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

Condition Update

Draft Evidence Report

April 27, 2018

Prepared for:

NEW ENGLAND CEPAC
COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL

AN ICER PROGRAM

ICER Staff/Consultants	University of Washington School of Pharmacy Modeling Group*
Reiner Banken, MD, MSc Senior Fellow **Foluso Agboola, MBBS, MPH** Research Scientist **Alexandra Ellis, MSc, AM** Senior Scientist, HTA and Economic Evaluation Institute for Clinical and Economic Review **Rick Chapman, PhD, MS** Director of Health Economics Institute for Clinical and Economic Review **Celia Segel, MPP** Director of CER Policy Development Institute for Clinical and Economic Review **Katherine Fazioli, BS** Research Assistant Institute for Clinical and Economic Review **Daniel A. Ollendorf, PhD** Chief Scientific Officer **Steven D. Pearson, MD, MSc** President Institute for Clinical and Economic Review	**David L. Veenstra, PharmD, PhD** Professor and Associate Director Pharmaceutical Outcomes Research and Policy Program **Nathaniel Hendrix, PharmD** Pharmaceutical Outcomes Research and Policy Program *The role of the University of Washington School of Pharmacy Modeling Group is limited to the development of the cost-effectiveness model, and the resulting ICER reports do not necessarily represent the views of UW.

DATE OF PUBLICATION: April 27, 2018

Reiner Banken served as the lead author for the report. Foluso Agboola led the systematic review, network meta-analysis and authorship of the comparative clinical effectiveness section. Katherine Fazioli assisted with the systematic review and network meta-analysis. Rick Chapman was responsible for oversight of the cost-effectiveness analyses and developed the budget impact model. Celia Segel authored the section on coverage policies and clinical guidelines. Alexandra Ellis, Daniel Ollendorf, and Steven Pearson provided methodologic guidance on the clinical and economic evaluations. The role of the University of Washington (UW) School of Pharmacy Modeling Group is limited to the development of the cost-effectiveness model, and the resulting ICER reports do not necessarily represent the views of the UW. We would also like to thank Erin Lawler and Matt Seidner for their contributions to this report.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs.

The funding for this report comes from government grants and non-profit foundations, with the largest single funder being the Laura and John Arnold Foundation. No funding for this work comes from health insurers, pharmacy benefit managers, or life science companies. ICER receives approximately 15% of its overall revenue from these health industry organizations to run a separate Policy Forum program, with funding approximately equally split between insurers/PBMs and life science companies. For a complete list of funders and for more information on ICER's support, please visit http://www.icer-review.org/about/support/

Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at http://www.icer-review.org

About New England CEPAC

The New England Comparative Effectiveness Public Advisory Council (New England CEPAC) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. New England CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The New England CEPAC is an independent committee of medical evidence experts from across New England, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Council members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about New England CEPAC is available at http://icer-review.org/programs/new-england-cepac/.

The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results.

This is an ICER update. The first report was issued in December 2016 and can be found here: https://icer-review.org/material/pso-final-report/.

In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers and other stakeholders. The following clinical experts provided input 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 input, please visit: https://icer-review.org/material/psoriasis-stakeholder-list/

Expert Reviewers

Alexa B. Kimball, MD
Harvard Medical Faculty Physicians
Beth Israel Deaconess Medical Center

Conflict of Interest Declaration: *Alexa B. Kimball is a consultant for Novartis, AbbVie, UCB, Lilly, Janssen. Investigator to AbbVie, and UCB. Fellowship funding from Janssen and AbbVie. President of the International Psoriasis Council.*

Joseph F. Merola, MD MMSc
Assistant Professor, Director of the Center for Skin and Related Musculoskeletal Disease
Dept of Dermatology and Medicine Division of Rheumatology
Harvard Medical School, Brigham and Women's Hospital

Conflict of Interest Declaration: *J. F. Merola is a consultant and/or investigator for the following relevant companies: AbbVie, Amgen, Eli Lilly, Novartis, Pfizer, Janssen, UCB, Celgene.*

Leah McCormick Howard, J.D.
Chief Operating Officer
National Psoriasis Foundation

Conflict of Interest Declaration: *The National Psoriasis Foundation works with all the manufacturers that have a therapy in the psoriatic disease space, including AbbVie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, Merck, Novartis, Ortho Dermatologics, Pfizer, Sandoz, Sun Pharma, and UCB. A full list of their funders can be found in their Annual Report.*

Bram Ramaekers, PhD
Senior Researcher Health Economics
Department of Clinical Epidemiology and Medical Technology Assessment (KEMTA)
Maastricht University Medical Center

Conflict of Interest Declaration: *Bram Ramaekers did consulting for Janssen, but the consulting fee was <$5,000.*

Table of Contents

List of Acronyms Used in this Report

AAD	American Academy of Dermatology
AE	Adverse Event
BI	Budget impact
BSA	Body Surface Area
CMS	Centers for Medicare and Medicaid Services
CUA	Cost utility analysis
DC	Discontinuation
DIC	Deviance information criterion
DLQI	Dermatology Life Quality Index
dPGA	Dynamic Physician Global Assessment
EADV	European Association for Dermatology and Venereology
ERG	Evidence Review Group
EQ-5D	EuroQol five-dimension questionnaire
GDP	Gross domestic product
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IGA	Investigator's Global Assessment
IPC	International Psoriasis Council
LY	Life year
MACE	Major adverse cardiac events
MCS	Mental component score
NHE	National Health Expenditures
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMSC	Non-melanoma skin cancer
PASI	Psoriasis Area and Severity Index
PCS	Physical component score
PDI	Psoriasis Disability Index
PGA	Physician Global Assessment
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSD	Psoriasis Symptom Diary
PSI	Psoriasis Symptom Inventory
PSOLAR	Psoriasis Longitudinal Assessment and Registry
PUVA	Psoralen and ultraviolet A radiation
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
Resdev	Residual deviance
SF-36	Short Form-36
sPGA	Static Physician Global Assessment
TB	Tuberculosis
TNF	Tumor necrosis factor
USPSTF	U.S. Preventative Services Task Force
UVB	Ultraviolet B
VAS	Visual Analog Scale
WAC	Wholesale acquisition cost
WLQ	Work Limitations Questionnaire
WPAI	Work Productivity and Activity Impairment
WPI	Worker Productivity Index

Condition Update

In November 2016, the New England CEPAC Panel deliberated on the available evidence to help patients, clinicians, and payers address important questions related to the use of targeted immunomodulators for the treatment of patients with moderate-to-severe chronic plaque psoriasis. Following the evidence presentation and public comments, the New England CEPAC Panel voted on key questions concerning the comparative clinical effectiveness and comparative value of these agents. The final 2016 report can be found here.

Since the publication of the report in 2016, three new drugs have been approved, and two drugs are under FDA review for this condition. One of the drugs, brodalumab, was included in our 2016 review, but was not yet approved at the time of our deliberations. The other two drugs, guselkumab and tildrakizumab, were not included and specifically target IL-23, which represents a novel method of action. Certolizumab pegol, a TNFα inhibitor already approved by the FDA for other autoimmune conditions, is likely to be approved for plaque psoriasis before mid-2018, when this report update will be discussed at a public meeting. Finally, risankizumab, another novel IL-23 inhibitor, was filed with the FDA for review on April 25, 2018.

ICER has therefore decided to revisit its 2016 report in a "Condition Update" for adults with moderate-to-severe plaque psoriasis. In our Condition Update, we have performed a full systematic review of new treatments that have emerged since our 2016 report and have identified new evidence that has emerged on the treatments already included in the original assessment. In the following report, we integrate these new data in updated syntheses of the clinical evidence as well as our evaluations of long-term cost-effectiveness and budgetary impact.

1. Introduction

1.1 Background

Psoriasis

Plaque psoriasis is a common, chronic disease that manifests itself by itchy pruritic, red, scaly, raised lesions on the skin, most commonly on the scalp, elbows, knees, scalp, and back extensor extremities and trunk.[1] Psoriasis affects about 3% of the population and generally occurs before age 35.[2,3] In this T cell-mediated autoimmune and inflammatory disease genetic predispositions play a major role.[4,5] The pathogenesis is driven by multiple cytokine-mediated pathways, including tumor necrosis factor-α (TNF-α) and interleukin (IL)-23 and IL-17 cytokines.[5] It is associated with systemic diseases including other autoimmune diseases (e.g., inflammatory bowel disease), metabolic syndrome, and cardiovascular disease.[6,7] In addition, up to 30% of patients with plaque psoriasis have at least some manifestations of psoriatic arthritis,[8-10] and may reach up to 40% among patients treated with biologics.[8,11]

Plaque psoriasis accounts for about 80% to 90% of all patients with psoriasis.[12-14] Other types of cutaneous psoriasis include inverse psoriasis (affecting the skin folds, particularly the genital area), guttate psoriasis (small spots all over the body), palmar-plantar psoriasis (on the hands and feet), nail psoriasis, erythrodermic psoriasis (where the entire body may turn red), and pustular psoriasis (sterile pustules).[1,4,15]

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 patient's 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).[16,17]

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), social functioning (e.g., the face) or sexual activities (genital areas).[18-20] Patients with severe psoriasis have increased mortality, mainly due to cardiovascular disease.[9] These patients have an additional 6.2% absolute risk for major adverse cardiac events over 10 years relative to the general population,[7] and cardiovascular mortality is the main driver for the three to four-year reduction in life expectancy for patients with severe psoriasis.[21]

The direct annual medical costs of psoriasis, excluding the cost of co-morbidities, have been estimated to cost the United States $52 billion to $63 billion and indirect costs of lost work productivity have been estimated to range between $24 billion and $35 billion.[22]

Treatments

Treatments for psoriasis can be grouped within four broad categories:

1. Topical therapies such as steroids, vitamin D analogs, retinoids, and calcineurin inhibitors;
2. Older systemic therapies, such as acitretin, cyclosporine, and methotrexate;
3. Phototherapy, most commonly narrow-band ultraviolet B light (NBUVB); 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 or nail 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-α inhibitors.
- *Cyclosporine* is a T cell inhibitor. It works rapidly but causes hypertension and may be associated with lymphoma and skin cancer (especially when combined with psoralen and ultraviolet A radiation [PUVA]). Cyclosporine is also associated with nephrotoxicity, liver disease, hypertrichosis, gingival changes, GI symptoms, and neurologic symptoms. Drug interactions are common and there are many contraindications. Current US guidelines limit the continuous use of cyclosporine to one-year; European guidelines to two years.[23] 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 (PUVA) treatment. Narrowband UVB is more effective than broadband UVB; both can be delivered at home. 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; as such, UVB by far the most common form of phototherapy delivered in current clinical practice. A final form of phototherapy involves the use of excimer lasers for focused UVB light therapy.

Targeted immunomodulators

Targeted immunomodulators include the monoclonal antibodies reducing the level of the pathogenic cytokines, specifically TNF-α and interleukin (IL)-23 and IL-17 cytokines, and the PDE4 inhibitor apremilast reducing the production of proinflammatory mediators.[5]

Monoclonal antibodies are part of the class of drugs called biological products or biologics, large, complex molecules that are produced through biotechnology in a living system, such as a microorganism.[24] The FDA calls the first approved specific biologic product the Reference Product, often simply called Biologic, and the subsequent product the Biosimilar Product or simply Biosimilar. When approving a biosimilar, the FDA determines that there are no clinically meaningful differences from an existing FDA-approved reference product.[24] Since 2015, the FDA has added four-letter meaningless suffixes at the end of all non-proprietary names of biosimilars. Starting in November 2017, these suffixes are also added to all newly approved reference biologics' nonproprietary names.[25] In this report, we will be using the nonproprietary names as used by the FDA for reference biologics and biosimilars.

Table 1.1 provides an overview of the targeted immunomodulators approved, expected to be approved or submitted to the FDA for approval, by July 2018 for the treatment of moderate-to-severe plaque psoriasis. Of note, several of these agents are newly available or under FDA review since ICER's 2016 review, including three agents in a new class of selective IL-23 inhibitors (guselkumab, tildrakizumab, and risankizumab), as well an IL 17 inhibitor (brodalumab), a TNFα inhibitor (certolizumab pegol) and a second biosimilar for infliximab.

Table 1.1. Targeted Immunomodulators for Moderate-to-Severe Plaque Psoriasis[1]

Mechanism of Action	Name and Company	FDA approval for plaque psoriasis	Market availability	FDA recommended dosing
TNFα	adalimumab / Humira® AbbVie	Reference Biologic 2008/01/18	Available	80mg subcutaneously, then 40mg every other week starting 1 week after initial dose
	etanercept / Enbrel® Amgen	Reference Biologic 2004/04/30	Available	50mg subcutaneously 2x/week for 3 months, then 50mg 1x/week
	infliximab (dyyb/abda) Remicade®| Janssen Inflectra® | Pfizer Renflexis® | Merck	Reference Biologic: 2006/09/26 Biosimilars: 2016/04/05 2017/04/24	Available	5mg/kg intravenously at weeks 0, 2, and 6, then every 8 weeks
	certolizumab pegol / Cimzia® UCB	Reference Biologic, under FDA review for moderate to severe psoriasis indication	Available for other indications	n/a
IL 12/23	ustekinumab / Stelara® Janssen	Reference Biologic 2009/09/25	Available	Patients ≤100kg/>100kg: 45mg/90mg subcutaneously at week 0 and 4, then every 12 weeks
IL 23	guselkumab/ Tremfya® Janssen	Reference Biologic 2017/07/13	Available	100mg subcutaneously at weeks 0, week 4, then every 8 weeks
	tildrakizumab-asmn / Ilumya® Sun/Merck	Reference Biologic 2018/03/20	Not yet launched	100 mg subcutaneously at weeks 0, 4, then every twelve weeks
	risankizumab AbbVie	Submitted to the FDA on April 25, 2018	n/a	n/a
IL 17	secukinumab / Cosentyx® Novartis	Reference Biologic 2015/01/21	Available	300mg subcutaneously at weeks 0, 1, 2, 3, 4 then 300mg every 4 weeks
	ixekizumab / Taltz® Eli Lilly	Reference Biologic, 2016/03/22	Available	160mg subcutaneously at week 0, then 80mg at weeks 2, 4, 6, 8, 10, 12, then 80mg every 4 weeks
	brodalumab / Siliq® Valeant	Reference Biologic 2017/02/15	Available	210mg subcutaneously, every 2 weeks*
PDE-4	Apremilast / Otezla® Celgene	Reference Biologic 2014/09/23	Available	5-day titration then 30mg orally 2x/day thereafter

[1] This table include all reference biologics approved or submitted for approval, but only biosimilars that are currently available.

Aspects of Treatment

Non-Standard Dosing: Many psoriatic drugs appear to have waning effectiveness with continued use, known as biologic fatigue.[26] To maintain effectiveness, physicians often prescribe increasing doses of psoriatic treatments. Occasionally physicians prescribe *lower* doses of effective medications 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%;[27] 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. This may be due to a lack of efficacy, to coverage changes or other reasons. In an examination of infliximab use, 26% of treatment courses involved use of a greater-than-initially-recommended dose.[28]

A more recent study also evaluated claims over 12 months for 7,527 patients receiving adalimumab, etanercept, or ustekinumab. The study found rates of dose escalation with adalimumab, etanercept, and ustekinumab of 8%, 31%, and 18%; discontinuations of 53%, 56%, and 39%; restarts of the same medication following discontinuation of 18%, 23%, and 9%; and switching to a different medication of 21%, 22%, and 15%, respectively. Among patients who continued receiving ustekinumab, only 0.5% decreased their dose (from 90 mg to 45 mg) during the study period.[29]

Combination Therapy: The role of combination therapy – for example, the use of topical therapies with targeted immunomodulators or use of methotrexate as an adjunctive systemic therapy – has not been rigorously evaluated, but such use might provide enhanced effectiveness and is typical in clinical practice.[30] Combination therapy seems likely to be discussed in a forthcoming guideline from the American Academy of Dermatology and the National Psoriasis Foundation.

Previous Biologic Therapy Exposure: Generally, patients receiving a second TNFα inhibitor after not having responded to another TNFα inhibitor have a lower effectiveness of this second drug compared to patients who never received an agent from this class of drugs before.[31,32] The response of biologic experienced patients seems to be slightly lower overall compared to biologic naive patients, however these studies often involve small patient populations.[32] Considerable uncertainty persists as to the differences between first and second line effectiveness with different agents and biologic drug classes.[32-34]

Biosimilars

As of April 2018, the FDA has approved six biosimilars for use in plaque psoriasis, [35] but only two have been launched. The delays for launching biosimilars despite FDA approval are mainly due to patent litigation.[36,37] When approving a biosimilar, the FDA determines that there are no clinically meaningful differences from an existing FDA-approved reference product.[24] Head to head studies

and registry studies for TNF-α therapy have shown that biosimilars can be interchanged with the reference biologic without losing effectiveness.[38-42] Switching studies have confirmed that TNF-α biosimilars do not trigger immune responses that could diminish the long-term effectiveness of biologic therapy for psoriasis.[5] However, for biosimilars to be substituted for the reference product without the involvement of the prescriber, additional requirements have to be fulfilled.[24,43] Currently none of the FDA approved biosimilars has been recognized as an interchangeable product.[44]

Safety aspects of treatment with biologics

The biologic systemic treatments that are the subject of the present assessment act on specific pathways in the immune system, multiple cytokine-mediated pathways, including tumor necrosis factor-α (TNF-α) and IL-23 and IL-17 cytokines.[5] Safety concerns for these agents are primarily related to effects on the immune system: a range of infections, including tuberculosis, and malignancies, especially skin cancer and lymphoma. Such safety concerns are studied using registries that provide real world evidence in large patient cohorts; such evidence is of course not yet available for the newer agents.

It is known that the use of TNF-α agents is associated with increased risk of reactivation of latent tuberculosis infections, leading in most cases to disseminated or extrapulmonary disease, and tuberculosis screening has become mandatory prior to treatment with biologics. Cohort studies have shown however that the risk of tuberculosis reactivation in patients receiving biologics not targeting TNF is almost negligible.[5] TNFα inhibitor treatment can also induce new autoimmune diseases, such as lupus erythematosus.[45]

IL-23 and IL-17 are required for optimal skin host defense against Candida albicans.[46] Not surprisingly, Candida infections are more common with the use of IL-17 agents (secukinumab and ixekizumab), but they are superficial, not systemic.[5,47] The use of brodalumab, the third IL-17 agent, carries an increased risk of suicide[48] and a Risk Evaluation and Mitigation Strategy (REMS) has been requested by the FDA before the approval.[49]

Registry studies have shown that increased risks of major adverse cardiovascular events and cancer, especially lymphoma and nonmelanoma skin cancer, initially attributed to biologic therapy, are most likely related to psoriasis itself and not to the treatment.[50,51]

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. For elderly patients the diarrhea and weight loss can be of particular concern. Other adverse effects include mood disorders, upper respiratory tract infection and nasopharyngitis.[52]

Emerging therapies

As mentioned in the 2016 report,[53] tofacitinib and baricitinib are oral first-generation Janus kinase (JAK) inhibitors that have been shown to be effective for moderate-to-severe plaque psoriasis in randomized controlled trials.[54,55] They are part of a large number of novel therapies for immune-mediated inflammatory diseases targeting different pathways such as type I and II interferons, cellular adhesion processes, B-cells, regulatory T-cells and bispecific antibodies.[56]

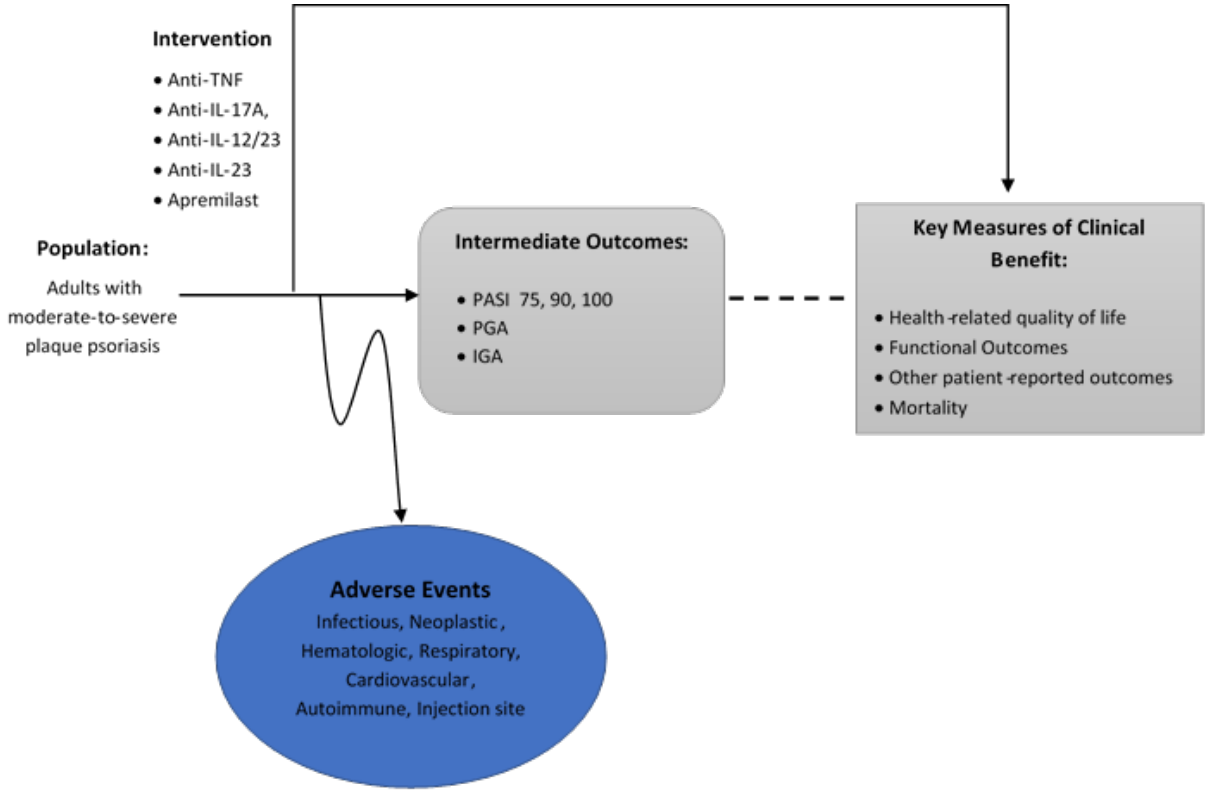
1.2 Scope of the Assessment

The scope for this update followed the approach used in 2016 and is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence was collected from available randomized controlled trials as well as high-quality systematic reviews; higher-quality comparative cohort studies will also be evaluated as necessary. We did not restrict studies according to study duration or study setting; however, we limited our review to those that captured the key outcomes of interest. We supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Analytic Framework

The analytic framework for assessment of anti-plaque psoriasis medications is depicted in Figure 1.1 below.

Figure 1.1. Analytic Framework: Management of Moderate-to-Severe Chronic Plaque Psoriasis



PASI = psoriasis area severity index; PGA = physician global assessment; IGA = Investigator Global Assessment

The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes: those within the rounded boxes are intermediate outcomes (e.g., PASI 75, 90, and 100), and those within the squared-off boxes are key measures of benefit (e.g., health-related quality of life). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment which are listed within the blue ellipsis.[57]

Populations

The population of focus for this review included adults with moderate-to-severe chronic plaque psoriasis. Although not a focus of the review, we did not exclude patient populations with other concomitant psoriasis types or psoriatic arthritis and evaluated psoriasis outcomes in these subgroups if data were available. Additionally, we attempted to distinguish outcomes for patients who have and have not been previously treated with a targeted immunomodulator.

Subgroup analyses conducted in the 2016 report were updated: patients with concomitant psoriatic arthritis, patients who had previous used biologic therapy, and results from Asian studies.

Interventions

The interventions of interest were the targeted immunomodulators (biologics and apremilast) approved, expected to be approved or submitted to the FDA for approval, by July 2018 for the treatment of moderate-to-severe plaque psoriasis:

- **TNF-α inhibitors**: adalimumab, etanercept, infliximab, certolizumab pegol
- **IL-17 agents**: secukinumab, ixekizumab, brodalumab
- **IL-12/23 agent**: ustekinumab
- **IL-23 agents**: guselkumab (approved in 2017), tildrakizumab (approved in March 2018), risankizumab (submitted to the FDA on April 25, 2018)
- **Anti-PDE-4 agent**: apremilast

Comparators

We compared to placebo, and wherever possible, we evaluated head-to-head trials of these interventions.

Outcomes

This review examined key clinical outcomes, including outcomes common to plaque psoriasis trials (a list of outcomes is included on the next page). We examined available data for evidence about the comparative effectiveness of targeted immunomodulators in affecting domains such as itch, scaling, pain, quality of life, work productivity, and satisfaction with treatment.

Clinical Trial and Study Outcomes

- Psoriasis Area and Severity Index (PASI): 50, 75, 90, 100
- Physician Global Assessment (PGA)
- Investigator Global Assessment (IGA)
- Treatment-related adverse events

Patient-Reported Outcomes

- Dermatology Life Quality Index (DLQI)
- Other measures of health-related quality of life (e.g., Psoriasis Symptoms and Signs Diary)
- Psoriasis Symptom Inventory (PSI)
- Symptom control
- Treatment tolerability

We updated the evidence tables with data from the newly selected studies and results were summarized in a qualitative fashion. As in the 2016 review, network meta-analyses to combine direct and indirect evidence on PASI 50, PASI 75 and PASI 90 scores were conducted, and were updated based on new direct and indirect evidence.

Timing

Evidence on intervention effectiveness and harms were 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.

1.3 Definitions

Psoriasis Area and Severity Index (PASI)

The PASI is a measure of the percent body surface area with psoriatic lesions in each of four regions (head, trunk, arms, and legs) as well as the degree of erythema, induration, and scale of the lesions in each area. PASI scores range from 0 to 72. Higher numbers indicate more 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) and Investigator's Global Assessment (IGA)

The Static Physician Global Assessment (sPGA) and the Investigator's Global Assessment (IGA) are similar, being scored by the treating or evaluating physician and only considers the time of evaluation. Scores usually range from 0 to 7 with higher scores indicating worse severity, but 5-point, 6-point and 7-point scales have all been used. 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, considers 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.

The IGA is a modified version of the PGA, and 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 Life Quality Index (DLQI)

The DLQI was the first dermatology-specific health-related quality-of-life (HRQoL) instrument introduced in 1994.[58] It comprises 10 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 representing better quality of life. A DLQI change of 5-points is the minimal amount of change needed to establish meaningful clinical significance in health-related quality of life (HRQL).

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 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.[59] 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 impairment. The PDI can also be expressed as a proportion of total possible score.

Visual Analog Scale (VAS)-skin pain

VAS is a commonly used measure of pain, which is also 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 pruritus (0 points) to severe pruritus (5 points).

Psoriasis Symptom Inventory (PSI)

The PSI is an 8-item measurement 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.

Psoriasis Symptom Diary (PSD)

The PSD measures the impact of psoriasis treatments on daily activities. Patients report disease severity on a scale of 0 to 10 on 20 psoriasis-specific signs and symptoms, including itching, pain, scaling, flaking, and changes in skin appearance.

Psoriasis Symptom and Sign Diary (PSSD)

The PSSD is a patient-reported instrument that assesses severity of six psoriasis symptoms (itch, skin tightness, burning, stinging, and pain,) and five signs (dryness, cracking, scaling, shedding/flaking, redness, and bleeding) with a summary score between 0 and 100.

Hospital Anxiety and Depression Scale (HADS)

The HADS is a 14-item scale that scores anxiety and depression. Seven items are related to anxiety and seven are related to depression. Each item is scored 0 to three to generate anxiety or depression scores of 0 to 21, with higher scores indicting more anxiety or depression. A score above eight 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 six questions about current employment and, in the past seven days, hours missed due to health problems, hours missed for other reasons, hours worked, productivity impairment at work ("presenteeism"), and productivity impairment in unpaid 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.[60]

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 scale, indicating no impact to severe impact on productivity at school, home, or work.

1.4 Insights Gained from Discussions with Patients and Patient Groups

In the development of the 2016 report,[53] ICER had conversations with and received input from patient advocacy groups, including the National Psoriasis Foundation, and individual patients.[61] These conversations highlighted the shortcomings associated with clinical trial outcomes in many studies of psoriasis therapies, frustrations with the healthcare system, as well as the social, emotional, and financial impact of psoriasis. These issues were presented by the National Psoriasis Foundation at the ICER public meeting on the topic.[62,53]

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). At an FDA meeting in 2017 on Patient-Focused Drug Development for Psoriasis, patients rated flaking/scaling and itching as a having a more significant impact on their quality of life than the rash itself.[63] Simple body surface area (BSA) measurements of psoriasis involvement do not consider the greater effect that lesions in particular areas –such as the nails, genitals, scalp, face, flexural areas, palms, and soles of the feet— 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.[19,64] 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.[19] 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.

In addition to delayed diagnosis, racial and ethnic minorities appear to have a higher prevalence of psoriasis, more severe disease, more common misdiagnosis, and more frequent non-treatment; they are less likely to be included in clinical trials. Furthermore, in a Medicare population, black patients were 70% less likely to have received biologics for their psoriasis compared to white patients.[65]

For all patients, treatments for plaque psoriasis may be challenging. 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. Patients need to consider time and travel for administration of phototherapy and infused therapy. Psoriasis is a chronic disease that requires management over a lifetime, potentially during the treatment of other chronic conditions, including cancer.

Psoriasis affects social functioning. Patients with psoriasis often feel the need to make different clothing choices to hide psoriatic skin. 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.[66] Psoriasis is associated with a higher likelihood of having depression, anxiety, and suicidal ideation.[20,67] Some patients reported somatic manifestations of psychiatric disease or emotional difficulties, including GI symptoms and hypertension.

Patients are concerned about lack of access to treatment because of inadequate insurance coverage, out of pocket costs, and future availability of drugs to treat their disease. About half of patients with psoriasis are either undertreated or not treated,[64] 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. Patients are also frustrated by a lack of clarity in the exception process and timing in many plans, reporting that their physicians are not always sure how to get through a step therapy process even when that patient is an appropriate candidate to move on to a more advanced treatment. In addition, switching insurance or within-plan coverage changes 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 autoimmune conditions, like rheumatoid arthritis, which is a listed indication for many of the drugs of interest for this review.

1.5. Potential Cost-Saving Measures in Psoriasis

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) currently used for people with psoriasis that could be reduced, eliminated, or made more efficient.

We did not receive any suggestions in response to the final scoping document. We also did not identify recommendation from professional organizations such as Choosing Wisely, American Academy of Dermatology or US Preventive Services Task Force. However, we continue to seek such input from all stakeholders during our public comment period.

2. Summary of Coverage Policies and Clinical Guidelines

2.1 Coverage Policies

We analyzed insurance coverage for treatment options for patients with moderate-to-severe plaque psoriasis in six New England state Medicaid programs, and 13 silver-tiered insurance plans on individual marketplaces across New England. A complete listing of plans surveyed, and key formulary designs, are included as tables in Appendix H.

Across all plans, we analyzed formulary exclusions, preferred agents, benefit design, and step protocols. All plans required an initial trial or contraindication to systemic therapy such methotrexate or phototherapy. After the trial with systemic therapy, all plans covered at least one TNFα inhibitor as a preferred agent; nearly half of plans covered an IL-17 as preferred; and over two-thirds of plans covered either an IL-17 or an IL-12/23 therapy as a preferred therapy. Preferred therapies still required prior authorization and required a trial of systemic therapy, but had lower cost-sharing than their non-preferred counterparts. Certain non-preferred therapies, such as ixekizumab, guselkumab or apremilast, often required trials of systemic therapy, followed by one, two, or three other specialty medications, before gaining access to the drug therapy. Some non-preferred therapies required up to five trials with other drug therapies for treating moderate-severe psoriasis. Our analysis of formulary designs is summarized in Table 2.1 below.

Importantly, it appears that a marked shift in coverage policy has occurred since our 2016 review. At that time, TNFα inhibitors were the only preferred agents in nearly all plans, and most insurers required patients to step through adalimumab and/or etanercept before attempting treatment with an agent from another class. In fact, in our 2016 analysis, only two plans offered secukinumab and ustekinumab as preferred drug therapies for treatment. In 2018, the landscape has shifted so that nearly two-thirds of plans surveyed offer at least one other preferred agent outside the TNFα inhibitor class.

Still, newer agents, such as brodalumab and guselkumab, remain unlikely to be covered; and apremilast and ixekizumab are most likely to see several step requirements. Table 2.1 presents key findings from our survey of commercial plans.

Medicaid

A few New England Medicaid programs have also evolved in their coverage policies since our analysis in 2016. Five of the six states continue to prefer adalimumab and etanercept on their drug list. However, two states – Vermont and Maine – added secukinumab to their list of preferred drugs after treatment failure with adalimumab. Coverage policies for New England state Medicaid programs are summarized in Appendix H in Table H2.

Table 2.1. Benefit Design for Treating Moderate-Severe Plaque Psoriasis across New England Commercial Payers

			# of Step edits				
	% of Plans Excluding Drug from Coverage	% of Plans Covering Drug under Medical Benefit	0	1	2	3+	% of Plans Covering as Preferred Agents
TNFα inhibitors							
etanercept	0%	0%	92%	8%	0%	0%	92%
infliximab	0%	54%	23%	8%	15%	0%	38%
adalimumab	0%	0%	100%	0%	0%	0%	100%
certolizumab pegol	92%	0%	0%	100%	0%	0%	0%
IL-17							
secukinumab	0%	0%	46%	23%	31%	0%	38%
ixekizumab	38%	0%	0%	38%	38%	13%	13%
brodalumab*	54%	0%	0%	0%	33%	0%	0%
IL-12/23							
ustekinumab	15%	23%	55%	27%	0%	0%	73%
IL-23							
guselkumab*	69%	0%	0%	25%	25%	0%	25%
risankizumab	*Investigational; Submitted to the FDA in April 2018*						
tildrakizumab	*Tildrakizumab was approved in March 2018; formulary status currently unknown*						
PDE-4							
Apremilast*	31%	0%	22%	44%	11%	0%	33%
**** brodalumab, guselkumab, and apremilast had incomplete information on step criteria.***							

2.2 Clinical Guidelines & Statements on Managing Care

From the Medical Board of the National Psoriasis Foundation: Treatment Targets for Plaque Psoriasis
http://www.jaad.org/article/S0190-9622(16)30909-4/pdf

In February 2017, the National Psoriasis Foundation published a paper in the Journal of the American Academy of Dermatology (JAAD) encouraging clinicians to establish treatment targets for their patients with plaque psoriasis in order to monitor disease progression and evaluate patient response to drug interventions. Based on consensus among dermatologists, and patient focus groups, the guidelines recommended that dermatologists measure body surface area (BSA) as the most practical outcome for monitoring response to treatment. The panel of experts defined an acceptable treatment response to a medical intervention within three months as BSA of 3% or less; or 75% improvement from baseline. Over maintenance therapy every six months, they suggested a treatment target of BSA 1% or less. In their discussion, the authors recognized the barriers to care in a real world setting and encouraged payers to improve accessibility to therapeutic options in order to help patients achieve treatment success. They do not suggest any specific drugs or sequencing of drug therapies as that is not the intended purpose of these treatment goals. Rather the purpose is to encourage a paradigm shift in care strategy to improve health outcomes.

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

The American Academy of Dermatology (AAD) were published in 2011 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 targeted immunomodulators (biologics) available at the time they were written. The AAD is preparing an update to their guideline specific to combination therapy for 2018.

NICE Guidelines
https://www.nice.org.uk/guidance/cg153?unlid=389903762016517237 35

The UK National Institute for Health and Care Excellence (NICE) reviewed therapies and offered guidance for treatment. The guidelines were most recently updated in September 2017. NICE recommends progression from topical (mostly steroid) to systemic non-biologic therapy such as phototherapy, methotrexate or cyclosporine before moving on to treatment with a targeted immunomodulator. After failure of non-biological treatment, they recommend a trial period of etanercept, ixekizumab, or secukinumab for 12 weeks; or adalimumab or ustekinumab for 16 weeks. Treatment response is considered a 75% improvement from baseline in the PASI. NICE also recommends secukinumab if a discount is available from the company. Infliximab is recommended after failure of first-line treatment for those patients with a PASI >20 ("very severe psoriasis"). In October 2016, NICE released a new determination recommending apremilast for severe disease if systemic therapy fails to achieve treatment response and apremilast is provided at a discount.

European Guideline on Systemic Treatment of Psoriasis Vulgaris, 2017 Update
http://www.euroderm.org/edf/index.php/edf-guidelines/category/5-guidelines-miscellaneous?download=79:psoriasis-update-2017-incl-grade-tables

An expert European panel updated their 2015 guidelines with an addendum in September 2017. They stated that systemic treatments have many unwanted side effects and toxicity but should be first-line therapy. If phototherapy and older systemic agents are ineffective, contraindicated, or not tolerated, they recommended treatment with TNF-α inhibitors or secukinumab. Ustekinumab and apremilast were recommended as second-line therapy. Ixekizumab and brodalumab were not included in the review.

British Association of Dermatologists Guidelines for Biologic Therapy for Psoriasis 2017
https://onlinelibrary.wiley.com/doi/epdf/10.1111/bjd.15665

In their 2017 guidelines, the British Association of Dermatologists updated treatment guidelines for biologics, recommending first line treatment with systemic therapy, unless not well tolerated or contraindicated; or moving directly to biologic treatment if the patient has either a BSA or PASI score of >10 or has severe localized psoriasis associated with functional impairment. As first line biologic treatment, they recommend ustekinumab, adalimumab (especially for patients with psoriatic arthropathy), and secukinumab. For second line treatment, they do not recommend a particular treatment. However, they suggest reserving treatment with infliximab for patients with severe disease when other biologics are ineffective. When biologic therapy fails, they suggest supplementing treatment with lifestyle interventions, systemic therapy, alternative biologic therapy, or alternative methods of administration of therapy. The guidelines also make recommendations for when to escalate dosage based on inadequate response and how to transition between biologic therapy.

3. Comparative Clinical Effectiveness

3.1 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 Table 1.1.

We included evidence from placebo-controlled trials, but concentrated on evidence about the comparative clinical effectiveness of these treatments compared to each other. 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], Psoriasis Symptom Inventory [PSI])
- Harms
    - Treatment-related adverse events (e.g., rate of infections)
    - Treatment tolerability (i.e., discontinuation due to adverse events)

3.2 Methods

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.[68] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[69] The PRISMA guidelines include a checklist of 27 items, further details of which is available in Appendix Table A1.

Since this was an update of the review conducted in 2016, we searched MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials for relevant studies from the date of the last search

(June 28th, 2016) to January 2, 2018 to update the evidence on the drugs included in the 2016 review (Appendix A). For the four new drugs added to the current review (guselkumab, tildrakizumab, risankizumab and certolizumab pegol), our search of the electronic databases spanned from January 1996 to January 2, 2018 (Appendix A). We limited each search to English language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. 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 submissions from manufacturers of psoriasis therapies that were not otherwise publicly available, as well as data recently presented during the American Academy of Dermatology conference from February 16-20, 2018.

Study Selection

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. 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 conference proceedings or regulatory documents on the TNF-α therapies given that these treatments have been available for at least a decade and primarily have peer-reviewed data available.

Data Synthesis and Statistical Analyses

Data were abstracted and summarized into evidence tables for all outcomes (see Appendix B, Tables B1-B3) and are synthesized in the text below. In addition, because the treatments of interest have usually not been directly compared, we developed quantitative, indirect comparisons among all agents using a Bayesian network meta-analysis (NMA) for the PASI outcome. Consistent with prior published methods,[70] PASI 50,75 and 90 response outcomes from clinical trials were tabulated to create numbers of patients in mutually exclusive categories (i.e., <50, <75, 50-74,75-89, ≥90);

these data were analyzed using a random-effects, multinomial likelihood model to generate proportions of patients in each category. An adjusted model was specified with a covariate for placebo response rate which was assumed to be common across all treatments and provided a control for known and unknown differences between study populations.

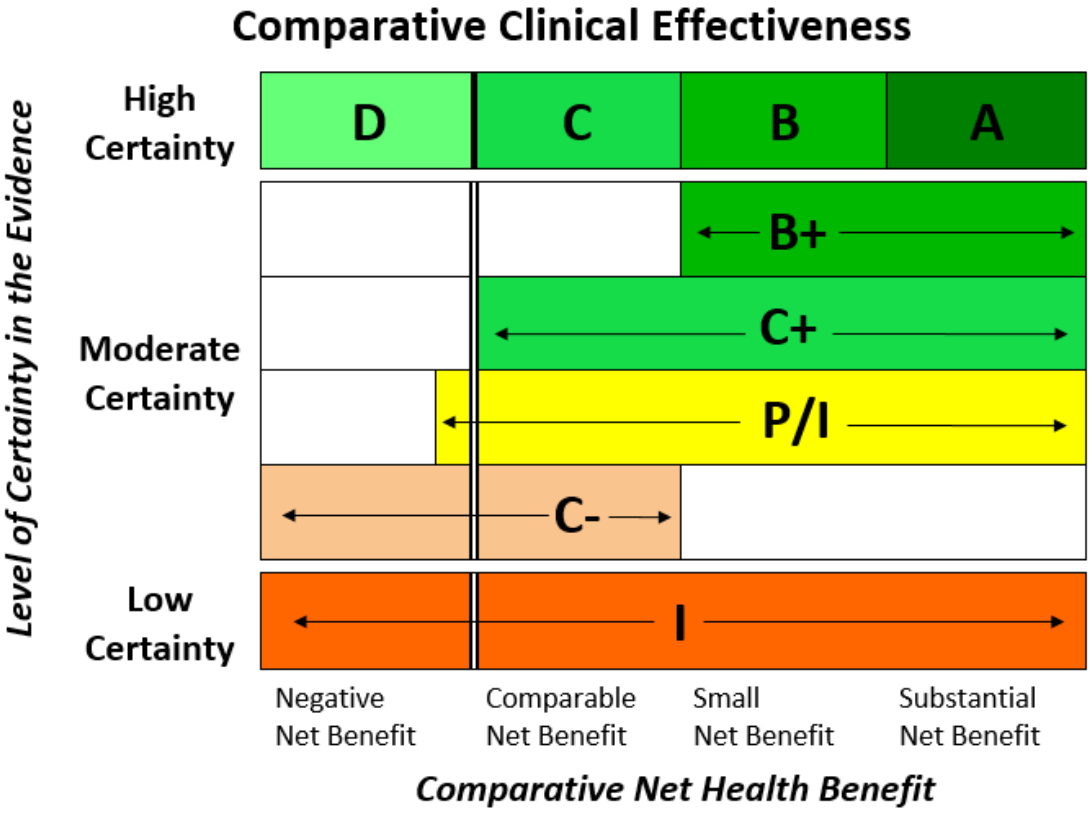
The NMA was conducted using JAGS software (version 4.3.0) via R using the R2jags package.[71] Criteria for trial selection, statistical methods and R code are detailed in Appendix F.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix (see Figure 3.1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

a) 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
b) The level of **certainty** in the best point estimate of net health benefit.[72]

Figure 3.1. 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
C- = "Comparable or Inferior" - Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior
I = "Insufficient" - Any situation in which the level of certainty in the evidence is low

3.3 Results

Study Selection

Our updated literature search identified 1,379 potentially relevant references (see Appendix A), of which 43 references, relating to 16 RCTs and two observational studies (29 publications and 14 abstracts/conference presentations) met our inclusion criteria. In addition, we included all 80 references relating to 36 individual RCTs and eleven observational study from the previous review.[53] In total, we included 123 references of 52 RCTs and 13 observational studies. Primary reasons for study exclusion included the evaluation of study populations or outcomes related specifically to patients with psoriatic arthritis or other types of psoriasis (e.g., erythrodermic), and non-comparative study design. Ustekinumab and the TNF-α therapies were the only treatments for which we found 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 3.1.

Quality of Individual Studies

As noted in the previous review, all the identified trials were rated to be of good or fair quality using criteria from U.S. Preventive Services Task Force (USPSTF).[73] We rated 13 of the newly identified trials, of which seven were Phase III, to be of good or fair quality using the same criteria. 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. The two observational studies were judged to be of fair quality. We did not assign a quality rating to the remaining Phase III trials (three risankizumab trials) that were only available in the grey literature.

Included Studies

Of the 52 individual RCTs, 47 were Phase III trials while the remaining five were Phase II trials that presented data on subpopulations of interest. Thirteen of the of the 47 Phase III trials are newly identified trials, of which 10 relate to the four new drugs of interest (three on certolizumab pegol; three on risankizumab; two on guselkumab; and two on tildrakizumab), and the remaining three relate to new studies on three drugs in the 2016 review (adalimumab, infliximab and head-to-head between infliximab and etanercept).

We identified six head-to-head trials on the new drugs: etanercept versus (certolizumab pegol [CIMPACT] and tildrakizumab [RESURFACE 2]); ustekinumab versus risankizumab [ULTIMMA 1 & 2]; and adalimumab versus guselkumab [VOAYAGE 1 and 2]. All six studies included a placebo-controlled arm.

In addition, we included nine head to head trials on the previously reviewed drugs: etanercept versus (ustekinumab [ACCEPT], secukinumab [FIXTURE], ixekizumab [UNCOVER 2 and 3], and infliximab [PIECE]); ustekinumab versus (brodalumab [AMAGINE 2 and 3], secukinumab [CLEAR], and ixekizumab [IXORA-S]). Four of these studies (ACCEPT, CLEAR, IXORA-S, and PIECE) did not include a placebo arm.

All the phase III studies were multicenter, double-blind, RCTs, except for the PIECE trial (etanercept versus infliximab) and the active comparator arms of the CIMPACT trial (etanercept versus certolizumab pegol). PIECE was an investigator initiated multicenter single-blind study, while the active comparator arms CIMPACT was single-blinded. Many of the trials removed blinding following the induction period, and some also re-randomized 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 beyond the induction phase. Most studies required washout of prior therapies and prohibited concurrent use of these treatments throughout the trials. Study populations had similar inclusion criteria (≥18 years old, BSA ≥10%, PASI score ≥12, ±PGA/IGA ≥ 3, ≥6 months of plaque psoriasis diagnosis, and were candidates for phototherapy or systemic therapy.

Studies were comparable with respect to age (range of means: 39-50 years, median: 45) and duration of psoriasis (range of means: 11-22 years, median: 18). Across all studies, an average of 21% of patients (range of means: 3% to 37%) had psoriatic arthritis at baseline and an average of 16.5% (range of means: 0% to 57%) of patients received prior biologic therapy. Of note, fewer patients were generally biologic-experienced in the studies of the older TNF-α drugs relative to the newer therapies (Median 0% vs 16.5%). Baseline PASI scores across trials ranged from 15 to 33 (median: 20). Given potential between-trial heterogeneity, we adjusted for the placebo response rate in our network meta-analysis which, to some degree, accounts for baseline patient differences between studies as well as possible unknown confounders. In addition, we also conducted a subgroup scenario analysis in our network meta-analysis adjusting for other baseline variations such as prior biologic exposure; the details and results of this analysis are discussed in Appendix F.

Subgroups

In the 2016 report, several populations were identified as being of special interest to stakeholders as described in the subgroups section of this report. [53] We have updated the analyses for these subgroups for the present report (see Appendix E). The characteristics of these subgroups are as follows:

Asian Studies: We separately considered and described the outcomes in seven trials (five phase III and two phase II) that were conducted exclusively in Asia (i.e., Japan, Korea, China, and Taiwan), plus a subgroup analysis of the ERASURE study. These trials were generally smaller (with the

exception of LOTUS, n=322)[74] with patients who had a briefer duration of psoriasis (Median: 15 years vs. 18 years from other studies), higher PASI score (Median: 28 vs. 20 in the other studies), less prior experience with biologic therapy (proportion of previous biologics, median: 0% vs. 21% in other studies) and lower BMI. We considered the Asian trials as a subgroup because of the generally smaller study size and differences in patient characteristics from the worldwide studies.

Patients with Previous Biologic Therapy Exposure: We also examined subgroups of patients who had and had not been previously treated with a targeted immunomodulator. As noted above, fewer patients were biologic-experienced in the studies of the older TNF-α drugs relative to the newer therapies. Patients who previously used biologic therapy might be less likely to respond to a subsequent targeted immunomodulator. Thus, we describe the results of 10 trials reporting this subgroup analysis below.

Patients with Psoriatic Arthritis: Because up to a third of patients with psoriasis develop psoriatic arthritis, we evaluated subgroup analysis of psoriasis patients with and without psoriatic arthritis. Patients with concomitant psoriatic arthritis might have more severe skin disease and might respond better or worse to targeted immunomodulators than patients without psoriatic arthritis.

Table 3.1. All Phase III Studies (New Studies are Bolded)

Drug	Trials	Total patients	Induction period (weeks)	PASI, (mean)	Age (years)	Psoriasis duration (years)	Previous biologics, %	PsA, %
Placebo Controlled Studies with or without Active Comparators								
Adalimumab [75-78]	REVEAL CHAMPION Asahina, 2010† **Cai, 2017†¥**	2,077	16/12	24	44	16	2	20
Etanercept [79-85]	Papp, 2005 Leonardi, 2003 Tyring, 2006 Strober, 2011 Gottlieb, 2011 Bagel, 2012 Bachelez, 2015	3,775	12	20	44	17	6	25
Infliximab[86-89]	EXPRESS I & II Yang, 2012† **Torii, 2010†¥**	1,396	10	23	43	17	8	25
Certolizumab Pegol[¥ 90,91]	**CIMPASI 1 & 2** **CIMPACT**	1,020	16/12	20	46	18	30	18
Ustekinumab [74,92-95]	PHOENIX 1 & 2 Igarashi, 2012† PEARL† LOTUS†	2,566	12	23	44	17	25	21
Secukinumab[96-98]	FEATURE JUNCTURE ERASURE FIXTURE	2,403	12	22	45	18	26	20
Ixekizumab[99,100]	UNCOVER 1, 2 & 3	3,866	12	24	46	19	27	NR
Brodalumab[101,102]	AMAGINE 1, 2 & 3	4,373	12	23	45	19	33	22
Apremilast [103,104]	ESTEEM 1 & 2 LIBERATE	1,505	16	19	46	19	31	NR
Guselkumab[¥ 105,106]	**VOYAGE 1 & 2**	1,829	16	22	44	18	21	19
Tildrakizumab[¥ 107]	**RESURFACE 1 & 2**	1, 862	12	20	46	NR	17	NR
Risankizumab[¥ 108 109]	**UltIMMA-1* & 2*, IMMhance***	1,504	16	20	48	NR	42	NR
Head-to Head Studies								
Etanercept/ Infliximab[¥110]	**PIECE**	48	12	17	44	20	15	11
Etanercept/Ustekinumab[111]	ACCEPT	903	12	20	45	19	11	28
Ustekinumab/ Secukinumab[112]	CLEAR	679	12	22	45	18	14	19
Ustekinumab/ Ixekizumab[113]	IXORA-S	302	12	20	44	18	14	NR

*Only available in the grey literature.; †Asian population only; ¥New drugs/studies (not in 2016 review)

Clinical Benefits

As in the 2016 review, the primary endpoint for most trials was the proportion of patients achieving PASI 75 at the end of the induction period. However, five new trials relating to guselkumab (VOYAGE 1 &2) and risankizumab (ULTIMMA 1 & 2, IMMHANCE); and one head-to-head trial between ixekizumab and ustekinumab (IXORA-S) from our original review specified PASI 90 as their primary endpoint. The duration of the induction period varied by agent: week 10 for infliximab; week 12 for etanercept, ustekinumab, secukinumab, ixekizumab, brodalumab, and tildrakizumab; week 16 for apremilast, guselkumab, and risankizumab; week 12 or 16 for adalimumab and certolizumab pegol. Other clinical outcomes included the proportion of patients meeting additional PASI thresholds (e.g., 50, 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 not 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 not 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 used in the NMA are based on the FDA-approved or proposed dosing at the end of the induction period for each drug with the two exceptions. First, for secukinumab, while the drug label indicates that 150mg may be appropriate for some patients, we included just the 300mg dose in our NMA. Second, although FDA-approved dosing for ustekinumab is weight-based, neither the placebo-controlled trials nor the ACCEPT study randomized participants based on weight; other direct comparison trials (i.e., IXORA-S, AMAGINE 2 and 3, and CLEAR) assigned patients their appropriate weight-based dose. So, we present the data separately for the ustekinumab doses in the description of the placebo-controlled trials in Appendix E and F and pooled all arms into one for the network meta-analysis.

Psoriasis Area Severity Index (PASI)

PASI

- ***All targeted immunomodulators showed statistically-significantly higher PASI 75, PASI 90 and PASI 100 response rates in comparison to placebo at the end of induction (10 to 16 weeks, depending on agent).***
- ***In direct comparative trials of the new agents, guselkumab was superior to adalimumab; tildrakizumab was superior to etanercept; and risankizumab was superior to ustekinumab. Certolizumab pegol 200mg was not significantly different from etanercept.***

- ***Direct comparative trials of the older agents showed that ustekinumab, secukinumab, ixekizumab and infliximab were superior to etanercept; secukinumab, ixekizumab, and brodalumab were superior to ustekinumab.***

The percentages of patients achieving PASI 75, PASI 90 and PASI 100 response rates at the end of the induction period was statistically-significantly greater for all immunomodulators compared to placebo. The range of PASI responses in the intervention and placebo groups across trials for the new drugs (guselkumab, tildrakizumab, risankizumab and certolizumab pegol) are shown in Table 3.2. None of the new agents reported PASI 50. In individual placebo-controlled RCTs, the incremental proportion of patients achieving PASI 75 above placebo within trials was 61% to 69% for certolizumab pegol (three trials); [114,115] 78% to 85% for guselkumab (two trials);[105,106] 56% to 60% for tildrakizumab (two trials);[107] and 80% for risankizumab.[109] The incremental proportion of patients achieving PASI 75 for the other drugs compared to placebo did not change from what was previously reported in the 2016 report (see Appendix E, Table E2 for PASI responses on all drugs).

