizumab improves patient-reported outcomes up to 52 weeks in bDMARD-naive patients with active psoriatic arthritis (SPIRIT-P1). *Rheumatology.* 2018;57(10):1777-1788. doi: 10.1093/rheumatology/key161.
- Khatri A, Klunder B, Peloso PM, Othman AA. Exposure-response analyses demonstrate no evidence of interleukin 17A contribution to efficacy of ABT-122 in rheumatoid or psoriatic arthritis. *Rheumatology.* 2019;58(2):352-360. doi: 10.1093/rheumatology/key312.
- Kim J, Tomalin L, Lee J, et al. Reduction of inflammatory and cardiovascular proteins in the blood of patients with psoriasis: differential responses between tofacitinib and etanercept after 4 weeks of treatment. *J Invest Dermatol.* 2018;138(2):273-281. doi: 10.1016/j.jid.2017.08.040.
- Kimball AB, Luger T, Gottlieb A, et al. Long-term impact of ixekizumab on psoriasis itch severity: results from a phase iii clinical trial and long-term extension. *Acta Derm Venereol.* 2018;98(1):98-102. doi: 10.2340/00015555-2801.
- Korber A, Papavassilis C, Bhosekar V, Reinhardt M. Efficacy and safety of secukinumab in elderly subjects with moderate to severe plaque psoriasis: a pooled analysis of phase iii studies. *Drugs Aging.* 2018;35(2):135-144. doi: 10.1007/s40266-018-0520-z.
- Lee MG, Huang YH, Lee JH, et al. Secukinumab demonstrates superior efficacy and a faster response in clearing skin in Asian subjects with moderate to severe plaque psoriasis compared with ustekinumab: Subgroup analysis from the CLEAR study. *J Dermatol.* 2019;25:25. doi: 10.1111/1346-8138.15004.
- Leonardi C, Maari C, Philipp S, et al. Maintenance of skin clearance with ixekizumab treatment of psoriasis: Three-year results from the UNCOVER-3 study. *J Am Acad Dermatol.* 2018;79(5):824-830.e822. doi: 10.1016/j.jaad.2018.05.032.
- Li N, Teeple A, Muser E, et al. Work/study productivity gain and indirect cost savings with guselkumab compared with adalimumab in moderate to severe psoriasis: results from the voyage 1 study. *J Manag Care Spec Pharm.* 2018;24(10 a):S81. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01670028/full.
- Mease P, Coates LC, Helliwell PS, et al. Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active psoriatic arthritis (EQUATOR): results from a randomised, placebo-controlled, phase 2 trial. *Lancet.* 2018;392(10162):2367-2377. doi: 10.1016/S0140-6736(18)32483-8.

