Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value

Draft Evidence Report

September 29, 2016

Prepared for

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In the development if this report, ICER's researchers consulted with a number of clinical experts, patients, manufacturers and other stakeholders. The following clinical experts provided input and/or feedback that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested feedback, please visit:
http://icer-review.org/material/psoriasis-stakeholder-list/

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List of Acronyms Used in this Report

TNF	Tumor necrosis factor
PASI	Psoriasis Area and Severity Index
PGA	Physician Global Assessment
IGA	Investigator's Global Assessment
DLQI	Dermatology Life Quality Index
VAS	Visual Analog Scale
PSI	Psoriasis Symptom Inventory
PUVA	Psoralen and ultraviolet A radiation
UVB	Ultraviolet B
TB	Tuberculosis
PDI	Psoriasis Disability Index
sPGA	Static Physician Global Assessment
dPGA	Dynamic Physician Global Assessment
HRQL	Health-related quality of life
PCS	Physical component score
MCS	Mental component score
WPAI	Work Productivity and Activity Impairment
WPI	Worker Productivity Index
WLQ	Work Limitations Questionnaire
CMS	Centers for Medicare and Medicaid Services
AAD	American Academy of Dermatology
NICE	National Institute for Health and Care Excellence
EADV	European Association for Dermatology and Venereology
IPC	International Psoriasis Council
RCT	Randomized controlled trial
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
USPSTF	U.S. Preventative Services Task Force
NMA	Network meta-analysis
PSOLAR	Psoriasis Longitudinal Assessment and Registry
EQ-5D	EuroQol five-dimension questionnaire
AE	Adverse Event
NMSC	Non-melanoma skin cancer
MACE	Major adverse cardiac events
QALY	Quality-adjusted life year
LY	Life year
ICER	Incremental cost-effectiveness ratio
WAC	Wholesale acquisition cost
CUA	Cost utility analysis
DC	Discontinuation
GDP	Gross domestic product
NHE	National Health Expenditures
BI	Budget impact
DIC	Deviance information criterion
Resdev	Residual deviance

Executive Summary

An executive summary will be provided as part of the full Evidence Report.

1. Background

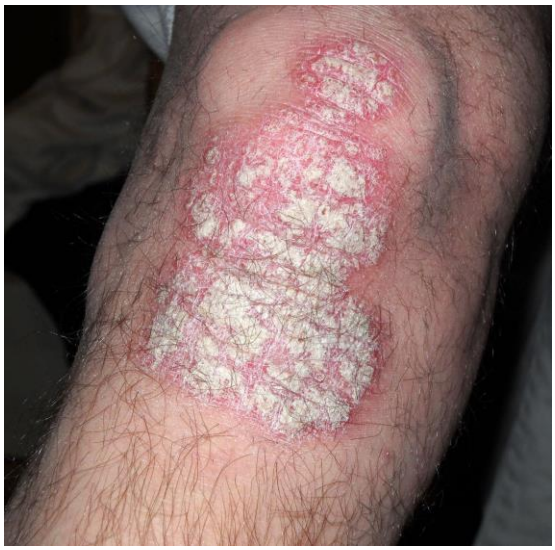
1.1 Introduction

Background

Plaque psoriasis is a common disease that causes itchy, red, scaly, raised lesions on the skin, most commonly on the elbows, knees, scalp, and back.[1] Psoriasis affects about 3% of the population and generally occurs before age 35.[2,3] Risk factors for development of psoriasis include a family history of psoriasis, smoking, alcohol use, and obesity.

Chronic plaque psoriasis accounts for about 80% to 90% of all patients with psoriasis[4-6]. Plaque psoriasis is one of the cutaneous psoriasis types; others include guttate psoriasis, pustular psoriasis, inverse psoriasis, nail psoriasis, and erythrodermic psoriasis. Psoriasis is associated with systemic diseases including other autoimmune diseases (e.g., inflammatory bowel disease), metabolic syndrome, and cardiovascular disease.[7] In addition, up to 30% of patients with plaque psoriasis have at least some manifestations of psoriatic arthritis.[8,9] Symptoms of psoriatic arthritis include inflammation in multiple small or large joints, involvement of the distal joints in the hand, as well as inflammation of tendons, tendon insertions, and fingers.

Figure 1. Typical psoriatic plaque on the knee



Plaque psoriasis significantly decreases health-related quality of life, particularly if lesions are in areas that can affect daily functioning (e.g., the hands or soles of the feet) or social functioning (e.g., the face).[10-12] Psoriasis itself is not a direct cause of increased mortality, but patients with severe psoriasis have increased mortality due to cardiovascular disease and infection.[13]

There is no cure for plaque psoriasis, but it can be managed with topical therapies, phototherapy, and systemic therapies. Systemic therapies include older agents such as methotrexate and cyclosporine as well as newer "targeted immunomodulators," which include biologic agents and the small molecule apremilast. Clinical interest in targeted immunomodulators is high, as many patients with chronic plaque psoriasis do not achieve adequate or durable benefit from older systemic therapies or phototherapy. The newer targeted immunomodulators are generally more expensive than older medications and there are questions regarding how these costs align with the clinical value brought to patients.

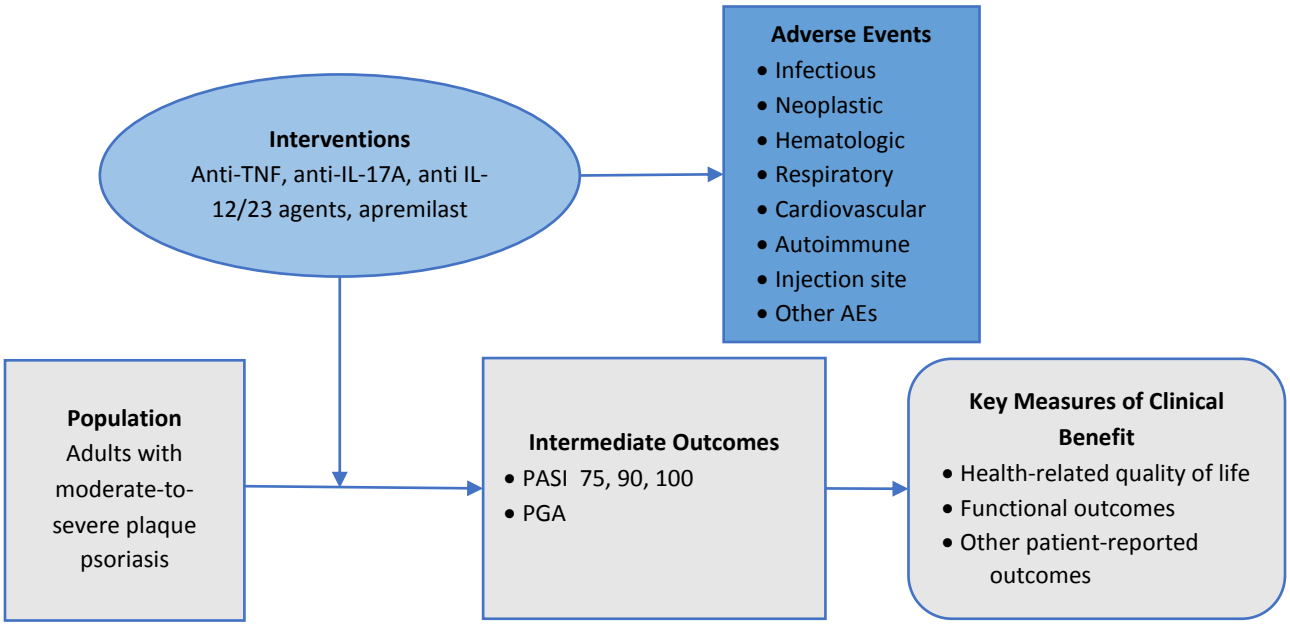
Scope of the Assessment

This project evaluated the health and economic outcomes of targeted immunomodulators (biologics plus apremilast) for adults with moderate-to-severe plaque psoriasis. The scope for these assessments is described below using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. To evaluate comparative clinical effectiveness, we examined randomized controlled trials as well as high-quality systematic reviews. To evaluate other measures of potential benefit as well as adverse events, we examined higher-quality comparative cohort studies, other articles from the published medical literature, information from the grey literature, and information received from patient groups.

Analytic Framework

The analytic framework for this assessment is depicted in Figure 2.

Figure 2. Analytic Framework:



Population

The population of focus for this review was adults with moderate-to-severe chronic plaque psoriasis. Although not a focus of the review, we did not exclude evidence from patient populations with other concomitant psoriasis types or psoriatic arthritis. We evaluated psoriasis outcomes in subgroups where data were available, including patients who have and have not been previously treated with a targeted immunomodulatory, and those with and without psoriatic arthritis.

Interventions

The interventions of interest were the targeted immunomodulators (biologics and apremilast) all but one of which has been approved for the treatment of moderate-to-severe plaque psoriasis:

- ***Anti-TNF-α agents:*** adalimumab, etanercept, infliximab (approved only for severe plaque psoriasis)
- ***Anti IL-12/23 agent:*** ustekinumab
- ***Anti IL-17A agents:*** secukinumab, ixekizumab, brodalumab (not yet approved)
- ***Anti PDE-4 agent:*** apremilast

Comparators

Wherever possible, we evaluated head-to-head trials of these interventions. Other comparators included placebo or other active treatments not listed above.

Outcomes

This review examined key clinical outcomes, including outcomes common to plaque psoriasis trials. Discussions with patients, patient groups, clinicians, and industry, as well as publications from academic research groups, indicated that people with psoriasis have symptoms and burdens that are not well-captured by standard trial outcomes.[11,14] Standard trial outcomes are generally not used or feasible to employ in actual clinical practice. We examined available data for evidence about the comparative effectiveness of targeted immunomodulators in affecting outcomes such as itch, scaling, pain, quality-of-life, and work productivity. Outcomes for which we were able to find evidence included:

- Clinical Benefits
  - Trial Outcomes
    - Psoriasis Area and Severity Index (PASI): 50, 75, 90, 100
    - Physician Global Assessment (PGA) or Investigator's Global Assessment (IGA)
  - Patient-Reported Outcomes
    - Dermatology Life Quality Index (DLQI)
    - Other measures of health-related quality of life (e.g., Short Form [SF]-36)
    - Symptom control (e.g., Visual Analog Scale [VAS]-itch, Psoriasis Symptom Inventory [PSI])
- Harms
  - Treatment-related adverse events (e.g., rate of infections)
  - Treatment tolerability (i.e., discontinuation due to adverse events)

For most outcomes, we summarized results qualitatively and descriptively. For the PASI, we examined direct evidence of comparative clinical effectiveness and performed a network meta-analysis to evaluate comparative clinical effectiveness through indirect comparison.

Timing

Evidence on intervention effectiveness and harms was derived from studies of any duration. Because psoriasis is a chronic condition with no cure, we were particularly interested in evidence of durability of response to medications, as well as long-term safety.

Settings

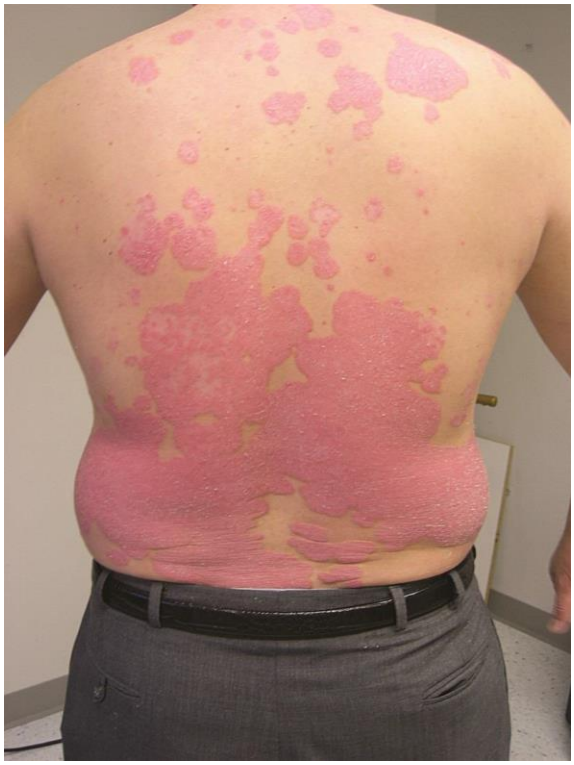
Plaque psoriasis is generally treated in outpatient and/or clinic settings, which was the focus of our review.

2. The Topic in Context

2.1 Overview

Roughly 70% to 80% of patients with plaque psoriasis have mild disease that can be adequately managed with topical therapy. Definitions of "moderate-to-severe" plaque psoriasis vary, but generally consist of psoriasis that affects at least 5% to 10% of a patients' body surface; produces lesions that have significant redness, thickness, and scale; or significantly reduces quality of life (e.g., lesions on the face, palm, or soles of the feet).[15,16] Moderate-to-severe plaque psoriasis is generally treated with systemic therapies.

Figure 3. Psoriatic involvement of the back involving about 10% of body surface area



Pictures from the US Food and Drug Administration Public Meeting on Patient-Focused Drug Development for Psoriasis: An Overview of Psoriasis. March 17, 2016. Available at: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm470608.htm

2.2 Treatments

Treatments for psoriasis can be grouped within 4 broad categories:

1. Topical therapies such as steroids, vitamin D analogs, retinoids, and calcineurin inhibitors;
2. Older systemic therapies, such as acetretin, cyclosporine, and methotrexate;
3. Phototherapy such as psoralen and ultraviolet A radiation (PUVA); and
4. "Targeted immunomodulators" including biologics and apremilast

Topical Treatments include emollients; topical corticosteroids of varying strength; vitamin D analogs (e.g., calcipotriene, calcitriol); coal tar products which are usually available without a prescription; topical retinoids (tazarotene); topical calcineurin inhibitors (e.g., tacrolimus or pimecrolimus), which can be useful for treatment of the face and intertriginous areas; and anthralin. Topical treatments are usually in the forms of creams, ointments, or lotions, but can also be gels, foams, sprays, and shampoos. Topical treatment can be impractical for patients with psoriasis that affects a large area or for patients who have significant scalp involvement. Higher potency topical corticosteroids can cause skin atrophy if used on non-psoriatic skin, particularly on areas of thinner skin, such as the face. Topical calcineurin inhibitors may be associated with skin cancer.

Older Systemic Therapy includes methotrexate, cyclosporine, and acitretin.

- *Methotrexate* is a folic acid inhibitor. It is effective but is associated with hepatotoxicity, requires close, potentially invasive (i.e., liver biopsy) monitoring, cannot be used in patients with liver disease or kidney disease, and is an abortifacient. Drug interactions are common; bone marrow suppression is a possibility. Methotrexate is generally given weekly and many patients describe a post-dose fatigue that can last for several days ("methotrexate fog"). Patients often get stomatitis, nausea, and vomiting and, more rarely, can have lung complications. Methotrexate can be combined with TNF-alpha inhibitors.
- *Cyclosporine* is a T cell inhibitor and works rapidly, but causes hypertension and may be associated with lymphoma and skin cancer (especially when combined with PUVA). Cyclosporine is also associated with kidney disease, liver disease, hypertrichosis, gingival changes, GI symptoms, and neurologic symptoms. Drug interactions are common and there are many contraindications. Some European guidelines only recommend use for 2 years. Cyclosporine cannot be combined with other systemic treatments (other than phototherapy).
- *Acitretin,* a retinoid, vitamin A analogue is highly teratogenic, associated with dry eyes and dry mouth, hair loss, as well as elevated triglycerides and musculoskeletal problems. Acitretin can be combined with phototherapy and, unlike many other psoriasis treatments, is not immunosuppressive.

Phototherapy includes sun exposure, broadband ultraviolet B (UVB), narrowband UVB, and psoralen with ultraviolet A (UVA) treatment (PUVA). Narrowband UVB is more effective than

broadband UVB; both can be delivered at home. There is a perception that PUVA is generally more effective than narrowband UVB, but evidence is mixed.[17] Psoralen, a photosensitizing drug, can be used orally or topically, as a bath, to the affected areas. Psoralen is associated with nausea, and PUVA is associated with increased squamous cell cancer and possibly melanoma. One final form of phototherapy is the use of excimer lasers for focused light therapy.

Targeted immunomodulators that have been approved, or are nearing approval, for the treatment of moderate-to-severe plaque psoriasis in the United States consist of medications with activity against the following targets:

- ***TNF-α:*** adalimumab (Humira®), etanercept (Enbrel®), infliximab (Remicade®)
- ***IL-12/23:*** ustekinumab (Stelara®)
- ***IL-17A:*** secukinumab (Cosentyx®), ixekizumab (Taltz®), brodalumab (investigational)
- ***Phosphodiesterase (PDE)-4:*** apremilast (Otezla®) Although not technically a biologic, apremilast is a novel, targeted, oral agent also approved for treatment of patients with moderate-to-severe plaque psoriasis.

[Note: Certolizumab pegol (Cimzia®) and golimumab (Simponi®, Simponi ARIA) are anti-TNF agents that have been approved for the treatment of psoriatic arthritis, but not plaque psoriasis. Alefacept (Amevive®) and efalizumab (Raptiva®) were T cell based biologics that were removed from the US market.]

Interventions

Table 1. Targeted Immunomodulators for Moderate-to-Severe Plaque Psoriasis

MOA	Name (generic/trade)	Dosing
Anti-TNFα	adalimumab/Humira	80mg subcutaneously, then 40mg every other week starting 1 week
	etanercept/Enbrel	50mg subcutaneously 2x/week for 3 months, then 50mg 1x/week
	infliximab/Remicade	5mg/kg intravenously at weeks 0, 2, and 6, then every 6 weeks
IL 12/23	ustekinumab/Stelara	Patients ≤100kg/>100kg: 45mg/90mg subcutaneously at week 0 and 4, then every 12 weeks
IL 17-A	secukinumab/Cosentyx	300mg subcutaneously at weeks 0, 1, 2, 3, 4 then 300mg every 4 weeks

	ixekizumab/Taltz	160mg subcutaneously at week 0, then 80mg at weeks 2, 4, 6, 8, 10,
	brodalumab/NA	210mg subcutaneously, every 2 weeks*
PDE-4	apremilast/Otezla	5-day titration then 30mg orally 2x/day thereafter

For all the biologics, infections may require interruption of treatment, discontinuation, or there may be contraindications to starting these agents.

Adverse events and concerns in use of TNF-alpha inhibitors include injection site reactions (for etanercept and adalimumab), infusion reactions (for infliximab), malignancies (especially skin cancer, lymphoma), infection (especially reactivation of tuberculosis and hepatitis B), congestive heart failure, demyelinating disease (e.g., multiple sclerosis), and autoimmune diseases, including a rare, lupus-like syndrome. TNF-alpha inhibitors are associated with an increased rate of severe infections. Because of the impaired immune response, vaccines should be given prior to initiating anti-TNF-alpha therapy.

For the anti IL-17A agents, concerns have included infections and reactivation of latent TB for secukinumab; neutropenia, candidal infection, and inflammatory bowel disease for ixekizumab (approved in March 2016); and candidal infections, neutropenia, and an increased risk of suicide for brodalumab (not yet approved although the FDA Dermatologic and Opthalmic Drugs Advisory Committee recommended its approval in July 2016).

Ustekinumab, an anti IL-12/23 Agent, has been associated with skin cancer, lymphoma, and severe infections. Although there has been concern for an increased risk of major cardiovascular events, several observational studies have not confirmed an effect.[18,19] Anti-ustekinumab antibodies occur in a few patients and are of unclear clinical significance.

Apremilast, an *anti-phosphodiesterase-4 agent,* is the only available oral targeted immunotherapy. Apremilast is associated with diarrhea, especially at initiation, that is lessened by titrating up the dose gradually. Additional possible adverse effects include depression and weight loss.

2.3. Other Aspects of Treatment

Non-Standard Dosing: many psoriatic drugs appear to have waning effectiveness with continued use. To maintain effectiveness physicians often prescribe increasing doses of psoriatic treatments. Occasionally physicians prescribe *lower* doses of effective medications in an attempt to decrease out-of-pocket costs. A US commercial database that evaluated claims from 2007 to 2012 found that

in the 12 months after the dose titration period, there were dose escalation rates with etanercept, adalimumab, and ustekinumab of 41%, 37%, and 36%,[20] ; dose reductions of 49%, 54%, and 37%; and discontinuation rates of 15%, 10%, and 5%, respectively. Within the same 12 months, many patients discontinued, restarted, and switched biologic treatments. In an examination of infliximab use, 26% of treatment series involved use of a greater-than-initially-recommended dose.[21]

Ordering: It is uncertain whether early aggressive treatment with anti-inflammatory agents can alter the natural history of psoriasis and/or mitigate the increased cardiovascular risk seen with the disease.

Emerging Therapies: Biologic "biosimilar" medications are becoming available, including recently-approved biosimilars for adalimumab (Amjevita®) and etanercept (Erelzi®). The equivalence of the etanercept biosimilar for moderate-to-severe plaque psoriasis has been reported in a single conference abstract.[22] Briakinumab is an additional anti-IL 12/23 that has been evaluated, but it is unclear if it will come to market. Tofacitinib, a small molecule treatment already approved for the treatment of rheumatoid arthritis, has been shown to be effective for moderate-to-severe plaque psoriasis in randomized controlled trials.

2.4 Insights Gained from Discussions with Patients and Patient Groups

ICER had conversations with and received input from patient advocacy groups, including the National Psoriasis Foundation, and with individual patients (please see online Stakeholder document). These conversations highlighted the shortcomings associated with clinical trial outcomes in many studies of psoriasis therapies (as previously noted), frustrations with the healthcare system, as well as the social, emotional, and financial impact of psoriasis.

Certain aspects of research into psoriasis are not patient-centered. Many of the tools developed to measure outcomes were not developed with patients in mind, and psoriasis-specific patient-centered outcome measures are limited (although the Psoriasis Symptom Inventory (PSI) and the Psoriasis Disability Index (PDI) are being used; see below). For example, PASI is cumbersome and is not generally used in clinical practice and the DLQI is not psoriasis-specific. Patients at a recent FDA meeting rated flaking/scaling and itching as a having a more significant impact on their quality of life than the rash itself. Simple body surface area measurements of psoriasis involvement do not take into account the greater effect that lesions in particular areas, such as the nails, genitals, scalp, face, flexural areas, palms, and soles of the feet, may have on an individual's quality of life. Patients also pointed out that average treatment responses described in clinical trials may not capture individual patient variability.

Up to half of patients are dissatisfied with their psoriasis treatment.[11,23] Dissatisfaction may be due to the unpredictable effectiveness of many agents to treat psoriasis, poor tolerability, lack of

durable response, and lack of access to medications because of coverage restrictions or costs.[11] Patients also expressed frustration with misdiagnoses and delayed diagnoses. The time from onset to diagnosis for plaque psoriasis averages two years. A psoriasis diagnosis may be delayed even further in those with darker skin tones.

Treatments for plaque psoriasis can be challenging for many patients. It can be difficult to apply topical therapies, especially when the affected area involves the scalp or covers a large part of the body. Therapies can also be inconvenient to use; some require multiple injections on a daily or weekly basis, especially initially, during induction.

Psoriasis affects social functioning. Patients with psoriasis often feel the need to make different clothing choices to hide psoriatic skin; we heard that this can be particularly challenging for women. Patients with psoriasis may moderate choices of activities, such as swimming. Because of different clothing choices, the manifestations and difficulties faced by people with psoriasis may not be visible to others. Children with psoriasis, especially teens, face teasing, bullying, and shunning because of the visible effect of the disease. Many find that some people seeing the lesions conclude the patient has a communicable disease.

Plaque psoriasis has both psychological and emotional effects. The psychological impact of severe psoriasis is comparable to that of diabetes or depression.[24] Psoriasis is associated with increased rates of depression and suicidal ideation. Some patients reported somatic manifestations of psychiatric disease or emotional difficulties, including GI symptoms and hypertension.

Patients are concerned about lack of access, the cost of treatment, affordability, and future availability of drugs to treat their disease. About half of patients with psoriasis are either undertreated or not treated,[23] and one of the main reasons is the cost of therapy. Patients are frustrated that they are being forced to start treatment with less efficacious medications due to insurance requirements for “step therapy” that mandates use of “preferred medications” first. In addition, switching insurance might require movement to another step therapy approach, which often requires patients to “start over” with previously-tried medications. Patients are anxious that individual drugs will stop working for them and want access to alternatives. Another source of frustration is that coverage decisions for biologics often seem to be dictated by other, non-psoriasis conditions, like rheumatoid arthritis, which is a listed indication for many of the drugs of interest for this review.

2.5 Definitions

Psoriasis Area and Severity Index (PASI)

The PASI is a measure of the percent body surface area with psoriatic lesions in each of 4 regions (head, trunk, arms, and legs) as well as the degree of erythema, induration, and scale of the lesions in each area. PASI scores can range from 0 to 72, with higher numbers indicating greater surface involvement and severity of lesions. The PASI is generally reported as the percentage reduction in the PASI score from baseline to follow-up. The most consistently reported result in clinical trials is PASI 75, i.e., a 75% reduction in the PASI score. For these outcomes, higher numbers indicate a greater percentage improvement: PASI 90 is a 90% improvement in the PASI score; PASI 100 indicates full disease clearance, or a follow-up PASI score of zero.

Physician Global Assessment (PGA)

The *Static Physician Global Assessment (sPGA)* is scored by the treating or evaluating physician and only considers the time of evaluation. Scores range from 0 to 7 with higher scores indicating worse severity. A good response in clinical trials in treatment generally requires sPGA scores of 0 ("clear") or 1 ("almost clear"). The Dynamic Physician Global Assessment (dPGA), also scored from 0 to 7, takes into account a patient's change from their baseline status, and is used less frequently. Unless otherwise noted, "PGA" in this report refers to the Static Physician Global Assessment.

Investigator's Global Assessment (IGA)

The IGA is a modified version of the PGA, and has recently being touted as more valid measure of disease severity in psoriasis. It is based on a 5-point rather than a 6- or 7-point scale; the proportion of patients achieving a score of 0 or 1 ("clear/almost clear") are often considered "responders" in clinical trials.

Dermatology Quality of Life Index (DLQI)

The DLQI is ten questions relating to symptoms, feelings, daily activities, leisure, work, school, social interactions, clothing choice, sexual difficulties, and treatment problems. DLQI scores range from 0 to 30 with lower scores being better. A 5-point change in the DLQI is a minimal clinically meaningful change in health-related quality of life (HRQL).

The NICE Guideline defines mild disease as a PASI, BSA, and DLQI all ≤ 10 and moderate-to-severe disease as (PASI > 10 or BSA > 10) and DLQI > 10.

EuroQol Five Dimensions (EQ-5D)

The EQ-5D is a standardized, self-reported questionnaire for evaluating a patient's health status across disease states, and is based on five dimensions: self-care, pain/discomfort,

anxiety/depression, mobility, and usual care activities. It is often used to compute a quality-adjusted life year.

Short Form-36 (SF-36)

The SF-36 is a 36 item, quality of life instrument that captures eight domains and is reported as a score from 0 to 100 with higher scores indicating better functioning. The SF-36 also has summary component scores for physical functioning (physical component score, or PCS) and mental functioning (mental component score or MCS). Scores can be standardized to a population reference, such that the population mean score is 50 with a standard deviation of 10.

Psoriasis Disability Index (PDI)

The Psoriasis Disability Index assesses is a 15-question instrument that assesses five domains of health-related quality of life: daily activities; work or school performance; personal relationships; leisure; and treatment.[25] Each question is scored from 0 to 3 and the individual items are summed to a total score of 0 to 45 with higher scores indicating greater imapirment. The PDI can also be expressed as a proportion of total possible score.

Visual Aanalog Scale (VAS)-skin pain

VAS is a commonly used measure of pain, and can also be used to assess the skin pain associated with scaly plaques in psoriatic patients, which can have a serious impact on quality of life. This modified version of the VAS is based on a score of 0 (no skin pain) to 100 (severe skin pain).

Visual Analog Scale (VAS)-itch

The VAS is also used to as a measure of pruritus assessment. Patients are asked to rate the severity of their itching on a five-point scale, from no prurtitus (0 points) to severe pruritus (5 points).

Psoriasis Symptom Inventory (PSI)

The psoriasis symtom inventory is an 8-item in which patients rate the severity of signs and symptoms of psoriasis from the past 24 hours. Each item is scored 0 to 4. Individual scores are summed and a total score can range from 0 to 32 with higher scores indicating worse symptoms.

Hospital Anxiety and Depression Scale (HADS)

The HADS is a 14-item scale with 7 items related to anxiety and 7 related to depression. Each item is scored 0 to 3 to generate anxiety or depression scores of 0 to 21, with higher scores indicting more anxiety or depression. A score above 8 is a generally-used cutoff indicating a possible diagnosis of anxiety or depression. The HADS is used for screening only, and does not represent a clinical diagnosis.

Work Productivity and Activity Impairment (WPAI)

The WPAI consists of 6 questions about current employment and, in the past 7 days, hours missed due to health problems, hours missed for other reasons, hours worked, productivity impairment at work ("presenteeism"), and productivity impairment in upaid activities. Results are reported on a percentage scale from 0 to 100 in four domains: percent work time missed due to health; percent impairment while working; percent overall work impairment; and percent impairment due to health.

Worker Productivity Index (WPI)

The WPI combines an objective absenteeism measure and a subjective presenteeism (i.e., attending work while ill) measure into a measure of "total lost hours per week."

Work Limitations Questionnaire (WLQ)

The WLQ is a self-administered instrument of 25 items, which measures four domains of work limitations, including physical, time management, mental-interpersonal, and output demands.[26]

Visual Analog Scale-productivity

Although more frequently used in arthritis patients, the VAS-productivity scale can also be used to measure work productivity in psoriasis. VAS-productivity is measured on a 0-10 cm scale, indicating no impact to severe impact on productivity at school, home, or work.

3. Summary of Coverage Policies and Clinical Guidelines

To understand the insurance landscape for therapies for moderate to severe plaque psoriasis, we reviewed publicly available coverage policies and formularies at the six New England state Medicaid programs, Centers for Medicare and Medicaid Services (CMS) and all major insurance carriers available in New England.

All public and private carriers in New England manage utilization of the seven approved medications under review through tiering, step therapy and excluding drugs from coverage (see Table 2). In nearly every plan, systemic therapies (such as phototherapy or methotrexate) are on the lowest tier or are considered the first line of therapy before treatment with biologics or apremilast. Etanercept and adalimumab are most often the preferred second-line treatment and are commonly placed on lower tiers than other therapies in this review. Carriers often have discounting arrangements for etanercept and adalimumab that are driven by other conditions, most commonly rheumatoid arthritis.

Nearly all private carriers in New England require prior authorization for all drugs under review, and require step therapy. Of the 19 plans reviewed, etanercept and adalimumab were listed as preferred agents in roughly two-thirds of the plans. Ixekizumab was excluded from roughly a quarter of the plans. Infliximab is commonly covered as a medical benefit because of its administration as an infused agent. Ustekinumab, secukinumab and ixekizumab, and apremilast are more likely to be excluded from formularies.

There are no national or local requirements for Medicare coverage of the products under review. Nationally, Medicare providers are required to cover topical therapy, ultraviolet light therapy, and coal tar in advance of PUVA therapy, which the Medicare provider must document.

Aside from systemic therapies (such as methotrexate), all but one of the New England state Medicaid programs list adalimumab and etanercept as the preferred therapies. All other therapies under review require prior authorization. Massachusetts is the exception—there are no preferred agents and all therapies under review require prior authorization.

Clinical Guidelines

American Academy of Dermatology
https://www.aad.org/practice-tools/quality-care/clinical-guidelines/psoriasis

The most recent clinical guidelines from the American Academy of Dermatology (AAD) were published in 2010 and precede FDA approval of ustekinumab, secukinumab, ixekizumab, and apremilast.

The AAD guidelines recommend that patients with limited disease be treated with topicals and/or targeted phototherapy. They do not recommend treating patients with limited disease with systemic therapies that have higher levels of risk. Methotrexate, for instance, carries the risk of hepatotoxicity, is contraindicated for several conditions, and can have drug interactions. For extensive disease, the guidelines recommend treatment with topical treatments, phototherapy, systemic therapies, and biologics, but do not prioritize among the biologics available at the time they were written.

National Psoriasis Foundation/Canadian Guidelines
https://www.ncbi.nlm.nih.gov/pubmed/22250239

In 2012, the National Psoriasis Foundation reviewed the Canadian Guidelines for the Management of Plaque Psoriasis.[27] In their review, they recognized adalimumab, etanercept and ustekinumab as first line systemic treatments for plaque psoriasis. They recognize infliximab as a second or third line treatment for plaque psoriasis. They did not prioritize among the then available biologics. No other drugs were reviewed at the time of the report.

NICE Guidelines
https://www.nice.org.uk/guidance/cg153?unlid=389990376201651723735

The UK National Institute for Health and Care Excellence (NICE) reviewed therapies and offers guidance for treatment. NICE recommends progression from topical (mostly steroid) to systemic non-biologic therapy such as phototherapy, methotrexate or cyclosporine before moving on to biologic treatment. After failure of non-biological treatment, they recommend etanercept or adalimumab for patients with a PASI >10. NICE also recommends secukinumab if a discount is available and ustekinumab at the higher dose only if provided at the same cost as for the lower dose. Infliximab is recommended after failure of first line treatment for those patients with a PASI >20 ("very severe psoriasis"). NICE does not recommend apremilast, which it felt was poor value. NICE recommends switching therapies after treatment failure of 10 weeks for infliximab; 12 weeks for etanercept and secukinumab; and 16 weeks for adalimumab and ustekinumab.

NICE is expected to release its recommendations for ixekizumab in April 2017.

European Guideline on Systemic Treatment of Psoriasis Vulgaris, 2015 Update
https://www.ncbi.nlm.nih.gov/pubmed/26481193

An expert panel nominated by the European Dermatology Forum, the European Association for Dermatology and Venereology (EADV) and the International Psoriasis Council (IPC) stated that all treatments should be preceded by objective assessment of disease and health-related quality of life (HRQL). They stated that older treatments have many unwanted side effects and toxicity, but should be first-line systemic therapy. If phototherapy and older systemic agents are ineffective,

contraindicated, or not tolerated, they recommended treatment with TNF-alpha inhibitors. Ustekinumab was recommended as "second line therapy," but there was "no strong consensus" as to where in the ordering of therapy, relative to TNF-alpha inhibitors, ustekinumab should fall. Secukinumab, apremilast, and brodalumab were not included in the review.

Canadian Guidelines for the Management of Plaque Psoriasis
http://www.dermatology.ca/media/guidelines/

The Canadian Guidelines were supported by Abbott Laboratories, Amgen Canada Inc., Astellas Pharma Canada Inc, Isotechnika Inc, Janssen-Ortho Inc, Leo Pharma, Schering-Plough Canada Inc, and Wyeth. This guideline did not prioritize among the then available biologic therapies, but stated that there was no reason to reserve biologic agents for second-line use.

Table 2. Representative Private Payer Policies for Plaque Psoriasis in New England

	Connecticut		Massachusetts			Maine		New Hampshire		Rhode Island		Vermont	
	Anthem	**United**	**BCBS**	**Harvard Pilgrim**	**Tufts Health Plan**	**Anthem**	**Aetna**	**Anthem**	**MVP Health**	**BCBS**	**Cigna**	**BCBS**	**Cigna**
Methotrexate													
Tier	1	1	1	1	1	1	1	1	1	1	1	1	1
Step Therapy	No	No	No	No	No	No	No	No	No	No	No	No	No
PA	No	No	No	No	No	No	No	No	No	No	No	No	No
Preferred Agent	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Etanercept													
Tier	3	3	2	2	2	3	2	3	2	4	2	2	2
Step Therapy	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
PA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Preferred Agent	No	No	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes
Adalimumab													
Tier	3	2	2	2	2	3	4	3	2	5	2	2	2
Step Therapy	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
PA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Preferred Agent	No	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	Yes
Infliximab													
Tier	3	3	2	Med	Med	3	4	3	Med	5	3	3	3

Step Therapy	Yes	Med	Yes	Med	Med	Yes	Yes	Yes	Med	Yes	Yes	Yes	Yes
PA	Yes	Med	Yes	Med	Med	Yes	Yes	Yes	Med	Yes	Yes	Yes	Yes
Preferred Agent	No	No	Yes	Med	Med	No	No	No	Med	No	No	No	No
Ustekinumab													
Tier	3	3	3	3	2	3	4	3	Med	5	4	3	3
Step Therapy	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Med	Yes	Yes	Yes	Yes
PA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Med	Yes	Yes	Yes	Yes
Preferred Agent	No	No	No	No	Yes	No	No	No	Med	No	No	No	No
Secukinumab													
Tier	NF	3	3	3	2	3	4	3	3	5	4	3	3
Step Therapy	NF	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
PA	NF	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Preferred Agent	NF	No	No	No	Yes	No	No	No	No	No	No	No	No
Ixekizumab													
Tier	3	3	NF	3	3	3	4	3	3	4	NF	3	NF
Step Therapy	Yes	Yes	NF	Yes	No	Yes	Yes	Yes	No	No	NF	Yes	NF
PA	Yes	Yes	NF	Yes	Yes	Yes	Yes	Yes	Yes	No	NF	Yes	NF
Preferred Agent	No	No	NF	No	No	No	No	No	No	No	NF	No	NF
Apremilast													
Tier	3	3	3	3	2	3	4	3	3	4	4	3	3

Step Therapy	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
PA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Preferred Agent	No	No	No	No	Yes	No	No	No	No	No	No	No	No

4. Comparative Clinical Effectiveness

4.1 Overview

To inform our analysis of the comparative clinical effectiveness of targeted immunomodulators for moderate-to-severe chronic plaque psoriasis, we abstracted evidence from available clinical studies, whether in published, unpublished, or abstract form. The drugs and regimens of interest are included in the table below:

Table 3. Drugs and regimens of interest

MOA	Name (generic/trade)	Dosing
Anti-TNFα	adalimumab/Humira	80mg subcutaneously, then 40mg every other week starting 1 week after initial dose
	etanercept/Enbrel	50mg subcutaneously 2x/week for 3 months, then 50mg 1x/week
	infliximab/Remicade	5mg/kg intravenously at weeks 0, 2, and 6, then every 6 weeks
IL 12/23	ustekinumab/Stelara	Patients ≤100kg/>100kg: 45mg/90mg subcutaneously at week 0 and 4, then every 12 weeks
IL 17-A	secukinumab/Cosentyx	300mg subcutaneously at weeks 0, 1, 2, 3, 4 then 300mg every 4 weeks
	ixekizumab/Taltz	160mg subcutaneously at week 0, then 80mg at weeks 2, 4, 6, 8, 10, 12, then 80mg every 4 weeks
	brodalumab/NA	210mg subcutaneously, every 2 weeks*
PDE-4	apremilast/Otezla	5-day titration then 30mg orally 2x/day thereafter

*Not yet FDA-approved

As described in the Background section, we included evidence from placebo-controlled trials, but focused on evidence about the comparative clinical effectiveness of these treatments compared to each other or to other active treatments not listed above. Our review focused on key clinical outcomes common to plaque psoriasis trials, as well as symptoms and burdens of psoriasis that are not well-captured by standard trial outcomes.

- Clinical Benefits
  - Trial Outcomes
    - Psoriasis Area and Severity Index (PASI): 50, 75, 90, 100
    - Physician Global Assessment (PGA) or Investigator's Global Assessment (IGA)
  - Patient-Reported Outcomes
    - Dermatology Life Quality Index (DLQI)
    - Other measures of health-related quality of life (e.g., Short Form [SF]-36)
    - Symptom control (e.g., Visual Analog Scale [VAS]-itch, Psoriasis Symptom Inventory [PSI])
- Harms
    - Treatment-related adverse events (e.g., rate of infections)
    - Treatment tolerability (i.e., discontinuation due to adverse events)

4.2 Methods

We included evidence from randomized controlled trials (RCTs), comparative observational studies, and high-quality systematic reviews where available. We excluded single-arm studies and studies from an early clinical development phase (i.e., Phase I). We included phase II studies only if they evaluated unique subpopulations or outcomes not otherwise available in Phase III data. We also excluded studies that only examined regimens not approved by the FDA. Data from studies which included other active treatments (e.g., tofacitinib) were included in the NMA to extend indirect comparisons, but these comparisons are not discussed in detail. Finally, we did not include studies that evaluated targeted immunomodulators as part of combination treatment.

In recognition of the evolving evidence base for psoriasis, we supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature that met ICER standards for review (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/). We excluded abstracts which reported duplicative data available in published articles, or reported results from observational studies since it would be difficult, if not impossible, to evaluate the methodological quality of these studies. We also did not include any outcomes from the conference proceedings or regulatory documents on the anti-TNF therapies given that these

treatments have been available for at least a decade and primarily have peer-reviewed data available.