Table 3.2. Placebo-Controlled Trials on New Drugs: Ranges of PASI Response Rates across Trials*

Treatment	PASI 50		PASI 75		PASI 90		PASI 100	
	Tx	Placebo	Tx	Placebo	Tx	Placebo	Tx	Placebo
Certolizumab*	NR	NR	67-81	4-12	36-53	0-5	NR	NR
Guselkumab	NR	NR	86-91	6-8	70-73	2-3	34-37	1
Tildrakizumab	NR	NR	62-66	6	35-37	1-3	12-14	0-1
Risankizumab	NR	NR	89	8	73-75	2-5	47	1

*200mg certolizumab pegol. See text for result of 400mg certolizumab pegol

We identified six head-to-head RCTs on the new drugs, and three of the trials showed statistically-significant differences between treatments in PASI 75 responses after the induction period (Table 3.3) Guselkumab was superior to adalimumab in two trials (70% & 73% vs. 47% & 50%, p<0.001); [105,106] and tildrakizumab was superior to etanercept in one trial (61% vs. 48%; p<0.001). [107]

In the CIMPACT trial, although a higher proportion of patients on 200mg certolizumab achieved PASI 75 compared to etanercept at 12 weeks (61% vs. 53%), there was no statistical significant difference between the two agents.[91] However, the 400mg dose of certolizumab pegol was significantly better than etanercept in achieving PASI 75 (67% vs. 53%; p=0.02).[91] We found no publicly available PASI 75 data for ULTIMMA 1 & 2 (risankizumab vs. ustekinumab), however, PASI 90 results from these trials were presented in a conference abstract, and risankizumab was shown to be superior to ustekinumab in the two trials (ULTIMMA 1: 75% vs. 42%; ULTIMMA 2: 75% vs. 48%; all p<0.001).[109]

Longer term results available on three trials on the new agents showed that guselkumab remained superior to adalimumab at week 48 (PASI 90: 76% vs. 48%; p<0.001) in one trial,[105] and risankizumab remained superior to ustekinumab at week 52 in two trials (PASI 90: 82% & 81% vs. 44% & 51%, respectively; p<0.001).[109]

As noted above, four of the head-to-head trials on the new drugs relating to guselkumab (two trials: guselkumab vs. adalimumab) and risankizumab (two trials: risankizumab vs. ustekinumab) specified the PASI 90 response as their primary endpoint. All four showed statistically-significant differences between treatments in PASI 90 responses in favor of the new agents (see Table 3.3). In addition, tildrakizumab was also shown to be superior to etanercept. However, inferential statistical comparisons of certolizumab pegol and etanercept was not conducted on PASI 90 response in the CIMPACT trial.

In addition to the above trials, we identified one new investigator initiated head-to-head trial between infliximab and etanercept. Infliximab was found to be significantly different to etanercept in achieving PASI 75 response (76% vs. 22%, p<0.0001),[110] but there was no statistical significant difference between both agents in achieving PASI 90 (see Table 3.3). Findings on the eight other head-to-head trials on the other agents included in the 2016 review showed that ustekinumab, secukinumab, and ixekizumab were superior to etanercept; and secukinumab, ixekizumab, and brodalumab were superior to ustekinumab (see Appendix E, Table E3).

Table 3.3. Comparative Trials: PASI Responses

Trial	Treatment	PASI 75	p-value	PASI 90	p-value	PASI 100	p-value
New Drugs							
VOYAGE 1	Adalimumab	73	<0.001	50	<0.001	21	<0.001
	Guselkumab	91		73		37	
VOYAGE 2	Adalimumab	69	<0.001	47	<0.001	17	<0.001
	Guselkumab	86		70		34	
CIMPACT	Etanercept	61	NS	27.1	NR	NR	NR
	Certolizumab Pegol†	53		31.2		NR	
RESURFACE 2	Etanercept	48	<0.001	21	<0.001	5	<0.001
	Tildrakizumab	61		39		12	
ULTIMMA 1*	Ustekinumab	Redact 14	N/A	42	<0.001	12	<0.001
	Risankizumab	Redact 11		75		36	
ULTIMMA 2*	Ustekinumab	Redact 13	N/A	48	<0.001	24	<0.001
	Risankizumab	Redact 15		75		51	
New Evidence on Old Drugs							
PIECE	Etanercept	22	0.0	0	0.05	0	NS
	Infliximab	76		20		4	

*Only available in the grey literature as of April 2016; †200mg certolizumab pegol; See Appendix E for other comparative trials; NR- not reported

Network Meta-Analysis of PASI Results

Given the paucity of head-to-head data comparing treatments, we performed indirect comparisons of PASI response using Bayesian network meta-analyses (NMAs). An NMA was felt to be appropriate, as the populations of the individual trials were sufficiently similar. We included all identified Phase III trials, including the studies conducted in exclusively Asian populations in the NMA. Further details on our methods, including data input tables, network diagrams, and league tables of results, can be found in Appendix F. Briefly, we used a random-effects approach. For the primary analysis, we also adjusted for the placebo response rate in each study to account for baseline patient differences between studies (for example, given the baseline severity and the proportion of study subjects who previously used a biologic treatment) as well as possible unknown confounders.

Our base case network meta-analysis confirmed our descriptive findings, namely that all immunomodulators were significantly more likely to achieve PASI 50, PASI 75, PASI 90 and PASI 100 responses compared to placebo (see Table 3.4). All biologics were approximately 10-18 times more likely to achieve PASI 75 or better response when compared to placebo, while apremilast was about six times more likely to achieve PASI 75 or better.

Results of the head-to-head comparisons were consistent with the direct evidence from the head-to-head trials, showing that guselkumab was statistically significantly better than adalimumab; infliximab, ustekinumab, secukinumab, ixekizumab, and tildrakizumab were statistically significantly better than etanercept; and secukinumab, ixekizumab, brodalumab, and risankizumab were statistically significantly better than ustekinumab (see Tables 3.5).

Although ixekizumab had the highest relative of relative effectiveness at every level (measured as relative risk (RR) of achieving PASI 50, 75 or 90 response during induction), all three IL-17 agents (ixekizumab, brodalumab and secukinumab), two of the anti-IL-23 agents (guselkumab and risankizumab), and infliximab were clearly all top performers. These agents did not differ statistically, as the likelihood of achieving PASI 75 or PASI 90 response included 1.0 (no difference) in the 95% credible intervals (see Tables 3.5). These agents were followed by ustekinumab 45/90 mg, adalimumab, tildrakizumab, certolizumab and apremilast, respectively.

However, it's important to note that all data on risankizumab included in the NMA were obtained from grey literature or data submitted as "academic in confidence" by the manufacturer.

We also conducted two subgroup analyses: 1) we assessed multi-national studies separately, by excluding all seven Asian studies; and 2) we assessed the biologic experienced studies separately, by excluding studies 11 studies that had only biologic naïve patients or had previous biologic exposure in less than 5% of their patient population. The results of the two subgroup analyses were generally

similar to our base case NMA (see Appendix F), and the relative ranking of the agents were preserved, demonstrating that these characteristics did not meaningfully impact our analyses.

Table 3.4. Relative Risks and Credible Intervals of Treatments Compared to Placebo

Treatments	PASI 50			PASI 75			PASI 90		
	RR	95% CrI		RR	95% CrI		RR	95% CrI	
Ixekizumab	6.24	4.86	8.18	18.34	13.29	25.99	49.58	34.00	73.52
Risankizumab*¥	6.19	4.84	8.06	17.89	13.04	25.17	47.23	32.44	70.33
Brodalumab	6.15	4.82	7.99	17.60	12.77	24.58	45.80	31.33	67.37
Infliximab	6.10	4.79	7.93	17.21	12.58	24.20	44.04	30.48	65.64
Guselkumab¥	6.07	4.78	7.85	16.99	12.53	23.61	43.12	30.06	63.68
Secukinumab	6.06	4.77	7.89	16.99	12.47	23.63	43.12	30.13	63.69
Ustekinumab(45/90)	5.61	4.47	7.12	14.13	10.66	18.96	31.99	23.18	44.63
Adalimumab	5.32	4.28	6.67	12.66	9.66	16.84	27.07	19.62	37.43
Tildrakizumab¥	5.29	4.24	6.69	12.54	9.29	17.10	26.64	18.22	38.50
Certolizumab¥	5.26	4.23	6.64	12.42	9.33	16.99	26.28	18.38	38.96
Etanercept	4.77	3.91	5.89	10.32	8.02	13.30	20.03	14.90	26.79
Apremilast	3.44	2.82	4.26	5.94	4.47	7.95	9.40	6.57	13.53

*Input for NMA was exclusively from unpublished grey literature and supplementary data submitted by the manufacturer; ¥New drugs; CrI: credible interval

Table 3.5. Base Case NMA: League Table of PASI 75 Response

Ixekizumab											
1.02 (0.97, 1.1)	Risankizumab*										
1.05 (0.99, 1.12)	1.02 (0.95, 1.1)	Brodalumab									
1.06 (0.99, 1.17)	1.04 (0.95, 1.14)	1.02 (0.93, 1.12)	Infliximab								
1.08 (1, 1.17)	1.05 (0.97, 1.15)	1.03 (0.95, 1.12)	1.01 (0.91, 1.12)	Guselkumab							
1.08 (1.02, 1.17)	1.05 (0.98, 1.14)	1.03 (0.96, 1.12)	1.01 (0.92, 1.11)	1 (0.91, 1.1)	Secukinumab						
1.3 (1.2, 1.42)	**1.26 (1.17, 1.39)**	**1.24 (1.16, 1.35)**	**1.22 (1.1, 1.35)**	**1.2 (1.1, 1.33)**	**1.2 (1.12, 1.31)**	Ustekinumab†					
1.44 (1.29, 1.68)	**1.41 (1.25, 1.64)**	**1.38 (1.23, 1.59)**	**1.36 (1.19,1.57)**	**1.34 (1.21, 1.52)**	**1.34 (1.19, 1.54)**	1.11 (1, 1.26)	Adalimumab				
1.46 (1.25, 1.81)	**1.43 (1.22, 1.76)**	**1.4 (1.2, 1.72)**	**1.37 (1.17, 1.68)**	**1.35 (1.15, 1.68)**	**1.35 (1.16, 1.66)**	1.13 (0.98, 1.35)	1.01 (0.85, 1.24)	Tildrakizumab			
1.47 (1.26, 1.8)	**1.43 (1.23, 1.76)**	**1.4 (1.2, 1.71)**	**1.38 (1.18, 1.7)**	**1.36 (1.16, 1.68)**	**1.36 (1.17, 1.66)**	1.14 (0.98, 1.36)	1.02 (0.85, 1.24)	1.01 (0.8, 1.23)	Certolizumab		
1.78 (1.57, 2.06)	**1.74 (1.52, 2.02)**	**1.7 (1.5, 1.97)**	**1.67 (1.47, 1.95)**	**1.65 (1.45, 1.92)**	**1.65 (1.46, 1.89)**	**1.37 (1.24, 1.54)**	**1.23 (1.08, 1.42)**	**1.22 (1.03, 1.41)**	**1.21 (1.01, 1.42)**	Etanercept	
3.08 (2.35, 4.27)	**3.01 (2.27, 4.12)**	**2.95 (2.23, 4.06)**	**2.89 (2.18, 4)**	**2.85 (2.17, 3.9)**	**2.85 (2.18, 3.86)**	**2.37 (1.84, 3.17)**	**2.12 (1.63, 2.86)**	**2.11 (1.53, 2.93)**	**2.09 (1.54, 2.86)**	**1.72 (1.33, 2.31)**	Apremilast
18.34 (13.29, 25.99)	**17.89 (13.04, 25.17)**	**17.6 (12.77, 24.58)**	**17.21 (12.58, 24.2)**	**16.99 (12.53, 23.61)**	**16.99 (12.47, 23.63)**	**14.13 (10.66, 18.96)**	**12.66 (9.66, 16.84)**	**12.54 (9.29, 17.1)**	**12.42 (9.33, 16.99)**	**10.32 (8.02, 13.3)**	**5.94 (4.47, 7.95)**	PBO

*Input for NMA was exclusively from unpublished grey literature and supplementary data submitted by the manufacturer; †dosing by weight; PBO: placebo; Bolded results are statistically significant

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

Physician Global Assessment (PGA) or Investigators Global Assessment (IGA) were generally consistent with the PASI results. All immunomodulators showed statistically significantly higher PGA or IGA of 'clear/almost clear' than placebo at the primary endpoint of each trial. In head-to-head trials of the new drugs, guselkumab was superior to adalimumab; and risankizumab was superior to etanercept. Tildrakizumab was not significantly different from etanercept.

Head-to-head trials of the older agents showed that ustekinumab, secukinumab, and ixekizumab were superior to etanercept; secukinumab, ixekizumab, and brodalumab were superior to ustekinumab.

All immunomodulators showed statistically significantly higher efficacy on PGA/IGA compared to placebo. Across the trials on the new drugs, the ranges of PGA/IGA response rates were 1% to 9% for placebo, 84% to 85% for guselkumab,[105,106] 48% to 58% for tildrakizumab,[107] 75% to 84% for risankizumab,[108,109] and 48% to 67% for 200mg certolizumab pegol.[90,91]

All six head-to-head RCTs on the new drugs reported IGA or PGA response, of which four found statistically significant differences between treatments following the induction period. The pattern of response rates and differences between treatments were similar to those of PASI response. Guselkumab had a higher proportion of patients achieve IGA scores of 0/1 than adalimumab in two trials (85% vs. 66% in VOYAGE 1 and 84% vs. 64% in VOYAGE 2; p<0.001), [105,106] and risankizumab had a higher proportion of patients achieving static PGA (sPGA) in two trials (63% vs. 88% in ULTIMMA 1 and 62% vs. 84% in ULLTIMMA 2).[109] There was no statistical significant difference between tildrakizumab and etanercept on the proportion of patients achieving PGA scores of 0/1 at 12 weeks (55% vs. 48%; p=0.07).[107] The sixth head-to-head trial (CIMPACT) did not report inferential statistical comparisons of 200mg certolizumab pegol and etanercept on the proportion of patients achieving PGA scores of 0/1 at 12 weeks, however, the result was numerically the same (39% vs. 39%).[91]

Longer term results showed that guselkumab remained superior to adalimumab at week 48 (IGA 0/1: 81% vs. 55%; p<0.001) in one trial,[105] and risankizumab remained superior to ustekinumab at week 52 in two trials (sPGA 0/1: 86% & 83% vs. 54% & 56%, respectively; p<0.001).[109]

Findings from the new head-to head trial between infliximab and etanercept (PIECE) showed that infliximab had a higher proportion of patients achieving IGA score of 0/1 t compared to etanercept (68% vs. 9%; p<0.001).[110]

As previously reported, evidence on all the other drugs were similar to the PASI responses, and showed that ustekinumab, secukinumab, and ixekizumab were superior to etanercept; and secukinumab, ixekizumab, and brodalumab were superior to ustekinumab.[53]

Dermatology Life Quality Index (DLQI)

DLQI results were generally consistent with PASI results. All targeted immunomodulators statistically significantly improved quality of life relative to placebo. In head-to-head trials of new agents, guselkumab was superior to adalimumab; and risankizumab was superior to ustekinumab.

Head-to-head trials of the older agents showed that secukinumab and ixekizumab were superior to both etanercept and ustekinumab.

Quality of life was measured in the majority of studies we identified in our search, primarily using the DLQI instrument. As noted in previous report, all targeted immunomodulators statistically significantly improved quality of life relative to placebo.[53] Some studies evaluated the mean DLQI change (MCID: defined as at least a 5-point reduction), others evaluated the proportion of patients achieving a DLQI score of 0 or 1 (indicating very little to no effect on quality of life), and some evaluated both measures.

The mean DLQI change was reported on two of the new drugs (certolizumab and guselkumab). The mean absolute difference between these interventions and the placebo group were as follows: certolizumab (-5.6 to -8.2; p<0.01),[90] guselkumab (-8.7 to -10.6; p<0.01).[105,106]

Mean DLQI change was not measured in any of the tildrakizumab and risankizumab trials. Instead, these trials reported the proportion of patients achieving a DLQI score of 0/1, and all trials resulted in a statistically significant greater proportion in favor of the intervention compared to placebo. The absolute differences between these agents and placebo were as follows: tildrakizumab (32% to 37%; p<0.001);[107] risankizumab (58% to 63%; p<0.001). In addition, the proportion of patients with a score of 0/1 was reported in the guselkumab trials. There was also a significant difference in favor of guselkumab compared to placebo (absolute difference: 49% to 52%; p<0.001)

In the head-to-head comparisons, guselkumab achieved a statistically significantly greater improvement on DLQI than adalimumab at 16 weeks in two trials; and significantly greater proportion of patients on risankizumab achieved DLQI 0/1 compared to ustekinumab (Table 3.6). There was no significant difference between tildrakizumab and etanercept at 12 weeks.

As previously reported, head-to-head evidence on the old drugs showed that secukinumab and ixekizumab were superior to both etanercept and ustekinumab. See Appendix E, Table E3 for results of the other head-to-head comparisons.

Table 3.6. DLQI Outcomes Across Direct Comparative Trials

Trial	Drug	Mean change	p-value	DLQI 0/1 (%)	p-value
VOYAGE 1	Adalimumab	-9.3	P<0.001	56	P<0.01
	Guselkumab	-11.2		39	
VOYAGE 2	Adalimumab	-9.7		52	P<0.01
	Guselkumab	-11.3	P<0.001	39	
RESURFACE 2	Etanercept	NR	NR	36	NS
	Tildrakizumab	NR		40	
ULTIMMA 1*	Ustekinumab	NR	NR	43	P<0.001
	Risankizumab	NR		66	
ULTIMMA 2*	Ustekinumab	NR	NR	43	P<0.001
	Risankizumab	NR		66	

*Only available in the grey literature; see Appendix E for other comparative trials

Symptom Control

Measures of symptom control were inconsistently reported across trials and used a variety of instruments. Guselkumab demonstrated a statistically significant benefit over placebo using PSSD measure.

As noted in our previous report, measures of symptom control were inconsistently reported across trials. In addition, a variety of instruments which includes a single symptom or a group of symptoms, were used to assess symptom control. These instruments include: Psoriasis Symptom Inventory (PSI), Psoriasis Symptom Diary (PSD), Psoriasis Symptom and Sign Diary (PSSD), pruritus VAS, Pain VAS, scaling etc.

We identified the two new placebo-controlled trials on guselkumab (VOYAGE 1 &2), assessing the improvement from baseline in psoriasis symptom and sign diary (PSSD) score. Guselkumab resulted in significantly greater improvement on PSSD score, compared to placebo (mean change -41.9 vs -3.0; p<0.01).[105]

In addition, new data on one head-to head trial (IXORA-S), showed that mean changes from baseline in itch NRS and skin pain VAS, were not significantly different between ixekizumab and ustekinumab. However, ixekizumab-treated patients reported faster improvements than ustekinumab-treated patients in itch and skin pain.[113]

Data previously reported on the old agents showed that brodalumab, secukinumab and apremilast all demonstrated an improvement in symptom control using one or more of the instrument listed above when compared to placebo.[53] In addition, head-to-head comparisons showed secukinumab to be better than ustekinumab (on itching, pain and scaling relief), and ixekizumab to be better than over etanercept VAS-skin pain.[53]

Worker Productivity

Positive effects on productivity were seen in the few studies that measured it. We found no data on productivity on any of the new drugs.

Very few studies measured worker productivity. Instruments used to measure productivity in the few trials that measured it include: Work Productivity and Activity Impairment (WPAI), Worker Productivity Index (WPI), Work Limitations Questionnaire (WLQ). See the Definitions section of the report for details about the productivity instruments.

We found no data on productivity for any of the new drugs.

In the previous report, data was found on four agents (adalimumab, infliximab, ustekinumab and apremilast), and all showed significant improvements compared to placebo using different measures of productivity.[53] In addition, findings from head-to-head trials showed that ixekizumab demonstrated a statistically significant improvement over etanercept using WPAI and work productivity loss; and secukinumab was statistically significantly better than ustekinumab in reducing presenteeism, work productivity loss and activity impairment on the WPAI.

Sexual Function

Very few studies reported sexual function as an outcome. We found no data on sexual function on any of the new drugs.

We identified no data on sexual function for any of the new drugs.

In the previous review we identified two abstracts of head to head studies that included data showing superiority of ixekizumab over etanercept and secukinumab over ustekinumab; [116,117] and one published pooled analysis showed superiority of secukinumab over etanercept. [118]

Subgroup Analyses

Limitations in the evidence base preclude determining whether there are meaningful differences in effectiveness within the subgroups of interest. Outcomes were statistically significantly in favor for all the agents available for review relative to placebo across subgroups.

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. Detailed discussions of these analyses are available in the Appendix E.

Harms

Severe or serious adverse events were rare during treatment. Nasopharyngitis, upper respiratory tract infections, and headaches were the most common side effects noted during the trials of guselkumab, tildrakizumab, tildrakizumab and certolizumab pegol. There was no indication of increased rates of serious infections, malignancies, and major cardiovascular events for any of the agents.

Adverse Events During Induction

Common adverse events (AEs) that occurred in ≥5% of patients as well as specific AEs of interest in the guselkumab, tildrakizumab, risankizumab, and certolizumab trials are shown as trial-weighted averages in Table 3.7 (see Appendix E, Table E5 for all agents). We had limited data on the AEs occurring in the unpublished risankizumab trials.

Most adverse events were mild or moderate. Severe or serious adverse events, death, and AEs leading to discontinuation were rare and generally 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, headache; and nausea. There was no evidence of increased risk of serious infections or malignancies. Incident rates of candidiasis and other opportunistic infections were reported to be low and comparable between groups in all trials. There were no reports of tuberculosis, demyelinating disease, or lymphoma in these trials. We also did not find differences in risk of major adverse cardiac events (MACE).

The types and patterns of AEs reported for these agents at longer timepoints (48-52 weeks) were similar to those reported during the placebo-controlled periods. In addition, comparative trials reported generally similar rates and types of AEs. At 48 weeks in VOYAGE 1, proportion of patients with AEs (74% vs. 75%), AEs leading to discontinuation (3% vs. 4%) and serious AEs (5% vs. 5%) were similar in the guselkumab and adalimumab group.[105] Similar pattern was observed between risankizumab and ustekinumab in ULTIMMA 1 & 2 at 52 weeks.[109]

Table 3.7. Adverse Events During the Placebo-Controlled Period

%	Guselkumab	Tildrakizumab	Risankizumab	Certolizumab	Placebo
Any AE	49	46	47	53	50
Tx-related death	NR	0.1	NR	0	0
D/C due to AEs	1.3	0.5	0.5	1.1	1.3
Serious AEs	1.9	1.5	2	1.4	2.5
≥Grade 3 AEs	NR	NR	NR	NR	NR
Common AEs occurring in ≥5% in one or more agent					
Any Infections	24	NR	NR	29	24
Nasopharyngitis	8	10	NR	12	7.6
Upper respiratory tract infection	4.5	1.5	NR	4.9	4.1
Headache	5	NR	NR	NR	3.3
AEs of Interest					
Malignancy excluding NMSC	0	NR	0.5	0	0
NMSC	0.1	0.1	0.2	0	0.1
MACE	0.1	0.2	0	NR	0.1
Serious Infections	0.1	0.5	0.4	0	0.3

Long-term Adverse Events from observational studies

As expected, there is currently no long-term safety observational data on any of the new agents. We previously reported long-term safety data from PSOLAR (Psoriasis Longitudinal Assessment and Registry) in our 2016 report.[53] Data from the identified studies suggest an increased rate of serious infections for infliximab and other biologic agents relative to nonbiologic therapy, although not for ustekinumab.[119,120] There were no material differences on other safety concerns among the biologic agents or in comparison with nonbiologic therapy. In addition, we identified one study that assessed drug survival, which is defined as the time from initiation of a biologic to discontinuation.[121] Result of the analysis showed that infliximab (Harzard ratio[HR]: 2.73;P = 0.0014); adalimumab [HR: 4.16; P < 0.0001]; and etanercept [HR: 4.91; P < 0.0001] have statistically significantly shorter times to discontinuation in first-time biologic users, when compared with ustekinumab.[121]

Table 3.8: Incidence of Adverse Events from the PSOLAR Registry[120]

Adverse Event	Ustekinumab	Infliximab	Other biologics	Nonbiologics
	Per 100 person-years			
All-Cause Mortality	0.36	0.45	0.42	0.70
MACE	0.34	0.38	0.33	0.45
Malignancy	0.51	0.64	0.74	0.81
Serious infections	0.95	2.78	1.80	1.26

MACE = major adverse cardiovascular events

Controversies and Uncertainties

Across the 52 RCTs identified for this review, only fifteen were based on head-to-head comparisons of the drugs of interest. As such, our network meta-analyses of PASI response are largely driven by indirect evidence; however, our findings are consistent with the results of head-to-head studies as well as with our assessment of relative differences in PASI response in comparison to placebo, and our NMA findings are also comparable to other recent assessments of the evidence. Although PASI 75 or PASI 90 was reported as the primary endpoint in nearly all studies, all other clinical outcomes, including PGA/IGA, DLQI were inconsistently reported across trials making 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 were only available for ustekinumab, secukinumab, and the TNF-α therapies, which limited our understanding of real-world effectiveness and durability of benefit for many of these therapies.

Trials required washout of non-study treatments prior to initiating targeted immunomodulators and prohibited non-study treatments during the trials. Prohibition of non-trial treatments permits direct comparative evaluation of targeted immunomodulators with placebo or one another, but it does not represent actual practice in which combination therapy (e.g., topical use during targeted immunomodulator treatment) is common.

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 is some data suggesting that diminishing the psoriasis-related inflammation in the skin also decreases the risk of cardiovascular disease,[5,122,123] while other

studies have suggested an associated between targeted immunomodulators and increased risk of major adverse cardiovascular events.[124] This is a controversial topic, however, and larger and more long term studies are needed to better understand the impact of biologic therapies on cardiovascular outcomes in patients with moderate to severe psoriasis.[125,126]

There are also concerns with the reporting of patient-centered outcomes. DLQI was evaluated in 25 of the 52 total clinical trials comprising our original review and this update, 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 (e.g., patients with psoriatic arthritis or prior biologic experience). Concerning the choice of the appropriate first-line biologic therapy, there are current evidence-based recommendations available for some comorbid conditions in clinical practice. For example, in the presence of severe psoriatic arthritis, TNF-α inhibitors are recommended to be the preferred options, while they are to be avoided for patients with multiple sclerosis.[127] Expert opinion, clinical judgment and patient preferences will often determine the choice of the most appropriate therapeutic option for many comorbidities.[127] Future studies should be pragmatic in nature, including patients with these type of comorbid conditions encountered in routine clinical practice.

3.4 Summary and Comment

Using the ICER evidence rating matrix, our evidence ratings for the comparisons of interest are provided in Table 3.9; ratings are presented for the targeted immunomodulator listed in each row relative to the comparator listed in each column. Note that comparisons 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 these 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 F). 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.

ICER Ratings

There were two head-to-head trials comparing guselkumab and adalimumab (VOYAGE 1 &2), both of which showed incremental benefit for guselkumab over adalimumab 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 small net benefit for guselkumab ("B") and an inferior net health benefit ("D") for adalimumab in this comparison.

Similarly, unpublished evidence from two trials (ULTIMMA 1 & 2) comparing risankizumab to ustekinumab consistently showed greater benefit for risankizumab. Although there are currently no peer reviewed publications of these two Phase III trials, the consistency of the results with the published Phase II trial,[128] and the magnitude of benefit when the indirect evidence was included, gave us a *high certainty* of a small net benefit for risankizumab ("B") when compared to ustekinumab.

In the one head-to-head comparisons between tildrakizumab and etanercept (RESURFACE 2), tildrakizumab resulted in a modestly better PASI outcome (supported by network meta-analysis), and no difference on PGA and DLQI outcome, so we judged the evidence of tildrakizumab versus etanercept to represent a comparable or better net health benefit ("C+"), and "C-" (comparable or inferior) for etanercept in this comparison.

The head-to-head trial comparing 200mg certolizumab pegol and etanercept (CIMPACT) was a single blind study which found no statistically significant difference between the two agents on PASI outcome, but inclusion of indirect evidence yielded a modest but significant improved outcome for certolizumab. As such, we rated the evidence "C+" (comparable or better) for certolizumab and "C" (comparable or inferior) for etanercept in this comparison.

Ratings based on indirect evidence alone are highlighted in blue in the table. For these 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 "C-"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.

We also considered the 'second-order' effect in our evidence ratings. For example, since we have *moderate certainty* of an incremental or better net health benefit of risankizumab over ustekinumab, and moderate certainty that ustekinumab provides an incremental or better benefit over etanercept and apremilast, we conclude that there is moderate certainty that risankizumab would also provide an incremental benefit over etanercept or apremilast.

ICER Rating on the Drugs Included in the 2016 Review

Our ratings on the old drugs in the 2016 review remain mostly unchanged, except in two instances. The first is the rating of secukinumab versus adalimumab which we rated as "I" based on indirect evidence. We have now changed the rating to "C+" based on the result of the updated NMA which shows evidence of net health benefit. The second is a comparison of infliximab versus etanercept. In this instance, the rating between the two drugs did not change, however, it is now highlighted in green in the table because we found data from one head-to-head trial which provides additional direct evidence.

Table 3.9. ICER Evidence Ratings for Available Head-to-Head Comparisons

Treatment	Comparator								New comparators			
	Adalimumab	Apremilast	Brodalumab	Etanercept	Infliximab	Ixekizumab	Secukinumab 300	Ustekinumab 45/90	Certolizumab pegol	Guselkumab	Risankizumab	Tildrakizumab
Adalimumab	-	B+	C-	C+	C-	C-	**C-***	I	**I**	**D (2)**	**C-**	**I**
Apremilast	C-	-	D	I	C-	C-	C-	C-	**C-**	**C-**	**C-**	**C-**
Brodalumab	C+	B	-	B	I	I	I	B (2)	**C+**	**I**	**I**	**C+**
Etanercept	C-	C+	D	-	**C- (1)†**	D (2)	C- (1)	C- (1)	**C- (1)**	**C-**	**C-**	**C-(1)**
Infliximab	C+	B+	I	**B+ (1)†**	-	I	I	C+	**C+**	**I**	**I**	**C+**
Ixekizumab	C+	B+	I	A (2)	I	-	C+	B+ (1)	**C+**	**I**	**I**	**C+**
Secukinumab 300	**C+***	B+	I	B+ (1)	I	C-	-	C+ (1)	**C+**	**I**	**I**	**C+**
Ustekinumab 45/90	I	B+	D (2)	B+ (1)	C-	C- (1)	C- (1)	-	**I**	**C-**	**D (2¥)**	**I**
New agents												
Certolizumab pegol	**C-**	**B+**	**C-**	**C+ (1)**	**C-**	**C-**	**C-**	**I**	-	**C-**	**C-**	**I**
Guselkumab	**B (2)**	**B+**	**I**	**C+**	**I**	**I**	**I**	**C+**	**C+**	-	**I**	**C+**
Risankizumab¥	**C+**	**B**	**I**	**B**	**I**	**I**	**I**	**B (2¥)**	**C+**	**I**	-	**C+**
Tildrakizumab	**I**	**B+**	**C-**	**C+ (1)**	**C-**	**C-**	**C-**	**I**	**I**	**C-**	**C-**	-

Note: The table should be read row-to-column. For example, there is moderate certainty that adalimumab has a small net benefit compared to apremilast (B+). Conversely, there is moderate certainty that the point estimate for comparative net health benefit of apremilast is either comparable or inferior to adalimumab (C-).

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

Number of head-to-head studies in parentheses

*Rating of secukinumab vs. adalimumab changed from the previous review from I to C+ based on the result of the updated NMA;

†Rating of infliximab vs. etanercept did not change from previous report, however the rating is now highlighted in green in the table because we found evidence on 1 head-to-head trial; ¥Based on unpublished grey literature

4. Long-Term Cost Effectiveness

4.1 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. All treatments included in the NMA, except for risankizumab and tildrakizumab, are included in the cost-effectiveness model. We developed a decision-analytic model, based originally on the York psoriasis cost-effectiveness model,[129] 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 analysis uses a healthcare system perspective with ten-year and lifetime time horizons, both using a 3% annual discount rate for costs and outcomes. The outcomes of the model include total costs, quality-adjusted life years (QALYs), months spent in health states of PASI improvement greater than or equal to 75% and 90%, and incremental cost-effectiveness ratios. Uncertainty in the data inputs and assumptions were evaluated using sensitivity and scenario analyses.

Since our prior report on targeted treatments for plaque psoriasis, we have made the following changes to the model:

- Updated discontinuation rates based on new data.
- Modeled treatment sequences in which second-line targeted treatment depends on first-line targeted treatment.
- Updated all costs.
- Updated the rate of switching to a second-line targeted treatment (vs. non-targeted) from 50% to 75% upon discontinuation from the first-line targeted treatment.
- In light of increasingly different discounts and pricing strategies, we have switched from using class-based discounts off WAC to drug-specific discounts.
- Switched to using average selling price (ASP) plus mark-up for infliximab to more closely reflect the way that office-administered products are reimbursed.

4.2 Methods

Model Structure

The general model structure is unchanged since our prior report. Please see Comparative Value Appendix G for a detailed discussion. 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 based on their percent improvement in PASI score over baseline: PASI 90 and higher, PASI 75-89, PASI 50-74, and PASI <50.

Patients with a PASI improvement of at least 75% after the initiation periods continued on first-line therapy after the initiation period. However, we applied a drug-specific discontinuation rate to each initial targeted drug which determines the rate of discontinuation due to all causes (e.g., loss of efficacy, development of adverse effects) after the end of the initiation period. This rate differed between the first and subsequent years of treatment. After discontinuing their first-line treatment, these patients transition to either second line targeted therapy or non-targeted therapy.

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, except for risankizumab and tildrakizumab, for which there was no pricing information at the time of the report.

We modeled sequential targeted treatments and targeted treatment discontinuation. Patients with response below 75% improvement after the initiation period (16 weeks for adalimumab, apremilast, and guselkumab, 10 weeks for infliximab, and 12 weeks for all other drugs) were assumed to discontinue the first-line therapy in the base-case (this assumption was evaluated in a scenario analysis, described below). 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 targeted therapy varied based on first-line targeted treatment: those patients taking an IL-17 drug switched to guselkumab; patients using guselkumab switched to a market basket representing the average of all IL-17 drugs; all other patients switched to a market basket of all IL-17 drugs plus guselkumab.

The administration schedules for included drugs are listed below. Each of these therapies includes an initial period with dosing that differs from the maintenance dose. Regimens are based on labeled dosing recommendations for all currently marketed drugs.

Table 4.1. Medication Dosing Schedules

Drug	Initial dosing	Maintenance dosing
Adalimumab	80 mg once	40 mg every other week, starting one week after initial dose
Apremilast	Day 1: 10 mg in morning; Day 2: 10 mg in morning and 10 mg in evening; Day 3: 10 mg in morning and 20 mg in evening; Day 4: 20 mg in morning and 20 mg in evening; Day 5: 20 mg in morning and 30 mg in evening	30 mg twice daily
Brodalumab	210 mg at weeks 0, 1, and 2	210 mg every two weeks
Certolizumab pegol	400 mg at weeks 0, 2, and 4	400 mg once a month
Etanercept	50 mg twice weekly for three months	50 mg once weekly
Guselkumab	100 mg at weeks 0 and 4	100 mg every eight weeks
Infliximab	5 mg/kg at weeks 0, 2, and 6	5 mg/kg every eight weeks
Ixekizumab	160 mg at week 0, then 80 mg at weeks 2, 4, 6, 8, 10, and 12	80 mg every four weeks
Secukinumab	300 mg at weeks 0, 1, 2, 3, and 4	300 mg every 4 weeks
Ustekinumab	45 mg at weeks 0 and 4 (90 mg for weight ≥ 100 kg)	45 mg every 12 weeks (90 mg for weight ≥ 100 kg)

Key Model Characteristics and Assumptions

Table 4.2. Key Model Assumptions

Assumption	Rationale
A patient cannot transition between effectiveness (PASI improvement) levels.	There is only modest improvement in effectiveness beyond the trial period, and discontinuation rate accounts for decline in effectiveness over time.
Probability of discontinuing first-line therapy is drug-specific as supported by available data	Empirical evidence indicates discontinuation rates beyond the initiation period are higher for infliximab and etanercept, and differs in year 1 vs. years 2+. (See section *Drug discontinuation and switching* section below for details.)
All discontinuation in the first year is due to lack of effectiveness at the end of the initiation period, except for infliximab	Our assumption in the base-case is that patients who receive benefit of less than PASI 75 from initial targeted treatment will discontinue that treatment at the end of the initiation period. The one exception to this is infliximab, which has a greater discontinuation in year one than indicated by drug response alone. This assumption was evaluated in a scenario analysis.

Probability of discontinuing newer drugs (brodalumab, certolizumab pegol, guselkumab, ixekizumab, tildrakizumab) is the same as ustekinumab in years 2+	There are limited to no data on discontinuation rates for the newer agents. This assumption was evaluated in a sensitivity analyses.
Seventy-five percent of patients discontinuing first line targeted drug therapy receive second line targeted drug and remainder receive non-targeted drug.	Recently published data[32] and expert clinical opinion suggest that, among those patients who discontinue their first-line targeted drug, approximately 75% begin a different targeted drug.
Second-line targeted treatment was assumed vary by first-line treatment as follows: patients receiving an IL-17 drug first-line receive guselkumab second-line; patients receiving guselkumab first-line receive a market basket equivalent to the average of all IL-17 drugs second-line; patients receiving any other first-line drug receive a market basket equivalent to the average of all IL-17 drugs plus guselkumab.	Clinical experts indicated that second-line treatment is likely to vary according to the choice of first-line agent and suggested this allocation of treatments. Different second-line targeted drug baskets were assessed in scenario analyses.
Second-line targeted treatments have a 10% lower probability of achieving PASI 75-100 (i.e., 5% lower probability of PASI 75-89, 5% lower probability of PASI 90-100, 5% higher probability of PASI 50-74, and 5% higher probability of PASI < 50).	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.	There is no clear evidence supporting an improvement in survival with targeted treatments for psoriasis.
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 dose and by the patient themselves during the maintenance period.	Allows for patient instruction while acknowledging that patients will self-administer the vast majority of their doses.
Drug cost discount was applied on a drug-by-drug (rather than class) basis. Guselkumab received the average discount of all drugs included in this report (33%).	There is significant heterogeneity in the amount that each drug is discounted within classes. Therefore, we have chosen to calculate each drug's net price using drug-specific discounts. Guselkumab had insufficient data to collect actual discount percentages and was therefore assumed to have the average discount of all other drugs in this analysis.
No additional months in PASI states > 0% improvement, on average, are attributable to non-targeted treatment	The population for this model has already not seen adequate improvement with non-targeted treatment alone and thus is eligible for targeted treatment. While some individuals who continue on non-targeted treatment may temporarily improve in PASI status, some will get worse. We therefore did not attribute

	any change in average PASI status to continued use of non-targeted drugs.

Model Inputs

Clinical Inputs

Clinical Probabilities/Response to Treatment

First-line targeted drug response

First-line targeted drug effectiveness is taken from the results of the network meta-analysis described above.

Table 4.3. Probability of PASI Response as First-Line Targeted Treatment

Drug	PASI < 50	PASI 50-74	PASI 75-89	PASI 90-100
Adalimumab	0.18	0.21	0.20	0.41
Apremilast	0.47	0.25	0.14	0.14
Brodalumab	0.05	0.10	0.15	0.70
Certolizumab pegol	Redacted, confidential	Redacted, confidential	Redacted, confidential	Redacted, confidential
Etanercept	0.26	0.24	0.19	0.31
Guselkumab	0.06	0.11	0.16	0.67
Infliximab	0.05	0.12	0.15	0.68
Ixekizumab	0.03	0.09	0.12	0.76
Secukinumab	0.06	0.11	0.16	0.67
Ustekinumab	0.13	0.19	0.19	0.49

Second-line targeted treatment effectiveness

No randomized controlled clinical trials have been conducted in an exclusively second-line patient population. Warren et al[130] did recently study secukinumab 150 and 300mg in a second-line (first-line non-responder) population (no placebo group). The 16-week PASI 75 response for 300mg (N=118) was 71% for patients with one previous non-response, and 48% in patients who had failed more than one TNFα drug; in contrast the first-line PASI 75 response was 83% in the NMA. Griffiths et al[131] evaluated outcomes with guselkumab among adalimumab PASI 90 non-responders, and found ~60% of patients achieved PASI 90 after 16 weeks of treatment; in contrast, 83% of all patients initiated on guselkumab achieved PASI 90 in the NMA. Papp et al[132] studied the effect of previous targeted drug use on brodalumab and ustekinumab outcomes; 27% and 26% of patients had previously received a targeted agent, respectively, and 12% and 10% had previously failed

targeted agent. For brodalumab, PASI 100 was achieved in 41.7% and 32.0% of patients in whom prior targeted therapy had been successful or failed; the corresponding results for ustekinumab were 21.1% and 11.3%.

These findings indicate that prior experience, and in particular prior failure, with targeted drugs is associated with a lower response rate. We assumed the PASI 75 response for second-line therapy was 10% lower than for findings in the NMA, which included studies primarily enrolling patients who were targeted drug naïve and were adjusted for placebo group differences.

Drug discontinuation and switching

Data for targeted drug discontinuation (switching to another targeted agent or discontinuation of targeted therapy) is heterogeneous, dependent on data source and healthcare setting, and limited to non-existent for newer drugs.[133] Please refer to Appendix G for details.

Based on the comparative evidence within each data source, several conclusions can be drawn about drug discontinuation and switching:

- Discontinuation rates are higher in year 1 than subsequent years, are primarily driven by lack of effectiveness (except for infliximab), and vary across drugs;
- Discontinuation rates in years 2+ are somewhat similar across drugs, but higher for infliximab and etanercept;
- Discontinuation rates are higher in patients previously exposed to targeted agents;
- The majority of patients who discontinue drug switch to another targeted agent.

Based on these general findings, we made the following assumptions:

- Year one discontinuation rates were determined by drug effectiveness - in the base-case, patients who do not achieve PASI 75 by the end of treatment induction discontinue first-line targeted therapy;
- The year two-plus annual discontinuation rate was 5%, except 10% for etanercept and infliximab;
- The annual discontinuation rate for second-line treatment was 10%;
- 75% of patients who discontinue first-line therapy switch to another targeted agent.

Mortality

There is no clear evidence that the modification of psoriasis-related health state alters mortality risk. As such, mortality depends upon age alone.

Utilities

Our base case uses considers the utility of each level of PASI improvement to be represented by the estimated mean utility weight as derived by co-administration of the generic quality of life instrument, the EQ-5D, with the PASI in five clinical trials.[134]

- Non-targeted treatment: 0.660
- PASI <50: 0.718
- PASI 50-74: 0.827
- PASI 75-89: 0.856
- PASI 90-100: 0.903

See the Comparative Value Appendix Table G3-G4 for a complete list of the utility values contributing to these estimates.

Adverse Events

As serious adverse event frequencies are similar across all drugs, most previously published cost-effectiveness analyses in plaque psoriasis have not included adverse events, and our previous analysis indicated inclusion of serious infection had little effect on results, they are not included in the base case scenario. We have included an analysis of the hypothetical impact of suicidality associated with brodalumab in a scenario analyses.

Economic Inputs

Drug Acquisition Costs

The below table refers to drug acquisition cost alone, not including administration costs or the cost of required laboratory tests. Two drugs – infliximab and ustekinumab – are dosed by weight. Infliximab is dosed at 5 mg/kg. We assumed that vials are not shared and that an average of five vials will be used per patient. The dose of ustekinumab is doubled from its baseline of 45 mg for patients weighing over 100 kg. Based on the clinical trials, we assumed that 30% of patients would receive the 90 mg dose.

In order to reflect differential discount and pricing strategies, we used net price in the cost-effectiveness model. With the exception of infliximab, the net price refers to wholesale acquisition cost (WAC) minus a discount percent, which we derived by averaging the difference between the actual cost of the drug and the WAC over the past year.[135] In contrast to the 2016 report, when we used discounts based on drug class, we used drug-specific discounts in this model. This is due to heterogeneity that has arisen within classes. For example, brodalumab combines a smaller discount with a lower WAC to arrive at an overall annual maintenance cost that is only slightly lower

than other members of the IL-17 class. Guselkumab had insufficient data on discounts and therefore was assumed to have the average discount of all other drugs in this analysis (33%).

Infliximab is a unique drug within this set, as it is the only drug administered intravenously. Because the drug is not being dispensed directly to the patient, we used average selling price (ASP) plus a 9.5% markup representing the mean markup by physicians' offices and hospital outpatient units.[136]

Non-targeted cost includes the cost of topical medications such as corticosteroids, non-targeted oral medications such as methotrexate, and hospitalization. The cost was determined from a claims analysis published in 2009 with its results recalculated to 2017 US dollars using the medical inflation rate.[137]

Table 4.4. Drug Cost Inputs

Intervention	Unit	WAC per Unit/Dose*	Discount %	Net price per Unit	Cost of first year	Annual cost of year 2+
Adalimumab	40 mg	$2,436.02	31%	$1,674.64	$43,702.20	$40,340.49
Apremilast	30 mg	$51.67	22%	$40.09	$26,881.83	$27,083.35
Brodalumab	210 mg	$1,750.00	20%	$1,400.00	$35,000.00	$33,600.00
Certolizumab pegol	400 mg	$4,044.32	36%	$2,583.70	$36,237.11	$31,060.38
Etanercept	50 mg	$1,218.00	31%	$837.69	$50,425.20	$40,340.16
Guselkumab	100 mg	$10,158.52	33%	$6,806.21	$47,641.02	$40,835.16
Infliximab	40 mg	$1,167.82	22%**	$911.99	$36,479.60	$27,359.70
Ixekizumab	80 mg	$5,161.60	44%	$2,888.74	$49,825.13	$35,060.11
Secukinumab	300 mg	$4,712.38	38%	$2,926.22	$43,825.13	$35,060.11
Ustekinumab	45 / 90 mg (see above)	$10,292.15 / $20,584.30	27%	$7,532.84 / $15,063.47	$66,417.30	$45,882.80

*WAC as of 3/28/2018; **Due to its distribution to physicians' offices and outpatient hospital units, infliximab is priced using average selling price (ASP) plus a 9.5% markup; WAC is included here for context only

Administration and Monitoring Costs

All drugs except for apremilast and infliximab are administered subcutaneously. Apremilast is an oral medication, and infliximab is intravenously administered over a two-hour period.

As stated above, our assumption is that only the first administration of a subcutaneously-administered drug is performed in a clinic. The 2017 national payment for a subcutaneously administration (CPT code 96372) is $25.84. Intravenous administration over two hours is

represented by two CPT codes – 96413 for the first hour and 96415 for the second hour – and costs a total of $183.89.

Health Care Utilization Costs

Psoriasis patients receiving certain targeted drugs require monitoring for potential infection. Some drugs 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 below. 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. In addition to these laboratory tests, each patient was assumed to receive four physician visits (CPT code 99213, $80.77) per year related to the disease.

Costs for the laboratory tests are:

- Latent TB screen (CPT 71010): $25.08
- Active TB screen (CPT 86580): $9.02
- Complete blood count (CPT 85025): $14.41
- Hepatitis B test (CPT 86317): $27.79
- Liver function test (CPT 80076): $15.15
- Renal function test (CPT 80069): $16.10

Table 4.5. Laboratory Test Schedule

Intervention	Latent TB	Active TB	CBC	HBV	LFT	Renal function
Adalimumab	Annually		Quarterly	Once		
Apremilast						Annually
Brodalumab	Once					
Certolizumab pegol	Annually		Quarterly	Once		
Etanercept	Annually		Quarterly	Once		
Guselkumab	Annually					
Infliximab	Annually	Annually	Quarterly	Once	Quarterly	
Ixekizumab		Annually				
Secukinumab		Annually				
Ustekinumab	Annually		Quarterly			

Test abbreviations: TB = tuberculosis, CBC = complete blood count, HBV = hepatitis B virus, LFT = liver function test

Sensitivity Analyses

We ran one-way sensitivity analyses to identify the key drivers of model outcomes, using reasonable ranges for each input described in the model inputs section above. We chose to compare ixekizumab to non-targeted treatment in order to focus on the comparison between the most effective therapy and the least effective. We also included a comparison of ixekizumab versus etanercept, as it compares a more effective to a less effective but commonly used targeted drug.

Scenario Analyses

We conducted a variety of scenario analysis to assess the assumptions in our base-case analysis.

- *Continuation of treatment in PASI 50-74 group:* In this scenario, we allowed 2% of individuals in the PASI 50-74 group to improve to PASI 75-89 per month in the first year after the initiation period. In this group, 10% of patients discontinued their first-line treatment per month as well. All patient in this PASI category discontinue targeted treatment by the end of year one

- *Effect of net price increases:* We used net prices from the 2016 report in this model in order to isolate the effect of price increases since that time.

- *Completed suicides with brodalumab:* Four participants among the 4,464 (0.09%) in the brodalumab arm of that drug's trials completed suicide, compared to zero completed suicides in the control arm. In acknowledgment of the severity of this event, we conducted a scenario analysis that, pessimistically, assumes completed suicide takes place immediately after the first month of brodalumab.

- *Dose escalation:* According to Egeberg 2018,[138] approximately 25% of patients taking etanercept increase their dosage by 50% or more. We assumed that patients who escalate their dosage will come from the group of patients with PASI 50-74 (approximately 25% of patients) and that they will increase their dosage by 50% immediately after the 12-week induction period. At that point, they will improve to PASI 75-89. This strategy of dose escalation was compared to first-line targeted treatment with a high-performing IL-17 drug such as ixekizumab, and to etanercept without dose escalation. As in our scenario where PASI 50-74 patients continued treatment, 2% of etanercept patients in this scenario improve to PASI 75-89 per month while 10% will switch to a second-line targeted treatment or non-targeted.

- *Second-line market baskets:* We assessed the effect of including all non-first-line drugs in the second-line basket; that is, we averaged the costs and effectiveness of all eleven drugs

(with the second-line penalty mentioned in the assumptions) and use this as the second-line market basket for all drugs.

- *Inclusion of productivity costs and benefits:* It is well known that psoriasis affects productivity. We evaluated a scenario using a limited societal perspective in which productivity benefits of psoriasis treatment and the productivity loss associated with intravenous administration of a drug are accounted for. Productivity cost offsets were derived from work productivity impact measures in RCTs of adalimumab and ixekizumab.[139,140] 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.[141] 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.

- Additionally, we performed a threshold analysis by systematically altering the price of all drugs to estimate the maximum prices that would correspond to given willingness to pay (WTP) thresholds. Risankizumab, an IL-23 drug expected to be approved by the FDA in 2018, and tildrakizumab, another IL-23 drug that was recently approved but does not have an official price, have been included in this threshold analysis.

Model Validation

We used several approaches to validate the model. First, we provided preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model. Second, we varied model input parameters to evaluate face validity of changes in results. We developed a simple back-of-the-envelope model using only drug costs and trial drug response data and compared to our full model results. We compared results to other cost-effectiveness models in this therapy area. Finally, an external health economist with expertise in psoriasis assessed the modeling approach and draft results.

4.3 Results

Base Case Results

The results below should be interpreted not as treatments with a single targeted drug, but as sequences of targeted drugs. Treatments beginning with guselkumab continue to IL-17 and/or non-

targeted drugs upon discontinuation; treatments beginning with IL-17 drugs continue upon discontinuation of first-line targeted treatment to guselkumab and/or non-targeted drugs. All other drugs are followed by a market basket of IL-17 drugs and guselkumab upon discontinuation from the first-line targeted treatment.

Because pricing information was not available for tildrakizumab or risankizumab at the time of this report, model outcomes and pricing thresholds are reported in scenario analyses below.

Our results suggest that ixekizumab and brodalumab are the most effective initial treatments, while apremilast and etanercept are the least effective. Apremilast and infliximab are the initial targeted treatments with the lowest cost, while guselkumab and ixekizumab are likely to be the most expensive initial targeted treatments.

Table 4.6. Results for the Base Case for Targeted Treatments Over 10 years

First-line Treatment	Total Cost	Total QALYs	Months spent in PASI 90+*	Months spent in PASI 75+*
Non-targeted treatment	$67,789	5.704	0.0	0.0
Adalimumab	$272,617	7.075	48.8	68.0
Apremilast	$190,708	6.704	32.1	47.2
Brodalumab	$268,862	7.369	68.6	83.0
Certolizumab pegol	$232,265	7.073	48.8	68.1
Etanercept	$251,521	6.875	40.3	56.8
Guselkumab	$308,848	7.348	66.9	82.0
Infliximab	$225,074	7.019	53.1	63.6
Ixekizumab	$291,411	7.415	73.2	84.9
Secukinumab	$286,522	7.342	66.4	81.7
Ustekinumab	$289,938	7.159	54.3	72.5

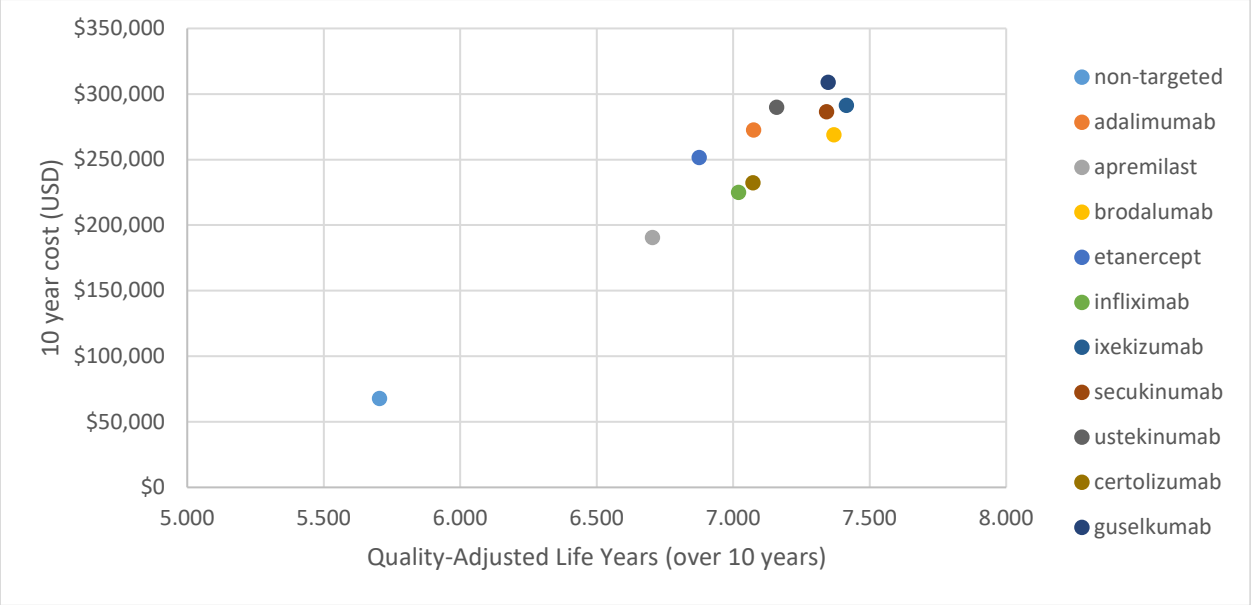
* Time spent in PASI health states is discounted at the same rate at costs and other outcomes.