- Mease P, Hall S, FitzGerald O, *et al.* Efficacy and safety of tofacitinib, an oral Janus kinase inhibitor, or adalimumab in patients with active psoriatic arthritis and an inadequate response to conventional synthetic disease-modifying antirheumatic drugs: OPAL Broaden, a randomized, placebo-controlled, phase 3 trial. *J Am Acad Dermatol.* 2017;76(6):Ab114-. doi: 10.1016/j.jaad.2017.04.452.
- Ozen G, Pedro S, Schumacher R, Simon TA, Michaud K. Safety of abatacept compared with other biologic and conventional synthetic disease-modifying antirheumatic drugs in patients with rheumatoid arthritis: data from an observational study. *Arthritis Res Ther.* 2019;21(1):141. doi: 10.1186/s13075-019-1921-z.
- Papp KA, Leonardi CL, Blauvelt A, et al. Ixekizumab treatment for psoriasis: integrated efficacy analysis of three double-blinded, controlled studies (UNCOVER-1, UNCOVER-2, UNCOVER-3). *Br J Dermatol.* 2018;178(3):674-681. doi: 10.1111/bjd.16050.
- Papp KA, Merola JF, Gottlieb AB, et al. Dual neutralization of both interleukin 17A and interleukin 17F with bimekizumab in patients with psoriasis: Results from BE ABLE 1, a 12-week randomized, double-blinded, placebo-controlled phase 2b trial. *J Am Acad Dermatol.* 2018;79(2):277-286.e210. doi: 10.1016/j.jaad.2018.03.037.
- Paul C, Guenther L, Torii H, et al. Impact of ixekizumab on facial psoriasis and related quality of life measures in moderate-to-severe psoriasis patients: 12-week results from two phase III trials. *J Eur Acad Dermatol Venereol.* 2018;32(1):68-72. doi: 10.1111/jdv.14581.
- Potenza MC, Peris K, Berardesca E, et al. Use of biological drugs in patients with psoriasis and psoriatic arthritis in Italy: results from the PSONG survey. *Dermatol Ther* 2018;31(1). doi: 10.1111/dth.12565.
- Puig L, Augustin M, Blauvelt A, et al. Effect of secukinumab on quality of life and psoriasis-related symptoms: A comparative analysis versus ustekinumab from the CLEAR 52-week study. *J Am Acad Dermatol.* 2018;78(4):741-748. doi: 10.1016/j.jaad.2017.10.025.
- Puig L, Lebwohl M, Bachelez H, Sobell J, Jacobson AA. Long-term efficacy and safety of brodalumab in the treatment of psoriasis: 120-week results from the randomized, double-blind, placebo- and active comparator-controlled phase 3 AMAGINE-2 trial. *J Am Acad Dermatol.* 2019;05:05. doi: 10.1016/j.jaad.2019.05.095.
- Quartuccio L, Zabotti A, Del Zotto S, Zanier L, De Vita S, Valent F. Risk of serious infection among patients receiving biologics for chronic inflammatory diseases: Usefulness of administrative data. *J Adv Res.* 2019;15:87-93. doi: 10.1016/j.jare.2018.09.003.
- Reich K, Armstrong A, Foley P, et al. Efficacy and safety of guselkumab compared with adalimumab for the treatment of moderate-to-severe psoriasis: results from the phase 3, double-blind, placebo-and active comparatorcontrolled VOYAGE 2 trial. *J Am Acad Dermatol.* 2017;76(6):Ab111-. doi: 10.1016/j.jaad.2017.04.442.
- Reich K, Gooderham M, Bewley A, et al. Safety and efficacy of apremilast through 104 weeks in patients with moderate to severe psoriasis who continued on apremilast or switched from etanercept treatment: findings from the LIBERATE study. *J Eur Acad Dermatol Venereol.* 2018;32(3):397-402. doi: 10.1111/jdv.14738.
- Reich K, Gooderham M, Thaçi D, et al. Risankizumab compared with adalimumab in patients with moderate-to-severe plaque psoriasis (IMMvent): a randomised, double-blind, active-comparator-controlled phase 3 trial. *Lancet.* 2019;394(10198):576-586. doi: 10.1016/S0140-6736(19)30952-3.

- Reich K, Papp KA, Armstrong AW, et al. Safety of guselkumab in patients with moderate-to-severe psoriasis treated through 100 weeks: a pooled analysis from the randomized VOYAGE 1 and VOYAGE 2 studies. *Br J Dermatol.* 2019;180(5):1039-1049. doi: 10.1111/bjd.17454.
- Reich K, Pinter A, Lacour JP, et al. Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24-week results from IXORA-S, a phase III study. *Br J Dermatol.* 2017;177(4):1014-1023. doi: 10.1111/bjd.15666.
- Schmieder GJ, Draelos ZD, Pariser DM, et al. Efficacy and safety of the Janus kinase 1 inhibitor PF-04965842 in patients with moderate-to-severe psoriasis: phase II, randomized, double-blind, placebo-controlled study. *Br J Dermatol.* 2018;179(1):54-62. doi: 10.1111/bjd.16004.
- Spindeldreher S, Maillere B, Correia E, et al. Secukinumab demonstrates significantly lower immunogenicity potential compared to ixekizumab. *Dermatol Ther.* 2018;8(1):57-68. doi: 10.1007/s13555-018-0220-y.
- Stull DE, Griffiths CEM, Gilloteau I, et al. Differential effects of secukinumab vs. ustekinumab for treatment of psoriasis on quality of life, work productivity and activity impairment: a structural equation modelling analysis. *Br J Dermatol.* 2018;178(6):1297-1307. doi: 10.1111/bjd.16366.
- Svecova D, Lubell MW, Casset-Semanaz F, Mackenzie H, Grenningloh R, Krueger JG. A randomized, double-blind, placebo-controlled phase 1 study of multiple ascending doses of subcutaneous M1095, an anti-interleukin 17A/F nanobody, in moderate-to-severe psoriasis. *J Am Acad Dermatol.* 2019;81(1):196-203. doi: 10.1016/j.jaad.2019.03.056.

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