We also looked for studies evaluating biosimilar forms of the anti-TNF agents. No peer-reviewed data are available, but a brief description ofof an etanercept and adalimumab biosimilars areareare biosimilar are described in the Emerging Therapies section of this report.

Data were abstracted and summarized data into evidence tables for all outcomes listed above. For most outcomes, we summarized findings qualitatively and descriptively. However, we quantitatively synthesized evidence for PASI 50, 75, and 90 measures through the conduct of a Bayesian network meta-analysis (see Appendix G).

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on targeted immunomodulators for moderate-to-severe plaque psoriasis followed established best methods used in systematic review research.[28] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[29] The PRISMA guidelines include a checklist of 27 items, further detail of which is available in Appendix Table A1.

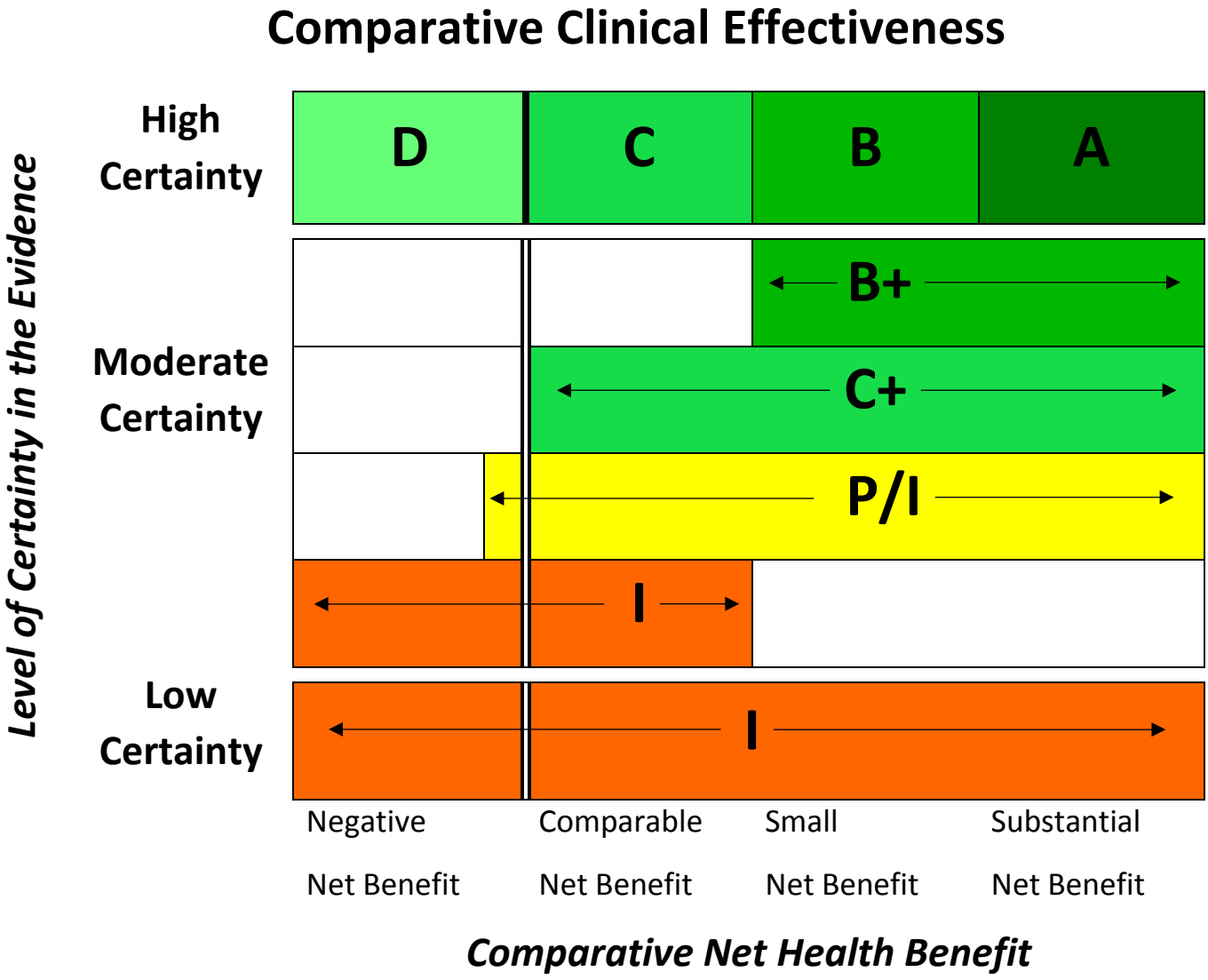
The timeframe for our search spanned the period from January 1996 to June 28, 2016 and focused on MEDLINE, EMBASE, and Cochrane-indexed articles. We limited each search to studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We did not conduct a *de novo* search for the anti-TNF agents. Rather, data from the key comparative studies not captured in the initial survey of the literature were abstracted from recently published high-quality systematic reviews. To supplement the above searches and ensure optimal and complete literature retrieval, we performed a manual check of the references of recent relevant reviews and meta-analyses. Other grey literature sources included data submissions from the manufacturer of psoriasis therapies that were not otherwise publicly available. Further details on the search algorithms, methods for study selection, data extraction, quality assessment, assessment for publication bias, and our approach to meta-analyses of the data are available in Appendix A.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix (see Figure 4) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
The level of **certainty** in the best point estimate of net health benefit.[30]

Figure 4. ICER Evidence Rating Matrix



A = "Superior" **-** High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" **-** High certainty of a small net health benefit
C = "Comparable"**-** High certainty of a comparable net health benefit
D = "Negative"**-** High certainty of an inferior net health benefit
B+ = "Incremental or Better" **-** Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit
C+ = "Comparable or Better" **-** Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit
P/I = "Promising but Inconclusive" **-** Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit
I = "Insufficient" **-** Either moderate certainty that the best point estimate of comparative net health benefit is comparable or inferior; or any situation in which the level of certainty in the evidence is low

4.3 Results

Study Selection

Our literature search identified 1,392 potentially relevant references. Key comparative studies of the anti-TNF agents were gathered and cross-checked from six recent high-quality systematic reviews.[31-36] A total of 69 references met our inclusion criteria; these citations related to 36 publications of 35 individual RCTs, of which 33 were Phase III RCTs, 22 abstracts, and 11 observational studies. Primary reasons for study exclusion included use of a regimen not approved by the FDA, study population or outcomes related specifically to patients with psoriatic arthritis or other types of psoriasis (e.g., eythrodermic), and non-comparative study design. We prioritized reporting information we identified as part of our literature search, and supplemented our presentation of the evidence with data available from the grey literature. Ustekinumab and the anti-TNF therapies were the only treatments for which we were able to find comparative observational data that met our inclusion criteria. Additional details of the included references are described in Appendix B, and the key studies are summarized in Table 4.

Quality of Individual Studies

We rated all 35 trials to be of good or fair quality using criteria from U.S. Preventive Services Task Force (USPSTF).[37] Trials of good quality had study arms that were comparable at baseline, the authors used valid instruments to evaluate outcomes, and no differential attrition was observed. Fair quality studies typically used modified intention-to-treat (mITT) as the primary method of analysis. Of the 11 observational studies, five were judged to be good, three fair, and three poor quality. As previously mentioned, we did not assign a quality rating to references that were obtained from the grey literature.

Key Studies

Of the 35 individual RCTs, we identified 28 key clinical studies evaluating at least one of the eight therapies of interest for this review. Two of the remaining studies were Phase II, and five were conducted exclusively in Asia which are discussed separately in the subgroups section of this report. Only two studies (ACCEPT and CLEAR) did not include a placebo arm. Eight studies included head-to-head trials of the drugs of interest for this review (etanercept vs. ustekinumab [ACCEPT], secukinumab [FIXTURE], and ixekizumab [UNCOVER 2 and 3]; and ustekinumab vs. brodalumab [AMAGINE 2 and 3] and secukinumab [CLEAR]), including a Phase IIIb trial [LIBERATE] comparing apremilast to a maintenance dose of etanercept that has not yet been published but was available in the grey literature. We also included five studies which evaluated one of the drugs of interest to another active comparator (1 of methotrexate vs. adalimumab, 2 of briakinumab vs. etanercept,

and 1 of tofacitinib vs. etanercept); for purposes of this review, we only considered comparisons to placebo in these trials.

All of the key studies were multicenter, double-blind, Phase III RCTs, though some removed blinding following the induction period for each drug. Many trials also rerandomized patients to different treatment groups and measured outcomes at various timepoints, making it difficult to evaluate the comparative durability of effect and harms across therapies. Trial populations had similar inclusion criteria (≥18 years old, BSA ≥10%, PASI score ≥12, ≥6 months of plaque psoriasis diagnosis, and candidates for phototherapy or systemic therapy) and were comparable with respect to age (range: 41-46 years, median: 45) and duration of psoriasis (range: 14-21 years, median: 19). Baseline PASI scores varied substantially across trials (range: 16-33, median: 23). Given potential other cross-trial heterogeneity, we conducted a sensitivity analysis in our network meta-analysis adjusting for baseline variations; the details and results of this analysis are discussed in Appendix G.

Subgroups

Several populations were identified as being of special interest to stakeholders, and are described in the subgroups section of this report. The characteristics of these subgroups are as follows:

Asian Studies: As previously mentioned, we separately considered five trials that were conducted exclusively in Asia (i.e., Japan, Korea, China, and Taiwan). These trials were generally smaller (with the exception of LOTUS, n=322)[38] with patients who were slightly younger (range: 40-50 years, median: 43) had a briefer duration of psoriasis (range: 13-16 years, median: 15), and lower BMI than the other trials.

Patients with Previous Biologic Therapy Exposure: We also examined subgroups of patients who had and had not been previously treated with a targeted immunomodulator. Fewer patients were biologic-experienced in the studies of the older anti-TNF drugs relative to the newer therapies. Across all studies, an average of 20% (range: 0% to 51%) of patients received prior biologic therapy.

Patients with Psoriatic Arthritis: Because up to a third of patients with psoriasis develop psoriatic arthritis, we evaluated subgroups of psoriasis patients with and without psoriatic arthritis. Among those studies that reported the number of patients with arthritis at baseline, 25% (range: 15% to 34%) had psoriatic arthritis.

Table 4. Key Studies

Drug	Trials	Total # of patients	Induction period (weeks)	PASI, (mean)	Age (years)	Psoriasis duration (years)	Previous biologics (%)	PsA (%)
Adalimumab	REVEAL CHAMPION	1,483	16	22	43	19	6	24
Etanercept	Papp, 2005 Leonardi, 2003 Tyring, 2006 Strober, 2011 Gottlieb, 2011 Bagel, 2012 Bachelez, 2015	3,775	12	20	44	17	6	25
Infliximab	EXPRESS I EXPRESS II	1,219	10	25	44	19	7	30
Ustekinumab	ACCEPT PHOENIX 1 PHOENIX 2	2,899	12	30	45	20	33	29
Secukinumab	FEATURE CLEAR JUNCTURE ERASURE FIXTURE	3,079	12	28	45	18	25	20
Ixekizumab	UNCOVER 1 UNCOVER 2 UNCOVER 3	3,866	12	24	46	19	27	NR
Brodalumab	AMAGINE 1 AMAGINE 2 AMAGINE 3	4,373	12	23	45	19	33	22
Apremilast	ESTEEM 1 ESTEEM 2 LIBERATE	1,505	16	19	46	19	31	NR

Clinical Benefits

The primary outcome of all trials was the proportion of patients achieving PASI 75 (also referred to as PASI response rate) at the end of the induction period. The duration of the induction period varied by agent: week 10 for infliximab; week 12 for ixekizumab, secukinumab, ustekinumab, and etanercept; and week 16 for adalimumab and apremilast. Other clinical outcomes included the proportion of patients meeting additional PASI thresholds (e.g., 50, 90, 100), or achieving a score of 0 or 1 ("cleared or minimal") on the Physician Global Assessment (PGA) or Investigator's Global Assessment (IGA), although these were less consistently reported. Patient-reported outcomes, including quality of life, were primarily based on mean change or proportion of patients achieving a score of 0 or 1 on the DLQI (indicating very little to no disease effect on quality of life); other quality of life instruments, such as the SF-36, were less commonly used. Measures of symptom control, such as VAS scales for itch or skin pain, as well as a recently validated tool for assessing symptom control in psoriasis patients (Psoriasis Symptom Inventory [PSI]), were infrequently employed. All data are reported based on the FDA-approved or proposed dosing at the end of the induction period for each drug with the following three exceptions: first, for secukinumab, while the drug label indicates that 150mg may be appropriate for some patients, we only describe outcomes for the 300mg dose. In addition, although FDA-approved dosing for ustekinumab is weight-based, none of trials randomized participants based on weight so many patients did not receive their appropriate weight-based dose. Finally, although the LIBERATE trial included the approved dose of apremilast, patients in the etanercept arm received a maintenance dose (i.e., 50 mg once weekly).

Psoriasis Area Severity Index (PASI)

PASI 75

All targeted immunomodulators showed statistically-significantly higher PASI 75 response rates in comparison to placebo at the end of induction (10 to 16 weeks, depending on agent). In direct comparative trials, ustekinumab, secukinumab, and ixekizumab were superior to etanercept; secukinumab and brodalumab were superior to ustekinumab; and there was no significant difference between etanercept and apremilast.

All immunomodulators showed a statistically significantly higher absolute percentage of PASI 75 responders compared to placebo. The range of PASI 75 responses in the intervention and placebo groups across trials is shown in Table 5. In individual placebo-controlled RCTs, the absolute proportion of patients achieving PASI 75 above placebo within trials was 62% to 64% for adalimumab (2 trials);[39,40] 33% to 54% for etanercept (7 trials);[41-47] 74% to 77% for infliximab (2 trials);[48,49] 80-88% for ixekizumab (3 trials);[50-52] 63%-64% for ustekinumab 45 mg (2 trials);[53,54] 63% to 72% for ustekinumab 90 mg (2 trials);[53,54] 72% to 84% for secukinumab at 12 weeks (4 trials);[55-57] 78% to 80% for brodalumab (3 trials);[58,59][Papp 2016] and 13% to 18% for apremilast (2 trials).[60,61])

Additionally, a newly approved biosimilar to etanercept, Erelzi, had a PASI 75 response very similar to etanercept (73.4% with Erelzi vs. 75% with etanercept).[22]

We identified eight head-to-head RCTs, all, but one of which showed statistically-significant differences between treatments in PASI 75 response (Table 6). In four trials, three agents were superior to etanercept: ustekinumab (57% vs. 68% and 74% for ustekinumab 45 mg and 90 mg, respectively);[62] secukinumab 300 mg (44% vs. 77%);[55] and ixekizumab (42% vs. 90% in UNCOVER 2[63] and 53% vs. 87% in UNCOVER 3).[52] In three trials, two agents were superior to ustekinumab: secukinumab (79% vs. 91% for secukinumab 300 mg at 12 weeks; 83% vs. 93% at 16 weeks)[64] and brodalumab (70% vs. 86% in AMAGINE 2 and 69% vs. 85% in AMAGINE 3).[59] In one trial, there was no statistically significant difference between etanercept and ampremilast (48% vs. 40%; p = 0.26).[65]

Table 5. Placebo-Controlled Trials: Ranges of PASI 50/75/90/100 Response Rates across Trials

Treatment	PASI 75		PASI 50		PASI 90		PASI 100	
	Tx	Placebo	Tx	Placebo	Tx	Placebo	Tx	Placebo
Adalimumab	71-80	7-19	88	30	45-52	2-11	17-20	1-2
Etanercept	40-59	3-7	71-85	7-21	19-32	1-2	6-7	0
Infliximab	76-80	2-3	91	8	45-57	1	NR	NR
Ustekinumab 45 mg	67	3-4	84	10	16-37	1-2	11-18	0
Ustekinumab 90 mg	66-76	3-4	86-89	10	42	1-2	13-18	0
Secukinumab	76-87	0-5	88-94	5-15	54-60	0-2	24-43	0-1
Ixekizumab	87-90	2-7	NR	NR	68-71	1-3	35-41	0-1
Brodalumab	83-86	3-8	NR	NR	69-70	1-3	37-44	0-2
Apremilast	29-33	6-15	56-59	17-20	9-94	0-2	NR	NR

Table 6. Comparative Trials: PASI Responses

Trial	Treatment	PASI 75	PASI 90	PASI 100
Accept	Etanercept	57	23	NR

	Ustekinumab 45 mg	68	36	NR
	Ustekinumab 90 mg	74	45	NR
FIXTURE	Etanercept	44	21	4
	Secukinumab 300 mg	77	54	24
UNCOVER 2&3	Etanercept	42-53	19-26	5-7
	Ixekizumab	87-90	68-70	38-41
CLEAR	Ustekinumab WBD	79	53	26
	Secukinumab 300 mg	91	73	39
AMAGINE 2&3	Ustekinumab WBD	69-70	47-48	19-22
	Brodalumab 210 mg	85-86	69-70	37-44
LIBERATE	Etanercept	48	NR	NR
	Apremilast	40	NR	NR

An additional three observational studies directly comparing anti-TNFα agents either reported non-significant findings [66] or did not conduct statistical tests on PASI 75 between groups.[67,68]

Given the paucity of head-to-head data comparing treatments, we performed indirect comparisons of PASI response using Bayesian network meta-analyses (NMAs). NMA was felt to be appropriate as the populations of the individual trials were sufficiently similar. Detailed descriptions of methods and results can be found in Appendix G. Our network meta-analysis showed that all immunomodulators had a statistically significantly higher efficacy on PASI 75 than placebo. In head-to-head comparisons, ixekizumab had the highest relative effectiveness [measured as relative risk (RR)] of achieving initial PASI 75 reponse during induction, followed by brodalumab, infliximab, secukinumab 300 mg, and ustekinumab 45/90 mg, and other anti-TNFα agents (in the order of adalimumab, etanercept, and Erelzi). Apremilast had the lowest RR. (see Appendix G5)

Other PASI Thresholds

All target immunomodulators showed statistically significantly higher PASI 50, 90, and 100 rates than placebo (except that no published PASI 50 results were found for ixekizumab). In direct comparative trials, ustekinumab, secukinumab, and ixekizumab were superior to etanercept for PASI 90 and 100. Secukinumab and brodalumab were superior to ustekinumab in PASI 90 and 100.

Similar to PASI 75 results, all targeted immunomodulators showed a statistically significantly higher percentage of patients achieving PASI 50, 90, and 100 compared to placebo, except for ixekizumab, which did not include PASI 50 in available trials (Table 5). Absolute rates were higher given the lower threshold for improvement with PASI 50, but generally ranged between 7% to 21% for placebo, 70% to 90% for biologics, and 55% to 60% for apremilast. PASI 90 response rates ranged between 0% to 11% for placebo, 16% to 70% for biologics, and 9% to 10% for apremilast. PASI 100 response rates ranged between 0% to 2% for placebo, 6% to 43% for biologics, and were not reported for apremilast.

Seven head-to-head RCTs showed statistically significant differences between treatments on PASI 90 and PASI 100. For PASI 90, four trials showed that ustekinumab, secukinumab, and ixekizumab were superior to etanercept. For PASI 100, three trials found that ustekinumab, secukinmab and ixekizumab were superior to etanercept. For both PASI 90 and 100, secukinumab and brodalumab were superior to ustekinumab. Table 6 summarizes the comparisons and Appendix G provides more details.

The direct comparative trials did not report PASI 50. However, we did identify two observational studies that compared PASI 50 response between treatments. One of them was a prospective, multi-center study in 162 patients (mean age 47, 68% male, mean duration of psoriasis 18 years, mean PASI 17.5) who received either infliximab or ustekinumab that found no statistically significant between-group difference in PASI 50 at seven months (96% vs. 82%).[66] The other was a retrospective analysis in 89 elderly patients (mean age 70, 55% male, mean duration of psoriasis 28 years, mean PASI 11) treated with etanercept or adalimumab, finding that adalimumab had higher response rates at 12 weeks (86% vs. 82%) but lower at 24 weeks (82% vs. 90%), one year (79% vs. 90%), two years (82% vs. 92%), and three years (82% vs. 92%). However, the statistical significance of these differences was not tested.[68]

Our network meta-analysis showed that all targeted immunomodulators were statistically significantly better than placebo on PASI 50. The effect sizes were similar among treatments, with RR ranging from 3.4 to 6.9. Pair-wise comparisons showed no difference between treatments (see Appendix G). Similarly, all immunomodulators had a statistically significantly higher efficacy on PASI 90 and 100. In head-to-head comparisons for initial PASI 90 and PASI 100, infliximab had the highest initial RR, followed by anti-interleukin agents (in the order of brodalumab, ixekizumab,

secukinumab 300 mg, ustekinumab 45/90 mg combined), and other anti-TNFα agents (in the order of adalimumab, etanercept, and Erelzi). Apremilast had the lowest RR (Appendix G).

Physician Global Assessment or Investigator Global Assessment "Clear/Almost Clear"

All immunomodulators showed statistically significantly higher proportions of patients with Physician Global Assessment (PGA) or Investigator's Global Assessment (IGA) of 'clear/almost clear' than placebo at the primary end point of each trial. Head-to-head trials found that etanercept and utsekinumab had lower PGA response rates than biologic comparators.

All immunomodulators showed statistically significantly higher efficacy on PGA/IGA compared to placebo. Across trials, the ranges of PGA/IGA response rates were 1% to 18% for placebo, 60% to 73% for adalilumab,[39,40] 40% to 66% for etanercept,[41,42,44-47] 76% to 83% for infliximab,[48,49] 60% to 74% for ustekinumab,[53,54] 65% to 74% for secukinumab,[55-57] 76-85% for brodalumab,[58,59] and 20% to 47% for apremilast.[60,61]

Seven of eight head-to-head RCTs also reported PGA response. All found statistically significant differences between treatments. The pattern response rates and differences between treatments were similar to those of PASI 75 response. In four trials, three agents had a higher proportion of patients achieve PGA scores of 0/1 than etanercept: ustekinumab (49% vs. 65% and 71% for ustekinumab 45 mg and 90 mg, respectively);[62] secukinumab (27% vs. 63%);[55] and ixekizumab (36% vs. 83% in UNCOVER 2[63] and 42% vs. 81% in UNCOVER 3;[52] both $p<0.0001$). In three trials, two agents had a significantly higher proportion of patients with PGA scores of 0/1 than ustekinumab: secukinumab (65% vs. 81% at 12 weeks; 68% vs. 83% at 16 weeks)[64] and brodalumab (61% vs. 79% in AMAGINE 2 and 69% vs. 85% in AMAGINE3[59]).

Two observational studies, adjusted for clinical and sociodemographic factors, compared PGA among drugs. One cross-sectional study in the U.S. with a sample size of 713 (mean age 49, 51% male, mean duration of psoriasis 19 years) showed that adalimumab had better adjusted PGA response compared to etanercept and ustekinumab (48% vs. 34% and 36%, $p<0.001$[69]). The PSOLAR registry (N=2076, mean age 47, 57% male, mean duration of psoriasis 17 years) found ustekinumab had better PGA response than infliximab (60% vs. 42%) at 12 months, but found no difference compared with etanercept or adalimumab.[70]

Dermatology Quality of Life Index (DLQI)

All targeted immunomodulators under review statistically significantly improved quality of life relative to placebo, with infliximab producing the overall greatest relative benefit and apremilast producing the smallest. Comparative trials demonstrated superior improvements in quality of life for secukinumab, ixekizumab, and apremilast compared to etanercept; secukinumab was also better than ustekinumab in one trial.

Quality of life was measured in the majority of studies we identified in our search, primarily using the DLQI instrument. Overall, 17 of the 28 key studies evaluated mean DLQI change, while eight evaluated the proportion of patients achieving a DLQI score of 0 or 1 (indicating very little to no effect on quality of life); six included both measures.

The 13 placebo-controlled trials reporting the mean DLQI change also showed a statistically significantly greater improvement for all therapies. Mean absolute difference between the intervention and placebo group improvement compared to placebo across the available studies for to each drug were as follows: adalimumab (-5.7),[71], etanercept (-5.5 to -5.6),[42,43] infliximab (-9.0),[49] (all outcomes, p<0.01), ustekinumab (-7.4 to -8.8 and -8.1 to -9.5 for 45 or 90mg, respectively),[53,54] ixekizumab (-8.4),[52] secukinumab (-8.8),[55] and apremilast (-3.9 to -4.5).[61,72]

Brodalumab was the only agent for which no study measured mean DLQI change, though an abstract based on the AMAGINE 1 trial did report the proportion of patients achieving a DLQI score of 0/1, which was statistically significant in favor of brodalumab (absolute difference: 50.9%, p<0.001).[73] Among those three placebo-controlled trials that also reported the proportion of patients with a score of 0/1, secukinumab (absolute difference: 48.3%, p<0.001)[55] and ustekinumab (47.1%-52.1%/46.4%-53.2 for 45/90mg)[53,54] were statistically significantly greater than placebo (all outcomes, p<0.0001).

Among the eight head-to-head trials, five studies evaluated improvements on the DLQI: CLEAR, FIXTURE, UNCOVER 2 and 3, and LIBERATE. In four trials, secukinumab, ixekizumab, and apremilast achieved a statistically significantly greater improvement on the DLQI than etanercept. In the CLEAR study, secukinumab also had a statistically significantly higher proportion of patients with a DLQI score of 0/1 relative to ustekinumab. The table below presents the data from these trials

Table 7. DLQI Outcomes Across Direct Comparative Trials

Trial		Mean change	p-value	DLQI 0/1 (%)	p-value
CLEAR	ustekinumab	NR	NR	56.5	p=0.0109
	secukinumab	NR		66.2	
FIXTURE	etanercept	-7.9	p<0.001	34.5	p<0.001
	secukinumab	-10.4		56.7	
UNCOVER 2	etanercept	-7.7	p<0.0001	33.8	p<0.0001
	ixekizumab	-10.4		64.1	
UNCOVER 3	etanercept	-8.0	p<0.0001	43.7	p<0.0001

	ixekizumab	-10.2		64.7	
LIBERATE	etanercept	-7.8	p=0.0004	NR	NR
	apremilast	-8.3		NR	

Data on clinically-meaningful improvements on the DLQI (defined as at least a 5-point reduction) were available for four drugs: etanercept, ustekinumab, brodalumab, and apremilast. An abstract based on the AMAGINE-1 trial reported that brodalumab was significantly better than placebo (66% mean absolute difference, p<0.001).[73] A pooled analysis of both PHOENIX 1 and 2, found that both doses of ustekinumab had a clinically-meaningful improvement on the DLQI compared to placebo (absolute difference: 54.6% and 59.4% for the 45mg and 90mg doses, respectively), though this outcome was reported in only one abstract.[74] Additionally, neither ESTEEM trial showed statistically significant improvements of apremilast relative to placebo.[61,72]

The LIBERATE trial comparing apremilast and etanercept was the only available head-to-head study. The proportion of patients achieving a minimum 5-point DLQI reduction for patients with at least a score of 5 on the DLQI at baseline was reported in one abstract, not statistically evaluated, and numerically the same as etanercept (23%).[75]

Other Quality of Life Measures

Few studies used other instruments to measure quality of life. One Phase II publication each for brodalumab and apremilast reported SF-36 scores. Brodalumab was associated with statistically significant improvement compared to placebo in the SF-36 PCS (+4.0 vs. +1.5) and MCS (+5.0 vs. +1.7).[76] Apremilast failed to demonstrate any significant improvement relative to placebo, although improvement from baseline on the MCS was statistically significant (+2.9, p=0.0045) and numerically higher than the placebo group, which worsened (-0.8).[77] Both brodalumab (+0.25 vs. -0.01, for placebo, p<0.001)[78] and adalimumab (+0.20 vs. +0.10 for placebo, p<0.01) demonstated statistically significant improvements compared to placebo on the EQ-5D,[71] though only the former was available in the peer-reviewed literature.

Symptom Control

Measures of symptom control were inconsistently reported across trials. Brodalumab was also the only agent to measure PSI outcomes, and demonstrated a statistically significant benefit over placebo. Two secukinumab trials measured improvements on the PSD, and improved itching, pain and scaling better than placebo. In head-to-head trials, ixekizumab demonstrated superiority over etanercept for VAS-skin pain, while apremilast was numerically similar to etanercept on the VAS-itch; apremilast wasbetter than placebo, however.

One trial of brodalumab and one of ustekinumab measured improvements in anxiety and depression on the HADS scale relative to placebo. In the publication of the AMAGINE 1 study, brodalumab improved both anxiety (-2.3) and depression (-2.0) relative to placebo (-0.7 and -0.4, respectively, treatment difference: -1.5 and -2.1, p<0.001 for both outcomes).[58] In a secondary analysis of PHOENIX 2, Langley and colleagues also reported a statistically significant improvement of both doses (45/90mg) of ustekinumab for anxiety (-1.6/-1/7 vs. -0.11) and depression (-1.7/-2.1 vs. -0.21) over placebo (both outcomes, p<0.001).[79]

Across the two ESTEEM RCTs, apremilast demonstrated a statistically significant absolute improvement over placebo for pruritus VAS of 21.0mm-24.2mm (p<0.001).[61,72] On the PSI, significantly more patients in the brodalumab group were PSI responders compared to placebo in the AMAGINE 1 study (absolute difference: 57%, p<0.001).[58] The proportion of responders (defined as a minimum of 2.2 reduction on all scales) receiving secukinumab was statisticaly significantly greater than placebo on the PSD for itching (83.0% vs. 16.9%), pain (72.8% vs. 15.6%), and scaling (83.0% vs. 13.8%) in the ERASURE and FIXTURE studies (p<0.05).[80]

In direct comparison trials, an abstract reported that ixekizumab was statistically significantly better than etanercept for VAS-skin pain (least mean change from baseline: -42.2 vs. -29.0, p<0.001).[81] In the LIBERATE trial, patients experienced a statistically significantly greater mean reduction on the VAS-itch scale from baseline for both apremilast (-35.6mm, p=0.00261) and etanercept (-36.4cm, p<0.0001) compared to placebo; the active intervention groups were not compared statistically, however, and the decrease was numerically higher for etanercept.[75] A single publication reporting results from the AMAGINE 2 and 3 trials found that numerically more patients were PSI responders (defined as PSI score ≤8, with no item having a score >1) in the brodalumab group compared to ustekinumab group (68% vs. 55% [AMAGINE 2] and 61% vs. 52% [AMAGINE 3], respectively); groups were not compared statistically for this particular outcome in either trial, however.[59]

Other Patient-Reported Outcomes

Compared to placebo, both brodalumab and ustekinumab were superior for improving anxiety and depression on HADS. Most of the data available on other patient-reported outcomes were the result of post hoc analyses of the key trials. Comparisons to placebo based on several different scales were also statistically significant for adalimumab, infliximab, and ustekinumab; data on apremilast was variable. Only two trials, one of brodalumab and one of etanercept, reported treatment satisfaction, which was better for both interventions than placebo. Work productivity statistically significantly improved for patients taking ixekizumab versus etanercept. Sexual function also was statistically significantly improved for ustekinumab versus placebo and for ixekizumab versus etanercept.

In addition to the above-described patient-reported outcomes, we identified three others that were available in the literature: work productivity loss (as measured on the Work Productivity and Activity Impairment [WPAI], Work Limitations Questionnaire [WLQ], or VAS-productivity), impaired sexual function (measured as score of 2 or 3 on DLQI item 9), and treatment satisfaction.

Work Productivity

With regard to work productivity, we identified three publications that were secondary analyses of Phase III placebo-controlled RCTs, including REVEAL, EXPRESS, PHOENIX 2, as well as an abstract pooling data from the ESTEEM trials. The secondary analysis of the REVEAL trial[82] demonstrated a statistically significant improvement for adalimumab relative to placebo on the WPAI for total work productivity impairment (15.1%, p<0.001); the data for the placebo group were not reported, however. Infliximab was statistically significantly better than placebo on VAS productivity scores in the EXPRESS trial, with a mean 22.5% increase in the intervention group compared to a 1.1% decrease change in the placebo group; a similar trend was observed on the SF-36 physical (+12.1 vs. -5.2) and emotional domain scores (+18.5 vs. -2.2) (all outcomes, p<0.001).[83]

The secondary analysis of PHOENIX 2 also demonstrated statistically significant improvements of ustekinumab 45/90mg based on WLQ domains for output demands (6.8/7.0 vs. 1.1) mental-interpersonal (7.8/7.5 vs. -1.1), and time management (6.6/9.1 vs. -0.7) compared to placebo (all outcomes, p<0.001). An abstract that pooled data from the ESTEEM trials also used the WLQ tool but found apremilast to be statistically significantly improved based on two of the four domains relative to placebo: time management (-2.1 vs. +2.8, p=0.002) and output demands (-1.5 vs. +1.0, p=0.046).[60] Finally, median percent improvements from baseline in productivity VAS better for ustekinumab 45/90mg (72.6%/71.4%) compared to no change for placebo, but groups were not compared statistically.[84]

A secondary analysis of the UNCOVER trials, which included head-to-head data on ixekizumab and etanercept.[85] Outcomes were evaluated based on the WPAI and demonstrated a statistically significant improvement over placebo in UNCOVER 1 (-19.8 vs. -0.8), and over etanercept and placebo in UNCOVER 2 (-19.5 vs. -13.7 and -2.0) and UNCOVER 3 (-19.3 vs. -17.4 and +0.6) for work productivity loss (least mean squares, p<0.001 for all outcomes).

Sexual Function

Very few studies reported sexual function as an outcome, with data available only for ustekinumab and ixekizumab. In a secondary analysis of the UNCOVER trials, one abstract reported that statistically significantly more patients reported improvements in sexual function with the ixekizumab compared to etanercept or placebo in both UNCOVER 1 (80%, 51%, and 24%) and UNCOVER 2 (81%, 69%, and 27% respectively).[86] In addition, a publication which pooled patients

from PHOENIX 1 and 2 reported that the proportion of patients with improved sexual function was statistically significantly higher with ustekinumab 45/90mg (22.8/22.1%) than placebo which remained unchanged from baseline (23.0%, p<0.001.[87]

Treatment Satisfaction

Only two studies reported treatment satisfaction. The proportion of patients who were "satisfied" or "very satisfied" with treatment was statistically significantly higher in the etanercept group versus placebo (76% vs. 18%, p<0.0001).[44] While one abstract reported that treatment satisfaction was statistically significantly higher in the brodalumab group relative to placebo (p<0.001), no additional data were reported.[73]

Harms

Severe or serious adverse events were rare during the induction phase of treatment. Infections (e.g. nasopharyngitis, upper respiratory tract infections, etc.), injection site reactions or infusion reaction, headache, and nausea were the most common side effects with biologics. Infliximab appears to have higher rates of these events than other drugs. Long-term safety data on all-cause mortality, MACE, malignancy, and serious infections are available for anti-TNFα agents and ustekinumab but not for the other drugs of interest for this review.

Adverse Events During Induction

Adverse events (AEs) that occurred in ≥5% of patients in any treatment group as well as specific AEs of particular interest are shown as trial-weighted averages in Table 8. Most adverse events were mild or moderate. Severe or serious adverse events, death, and AEs leading to discontinuation were rare and comparable between the treatment and placebo groups.

The most common AEs included mild infections (e.g. nasopharyngitis, upper respiratory tract infections, etc.); injection site reactions for subcutaneously administered drugs and infusion reaction for infliximab; headache; and nausea. There was no evidence of increased risk of serious infections or malignancies. There were no reports of tuberculosis, opportunistic infections, demyelinating disease, or lymphoma in these trials. We also did not find differences in risk of major adverse cardiac events (MACE).

Table 8. Adverse events during the placebo-controlled period

%	adalimumab	etanercept	infliximab	ustekinumab	secukinumab	ixekizumab	brodalumab	apremilast	placebo
Any AE	65	57	71	53	58	58	58	69	52
Tx-related death	0	0	0	0.1	0	0	0.1	0.1	0
D/C due to AEs	2	2	7	1	1	2	1	5	2
Serious AEs	2	2	3	1	2	2	1	2	2
Serious Infections	1	0.5	6	0.6	NR	0.4	0.5	NR	0.3
≥Grade 3 AEs	2	2	NR	NR	NR	NR	4	4	3
common AEs, %									
Any Infections	32	27	36	36	29	27	NR	NR	25
Nasopharyngitis	8	8	NR	12	11	10	9	7	8
Upper respiratory tract infection	7	6	14	5	3	4	6	8	5
Headache	6	7	13	7	6	4	4	6	4
Nausea	4	2	4	NR	5	NR	NR	17	4
Injection site reactions	19	14	NA	4	NR	10	1	NA	2
Infusion Reaction	NA	NA	10	NA	NA	NA	NA	NA	7
Malignancy excluding NMSC	0.2	0.5	1	0.2	NR	0.1	NR	NR	0.2
NMSC	0.5	0.3	NR	0.4	NR	0.1	NR	NR	0.2
MACE	NR	0.2	NR	0.2	NR	0	0	NR	0

* Values represent weighted averages across key trials; D/C=discontinuation; AEs=adverse events; NMSC=nonmalenoma skin cancer

Long-term Adverse Events

In AMAGINE 2 and AMAGINE 3, patients were randomized to brodalumab or ustekinumab and followed for 52 weeks.[Lebwohl 2015] For the AMAGINE 2 and AMAGINE 3 trials, 52 week rate of serious AEs for brodalumab and ustekinumab were 8.3 per 100 person-years (P-Y) and 7.9 per 100 P-Y and for ustekinumab were 13.0 per 100 P-Y and 4.0 per 100 P-Y; the rates of serious infections for brodalumab were 1.0 per 100 P-Y and 1.3 per 100 P-Y and for ustekinumab were 0.8 per 100 P-Y and 1.2 per 100 P-Y; cardiac disorders for brodalumab were 1.2 per 100 P-Y and 0.9 per 100 P-Y and for ustekinumab were 1.2 per 100 P-Y and 0.0 per 100 P-Y, respectively. Five deaths occurred, two in the brodalumab group and three in the placebo group.

In FIXTURE, patients randomized to secukinumab or etanercept were followed for 52 weeks. The rates of serious AEs for secukinumab 300 mg and etanercept were 6.8 per 100 P-Y and 7.0 per 100 P-Y ; for infections were 105.4 per 100 P-Y and 91.4 per 100 P-Y; and for AEs leading to discontinuation were 14 per 100 P-Y, and 12 per 100 P-Y, respectiely. No deaths occurred. [88]

For ustekinumab, the PHOENIX 1 trial (n = 517 patients; mean age, 45 years old) and the PHOENIX 2 trial (n = 1212 patients; mean age, 46 years old) had long-term follow up of up to 5 years. In PHOENIX 1 and PHOENIX 2, the rates of serious adverse events were 5 per 100 P-Y and 7 per 100 P-Y; serious infections were 1 per 100 P-Y and 1 per 100 P-Y; malignancies were 1 per 100 P-Y and 1 per 100 P-Y; and MACE were 0.3 per 100 P-Y and 0.5 per 100 P-Y, respectively.

Long-term safety data are also available from large observational studies and registries. PSOLAR is a multicenter, longitudinal, psoriasis-based registry study evaluating the risk of infection in biologics and other systemic therapies. The overall population was 55% male, with a mean age of 49 and a mean duration of disease of 18 years. We identified two publications describing PSOLAR results for serious infections,[89] all-cause mortality, MACEs, and malignancy excluding NMSC.[90] PSOLAR had a total enrollment of 11,466 patients with 22,311 P-Y of follow-up to evaluate the serious infection rate and 12,095 patients with 31,818 P-Y of follow-up for the other rates. Nonbiologics were associated with a significantly higher rate of AE rates than biologics on all-cause mortality (nonbiologics, 0.70 per 100 P-Y; infliximab, 0.45 per 100 P-Y; ustekinumab, 0.36 per 100 P-Y; and other biologics [mostly adalimumab per etanercept], 0.42 per 100 P-Y]; MACE (nonbiologics, 0.45 per 100 P-Y; infliximab, 0.38 per 100 P-Y; ustekinumab, 0.34 per 100 P-Y; other biologics, 0.33 per 100 P-Y); and malignancy (nonbiologics, 0.81 per 100 P-Y; infliximab, 0.64 per 100 P-Y; ustekinumab, 0.51 per 100 P-Y; and other biologics, 0.74 per 100 P-Y). Biologics, except ustekinumab, had a higher rate of serious infections (nonbiologics, 1.05-1.28 per 100 P-Y; infliximab, 2.49 per 100 P-Y; ustekinumab, 0.83 per 100 P-Y; etanercept, 1.47 per 100 P-Y; and adalimumab, 1.97 per 100 P-Y).

For the other drugs, including ixekizumab, secukinumab, brodalumab, and apremilast, no long-term safety data beyond the duration of clinical trials were published.

Subgroup Analyses

Limitations in the evidence base preclude determining whether there are meaningful differences in effectiveness within the subgroups of interest. Although outcomes were statistically significantly in favor for all the agents available for review relative to placebo, data comparing subgroup results between agents were only available in one observational study.