Table 4.7. Incremental Cost-Effectiveness Ratios for the Base Case, Compared to Non-Targeted Treatment

First-line Treatment	Cost / QALY	Cost / month in PASI 90+	Cost / month in PASI 75+
Adalimumab	$149,385	$4,200	$3,010
Apremilast	$122,882	$3,826	$2,603
Brodalumab	$120,750	$2,932	$2,423
Certolizumab pegol	$120,158	$3,369	$2,415
Etanercept	$156,863	$4,556	$3,232
Guselkumab	$146,638	$3,603	$2,940
Infliximab	$119,572	$2,964	$2,471

Ixekizumab	$130,695	$3,056	$2,634
Secukinumab	$133,527	$3,295	$2,677
Ustekinumab	$152,678	$4,091	$3,064

Figure 4.1. Cost-Effectiveness of Initial Targeted Therapies Over 10 Years



Drugs that are farther to the right provide the greatest clinical benefit and drugs higher on the y-axis are more expensive.

Sensitivity Analysis Results

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges to evaluate changes in cost per additional QALY comparing ixekizumab to non-targeted treatment. In the base case, ixekizumab has an ICER of $130,695 per QALY compared to non-targeted and $73,906 per QALY compared to etanercept.

Figure 4.2. One-Way Sensitivity Analyses of ICER for Ixekizumab Versus Non-Targeted

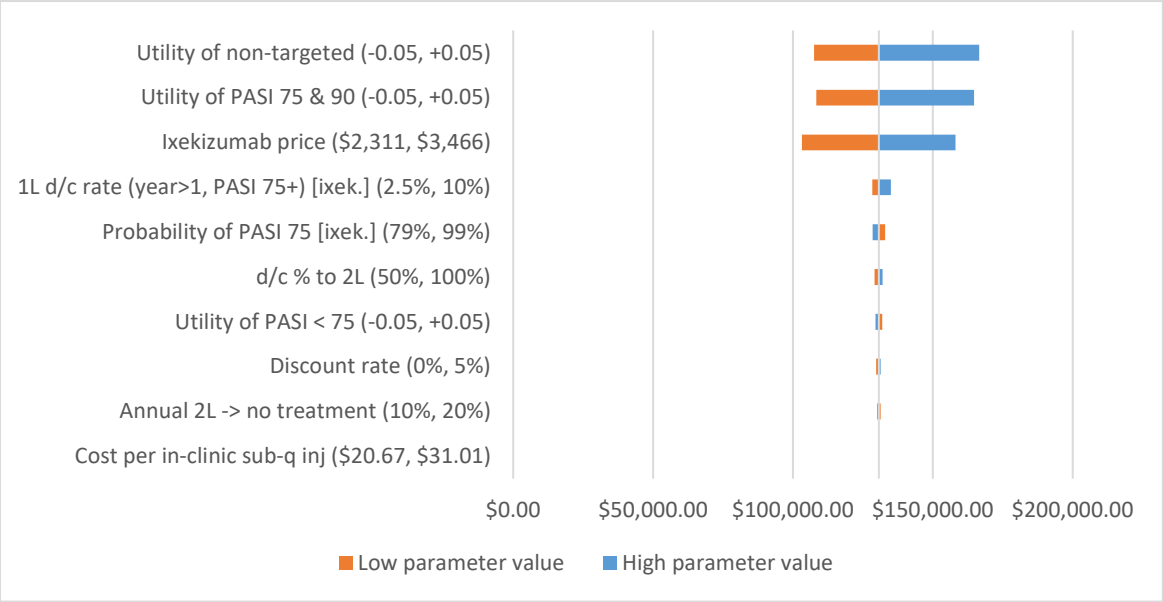
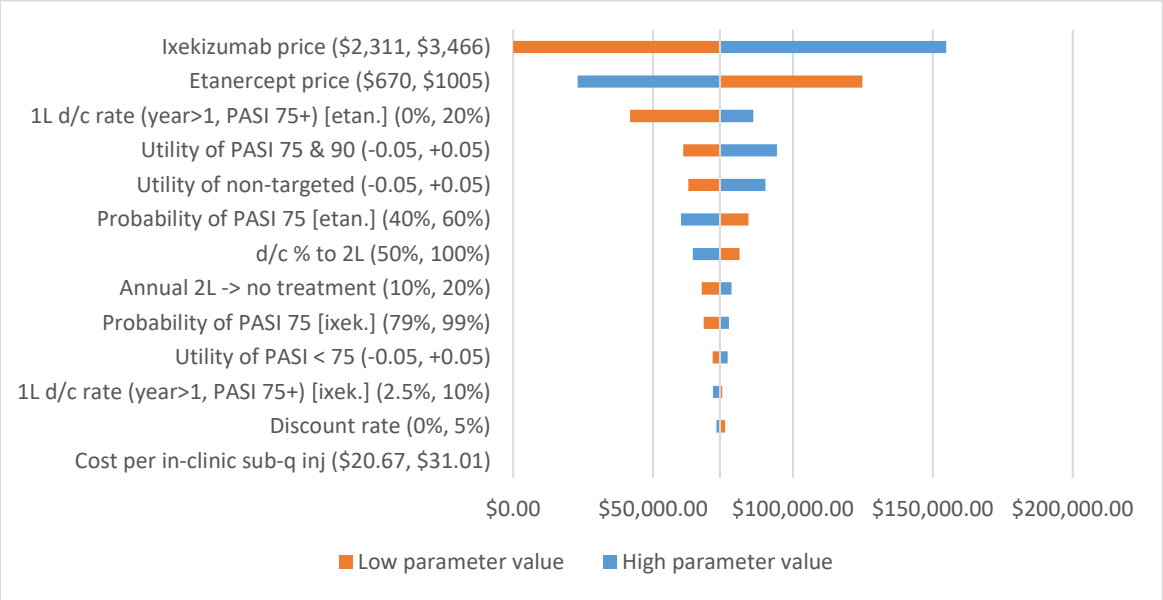


Figure 4.3. One-Way Sensitivity Analyses of ICER for Ixekizumab Versus Etanercept (Note: Ixekizumab Dominates Etanercept at a Price of $2,311 Per Unit)



Scenario Analyses Results

Improvements in PASI 50-74 group

When we assumed patients in the PASI 50-74 group continued therapy with small improvement and relatively higher discontinuation, the results for costs and QALYs changed by 0.2 to 3.5%, and the conclusions were unchanged. Results can be found in Appendix G, Table G11.

Effect of Net Price Changes

This scenario analysis is intended to isolate the effect of net price changes from other changes that have been made to the model since the 2016 report. Only drugs that were included in last year's analysis have been included here. The brodalumab price was estimated in 2016 and has not been included. In all cases, total costs of treatment increased by between 1% and 13% based on increases in net prices alone.

Table 4.8. Results (% Change in Results) Over 10 Years of this Year's Base Case Versus When Prices from the 2016 Report are Substituted

Treatment	Total Cost	Net price, 2016	Net price, 2018
Adalimumab	$242,952 (10.9%)	$1,434	$1,675
Apremilast	$176,923 (7.2%)	$34	$40.09
Etanercept	$227,710 (9.5%)	$717	$838
Infliximab	$204,659 (9.1%)	$779	$912*
Ixekizumab	$274,519 (5.8%)	$2,681	$2,889
Secukinumab	$249,419 (12.9%)	$2,439	$2,926
Ustekinumab	$286,637 (1.1%)	$7,514	$7,533

* Net price for infliximab was previously estimated by a discounted WAC; however, we have changed to estimating it by APC plus a mark-up, as this better replicate how intravenously administered drugs are reimbursed.

Completed suicides with brodalumab

In the most pessimistic scenario, completed suicides would be expected to reduce the number of QALYs gained with brodalumab use over 10 years from 7.369 to 7.362, or a decrease of 0.1%.

Dose escalation with etanercept

When etanercept patients with PASI 50 to 74 escalate their dose rather than immediately switching treatments, the costs for this treatment sequence rise to $261,189 over 10 years (3.8% increase)

with outcomes equivalent to 6.905 QALYs (0.4% increase). The ICER compared to non-targeted treatment rises to $160,955 per incremental QALY (2.6% increase).

Time to onset

While our base case assumption was that drug response is immediate with the first administration of the drug, we examined onset of response at months two and three for secukinumab as an illustrative example. ICERs compared to non-targeted were:

- Onset at month 1: $133,527
- Onset at month 2: $134,609
- Onset at month 3: $135,708

Second-line market baskets

Changing the second-line targeted treatment to a market basket represented by an average of all 10 targeted drugs changed total costs and QALYs by 0.1% to -2.5% (see Appendix G, Table G12) for details).

Productivity

Including productivity offsets led to 10-13% decreases in total costs, and ICER's compared to non-targeted that were notably lower than in the base case (i.e., $100-135K/QALY rather than $125-$155K/QALY).

Table 4.9. Inclusion of Productivity Offsets

Treatment	Total Cost	Cost per QALY, compared to non-targeted
Adalimumab	$242,075 (-11.2%)	$127,100
Apremilast	$167,075 (-12.4%)	$99,256
Brodalumab	$233,343 (-13.2%)	$99,420
Certolizumab pegol	$201,847 (-13.1%)	$97,936
Etanercept	$224,885 (-10.6%)	$134,079
Guselkumab	$273,699 (-11.4%)	$125,241
Infliximab	$201,191 (-10.6%)	$101,416
Ixekizumab	$255,254 (-12.4%)	$109,533
Secukinumab	$251,428 (-12.2%)	$112,103
Ustekinumab	$258,032 (-11.0%)	$130,750

Threshold analysis results

To estimate the maximum prices that would correspond to given willingness to pay thresholds, we systematically altered the price of each drug in the base case scenario in order to match that threshold. Prices for each drug that would achieve cost-effectiveness thresholds ranging from $50,000 to $150,000 per QALY gained are presented in Table 4.10.

In most cases, discounts from WAC would be required to achieve cost-effectiveness thresholds of $50,000 or $100,000 per QALY, while premiums on price could be charged for some drugs and remain below $150,000 per QALY. For apremilast, there was no positive price that could be charged to achieve a level of cost-effectiveness of $50,000/QALY. This occurs primarily because most patients who initiate treatment with apremilast quickly move on to second-line treatment which is more expensive, making it impossible to achieve a cost-effectiveness threshold of $50,000/QALY unless second-line treatment were discounted as well. Second-line treatment is more influential for apremilast than for the other drugs because approximately 70% of patients discontinue after the apremilast initiation period.

Table 4.10. Threshold Analysis Results

Intervention	WAC per Unit/Dose*	Net price per Unit	Price needed for $50k/QALY	Price needed for $100k/QALY	Price needed for $150k/QALY
Adalimumab	$2,436.02	$1,674.64	$447	$1,067	$1,687
Apremilast	$51.67	$40.09	< $0	$26	$58
Brodalumab	$1,750.00	$1,400.00	$611	$1,172	$1,731
Certolizumab pegol	$4,044.32	$2,583.70	$905	$2,119	$3,332
Etanercept	$1,218.00	$837.69	$78	$434	$790
Guselkumab	$10,158.52	$6,806.21	$2,531	$4,747	$6,963
Infliximab	$1,167.82	$911.99	$182	$711	$1,238
Ixekizumab	$5,161.60	$2,888.74	$1,207	$2,255	$3,302
Secukinumab	$4,712.38	$2,926.22	$1,127	$2,204	$3,282
Ustekinumab	$10,292.15 / $20,584.30	$7,532.84 / $15,063.47	$2,527 / $5,056	$4,970 / $9,940	$7,415 / $14,830

*WAC prices as of 3/28/18; infliximab pricing is based on mark-up from ASP due to its in-office administration

Risankizumab threshold analysis

The forthcoming IL-23 drug risankizumab was included in the NMA. The results were as follows:

- PASI < 50: 0.04

- PASI 50-74: 0.08
- PASI 75-89: 0.16
- PASI 90-100: 0.72

No WAC will be announced for this product for some time, and the approved dosing is not certain. Assuming discontinuation parameters identical to guselkumab, we have calculated the following value-based *monthly* maintenance prices:

- $50k / QALY: $1,235
- $100k / QALY: $2,288
- $150k / QALY: $3,342

Tildrakizumab threshold analysis

The recently-approved IL-23 drug tildrakizumab was included in the NMA, but its pricing has not yet been released. The results of the NMA were as follows:

- PASI < 50: 0.18
- PASI 50-74: 0.21
- PASI 75-89: 0.19
- PASI 90-100: 0.42

Tildrakizumab was approved to be dosed at 100 mg every 12 weeks, following initiation doses of 100 mg at weeks zero and four. Using this dosing information, we have calculated per-unit pricing (i.e., per every 12 weeks) for tildrakizumab as follows:

- $50k / QALY: $2,607
- $100k / QALY: $6,065
- $150k / QALY: $9,253

4.4 Summary and Comment

The most effective treatments in this analysis were, in descending order, ixekizumab (7.415 QALYs), brodalumab (7.369 QALYs), and guselkumab (7.348 QALYs). The least effective treatment was apremilast (6.704 QALYs).

The least costly treatments, over 10 years, were apremilast ($191,084), infliximab ($225,074), and certolizumab ($232,265). The most expensive treatment was guselkumab ($308,848).

The values of the eleven included drugs compared to non-targeted treatment are remarkably similar when considered on a cost per QALY basis - most of them are between $100,000 and $150,000 per QALY. However, guselkumab is at the higher end of the value spectrum (using an estimated drug price discount), and brodalumab is at the lower (more favorable) end of the spectrum. The value of tildrakizumab and risankizumab will be dependent on their final list price and discounts provided in the marketplace.

In our 2016 analysis, we concluded that IL-17 drugs were a reasonable first-line targeted treatment due to their high efficacy and reasonable economic value – even in comparison to step therapy using a less effective and slightly less expensive targeted drug first line. This conclusion remains valid – for example, in the base case, ixekizumab has an ICER of $ $73,906 per QALY compared to etanercept.

However, the IL-17 drugs have increased in price across the board, leading to less favorable value than in our 2016 report. Other contributing factors are revised estimates of quality of life impacts and increased use of targeted drugs second line.

Limitations

We currently lack robust data on treatment patterns and discontinuation rates in the U.S. setting. While we have some data from psoriasis registries in other countries, the choice of what drug to switch to is largely determined by policies unique to each locale. This issue becomes even more complicated when there is the possibility of increasing the dosage of the first-line targeted drug to titrate the treatment to be more effective. The model is fairly sensitive to these parameters, although the fundamental conclusions are not changed.

Next, while we have evidence that suggests a 10% decrease in effectiveness for second-line targeted treatments is approximately correct, data on this subject has not been collected in a well-controlled setting that eliminates the influence of unobserved confounding factors.

Perhaps most importantly, though, we were limited by the existing data on the utility of response to treatment. Our model, like the clinical trials for each of these drugs, used the percent change in PASI from baseline, but this approach is problematic. One issue is that there is likely to be poorly characterized heterogeneity in the participants between these studies. Another is that, even within a given level of PASI response, there may be different distributions of response. For example, two drugs may have the same percentage responding with PASI 75-90, although the average response within that grouping may be closer to 75% improvement for one drug and closer to 90% for the other. The ideal solution to this issue would be to collect directly-elicited utility data from a generic or psoriasis-specific instrument before and after treatment with each drug.

Conclusions

Targeted drugs for plaque psoriasis generally represent good value compared to non-targeted treatment, as most drugs fall between $100,000 and $150,000 per incremental QALY. Only etanercept and ustekinumab exceeded the $150,000 per QALY threshold. Recent price increases, particularly those for adalimumab and etanercept, have made these drugs notably less cost-effective than they were in our previous report.

The results of our model indicate that initial treatment with apremilast, infliximab, certolizumab, and brodalumab have similar cost effectiveness compared to non-targeted treatment, but brodalumab offers the highest effectiveness. Indeed, initial treatment with either brodalumab, ixekizumab, secukinumab, or guselkumab is considerably more effective than initial (step) therapy with less effective agents.

5. Additional Considerations

Our reviews seek to provide information on other benefits 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. These general elements are listed in the table below, and the subsequent text provides detail about the elements that are applicable to the comparison of targeted immunomodulators to each other.

Table 5.1. Potential Other Benefits or Contextual Considerations (Not Specific to Any Disease or Therapy)

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to systemic therapies, there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to systemic therapies, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

As described in Section 1.4., many aspects of patients' lives are affected by plaque psoriasis. For example, many psoriasis patients reported difficulties in finding and/or maintaining a job and socialization with family members and friends. In addition, many patients with psoriasis have serious emotional and psychological issues. Psoriasis is associated with a higher likelihood of having depression, anxiety, and suicidal ideation. Data from clinical effectiveness shows that the use of targeted immunomodulators offers patients better treatment potential in regard to greater skin

clearance and overall improved quality of life. Although we have very limited data on the evaluating the effect of these drugs on patients' quality of life, there is reason to believe that for some patients with psoriasis, targeted immunomodulators may make many aspects of day-to-day living easier.

All of the targeted immunomodulators are administered subcutaneously except for apremilast (oral) and infliximab (intravenous). Subcutaneous route of administration is less burdensome and has reduced complexity, which is likely to improve adherence as well as the ability for some patients with limited mobility to self-administer prophylaxis. Further, patients may favor the convenience of an oral drug like apremilast. Although infliximab has a relatively better efficacy in our evidence review, patients might be disinclined to use an intravenous medication that is associated with administration time and discomfort.

In addition, patients could favor agents that need to be taken less frequently. The frequency of administration during maintenance is greatest for apremilast (twice a day). Other targeted immunomodulators are taken weekly (adalimumab, etanercept), every two weeks (brodalumab), every four weeks (secukinumab and ixekizumab), every 8 weeks (infliximab, guselkumab), and every 12 weeks (ustekinumab, tildrakizumab, risankizumab).

Psoriasis is chronic condition requiring long term treatment. Therefore, there is a need to understand the potential risks for serious events or events with long-latency periods that may be associated with the use of targeted immunomodulators. Observation data on the drugs that have been around for longer periods (TNFα inhibitors) have been generally reassuring. The long-term risks of the newer agents (IL-17s and IL-23s) will only become apparent with ongoing use in a large number of treated individuals. Current data from the short-term trials, and extension studies on these agents have generally been positive, however, it will be important to follow the safety profile of these drugs in post-marketing registries to ensure their long-term safety.

Finally, longer term data have shown that that loss of effect over time is a very common problem with these drugs. In fact, switching treatment is generally expected among patients. However, due to limited guidance in clinical practice, there is some uncertainty about the best choice of second-line biologic agent needed to achieve optimal outcomes.

6. Value-Based Price Benchmarks

Value-based price benchmarks will be included in the revised Evidence Report that will be released on/around June 8, 2018.

7. Potential Budget Impact

7.1 Overview

We used results from the same model employed for the cost-effectiveness analyses to estimate the total potential budgetary impact of the two novel treatments for psoriasis patients: certolizumab pegol (not yet approved for this indication) and guselkumab (approved in July 2017). We used the WAC for each drug, an estimate of discounted WAC, and the cost-effectiveness threshold prices at $50,000, $100,000, and $150,000 per QALY in our estimates of budget impact. We did not include the other therapies modeled above in this potential budget impact analysis, given their established presence on the market.

7.2 Methods

Potential budget impact was defined as the total incremental cost of using the new therapies 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 a five-year time horizon, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapies.

The potential budget impact analysis included the entire candidate population for treatment, which included 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 certolizumab pegol or guselkumab, we first determined the estimated incidence of psoriasis in the U.S. We did not include brodalumab in our analysis given its presence on the market for nearly two years, and we could not estimate budget impact for tildrakizumab or risankizumab in the absence of an established price.

As in our 2016 report, 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.[12] The proportion of psoriasis patients with plaque psoriasis has been estimated to be 79%.[12] 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 2018-2022 U.S. adult population results in an average estimate of 29,342 incident cases of moderate-severe plaque psoriasis in the US per year, or approximately 146,710 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 are described in detail here. The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy. Briefly, we evaluate a new drug that would take market share from one or more drugs and calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. For this analysis, we assumed that certolizumab pegol or guselkumab would replace non-targeted therapy in the eligible patients being treated.

Using this approach to estimate potential budget impact, we then compared our estimates to an updated 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 (http://icer-review.org/wp-content/uploads/2018/03/ICER-value-assessment-framework-update-FINAL-062217.pdf), 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 over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending. Calculations are performed as shown in Table 7.1.

For 2017-18, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $915 million per year for new drugs.

Table 7.1. Calculation of Potential Budget Impact Threshold

Item	Parameter	Estimate	Source
1	Growth in US GDP, 2017 (est.) +1%	3.20%	World Bank, 2016
2	Total health care spending, 2016 ($)	$2.71 trillion	CMS NHE, 2014
3	Contribution of drug spending to total health care spending (%)	17.7%	CMS National Health Expenditures (NHE), 2016; Altarum Institute, 2014
4	Contribution of drug spending to total health care spending ($) (Row 2 x Row 3)	$479 billion	Calculation
5	Annual threshold for net health care cost growth for ALL new drugs (Row 1 x Row 4)	$15.3 billion	Calculation
6	Average annual number of new molecular entity approvals, 2015-2016	33.5	FDA, 2017
7	Annual threshold for average cost growth per individual new molecular entity (Row 5 ÷ Row 6)	$457.5 million	Calculation
8	Annual threshold for estimated potential budget impact for each individual new molecular entity (doubling of Row 7)	$915 million	Calculation

7.3 Results

Table 7.2 illustrates the per-patient budget impact calculations for certolizumab pegol in adults with moderate to severe plaque psoriasis, compared to non-targeted therapy. Potential budget impact is presented based on WAC ($4,044 per 200mg), discounted WAC ($2,584), and the prices to reach $150,000, $100,000, and $50,000 per QALY in this population ($3,332, $2,119, and $905, respectively).

Table 7.2. Per-Patient Budget Impact Calculations Over a Five-Year Time Horizon for Certolizumab Pegol in Adults with Moderate to Severe Plaque Psoriasis

	Average Annual Per Patient Budget Impact				
	WAC	Discounted WAC	$150,000/ QALY	$100,000/ QALY	$50,000/ QALY
Certolizumab pegol	$50,383	$32,220	$39,655	$26,636	$12,898
Non-targeted therapy	$7,811				
Difference	$42,572	$24,409	$31,844	$18,824	$5,087

WAC: wholesale acquisition cost; QALY: quality adjusted life year

The average potential budgetary impact when using the WAC was an additional per-patient cost of approximately $42,600 and approximately $24,400 using the discounted WAC. At the three cost-

effectiveness threshold prices (at $50,000, $100,000 and $150,000 per QALY), the average annual budget impact ranged from approximately $31,800 per patient using the price ($3,332 per 200mg) to achieve $150,000 per QALY to approximately $5,100 using the price ($905) to achieve a $50,000 per QALY cost-effectiveness threshold.

Table 7.3 illustrates the per-patient budget impact calculations for guselkumab in adults with moderate to severe plaque psoriasis, compared to non-targeted therapy. We present the potential budget impact results based on WAC ($10,159 per 100mg), assumed discounted WAC ($6,806), and the prices for guselkumab to reach $150,000, $100,000, and $50,000 per QALY ($6,963, $4,747, and $2,531, respectively).

Table 7.3. Per-Patient Budget Impact Calculations Over a Five-Year Time Horizon for Guselkumab in Adults with Moderate to Severe Plaque Psoriasis

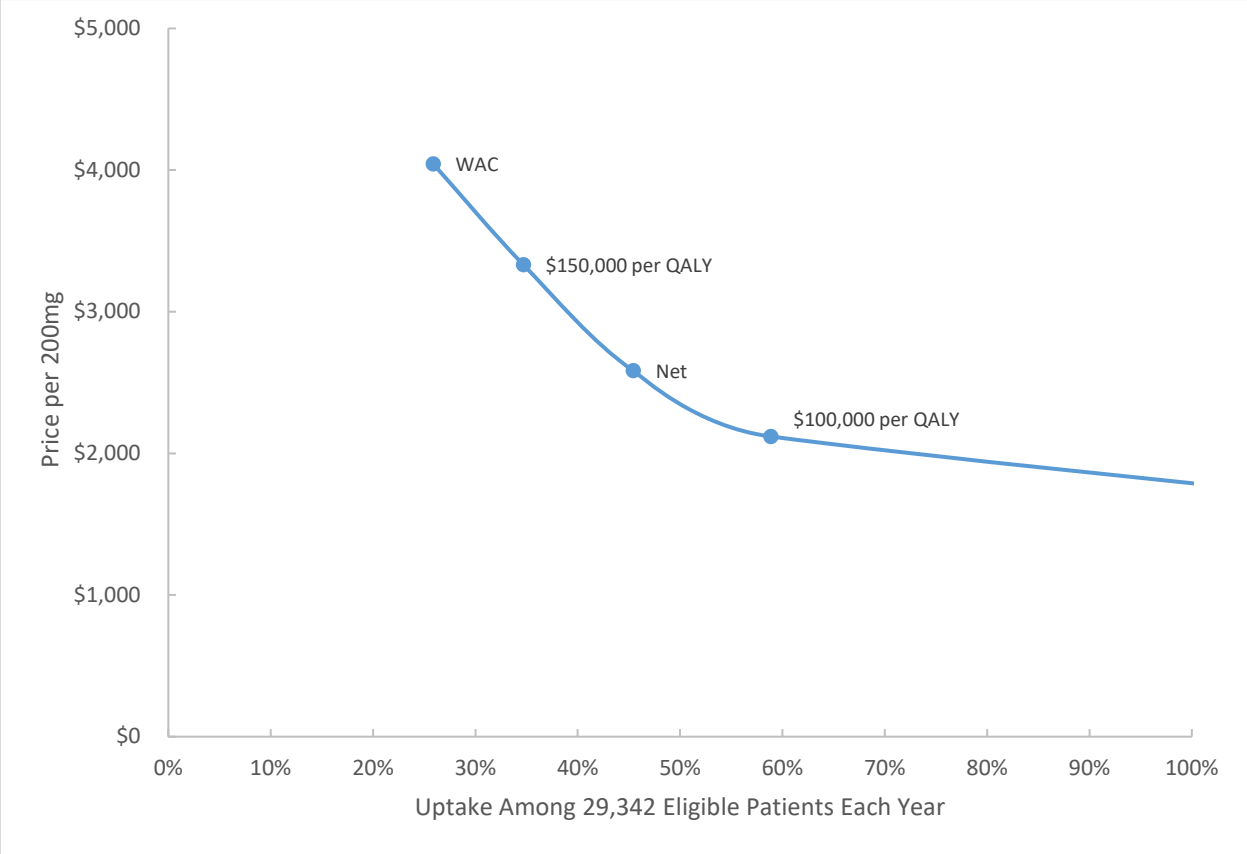
	Average Annual Per Patient Budget Impact				
	WAC	Discounted WAC	$150,000/ QALY	$100,000/ QALY	$50,000/ QALY
Guselkumab	$63,074	$41,712	$43,941	$30,204	$16,464
Non-targeted therapy	$7,811				
Difference	$55,263	$33,900	$36,130	$22,393	$8,653

WAC: wholesale acquisition cost; QALY: quality-adjusted life year

The average potential budgetary impact when using the WAC was an additional per-patient cost of approximately $55,300 and approximately $33,900 using the assumed discount from WAC. At the three cost-effectiveness threshold prices (at $50,000, $100,000 and $150,000 per QALY), the average annual budget impact ranged from approximately $36,100 per patient using the price to achieve $150,000 per QALY to approximately $8,700 using the price to achieve a $50,000 per QALY cost-effectiveness threshold.

For certolizumab pegol, as shown in Figure 7.1, approximately 26% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $915 million at total treatment costs using WAC ($4,044 per 200mg), and approximately 45% using the discounted WAC. Approximately 35% of patients could be treated in a given year without crossing the budget impact threshold at the $150,000 per QALY threshold price ($3,332), while 59% of the population could be treated without crossing the threshold at the $100,000 per QALY threshold price ($2,119). At the $50,000 per QALY threshold price ($905), the entire eligible cohort could be treated without exceeding the $915 million threshold, reaching only 45% of the threshold.

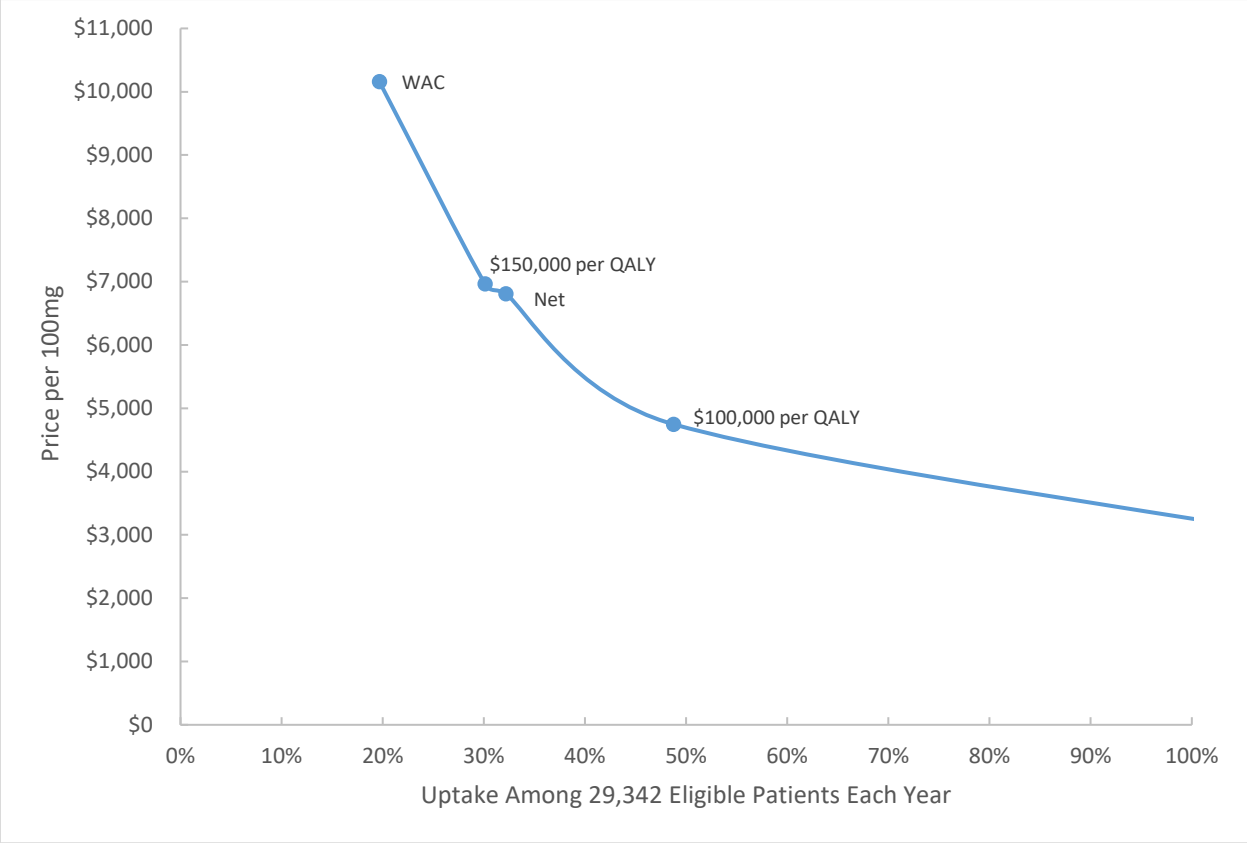
Figure 7.1. Potential Budget Impact Scenarios at Different Prices for Certolizumab Pegol in Adults with Moderate to Severe Plaque Psoriasis*



*Graph shows the relation between price per 200mg and proportion of patients eligible for treatment with certolizumab pegol who could be treated over five years without crossing $915-million budget impact threshold.

For guselkumab (Figure 7.2), approximately 20% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $915 million at total treatment costs using WAC ($10,159 per 100mg), and approximately 32% using the assumed discounted WAC. Approximately 30% of patients could be treated in a given year without crossing the budget impact threshold at the $150,000 per QALY threshold price ($6,963), while 49% of the population could be treated without crossing the threshold at the $100,000 per QALY threshold price ($4,747). At the $50,000 per QALY threshold price ($2,531), the entire eligible cohort could be treated without exceeding the $915 million threshold (at 78% of the total).

Figure 7.2. Potential Budget Impact Scenarios at Different Prices for Guselkumab in Adults with Moderate to Severe Plaque Psoriasis*



*Graph shows the relation between price per 100mg and proportion of patients eligible for treatment with guselkumab who could be treated over five years without crossing $915-million budget impact threshold.

In summary, the annual budget impact over a five-year time-horizon for treating eligible patients with moderate to severe plaque psoriasis with certolizumab pegol rather than non-targeted therapy was estimated to be approximately $24,400 per patient using net price, and approximately $33,900 per patient using net price for guselkumab. The total annual potential budget impact is estimated to exceed ICER's annual $915 million budget impact threshold using WAC, discounted WAC, and prices to achieve cost-effectiveness thresholds from $100,000 to $150,000 per QALY gained. At the price to achieve a cost-effectiveness threshold of $50,000 per QALY, the total annual budget would not exceed ICER's $915 million annual budget impact threshold for either certolizumab pegol or guselkumab.

****

This is an ICER update evaluating targeted immunomodulators for treating moderate-to-severe plaque psoriasis. This is ICER's first update of the topic, which was originally reviewed in 2016.

References

1. Bergstrom KG, Kimball AB. *100 questions & answers about psoriasis.* 2nd ed. Sudbury, Mass.: Jones and Bartlett; 2011.
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. Menter A. *An Overview of Psoriasis, Chapter 1 in Koo, John Y. M. editor Moderate to severe psoriasis.* Fourth edition ed: CRC Press; 2014.
5. Conrad C, Gilliet M. Psoriasis: from Pathogenesis to Targeted Therapies. *Clinical reviews in allergy & immunology.* 2018;54(1):102-113.
6. Boehncke WH, Schon MP. Psoriasis. *Lancet.* 2015;386(9997):983-994.
7. Lockshin B, Balagula Y, Merola JF. Interleukin-17, Inflammation, and Cardiovascular Risk in Patients With Psoriasis. *J Am Acad Dermatol.* 2018.
8. Ibrahim G, Waxman R, Helliwell PS. The prevalence of psoriatic arthritis in people with psoriasis. *Arthritis Rheum.* 2009;61(10):1373-1378.
9. 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.
10. Mease PJ, Gladman DD, Papp KA, et al. Prevalence of rheumatologist-diagnosed psoriatic arthritis in patients with psoriasis in European/North American dermatology clinics. *J Am Acad Dermatol.* 2013;69(5):729-735.
11. Strober B, Karki C, Mason M, et al. Characterization of disease burden, comorbidities, and treatment use in a large, US-based cohort: Results from the Corrona Psoriasis Registry. *J Am Acad Dermatol.* 2018;78(2):323-332.
12. 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.
13. 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.
14. 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.
15. Merola JF, Li T, Li WQ, Cho E, Qureshi AA. Prevalence of psoriasis phenotypes among men and women in the USA. *Clin Exp Dermatol.* 2016;41(5):486-489.
16. 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.
17. 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.

18. 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.
19. 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. *Journal of the American Academy of Dermatology.* 2014;70(5):871-881 e871-830.
20. Rapp SR, Feldman SR, Exum ML, Fleischer AB, Jr., Reboussin DM. Psoriasis causes as much disability as other major medical diseases. *Journal of the American Academy of Dermatology.* 1999;41(3 Pt 1):401-407.
21. Reich K. The concept of psoriasis as a systemic inflammation: implications for disease management. *J Eur Acad Dermatol Venereol.* 2012;26 Suppl 2:3-11.
22. Brezinski EA, Dhillon JS, Armstrong AW. Economic Burden of Psoriasis in the United States: A Systematic Review. *JAMA Dermatol.* 2015;151(6):651-658.
23. Amor KT, Ryan C, Menter A. The use of cyclosporine in dermatology: part I. *J Am Acad Dermatol.* 2010;63(6):925-946; quiz 947-928.
24. FDA. Biological Product Definitions. In: U.S. Department of Health & Human Services; 2018: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM581282.pdf. Accessed 2018-03-11.
25. RAPS. FDA Begins Adding Suffixes to Newly Approved Biologics' Names. 2017; https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2017/11/fda-begins-adding-suffixes-to-newly-approved-biologics-names. Accessed March 11, 2018.
26. Levin EC, Koo JY. *Biologic Fatigue, Chapter 15 in Koo, John Y. M. editor Moderate to severe psoriasis.* Fourth edition ed: CRC Press; 2014.
27. 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.
28. Mehren CR, Gniadecki R. Dose-creep of Infliximab during psoriasis treatment: an observational study. *Acta dermato-venereologica.* 2012;92(4):355-357.
29. Carter C, Wilson KL, Smith D, Lee S. Comparative Treatment Patterns Among Psoriasis Patients Using Adalimumab, Etanercept, or Ustekinumab. *Am J Pharm Benefits.* 2016;8(5):191-198.
30. Busard CI, Cohen AD, Wolf P, et al. Biologics combined with conventional systemic agents or phototherapy for the treatment of psoriasis: real-life data from PSONET registries. *J Eur Acad Dermatol Venereol.* 2018;32(2):245-253.
31. 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.
32. Iskandar IYK, Warren RB, Lunt M, et al. Differential Drug Survival of Second-Line Biologic Therapies in Patients with Psoriasis: Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *J Invest Dermatol.* 2018;138(4):775-784.
33. Seale L, Cardwell LA, Feldman SR. Adherence to biologics in patients with psoriasis. *Expert Rev Clin Immunol.* 2018;14(2):155-161.
34. Raychaudhuri SP, Kundu-Raychaudhuri SK, Bagchi D. *Psoriasis and psoriatic arthritis : pathophysiology, therapeutic intervention, and complementary medicine.* Boca Raton, FL: CRC Press/Taylor & Francis Group; 2018.

35. FDA. Biosimilar Product Information. 2018; https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580432.htm. Accessed March 11, 2018.
36. Brennan Z. Top-Selling Drugs in 2018: Biosimilar Competition is FDA Approved but Not Marketed. *Regulatory Focus* 2018; https://www.raps.org/news-and-articles/news-articles/2018/2/top-selling-drugs-in-2018-biosimilar-competition. Accessed March 11, 2018.
37. Sagonowsky E. AbbVie's Humira gets biosim reprieve—and Amgen wins copycat advantage—in patent deal with Samsung Bioepis. 2018; https://www.fiercepharma.com/legal/abbvie-biogen-agree-2023-date-for-u-s-humira-biosim-launch. Accessed April 6, 2018.
38. Griffiths CEM, Thaci D, Gerdes S, et al. The EGALITY study: a confirmatory, randomized, double-blind study comparing the efficacy, safety and immunogenicity of GP2015, a proposed etanercept biosimilar, vs. the originator product in patients with moderate-to-severe chronic plaque-type psoriasis. *The British journal of dermatology.* 2017;176(4):928-938.
39. Papp K, Bachelez H, Costanzo A, et al. Clinical similarity of the biosimilar ABP 501 compared with adalimumab after single transition: long-term results from a randomized controlled, double-blind, 52-week, phase III trial in patients with moderate-to-severe plaque psoriasis. *The British Journal of Dermatology.* 2017;177(6):1562-1574.
40. Gisondi P, Bianchi L, Conti A, et al. Infliximab biosimilar CT-P13 in the treatment of chronic plaque psoriasis: data from the Psobiosimilars registry. *The British Journal of Dermatology.* 2017;177(6):e325-e326.
41. Jorgensen KK, Olsen IC, Goll GL, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. *Lancet.* 2017;389(10086):2304-2316.
42. Chingcuanco F, Segal JB, Kim SC, Alexander GC. Bioequivalence of Biosimilar Tumor Necrosis Factor-alpha Inhibitors Compared With Their Reference Biologics: A Systematic Review. *Ann Intern Med.* 2016;165(8):565-574.
43. FDA. Considerations in Demonstrating Interchangeability With a Reference Product-Guidance for Industry Draft Guidance. 2017; https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf. Accessed April 10, 2018.
44. FDA. Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations. 2018; https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm411418.htm. Accessed March 11, 2018.
45. De Bandt M, Sibilia J, Le Loet X, et al. Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: a French national survey. *Arthritis Res Ther.* 2005;7(3):R545-551.
46. Kagami S, Rizzo HL, Kurtz SE, Miller LS, Blauvelt A. IL-23 and IL-17A, but not IL-12 and IL-22, are required for optimal skin host defense against Candida albicans. *J Immunol.* 2010;185(9):5453-5462.
47. Papp KA, Bachelez H, Blauvelt A, et al. Infections from seven clinical trials of ixekizumab, an anti-interleukin-17A monoclonal antibody, in patients with moderate-to-severe psoriasis. *The British Journal of Dermatology.* 2017;177(6):1537-1551.
48. Danesh MJ, Kimball AB. Brodalumab and suicidal ideation in the context of a recent economic crisis in the United States. *J Am Acad Dermatol.* 2016;74(1):190-192.

49. FDA. Approved Risk Evaluation and Mitigation Strategies (REMS) - Siliq (brodalumab). 2018; https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=362. Accessed April 25, 2018.
50. Bissonnette R, Kerdel F, Naldi L, et al. Evaluation of Risk of Major Adverse Cardiovascular Events With Biologic Therapy in Patients With Psoriasis. *Journal of Drugs in Dermatology : JDD.* 2017;16(10):1002-1013.
51. Kimball AB, Sundaram M, Cloutier M, et al. Increased Prevalence of Cancer in Adult Patients With Psoriasis in the United States: A Claims Based Analysis. *Journal of Drugs in Dermatology : JDD.* 2018;17(2):180-186.
52. Papp K, Reich K, Sobell JM, et al. Two-year safety of apremilast in patients with moderate to severe plaque psoriasis: Results from ESTEEM 1. *Australasian Journal of Dermatology.* 2016;57:67.
53. Linder J, Pearson S, Ollendorf D, et al. Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value. In: Institute for Clinical and Economic Review, ed. Boston2016: https://icer-review.org/wp-content/uploads/2016/11/NE_CEPAC_Psoriasis_Evidence_Report_FINAL_012317.pdf. Accessed 2017-11-27.
54. Feldman SR, Traci D, Gooderham M, et al. Tofacitinib improves pruritus and health-related quality of life up to 52 weeks: Results from 2 randomized phase III trials in patients with moderate to severe plaque psoriasis. *J Am Acad Dermatol.* 2016.
55. Papp KA, Menter MA, Raman M, et al. A randomized phase 2b trial of baricitinib, an oral Janus kinase (JAK) 1/JAK2 inhibitor, in patients with moderate-to-severe psoriasis. *The British Journal of Dermatology.* 2016;174(6):1266-1276.
56. Baker KF, Isaacs JD. Novel therapies for immune-mediated inflammatory diseases: What can we learn from their use in rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, psoriasis, Crohn's disease and ulcerative colitis? *Ann Rheum Dis.* 2018;77(2):175-187.
57. Woolf S. An organized analytic framework for practice guideline development: using the analytic logic as a guide for reviewing evidence, developing recommendations, and explaining the rationale. *Clinical Practice Guideline Development: Methodology Perspectives. AHCPR Pub* 1994; 105-113. Available at: https://ntrl.ntis.gov/NTRL/ under number PB95195848.
58. Nijsten T. Dermatology life quality index: time to move forward. *J Invest Dermatol.* 2012;132(1):11-13.
59. Finlay AY, Kelly SE. Psoriasis--an index of disability. *Clin Exp Dermatol.* 1987;12(1):8-11.
60. Lerner D, Amick BC, 3rd, Rogers WH, Malspeis S, Bungay K, Cynn D. The Work Limitations Questionnaire. *Med Care.* 2001;39(1):72-85.
61. Institute for Clinical and Economic Review. Key Stakeholder Organizations for 2016 ICER Psoriasis Report. 2016; https://icer-review.org/wp-content/uploads/2016/10/NECEPAC_Psoriasis_Stakeholder_List_092916.pdf.
62. Siegel M. Comment of the National Psoriasis Foundation at the ICER public meeting on Treatment Options for Plaque Psoriasis, November 18, 2016. [YouTube video]. 2016; https://youtu.be/Rl7Fa9Ex2ts. Accessed March, 19, 2018.
63. FDA. Public Meeting on Patient-Focused Drug Development for Psoriasis. 2018; https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm470608.htm. Accessed March 31, 2018.
64. 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.
65. Takeshita J, Gelfand JM, Li P, et al. Psoriasis in the US Medicare Population: Prevalence, Treatment, and Factors Associated with Biologic Use. *J Invest Dermatol.* 2015;135(12):2955-2963.
66. 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.
67. Korman NJ, Zhao Y, Pike J, Roberts J. Relationship between psoriasis severity, clinical symptoms, quality of life and work productivity among patients in the USA. *Clin Exp Dermatol.* 2016;41(5):514-521.
68. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med.* 1997;126(5):376-380.
69. 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.
70. Dias S, Welton NJ, Sutton AJ, Ades AE. *NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of. Randomised Controlled Trials.* 2011 (updated 2014).
71. Yu-sung S, Masanao Y. R2jags: Using R to Run 'JAGS'. R package version 0.5-7. 2015; https://CRAN.R-project.org/package=R2jags.
72. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Med Care.* 2010;48(6 Suppl):S145-152.
73. U.S. Preventative Services Task Force. *Procedure Manual. Agency for Healthcare Research and Quality.* 2008.
74. 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). *Journal of Drugs in Dermatology : JDD.* 2013;12(2):166-174.
75. 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.
76. 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.
77. 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.
78. Cai L, Gu J, Zheng J, et al. Efficacy and safety of adalimumab in Chinese patients with moderate-to-severe plaque psoriasis: results from a phase 3, randomized, placebo-controlled, double-blind study. *J Eur Acad Dermatol Venereol.* 2017;31(1):89-95.
79. 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.
80. Leonardi CL, Powers JL, Matheson RT, et al. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med.* 2003;349(21):2014-2022.
81. 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.

82. 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.
83. 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.
84. 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.
85. 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.
86. 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.
87. 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.
88. 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. *Chinese medical journal.* 2012;125(11):1845-1851.
89. Torii H, Nakagawa H. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-controlled multicenter trial. *J Dermatol Sci.* 2010;59(1):40-49.
90. Gottlieb AB, Blauvelt A, Thaci D, et al. Certolizumab Pegol for the Treatment of Chronic Plaque Psoriasis: Results through 48 Weeks from Two Phase 3, Multicenter, Randomized, Double-Blinded, Placebo-Controlled Studies (CIMPASI-1 and CIMPASI-2). *J Am Acad Dermatol.* 2018.
91. Lebwohl M, Blauvelt A, Paul C, et al. Certolizumab Pegol for the Treatment of Chronic Plaque Psoriasis: Results Through 48 Weeks of a Phase 3, Multicenter, Randomized, Double-Blinded, Etanercept- and Placebo-Controlled Study (CIMPACT). *J Am Acad Dermatol.* 2018.
92. 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.
93. 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.
94. 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.
95. 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). *J Dermatol Sci.* 2011;63(3):154-163.
96. 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.

97. 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.
98. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. *New England Journal of Medicine.* 2016;371(4):326-338.
99. Gordon K, Leonardi C, Blauvelt A, et al. Efficacy and safety of ixekizumab over four years of open-label treatment in a Phase 2 study in chronic plaque psoriasis. *Experimental Dermatology.* 2016;25:39.
100. 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.
101. Lebwohl M, Reich K, Paul C, Rosen M, Hansen K. Brodalumab is efficacious in patients with moderate-to-severe psoriasis irrespective of prior use of, and response to, other biological therapies. *British Journal of Dermatology.* 2017;177:64-65.
102. 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.
103. 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.
104. Reich K, Gooderham M, Green L, et al. The efficacy and safety of apremilast, etanercept and placebo in patients with moderate-to-severe plaque psoriasis: 52-week results from a phase IIIb, randomized, placebo-controlled trial (LIBERATE). *Journal of the European Academy of Dermatology and Venereology : JEADV.* 2016(pagination).
105. Blauvelt A, Papp KA, Griffiths CEM, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *Journal of the American Academy of Dermatology.* 2016.
106. Reich K, Armstrong AW, Foley P, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. *J Am Acad Dermatol.* 2017;76(3):418-431.
107. Reich K, Papp KA, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. *The Lancet.* 2017;390(10091):276-288.
108. Blauvelt A, Papp K, Gooderham M, et al. Efficacy and safety of risankizumab, an IL-23 inhibitor, in patients with moderate-to-severe chronic plaque psoriasis: 16-week results from the phase 3 IMMhance trial. Paper presented at: Psoriasis: from gene to clinic. 2017; London, UK.
109. Gordon K, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab: results from two double-blind, placebo- and ustekinumab-controlled, phase 3 trials in moderate-to-severe plaque psoriasis. Paper presented at: AAD Annual Meeting 2018; San Diego, CA.
110. de Vries AC, Thio HB, de Kort WJ, et al. A prospective randomized controlled trial comparing infliximab and etanercept in patients with moderate-to-severe chronic plaque-type psoriasis:

the Psoriasis Infliximab vs. Etanercept Comparison Evaluation (PIECE) study. *The British Journal of Dermatology.* 2017;176(3):624-633.
111. Griffiths CE, Strober BE, van de Kerkhof P, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *N Engl J Med.* 2010;362(2):118-128.
112. 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.
113. Reich K, Pinter A, Lacour JP, et al. Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24-week results from IXORA-S, a phase III study. *British Journal of Dermatology.* 2017;177(4):1014-1023.
114. Reich K, Blauvelt A, Thac¸i D, Leonardi C, Gottlieb A. Maintenance of Response with Certolizumab Pegol for the Treatment of Chronic Plaque Psoriasis: 48-Week Results from Two Ongoing Phase 3, Multicenter, Randomized, Placebo-Controlled Studies (CIMPASI-1 and CIMPASI-2). European Academy of Dermatology and Venereology (EADV) Congress; 2017; Geneva, Switzerland.
115. Lebwohl M, Paul C, Piguet V, et al. Certolizumab Pegol for the Treatment of Chronic Plaque Psoriasis: Primary Results from an Ongoing Phase 3, Multicenter, Randomized, Active- and Placebo-Controlled Study. Paper presented at: 13th Annual Maui Derm for Dermatologists 2017; March 20 -24, 2017; Maui Hawaii.
116. Blauvelt A, Mehlis S, Vanaclocha F, al. E. Secukinumab provides greater 52-week sustained relief from dermatology-related quality of life impact on clothing choice and sexual function than ustekinumab. Paper presented at: 25th European Academy of Dermatology and Venereology Congress2016; Vienna, Austria.
117. 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.
118. Korman NJ, Sofen H, Fretzin S, et al. Secukinumab provides better relief from the impact of psoriasis on daily activities and personal relationships than etanercept: results of two phase 3 placebo-controlled randomized clinical trials in moderate-to-severe psoriasis. *J Dermatolog Treat.* 2017;28(5):384-389.
119. 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.
120. Papp K, Gottlieb AB, Naldi L, et al. Safety Surveillance for Ustekinumab and Other Psoriasis Treatments From the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *Journal of drugs in dermatology : JDD.* 2015;14(7):706-714.
121. Menter A, Papp KA, Gooderham M, et al. Drug survival of biologic therapy in a large, disease-based registry of patients with psoriasis: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *J Eur Acad Dermatol Venereol.* 2016;30(7):1148-1158.
122. Wu JJ, Guerin A, Sundaram M, Dea K, Cloutier M, Mulani P. Cardiovascular event risk assessment in psoriasis patients treated with tumor necrosis factor-alpha inhibitors versus methotrexate. *J Am Acad Dermatol.* 2017;76(1):81-90.
123. Gulliver WP, Young HM, Bachelez H, Randell S, Gulliver S, Al-Mutairi N. Psoriasis Patients Treated With Biologics and Methotrexate Have a Reduced Rate of Myocardial Infarction: A Collaborative Analysis Using International Cohorts. *J Cutan Med Surg.* 2016;20(6):550-554.

124. Hu SC, Lan CE. Psoriasis and Cardiovascular Comorbidities: Focusing on Severe Vascular Events, Cardiovascular Risk Factors and Implications for Treatment. *Int J Mol Sci.* 2017;18(10).
125. Rungapiromnan W, Yiu ZZN, Warren RB, Griffiths CEM, Ashcroft DM. Impact of biologic therapies on risk of major adverse cardiovascular events in patients with psoriasis: systematic review and meta-analysis of randomized controlled trials. *The British journal of dermatology.* 2017;176(4):890-901.
126. Gelfand JM. Does biologic treatment of psoriasis lower the risk of cardiovascular events and mortality? A critical question that we are only just beginning to answer. *J Am Acad Dermatol.* 2018.
127. Amin M, No DJ, Egeberg A, Wu JJ. Choosing First-Line Biologic Treatment for Moderate-to-Severe Psoriasis: What Does the Evidence Say? *Am J Clin Dermatol.* 2018;19(1):1-13.
128. Papp KA, Blauvelt A, Bukhalo M, et al. Risankizumab versus Ustekinumab for Moderate-to-Severe Plaque Psoriasis. *N Engl J Med.* 2017;376(16):1551-1560.
129. Woolacott N, Hawkins N, Mason A, et al. Etanercept and efalizumab for the treatment of psoriasis: a systematic review. *Health technology assessment (Winchester, England).* 2006;10(46):1-233, i-iv.
130. Warren RB, Barker J, Burden AD, et al. Secukinumab has demonstrated efficacy and safety in hard-to-treat anti-TNFα failure patients from the UK and Republic of Ireland: Results of the SIGNATURE study. Annual Meeting of the American Academy of Dermatology; February 16-20, 2018; San Diego, CA.
131. Griffiths CEM, Radtke MA, Youn SW, et al. Clinical response after guselkumab treatment among adalimumab PASI 90 non-responders: results from the VOYAGE 1 and 2 trials. Annual meeting of the American Academy of Dermatology; February 16-20, 2018; San Diego, CA.
132. Papp K, Gordon K, Langley R, et al. Impact of previous biologic use on efficacy and safety of brodalumab and ustekinumab in patients with moderate-to-severe plaque psoriasis: integrated analysis of AMAGINE-2 and AMAGINE-3. *British Journal of Dermatology.* 2018.
133. No DJ, Inkeles MS, Amin M, Wu JJ. Drug survival of biologic treatments in psoriasis: a systematic review. *J Dermatolog Treat.* 2017:1-7.
134. 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.
135. SSRHealth. US Brand Rx Net Price. *Access-restricted document.* 2018.
136. Wiatrowski A, Stockman C, Reimers K, et al. *Medical Pharmacy Trends Report.* Scottsdale, AZ: Magellan Rx Management;2015.
137. Yu AP, Tang J, Xie J, et al. Economic burden of psoriasis compared to the general population and stratified by disease severity. *Curr Med Res Opin.* 2009;25(10):2429-2438.
138. Egeberg A, Ottosen MB, Gniadecki R, et al. Safety, efficacy and drug survival of biologics and biosimilars for moderate-to-severe plaque psoriasis. *The British journal of dermatology.* 2018;178(2):509-519.
139. 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.
140. 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.

141. Bureau of Labor Statistics. May 2015 National Occupational Employment and Wage Estimates United States. *Occupational Employment Statistics.* 2015. http://www.bls.gov/oes/current/oes_nat.htm#00-0000.
142. Reich K, Ortonne JP, Gottlieb AB, et al. Successful treatment of moderate to severe plaque psoriasis with the PEGylated Fab' certolizumab pegol: results of a phase II randomized, placebo-controlled trial with a re-treatment extension. *British Journal of Dermatology.* 2012;167(1):180-190.
143. Kimball A, Papp K, Tyring S, et al. Efficacy of tildrakizumab, an anti-IL23p19 monoclonal antibody, stratified by prior exposure to biologics in a randomized, placebo-controlled phase 3 clinical trial. *Journal of the American Academy of Dermatology.* 2017;76(6):AB121.
144. Reich K, Papp K, Thaçi D, et al. Safety and tolerability of tildrakizumab, an anti-IL-23p19 monoclonal antibody, in patients with chronic plaque psoriasis over two years of treatment: results from long-term extensions of two phase III clinical studies (reSURFACE 1 and reSURFACE 2). 2018.
145. Gordon KB, Duffin KC, Bissonnette R, et al. A Phase 2 Trial of Guselkumab versus Adalimumab for Plaque Psoriasis. *New England Journal of Medicine.* 2015;373(2):136-144.
146. Langley RG, Tsai TF, Flavin S, et al. Efficacy and safety of guselkumab in patients with psoriasis who have an inadequate response to ustekinumab: Results of the randomized, double-blind, phase III NAVIGATE trial. *British Journal of Dermatology.* 2017.
147. Burge RT, Papadimitropoulos M, Henneges C, Garcia EG, Romiti R. Ixekizumab treatment leads to early resolution of bothersome symptoms versus ustekinumab. *Value in Health.* 2017;20(9):A902.
148. 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.
149. 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.
150. 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.
151. 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.
152. 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 (Basel, Switzerland).* 2012;225(4):312-319.
153. Gisondi P, Cotena C, Tessari G, Girolomoni G. Anti-tumour necrosis factor-alpha therapy increases body weight in patients with chronic plaque psoriasis: a retrospective cohort study. *J Eur Acad Dermatol Venereol.* 2008;22(3):341-344.
154. Blauvelt A, Reich K, Mehlis S, et al. Secukinumab demonstrates greater sustained improvements in daily activities and personal relationships than ustekinumab in patients with moderate-to-severe plaque psoriasis: 52-week results from the CLEAR study. *Journal of the European Academy of Dermatology and Venereology.* 2017;31(10):1693-1699.
155. Thaci D, Kimball A, Foley P, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, improves patient-reported outcomes in the treatment of moderate to severe psoriasis: results of two

phase III randomized, controlled trials. *Journal Of The European Academy Of Dermatology And Venereology : JEADV.* 2016(pagination).
156. Lacour JP, Paul C, Jazayeri S, et al. Secukinumab administration by autoinjector maintains reduction of plaque psoriasis severity over 52 weeks: results of the randomized controlled JUNCTURE trial. *Journal of the European Academy of Dermatology and Venereology.* 2017;31(5):847-856.
157. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. *N Engl J Med.* 2014;371(4):326-338.
158. 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.
159. 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.
160. 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.
161. Wu NL, Hsu CJ, Sun FJ, Tsai TF. Efficacy and safety of secukinumab in Taiwanese patients with moderate to severe plaque psoriasis: Subanalysis from ERASURE phase III study. *Journal of Dermatology.* 2017;44(10):1129-1137.
162. Sigurgeirsson B, Gottlieb AB, Langley RG, et al. Effect of secukinumab on psoriasis symptoms and physical functioning compared with placebo and etanercept in subjects with moderate-to-severe plaque psoriasis and concomitant psoriatic arthritis: A subanalysis from the phase 3 fixture study. *Scandinavian Journal Of Rheumatology.* 2014;43:64-65.
163. 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.
164. Lee JH, Morita A, Tsai TF, et al. Secukinumab efficacy and safety in Asian subjects with moderate to severe plaque psoriasis: Pooled analysis from the FIXTURE and ERASURE phase III clinical studies. *Journal of the American Academy of Dermatology.* 2015;72(5 SUPPL. 1):AB249.
165. van de Kerkhof PC, Griffiths CE, Reich K, et al. Secukinumab long-term safety experience: A pooled analysis of 10 phase II and III clinical studies in patients with moderate to severe plaque psoriasis. *Journal of the American Academy of Dermatology.* 2016;75(1):83-98.e84.
166. 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.
167. 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.
168. Imafuku S, Torisu-Itakura H, Nishikawa A, Zhao F, Cameron GS. Efficacy and safety of ixekizumab treatment in Japanese patients with moderate-to-severe plaque psoriasis: Subgroup analysis of a placebo-controlled, phase 3 study (UNCOVER-1). *Journal of Dermatology.* 2017;44(11):1285-1290.
169. 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.

170. Blauvelt A, Gooderham M, Iversen L, et al. Efficacy and safety of ixekizumab for the treatment of moderate-to-severe plaque psoriasis: results through 108 weeks of a randomized, controlled phase 3 clinical trial (UNCOVER-3). *Journal Of The American Academy Of Dermatology.* 2017.
171. Leonardi C, Maari C, Philipp S, et al. Long-term Efficacy and Safety of Ixekizumab for the Treatment of Moderate-to-Severe Plaque Psoriasis Sustained for 3 Years: Results of a Randomized, Controlled Phase 3 Study (UNCOVER-3). 2018.
172. Gottlieb AB, Lacour JP, Korman N, et al. Treatment outcomes with ixekizumab in patients with moderate-to-severe psoriasis who have or have not received prior biological therapies: an integrated analysis of two Phase III randomized studies. *Journal Of The European Academy Of Dermatology And Venereology : JEADV.* 2016.
173. Guenther L, Warren RB, Cather JC, et al. Impact of ixekizumab treatment on skin-related personal relationship difficulties in moderate-to-severe psoriasis patients: 12-week results from two Phase 3 trials. *Journal of the European Academy of Dermatology and Venereology.* 2017;31(11):1867-1875.
174. Kimball AB, Luger T, Gottlieb A, et al. Impact of ixekizumab on psoriasis itch severity and other psoriasis symptoms: Results from 3 phase III psoriasis clinical trials. *Journal of the American Academy of Dermatology.* 2016;75(6):1156-1161.
175. 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-to-severe psoriasis. *Journal of the American Academy of Dermatology.* 2016;74(5):AB253.
176. 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.
177. 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. *Journal of Investigative Dermatology.* 2015;135:S26.
178. Papp KA, Leonardi C, Menter A, et al. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *New England Journal of Medicine.* 2012;366(13):1181-1189.
179. Papp K, Leonardi C, Menter A, et al. Maintenance of clinical response with long-term brodalumab (AMG 827) therapy for psoriasis: Week 144 results from an open-label extension study. *Australasian Journal Of Dermatology.* 2015;56(52).
180. 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.
181. 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.
182. 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.
183. Lebwohl M, Strober B, Menter A, et al. Phase 3 Studies Comparing Brodalumab with Ustekinumab in Psoriasis. *New England Journal of Medicine.* 2015;373(14):1318-1328.
184. Umezawa Y, Nakagawa H, Niiro H, Ootaki K, Japanese Brodalumab Study G. Long-term clinical safety and efficacy of brodalumab in the treatment of Japanese patients with moderate-to-severe plaque psoriasis. *J Eur Acad Dermatol Venereol.*30(11):1957-1960.

185. Langley R, Lebwohl M, Krueger G, et al. Long-term efficacy and safety of ustekinumab, with and without dosing adjustment, in patients with moderate-to-severe plaque psoriasis: results from the PHOENIX 2 study through 5 years of follow-up. *British Journal of Dermatology.* 2015;172(5):1371-1383.
186. 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.
187. 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. *J Dermatolog Treat.* 2011;22(6):337-347.
188. 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.
189. 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.
190. Zhang W, Islam N, Ma C, Anis AH. Systematic review of cost-effectiveness analyses of treatments for psoriasis. *PharmacoEconomics.* 2015;33(4):327-340.
191. 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. *Archives of Dermatology.* 2012;148(4):487-494.
192. 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.
193. 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.
194. Iskandar IYK, Ashcroft DM, Warren RB, et al. Comparative effectiveness of biological therapies on improvements in quality of life in patients with psoriasis. *British Journal of Dermatology.* 2017;177(5):1410-1421.
195. 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.
196. Papp KA, Langley RG, Sigurgeirsson B, et al. Efficacy and safety of secukinumab in the treatment of moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled phase II dose-ranging study. *The British journal of dermatology.* 2013;168(2):412-421.
197. 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.
198. Crowley J, Thaci D, Joly P, et al. Long-term safety and tolerability of apremilast in patients with psoriasis: pooled safety analysis for >156 weeks from 2 phase 3, randomized, controlled trials (ESTEEM 1 and 2). *Journal Of The American Academy Of Dermatology.* 2017(pagination).
199. 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.
200. Reich K, Gooderham M, Bewley A, et al. Safety and efficacy of apremilast through 104 weeks in patients with moderate to severe psoriasis who continued on apremilast or switched from etanercept treatment: findings from the LIBERATE study. *J Eur Acad Dermatol Venereol.* 2017.
201. 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.
202. Ohtsuki M, Okubo Y, Komine M, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in the treatment of Japanese patients with moderate to severe plaque psoriasis: Efficacy, safety and tolerability results from a phase 2b randomized controlled trial. *Journal of Dermatology.* 2017;44(8):873-884.
203. National Institute for Health and Care Excellence (NICE). Brodalumab for treating moderate to severe plaque psoriasis. 2018;Technology appraisal guidance.
204. Ramaekers BLT, Wolff RF, Pouwels X, et al. Ixekizumab for Treating Moderate-to-Severe Plaque Psoriasis: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. *PharmacoEconomics.* 2018.
205. Hinde S, Wade R, Palmer S, Woolacott N, Spackman E. Apremilast for the Treatment of Moderate to Severe Plaque Psoriasis: A Critique of the Evidence. *PharmacoEconomics.* 2016;34(6):587-596.
206. National Institute for Health and Care Excellence (NICE). Secukinumab for treating moderate to severe plaque psoriasis. In*.* Vol TA350. 22 July 2015 ed: NICE; 2015.
207. Turner D, Picot J, Cooper K, Loveman E. Adalimumab for the treatment of psoriasis. *Health technology assessment (Winchester, England).* 2009;13 Suppl 2:49-54.
208. Loveman E, Turner D, Hartwell D, Cooper K, Clegg A. Infliximab for the treatment of adults with psoriasis. *Health technology assessment (Winchester, England).* 2009;13 Suppl 1:55-60.
209. Gospodarevskaya E, Picot J, Cooper K, Loveman E, Takeda A. Ustekinumab for the treatment of moderate to severe psoriasis. *Health technology assessment (Winchester, England).* 2009;13 Suppl 3:61-66.
210. (NICE) NIfHaCE. Etanercept and efalizumab for the treatment of adults with psoriasis. 2006.
211. U.S. Preventive Services Task Force. *Procedure Manual.* Agency for Healthcare Research and Quality;2008.
212. Dias S, Sutton AJ, Welton NJ, Ades AE. Evidence synthesis for decision making 3: heterogeneity--subgroups, meta-regression, bias, and bias-adjustment. *Med Decis Making.* 2013;33(5):618-640.
213. 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.
214. Nakagawa H, Niiro H, Ootaki K, Japanese brodalumab study g. Brodalumab, a human anti-interleukin-17-receptor antibody in the treatment of Japanese patients with moderate-to-severe plaque psoriasis: Efficacy and safety results from a phase II randomized controlled study. *J Dermatol Sci.*81(1):44-52.
215. Mrowietz U, Leonardi C, Girolomoni G, et al. Secukinumab retreatment-as-needed versus fixed-interval maintenance regimen for moderate to severe plaque psoriasis: a randomized, double-

blind, noninferiority trial (SCULPTURE). *Journal of the American Academy of Dermatology.* 2015;73(1):27-36.
216. Bissonnette R, Luger T, Thac¸i D, et al. Secukinumab sustains good efficacy and favourable safety in moderate to severe psoriasis patients up to 3 years of treatment: results from a double-blind extension study. *British Journal of Dermatology.* 2017;177(4):1033-1042.
217. Gordon K, Menter A, Ferris L, et al. Consistency of response (PASI 90 or 100 and IGA 0/1 or 0) in patients with moderate to severe psoriasis treated with guselkumab: results from the VOYAGE 1 and 2 trials. Annual meeting of the American Academy of Dermatology; February 16-20, 2018; San Diego, CA.
218. Cao Z, Carter C, Wilson KL, Schenkel B. Ustekinumab dosing, persistence, and discontinuation patterns in patients with moderate-to-severe plaque psoriasis. *J Dermatolog Treat.* 2015;26(2):113-120.
219. Feldman S, Zhao Y, Gray S, Montejano L, Lin F, Herrera V. Adherence and persistence among U.S. patients initiating secukinumab for the treatment of moderate to severe psoriasis. 2017.
220. Bagel J, Liao W, Palmer J, et al. Persistence and adherence of secukinumab and subcutaneously administered anti-TNF treatments among biologic-naive and biologic experienced patients with plaque psoriasis: analyses from a US claims database. 2017.

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. Updated Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials on the 2016 Review

1	Psoriasis/	18421
2	psoria$.ti,ab.	28290
3	(secukinumab or cosentyx).ti,ab.	518
4	(ustekinumab or stelara).ti,ab.	979
5	(ixekizumab or taltz).ti,ab.	234
6	brodalumab.ti,ab.	138
7	(apremilast or otezla).ti,ab.	334
8	1 or 2	30099
9	3 or 4 or 5 or 6 or 7	1953
10	8 and 9	1541
11	limit 10 to english language	1468
12	limit 11 to humans	1467
13	(abstract or addresses or autobiography or bibliography or biography or clinical trial, phase I or case report or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video-audio media).pt.conference or congresses).pt.	3057911
14	12 not 13	1059
15	remove duplicates from 14	884
16	limit 15 to ed=20160628-20180102	632
Date of Search: January 2, 2018		

Table A3. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials on New Drugs

1	Psoriasis/	18421
2	psoria$.ti,ab.	28290
3	(certolizumab pegol or cimzia).ti,ab.	647
4	(guselkumab or tremfya).ti,ab.	42
5	tildrakizumab.ti,ab.	28
6	risankizumab.ti,ab.	15
7	1 or 2	30099
8	3 or 4 or 5 or 6	705
9	7 and 8	154
10	limit 9 to english language	152
11	limit 10 to humans	152
12	(guideline or practice guideline or letter or editorial or news or case reports or clinical conferences or congresses).pt	2049847

13	11 not 12	149
14	remove duplicates from 13	129
Date of Search: January 2, 2018		

Table A4. Updated Search Strategy in EMBASE on the 2016 Review

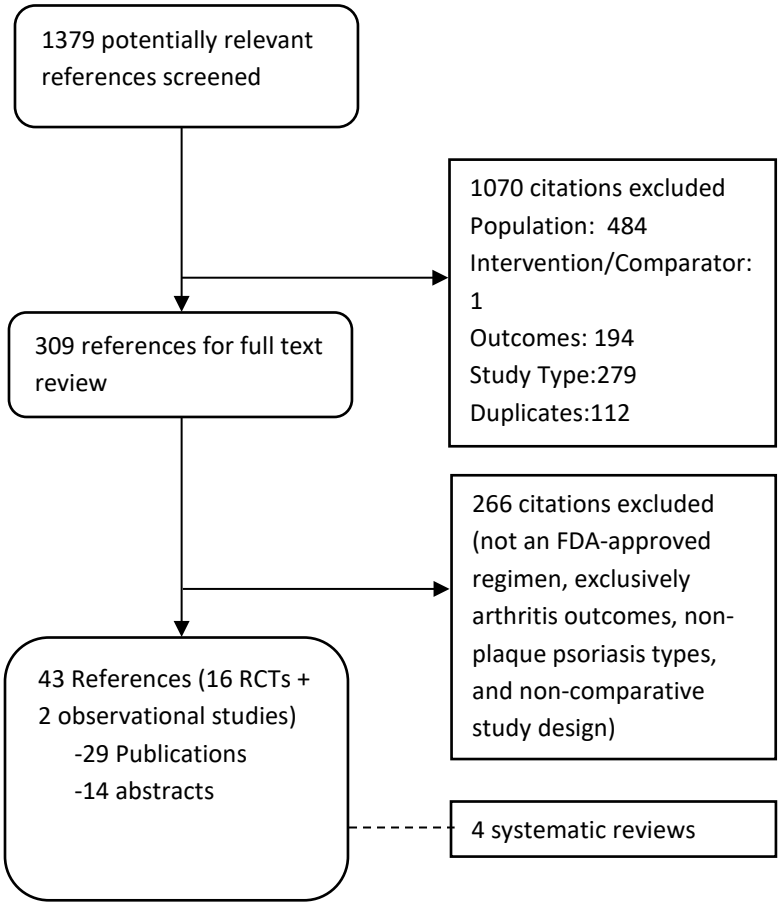
1	'psoriasis vulgaris'	8040
2	psorias*:ab,ti OR psoriat*:ab,ti	57572
3	#1 OR #2	58457
4	'secukinumab':ab,ti OR 'cosentyx':ab,ti	399
5	'ustekinumab':ab,ti OR 'stelara':ab,ti	1454
6	'ixekizumab':ab,ti OR 'taltz':ab,ti	156
7	'apremilast':ab,ti OR 'otezla':ab,ti	331
8	'brodalumab':ab,ti	127
9	#4 OR #5 OR #6 OR #7 OR #8	2235
10	#3 AND #9	1805
11	#3 AND #9 AND ([editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim)	122
12	#10 NOT #11	1683
13	#12 AND [english]/lim	1622
14	#12 AND [medline]/lim	413
15	#13 NOT #14	1224
16	#15 AND [animals]/lim	40
17	#15 AND [humans]/lim AND [animals]/lim	32
18	#15 NOT #16 NOT #17	1184
19	#18 NOT 'case report' NOT 'case study'	1679
20	#19 AND [humans]/lim	1568
21	#20 AND [28-6-2016]/sd	712
Date of Search: January 2, 2018		

Table A5. Search Strategy in EMBASE on New Drugs

1	'psoriasis vulgaris'	8040
2	psorias*:ab,ti OR psoriat*:ab,ti	57572
3	#1 OR #2	58457
4	'guselkumab':ab,ti OR 'tremfya':ab,ti	61
5	'tildrakizumab':ab,ti	40
6	'certolizumab pegol':ab,ti OR 'cimzia':ab,ti	1463
7	‘risankizumab’:ab,ti	21
8	#4 OR #5 OR #6 OR #7	1546
9	#3 AND #8	1805
10	#3 AND #8 AND ([editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim)	122
11	#9 NOT #8	1683

12	#11 AND [english]/lim	1622
13	#11 AND [medline]/lim	413
14	#12 NOT #13	1224
15	#14 AND [animals]/lim	40
16	#14 AND [humans]/lim AND [animals]/lim	32
17	#14 NOT #15 NOT #16	1184
18	#17 NOT 'case report' NOT 'case study'	1679
19	#18 AND [humans]/lim	211
Date of Search: January 2, 2018		

Figure A1. PRISMA Flow Chart Showing Results of Literature Search



Appendix B. Evidence Summary Tables

Table B1. Evidence Summary Tables for New Drugs

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
TNFα inhibitors						
Certolizumab Pegol						
Reich, 2012[142] **(NCT00245765)** ***Good quality publication***	Phase II, randomized, controlled, double-blind multicenter trial 15 sites in France and Germany ITT, NRI	1) Certolizumab 200 mg q2w after 400 mg at weeks 0, 2, and 4 (n=59) 2) Certolizumab 400 mg q2w (n=58) 3) Placebo (n=59)	Inclusion: Adult patients (>18 years) with moderate-to-severe plaque psoriasis (PASI ≥12, BSA ≥10%) who were candidates for systematic therapy or phototherapy Exclusion: Other major forms of psoriasis; previous or recent serious infection; any disease that that could be impacted by certolizumab or the investigator thinks will make the subject unsuitable for inclusion	Age, mean 1)43.3; 2)43.6; 3)43.3 Male, % 1)75.0; 2)72.0; 3)63.0 Caucasian, % 1)97; 2)100; 3)97 Duration of PsO, years 1)21.0; 2)19.6; 3)19.7 With PsA, % NR Previous TNFα, % 1)22.0; 2)24.0; 3)23.0 PGA severe, % 1)36; 2)30; 3)36 PASI, mean (SD) 1)21.4 (8.8) 2)22.0 (8.1) 3)22.6 (8.8)	**At 12 weeks** PASI 75, %: 1)74.6; 2)82.8; 3)6.6 PASI 90, % 1)39.0; 2)46.6; 3)1.7 PGA 0/1, % 1)52.5; 2)72.4; 3)1.7 *For all above, p<0.001 for certolizumab 200 mg and 400 mg vs. placebo* DLQI 0/1, % 1)56.6; 2)68.6; 3)15.0 DLQI change from baseline, mean 1)-8.3; 2)-9.9; 3)-0.8	**0-12 weeks** Any AE, %: 1)72 2)71 3)70 Serious AE, %: 1)3 2)5 3)2 AE leading to discontinuation, % 1)3 2)4 3)5 Infection, % 1)2 2)4 3)0

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Gottlieb, 2018[90] **(NCT02326298)** **CIMPASI-1** ***Good quality publication***	Phase III, double-blind, placebo-controlled, multicenter trial Sites in North America and Europe ITT, MI & LOCF	1) Certolizumab 200 mg q2w after 400 mg at weeks 0, 2, and 4 (n=95) 2) Certolizumab 400 mg q2w (n=88) 3) Placebo (n=51) At 16 weeks, patients continued to receive treatment to 48 weeks based on their PASI response: All patients on certolizumab with PASI 50 response continued treatment; placebo PASI 75 responders continued placebo; placebo PASI 50-75 responders received 200 mg; all PASI 50 non-responders entered escape arm and received unblinded 400mg	Inclusion: Adult patients (≥18 years) with moderate-to-severe plaque psoriasis (PASI ≥12, BSA ≥10%, PGA≥3 on a 5-point scale) who were candidates for systematic therapy or phototherapy Exclusion: Previous treatment with certolizumab or >2 biologics (including TNFα); history of primary failure to any biologic or secondary failure to >1 biologic; erythrodermic, guttate, or generalized pustular form of psoriasis	Age, mean 1)44.5; 2)43.6; 3)47.9 Male, % 1)70.5; 2)68.2; 3)68.6 Caucasian, % 1)91.6; 2)89.8; 3)88.2 Duration of PsO, years 1)16.6; 2)18.4; 3)18.5 With PsA, % 1)10.5; 2)17.0; 3)7.8 Previous biologic, % 1)31.6; 2)33.0; 3)29.4 PGA severe(4), % 1)34.7; 2)26.1; 3)31.4 PASI, mean (SD) 1)20.1 (8.2) 2)19.6 (7.9) 3)19.8 (7.5) DLQI, mean (SD) 1)13.3 (7.4) 2)13.1 (6.5) 3)13.9 (8.3)	**At 16 weeks** PASI 75, % 1)66.5; 2)75.8; 3)6.5 PASI 90, % 1)35.8; 2)43.6; 3)0.4 PGA 0/1, % 1)47.0; 2)57.9; 3)4.2 DLQI, change from baseline, mean 1)-8.9; 2)-9.6; 3)-3.3 *For all above, p<0.0001 for certolizumab 200 mg & 400 mg vs. placebo*	**0-16 weeks** Any TEAE, % (IR/100PY) 1)54.7 (292.3) 2)64.8 (375.9) 3)54.9 (279.1) Serious AE, % (IR/100PY) 1)2.1 (6.9) 2)5.7 (19.0) 3)2.0 (6.8) TEAE leading to discontinuation, % 1)0 2)2.3 3)0 Serious infection, % (IR/100PY) 1)0 2)0 3)0 Malignancy, % (IR/100PY) 1)0 2)0 3)0 Depression, % (IR/100PY) 1)0 2)1.1 (3.7) 3)0

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Gottlieb, 2018[90] **(NCT02326272)** **CIMPASI-2** ***Good quality publication***	Phase III, double-blind, placebo-controlled, multicenter trial Sites in North America and Europe ITT, MI	1) Certolizumab 200 mg q2w after 400 mg at weeks 0, 2, and 4 (n=91) 2) Certolizumab 400 mg q2w (n=87) 3) Placebo (n=49) At 16 weeks, patients continued to receive treatment to 48 weeks based on their PASI response: All patients on certolizumab with PASI 50 response continued treatment; placebo PASI 75 responders continued placebo; placebo PASI 50-75 responders received 200 mg; all PASI 50 non-responders entered escape arm and received unblinded 400mg	*See CIMPASI-1*	Age, mean 1)46.7; 2)46.4; 3)43.3 Male, % 1)63.7; 2)49.4; 3)53.1 Caucasian, % 1)94.5; 2)93.1; 3)89.8 Duration of PsO, years 1)18.8; 2)18.6; 3)15.4 With PsA, % 1)24.2; 2)29.9; 3)18.4 Previous biologic, % 1)35.2; 2)34.5; 3)28.6 PGA severe(4), % 1)27.5; 2)29.9; 3)24.5 PASI, mean (SD) 1)18.4 (5.9) 2)19.5 (6.7) 3)17.3 (5.3) DLQI, mean (SD) 1)15.2 (7.2) 2)14.2 (7.2) 3)12.9 (7.3)	**At 16 weeks** PASI 75, % 1)81.4; 2)82.6; 3)11.6 PASI 90, % 1)52.6; 2)55.4; 3)4.5 PGA 0/1, % 1)66.8; 2)71.6; 3)2.0 DLQI, change from baseline, mean 1)-11.1 2)-10.0; 3)-2.9 *For all above, p<0.0001 for certolizumab 200 mg & 400 mg vs. placebo*	**0-16 weeks** Any TEAE, % (IR/100PY) 1)60.0 (308.7) 2)69.0 (405.7) 3)67.3 (388.9) Serious AE, % (IR/100PY) 1)2.2 (7.4) 2)4.6 (15.3) 3)0 TEAE leading to discontinuation, % 1)3.3 2)1.1 3)0 Serious infection, % (IR/100PY) 1)0 2)1.1 (3.8) 3)0 Malignancy, % (IR/100PY) 1)0 2)1.1 (3.8) 3)0 Depression, % (IR/100PY) 1)1.1 (3.7) 2)1.1 (3.8) 3)0

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Lebwohl 2018[91] **(NCT02346240)** **CIMPACT** ***Good quality publication***	Phase III, double-blind, placebo- and active-controlled multicenter trial ITT, MI	1) Certolizumab 200 mg q2w after 400 mg at weeks 0, 2, and 4 (n=165) 2) Certolizumab 400 mg q2w (n=167) 3) Etanercept 50 mg BIW (n=170) 4) Placebo (n=57) Etanercept was single-blind (outcomes assessor). At week 16, patients achieving PASI 75 in the certolizumab arms were rerandomized to continue treatment or receive placebo. Patients achieving PASI 75 in the placebo arm continued to receive placebo, and patients achieving PASI 75 in the etanercept arm were rerandomized to certolizumab 200 mg or placebo. PASI 75 nonresponders entered the escape arm and received certolizumab 400 mg.	Inclusion: Adult patients (≥18 years) with moderate-to-severe chronic plaque psoriasis for ≥6 months and PASI ≥12, BSA ≥10%, PGA≥3 at baseline who were candidates for systematic therapy, phototherapy, or photochemotherapy Exclusion: Previous treatment with certolizumab (or etanercept or > 2 biologics (including TNFα); history of primary failure to any biologic or secondary failure to >1 biologic; erythrodermic, guttate, or generalized pustular form of psoriasis	Age, mean 1)46.7; 2)45.4; 3)44.6; 4)46.5 Male, % 1)68.5; 2)64.1; 3)74.7; 4)59.6 Caucasian, % 1)95.8; 2)97.0; 3)95.9; 4)100 Duration of PsO, years 1)19.5; 2)17.8; 3)17.4; 4)18.9 With PsA, % 1)16.4; 2)14.4; 3)15.9; 4)21.1 Previous biologic, % 1)26.7; 2)28.7; 3)30.0; 4)19.3 PGA, severe(4), % 1)30.9; 2)32.3; 3)32.4; 4)29.8 PASI, mean (SD) 1)21.4 (8.8); 2)20.8 (7.7) 3)21.0 (8.2); 4)19.1 (7.1) DLQI, mean (SD) 1)12.8 (7.0); 2)15.3 (7.3) 3)14.1 (7.4); 4)13.2 (7.6)	**At 12 weeks** PASI 75, % 1)61.3; 2)66.7; 3)53.3; 4) 5.0, *p=0.015 for certolizumab 400 mg vs. etanercept* PASI 90, % 1)31.2; 2)34.0; 3)27.1; 4)0.2 PGA 0/1, % 1)39.8; 2)50.3; 3)39.2; 4)1.9, *p<0.05 for certolizumab 200 mg vs. placebo* **At 16 weeks** PASI 75, % 1)68.2; 2)74.7; 4)3.8 PASI 90, % 1)39.8; 2)49.1; 4)0.3 PGA 0/1, % 1)48.3; 2)58.4; 4)3.4 *For all above, p<0.0001 for certolizumab 200 mg and 400 mg vs. placebo unless otherwise stated*	**0-12 weeks** Any TEAE, % (IR/100PY) 1)47.3 (299.5) 2)49.1 (309.2) 3)46.4 (295.6) 4)56.1 (393.3) Serious AE, % (IR/100PY) 1)0.6 (2.7) 2)2.4 (10.6) 3)0.6 (2.7) 4)8.8 (41.0) AE leading to discontinuation, % 1)0.6 2)0.6 3)2.4 4)0 Serious infection, % (IR/100PY) 1)0 2)0.6 (2.6) 3)0 4)0 Malignancy, % (IR/100PY) 1)0; 2)0; 3)0; 4)0 Depression, % (IR/100PY) 1)0.6 (2.7); 2)0; 3)0; 4)0

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Anti-IL-23 Agents						
Tildrakizumab						
Reich, 2017[107] **(NCT01722331)** **reSURFACE 1** ***Good quality publication***	Phase III, randomized, controlled, double-blind, parallel-group, multicenter trial 118 global sites FAS, NRI	1) Tildrakizumab 200 mg (n=308) 2) Tildrakizumab 100 mg (n=309) 3) Placebo (n=155) Tildrakizumab was given at weeks 0, 4 and subsequently every 12 weeks. Patients on placebo crossed over to tildrakizumab at week 12 through week 28 followed by randomized treatment withdrawal through week 64 for all patients.	Inclusion: Adult patients (≥18 years) with moderate-to-severe chronic plaque psoriasis (PGA ≥3, PASI≥12, BSA ≥10%) at baseline who were candidates for systematic therapy or phototherapy Exclusion: Severe infection (within 2 weeks); live vaccination (within 4 weeks); active or latent TB; previous malignancy; previous use of any anti-IL-23 or anti-IL-17 agents	Age, mean 1)46.9; 2)46.4; 3)47.9 Male, % 1)73.0; 2)67.0; 3)65.0 Caucasian, % 1)68.0; 2)70.0; 3)65.0 Previous biologics, % 1)23.0; 2)23.0; 3)23.0 Duration of PsO & w/PsA NR PASI, mean (SD) 1)20.7 (8.5); 2)20.0 (7.9); 3)19.3 (7.1) DLQI, mean (SD) 1)13.2 (6.9); 2)13.9 (6.7) 3)13.2 (7.3)	**At 12 weeks** PASI 75, % 1)62.0; 2)64.0; 3)6.0 PASI 90, % 1)35.0; 2)35.0; 3)3.0 PASI 100, % 1)14.0; 2)14.0; 3)1.0 PGA 0/1, % 1)59.0; 2)58.0; 3)7.0 DLQI 0/1, % 1)44.0; 2)42.0; 3)5.0 *For all above, p<0.0001 for tildrakizumab 200 mg and 100 mg vs. placebo*	**0-12 weeks** Any AE, %: 1)42; 2)47; 3)48 Serious AE, %: 1)3; 2)2; 3)1 AE leading to discontinuation, % 1)2; 2)0; 3)1 Severe infection, % 1)<1; 2) <1; 3)0 MACE, % 1)0; 2)<1; 3)0
Kimball, 2017 [143] **(NCT01722331)** **reSURFACE 1** ***Abstract***	*Subgroup analysis of reSURFACE 1: previous vs. no previous biologic use*	1) Tildrakizumab 200 mg (n=308) 2) Tildrakizumab 100 mg (n=309) 3) Placebo (n=155)	*See Reich, 2017*[107]	*See Reich, 2017*[107]	**At 12 weeks** *Prior biologic* PASI 75, % 1)56; 2)55; 3)0, *p=NR* PGA 0/1, % 1)51; 2)49; 3)3, *p=NR* *No prior biologic* PASI 75, % 1)64; 2)66; 3)8, *p=NR* PGA 0/1, % 1)62; 2)61; 3)8, *p=NR*	NR

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Reich, 2017[107] **(NCT01729754)** **reSURFACE 2** ***Good quality publication***	Phase III, randomized, controlled, double-blind, parallel-group, multicenter trial 132 global sites FAS, NRI	1) Tildrakizumab 200 mg (n=314) 2) Tildrakizumab 100 mg (n=307) 3) Etanercept 50 mg BIW (n=313) 4) Placebo (n=156) *Same dosing schedule as reSURFACE 1 except patients receiving etanercept reduced dosing to once weekly at week 12.*	*Same inclusion and exclusion criteria as reSURFACE 1* Reich, 2017[107] *except reSURFACE 2 also excluded patients with previous etanercept use.*	Age, mean 1)44.6; 2)44.6; 3)45.8; 4)46.4 Male, % 1)72.0; 2)72.0; 3)71.0; 4)72.0 Caucasian, % 1)90.0; 2)91.0; 3)92.0; 4)92.0 Duration of PsO, years NR With PsA, % NR Previous biologics, % 1)12.0; 2)13.0; 3)12.0; 4)13.0 PASI, mean (SD) 1)19.8 (7.5) 2)20.5 (7.6) 3)20.2 (7.4) 4)20.0 (7.6) DLQI, mean (SD) 1)13.2 (7.0) 2)14.8 (7.2) 3)14.5 (7.2) 4)13.7 (7.0)	**At 12 weeks** PASI 75, % 1)66.0; 2)61.0; 3)48.0; 4)6.0 PASI 90, % 1)37.0; 2)39.0; 3)21.0; 4)1.0 PASI 100, % 1)12.0; 2)12.0; 3)5.0; 4)0 *For all above, p<0.0001 for tildrakizumab 200 mg and 100 mg vs. placebo & p≤0.001 for tildrakizumab 200 mg and 100 mg vs. etanercept.* PGA 0/1, % 1)59.0; 2)55.0; 3)48.0; 4)4.0 DLQI 0/1, % 1)47.0; 2)40.0; 3)36.0; 4)8.0 *For all above, p<0.0001 for tildrakizumab 200 mg and 100 mg vs. placebo*	**0-12 weeks** Any AE, %: 1)49 2)44 3)54 4)55 Serious AE, %: 1)2 2)1 3)2 4)3 AE leading to discontinuation, % 1)1 2)1 3)2 4)1 Severe infection, % 1)<1 2)0 3)0 4)<1 Malignancies, % 1)<1 2)<1 3)<1 4)0 Deaths, % 1)0; 2)<1; 3)0; 4)0

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Reich, 2018 [144] **(NCT01722331 & NCT01729754)** **reSURFACE -1 & -2** ***Abstract***	Phase III, randomized, controlled, double-blind, parallel-group, multicenter trials	Patients who completed reSURFACE -1 or -2 base studies and achieved at least PASI 50 received tildrakizumab in an OLE. reSURFACE 1 1) Tildrakizumab 100 mg (n=256) 2) Tildrakizumab 200 mg (n=267) reSURFACE 2 3) Tildrakizumab 100 mg (n=399) 4) Tildrakizumab 200 mg (n=454)	*See Reich, 2017*[107]	*See Reich, 2017*[107]	NR	**0-104 weeks** Total PYs 1)662.3; 2)750.0; 3)825.9; 4)807.2 Severe infections, EAR/100 PY 1)0.8; 2)0.8; 3)0.8; 4)1.1 Malignancies, EAR/100 PY 1)0.9; 2)0.3; 3)0.5; 4)0.9 NMSC, EAR/100 PY 1)0.3; 2)0.3; 3)0.4; 4)0.5 MACE, EAR/100 PY 1)0.5; 2)0.3; 3)0.0; 4)0.1 Death, EAR/100 PY 1)0.0; 2)0.0; 3)0.2; 4)0.1

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Guselkumab						
Blauvelt, 2016[105] **(NCT02207231)** **VOYAGE 1** ***Good quality publication***	Phase III, randomized double-blind, placebo- and active-controlled, multicenter trial 101 global sites ITT, NRI (binary) & mLOCF (continuous)	1) Guselkumab 100 mg at week 0, 4, and then every 8 weeks (n=329) 2) Adalimumab 80 mg at week 0, 40 mg at week 1, and then 40 mg q2w (n=334) 3) Placebo (n=174) Patients on placebo crossed over to guselkumab after 16 weeks through week 48.	Inclusion: Adult patients (≥18 years) with moderate-to-severe plaque psoriasis (IGA ≥3, PASI ≥12, BSA ≥10%) for ≥6 months who were candidates for systematic therapy or phototherapy Exclusion: Previous or current signs of severe medical condition or malignancy; active TB; previous use of guselkumab or adalimumab, other TNFα agents (3 months), IL-12/23, IL-17, or IL-23 agents (6 months), or other systemic therapies (4 weeks)	Age, mean 1)43.9; 2)42.9; 3)44.9 Male, % 1)72.9; 2)74.6; 3)68.4 Caucasian, % 1)79.6; 2)82.9; 3)83.3 Duration of PsO, years 1)17.9; 2)17.0; 3)17.6 With PsA, % 1)19.5; 2)18.6; 3)17.2 Previous biologics, % 1)21.6; 2)21.0; 3)19.5 IGA, severe(4), % 1)23.4; 2)26.9; 3)24.7 PASI, mean (SD) 1)22.1 (9.5) 2)22.4 (9.0) 3)20.4 (8.7) DLQI, mean (SD) 1)14.0 (7.5) 2)14.4 (7.3) 3)13.3 (7.1)	**At 16 weeks** PASI 75, % 1)91.2; 2)73.1; 3)5.7 PASI 90, % 1)73.3; 2)49.7; 3)2.9 PASI 100, % 1)37.4; 2)17.1; 3)0.6 IGA 0/1, % 1)85.2; 2)65.9; 3)6.9 DLQI change from baseline, mean 1)-11.2; 2)-9.3; 3)-0.6 DLQI 0/1, % 1)56.3; 2)38.6; 3)4.2 *For all above, p<0.001 for guselkumab vs. placebo*	**0-16 weeks** Any AE, %: 1)51.7 2)51.1 3)49.4 Serious AE, %: 1)2.4 2)1.8 3)1.7 AE leading to discontinuation, % 1)1.2 2)0.9 3)1.1 Serious infection, % 1)0 2)0.6 3)0 NMSC, % 1)0.3 2)0 3)0 MACE, % 1)0.3 2)0.3 3)0

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Reich, 2016[106] **(NCT02207244)** **VOYAGE 2** ***Good quality publication***	Phase III, randomized double-blind, placebo- and active-controlled multicenter trial 115 global sites ITT, NRI	1) Guselkumab 100 mg at weeks 0, 4, and then every 8 weeks (n=496) 2) Adalimumab 80 mg at week 0, 40 mg at week 1, and then 40 mg q2w (n=248) 3) Placebo (n=248) Patients on placebo crossed over to guselkumab after 16 weeks. At week 28, patients on guselkumab & adalimumab were re-randomized based on PASI response level.	*Same inclusion and exclusion criteria as VOYAGE 1*[105]	Age, mean 1)43.7; 2)43.2; 3)43.3 Male, % 1)70.4; 2)68.5; 3)69.8 Caucasian, % 1)82.3; 2)80.6; 3)83.1 Duration of PsO, years 1)17.9; 2)17.6; 3)17.9 With PsA, % 1)17.9; 2)17.7; 3)18.5 Previous biologics, % 1)20.4; 2)19.8; 3)21.8 IGA severe(4), % 1)23.2; 2)21.4; 3)23.0 PASI, mean (SD) 1)21.9 (8.8) 2)21.7 (9.0) 3)21.5 (8.0) DLQI, mean (SD) 1)14.7 (6.9) 2)15.0 (6.9) 3)15.1 (7.2)	**At 16 weeks** PASI 75, % 1)86.3; 2)68.5; 3)8.1, *p=NR* PASI 90, % 1)70.0; 2)46.8; 3)2.4, *p<0.001 for guselkumab vs. placebo* PASI 100, % 1)34.1; 2)20.6; 3)0.8, *p=NR* IGA 0/1, % 1)84.1; 2)67.7; 3)8.5 *p<0.001 for guselkumab vs. placebo* DLQI 0/1, % 1)51.7; 2)39.0; 3)3.3, *p=NR* DLQI change from baseline 1)-11.3; 2)-9.7; 3)-2.6, *p=NR*	**0-16 weeks** Any AE, %: 1)47.6 2)48.4 3)44.8 Serious AE, %: 1)1.6 2)2.4 3)1.2 AE leading to discontinuation, % 1)1.4 2)1.6 3)0.8 Serious infection, % 1)0.2 2)0.8 3)0.4 MACE, % 1)0 2)0.4 3)0

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Gordon, 2015[145] **(NCT01483599)** **X-PLORE** ***Fair quality publication***	Phase II, randomized double-blind, placebo- and active-controlled multicenter trial 31 sites in North America and 12 sites in Europe ITT, NRI	1) Guselkumab (n=208) a) 5 mg b) 15 mg c) 50 mg d) 100 mg every 8 weeks (n=42) e) 200 mg at weeks 0, 4 and every 12 weeks thereafter (n=42) 2) Adalimumab 40 mg q2w following 80 mg loading dose (n=43) 3) Placebo (n=42) Patients randomized to guselkumab received one of 5 doses listed above. At week 16, patients on placebo crossed over to guselkumab 100 mg group. Adalimumab was not administered in a blinded, placebo-controlled manner.	Inclusion: Adult patients (≥18 years) with moderate-to-severe plaque psoriasis (PGA ≥3, PASI ≥12, BSA ≥10%) for ≥6 months who were candidates for systematic therapy or phototherapy Exclusion: Previous exposure to adalimumab or guselkumab	Age, median 1)44.0; 2)50.0; 3)46.5 Male, % 1)72.0; 2)70.0; 3)67.0 Caucasian, % 1)91.0; 2)91.0; 3)93.0 Duration of PsO, years 1)18.5; 2)19.3; 3)18.0 With PsA, % 1)25.0; 2)26.0; 3)29.0 Previous biologics, % 1)41.0; 2)60.0; 3)36.0 PGA, severe(5), % 1)5.0; 2)9.0; 3)2.0 PASI, mean (SD) 1)20.9 (8.1) 2)20.2 (7.6) 3)21.8 (10.0)	**At 16 weeks** PASI 75, % 1d)79.0; 1e)81.0 2)70.0; 3)5.0 PASI 90, % 1d)62.0; 1e)57.0 2)44.0; 3)2.0 PASI 100, % 1d)33.0; 1e)29.0 2)26.0; 3)0 PGA 0/1, % 1d)86.0; 1e)83.0 2)58.0; 3)7.0 DLQI 0/1, % 1d)62; 1e)70; 2)49; 3)7 DLQI change from baseline, mean 1d)-10.8; 1e)-11.4 2)-10.1; 3)-2.3 *For all above, p<0.001 for guselkumab 100 mg, 200 mg, & adalimumab vs. placebo*	**0-16 weeks** Any AE, %: 1)50.0 2)56.0 3)52.0 Serious AE, %: 1)1.0 2)2.0 3)2.0 AE leading to discontinuation, % 1)2.0 2)7.0 3)7.0 Serious infection, % 1)1.0 2)0 3)0

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Langley, 2017[146] **(NCT02203032)** **NAVIGATE** ***Fair quality publication***	Phase III, randomized, double-blind, active-controlled multicenter trial 100 global sites ITT, NRI	All patients received open-label ustekinumab dosed by weight at weeks 0 and 4. At week 16, patients with IGA≥2 were randomized to guselkumab 100 mg at weeks 16, 20, and every 8 weeks thereafter or to continue ustekinumab at week 16 and every 12 weeks thereafter. Patients with an IGA of 0 or 1 continued receiving open-label ustekinumab at week 16 and every 12 weeks thereafter. *Non-randomized* 1) Open-label ustekinumab continuation (n=585) *Randomized* 2) Guselkumab 100 mg (n=135) 3) Ustekinumab (n=133)	Inclusion: Adults (≥18 years) with moderate-to-severe plaque psoriasis (PASI≥12, IGA≥ 3, BSA≥ 10%) for ≥ 6 months who were candidates for phototherapy or systemic treatment Exclusion: Severe medical conditions; history of malignancy within 5 years (except NMSC); history of active TB; positive for hepatitis B or seropositive for antibodies to hepatitis C; prior treatment with guselkumab or ustekinumab, IL-12, IL-17 or IL-23 agents (6 months), TNFα (3 months or 5 half-lives), or any systemic immunosuppressants or phototherapy (4 weeks)	Age, mean 1)42.9; 2)44.2; 3)43.0 Male, % 1)63.6; 2)70.4; 3)66.2 Caucasian, % 1)89.4; 2)80.7; 3)74.4 Weight>100 kg, % 1)25.5; 2)27.4; 3)27.8 Duration of PsO, years 1)16.7; 2)18.2; 3)15.6 With PsA, % 1)13.2; 2)20.7; 3)15.8 Previous TNFα, % 1)10.8; 2)23.7; 3)19.5 IGA, severe(4), % 1)18.5; 2)23.7; 3)24.8 PASI, mean (SD) 1)21.1 (9.2) 2)22.6 (9.3) 3)22.8 (9.4) DLQI, mean (SD) 1)14.2(7.1) 2)15.5(7.9) 3)14.4(6.7)	**At week 28** PASI 75, % 2)81.4; 3)50.3; *p=NR* PASI 90, % 2)48.1; 3)22.6; *p≤0.001* PASI 100, % 2)11.3; 3)5.6; *p=NR* IGA, 0/1, % 2)31.1; 3)14.3; *p=0.001* **At week 52** PASI 75, % 2)76.9; 3)53.8; *p=NR* PASI 90, % 2)51.1; 3)24.1; *p<0.001* PASI 100, % 2)20.0; 3)7.5; *p=0.003* IGA, 0/1, % 2)36.3; 3)17.3; *p<0.001* DLQI 0 or 1, % 2)38.8; 3)19.0; *p=0.002*	**16- 60 weeks** Any AE, %: 1)41.4 2)64.4 3)55.6 Serious AE, % 1)3.4 2)6.7 3)4.5 AE leading to discontinuation, % 1)1.2 2)2.2 3)1.5 Serious infection, % 1)0.9 2)0.7 3)0 NMSC, n 1)2 2)0 3)0 Malignancy other than NMSC, n 1)2; 2)2; 3)0 MACE, % 1)0.2; 2)1.5; 3)0.8

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Risankizumab						
Blauvelt, 2017[108] **(NCT02672852)** **IMMhance** ***Abstract***	Phase III, randomized, double-blinded, placebo-controlled multicenter trial Sites in Australia, Belgium, Canada, Czechia, France, Germany, Japan, Korea, and United States NRI	1) Risankizumab 150 mg at weeks 0 and 4 (n=407) 2) Placebo (n=100) At week 16, patients receiving risankizumab with sPGA≥2 continued treatment and those with sPGA 0 or 1 were rerandomized to continue treatment or receive placebo. Patients receiving placebo during the double-blind phase were treated with risankizumab at week 16 and thereafter.	Inclusion: Adults (≥ 18 years) with chronic plaque psoriasis for >6 months and moderate-to-severe chronic plaque psoriasis (PASI≥ 12, sPGA≥3, BSA≥ 10%) at baseline who were candidates for systemic therapy or phototherapy Exclusion: Non-plaque or drug-induced psoriasis; active inflammatory disease other than psoriasis or PsA	Age, mean 1)49.6; 2)47.6 Male, % 1)69.5; 2)73 Caucasian, % 1)78.6; 2)82 Duration of PsO, years NR With PsA, % NR Prior TNFα, % 1)36.9; 2)35 Prior biologics, % 1)56.5; 2)51.0 sPGA severe, % 1)20.6; 2)23 PASI, mean (SD) 1)19.9 (7.9) 2)21.2 (8.7)	**At 16 weeks** PASI 75, % 1)88.7; 2)8.0 PASI 90, % 1)73.2; 2)2.0 PASI 100, % 1)47.2; 2)1.0 sPGA 0/1, % 1)83.5; 2)7.0 sPGA 0, % 1)46.4; 2)1.0 DLQI 0/1, % 1)65.4; 2)3.0 *For all above, p<0.001*	**0-16 weeks** Any AE, % 1)45.5; 2)48.0 Serious AE, % 1)2.0; 2)8.0 AE leading to discontinuation, % 1)0.5; 2)4.0 Serious infection, % 1)0; 2)1.0 MACE, % 1)0; 2)1.0 Malignancies, % 1)0.7; 2)0 Malignancies excluding NMSC, % 1)0.5; 2)0

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Gordon, 2018[109] **(NCT02684370)** **UltIMMa-1** ***Abstract***	Phase III, randomized, triple-blinded, placebo- and active-controlled, multicenter trial Sites in Australia, Canada, Czechia, France, Germany, Japan, Korea, and United States NRI	1) Risankizumab 150 mg at weeks 0 and 4 (n=304) 2) Ustekinumab 45/90 mg dosed by weight at weeks 0 and 4 (n=100) 3) Placebo (n=102) At week 16, patients receiving risankizumab and ustekinumab continued treatment and patients receiving placebo switched to treatment with risankizumab.	Inclusion: Adults (≥18 years) with chronic plaque psoriasis for ≥6 months and moderate-to-severe chronic plaque psoriasis (PASI≥ 12, sPGA≥3, BSA≥ 10%) at baseline who were candidates for systemic therapy or phototherapy Exclusion: Non-plaque or drug-induced psoriasis; active inflammatory disease other than psoriasis or PsA; prior exposure to risankizumab or ustekinumab	Age, mean 1)48.3; 2)46.5; 3)49.3 Male, % 1)69.7; 2)70; 3)77.5 Caucasian, % 1)65.8; 2)74.0; 3)69.6 Weight>100 kg, % 1)25.7; 2)26.0; 3)25.5 Duration of PsO, years NR With PsA, % NR Prior biologic, % 1)34.2; 2)30.0; 3)39.2 sPGA severe, % 1)15.8; 2)15.0; 3)15.7 PASI, mean 1)20.6 2)20.1 3)20.5	**At 16 weeks** PASI 90, % 1)75.3; 2)42.0; 3)4.9 PASI 100, % 1)35.9; 2)12.0; 3)0 sPGA 0/1, % 1)87.8; 2)63.0; 3)7.8 sPGA 0, % 1)36.8; 2)14.0; 3)2.0 DLQI 0/1, % 1)65.8; 2)43.0; 3)7.8 *For all above, p<0.001*	**0-16 weeks** Any AE, % 1)49.7; 2)50.0; 3)51.0 Serious AE, % 1)2.3; 2)8.0; 3)2.9 AE leading to discontinuation, % 1)0.7; 2)2.0; 3)3.9 Serious infection, % 1)0.3; 2)3.0; 3)0 MACE, % 1)0; 2)0; 3)0 Malignancies, % 1)0.3; 2)0; 3)1.0 Malignancies excluding NMSC, % 1)0; 2)0; 3)0

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Gordon, 2018[109] **(NCT02684357)** **UltIMMa-2** ***Abstract***	Phase III, randomized, double-blinded, placebo- and active-controlled, multicenter trial Sites in Austria, Belgium, Canada, France, Germany, Mexico, Poland, Portugal, Spain, and United States NRI	1) Risankizumab 150 mg at weeks 0 and 4 (n=294) 2) Ustekinumab 45/90 mg dosed by weight at weeks 0 and 4 (n=99) 3) Placebo (n=98) At week 16, patients receiving risankizumab and ustekinumab continued treatment and patients receiving placebo switched to treatment with risankizumab.	*See UltIMMa-1*	Age, mean 1)46.2 2)48.6; 3)46.3 Male, % 1)69.0 2)66.7; 3)68.4 Caucasian, % 1)86.7 2)91.9; 3)88.8 Weight>100 kg, % 1)31.0; 2)30.3; 3)31.6 Duration of PsO, years NR With PsA, % NR Prior biologic, % 1)40.1; 2)43.4; 3)42.9 sPGA severe, % 1)22.4; 2)18.2; 3)21.4 PASI, mean 1)20.5; 2)18.2; 3)18.9	**At 16 weeks** PASI 90, % 1)74.8; 2)47.5; 3)2.0 PASI 100, % 1)50.7; 2)24.2; 3)2.0 sPGA 0/1, % 1)83.7; 2)61.6; 3)5.1 sPGA 0, % 1)51.0; 2)25.3; 3)3.1 DLQI 0/1, % 1)66.7; 2)46.5; 3)4.1 *For all above, p<0.001*	**0-16 weeks** Any AE, % 1)45.6; 2)53.5; 3)45.9 Serious AE, % 1)2.0; 2)3.0; 3)1.0 AE leading to discontinuation, % 1)0.3; 2)0; 3)1.0 Serious infection, % 1)1.0; 2)1.0; 3)0 MACE, % 1)0; 2)0; 3)0 Malignancies, % 1)0.3; 2)0; 3)0 Malignancies excluding NMSC, % 1)0; 2)0; 3)0 Non-treatment emergent deaths, % 1)0.3; 2)0; 3)0

AE: adverse event; BSA: body surface area; DLQI: Dermatology Life Quality Index; EAR: exposure-adjusted rate; FAS: full analysis set; IGA: Investigator's Global Assessment; IR: incidence rate; ITT: intention-to-treat; LOCF: last observation carried forward; MACE: major adverse cardiac events; MI: multiple imputation; mLOCF: modified last observation carried forward; BIW: twice weekly; NMSC: non-melanoma skin cancer; NR: not reported; NRI: nonresponder imputation; PASI: Psoriasis Area Severity Index; PGA: Physician's Global Assessment; PsA: psoriatic arthritis; PsO: psoriasis; PY: patient years; q2w: every two weeks; q4w: every four weeks; SAE: serious adverse event; SD: standard deviation; sPGA: static Physician's Global Assessment; TB: tuberculosis; TEAE: treatment emergent adverse event