As previously mentioned, three subgroups were identified as being of particular interest to stakeholders: patients with psoriatic arthritis; patients who have or have not previously received biologic agents; and studies that were conducted in Asia.

Patients with Psoriatic Arthritis

We identified five secondary analyses evaluating outcomes for patients with psoriatic arthritis, four of which were from the grey literature.[74,91-94] No data were available for the anti-TNFs or apremilast. One post hoc analysis of a Phase IIb study in brodalumab reported outcomes for those with and without psoriatic arthritis, but between group comparisons were not statistically evaluated.

Three placebo-controlled RCTs included secukinumab, ixekizumab, and ustekinumab, and brodalumab and reported results among patients with psoriatic arthritis. All agents were statistically significantly better relative to placebo on the PASI 75 among patients with psoriatic arthritis (Table 9).

One abstract reported results of the FIXTURE trial among patients with psoriatic arthritis. Patients with plaque psoriasis and psoriatic arthritis receiving secukinumab had a statistically significantly higher rate of achieiving PASI 75 (72% vs. 39% and 2%) and PASI 90 (44% and 39% vs. 18% and 2%) compared to etanercept and placebo, respectively ($p<0.01$). These differences were similar to those observed for the overall trial population.[94]

Table 9. Proportion of patients with and without psoriatic arthritis reaching PASI 75

Drug (Trial)	# of PsA patients	PsA Achieving PASI 75 (%)		Overall Population	
		Intervention	Placebo	Intervention	Placebo
Secukinumab (FIXTURE)	175	72	2	82	5
Etanercept (FIXTURE)	Same trial	39	4	44	Same trial
Secukinumab (ERASURE)	171	70	4	82	5

Ustekinumab 45/90mg (PHOENIX 1 and 2)	563	63/62	4	67/66	3
Ixekizumab (all UNCOVER trials)	749	90	3	87-90	4
Brodalumab (Phase IIb)	198	92	0	82	0

The secondary analysis of a Phase IIb trial of brodalumab was the only one that reported outcomes for patients with and without psoriatic arthritis. Patients with psoriatic arthritis (n=46) had numerically similar proportions of achieving PASI 75 compared to patients without psoriatic arthritis (n=152; 92% and 79% vs. no change for placebo), PASI 90 (83% and 71% vs. no change for placebo), a DLQI response (defined as a ≥5-point improvement; 100% vs. 79% vs. 0% and 42% for placebo), and a PSI response (defined as a score ≤8, with no item having a score >1; 94% and 79% vs. 14% and 13% for placebo) The authors stated that adverse events were similar between subgroups, no data were included.[93]

One abstract evaluated SF-36 outcomes based on pooled data from the UNCOVER trials for ixekizumab,[92] and found that patients with psoriatic arthritis who received ixekizumab, relative to patients who received placebo, achieved statistically significantly greater improvements on the MCS (5.2 vs. 0.8) and PCS (5.4 vs. -1.1) subscales (both outcomes, p<0.001).

Patients with Previous Biologic Therapy Exposure

We identified seven studies that evaluated outcomes in patients who were and were not previously exposed to biologic therapy.[61,89,95-99] Subgroup analyses from four RCTs were primarily reported in the grey literature, though we found two peer-reviewed publications:one a key clinical trial of apremilast (ESTEEM 2) and one Phase II study on brodalumab. No head-to-head data were available. Across placebo-controlled studies, a statistically significantly greater proportion of patients achieved a PASI 75 reponse with the intervention for patients with and without prior biologic therapy. Rates between groups were numerically similar, but not compared statistically, and other outcomes (PASI 50, 90, and sPGA score of 0/1) followed the same trend where reported).

Table 10. Proportion of patients reaching PASI 75 in the bio-exposed and bio-naïve groups

Drug	Exposed (%)	Naïve (%)
Apremilast	22.8	31.9
Placebo	4.5	6.5
***p-value*[61]**	*=0.0069*	*<0.001*

Brodalumab	88	79
Placebo	0	0
***p-value*[95]**	*<0.001*	*<0.001*
Ixekizumab	89.5	88.4
Placebo	2.7	5.2
***p-value*[96]**	*<0.001*	*<0.001*
Secukinumab	75.7	84.0
Placebo	4.1	4.6
***p-value*[97]**	*<0.0001*	*<0.0001*

In addition to the above-described analyses from RCTs, we identified three observational studies. One small database study (DERMBIO) evaluated efficacy outcomes associated with subgroups of Danish patients (n=179, 51.4% male, age 43.4 years, mean PASI 10.9) taking ustekinumab who were and were not previously exposed to anti-TNFs, or who failed previous anti-TNF therapy.[98] There were no statistical differences in PASI 75 response for patients taking one, two, or three prior anti-TNFs. Although patients who had previously been exposed to anti-TNFs achieved PASI 75 response 20 days sooner than those patients who were anti-TNF-naïve, the difference was also not statistically significant. Data for each subgroup were not reported in the publication, though 80% of all patients overall achieved PASI 75 at the end of the study period.[98]

Another study from the same database evaluated the three anti-TNFs and ustekinumab and found that patients (n=1,867, mean age 45.1, 64.5% male, mean PASI 12.8) taking adaliumumab (OR: 1.8, 95% CI 1.4-2.3), etanercept (OR: 2.6, 95% CI 0-3.3), or infliximab (OR: 1.990, 95% CI 1.5-2.6) were statistically significantly more likely to terminate treatment than those on ustekinumab after adjusting for sex and previous biologic treatment at baseline (all outcomes, p<0.0001).[99] The authors note, however, all patients who were previously exposed to biologic therapy had a higher probability of treatment discontinuation (primarily due to loss of efficacy) across all agents (OR: 1.24, 95% CI 1.05-1.46, p=0.011).[99]

The final observational study was a large database study (PSOLAR) comparing rates of serious infections among patients (n=11,466, 55.4% male, age 48.4 years, mean psoriasis diagnosis 17.6 years) taking anti-TNFs or ustekinumab.[89] The investigators evaluated the rate of serious infections

across patients taking adalimumab, etanercept, infliximab, and ustekinumab and found that infliximab and adalimumab has the highest rates of infections (2.49 per 100 P-Y and 1.97 per 100 P-Y) while etanercept and ustekinumab had the lowest (1.47 per 100 P-Y and 0.83 per 100 P-Y). When divided into subgroups of patients who were biologic-exposed and biologic-naïve across agents, incidence rates were 1.35 per 100 P-Y and 1.12 per 100 P-Y, respectively; the trend was similar to the overall rates when evaluated according to drug but were not compared statistically across agents.[89]

Asian Studies

We identified six placebo-controlled RCTs that were conducted in Asia, including a subanalysis of the Japanese portion of the ERASURE study. No head-to-head Asian studies were available.[38,100-104] Three distinct trials of ustekinumab included patients in Japan,[101] China (LOTUS),[38] and Taiwan and Korea (PEARL) patients,[103] while the subgroup analysis for the secukinumab trial[102] included Japanese patients, and the trial for infliximab[104] included Chinese patients. We did not identify any trials conducted in Asia for ixekizumab, apremilast, or brodalumab.

As in multinational studies, all studies demonstrated statistically significant differences on all PASI measures (where reported) for each therapy compared to placebo; these results are presented in the table below. The proportion of patients achieving a PASI 75 response across RCTs of adalimumab (71-80%), infliximab (76-80%), secukinumab (76-91%), and ustekinumab 45mg (67-68%) and 90mg (66-76%) did not demonstrate any identifiable differences. Other commonly reported outcomes included improvements on the DLQI and the proportion of patients achieving a PGA or IGA score of 0/1, which were consistent with PASI score improvement. One of the studies evaluating ustekinumab also measured SF-36, and was the only trial that met our inclusion criteria to include PDI outcomes; these results are available in the summary evidence tables in Appendix B.[101]

Table 11. Proportion of patients Achieving PASI Scores across Asian Studies

Study	Study group	PASI 50	p-value	PASI 75	p-value	PASI 90	p-value	PASI 100	p-value
Asahina, 2010	Adalimumab	81	<0.001	63	<0.001	40	<0.001	NR	NR
	Placebo	20		4		0		NR	
Igarashi, 2012	Ustekinumab 45mg	83	<0.001	59	<0.001	33	<0.001	NR	NR
	Ustekinumab 90mg	84		68		44		NR	
	Placebo	13		7		3		NR	
Tsai, 2011	Ustekinumab 45mg	84	<0.001	67	<0.001	49	<0.001	8	=0.024

	Placebo	13		5		2		0	
Zhu, 2013	Ustekinumab 45mg	91	<0.001	83	<0.001	67	<0.001	24	<0.001
	Placebo	20		11		3		1	
Yang, 2012	Infliximab	94	<0.001	81	<0.001	57	<0.001	NR	NR
	Placebo	13		2		0		NR	
Ohtsuki, 2014	Secukinumab	NR	NR	83	<0.0001	62	<0.0001	28	<0.01
	Placebo	NR		7		0		0	

*NA=not available; NR=not reported

Across the ustekinumab trials, the mean absolute difference in improvement on the DLQI ranged from -7.4 to -10.7, with all studies reporting outcomes that were statistically significantly better than placebo (p<0.001).[38,101,103] Adalimumab also demonstrated a statistically significant improvement (-6.1, p<0.001),[100] as did infliximab (-6.6, p<0.001).[104] Rather than mean DLQI change, Ohtsuki and colleagues only reported the proportion of patients with a DLQI score of 0 or 1 which was statistically significant in favor of secukinumab in the ERASURE study (71.4% vs. 24.1% for placebo, p<0.001).[102]

The absolute mean proportion of patients achieving a score of 0 or 1 on the PGA across the placebo-controlled studies that reported PGSAwas 48% to 64% higher with ustekinumab, 51.8% higher with apremilast, 81.4% higher with infliximab (all p<0.001). The subgroup analysis of the ERASURE trial was the only study to report outcomes based on the modified IGA measure and found that statistically significantly more patients were responders (a score of 0/1) in the secukinumab group compared to those receiving placebo (55.2% vs. 3.4%, p<0.0001).[102]

Two studies conducted in Japan, one of ustekinumab[101] and one of adalimumab,[100] reported SF-36 outcomes. For ustekinumab, both doses were statistically significantly better than placebo on the PCS of the SF-36 (7.8/5.1 vs. -0.95, p=0.0033 and p=0.0164 for 45mg and 90mg of ustekinumab, respectively). There were no significant differences for the MCS. For adalimumab compared to placebo, there were significant improvements in the PCS (4.6 vs. -0.4; p < 0.01) and MCS (2.4 vs. -2.6; p < 0.05).

The Ohtuski study also reported outcomes for patients with and without prior exposure to biologic therapy. Patients who were biologic-exposed in the secukinumab group had a statistically significantly greater proportion of patients achieving PASI 75 (83.3%) and PASI 90 (50.0%) than the placebo group (0%), with a similar trend in the biologic-naïve secukinumab patients (82.6% and 65.2% vs. 8.7% and 0% for PASI 75 and PASI 90, respectively). The groups were not compared statistically, however.

The most common treatment-related adverse events consistent with those reported in the main trials for the agents of interest, and no new safety concerns arose for any of the agents in this population.

Controversies and Uncertainties

Across the 28 Phase III RCTs identified for this review, only eight included head-to-head comparisons for the drugs of interest. The network meta-analysis extendend comparisons to those between all agents, but is based on indirect comparisons. Our results are largely consistent with the comparative data, other meta-analyses, and other network meta-analyses. Although PASI 75 was reported as the primary endpoint in all studies, all other clinical outcomes, including PASI 50, 90, 100 and PGA/IGA, were inconsistently reported across trials, many cross-drug comparisons difficult. Longer-term data on both drug effectiveness and harms were also variable; many studies reassigned patients to different groups (mostly cross-over to the intervention) and evaluated outcomes at different time periods. Observational data was only available for ustekinumab and the anti-TNFs, which limited our understanding of real-world effectiveness and durability for many of these therapies.

Assessments of real-world effectiveness also are limited by lack of comparative data on non-standard dosing, whether increased (to preserve effectiveness) or decreased (to reduce costs). Treatment durability and cost are both important factors in choosing a treatment for psoriasis. This uncertainty hinders our understanding of the relative effectiveness of these agents. We also did not identify any studies evaluating the potential association between early aggressive treatment and cardiovascular risk.

There are also concerns with the reporting of patient-centered outcomes. DLQI was evaluated in 17 of the 28 clinical trials, not all trials used the same standard of measurement, and other scales were not uniformly employed. Additionally, many of the tools developed to measure outcomes were not developed with patients in mind, and psoriasis-specific instruments are limited.

Finally, subgroup data were primarily reported in conference abstracts and the interventions were only compared statistically to placebo, thereby limiting our understanding of how outcomes may differ across population types.

Summary

ICER evidence ratings for the comparisons of interest are provided in Table 12; ratings are presented for the targeted immunomodulator listed in each row relative to the comparator listed in each column. Note that comparsions to placebo are not included in the table. As described previously, findings from placebo-controlled trials indicated substantial improvements in clinical

measures for all agents, so these would all receive a letter grade of "A" (i.e., high certainty of substantial net health benefit) relative to placebo.

The presence of some direct comparisons allowed us to be reasonably confident about the relative net health benefit for some between-agent comparisons. However, because of the lack of many head-to-head comparisons, we relied on a network meta-analysis to estimate the comparative clinical effectiveness between many targeted immunomodulators (see Appendix G). Ratings based on a combination of direct and indirect evidence are highlighted in green in the table along with the number of head-to-head studies that informed the rating. There were two head-to-head trials comparing ixekizumab and etanercept, both of which showed substantial improvement in the percentage of patients achieving various PASI thresholds, and a similar magnitude of benefit when indirect evidence was included. We felt that the consistency of results across the two trials represented high certainty of a substantial net benefit for ixekizumab ("A") and an inferior net health benefit ("D") for etanercept in this comparison. Similarly, findings from two trials comparing brodalumab to ustekinumab showed consistent benefit for brodalumab, albeit at an incremental level (ratings of "B" and "D" for brodalumab and ustekinumab respectively).

The remaining comparisons were based on single head-to-head trials, making certainty in our estimates only moderate. Comparisons of ustekinumab and secukinumab showed clinical improvement over etanercept that was supported by indirect comparison, yielding a rating of "B+" (incremental or better). Etanercept was rated an "I" for both comparisons, given moderate certainty that net health benefit is either comparable or inferior. Findings from a single trial of secukinumab vs. ustekinumab showed improved clinical outcomes at all PASI thresholds for secukinumab, but inclusion of indirect evidence yielded a nonsignificant difference in treatment effect. As such, we rated the evidence "C+" (comparable or better) for secukinumab and "I" for ustekinumab in this comparison. Finally, a single, unpublished comparison of etanercept to apremilast showed no statistically-significant difference in the proportion of patients achieving PASI 75, although the etanercept dose used was lower than in product labeling. While addition of indirect evidence suggests an incremental benefit for etanercept, we feel that indirect findings can only confirm or downgrade certainty in evidence ratings. As such, we judge the evidence to be insufficient (I*) to distinguish between etanercept and apremilast, and given that both agents are consistently ranked together in our network meta-analyses, consider them functionally equivalent for all other comparisons.

Table 12. ICER evidence ratings for available head-to-head comparisons

	Adalimumab	Apremilast	Brodalumab	Etanercept	Infliximab	Ixekizumab	Secukinumab 300	Ustekinumab 45/90
Adalimumab	-	C+	I	C+	I	I	I*	I*
Apremilast	I	-	D	I* (1)	I	I	I	I
Brodalumab	C+	B	-	B	I*	I*	I*	B (2)
Etanercept	I	I* (1)	D	-	I	D (2)	I (1)	I (1)
Infliximab	C+	B+	I*	B+	-	I*	I*	C+
Ixekizumab	C+	B+	I*	A (2)	I*	-	C+	C+
Secukinumab 300	I*	B+	I*	B+ (1)	I*	I	-	C+ (1)
Ustekinumab 45/90	I*	B+	D (2)	B+ (1)	I	I	I (1)	-

Table key: green=direct + indirect evidence; blue=indirect evidence only

Number of head-to-head studies in parentheses

I*: insufficient evidence on comparative net health benefit; I: moderate certainty that net health benefit is comparable or inferior

Ratings based on indirect evidence alone are highlighted in blue in the table. In one instance, certainty in the ratings remained high due to a "second-order" effect. Specifically, because we have high certainty that brodalumab provides an incremental net health benefit over ustekinumab, and moderate certainty that ustekinumab provides an incremental or better benefit over etanercept, we conclude that there is high certainty that brodalumab would also provide an incremental benefit over etanercept or apremilast (its functional equivalent). For all other ratings, results of the network meta-analyses represented the only guide with which to judge the evidence. Drugs with evidence of net health benefit were judged B+ or C+ based on the observed magnitude of benefit, and their comparators received an I rating (moderate certainty of comparable or inferior net health benefit).In situations where the credible interval (the Bayesian equivalent of the confidence interval) crossed 1.0, the evidence was rated I* (insufficient) for both directions of the comparison.

5. Other Benefits or Disadvantages

Our reviews seek to provide information on other benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples include but are not limited to:

1. Methods of administration that improve or diminish patient acceptability and adherence
2. A public health benefit, e.g., reducing new infections
3. Treatment outcomes that reduce disparities across various patient groups
4. More rapid return to work or other positive effects on productivity (if not considered a benefit as part of comparative clinical effectiveness)
5. New mechanisms of action for treatments of clinical conditions for which the response to currently available treatments varies significantly among patients for unknown reasons (substantial heterogeneity of treatment effect)

Beyond the effectiveness and safety of targeted immunomodulators described in the Comparative Clinical Effectiveness section, method of administration and rapidity of effect may be important considerations. Regarding method of administration, all of the targeted immunomodulators are given subcutaneously except for infliximab (intravenous) and apremilast (oral). For patients who require rapid clearing of moderate-to-severe plaque psoriasis, cyclosporine, an older systemic agent, not a focus of this review, and infliximab appear to be superior to other treatments.

6. Comparative Value

6.1 Overview

The aim of this analysis was to estimate the cost-effectiveness of treatments for patients with moderate to severe plaque psoriasis who have failed topical treatment and phototherapy. To conduct the cost-effectiveness analysis, we developed a simulation model to assess the clinical and economic outcomes of the treatments of interest. Model parameters were estimated from the network meta-analyses described earlier in this report and the published literature. The outcomes of the model include total costs, quality-adjusted life years (QALYs), life years (LYs), and incremental cost-effectiveness ratios. Uncertainty in the data inputs and assumptions were evaluated using sensitivity and scenario analyses.

6.2 Cost-Effectiveness Model: Methods

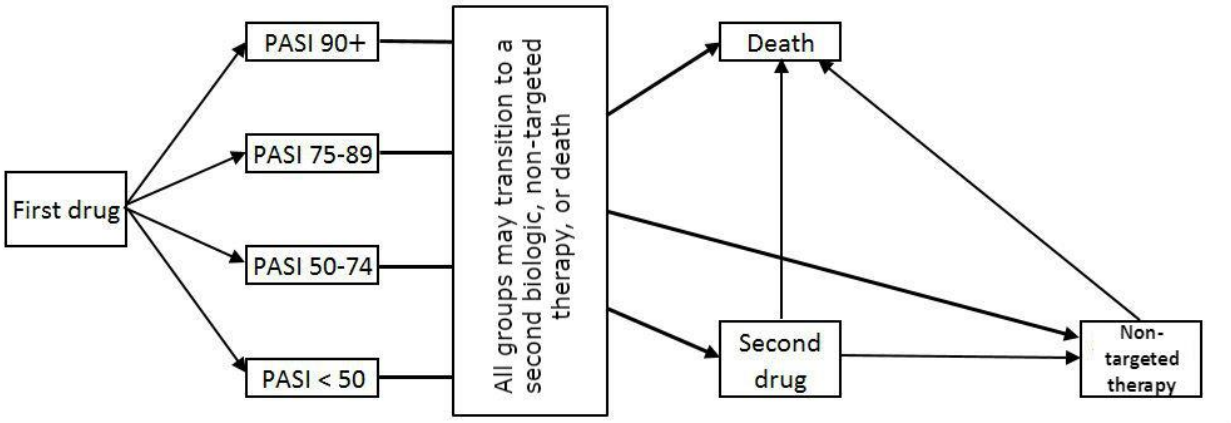
Cost-Effectiveness Model: Methods

Model Structure

We developed a Markov model with eight health states, as shown in Figure 5; patients could transition between states every month. After the initiation period of the first-line targeted therapy, defined as the point in time at which the primary trial outcome was measured, typically 12-16 weeks, patients were categorized into one of four health states: PASI 90 and higher, PASI 75-89, PASI 50-74, and PASI <50. Although no transition between PASI improvement states was allowed in the model, decreased treatment response and drug discontinuation over time could occur.

Patients with response below 75% improvement after the initiation period (16 weeks for adalimumab and apremilast, 12 weeks for all other drugs) were assumed to discontinue the first-line therapy. A proportion of these patients then begin second-line targeted therapy and the remainder received non-targeted therapy (i.e., topical therapy, other systemic therapy, and phototherapy). Second-line therapy was defined as an average of all available targeted therapies.

Figure 5: Markov model of psoriasis treatment and response



Patients with a PASI improvement of at least 75% after the initiation periods continued on first-line therapy, but could discontinue therapy over time and transition to either second line targeted therapy or non-targeted therapy.

All health states were assumed to have an equal hazard of death, which the model treats as a function of age alone (i.e., no increased mortality from the psoriasis disease state or treatment). The health state utilities (quality of life) were based on percent improvement in PASI score for the four response strata: 90-100, 75-89, 50-74, and less than 50. These utilities are the same across therapies in the base case.

The time horizon for the base case analysis was 10 years, to facilitate comparison with previous analyses, and to provide greater focus on effects of first line vs. second line treatment.

Target Population

The population of focus for this review was adult patients with moderate to severe plaque psoriasis who failed topical treatment and phototherapy. Consistent with the patient populations in the key clinical trials, the mean age of patients in the base case is 45 years and mean weight is 90 kg.

Treatment Strategies

The interventions included for review are those assessed in the evidence review and NMA; their administration schedules are listed in Appendix F. Each of these therapies includes an initiation period. Regimens are based on labeled dosing recommendations for all currently marketed drugs;[18,105-109] dosing for brodalumab is based on the approach used in the key clinical trials.[110]

Modeling Overview

Model type and structure

Key model choices and assumptions

The model used a health system perspective and all future costs, QALYs and LYs were discounted at 3% per year. The model was informed by a number of assumptions, which are represented in Table 13 along with the rationale for each assumption.

Table 13. Key model assumptions

Assumption	Rationale
A patient cannot transition between effectiveness (PASI improvement) levels.	Drug response does not show significant improvement past the trial period; discontinuation rate accounts for decline in effectiveness over time.
Probability of discontinuing first-line therapy is drug specific	Empirical evidence indicates discontinuation rates beyond the initiation period differ across drugs, and differs in year 1 vs. years 2+
Probability of discontinuing newer drugs (secukinumab, ixekizumab, and brodalumab) is the same as ustekinumab	There are limited to non-existent data on discontinuation rates for the newer agents. This assumption was evaluated in a sensitivity analyses.
Half of patients discontinuing first line targeted drug therapy receive second line targeted drug and remainder receive non-targeted drug.	There are limited data on proportion of patients receiving second line targeted treatment, particulary in current treatment paradigm with newer agents. This assumption was evaluated in sensitivity analyses.
Second line targeted therapy was assumed to be an average of all available targeted agents	There are no RCTs of second line targeted therapy and limited data on second line targeted therapy response in general.
Risk of death is based on age alone.	Evidence suggesting that treatment of psoriasis improves survival is very weak.
Patients remain on first-line therapy during the trial period.	A full trial period (16 weeks for adalimumab and apremilast, 12 weeks for all others) is needed to determine whether the drug will produce an adequate response.
Subcutaneous drugs are administered in-clinic during the initiation period and by the patient themselves during the maintenance period.	Balance between assuming SQ drugs are always self-administered vs. always administered in clinic.

Economic inputs

Costs

Monthly costs included those of drug acquisition, administration, clinic visits, and labs for all surviving patients. Costs for adverse events were not included in the base case analysis but were explored in a sensitivity analysis.

Drug acquisition costs

For each cycle of the model, surviving patients are assumed to receive one of the included drug therapies. Therefore, if patients discontinued first-line targeted therapy and was still alive, they would incur costs for either a second-line targeted therapy or for non-targeted therapy. Wholesale acquisition cost (WAC) was used for the unit cost of each drug.[111]

Table 14: Drug acquisition costs

Treatment	Unit cost	Cost of initiation period	Monthly cost of maintenance	Source
adalimumab (per 40mg)	$2,048.54	$8,194 (1 mo.)	$4,097	WAC
apremilast (per 30mg)	$43.11	$2,457 (1 mo.)	$2,629	WAC
brodalumab* (per 210mg)	[$4,084.11]	[$24,504] (2 mo.)	[$4,084]	Assumed average of ixekizumab and secukinumab
etanercept (per 50mg)	$1,024.44	$24,581 (3 mo.)	$4,097	WAC
infliximab (per 5mg/kg)	$53.57	$16,072 (2 mo.)	$2,143	WAC
ixekizumab (per 80mg)	$4,103.65	$32,829 (3 mo.)	$4,104	WAC
secukinumab (per 300mg)	$4,064.57	$16,258 (1 mo.)	$4,065	WAC
ustekinumab (per 70% 45mg/30% 90mg))	$8,840.22	$22,984 (1 mo.)	$3,831	WAC
2nd line targeted drug (per cycle)	$3,264.68	$10,500**	$3,264.68	Average monthly cost of above drugs
non-targeted therapy (per cycle)	$990	n/a	$990	Yu, Curr Med Res Opin, 2009 (inflated to 2016 dollars)[112]

*assumed cost for draft report

**switching cost

Infliximab and ustekinumab are dosed based on body weight. We assumed that each infliximab administration used five 100 mg vials to account for incomplete vial usage (drug wastage). Based on data from the ustekinumab trials, we assumed that 30% of patients were greater than 100kg and therefore would receive a 90 mg rather than the standard 45 mg dose.

The cost of second-line targeted therapy was calculated as the average of of first line targeted therapies. A switching cost was assigned to the first month of second line therapy to reflect the additional cost of initiation above and beyond maintenance therapy, based on the average incremental cost across first line therapies.

The cost for non-targeted therapy was roughly estimated from a study by Yu et al.[112] Yu and colleagues analyzed medical care costs for patients with psoriasis using 2003 claims data and found that incremental adjusted total costs for patients with moderate to severe psoriasis vs. mild psoriasis were approximately $10,000 per year in 2016 US dollars. These costs include utilization of non-topical systemic therapies and phototherapy. Given the uncertainty in the costs of patients on non-targeted therapy (e.g., non-topical systemic treatment included two targeted therapies), the cost of non-targeted therapy was varied by +/- 50% in sensitivity analyses.

Although in clinical practice patients can experience dose changes in response to changes in effectiveness or adverse effects, we did not include dose decreases or increases because a recent study indicated that dose increases were as common as dose decreases, and the majority of dose increases were followed by dose decreases or drug discontinuation.[113] Treatment failures are captured in the model by transitions to second line targeted therapy or non-targeted therapy.

Administration costs

All targeted therapies in this comparison other than apremilast were injectable drugs. For subcutaneous drug therapies, we assumed that the injection was administered at a clinic during the initiation phase, but was self-administered by the patient during the maintenance phase. Cost per subcutaneous injection administration at a clinic, obtained from the Redbook (CPT code 96372), was $25.44.[111]

Infliximab, the only drug in the analysis that requires intravenous administration, is delivered over a two-hour infusion. Each administration was assumed to cost $164.54: $136.15 for the first hour (CPT code 96413) and $28.39 for the second hour (CPT code 96415). We also included the cost of one day lost from work ($193) to account for patient time cost related to IV administration. [114]

Monthly costs for administration of second-line therapy were estimated by averaging the monthly administration costs for all first-line drugs during their maintenance phases. Non-targeted therapy consisted mostly of topical treatments, which meant that there were no administration costs. Likewise, there were no administration costs for the only oral medication in the analysis, apremilast.[114]

Laboratory and clinic visit costs

Due to the interaction of the targeted therapies with the immune system, many psoriasis patients require monitoring for potential infection. Some also require testing of physiologic systems, such as hepatic function. The costs for each of the laboratory tests required by one or more targeted psoriasis therapies and the schedule of laboratory tests indicated for each drug are provided in Appendix F. When possible, the indicated laboratory tests were obtained from the drug's labeling; otherwise, they were gathered by examination of the therapeutic protocol in the pivotal trials.[114] In

addition to these laboratory tests, each patient was assumed to receive four physician visits per year related to the disease.

Productivity costs

Productivity cost offsets were derived from work productivity impact measures in RCTs of adalimumab and ixekizumab.[82,85] We estimated that patients achieving a PASI 75 improvement who were employed had a 15% improvement in total work productivity (primarily presenteeism vs. absenteeism). We also estimated that 60% of patients were employed full-time and 15% half-time based on baseline characteristics of study participants. We used an average 2015 US income of $48,320.[115] We assumed presenteeism improvements were valued equally to absenteeism improvements, and that presenteeism effects were not already captured by quality of life (EQ-5D) measurements.

The cost offset per year for a patient achieving a PASI 75 improvement was thus $4900. We estimated a $4400 productivity cost offset for 2L based on an estimated 10% lower effectiveness in second line.

Clinical Inputs

Utilities

Utilities for the base case scenario were obtained from an analysis of EQ-5D data in 3,231 patients enrolled in five RCTs evaluating secukinumab in moderate to severe psoriasis.[36] The EQ-5D is one of the most commonly used generic health status measurement, and has good validity and reliability in various health conditions, including psoriasis. The EQ-5D includes questions across five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D was measured alongside PASI in the secukinumab RCTs, and the relationship between PASI improvement and EQ-5D was evaluated to derive the estimates shown in Table 15.

These utilities were selected because they were derived from relatively recent clinical trials, were used in a NICE technology assessment of secukinumab, and are representative of utility scores derived from multiple previous studies.[36]

Table 15. Utility by health state

State	Utility	Source
PASI 90-100	0.906	NICE, secukinumab submission
PASI 75-89	0.868	NICE, secukinumab submission
PASI 50-74	0.835	NICE, secukinumab submission
PASI <50	0.751	NICE, secukinumab submission

Second-line therapy	0.846	Estimated
Non-targeted therapy	0.642	NICE, secukinumab submission

The utility of second-line therapy was calculated based on estimated second-line response across all available targeted therapies. We assumed second-line treatment had a 10% absolute lower probability of achieving PASI 75;[97,116,117] this was applied as a 5% decrease in PASI 90 and PASI 75-89, and a 5% increase in PASI <50 and PASI 50-74. We then calculated the utility for each drug and averaged across drugs.

Due to similar adverse event profiles between drugs and the absence of their utility evaluation in other cost-effectiveness analyses in psoriasis, we did not include any adverse event associated disutilities.

Clinical probabilities

Patient response to first-line targeted therapy was derived from the network meta-analysis (NMA) (see Appendix G).

Several recent studies provide drug-specific discontinuation rates. Discontinuation rates during the first year, after the initiation period, were derived from a study be Feldman et al., who conducted a retrospective analysis using claims data 2007-2012 of 4,309 psoriasis patients.[113] The majority of patients received etanercept or adalimumab, and a small number (N=195) received ustekinumab. Over the follow-up period 35%, 27%, and 16% of etanercept, adalimumab, and ustekinumab patients discontinued therapy. We assumed the discontinuation rate for infliximab was similar to etanercept and adalimumab (30%) and that secukinumab, ixekizumab, and brodalumab had the same rate as ustekinumab (16%).

Discontinuation rates after year one were estimated from a long term Danish cohort study (DERMBIO).[118] There were 1867 treatment series (adalimumab n = 774, etanercept n = 449, infliximab n = 253, ustekinumab n = 391) administered in 1277 patients for up to 10 years. Based on a multivariate Cox model, approximately 15% of adalimumab, etanercept, and infliximab patients discontinued treatment each year, while 5% of ustekinumab patients did. We assumed secukinumab, ixekizumab, and brodalumab were the same as ustekinumab. Based on the same study we estimated the discontinuation rate from second line therapy was 15% per year.

The impact of the cost of one serious adverse event, pneumonia, was included in sensitivity and scenario analyses to assess its relative importance. Pneumonia incidence was taken from the prescribing information of each drug that has already entered the market, and a meta-analysis of phase III trials for brodalumab.[113] Due to non-standard language, the figure for each drug reflected the incidence of 'pneumonia', 'serious infection', or 'serious respiratory infection.' In the case of

apremilast, no mention of serious infection was found in the prescribing information and so we assumed that it did not increase risk of pneumonia. Absolute rates, rather than placebo-adjusted rates, were used. A cost of $5,873 was used based on Medicare reimbursement rates.

Model validation

We used several approaches to validate the model. First, we provided information on the preliminary model approach, inputs, and results with the manufacturers of the targeted drugs. Feedback from these companies resulted in the identification of an error in drug cost, and revisions to the model including addition of drug-specific discontinuation rates, modification of average patient weight, and inclusion of a switching cost for second line targeted drug treatment. We also added scenario analyses to assess the patient-centered impacts of achieving PASI 100 and improvement in work productivity.

Second, we developed a simple 'back-of-the-envelope' model to assess one-year clinical and economic outcomes based on first line targeted therapy only. The results of the two models were similar after identification and correction of a drug administration cost error. Third, we compared our results with an independently developed (unpublished) model based on the York et al model framework. The results from these two models were similar. Lastly, we conducted various sensitivity and scenario analyses as described below to assess model behavior.

Sensitivity analyses

We conducted various sensitivity and scenario analyses to assess the impact of model input uncertainty and key assumptions:

1. We evaluated the impact of uncertainty in each model parameter using one-way sensitivity analyses in which the parameters were varied over plausible ranges. These analyses were conducted for key comparators that were most likely to be cost effective or most effective.
2. We assessed the impact of quality of life of PASI 100 on the results.
3. We evaluated the influence of a 20% drug rebate.

6.4 Cost-Effectiveness Model: Results

Base Case Results

Total costs, quality-adjusted life years, and life years for each therapy accrued over the 10-year time horizon of the model are shown in Table 16 below. Additionally, we show the incremental cost-effectiveness ratio for each of the targeted therapies compared to non-targeted therapy.

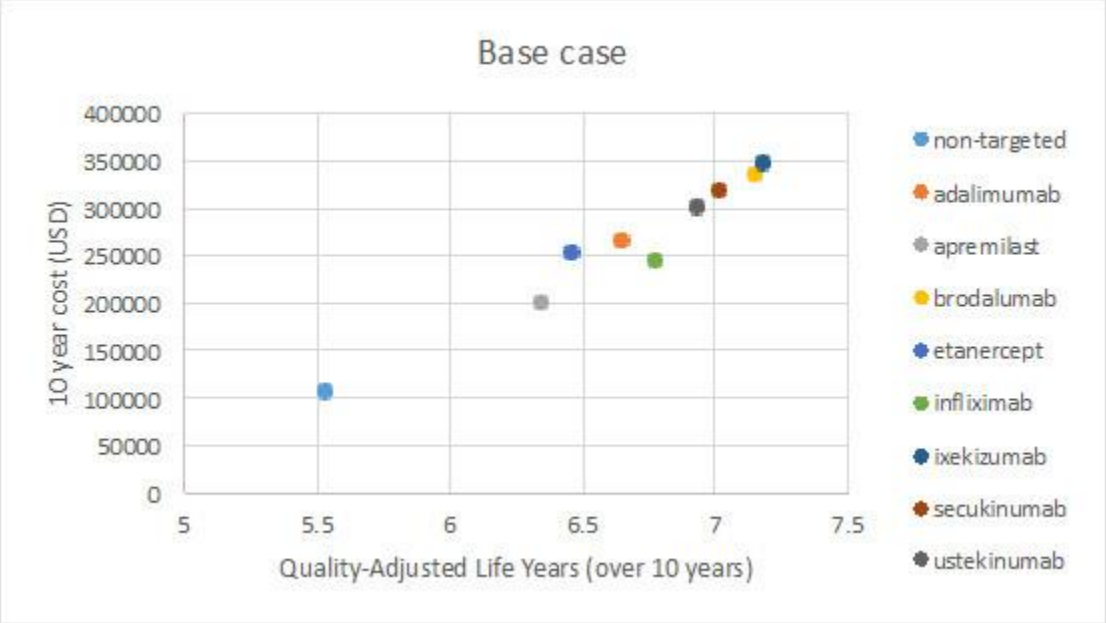
Table 16. Results for the base case

	Cost	QALYs	LYs	ICER vs non-target
non-targeted	$105,727	5.53	8.64	
adalimumab	$266,021	6.65	8.64	$143,367
apremilast	$199,553	6.35	8.64	$114,263
brodalumab	$336,222	7.15	8.64	$142,297
etanercept	$253,404	6.47	8.64	$157,723
infliximab	$243,320	6.78	8.64	$110,431
ixekizumab	$345,576	7.19	8.64	$144,874
secukinumab	$316,744	7.02	8.64	$141,885
ustekinumab	$301,327	6.93	8.64	$139,797

*results for brodalumab are tentative, as pricing is not available

The base-case results indicate that treatment with targeted drugs, over a 10-year time frame that includes drug discontinuation, leads to QALY improvements ranging from 0.8 (apremilast) to 1.7 (ixekizumab, brodalumab). Infliximab is the most cost effective drug because it provides moderate benefit and a relatively low cost. Although infliximab has good initial effectiveness, it also has a high discontinuation rate.

Figure 6: Cost-effectiveness plane for all comparators (base case)*



*results for brodalumab are tentative, as pricing is not available

The base-case results shown in the Table 16 are also graphed in the Figure 6. Drugs that are further to the right provide the greatest clinical benefit, and drugs higher on the y-axis are more expensive. Infliximab is the most cost-effective drug because it provides the greatest clinical benefit per dollar spent – that is, the slope between non-targeted therapy and infliximab is the lowest. Moving from infliximab to the four most effective agents (ustekinumab, secukinumab, brodalumab, and ixekizumab) is a steeper slope, and above the $150,000/QALY threshold. However, if these agents are compared to non-targeted therapy directly (ignoring infliximab), the slope for each is just below $150,000/QALY.

Sensitivity Analysis Results

The impacts of varying each of the parameters in the model over ranges reflecting their uncertainty are shown in the Figure 7. The cost of non-targeted therapy, the dosing during maintenance, and the cost of first and second-line targeted therapies were associated with the greatest uncertainty in the model. The incremental results for infliximab versus non-targeted therapy ranged from approximately $85,000000 to $128,000/QALY gained.

Figure 7. One-way sensitivity analysis: Infliximab versus non-targeted therapy

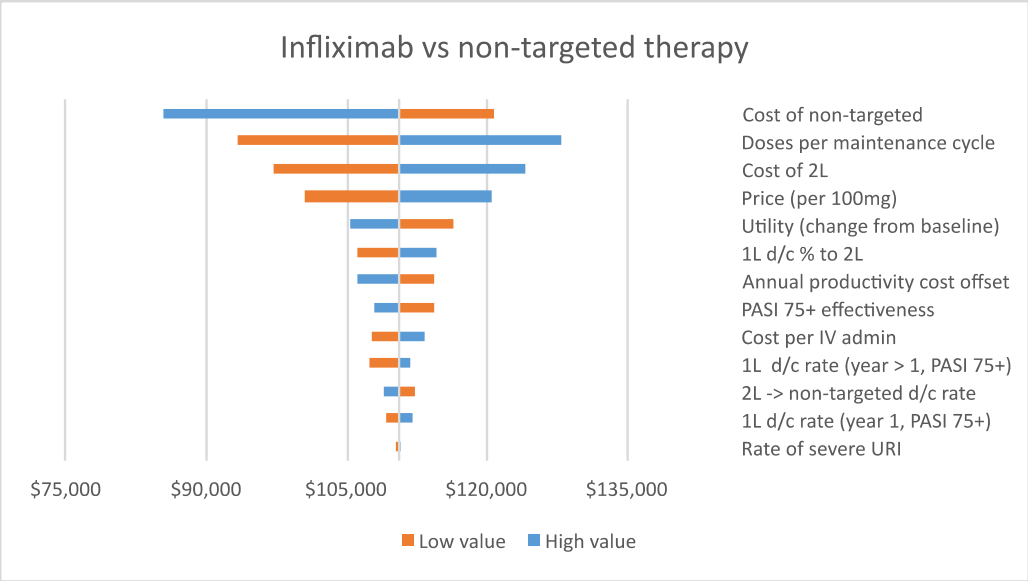
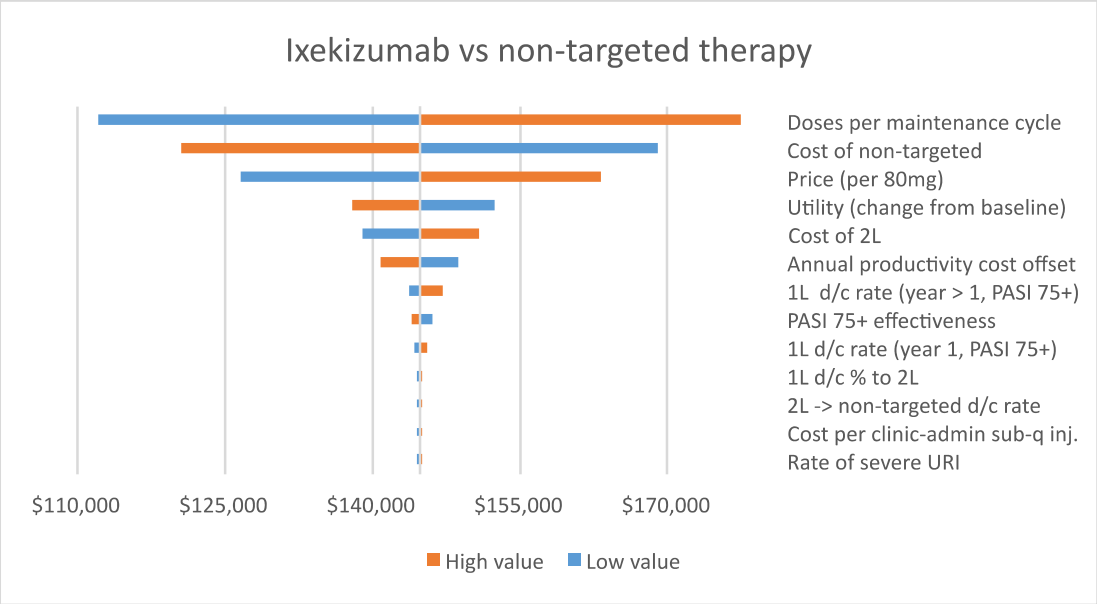


Figure 8 demonstrates the impact of varying these same parameters on the cost effectiveness of ixekizumab versus non-targeted therapy. The greatest uncertainty arises from the maintenance dosing, cost of non-targeted therapy, cost of first and second line drug therapy, and the utility (quality of life) benefit. The annual productivity cost offset was also a moderate factor. The

incremental cost-effectiveness ratio ranged from approximately $112,000 to $177,000/QALY gained.

Figure 8. One-way sensitivity analysis: Ixekizumab versus non-targeted therapy



Results when when PASI 100 is taken into account

Assessment of the impact of PASI 100 by stratifying the PASI 90+ group into PASI 90-99 and PASI 100 necessitated the use of utility estimates derived using a novel instrument based on the EQ-5D designed specifically for psoriasis (the EQ-PSO).[119] This instrument includes the domains of skin irritation and self confidence in addition to those of the EQ-5D. Validation of the novel instrument was somewhat challenging. Utilities derived from the ixekizumab clinical trials using the EQ-PSO indicated there is a benefit to achieving PASI 100 vs PASI 90-99, but also surprisingly suggested PASI 75-89 had better quality of life than PASI 90-99.[120] When we switched to using these utilities, the ratio for ixekizumab relative to non-targeted therapy, for example, increased to $227,740/QALY gained because the gains relative to baseline are smaller for this utility set. When we then used drug-specific utilities that accounted for the proportion of patients achieving PASI 100 (estimated for drugs without PASI 100 data), the incremental cost-effectiveness ratio for ixekizumab improved to $217,611/QALY gained. We conclude from this scenario analysis that 1) developing a novel utility instrument for psoriasis is challenging, as noted by the authors, and 2) the impact of achieving PASI 100 relative to PASI 90-99 is unlikely to meaningfully impact the overall economic value of psoriasis treatments.[120]

Table 17: Results when a 20% rebate on drug cost assumed

	Cost	QALYs	LYs	ICER vs non-target
non-targeted	$85,189	5.53100	8.64	
adalimumab	$209,133	6.64907	8.64	$110,856
apremilast	$156,977	6.35215	8.64	$87,424
brodalumab	$263,358	7.15082	8.64	$109,993
etanercept	$199,838	6.46731	8.64	$122,447
infliximab	$193,821	6.77697	8.64	$87,187
ixekizumab	$270,755	7.18657	8.64	$112,086
secukinumab	$248,241	7.01824	8.64	$109,634
ustekinumab	$236,245	6.93017	8.64	$107,961

***results for brodalumab are tentative, as pricing is not available**

Drug rebates for some of the drugs studied in this analysis have been reported in the press to be in the range of 20%. When the targeted drug costs were decreased by 20%, all targeted drugs were less than $150,000/QALY, and several approached or were below $100,000/QALY.[121]

6.5 Potential Budget Impact

We also used the cost-effectiveness model to estimate the potential total budgetary impact of the two novel treatments for psoriasis patients, based on assumed patterns of product uptake: ixekizumab (approved in March 2016) and brodalumab (not yet approved). We did not include the other therapies modeled above in this potential budget impact analysis, given their established presence on the market.

Potential Budget Impact Model: Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total incremental cost of using the new therapy rather than non-targeted therapy for the treated population, calculated as incremental health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time.

The potential budget impact analysis included the entire candidate population for treatment, which was considered to be adults with moderate to severe plaque psoriasis who are taking a biologic agent for psoriasis for the first time. To estimate the size of the potential candidate population for treatment with brodalumab or ixekizumab, we first determined the estimated incidence of psoriasis in the US. (We used incidence rather than prevalence because we were interested only in patients who were taking a biologic for the first time.) Psoriasis incidence in the United States has been estimated at 78.9 cases per 100,000 persons.[4] The proportion of psoriasis patients with plaque psoriasis has been estimated to be 79%.[4] Helmick found that 18.2% of psoriasis patients have moderate-to-severe disease, defined as involving greater than 3% of body surface area.[3] Applying these proportions to the projected 2016 U.S. population results in an estimate of approximately 36,750 incident cases of moderate-severe plaque psoriasis in the US per year, or approximately 183,750 incident cases over five years, assuming equal incidence rates for each of the five years in our analysis. This was assumed to be the candidate population for treatment with these novel agents.

ICER's methods for estimating potential budget impact and calculating value-based benchmark prices are described in detail elsewhere. Briefly, our calculations assume that the utilization of new drugs occurs without any payer, provider group, or pharmacy benefit management controls in place, to provide an estimate of "unmanaged" drug uptake by five years after launch.

In general, we examine six characteristics of the drug or device and the marketplace to estimate "unmanaged" uptake. These characteristics are listed below:

- Magnitude of improvement in clinical safety and/or effectiveness
- Patient-level burden of illness
- Patient preference (ease of administration)
- Proportion of eligible patients currently being treated
- Primary care versus specialty clinician prescribing/use
- Presence or emergence of competing treatments of equal or superior effectiveness

Based on our assessment of these criteria, we assign a new drug or device to one of four categories of unmanaged drug uptake patterns: 1) very high (75% uptake by year 5); 2) high (50% uptake by year 5); 3) intermediate (25% uptake by year 5); and 4) low (10% uptake by year 5). In this analysis, we assumed a 10% uptake pattern for ixekizumab and a 10% uptake for brodalumab in the eligible population. We assumed that uptake would be low for ixekizumab and brodalumab because they would be the second and third 1L-17 inhibitor therapies for psoriasis patients to enter what is considered "an increasingly saturated market."[122]

Using this approach to estimate potential budget impact, we then compared our estimates to a budget impact threshold that represents a potential trigger for policy mechanisms to improve

affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation, this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA each year, and the contribution of spending on retail and facility-based drugs to total health care spending. Calculations are performed as shown in Table 18.

For 2015-16, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage affordability is calculated to total approximately $904 million per year for new drugs.

Table 18. Calculation of Potential Budget Impact Threshold

Item	Parameter	Estimate	Source
1	Growth in US GDP, 2015-2016 (est.) +1%	3.75%	World Bank, 2015
2	Total health care spending ($)	$3.08 trillion	CMS NHE, 2014
3	Contribution of drug spending to total health care spending (%)	13.3%	CMS National Health Expenditures (NHE), Altarum Institute, 2014
4	Contribution of drug spending to total health care spending ($) (Row 2 x Row 3)	$410 billion	Calculation
5	Annual threshold for net health care cost growth for ALL new drugs (Row 1 x Row 4)	$15.4 billion	Calculation
6	Average annual number of new molecular entity approvals, 2013-2014	34	FDA, 2014
7	Annual threshold for average cost growth per individual new molecular entity (Row 5 ÷ Row 6)	$452 million	Calculation

8	Annual threshold for estimated potential budget impact for each individual new molecular entity (doubling of Row 7)	$904 million	Calculation

Potential Budget Impact Model: Results

Table 19 below presents the potential budget impact of one year and five years of brodalumab and ixekizumab in the candidate population, assuming the uptake patterns previously described. Results are presented for both one-year and five-year time horizons.

Results from the potential budget impact model showed that, with the uptake pattern assumptions mentioned above, an estimated 3,675 individuals would receive brodalumab in the first year, and an estimated 3,675 would receive ixekizumab in the first year. After one year of treatment with brodalumab, with net annual costs of approximately $50,500 per patient, one-year budget impact is estimated to be approximately $185.4 million. After one year of treatment with ixekizumab, net annual costs were estimated as approximately $55,200 per patient, and one-year budget impact as approximately $202.8 million.

Over the entire five-year time horizon, we estimate that "unmanaged" uptake would lead to approximately 18,375 persons taking brodalumab and 18,375 taking ixekizumab. Across the full five-year time horizon, the weighted potential budgetary impact (i.e., adjusted for differing periods of drug utilization and associated cost-offsets) is approximately $102,500 per patient taking brodalumab, and approximately $108,500 per patient taking ixekizumab. Total potential budgetary impact of brodalumab over five years is approximately $1.88 billion, with an average budget impact per year of approximately $376.7 million. For ixekizumab, total potential budgetary impact over five years is approximately $1.99 billion, with an average budget impact per year of approximately $398.7 million. The annualized potential budget impact of brodalumab is 42% of the budget impact threshold of $904 million for a new drug, while the annualized potential budget impact of ixekizumab is 44% of the threshold.

Table 19. Estimated Total Potential Budget Impact (BI) of Brodalumab and Ixekizumab for Treatment of Plaque Psoriasis

		Analytic Horizon = 1 Year			Analytic Horizon = 5 Years		
	Eligible Population	Number Treated	Annual BI per Patient*	Total BI (millions)	Number Treated	Weighted BI per Patient*	Average BI per year (millions)

Brodalumab	183,750	3,675	$50,500	$185.4	18,375	$102,500	$376.7
Ixekizumab	183,750	3,675	$55,200	$202.8	18,375	$108,500	$398.7

*Weighted budget impact calculated by subtracting cost offsets from drug costs for one-year horizon. For five-year horizon, drug costs and cost offsets apportioned assuming 20% of patients in uptake target initiate therapy each year. Those initiating in year 1 receive full drug costs and cost offsets, those initiating in year 2 receive 80% of drug costs and cost offsets, etc.

6.6 Draft Value-based Benchmark Prices

Value-based price benchmarks will be provided as part of the full Evidence Report.

6.7 Summary and Comments

We have attempted to both model psoriasis treatment accurately and accommodate the limits of available data. The latter necessity has placed some restrictions on how accurately we can model the course of psoriasis treatment. First, we would have preferred direct utility elicitation data from clinical trials. Instead, we have had to surmise quality of life from improvements in PASI score. We believe that this is not an invalid method, but the uncertainty that it introduces into the model is greater than would be seen in a model that included direct patient reports of utility.

Next, the course and effects of therapy sequencing is not clear. We have assumed that, after first-line therapy, half of patients take up a second-line targeted therapy while half de-escalate therapy and move to a non-targeted therapy. We have also assumed a 20% annual rate of transition from second-line therapy to non-targeted therapy, based on the rate of discontinuation of first-line therapy. While we weighted all first-line agents equally for purposes of estimating the costs and utility of second-line therapy, there is no doubt that some agents are preferred over others as second-line treatment. However, there are limited data to understand second-line therapy choice, so we have explored the effect of our assumptions on the results in scenario analyses.

The uncertainty around course of therapy extends to the pattern of drug dose escalation and holidays. While we know that real world drug dosing varies from clinical trials, available data on the relationship between dose changes and effectiveness are extremely limited. We have therefore built our model without the possibility of drug holidays as a conservative assumption which reports on the maximum number of doses possible under the labeled regimen. To balance this somewhat, we have not included any dose escalation—another known phenomenon that both contradicts labeled dosing recommendations and which is poorly characterized in the scientific literature.

There are three main findings of our analyses. First, infliximab appears to be the most cost-effective targeted agent for psoriasis treatment, despite the necessity for intravenous administration. This result is robust to several scenario analyses that explored the uncertainty in the model. Second, targeted agents other than infliximab do not represent good economic value unless drug rebates and work productivity impacts are assessed, in which case they are moderately cost effective. Third, differentiating which targeted agent should be used first-line is highly dependent on the rate of second-line targeted drug use. Under assumptions of moderate second-line targeted drug use, agents with the highest PASI improvement provide the greatest benefit (QALYs) atsimilar cost effectiveness to less effective agents. If second-line targeted drug use is high, our findings suggest the main means of discriminatiosn among agents should be price.

References

1. *World Health Organization. Global Report on Psoriasis.* 2016.
2. Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the United States. *J Am Acad Dermatol.* 2014;70(3):512-516.
3. Helmick CG, Lee-Han H, Hirsch SC, Baird TL, Bartlett CL. Prevalence of psoriasis among adults in the U.S.: 2003-2006 and 2009-2010 National Health and Nutrition Examination Surveys. *Am J Prev Med.* 2014;47(1):37-45.
4. Icen M, Crowson CS, McEvoy MT, Dann FJ, Gabriel SE, Maradit Kremers H. Trends in incidence of adult-onset psoriasis over three decades: a population-based study. *J Am Acad Dermatol.* 2009;60(3):394-401.
5. Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol.* 2008;58(5):826-850.
6. Gottlieb A, Korman NJ, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 2. Psoriatic arthritis: overview and guidelines of care for treatment with an emphasis on the biologics. *J Am Acad Dermatol.* 2008;58(5):851-864.
7. Boehncke WH, Schon MP. Psoriasis. *Lancet.* 2015;386(9997):983-994.
8. Ibrahim G, Waxman R, Helliwell PS. The prevalence of psoriatic arthritis in people with psoriasis. *Arthritis Rheum.* 2009;61(10):1373-1378.
9. Mease P. Non-anti-TNF biologics in PSA. *Annals of the Rheumatic Disease.* 2013;71.
10. Lee YW, Park EJ, Kwon IH, Kim KH, Kim KJ. Impact of Psoriasis on Quality of Life: Relationship between Clinical Response to Therapy and Change in Health-related Quality of Life. *Ann Dermatol.* 2010;22(4):389-396.
11. Lebwohl MG, Bachelez H, Barker J, et al. Patient perspectives in the management of psoriasis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey. *J Am Acad Dermatol.* 2014;70(5):871-881 e871-830.
12. Rapp SR, Feldman SR, Exum ML, Fleischer AB, Jr., Reboussin DM. Psoriasis causes as much disability as other major medical diseases. *J Am Acad Dermatol.* 1999;41(3 Pt 1):401-407.
13. Abuabara K, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Cause-specific mortality in patients with severe psoriasis: a population-based cohort study in the U.K. *The British journal of dermatology.* 2010;163(3):586-592.
14. Paek SY, Thompson JM, Qureshi AA, Merola JF, Husni ME. Comprehensive Assessment of the Psoriasis Patient (CAPP): A Report from the GRAPPA 2015 Annual Meeting. *J Rheumatol.* 2016;43(5):961-964.
15. Mrowietz U, Kragballe K, Reich K, et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. *Arch Dermatol Res.* 2011;303(1):1-10.
16. Nast A, Jacobs A, Rosumeck S, Werner RN. Efficacy and Safety of Systemic Long-Term Treatments for Moderate-to-Severe Psoriasis: A Systematic Review and Meta-Analysis. *J Invest Dermatol.* 2015;135(11):2641-2648.
17. Chen Y, Liu Y, Huang Y, et al. Immune activating effects of stimulation of TLR agonists and cytokines on keratinocytes from a patient with a CARD14 mediated pustular psoriasis (P6283). *J Immunol.* 2013;190(1).

18. Gottlieb AB, Kalb RE, Langley RG, et al. Safety observations in 12095 patients with psoriasis enrolled in an international registry (PSOLAR): experience with infliximab and other systemic and biologic therapies. *J Drugs Dermatol.* 2014;13(12):1441-1448.
19. Papp KA, Griffiths CE, Gordon K, et al. Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. *Br J Dermatol.* 2013;168(4):844-854.
20. Feldman SR, Tencer T, Clancy Z, Zhang F. Cost per responder of apremilast versus etanercept, adalimumab, and ustekinumab in patients with moderate to severe psoriasis. *Journal of the American Academy of Dermatology.* 2015;72(5):AB229.
21. Mehren CR, Gniadecki R. Dose-creep of Infliximab during psoriasis treatment: an observational study. *Acta Derm Venereol.* 2012;92(4):355-357.
22. Griffiths C, Thac¸i D, Gerdes S, et al. GP2015, a proposed etanercept biosimilar, has equivalency, safety and immunogenicity to etanercept originator product in patients with chronic plaque-type psoriasis: 12 week results from the phase 3 EGALITY study. *5th Congress of the Psoriasis International Network.*P222.
23. Armstrong AW, Robertson AD, Wu J, Schupp C, Lebwohl MG. Undertreatment, treatment trends, and treatment dissatisfaction among patients with psoriasis and psoriatic arthritis in the United States: findings from the National Psoriasis Foundation surveys, 2003-2011. *JAMA Dermatol.* 2013;149(10):1180-1185.
24. Sampogna F, Chren MM, Melchi CF, et al. Age, gender, quality of life and psychological distress in patients hospitalized with psoriasis. *The British journal of dermatology.* 2006;154(2):325-331.
25. Finlay AY, Kelly SE. Psoriasis--an index of disability. *Clin Exp Dermatol.* 1987;12(1):8-11.
26. Lerner D, Amick BC, 3rd, Rogers WH, Malspeis S, Bungay K, Cynn D. The Work Limitations Questionnaire. *Med Care.* 2001;39(1):72-85.
27. Hsu S, Papp KA, Lebwohl MG, et al. Consensus guidelines for the management of plaque psoriasis. *Arch Dermatol.* 2012;148(1):95-102.
28. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med.* 1997;126(5):376-380.
29. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *International journal of surgery (London, England).* 2010;8(5):336-341.
30. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Medical care.* 2010;48(6 Suppl):S145-152.
31. Gomez-Garcia F, Epstein D, Isla-Tejera B, Lorente A, Velez Garcia-Nieto A, Ruano J. Short-term efficacy and safety of new biologic agents targeting IL-23/Th17 pathway for moderate to severe plaque psoriasis: a systematic review and network meta-analysis. *The British journal of dermatology.* 2016.
32. Lin VW, Ringold S, Devine EB. Comparison of Ustekinumab With Other Biological Agents for the Treatment of Moderate to Severe Plaque Psoriasis: A Bayesian Network Meta-analysis. *Arch Dermatol.* 2012;148(12):1403-1410.
33. Reich K, Burden AD, Eaton JN, Hawkins NS. Efficacy of biologics in the treatment of moderate to severe psoriasis: a network meta-analysis of randomized controlled trials. *The British journal of dermatology.* 2012;166(1):179-188.

34. Signorovitch JE, Betts KA, Yan YS, et al. Comparative efficacy of biological treatments for moderate-to-severe psoriasis: a network meta-analysis adjusting for cross-trial differences in reference arm response. *The British journal of dermatology.* 2015;172(2):504-512.
35. Zweegers J, Otero ME, van den Reek JM, et al. Effectiveness of Biologic and Conventional Systemic Therapies in Adults with Chronic Plaque Psoriasis in Daily Practice: A Systematic Review. *Acta Derm Venereol.* 2016;96(4):453-458.
36. National Institute for Health and Care Excellence. Single Technology Appraisal: Secukinumab for the treatment of moderate to severe plaque psoriasis. *Manufacturer Submission of Evidence.* December 2014.
37. U.S. Preventive Services Task Force. *Procedure Manual.* Agency for Healthcare Research and Quality;2008.
38. Zhu X, Zheng M, Song M, et al. Efficacy and safety of ustekinumab in Chinese patients with moderate to severe plaque-type psoriasis: results from a phase 3 clinical trial (LOTUS). *J Drugs Dermatol.* 2013;12(2):166-174.
39. Saurat JH, Stingl G, Dubertret L, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *The British journal of dermatology.* 2008;158(3):558-566.
40. Menter A, Tyring SK, Gordon K, et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. *J Am Acad Dermatol.* 2008;58(1):106-115.
41. Papp KA, Tyring S, Lahfa M, et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *The British journal of dermatology.* 2005;152(6):1304-1312.
42. Leonardi CL, Powers JL, Matheson RT, et al. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med.* 2003;349(21):2014-2022.
43. Tyring S, Gottlieb A, Papp K, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet.* 2006;367(9504):29-35.
44. Bagel J, Lynde C, Tyring S, Kricorian G, Shi Y, Klekotka P. Moderate to severe plaque psoriasis with scalp involvement: a randomized, double-blind, placebo-controlled study of etanercept. *J Am Acad Dermatol.* 2012;67(1):86-92.
45. Gottlieb AB, Leonardi C, Kerdel F, Mehlis S, Olds M, Williams DA. Efficacy and safety of briakinumab vs. etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. *The British journal of dermatology.* 2011;165(3):652-660.
46. Strober BE, Crowley JJ, Yamauchi PS, Olds M, Williams DA. Efficacy and safety results from a phase III, randomized controlled trial comparing the safety and efficacy of briakinumab with etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. *British Journal of Dermatology.* 2011;165(3):661-668.
47. 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.
48. Reich K, Nestle FO, Papp K, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet.* 2005;366(9494):1367-1374.

49. Menter A, Feldman SR, Weinstein GD, et al. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *J Am Acad Dermatol.* 2007;56(1):31.e31-15.
50. Langley R, Feldman SR, Paul C, et al. Treatment with ixekizumab over 60 weeks provides sustained improvements in health-related quality of life: Results from UNCOVER-1, a randomized phase 3 trial. *Journal of the American Academy of Dermatology.* 2016;74(5):AB279.
51. Griffiths C, Fava M, Miller A, et al. Impact of ixekizumab treatment on depressive symptoms: An integrated analysis of three phase 3 clinical studies in patients with moderate-tosevere psoriasis. *Journal of the American Academy of Dermatology.* 2016;74(5):AB253.
52. Gordon KB, Blauvelt A, Papp KA, et al. Phase 3 Trials of Ixekizumab in Moderate-to-Severe Plaque Psoriasis. *N Engl J Med.* 2016;375(4):345-356.
53. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1).[Erratum appears in Lancet. 2008 May 31;371(9627):1838]. *Lancet.* 2008;371(9625):1665-1674.
54. Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet.* 2008;371(9625):1675-1684.
55. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. *N Engl J Med.* 2016;371(4):326-338.
56. Blauvelt A, Prinz JC, Gottlieb AB, et al. Secukinumab administration by pre-filled syringe: efficacy, safety and usability results from a randomized controlled trial in psoriasis (FEATURE). *British Journal of Dermatology.* 2015;172(2):484-493.
57. Paul C, Lacour JP, Tedremets L, et al. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: A randomized, controlled trial (JUNCTURE). *Journal of the European Academy of Dermatology and Venereology.* 2015;29(6):1082-1090.
58. Papp KA, Reich K, Paul C, et al. A prospective phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. *The British journal of dermatology.* 2016.
59. 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.
60. Papp K, Zhang F, Tencer T, Li S. The impact of apremilast therapy on work productivity among patients with moderate to severe plaque psoriasis: Pooled analysis of 2 phase 3 studies. *Journal of the American Academy of Dermatology.* 2015;72(5):AB255.
61. Paul C, Cather J, Gooderham M, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: A phase III, randomized controlled trial (ESTEEM 2). *British Journal of Dermatology.* 2015;173(6):1387-1399.
62. Griffiths CE, Strober BE, van de Kerkhof P, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *N Engl J Med.* 2016;362(2):118-128.

63. 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;386(9993):541-551.
64. 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. *Journal of the American Academy of Dermatology.* 2015;73(3):400-409.
65. Reich K, Soung J, Gooderham M, Zhang Z, Nograles K, Goodfield M. Sustained efficacy of apremilast in patients with moderate to severe psoriasis who continued on apremilast or switched from etanercept treatment: 52-week results from the LIBERATE study. *Journal of the American Academy of Dermatology.* 2016;74(5):AB276.
66. Gisondi P, Conti A, Galdo G, Piaserico S, De Simone C, Girolomoni G. Ustekinumab does not increase body mass index in patients with chronic plaque psoriasis: a prospective cohort study. *The British journal of dermatology.* 2013;168(5):1124-1127.
67. Piaserico S, Conti A, Lo Console F, et al. Efficacy and safety of systemic treatments for psoriasis in elderly patients. *Acta Dermato-Venereologica.* 2014;94(3):293-297.
68. Esposito M, Giunta A, Mazzotta A, et al. Efficacy and safety of subcutaneous anti-tumor necrosis factor-alpha agents, etanercept and adalimumab, in elderly patients affected by psoriasis and psoriatic arthritis: an observational long-term study. *Dermatology.* 2012;225(4):312-319.
69. Gelfand JM, Wan J, Callis Duffin K, et al. Comparative effectiveness of commonly used systemic treatments or phototherapy for moderate to severe plaque psoriasis in the clinical practice setting. *Arch Dermatol.* 2012;148(4):487-494.
70. Strober BE, Bissonnette R, Fiorentino D, et al. Comparative effectiveness of biologic agents for the treatment of psoriasis in a real-world setting: Results from a large, prospective, observational study (Psoriasis Longitudinal Assessment and Registry [PSOLAR]). *Journal of the American Academy of Dermatology.* 2016;74(5):851-861e854.
71. Revicki D, Willian MK, Saurat JH, et al. Impact of adalimumab treatment on health-related quality of life and other patient-reported outcomes: results from a 16-week randomized controlled trial in patients with moderate to severe plaque psoriasis. *The British journal of dermatology.* 2008;158(3):549-557.
72. Papp K, Reich K, Leonardi CL, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). *Journal of the American Academy of Dermatology.* 2015;73(1):37-49.
73. Strober B, Gordon K, Augustin M, et al. Improvements in patient-reported outcomes (PROs) among moderate to severe plaque psoriasis patients treated with brodalumab: Results from AMAGINE-1. *Journal of the American Academy of Dermatology.* 2016;74(5):AB256.
74. Sofen H, Wasel N, Yeilding N, Lee S, Zhao N, Mendelsohn A. Ustekinumab improves overall skin response and healthrelated quality of life in a subset of moderate to severe psoriasis patients with psoriatic arthritis: Analysis of phoenix 1 and 2. *Value in Health.* 2010;13(3):A130.
75. Green L, Thaci D, Zhang Z, Goncalves J, Nograles K, Nikkels A. Effect of apremilast and etanercept on pruritus and health-related quality of life in patients with moderate to severe

plaque psoriasis: Results from the LIBERATE study. *Journal of the American Academy of Dermatology.* 2016;74(5):AB245.
76. Papp KA, Leonardi C, Menter A, et al. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *N Engl J Med.* 2012;366(13):1181-1189.
77. Papp K, Cather JC, Rosoph L, et al. Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial. *The Lancet.* 2012;380(9843):738-746.
78. Paul C, Barker J, Klekotka P, et al. Improvements in health-related quality of life measured by SF-36 and EQ-5D in patients with moderate to severe plaque psoriasis treated with brodalumab. *Journal of the American Academy of Dermatology.* 2016;74(5):AB256.
79. Langley RG, Feldman SR, Han C, et al. Ustekinumab significantly improves symptoms of anxiety, depression, and skin-related quality of life in patients with moderate-to-severe psoriasis: Results from a randomized, double-blind, placebo-controlled phase III trial. *Journal of the American Academy of Dermatology.* 2010;63(3):457-465.
80. Strober B, Sigurgeirsson B, Popp G, et al. Secukinumab improves patient-reported psoriasis symptoms of itching, pain, and scaling: Results of two phase 3, randomized, placebo-controlled clinical trials. *International Journal of Dermatology.* 2016;55(4):401-407.
81. Gottlieb A, Luger T, Sanz LP, et al. Impact of ixekizumab on skin pain in patients with moderate to severe psoriasis compared to placebo and etanercept in UNCOVER-2. *Journal of the American Academy of Dermatology.* 2016;74(5):AB57.
82. Kimball AB, Yu AP, Signorovitch J, et al. The effects of adalimumab treatment and psoriasis severity on self-reported work productivity and activity impairment for patients with moderate to severe psoriasis. *J Am Acad Dermatol.* 2012;66(2):e67-76.
83. Reich K, Nestle FO, Wu Y, et al. Infliximab treatment improves productivity among patients with moderate-to-severe psoriasis. *European journal of dermatology : EJD.* 2007;17(5):381-386.
84. Reich K, Schenkel B, Zhao N, et al. Ustekinumab decreases work limitations, improves work productivity, and reduces work days missed in patients with moderate-to-severe psoriasis: results from PHOENIX 2. *Journal of Dermatological Treatment.* 2011;22(6):337-347.
85. Armstrong AW, Lynde CW, McBride SR, et al. Effect of Ixekizumab Treatment on Work Productivity for Patients With Moderate-to-Severe Plaque Psoriasis: Analysis of Results From 3 Randomized Phase 3 Clinical Trials. *JAMA Dermatol.* 2016;152(6):661-669.
86. Guenther L, Sofen H, Cathers J, et al. Impact of ixekizumab treatment on sexual function in moderate-to-severe psoriasis patients: 12 week results from two phase 3 trials UNCOVER-2 and UNCOVER-3. *Journal of the American Academy of Dermatology.* 2016;74(5):AB254.
87. Guenther L, Han C, Szapary P, et al. Impact of ustekinumab on health-related quality of life and sexual difficulties associated with psoriasis: results from two phase III clinical trials. *J Eur Acad Dermatol Venereol.* 2011;25(7):851-857.
88. Langley R, Reich K, Griffiths C, et al. Secukinumab compared with placebo and etanercept: The first 52-week head-to-head comparison of two biologics in a randomized, double-blind phase 3 study in subjects with moderate-to-severe plaque psoriasis (FIXTURE). *JDDG - Journal of the German Society of Dermatology.* 2014;12(14).
89. Kalb RE, Fiorentino DF, Lebwohl MG, et al. Risk of Serious Infection With Biologic and Systemic Treatment of Psoriasis: Results From the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *JAMA Dermatology.* 2015;151(9):961-969.

90. Papp K, Gottlieb AB, Naldi L, et al. Safety surveillance for ustekinumab and other psoriasis treatments from the psoriasis longitudinal assessment and (PSOLAR). *Journal of Drugs in Dermatology.* 2015;14(7):706-714.
91. Blauvelt A, Gottlieb A, Sigurgeirsson B, Papavassilis C, Martin R. Secukinumab efficacy in subjects with moderate-to-severe plaque psoriasis and concomitant psoriatic arthritis: A subanalysis of the ERASURE study. *Journal of the American Academy of Dermatology.* 2014;70(5 SUPPL. 1):AB2.
92. Gottlieb A, Papp K, Duffin KC, et al. Ixekizumab in patients with psoriasis and psoriatic arthritis: Pooled analysis of three phase 3 studies in moderate-to-severe psoriasis. *J Invest Dermatol.* 2015;135:S26.
93. Papp K, Menter A, Strober B, et al. Efficacy and safety of brodalumab in subpopulations of patients with difficult-to-treat moderate-to-severe plaque psoriasis. *Journal of the American Academy of Dermatology.* 2014;72(3):436-439.e431.
94. Gottlieb A, Langley R, Philipp S, Martin R, Papavassilis C, Mpfofu S. Improvement in psoriasis symptoms and physical functioning with secukinumab compared with placebo and etanercept in subjects with moderate-to-severe plaque psoriasis and psoriatic arthritis: Results of a subanalysis from the phase 3 fixture study. *Arthritis and Rheumatism.* 2013;65(12):3322.
95. Papp K, Menter A, Strober B, et al. Improvement of psoriasis in patients with and without prior biologic experience: Subanalysis of a brodalumab (AMG 827) phase 2 study for moderate to severe plaque psoriasis. *Journal of the American Academy of Dermatology.* 2015;72(5 SUPPL. 1):AB238.
96. Gottlieb AB, Gerdes S, Lacour JP, et al. Efficacy of ixekizumab in moderate to severe psoriasis patients who have or have not received prior biologic therapies: An integrated analysis of 3 phase 3 studies. *Journal of the American Academy of Dermatology.* 2016;74(5):AB247.
97. Papp K, Karpov A, Papavassilis C, Melendez E, Nakagawa H. Secukinumab efficacy in relationship with response to previous biologic psoriasis therapy: A subanalysis from the ERASURE Study. *Journal of the American Academy of Dermatology.* 2014;70(5 SUPPL. 1):AB186.
98. Clemmensen A, Spon M, Skov L, Zachariae C, Gniadecki R. Responses to ustekinumab in the anti-TNF agent-naive vs. anti-TNF agent-exposed patients with psoriasis vulgaris. *J Eur Acad Dermatol Venereol.* 2011;25(9):1037-1040.
99. Gniadecki R, Bang B, Bryld LE, Iversen L, Lasthein S, Skov L. Comparison of long-term drug survival and safety of biologic agents in patients with psoriasis vulgaris. *British Journal of Dermatology.* 2014;172(1):244-252.
100. Asahina A, Nakagawa H, Etoh T, Ohtsuki M. Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: efficacy and safety results from a Phase II/III randomized controlled study. *The Journal of dermatology.* 2010;37(4):299-310.
101. Igarashi A, Kato T, Kato M, Song M, Nakagawa H, Japanese Ustekinumab Study G. Efficacy and safety of ustekinumab in Japanese patients with moderate-to-severe plaque-type psoriasis: long-term results from a phase 2/3 clinical trial. *Journal of Dermatology.* 2012;39(3):242-252.

102. Ohtsuki M, Morita A, Abe M, et al. Secukinumab efficacy and safety in Japanese patients with moderate-to-severe plaque psoriasis: Subanalysis from ERASURE, a randomized, placebo-controlled, phase 3 study. *Journal of Dermatology.* 2014;41(12):1039-1046.
103. Tsai TF, Ho JC, Song M, et al. Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: a phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL). *Journal of Dermatological Science.* 2011;63(3):154-163.
104. Yang HZ, Wang K, Jin HZ, et al. Infliximab monotherapy for Chinese patients with moderate to severe plaque psoriasis: a randomized, double-blind, placebo-controlled multicenter trial. *Chin Med J (Engl).* 2012;125(11):1845-1851.
105. Taltz(R) [package insert]. *Eli Lilly and Company.* 2016(Indianapolis, IN).
106. Stelara(R) [package insert]. *Janssen Biotech Inc.* 2016(Horsham, PA).
107. Remicade(R) [package insert]. *Janssen Biotech Inc.* 2015(Horsham, PA).
108. Enbrel(R) [package insert]. *Amgen.* 2015(Thousand Oaks, CA).
109. Cosentyx(R) [package insert]. *Novartis Pharmaceutical Corporation.* 2016(East Hanover, NJ).
110. Farahnik B, Beroukhim K, Abrouk M, et al. Brodalumab for the Treatment of Psoriasis: A Review of Phase III Trials. *Dermatology and therapy.* 2016;6(2):111-124.
111. Redbook Online [online database]. *Truven Health Analytics* accessed 2016 Aug 23(Greenwood Village, CO).
112. Yu AP, Tang J, Xie J, et al. Economic burden of psoriasis compared to the general population and stratified by disease severity. *Current medical research and opinion.* 2009;25(10):2429-2438.
113. Feldman SR, Zhao Y, Shi L, Tran MH, Lu J. Economic and comorbidity burden among moderate-to-severe psoriasis patients with comorbid psoriatic arthritis. *Arthritis Care Res (Hoboken).* 2015;67(5):708-717.
114. PINC-01. Selected Characteristics of People 15 Years and Over, by Total Money Income, Work Experience, Race, Hispanic Origin, and Sex. Accessed September 22, 2016.
115. Bureau of Labor Statistics. May 2015 National Occupational Employment and Wage Estimates United States. *Occupational Employment Statistics.* http://www.bls.gov/oes/current/oes_nat.htm#00-0000.
116. E. R. Abstract 1654. *European Academy of Dermatology and Venereology.* 2014.
117. Griffiths C, Papp K, Zaldivar ER, et al. Secukinumab shows efficacy in subjects regardless of previous exposure to biologic therapy: A pooled subanalysis from four phase 3 clinical trials in psoriasis. *Journal of the American Academy of Dermatology.* 2015;72(5):AB251.
118. Gniadecki R, Bang B, Bryld LE, Iversen L, Lasthein S, Skov L. Comparison of long-term drug survival and safety of biologic agents in patients with psoriasis vulgaris. *The British journal of dermatology.* 2015;172(1):244-252.
119. Swinburn P, Lloyd A, Boye KS, Edson-Heredia E, Bowman L, Janssen B. Development of a disease-specific version of the EQ-5D-5L for use in patients suffering from psoriasis: lessons learned from a feasibility study in the UK. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2013;16(8):1156-1162.
120. Pickard AS, Gooderham M, Hartz DS, Nicolay C. EQ-5D health utilities: Exploring ways to improve upon responsiveness in psoriasis. *J Med Econ.* 2016:1-31.
121. Thomas K. A Push to Lower Drug Prices That Hit Insurers and Employers the Hardest. *New York Times.* September 8, 2016.

122. Vasiliou C. Psoriasis Forecast. *Datamonitor Healthcare.* 2015.
123. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ (Clinical research ed).* 2005;331(7521):897-900.
124. National Institute for Health and Care Excellence. A general linear modelling framework for pair-wise and network meta-analysis of randomised controlled trials *Decision Support Unit, ScHARR, University of Sheffield, Regent Court, 30 Regent Street Sheffield, S1 4DA.* 2016;2.