*p-values only reported if significant

Table B2. Evidence Summary Tables for New Head-to-Head Trials

Study, *Quality rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Reich, 2017[113] ***Also see Burge, 2017 (conference abstract)*** [147] **(NCT02561806)** **IXORA-S** ***Good quality publication***	Phase IIIb, randomized, double-blind, controlled, parallel-group, multicenter trial 51 global sites ITT, NRI (binary) & mLOCF (continuous)	1) Ixekizumab: 160 mg at week 0, 80 mg q2w through week 12, and then 80 mg q4w (n= 136) 2) Ustekinumab dosed by weight at weeks 0, 4, and then every 12 weeks (n=166)	Inclusion: Adult patients (≥18 years) with chronic plaque psoriasis (PASI≥10) for ≥6 months who had previously failed or had a contraindication or intolerability to at least one systemic therapy Exclusion: Predominant presence of nonplaque psoriasis; contraindication for ustekinumab; prior treatment with ustekinumab, ixekizumab, or any other IL-17 or IL-12/23 antagonists	Age, mean 1)42.7; 2)44.0 Male, % 1)66.2; 2)67.5 Caucasian, % 1)93.3; 2)95.7 Weight>100 kg, % 1)23.0; 2)27.1 Duration of PsO, years 1)18.0; 2)18.2 Previous biologics, % 1)13.2; 2)15.1 PASI, mean (SD) 1)19.9 (8.2) 2)19.8 (9.0) DLQI total, mean (SD) 1)11.1 (7.2) 2)12.0 (7.3) Itch NRS, mean (SD) 1)6.3(2.7); 2)6.2 (2.6) Skin pain VAS, mean (SD) 1)42.9 (33.3) 2)39.4 (30.8)	**At 12 weeks** PASI 75, % 1)88.2; 2)68.7, *p<0.001* PASI 90, % 1)72.8; 2)42.2, *p<0.001* PASI 100, % 1)36.0; 2)14.5, *p<0.01* DLQI 0/1, % 1)61.0; 2)44.6, *p<0.01* sPGA 0/1, % 1)83.6; 2)57.2, *p<0.001* Itch NRS, change from baseline, mean (SD) 1)-4.8(3.0); 2)-4.2(3.0) Skin pain VAS, change from baseline, mean (SD) 1)-35.4 (32.1); 2)-29.1 (30.7)	**0-24 weeks** Any TEAE, % 1)69.6 2)75.3 Serious TEAE, % 1)4.4 2)6.0 Serious AE, % 1)2.2 2)3.0 AE leading to discontinuation, % 1)1.5 2)0.6 Infection, % 1)42.2 2)52.4

Study, *Quality rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
de Vries, 2017[110] **(Netherlands registry: NTR 1559)** **PIECE** ***Fair quality publication***	Investigator-initiated, single-blind, multicenter trial Sites in the Netherlands ITT, LOCF	1) Etanercept 50 mg BIW (n=23) 2) Infliximab 5 mg/kg at weeks 0, 2, 6 and every 8 weeks thereafter (n=25) If patient discontinued due to adverse events or insufficient response (less than 50% improvement in PASI) up to week 12, they could switch to other treatment arm. At week 12 patients with insufficient response could crossover to other treatment arm.	Inclusion: Adult patients (≥18 years) with moderate-to-severe plaque psoriasis (PASI≥10 or BSA ≥10% or PASI ≥8 and Shindex-29 score≥35) who have failed, were contraindicated for, or intolerant to UV therapy and methotrexate or ciclosporin Exclusion: Malignancy within previous 10 years; active/chronic infections; demyelinating disease; congestive heart failure; liver or kidney function disorders; prior etanercept or infliximab treatment failure	Age, mean 1)42.4; 2)45.9 Male, % 1)56; 2)72 Duration of PsO, years 1)10.6; 2)12.9 With PsA, % 1)13; 2)8 PASI, mean (SD) 1)15.9 (5.1) 2)17.8 (9.7) IGA, mean (SD) 1)3.3 (0.65) 2)3.2 (0.52)	**At 12 weeks** PASI 50, % 1)61; 2)96, *p=0* PASI 75, % 1)22; 2)76, *p=0* PASI 90, % 1)0; 2)20, *p=0.05* PASI 100, % 1)0; 2)4 IGA 0/1, % 1)9; 2)68, *p=0*	**0-24 weeks** Any AE, % 1)100 2)96 Any treatment-related AE, % 1)12 2)8 Any SAE, % 1)0.7 2)0.5 AE leading to discontinuation, n 1)2 2)3

AE: adverse event; BIW: twice weekly; BSA: body surface area; DLQI: Dermatology Life Quality Index; IGA: Investigator's Global Assessment; ITT: intention-to-treat; LOCF: last observation carried forward; mLOCF: modified last observation carried forward; NRI: nonresponder imputation; PASI: Psoriasis Area Severity Index; PsA: psoriatic arthritis; PsO: psoriasis; q2w: every two weeks; SAE: serious adverse event; SD: standard deviation; sPGA: static Physician's Global Assessment; TEAE: treatment emergent adverse event

*p-values only reported if significant

Table B3. Updated Evidence Summary Tables for Older Drugs

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
TNFα Inhibitors						
Adalimumab						
Saurat, 2008[76] and Revicki, 2008[148] **(NCT00235820)** **CHAMPION** ***Good quality publication***	Phase III, randomized, controlled, double-blind, multicenter trial 28 study sites in Europe and Canada ITT with NRI	1) Adalimumab 40 mg q2w following an 80 mg dose (n=108) 2) Placebo (n=53) 3) Methotrexate 7.5 to 25 mg once weekly (n=110)	Inclusion: Psoriasis for ≥12 months and stable moderate to severe chronic plaque psoriasis (PASI≥10 and BSA≥10%) at baseline; candidate for systematic therapy or phototherapy Exclusion: Previous systemic TNFα 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 Duration of PsO (year), mean 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 (SD) 1) 20.2 (7.5) 2) 19.2 (6.9) DLQI, mean (SD) 1)11.8 (6.6) 2)11.7 (7.0) ED-5D index score, mean (SD) 1)0.7 (0.3) 2)0.7 (0.3)	**At 16 weeks** PASI 50, % 1)88 2)30.2 PASI 75, % 1)79.6 2)18.9 PASI 90, % 1)51.9 2)11.3 PASI 100, % 1)16.7 2)1.9; *p=0.004* PGA 0/1. % 1) 73.1 2) 11.3 DLQI, change from baseline, mean (95% CI) 1)-9.1 (-10.4, -7.8) 2)-3.4 (-5.2, -1.6) ED-5D index score, change from baseline, mean (95% CI) 1)0.2 (0.2, 0.3) 2)0.1 (0.0, 0.2), *p<0.01* *p<0.001 unless otherwise specified*	**0-16 weeks** SAEs, % 1)1.9 2)1.9 AEs leading to discontinuation, % 1)0.9 2)1.9

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Menter, 2008[75] **(NCT00237887)** **REVEAL** ***Good quality publication***	Phase III, multicenter, double-blind RCT 67 centers in the United States and 14 centers in Canada ITT with NRI	1) Adalimumab: 40 mg q2w following an 80 mg dose (n=814) 2) Placebo (n=398)	Inclusion: Psoriasis for ≥6 months, stable moderate-to-severe plaque psoriasis for ≥ 2 months (PASI≥12, BSA≥10% and PGA of at least moderate severity); Exclusion: A history of CNS disease, cancer or lymphoproliferative disease	Age, mean 1)44.1 2)45.4 Male, % 1)67.1 2)64.6 Caucasian, % 1)91.2 2)90.2 Duration of PsO (years), mean 1)18.1 2)18.4 With PsA, % 1)27.5 2)28.4 Previous systemic biologic, % 1)11.9 2)13.3 PASI, mean (SD) 1) 19.0 (7.08) 2) 18.8 (7.09)	**At 16 weeks** PASI 75, % 1)71; 2)7 P<0.001 PASI 90, %: 1)45; 1)2 P<0.01 PASI 100, %: 1)20; 2)1 P<0.01	**0-16 weeks** SAEs,% 1)1.8 2)1.8 Serious infectious, % 1)0.6 2)1.0 AEs leading to discontinuation, % 1)1.7 2)2.0

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Asahina, 2010[77] ***Good quality publication***	Phase II/III, multicenter, double-blind RCT 42 sites in Japan ITT with NRI	1) Adalimumab 40 mg q2w (n=38) 2) Adalimumab 80 mg at week 0 and 40 mg q2w thereafter (n=43) 3) Adalimumab 80 mg q2w (n=42) 4) Placebo (n=46)	Inclusion: Moderate-to-severe chronic plaque psoriasis ≥6 months stable for ≥2 months (PASI≥12, and BSA≥10%) Exclusion: Previous TNFα therapy, other major disease or infection	Age, mean 2)44.2 4)43.9 Male, % 2)35 4)41 Duration of PsO (year), mean 2)14.0 4)15.5 Previous systemic non-biologic, % 2)41.9 4)37.0 PASI, mean (SD) 2)30.2 (10.9) 4)29.1 (11.8)	**At 16 weeks** PASI 50, %: 2)81.4; 4)19.6 PASI 75,%: 2)62.8; 4)4.3 PASI 90,%: 2)39.5; 4)0 PGA 0/1, % 2) 60.5; 4) 8.7 DLQI, change from baseline, mean (SD) 2)-5.1 (5.7); 4)1.0 (7.0) *p<0.001 for all*	**0-16 weeks** SAEs, % 2)2.3 4)2.2 AEs leading to discontinuation, 2)11.6 4)10.9

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Cai, 2017[78] **(NCT01646073)** ***NEW EVIDENCE***	Phase III, randomized, controlled, double-blind multicenter trial 16 sites in China ITT, NRI (categorical) & LOCF (continuous)	1) Adalimumab 40 mg q2w following 80 mg loading dose (n=338) 2) Placebo (n=87) At week 13, all patients received adalimumab 40 mg q2w, following an 80 mg loading dose only for patients originally randomized to placebo.	Inclusion: Adult patients (≥18 years) with psoriasis for at least 6 months, plaque psoriasis for at least 2 months, and moderate-to-severe plaque psoriasis at baseline for whom previous systemic therapy has failed. Exclusion: Previous exposure to a biologic treatment or received other systemic treatment within one month of baseline	Age, mean 1)43.1; 2)43.8 Male, % 1)75.1; 2)66.7 Duration of Pso (years), mean 1)14.8; 2)15.8 History of PsA, % 1)12.7; 2)11.5 PASI, mean (SD) 1) 28.2 (12.0); 2) 25.6 (10.98) PGA, moderate (3), % 1)63.5; 2)65.5 PGA, marked (4), % 1)32.5; 2)32.2 PGA, severe (5), % 1)4.1; 2)2.3 DLQI, mean (SD) 1)14.7 (7.1); 2)13.4 (7.1)	**At 12 weeks** PASI 75, % 1)77.8;2)11.5 PASI 90, % 1)55.6; 2)3.4 PASI 100, % 1)13.3; 2)1.1 *p≤0.001 for all above* PGA 0/1, % 1)80.5; 2)14.9, p=NR *See publication for efficacy data through 24 weeks.*	**0-12 weeks** Any AE, % 1)46.7; 2)37.9 AE leading to discontinuation, % 1)0.6; 2)0 Serious AE, % 1)1.2; 2)3.4 Infection, % 1)17.5; 2)16.1 Serious Infection, % 1)0; 2)0

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Etanercept						
Papp, 2005[79] ***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 (n=203) 2) Etanercept 25 mg BIW (n=204) 3) Placebo (n=204)	Inclusion: Active and clinically stable plaque psoriasis with ≥10% BSA involvement; baseline PASI≥10; at least one previous phototherapy or systemic therapy; adequate hematological, renal, and hepatic function Exclusion: Active severe infection; other skin conditions; previous TNFα therapy	Age, median 1)44.5; 3)44.0 Male, % 1)67; 3)64 Duration of PsO, yr 1)18.1; 3)17.5 History of PsA, % 1)26; 3)26 PASI, median (range) 1)16.1 (7.0-57.3) 3)16.0 (7.0-62.4)	**At 12 weeks** PASI 50, % 1)72; 3)9 P<0.0001 PASI 75, % 1)46; 3)3 P<0.0001 PASI 90,% 1)19; 3)<1 P<0.0001 sPGA "clear" or "almost clear," % 1)54; 3)3 *p<0.0001 for all*	**0-12 weeks** Grade 3 or 4 laboratory abnormalities at week 24, n 1)1 3)1
Leonardi, 2003[80] ***Fair quality publication***	Phase III, multicenter, double-blind RCT 47 sites in the US mITT with LOCF	1) Etanercept 25 mg once weekly (n=160) 2) Etanercept 25 mg BIW (n=162) 3) Etanercept 50 mg BIW (n=164) 4) Placebo (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 TNFα therapy	Age, median 3)44.8; 4)45.6 Male, % 3)65; 4)63 Caucasian, % 3)87; 4)90 Duration of PsO, yr 3)18.6; 4)18.4 History of PsA, % 22 Prior systemic therapy/ phototherapy, % 76 PASI, median (SE) 3)18.4 (0.7); 4)18.3 (0.6)	**At 12 weeks** PASI 50, %: 3)74; 4)14 PASI 75, % 3)49; 4)4 PASI 90, % 3)22; 4)1 sPGA "clear" or "almost clear" at week 12,%: 3)49; 4)5 % improvement DLQI, mean (SD) 3)61.0 (4.3) 4)10.9 (4.8) *p<0.001 for all*	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Tyring, 2006[81] **(NCT00111449)** ***Fair quality publication***	Phase III, multicenter, double-blind RCT 39 sites in the US and Canada mITT with LOCF	1) Etanercept 50 mg BIW (n=300) 2) Placebo (n=300)	Inclusion: Active, clinically stable plaque psoriasis with PASI≥10 and BSA≥10%; previous systemic therapy or phototherapy, or candidate for such therapy; adequate hematological, renal, and hepatic function Exclusion: History of psychiatric disease; active guttate, erythrodermic, or pustular psoriasis; previous TNFα therapy	Age, median 1)45.8 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 PASI, median (SD) 1)18.3 (7.6) 2)18.1 (7.4)	**At week 12** PASI 50, % 3)74; 4)14 PASI 75, % 3)47; 4)5 PASI 90, % 3)21; 4)1, *p<0.001* % improvement DLQI, mean (SD) 3)69.1 4)22.1 *All p<0.0001 unless otherwise stated*	**0-12 weeks** SAE,% 1)0; 2)0.3 AEs leading to discontinuation through 12 weeks, % 1)1.3; 2)1.6
Bagel, 2012[84] ***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 psoriasis; significant medical problems; a history of tuberculosis; or a history of cancer 5 years or less before enrollment	Age, median 1)39; 2)42 Male, % 1)53.2; 2)58.1 Caucasian, % 1)69.4; 2)75.8 Duration of PsO, yr 1)17.5; 2)11.9 Previous biologic therapy, % TNFα 1)6.8; 2)6.5 PASI, median (range) 1)15.5 (8,46) 2)15.2 (10,41)	**At week 12** PASI 50, % 1)85 2)7 P<0.0001 PASI 75, % 1)59 2)5 P<0.0001 PASI 90, % 1)25 2)2 P<0.0001 PGA 0/1, % 1)54 2)5 P<0.0001	**0-12 weeks** SAEs, % 1)0 2)0 AEs leading to discontinuation, % 1)3.2 2)0

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Gottlieb, 2011[83] **(NCT00691964)** ***Good quality publication***	Phase III, multicenter, double-blind RCT 33 sites in the United States ITT with NRI & LOCF	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 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)	**At 12 weeks** PASI 75, % 2)56.0 3)7.4 P<0.001 PASI 90, % 2)23 3)1.4 P≤0.002 PASI 100, % 2)6.7 3)0 p≤0.002 PGA 0/1 at, % 2)39.7; 3)2.9, p<0.0001 DLQI of 0, % 2)21.3; 3)2.9, p≤0.008	**0-12 weeks** Severe AE, % 2)2.1 3)4.3 Serious, % 2)0.7 3)2.9 AEs leading to discontinuation, % 2)2.8 3)0
Strober, 2011[82] **(NCT00710580)** ***Good quality publication***	Phase III, multicenter, double-blind RCT 41 sites in the US ITT with NRI &LOCF	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: Previous systemic anti-IL-12/23p40 therapy, etanercept, or inability to discontinue topical therapy, phototherapies, or systemic therapies	Age, median 2)45.2; 3)45.0 Male, % 2)61.2; 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, % 2)7.9; 3)4.2 PASI, mean (SD) 2)18.5 (6.0); 3)18.3 (6.4)	**At 12 weeks** PASI 75, % 2)39.6 3)6.9 PASI 90, % 2)13.7 3)4.2 PASI 100, % 2)5.8 3)0 PGA 0-1, % 2)39.7; 3)2.9, P<0.0001 DLQI of 0, % 2)29.5; 3)4.2	Severe AE at week 12, % 2)0.7 3)2.8 Serious AE at week 12, % 2)0.7 3)2.8 AEs leading to discontinuation through 12 weeks, % 2)2.9 3)2.8

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Bachelez, 2015[85] **(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 to etanercept, previously not responded to TNFα therapy, active infection, previous tofacitinib	Age, median 3)42.0 4)46.0 Male, % 3)70 4)66 Caucasian, % 3)87 4)84 Duration of PsO, yr 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)	**At 12 weeks** PASI 50, % 3)80.3 4)20.6 PASI 75, % 3)58.8 4)5.6 PASI 90, % 3)32.2 4)0.9 PGA 0-1, % 3)66.3 4)15.0 PGA 0, % 3)19.4 4)1.9 DLQI reduction ≥5 from baseline, % 3)74.7 4)31.8	**0-12 weeks** Severe TEAE, % 2)2 3)5 Serious TEAE, % 2)2 3)2 AEs leading to discontinuation, % 2)3 3)4

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Infliximab						
Reich, 2005[86] **EXPRESS I** ***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 TNFα 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 With PsA, % 1)31 2)29 Previous biologic therapy, % NR PASI, mean (SD) 1)22.9 2)22.8	**At 10 weeks** PASI 50, % 1)91 2)8 PASI 75, % 1)80 2)3 PASI 90, % 1)57 2)1 PGA of 0-1, % 1)83 2)4 *All p<0.0001* Change in DLQI from baseline, mean** 1)10.3 2)0.4 *p<0.001* **Reported in Reich 2006	**0-24 weeks** Serious AEs % 1)6 2)3 AEs leading to discontinuation,% 1)9 2)7
Reich, 2006[149] **EXPRESS I**	*See above* Work productivity outcomes from EXPRESS	*See above*	*See above*	**Additional characteristics:** Productivity VAS 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	**At 10 weeks** Productivity VAS 1) -0.1; 2) 2.7 SF-RP (role physical) 1) -5.2; 2) 20.6 SF-RE (role emotional) 1) -2.2; 2) 18.2 *All p<0.001*	Discontinuation due to AEs through week 50 (%) Placebo/INF: 10.4 INF/INF: 11.3 Discontinuation due to unsatisfactory therapeutic effects (%) Placebo/INF: 9.7 INF/INF: 4.7

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Menter, 2007[87] **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) 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	Inclusion: A diagnosis of moderate-to-severe plaque psoriasis; 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 TNFα treatment	Age, median 2)44.5 3)44.4 Male, % 2)65.0 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 PASI, mean (SD) 2)20.4 (18.6) 3)19.8 (17.4)	**At 10 weeks** PASI 75, % 2)75.5 3)1.9 PASI 90, % 2)45.2 3)0.5 PGA of 1-2, % 2)76.0 3)1.0 DLQI of 0, % 2)39.0 3)1.0 DLQI mean change 2) -9.0 3) 0 *p<0.001* *PGA ranging from 1 to 6	**0-14 weeks** Any SAE, % 2) 2.9 3) 2.4 AEs leading to discontinuation, % 1)5.1 2)2.4

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Yang, 2012[88] ***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 history of malignancy within 5 years	Age, median 1)39.4 2)40.1 Male, % 1)71.4 2)77.8 White, % NR Duration of PsO, yr 1)16.0 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	**At 10 weeks** PASI 50, % 1)94.0 2)13.3 PASI 75, % 1)81.0 2)2.2 PASI 90, % 1)57.1 2)0 PGA of 0-1, % 1)88.1 2)6.7 DLQI mean 1) 6.5 2) 13.1 *P<0.001 for all*	Serious AEs at week 10, % 1)1.2 2)0 AEs leading to discontinuation through 26 weeks, % 1)6.7 2)NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Torii, 2010[89] ***Fair quality publication*** ***NEW EVIDENCE***	Phase III, randomized, controlled, double-blind multicenter trial 28 sites in Japan ITT, NRI	1) Infliximab 5 mg/kg at weeks 0, 2, and 6 (n=35) 2) Placebo (n=19)	Inclusion: Patients with moderate-to-severe plaque psoriasis (PASI≥12, BSA≥10%) for at least 6 months requiring systematic therapy or phototherapy Exclusion: History or risk of serious infection, lymphoproliferative disease, or active TB	Age, mean 1)46.9; 2)43.3 Male, % 1)62.9; 2)73.7 Duration of Pso, years 1)14.2; 2)11.1 With PsA, % 1)28.6; 2)36.8 PASI, mean (SD) 1) 31.9 (12.8) 2) 33.1 (15.6) PGA moderate, % 1)40.0; 2)52.6 PGA marked, % 1)45.7; 2)36.8 PGA severe, % 1)8.6; 2)5.3 DLQI, mean (SD) 1) 12.7 (6.8) 2) 10.5 (6.8)	**At week 10** PASI 50, % 1)82.6; 2)10.8 PASI 75, % 1)68.6; 2)0 PASI 90, % 1)54.6; 2)0 PGA, cleared or minimal, % DLQI, change from baseline, mean (SD) 1) -9.9 (7.1); 2)-0.4 (6.2) *p<0.001 for all above* *See publication for efficacy data up to week 66.*	**0-14 weeks** Duration of follow-up (days), mean 1)101.3; 2)105.5 Any AE, % 1)97.1; 2)57.9 AE leading to discontinuation, % 1)2.9; 2)5.3 SAE, % 1)2.9; 2)5.3 Infection, % 1)62.9; 2)21.1 Serious infection, % 1)0; 2)5.3 Infusion reaction, % 1)8.6; 2)5.3 Serious infusion reaction, % 1)2.9; 2)0 *See publication for safety data up to week 78.*

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Observational Studies						
Gisondi, 2013[150] ***Good quality publication***	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, cyclosporine, 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, mean (SD) 1) 16.5 (9.1) 2) 18.4 (8.2)	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 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	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Piaserico, 2014[151] ***Fair quality publication***	Observational, prospective study Adjustment: for the presence of comorbidities, smoking, steroid use and disease severity	1) etanercept (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	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) 4)17.2 (1.9)	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
Esposito, 2012[152] ***Poor quality publication***	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 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 Previous biologic therapy, % 1) Adalimumab: 1.6	**At week 12** PASI 50, % 1)82.0 2)85.7 PASI 75, % 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 PASI 50 at year 1, % 1)90.2 2)78.6 PASI 75 at year 1, %	Severe AEs leading to discontinuation, % 1)4.9 2)7.1

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
				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) 2)10.4 (0.4-23.8)	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 PASI 75 at year 3, % 1)83.6 2)71.4	
Gisondi, 2008[153] ***Poor quality publication***	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)	Inclusion: psoriatic patients affected by chronic plaque psoriasis consecutively admitted to the outpatient 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, cyclosporine, acitretin or phototherapy Exclusion: patients diagnosed with PsA	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 2) 17.5 3) 18.6 Previous biologic therapy, % 0 PASI, mean (SD) 1) 18.8 (7.4) 2) 17.7 (7.3)	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

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
				3) 8.2 (3.1)		
Anti IL-17A Agents						
Secukinumab (Cosentyx)						
Blauvet, 2015[96] **(NCT01555125)** **FEATURE** ***Good quality publication***	Phase III RCT Double-blind Multicenter 32 sites in North America and Europe ITT with NRI	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 every 4 weeks starting from week 4 (n=59) 3) placebo (n=59) Maintenance: dosing every 4 weeks from week 12 to week 52	Inclusion: Plaque psoriasis for ≥6 months; moderate-to-severe disease defined by baseline PASI≥12, IGA mod 2011≥3, and BSA≥10%; inadequately controlled by topical treatment, phototherapy, or previous systemic therapy Exclusion: Non-chronic-plaque psoriasis, except for palmoplantar psoriasis; prior anti-IL-17A therapy; medical conditions that confound the evaluation or risky for immunotherapy; active infections or history of infections; history of lymphoproliferative diseases or malignancy; pregnancy	Age, mean 1) 45.1 2) 46.0 3) 46.5 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) 2) 20.5 (8.29) 3) 21.1 (8.49) Previous biologic, % 1) 39.0 2) 47.5 3) 44.1	**At 12 weeks** PASI 75, % 1) 75.9 2) 69.5 3) 0 PASI 90, % 1) 60.3 2) 45.8 3) 0 PASI 100, % 1) 43.1 2) 8.5 3) 0 IGA mod 2011 0/1 response, % 1) 69.0 2) 52.5 3) 0 *p<0.0001 for all secukinumab vs. placebo comparisons*	**0-12 weeks** Serious AE at week 12, % 1) 5.1 2) 0 3) 1.7 AE leading to discontinuation at week 12, % 1) 1.7 2) 0 3) 1.7

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Thaci, 2015[112] **(NCT02074982)** **CLEAR** ***Good quality publication***	Phase IIIb RCT Double-blind Multicenter 134 sites worldwide ITT with NRI	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 16-40 (placebo given at other wks) (n=339)	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: Previous biologics targeting IL-17A or IL-12/IL-23	Age, mean 1) 45.2; 2) 44.6 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) 14.2; 2) 13.0	**At 16 weeks** PASI 75, % 1)93.1 2)82.7 PASI 90, % 1)79.0 2)57.6 PASI 100, % 1)44.3 2)28.4 IGA mod 2011 0/1, % 1)82.9; 2)67.5 DLQI 0/1, % 1)71.9; 2)57.4 *p≤0.0001 for all*	At week 16 Nonfatal serious AE, % 1)3.0 2)3.0 AE leading to discontinuation at week 16, % 1)0.9 2)1.2
Blauvelt, 2017 [154] **(NCT02074982)** **CLEAR** ***NEW EVIDENCE***	Phase IIIb, randomized, controlled, double-blind, multicenter trial	1) Secukinumab 300 mg (n=336) 2) Ustekinumab dosed by weight (n=339)	*See Thaci, 2015* [155]	*See Thaci, 2015* [155] **Additional patient characteristics:** DLQI, daily activities domain total, mean (SD) 1)2.9 (1.88); 2) 2.8 (1.83) DLQI, PRD total, mean (SD) 1)1.8 (1.90); 2)1.9 (1.94)	**At 16 weeks** DLQI, change from baseline in daily activities total, mean 1)-2.63; 2)-2.43, *p<0.001* DLQI, daily activities total responders, % 1)83.6; 2)73.1, p*<0.01* DLQI, change from baseline in PRD, mean 1)-1.67; 2)-1.49, p*<0.01* DLQI, PRD total responders, % 1)86.5; 2)75.4, p*<0.01*	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
					Total responders defined as patients reporting no impact	
Paul, 2015[97] **(NCT01636687)** **JUNCTURE** ***Fair quality publication***	Phase III RCT Double-blind Multicenter 38 sites worldwide ITT, NRI	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 or drug-induced psoriasis; ongoing prohibited treatment; prior exposure IL-17 agents; systemic infection, tuberculosis, history of HIV, Hep B, Hep C; immunocompromised	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 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; 2) 26.2; 3) 19.7	**At 12 weeks** PASI 75, % 1)86.7 2)71.7 3)3.3 PASI 90, % 1)55.0 2)40.0 3)0 PASI 100, % 1)26.7 2)16.7 (p=0.0006 vs. (3)) 3)0 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*	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
Lacour, 2017 [156] **(NCT01636687)** **JUNCTURE** ***Good quality publication*** ***NEW EVIDENCE***	Phase III, randomized, controlled, double-blind, parallel-group, multicenter trial	1) Secukinumab 150 mg (n=61) 2) Secukinumab 300 mg (n=60) 3) Placebo (n=61) *See Paul, 2015* [97]	*See Paul, 2015* [97]	*See Paul, 2015* [97] **Additional patient characteristics:** mIGA, moderate (3), % 1)57.4; 2)65.0; 3)62.3 mIGA, severe (4), % 1)42.6; 2)35.0; 3)37.7	**At 52 weeks** PASI 75, % 1)70; 2)80 PASI 90, % 1)53.3; 2)63.3 PASI 100, % 1)30.0; 2)38.3 mIGA 0 or 1, %	**0-52 weeks** Any AE, % 1)78.7; 2)88.6 Serious AEs, % 1)13.5; 2)8.0 AE discontinuation, % 1)1.1; 2)0 Serious infections, % 1)3.4; 2)2.3

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
					1)55.0; 2)68.3 MACE, % 1)1.1; 2)0	
Langley, 2014[157] **(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 excluded from analysis	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: Non-plaque or drug induced psoriasis	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 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 Previous biologic, % 1) 28.6 2) 29.8 3) 29.4	**At 12 weeks** PASI 75, % 1) 81.6 2) 71.6 3) 4.5 IGA 0/1, % 1) 65.3 2) 51.2 3) 2.4 PASI 90, % 1) 59.2 2) 39.1 3) 1.2 DLQI, change in mean score 1) -11.4 2) -10.1 3) -1.1 DLQI, score of 0/1, % 1) 58.8 2) 46.1 3) 10.3 **all p<0.001 for comparisons with placebo*	**0-12 weeks** 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

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Ohtsuki, 2014[158] **ERASURE**	*Sub analysis of Japanese patients (18 sites in Japan) enrolled in ERASURE trial*	*See Langley, 2014[157]* Bio-naïve 1) 23 2) 24 3) 23 Bio-exposed 1) 6 2) 5 3) 6	*See Langley, 2014[157]*	Age 1) 51.9 2) 48.2 3) 50.2 Male, % 1) 89.7 2) 79.3 3) 79.3 Mean PASI 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 3) 20.7	**At 12 weeks** 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 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: 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	AEs (%) 1) 48.3 2) 55.2 3) 41.4 SAEs (per 100 PYs) 1) 2.7 2) 8.5 3) 0
Blauvelt, 2014[159] **ERASURE**	*See Langley, 2014[157]*	*See Langley, 2014[157]* 1)secukinumab 300 mg 2)secukinumab 150 mg	*See Langley, 2014[157]*	PsA patients (n=171)	**At 12 weeks** PASI 75,% 1) 68; 2) 70; 3)4	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Abstract	*Reports outcomes of subpopulation w/ PsA*	3)placebo			PASI 90,% 1) 53; 2) 44; 3) 0	
Papp, 2014[160] **ERASURE** ***Abstract***	*See Langley, 2014[157]* Reports outcomes based on prior biologic exposure	*See Langley, 2014[157]*	*See Langley, 2014[157]*	Previous exposure to biologic (n=216/738) Previous inadequate response to biologic (n=72/216)	**At 12 weeks** No prior exposure PASI 75, % 1) 84.0; 2) 74.7; 3) 4.6 IGA 0/1, % 1) 67.4; 2) 55.0; 3) 2.9 Prior exposure PASI 75, % 1) 75.7; 2) 64.4; 3) 4.1 IGA 0/1, % 1) 60.0; 2) 42.5; 3) 1.4 **p<0.0001 for each secukinumab dose vs. placebo*	NR
Wu, 2017 [161] **(NCT01365455)** **ERASURE** ***Good quality publication*** ***NEW EVIDENCE***	Phase III, randomized, controlled, double blind, multicenter trial *Subgroup analysis-Taiwanese patients in ERASURE*	1) Secukinumab 150 mg q4w (n=20) 2) Secukinumab 300 mg q4w (n=16) 3) Placebo (n=15) SEC was administered at week 0, 1, 2, 3, 4 and then q4w through week 48. In the placebo arm, patients who did not achieve PASI 75 were rerandomized to received SEC 150 mg or 300 mg at week 12. Those patients who	*See Langley, 2014 [157]*	Age, mean 1)39.5; 2)38.1;3)40.6 Male, % 1)70; 2)87.5; 3)86.7 With PsA, % 1)15; 2)18.8; 3)26.7 Duration of PsO, yr 1)14.5 (5.8); 2)13.6 (6.9); 3)8.3 (5.8) Previous TNFα, % 1)25; 2)25; 3)6.7 PASI, mean (SD) 1)20.9 (7.7); 2)24.7 (8.5); 3)21.1 (6.5)	**At 12 weeks** PASI 75, % 1)70; 2)87.5; 3)0 *p<0.001 for SEC 150, SEC 300 vs. PBO* PASI 90, % 1)45; 2)68.8; 3)0 *p=0.004 for SEC 150 and p<0.001 for SEC 300 vs. PBO* PASI 100, % 1)15; 2)31.3; 3)0 *p<0.05 for SEC 300 vs. PBO* mIGA 0 or 1, %	**0-12 weeks** Any AE, % 2)80; 2)93.8; 3)80 Serious AE, % 1)0; 2)0; 3)0 AE leading to discontinuation, % 1)0; 2)0; 3)0

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
		achieved PASI 75 underwent continuous placebo treatment.		mIGA, severe (4), % 1)20; 2)12.5; 3)33.3	1)65; 2)68.8; 3)0 *p<0.001 for SEC 150, SEC 300 vs. PBO.*	
Langley, 2014[157] **(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: Non-plaque or drug induced psoriasis; previous etanercept	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 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 Previous biologic, % 1) 11.6 2) 13.8 3) 13.8 4) 10.7	**At 12 weeks** PASI 75, % 1) 77.1 2) 67.0 3) 44.0 4) 4.9 IGA 0/1, % 1) 62.5 2) 51.1 3) 27.2 4) 2.8 PASI 90, % 1) 54.2 2) 41.9 3) 20.7 4) 1.5 DLQI, change in mean score 1) -10.4 2) -9.7 3) -7.9 4) -1.9 **all p<0.001 for comparisons between secukinumab and etanercept/placebo* DLQI, score of 0/1, % 1) -10.4 2) -9.7 3) -7.9	**0-12 weeks** 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 2) 10 3) 12 4) 3

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
					4) -1.9	
Sigurgeirsson, 2014 [162] **(NCT01358578)** **FIXTURE** ***Abstract*** ***NEW EVIDENCE***	Phase III, randomized, controlled, double-blind, multicenter trial *Subgroup analysis- Concomitant PsA*	1) Secukinumab 150 mg q4w (n=49) 2) Secukinumab 300 mg q4w (n=50) 3) Etanercept 50 mg biw until week 12, then once weekly thereafter (n=44) 4) Placebo (n=47) Secukinumab was administered at weekly for 4 weeks and then q4w thereafter.	*See Langley, 2014* [157]	*See Langley, 2014* [157]	**At 12 weeks** PASI 75, % 1)59; 2)72; 3)39; 2)2 *p<0.01 for secukinumab 150, secukinumab 300 vs. PBO. p<0.01 for secukinumab 300 vs. ETN.* PASI 90, % 1)39; 2)44; 3)18; 2)2 *p<0.01 for secukinumab 150, secukinumab 300 vs. PBO. p<0.01 for secukinumab 300 vs. ETN.*	NR
Strober, 2016[163] **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) 2) secukinumab 150mg (n=229) 3) placebo (n=225)	See ERASURE and FIXTURE	Age (yr), mean 1) 43.0; 2) 45.7; 3) 43.1 Male, % 1) 62.5; 2) 65.9; 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)	**At week 12** Response rate* for itching, % 1) 83.0; 2) 78.2; 3) 16.9 Response rate* for pain % 1) 72.8; 2) 65.5; 3) 15.6 Response rate* for scaling, % 1) 83.0; 2) 78.2; 3) 13.8 *reduction of ≥2.2 points from baseline	*NR*

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
				PSD, scaling mean (SD) 1) 6.4 (2.6); 2) 6.5 (2.4) 3) 6.2 (2.4)		
Lee, 2015 [164] **ERASURE & FIXTURE** **(NCT01365455& NCT01358578)** ***Abstract*** ***NEW EVIDENCE***	Phase III, randomized, controlled, double-blind, multicenter trials *Pooled, subgroup analysis- Asian patients*	1) Secukinumab 150 mg (n=NR) 2) Secukinumab 300 mg (n=NR) 3) Etanercept 50 mg BIW (n=NR) 4)Placebo (n=NR) Secukinumab administered at weeks 0, 1, 2, 3, 4 and then q4w thereafter.	*See Langley, 2014* [157]	*See Langley, 2014* [157]	**At 12 weeks** PASI 75, % 1)67.5; 2)74.4; 3)27.4; 4)6.8 *p<0.0001 for SEC 150, SEC 300 vs. PBO and ETN* PASI 90, % 1)40.5; 2)53.6; 3)13.7; 4)0.9, *p=NR* IGA, 0 or 1, % 1)46.0; 2)52.8; 3)17.8; 4)2.6 *p<0.0001 for SEC 150, SEC 300 vs. PBO and ETN*	NR
Korman, 2017 [118] **ERASURE & FIXTURE** **(NCT01365455& NCT01358578)** ***Good quality publication*** ***NEW EVIDENCE***	Phase III, randomized, controlled, double-blind, multicenter trials *Pooled analysis*	1) Secukinumab 300 mg (n=572) 2) Etanercept (n=326) 3)Placebo (n=572) Secukinumab administered at weeks 0, 1, 2, 3, 4 and then q4w thereafter. Subjects randomized to placebo and those who did not respond were	*See Langley, 2014* [157]	Age, mean (SD) 1)44.5 (13.5); 2)42.9 (12.9); 3)44.8 (12.9) Male, % 1)68.7; 2)71.2; 3)71.2 PASI, mean (SD) 1) 23.3 (9.7) 2) 23.2 (9.8) 3) 22.9 (10.0) DLQI total, mean (SD) 1) 13.6 (7.3) 2) 13.4 (7.3)	**At 12 weeks** DLQI PRD score, change from baseline, mean (SD) 1)-1.5 (1.7); 2)-1.2 (1.8); 3)-0.1 (1.4) *p<0.05 for SEC vs. ETN, p<0.0001 for SEC vs. PBO* DLQI PRD score 0, % 1)47.5; 2)37.6; 3)15.5 *p<0.01 for SEC vs. ETN, p<0.0001 for SEC vs. PBO*	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
		rerandomized to secukinumab at week 12.		3) 12.8 (7.1) DLQI PRD score, mean (SD) 1)1.9 (1.9); 2)2.1 (1.9); 3)1.8 (1.8) DLQI skin-related sexual difficulties, mean (SD) 1)1.2 (1.1); 2)1.1 (1.1); 3)1.1 (1.0)	DLQI skin-related sexual difficulties, change from baseline, mean (SD) 1)-1.0; 2)-0.7; 2)0 *p<0.01 for SEC vs. ETN, p<0.0001 for SEC vs. PBO* DLQI skin-related sexual difficulties 0, % 1)36.7; 2)34.0; 3)9.7 *p<0.0001 for SEC vs. PBO* **At 52 weeks*** DLQI PRD score, change from baseline, mean (SD) 1)-1.62; 2)-1.40 DLQI PRD score 0, % 1)54.6; 2)48.6; *p<0.05* DLQI skin-related sexual difficulties, change from baseline, mean (SD) 1)-1.0; 2)-0.8; *p<0.01* DLQI skin-related sexual difficulties 0, % 1)39.8; 2)35.5 *See publication for number analyzed at 52 weeks.	

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
van de Kerkhof, 2016 [165] **ERASURE, FIXTURE, FEATURE, JUNCTURE, SCULPTURE, STATURE, and 4 phase II trials** **(NCT01365455, NCT01358578, NCT01555125, NCT0163668, NCT01406938, NCT01412944, NCT00941031, NCT01132612, NCT01071252, NCT00805480)** ***Good quality publication*** ***NEW EVIDENCE***	Phase II and III, randomized, double-blind trials All studies except two phase III trials were not placebo-controlled *Pooled analysis*	1) Secukinumab 300 mg (n=1173)* 2) Secukinumab 150 mg(n=1174)* 3) Secukinumab 300 or 150 mg (n=2877)† 4) Etanercept (n=323)‡ 5) Placebo (n=793) *Includes subjects from phase III studies only who were randomized to the specified secukinumab dose at the study start. †Includes subjects from phase II and III studies who were randomized to any secukinumab dose at the study start. ‡Etanercept data are from one phase III trial (FIXTURE).	NR *See van de Kerkhof, 2016* [165] *for additional information*	Age, mean 1)45.6; 2)45.2; 3)45.2; 4)43.8; 5)44.6 Male, % 1)68.9; 2)67.3; 3)69.8; 4)70.9; 5)69.6 Caucasian, % 1)72.2; 2)72.2; 3)75.1; 4)66.9; 5)74.8 With PsA, % 1)22.7; 2)32.6; 3)29.3; 4)17.9 Duration of PsO, yr 1)18.8; 2)18.9; 3)19.2; 4)13.6; 5)18.8 Previous biologics, % 1)24.5; 2)24.7; 3)25.4; 4)13.9; 5)22.0 PASI, mean (SD) 1) 22.9 (9.5); 2) 23.3 (10.2); 3) 22.6 (9.6); 4) 23.3 (9.8); 5) 22.2 (9.6)	NR	**0-12 weeks** Any AE, % 1)54.2; 2)56.3; 3)56.3; 4)57.6; 5)50.4 Nonfatal SAE, % 1)2.0; 2)1.9; 3)2.2; 4)0.9; 5)1.6 AEs leading to discontinuation, % 1)1.5; 2)1.5; 3)1.5; 4)1.9; 5)1.3 **0-52 weeks** Total P-Y 1) 117.5; 2) 1142.0 3) 2724.6; 4) 293.5 Any AE, IR/100 PY 1)236.1; 2)239.9; 3)252.9; 4)243.4 Nonfatal SAE, IR/100 PY 1)7.4; 2)6.8; 3)7.8; 4)7.0 AEs leading to discontinuation, n 1)46; 2)43; 3)118; 4)12

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
						Death, n 1)0; 2)1; 3)1; 4)0
Ixekizumab (Taltz)						
Gordon, 2016[166] **(NCT01474512)** **UNCOVER-1** ***Good quality publication***	Phase III RCT Double-blind Multicenter 100 sites worldwide ITT with NRI	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* 2a) maintained on ixekizumab 80mg Q4W 2b) switch to ixekizumab 80mg Q2W	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 <100kg, % 1) 67.1, 2) 66.5, 3) 66.5 PsO duration, years 1) 20, 2) 19, 3) 20 PASI score 1) 20, 2), 20, 3) 20 Previous biologics (%): 1) 42.0, 2) 38.9, 3) 40.0	**At 12 weeks** 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* **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	0-**12 weeks** (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 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[167] **(NCT01474512)** **UNCOVER-1** ***Abstract***	*Reports improvement in HRQoL for IXE Q4W*	See above	See above	See above	DLQI, mean change at 12 weeks: -11.3* DLQI, mean change at 60 weeks: -11.2*	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
					DLQI, score of 0/1 at 60 weeks (%): 66.4 *p<0.001 from baseline	
Imafuku, 2017 [168] **(NCT01474512)** **UNCOVER-1** ***Good quality publication*** ***NEW EVIDENCE***	Phase III, randomized, controlled, double-blind, multicenter trial *Subgroup analysis-Japanese patients*	1) Ixekizumab 80 mg q4w after 160 mg loading dose (n=12) 2) Ixekizumab 80 mg q2w after 160 mg loading dose (n=8) 3) Placebo (n=13)	*See Gordon, 2016* [166]	Age, mean 1)44.5 (10.6); 2)45.5 (10.4); 3)51.4 (14.9) Male, % 1)83.3; 2)100; 3)69.2 Duration of PsO, yr 1)18.7; 2)13.9; 3)13.2 Previous biologics, % 1)0; 2)0; 3)0 PASI, mean (SD) 1) 22.3 (9.4) 2) 27.6 (14.7) 3) 24.8 (12.9) sPGA, moderate (3), % 1)41.7; 2)50.0; 3)46.2 sPGA, severe (4), % 1)58.3; 2)37.5; 3)38.5 sPGA, very severe (5), % 1)0; 2)12.5; 3)15.4 DLQI total, mean (SD) 1) 11.5 (7.6) 2) 13.9 (8.0)	**At 12 weeks** PASI 75, % 1)75; 2)100; 3)0 PASI 90, % 1)58.3; 2)75; 3)0 PASI 100, % 1)33.3; 2)37.5; 3)0 sPGA (0, 1), % 1)66.7; 2)100; 3)0 DLQI, change from baseline, mean (SD) 1) -9.0 (6.91 2) -13.3 (7.38) 3) -2.6 (8.22)	**0-12 weeks** Any TEAE, % 1)75; 2)87.5; 3)76.9 SAE, % 1)8.3; 2)0; 3)7.7 TEAE leading to discontinuation, % 1)25; 3)0; 3)7.7 Infection, % 1)25; 3)25; 3)23.1

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
				3) 12.9 (7.9)		
Griffiths, 2015[100] and Gordon, 2016[166] **(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 ITT	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 randomized withdrawal period*	Inclusion: ≥18 years BSA ≥10%, PASI ≥12 sPGA ≥3 ≥6 months of plaque psoriasis diagnosis Candidates for phototherapy or systemic therapy Exclusion: Patients who had used etanercept at any time before screening	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): 1) 19, 2) 19, 3) 19, 4) 18 PASI: 1) 21, 2) 19, 3) 20, 4) 19 Previous biologics (%): 1) 25.6, 2) 21.2, 3) 24.5, 4) 23.9	**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 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*	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 (%): 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[169] **(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

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Griffiths, 2015[100] and Gordon, 2016[166] **(NCT01646177)** **UNCOVER-3** ***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 ITT	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 ≥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 Previous biologics (%): 1) 17.1, 2) 15.7, 3) 15.0, 4) 15.1	**At 12 weeks** 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 (%): 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 above

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Blauvelt, 2017 [170] **UNCOVER-3** **(NCT01646177)** ***Good quality publication*** ***NEW EVIDENCE***	Phase III, randomized, controlled, double-blind, multicenter trial *Long term safety*	1) Ixekizumab 80 mg q2w (0-12 weeks), IXE 80 mg q4w (12-108 weeks) (n=385 for efficacy; n=362 for safety) 2) Ixekizumab 80 mg q4w (0-12 weeks), IXE 80 mg q4w (12-108 weeks) (n=360) 3) Etanercept 50 mg BIW (0-12 weeks), IXE 80 mg q4w (12-108 weeks) (n=369) 4) Placebo (0-12 weeks), IXE 80 mg q4w (12-108 weeks) (n=183) After the 12-week induction period, patients entered the LTE and received IXE 80 mg q4w. After week 60, patients could increase dose to IXE 80 mg q2w at the investigator's discretion.	*See Griffiths, 2015* [100] *and Gordon, 2016* [166]	*See Griffiths, 2015* [100] *and Gordon, 2016* [166]	**At 108 weeks** PASI 75, % 1)83.6 PASI 90, % 1)70.3 PASI 100, % 1)48.9 sPGA 0 or 1, % 1)74.1 * Efficacy results are only reported for patients who received recommended dose of IXE 80 mg q2w during the induction period and IXE 80 mg q4w during the LTE. Safety results are reported for all treatment arms.	**At 108 weeks** Any TEAE, % 1)84.5; 2)84.7; 3)84.8; 4)83.6 Any severe TEAE, % 1)9.9; 2)14.4; 3)14.1; 4)14.8 Any serious AE, % 1)8.3; 2)11.9; 3)12.7; 4)15.3 Candida infections, % 1)3.3; 2)5.0; 3)3.0; 4)4.4 Malignancies, % 1)1.4; 2)2.8; 3)1.4; 4)1.1 Cerebrocardiovascular events, % 1)1.9; 2)1.7; 3)2.7; 4)4.4 Death, n 1)1; 2)1; 3)2; 4)1

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Leonardi, 2018 [171] **UNCOVER-3** **(NCT01646177)** ***Abstract*** ***NEW EVIDENCE***	Phase III, randomized, controlled, double-blind, multicenter trial *Long term safety*	After the 12-week induction period, patients entered the LTE and received IXE 80 mg q4w. After week 60, patients could increase dose to IXE 80 mg q2w at the investigator's discretion. 1) Ixekizumab 80 mg q2w (0-12 weeks), IXE 80 mg q4w (12-156 weeks)* (n=385 for efficacy, 362 for safety) 2) Ixekizumab 80 mg q4w (0-12 weeks), IXE 80 mg q4w (12-156 weeks) (n=360) 3) Etanercept 50 mg BIW (0-12 weeks), IXE 80 mg q4w (12-156 weeks) (n=369) 4) Placebo (0-12 weeks), IXE 80 mg q4w (12-156 weeks) (n=183) *Patients randomized to IXE q2w/IXE q4w were considered for primary efficacy analysis	*See Griffiths, 2015* [100] *and Gordon, 2016* [166]	*See Griffiths, 2015* [100] *and Gordon, 2016* [166]	**At 156 weeks** PASI 75, % 1)80.5 PASI 90, % 1)66.0 PASI 100, % 1)45.1 sPGA 0/1, % 1)67.4 sPGA 0, % 1)48.5 *Results presented here are for patients who received IXE 80 mg q4w during entire OLE. See publication for results including patients who increased dose to IXE 80 mg q2w.*	**0-156 weeks** Any TEAE, % 1)87.8; 2)86.4; 3)87.0; 4)88.5 Severe TEAE, % 1)11.6; 2)16.9; 3)16.8; 4)19.7 Discontinuation due to AE, % 1)6.4; 2)8.3; 3)7.9; 4)8.2 Viral upper respiratory tract infection, % 1)28.5; 2)25.3; 3)28.2; 4)29.0 Upper respiratory tract infection, % 1)8.8; 2)11.1; 3)7.9; 4)8.7 Injection-site reaction, % 1)6.4; 2)8.9; 3)6.5; 4)9.3 Candida infection, % 1)3.6; 2)6.1; 3)4.1; 4)4.9 Death, % 1)0.6; 2)0.3; 3)0.5; 4)1.1

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Gottlieb, 2016 [172] **(NCT01597245 & NCT01646177)** **UNCOVER -2 and -3** ***NEW EVIDENCE***	Phase III, randomized, controlled, double-blind, multicenter trials *Pooled analysis*	*Prior biologic* 1) Ixekizumab 80 mg q4w after 160 mg loading dose (n=143) 2) Ixekizumab 80 mg q2w after 160 mg loading dose (n=142) 3) Etanercept 50 mg BIW (n=136) 4) Placebo (n=76) *No prior biologic* 5) Ixekizumab 80 mg q4w after 160 mg loading dose (n=590) 6) Ixekizumab 80 mg q2w after 160 mg loading dose (n=594) 7) Etanercept 50 mg BIW (n=604) 8) Placebo (n=284)	*See Griffiths, 2015* [100] *and Gordon, 2016* [166]	*See Griffiths, 2015* [100] *and Gordon, 2016* [166]	**At 12 weeks** PASI 75, % 1)76.2; 2)91.5; 3)34.6; 5)82.2; 6)87.7; 7)50.7 PASI 90, % 1)55.2; 2)76.1; 3)13.2; 5)64.4; 6)67.7; 7)24.3 PASI 100, % 1)25.2; 2)47.2; 3)3.7; 5)34.9; 6)37.0; 7)7.0 Itch NRS responders*, % 1)80.3; 2)82.4; 3)55.0; 5)77.9; 6)84.1; 7)62.4 *p<0.001 for all IXE vs. ETN* *Total number of patients analyzed differs for this outcome. See publication for details.	**0-12 weeks** Any TEAE, % 1)55; 2)55; 3)56; 4)45; 5)58; 6)58; 7)54; 8)44 Any SAE, % 1)1.4; 2)1.4; 3)1.5; 4)1.3; 5)2.0; 6)2.0; 7)2.0; 8)2.1 Infections, % 1)27; 2)25; 3)24; 4)25; 5)26; 6)26; 7)21; 8)19

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Guenther, 2017 [173] **(NCT01597245 & NCT01646177)** **UNCOVER -2 and -3** ***Good quality publication*** ***NEW EVIDENCE***	Phase III, randomized, controlled, double-blind, multicenter trials *Pooled analysis*	1) Ixekizumab 80 mg q4w after 160 mg loading dose (n=733) 1) Ixekizumab 80 mg q2w after 160 mg loading dose (n=736) 3) Etanercept 50 mg BIW (n=740) 4) Placebo (n=361)	*See Griffiths, 2015* [100] *and Gordon, 2016* [166]	*See Griffiths, 2015* [100] *and Gordon, 2016* [166] **Additional patient characteristics:** DLQI personal relationship domain (PRD) score, mean (SD) 1) 1.6 (1.8) 2) 1.7 (1.8) 3) 1.7 (1.8) 4) 1.8 (1.9)	**At 12 weeks** Change in PRD score, mean (SE) 1)-1.3 (0.05); 2)-1.4 (0.04); 3)-1.1 (0.03); 4)-0.1 (0.05) *p<0.001 for IXE q4w, IXE q2w vs. ETN & PBO* Skin-related sexual difficulties, % 1)18.1; 2)12.9; 3)23.6; 4)49.3 *p≤0.001 for IXE q4w, IXE q2w vs. ETN & PBO* Improvement in skin-related sexual difficulties, % 1)71.7; 2)79.6; 3)59.4; 4)24.7, *p=NR* Sexual health impairment, % 1)3.8; 2)1.8; 3)5.0; 4)18.8 *p<0.001 for IXE q4w, IXE q2w vs. PBO; p<0.001 for IXE q2w vs. ETN* Improvement in skin-related sexual health impairment, % 1)83.4; 2)91.2; 3)77.9; 3)48.5, *p=NR*	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Kimball, 2016 [174] **(NCT01474512, NCT01597245, & NCT01646177)** **UNCOVER -1, -2, & -3** ***Good quality publication*** ***NEW EVIDENCE***	Phase III, randomized, controlled, double-blind, multicenter trials	UNCOVER-1 1) Ixekizumab 80 mg q4w after 160 mg loading dose 1) Ixekizumab 80 mg q2w after 160 mg loading dose 3) Placebo UNCOVER-2 and -3 1) Ixekizumab 80 mg q4w after 160 mg loading dose 1) Ixekizumab 80 mg q2w after 160 mg loading dose 3) Etanercept 50 mg BIW 4) Placebo	*See Gordon, 2016* [166] *for UNCOVER-1,* *See Griffiths, 2015* [100] *and Gordon, 2016* [166] *for UNCOVER-2 and -3*	*See Gordon, 2016* [166] *for UNCOVER-1,* *See Griffiths, 2015* [100] *and Gordon, 2016* [166] *for UNCOVER-2 and -3* **Additional patient characteristics:** UNCOVER-1 Itch NRS, range 7.0-7.2 Skin pain VAS, range 46.9-48.9 UNCOVER-2 Itch NRS, range 6.4-6.7 Skin pain VAS, range 43.3-46.9 UNCOVER-3 Itch NRS, range 6.2-6.5 Skin pain VAS, range 38.4-43.2	**At 12 weeks** UNCOVER-1 Itch NRS, mean 1)1.38; 2)1.38; 3)6.67 *p<0.001 for IXE q4w, IXE q2w vs. PBO* Skin pain VAS, mean 1)8.18; 2)6.62; 3)47.3 *p<0.001 for IXE q4w, IXE q2w vs. PBO* UNCOVER-2 Itch NRS, mean 1)1.67; 2)1.38; 3)2.94; 4)6.10 *p<0.001 for IXE q4w, IXE q2w vs. PBO* Skin pain VAS, mean 1)9.44; 2)6.78; 3)17.4; 4)44.3 *p<0.001 for IXE q4w, IXE q2w, ETN vs. PBO* UNCOVER-3 Itch NRS, mean 1)1.57; 2)1.14; 3)2.42; 4)5.86 *p<0.001 for IXE q4w, IXE q2w vs. PBO* Skin pain VAS, mean 1)7.66; 2)5.15; 3)12.5; 4)40.4 *p<0.001 for IXE q4w, IXE q2w, ETN vs. PBO*	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Armstrong, 2016[139] **UNCOVER trials (all)** ***Good quality publication***	See above Secondary analysis to evaluate change in work productivity from baseline as measured by WPAI-PSO scores	N=3866	See main trials	See main trials	WPAI-PSO* *UNCOVER-1* Absenteeism: 1)0.2, 2)-3.5, *p< 0.001 vs.1*, 3)-2.6, *p=0.003 vs.1* Presenteeism: 1) 0.5 2) -18.8, 3) -18.3 *2 and 3 vs. 1, p<0.001* Work productivity loss: 1) -0.8, 2) -20.6, 3) -19.8 *2 and 3 vs. 1, p<0.001* Activity impairment: 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 -3, with the exception of absenteeism with ixekizumab Q4W in UNCOVER-2* *UNCOVER-2 (from graph)* Work productivity loss: 1)-2, 2) -14, 3) -19, 4) -19.5 *2 and 3 vs. 1 and 2, p<0.001* *UNCOVER-3 (from graph)* Work productivity loss: 1) +0.7, 2) -17, 3) -16, 4) -19 *4 vs. 1, p<0.001; all other comparisons NS* **Data presented as LSM change from baseline relative to placebo*	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Griffiths, 2016[175] **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* **Outcomes presented for NRI analysis*	NR
Gottlieb, 2016[176] **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	**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

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Gottlieb, 2015[177] **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 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*	NR
2016 **IXORA-S** **(NCT02561806)** ***Abstract***	Phase III RCT Double-blind Multicenter	N=302 1)ixekizumab, 80mg Q2W (n=136) 2)ustekinumab, dosed by weight according to the label(n=166)	Inclusion: ≥6 months of plaque psoriasis diagnosis Failure of at least 1 systemic therapy Baseline PASI ≥10 Exclusion: Prior use of ustekinumab, prior use of IL-17A or IL12/23 antagonists, use of biologics within washout periods, ongoing or serious infection.	NR	PASI 75 (%): 1)91% 2)69% PASI 90 (%): 1)75 2)42 PASI 100(%); 1)37 2)15 sPGA of 0 (%): 1)43 2)18 DLQI of 0/1 (%): 1)63; 2)45	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Brodalumab						
Papp, 2012[178] **(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) Also evaluated 280mg brodalumab monthly	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) 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 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 (%): Etanercept- 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	**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 (%): 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* 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*	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 Discontinuation due to AEs (%): 1) 0, 2) 0, 3) 5, 4) 3 Deaths: NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Papp, 2015 [179] **(NCT00975637)** ***Abstract*** ***NEW EVIDENCE***	Phase II, double-blind, randomized, controlled, multicenter trial with open-label extension 23 international sites	1) Brodalumab 140 mg or 210 mg (n=181) Subjects previously received placebo or brodalumab 70, 140, 210 mg q2w or 280 mg q4w. Subjects enrolled in OLE initially received brodalumab 210 mg q2w. A protocol amendment after 1 year reduced the dose to 140 mg for subjects ≤100 kg (n=119). A subsequent protocol amendment allowed for subjects with inadequate response to 140 mg to increase to 210 mg (n=19).	*See Papp, 2012* [178]	*See Papp, 2012* [178]	**Week 12 OLE** PASI 75, % 1)95.4 PASI 90, % 1)85.1 PASI 100, % 1)62.9 **Week 48 OLE** PASI 75, % 1)93.3 PASI 90, % 1)83.0 PASI 100, % 1)61.8 **Week 144 OLE** PASI 75, % 1)85.4 PASI 90, % 1)73.6 PASI 100, % 1)51.4	**0-144 weeks** Any TEAE, % 1)94.5 Most frequently reported AEs were nasopharyngitis (26.5%), upper respiratory tract infection (19.9%), arthralgia (17.1%), back pain (11.0%), and influenza (10.5%).