APPENDICES

Appendix A. Evidence Review Methods and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.
From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097		

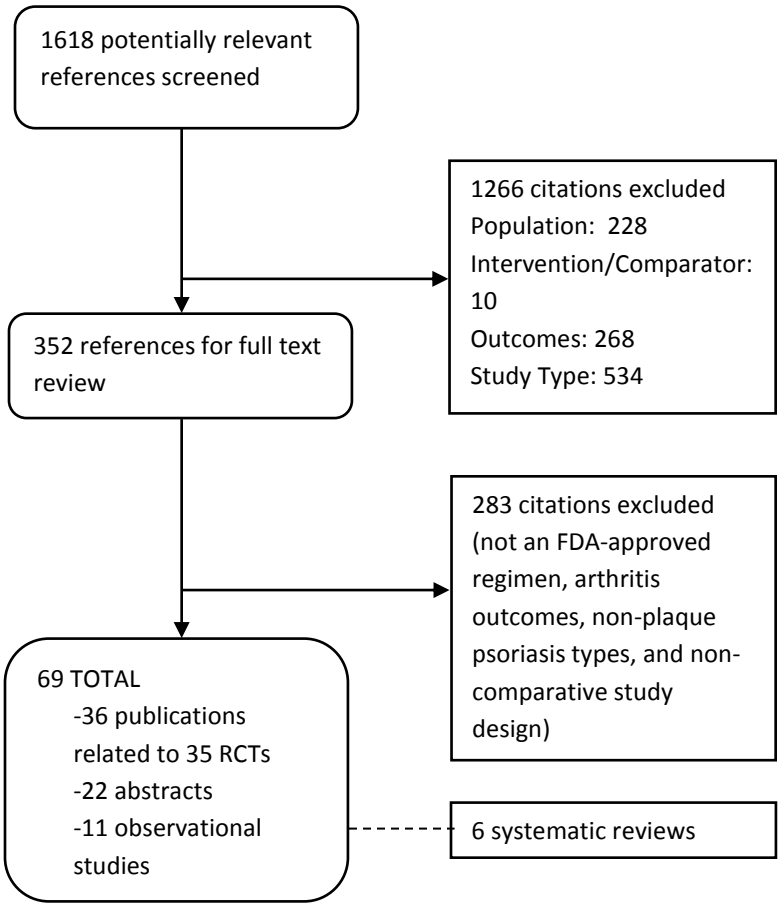
Table A2. Search Strategy of Medline 1996 to Present with Daily Update, EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Cochrane Central Register of Controlled

1	Psoriasis/	16220
2	psoria$.ti,ab.	24352
3	(secukinumab or cosentyx).ti,ab.	222
4	(ustekinumab or stelara).ti,ab.	649
5	(ixekizumab or taltz).ti,ab.	64
6	brodalumab.ti,ab.	77
7	(apremilast or otezla).ti,ab.	179
8	1 or 2	26043
9	3 or 4 or 5 or 6 or 7	1094
10	8 and 9	861
11	limit 10 to english language	824
12	limit 11 to humans	824
13	(guideline or practice guideline or letter or editorial or news or case reports or clinical	1931126
14	12 not 13	700
15	remove duplicates from 14	601
Date of Search: June 28, 2016		

Table A3. Search Strategy of Embase on June 28, 2016

#20	#19 AND [humans]/lim	1017
#19	#18 NOT 'case report' NOT 'case study'	1124
#18	#15 NOT #16 NOT #17	1184
#17	#15 AND [humans]/lim AND [animals]/lim	32
#16	#15 AND [animals]/lim	40
#15	#13 NOT #14	1224
#14	#12 AND [medline]/lim	413
#13	#12 AND [english]/lim	1622
#12	#10 NOT #11	1683
#11	#3 AND #9 AND ([editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR	122
#10	#3 AND #9	1805
#9	#4 OR #5 OR #6 OR #7 OR #8	2235
#8	'brodalumab':ab,ti	127
#7	'apremilast':ab,ti OR 'otezla':ab,ti	331
#6	'ixekizumab':ab,ti OR 'taltz':ab,ti	156
#5	'ustekinumab':ab,ti OR 'stelara':ab,ti	1454
#4	'secukinumab':ab,ti OR 'cosentyx':ab,ti	399
#3	#1 OR #2	58457
#2	psorias*:ab,ti OR psoriat*:ab,ti	57572
#1	'psoriasis vulgaris'	8040

Figure A1. PRISMA Flow Chart Showing Results of Literature Search



Appendix B. Evidence Summary Tables

Study, *Quality rating*	Study Design	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Anti-TNF Agents						
Adalimumab						
Sauret, 2008 **(NCT00235820)** **CHAMPION** ***Good quality publication***	Phase III RCT Double-blind Multicenter 28 study sites in Europe and Canada ITT with NRI	**1)Adalimumab: 40 mg every other week following an 80 mg dose (n=108)** **2)placebo (n=53)** 3) Methotrexate: 7.5 to 25 mg once weekly (n=110) For 16 weeks	Inclusion: a diagnosis of psoriasis for at least 12 months and stable moderate to severe chronic plaque psoriasis (PASI≥10 and BSA≥10%); candidate for systematic therapy or phototherapy; Exclusion: Previous systemic anti-TNF therapy or methotrexate; pregnancy	Age, mean 1)42.9 2)40.7 Male, % 1)64.8 2)66.0 Caucasian, % 1)95.4 2)92.5	PASI 50 at 16 weeks (%): 1)88 2)30.2 PASI 75 at 16 weeks (%): 1)79.6 2)18.9 PASI 90 at 16 weeks (%): 1)51.9	Serious AEs at 16 weeks, %: 1)1.9 2)1.9 AEs leading to discontinuation at 16 weeks, % 1)0.9 2)1.9

				Duration of PsO, yr 1)17.9 2)18.8 With PsA, % 1)21.3 2)20.8 Previous systemic and/or phototherapy, % 1)82.2 2)90.4 PASI, mean (range) 1)20.2 (10.4-52.9) 2)19.2 (6.5-38.1)	2)11.3 PASI 100 at 16 weeks (%): 1)16.7 (p=0.004) 2)1.9 PGA of 'clear' or 'minimal' at 16 weeks: 1) 73.1 2) 11.3 *PGA ranging from 0 to 5 †P<0.001 vs. placebo unless specified otherwise	
Revicki, 2008	See above	See above	See above	See above	At week 16:	NR

(NCT00235820) **CHAMPION** ***Good quality publication***					DLQI, mean change 1) -3.4 3) -9.1 *1 vs. 3, p<0.001* ED-5D 1) 0.1 3) 0.2 *1 vs. 3, p<0.01* VAS pruritus 1) -1.7 3) -4.8 *1 vs. 3, p<0.001*	
Menter, 2008 **(NCT00237887)**	Phase III, multicenter, double-blind RCT	Period A (16 wk) 1)Adalimumab: 40 mg every other week following an 80 mg dose (n=814)	Inclusion: A diagnosis of psoriasis of at least 6 months, stable moderate to severe plaque psoriasis for at	Age, mean 1)44.1 2)45.4	PASI 75, %: 1)68 at wk 12, 71 at wk 16	SAE through 16 weeks,% 1)1.8 2)1.8

REVEAL ***Good quality publication***	67 centers in the United States and 14 centers in Canada ITT with NRI	2)placebo (n=398)	least 2 months(PASI≥12, BSA≥10% and PGA of at least moderate severity); Exclusion: A history of CNS disease, cancer or lymphoproliferative disease	Male, % 1)67.1 2)64.6 Caucasian, % 1)91.2 2)90.2 Duration of PsO, yr 1)18.1 2)18.4 With hx of PsA, % 1)27.5 2)28.4	2)5 at wk 12, 7 at wk 16 P<0.001 for both PASI 90, %: 1)37 at wk 12, 45 at wk 16 2)2 at wk 12, 2 at wk 16 P<0.01 for both PASI 100, %: 1)14 at wk 12, 20 at wk 16 2)<1 a wk 12, 1 at wk 16 P<0.01 for both PGA of 'clear' or 'minimal' at 12 weeks, %:	Serious infectious AE through 16 weeks, % 1)0.6 2)1.0 AEs leading to discontinuation through 16 weeks, % 1)1.7 2)2.0

				Previous systemic biologic, % 1)11.9 2)13.3 PASI, mean (SD) 1)19.0 (7.08) 2) 18.8 (7.09)	1)60 2)4 P<0.01 PGA of 'clear' at 12 weeks, %: 1)16 2)<1 P<0.01 *patients with missing PASI scores were considered nonresponders †PGA ranging from 0 to 5	
Kimball, 2010 **(NCT00237887)** **REVEAL**	Work productivity outcomes from REVEAL	See above	See above	See above TWPI (%) 1) 18.5 2) 17.9	At 16 weeks TWPI (total work productivity impairment) 1) -13.4 3) -2.3	NR

Good quality publication				Presenteeism (%) 1) 17.8 2) 16.8 Absenteeism (%) 1) 3.3 2) 2.6 p=NS	Absolute difference: 11.1% TAI (total activity impairment) 1) -18.8 3) -3.3 Absolute difference: 15.5% Impairment while working owing to presenteeism 1) -12.9 3) -1.5 Absolute difference: 11.4% All outcomes, p<0.0001	

					Employment and absenteeism measures = NS	
Asahina, 2010 ***Good quality publication***	Phase II/III, multicenter, double-blind RCT 42 sites in Japan ITT with NRI	1)adalimumab 40 mg eow (n=38) **2)adalimumab 80mg at week 0 and 40 mg eow starting week 2 (n=43)** 3)adalimumab 80 mg eow (n=42) **4)placebo eow (n=46)** for 24 wk	Inclusion: a clinical diagnosis of moderate to severe chronic plaque psoriasis for at least 6 months, stable for at least the recent 2 months (PASI≥12, and BSA≥10%) Exclusion: Previous anti-TNF therapy, other skin diseases or infection, systemic lupus erythematosus, scleroderma or rheumatoid Arthritis; a history of CNS disease, cancer, lymphoma, leukemia, tuberculosis, or lymphoproliferative	Age, mean 2)44.2 4)43.9 Male, % 2)35 4)41 Caucasian, % NR, trial in Japan Duration of PsO, yr 2)14.0 4)15.5	PASI 50 at week 16, %: 2)81.4 4)19.6 P<0.001 PASI 75,%: 2)53.3 at wk 12, 62.8 at wk 16 4)2.2 at wk 12, 4.3 at wk 16 P<0.001 for both PASI 90,%: 2)30.2 at wk 12, 39.5 at wk 16 4)0 at wk 12 and wk 16	Any SAE at 16 weeks, %: 2) 2.3 4) 2.2 AEs leading to discontinuation through 16 weeks, % 2)11.6 4)10.9

			disease; positive serology for HIV, Hep B, Hep C, infectious disease, immunosuppressive disease or abnormal hematological, hepatic, or renal values	With hx of PsA, % NR Previous systemic non-biologic, % 2)41.9 4)37.0 PASI, mean (SD) 2)30.2 (10.9) 4)29.1 (11.8)	P<0.001 for both PGA "clear" or "minimal" at week 16,%: 2) 60.5 4) 8.7 P<0.001 Change in QoL at wk 16, mean (SD) 2) DLQI -5.1 (5.7); SF-36 physical 4.6 (7.6);mental 2.4 (10.2) 4) DLQI 1.0 (7.0); SF-36 physical -0.4 (7.3); mental -2.6 (10.6) P<0.001 for DLQI, p<0.01 for SF-36 physical, p<0.05 for SF-36 mental	

					*missing data were imputed by LOCF †PGA ranging from 0 to 5	
Etanercept						
Papp, 2005 ***Fair quality publication***	Phase III, multicenter, double-blind RCT 50 sites in the US, Canada, and Europe mITT with LOCF	**1)etanercept 50 mg BIW (203)** 2)etanercept 25 mg BIW (204) **3)placebo (204)**	Inclusion: Active and clinically stable plaque psoriasis with ≥10% BSA involvement; baseline PASI≥10; at least one previous phototherapy or systemic therapy; adequate haematological, renal, and hepatic function Exclusion: Active severe infection; other skin conditions; active guttate, erythrodermic or pustular psoriasis;	Age, median 1)44.5 3)44.0 Male, % 1)67 3)64 Caucasian, % NR Duration of PsO, yr 1)18.1	PASI 50 at week 12, %: 1)72 3)9 P<0.0001 PASI 75 at week 12,%: 1)46 3)3 P<0.0001 PASI 90 at week 12,%: 1)19 3)<1	SAE NR Grade 3 or 4 laboratory abnormalities at week 24, n 1)1 3)1

			previous anti-TNF therapy	3)17.5 With hx of PsA, % 1)26 3)26 Previous systemic therapy, % Oral retinoids 1)23 3)24 Oral retinoids 1)38 3)39 Oral retinoids 1)18 3)16	P<0.0001 sPGA “clear” or “almost clear” at week 12,%: 1) 54 3) 3 P<0.0001 *missing data were imputed by LOCF †PGA ranging from 0 to 5	

				PASI, median (range) 1)16.1 (7.0-57.3) 3)16.0 (7.0-62.4)		
Leonardi, 2003 ***Fair quality publication***	Phase III, multicenter, double-blind RCT 47 sites in the US mITT with LOCF	1) etanercept 25 mg QW for 24 wk (n=160) 2) etanercept 25 mg BIW for 24 wk (n=162) 3) etanercept 50 mg BIW for 24 wk (n=164) 4) placebo BIW for 12 wk 25 mg BIW after wk 12 (n=166)	Inclusion: Active but clinically stable moderate-to-severe plaque psoriasis (PASI≥10 and BSA≥10%); previous phototherapy or systemic therapy, or candidate for such therapy Exclusion: guttate, erythrodermic, or pustular psoriasis; active skin conditions; previous anti-TNF therapy	Age, median 3)44.8 4)45.6 Male, % 3)65 4)63 White race, % 3)87 4)90 Duration of PsO, yr 3)18.6	PASI 50 at week 12, %: 3)74 4)14 P<0.001 PASI 75 at week 12,%: 3)49 4)4 P<0.001 PASI 90 at week 12,%: 3)22 4)1 P<0.001	SAE NR

				4)18.4 With hx of PsA, % 22 Previous systemic therapy or phototherapy, % 76 PASI, median (SE) 3)18.4 (0.7) 4)18.3 (0.6)	sPGA "clear" or "almost clear" at week 12,%: 3) 49 4) 5 P<0.001 %improvement DLQI, mean (SD) 3)61.0 (4.3) 4)10.9 (4.8) P<0.001 *missing data were imputed by LOCF †PGA ranging from 0 to 5	
Tyring, 2006	Phase III, multicenter, double-blind RCT	*1)50 mg BIW (n=300)* *2)placebo (n=300)*	*Inclusion:* *Active, clinically stable plaque psoriasis with*	Age, median 1)45.8	PASI 50 at week 12, %: 3)74	SAE at 12 weeks,% 1)0

(NCT00111449) ***Fair quality publication***	39 sites in the US and Canada mITT with LOCF	*For 12 wk*	*PASI≥10 and BSA≥10%; previous systemic therapy or phototherapy, or candidate for such therapy; adequate haematological, renal, and hepatic function* *Exclusion:* *History of psychiatric disease; active guttate,* *erythrodermic, or pustular psoriasis; preivous snit-TNF therapy*	2)45.6 Male, % 1)65 2)70 Duration of PsO, yr 1)20.1 2)19.7 With hx of PsA, % 1)35 2)33 Previous systemic therapy or phototherapy, % NR	4)14 P<0.0001 PASI 75 at week 12,%: 3)47 4)5 P<0.0001 PASI 90 at week 12,%: 3)21 4)1 P<0.001 %improvement DLQI, mean (SD) 3)69.1 4)22.1 P<0.0001	2)0.3 AEs leading to discontinuation through 12 weeks, % 1)1.3 2)1.6

				PASI, median (SD) 1)18.3 (7.6) 2)18.1 (7.4) Other outcomes reported: FACIT-F, Ham-D, and BDI	*missing data were imputed by LOCF	
Bagel, 2012 ***Good quality publication***	Phase III, multicenter, double-blind RCT Conducted in North America mITT with LOCF	*1)etanercept 50 mg BIW through week 12, followed by etanercept 50 mg QW and placebo QW through week 24 (n=62)* *2)placebo BIW through week 12, followed by etanercept 50 mg BIW (n=62)*	*Inclusion:* *Stable moderate to severe plaque psoriasis with BSA≥10% for ≥ 6 months; PASI ≥10 and SSA ≥ 30% with PSSI ≥15; candidates for phototherapy or systemic therapy* *Exclusion:* *guttate,* *erythrodermic, or pustular*	Age, median 1)39 2)42 Male, % 1)53.2 2)58.1 White or caucasian, % 1)69.4 2)75.8	PASI 50 at week 12, %: 1)85 2)7 P<0.0001 PASI 75 at week 12,%: 1)59 2)5 P<0.0001 PASI 90 at week 12,%: 1)25	SAE at week 12,% 1)0 2)0 AEs leading to discontinuation through 12 weeks, % 1)3.2 2)0

			psoriasis; significant medical *problems; a history of tuberculosis;* *or a history of cancer* *5 years or less before enrollment*	Duration of PsO, yr 1)17.5 2)11.9 With hx of PsA, % NR Previous biologic therapy, % Anti-TNF 1)6.8 2)6.5 Non-anti-TNF 1)3.2 2)4.8 PASI, median (range) 1)15.5 (8,46)	2)2 P<0.0001 PGA 0-1 at week 12, % 1)54 2)5 P<0.0001 *missing data were imputed by LOCF

				2)15.2 (10,41)		
Gottlieb, 2011 **(NCT00691964)** ***Good quality publication***	Phase III, multicenter, double-blind RCT 33 sites in the United States ITT with NRI	*1)briakinumab 200 mg at week 0 and 4, followed by 100 mg at week 8 (n=138)* *2)etanercept 50 mg BIW at week 0-11 (n=141)* *3)placebo (n=68)*	*Inclusion:* *A diagnosis of chronic plaque psoriasis for ≥6months, stable for ≥2 months; BSA ≥ 10%; PGA at least moderate (≥3); PASI ≥ 12* *Exclusion:* *Previous systemic anti-IL-12/23p40 therapy, etanercept, or inability to discontinue topical therapy, phototherapies, or systemic therapies*	Age, median 2)43.1 3)44.0 Male, % 2)69.5 3)69.1 Caucasian, % 2)90.1 3)95.6 Duration of PsO, yr 2)17.0 3)19.1	PASI 75 at week 12, %: 2)56.0 3)7.4 P<0.001 PASI 90 at week 12, %: 2)23 3)1.4 P≤0.002 PASI 100 at week 12, %: 2)6.7 3)0 p≤0.002 PGA 0-1 at week 12, %	Severe AE at 12 weeks, % 2)2.1 3)4.3 Serious AE at 12 weeks, % 2)0.7 3)2.9 AEs leading to discontinuation through 12 weeks, % 2)2.8 3)0

				With hx of PsA, % 2)22.7 3)20.6 Previous biologic therapy, % 2)14.2 3)14.7 PASI, mean (SD) 2)20 (14.2) 3)10 (14.7)	2)39.7 3)2.9 P<0.0001 DLQI of 0 at week 12, % 2)21.3 3)2.9 p≤0.008 *missing data were imputed by LOCF	
Strober, 2011 **(NCT00710580)** ***Good quality publication***	Phase III, multicenter, double-blind RCT 41 sites in the US ITT with NRI	*1)briakinumab 200 mg at week 0 and 4, followed by 100 mg at week 8 (n=139)* *2)etanercept 50 mg BIW at week 0-11 (n=139)* *3)placebo (n=72)*	*Inclusion:* *A diagnosis of chronic plaque psoriasis for ≥6months, stable for ≥2 months; BSA ≥ 10%; PGA at least moderate (≥3); PASI ≥ 12* *Exclusion:*	Age, median 2)45.2 3)45.0 Male, % 2)61.2	PASI 75 at week 12, %: 2)39.6 3)6.9 PASI 90 at week 12, %: 2)13.7	Severe AE at week 12, % 2)0.7 3)2.8 Serious AE at week 12, %

			Previous systemic anti-IL-12/23p40 therapy, etanercept, or inability to discontinue topical therapy, phototherapies, or systemic therapies	3)63.9 Caucasian, % 2)91.4 3)93.1 Duration of PsO, yr 2)15.2 3)15.5 With hx of PsA, % 2)33.1 3)20.8 Previous biologic therapy, % 2)7.9 3)4.2	3)4.2 PASI 100 at week 12, %: 2)5.8 3)0 PGA 0-1 at week 12, % 2)39.7 3)2.9 P<0.0001 DLQI of 0 at week 12, % 2)29.5 3)4.2 *missing data were imputed by LOCF	2)0.7 3)2.8 AEs leading to discontinuation through 12 weeks, % 2)2.9 3)2.8

				PASI, mean (SD) 2)18.5 (6.0) 3)18.3 (6.4)		
Bachelez, 2015 (NCT01241591) ***Good quality publication***	*Phase III, multicenter, double-blind RCT* 122 sites worldwide (not included the US and Canada) ITT with NRI	*1)tofacitinib 5 mg twice daily (n=329)* *2) tofacitinib 10 mg twice daily (n=330)* *3)etanercept 50 mg BIW at week 0-11 (n=335)* *4)placebo (n=107)*	*Inclusion:* *Chronic stable plaque psoriasis for ≥ 12 months; candidates for systemic therapy or phototherapy; PASI ≥12 and PGA of moderate or severe; BSA ≥10%; failed to respond or had a contraindication to or were intolerant to at least one conventional systemic therapy* *Exclusion:* *Non-plaque or drug-induced forms of psoriasis, could not continue systemic therapies, previous or had a contraindication*	Age, median 3)42.0 4)46.0 Male, % 3)70 4)66 Caucasian, % 3)87 4)84 Duration of PsO, yr	PASI 50 at week 12, %: 3)80.3 4)20.6 PASI 75 at week 12, %: 3)58.8 4)5.6 PASI 90 at week 12, %: 3)32.2 4)0.9	Severe TEAEs at week 12, % 2)2 3)5 Serious TEAEs at week 12, % 2)2 3)2 AEs leading to discontinuation through 12 weeks, % 2)3 3)4

			to etanercept, previously not responded to anti-TNF therapy, active infection, previous tofacitinib	3)18.0 4)17.0 With hx of PsA, % 3)21 4)24 Previous biologic therapy, % 3)11 4)11 PASI, median (range) 3)19.4 (12.0-63.6) 4)19.5 (12.4-54.6)	PGA 0-1 at week 12, % 3)66.3 4)15.0 PGA 0 at week 12, % 3)19.4 4)1.9 DLQI reduction ≥*5 from baseline* at week 12, % 3)74.7 4)31.8 *patients with missing data were considered non-responders †PGA ranging from 0 to 4	

Infliximab						
Reich, 2005 **EXPRESS** ***Fair quality publication***	Phase III, multicenter, double-blind RCT 32 sites (countries NR) ITT and NRI only for PASI measures only	*1) infusions of infliximab 5mg/kg at weeks 0,2 and 6, then every 8 weeks to week 46 (n=301)* *2) infusions of placebo at weeks 0,2 and 6, then every 8 weeks to week 46 (n=77)* *Crossover at week 24*	*Inclusion:* *A diagnosis of moderate-to-severe plaque psoriasis for ≥6 moths; candidates for phototherapy or systemic therapy; PASI≥12 and BSA≥10%* *Exclusion:* *A history or risk of serious infection, lymphoproliferative disease, or active tuberculosis; previous anti-TNF treatment*	Age, median 1)42.6 2)43.8 Male, % 1)69 2)79 White, % NR Duration of PsO, yr 1)19.1 2)17.3	PASI 50 at week 10, % 1)91 2)8 PASI 75 at week 10, % 1)80 2)3 PASI 90 at week 10, % 1)57 2)1 PGA of 0-1 at week 10, % 1)83 2)4	Serious AEs at week 24, % 1)6 2)3 AEs leading to discontinuation through 24 weeks, % 1)9 2)7

				With PsA, % 1)31 2)29 Previous biologic therapy, % NR PASI, mean (SD) 1)22.9 2)22.8	All p<0.0001 Change in DLQI from baseline at week 10, mean** 1)10.3 2)0.4 P<0.001 *ITT analysis results, per-protocol is not presented here †PGA ranging from 0 to 5 **Reported in Reich 2006	
Reich, 2006 **EXPRESS**	Work productivity outcomes from EXPRESS	*See above*	*See above*	See above Productivity VAS	At week 10 Productivity VAS 1) -0.1	Discontinuation due to AEs through week 50 (%) Placebo/INF: 10.4

Fair quality publication				1) 5.8 2) 6.3 SF-RP (role physical) 1) 64.8 2) 69.8 SF-RE (role emotional) 1) 72.1 2) 71.9	2) 2.7 SF-RP (role physical) 1) -5.2 2) 20.6 SF-RE (role emotional) 1) -2.2 2) 18.2 All outcomes, p<0.001 at week 10 and 24	INF/INF: 11.3 Discontinuation due to unsatisfactory therapeutic effects (%) Placebo/INF: 9.7 INF/INF: 4.7
Menter, 2007 **EXPRESS II** ***Good quality publication***	Phase III, multicenter, double-blind RCT 63 sites in the US, Canada, and Europe ITT with NRI	*1)infusions of infliximab 3mg/kg at weeks 0,2 and 6 (n=313)* *2)infusions of infliximab 5mg/kg at weeks 0,2 and 6 (n=314)*	*Inclusion:* *A diagnosis of moderate-to-severe plaque psoriasis; candidates for phototherapy or systemic therapy; PASI≥12 and BSA≥10%*	Age, median 2)44.5 3)44.4 Male, % 2)65.0	PASI 75 at week 10, % 2)75.5 3)1.9 PASI 90 at week 10, % 2)45.2	≥1 SAE at week 14, % 2) 2.9 3) 2.4 AEs leading to discontinuation through 14 weeks, %

		3)infusions of placebo at weeks 0,2 and 6 (n=208) *1) and 2) were re-randomized to receive either every-8-week continuous maintenance therapy or intermittent as-needed maintenance therapy; 3)crossed over to receive infliximab 5mg/kg at weeks 16,18,and 22, and every 8 weeks thereafter*	*Exclusion:* *A history or risk of serious infection, lymphoproliferative disease, or active tuberculosis; previous anti-TNF treatment*	3)69.2 Caucasian, % 2)93.3 3)90.9 Duration of PsO, yr 2)19.1 3)17.8 With PsA, % 2)28.3 3)26.0 Previous biologic therapy, % 2)14.3 3)13.0	3)0.5 PGA of 1-2 at week 10, % 2)76.0 3)1.0 DLQI of 0 at week 10, % 2)39.0 3)1.0 DLQI mean change at week 10, % 2) -9.0 3) 0 p<0.001	1)5.1 2)2.4

				PASI, mean (SD) 2)20.4 (18.6) 3)19.8 (17.4)	*PGA ranging from 1 to 6	
Yang, 2012 ***Fair quality publication***	Phase III, multicenter, double-blind RCT ITT; handling of missing data NR	*1)infusion of infliximab 5mg/kg at weeks 0,2, and 6, then at weeks 14 and 22 (n=84)* *2)placebo at weeks 0,2, and 6, then infliximab 5mg/kg at weeks 10,12, and 16 (n=45)*	*Inclusion:* *A diagnosis of plaque psoriasis for ≥6 months; had failed to respond to conventional systemic treatment; PASI≥12 and BSA≥10%;* *Exclusion:* *Non-plaque psoriasis; a history of chronic infectious disease or opportunistic infection or lymphoproliferative disease; a serious infection within 2 months; active or latent tuberculosis; pregnancy or planned pregnancy within 12 months; an active malignancy or a*	Age, median 1)39.4 2)40.1 Male, % 1)71.4 2)77.8 White, % NR Duration of PsO, yr 1)16.0	PASI 50 at week 10, % 1)94.0 2)13.3 PASI 75 at week 10, % 1)81.0 2)2.2 PASI 90 at week 10, % 1)57.1 2)0 PGA of 0-1 at week 10, %	Serious AEs at week 10, % 1)1.2 2)0 AEs leading to discontinuation through 26 weeks, % 1)6.7 2)NR

			history of malignancy within 5 years	2)16.0 With PsA, % NR Previous psoriasis therapy, % 1) 40.5 2) 31.1 PASI, mean (SD) NR DLQI, mean 1)14.4 2)14.4	1)88.1 2)6.7 DLQI at week 10, mean 1) 6.5 2) 13.1 P<0.001 for all	
Observational Studies						

Gisondi, 2013 ***Good quality***	*Observational, prospective, multi-center study*	*1)infliximab 5 mg/kg at weeks 0,2, and 6 and every 8 weeks thereafter (n=83)* *2)ustekinumab 45 mg for patients ≤100 kg and 90 mg for patients > 100 kg at weeks 0, 4, and every 12 weeks thereafter (n=79)*	*Inclusion:* *Patient data recoded at four tertiary referral psoriasis* *centers in Italy (Universities of Verona, Modena and Padua,* *and Catholic University of Rome); a diagnosis of chronic plaque psoriasis; all patients who received etanercept or infliximab were biological therapy naïve, with PASI≥10 and BSA ≥10% and resistance to methotrexate, cycloporin, acitretin or phototherapy* *Exclusion:* ***Patients diagnosed with PsA***	Age, mean 1) 47.8 2) 45.7 Male, % 1) 64 2) 72 White, % NR Duration of PsO, yr 1) 17.5 2) 18.6 Previous biologic therapy, % 0	PASI at 1 month, mean (SD) 1) 4.1 (4.7) 2) 2.1 (3.2) PASI at 7 months, mean (SD) 1) 8.1 (5.2) 2) 4.1 (5.5) Improvement in PASI at 1 month, % 1) 64 2) 60 Improvement in PASI at 7 months, % 1) 85 2) 82	NR

				PASI, mean (SD) 1) 16.5 (9.1) 2) 18.4 (8.2)	PASI 75 at 1 month, % 1) 32 2) 28 PASI 50 at 7 months, % 1) 96 2) 82 PASI 75 at 7 months, % 1) 69 2) 58 *between-group PASI 50 and PASI 75 are not statistically significant	

Publication *Piaserico, 2014* *Fair quality*	*Observational, prospective study* *Adjustment:* *for the presence of comorbidities, smoking, steroid use* *and disease severity*	*1) etancercept (n=83)* *2) adalimumab (n=18)* *3) infliximab (n=16)* *4) ustekinumab (n=4)*	*Inclusion:* *All patients who received a new treatment with systemic traditional* *drugs or biologics for chronic plaque psoriasis in various* *Italian Dermatology Departments* *Exclusion:*	Age, mean 71.3 Male, % 58.3 White, % NR Duration of PsO, yr 22.1 Previous biologic therapy, % 26.2 PASI, mean (SD) 1)14.9 (6.4) 2)14.3 (4.1) 3)14.8 (5.7)	PASI 75 at week 12, % 1) 64 2) 65 3) 93 4) 100	Serious AEs, % 1)7.2 2)0 3)12.5 4)0

				4)17.2 (1.9) Not compared between groups		
Publication *Esposito, 2012* *Poor quality*	*observational, retrospective study* *adjustment: none*	*1) etanercept: 50 mg weekly as continuous regimen for PsA and 50 mg twice weekly for 12 weeks for PsO (n=61)* *2) adalimumab: a loading dose of 80 mg followed by 40 mg every other week for PsA and PsO (n=28)*	*Inclusion:* *Patients with PsO with/without PsA, ≥65 years undergoing anti-TNF-α therapy (i.e. adalimumab or etanercept) for at least 6 months in the outpatient collaborative* *Dermatology and Rheumatology Unit of the University of* *Rome*	Age, mean (range) 1) 70 (65-82) 2) 69 (65-75) Male, % 1)54 2)57 White, % NR Duration of PsO, yr 1)29.2 2)24.1	PASI 50 at week 12, % 1)82.0 2)85.7 PASI 75 at week 12, % 1)54.1 2)60.7 PASI 50 at week 24, % 1)90.2 2)82.1 PASI 75 at week 24, % 1)78.7 2)71.4	Severe AEs leading to discontinuation, % 1)4.9 2)7.1

				With PsA, % 1) 2) Previous biologic therapy, % 1) Adalimumab: 1.6 Efalizumab: 9.8 Infliximab: 9.8 2) Efalizumab: 25.0 Etanercept: 67.9 Infliximab: 50.0 PASI, mean (range) 1)11.3 (0.4-68.3)	PASI 50 at year 1, % 1)90.2 2)78.6 PASI 75 at year 1, % 1)83.6 2)67.9 PASI 50 at year 2, % 1)91.8 2)82.1 PASI 75 at year 2, % 1)86.9 2)71.4 PASI 50 at year 3, % 1)91.8 2)82.1	

				2)10.4 (0.4-23.8) Not statistically compared between groups	PASI 75 at year 3, % 1)83.6 2)71.4	
Publication *Gisondi, 2008* *Poor quality*	*Observational, retrospective study* *Adjustment: none*	*1)**etanercept 25 mg twice weekly (n=58)*** *2) infliximab 5 mg/kg at week 0,2,and 6 and then every 8 weeks (n=40)* *3)methotrexate 15 mg once weekly (n=43)* **doses NR*	*Inclusion:* *psoriatic patients affected by chronic plaque psoriasis consecutively* *admitted to the outpatients clinics of the University* *Hospital of Verona; all patients who received etanercept or infliximab were biological therapy naïve, with PASI≥10 and BSA ≥10% and resistance to methotrexate, cycloporin, acitretin or phototherapy*	Age, mean 1) 50.2 2) 46.8 3) 53.1 Male, % 1) 67 2) 70 3) 60 White, % NR Duration of PsO, yr 1) 22	PASI at 6 months, mean (SD) 1) 4.8 (4.7) 2) 2.1 (3.2) 3) 4.3 (6) Improvement in PASI, % 1) 74.5 2) 88.8 3) 47.6	Severe AEs, 0

			Exclusion: ***patients diagnosed with PsA***	2) 17.5 3) 18.6 Previous biologic therapy, % 0 PASI, mean (SD) 1) 18.8 (7.4) 2) 17.7 (7.3) 3) 8.2 (3.1)		
Anti IL-17A Agents						
Secukinumab (Cosentyx)						
Publication Blauvet, 2015	Phase III RCT Double-blind Multicenter	1) secukinumab 300mg at week 0,1,2,3, and then every 4 weeks starting from week 4 (n=59) 2) secukinumab 150mg at week 0,1,2,3, and then	Inclusion: Plaque psoriasis for ≥6 months; moderate-to-severe disease defined by baseline PASI≥12, IGA mod 2011≥3, and BSA≥10%;	Age, mean 1) 45.1 2) 46.0 3) 46.5	PASI 75 at week 12, % 1) 75.9 2) 69.5 3) 0	Serious AE at week 12, % 1) 5.1 2) 0 3) 1.7

(FEATURE NCT01555125) *Good quality publication*	32 sites in North America and Europe ITT with NRI	every 4 weeks starting from week 4 (n=59) 3) placebo (n=59) Maintenance: dosing every 4 weeks from week 12 to week 52	inadequately controlled by topical treatment, phototherapy, or previous systemic therapy Exclusion: Non-chronic-plaque psoriasis, except for palmoplantar psoriasis; prior anti-IL-17 therapy; medical conditions that confound the evaluation or risky for immunotherapy; active infections or history of infections; history of lymphoproliferative diseases or malignancy; pregnancy	Male, % 1) 64.4 2) 67.8 3) 66.1 White, % 1) 91.5 2) 86.4 3) 96.6 Duration of PsO (yr), mean 1) 18.0 2) 20.4 3) 20.2 PASI, mean (SD) 1) 20.7 (7.95)	PASI 90 at week 12, % 1) 60.3 2) 45.8 3) 0 PASI 100 at week 12, % 1) 43.1 2) 8.5 3) 0 IGA mod 2011 0/1 response at week 12, % 1) 69.0 2) 52.5 3) 0	AE leading to discontinuation at week 12, % 1) 1.7 2) 0 3) 1.7

				2) 20.5 (8.29) 3) 21.1 (8.49) Previous biologic, % 1) 39.0 2) 47.5 3) 44.1	*p<0.0001 for all secukinumab vs. placebo comparisons	
Publication Thaci, 2015	Phase IIIb RCT Double-blind Multicenter	1) secukinumab SQ 300mg dosed at Week 0, 1, 2, 3, & q4wks to Week 48 (n=337) 2) ustekinumab SQ weight-based dosing at Week 0, 4, & q12wks from Wk 16-	Inclusion: Moderate-to-severe psoriasis defined by baseline PASI≥12, IGA mod 2011 of 3 or 4, and BSA≥10%; a diagnosis of psoriasis for ≥6 months; had	Age, mean 1) 45.2 2) 44.6	PASI 75 at week 12, % 1)91.0 2)79.1 PASI 75 at week 16, %	At week 16 Nonfatal serious AE, % 1)3.0 2)3.0

(CLEAR NCT02074982) *Good quality publication*	134 sites worldwide ITT with NRI	40 (placebo given at other wks) (n=339)	been inadequately controlled by topical treatment, phototherapy, and/or previous systemic therapy Exclusion: Previous biologics targeting IL-17 or IL-12/IL-23	Male, % 1) 68.0 2) 74.3 Caucasian, % 1) 88.7 2) 85.0 Duration of PsO (yr), mean 1) 19.6 2) 16.1 PASI, mean (SD) 1) 21.7 (8.50) 2) 21.5 (8.07) Previous biologic, %	1)93.1 2)82.7 P=0.0001 PASI 90 at week 12, % 1)72.8 2)53.4 PASI 90 at week 16, % 1)79.0 2)57.6 PASI 100 at week 12, % 1)38.9 2)25.7 P=0.0003 PASI 100 at week 16, %	AE leading to discontinuation at week 16, % 1)0.9 2)1.2

				1) 14.2 2) 13.0	1)44.3 2)28.4 IGA mod 2011 0/1 at week 12, % 1)80.8 2)65.1 IGA mod 2011 0/1 at week 16, % 1)82.9 2)67.5 DLQI 0/1 at week 12, % 1)66.2 2)56.5 P=0.0109 DLQI 0/1 at week 16, %	

					1)71.9 2)57.4 Subject-reported sx, absolute change at week 16 from baseline, mean Pain 1)-3.3 2)-2.8 P=0.0414 Itching 1)-5.0 2)-4.6 P=0.0053 Scaling 1)-5.7 2)-5.2 P=0.0001	

					*p<0.0001 unless specified otherwise	
Paul, 2015 (NCT01636687) JUNCTURE *Fair quality publication*	Phase III RCT Double-blind Multicenter 38 sites worldwide Did not specify handling of missing data	1) secukinumab 300 mg at week 0,1,2,3, and then every 4 weeks starting from week 4(n=60) 2) secukinumab 150mg at week 0,1,2,3, and then every 4 weeks starting from week (n=61) 3) placebo (n=61) Maintenance: dosing every 4 weeks, week 12-52 OTE: week 52-208 and an 8-week treatment-free FU	Inclusion: Moderate-to-severe psoriasis defined by baseline PASI≥12, IGA mod 2011 of 3 or 4, and BSA≥10%; a diagnosis of psoriasis for ≥6 months; had been inadequately controlled by topical treatment, phototherapy, and/or previous systemic therapy Exclusion: Non-plaque type or drug-induced psoriasis; ongoing use of any prohibited treatment; prior exposure to biologics targeting IL-17; medical conditions	Age, mean 1) 46.6 2) 43.9 3) 43.7 Male, % 1) 76.7 2) 67.2 3) 62.3 Caucasian, % 1) 93.3 2) 95.1 3) 96.7	PASI 75 at week 12, % 1)86.7 2)71.7 3)3.3 PASI 90 at week 12, % 1)55.0 2)40.0 3)0 PASI 100 at week 12, % 1)26.7 2)16.7 (p=0.0006 vs. (3)) 3)0	At week 12, Nonfatal serious AEs, % 1)1.7 2)4.9 3)1.6 AE leading to discontinuation, % 1)0 2)0 3)1.6

			including active systemic infection, tuberculosis, history of HIV, Hep B, Hep C, or other conditions immunocompromising patients.	Duration of PsO (yr), mean 1) 21.0 2) 20.6 3) 19.86 PASI, mean (SD) 1) 18.9 (6.37) 2) 22.0 (8.85) 3) 19.4 (6.70) Previous biologic, % 1) 25.0 2) 24.6 3) 21.3 PsA reported, % 1) 23.3	IGA mod 2011 0/1 response 1)73.3 2)53.3 3)0 *P<0.0001 for secukinumab vs. placebo comparisons unless specified otherwise	

				2) 26.2 3) 19.7		
Langley, 2014 (NCT01365455) ERASURE *Good quality publication*	Phase III RCT Double-blind Multicenter 88 sites worldwide ITT with NRI	1) secukinumab 300mg (n=245) 2) secukinumab 150mg (n=245) 3) placebo (n=248) Administered once weekly and at week 1, 2, 3, 4, then q4wks until week 48 At week 12, placebo pt who did not exceed PASI75 were randomized to secukinumab, and these patients were	Inclusion: Adults w/ moderate-to-severe plaque psoriasis PASI score ≥ 12, IGA of 3 or 4, and BSA ≥10%; a diagnosis of psoriasis for ≥6 months; poorly controlled with topical treatments, phototherapy, systemic therapy, or a combination of these therapies Exclusion:	Age (yr), mean 1) 44.9 2) 44.9 3) 45.4 Male, % 1) 69.0 2) 68.6 3) 69.4 White, % 1)69.8	PASI75 at 12 weeks, % 1) 81.6 2) 71.6 3) 4.5 IGA 0/1 at week 12, % 1) 65.3 2) 51.2 3) 2.4 PASI90 at week 12, % 1) 59.2	At week 12 Nonfatal serious AE, % 1) 1.2 2) 2.1 3) 0.9 AE leading to discontinuation, % 1)1.2 2)0.6 3)1.9

		excluded from analysis	Non-plaque or drug induced psoriasis	2)69.8 3)71.0 PASI score, mean (SD) 1) 22.5 (9.2) 2) 22.3 (9.8) 3) 21.4 (9.1) Body surface area involved, % (SD) 1) 32.8 (19.3) 2) 33.3 (19.2) 3) 29.7 (15.9) Psoriatic arthritis, % 1) 23.3 2) 18.8 3) 27.4	2) 39.1 3) 1.2 DLQI, change in mean score at Wk12 1) -11.4 2) -10.1 3) -1.1 DLQI, score of 0/1 at Wk12 1) 58.8 2) 46.1 3) 10.3 *all p<0.001 for comparisons with placebo	

				Previous biologic, % 1) 28.6 2) 29.8 3) 29.4		
Langley, 2014 (same as above) NCT01358578 FIXTURE *Good quality publication*	Phase III RCT Double-blind Multicenter 88 sites worldwide ITT with NRI	1) secukinumab 300mg (n=327) 2) secukinumab 150mg (n=327) 3) etanercept 50mg BIW until week 12, then QW until week 51 (n=326) 4) placebo (n=326) Secukinumab was administered once weekly and at week 1, 2, 3, 4, then q4wks until week 48	Inclusion: Adults w/ moderate-to-severe plaque psoriasis PASI score ≥ 12, IGA of 3 or 4, and BSA ≥10%; a diagnosis of psoriasis for ≥6 months; poorly controlled with topical treatments, phototherapy, systemic therapy, or a combination of these therapies Exclusion:	Age (yr), mean 1) 44.5 2) 45.4 3) 43.8 4) 44.1 Male, % 1) 68.5 2) 72.2 3) 71.2 4) 72.7	PASI 75 at week 12, % 1) 77.1 2) 67.0 3) 44.0 4) 4.9 IGA 0/1 at week 12, % 1) 62.5 2) 51.1 3) 27.2 4) 2.8	At week 12 Nonfatal serious AE, # events/100 person-year 1) 6.8 2) 6.0 3) 7.0 4) 8.3 AE leading to discontinuation, # events 1) 14