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
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 2 and 3 vs. 4, p<0.0001; 1 vs. 4, p=0.042	NR
Papp, 2014[180] **(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 (%) 1) 100, 2) 0, 3) 24.3, 4) 22.7 Previous biologics (%): TNFα- 1) 32.6, 2) 21.7, 3) 68.6, 4) 0 Ustekinumab- 1) 4.3, 2) 13.8, 3) 32.9, 4) 0	**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 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 vs. placebo were SS.* *Outcomes not compared between subgroups*	AEs of any grade were higher among patients who received brodalumab versus placebo and were similar among subgroups (data NR)

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Papp, 2015[181] **(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[102] **(NCT01708590)** **AMAGINE 1** ***Good quality publication***	Phase III RCT Double-blind Multicenter 73 sites in the US, Canada, and Europe ITT (all randomized patients)	N=661 1) brodalumab 140mg Q2W (n=219) 2) brodalumab 210mg Q2W 3) placebo (n=222) Patients who achieved sPGA success (≥2) at week 12 were rerandomized to their induction doses of brodalumab or placebo	Inclusion: 18 - 75years BSA ≥10%, PASI ≥12 sPGA ≥3 ≥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)	Age (years): 1) 46, 2) 46, 3) 47 % male: 1) 74, 2) 73, 3) 73 Weight (kg): 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	**At week 12:** PASI 75 (%): 1) 60, 2) 83, 3) 3 PASI 90 (%): 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) 53, 2) 61, 3) 4	Primary outcomes at week 12: AEs ≥1 (%): 1) 58, 2) 59, 3) 51 SAEs (%): 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 brodalumab 210mg group)

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Strober, 2016[182] **(NCT01708590)** **AMAGINE 1** ***Abstract***	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 **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	NR
Lebwohl, 2015[183] **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 rerandomization to receive one of four brodalumab maintenance regimens	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): 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	**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 (%) 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)	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 (%): 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) 2 additional attempted suicides in the same patient as the induction period and 1 in the UST group at 52 weeks

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Lebwohl, 2015[183] **(NCT01708629)** **AMAGINE-3** ***Good quality publication***	Phase III RCT Double-blind Multicenter 142 international sites (US, Canada, Europe, Australia) ITT	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): 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	**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 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* **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	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 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
Lebwohl, 2017 [101] **AMAGINE 1, 2, 3**	Phase III, randomized, controlled, double-blind, multicenter trials *Pooled analysis*	1) Placebo (n=844) 2) Brodalumab 140 mg (n=1458)	*See Papp, 2016 for AMAGINE 1[102] and Lebwohl, 2015[183] for AMAGINE 2 and 3*	*See Papp, 2016 for AMAGINE 1[102] and Lebwohl, 2015[183] for AMAGINE 2 and 3*	**At 12 weeks** *Prior biologic use* PASI 75, % 1) 2.6 2) 60.7 3) 83.1	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
(NCT01708590 & NCT01708603 & NCT01708629) ***Abstract*** ***NEW EVIDENCE***		3) Brodalumab 210 mg (n=1458)			PASI 90, % 1) 0.4 2) 43.2 3) 66.7 PASI 100, % 1) 0.0 2) 20.3 3) 40.3 *No prior biologic use* PASI 75, % 1) 7.5 2) 69.3 3) 86.3 PASI 90, % 1) 2.8 2) 52.2 3) 70.9 PASI 100, % 1) 0.7 2) 28.3 3) 40.9	
Nakagawa, 2016[98] ***Good quality publication*** ***NEW EVIDENCE***	Phase II, randomized, controlled, double-blind multicenter trial Sites in Japan	1) Brodalumab (210mg) (n=37) 2) Brodalumab (140mg) (n=37)	Inclusion: Adult patients (20-70 years) with moderate to severe plaque psoriasis (PASI ≥12, BSA ≥10%) for at least 6 months and	Age, mean 1)46.4; 2)46.4; 3)43.4; 4) 46.6 Male, % 1)75.0; 2)72.0; 3)63.0	**At 12 weeks** PASI 75 (%): 1)94.6*; 2)78.4*; 3)25.6; 4)7.9 PASI 90 (%):	**0-12 weeks** Any AE. % 1) 73 2) 57 3) 54 4) 45

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
		3) Brodalumab (70mg) (n=39) 4) Placebo (n=38)	were candidate for systematic therapy or phototherapy. Negative HBV, HCV, HIV, TB & human T-cell lymphotropic virus tests were required Exclusion: Erythrodermic, guttate, pustular, or dug induced psoriasis, CHF, MI, unstable angina (within a year), current or previous history of malignancy (within 5 years). Previous use of systemic therapy, phototherapy, or biologic agents were allowed after washout.	Caucasian, % 1)78.4; 2)81.1; 3)87.2; 4)71.1 Duration of PsO, yr 1)15.0; 2)14.5; 3)13.3; 4)16.9 With PsA, % 1)13.5; 2)16.2; 3)15.4; 4)18.4 Prior Biologic, % 1)13.5; 2)8.1; 3)12.8; 3)7.9 PASI, mean (SD) 1)28.0 (14.4) 2)28.5 (10.7) 3)27.6 (11.6) 4)24.0 (8.9)	1)91.9*; 2)64.9*; 3)15.4; 4)2.6 PASI 100 (%): 1) 59.5*; 2) 35.1*; 3) 2.6; 4) 0 sPGA of '0' or '1' (%) 1)94.6*; 2)78.4*; 3)25.6†; 4)5.3 *Change from baseline* DLQI 1) -9.0*; 2)-8.4*; 3) -2.2; 4) -2.0 SF36 - (PC) 1) -8.1†; 2)-3.8; 3) -1.8; 4)-0.2 SF36 - (MC) 1) -5.0†; 2)-7.0†; 3) -1.9; 4)-1.1 *†p<0.05 vs placebo* **P<0.001 vs placebo*	Serious AE, % 1) 2.7 2) 0 3) 5.1 4) 2.6
Umezawa, 2016[184] ***Good quality publication*** ***NEW EVIDENCE***	Phase II, randomized, controlled, double-blind multicenter trial with open label extension *See Nakagawa, 2016[98]*	**Week 0 – 12** 1) Brodalumab (210mg) (n=37) 2) Brodalumab (140mg) (n=37)	*See Nakagawa, 2016[98]*	*See Nakagawa, 2016[98]*	**Week 52** PASI 75 (%): 1)94.4; 2)78.1 PASI 90 (%): 1)87.5; 2)71.2	**0-52 weeks** Any AE, % 1) 92 2) 86

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
		3) Brodalumab (70mg) (n=39) 4) Placebo (n=38) At 12 weeks, patients in the 70mg brodalumab or placebo group in the main RCT were allocated to either the 140mg or 210mg brodalumab group. **After Week 12** 1) Brodalumab (210mg) (n=73) 2) Brodalumab (140mg) (n=72)			PASI 100 (%): 1) 55.6; 2) 43.8 sPGA of 'clear' or 'minimal' (%) 1)91.7; 2)69.9 *Change from baseline* DLQI 1) -7.9; 2)-8.3 SF36 - (PC) 1) -6.4; 2)-5.8 SF36 - (MC) 1) -6.8; 2)-3.6	Discontinuation due to AE, % 1) 0 2) 0 No death
Anti IL-12/13 Agent						
Ustekinumab (Stelara)						
Griffiths, 2010[111] **(NCT00454584)**	Phase III RCT Multicenter	N=903 1) ustekinumab 45mg (n=209)	Inclusion: ≥18 years BSA ≥10%, PASI ≥12, sPGA ≥3	Age (years): 1) 45.1, 2) 44.8, 3) 45.7 % male: 1) 63.6, 67.4, 3) 70.9	**Week 12:** PASI 75 (%) 1) 67.5 2) 73.8, 3) 56.8 *1 vs. 3, p=0.01*	Primary outcomes at week 12: AEs ≥1 (%): 1) 66.0, 2) 69.2), 3) 70.0

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
ACCEPT ***Fair quality publication***	*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	2) ustekinumab 90mg (n=347) 3) etanercept 50mg (n=347) *Patients who did not respond on etanercept crossed over to receive ustekinumab*	≥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	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 Previous biologics (%): 1) 12.4, 2) 10.4, 3) 11.8	*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 PGA- cleared or minimal (%): 40.4	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 were similar in the lower-dose and higher-dose ustekinumab groups and also before and after crossover from etanercept to ustekinumab
Leonardi, 2008[93] **(NCT00267969)** **PHOENIX 1** ***Good quality publication***	Phase III RCT Double-blind Multicenter 48 sites in the US, Canada, and Belgium	N=766 1) ustekinumab 45mg (n=255) 2) ustekinumab 90mg (n=256) 3) placebo (n=255)	Inclusion: ≥18 years PASI ≥12 BSA ≥10% ≥6 months of plaque psoriasis diagnosis	Age: 1) 44.8, 2) 46.2, 3) 44.8 % male: 1) 68.6, 2) 67.6, 3) 71.8 Weight (kg):	Primary outcomes at wk 12: PASI 75 (%) 1) 67.1, 2) 66.4, 3) 3.1 PASI 50 (%) 1) 83.5, 2) 85.9, 3) 10.2 PASI 90 (%)	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 (%):

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
	ITT with NRI	Ustekinumab patients with PASI ≥75% improvement re-randomized at wk 40 1) maintenance (n=162) 2) withdrawal (n=160) *Cross-over to ustekinumab 45 or 90 mg at week 12*	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 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	1) 93.7, 2) 93.8, 3) 94.2 PsO duration (years): 1)19.7, 2) 19.6, 3) 20.4 PASI: 1) 20.5, 2) 19.7, 3) 20.4 DLQI: 1) 11.1, 2) 11.6, 3) 11.8 PsA: 1) 29.0, 2) 36.7, 3) 35.3 Previous biologics (%): 1) 52.2, 2) 50.8, 3) 50.2	1) 41.6, 2) 36.7, 3) 2.0 *All UST groups vs. placebo, p<0.0001* PGA- cleared or minimal (%): 1) 60.4, 2) 61.7, 3) 3.9 *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*	1) 0.8, 2) 1.6, 3) 0.8 Infections (%): 1) 31.4, 2) 25.9, 3) 26.7 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
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 100 (%) 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[92] **PHOENIX 2** ***Good quality publication***	Phase III RCT Double-blind Multicenter 70 sites in Europe and North	N=766 1) ustekinumab 45mg (n=409) 2) ustekinumab 90mg (n=411) 3) placebo (n=410)	Inclusion: ≥18 years PASI ≥12 BSA ≥10% ≥6 months of plaque psoriasis diagnosis	Age (years): 1) 45.1, 2) 46.6, 3) 47.0 % male: 1) 69.2, 2) 66.7, 3) 69.0 Weight (kg): 1) 90.3, 2) 91.5, 3) 91.1 PsO duration (years):	**At wk 12:** PASI 75 (%): 1) 66.7, 2) 75.7, 3) 3.7 PASI 50 (%): 1) 83.6, 2) 89.3, 3) 10.0 PASI 90 (%): 1) 42.3, 2) 50.9, 3) 0.7	Primary outcomes at week 12: AEs ≥1 at wk 12 (%): 1) 53.1, 47.9, 3) 49.8 URIs (%): 1) 4.4, 2) 2.9, 3) 3.4 SAEs (%):

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
	America ITT with NRI	*Partial responders (i.e., patients achieving ≥50% but <75% improvement from baseline in PASI) were re-randomized at week 28*	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) 19.3, 2) 20.3, 3) 20.8 PASI: 1) 19.4, 2) 20.1, 3) 19.4 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 Baseline characteristics for partial responders at wk 28 also reported	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*	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. 1 death (cardiac-related)
Langley, 2015[185] **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	BSA (%): a) 29.0, b) 22.9 PASI: a) 20.5, b) 18.4 Hyperlipidemia a) 24.6, b) 16.4 Hypertension (%)ǂ: a) 29.6, b) 24. PsA (%)*: a) 28.7, b) 21.9 Systemic therapies: a) 63.2, b) 47.8 Previous biologics (%): a) 44.4, b) 30.3 **p=0.009, ǂp=0.046, all other comparisons p<0.001*	**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) 195, 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) 6.57, b) 7.43, c) 7.02 *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 ** per 100 patient-years*
Langley, 2010[186] **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	**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

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
					DLQI, mean 1) -9.3, 2) -10.0, 3) -0.5 *UST vs. placebo, p<0.001*	
Reich, 2011[187] **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	**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 *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)*	NR
Sofen, 2010[188] **PHOENIX 1 and 2** ***Abstract***	Pooled analysis of patients from PHOENIX 1 and 2 for a subgroup with PsA	N=563	See original studies	PASI: 20.7 DLQI: 12.6	**At wk 12:** Primary: PASI 75 (%): 1) 63.0, 2) 61.5, 3) 3.6 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*	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Guenther, 2011[189] **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	**At wk 12**: 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	NR
Igarashi, 2012[94] ***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	**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)	Primary outcomes at wk 12: AEs ≥1 (%): 1) 65.6, 2) 59.7, 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)

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
				Previous biologics (%): 1) 1.6, 2) 0.0, 3) 0.0	1) -38.5, 2) -9.3. 3) +8.0 *p=NR* *Other outcomes reported: DLQI mean change, SF-36 summary, MCS, and PDI scores also included through wk 64*	No deaths through wk 72
Tsai, 2011[95] **PEARL** ***Good quality publication***	Phase 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) 11.9, 13.9 PASI: 1) 25.2, 2) 22.9 DLQI: 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	**At 12 weeks** PASI 75 (%): 1) 67.2, 2) 5.0 *p<0.001* PASI 50 (%): 1) 83.6, 2) 13.3 *p<0.001* PASI 90 (%): 1) 49.2, 2) 1.7 *p<0.001* PASI 100 (%): 1) 8.2, 2) 0.0 *p=0.024* PGA, cleared/minimal (%): 1) 70.5, 2) 8.3 *p<0.001*	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) 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 (%):

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
				(49.6%) and Korean (50.4%)	DLQI, mean change: 1) -11.2, 2) -0.5 *p<0.001*	Placebo/UST, 3.6 UST45, 8.5 Discontinuation from AEs (%): Placebo/UST, 0.0 UST45, 1.6 Infections (%): Placebo/UST, 25.5 UST45, 32.2 No deaths during the study
Zhu, 2013[190] **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 (%): 1)8.8, 2)8.6 Previous biologics (%): 1) 11.9, 6.8	**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* Response was maintained through wk 28	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 No deaths, serious infections, malignancies, or cardiovascular events reported through wk 36

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Observational Studies						
Clemmensen, 2011[31] **DERMBIO** ***Poor quality***	Database of Danish patients to evaluate drug adherence in TNFα-naïve vs. TNFα exposed over 1 year	N=179 1) All ustekinumab (n=71) 2) ustekinumab TNFα-naïve (n=24) 3) ustekinumab TNFα exposed (n=37) 4) TNFαs (n=47)	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 patients, PASI >10 or DLQI >10	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 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*	"No difference in the PASI75 response between the subjects exposed to 1, 2 or 3 TNFαa agents (data NR)" "Previous failure to one or more TNFα inhibitors did not influence treatment responses measured by the time to PASI 75 or the proportion of patients achieving PASI 75"	Discontinuation (%): Ustekinumab survival was significantly better than the adherence to TNFα drugs (p<0.001, HR 0.32, 95% CI 0.15–0.67)
Gelfand, 2012[191] ***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 Previous biologics (%): 37.3	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): 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	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
					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[192] **DERMBIO** ***Good quality***	Database of Danish patients to evaluate long-term drug survival (time to drug discontinuation) 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 *The choice of drug was the decision of the physician*	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 PsO duration (years): 1) 18.7, 2) 19.5, 3) 18.7, 4) 17.9 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	*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 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*	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Goren, 2015 ***Fair quality***	Web-based survey from a US claims database study evaluating differences between ustekinumab and adalimumab for patients previously or not previous on etanercept	N=250 1) bio-naïve (n=68) 1a) ADA (n=26) 1b) UST (n=42) 2) etanercept-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 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	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, the results were still significant. Adjusting for covariates, no significant overall differences were realized on health outcomes across UST and ADA users.	NR
Kalb, 2013[119] **PSOLAR** ***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. *Treatment dosing was determined by the treating physician*	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 *SS differences between the biologics and nonmethotrexate/ nonbiologics cohorts (age, sex, BMI, and disease characteristics [PGA score, PsO duration]), as well as*	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 and bio-naive populations (i.e., lowest rates for the ustekinumab or etanercept cohorts, followed by either the infliximab or adalimumab cohort)*

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
				among the individual biologic groups (higher prevalence of psoriatic arthritis, history of serious infection)		*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[120] **PSOLAR** ***Good quality***	Multicenter, longitudinal, psoriasis-based registry study evaluating adverse events in a real-world setting for 8 years (06/2007-08/2013) Missing values for covariates were imputed	N=12094 1) UST (n=4134) 2) INF (n=1435) 3) ŧother biologics (n=2151) 4) *non-biologics (n=2151) (31,818 patient-years)	NR *Treatment dosing was determined by the treating physician*	Age (years): 1) 47.2, 2) 49.2, 3) 48.4, 4) 51.2 % 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	NR	*Cumulative incidence rates 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

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
	as the mean for continuous factors and as the median for categorical factors.	ǂ4188 were treated with adalimumab and/or etanercept *511 were exposed to methotrexate		Previous biologics (%): 1) 88.4, 2) 94.8, 3) 85.8, 4) 0.0		Serious infections (overall): 1.50 1) 0.95, 2) 2.78, 3) 1.80, 4) 1.26 ** rate/100 patient-years*
Strober, 2016[193] **PSOLAR** ***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) 46.8, 3) 46.7, 4) 47.9 % male: 1) 56.8, 2) 56.0, 3) 58.0, 4) 62.9 PsO duration (years): 1) 19.1, 2) 14.7, 3) 16.1, 4) 17.2 PsA (%): 1) 33.5, 2) 35.8, 3) 35.0, 4) 44.0 *Baseline clinical values numerically reflected more severe disease in the infliximab group.*	**12 Month Analysis** 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 *No other comparisons to UST were SS* *Adjusted multivariate analysis *Missing data excluded in the analysis* *Other outcomes reported: 6-month data and BSA*	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Iskandar, 2017[194] **BADBIR** ***Good quality publication*** ***NEW EVIDENCE***	Prospective observational cohort registry that compares two adult psoriasis cohorts: patients treated with biologics, and a second comparator group with similar disease characteristics but exposed only to nonbiologic systemic therapies. This study focused on evaluating the impact of biologics on quality of life.	N=2152 1) Etanercept (n=517) 2) Adalimumab (n= 1239) 3) Ustekinumab (n=396)	Inclusion: Adult patients with chronic plaque psoriasis, receiving adalimumab, etanercept or ustekinumab with follow-up data ≥6months	Age, mean 1)45.1; 2)44.8; 3)46.7 Female, % 1)42.0; 2)39.1.0; 3)36.6 Duration of PsO, yr 1)22.9; 2)22.3; 3)22.0 With PsA, % 1) 25.0; 2)25.3; 3)21.2 Biologic naive, % 1)93.0; 2)83.1; 3)57.1 DLQI total score, median 1) 18 2) 18 3) 19 DLQI "0' or '1', % 1) 1.6 2) 1.7 3) 1.9 EQ-5D utility score, median (IQR) 1) 0.73 (0.52, 0.8) 2) 0.73 (0.62, 0.8) 3) 0.73 (0.59, 0.8)	**At 6 months** DLQI change from baseline, median (IQR) 1) -11 (-17, -6) 2) -14 (-20, -7) 3) -14 (-19, -7) DLQI, '0' or '1', % 1) 29.5 2) 51.9 3) 46.8 All p<0.001 vs. baseline EQ-5D change from baseline, median (IQR) 1) 0.07 (0, 0.24) 2) 0.11 (0, 0.27) 3) 0.07 (0, 0.24)	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Anti-PDE4 Agent						
Apremilast (Otezla)						
Papp, 2012[195] **(NCT00773734)** ***Good quality publication***	Phase IIb RCT Double-blind Multicenter 35 sites in the US and Canada ITT with LOCF	N=352 1) placebo (n=88) 2) apremilast 10mg BID (n=89) 3) apremilast 20mg BID (n=87) 4) apremilast 30mg BID (n=88) 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)	Inclusion: ≥18 years BSA ≥10%, PASI ≥12 ≥6 months of plaque psoriasis diagnosis 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	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): 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]	**At week 16*:** PASI 50 (%): 1) 25, 2) 38.2, 3) 47.1, 4) 60.2 *2 vs. 1, p=NS* *3 & 4 vs. 1, p<0.002* 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* PASI 100 (%): 1) 1, 2) 0, 3) 3.4, 4) 2.3 *p=NS* sPGA score of 0/1 (%): 1) 12.5, 2) 10.1, 3) 24.1, 4) 33.0 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 (%):	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 (%): 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): 2) 4, 3) 0, 4) 0 Deaths (n): None

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
					1) -6.1, 2) -10.2, 3) -35.5, 4) -43.7 *2 vs. 1, p=NS* *3 &4 vs. 1, p<0.005* DLQI ≥ 5-point decrease (only patients with score >5) (%): 1) 25, 2) 34, 3) 49, 4) 44 2 vs. 1, p=NR 3& 4 vs. 1, p=0.01	
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[196] **(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

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Papp, 2015[103] **(NCT01194219)** **ESTEEM 1** ***Good quality publication***	Phase III RCT Double-blind Multicenter 72 sites in the US, Canada, and Europe ITT with LOCF and NRI results	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 Candidates for phototherapy or systemic therapy Exclusion: use of biologics within 12 to 24 weeks	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 PASI: 1) 19.4, 2) 18.7 DLQI: 1) 12.1, 2) 12.7 PsA (%): NR Previous biologics (%): 1) 28.4, 28.8	**At week 16:** PASI 50 (%): 1) 17.0, 2) 58.7ǂ PASI 75 (%)*: 1) 5.3, 2) 33.1ǂ PASI 90 (%): 1) 0.4, 2) 9.8 sPGA score of 0/1 with ≥2-point reduction (%)*: 1) 3.9, 2) 21.7ǂ 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* *Patients remaining on APR over 52 weeks maintained or continued improvement.* *Other outcomes reported: NPSI, c, BSA mean change, PASI mean % improvement*	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 (%): 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

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Thaci, 2017 [155] **(NCT01194219)** **ESTEEM 1** ***Fair quality publication*** ***NEW EVIDENCE***	Phase III, randomized, double-blind, placebo-controlled, multicenter trial *See Papp, 2015*[103]	1) Placebo (n=282) 2) Apremilast 30 mg BID (n=562)	*See Papp, 2015*[103]	*See Papp, 2015*[103] **Additional patient characteristics:** SF-36v2 MCS, mean (SD) 1)47.0 (11.6) 2)45.8 (12.5) SF-36v2 PCS, mean (SD) 1)48.8 (8.9) 2)48.8 (9.7) WLQ-25, mean (SD) 1)0.037 (0.043) 2)0.040 (0.048)	**At 16 weeks** DLQI, change from baseline, mean (SD) 1)-2.1 (5.69) 2)-6.6 (6.66) *p<0.0001* DLQI 0 or 1, % 1) 6.7 2) 25.8 *p≤0.0095* SF-36v2 MCS, change from baseline, mean (SD) 1)-1.0 (9.16) 2)2.4 (9.50) *p<0.0001* SF-36v2 PCS, change from baseline, mean (SD) 1)0.17 (6.22) 2)1.15 (7.20) WLQ-25 change from baseline, mean (SD) 1)0.006 (0.036) 2)-0.004 (0.039) *p=0.0148*	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Papp, 2016[52] (NCT01194219) **ESTEEM 1** ***Good quality publication*** ***NEW EVIDENCE***	Phase III randomized trial with an open-label extension *See Papp, 2015[103]*	**Week 0 – 16** 1) Placebo (n=282) 2) Apremilast 30mg BID (n=562) At week 16, the placebo group switched to apremilast through week 32, followed by a randomized treatment withdrawal phase to week 52 LTE was continued for up to 5 years	*See Papp, 2015[103]*	*See Papp, 2015[103]*	NR	**Harms from apremilast 0-52 weeks (N=804)** Serious AEs, %: 4.5 AEs leading to discontinuation, %: 7.8 Depression, %: 2 Serious infection, %:0 Suicidal ideation, %: 0 Death: 1 case **>52 - 104 weeks (N=444)** Serious AEs, %: 5.4 AEs leading to discontinuation, %: 2.9 Depression, %: 0.5 Serious infection, %:1.4 Suicidal ideation, %: 0 Death: 1 case

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Paul, 2015[197] **(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 Exclusion: use of biologics within 12 to 24 weeks	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: NR PsA (%): NR Previous biologics (%): 1) 32.1, 2) 33.6	**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: 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 (%): Biologic naïve- 1) 6.5, 2) 31.9 1 vs. 2, p<0.001 Biologic-experienced- 1) 4.5, 2) 22.8	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 At week 52: AEs ≥1 (%): Apremilast- 77.9 SAEs ≥1 (%): Apremilast- 4.7 Discontinuation due to AEs (%): Apremilast- 7.1 Deaths (n): Apremilast- 0

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
					1 vs. 2, p=0.0069 *Other outcomes reported: NPSI, ScPGA, PASI mean % improvement*	
Thaci, 2017 [155] **(NCT01232283)** **ESTEEM 2** ***Fair quality publication*** ***NEW EVIDENCE***	Phase III, randomized, double-blind, placebo-controlled, multicenter trial *See Paul, 2015*[197]	1) Placebo (n=137) 2) Apremilast 30 mg BID (n=274)	*See Paul, 2015*[197]	*See Paul, 2015*[197] **Additional patient characteristics:** DLQI, mean (SD) 1)12.8 (7.1) 2)12.5 (7.1) SF-36v2 MCS, mean (SD) 1)45.3 (12.4) 2)45.4 (12.8) SF-36v2 PCS, mean (SD) 1)48.5 (9.5) 2)48.5 (9.1) WLQ-25, mean (SD) 1)0.038 (0.046) 2)0.045 (0.046)	**At 16 weeks** DLQI, change from baseline, mean (SD) 1)-2.8 (7.22) 2)-6.7 (6.95) *p<0.0001* DLQI 0 or 1, % 1)8.0 2)28.1 *p≤0.0095* SF-36v2 MCS, change from baseline, mean (SD) 1)0.0 (10.50) 2)2.6 (10.13) *p≤0.0095* SF-36v2 PCS, change from baseline, mean (SD) 1)0.28 (7.29) 2)1.60 (7.24) WLQ-25 change from baseline, mean (SD) 1)-0.005 (0.036) 2)-0.006 (0.039)	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Crowley, 2017[198] (NCT01194219 & NCT01232283) **ESTEEM 1 & 2** ***Fair quality publication*** ***NEW EVIDENCE***	2 Phase III, randomized, double-blind, placebo-controlled, multicenter trial *See Papp, 2015[103]* *See Paul, 2015[197]* Pooled analysis of the LTE	**Week 0 – 16** 1) Placebo (n=418) 2) Apremilast 30 mg BID (n=832) **Week 16 - 156** 1) Apremilast BID (n=1184) Patient-years=1902.2	*See Papp, 2015[103]* *See Paul, 2015[197]*	*See Papp, 2015[103]* *See Paul, 2015[197]*	NR	**0 – 156 weeks** Any AE, % (100 PY): 83.2 (237.5) AEs leading to discontinuation, % (100 PY): 11.1 (7) Any AE leading to death, % (100 PY): 0.3 (0.2) Serious AE, % (100 PY): 9 (5.9) MACE: 0.5/100 PY Malignancies: 1.2/100 PY Serious infection: 0.9/100 PY Depression: 1.8/100 PY

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Reich, 2016 [104] **(NCT01690299)** **LIBERATE** ***Good quality publication*** ***NEW EVIDENCE***	Phase IIIb, randomized, controlled, double-blind, multicenter trial LOCF	1) Apremilast 30 mg BID (n=83) 2) Etanercept 50 mg QW (n=83) 3) Placebo (n=84)	Inclusion: Adults (≥18 years) with chronic plaque psoriasis for ≥12 months (PASI≥12, BSA ≥10%, sPGA ≥3) who had inadequate response to ≥1 conventional systemic agent, were candidates for phototherapy or systemic therapy, and had no prior exposure to biologics. Exclusion: Prior failure of >3 systemic agents; history of demyelinating diseases or history of or concurrent congestive heart failure; other clinically significant or major uncontrolled disease; serious infection; latent, active or history of incompletely treated tuberculosis.	Age, mean 1)46.0; 2)47.0; 3)43.4 Male, % 1)59.0; 2)59.0; 3)70.2 Caucasian, % 1)95.2; 2)90.4; 3)95.2 Duration of PsO in years, mean 1)19.7; 2)18.1; 3)16.6 PASI, mean (SD) 1) 19.3 (7.0) 2) 20.3 (7.9) 3) 19.4 (6.8) DLQI, mean (SD) 1) 13.6 (6.7) 2) 12.5 (7.0) 3) 11.4 (6.3) sPGA severe (4), % 1)20.5; 2)15.7; 3)27.4 Prior use of conventional systemic therapies, % 1)79.5; 2)69.9; 3)83.3	**At 16 weeks** PASI 50, % 1)62.7; 2)83.1; 3)33.3 *p<0.0001 for ETN vs. PBO, p=0.0002 for APR vs. PBO* PASI 75, % 1)39.8; 2)48.2; 3)11.9 *p<0.0001 for APR, ETN vs. PBO* PASI 90, % 1)14.5; 2)20.5; 3)3.6 *p<0.001 for ETN vs. PBO, p=0.017 for APR vs. PBO* sPGA 0/1 and ≥2 reduction from baseline, % 1)21.7; 2)28.9; 3)3.6 *p<0.0001 for ETN vs. PBO, p=0.0005 for APR vs. PBO* DLQI, change from baseline, mean (SD) 1)-8.3 (7.7); 2)-7.8 (6.5); 3)-3.5 (5.6)	**0-16 weeks** Any AE, % (EAIR/100 PY) 1) 71.1 (469.0) 2) 53.0 (288.8) 3) 53.6 (292.0) Serious AE, % 1) 3.6 (12.6) 2) 2.4 (7.9) 3) 0.0 (0.0) AE leading to discontinuation, % 1) 3.6 (12.5) 2) 2.4 (7.9) 3) 2.4 (8.3)

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
					p<0.0001 for ETN vs. PBO, p=0.0004 for APR vs. PBO	
Green, 2016[199] **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	**At week 16:** DLQI (mean change): 1) -3.8, 2) -8.3, 3) -7.8 *1 & 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 & 3 , p=0.002* % 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	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Reich, 2017[200] **(NCT01690299)** **LIBERATE** ***Good quality publication*** ***NEW EVIDENCE***	Phase III randomized trial with an open-label extension *See Reich, 2016[201]*	At week 16 of the main trial, the placebo and etanercept group switched to apremilast; apremilast patients continued through week 104 **Week 16 -104** 1) Apremilast/ apremilast (n=74) Patient-years =89.4 2) Etanercept/ apremilast (n=79) Patient-years=102.3 3) Placebo/ apremilast (n=73) Patient-years=95.6	*See Reich, 2016[201]*	*See Reich, 2016[201]*	**At 104 weeks** PASI 75, %: 1) 45.9 2) 51.9 3) 50.7 sPGA 'clear' or 'minimal', %: 1) 18.9 2) 26.6 3) 27.4 DLQI, change from baseline, mean (SD): 1) -7.5 (7.0) 2) -5.2 (7.3) 3) -5.6 (6.3) Pruritus VAS change from baseline, mean (SD) 1) -26.6 (29.1) 2) -24.4 (31.2) 3) -32.3 (33.4)	**16-104 weeks** Any AE, % (PY): 1) 49 (0.54) 2) 54 (0.53) 3) 45 (0.47) Serious AEs, % (PY): 1) 4.1 (0.034) 2) 5.1 (0.039) 3) 6.8 (0.052) AEs leading to discontinuation, % (PY): 1) 5.4 (0.045) 2) 2.5 (0.020) 3) 4.1 (0.031) AE leading to death, % (PY): 1) 0 2) 0 3) 0

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Ohtsuki, 2017 [202] **(NCT01988103)** ***Fair quality publication*** ***NEW EVIDENCE***	Phase IIb, randomized, placebo-controlled, double-blind, multicenter trial Sites in Japan	1) Apremilast 20 mg BID (n=85) 2) Apremilast 30 mg BID (n=85) 3) Placebo (n=84)	Inclusion: Adults (≥20 years) with chronic moderate to severe plaque psoriasis (PASI ≥12, BSA ≥10%) for ≥ 6 months and was inappropriate for or inadequately controlled by topical therapy. Exclusion: Major illness; history of suicide attempt, or major psychiatric illness requiring hospitalization (within last 3 years); significant infection; active or latent TB; prolonged UV exposure; or previous use of biologics (12– 24 weeks), other systemic treatment or phototherapy (4 weeks), or active topical treatments (2 weeks).	Age, mean 1)52.2; 2)51.7; 2)48.3 Male, % 1)81.2; 2)83.5; 3)73.8 Duration of PsO, yr 1)12.6; 2)13.9; 3)12.4 With PsA, % NR Previous biologics, % 1)3.5; 2)2.4; 3)4.8 PASI, mean (SD) 1)22.1(9.6) 2)21.6 (8.9) 3)19.9 (8.9) DLQI total, mean (SD) 1)7.4 (5.6) 2)7.4 (5.7) 3)7.5 (5.3)	**At 16 weeks** PASI 50 (%) 1)37.6; 2)48.2; 3)21.4 PASI 75 (%) 1)22.4; 2)28.2; 3)7.1 *(PASI 50, 75, p<0.05 APR20 vs. placebo, p≤0.0003 APR30 vs. placebo)* PASI 90 (%) 1)7.1; 2)14.1; 3)1.2 sPGA 0 or 1 (%) 1)23.9; 2)26.8; 3)8.8 *(p<0.05 for APR20 & APR30 vs. placebo)* DLQI, change from baseline, mean (SD) 1)-0.4(5.3); 2)-2.2(5.0); 3)+1.3(5.7) *(p<0.05 APR20 vs. placebo, p<0.0001 APR30 vs. placebo)*	**0-16 weeks** Any AEs, % 1)57.6 2)51.8 3)41.7 Serious AEs, % 1)4.7 2)0.0 3)0.0 AEs leading to discontinuation, % 1)11.8 2)7.1 3)4.8 **0-68 weeks** Any AEs, % 1)77.7 2)74.2 Serious AEs, % 1)9.1 2)1.7 AEs leading to discontinuation, % 1) 15.7; 2)8.3 AE leading to death, n 1)1; 2)0

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Komine, 2017[202] **(NCT01988103)** ***Abstract*** ***NEW EVIDENCE***	Phase II randomized trial with an open-label extension *See Ohtsuki, 2017* [202]	1) Apremilast 20 mg BID (n=85) 2) Apremilast 30 mg BID (n=85) 3) Placebo (n=84) At week 16, patients on placebo were re-randomized to either apremilast 20mg or apremilast 30mg	*See Ohtsuki, 2017* [202]	*See Ohtsuki, 2017* [202]	**AT 68 weeks** PASI 75 (%) 1) 30.6 2) 41.2 sPGA 0 or 1 (%) 1) 36.6 2) 39.4	NR

AE: adverse event; BSA: body surface area; DLQI: Dermatology Life Quality Index; EAR: exposure-adjusted rate; IGA: Investigator's Global Assessment; IR: incidence rate; ITT: intention-to-treat; LOCF: last observation carried forward; MACE: major adverse cardiac events; MI: multiple imputation; mLOCF: modified last observation carried forward; BIW: twice weekly; NR: not reported; NRI: nonresponder imputation; PASI: Psoriasis Area Severity Index; PGA: Physician's Global Assessment; PsA: psoriatic arthritis; PsO: psoriasis; PY: patient years; q2w: every two weeks; q4w: every four weeks; SAE: serious adverse event; SD: standard deviation; sPGA: static Physician's Global Assessment; TB: tuberculosis; TEAE: treatment emergent adverse event

*****p-values only reported if significant

Appendix C. Previous Systematic Reviews and Technology Assessments

We identified five systematic reviews, four of which conducted network meta-analyses, and eight health technology appraisals conducted by the National Institute for Health and Care Excellence (NICE) comparing the effectiveness of targeted immunomodulators in moderate-to-severe psoriasis.

Sbidian, E., et al. (2017). "Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis." Cochrane Database of Systematic Reviews, Issue 12, Art. No.: Cd011535.

The authors of this systematic review identified 109 randomized controlled trials (RCTs) conducted in adults with moderate-to-severe psoriasis. Interventions of interest included all drugs of interest in our review (except risankizumab) in addition to conventional systemic treatments (acitretin, ciclosporin, fumaric acid esters, methotrexate), other small molecules (tofacitinib, ponesimod), and other biologics (alefacept, itolizumab). Two-thirds of the identified studies were placebo-controlled trials, 23% were head-to-head trials, and 10% were multi-armed trials (including both active comparator and placebo arms). Collectively, these trials enrolled approximately 40,000 patients, 68% of which were men, and the mean PASI score at baseline was 20. Using network meta-analyses, all 19 interventions were compared and ranked according to their effectiveness as measured by proportion of patients achieving PASI 90 and incidence of serious adverse events (SAEs). The analyses showed that all interventions, on both class- and drug-levels, were superior to placebo in achieving PASI 90. Ranking on the class-level showed that anti-IL-17 agents were the most effective treatments (versus placebo RR: 30.81), followed by anti-IL-12/23 agents (23.16), anti-IL-23 agents (16.53), TNFα agents (11.58), small molecules (8.76), other biologics (4.78), then conventional systemic agents (3.78). On the drug-level, ixekizumab had the highest probability of achieving PASI 90 (versus placebo RR 32.45), followed by secukinumab (26.55), brodalumab (25.45), certolizumab (24.58), guselkumab (21.03), ustekinumab (19.91), then tildrakizumab (15.63). Results from the network meta-analysis for SAEs showed there was no statistically significant difference in the risk of SAEs between all the interventions and placebo. Compared to conventional systemic therapies, anti-IL-17 agents and TNFα agents were associated with a higher risk of SAEs (RR: 2.31 and 2.06, respectively). Generally, more effective treatments were associated with a higher risk of SAEs when compared to other treatments. The authors noted that the evidence for SAEs was of very low to moderate quality and recommended researchers to analyze data from non-randomized or post-marketing studies to assess the long-term risk of SAEs associated with these interventions.

Sawyer, L., et al. (2018). "The comparative efficacy of brodalumab in patients with moderate-to-severe psoriasis: a systematic literature review and network meta-analysis." Journal of Dermatological Treatment.

This systematic review and network meta-analysis assessed the efficacy of brodalumab relative to other biologic therapies (adalimumab, etanercept, infliximab, ixekizumab, secukinumab, and ustekinumab) and apremilast for the treatment of moderate-to-severe chronic plaque psoriasis. Sixty-two publications relating to 54 RCTs met the inclusion criteria for the network meta-analysis. A Bayesian network meta-analysis and an ordered probit model was used to generate the likelihood of achieving PASI response levels (50, 75, 90 and 100). The primary analysis excluded studies with a non-biologic systemic therapy arm and only included the doses of biologics licensed by the European Medicine Agency or recommended by NICE except for brodalumab 140 mg. As a result, the evidence network for the primary analysis included 41 RCTs, and a sensitivity analysis was conducted including all 54 RCTs. Results from the primary analysis with placebo-response adjustment showed that ixekizumab and brodalumab 210 mg were the most effective treatments, followed by secukinumab and infliximab for PASI 50, 75, 90, and 100 when compared to placebo. Specifically, the primary analysis of PASI 75 showed treatment with ixekizumab and brodalumab 210 mg had the highest likelihood of reaching PASI 75 (versus placebo RR: 16.51 and 16.48, respectively), followed by secukinumab (15.27) and infliximab (14.96). Results from the sensitivity analysis including all 54 RCTs showed similar results with anti-IL-17 agents outperforming all other therapies. The primary analysis also demonstrated brodalumab 210 mg was associated with a higher likelihood of achieving PASI 50, 75, 90, and 100 than adalimumab, apremilast, brodalumab 140 mg, etanercept, ustekinumab, infliximab, and secukinumab.

Gomez-Garcia, F., et al. (2017). "Short-term efficacy and safety of new biological agents targeting the interleukin-23-T helper 17 pathway for moderate-to-severe plaque psoriasis: a systematic review and network meta-analysis." Br J Dermatol 176(3): 594-603.

This systematic review and network meta-analysis evaluated the effectiveness and safety of secukinumab, ustekinumab, and TNFα agents. Efficacy measures, including PASI 75 and 90, and safety data at week 10-16 from 27 RCTs were analyzed using frequentist method to generate odds ratios (OR) of direct and indirect comparisons. Other efficacy outcomes such as IGA, PGA, and DLQI were also analyzed but not presented as main results due to missing data for some interventions. All biologics showed superior efficacy compared to placebo but also had higher ORs for adverse events. Based on PASI 75 and 90, infliximab (versus placebo OR 118.89 and 84.11, respectively) and secukinumab (87.07 and 96) were found to be the most effective but also the most likely to produce adverse events. Ustekinumab 90 mg ranked third in effectiveness in terms of achieving PASI 75 and 90 (versus placebo OR 73.67 and 61.34, respectively) and was the only agent showing no increased risk for all safety outcomes compared to placebo. Of the remaining drugs analyzed,

ustekinumab 45 mg was associated with the highest likelihood of achieving PASI 75 and 90 (versus placebo OR 56.16 and 55.95), followed by adalimumab (30.69 and 22.11), then etanercept (17.88 and 16.53). Mixed treatment comparisons based on PASI 75 showed no difference between infliximab and secukinumab, but both were significantly more effective than the other biologics. Etanercept had significantly lower effectiveness compared to other biologics, and adalimumab and ustekinumab were not distinguished from each other.

Zweegers, J., et al. (2016). "Effectiveness of Biologic and Conventional Systemic Therapies in Adults with Chronic Plaque Psoriasis in Daily Practice: A Systematic Review." Acta Derm Venereol 96(4): 453-458.

The authors conducted a literature review of prospective and retrospective observational studies of TNFα agents, ustekinumab, and conventional systemic therapies from 1990 to 2014. A total of 32 studies were identified including two retrospective and two prospective studies comparing PASI responses of biologics of interest. 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 among agents.

Signorovitch, J. E., et al. (2015). "Comparative efficacy of biological treatments for moderate-to-severe psoriasis: a network meta-analysis adjusting for cross-trial differences in reference arm response." Br J Dermatol 172(2): 504-512.

This systematic review identified 15 phase II or III trials of biologic treatments for moderate-to-severe psoriasis conducted in the U.S. or Europe. The authors proposed a network meta-analysis model adjusted for placebo response rate to control for measured and unmeasured patient- and trial-level characteristics. The network meta-analysis results showed all biologics were more effective than placebo with infliximab associated with the highest likelihood of achieving PASI 75 (versus placebo RR 19.49), followed by ustekinumab 90 mg (17.54), ustekinumab 45mg (16.33), adalimumab (16.01), then etanercept (12.54). Etanercept had statistically significant lower effectiveness than the other biologics, and the differences between the others were not statistically significant.

NICE health technology appraisals

NICE has issued technology appraisals for brodalumab, ixekizumab, apremilast, secukinumab, adalimumab, infliximab, ustekinumab, and etanercept for the treatment of moderate-to-severe psoriasis. During the technology appraisal process, a selected academic evidence review group (ERG) evaluates evidence submitted by the intervention technology company and generates a

report on the clinical and cost-effectiveness of the technology. The ERG report is sent to an appraisal committee who issues either an appraisal consultation document or a final appraisal determination with their recommendations.

The company's brodalumab submission[203] showed the treatment sequence starting with brodalumab dominated or had an ICER less than £25,000/QALY versus the sequences starting with other biologics, apremilast, or dimethyl fumarate. Since the cost-effectiveness of a treatment included early in a sequence would be driven by avoiding potentially cost-ineffective treatments later in the sequence, the committee considered the results from the ERG model that compared individual treatments and best supportive care to determine the cost-effectiveness of brodalumab. Results from the ERG model showed brodalumab was cost-effective, and the committee recommended brodalumab as a treatment option for patients with severe disease (PASI≥10) who have not responded to systemic therapy.

The company's ixekizumab submission[204] reported an ICER of £32,541/QALY for the sequence of treatments with ixekizumab as first-line therapy versus the sequence beginning with etanercept. After reviewing the company's model, the ERG added another sequence with ixekizumab as a second-line therapy following adalimumab which the ERG felt was a treatment sequence more likely to be used in real world practice. Results from the ERG model showed the sequence with ixekizumab as a second-line therapy had an ICER of £25,532/QALY versus the etanercept sequence, and the sequence with ixekizumab as a first-line therapy had an ICER of £39,129/QALY versus the second-line ixekizumab sequence. The appraisal committee concluded the cost-effectiveness of ixekizumab was similar to that of other biologics and recommended ixekizumab as a treatment for adults with severe disease (PASI≥10 and DLQI>10) who have not responded to systemic therapy.

Results from the company's apremilast model[205] suggested the sequence of treatments including apremilast dominated the comparator sequence in both modeled populations, distinguished by DLQI>10 or DLQI≤10. Upon review of the company's submission, the ERG noted the company used a high cost of basic supportive care, a US EQ-5D measure instead of a UK measure for utility estimates, and a lower number of annual physician visits than seen in real world practice. Correcting for these and other assumptions, the ERG's model showed apremilast was more clinically effective in both populations but not cost-effective. The ERG's final guidance stated the sequence including apremilast had an ICER of £30,300/QALY in the DLQ1>10 population and £60,000/QALY in the DLQ1≤10 population.

The company's secukinumab model.[206] showed secukinumab dominated adalimumab, ustekinumab 45 mg and 90 mg, and infliximab. Additionally, the company found secukinumab had an ICER of £2,515/QALY versus etanercept and £7,231/QALY versus best supportive care. The ERG performed an exploratory analysis of the company's base case by correcting for assumptions including rates of

mortality, cost of serious adverse events, and cost for best supportive care. Due to structural and parameter uncertainties, the appraisal committee was unable to determine a precise ICER but recommended secukinumab as a cost-effective therapy.

The company's adalimumab submission[207] reported an ICER of £30,538/QALY for adalimumab versus supportive care. The number of hospitalization days avoided influenced model outcomes significantly with no days avoided resulting in an ICER of £60,600/QALY and 39 days avoided resulting in a ICER of £4,800/QALY. The ERG expressed uncertainty of this model input and noted it to be a key factor driving model results. NICE issued an appraisal consultation document and recommended treatment with adalimumab for patients with PASI>10 and DLQI>10 who have not responded to systemic therapy.

Results from the company's infliximab model[208] showed infliximab to be cost-effective when compared to etanercept with an ICER of £26,095/QALY. The ERG notes the company's model defines the population as patients with DLQI scores in the fourth quartile which does not clearly indicate if these patients fall under the moderate-to-severe psoriasis category. NICE recommended treatment with infliximab for patients with very severe disease (PASI>20 and DLQI>18) in appraisal consultation document.

The company's ustekinumab submission[209] reported an ICER of £29,587/QALY for ustekinumab versus supportive care. The model assumed 80% of the population weighed less than 100 kg and were treated with 45 mg of ustekinumab, and the remaining patients received 90 mg of ustekinumab. In the base case, the manufacturer proposed a patient access scheme that discounted the cost of ustekinumab 90 mg to that of ustekinumab 45 mg. ERG analysis showed the probability of ustekinumab being cost-effective at £20,000/QALY and £30,000/QALY was 10% and 47%, respectively.

The manufacturer of etanercept modelled etanercept 25 mg and 50 mg over 12- and 96-week periods. The model[210] showed the ICER for etanercept 25 mg versus no systematic therapy was almost £125,000/QALY in the 12-week model and £37,2000 in the 96-week model. The respective ICERs for etanercept 50 mg were substantially higher. The assessment group at NICE found the ICER for etanercept 25 mg to be £65,320/QALY over a longer time horizon and the ICER for etanercept 50 mg to be substantially higher.