			Non-plaque or drug induced psoriasis; previous etanercept	White, % 1)68.5 2)67.0 3)67.2 4)66.9 PASI score, mean (SD) 1) 23.9 (9.9) 2) 23.7 (10.5) 3) 23.2 (9.8) 4) 24.1 (10.5) Psoriatic arthritis, % 1) 15.3 2) 15.0 3) 13.5 4) 15.0	PASI 90 at Wk12, % 1) 54.2 2) 41.9 3) 20.7 4) 1.5 DLQI, change in mean score at week 12 1) -10.4 2) -9.7 3) -7.9 4) -1.9 *all p<0.001 for comparisons between secukinumab and etancercept/placebo	2) 10 3) 12 4) 3

				Previous biologic, % 1) 11.6 2) 13.8 3) 13.8 4) 10.7	DLQI, score of 0/1 (%) 1) -10.4 2) -9.7 3) -7.9 4) -1.9	
Publication Ohtsuki, 2014 (ERASURE)	Subanalysis of Japanese patients (18 sites in Japan) enrolled in ERASURE trial	See original trial Bio-naïve 1) 23 2) 24 3) 23 Bio-exposed 1) 6 2) 5	See original trial	Age 1) 51.9 2) 48.2 3) 50.2 %male 1) 89.7 2) 79.3 3) 79.3 Mean PASI	Wk 12: PASI 75 (%) 1) *82.8, 2) *86.2, 3) 6.9 PASI 90 (%) 1) *62.1, 2) *55.2, 3) 0 PASI 100 PASI 100 (%) 1) **27.6, 2) 10.3, 3) 0	AEs (%) 1) 48.3 2) 55.2 3) 41.4 SAEs (per 100 PYs) 1) 2.7 2) 8.5 3) 0

		3) 6		1) 26.7 2) 28.2 3) 21.4 PsO duration (years) 1) 15.6 2) 15.6 3) 14.1 PsA 1) 13.8 2) 17.2 3) 13.8 Previous biologic: 1) 20.7 2) 17.2	IGA mod 0/1 (%) 1) *55.2, 2) *55.2, 3) 3.4 *p<0.0001, **p<0.01 DLQI score of 0/1 (%) 1) 71.4, 2) 65.5, 3) 24.1 *1 vs. 3, p<0.001* *2 vs. 3, p<0.01* **Improvements persisted after one year** PASI 75 Bio-naïve:	

				3) 20.7	1) 82.6, 2) 83.3, 3) 8.7 Bio-exposed: 1) 83.3, 2) 100, 3) 0 PASI 90 Bio-naïve: 1) 65.2, 2) 54.2, 3) 0 Bio-exposed: 1) 50, 2) 60, 3) 0	
Blauvelt, 2014 ERASURE *Abstract*	*See ERASURE*	*See ERASURE* *1)secukinumab 300 mg* *2)secukinumab 150 mg* *3)placebo* Reports outcomes of subpopulation w/ PsA	See ERASURE	PsA patients (n=171)	PASI 75 at week 12,% 1) 68 2) 70 3) 4 PASI 90 at week 12,% 1) 53 2) 44	NR

					3) 0	
Papp, 2014 ERASURE *Abstract*	*As above*	*As above* Reports outcomes based on prior biologic exposure	See ERASURE	Previous exposure to biologic (n=216/738) Previous inadequate response to biologic (n=72/216)	no prior biologic exposure PASI 75 at week 12, % 1) 84.0 2) 74.7 3) 4.6 IGA 0/1 at week 12, % 1) 67.4 2) 55.0 3) 2.9 w/ prior biologic exposure PASI 75 at week 12, % 1) 75.7% 2) 64.4% 3) 4.1%	NR

					IGA 0/1 at week 12, % 1) 60.0% 2) 42.5% 3) 1.4% *p<0.0001 for each secukinumab dose vs. placebo	
Strober, 2016 (ERASURE and FIXTURE) *Good quality publication*	*Secondary analysis*	*As above* 39% patients who (n=678/1718) completed Psoriasis Symptom Diary (PSD) were included in this analysis 1) secukinumab 300mg (n=224)	See ERASURE and FIXTURE	Age (yr), mean 1) 43.0 2) 45.7 3) 43.1 Male, % 1) 62.5 2) 65.9	Response rate for itching (reduction of ≥2.2 points from baseline) at week 12, % 1) 83.0 2) 78.2 3) 16.9 Response rate for pain (reduction of	*NR*

		2) secukinumab 150mg (n=229) 3) placebo (n=225)		3) 71.1 PASI, mean (SD) 1) 21.9 (9.0) 2) 21.8 (9.0) 3) 21.6 (8.7) PSD, itching mean (SD) 1) 6.4 (2.4) 2) 6.5 (2.4) 3) 6.1 (2.5) PSD, pain mean (SD) 1) 5.5 (3.0) 2) 5.3 (3.1) 3) 5.0 (3.0)	≥2.2points from baseline) at week 12, % 1) 72.8 2) 65.5 3) 15.6 Response rate for scaling (reduction of ≥2.2points from baseline) at week 12, % 1) 83.0 2) 78.2 3) 13.8	

				PSD, scaling mean (SD) 1) 6.4 (2.6) 2) 6.5 (2.4) 3) 6.2 (2.4)		
Ixekizumab (Taltz)						
Gordon, 2016 (NCT01474512) UNCOVER-1 *Good quality publication*	Phase III RCT Double-blind Multicenter 100 sites worldwide ITT with NR	N=1296 1) placebo (n=431) 2) ixekizumab, 80mg Q4W (n=432) 3) ixekizumab, 80mg Q2W (n=433) *Patients who had an sPGA score of* *0 or 1 at week 12 and entered the randomized withdrawal period through 60 weeks*	Inclusion: ≥18 years BSA ≥10%, PASI ≥12 sPGA ≥3 ≥6 months of plaque psoriasis diagnosis Candidates for phototherapy or systemic therapy	**Age (years):** 1) 46, 2) 46, 45 **% male:** 1) 70.3, 2) 66.9, 3) 67.2 **Weight (kg):** <100kg- 1) 67.1, 2) 66.5, 3) 66.5 ≥100kg- 1) 32.9, 2) 32.9, 3) 33.5 **PsO duration (years):** 1) 20, 2) 19, 3) 20 **PASI:**	Primary outcomes at week 12: **PASI 75 (%):** 1) 3.0, 2) 82.6, 3) 89.1 **PASI 90 (%):** 1)0.5 2) 64.6, 3) 70.9 **PASI 100 (%):** 1) 0.0, 2) 33.6, 3) 35.3 **sPGA score of 0/1 (%):** 1) 3.2, 2) 76.4, 3) 81.8 *All IXE groups vs. placebo, p<0.001*	Primary outcomes at week 12 (pooled across UNCOVER trials): **AEs (%):** 1) 46.8, 2) 58.3, 3) 58.4 All IXE- 80.9 **SAEs (%):** 1) 1.5, 2) 2.2, 3) 1.7 All IXE (wk 0-60)- 6.7 **Discontinuation of study due to AEs (%):** 1) 1.1, 2) 2.1, 3) 2.1

		2a) maintained on ixekizumab 80mg Q4W 2b) switch to ixekizumab 80mg Q2W		1) 20, 2), 20, 3) 20 **DLQI:** NR **PsA (%):** NR **Previous biologics (%):** 1) 42.0, 2) 38.9, 3) 40.0	At wk 60 (pooled UNCOVER-1 and -2): **PASI 75 (%):** 2a) 80, 2b) 83 **PASI 90 (%):** 2a) 71, 2b) 73 **sPGA score of 0/1 (%):** 2a) 73, 2b) 75	All IXE (wk 0-60)- 4.4 **Infections (%):** 1) 22.9, 2) 27.4, 3) 27.0 All IXE (wk 0-60)- 55.2 **MACE (%):** 1) 0.1, 2) 0.2, 3) 0.0 All IXE (wk 0-60)- 0.6 **Grade 3 or 4 neutropenia (n):** 1) 1, 2) 1, 3) 2 All IXE (wk 0-60)- 10 **Deaths (n):** 0 in all groups All IXE (wk 0-60)- 0.1 (3 patients)
Langley, 2016 (NCT01474512)	Reports improvement in HRQoL for IXE Q4W	See above	See above	See above	**DLQI, mean change at 12 weeks:** -11.3*	NR

UNCOVER-1 *Abstract*					**DLQI, mean change at 60 weeks:** -11.2* **DLQI, score of 0/1 at 60 weeks (%):** 66.4 *p<0.001 from baseline	
Griffiths, 2015 and Gordon, 2016 (NCT01597245) UNCOVER-2 *Good quality publication*	Phase III RCT Double-blind Multicenter Sites in USA, Canada, Mexico, Argentina, Chile, Europe, Czech Republic, Hungary, Romania, Russia, Australia, and Japan	N=1224 1) placebo (n=168) 2) etanercept (n=358) 3) ixekizumab 80mg Q4W (n=347) 4) ixekizumab, 80mg Q2W (n=351) *Patients who had an sPGA score of* *0 or 1 at week 12 and entered the*	Inclusion: ≥18 years BSA ≥10%, PASI ≥12 sPGA ≥3 ≥6 months of plaque psoriasis diagnosis Candidates for phototherapy or systemic therapy	**Age (years):** 1) 45, 2) 45, 3), 45, 4), 45 **% male:** 1) 71.4, 2) 65.9, 3) 70.3, 4) 63.0 **Weight (kg):** <100kg- 1) 66.9, 2) 65.0, 3) 65.6, 4) 72.9 ≥100kg- 1) 33.1, 2) 35.0, 3) 34.4, 4) 27.1 **PsO duration (years):**	Primary outcomes at week 12: **PASI 75 (%):** 1) 2.4, 2) 41.6‡, 3) 77.5‡§, 4) 89.7‡§ **PASI 90 (%):** 1) 0.6, 2) 18.7‡, 3) 59.7‡§, 4) 70.7‡§ **PASI 100 (%):** 1) 0.6, 2) 5.3, 3) 30.8, 4) 40.5	Primary outcomes at week 12 (pooled across UNCOVER-1 and -2 trials): **AEs (%):** 1) 44, 2) 54, 3) 58, 4) 58 **SAEs (%):** 2% in all groups **Discontinuation of study due to AEs (%):**

	ITT	*randomized withdrawal period*	Exclusion: Patients who had used etanercept at any time before screening	1) 19, 2) 19, 3) 19, 4) 18 **PASI:** 1) 21, 2) 19, 3) 20, 4) 19 **DLQI:** NR **PsA (%):** NR **Previous biologics (%):** 1) 25.6, 2) 21.2, 3) 24.5, 4) 23.9	**sPGA score of 0/1 with ≥2-point reduction (%):** 1) 2.4, 2) 36.0‡§, 3) 72.9‡§, 4) 83.2‡§ **DLQI, score of 0/1 (%):** 1) 6.0, 2) 33.8‡, 3) 59.9‡§, 4) 64.1‡§ *‡p<0·0001 compared with placebo* *§p<0·0001 compared with etanercept (see Table 2 in publication for differences between groups and 97.5% CI)* ***Other outcomes reported: sPGA score of 0, PASI % improvement, DLQI mean change, Itch NRS***	1) 0.01, 2) 0.07, 3) 0.05, 4) 0.03 **URIs (%):** 1) 3, 2) 5, 3) 3, 4) 4 **Deaths (n):** 0 in all groups

Gottlieb, 2016 (NCT01597245) UNCOVER-2 *Abstract*	Reports improvement in skin pain VAS	See above	See above	See above **Mean VAS** 1) 49.2	**Skin pain VAS at 12 weeks:** 1) 44.5, 2) 18.9, 3) 10.3, 4) 7.2 *Least squares mean change from baseline:* 1) -4.6, 2) -29, 3) -37.7, 4) -42.2 *All comparisons, p<0.001*	NR
Papp, 2016 (NCT01597245) UNCOVER-2 *Abstract*	Reports outcomes for patients who failed etanercept (sPGA≤2) during the induction period and began received IXE Q4W	N=200	NR	NR	Outcomes after 12 weeks: **PASI 75 (%):** 83.5 **PASI 90 (%):** 57.0 **PASI 100 (%):** 22.0 **sPGA score of 0/1 (%):** 73	**SAEs ≥1 (%):** 4.5 **Discontinuation of study due to AEs (%):** 4 Most AEs were mild or moderate and were similar placebo non-

					Outcomes after 44 weeks of IXE (at 60 weeks): **PASI 75 (%):** 82.5 **PASI 90 (%):** 68.5 **PASI 100 (%):** 43.5 **DLQI, score of 0/1 (%): 58** *No outcomes were statistically measured*	responders who also started IXE Q4W *No outcomes were statistically measured*
Griffiths, 2015 and Gordon, 2016 (same as above) (NCT01646177) UNCOVER-3	Phase III RCT Double-blind Multicenter Sites in USA, Canada, Mexico, Argentina, Chile, Europe, Czech Republic, Hungary,	N=1346 1) placebo (n=193) 2) etanercept (n=382) 3) ixekizumab, 80mg Q4W (n=386) 4) ixekizumab, 80mg Q2W (n=385)	Same as UNCOVER-2	**Age (years):** 1) 46, 2) 46, 3), 46, 4), 46 **% male:** 1) 71.0, 2) 70.4, 3) 66.8, 4) 66.0 **Weight (kg):** <100kg- 1) 71.9, 2) 67.0, 3) 71.9, 4) 71.6	Primary outcomes at week 12: **PASI 75 (%):** 1) 7.3, 2) 53.4†, 3) 84.2†‡, 4) 87.3†‡ **PASI 90 (%):** 1) 3.1, 2) 25.7†, 3) 65.3†‡, 4) 68.1†‡ **PASI 100 (%):**	See above

Good quality publication	Romania, Russia, Australia, and Japan ITT			≥100kg- 1) 28.1, 2) 33.0, 3) 28.1, 4) 28.4 **PsO duration (years):** 1) 18, 2) 18, 3), 18, 4) 18 **PASI:** 1) 21, 2), 21, 3) 21, 4) 21 **DLQI:** NR **PsA (%):** NR **Previous biologics (%):** 1) 17.1, 2) 15.7, 3) 15.0, 4) 15.1	1) 0.0, 2) 7.3†, 3) 35.0†‡, 4) 37.7†‡ **sPGA score of 0/1 with ≥2-point reduction (%):** 1) 6.7, 2) 41.6†, 3) 75.4†‡, 4) 80.5†‡ **DLQI, score of 0/1 (%):** 1) 7.8, 2) 43.7‡, 3) 63.7‡§, 4) 64.7‡§ *†p<0·0001 compared with placebo* *‡p<0·0001 compared etanercept* *(see Table 2 in publication for differences between groups and 97.5% CI)* ***Other outcomes reported: sPGA score of 0, PASI %***	

					improvement, DLQI mean change, Itch NRS	
Guenther, 2016 UNCOVER-2 and -3 *Abstract*	Secondary analysis to evaluate improvement in sexual difficulties using DLQI Item 9	See main trials	See main trials	See main trials	**Primary outcomes at week 12:** *UNCOVER-2* **Improvement in sexual difficulties (%):** 1) 24, 2) 51, 3) 68, 4) 80 3 and 4 vs. 1 and 2, p<0.001 *UNCOVER-3* 1) 27, 2) 69, 3) 78, 4) 81 3 and 4 vs. 2, p<0.05 3 and 4 vs. 1, p<0.001	NR
Armstrong, 2016 UNCOVER trials (all)	See above Secondary analysis to evaluate change in work productivity	N=3866	See main trials	See main trials	**WPAI-PSO*** *UNCOVER-1* <u>Absenteeism:</u>	NR

Good quality publication	from baseline as measured by WPAI-PSO scores				1) 0.2, 2) -3.5, *p< 0.001 vs. 1*, 3) -2.6, *p= 0.003 vs. 1* <u>Presenteeism:</u> 1) 0.5 2) -18.8, 3) -18.3 *2 and 3 vs. 1, p<0.001* <u>Work productivity loss:</u> 1) -0.8, 2) -20.6, 3) -19.8 *2 and 3 vs. 1, p<0.001* <u>Activity impairment:</u> 1) 0.8, 2) -24.5, 3) -25.2 *2 and 3 vs. 1, p<0.001* "Similar results were obtained for UNCOVER-2 and UNCOVER-3, with the exception of absenteeism with	

					ixekizumab Q4W in UNCOVER-2” *UNCOVER-2 (from graph)* <u>Work productivity loss:</u> 1)-2, 2) -14, 3) -19, 4) -19.5 *2 and 3 vs. 1 and 2, p<0.001* *UNCOVER-3 (from graph)* <u>Work productivity loss:</u> 1) +0.7, 2) -17, 3) -16, 4) -19 *4 vs. 1, p<0.001; all other comparisons NS*	

					**Data presented as least squares* *mean change from baseline relative to placebo*	
Griffiths, 2016 Pooled UNCOVER trials (all) *Abstract*	Secondary analysis to evaluate improvement in depression (etanercept group not included)	N=3119 1) placebo (n=791) 2) ixekizumab, 80mg Q4W (n=1161) 3) ixekizumab, 80mg Q2W (n=1167)	See main trials	**QIDS-SR16 median score:** 14.0 (no difference b/w groups)	Primary outcomes at week 12: **QIDS-SR16 mean change:** 1) -3.6, 2) -6.5, 3) -6.9 *2 and 3 vs. 1, p<0.001* **QIDS-SR16 ≥50% improvement from baseline (%)*:** 1) 27.1, 2) 49.1, 3) 59.8 *2 and 3 vs. 1, p≤0.001* **QIDS-SR16 remission (score ≤5) (%)*:** 1) 17.8, 2) 33.5, 3) 45.2 *2 and 3 vs. 1, p<0.05*	NR

					**Outcomes presented for NRI analysis*	
Gottlieb, 2016 Pooled UNCOVER trials (all) *Abstract*	Secondary analysis to evaluate subgroups of patients who were biologic-naïve vs. biologic-experienced	N=3126 1) placebo (n=792) 2) ixekizumab, 80mg Q4W (n=1165) 3) ixekizumab, 80mg Q2W (n=1169) a) biologic-experienced (n=883) b) biologic-naïve (n=2243)	See main trials	NR	Primary outcomes at week 12: **PASI 75 (%):** 1a) 2.7, 1b) 5.2, 2a) 77.5, 2b) 83.1, 3a) 89.5, 3b) 88.4 **PASI 90 (%):** 1a) 0, 1b) 1.7, 2a) 53.7, 2b) 66.9, 3a) 73.0, 3b) 68.7 **PASI 100 (%):** 1a) 0, 1b) 0.3, 2a) 32.0, 2b) 34.7, 3a) 36.6, 3b) 39.1 *All IXE groups vs. placebo, p<0.001*	NR

Gottlieb, 2015 Pooled UNCOVER trials (all) *Abstract*	Secondary analysis to evaluate subgroups of patients with PsA (etanercept group not included)	N=792	See main trials	**Joint Pain VAS:** 49.6 **PASI:** 21.6 **DLQI:** 14.2	**Joint Pain VAS, mean change:** Placebo, +1.1 IXE Q4W, -25.2 IXE Q2W, -26.8 **DLQI, mean change:** Placebo, -0.8 IXE Q4W, -10.5 IXE Q2W, -11.8 **PASI 75 (%):** Placebo, 2.9 IXE Q4W, 81.1 IXE Q2W, 89.8 **SF-36 MCS, mean score:** Placebo, +0.8 IXE Q4W, +4.2	NR

					IXE Q2W, +5.2 **SF-36 PCS, mean score:** Placebo, -1.1 IXE Q4W, +5.1 IXE Q2W, +5.4 *IXE groups vs. placebo for all outcomes, p<0.001*	
Brodalumab						
Papp, 2012 (NCT00975637) *Good quality publication*	Phase II RCT Double-blind Multicenter 23 international sites ITT	N=198 1) brodalumab 70mg (n=39) 2) brodalumab 140mg (n=39) 3) brodalumab 210mg (n=40) 4) placebo (n=38)	Inclusion: ≥18 years BSA ≥10%, PASI ≥12 sPGA ≥3 ≥6 months of plaque psoriasis diagnosis	**Age (years):** 1) 42.1, 2) 44.0, 3) 42.1, 4) 41.8 **% male:** 1) 56, 2) 72, 3) 62, 4) 58 **Weight (kg):** 1) 88.8, 2) 92.4, 3) 88.8, 4) 86.9	Primary outcomes at week 12: **PASI 75 (%):** 1) 33, 2) 77, 3) 82, 4) 0 **PASI 50 (%):** 1) 51, 2) 90, 3) 90, 4) 16 **PASI 90 (%):**	Primary outcomes at week 12: **AEs ≥1 (%):** 1) 68, 2) 69, 3) 82, 4) 62 **URIs (%):** 1) 8, 2) 8, 3) 5, 4) 5 **SAEs ≥1 (%):** 1) 3, 2) 0, 3) 2, 4) 3

		Also evaluated 280mg brodalumab monthly	Candidates for phototherapy or systemic therapy Exclusion: patients could not have received biologic agents within 3 months, and no previous treatment with ustekinumab or etanercept	**PsO duration (years):** 1) 20.7, 2) 19.2, 3) 17.1, 4) 18.3 **PASI:** 1) 18.8, 2) 19.4, 3) 20.6, 4) 18.9 **DLQI:** 1) 12.4, 2) 11.1, 11.4, 13.3 **PsA (%):** 1) 21, 2) 28, 3) 30, 4) 18 **Previous biologics (%):** Entanercept- 1) 18, 2) 8, 3) 10, 4) 18 Adalimumab- 1) 8, 2) 13, 3) 18, 4) 11 Ustekinumab- 1) 15, 2) 5, 3) 15, 13	1) 18*, 2) 72, 3) 75, 4) 0 **sPGA score of 0/1 (%):** 1) 26*, 2) 85, 3) 80, 4) 3 *All BROD groups vs. placebo for both outcomes, p<0.001; *p<0.01* **DLQI, mean change:** 1) -5.9*, 2) -9.1, 3) -9.4, 4) -3.0 *All BROD groups vs. placebo, p<0.001; *p<0.01* **SF-36, Physical:** 1) +1.7, 2) +4.2, 3) +4.0, 4) +1.5 *2 vs. placebo, p<0.01*	**Discontinuation due to AEs (%):** 1) 0, 2) 0, 3) 5, 4) 3 **Deaths: NR**

					SF-36, Mental: 1) +2.4, 2) +4.4, 3) +5.0, 4) +1.7 *2 vs. placebo, p<0.05;* *3 vs. placebo, p<0.01* ***Other outcomes reported: Mean % BSA***	
Gordon, 2013 (NCT00975637) *Good quality publication*	Secondary analysis of Phase II data evaluating quality of life	See above	See above	See above	Primary outcomes at week 12: **PSI total score = 0 (%):** 1) 18, 2) 41, 3) 55, 4) 0 2 and 3 vs. 4, p<0.0001; 1 vs. 4 p=0.006 **PSI change:** 1) 8.5, 2) 15.8, 3) 16.2, 4) 4.8	NR

					2 and 3 vs. 4, p<0.0001; 1 vs. 4, p=0.042 Other outcomes reported: Includes further breakdown of PSI and DLQI components at weeks 2, 4, 8	
Papp, 2014 (NCT00975637) *Fair quality publication*	Secondary analysis of Phase II data evaluating subgroups with and without PsA and with and without previous biologic use Subgroups were not compared statistically due to low statistical power	1) PsA- yes (n=46) 2) PsA- no (n=152) 3) Biologic use- yes (n=70) 4) Biologic use- no (n=158) a) placebo b) brodalumab 140mg c) brodalumab 210mg	See original trial	**Age (years):** 1) 89.7, 2) 90.1, 3) 93, 4) 21.3 **PsO duration (years):** 1) 24.3, 2) 17.3, 3) 21.4, 4) 17.6 **PASI:** 1) 26.6, 2) 22.9, 3) 26.5, 4) 22.2 **DLQI:** 1) **PsA (%)**	Primary outcomes at week 12: **PASI 75 (%):** 1a) 0, 1b) 82, 1c) 92 2a) 0, 2b) 75, 2c) 79 3a) 0, 3b) 70, 3c) 88 4a) 0, 4b) 60, 4c) 79 **PASI 90 (%):** 1a) 0, 1b) 73, 1c) 83 2a) 0, 1b) 71, 2c) 71 3a) 0, 1b) 70, 1c) 81	AEs of any grade were higher among patients who received brodalumab versus placebo and were similar among subgroups (data NR)

				1) 100, 2) 0, 3) 24.3, 4) 22.7 **Previous biologics (%):** Anti-TNF- 1) 32.6, 2) 21.7, 3) 68.6, 4) 0 Ustekinumab- 1) 4.3, 2) 13.8, 3) 32.9, 4) 0	4a) 0, 1b) 72, 3c) 71 **DLQI response:** 1a) 0, 1b) 100, 1c) 100 2a) 42, 2b) 75, 2c) 79 3a) 33, 3b) 80, 3c) 94 4a) 35, 4b) 83, 4c) 79 **PSI score ≤8, with no item having a score >1 (%):** 1a) 14, 1b) 100, 1c) 94 2a) 13, 2b) 86, 2c) 79 3a) 8, 3b) 100, 3c) 86 4a) 15, 4b) 94, 4c) 79 *All BROD groups vs. placebo were SS* Outcomes not compared between subgroups	

					Other outcomes reported: PASI 100	
Papp, 2015 (NCT00975637) *Abstract*	Secondary analysis of Phase II data evaluating subgroups with and without previous biologic use	1) Biologic use- yes (n=70) 2) Biologic use- no (n=158) a) brodalumab 70mg b) brodalumab 140mg c) brodalumab 210mg d) placebo	See original trial	See original trial	Primary outcomes at week 12: **sPGA score of 0/1 (%):** 1a) 8, 1b) 80, 1c) 81, 1d) 0 2a) 35, 2b) 86, 2c) 79, 2d) 4 *No outcomes were evaluated statistically* Other outcomes reported: sPGA score of 0	**AEs at week 12 (%):** 1) brodalumab (combined) – 79% placebo – 67% 2) brodalumab (combined) – 70% placebo – 60%
Papp, 2016 (NCT01708590) AMAGINE 1	Phase III RCT Double-blind Multicenter	N=661 1) brodalumab 140mg Q2W (n=219) 2) brodalumab 210mg Q2W 3) placebo (n=222)	Inclusion: 18 - 75years BSA ≥10%, PASI ≥12 sPGA ≥3	**Age (years):** 1) 46, 2) 46, 3) 47 **% male:** 1) 74, 2) 73, 3) 73 **Weight (kg):**	Primary outcomes at week 12: **PASI 75 (%):** 1) 60, 2) 83, 3) 3 **PASI 90 (%):**	Primary outcomes at week 12: **AEs ≥1 (%):** 1) 58, 2) 59, 3) 51 **SAEs (%):**

Good quality publication	73 sites in the US, Canada, and Europe ITT (all randomized patients)	Patients who achieved sPGA success (≥2) at week 12 were rerandomized to their induction doses of brodalumab or placebo	≥6 months of plaque psoriasis diagnosis Candidates for phototherapy or systemic therapy Exclusion: A washout period was required for patients receiving specific drugs (reported in supplementary appendix)	1) 90.6, 2) 91.4, 3) 90.4 **PsO duration (years):** 1) 19, 2), 20, 3) 21 **PASI:** 1) 19.7, 2) 18.9, 3) 19.0 **DLQI:** NR **PsA (%):** 1) 27, 2) 26, 3) 29 **Previous biologics (%):** 1) 45, 2) 47, 3) 46	1) 42.5, 70.3, 2) 0.9 **PASI 100 (%):** 1) 0.5, 2) 23.3, 3) 41.9 **sPGA score of 0/1 (%):** 1) 54, 2) 76, 3) 1 **HADS-A (treatment difference, after imputation):** 1) -1.3, 2) -1.5 *BROD vs. placebo, p<0.001* **HADS-D (treatment difference, after imputation):** 1) -1.9, 2) -2.1 *BROD vs. placebo, p<0.001* **PSI responder (score ≤8, with no item having a score >1) (%):**	1) 2.7, 2) 1.4, 3) 1.8 **Discontinuation due to AEs (%):** 1) 1.8, 2) 0.9, 3) 1.4 **Depression (%)** 1) 0.5, 2) 0.5, 3) 0.5 **URIs (≥5% in any group):** 1) 8.2, 2) 8.1, 3) 6.4 **No deaths** **AE outcomes at week 52** reported based on number of patients with exposure-emergent adverse events per 100 patient-years **5 deaths** (2 suicides, 1 in the placebo group and 1 in the

					1) 53, 2) 61, 3) 4 At week 52: **PASI 90 (%):** BROD 210/BROD 210, 78.3 BROD210/placebo, 0.0 BROD 140/BROD 140, 66.7 BROD140/placebo, 3.4 **PASI 100 (%):** BROD 210/BROD 210, 67.5 BROD210/placebo, 0.0 BROD 140/BROD 140, 43.9 BROD140/placebo, 1.7	brodalumab 210mg group)

					sPGA score ≥2 (%): BROD 210/BROD 210, 83.1 BROD210/placebo, 0.0 BROD 140/BROD 140, 70.2 BROD140/placebo, 5.1 *All BROD vs. placebo, p<0.001* ***Other outcomes reported: sPGA score of 0***	
Strober, 2016 (NCT01708590) AMAGINE 1	PROs from AMAGINE-1	See original trial	See original trial	See original trial	Primary outcomes at week 12: **DLQI improvement ≥5 (%)** 1) 74, 2) 84, 3) 22	NR

Abstract					**DLQI score of 0/1 (%)** 1) 43, 2) 56, 3) 5 **PSI score = 0 (%)** 1) 17, 2) 22, 3) 1 *All BROD groups vs. placebo, p<0.001* PSI responder data same as Papp, 2016	
Lebwohl, 2015 NCT01708603 AMAGINE-2 *Good quality publication*	Phase III RCT Double-blind Multicenter 142 international sites (US, Canada, Europe, Australia) ITT	N=2,492 1) placebo (n=309) 2) ustekinumab (n=300) 3) brodalumab 140mg Q2W (n=610) 4) brodalumab 210mg Q2W (n=612) At week 12, patients receiving brodalumab underwent	Inclusion: 18 - 75years BSA ≥10%, PASI ≥12 sPGA ≥3 ≥6 months of plaque psoriasis diagnosis Candidates for phototherapy or systemic therapy	**Age (years):** 1) 44, 2) 45, 3) 45, 4) 45 **% male:** 1) 71, 2) 68, 3) 68, 4) 69 **Weight (kg):** 1) 92, 2), 91, 3) 92, 4) 91 **PsO duration (years):**	Primary outcomes at week 12: **PASI 75 (%)** 1) 8, 2) 70, 3) 67, 4) 86 **PASI 90 (%)** 1) 3, 2) 47, 3) 49, 4) 70 **PASI 100 (%)** 1), 2, 2) 22, 3) 26, 4) 44 **sPGA score of 0 or 1 (%)**	Primary outcomes at week 12: ***AMAGINE-2*** **AEs ≥1 (%):** 1) 53.4, 2) 59.0, 3) 60.1, 4) 57.8 **SAEs (%):** 1) 2.06, 2) 1.3, 3) 2.1, 4) 1.0 **Discontinuation due to AEs (%):**

		rerandomization to receive one of four brodalumab maintenance regimens		1) 18, 2) 19, 3) 19, 4) 19 **PASI:** 1) 20.4, 2) 20.0, 3) 20.0, 4) 20.3 **DLQI:** NR **PsA (%):** 1) 17, 2) 17, 3), 21, 4) 19 **Previous biologics (%):** 1)29, 2) 28, 3) 29, 4) 29	1) 4, 2) 61, 3) 58, 4) 79 **p1 (%)** 1) 7, 2) 55, 3) 51, 4) 68 *All BROD groups vs. placebo, p<0.001* *BROD 210mg was SS better than UST in both trials on PASI 75, 90, 100 and sPGA score of 0/1 (p-values in Table 2; no comparison b/w BROD and UST for PSI) ***Other outcomes reported: sPGA score of 0*** At week 52 (after switching to brodalumab 210 mg):	1) 0.3, 2) 1.3, 3) 1.2, 4) 1.2 **1 attempted suicide** in the brodalumab 210mg group **1 death** in the brodalumab 210mg group (cerebral infarction) **AE outcomes at week 52:** Based on number of patients with exposure-emergent adverse events per 100 patient-years (reported in supplementary appendix) **2 additional attempted suicides** in

					PASI 75 (%) 1) 94, 2) 91 **PASI 100 (%)** 1) 62, 2) 46 **sPGA score of 0/1 (%)** 1) 87, 2) 73 **PSI score ≤8, with no item having a score >1 (%)** 1) 81, 2) 84	the same patient as the induction period and 1 in the UST group
Lebwohl, 2015 (same as above) (NCT01708629) AMAGINE-3 *Good quality publication*	Phase III RCT Double-blind Multicenter 142 international sites (US, Canada, Europe, Australia)	N=1,881 1) placebo (n=315) 2) ustekinumab (n=313) 3) brodalumab 140mg Q2W (n=629) 4) brodalumab 210mg Q2W (n=624)	See above	**Age (years):** 1) 44, 2) 45, 3) 45, 4) 45 **% male:** 1) 66, 2) 68, 3) 70, 4) 69 **Weight (kg):** 1) 89, 2), 90, 3) 89, 4) 90 **PsO duration (years):**	Primary outcomes at week 12: **PASI 75 (%)** 1) 69, 2) 85*, 3) 69, 4) 6 **PASI 90 (%)** 1) 2, 2) 48, 3) 52, 4) 69 **PASI 100 (%)** 1) 0.3, 2)19, 3) 27, 4) 37	**AEs ≥1 (%):** 1) 48.6, 2) 53.7, 3) 52.6, 4) 56.8 **SAEs (%):** 1) 1.0, 2) 0.6, 3) 1.6, 4) 1.4 **Discontinuation due to AEs (%):** 1) 1.0, 2) 0.6, 3) 0.8, 4) 1.1

	ITT			1) 18, 2), 18, 3) 17, 4) 18 **PASI:** 1) 20.1, 2) 20.1, 3) 20.1, 4) 20.4 **DLQI:** NR **PsA (%):** 1) 19, 2) 20, 3) 21, 4) 20 **Previous biologics (%):** 1) 24, 2) 24, 3) 25, 4) 25	**sPGA score of 0/1 (%):** 1) 6), 2) 69, 3) 69, 4) 85 **PSI score ≤8, with no item having a score >1 (%)** 1) 6, 2) 52, 3) 53, 4) 61 *All BROD groups vs. placebo, p<0.001* *BROD 210mg was SS better than UST in both trials on PASI 75, 90, 100 and sPGA score of 0/1 (p-values in Table 2; no comparison b/w BROD and UST for PSI) ***Other outcomes reported: sPGA score of 0***	**AE outcomes at week 52** based on number of patients with exposure-emergent adverse events per 100 patient-years (reported in supplementary appendix) **No attempted suicides at any point during the study**

					At week 52 (after switching to brodalumab 210 mg): **PASI 75 (%)** 1) 93 2) 92 **PASI 100 (%)** 1) 68 2) 40 **sPGA score of 0/1 (%)** 1) 90 2) 70 **PSI score ≤8, with no item having a score >1 (%)** 1) 86 2) 73	
Anti IL-12/13 Agent						
Ustekinumab (Stelara)						

Griffiths, 2010 (NCT00454584) ACCEPT *Fair quality publication*	Phase III RCT Multicenter *Dose of UST was blinded, but otherwise patients knew which drug they were receiving* 67 sites worldwide ITT but unclear about handling of missing data	N=903 1) ustekinumab 45mg (n=209) 2) ustekinumab 90mg (n=347) 3) etanercept 50mg (n=347) *Patients who did not respond on etanercept crossed over to receive ustekinumab*	Inclusion: ≥18 years BSA ≥10%, PASI ≥12, sPGA ≥3 ≥6 months of plaque psoriasis diagnosis Candidates for phototherapy or systemic therapy Exclusion: patients could not have received biologic agents within 3 months, and no previous treatment with ustekinumab or etanercept	**Age (years):** 1) 45.1, 2) 44.8, 3) 45.7 **% male:** 1) 63.6, 67.4, 3) 70.9 **Weight (kg):** 1) 90.4, 2) 91.0, 3) 90.8 **PsO duration (years):** 1) 18.9, 2) 18.7, 3) 18.8 **PASI:** 1) 20.5, 2) 19.9, 3) 18.6 **DLQI:** NR **PsA (%):** 1) 29.7, 2) 27.4, 3) 27.4	Primary outcomes at wk 12: **PASI 75 (%)** 1) 67.5 2) 73.8, 3) 56.8 *1 vs. 3, p=0.01* *2 vs. 3, p<0.001* **PASI 90 (%)** 1) 36.4, 2) 44.7, 23.1 **sPGA score of 0/1 (%)** 1) 65.1, 2) 70.6, 3) 49.0 *Both UST groups vs. ETN, p<0.001* Patients who did not respond on ETN and crossed over to UST 90mg: **PASI 75 (%)**: 48.9 **PASI 90 (%):** 23.4	Primary outcomes at week 12: **AEs ≥1 (%):** 1) 66.0, 2) 69.2), 3) 70.0 **URIs (%):** 1) 6.2, 2) 6.3, 3) 5.8 **SAEs ≥1 (%):** 1) 1.9, 2) 1.2, 3) 1.2 **Infections (%):** 1) 30.6, 2) 29.7, 3) 29.1 **Discontinuation due to AEs (%):** 1) 1.9, 2) 2.0, 3) 2.3 **3 deaths**, 1 in each active treatment arm **Common AEs at wk 64:** adverse events

				Previous biologics (%): 1) 12.4, 2) 10.4, 3) 11.8	**PGA- cleared or minimal (%):** 40.4 ***Other outcomes reported: PGA cleared***	were similar in the lower-dose and higher-dose ustekinumab groups and also before and after crossover from etanercept to ustekinumab
Leonardi, 2008 (NCT00267969) PHOENIX 1 *Good quality publication*	Phase III RCT Double-blind Multicenter 48 sites in the US, Canada, and Belgium ITT with NRI	N=766 1) ustekinumab 45mg (n=255) 2) ustekinumab 90mg (n=256) 3) placebo (n=255) Ustekinumab patients with PASI ≥75% improvement re-randomized at wk 40 1) maintenance (n=162) 2) withdrawal (n=160)	Inclusion: ≥18 years PASI ≥12 BSA ≥10% ≥6 months of plaque psoriasis diagnosis Candidates for phototherapy or systemic therapy Exclusion: previous treatment with any agent that targets IL-12 or -23, received biological or investigational agents within previous 3	**Age:** 1) 44.8, 2) 46.2, 3) 44.8 **% male:** 1) 68.6, 2) 67.6, 3) 71.8 **Weight (kg):** 1) 93.7, 2) 93.8, 3) 94.2 **PsO duration (years):** 1)19.9, 2) 19.6, 3) 20.4 **PASI:** 1) 20.5, 2) 19.7, 3) 20.4	Primary outcomes at wk 12: **PASI 75 (%)** 1) 67.1, 2) 170 (66.4), 3) 3.1 **PASI 50 (%)** 1) 83.5, 2) 85.9, 3) 10.2 **PASI 90 (%)** 1) 41.6, 2) 36.7, 3) 2.0 *All UST groups vs. placebo, p<0.0001* **PGA- cleared or minimal (%):**	Primary outcomes at week 12: **AEs ≥1 (%):** 1) 57.6, 2) 51.4, 3) 48.2 **URIs (%):** 1) 7.1, 2) 6.3, 3) 6.3 **SAEs (%):** 1) 0.8, 2) 1.6, 3) 0.8 **Infections (%):** 1) 31.4, 2) 25.9, 3) 26.7

		Cross-over to ustekinumab 45 or 90 mg at week 12	months, had received conventional systemic psoriasis therapy, or phototherapy within the previous 4 weeks, or had received topical psoriasis treatment within the previous 2 weeks	**DLQI:** 1) 11.1, 2) 11.6, 3) 11.8 **PsA:** 1) 29.0, 2) 36.7, 3) 35.58 **Previous biologics (%):** 1) 52.2, 2) 50.8, 3) 50.2	1) 60.4, 2) 52.4, 3) 105 (n) *1 vs. 3: 56.5%, 95% CI 50.0–62.9, p<0.0001* *2 vs. 3: 57.8%, 95% CI 51.4–64.2, p<0.0001* **DLQI score of 0 or 1 (%):** 1) 53.1, 2) 52.4, 3) 6.0 *1 and 2 vs. 3: p<0.0001* Maintenance vs. withdrawal on PASI and PGA (data NR): *p<0.0001* ***Other outcomes reported: PGA clear and marked or severe and DLQI mean change also reported at week 12 and 28,***	No dose response was seen in the rates of adverse events, serious adverse events, or adverse events leading to study agent discontinuation Similar AEs in withdrawal phase AEs also reported wk 12-40 (crossover) and wk 40-74 (withdrawal) **3 deaths**, 1 in the 45mg and 2 in the placebo groups

					DLQI mean change reported at wk 28	
Kimball, 2013 PHOENIX 1	5-year long-term safety extension of PHOENIX 1	N=517 (those who received one dose of ustekinumab) 1) ustekinumab 45mg (n=259) 2) ustekinumab 90mg (n=258)	See above	Similar to original trial	At wk 244: **PASI 75 (%)** 1) 63.4, 2) 72.0 **PASI 90 (%)** 1) 39.7, 2) 49.0 **PASI 10 (%)** 1) 21.6, 2) 26.4 **PGA- score of 0/1 (%):** 1) 42.5, 2) 51.0 ***Other outcomes reported: % PASI improvement***	**Serious infections (n):** 1) 13, 2) 19 (in 30 patients) **MACE (n):** 1) 8, 2) 2 (reported in 10 patients) **Discontinuation**: 68.7% of ustekinumab-treated patients completed the 5-year f/u **5 deaths** unrelated to treatment
Papp, 2008 PHOENIX 2	Phase III RCT Double-blind Multicenter	N=766 1) ustekinumab 45mg (n=255) 2) ustekinumab 90mg (n=256)	Inclusion: ≥18 years PASI ≥12 BSA ≥10%	**Age (years):** 1) 45.1, 2) 46.6, 3) 47.0 **% male:**	Primary outcomes at wk 12: **PASI 75 (%):** 1) 66.7, 2) 75.7, 3) 3.7	Primary outcomes at week 12: **AEs ≥1 at wk 12 (%):** 1) 53.1, 47.9, 3) 49.8

Good quality publication	70 sites in Europe and North America ITT with NRI	3) placebo (n=255) *Partial responders (i.e., patients achieving ≥50% but <75% improvement from baseline in PASI) were re-randomized at week 28*	≥6 months of plaque psoriasis diagnosis Exclusion: patients who had received treatment with any agent that specifically targeted IL-12 or -23, had received biological or investigational agents within the previous 3 months	1) 69.2, 2) 66.7, 3) 69.0 **Weight (kg):** 1) 90.3, 2) 91.5, 3) 91.1 **PsO duration (years):** 1) 19.3, 2) 20.3, 3) 20.8 **PASI:** 1) 41.3, 2) 38.7, 3) 39.0 **DLQI:** 1) 12.2, 2) 12.6, 3) 12.3 **PsA (%):** 1) 26.2, 2) 22.9, 3) 25.6 **Previous biologics (%):** 1) 38.4, 2) 36.5, 3) 38.8	**PASI 50 (%):** 1) 83.6, 2) 89.3, 3) 10.0 **PASI 90 (%):** 1) 42.3, 2) 15.9, 3) 0.7 **PGA, cleared/minimal (%):** 1) 68.0, 2) 73.5, 3) 4.9 **DLQI, score of 0/1 (%):** 1) 55.3, 2) 56.4, 3) 3.2 *All UST groups vs. placebo, p<0.0001* ***Other outcomes reported: PGA clear and marked or severe and DLQI mean change also reported at week 12 and 28,***	**URIs (%):** 1) 4.4, 2) 2.9, 3) 3.4 **SAEs (%):** 1) 2.0, 1.2, 3) 2.0 **Infections (%):** 1) 21.5, 2) 22.4, 3) 20.0 **Discontinuation due to AEs (%):** NR *Patients not achieving PASI 50 at wk 28 discontinued the study* **AEs at wk 52:** No dose response had been observed in rates of adverse events, serious adverse events, or adverse events leading to treatment discontinuation.

				Baseline characteristics for partial responders at wk 28 also reported	***DLQI mean change reported at wk 28*** ***PASI 50, 90, 100 scores also reported at week 28***	**1 death (cardiac-related)**
Langley, 2015 PHOENIX 2	5-year long-term safety extension of PHOENIX 2 Also compared dose adjusters to non-adjusters after wk 28	N=1212 1) ustekinumab 45mg (n=606) 2) ustekinumab 90mg (n=606) 3) combined N=1112 a) adjusters (n=544) b) non-adjusters (n=568) c) combined	See above	**Weight (kg):** a) 94.6, b) 85.7 **BSA (%):** a) 29.0, b) 22.9 **PASI:** a) 20.5, b) 18.4 **Hyperlipidaemia** a) 24.6, b) 16.4 **Hypertension (%)ǂ:** a) 29.6, b) 24. **PsA (%)*:** a) 28.7, b) 21.9	At wk 244: **PASI 75 (%):** 1) 76.5, 2) 78.6 **PASI 90 (%):** 1) 50.0, 2) 55.5 **PASI 100 (%):** 1) 28.1, 2) 31.3 **PGA, cleared/minimal (%):** 1) 54.0, 2) 58.6	**AEs at wk 264 (n):** 1) 222, 2) 165, 3) 206 a) 187, 216, 3) 202 ***Discontinuation due to AEs (%):** 1) 2.17, 2) 2.58, 3) 2.43 a) 2.51, b) 1.66, c) 2.06 ***SAEs (%):** 1) 7.99, 2) 6.87, 3) 2.43 a) 2.57, b) 7.43, c) 7.02

				Systemic therapies: a) 63.2, b) 47.8 **Previous biologics (%):** a) 44.4, b) 30.3 **p=0.009, ŧp=0.046, all other comparisons p<0.001*	"The greatest incidence of dosing adjustments occurred among patients weighing > 100 kg originally randomized to 45 mg"	***MACE (%):** 1) 0.56, 2) 0.42, 3) 0.48 a) 0.38, b) 0.54, c) 0.46 ***Infections (%):** 1) 85.6, 2) 75.9, 3) 79.7 a) 22.5, b) 25.9, c) 24.3 **Results presented per 100 patient-years*
Langley, 2010 PHOENIX 2 *Good quality publication*	Secondary analysis of patients from PHOENIX 2 evaluating anxiety, depression and QoL	See original study	See original study	See original study	Primary outcomes at wk 12: **HADS-A, mean** 1) -1.6, 2) -1.6, 3) -0.11 **HADS-D, mean** 1) -1.7, 2) -2.1, 3) -0.21	All psychologic AEs were mild and did not result in treatment discontinuation

					DLQI, mean 1) -9.3, 2) -10.0, 3) -0.5 *UST vs. placebo, p<0.001* ***Other outcomes reported: % of patients with symptoms of depression and anxiety***	
Reich, 2011 PHOENIX 2 *Good quality publication*	Secondary analysis of patients from PHOENIX 2 evaluating productivity	See original study	See original study	See original study **Median productivity VAS score:** 1) 2.7, 2) 3.2, 3) 2.6	Primary outcomes at wk 12: **Median improvement from baseline in work days missed (%):** 1) 81.6, 2) 78.4, 3) 10.6 **Median improvement from baseline in productivity VAS (%):** 1) 72.6, 2) 71.4, 3) 0.0	NR

					***WLQ-physical demands** 1) 7.6, 2) 5.1ǂ, 3) 0.2 ***WLQ-time management** 1) 6.6, 2) 9.1, 3) -0.7 ***WLQ-mental-interpersonal** 1) 7.8, 2) 7.5, 3) -1.1 ***WLQ-output demands** 1) 6.8, 2) 7.0, 3) -1.1 *UST vs. placebo, p<0.001 (ǂ=NS)* At wk 24: **Median improvement from baseline in work days missed (%):** Placebo/UST45, 87.2 Placebo/UST90, 72.6	

					UST45, 83.3 UST90, 80.7 **Median productivity VAS (%):** Placebo/UST(combined), 1.29 UST(combined), 1.31 ***WLQ-physical demands** Placebo/UST45, 5.8 Placebo/UST90, 5.6 UST45, 8.6 UST90, 10.6 ***WLQ-time management** Placebo/UST45, 10.8 Placebo/UST90, 9.7 UST90, 8.0 UST45, 10.2	

					***WLQ-mental-interpersonal** Placebo/UST45, 9.2 Placebo/UST90, 8.1 UST45, 8.0 UST90, 9.1 ***WLQ-output demands** Placebo/UST45, 7.5 Placebo/UST90, 8.0 UST90, 7.8 UST45, 7.8 *Mean improvement from baseline, not measure statistically	
Sofen, 2010 PHOENIX 1 and 2	Pooled analysis of patients from PHOENIX 1 and 2 for a subgroup with PsA	N=563	See original studies	**PASI:** 20.7 **DLQI:**	Primary outcomes at wk 12: **Primary: PASI 75 (%):** 1) 63.0, 2) 61.5, 3) 3.6	NR

Abstract				12.6	**DLQI, mean score:** 1) -9.2, 2) -9.7, 3) -0.01 **DLQI, ≥5 improvement:** 1) -9.2, 2) -9.7, 3) -0.01 *All UST groups vs. placebo, p<0.001*	
Guenther, 2011 PHOENIX 1 and 2 *Good quality publication*	Pooled analysis of patients from PHOENIX 1 and 2 for patients with sexual difficulties	See original trials	See original trials	**Impaired sexual function (score of 2 or 3 on DLQI item 9) (%):** All UST, 22.6 UST45, 22.8 UST90, 22.1 Placebo, 23.0	Primary outcomes at wk 12: **DLQI, mean change:** UST, -9.13 Placebo, -0.53 TE (Cohen's *d* score): -1.36 **DLQI, ≥5:** UST45, 69.0 UST90, 74.7 Placebo, 20.1	NR

					UST vs. placebo, p<0.001 **Patients with impaired sexual function (%):** UST, 2.7 UST45, 2.6 UST90, 2.8 Placebo, no change (23.0) *UST vs. placebo, p<0.001* At wk 28: **Patients with impaired sexual function (%):** UST (crossover), 4.4 UST45, 3.4 UST, 90, 2.3	

Igarashi, 2012 *Good quality publication*	Phase II/III RCT Double-blind Multicenter *35 sites in Japan* ITT with NRI	N=158 1) ustekinumab 45mg (n=64) 2) ustekinumab 90mg (n=62) 3) placebo (n=32) *Cross-over to ustekinumab 45 or 90 mg at week 12*	Inclusion: ≥20 years PASI ≥12 BSA ≥10% ≥6 months of plaque psoriasis diagnosis	**Age (years):** 1) 45, 2) 44, 3) 49 **% male:** 1) 82.8, 2) 75.8, 3) 83.9 **Weight (kg):** 1) 73.2, 2) 71.1, 3) 71.2 **PsO duration (years):** 1) 15.8, 2) 17.3, 3) 16.0 **PASI:** 1) 30.1, 2) 28.7, 3) 30.3 **DLQI:** 1) 11.4, 2) 10.7, 10.5 **PsA (%):** 1) 9.4, 2) 11.3, 3) 3.1 **Previous biologics (%):**	Primary outcomes at wk 12: **PASI 75 (%):** 1) 59.4, 2) 67.7, 3) 6.5 **PASI 50 (%):** 1) 82.8, 2) 83.9, 3) 12.9 **PASI 90 (%):** 1) 32.8, 2) 43.5, 3) 3.2 **PGA, cleared/minimal (%):** 1) 57.8, 2) 69.4, 3) 9.7 **DLQI score of 0/1 (%):** 1) 30.6, 2) 32.8, 3) 6.7 *All UST groups vs. placebo, p<0.0001* **VAS improvement (mean)** 1) -38.5, 2) -9.3. 3) +8.0	Primary outcomes at wk 12: **AEs ≥1 (%):** 1) 65.6, 2) 65.6, 3) 65.6 **SAEs (%):** 1) 0.0, 2) 4.8, 3) 6.3 **Infections (%):** 1) 20.3, 2) 24.2, 3) 18.8 **Discontinuation from AEs (%):** 1) 0.0, 2) 6.5, 3) 6.3 AEs also reported through wk 72 (generally comparable between groups) **No deaths** through wk 72

				1) 1.6, 2) 0.0, 3) 0.0	*p=NR* ***Other outcomes reported: DLQI mean change, SF-36 summary, MCS, and PDI scores also included through wk 64***	
Tsai, 2011 PEARL *Good quality publication*	Phase II/III RCT Double-blind Multicenter *Conducted at 13 sites in Korea and Taiwan* ITT with NRI	N=121 1) ustekinumab 45mg (n=61) 2) placebo (n=60) *Placebo group crossed-over to ustekinumab 45mg at wk 12-36*	Inclusion: ≥20 years PASI ≥12 BSA ≥10% ≥6 months of plaque psoriasis diagnosis Exclusion: patients could not have received biologic agents within 3 months	**Age (years):** 1) 40.9, 2) 40.4 **% male:** 1) 82.0, 2) 88.3 **Weight (kg):** 1) 73.1, 2) 74.6 **PsO duration (years):** 1) 11.0, 13.9 **PASI:** 1) 25.2, 2) 22.9 **DLQI:**	Primary outcomes at wk 12: **PASI 75 (%):** 1) 67.2, 2) 5.0 *1 vs. 2, p<0.001* **PASI 50 (%):** 1) 83.6, 2) 13.3 *1 vs. 2, p<0.001* **PASI 90 (%):** 1) 49.2, 2) 1.7 *1 vs. 2, p<0.001* **PASI 100 (%):**	Primary outcomes at wk 12: **AEs ≥1 (%):** 1) 65.6, 2) 70.0 **SAEs (%):** 1) 0.0, 2) 3.3 **URIs (%):** 1) 11.5, 2) 11.7 **Discontinuation from AEs (%):** 1) 0.0, 2) 5.0 **Infections (%):**

				1) 16.1, 15.2 **PsA (%):** 1) 16.4, 2) 11.7 **Previous biologics (%):** 1) 21.3, 2) 15.0 The population was evenly distributed Between Taiwanese/Chinese (49.6%) and Korean (50.4%)	1) 8.2, 2) 0.0 *1 vs. 2, p=0.024* **PGA, cleared/minimal (%):** 1) 70.5, 2) 8.3 *1 vs. 2, p<0.001* **DLQI, mean change:** 1) -11.2, 2) -0.5 *1 vs. 2, p<0.001* *At wk 28:* **PASI 75 (%):** Placebo/UST, 74.1 UST45, 72.4 **PASI 50 (%):** Placebo/UST, 87.0 UST45, 84.5 **PASI 90 (%):**	1) 32.8, 2) 23.3 At wk 36: **AEs ≥1 (%):** Placebo/UST, 67.3 UST45, 67.8 **SAEs (%):** Placebo/UST, 9.1 UST45, 3.4 **URIs (%):** Placebo/UST, 3.6 UST45, 8.5 **Discontinuation from AEs (%):** Placebo/UST, 0.0 UST45, 1.6 **Infections (%):** Placebo/UST, 25.5

					Placebo/UST45, 46.3 UST45, 60.3 **PASI 100 (%):** Placebo/UST45, 16.7 UST45, 20.7 **PGA, cleared/minimal (%):** **DLQI, mean change:** Placebo/UST45, 59.3 UST45, 69.0 *p-values for wk 28 outcomes=NR* ***Other outcomes reported: % PASI improvement, PGA cleared*** Also reported response at wk 12 and	UST45, 32.2 **No deaths** during the study

					28 by weight (≤70kg vs. >70kg)	
Zhu, 2013 LOTUS *Good quality publication*	Phase III RCT Double-blind *14 sites in China* ITT with NRI	N=322 1) ustekinumab 45mg (n=160) 2) placebo (n=162) Placebo patients crossed over to receive ustekinumab for wks 12-16	Inclusion: ≥18 years PASI ≥12 BSA ≥10% ≥6 months of plaque psoriasis diagnosis	**Age (years):** 1) 40.1, 2) 39.2 **% male:** 1) 78.1, 2) 75.9 **Weight (kg):** 1) 69.9, 2) 70.0 **PsO duration (years):** 1) 14.6, 14.2 **PASI:** 1) 23.2, 2) 22.7 **DLQI:** 1) 13.7, 2) 13.1 **PsA (%):** NR **Previous biologics (%):**	Primary outcomes at wk 12: **PASI 75 (%):** 1) 82.5 2) 11.1 **PASI 50 (%):** 1) 91.3 2) 19.8 **PASI 90 (%):** 1) 66.9 2) 3.1 **PGA, cleared/minimal (%)** 1) 78.8 2) 14.8 *All UST groups vs. placebo, p<0.001*	**At week 12:** AEs (%) 1) 42.5, 2) 38.5 SAEs (%) 1) 0.6 2) 0.6 Infections (%) 1) 19.3 2) 25.6 Discontinuation due to AEs (%) 1) 1.2 2) 1.9

				1) 11.9, 6.8	Response was maintained through wk 28	No deaths, serious infections, malignancies, or cardiovascular events reported through wk 36
Observational Studies						
Clemmensen, 2011 DERMBIO *Publication*	Database of Danish patients to evaluate drug adherence in anti-TNF-naïve vs. anti-TNF exposed over 1 year	N=179 1) All ustekinumab (n=71) 2) ustekinumab anti-TNF-naïve (n=24)	Inclusion: Failure of two or more conventional systemic agents or lack of efficacy or intolerance to methotrexate and narrow- band ultraviolet B; for biologic-naive	**Age (years):** 1) 43.1, 2) 41.8, 3) 43.7, 4) 43.7 **% male:** 1) 50.7, 2) 41.7, 3) 55.3, 4) 53.7	"No difference in the PASI75 response between the subjects exposed to 1, 2 or 3 anti-TNFa agents (data NR)"	**Discontinuation (%):** Ustekinumab survival was significantly better than the adherence to anti-TNF drugs (p<0.001, HR 0.32, 95% CI 0.15–0.67)

Poor quality		3) ustekinumab anti-TNF exposed (n=37) 4) Anti-TNFs (n=47)	patients, PASI >10 or DLQI >10	**PASI:** 1) 10.9, 2) 13.7, 3) 9.6, 4) 10.4 **Observation time (days):** 1) 142.6, 2) 132.8, 3) 147.5, 4) 173.1 *Differences between groups not measured statistically*	"Previous failure to one or more TNFa inhibitors did not influence treatment responses measured by the time to PASI 75 or the proportion of patients achieving PASI 75"	
Gelfand, 2012 *Publication* *Good quality*	Cross-sectional study of 10 outpatient dermatology sites across the US participating in the Dermatology Clinical Effectiveness Research Network	N=713 1) ADA (n=152) 2) ETN (n=191) 3) UST (n=73)	N/A	***No compared between groups*** **Age (years):** 48.6 **% male:** 50.6 **Weight (kg): NR** **PsO duration (years):** 19 **PsA (%):** 22.6	**PGA clear or almost clear (%):** 1) 47.7% 2) 34.2% 3) 36.1% p<0.001 **PGA clear or almost clear (*adjusted relative rates):**	NR

				Previous biologics (%): 37.3	1) 2.15; 95% CI, 1.60-2.90 2) 1.45; 95% CI 1.06-1.97 3) 1.57; 95% CI 1.06-2.32 **Differences in median PGA:** (p<0.001), PASI (p=.02), and BSA (p=0.01) across therapies Treatment doses were double the recommended doses in 36.1% of patients taking etanercept and 11.8% of those taking adalimumab; 10.6% of patients undergoing phototherapy received the	

					recommended treatment frequency *Adjusted for sex, race, ethnicity, body mass index, skin type, frequency of topical use, practice setting of dermatologist, marital status, income, and insurance	
Gniadecki, 2011 DERMBIO *Publication* *Good quality*	Database of Danish patients to evaluate long-term drug survival (time to drug discontin-uation) followed up to 10 years	N=1277 1) ADA (n=567) 2) ETN (n=364) 3) INF (n=176) 4) UST (n=170)	Inclusion: Patients on biologics with: PASI > 10 DLQI > 10 BSA > 10% in whom treatments previously failed or who have contraindications to topical therapies, ultraviolet B phototherapy and methotrexate	**Age (years):** 1) 44.4, 2) 46.3, 3) 45.5, 4) 44.6 **% male:** 1) 63.8, 2) 65.9, 67.6, 4) 60.6 **Weight (kg):** 1) 87.4, 2) 88.6, 3) 92.0, 4) 89.6 **PsO duration (years):** 1) 18.7, 2) 19.5, 3) 18.7, 4) 17.9	***OR for treatment termination:** 1 vs. 4: 1.77, 95% CI 1.39-2.26, p<0.0001 2 vs. 4: 2.55, 95% CI 1.98-3.29, p<0.0001 3 vs. 4: 1.99, 95% CI 1.5-2.63, p<0.0001 2 vs. 1: 1.42, 95% CI, 1.20-1.68, p<0.0001 2 vs. 3: 1.30, 95% CI 1.04-1.61, p=0.02	NR

			The choice of drug *was the decision of the physician*	**PASI:** 1) 12.5, 2) 12.6, 3) 15.8, 4) 11.4 **DLQI:** 1) 12.6, 2) 11.9, 3) 13.9, 4) 11.5 **PsA (%):** 1) 38.1, 2) 39.6, 3) 43.8, 4) 14.1 **Previous biologics (%):** NR	Bio-naïve vs. bio-exposed: 1.24, 95% CI 1.05-1.46, 0.011 Male vs. female: 1.51, 95% CI 1.31-1.74, p<0.0001 *Adjusted for covariates*	
Goren, 2015 *Publication* *Fair quality*	Web-based survey from a US claims database study evaluating differences between ustekinumab and adalimumab for patients previously or not previous on entanercept	N=250 1) bio-naïve (n=68) 1a) ADA (n=26) 1b) UST (n=42) 2) entanercept-experienced 2a) ADA (n=49) 2b) UST (n=65)	Inclusion: ≥18 years	**Age (years):** 1a) 45.8, 1b) 47.6, 2a) 51.1, 2b) 46.4 **% male:** 1a) 61.5, 1b) 54.8, 2a) 42.9, 2b) 55.4 **Weight (kg):** NR	Significantly higher proportion of bio-naïve ustekinumab users reported a score of 0 on the DLQI compared with bio-naïve adalimumab users (45.2% vs 19.2%, p<0.05). After adjusting for covariates in multivariable models,	NR

				PsO duration (years): 1a) 11.4, 1b) 18.5, 2a) 21.2, 2b) 17.9 Bio-naïve ADA patients had a significantly shorter duration of psoriasis then ustekinumab	the results were still significant. Adjusting for covariates, no significant overall differences were realized on health outcomes across UST and ADA users.	
Kalb, 2013 PSOLAR *Publication* *Good quality*	Multicenter, longitudinal, psoriasis-based registry study evaluating the risk of infection in biologics and other systemic therapies followed up to 8 years (June 20, 2007, through August 23, 2013)	N=11466 1) UST (n=3474) 2) ETN (n=1854) 3) ADA (n=2675) 4) INF (n=1151) Nonmethotrexate/nonbiologics, (n=1610) 5) Methotrexate/ nonbiologics, (n=490) (22,311 patient-years)	Inclusion: Non-biologic therapies included (but were not limited to) methotrexate, systemic retinoids, psoralen plus UV-A, and UV-B, which may also impact infection risk in different ways and to different degrees.	**Age (years):** 1) 47.2, 2) 48.7, 3) 47.6, 4) 48.5, 5) 50.1, 6) 55.1 **% male:** 1) 57.5, 2) 56.0, 3) 56.3, 4) 56.6, 5) 51.6, 6) 42.2 **PsA (%):** 1) 32.6, 2) 42.3, 3) 41.6, 4) 52.2, 5) 14.7, 6) 28.6 **Previous biologics (%):** 71.4	NR	***Incidence rate of serious infections (unadjusted):** Overall: 1.45 1) 0.83, 2) 1.47, 3) 1.97, 4) 2.49, 5) 1.05, 6) 1.28 Biologic-exposed (incident): 1.35 Bio-naïve: 1.12 *The trend was similar* *across the biologic cohorts in the incident*

			Treatment dosing was determined by the treating physician	*SS differences between the biologics and nonmethotrexate/* *nonbiologics cohorts (age, sex, BMI, and disease characteristics [PGA score, PsO duration]), as well as among the individual biologic groups (higher prevalence of psoriatic arthritis, history of serious infection)*		*and bio-naive populations* *(ie, lowest rates for the ustekinumab or etanercept cohorts,* *followed by either the infliximab or adalimumab cohort)* *Most common AEs: **Pneumonia:** 1) 0.19, 2) 0.27, 3) 0.39, 4) 0.44, 5) 0.21, 6) 0.16 **Cellulitis:** 1) 0.19, 2) 0.37, 3) 0.19, 4) 0.40, 5) 0.13, 6) 0.24 *per 100 patient-years for those that occurred at least 4

						times across treatment cohorts Multivariate analysis for the overall population: **Increasing age:** HR, 1.37; 95% CI, 1.24-1.52) **Presence of diabetes:** HR, 1.70; 95% CI, 1.25-2.32 **History of significant infections:** HR, 1.67; 95%CI, 1.28-2.18 *Increased risk of serious infections, all outcomes p<0.001*
Papp, 2015	Multicenter, longitudinal, psoriasis-based registry study evaluating adverse	N=12094 1) UST (n=4134)	NR	**Age (years):** 1) 47.2, 2) 49.2, 3) 48.4, 4) 51.2	NR	*Cumulative incidence rates

PSOLAR *Publication* *Good quality*	events in a real-world setting for 8 years (June 20, 2007, through August 23, 2013)	2) INF (n=1435) 3) ŧother biologics (n=2151) 4) *non-biologics (n=2151) (31,818 patient-years) ŧ4188 were treated with adalimumab and/or etanercept *511 were exposed to methotrexate	*Treatment dosing was determined by the treating physician*	**% male:** 1) 57.5, 2) 55.1, 3) 55.25, 4) 49.3 **PsA (%):** 1) 34.0, 2) 55.2, 3) 39.6, 4) 18.1 **Previous biologics (%):** 1) 88.4, 2) 94.8, 3) 85.8, 4) 0.0		**All-cause mortality (overall): 0.46** 1) 0.36, 2) 0.45, 3) 0.42, 4) 0.70 **MACE (overall): 0.36** 1) 0.34, 2) 0.38, 3) 0.33, 4) 0.45 **Serious infections (overall): 1.50** 1) 0.95, 2) 2.78, 3) 1.80, 4) 1.26 **Data are presented as rate/100 patient-years* Missing values for covariates were imputed as the mean for continuous factors and as the median for categorical factors.

Strober, 2016 PSOLAR *Publication* *Fair quality*	Multicenter, longitudinal, psoriasis-based registry study evaluating effectiveness of biologics in a real-world setting (June 20, 2007, through August 23, 2013)	N=2076 (patients initiating a new biologic) 1) UST (n=1041) 2) ETN (n=116) 3) ADA (n=662) 4) INF (n=257)	Inclusion: Patients may have been bio-naive or may have been exposed before enrollment to a biologic other than their newly initiated treatment in the registry Excluded: Patients restarting a biologic received before enrollment	**Age (years):** 1) 46.3, 2) 47.9, 3) 46.7, 4) 46.8 **% male:** 1) 56.8, 2) 62.9, 3) 58.0, 4) 56.0 **PsO duration (years):** 1) 19.1, 2) 17.2, 3) 16.1, 4) 14.7 **PsA (%):** 1) 33.5, 2) 44.0, 3) 35.0, 4) 35.8 *Baseline clinical values numerically reflected more severe disease in the infliximab group.*	12 Month Analysis (6 months also reported): **PGA of 0/1 (%):** 1) 59.9, 2) 57.6, 3) 56.5, 4) 42.0 ***Odds of achieving a PGA score of 0/1 (logistic regression):** 1 vs. 4: OR 0.449, 95% CI 0.260-0.774, p=0.040 *No other comparisons to UST were SS* ***DLQI mean improvement (least mean square):** 1 vs. 2: -5.011, 1.917 (95% CI 0.909-2.925), p=0.0002 1 vs. 3: -6.185, 0.743 (95% CI 0.025-1.492), p=0.427	NR

					No other comparisons to UST were SS *Adjusted multivariate analysis *Missing data excluded in the analysis* ***Other outcomes reported: 6-month data and BSA***	
Anti-PDE4 Agent						
Apremilast (Otezla)						
Papp, 2012 (NCT00773734) *Good quality publication*	Phase IIb RCT Double-blind Multicenter 35 sites in the US and Canada	N=352 1) placebo (n=88) 2) apremilast 10mg BID (n=89) 3) apremilast 20mg BID (n=87) 4) apremilast 30mg BID (n=88)	Inclusion: ≥18 years BSA ≥10%, PASI ≥12 ≥6 months of plaque psoriasis diagnosis	**Age (years):** 1) 44.1, 2) 44.4, 3) 44.6, 4) 44.1 **% male:** 1) 60, 2) 71, 3) 63, 4) 57 **Weight (kg):**	Primary outcomes at week 16*: **PASI 50 (%):** 1) 25, 2) 38.2, 3) 47.1, 4) 60.2 *2 vs. 1, p=NS* *3 vs. 1, p<0.001* *4 vs. 1, p=0.002*	Primary outcomes at week 16: **AEs ≥1 (%):** 1) 65, 2) 66, 3) 77, 4) 82 **SAEs ≥1 (%):** 1) 2, 2) 0, 3) 2, 4) 2 **Infections ≥1 (%):**

	ITT with LOCF	Patients in the placebo group were rerandomized to APR 20mg or 30mg (n=70); those in the APR groups continued to the active treatment phase wk 16-24 (n=210)	Candidates for phototherapy or systemic therapy Exclusion: use of *adalimumab*, *etanercept*, efalizumab, or *infliximab* within 12 weeks; or had used alefacept within 24 weeks of randomization	1) 90.4, 2) 95.9, 3) 20.2, 4) 91.4 **PsO duration (years):** 1) 19.6, 2) 18.0, 3) 19.2, 4) 19.2 **PASI:** 1) 18.1, 2) 18.1, 3) 18.5, 4) 19.1 **DLQI:** NR **PsA (%):** 1) 19, 2) 23, 3) 18, 4) 24 **Previous biologics (%):** NR [see exclusion criteria]	**PASI 75 (%):** 1) 5.7, 2) 11.2, 3) 28.7, 4) 40.9 *2 vs. 1, p=NS* *3 and 4 vs. 1, p<0.001* **PASI 90 (%):** 1) 1.1, 2) 4.5, 3) 9.2, 4) 11.4 *2 vs. 1, p=NS* *3 vs. 1, p=0.016* *4 vs. 1, p=0.005* **PASI 100 (%):** 1) 1, 2) 0, 3) 3.4, 4) 2.3 2 vs. 1, p=NR *3 and 4 vs. 1, p=NS* **sPGA score of 0/1 (%):** 1) 12.5, 2) 10.1, 3) 24.1, 4) 33.0	1) 33, 2) 33, 2) 41, 4) 48 **Discontinuation due to AEs (%):** 1) 5.7, 2) 2.2, 3) 9.2, 4) 11.47 **Deaths (n):** 1 in the placebo group At week 24 (those continuing apremilast): **AEs ≥1 (%):** 2) 39, 3) 39, 4) 46 **SAEs ≥1 (%):** 1) 1, 2-4) 0 **Infections ≥1 (%):** 2) 18, 3) 15, 4) 22 **Discontinuation due to AEs (n):**

					p=NR **sPGA mean change (%):** 1) -0.6, 2) -0.8, 3) -1.2, 4) 37.7 *2 vs. 1, p=NS* *3 and 4 vs. 1, p<0.001* **Pruritus VAS, mean % change (%):** 1) -6.1, 2) -10.2, 3) -35.5, 4) -43.7 *2 vs. 1, p=NS* *3 vs. 1, p=0.005* *4 vs. 1, p<0.001* **DLQI ≥ 5-point decrease (only patients with score >5) (%):** 1) 25, 2) 34, 3) 49, 4) 44 2 vs. 1, p=NR	2) 4, 3) 0, 4) 0 **Deaths (n):** None

					3 vs. 1, p=0.001 4 vs. 1, p=0.011 *All outcomes LOCF for missing data ***Other outcomes reported: BSA mean change, SF-36 domain scores at wk 16 and 24, DLQI mean change at wk 24***	
Strand, 2013 (NCT00773734) *Good quality publication*	Reporting of PRO measures	See above	See above	See above	At wk 16: **DLQI mean change (%):** 1) -1.9, 2) -3.2, 3), -5.9, 4) -4.4 ***Other outcomes reported: MCID between groups for PROs***	NR

Papp, 2013 (NCT00773734) Phase IIb *Abstract*	Reporting of symptom measures	See above	See above	See above	At wk 24 (those continuing apremilast): **Pruritus VAS, mean change (%):** 2) -36.7, 3) -41.5, 4) -41.0 p=NR ***Other outcomes reported: MCID between groups for pruritus VAS***	NR
Papp, 2015 (NCT01194219) ESTEEM 1 *Good quality publication*	Phase III RCT Double-blind Multicenter 72 sites in the US, Canada, and Europe	N=844 1) placebo (n=282) 2) apremilast 30mg BID (n=562)	Inclusion: ≥18 years BSA ≥10%, PASI ≥12 sPGA ≥3 ≥6 months of plaque psoriasis diagnosis	**Age (years):** 1) 46.5, 2) 45.8 **% male:** 1) 68.8, 2) 67.4 **Weight (kg):** 1) 93.7, 2) 93.2 **PsO duration (years):** 1) 18.7, 2) 19.8	Primary outcomes at week 16: **PASI 50 (%):** 1) 17.0, 2) 58.7ǂ **PASI 75 (%)*:** 1) 15.3, 2) 33.1ǂ **PASI 90 (%):** 1) 0.4, 2) 9.8	Primary outcomes at week 16: **AEs ≥1 (%):** 1) 55.7, 2) 69.3 **SAEs ≥1 (%):** 1) 2.8, 2) 2.1 **Discontinuation due to AEs (%):**

	ITT with LOCF and NRI results		Candidates for phototherapy or systemic therapy Exclusion: use of biologics within 12 to 24 weeks	**PASI:** 1) 19.4, 2) 18.7 **DLQI:** 1) 12.1, 2) 12.7 **PsA (%):** NR **Previous biologics (%):** 1) 28.4, 28.8	**sPGA score of 0/1 with ≥2-point reduction (%)*:** 1) 17.5, 2) 46.5ǂ **DLQI ≥ 5-point decrease (only patients with score >5)** 1) 33.5, 2) 70.2 **Pruritus VAS, mean change (mm)** 1) -7.3, 2) -31.5ǂ *ǂ1 vs. 2, p<0.0001* *LOCF for missing data (NRI also reported) *Patients remaining on APR over 52 weeks maintained or*	1) 3.2, 2) 5.3 **Deaths (n):** 1) 1, 2) 1 At week 52: **AEs ≥1 (%):** Apremilast- 78.7 **SAEs ≥1 (%):** Apremilast- 4.2 **Discontinuation due to AEs (%):** Apremilast- 7.3 **Deaths (n):** Apremilast- 1

					continued improvement. ***Other outcomes reported: NPSI,*** ***ScPGA, BSA mean change, PASI mean % improvement***	
Paul, 2015 (NCT01232283) ESTEEM 2 *Fair quality publication*	Phase III RCT Double-blind Multicenter 40 sites in the US, Canada, and Europe Modified ITT	N=411 1) placebo (n=137) 2) apremilast 30mg BID (n=274) At week 16, placebo patients switched to apremilast (N=380)	Inclusion: ≥18 years BSA ≥10%, PASI ≥12 sPGA ≥3 ≥6 months of plaque psoriasis diagnosis Candidates for phototherapy or systemic therapy	**Age (years):** 1) 45.7, 2) 45.3 **% male:** 1) 73.0, 2) 64.2 **Weight (kg):** 1) 90.5, 2) 91.4 **PsO duration (years):** 1) 18.7, 2) 17.9 **PASI:** 1) 20.0, 2) 18.9 **DLQI:**	Primary outcomes at week 16: **PASI 50 (%)*:** 1) 19.7, 2) 55.5 **PASI 75 (%)*:** 1) 5.8, 2) 28.8 **PASI 90 (%)*:** 1) 1.5, 2) 8.8 (p=0.0042) **sPGA score of 0/1 (%)*:** 1) 4.4, 2) 20.4 **DLQI, mean change:**	Primary outcomes at week 16: **AEs ≥1 (%):** 1) 60.3, 2) 68.0 **SAEs ≥1 (%):** 1) 2.2, 2) 1.8 **Discontinuation due to AEs (%):** 1) 5.1, 2) 5.5 **Deaths (n):** 1) 0, 2) 0

			Exclusion: use of biologics within 12 to 24 weeks	NR **PsA (%):** NR **Previous biologics (%):** 1) 32.1, 2) 33.6	1) -12.2, 2) -33.5 **DLQI ≥ 5-point decrease (only patients with score >5)** 1) 42.9, 2) 70.8 (p<0.001 from baseline only) **Pruritus VAS, mean change (mm)** 1) -12.5, 2) -33.5 *APR groups vs. placebo, p<0.001* *LOCF for missing data (NRI also reported for PASI 75 and 90) **PASI 75 by prior therapy (%):**	At week 52: **AEs ≥1 (%):** Apremilast- 77.9 **SAEs ≥1 (%):** Apremilast- 4.7 **Discontinuation due to AEs (%):** Apremilast- 7.1 **Deaths (n):** Apremilast- 0

					Biologic naïve- 1) 6.5, 2) 31.9 1 vs. 2, p<0.001 Biologic-experienced- 1) 4.5, 2) 22.8 1 vs. 2, p=0.0069 ***Other outcomes reported: NPSI,*** ***ScPGA, PASI mean % improvement***	
Foley, 2015 ESTEEM 1 and 2 *Abstract*	Pooled analysis for AEs	N=1250 1) placebo (n=418) 2) apremilast (n=832)	NR	NR	NR	At wk 16: **AEs ≥ 5%:** Diarrhea 1) 6.7%, 2) 17.8% Nausea 1) 6.7%, 2) 16.6% URTI

						1) 6.5%, 2) 8.4% Nasopharyngitis 1) 6.9%, 2) 7.3%) *Rates of tension headache and headache also reported.* **SAEs (%):** 1) 2.6, 2) 2.0
Reich, 2016 LIBERATE *Abstract*	Phase IIIb RCT Reports efficacy through wk 52	Through wk 16: 1) placebo (n=84) 2) apremilast 30mg BID (n=83) 3) etanercept 50mg QW (n=83) Wk 16-52 (crossover period):	All patients were biologic-naïve	NR	Primary outcomes at week 16: **PASI 75 (%):** 1) 11.9, 2) 39.8, 3) 48.2 1 and 2 vs. 3, p<0.0001 2 vs. 3, p=NS **sPGA score of 0/1 (%):**	NR

		1) placebo-apremilast (n=73) 2) apremilast-apremilast (n=74) 3) etanercept-apremilast (n=79)			1) 3.6, 2) 21.7, 3) 28.9 1 vs. 3, p=0.0005 2 vs. 3, p<0.0001 At week 52: **sPGA score of 0/1 (%):** 1) 24.1, 2) 24.1, 3) 25.3 p=NR ***Outcomes also reported: LS-PGA at wk 0-16, 16-52***	
Crowley, 2016 LIBERATE *Abstract*	As above Reports safety outcomes for wks 16 to ≤52 vs. 0-16	1) placebo-apremilast (n=73) 2) apremilast-apremilast (n=74) 3) etanercept-apremilast (n=79)	As above	NR	NR	**AEs in ≥5% of patients (%):** Diarrhea, nausea, headache did not increase for those continuing apremilast (data NR)

						SAEs: 4.11-9.16 across groups for wks 16-52 vs. 3.93 for etanercept and 12.47 for apremilast (wk 0-16) [per 100 patient-yrs] **Discontinuation due to AEs**: 4.11-6.78 across groups for wks 16-52 vs. 7.87-12.40 across groups (wk 0-16) [per 100 patient-yrs] **Rates of depression:** 2 patients wks 16-52 for apremilast-apremilast (both patients had baseline depression) 1 patient in apremilast-apremilast group developed

						suicidal ideation in wks 16-52 Weight loss also reported
Green, 2016 LIBERATE *Abstract*	*As above*	*As above* Reports pruritus and HrQOL up to wk 52	As above Patients who received ≥1 dose at baseline and f/u included in this analysis	NR	Primary outcomes at week 16: **DLQI (mean change):** 1) -3.8, 2) -8.3, 3) -7.8 *1 vs. 3, p<0.0001* *2 vs. 3, p=0.0004* **Pruritus VAS (mean change from baseline, mm):** 1) -22.5, 2) -35.6, 3) -36.4 *1 vs. 2, p=0.00261* *1 vs. 3, p<0.0001*	NR

					% of patients achieving MCID (p=NR): **DLQI (≥5 points):** 1) 41.7, 2) 65.1, 3) 65.1 **Pruritus VAS (>20% improvement):** 1) 53.6, 2) 79.5, 3) 83.1 Outcomes at week 52 (p=NR): **Pruritus VAS (>20% improvement):** 1) -35.8, 2) -35.9, 3) -34.6 **DLQI (mean change):** 1) -6.6, 2) -8.9, 3) -8.0 **DLQI (≥5 points):**	

					1) 59.4, 2) 75.7, 3) 71.2	

Appendix C. Previous Systematic Reviews and Technology Assessments

We identified five systematic reviews comparing the effectiveness of biologics in moderate-to-severe psoriasis, four of which also conducted NMAs. All reviews focused on PASI response rate at the end of induction phase as the measurement of effectiveness. Some included unapproved dosing but the results are not described below. Most NMAs used ordered multinomial models within a Bayesian framework to analyze PASI50, 75, and 90 jointly. Biologics were consistently found to have statistically significantly higher response rate than placebo. According to the NMAs, the ranking of biologics was similar among these analyses. Collectively, infliximab ranked the highest, followed by ustekinumab, adalimumab, and etanercept.