Appendix D. Ongoing Trials

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Anti-IL-17 agents					
Secukinumab					
Study of Efficacy and Safety of Secukinumab in Subjects with Moderate to Severe Chronic Plaque-type Psoriasis/Novartis (NCT03066609)	Phase III, randomized, parallel assignment, quadruple-blinded	1. Secukinumab 150 mg 2. Secukinumab 300 mg 3. Placebo	N=554 Inclusion: ≥18 years Chronic plaque-type psoriasis for at least 6 months Moderate-to-severe psoriasis at baseline (PASI≥12; IGA mod 2011≥3; BSA≥10%) Candidate for systemic therapy Exclusion: Previous exposure to biologic targeting IL-17 or IL-17 receptor	PASI 75 and IGA mod 2011 0/1 at week 12	October 30, 2018
A Study to Evaluate Clear Skin Effect on Quality of Life in Patients With Plaque Psoriasis (PROSE)/Novartis (NCT02752776)	Phase IV, non-randomized, single group assignment, open label	1. Secukinumab	N=1661 Inclusion: ≥18 years Moderate-to-severe plaque-type psoriasis for at least 3 months Exclusion: Previous use of biologic targeting IL-17 or IL-17 receptor	DLQI 0/1 responders at week 16	March 26, 2018

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Study of Secukinumab With 2 mL Pre-filled Syringes (ALLURE)/Novartis (NCT02748863)	Phase III, randomized, parallel assignment, quadruple-blinded	1. Secukinumab 150 mg 2. Secukinumab 300 mg 3. Placebo	N=210 Inclusion: ≥18 years Chronic plaque-type psoriasis for at least 6 months Moderate-to-severe psoriasis at baseline (PASI≥12; IGA mod 2011≥3; BSA≥10%) Candidate for systemic therapy Exclusion: Previous use of biologic targeting IL-17 or IL-17 receptor	PASI 75 responders and IGA mod 2011 0/1 responders at week 12	August 24, 2018
Ixekizumab					
A Study of Ixekizumab (LY2439821) in Chinese Participants With Moderate-to-Severe Plaque Psoriasis/Eli Lilly (NCT03364309)	Phase III, randomized, parallel assignment, double-blinded	1. Ixekizumab 2. Placebo	N=420 Inclusion: ≥18 years Chronic plaque psoriasis for at least 6 months PASI≥12; sPGA≥3; BSA≥10% at baseline Candidates for phototherapy and/or systemic therapy Exclusion: Previous use of biologic targeting IL-17 or IL-17 receptor	sPGA 0/1 responders and PASI 75 responders at week 12	June 15, 2020

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
A Study of Ixekizumab (LY2439821) in Participants With Moderate-to-Severe Plaque Psoriasis Naive to Systemic Treatment/Eli Lilly (NCT02634801)	Phase III, randomized, parallel assignment, single-blinded (outcomes assessor)	1. Ixekizumab 80 mg q2w until week 12, q4w until week 24 2. Fumaric acid esters 215 mg 1-3 times daily 3. Methotrexate 30 mg weekly	N=162 Inclusion: ≥18 years Moderate-to-severe chronic plaque-type psoriasis for at least 6 months PASI>10 or BSA>10% and DLQI>10 Candidates for and naïve to any systemic treatment Exclusion: Serious illness of disorder other than psoriasis or immunocompromised	PASI 75 responders at week 24	November 2017
Brodalumab					
Brodalumab in Subjects With Moderate to Severe Plaque Psoriasis Who Have Failed IL-17A Therapies/Icahn School of Medicine at Mount Sinai (NCT03403036)	Phase IV, single group assignment, open label	1. Brodalumab 210 mg q2w	N=40 Inclusion: ≥18 years sPGA≥3 and BSA>5% at baseline Previously failed treatment with an IL-17A agent Last dose of secukinumab or ixekizumab ≥ 28 days Exclusion: Use of most psoriasis treatments within previous 4 weeks Risk of suicide	PASI score at week 16 AEs through week 16	June 30, 2018

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
A Trial Comparing the Efficacy of Subcutaneous Injections of Brodalumab to Oral Administrations of Fumaric Acid Esters in Adults With Moderate to Severe Plaque Psoriasis/LEO Pharma (NCT03331835)	Phase IV, randomized, parallel assignment, single-blinded (outcome assessor)	1. Brodalumab 210 mg q2w 2. Fumaric acid esters 215 mg 1-3 times daily	N=240 Inclusion: ≥18 years Chronic plaque-type psoriasis for at least 6 months Moderate-to-severe psoriasis at baseline (PASI>10, BSA>10%, DLQI>10) Candidates for systemic therapies Exclusion: Previous use of systemic treatment for psoriasis Use of most psoriasis treatments within previous 4 weeks History of depressive disorder or suicidal behavior	PASI 75 responders and sPGA 0/1 responders at week 24	October 2018
Study to Assess the Long-Term Safety of Brodalumab Compared With Other Therapies in the Treatment of Adults With Moderate-to-Severe Psoriasis/Valeant (NCT03254667)	Prospective observational cohort	1. Brodalumab 2. Non-IL-17-inhibitor biologic medications	N=3500 Inclusion: ≥18 years Moderate-to-severe psoriasis Started on or switched to a systemic treatment within previous 12 months Exclusion: Participating in clinical trial	Incidence of malignancy through 8 years	November 2031

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
A Study of KHK4827 (Brodalumab) in Subjects With Moderate to Severe Psoriasis in Korea/ Kyowa Hakko Kirin Korea Co., Ltd. (NCT02982005)	Phase III, randomized, parallel assignment, triple-blinded	1. Brodalumab 2. Placebo	N=60 Inclusion: ≥20 years Moderate-to-severe chronic plaque-type psoriasis for at least 6 months PASI≥12; sPGA≥3; BSA≥10% at baseline Exclusion: Previous use of IL-17 antagonist History of suicidal ideation Severe depression at baseline	PASI 75 responders and sPGA 0/1 responders at week 12	December 2018
Anti-IL-12/23 agent					
Ustekinumab					
No ongoing trials identified					
Anti-IL-23 agents					
Guselkumab					
A Study to Compare the Efficacy of Guselkumab to Fumaric Acid Esters for the Treatment of Participants With Moderate to Severe Plaque Psoriasis (POLARIS)/Janssen (NCT02951533)	Phase III, randomized, parallel assignment, open label	1. Guselkumab 100 mg 2. Fumaric acid esters	N=119 Inclusion: ≥18 years Plaque-type psoriasis for at least 6 months PASI>10, BSA>10%, DLQI>10 at baseline	PASI 90 responders at week 24	February 14, 2019

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
An Efficacy and Safety of CNTO 1959 (Guselkumab) in Participants With Moderate to Severe Plaque-type Psoriasis/Janssen (NCT02325219)	Phase III, randomized, parallel assignment, double-blind	1. Guselkumab 50 mg 2. Guselkumab 200 mg 3. Placebo	N=226 Inclusion: ≥20 years Plaque-type psoriasis for at least 6 months PASI≥12; IGA≥3; BSA≥10% at baseline Candidate for phototherapy or systemic treatment	IGA 0/1 responders and PASI 90 responders at week 16	September 21, 2018
Tildrakizumab					
No ongoing trials identified					
Risankizumab					
A Study to Assess the Efficacy of Risankizumab Compared to FUMADERM® in Subjects With Moderate to Severe Plaque Psoriasis Who Are Naïve to and Candidates for Systemic Therapy/AbbVie (NCT03255382)	Phase III, randomized, parallel assignment, open label	1. Risankizumab 2. Fumaric acid ester	N=120 Inclusion: ≥18 years Chronic plaque psoriasis for at least 6 months Stable moderate to severe psoriasis at baseline Naïve to and candidate for systemic therapy Exclusion: Previously received systemic therapy	PASI 90 responders at week 24	June 27, 2018

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
BI 655066 (Risankizumab) Compared to Placebo in Japanese Patients With Moderate to Severe Chronic Plaque Psoriasis/AbbVie (NCT03000075)	Phase II, randomized, parallel assignment, double-blind	1. Risankizumab 'high dose' 2. Risankizumab 'low dose' 3. Placebo	N=171 Inclusion: ≥20 years Chronic plaque-psoriasis for at least 6 months Stable moderate to severe psoriasis (PASI≥12; sPGA≥3; BSA≥10%) at baseline Exclusion: Previous exposure to risankizumab	PASI 90 responders at week 16	June 2018
Extension Trial Assessing the Safety and Efficacy of BI 655066/ABBV-066/Risankizumab in Patients With Moderate to Severe Chronic Plaque Psoriasis/AbbVie (NCT02203851)	Phase II, single group assignment, open label	1. Risankizumab	N=104 Inclusion: ≥18 years Moderate to severe chronic plaque psoriasis Completed the preceding trial Exclusion: Experienced SAE during preceding trial	PASI 90 responders at week 48 AEs and SAEs through week 48	August 15, 2018

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Anti-PDE-4 agent					
Apremilast					
A Study of the Real-life Management of Psoriasis Patients Treated With Otezla® (Apremilast) in Belgium (OTELO)/Celgene (NCT03097003)	Prospective observational cohort	1. Apremilast	N=250 Inclusion: ≥18 years Moderate to severe chronic plaque psoriasis (PASI>10 BSA>10%) Exclusion: Received apremilast within last month	Patient Benefit Index for skin diseases responders at month 6	June 30, 2018
Observational Study of Apremilast in Patients With Psoriasis in The Netherlands (APRIL)/Celgene (NCT02652494)	Prospective observational cohort	1. Apremilast	N=200 Inclusion: ≥18 years Starting treatment for psoriasis with apremilast Exclusion: Prior exposure to apremilast PsA treated by rheumatologist	DLQI responders for up to 12 months	December 31, 2018
A Study of Real-World Experience of Psoriasis Patients Treated With Apremilast in Clinical Dermatology Practice (APPRECIATE)/Celgene (NCT02740218)	Retrospective observational cohort	1. Apremilast	N=515 Inclusion: ≥18 years Plaque psoriasis Initiated treatment with apremilast 6 months previously Exclusion: Participating in clinical trial	Patient Benefit Index score up to 7 months	February 28, 2018

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
A Study of Otezla® in Patients With Plaque Psoriasis Under Routine Conditions/Celgene (NCT02626793)	Prospective observational cohort	1. Apremilast	N=500 Inclusion: ≥18 years Moderate to severe plaque psoriasis Failed previous systemic treatment	DLQI score at 4 months	December 30, 2017
Post-Marketing Surveillance Study of OTEZLA/Celgene (NCT03284879)	Prospective observational case-only	1. Apremilast	N=1000 Inclusion: All ages Psoriasis vulgaris with an inadequate response to topical therapies or psoriasis arthropathica	AEs through 12 months, PGA and DLQI score at 12 months	August 31, 2021
TNF- α agents					
Adalimumab					
Comparative Clinical Trial of Efficacy and Safety of BCD-057 and Humira® in Patients With Moderate to Severe Plaque Psoriasis (CALYPSO)/Biocad (NCT02762955)	Phase III, randomized, parallel assignment, triple-blinded	1. BCD-057 (adalimumab biosimilar) 40 mg q2w 2. Adalimumab 40 mg q2w	N=344 Inclusion: 18-75 years Moderate to severe plaque psoriasis for at least 6 months PASI≥12; sPGA≥3; BSA≥10% at baseline Candidates for phototherapy or systemic treatments Exclusion: Previous use of TNFα therapy or previous use of 2 or more biologics Participating in clinical trial within 3 months before trial	PASI 75 responders at 16 weeks	December 2018

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Real-World Outcome of Psoriasis Subjects in Korea on Adalimumab (RAPSODI)/AbbVie (NCT03099083)	Prospective observational cohort	1. Adalimumab	N=100 Inclusion: ≥19 years Diagnosis of psoriasis by investigator Exclusion: Participating in clinical trial at enrollment	EQ-5D score at week 24	November 1, 2018
MAP Study: Methotrexate and Adalimumab in Psoriasis (MAP)/Jeffery J Crowley (NCT03217734)	Phase II/III randomized, parallel assignment, triple-blinded	1. Adalimumab 40 mg q2w 2. Adalimumab 40 mg q2w + methotrexate 10 mg weekly	N=56 Inclusion: ≥18 years Psoriasis for at least 6 months Moderate to severe psoriasis (PASI≥12; BSA≥10%) at baseline Exclusion: Previous exposure to adalimumab or adalimumab biosimilar	PASI score at week 16	October 10, 2018
A Study to Evaluate the Effectiveness and Patient-Reported Outcome of Adalimumab in Patients With Moderate to Severe Plaque Psoriasis in China (ADAPT)/AbbVie (NCT03236870)	Prospective observational cohort	1. Adalimumab	N=310 Inclusion: ≥18 years Patients with moderate to severe plaque psoriasis eligible to use adalimumab Exclusion: Participating in clinical trial at enrollment	PASI 75 responders at week 12	December 1, 2019

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Study of Efficacy and Safety of HLX03 in Subjects With Moderate to Severe Plaque Psoriasis/ Shanghai Henlius Biotech (NCT03316781)	Phase III, randomized, parallel assignment, quadruple-blinded	1. HLX03 (adalimumab biosimilar) 40 mg q2w 2. Adalimumab 40 mg q2w	N=216 Inclusion: 18-75 years Moderate to severe plaque psoriasis for at least 6 months and at baseline (PASI≥12; PGA≥3; BSA≥10%) Previously failed at least one traditional psoriasis treatment	PASI score at week 16	October 2018
Canadian Humira Post Marketing Observational Epidemiological Study: Assessing Effectiveness in Psoriasis (Complete-PS)/AbbVie (NCT01387815)	Prospective observational cohort	1. Topical agents 2. Traditional systemic agents 3. Adalimumab	N=662 Inclusion: ≥18 years Moderate to severe plaque psoriasis determined by physician Treating physician decided to change or add current treatment for any reason	PGA 0/1 responders at month 6	June 30, 2018

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
A Study to Provide Real-world Evidence on the Treatment Goal Achievement Rate, Adherence to and Utilization Patterns of Adalimumab in Patients With Moderate to Severe Plaque Psoriasis in Greece (CONCORDIA)/AbbVie (NCT02713295)	Prospective observational cohort	1. Adalimumab	N=280 Inclusion: ≥18 years Plaque psoriasis for at least 6 months Moderate to severe psoriasis at time of adalimumab treatment onset (BSA>10% or PASI>10 and DLQI>10) Exclusion: Initiated adalimumab more than 2 weeks prior to enrollment Previous exposure to adalimumab unless a period of at least 6 months from the last dose has elapsed	PASI 75 responders or DLQI≤5 responders at week 16	March 15, 2019
Documentation of Humira in Psoriasis Patients in Routine Clinical Practice (LOTOS)/AbbVie (NCT01077232)	Prospective observational case-only	1. Adalimumab	N=3000 Inclusion: ≥18 years Moderate to severe plaque psoriasis Failed other systemic therapy or photochemotherapy	PASI score and PASI 75 responders at 24, 48, and 60 months	October 31, 2020

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Chronic Plaque Psoriasis (Ps) Registry/AbbVie (NCT00799877)	Prospective observational	1. Adalimumab	N=6000 Inclusion: ≥18 years Chronic plaque psoriasis Initiated adalimumab within 4 weeks of enrollment or received continuous adalimumab treatment in the past with documentation of AEs since initiation	AEs, SAEs, and AEs leading to discontinuation every 6 months through 10 years	September 29, 2022
Etanercept					
Safety and Efficacy of Etanercept in Patients With Psoriasis/Chengdu PLA General Hospital (NCT02258282)	Randomized, parallel assignment, single-blinded	1. Etanercept 2. Placebo	N=80 Inclusion: 18 to 75 years old Plaque psoriasis Unsatisfactory response to traditional DMARDs Eligible for systemic therapy PGA≥3; BSA≥3% at baseline	PGA at 24 weeks	December 2022
Infliximab					
No ongoing trials identified					

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Certolizumab pegol					
A Study to Test the Efficacy and Safety of Certolizumab Pegol in Japanese Subjects With Moderate to Severe Chronic Psoriasis/UCB (NCT03051217)	Phase II/III, randomized, parallel assignment, quadruple-blinded	1. Certolizumab 200 mg q2w 2. Certolizumab 400 mg q2w 3. Placebo	N=149 Inclusion: ≥20 years Chronic plaque psoriasis for at least 6 months PASI≥12, PGA≥3; BSA≥10% at baseline Also includes patients with generalized pustular or erythrodermic psoriasis	PASI 75 responders at week 16	January, 2019
Head-to-head					
A Study to Evaluate the Comparative Efficacy of CNTO 1959 (Guselkumab) and Secukinumab for the Treatment of Moderate to Severe Plaque-type Psoriasis (ECLIPSE)/Janssen (NCT03090100)	Phase III, randomized, parallel assignment, double-blinded	1. Secukinumab 2. Guselkumab + placebo	N=1048 Inclusion: ≥18 years Plaque-type psoriasis for at least 6 months Exclusion: Previous use of guselkumab or secukinumab	PASI 90 responders at week 48	November 23, 2018
Risankizumab Versus Secukinumab for Subjects With Moderate to Severe Plaque Psoriasis/AbbVie (NCT03478787)	Phase III, randomized, parallel assignment, single-blinded (outcomes assessor)	1. Risankizumab 2. Secukinumab	N=310 Inclusion: ≥18 years Chronic plaque psoriasis for at least 6 months Moderate to severe psoriasis at baseline Candidate for systemic therapy Exclusion:	PASI 90 responders at week 16 and 52	May 27, 2020

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
			Previous exposure to risankizumab or secukinumab		
A Registry of Patients With Moderate to Severe Plaque Psoriasis (PURE)/Novartis (NCT02786186)	Prospective observational cohort	1. Secukinumab 2. Approved standard of care (other therapies including systemic, phototherapy, or biologic therapy)	N=2500 Inclusion: ≥18 years Moderate-to-severe chronic plaque-type psoriasis Patients initiating a treatment for psoriasis as per regional policy Exclusion: Participation in clinical trial within 30 days	Incidence of TEAE through month 60	December 30, 2024
The Corrona Psoriasis (PSO) Registry/Corrona, LLC. (NCT02707341)	Prospective observational cohort	1. Systemic psoriasis treatments	N=10000 Inclusion: ≥18 years Patients with psoriasis who have started or switched to a systemic psoriasis treatment within prior 12 months	Number of patients with AEs or SAEs through at least 8 years	December 2100
PsoBest - The German Psoriasis Registry/University Medical Center Hamburg-Eppendorf (NCT01848028)	Prospective observational cohort	1. Systemic psoriasis or psoriatic arthritis treatments	N=3500 Inclusion: ≥18 years Patients with plaque-type psoriasis or psoriatic arthritis initiating a systemic treatment for the first time Exclusion: Participating in clinical trial at enrollment	PASI score every 6 months for 10 years	July 2026
Psoriasis Longitudinal Assessment and Registry (PSOLAR)/Janssen	Prospective observational cohort	1. Infliximab 2. Ustekinumab	N=12052 Inclusion: ≥18 years Diagnosis of psoriasis	Number of patients with AEs or SAEs through at least 8 years	May 31, 2021

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
(NCT00508547)		And other systemic treatments	Candidates for or currently receiving systemic treatments for psoriasis Exclusion: Participating in clinical trial at enrollment		
Swiss Dermatology Network of Targeted Therapies (SDNTT)/SDNTT (NCT01706692)	Prospective observational cohort	1. Adalimumab 2. Etanercept 3. Infliximab 4. Ustekinumab And other systemic treatments	N=500 Inclusion: ≥18 years Plaque-type psoriasis or psoriatic arthritis confirmed by dermatologist Receiving specific systemic drug for the first time Exclusion: Participating in a clinical trial at day of registration	PASI score every 6 months for 5 years	June 2021
Spanish Registry of Systemic Treatments in Psoriasis (Biobadaderm)/Spanish Academy of Dermatology (NCT02075697)	Prospective observational cohort	1. Systemic treatments for psoriasis	N=1887 Inclusion Criteria: Any age Psoriasis patients who begin any biological or nonbiologic systemic treatment for the first time	SAEs through 5 years	October 2020
Ustekinumab Safety and Surveillance Program Using the Ingenix NHI Database/Janssen (NCT01081730)	Prospective observational cohort	1. Ustekinumab And other biological and nonbiologic psoriasis treatments	N=2000 Inclusion: All ages Complete medical coverage and pharmacy benefits Enrollment for at least 6 months	Serious infections and other AEs through at least 8 years	April 30, 2018

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date

AE: adverse event; BSA: body surface area; DLQI: Dermatology Life Quality Index; EQ-5D: EuroQol Five Dimensions; IGA: Investigator's Global Assessment; PASI: Psoriasis Area Severity Index; PsA: psoriatic arthritis; q2w: every two weeks; SAE: serious adverse event; sPGA: static Physician's Global Assessment

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. Two investigators 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. Two investigators 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) [211] 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. PASI Outcomes by Trial

Trial	Treatment	Week	N	PASI 50, %	p-value	PASI 75, %	p-value	PASI 90, %	p-value	PASI 100, %	p-value
CHAMPION	Adalimumab	16	108	88	<0.001	79.6	<0.001	51.9	<0.001	16.7	0.004
	placebo	16	53	30.2		18.9		11.3		1.9	
REVEAL	Adalimumab	16	814	NR	NR	71	<0.001	45	<0.001	20	<0.001
	placebo	16	398	NR		6.5		2		1	
Asahina 2010	Adalimumab	16	43	81.4	<0.001	62.8	<0.001	39.5	<0.001	NR	NR
	placebo	16	46	19.6		4.3		0		NR	
Cai 2017	Adalimumab	12	337	NR	NR	77.8	<0.001	55.6	<0.001	13.3	0.001
	placebo	12	87	NR		11.5		3.4		1.1	
CONSORT	Etanercept	12	203	72.4	<0.0001	46.3	<0.0001	19.2	<0.0001	NR	NR
	placebo	12	204	8.8		2.9		0.5		NR	
Leonardi 2003	Etanercept	12	164	73.8	<0.001	49.4	<0.001	22	<0.001	NR	NR
	placebo	12	166	14.5		3.6		0.6		NR	
Tyring 2006	Etanercept	12	311	73.6	<0.0001	47.3	<0.0001	20.9	<0.0001	NR	NR
	placebo	12	306	14.1		4.9		1.3		NR	
Strober 2011	Etanercept	12	139	NR	NR	39.6	NR	13.7	NR	5.8	NR
	placebo	12	72	NR		6.9		4.2		0	
Gottlieb 2011	Etanercept	12	141	NR	NR	56	NR	22.7	NR	7.1	NR
	placebo	12	68	NR		7.4		1.5		0	
Bagel 2012	Etanercept	12	62	85.5	<0.0001	59.7	<0.0001	25.8	<0.0001	NR	NR
	placebo	12	62	6.5		4.8		1.6		NR	
Bachelez 2015	Etanercept	12	335	80.3	<0.0001	58.8	<0.0001	32.2	<0.0001	NR	NR
	placebo	12	107	20.6		5.6		0.9		NR	
PIECE	Etanercept	12	23	60.9	0	21.7	0	0	0.05	0	1
	Infliximab	12	25	96		76		20		4	
EXPRESS 1	Infliximab	10	301	91	<0.0001	80.4	<0.0001	57.1	<0.0001	NR	NR
	placebo	10	77	7.8		2.6		1.3		NR	
EXPRESS 2	Infliximab	10	314	NR	NR	75.5	<0.001	45.2	<0.001	NR	NR
	placebo	10	208	NR		1.9		0.5		NR	
Yang 2012	Infliximab	10	84	94	<0.001	81	<0.001	57.1	<0.001	NR	NR
	placebo	10	45	13.3		2.2		0		NR	
Torii 2010	Infliximab	10	35	82.9	<0.001	68.6	<0.001	54.3	<0.001	NR	NR
	placebo	10	19	10.5		0		0		NR	
ACCEPT	Etanercept	12	347	NR	NR	56.8	≤0.01	23.1	<0.001	NR	NR
	Ustekinumab	12	556	NR		71.4		41.5		NR	
PHOENIX 1	Ustekinumab	12	511	84.7	<0.0001	66.7	<0.0001	39.1	<0.0001	11.7	<0.0001
	placebo	12	255	10.2		3.1		2		0	
PHOENIX 2	Ustekinumab	12	820	86.5	<0.0001	71.2	<0.0001	46.6	<0.0001	18.2	<0.0001
	placebo	12	410	10		3.7		0.7		0	
Igarashi 2012	Ustekinumab	12	126	83.3	<0.0001	63.5	<0.0001	38.1	≤0.001	NR	NR
	placebo	12	31	12.9		6.5		3.2		NR	
PEARL	Ustekinumab	12	61	83.6	<0.001	67.2	<0.001	49.2	<0.001	8.2	NS
	placebo	12	60	13.3		5		1.7		0	
LOTUS	Ustekinumab	12	160	91.3	<0.001	82.5	<0.001	66.9	<0.001	23.8	<0.001
	placebo	12	162	19.8		11.1		3.1		0.6	
FEATURE	Secukinumab	12	59	NR	NR	76.3	<0.0001	60.3	<0.0001	42.4	<0.0001
	placebo	12	59	NR		0		0		0	
CLEAR	Secukinumab	12	334	NR	NR	91	<0.0001	72.8	<0.0001	38.9	0.0003
	Ustekinumab	12	335	NR		79.1		53.4		25.7	

JUNCTURE	Secukinumab	12	60	NR	<0.0001	86.7	<0.0001	55	<0.0001	26.7	<0.0001
	placebo	12	61	NR		3.3		0		0	
ERASURE	Secukinumab	12	245	NR	NR	81.6	<0.001	59.2	<0.001	28.6	<0.001
	placebo	12	246	NR		4.5		1.2		0.8	
FIXTURE	Secukinumab	12	323	NR	NR	77.1	<0.001 vs. ETN and PBO	54.2	<0.001 vs. ETN and PBO	24.1	<0.01 vs. ETN
	Etanercept	12	323	NR		44		20.7		4.3	
	placebo	12	324	NR		4.9		1.5		0	
UNCOVER 1	Ixekizumab	12	433	NR	NR	89.1	<0.001	70.9	<0.001	35.3	<0.001
	placebo	12	431	NR		3.9		0.5		0	
UNCOVER 2	Ixekizumab	12	351	NR	NR	89.7	<0.0001 vs. ETN and PBO	70.7	<0.0001 vs. ETN and PBO	40.5	<0.0001 vs. ETN and PBO
	Etanercept	12	358	NR		41.6		18.7		5.3	
	placebo	12	168	NR		2.4		0.6		0.6	
UNCOVER 3	Ixekizumab	12	385	NR	NR	87.3	<0.0001 vs. ETN and PBO	68.1	<0.0001 vs. ETN and PBO	37.7	<0.0001 vs. ETN and PBO
	Etanercept	12	382	NR		53.4		25.7		7.3	
	placebo	12	193	NR		7.3		3.1		0	
IXORA-S	Ixekizumab	12	136	NR	NR	88.2	<0.001	72.8	<0.001	36	<0.001
	Ustekinumab	12	166	NR		68.7		42.2		14.5	
AMAGINE 1	Brodalumab	12	222	NR	NR	83.3	<0.0001	70.3	<0.0001	41.9	<0.0001
	placebo	12	220	NR		2.7		0.9		0.5	
AMAGINE 2	Brodalumab	12	612	NR	NR	86.3	<0.001 vs. PBO; NS vs. UST	69.9	NR	44.4	<0.001 vs. UST and PBO
	Ustekinumab	12	300	NR		70		47		21.7	
	placebo	12	309	NR		8.1		2.9		0.6	
AMAGINE 3	Brodalumab	12	624	NR	NR	85.1	<0.001 vs. PBO; 0.007 vs. UST	69.1	NR	36.7	<0.001 vs. UST and PBO
	Ustekinumab	12	313	NR		69.3		47.9		18.5	
	placebo	12	315	NR		6		1.9		0.3	
ESTEEM 1	Apremilast	16	562	58.7	<0.0001	33.1	<0.0001	9.8	NR	NR	NR
	placebo	16	282	17		5.3		0.4		NR	
ESTEEM 2	Apremilast	16	274	55.5	<0.001	28.8	<0.001	8.8	0.004	NR	NR
	placebo	16	137	19.7		5.8		1.5		NR	
LIBERATE	Apremilast	16	83	62.7	0.0002	39.8	<0.0001	14.5	NS	NR	NR
	placebo	16	84	33.3		11.9		3.6		NR	
VOYAGE 1	Guselkumab	16	329	NR	NR	91.2	<0.001 vs. ADA and PBO	73.3	<0.001 vs. ADA and PBO	37.4	<0.001 vs. PBO, NR vs. ADA
	Adalimumab	16	334	NR		73.1		49.7		17.1	
	placebo	16	174	NR		5.7		2.9		0.6	
VOYAGE 2	Guselkumab	16	496	NR	NR	86.3	<0.001 vs. ADA and PBO	70	<0.001 vs. ADA and PBO	34.1	<0.001 vs. PBO, NR vs. ADA
	Adalimumab	16	248	NR		68.5		46.8		20.6	
	placebo	16	248	NR		8.1		2.4		0.8	
reSURFACE 1	Tildrakizumab	12	308	NR	NR	63.8	<0.0001	34.6	<0.0001	13.9	<0.0001
	placebo	12	154	NR		5.8		2.6		1.3	
reSURFACE 2	Tildrakizumab	12	314	NR	NR	61.2	<0.0001 vs. PBO, 0.001 vs. ETN	38.8	<0.0001 vs. ETN and PBO	12.4	<0.0001 vs. PBO, 0.0006 vs. ETN
	Etanercept	12	313	NR		48.2		21.4		4.8	
	placebo	12	156	NR		5.8		1.3		0	
CIMPASI 1	Certolizumab	16	95	NR	NR	66.3	<0.0001	35.8	<0.0001	NR	NR
	placebo	16	51	NR		5.9		0		NR	
CIMPASI 2	Certolizumab	16	91	NR	NR	81.3	<0.0001	52.7	<0.0001	NR	NR
	placebo	16	49	NR		12.2		4.1		NR	

CIMPACT	Certolizumab	12	165	REDACT 4		61.2	<0.0001 vs. PBO, NR vs. ETN	31.2	<0.0001 vs. PBO, NR vs. ETN	NR	NR
	Etanercept	12	170	REDACT 3		53.5		27.1		NR	
	placebo	12	57	REDACT 2		5.3		0.2		NR	
IMMhance	Risankizumab	16	407	NR	NR	88.7	<0.001	73.2	<0.001	47.2	<0.001
	placebo	16	100	NR		8		2		1	
UltIMMa 1	Risankizumab	16	304	NR	NR	REDACT 11		75.3	<0.001 vs. UST and PBO	35.9	<0.001 vs. UST and PBO
	Ustekinumab	16	100	NR		REDACT 14		42		12	
	placebo	16	102	NR		REDACT 10		4.9		0	
UltIMMa 2	Risankizumab	16	294	NR	NR	REDACT 13		74.8	<0.001 vs. UST and PBO	50.7	<0.001 vs. UST and PBO
	Ustekinumab	16	99	NR		REDACT 15		47.5		24.2	
	placebo	16	98	NR		REDACT 12		2		2	

NR: not reported; NS: not significant

Additional Comparative Clinical Effectiveness Results

Table E2. Placebo-Controlled Trials: Ranges of PASI 50/75/90/100 Response Rates across Trials*

Treatment	PASI 50		PASI 75		PASI 90		PASI 100	
	Tx	Placebo	Tx	Placebo	Tx	Placebo	Tx	Placebo
Adalimumab	88	30	71-80	7-19	45-52	2-11	17-20	1-2
Etanercept	71-85	7-21	40-59	3-7	19-32	1-2	6-7	0
Infliximab	91	8	76-80	2-3	45-57	1	NR	NR
Certolizumab¥	NR	NR	67-81	4-12	36-53	0-5	NR	NR
Ustekinumab 45 mg	84	10	67	3-4	42	1-2	11-18	0
Ustekinumab 90 mg	86-89	10	66-76	3-4	37-51	1-2	13-18	0
Secukinumab	NR	NR	76-87	0-5	54-60	0-2	24-43	0-1
Ixekizumab	NR	NR	87-90	2-7	68-71	1-3	35-41	0-1
Brodalumab	NR	NR	83-86	3-8	69-70	1-3	37-44	0-2
Apremilast	56-63	17-33	29-40	5-12	9-15	0-4	NR	NR
Guselkumab¥	NR	NR	86-91	6-8	70-73	2-3	34-37	1
Tildrakizumab¥	NR	NR	62-66	6	35-37	1-3	12-14	0-1
Risankizumab¥	NR	NR	89	8	73-75	2-5	47	1

*Excludes trials conducted in exclusively Asian population; ¥New drugs

Table E3. Comparative Trials: PASI Responses

Trial	Treatment	PASI 75	p-value	PASI 90	p-value	PASI 100	p-value
VOYAGE 1 & 2¥	Adalimumab	69-73	<0.001	47-50	<0.001	17-21	<0.001
	Guselkumab	86-91		70-73		34-37	
PIECE¥	Etanercept	22	0.0	0	0.05	0	NS
	Infliximab	76		20		4	
CIMPACT*¥	Etanercept	61	NS	27.1	N/A	NR	NR
	Certolizumab Pegol	53		31.2		NR	
ACCEPT	Etanercept	57	≤0.01	23	<0.001	NR	NR
	Ustekinumab 45 mg	68		36		NR	

	Ustekinumab 90 mg	74		45		NR	
FIXTURE	Etanercept	44	<0.001	21	<0.001	4	<0.001
	Secukinumab 300 mg	77		54		24	
UNCOVER 2&3	Etanercept	42-53	<0.0001	19-26	<0.0001	5-7	<0.0001
	Ixekizumab	87-90		68-70		38-41	
RESURFACE 2¥	Etanercept	48	<0.001	21	<0.001	5	<0.001
	Tildrakizumab	61		39		12	
CLEAR	Ustekinumab WBD	79	0.0001	53	<0.0001	26	<0.0001
	Secukinumab 300 mg	91		73		39	
AMAGINE 2†&3	Ustekinumab WBD	69-70	0.007	47-48	<0.001	19-22	<0.001
	Brodalumab 210 mg	85-86		69-70		37-44	
IXORA-S	Ustekinumab	69	<0.001	42	<0.001	15	0.009
	Ixekizumab	91		75		37	
ULTIMMA 1* & 2*¥	Ustekinumab	Redact 13 & 14	N/A	42-48	<0.001	12-24	<0.001
	Risankizumab	Redact 11 & 15		75		36-51	

*Only available in the grey literature as of April 2016; †P-value NS for PASI 75 in in AMAGINE 2; ¥New trials

Table E4. DLQI Outcomes Across Direct Comparative Trials

Trial	Drug	Mean change	p-value	DLQI 0/1 (%)	p-value
VOYAGE 1	Adalimumab	-9.3	P<0.001	56	P<0.01
	Guselkumab	-11.2		39	
VOYAGE 2	Adalimumab	-9.7		52	P<0.01
	Guselkumab	-11.3	P<0.001	39	
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	
RESURFACE 2	Etanercept	NR	NR	36	NS
	Tildrakizumab	NR		40	
IXORA-S	ixekizumab	NR	NR	61	p<0.001
	ustekinumab	NR		45	
ULTIMMA 1*	Ustekinumab	NR	NR	43	P<0.001
	Risankizumab	NR		66	
ULTIMMA 2*	Ustekinumab	NR	NR	43	P<0.001
	Risankizumab	NR		66	

*Only available in the grey literature

Table E5. Adverse Events During the Placebo-Controlled Period

%	ADA	ETN	IFX	UST	SEC	IXE	BROD	GUS	TIL	RIS	CZP	APR	PBO
Any AE	65	57	71	53	58	58	58	49	46	47	53	69	51
Tx-related death	0	0	0	0.1	0	0	0.1	NR	0.1	NR	0	0.1	0
D/C due to AEs	2	2	7	1	1	2	1	1.3	0.5	0.5	1.1	5	2
Serious AEs	2	2	3	1	2	2	1	1.9	1.5	2	1.4	2	2
Serious Infections	1	0.5	6	0.6	NR	0.4	0.5	0.1	0.5	0.4	0	NR	0.3
≥Grade 3 AEs	2	2	NR	NR	NR	NR	4	NR	NR	NR	NR	4	3
Common AEs, %													
Any Infections	32	27	36	36	29	27	NR	24	NR	NR	29	NR	25
Nasopharyngitis	8	8	NR	12	11	10	9	8	10	NR	12	7	8
Upper respiratory tract infection	7	6	14	5	3	4	6	4.5	1.5	NR	4.9	8	5
Headache	6	7	13	7	6	4	4	5	NR	NR	NR	6	4
Nausea	4	2	4	NR	5	NR	NR	NR	NR	NR	NR	17	4
Injection site reactions	19	14	NA	4	NR	10	1	NR	NR	NR	NR	NA	2
Infusion Reaction	NA	NA	10	NA	NA	NA	NA	NA	NA	NA	NA	NA	7
AEs of Interest													
Malignancy excluding NMSC	0.2	0.5	1	0.2	NR	0.1	NR	0	NR	0.5	0	NR	0.2
NMSC	0.5	0.3	NR	0.4	NR	0.1	NR	0.1	0.1	0.2	0	NR	0.2
MACE	NR	0.2	NR	0.2	NR	0	0	0.1	0.2	0	NR	NR	0

Subgroup Analyses

Patients with Psoriatic Arthritis

We identified no new secondary analysis evaluating outcomes in patients with psoriatic arthritis. In the previous report, we identified and discussed in details five secondary analyses evaluating outcomes for patients with psoriatic arthritis, four of which were from the grey literature.[19,159,160,177,188,213]

All agents (secukinumab, ixekizumab, ustekinumab, and brodalumab) were statistically significantly better relative to placebo (or active comparator) on the PASI 75 among patients with psoriatic arthritis, and the differences were similar to those observed in the overall population (Table X). See the 2016 report for additional details.[53]

Table E6. 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

Patients with Previous Biologic Therapy Exposure

In total, we identified ten studies that evaluated outcomes in patients who were and were not previously exposed to biologic therapy.[31,101,119,143,160,169,172,181,192,197] Subgroup analyses from four RCTs were primarily reported in the grey literature, though we found three peer-reviewed publications: a key clinical trial of apremilast (ESTEEM 2), a Phase II study on brodalumab, and a pooled analysis of UNCOVER 2 & 3. Across placebo-controlled studies, a statistically significantly greater proportion of patients achieved a PASI 75 response with the intervention for patients with and without prior biologic therapy (except for tildrakizumab where p-value was not reported). 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. In one head-to-head comparison between ixekizumab and etanercept, ixekizumab remained superior to etanercept in both groups of patients with (90% vs. 35%, p<0.001) and without (88% vs. 51%; p<0.001) prior biologic use.

Table E7. 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[197]	=0.0069	<0.001
Brodalumab	88	79
Placebo	0	0
p-value[181]	<0.001	<0.001
Ixekizumab	89.5	88.4
Placebo	2.7	5.2
p-value[176]	<0.001	<0.001
Secukinumab	75.7	84.0
Placebo	4.1	4.6
p-value[160]	<0.0001	<0.0001
Tildrakizumab	55	66.4
Placebo	0	7.5
p-value	NR	NR

In addition to the above-described analyses from RCTs, we identified and described three observational studies in the previous report. All were database studies, of which two were based on one small database (DERMBIO registry), while one was based on a large database (PSOLAR registry). Similar to the RCTs, the studies did not find a statistical significant difference in the in PASI 75 response for patients taking one, two, or three prior TNF-α.[31] However, one study found that 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).[192] See the 2016 report for additional details. [53]

Asian Studies

We identified seven Phase III and two Phase II placebo-controlled RCTs that were conducted in Asia, plus a sub analysis of the Japanese portion of the ERASURE study. No head-to-head Asian studies were available.[74,77,88,94,95,158] Two trials of adalimumab included Chinese patients[78] and Japanese patients[77], three distinct trials of ustekinumab included patients in Japan,[94] China (LOTUS),[74] and Taiwan and Korea (PEARL) patients,[95] the subgroup analysis for the secukinumab trial[158] included Japanese patients, the trials for infliximab included Chinese[88] and Japanese patients,[89] while the phase II trials of brodalumab[214] and apremilast[202] included Japanese patients. We did not identify any trials conducted in Asia for etanercept, certolizumab, ixekizumab, guselkumab, tildrakizumab or risankizumab.

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%), ustekinumab 45mg (67-68%) and 90mg (66-76%), brodalumab (83-86%), and apremilast (29-40%) did not demonstrate any identifiable differences from the results reported in the Asian studies. 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. See the evidence table in Appendix B for details of the other outcomes reported in these studies.

Table E8. 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	
Cai, 2017	Adalimumab	NR	NR	78	0.002	56	0.002	13	0.002
	Placebo	NR		12		3		1.1	
Torii, 2010	Infliximab	83	<0.001	69	<0.001	55	<0.001	NR	NR
	Placebo	11		0		9		NR	
Yang, 2012	Infliximab	94	<0.001	81	<0.001	57	<0.001	NR	NR
	Placebo	13		2		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	
Ohtsuki, 2014	Secukinumab	NR	NR	83	<0.0001	62	<0.0001	28	<0.01
	Placebo	NR		7		0		0	
Nakagawa, 2016	Brodalumab	NR	NR	95	<0.001	92	<0.001	60	<0.001
	Placebo	NR		8		3		0	
Ohtsuki, 2017	Apremilast	48	<0.003	28	<0.003	14	<0.05	NR	NR
	Placebo	21		7		1		NR	

*NA=not available; NR=not reported

Appendix F. Network Meta-Analysis Supplemental Information

Network Meta-Analysis Methods

Network meta-analyses were conducted to determine comparative effectiveness using measures of treatment response based on the Psoriasis Area and Severity Index (PASI). For the NMA, we included Phase III RCTs that reported the proportion of patients with an improved PASI score at the end of induction period (10-16 weeks). RCTs were included if they reported one or more commonly used PASI benchmark scores (the proportion of patients with >50%, >75%, or >90% improvement on the PASI scale).

PASI outcomes are ordered categorical data with up to four distinct groups: i.e. PASI<50, PASI 50, PASI 75, and PASI 90, representing a reduction in the Psoriasis Area and Severity Index (PASI) of less than 50%, at least 50%, at least 75%, and at least 90% respectively. Using the PASI outcomes reported in studies, we created mutually exclusive groups by re-classifying the data as <50, 50-74, 75-89, 90-100. Therefore, a multinomial likelihood model with a probit link was used. Model functions have been previously published.[70] This model allows for the inclusion of data from trials that use different thresholds or a different number of thresholds. Our model adjusted for the placebo response rate in each study. Model assumptions are provided below.

Assumption (s):

1) PASI was a continuous variable which has been categorized by specifying cut-points (e.g., 50, 75, 90)
2) The distance (on a standard normal scale) between consecutive categories was the same for every trial and every treatment
3) Treatment effect was the same regardless of the PASI cut-off (i.e., 50 vs. 75 vs. 90).
4) Study-specific treatment effects came from a common distribution, and the amount of between-study variance (i.e., heterogeneity) was assumed to be constant across all treatment comparisons
5) The model includes a covariate for placebo response, which was assumed to be common across all treatments.

Two subgroup analyses were also conducted by: 1) excluding all Asian studies; and 2) excluding studies that had previous biologic exposure in less than 5% of their patient population.

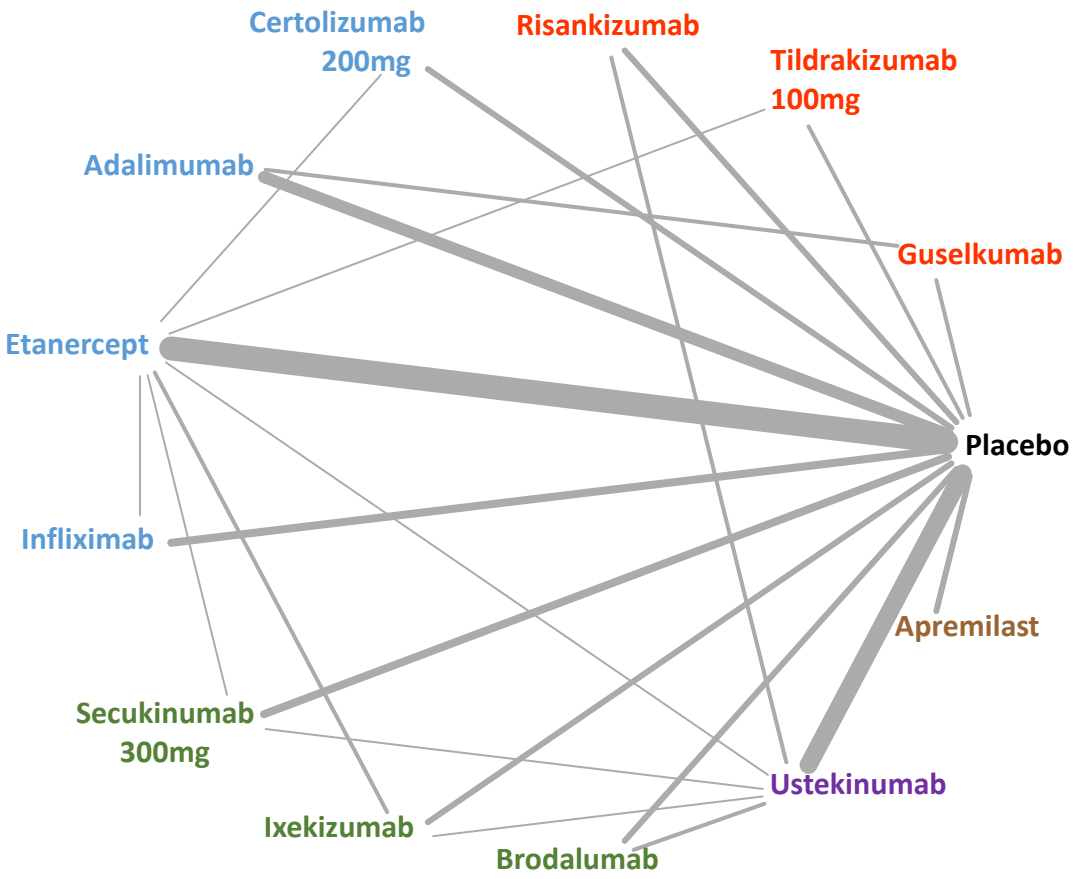
All statistical analyses were conducted within a Bayesian framework with JAGS software (version 4.3.0) via R using the R2jags package.[71] For all analyses we used noninformative prior distributions for all model parameters. We initially discarded the first 50,000 iterations as "burn-in" and base inferences on an additional 50,000 iterations using three chains. Convergence of chains was assessed visually using trace plots.

Relative risks and proportions of patients having a given PASI response state compared to placebo were generated. We based our analysis on existing code.[70,212]

Supplemental NMA Results

The network diagram (Figure E1), additional results on the base case NMA including league tables for PASI 50 and 90 and results of subgroup analyses are presented below. To interpret the network figures, note that the lines indicate the presence of a trial directly assessing the connecting interventions, with the thickness of the line corresponding to the number of trials. The location of treatments and the distances between them does not have any meaning.

Figure F1. Network of Studies Included in the NMA of PASI Outcome



Legend: The TNF inhibitors are depicted in blue, the Interleukin-17 inhibitors are depicted in green, the interleukin 12/23 agent is depicted in purple; the phosphodiesterase inhibitor (anti- PDE4) is depicted in brown; and the new class (interleukin-23 inhibitors) are depicted in red.

Table F2. Base Case NMA Proportions of Patients Having a Given PASI Response State at the End of Induction Period

Treatments	<50%	50%-75%	75%-90%	>90%
Ixekizumab	3.1%	8.0%	12.4%	76.5%
Risankizumab*¥	3.9%	9.3%	13.6%	73.2%
Brodalumab	4.6%	10.4%	14.5%	70.4%
Infliximab	5.3%	11.3%	15.2%	68.1%
Guselkumab¥	5.7%	11.8%	15.6%	66.8%
Secukinumab	5.8%	12.0%	15.7%	66.5%
Ustekinumab(45/90)	13.0%	18.5%	19.1%	49.2%
Adalimumab	17.5%	21.2%	19.6%	41.6%
Tildrakizumab¥	18.0%	21.4%	19.5%	41.0%
Certolizumab*¥	18.2%	21.5%	19.5%	40.6%
Etanercept	26.1%	24.1%	19.0%	30.6%
Apremilast	46.5%	24.6%	14.3%	14.5%
Placebo	84.5%	10.7%	3.3%	1.5%

Table F3. Base Case NMA: League Table of PASI 50 Response

Ixekizumab												
1.01 (0.99, 1.03)	Risankizumab*											
1.02 (1, 1.04)	1.01 (0.98, 1.04)	Brodalumab										
1.02 (1, 1.06)	1.01 (0.98, 1.05)	1.01 (0.97, 1.05)	Infliximab									
1.03 (1, 1.06)	1.02 (0.99, 1.06)	1.01 (0.98, 1.05)	1 (0.96, 1.04)	Guselkumab								
1.03 (1.01, 1.06)	1.02 (0.99, 1.05)	1.01 (0.98, 1.05)	1.01 (0.97, 1.04)	1 (0.96, 1.04)	Secukinumab							
1.11 (1.07, 1.17)	**1.1 (1.07, 1.16)**	**1.1 (1.06, 1.14)**	**1.09 (1.04, 1.14)**	**1.08 (1.04, 1.14)**	**1.08 (1.05, 1.13)**	Ustekinumab†						
1.17 (1.11, 1.27)	**1.16 (1.1, 1.26)**	**1.15 (1.09, 1.24)**	**1.15 (1.08, 1.24)**	**1.14 (1.09, 1.22)**	**1.14 (1.08, 1.23)**	1.05 (1, 1.12)	Adalimumab					
1.18 (1.09, 1.33)	**1.17 (1.08, 1.32)**	**1.16 (1.08, 1.3)**	**1.15 (1.07, 1.29)**	**1.15 (1.06, 1.29)**	**1.15 (1.07, 1.28)**	1.06 (0.99, 1.17)	1.01 (0.93, 1.12)	Tildrakizumab				
1.18 (1.1, 1.32)	**1.17 (1.09, 1.31)**	**1.16 (1.08, 1.29)**	**1.16 (1.07, 1.29)**	**1.15 (1.06, 1.29)**	**1.15 (1.07, 1.28)**	1.06 (0.99, 1.17)	1.01 (0.92, 1.12)	1.01 (0.89, 1.12)	Certolizumab*			
1.31 (1.22, 1.43)	**1.3 (1.21, 1.42)**	**1.29 (1.2, 1.41)**	**1.28 (1.19, 1.4)**	**1.27 (1.19, 1.39)**	**1.27 (1.19, 1.38)**	**1.18 (1.11, 1.26)**	**1.12 (1.04, 1.21)**	**1.11 (1.01, 1.2)**	**1.11 (1.01, 1.21)**	Etanercept		
1.81 (1.53, 2.24)	**1.8 (1.51, 2.21)**	**1.78 (1.5, 2.2)**	**1.77 (1.49, 2.18)**	**1.76 (1.49, 2.16)**	**1.76 (1.48, 2.16)**	**1.63 (1.38, 1.97)**	**1.54 (1.31, 1.87)**	**1.53 (1.28, 1.89)**	**1.53 (1.27, 1.87)**	**1.38 (1.18, 1.67)**	Apremilast	
6.24 (4.86, 8.18)	**6.19 (4.84, 8.06)**	**6.15 (4.82, 7.99)**	**6.1 (4.79, 7.93)**	**6.07 (4.78, 7.85)**	**6.06 (4.77, 7.89)**	**5.61 (4.47, 7.12)**	**5.32 (4.28, 6.67)**	**5.29 (4.24, 6.69)**	**5.26 (4.23, 6.64)**	**4.77 (3.91, 5.89)**	**3.44 (2.82, 4.26)**	PBO

*Input for NMA was exclusively from unpublished grey literature and supplementary data submitted by the manufacturer; †dosing by weight; PBO: placebo

Table F4. Base Case NMA: League Table of PASI 90 Response

Ixekizumab												
1.05 (0.94, 1.18)	Risankizumab*											
1.09 (0.98, 1.22)	1.04 (0.91, 1.18)	Brodalumab										
1.12 (0.98, 1.31)	1.07 (0.92, 1.26)	1.03 (0.89, 1.22)	Infliximab									
1.14 (1.01, 1.32)	1.09 (0.94, 1.27)	1.05 (0.91, 1.23)	1.02 (0.85, 1.21)	Guselkumab								
1.15 (1.03, 1.3)	1.1 (0.96, 1.26)	1.06 (0.93, 1.21)	1.02 (0.87, 1.21)	1 (0.85, 1.17)	Secukinumab							
1.55 (1.38, 1.76)	**1.48 (1.31, 1.7)**	**1.43 (1.28, 1.62)**	**1.38 (1.17, 1.62)**	**1.35 (1.17, 1.58)**	**1.34 (1.2, 1.54)**	Ustekinumab†						
1.83 (1.54, 2.25)	**1.75 (1.45, 2.17)**	**1.68 (1.41, 2.06)**	**1.63 (1.33, 2.04)**	**1.59 (1.38, 1.92)**	**1.59 (1.32, 1.95)**	1.18 (1, 1.41)	Adalimumab					
1.86 (1.46, 2.51)	**1.78 (1.39, 2.43)**	**1.71 (1.36, 2.3)**	**1.65 (1.29, 2.23)**	**1.62 (1.27, 2.22)**	**1.61 (1.29, 2.17)**	1.2 (0.96, 1.57)	1.02 (0.79, 1.38)	Tildrakizumab				
1.88 (1.49, 2.48)	**1.8 (1.41, 2.42)**	**1.73 (1.37, 2.28)**	**1.68 (1.31, 2.26)**	**1.64 (1.27, 2.22)**	**1.63 (1.28, 2.18)**	1.21 (0.97, 1.59)	1.02 (0.78, 1.38)	1.02 (0.71, 1.37)	Certolizumab			
2.48 (2.1, 3.01)	**2.37 (1.96, 2.91)**	**2.29 (1.91, 2.8)**	**2.22 (1.82, 2.73)**	**2.17 (1.8, 2.67)**	**2.16 (1.83, 2.61)**	**1.6 (1.39, 1.87)**	**1.36 (1.11, 1.67)**	**1.33 (1.04, 1.66)**	**1.32 (1.02, 1.68)**	Etanercept		
5.25 (3.64, 8)	**5.03 (3.41, 7.59)**	**4.84 (3.35, 7.27)**	**4.7 (3.18, 7.1)**	**4.59 (3.15, 6.94)**	**4.58 (3.2, 6.77)**	**3.4 (2.41, 4.94)**	**2.87 (2, 4.25)**	**2.83 (1.82, 4.39)**	**2.8 (1.83, 4.28)**	**2.11 (1.48, 3.11)**	Apremilast	
49.58 (34, 73.52)	**47.23 (32.44, 70.33)**	**45.8 (31.33, 67.37)**	**44.04 (30.48, 65.64)**	**43.12 (30.06, 63.68)**	**43.12 (30.13, 63.69)**	**31.99 (23.18, 44.63)**	**27.07 (19.62, 37.43)**	**26.64 (18.22, 38.5)**	**26.28 (18.38, 38.96)**	**20.03 (14.9, 26.79)**	**9.4 (6.57, 13.53)**	PBO

*Input for NMA was exclusively from unpublished grey literature and supplementary data submitted by the manufacturer; †dosing by weight; PBO: placebo

Table F5. Subgroup Analysis. Biologic Experienced Studies (Excludes 11 Studies With 5% or Less Biologic Experienced Patient Population), Proportions

Treatment	<50%	50%-74%	75%-90%	>90%
Ixekizumab	3.0%	7.9%	12.3%	76.9%
Risankizumab*¥	3.7%	9.0%	13.3%	74.0%
Brodalumab	4.5%	10.2%	14.4%	70.9%
Infliximab	5.0%	11.0%	15.0%	69.0%
Guselkumab¥	5.1%	11.2%	15.1%	68.4%
Secukinumab	5.6%	11.8%	15.6%	67.0%
Ustekinumab(45/90)	13.0%	18.7%	19.1%	49.1%
Adalimumab	16.0%	20.5%	19.4%	43.9%
Tildrakizumab¥	17.2%	21.2%	19.4%	42.0%
Certolizumab*¥	18.7%	21.8%	19.4%	39.7%
Etanercept	26.7%	24.4%	18.9%	29.9%
Apremilast	46.2%	24.8%	14.3%	14.6%
Placebo	85.6%	10.0%	3.0%	1.3%

*Input for NMA was exclusively from unpublished grey literature and supplementary data submitted by the manufacturer;¥New drugs

Table F6. Subgroup Analysis. Biologic Experienced Studies (Excludes 11 Studies With 5% Or Less Biologic Experienced Patient Population), Relative Risks Vs. Placebo

Treatment	PASI 50			PASI 75			PASI 90		
	RR	95% CrI		RR	95% CrI		RR	95% CrI	
Ixekizumab	6.74	5.25	9.06	20.56	14.89	30.00	56.92	38.85	88.07
Risankizumab*¥	6.69	5.23	8.96	20.11	14.54	29.10	54.62	37.26	84.15
Brodalumab	6.64	5.19	8.82	19.72	14.28	28.25	52.48	36.03	80.05
Guselkumab	6.60	5.16	8.84	19.29	14.13	27.76	50.81	34.97	77.43
Infliximab	6.58	5.12	8.77	19.30	13.76	28.11	50.67	32.98	80.24
Secukinumab	6.56	5.15	8.67	19.07	13.89	27.07	49.64	34.26	75.07
Ustekinumab(45/90)	6.05	4.85	7.86	15.77	11.98	21.89	36.38	26.30	52.41
Adalimumab	5.82	4.68	7.59	14.62	10.89	20.30	32.49	22.74	48.28
Tildrakizumab¥	5.72	4.56	7.45	14.14	10.37	20.00	30.92	20.68	47.67
Certolizumab*¥	5.64	4.52	7.30	13.66	10.17	19.31	29.43	20.48	45.25
Etanercept	5.08	4.15	6.49	11.28	8.72	15.22	22.22	16.18	31.56
Apremilast	3.72	2.95	4.69	6.64	4.75	9.18	10.77	6.99	16.25

*Input for NMA was exclusively from unpublished grey literature and supplementary data submitted by the manufacturer;¥New drugs

Table F7. Subgroup Analysis. Multi-National Studies (Excludes All 7 Asian Studies), Proportions

Treatment	<50%	50%-74%	75%-90%	>90%
Ixekizumab	3.2%	8.2%	12.6%	76.0%
Risankizumab*¥	4.0%	9.6%	13.9%	72.5%
Brodalumab	4.7%	10.6%	14.8%	69.8%
Infliximab	5.0%	11.0%	15.1%	68.9%
Guselkumab¥	5.6%	11.7%	15.6%	67.0%
Secukinumab	5.9%	12.1%	15.9%	66.0%
Ustekinumab(45/90)	13.5%	19.0%	19.3%	48.0%
Adalimumab	17.3%	21.2%	19.6%	41.7%
Tildrakizumab¥	17.8%	21.5%	19.5%	40.8%
Certolizumab*¥	18.1%	21.6%	19.6%	40.5%
Etanercept	26.3%	24.3%	19.1%	30.2%
Apremilast	45.9%	24.9%	14.5%	14.7%
Placebo	84.2%	10.9%	3.4%	1.6%

*Input for NMA was exclusively from unpublished grey literature and supplementary data submitted by the manufacturer;¥New drugs

NMA code

Model

```
model <- function() { # *** PROGRAM STARTS
  for(i in 1:ns){ # LOOP THROUGH STUDIES
    w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
    delta[i,1] <- 0 # treatment effect is zero for control arm
    mu[i] ~ dnorm(0,.001) # vague priors for all trial baselines (smaller than original)
    for (k in 1:na[i]) { # LOOP THROUGH ARMS
      p[i,k,1] <- 1 # Pr(PASI >0)
      for (j in 1:(nc[i]-1)) { # LOOP THROUGH CATEGORIES
        r[i,k,j] ~ dbin(q[i,k,j],n[i,k,j]) # binomial likelihood
        q[i,k,j] <- 1-(p[i,k,C[i,(j+1)]]/p[i,k,C[i,j]]) # conditional probabilities
        theta[i,k,j] <- mu[i] + delta[i,k] + z[j]+(beta[t[i,k]]-beta[t[i,1]])*(mu[i]-mx) # linear predictor
        rhat[i,k,j] <- q[i,k,j] * n[i,k,j] # predicted number events
        dv[i,k,j] <- 2 * (r[i,k,j]*(log(r[i,k,j])-log(rhat[i,k,j])) #Deviance contribution of each category
                    +(n[i,k,j]-r[i,k,j])*(log(n[i,k,j]-r[i,k,j]) - log(n[i,k,j]-rhat[i,k,j])))
      }
      dev[i,k] <- sum(dv[i,k,1:(nc[i]-1)]) # deviance contribution of each arm
      for (j in 2:nc[i]) { # LOOP THROUGH CATEGORIES
```

```
      p[i,k,C[i,j]] <- 1 - phi.adj[i,k,j] # link function
      # adjust link function phi(x) for extreme values that can give numerical errors
      # when x< -5, phi(x)=0, when x> 5, phi(x)=1
      phi.adj[i,k,j] <- step(5+theta[i,k,(j-1)])*(step(theta[i,k,(j-1)]-5)
                                    + step(5-theta[i,k,(j-1)])*phi(theta[i,k,(j-1)]) )
    }
  }
  for (k in 2:na[i]) { # LOOP THROUGH ARMS
    delta[i,k] ~ dnorm(md[i,k],taud[i,k])
    md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LHR distributions, with multi-arm trial correction
    taud[i,k] <- tau *2*(k-1)/k # precision of LHR distributions (with multi-arm trial correction)
    w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]]) # adjustment, multi-arm RCTs
    sw[i,k] <- sum(w[i,1:(k-1)])/(k-1) # cumulative adjustment for multi-arm trials
  }
  resdev[i] <- sum(dev[i,(1:na[i])]) # summed residual deviance contribution for this trial
}
z[1] <- 0 # set z50=0
for (j in 2:(Cmax-1)) { # Set priors for z, for any number of categories
  z.aux[j] ~ dunif(0,5) # priors
  z[j] <- z[j-1] + z.aux[j] # ensures z[j]~Uniform(z[j-1], z[j-1]+5)
}
totresdev <- sum(resdev[]) #Total Residual Deviance
d[1] <- 0 # treatment effect is zero for reference treatment
beta[1]<-0 # coefficient is zero for reference treatment


for (k in 2:nt){
  d[k] ~ dnorm(0,.0001) # vague priors for treatment effects
  beta[k]<-B #common covariate effect
}
B ~ dnorm(0,.0001) #vague prior for covariate effect

sd ~ dunif(0,5) # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)

A ~ dnorm(meanA,precA)
for (k in 1:nt) {
  # calculate prob of achieving PASI >50,>75,>90 on treatment k
  for (j in 1: (Cmax-1)) { T[j,k] <- 1 - phi(A + d[k] + z[j]) }
  # calculate prob of achieving PASI50,50-75,75-90,>90 on treatment k
  T50[k] <- phi(A + d[k] + z[1]+beta[k]*(A-mx))
  T50_75[k] <- phi(A + d[k] + z[2]+beta[k]*(A-mx))-T50[k]
  T75_90[k] <- phi(A + d[k] + z[3]+beta[k]*(A-mx))-T50_75[k]-T50[k]
  T90[k] <- 1- phi(A + d[k] + z[3]+beta[k]*(A-mx))
}

# calculate risk ratios for PASI >50, >75, >90
for (k in 1:(nt-1)){
  for (kk in (k+1):nt){
    rrPASI50[kk,k] <- T[1,kk]/T[1,k]
```

```
    rrPASI75[kk,k] <- T[2,kk]/T[2,k]
    rrPASI90[kk,k] <- T[3,kk]/T[3,k]

    rrPASI50[k,kk] <- T[1,k]/T[1,kk]
    rrPASI75[k,kk] <- T[2,k]/T[2,kk]
    rrPASI90[k,kk] <- T[3,k]/T[3,kk]
   }
  }
}
```

Analysis

```
NMAresults<- jags(data=datalist, inits=jaginits, parameters.to.save = c("d", "z", "T50", "T50_75","T75_90","T90",
                  "B","rrPASI50", "rrPASI75", "rrPASI90"), model.file = model,  n.iter = 100000)
```

Appendix G. Comparative Value Supplemental Information

Model structure

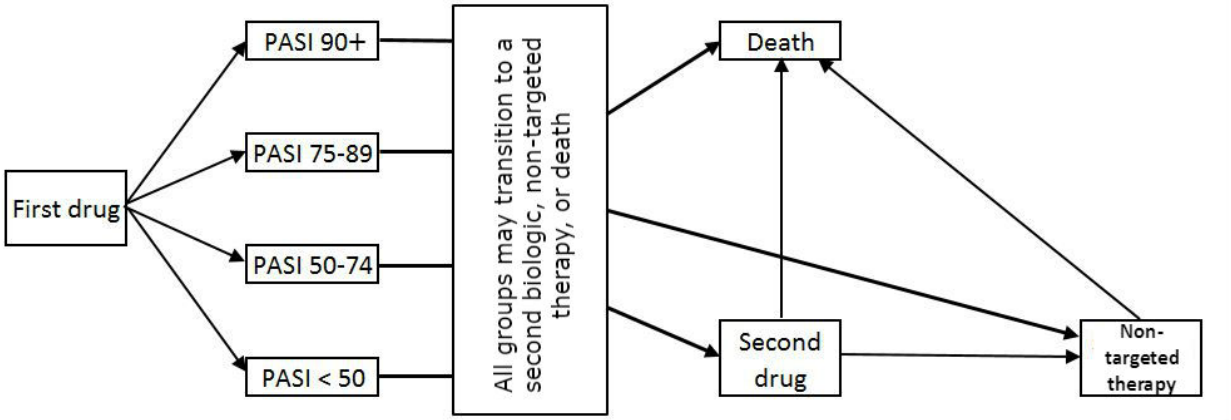
We developed a Markov model in Excel with eight health states, as shown in Figure X; patients could transition between states every month. After the initiation period of the first-line targeted therapy, defined as the point in time at which the primary trial outcome was measured, typically 12-16 weeks, patients were categorized into one of four health states based on their percent improvement in PASI score over baseline: PASI 90 and higher, PASI 75-89, PASI 50-74, and PASI <50. In the base-case analysis, no transition between PASI improvement states was allowed in the model, but drug switching and discontinuation over time could occur.

Patients with response below 75% improvement after the initiation period (16 weeks for adalimumab, apremilast, and guselkumab, 10 weeks for infliximab, and 12 weeks for all other drugs) were assumed to discontinue the first-line therapy in the base-case (this assumption was evaluated in a scenario analysis, described below). 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 varied based on first-line targeted treatment: those patients taking an IL-17 drug switched to guselkumab; patients using guselkumab switched to a market basket representing the average of all IL-17 drugs; all other patients switched to a market basket of all IL-17 drugs plus guselkumab.

Patients with a PASI improvement of at least 75% after the initiation periods continued on first-line therapy after the initiation period. However, we applied a drug-specific discontinuation rate to each

initial targeted drug which determines the rate of discontinuation due to all causes (e.g., loss of efficacy, development of adverse effects) after the end of the initiation period. This rate differed between the first and subsequent years of treatment. After discontinuing their first-line treatment, these patients transition to either second line targeted therapy or non-targeted therapy in the same proportion as those patients who did not have an adequate initial response to their first-line drug. All health states were assumed to have an equal risk of death, which is treated as a function of age alone (i.e., neither change in psoriasis disease state nor treatment alters mortality rate).

Figure G1. Model Framework



Drug discontinuation and switching

The three main data sources are 1) patient registries, 2) long-term trial follow-up, and 3) claims data. Some of the most exhaustive data come from Denmark, where all treated psoriasis patients in the country are enrolled in a long-term patient registry, known as Dermbio. Egeberg et al[138] reported real-world drug discontinuation based on a total of 3495 treatment series (adalimumab: 1332; etanercept: 579; infliximab: 333; ustekinumab: 1055 and secukinumab: 196). Targeted treatment-naïve patients had lower discontinuation rates than non-naïve patients. Infliximab and etanercept had the highest discontinuation rates (etanercept primarily due to lack of effectiveness; infliximab primarily due to causes other than lack of effectiveness) and ustekinumab had the lowest rate. Secukinumab, for which there were limited data, had a discontinuation rate similar to infliximab and etanercept. However, interpretation of these findings is complicated by dose increases for etanercept (29% patients were >50% higher than label) and ustekinumab (33% patients were >50% higher than label for patients <=100kg) compared to almost none for adalimumab and secukinumab, use of secukinumab primarily in patients who had previous exposure to targeted agents, and different definitions of treatment gaps due to dosing schedules. In contrast, Iskandar et al,[32] in a UK-based patient registry (BADBIR) of 2980 patients (adalimumab:

1675; etanercept: 996; ustekinumab: 309), found that ustekinumab and adalimumab had similar discontinuation rates. This finding may be explained by similar treatment gap definitions and lack of ustekinumab dose increases due to UK coverage policies. Of note, approximately 77% of patients with a treatment gap switched to another targeted therapy.

Long-term trial follow-up studies generally have found low rates of drug discontinuation. Interpretation of findings from these studies and comparison to real-world patient registry data is complicated by controlled trial settings, and these data are primarily useful for assessing the discontinuation rates of newer agents in relation to older agents across similar study designs. Langley et al[185] reported a ustekinumab discontinuation rate of 30% (363 of 1212 patients) over 4.7 years, with approximately half of patients receiving dose adjustments. Mrowietz et al[215] reported a 4% dropout during secukinumab induction, and 8% dropout for PASI 75 responders during remainder of year 1; Bissonnette et al[216] reported a secukinumab discontinuation rate from end of year 1 to end of year 3 of 19% (32 of 168 patients). Leonardi et al[171] reported 22% of (84/385) ixekizumab patients discontinued therapy or were lost to follow-up after 3 years (27% had dose adjustments). Blauvelt et al[105] reported a guselkumab discontinuation rate of 8.5% (28 of 329) after 48 weeks in the VOYAGER 1 RCT; Gordon et al[217] unfortunately did not report discontinuation rates at 100 weeks. While not definitive, results from these clinical trials suggest discontinuation rates for ustekinumab, secukinumab, and ixekizumab are generally similar.

Several studies have been conducted in the US using claims data. These studies suggest etanercept and infliximab have the highest discontinuation rates, and that secukinumab discontinuation is similar to ustekinumab. Cao et al ,[218] in a study of 1,000 ustekinumab treated patients (60% targeted treatment experienced), using a treatment gap period of 130 days, found 81% persistence with a mean follow-up ~6 mos. Feldman et al[219] in a study of 1504 secukinumab patients (mean follow-up ~6 months, 68% targeted treatment experienced) reported an 87% persistence. Bagel et al[220] evaluated discontinuation and persistence among targeted drug-naïve (N=3,584) and targeted drug-experienced patients (N=1,185) who initiated secukinumab, adalimumab, or etanercept. Mean follow-up ranged from 529-615 days across drugs. Discontinuation rates at 1 year for the three drugs were 35%, 42%, 47% for naïve and 32%, 41%, and 54% for experience patients, respectively. Adherence ranking at 1 year was analogous. These studies suggest ustekinumab and secukinumab discontinuation over the first 6 mos. are similar, secukinumab discontinuation in year 1 is lower than for adalimumab and etanercept, and discontinuation is higher for targeted drug experienced patients.

Table G1. 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 G2. 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 G3. Alternative Sources of Health State Utilities

Drug	Pickard	NICE adalimumab	NICE ustekinumab
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 G4. Utility Values for Health States

	Utility Value				
	Non-targeted treatment	PASI < 50	PASI 50-74	PASI 75-89	PASI 90-100
Adalimumab	0.660	0.723	0.838	0.838	0.968
Apremilast	0.660	0.710	0.830	0.850	0.870
Ixekizumab	0.660	0.689	0.785	0.826	0.844
Secukinumab	0.660	0.769	0.853	0.886	0.924
Ustekinumab	0.660	0.700	0.830	0.880	0.910
EQ-5D average (Pickard, 2016)	0.660	0.718	0.827	0.856	0.903
EQ-5D-PSO (secukinumab only) (Pickard, 2016)	0.696	0.723	0.798	0.847	0.867

Table G5. 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 G6. 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
ustekinumab	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

Sensitivity Analyses of Economic Model

One-Way Sensitivity Analysis

Below are one-way sensitivity analyses showing the incremental cost and QALYs for four comparisons: ixekizumab versus non-targeted, infliximab versus non-targeted, infliximab versus ixekizumab, and ixekizumab versus etanercept.

Table G7. 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

Table G8. 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

Figure G2. Incremental Costs of Ixekizumab Versus Non-Targeted Therapy

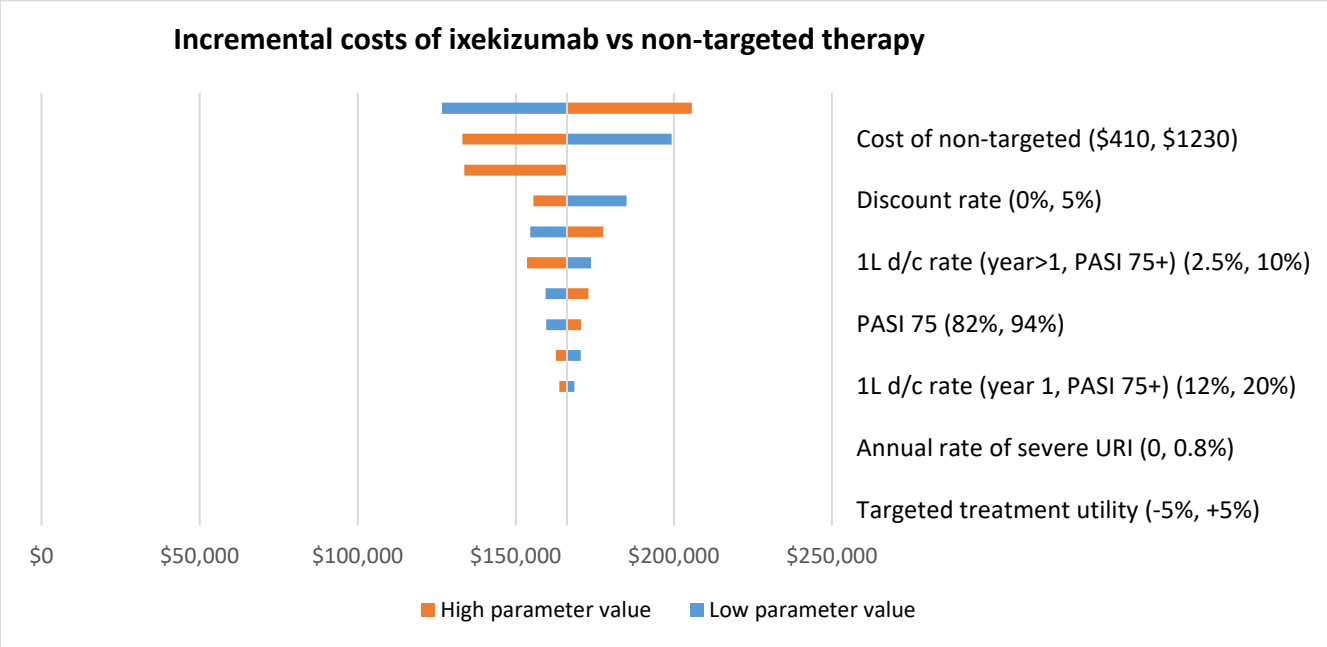


Figure G3. Incremental QALYs Of Ixekizumab Versus Non-Targeted Therapy

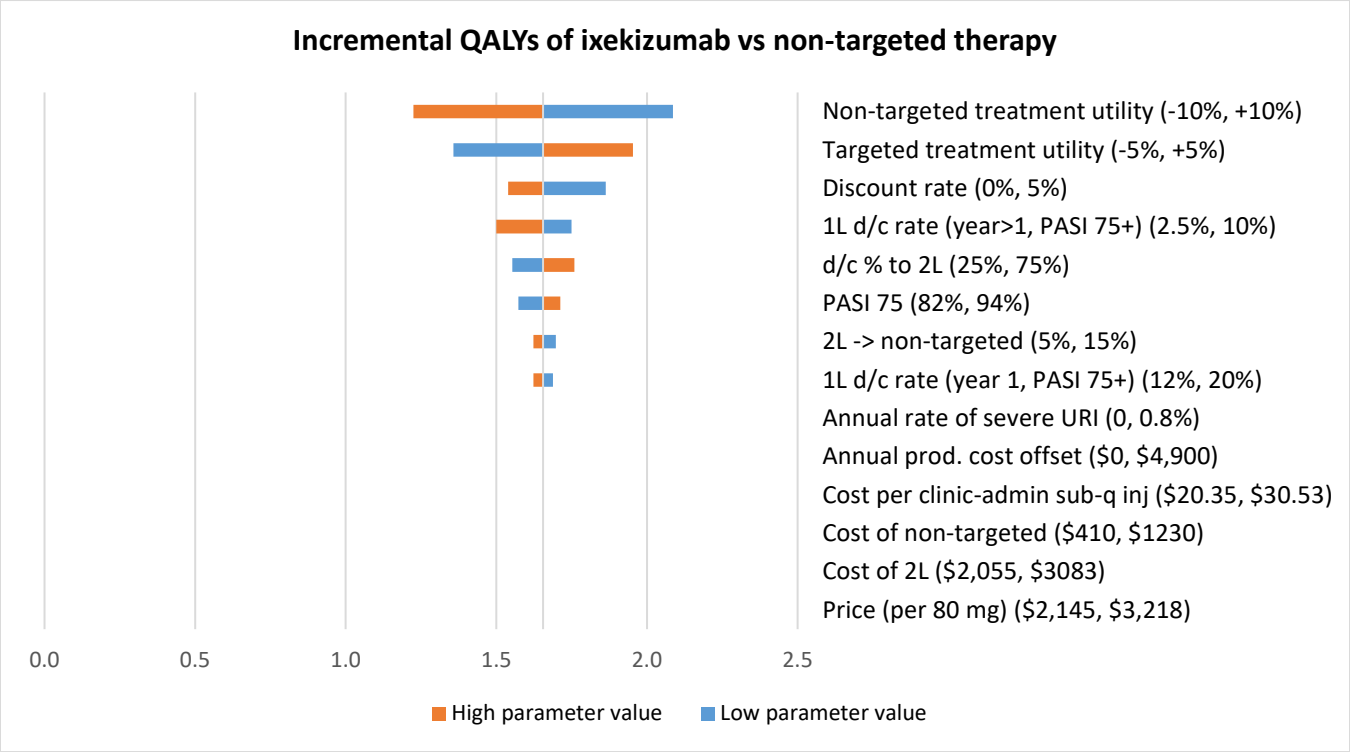


Figure G4. Incremental costs of infliximab versus non-targeted therapy

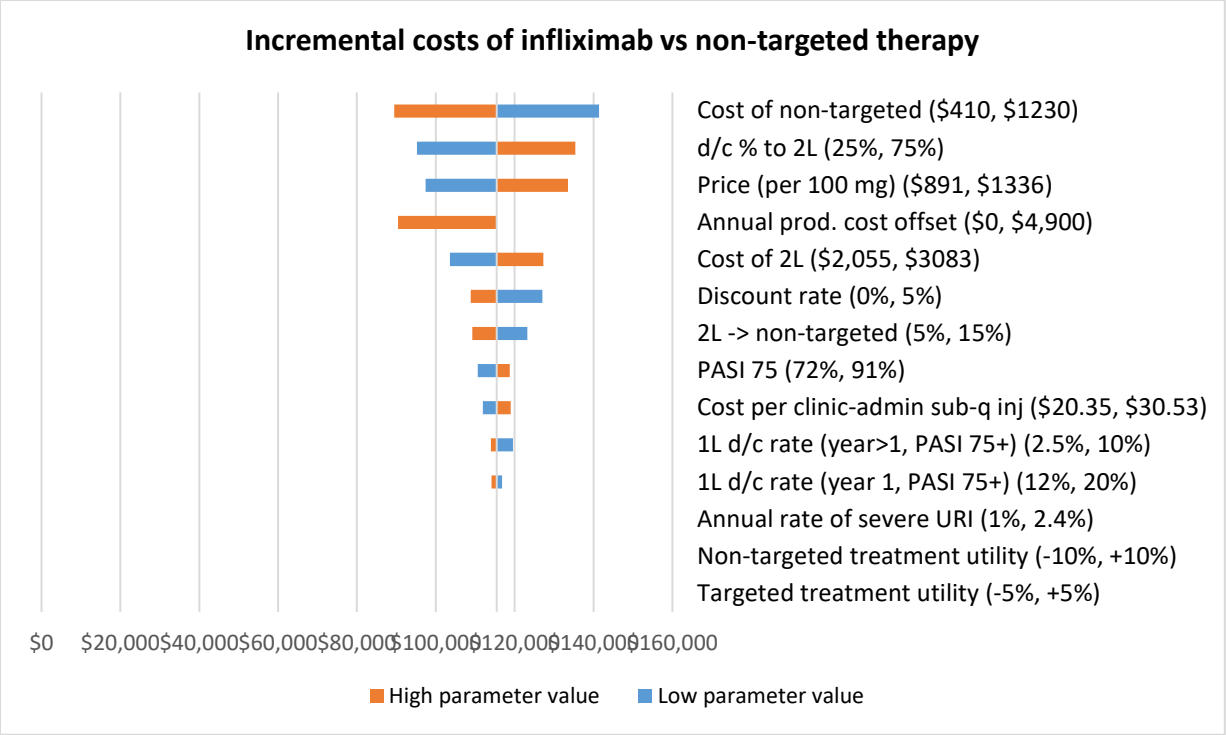


Figure G5. Incremental QALYs Of Infliximab Versus Non-Targeted Therapy

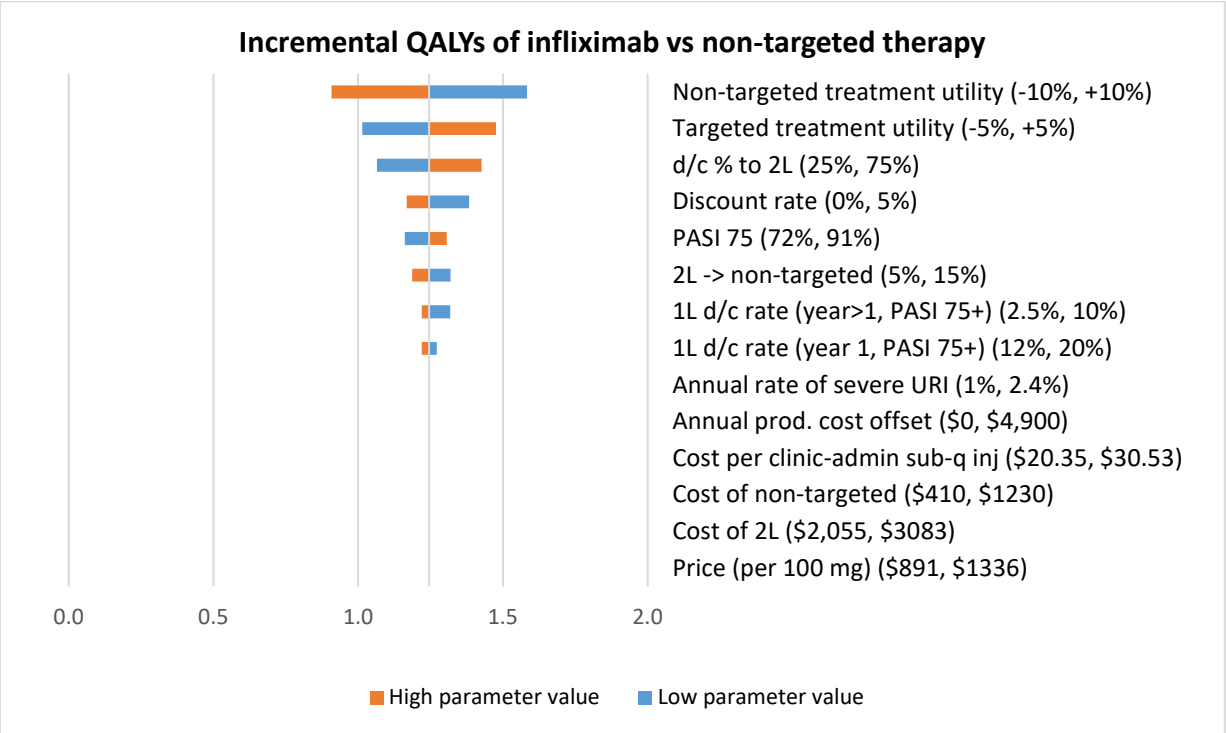


Figure G6. Incremental Costs of Ixekizumab Versus Infliximab

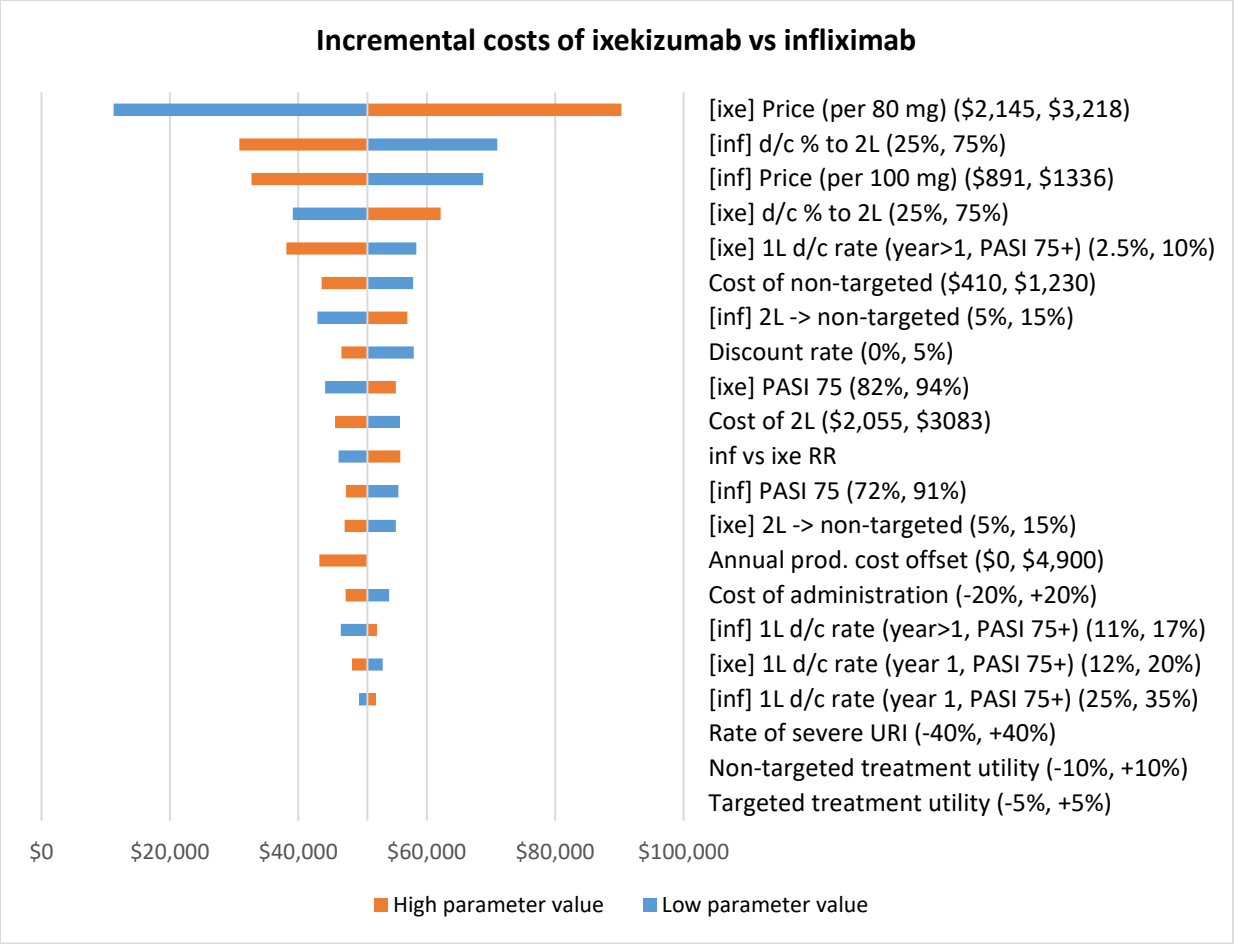


Figure G7. Incremental QALYs of Ixekizumab Versus Infliximab

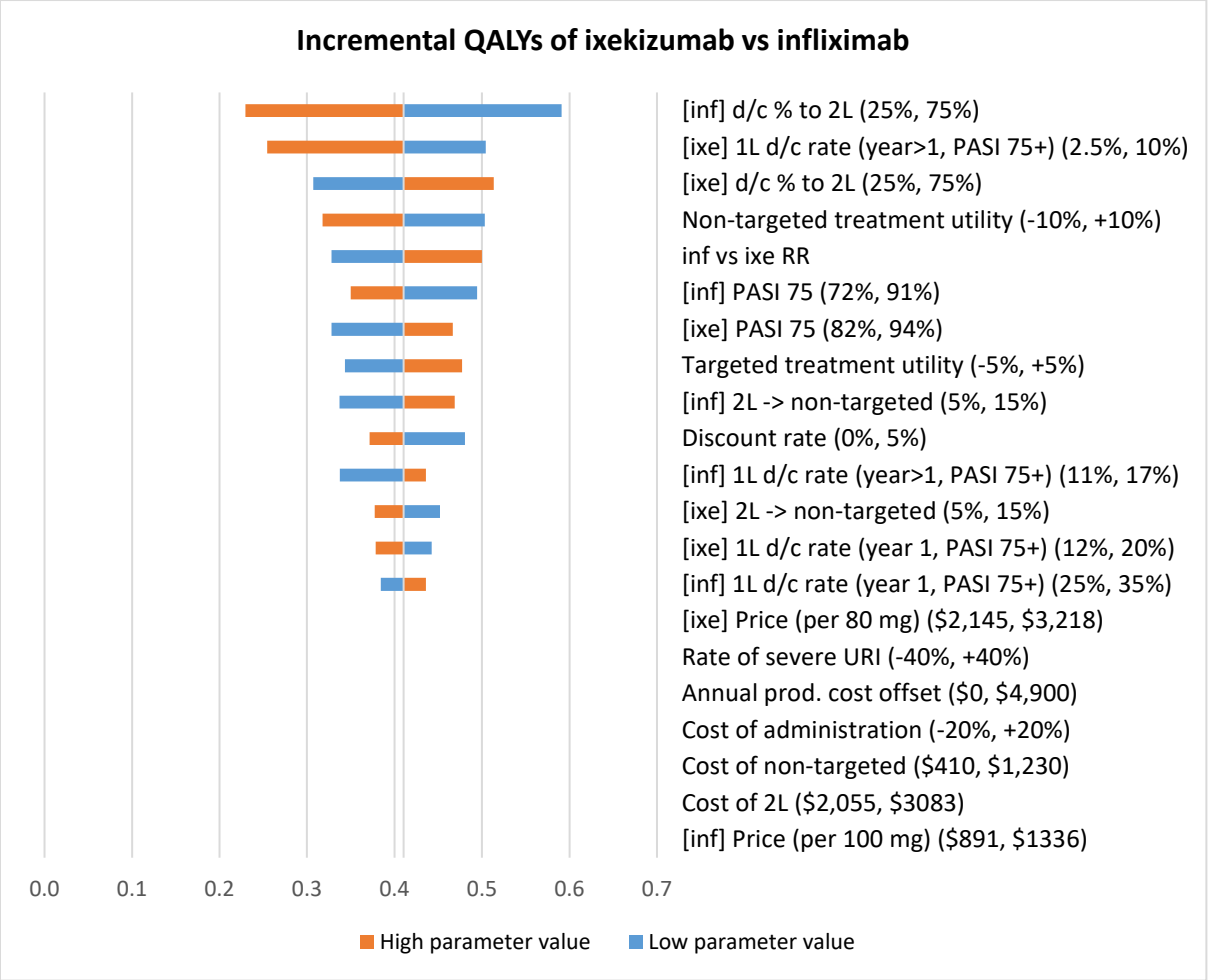


Figure G8. Incremental Costs Of Etanercept Versus Ixekizumab

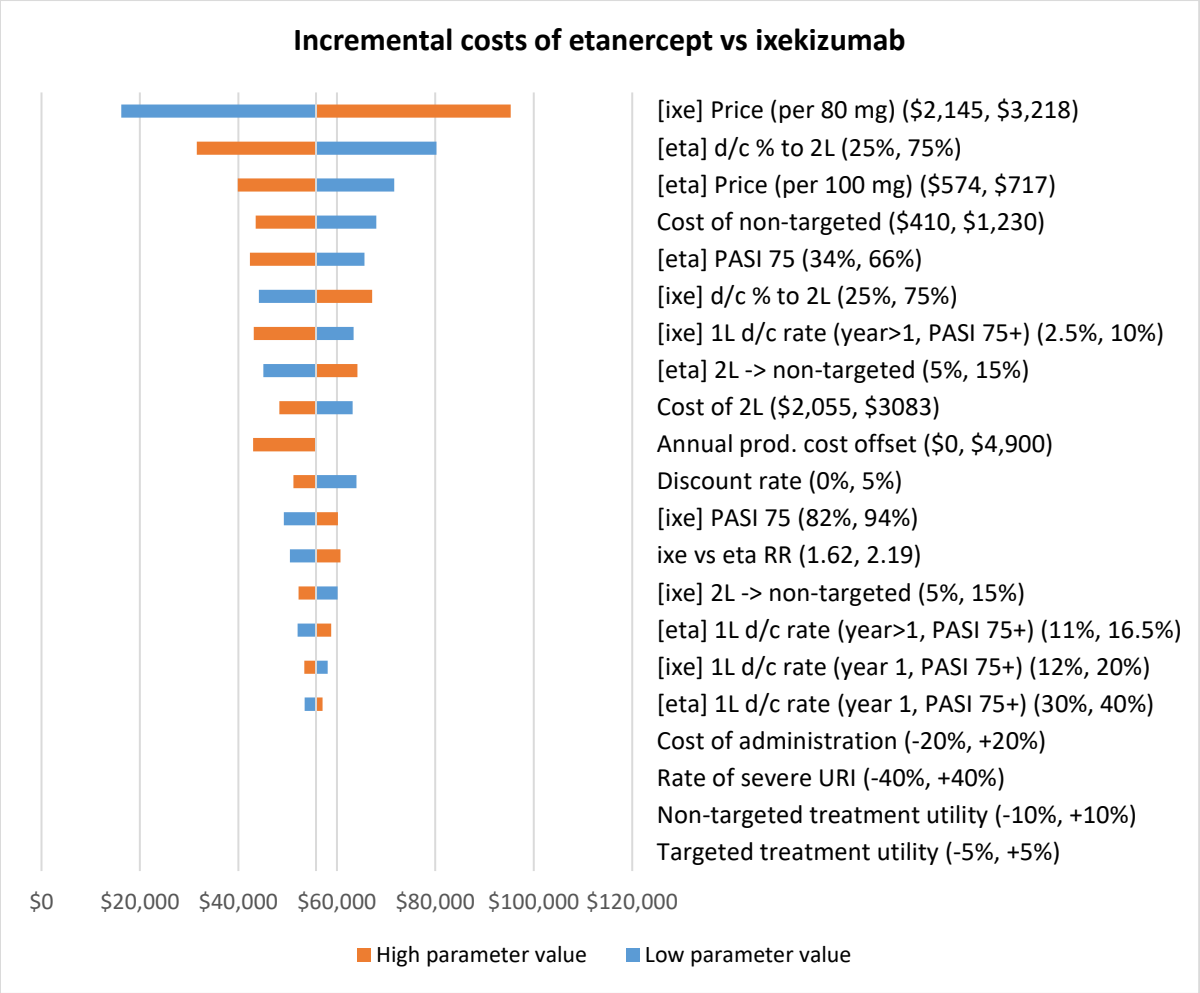
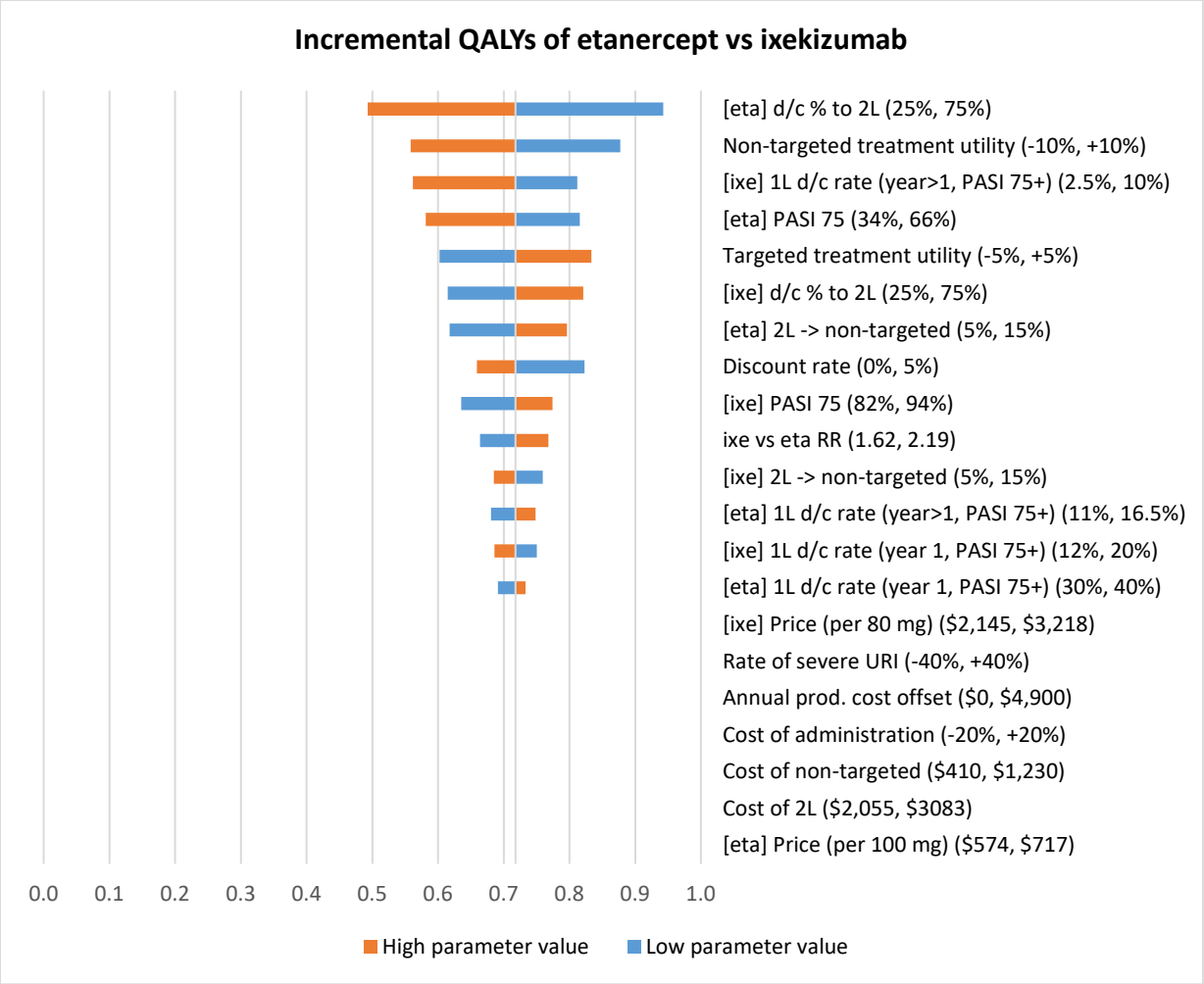


Figure G9. Incremental QALYs Of Etanercept Versus Ixekizumab



Scenario analysis

Table G9: Results Comparing Each Drug To Non-Targeted Therapy Using Non-Discounted WAC Prices

	Cost	QALYs	LYs	Incremental cost/QALY vs. non-target
Non-targeted therapy	$88,086	5.531	8.64	-
Adalimumab	$281,311	6.649	8.64	$172,821
Apremilast	$203,594	6.353	8.64	$140,529
Brodalumab	$363,916	7.151	8.64	$170,285
Etanercept	$263,757	6.469	8.64	$187,340
Infliximab	$268,224	6.776	8.64	$144,669
Ixekizumab	$374,055	7.187	8.64	$172,732
Secukinumab	$341,425	7.018	8.64	$170,342
Ustekinumab	$323,962	6.930	8.64	$168,583

Table G10: Results Comparing Each Drug To Non-Targeted Therapy Using A Lifetime Time Horizon

	Cost	QALYs	LYs	Incremental cost/QALY vs. non-targeted therapy
Non-targeted therapy	$220,024	13.81550	21.59	-
Adalimumab	$379,625	15.31003	21.59	$106,790
Apremilast	$319,243	14.90620	21.59	$90,968
Brodalumab	$474,113	16.59990	21.59	$91,254
Etanercept	$362,729	15.06425	21.59	$114,279
Infliximab	$374,606	15.48090	21.59	$92,820
Ixekizumab	$495,999	16.66841	21.59	$96,734
Secukinumab	$441,245	16.34461	21.59	$87,470
Ustekinumab	$511,815	16.17419	21.59	$123,709

Improvements in PASI 50-74 group

When we assumed patients in the PASI 50-74 group continued therapy with small improvement and relatively higher discontinuation, the results for costs and QALYs changed by 0.2 to 3.5%, and the conclusions were unchanged.

Table G11. Results (% Change Vs. Base Case) Over 10 Years When, During the First Year After the Initiation Period, 2% of Patients in the PASI 50-74 Group Improve to PASI 75-89 and 10% Discontinue Per Month

Treatment	Total Cost	Total QALYs	Base case cost	Base case QALYs
Adalimumab	$279,874 (2.7%)	7.102 (0.4%)	$272,617	7.075
Apremilast	$195,432 (2.5%)	6.736 (0.5%)	$190,708	6.704
Brodalumab	$272,228 (1.3%)	7.383 (0.2%)	$268,862	7.369
Certolizumab pegol	$238,401 (2.6%)	7.102 (0.4%)	$232,265	7.073
Etanercept	$260,419 (3.5%)	6.905 (0.4%)	$251,521	6.875
Guselkumab	$312,865 (1.3%)	7.362 (0.2%)	$308,848	7.348
Infliximab	$227,408 (1.0%)	7.032 (0.2%)	$225,074	7.019
Ixekizumab	$294,544 (1.1%)	7.427 (0.2%)	$291,411	7.415
Secukinumab	$290,386 (1.3%)	7.357 (0.2%)	$286,522	7.342
Ustekinumab	$297,398 (2.6%)	7.185 (0.4%)	$289,938	7.159

Second-line market baskets

Changing the second-line targeted treatment to a market basket represented by an average of all 10 targeted drugs changed total costs and QALYs by 0.1% to -2.5% (see Appendix for details).

Table G12. Results (% Change Vs. Base Case) Over 10 Years When Second-Line Treatment is a Market Basket Representing the Average Cost and Effectiveness of the 10 Included Drugs

Treatment	Total Cost	Total QALYs	Base case cost	Base case QALYs
Adalimumab	$269,347 (-1.2%)	7.035 (-0.6%)	$272,617	7.075
Apremilast	$185,859 (-2.5%)	6.644 (-0.9%)	$190,708	6.704
Brodalumab	$262,033 (-2.5%)	7.347 (-0.3%)	$268,862	7.369
Certolizumab pegol	$229,001 (-1.4%)	7.032 (-0.6%)	$232,265	7.073
Etanercept	$247,266 (-1.7%)	6.822 (-0.8%)	$251,521	6.875

Guselkumab	$309,272 (0.1%)	7.320 (-0.4%)	$308,848	7.348
Infliximab	$220,883 (-1.9%)	6.971 (-0.7%)	$225,074	7.019
Ixekizumab	$285,068 (-2.2%)	7.394 (-0.3%)	$291,411	7.415
Secukinumab	$279,371 (-2.5%)	7.319 (-0.3%)	$286,522	7.342
Ustekinumab	$287,010 (-1.0%)	7.123 (-0.3%)	$289,938	7.159

Appendix H. Coverage Policies in New England

Table H1. Coverage Policies in New England Commercial Plans

	Connecticut		Maine		Massachusetts			New Hampshire		Rhode Island		Vermont	
	Anthem (Wellpoint Inc Group)	Connecticare	Anthem (Wellpoint Inc Group)	HPHC Maine	BCBS of MA	Neighborhood Health Plan	Tufts Health Plan	Anthem (Wellpoint Inc Group)	HPHC New Hampshire	BCBS of RI	Neighborhood Health Plan of RI	BCBS of VT	MVP Grp
TNFα inhibitors													
etanercept (Tradename: Enbrel; Manufacturer: Amgen)													
Tier	4	5	4	3	2	3	2	4	3	4	3	2	2
Systemic therapies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
How many TNFs	0	0	0	0	1	0	0	0	0	0	0	0	0
How many trials of biologics?	0	0	0	0	1	0	0	0	0	0	0	0	0
Preferred Agent	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
infliximab (Tradename: Remicade; Manufacturer: Janssen)													
Tier	MB	5	MB	MB	MB	4	2	MB	MB	4	4	3	MB
Systemic therapies	MB	Yes	MB	MB	Yes	Yes	Yes	MB	MB	Yes	Yes	Yes	no info
How many TNFs	MB	0	MB	MB	2	0	0	MB	MB	0	2	2	no info
How many trials of biologics?	MB	0	MB	MB	2	1	0	MB	MB	0	5	2	no info
Preferred Agent	Yes	Yes	Yes	MB	No	No	Yes	Yes	MB	No	No	No	no info

adalimumab (Tradename: Humira; Manufacturer: AbbVie)													
Tier	4	5	4	3	2	3	2	4	3	4	3	2	2
Systemic therapies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
How many TNFs	0	0	0	0	0	0	0	0	0	0	0	0	0
How many trials of biologics?	0	0	0	0	0	0	0	0	0	0	0	0	0
Preferred Agent	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
certolizumab pegol (Tradename: Cimzia; Manufacturer: UCB)													
Tier	NF	5	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF
Systemic therapies	NF	Yes	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF
How many TNFs	NF	1	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF
How many trials of biologics?	NF	1	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF
Preferred Agent	NF	No	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF
IL17As													
secukinumab (Tradename: Cosentyx; Manufacturer: Novartis)													
Tier	4	5	4	4	2	3	2	4	4	4	4	2	3
Systemic therapies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
How many TNFs	2	1	2	1	0	0	1	2	1	2	0	0	0
How many trials of biologics?	2	1	2	1	0	0	2	2	1	0	0	0	0
Preferred Agent	No	No	No	No	Yes	Yes	No	No	No	Yes	Yes	Yes	No

ixekizumab (Tradename: Taltz; Manufacturer: Eli Lilly)													
Tier	NF	NF	NF	4	4	4	2	NF	4	4	NF	3	2
Systemic therapies	NF	NF	NF	Yes	Yes	Yes	Yes	NF	Yes	Yes	Yes	Yes	Yes
How many TNFs	NF	NF	NF	1	1	2	1	NF	1	2	2	1	1
How many trials of biologics?	NF	NF	NF	1	2	2	2	NF	1	3	5	PA- no info	1
Preferred Agent	NF	NF	NF	No	No	No	No	NF	No	No	No	No	Yes
brodalumab (Tradename: Siliq; Manufacturer: Valeant)													
Tier	NF	NF	NF	4	4	NF	4	NF	4		NF	3	NF
Systemic therapies	NF	NF	NF	Yes	Yes	NF	Yes	NF	Yes	Yes	NF	Yes	NF
How many TNFs	NF	NF	NF	no info	1	NF	1	NF	no info	2	NF	PA- no info	NF
How many trials of biologics?	NF	NF	NF	no info	2	NF	2	NF	no info	3	NF	PA- no info	NF
Preferred Agent	NF	NF	NF	no info	No	NF	No	NF	no info	No	NF	No	NF
IL12/23													
ustekinumab (Tradename: Stelara; Manufacturer: Janssen)													
Tier	NF	NF	4	MB	2	3	2	MB	MB	4	4	2	2
Systemic therapies	NF	NF	Yes	Yes	Yes	Yes	Yes	MB	Yes	Yes	Yes	Yes	Yes
How many TNFs	NF	NF	0	1	0	0	0	MB	1	0	0	PA- no info	1
How many trials of biologics?	NF	NF	0	1	0	0	0	MB	1	0	0	PA- no info	1
Preferred Agent	No	NF	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes

risankizumab (Tradename: *Investigational;* Manufacturer: AbbVie)													
Tier	investigational												
Systemic therapies													
How many TNFs													
How many trials of biologics?													
Preferred Agent													
IL23													
guselkumab (Tradename: Tremfya; Manufacturer: Janssen)													
Tier	NF	NF	NF	NF	3	NF	4	NF	NF		NF	3	NF
Systemic therapies	NF	NF	NF	NF	Yes	NF	Yes	NF	NF	Yes	NF	PA- no info	NF
How many TNFs	NF	NF	NF	NF	1	NF	1	NF	NF	2	NF	PA- no info	NF
How many trials of biologics?	NF	NF	NF	NF	1	NF	2	NF	NF	3	NF	PA- no info	NF
Preferred Agent	NF	NF	NF	NF	No	NF	No	NF	NF	No	NF	Yes	NF
tildrakizumab (Tradename: Ilumya; Manufacturer: Sun Pharma/Merck)													
Tier	*Approved in March 2018; Not included on any formularies at the time of survey*												
Systemic therapies													
How many TNFs													
How many trials of biologics?													
Preferred Agent													

PDE-4													
apremilast (Tradename: Otezla; Manufacturer: Celgene)													
Tier	NF	NF	NF	4	2	3	2	NF	4	4	4	2	3
Systemic therapies	NF	NF	NF	Yes	Yes	Yes	Yes	NF	Yes	Yes	Yes	Yes	Yes
How many TNFs	NF	NF	NF	1	0	no info	1	NF	1	1	0	PA- no info	0
How many trials of biologics?	NF	NF	NF	1	0	no info	2	NF	1	1	1	PA- no info	0
Preferred Agent	NF	NF	NF	No	Yes	Yes	No	NF	No	No	No	Yes	No

Table H2. New England Medicaid Policies for Drug Therapies to treat Moderate-Severe Plaque Psoriasis

	Massachusetts	Connecticut	Rhode Island	Vermont	New Hampshire	Maine
Prefers adalimumab and etanercept	No	Yes	Yes	Yes	Yes	Yes
Prefers secukinumab (after treatment failure with adalimumab)	No	No	No	Yes	No	Yes
Requires PA even for preferred drugs	N/A	Yes	No	Yes	Yes	Yes
# of trials required of systemic therapy	1	1	0	2	1	1