Reich 2011

This systematic review and network meta-analysis focused on the comparative effectiveness of biologic agents in moderate-to-severe psoriasis available in Europe. The outcomes of interest were PASI 50,75, and 90 response rates measured as the primary endpoints in RCTs (at 10-16 weeks). Nineteen placebo-controlled and head-to-head trials published between 1995-2008 were identified and included in the analysis, including 60-70% males, with a mean age of 44 to 47 years. A Bayesian hierarchical model on ordered probit scale was used to analyze PASI 50,75, and 90 jointly. The NMA showed that all biologics were more effective than placebo and infliximab had the highest probability of achieving PASI response, followed by ustekinumab 90 mg, ustekinumab 45 mg, adalimumab, etanercept 50 mg, and placebo (RRs for PASI 75 were 22.6, 20.9, 19.5, 16.5, 14.7, and 1.0, respectively; Risk Ratios (RR) for PASI 50 and 90 were also reported). When analyzed according to the dosing recommendations (45 mg in patients ≤100 kg and 90 mg in patients > 100 kg) in a sensitivity analysis, ustekinumab 45 mg showed a higher comparative effectiveness than ustekinumab 90 mg.

Lin 2012

This Bayesian network meta-analysis compared the effectiveness of ustekinumab to other biologics and placebo in moderate-to-severe psoriasis. Seventeen trials were identified from a systematic search of 1992 to 2012 and their primary endpoints within 10 to 16 weeks were analyzed. Patient characteristics were similar among trials, with mean age ranging from 41 to 47 years, mean disease duration from 14 to 21 years, mean BSA involvement at baseline from 20% to 50%, and baseline PASI from 13 to 33. PASI 75 was analyzed as the main outcome, but PASI 50 and 90 were analyzed separately as well. The odds of achieving PASI 75 for ustekinumab was higher compared to adalimumab [Odds Ratio (OR) 1.84], etanercept (OR 2.07), but lower than infliximab (OR 0.36), all

treatments given according to the FDA-approved dosing (table x in this report). Previous experience with biologics was not found to be a statistically significant predictor of PASI response in the adjusted model.

Signorovitch 2014

This systematic review and NMA looked at biologic treatments marketed in the U.S. and Europe for moderate-to-severe psoriasis. Fifteen phase II or III trials conducted in the U.S. and Europe were included. The authors proposed an NMA model adjusted for placebo response rate as a way to control for measured and unmeasured patient- and trial- level characteristics and reduce heterogeneity in the model. The NMA results were similar to the other publications, showing all biologics between than placebo, with infliximab ranked the highest (RR 19.49), followed by ustekinumab 90 mg (RR 17.54), ustekinumab 45mg (RR 16.33), adalimumab (RR 16.01), and etanercept (RR 12.54). Etanercept had statistically significantly lower effectiveness than the other biologics, but the differences between the others were not statistically significant.

Gomez-Garcia 2016

This systematic review and meta-analysis included secukinumab besides the older biologics and evaluated evidence on both effectiveness and adverse events. Efficacy outcomes, including PASI 75 and 90, and safety outcomes, including any AE, SAE, and infectious AE, at week 10-16 from 27 RCTs were analyzed in the NMAs using frequentist method to generate odds ratios (OR) of direct and indirect comparisons. Other efficacy outcomes, such as IGA, PGA, and DLQI data were also analyzed but not presented as main results due to missing data for some biologics. All biologics showed superior efficacy compared to placebo on all efficacy outcomes, but some biologics also had higher ORs for AEs. Based on PASI 75 and 90, Infliximab (OR 118.89 and 84.11 for PASI 75 and PASI 90, respectively) and secukinumab (OR 87.07 and 95) were found to be the most effective but also the most likely to produce any adverse events or infectious AE (OR 1.85 and 1.34 for any AE compared to placebo). Ustekinumab ranked the third in effectiveness (OR 73.67 and 61.34) and was the only agent showing no increased risk for all safety outcomes compared to placebo. The ranking of the others is: ustekinumab 45 mg (OR 59.16 and 55.95), adalimumab (OR 30.69 and 22.11), and etanercept (OR 17.88 and 16.53). Mixed treatment comparisons based on PASI 75 showed no difference between infliximab and secukinumab, but both were statisticaaly significantly more effective than the other biologics; etanercept had statistically significantly lower OR for PASI 75 than the others; adalimumab and ustekinumab were not distinguished from each other.

Zweegers 2016

The authors conducted a literature review of prospective and retrospective observational studies from 1990 to 2014 on the daily practice biologics and conventional systemic therapies. A total of 32

studies were identified, among which two retrospective and two prospective studies compared PASI responses of biologics of our interest, including adalimumab, infliximab, etanercept, and ustekinumab. Only one of these four studies found a statistically significant difference between biologics: percentage improvement in PASI at 24 weeks was greater with infliximab compared to etanercept (89% vs. 75%, p=0.02). The other studies either did not conduct statistical tests or found non-statistically significant results. The authors identified the gap in the availability of direct evidence on effectiveness between agents.

Appendix D. Ongoing Studies

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Adalimumab					
Phase 3 Study of M923 and Humira in Subjects with Chronic Plaque-type Psoriasis **NCT02581345**	Phase III RCT	1) M923 (adalimumab biosimilar) 2) Adalimumab 3) M923 and adalimumab	N = 827, ages ≥18 **Inclusion criteria:** - PsO duration ≥ 6 months **Exclusion criteria:** - Prior use of TNF inhibitors, or 2 or more non-TNF biologic therapies	PASI 75 at week 16 Selected secondary outcomes: PASI 50, 90; sPGA, DLQI, EQ-5D, clinically significant AEs	May 2017
MSB11022 in Moderate to Severe Chronic Plaque Psoriasis (AURIEL-PsO) **NCT02660580**	Phase III RCT	1) MSB11022 (adalimumab biosimilar) 80mg initial dose, 40mg Q2W starting week 1 2) adalimumab following same dosing schedule above	N = 406, ages ≥18 **Inclusion criteria:** - 10% BSA, sPGA ≥ 3, PASI ≥ 12 - Patients who have received > 1 biologic **Exclusion criteria:** - Patients who have previously received adalimumab or an investigational or licensed biosimilar of adalimumab	PASI 75 at week 16 Selected secondary outcomes: % PASI improvement, HrQoL, AEs and SAEs	September 2017
Comparison of CHS-1420 Versus Humira in Subjects with Chronic	Phase III RCT	1) CHS-1420 (adalimumab biosimilar) 80mg initial	N = 545, ages ≥18 **Inclusion criteria:**	PASI 75 at week 12	March 2017

Plaque Psoriasis (PsOsim) **NCT02489227**		dose, 40mg Q2W weeks 1 to study completion 2) Adalimumab 80mg initial dose, 40mg Q2W weeks 1-15, re-randomized to either arm weeks 17-23, CHS-1420 weeks 17 to study completion	-10% BSA, sPGA ≥ 3, PASI ≥ 12 **Exclusion criteria:** Presence of significant comorbid conditions	No other outcomes listed	
Etanercept					
Safety and Efficacy Study of Etanercept (Qiangke) to Treat Moderate to Severe Plaque Psoriasis **NCT02701205**	Phase III RCT	1) Etanercept biosimilar (Qiangke) 50mg 2) Etanercept biosimilar (Qiangke) 25mg 3) Placebo	N = 216, ages 18-65 **Inclusion criteria:** -10% BSA, sPGA ≥ 3, PASI ≥ 12, PsO duration ≥ 6 months **Exclusion criteria:** -Previous use of systemic therapy or phototherapy with inadequate response -No use of adjuvant therapy, including traditional Chinese medicine and acupuncture, during first two weeks of study -No use of TNF antagonists or other biologics within 6 weeks before baseline	PASI 75 at week 12 Selected secondary outcomes: PASI 50, 90; PGA, DLQI	December 2017

Infliximab					
Psoriasis Longitudinal Assessment and Registry (PSOLAR) **NCT00508547**	Obs. Cohort (Phase IIII study)	1) Infliximab 2) Ustekinumab 3) Other biologic agents 4) Conventional systemic agents	N = 12051, ages 18-99 **Inclusion criteria:** - Candidate for, or currently receiving, conventional systemic agents or biologic treatment for psoriasis **Exclusion criteria:** - No participation in clinical trial with non-marketed investigational agents	Number of patients with AEs or SAEs over 8 years Selected secondary outcomes: DLQI, EQ-5D, HADS	May 2021
Secukinumab					
Study of Secukinumab Compared to Ustekinumab in Subjects with Plaque Psoriasis (CLARITY) **NCT02826603**	Phase III RCT	1) Secukinumab 300mg 2) Ustekinumab 45mg or 90mg (weight-dependent)	N = 1100, ages ≥18 **Inclusion criteria:** - 10% BSA, IGA ≥ 3, PASI ≥ 12, PsO duration ≥ 6 months - Inadequate response to prior topical treatment, phototherapy, or systemic treatment **Exclusion criteria:** - Prior use of secukinumab or drugs targeting IL-17 receptor	PASI 90 at week 12 IGA score of 0 or 1 at week 12 Selected secondary outcomes: TEAEs	August 2018
Ixekizumab					
A Study Comparing Different Dosing	Phase III RCT	1) Ixekizumab 160mg initial dose, 80mg Q2W	N = 1227, ages ≥18 **Inclusion criteria:**	PASI 75 and sPGA score of 0 or 1 at week 52	September 2017

regimens of Ixekizumab (LY2439821) in Participants with Moderate to Severe Plaque Psoriasis (IXORA-P) **NCT02513550**		2) Ixekizumab 160mg initial dose, 80mg Q4W 3) 160 mg ixekizumab initial dose, 80mg ixekizumab Q4W with step-up to Q2W 4) Placebo	- 10% BSA, PGA ≥ 3, PASI ≥ 12, PsO duration ≥ 6 months **Exclusion criteria:** - No concurrent/recent use of biologic agent	Selected secondary outcomes: PASI 90, 100; sPGA score of 0, DLQI, Itch NRS, EQ-5D, VAS-skin pain	
A Study of Ixekizumab (LY2439821) in Participants with Moderate-to-Severe Plaque Psoriasis (IXORA-S) **NCT02561806**	Phase III RCT	1) Ixekizumab 160mg initial dose, 80mg Q2W 2) Ustekinumab 45 or 90mg (weight-dependent)	N = 300, ages ≥18 **Inclusion criteria:** - PASI ≥ 12, PsO duration ≥ 6 months - Failure, contraindication, or intolerability to at least 1 systemic therapy (including cyclosporine, methotrexate, or phototherapy) **Exclusion criteria:** - No concurrent/recent use of biologic agent - No prior use or contraindication to ustekinumab - No previous tx with ixekizumab or other IL-17 or IL-12/23 antagonists	≥ PASI 90 at week 12 Selected secondary outcomes: SF-36, PGA, EQ-5D, WPAI	May 2017

A Study in Japanese Participants with Moderate-to-Severe Psoriasis (UNCOVER-J) **NCT01624233**	Phase III (exten-sion study)	Ixekizumab 160mg initial dose, 80mg Q2W until week 12, Q4W until week 52, and up to 192 weeks following relapse during drug-free period	N = 90, ages ≥20 **Inclusion criteria:** - 10% BSA, PGA ≥ 3, PASI ≥ 12, PsO duration ≥ 6 months **Exclusion criteria:** - No prior use of etanercept - No concurrent/recent use of biologic agents	PASI at week 12 Selected secondary outcomes: PGA, PROs, efficacy in patients with PsA	December 2016
Brodalumab – no ongoing studies identified					
Apremilast					
A Phase 4 Study of Efficacy and Safety of Apremilast in Subjects With Moderate Plaque Psoriasis (UNVEIL) **NCT02425826**	Phase IIII RCT	1) Apremilast 30mg BID 2) Placebo After week 16, all subjects take apremilast 30mg until week 52	N = 197, ages ≥18 **Inclusion criteria:** - 5-10% BSA, sPGA=3, PASI ≥ 12, PsO duration ≥ 6 months **Exclusion criteria:** - No prior exposure to systemic or biologic treatment for psoriatic arthritis, psoriasis, or other indications that could impact psoriasis assessment - No prior apremilast treatment	Mean percentage change in BSA multiplied by sPGA at week 16 Selected secondary outcomes: PASI 50, 75; DLQI, TSQM, AEs	November 2016

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Appendix E. Comparative Clinical Effectiveness Supplemental Information

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table F2) [37] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention-to treat-analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Modified intention-to-treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention-to treat-analysis is lacking.*

Table E1. Table PASI outcomes by trial

Trial	treatment	Time point (weeks)	N	%PASI 75	P value	%PASI 50	P value	%PASI 90	P value	%PASI 100	P value
Head-to-head trials											
Griffiths 2010 ACCEPT	Etanercept	12	347	57		NR		23		NR	
	Ustekinumab 45 mg	12	209	68	0.01	NR		36	P<0.001	NR	
	Ustekinumab 90 mg	12	347	74	<0.001	NR		45	P<0.001	NR	
Langley 2014 FIXTURE	Etanercept	12	326	44		NR		21		4	
	Secukinumab 300 mg	12	327	77	P<0.001	NR		54	P<0.001	24	P<0.001
Griffiths 2015	Etanercept	12	358	42		NR		19		5	
UNCOVER 2	ixekizumab	12	351	90	P<0.0001	NR		71	P<0.0001	41	P<0.0001
Gordon 2015	Etanercept	12	382	53		NR		26		7	
UNCOVER 3	ixekizumab	12	385	87	P<0.0001	NR		68	P<0.0001	38	P<0.0001
Thaci 2015	Ustekinumab	12	339	79		NR		53		26	
CLEAR	Secukinumab 300 mg	12	337	91	P<0.0001	NR		73	P<0.0001	39	P<0.0001
	Ustekinumab WBD	16	339	83		NR		58		28	
	Secukinumab 300 mg	16	337	93	P=0.0001	NR		79	P<0.0001	44	P<0.0001
Lebwohl 2015	Ustekinumab WBD	12	300	70		NR		47		22	
AMAGINE 2	Brodalumab 210 mg	12	612	86	0.08	NR		70	P<0.001	44	P<0.001
Lebwohl 2015	Ustekinumab WBD	12	313	69		NR		48		19	
AMAGINE 3	Brodalumab 210 mg	12	624	85	0.007	NR		69	P<0.001	37	P<0.001
Placebo-controlled trials											
Sauret 2008	Adalimumab	16	108	80		88		52		17	
CHAMPION	placebo	16	53	19	P<0.001	30	P<0.001	11	P<0.001	2	P<0.01
Menter 2008	Adalimumab	16	814	71		NR		45		20	
REVEAL	placebo	16	398	7	P<0.001	NR		2	P<0.001	1	P<0.01
Papp 2005	Etanercept	12	203	46		72		19		NR	
	placebo	12	204	3	P<0.001	9	P<0.001	<1	P<0.001	NR	
Leonardi 2003	Etanercept	12	164	49		71		22		NR	
	placebo	12	166	4	P<0.001	14	P<0.001	1	P<0.001	NR	
Tyring 2006	Etanercept	12	300	47		74		21		NR	
	placebo	12	300	5	P<0.001	14	P<0.001	1	P<0.001	NR	
Bagel 2012	Etanercept	12	62	59		85		25		NR	
	placebo	12	62	5	P<0.001	7	P<0.001	2	P<0.001	NR	
Gottlieb 2011	Etanercept	12	141	56		NR		23		7	
M10-114	placebo	12	68	7	P<0.001	NR		1	P<0.001	0	NR
Strober 2011	Etanercept	12	139	40		NR		14		6	
M10-315	placebo	12	72	7	P<0.001	NR		4	P<0.001	0	NR
Bachelez 2015	Etanercept	12	335	59		80		32		NR	

	placebo	12	107	6	P<0.001	21	P<0.001	1	P<0.001	NR	
Griffiths 2016	Etanercept	12	241	75		NR		NR		NR	
EGALITY	Erelzi	12	239	73.4	NS	NR		NR		NR	
Reich 2015	Infliximab	10	301	80		91		57		NR	
	placebo	10	77	3	P<0.001	8	p<0.001	1	P<0.001	NR	
Menter 2007	Infliximab	10	314	76		NR		45		NR	
	placebo	10	208	2	P<0.001	NR		1	P<0.001	NR	
Langley 2016	ixekizumab	12	433	89		NR		71		35	
	placebo	12	431	3	P<0.001	NR		1	P<0.001	0	P<0.001
Griffiths 2015	ixekizumab	12	351	90		NR		71		41	
	placebo	12	168	2	P<0.0001	NR		1	P<0.0001	1	P<0.0001
Gordon 2015	ixekizumab	12	351	87		NR		68		38	
	placebo	12	168	7	P<0.0001	NR		3	P<0.0001	0	P<0.0001
Leonardi 2008	Ustekinumab 45 mg	12	255	67		84		37		11	
	Ustekinumab 90 mg	12	256	66	P<0.0001	86	p<0.0001	42	P<0.0001	13	P<0.0001
	placebo	12	255	3	P<0.0001	10	p<0.0001	2	P<0.0001	0	P<0.0001
Papp 2008	Ustekinumab 45 mg	12	255	67		84		16		18	
	Ustekinumab 90 mg	12	256	76	P<0.0001	89	P<0.0001	42	P<0.0001	18	P<0.0001
	placebo	12	255	4	P<0.0001	10	P<0.0001	1	P<0.0001	0	P<0.0001
Langley 2014	Secukinumab 300 mg	12	245	82		91		59		29	
ERASURE	placebo	12	248	5	P<0.001	9	P<0.001	1	P<0.001	1	P<0.001
	Secukinumab 300 mg	16	245	86		91		NR		42	
	placebo	16	248	NR	P<0.001	NR		NR		NR	
Langley 2014	Secukinumab 300 mg	12	327	77		92		54		24	
FIXTURE	placebo	12	326	5	P<0.001	15	P<0.001	2	P<0.001	0	P<0.0001
	Secukinumab 300 mg	16	327	87		94		NR		37	
	placebo	16	326	NR	P<0.001	NR		NR		NR	
Blauvet 2015	Secukinuab 300 mg	12	59	76		88		60		43	
	placebo	12	59	0	P<0.0001	5	P<0.0001	0	P<0.0001	0	P<0.001
Paul 2015	Secukinuab 300 mg	12	60	87		NR		55		27	
	placebo	12	61	3	P<0.0001	NR		0		0	P<0.001
Papp 2016	Brodalumab 210 mg	12	220	83		NR		70		42	
	placebo	12	222	3	P<0.001	NR		1	P<0.001	1	P<0.001
Lebwohl 2015	Brodalumab 210 mg	12	612	86		NR		70		44	
AMAGINE 2	placebo	12	309	8	P<0.001	NR		3	P<0.001	2	P<0.001
Lebwohl 2015	Brodalumab 210 mg	12	624	85		NR		69		37	
AMAGINE 3	placebo	12	315	6	P<0.001	NR		2	P<0.001	0	P<0.001
Papp 2015	Apremilast	16	562	33		59		9.8		NR	
	placebo	16	282	15	P<0.001	17	P<0.001	0	NS	NR	
Paul 2015	Apremilast	16	274	29		56		9		NR	
	placebo	16	137	6	P<0.001	20	P<0.001	2	P=0.004	NR	

Appendix F. Comparative Value Supplemental Information

Table F1. Targeted therapies with dosing regimens

Drug	Route	Initiation phase	Maintenance phase
Adalimumab	Subcutaneous	80 mg once	40 mg once every two weeks (starting one week after first dose)
Apremilast	Oral	10 mg once in the morning on the first day; increase by 10 mg per day to maintenance dose (6 days)	30 mg twice a day
Brodalumab	Subcutaneous	210 mg once every two weeks for eight weeks	210 mg once every four weeks
Etanercept	Subcutaneous	50 mg twice a week through week 12	50 mg once a week
Infliximab	Intravenous	5 mg / kg at weeks 0, 2, and 6	5 mg / kg once every 8 weeks
Ixekizumab	Subcutaneous	160 mg once, then 80 mg every 2 weeks until week 12	80 mg once every 4 weeks
Secukinumab	Subcutaneous	300 mg once a week through week 4	300 mg once every 4 weeks
Ustekinumab	Subcutaneous	45 mg at weeks 0 and 4 (90 mg if patient > 100 kg)	45 mg once every 12 weeks (90 mg if patient > 100 kg)

Table F2. Ranges of PASI 75 for selected targeted therapies

Drug	Low value	Baseline value	High value
Infliximab	0.132	0.221	0.310
Etanercept	0.158	0.254	0.350
Ixekizumab	0.141	0.220	0.299
Secukinumab	0.158	0.245	0.332

Table F3. Alternative sources of health state utilities

Drug	Pickard	NICE adalimumab	NICE ustekizumab
PASI 90-100	0.856	0.861	0.892
PASI 75-89	0.847	0.782	0.862
PASI 50-74	0.798	0.782	0.812
PASI < 50	0.723	0.696	0.682
Second-line	0.846	0.739	0.789
Non-targeted	0.696	0.642	0.642

Table F4. Costs for laboratory tests

Test	Baseline	Source
Latent TB screen	$22.56	CMS fee schedule, 2016 (71010)
Active TB screen	$7.88	CMS fee schedule, 2016 (86580)
CBC (2016)	$19.11	Hankin, Drug Ben Trends, 2005
Hepatitis B screen (2016)	$17.29	Eckman, Clin Inf Dis, 2011
Liver function test (2016)	$19.11	Hankin, Drug Ben Trends, 2005
Renal function test (2016)	$20.88	Hankin, Drug Ben Trends, 2005
Clinic visit (2016)	$87.90	Hankin, Drug Ben Trends, 2005

Table F5. Per-cycle laboratory regimens for anti-psoriasis drugs

Drug	Latent TB	Active TB	CBC	HBV	LFT	Renal
adalimumab	0.0	0.0	0.2	once*	0.3	0.0
apremilast	0.0	0.0	0.0	0.0	0.0	once
brodalumab	0.0	0.0	0.0	0.0	0.0	0.0
etanercept	once	0.3	0.2	once	0.3	0.0
infliximab	once	0.2	0.2	0.0	0.0	0.0
ixekizumab	once	0.2	0.0	0.0	0.0	0.0
secukinumab	once	0.2	0.0	0.0	0.0	0.0
ustekizumab	once	0.2	0.2	0.0	0.0	0.0

*Laboratory tests marked "once" indicate a single administration of the test at the initiation of therapy

Table F6. One-way SA results - Infliximab Vs. non-targeted therapy

Infliximab vs non-targeted							
Parameter	**Low value**	**Base value**	**High value**		**Low value**	**Base ICER**	**High value**
Rate of severe URI	1%	1.70%	2.40%		$110,514	$110,573	$110,632
1L d/c rate (year 1, PASI 75+)	25%	30%	35%		$109,254	$110,573	$111,915
2L -> non-targeted d/c rate	5.0%	10.0%	15.0%		$112,271	$110,573	$109,046
1L d/c rate (year > 1, PASI 75+)	11.25%	15%	16.50%		$107,386	$110,573	$111,779
Cost per IV admin	$286.03	$357.54	$429.05		$107,748	$110,573	$113,398
PASI 75	72.41%	83.05%	90.81%		$114,406	$110,573	$108,023
Annual productivity cost offset	$3,920.00	$4,900	$5,880.00		$114,303	$110,573	$106,126
d/c % to 2L	25%	50%	75%		$106,060	$110,573	$114,497
Utility (change from baseline)	-5%	0%	+5%		$116,392	$110,573	$105,307
Price (per 100mg)	$964.33	$1,071.48	$1,178.63		$100,596	$110,573	$120,549
Cost of 2L	$2,958.52	$3,698	$4,437.78		$97,200	$110,573	$123,945
Doses per maintenance cycle	2.0	2.5	3.0		$93,200	$110,573	$127,946
Cost of non-targeted	$495.09	$990	$1,485.28		$120,654	$110,573	$85,369

Table F7. One-way SA results – Ixekizumab vs. non-targeted therapy

Ixekizumab vs non-targeted							
Parameter	Low value	Base value	High value		Low value	Base ICER	High value
Rate of severe URI	0%	0.40%	0.80%		$144,874	$144,888	$144,903
Cost per clinic-admin sub-q inj.	$20.35	$25.44	$30.53		$144,863	$144,888	$144,913
2L -> non-targeted d/c rate	5.0%	10.0%	15.0%		$144,799	$144,888	$144,949
d/c % to 2L	25%	50%	75%		$144,578	$144,888	$145,129
1L d/c rate (year 1, PASI 75+)	12%	16%	20%		$144,272	$144,888	$145,501
PASI 75	81.98%	88.83%	93.64%		$146,182	$144,888	$144,022
1L d/c rate (year > 1, PASI 75+)	2.50%	5%	10.00%		$143,728	$144,888	$147,138
Annual productivity cost offset	$3,920.00	$4,900	$5,880.00		$148,688	$144,888	$140,780
Cost of 2L	$2,958.52	$3,698	$4,437.78		$138,996	$144,888	$150,781
Utility (change from baseline)	-5%	0%	+5%		$152,514	$144,888	$137,989
Price (per 80mg)	$3,693.29	$4,103.65	$4,514.02		$126,611	$144,888	$163,166
Cost of non-targeted	$495.09	$990	$1,485.28		$169,038	$144,888	$120,739
Doses per maintenance cycle	0.80	1	1.2		$112,298	$144,888	$177,479

Appendix G. Network Meta-Analysis Methods and Results

Network Meta-Analysis Methods

In addition to summary evidence tables, we performed quantitative indirect comparisons using Bayesian network meta-analysis (NMA) for PASI outcomes.[123] A ordinal multinomial model with a probit link for PASI 50, PASI 75, and PASI 90 was used. This model assumes the treatment effect is the same regardless of the PASI cut-off and allowed us to use the data efficiently when some PASI outcomes were missing. All the analyses were conducted in WINBUGS 1.4,3 using code from the NICE DSU technical support document. Review of the deviance information criterion (DIC) statistics as well as comparison of the residual deviance (resdev) to the number of unconstrained data points was used to assess the best model fit under multiple alternative assumptions.[124] Given the expectation of at least some degree of heterogeneity in patient populations and/or study design, there is a general preference for a random-effects approach. A total of 50,000 iterations each were employed for both "burn-in" (for model convergence) and model (for model results) simulations. Relative risks and probabilities of patients having a given PASI response state was generated.

We conducted a sensitivity analysis to assess ustekinumab 45 mg and 90 mg doses separately by excluding a head-to-head trial where the two doses were combined. We also conducted a sensitivity analysis in which placebo response rate in each trial was adjusted as a covariate in the above described model. The median and credible interval of the adjustment coefficient (β) of placebo response from a previous network meta-analysis was used as input to our model. The adjustment coefficient (β) was tested against zero.[34]

Table G1. Basecase NMA. Relative risks and credible intervals of treatments compared to placebo on PASI outcomes from the NMA

treatment	PASI 75	CrI	PASI 50	CrI	PASI 90	CrI
ixekizumab	17.89	12.68-25.94	7.359	5.619-9.884	75.22	47.87-121.7
brodalumab 210	17.25	11.94-25.39	7.232	5.49-9.75	69.85	40.62-118.9
infliximab	16.72	11.75-24.34	7.13	5.442-9.576	64.84	39.78-106.8
secukinumab 300	15.37	10.93-22.17	6.844	5.246-9.148	54.63	34.57-87.98
ustekinumab 45/90	13.99	10.02-20.0	6.509	5.014-8.654	45.62	29.37-72.65
adalimumab	13.01	8.977-19.27	6.242	4.74-8.418	40.16	23.6-69.32
secukinumab 150	12.98	9.116-18.79	6.241	4.773-8.325	39.97	24.45-65.41

entanercept	9.57	6.943-13.54	5.196	4.046-6.839	23.89	15.63-37.58
Erelzi	8.92	4.465-15.46	4.95	3.062-7.278	21.5	7.749-49.13
apremilast	6.148	3.807-9.804	3.874	2.731-5.473	12.14	6.179-23.34

Table G2. Base case NMA. Probabilities of patients having a given PASI response state at the end of induction period

Treatment	%PASI 0-50	%PASI 50-75	%PASI 75-90	%PASI90-100
placebo	87.0	8.1	4.0	0.9
adalimumab	18.3	16.9	27.7	37.2
apremilast	49.3	20.1	19.4	11.2
brodalumab 210	5.3	8.4	21.3	65.0
etanercept	32.3	20.3	25.5	22.0
infliximab	6.9	10.0	23.3	59.8
ixekizumab	4.1	7.1	19.4	69.5
secukinumab 150	18.5	17.0	27.7	36.8
secukinumab 300	10.8	13.0	26.0	50.3
ustekinumab 45/90	15.2	15.5	27.4	42.0
Erelzi	35.0	20.5	24.7	19.9

Table G3. Base case NMA: league table of PASI 75 response

ixekizumab										
1.03 (0.91-1.25)	brodalumab 210 mg									
1.07 (0.95-1.24)	1.04 (0.85-1.23)	infliximab								
1.16 (1.04-1.33)	1.13 (0.92-1.32)	1.09 (0.93-1.26)	secukinumab 300 mg							
1.28 (1.14-1.45)	**1.24 (1.01-1.45)**	**1.20 (1.02-1.38)**	1.1 (0.96-1.26)	ustekinumab 45/90 mg						
1.37 (1.14-1.74)	**1.15 (1.02-1.34)**	**1.28 (1.02-1.65)**	1.18 (0.95-1.52)	1.07 (0.87-1.37)	adalimumab					
1.37 (1.18-1.66)	**1.33 (1.06-1.64)**	**1.29 (1.07-1.56)**	**1.18 (1.04-1.37)**	1.08 (0.91-1.30)	1.00 (0.76-1.30)	secukinumab 150 mg				
1.87 (1.62-2.19)	**1.81 (1.45-2.19)**	**1.75 (1.45-2.10)**	**1.61 (1.36-1.91)**	**1.46 (1.25-1.73)**	**1.37 (1.05-1.71)**	1.36 (1.10-1.65)	entanercept			
1.99 (1.31-3.83)	**1.92 (1.22-3.73)**	**1.86 (1.20-3.59)**	**1.71 (1.11-3.30)**	**1.56 (1.01-3.00)**	1.45 (0.90-2.86)	1.45 (0.92-2.9)	1.07 (0.71-1.99)	Erelzi		
2.90 (2.03-4.46)	**2.79 (1.90-4.36)**	**2.70 (1.86-4.22)**	**2.49 (1.72-3.78)**	**2.26 (1.58-3.49)**	**2.11 (1.42-3.31)**	**2.10 (1.42-3.31)**	**1.55 (1.07-2.4)**	1.45 (0.70-2.64)	apremilast	
17.89 (12.68-25.94)	**17.25 (11.94-25.39)**	**16.72 (11.75-24.34)**	**15.37 (10.93-22.17)**	**13.99 (10.02-20.0)**	**13.01 (8.98-19.27)**	**12.98 (9.12-18.79)**	**9.57 (6.94-13.54)**	**8.92 (4.47-15.46)**	**6.15 (3.81-9.80)**	placebo

Table G4. Base case NMA: league table of PASI 50 response

ixekizumab										
1.01 (0.96-1.11)	brodalumab 210 mg									
1.03 (0.98-1.11)	1.02 (0.92-1.10)	infliximab								
1.07 (1.02-1.15)	1.06 (0.96-1.15)	1.04 (0.97-1.12)	secukinumab 300 mg							
1.13 (1.07-1.21)	**1.11 (1.01-1.21)**	**1.10 (1.01-1.18)**	**1.05 (0.98-1.13)**	ustekinumab 45/90 mg						
1.17 (1.06-1.35)	**1.15 (1.02-1.34)**	**1.14 (1.01-1.32)**	**1.09 (0.97-1.27)**	1.04 (0.93-1.20)	adalimumab					
1.18 (1.08-1.31)	**1.16 (1.03-1.30)**	**1.14 (1.04-1.28)**	**1.09 (1.02-1.20)**	1.04 (0.95-1.16)	1.00 (0.85-1.16)	secukinumab 150 mg				
1.41 (1.30-1.57)	**1.39 (1.24-1.56)**	**1.37 (1.23-1.54)**	**1.32 (1.19-1.47)**	**1.25 (1.14-1.39)**	**1.21 (1.03-1.38)**	1.20 (1.06-1.36)	entanercept			
1.47 (1.14-2.30)	**1.45 (1.11-2.27)**	**1.43 (1.10-2.23)**	**1.37 (1.06-2.14)**	**1.30 (1.01-2.03)**	1.25 (0.94-1.98)	1.25 (0.95-1.96)	1.04 (0.81-1.59)	Erelzi		
1.89 (1.50-2.57)	**1.86 (1.45-2.53)**	**1.83 (1.44-2.50)**	**1.76 (1.38-2.39)**	**1.67 (1.32-2.27)**	**1.61 (1.24-2.19)**	**1.61 (1.24-2.20)**	**1.34 (1.05-1.82)**	1.28 (0.78-1.90)	apremilast	
7.36 (5.62-9.88)	**7.23 (5.49-9.75)**	**7.13 (5.44-9.58)**	**6.84 (5.25-9.15)**	**6.51 (5.01-8.65)**	**6.24 (4.74-8.42)**	**6.24 (4.77-8.32)**	**5.20 (4.05-6.84)**	**4.95 (3.06-7.28)**	**3.87 (2.73-5.47)**	placebo

Table G5. Base case NMA: league table of PASI 90 response

ixekizumab										
1.07 (0.8-1.60)	brodalumab 210 mg									
1.16 (0.89-1.57)	1.08 (0.71-1.56)	infliximab								
1.38 (1.08-1.79)	1.29 (0.85-1.80)	1.19 (0.87-1.59)	secukinumab 300 mg							
1.65 (1.30-2.10)	**1.54 (1.02-2.12)**	**1.42 (1.04-1.89)**	1.20 (0.93-1.54)	ustekinumab 45/90 mg						
1.86 (1.31-2.83)	**1.74 (1.07-2.77)**	**1.61 (1.05-2.54)**	1.35 (0.91-2.10)	1.13 (0.77-1.74)	adalimumab					
1.88 (1.39-2.64)	**1.76 (1.12-2.61)**	**1.62 (1.14-2.31)**	**1.36 (1.08-1.77)**	1.14 (0.84-1.59)	1.01 (0.63-1.59)	secukinumab 150 mg				
3.15 (2.46-4.07)	**2.94 (1.91-4.17)**	**2.71 (1.93-3.75)**	**2.29 (1.70-3.05)**	**1.91 (1.46-2.51)**	**1.69 (1.09-2.50)**	1.67 (1.17-2.33)	entanercept			
3.48 (1.70-9.30)	**3.23 (1.46-8.91)**	**3.00 (1.41-8.12)**	**2.52 (1.21-6.80)**	**2.11 (1.02-5.65)**	1.86 (0.84-5.22)	1.85 (0.86-5.02)	1.11 (0.56-2.82)	Erelzi		
6.17 (3.57-11.6)	**5.73 (3.04-11.17)**	**5.32 (2.91-10.33)**	**4.48 (2.51-8.60)**	**3.74 (2.13-7.07)**	**3.3 (1.76-6.47)**	**3.28 (1.77-6.43)**	**1.96 (1.12-3.72)**	1.77 (0.59-4.51)	apremilast	
75.22 (47.87-121.7)	**69.85 (40.62-118.9)**	**64.84 (39.78-106.8)**	**54.63 (34.57-87.98)**	**45.62 (29.37-72.65)**	**40.16 (23.6-69.32)**	**39.97 (24.45-65.41)**	**23.89 (15.63-37.58)**	**21.5 (7.75-49.13)**	**12.14 (6.18-23.34)**	placebo

Table G6. Sensitivity analysis NMA. Ustekinumab 45 mg and 90 mg separately, relative risks

Treatment	PASI 75	CrI	PASI 50	CrI	PASI 90	CrI
infliximab	17.5	12.59-24.85	6.974	5.392-9.222	70.19	45.69-110.1
brodalumab 210	17.11	12.2-24.46	6.904	5.333-9.137	67.16	41.81-108.1
ixekizumab	17.08	12.42-23.97	6.903	5.356-9.087	66.48	44.44-101.3
secukinumab 300	15.7	11.52-21.84	6.638	5.185-8.663	55.85	37.55-84.99
ustekinumab 90	14.93	11.03-20.62	6.474	5.088-8.418	50.74	34.35-76.42
ustekinumab 45	14.12	10.52-19.33	6.294	4.972-8.128	45.73	31.44-67.82
secukinumab 150	13.61	10.08-18.79	6.172	4.867-7.975	42.79	28.73-65.04
adalumab	11.77	8.436-16.57	5.687	4.452-7.392	33.35	20.6-53.38
entanercept	9.708	7.552-12.69	5.08	4.145-6.321	24.18	17.56-33.82
Erelzi	9.088	4.991-14.67	4.852	3.253-6.759	21.89	8.968-44.91
apremilast	5.252	3.365-7.822	3.395	2.47-4.546	9.553	5.115-16.92

Table G7. Sensitivity analysis NMA. Ustekinumab 45 mg and 90 mg separately, probabilities

Treatment	%PASI 0-50	%PASI 50-75	%PASI 75-90	%PASI90-100
placebo	86.4	8.7	4.0	0.9
adalumab	21.9	19.3	27.1	31.6
apremilast	53.5	20.4	17.1	9.0
brodalumab 210	5.3	9.1	21.5	64.1
entanercept	30.6	21.2	25.4	22.8
infliximab	4.6	8.3	20.4	66.7
ixekizumab	5.7	9.5	21.9	62.9
secukinumab 150	15.6	16.7	27.2	40.6
secukinumab 300	9.3	12.7	25.1	52.9
ustekinumab 45	13.9	15.9	26.9	43.3
Erelzi	33.1	21.5	24.7	20.8
ustekinumab 90	11.4	14.3	26.2	48.1

Table G8. Sensitivity analysis NMA. Placebo response unjustment, relative risks

treatment	PASI 75	CrI	PASI 50	CrI	PASI 90	CrI
infliximab	17.7	12.78-25.21	6.962	5.39-9.221	70.9	46.21-111.9
brodalumab 210	17.35	12.41-24.91	6.896	5.339-9.152	68.17	42.56-110.0
ixekizumab	17.28	12.59-24.25	6.894	5.353-9.069	67.21	45.22-102.5
secukinumab 300	16.29	11.97-22.62	6.712	5.247-8.771	59.4	40.43-89.26
ustekinumab 45/50	14.38	10.78-19.58	6.312	4.999-8.139	46.8	32.62-68.38

secukinumab 150	14.08	10.45-19.42	6.24	4.933-8.077	45.09	30.48-68.1
adalumab	11.96	8.533-16.81	5.698	4.459-7.39	33.99	20.86-54.34
entanercept	9.801	7.616-12.84	5.077	4.144-6.329	24.41	17.7-34.21
Erelzi	9.202	5.01-14.82	4.864	3.245-6.753	22.2	8.962-45.5
apremilast	5.284	3.366-7.948	3.395	2.466-4.555	9.609	5.113-17.04

Table G9. Sensitivity analysis NMA. Placebo response adjustment, probabilities

Treatment	%PASI 0-50	%PASI 50-75	%PASI 75-90	%PASI90-100
placebo	86.4	8.8	4.0	0.9
adalumab	21.7	19.5	27.1	31.7
apremilast	53.5	20.7	16.9	8.9
brodalumab 210	5.3	9.2	21.5	64.1
entanercept	30.5	21.5	25.3	22.7
infliximab	4.6	8.5	20.5	66.4
ixekizumab	5.7	9.7	21.9	62.7
secukinumab 150	14.5	16.5	27.0	42.0
secukinumab 300	8.2	12.1	24.4	55.3
ustekinumab 45/90	20.4	19.1	27.3	33.3
Erelzi	55.7	20.2	16.0	8.0